Aseptically Safe and Fast Administration of Freeze-Dried Drug Products: Application for Emergency Cases and Tropical Diseases

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Dekan

For Paps, Oma & Yaël

for you are the ones that made me who I am today

It's the questions we can't answer that teach us the most.

They teach us how to think.

If you give a man an answer, all he gains is a little fact.

But give him a question and he'll look for his own answers.

– Patrick Rothfuss

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Im frühen 19. Jahrhundert wurde die Idee geboren, ein Medikament durch die Haut zu verabreichen und nicht über die oralen Wege oder die Inhalation von Tinkturen und Mischungen. Was mit der Entfernung äußerer Hautschichten zur Verabreichung von Umschlägen oder arzneimittelhaltigen Pflastern begann, wandelte sich schnell zur Verabreichung von Morphin durch Einstechen einer Impflanzette in die Haut. Um 1850 entwickelten der französische Tierarzt Charles Gabriel Pravaz und der schottische Arzt Alexander Wood, individuell, die frühe Version einer Spritze mit Hohlnadel und einem Spritzenzylinder aus Metall. Zu dieser Zeit glaubte man, dass die Injektion von Medikamenten in die Haut nur lokale Reaktionen hervorrufen würde, man wusste nicht, dass die Körperflüssigkeiten das applizierte Medikament systemisch in den Körper transportieren würden. Erst als Patienten eine Abhängigkeit von injiziertem Morphin und Opium zeigten, wurde die Annahme das eine Injektion nur lokalen Reaktion induziere überdacht. Heute gilt die Medikation von Patienten durch Verabreichung von Medikamenten über Injektionen und Infusionen als eine der Hauptsäulen der systemischen Therapie. Während subkutan und intramuskulär verabreichte Medikamente erst resorbiert und verteilt werden müssen, um systematisch wirksam zu sein, bietet der intravenöse (IV) Verabreichungsweg eine sofortige 100%ige Bioverfügbarkeit. Dies führt zu einem schnellen Wirkungseintritt und einer reduzierten oder verzögerten Metabolisierung des Wirkstoffs. Die Mehrheit der eingesetzten Medikamente während eines Krankenhausaufenthaltes wird über den IV-Weg verabreicht. Da nicht übertragbare Krankheiten (NCD)—Krankheiten, die nicht von Mensch zu Mensch übertragbar sind—wie z.B. Krebs, Herz-Kreislauf-Erkrankungen, Diabetes und chronische Lungenerkrankungen für etwa 70 % der weltweiten Todesfälle verantwortlich sind, ist die Behandlung oder Therapie dieser Krankheiten zunehmend auf die korrekte Verabreichung von Medikamenten über den IV-Weg angewiesen. Insbesondere, wenn ein Krankenhausaufenthalt erforderlich ist. Daher ist die korrekte Vorbereitung, Verabreichung und Sicherstellung der ordnungsgemäßen aseptischen Handhabung von Medikamenten entscheidend, wenn diese per IV Applikation verabreicht werden.

Diese Arbeit stellt die Generierung eines Instant Infusion Lyo Kits (IIK) zur komplikationsarmen und schnellen Herstellung von steril hergestellten Zubereitungen (CSP) vor. Dieses System soll bei gleichzeitiger Sicherstellung korrekter Dosis- und Lösungsmittelkombinationen auch die Aufrechterhaltung der Asepsis während der Zubereitung und Verabreichung sicherstellen. Durch den Einsatz der Gefriertrocknung als Herstellungsverfahren der Wahl, ist die Erzeugung mehrerer Arzneimittelformate als trockenes Pulver mit vergleichsweise langen Stabilitäten (aufgrund der Abwesenheit von Wasser) möglich. Verpackt in eine Medikationsvorrichtung, die das Arzneimittel und das Lösungsmittel in einem System umschließt, soll die sichere und schnelle Zubereitung und Verabreichung von CSPs gewährleistet werden.
Die erste notwendige Untersuchung diente zu Identifikation von CSP-bezogenen Medikationsfehlern (ME), die die Qualität und die Sicherheit von IV-Infusionen, die hospitalisierten Patienten verabreicht werden, beeinträchtigen. Es wurde angenommen, dass sich MEs Krankenhäusern lokalisiert in Ländern mit niedrigem und mittlerem Einkommen (LMIC) von den MEs unterscheiden würden, die in Krankenhäusern in Ländern mit hohem Einkommen identifiziert wurden. Es wurde jedoch festgestellt, dass die beobachteten Medikationsfehler, die in beiden

Umfeldern am häufigsten vorkommen, ähnlich sind und in LMIC- und HIC-Krankenhäusern und Pflegeeinrichtungen gemeinsam auftreten. Die fünf am häufigsten vorkommenden und hervorgehobenen MEs wurden daher extrahiert und ihre möglichen Ausweichstrategien diskutiert. Als am häufigsten wiederkehrende Fehler bei der Zubereitung und Verabreichung wurden die folgenden MEs identifiziert: "falsche Verabreichungsrate", "falsche Dosis", "nicht gemischt / falsch gemischt / falsche Rekonstitution", "falsches Lösungsmittel / falsche Zubereitungstechnik" und "falscher Zeitpunkt / falsche Frequenz". Zusätzlich wurden aseptische Handhabungsfehler wie unzureichendes "Händewaschen und Desinfizieren" und die Verletzung des langwierigen, aber notwendigen "30 Sekunden Vial/Ampullen-Septum abreiben" identifiziert. Der Einsatz von Schulungen, Kalkulationstabellen, Einführung von Aufbereitungsdiensten sowie software- und gerätebasierte Lösungen zur Umgehung dieser Fehler wurden genannt und diskutiert. Einige dieser Lösungen sind anwendbar und führten zu einer deutlichen Verringerung der Fehlerprävalenz. Es wurden aber auch technische Lösungen identifiziert, um einige der genannten MEs zu vermeiden. Die Verwendung von Adaptersystemen und proprietären Diluent- und Medikamentkombinations-systemen zur Umgehung der MES wurden als mögliche Umgehungsstrategien hervorgehoben und können zur Überwindung von "falsches Diluent"- oder "falsche Dosis"-Fehlern eingesetzt werden. Als technische Lösung, die die meisten potenziellen MEs zu vermeiden vermochte, wurde die Doppelkammerbeutel (DCB) Technologie identifiziert. Die gemeinsame Verpackung von Arzneimittel und Lösungsmittel in einem System, ermöglicht die korrekte Zubereitung und Rekonstitution eines Arzneimittels, ohne das potenzielle Auftreten von "falscher Dosis", "falschem Verdünnungsmittel / falscher Zubereitungstechnik" und "nicht gemischt / falsch gemischt / falsche Rekonstitution". Zusätzlich wird auch die mikrobielle Beeinträchtigung des CSPs potenziell umgangen, da kein Arzneimittelaliquot aus einem Vial entnommen und kein Septum 30 Sekunden lang mit Alkohol abgerieben werden muss. Die derzeit auf dem Markt befindlichen DCBs sind jedoch nur mit Antibiotikapulvern gefüllt. Die Dosierung des Medikaments innerhalb der DCB beruht auf einer Pulverdosierung, die voraussetzt, dass das Medikament als Pulver hergestellt werden kann, was im Allgemeinen mit hohen Temperaturen und Anwendung von Scherkräften während der Herstellung verbunden ist. Diese Umstände können die Qualität des Medikaments vor der Abfüllung beeinträchtigen, insbesondere wenn biologische Verbindungen wie Antikörper, Antikörper-Wirkstoff-Konjugate (ADC) und Oligonukleotide zur Abfüllung vorgesehen sind. Darüber hinaus erfordert die Abfüllung des Arzneimittels in die DCBs spezielle Abfüllumgebungen und -geräte, die den Einschluss des Antibiotika-Arzneimittelpulvers innerhalb der Fertigungslinie sicherstellen.

Durch die Einschränkung, dass die DCBs nur mit Medikamentenpulver gefüllt werden können, werden Möglichkeiten für andere Medikamente verpasst, die ebenfalls von diesen DCB-Medikationssystemen profitieren könnten. Wir untersuchten daher den möglichen Transfer von gefriergetrocknetem Material als flexiblen Gefriertrocknungskuchen für den Transfer in diese Medikationsvorrichtungen. Da die Gefriertrocknung dafür bekannt ist, flüssige Produkte auf schonende Weise in getrocknete Arzneimittel zu dehydrieren, untersuchten wir mögliche Designänderungen an den derzeitigen Arzneimittelbehältern, um einen vollständigen und expositionsarmen Transfer von Arzneimitteln in solche Medikationssysteme zu ermöglichen.

Als das bemerkenswerteste Behälterdesign, erwies sich eine dreidimensionale Matrixstruktur, in die das von uns für die Untersuchungen verwendete biologische Arzneimittelprodukt eingebettet werden konnte. Als Modellmolekül wurde ein monoklonaler Antikörper (mAb1) gewählt, der auf

verschiedene Weise abgebaut werden kann. Nach der Gefriertrocknung beherbergten diese porösen Strukturen das Arzneimittelprodukt in ihrer Matrix und ermöglichten den sicheren Transfer des Medikaments in ein potenzielles Medikationssystem. Vergleiche mit dem üblichen Behälterdesign—Serumfläschchen, die das Lyophilisat als Kuchen beherbergen—bewiesen die Gleichwertigkeit in Bezug auf Rekonstitutionszeit und das Aussehen des Kuchens. Zwar wurde keine äquivalente Restfeuchte erreicht, was aber auf die Extraktionsmethode zurückzuführen sein könnte, bei der die flexiblen Gefriertrocknungskuchen der feuchten Umgebung im Herstellungsbereich ausgesetzt waren. Die porösen Strukturen erwiesen sich jedoch dem allgemeinen Gefriertrocknungsprozess, wie er in Fläschchen beobachtet wurde, als überlegen, da die porösen Strukturversionen aus Edelstahl oder Aluminium den Trocknungsprozess beschleunigten und die Verarbeitungszeit auf weniger als 50% reduzierten. Darüber hinaus wurde eine signifikante Homogenität der Trocknung zwischen den Chargen innerhalb dieser Strukturen erreicht, wodurch die Anzahl der Ausschüsse potenziell reduziert werden könnte.

Da ein flexibler Gefriertrocknungskuchen in Form von porösen Strukturen zur Verfügung stand, wurden Untersuchungen zum Transfer in Medikationssysteme und zur Stabilität des biologischen Targets (mAb1) initiiert. Zwei unterschiedlich gestaltete Doppelkammerbeutel (DCB I und DCB II) wurden für die Untersuchung der Stabilität von mAb1 in Gegenwart von Lösungsmittel in der angrenzenden Kammer eingesetzt. Zusätzlich wurde die Stabilität der gleichen Formulierung in ihrer flüssigen und gefriergetrockneten Form in 20 ml Serumfläschchen bei der Lagerung untersucht. DCB I bestehen aus einem einzelnen Infusionsbeutel, der durch eine sandwichartige Trennung in zwei Kammern getrennt wurde. Die Trennung wird aufgehoben, indem ein Gummistab aus der Sandwichdichtung (Metallhülse - Infusionsbeutel – Gummistab) gezogen wird, der wiederum den Durchgang zwischen den beiden Kammern öffnet. DCB II besteht aus zwei Kammern, die durch eine Schweißnaht voneinander getrennt sind. Der Medikamentenbehälter ist auf einer Seite mit einer aluminierten Kunststofffolie und auf der gegenüberliegenden Seite mit einer durchsichtigen Kunststofffolie abgedeckt, welche temporär mit einer Aluminiumfolien-Abdeckung maskiert ist. Die Erzeugung eines Durchgangs zwischen den beiden Kammern, erfolgte durch Anwendung von Druck auf die Flüssigkeitskammer, um die Schweißnaht zu durchbrechen und die Rekonstitution des flexiblen Gefrierkuchens zu ermöglichen. Die generierten DCBs und Vials wurden gemeinsam bei unterschiedlichen Temperatur- und Feuchtigkeitsbedingungen gelagert, um den Einfluss des Behälterformats auf di Degradation des Modellmoleküls mAb1 zu untersuchen. Nach 24 Wochen Lagerung zeigten die Behälter unterschiedliche Befähigung, die Stabilität des Arzneimittels zu erhalten. DCB I-Behälter mit einer sandwichartigen Trenndichtung in der Mitte, welche die benachbarten Lösungsmittel- und Arzneimittelkammer des Infusionsbeutels trennte, wiesen eine geringere Stabilität auf als das flüssige Pendant in Serumfläschchen. Die DCB II-Behälter, die den flexiblen Lyophilisatkuchen durch eine aluminierte Kunststofffolie und eine Aluminiumfolien-Abdeckung auf der anderen Seite umschlossen, zeigten gleiche Stabilitätseigenschaften wie Serumfläschchen mit Lyophilisat.

Bemerkenswerterweise konnte die Verwendung einer temporären Aluminiumfolien-Abdeckung, die Verwendung einer aluminierten Kunststofffolie und die auf einer Schweißnaht basierende Trennversiegelung eine ähnliche Stabilität des Antikörpers in DCBs leisten, wie sie Serumfläschchen mit Lyophilisat bieten. Während die sandwichartige Trennversiegelung in DCB i -Behältern und das verwendete Folienmaterial ohne Aluminiumbarriere hingegen erhöhte Abbauraten zeigte, die jene in der flüssigen Serumfläschchen gefundenen Raten übertrafen.

Die Verwendung eines Designs, das Barrierematerialien wie Aluminium in die Umhüllung des Arzneimittels einschließt, ermöglichte eine bemerkenswerte Stabilisierung eines empfindlichen Arzneimittelprodukts, das anfällig für Aggregation und Oxidation ist. Durch eine weitere Verbesserung des Designs, der porösen Strukturen und der Verwendung verschiedener Ausgangsmaterialien (welche durch thermodynamische Modellierungen ermittelt werden könnten) können die Verarbeitungszeiten dieser flexiblen Lyophilisatkuchen potenziell weiter beschleunigt werden. Dies würde zu einem geringeren ökonomischen Fußabdruck dieser Medikationssysteme führen und damit zu einer breiteren Erschwinglichkeit. Darüber hinaus könnten die Untersuchungen zum Ersatz der Berechnung von Dosierungen basierend auf Alter, Stoffwechsel und Körperoberfläche durch die Verwendung von Dose-Banding Ansätzen und die Herstellung von nur einigen IIK-Formaten die Therapie bestimmter Patientengruppen drastisch erleichtern. Dadurch würde die Notwendigkeit einer genauen Dosisanpassung für jeden Patienten entfallen.

SUMMARY

In the early 19th century, the idea of administering a drug via the skin and not via oral routes or inhalation of mixtures was born. What started with the removal of outer skin layers to administer poultices or drug containing plasters, quickly changed to the administration of morphine by stitching a vaccination lancet into the skin. At around 1850 French veterinary surgeon Charles Gabriel Pravaz and the Scottish doctor Alexander Wood developed individually the early version of a syringe, including a hollow needle and a metal syringe barrel. At that time, the injection of medication into the skin was believed to only have local reactions, little was known that the body fluids would transport the applied drug systemically. Only when patients demonstrated a dependency on injected morphine and opium the assumption of a local only therapy was changed. Nowadays, the medication of patients by administration of drugs via injections and infusion is considered one of the main pillars of systemic therapy. While subcutaneous and intramuscular administered drugs need to be resorbed and distributed to be systematically effective the intravenous (IV) administration route offers 100% bioavailability immediately, leading to quick onset of effect and reduced metabolism of the active pharmaceutical ingredient (API). The majority of applied medications during hospitalization, is administered via the IV route. As non-communicable diseases (NCD)—disease that are not transmissible from one person to another—like cancer, cardiovascular diseases, diabetes, and chronic lung diseases are responsible for about 70% of the global death toll, the treatment or therapy of those illnesses is increasingly relying on the correct administration of drugs via the IV route, when hospitalization is necessary. Therefore, the correct preparation, administration and assurance of proper aseptic handling measure of medication is crucial when IV drugs are compounded and applied.

This work presents the generation of an Instant Infusion Lyo Kit (IIK) for the complication-reduced and fast preparation of compounded sterile preparations (CSP), while assuring correct dose and diluent combinations and the maintenance of asepsis during preparation and administration. By use of freeze-drying as manufacturing method of choice the generation of multiple drug formats as a dry powder with comparably long stabilities (due to the absence of water) is achievable. Packaged into a medication device that safely encloses the drug product and the diluent in one system, the safe and fast preparation and administration of CSPs should be guaranteed.

The first required assessment was the identification of CSP related medication errors (ME) that interfere with the quality and the safety of IV infusions administered to hospitalized patients. It was assumed that the MEs in hospital settings located in low- and middle income countries (LMIC) would differ from the MEs identified in high income country hospital settings. However, it was ascertained that the observed medication errors most prevalent in both settings, are similar and are shared in LMIC and HIC hospitals and care facilities. The five most occurring and highlighted MEs were thus extracted, and their potential evasion strategies discussed. As most recurring errors in the preparation and administration the following MEs of “wrong administration rate”, “wrong dose”, “not mixed / wrong mixed / wrong reconstitution”, “wrong diluent /wrong preparation technique”, and “wrong time / wrong frequency” were identified. Additionally aseptic handling errors like insufficient “hand washing and disinfection” and the violation of lengthy but necessary “30 second vial/ampoule septum swabbing” were also identified. The application of trainings,

calculation charts, introduction of preparation services and software and device based solutions for the circumnavigation of these errors were mentioned and discussed. Some of these solutions are applicable and led to significant reductions in the prevalence of errors. However, technical solutions were as well identified to avoid some of the mentioned MEs. The use of adapter systems and proprietary diluent and drug combination systems to circumnavigate the MEs were highlighted as possible evasion strategies and can be utilized to overcome “wrong diluent” or “wrong dose” errors. The technical solution that was capable to avoid the greatest number of potential MEs was identified as dual chamber bags (DCB). The co-packaging of drug and diluent in one system allows the correct preparation and reconstitution of a drug product without the potential occurrence of “wrong dose”, “wrong diluent / wrong preparation technique” and “not mixed / wrong mixed / wrong reconstitution”. Additionally, microbial impairment of the CSP is potentially evaded as well, as no drug aliquot from a vial must be extracted and no septum must be swabbed for 30 seconds. However, the currently marketed DCBs are only filled with antibiotic powders. The dosing of the drug within the DCB relies on powder dosing that requires the drug being suitable to be manufactured as a powder, which in general involves high temperatures and shear stress during manufacturing. These process parameters can compromise the drug quality prior filling, especially when biological compounds like antibodies, antibody-drug-conjugates (ADC) and oligonucleotides are intended for filling. Moreover, the filling of the drug product into the DCBs requires specialized filling environments and equipment, which assure the containment of the antibiotics drug powder within the manufacturing line.

By limiting the DCBs to only be filled with drug powder opportunities for other medications are missed that could as well benefit from these DCB medication devices. We therefore investigated the potential transfer of freeze-dried material as a flexible lyophilization cake for the transfer into these medication devices. As freeze-drying is known to desiccate liquid products into dried drug products in a gentle manner, we investigated possible design changes to the current drug containers to allow complete and exposure minimized transfer of drugs into such medication systems. The container design proven to be the most remarkable, was identified to be a three-dimensional matrix structure that can be embedded with the biological drug product we used for the investigations. A monoclonal antibody (mAb1) susceptible to degradation in multiple ways, was chosen as a model molecule. After freeze-drying, these porous structures housed the drug product in their matrix and allowed the safe transfer of the drug into a potential medication system. Comparisons to the common container design—vials that house the lyophilizate as cake—proved the equivalency in terms of reconstitution time and cake appearance. Although equivalent residual moisture levels were not achieved, these can be retraced to the extraction method, which exposed them to the humid environment in the manufacturing area. However, the porous structures proved to be superior to the general lyophilization process observed in vials, as the porous structure versions made from stainless steel or aluminum accelerated the desiccation process and reduced the processing time to less than 50%. Furthermore, a significant inter batch homogeneity of the drying within these structures was achieved, potentially reducing the number of rejects.

With a flexible lyophilization cake in the form of porous structures available, investigation into transferability and stability of the biological target (mAb1) were initiated. Two differently designed dual chamber bags (DCB I and DCB II) were employed for the investigation of mAb1 stability in the presence of diluent in the adjacent chamber. Additionally, the same formulation was investigated in their liquid and lyophilized dosage from stored in 20 ml glass vials. DCB I constitutes of a single

infusion bag that was separated into two chambers by a sandwich-like separation seal. The separation is removed by pulling a rubber rod from the sandwich seal of metal sleeve –infusion bag- rubber rod that in return opens the passageway between the two chambers. DCB II constitutes of two chambers that are separated from each other by a weld seam. The drug product container is covered on one side by an aluminized plastic foil and on the opposite side by a translucent plastic foil that is temporarily masked with an aluminum foil cover. Generation of a passageway between the two chambers was performed by pressurizing the liquid chamber, to rupture the weld seam and allow reconstitution of the flexible lyophilization cake. The generated drug housing DCBs and vials were stored at different temperature and humidity conditions to investigate the influence of the container format on the degradation behavior of mAb1. After 24 weeks of storage the containers presented different capabilities to maintain drug product stability. DCB I containers with a sandwich-like separation seal in the center separated the individual diluent and drug product chambers of the single infusion bag and demonstrated inferior stability than the liquid vial counterpart. The DCB II containers that enclosed the flexible lyophilizate cake by an aluminized plastic foil and an aluminum foil cover on the other side, demonstrated equal stability properties as lyophilizate vials. Remarkably the inclusion of a temporary aluminum foil cover, the use of an aluminized plastic foil and the separation seal based on a weld seam can promote similar stability retention in DCBs as observed in lyophilizate vials. While the sandwich-like separation seal and the used foil material without an aluminum barrier facilitated increased degradation rates, exceeding the rates found in liquid vials.

The use of a design that includes barrier materials as aluminum in the enclosure of the drug product facilitated a striking retention and stabilization of a delicate drug product, susceptible to aggregation and oxidation. By further improving the design of the porous structures and utilizing different source materials determined by thermodynamic modelling, the processing times of these flexible lyophilizate cakes can be potentially accelerated further. Resulting in a lower economic footprint of these medication systems and thus to a broader affordability. Further, the investigations into substituting the calculation of dosages based on age, metabolism, and body-surface-area by use of dose-banding approaches could facilitate the manufacturing of only some IIK formats for the therapy of specific patient groups, eliminating the need to accurately adjust the dose for each patient.

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LIST OF ABBREVIATIONS

ADC	Antibody-drug conjugate
API	Active pharmaceutical ingredient
COC	Cyclic Olefin Copolymer
CQA	Critical Quality Attribute
CSP	Compounded sterile preparation
DCB	Dual chamber bags
DSC	Differential scanning calorimetry
EVA	Ethylene-vinyl acetate
FDA	Food and Drug Administration
HMWs	High molecular weight species
HPBCD	Hydroxypropyl-betacyclodextrin
IEC	Ion exchange high performance liquid chromatography
IgG	Immunoglobulin
LC-ESI-MS	Liquid chromatography electrospray ionization mass spectrometry
mAb	Monoclonal antibody
ME	Medication error
MW	molecular weight
NCD	non-communicable disease
NMR	Nuclear magnetic resonance
Ph. Eur	European Pharmacopeia
pI	Isoelectric point
PP	Polypropylene
scf.	scaffold
SD	Standard deviation
SEC	Size exclusion high-performance liquid chromatography
SLM	Selective Laser Melting
SLS	Selective Laser Sintering
SS	stainless steel
T_c	Collapse temperature
T_g' / T_g	Glass transition temperature
T_p	Product temperature
T_s	Shelf temperature
twPETC	thin walled polyethylene-terephthalate
UK	United Kingdom
US	United States
USP	United States Pharmacopeia
w/v	Weight per volume
w/w	Weight per weight
µ-CT	Micro-computed tomography

SCOPE OF THE THESIS

The handling of medications is a parkour wired with complications in the preparation, administration, and aseptic handling of drugs. In Chapter I it is identified that such a gap exists, showing the need for a medication system that facilitates the safe medication preparation for patients while providing a system that minimizes exposure of drugs to healthcare professionals. The aim of this thesis was to find a transfer solution for lyophilizates, that enables the safe and fast preparation of an IV infusion in the absence of an aseptic environment. The focus of the thesis was therefore divided into three main work packages or chapters, with Chapter I intended as the introduction. An outline of the discussed questions can be found following:

- Chapter I: Challenges in the preparation and handling of intravenous medications and technical evasion strategies
  - What are the most common handling errors during IV medication preparation and which of these are regarded to have the most severe effect on patient health?
  - How are these handling and medication errors prevented and are there opportunities for drug manufacturers to mitigate such preparation errors in the first place?

- Chapter II: Part I: Significant reduction of lyophilization process times by using novel matrix based scaffolds
  - How could the transfer of a brittle lyophilizate into a medication system be accomplished while the complete dosage transfer is ensured?
  - Can the lyophilization outside of a confining container be facilitated and how are proper heat conduction and batch homogeneity facilitated?
  - Will generated flexible lyophilizate cakes be able to achieve the critical quality attributes set by lyophilizates prepared in vials? And if not, are there possibilities for improving the design?

- Chapter III: Part II: Matrix based scaffold lyophilization facilitates processing as a prerequisite for an innovative packaging system
  - Can a flexible lyophilizate be transferred into possible medication system allowing the safe reconstitution and preparation of an IV infusion?
  - How do different dual chamber bags perform? Are there key requirements in the design that need to be considered to provide a stabilizing environment for the incorporated drug product?
  - What mechanisms are leading to degradation within the dual chamber bags and how safe is the drug from experiencing premature reconstitution?

CHAPTER I

(Unpublished results)

Challenges in the preparation and handling of intravenous medications and technical evasion strategies

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Published: Chapter I is to be submitted as a review paper in an international peer-reviewed journal. The structure of Chapter I therefore follows the recommendations set forth for a review article.

Highlights: It is generally assumed that low and middle income countries are more likely to have a higher prevalence for medication errors such as aseptic omissions, incorrect dose preparations or wrong administration rates. In our non-systematic review we elucidate that common and frequent medication errors are observed in high income countries as well and are not only an issue of the respective health care system. Medication errors with the highest prevalence and severity were extracted from 24 observational studies and based on their number of mentions the five major medication error types were elaborated. Recommended strategies to mitigate errors such as "wrong mixing and wrong reconstitution" and "wrong administration rate" were then compared to potential technical solutions that could ultimately avoid these errors. Next to increased training efforts and the introduction of control systems, the usage of adapter systems and ready-to-use systems were identified to be the most beneficial technical solutions to prevent the occurrence of such medication errors. A technical solution superior in evading most of these was a system that combines diluent and drug product in one dual chamber infusion bag.

Abstract

The preparation of intravenous medicines is accompanied by numerous complications and challenges. The emergence of such complications is imposed by the environment in which the drug-preparation is compounded and also dictated by the dosage form and the inherent associated preparation steps and drug product-specific properties. To identify the challenges that healthcare professionals encounter during drug preparations in different settings, 24 observational studies of drug preparations in high-, middle- and low-income countries were analyzed. Medication errors associated with the preparation, administration and aseptic handling of drug products were observed in these studies. This review serves to summarize the most prevalent errors, along with proposing strategies to address knowledge and handling gaps for the correct compounding of sterile preparations. Additionally, technical solutions to minimize the occurrence of these errors and reduce potential patient harm are elucidated.

Keywords:

medication error, preparation error, administration error, aseptic error, low and middle income countries, high income countries, vial adapters, dual chamber infusion bags

Introduction

Every day millions of people receive either curative or palliative medical care to improve their medical conditions. Such care ranges from medications against simple inflammations to treatments of complicated metastatic cancer. Some of these treatments can be easily addressed by medication administered orally, while some treatments require intravenous (IV) administration. Although many drugs can be administered orally and are then resorbed within the gastrointestinal tract (GIT), some must be administered differently. Due to the degradation of some drugs by acids, bases, endogenous enzymes and the first pass metabolism—potentially reducing the efficacy of the treatment—some drugs need to be administered parenterally to the patient. This can be facilitated by intravenous bolus injections, or in the case of larger quantities and maintained serum levels, by IV infusion. Novel drugs based on peptides, proteins, oligonucleotides, or other biological compounds are often subject to degradation in the GIT and thus must be administered parenterally. Aside from the uptake of drugs, the immediate bioavailability of the treatment is also of importance. The immediate efficacy of parenterally applied medicines can be a blessing or curse; the former applies when the right medicine in the proper dose is applied correctly, but the latter applies if the medicine is unsterile, the incorrect drug is used, or the calculated dose is determined incorrectly.

The National Coordinating Council for Medication Error Reporting and Prevention defines medication errors (MEs) as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer" [1]. These MEs are one of the main reasons for prolonged hospitalization, and in some cases, for fatalities. For example, around 98'000 patient deaths are estimated to stem from MEs every year in the United States alone [2]. Another study by John Hopkins estimates the number of patient deaths originating from MEs to be greater than 250'000 every year. With this number of patient deaths medication errors represent the third leading cause of deaths in the United States after heart diseases and cancer, but ahead of respiratory diseases [3]. The aim of our non-systematic review was therefore intended to elaborate on the five most common MEs during preparation and administration of CSPs, and to include the most common aseptic handling errors. These most prevalent MEs should then be linked to technical evasion strategies for improved CSP preparation and administration that would facilitate a better alignment with the recommendations and guidelines for preparation of IV medications in all relevant environments.

Factors influencing medical treatment success

1. Aspects of the social setting for medical treatment success

Social factors have a significant impact on the patient's treatment outcome and must be regarded to assess the potential treatment success of a patient. The burden in terms of the price barrier for medications was shown to be a great social setting factor, leaving a third of the global population unable to afford medications and treatments for their medical conditions [4-8]. Only a few approaches are in place to subsidize the costs involved for medications and treatments, and these hurdles in affordability are not only locally confined to low and middle income countries (LMICs) in the sub-Saharan or tropical regions, but can also be found in the European Union (EU), where drug

prices differ among the high income countries (HICs) and the low to middle income countries in the European Union. Prices for some medicines were shown to be at least twofold higher for some EU countries, thus making some necessary treatments unaffordable even in countries with existing primary healthcare frameworks [9, 10]. In some LMICs, patients can face retail prices that are up to 552% higher than international reference prices [11, 12]. Under worst-case conditions, the access to basic medical care is furthermore restricted in LMICs by the distance that must be travelled in order to receive a respective treatment [11-16].

2. Aspects of the clinical setting for medical treatment success

The clinical setting of a patient is equally as important as the social factors in terms of the impact on the patient's treatment outcome. A crucial determinant for the treatment success, aside from the correct drug administration route and the patient's condition, is the environment in which the patient receives the treatment[17, 18]. The location of the patient in need of a treatment is therefore a key factor for success of therapy. Citizens from HICs benefit from strong healthcare systems with excellent primary healthcare. These systems consist of well-organized supply chains, medical infrastructure, highly educated physicians/nurses/pharmacists and pharmacies with adequate storage conditions for drugs [19]. In comparison, patients suffering from diseases in LMICs are less likely to have access to such healthcare systems. Hospitalizations in both HIC and LMIC settings are generally connected to therapies that local physicians are unable to perform. In some cases, these treatments even require the consultation of specialists for dedicated surgeries or preparations. For example, some therapies require the intravenous administration of drug preparations that need to be tailored to the patients' weight, body surface area, and metabolism. During the preparation and also during the administration of these medications, the healthcare professional may be confronted with complications that potentially lead to MEs, e.g. due to parenteral preparations that are prepared incorrectly or unsterile. The handling of intravenous preparations, also referred to as compounded sterile preparations (CSPs), is expected to follow specific guidelines, exemplarily laid down in Chapter 797 of the USP "Guidebook to Pharmaceutical Compounding: Sterile Preparations", along with other guidelines such as the "Concepts in Sterile Preparation and Aseptic Technique" or the "Guidelines on Compounding Sterile Preparations" from the American Society of Health-System Pharmacists, which are intended to support the preparation of CSPs and advise where certain complications can be expected [20-22]. The described techniques and handling guidelines for the preparation of CSPs herein are intended to apply wherever CSPs are prepared, i.e. not only in pharmacy settings and tertiary care facilities, but also in hospital wards. However, they may potentially not apply outside of the United States [20]. While these recommendations and directives for aseptic handling to facilitate accurate manufacturing of CSPs are regularly verified and validated to be in place in hospital pharmacies, these guidelines might not be effective in hospitals without dedicated CSP areas that lack cleanrooms or laminar air flow hoods. The directive regarding compliance of recommended hand washing routines or the guidelines of when to wear sterile gloves is incomplete. A patient might be harmed if the sterility of a CSP is compromised and the preparation is administered, particularly when the preparation of such CSPs occurs in patient rooms or wards, both of which are unsterile environments [23-26]. Some IV preparations are compounded well in advance of administration, although these directives specify for example that reconstitution of medicines should be performed shortly before administration to prevent microbial contamination in these CSPs. In

severe cases, during a simple treatment, these types of omissions can cause nosocomial infections, creating further complications for the patient [23].

To avoid such incidents, the WHO recommends the use of their "Tool C" for infusions and injections. In this document, recommendations and simplified approaches are described that enable the healthcare professional to prepare and administer drugs safely in a broad range of preparation environments. Example cases are described, how needle-stick injuries or the contamination of medicines or fluids in infusions can be avoided, but recommendations are also provided on when to use alcohol disinfection or when simple hand washing is sufficient [27].

Complications during preparation and administration of intravenous medications

The imbalance of the standards found in developed clinical settings compared to the standards found in low and middle income settings are only partially mirrored by the complications during drug preparation, administration, and aseptic handling of CSPs.

Many different possibilities for MEs exist in the preparation of medications, during the sterile handling and in their administration. As the premises and preconditions such as adherent pharmacies, special preparation rooms and controlled storage spaces differ between hospitals and clinical facilities in HICs and LMICs, the possibilities for errors also differ. Aside from the working environment and workload of the individual, the level of education, amount of experience, access to information sources, and opportunity for further training need to be taken into consideration in the occurrence and prevalence of MEs [28-30]. For example, nurses were less likely to perform errors with each additional year of experience. This was linked to a 10.9% reduction of errors, and an averaged 18.5% reduction of serious errors per additional year of experience; however, this was only applicable only during the first 6 years of nursing experience. Minor errors were connected to an increased level of care or to the referral of the patient to another clinician, while serious errors were linked to the permanent reduction of body functions or even surgical interventions [31].

The National Coordinating Council of Medication Error Reporting and Prevention (NCC MERP) categorizes MEs into nine categories according to their degree of severity, ranging from Category A (circumstances able to cause error) to Category I (errors that may cause or result in patient death) [1]. These categories specify the severity of MEs for the patient, and several studies discussed the need for and introduced additional subcategories to increase the granularity of these initially defined categories. These were included in these studies to allow deeper specification and finer classification of medication errors observed in the clinical environment [32-35]. Despite the categorization, a comparative analysis on the prevalence of MEs observed during stays within clinical environments and hospitals in different HIC and LMIC settings is missing. To address this gap, we reviewed and compared 24 studies on the five main MEs found in the respective clinical environments of each study. We focused primarily on intensive care units (ICU), teaching hospitals and tertiary care hospitals in LMICs and HICs in which these MEs were observed. The total number of doses prepared or administered were associated with the incidents of errors observed during preparation, administration, and sterile handling. In the event medications had to be discarded or were accidentally damaged prior to administration, these observations were removed from these

confrontations to avoid including any additional preparation bias. The five most prevalent MEs in each study were identified and aligned with the ME type categories defined in Table I. The definitions and error types described have been adapted from Nguyen et al. and Blandford et al., and have been expanded upon through the addition of sterile handling MEs [28, 36].

Table I *List of error types observed during preparation, administration and sterile handling of drugs in clinical environments and hospitals*

Medication error type	Definition
Preparation errors	
Wrong drug	Drug prescribed differs from the drug administered
Wrong dose	Prescribed drug dose differs from the drug amount administered (±10%)
Wrong dosage form	Compounded drug deviates from prescribed drug formulation including wrong concentration
Deteriorated drug / precipitated drug	Drug integrity prior administration was comprised due to long storage at wrong conditions or lag time prior administration
Expired drug	Use of drug product which exceeded the shelf life declaration of drug manufacturer
Wrong diluent / wrong preparation technique	Use of wrong diluent for dilution, dissolution or reconstitution of drug Incorrect preparation technique or deviation from package insert / hospital policy (wrong volume, possible incompatibility)
Not mixed / wrong mixed / wrong reconstitution	Drug and diluent not mixed, mixing time was insufficient or reconstitution was performed incorrect; leaving inhomogeneous solutions or undiluted particles
Labelling error	Missing or incorrect information on the label or outside of the drug container
Prescription error	Missing drug and patient information on prescription, errors in transcribing, and errors in frequency or timing
Missed dose / omitted dose	Failure to administer an ordered dose to a patient or omission of dose administration
Unordered drug	Administered medication that was not prescribed earlier
Aseptic errors	
No hand washing / no hand disinfection	Missed hand washing and hand disinfection, missed use of gloves, missed disinfection of intravenous ports, skin antisepsis before injection/infusion
Working environment not cleaned or not disinfected	No work space cleaning with detergents and disinfectant or drug preparation not in laminar flow hood, contact of sterile equipment or products with unsterile surfaces
Vial / ampoule surface not swabbed	Surface of vial septum or neck not rubbed with disinfectant or duration of insufficient disinfection duration

According to the description and emphasis of the authors in their respective studies, the most frequently observed MEs were identified and categorized into 17 error type subcategories. These 17 individual subcategories were further distributed under three top-level medication error types: preparation, administration and aseptic errors. These 17 subcategories for the MEs were then weighted according to their described severity in patient harm. A ME of a certain study that was found to show the most frequent prevalence, or described as the most frequently observed ME with the most significant impact on patient health, was thereby weighted as the ME with the

highest prevalence and severity—a first degree medication error (#1-ME). Less frequent errors were weighted accordingly as #2-ME, #3-ME, #4-ME and #5-ME. These less frequent errors were nevertheless of high clinical relevance and frequently recurring in these studies. Due to the different motivations and aims of the studies, the observed MEs were discussed and categorized differently within these articles. Some articles discussed each ME exhaustively according to their occurrence and rated them by the NCC MERP categories, while others referred only to the first and second most prevalent ME observed during their evaluations (#1-ME and #2-ME). Therefore, the mention of MEs varied in each article between two and five MEs among the evaluated studies. For our assessment, each reported ME was collected and only the five most frequently observed MEs were retained for each study. In a first step, these MEs were matched to one of the 17 subcategories of MEs. If no accurate subcategorization was possible, or no accurate subcategorization was given, the respective ME was assigned to the top level category best fitting its nature. In a second step, the mentioned ME was weighted into one of the five prevalence categories based on the authors' perspective on the prevalence and severity of the ME. To assess the ME with the highest prevalence and greatest severity of all the analyzed studies, a numerical weight was assigned to each prevalence category. This numerical value was used to eventually identify the error type with the most frequent observation, highest prevalence and severity rate among the individual studies. In two cases, the most prevalent ME occurrences were intertwined—wrong reconstitution was connected with a wrong preparation technique due to use of the wrong diluent—and the authors described them as severe. Therefore, both MEs were rated with the prevalence category #1-ME. Through the allocation of weighting points to these MEs, a connection between the distinct error and their occurrence could be established. The listing of the extracted (most prevalent and severe) MEs and their respective weightings is shown in Table II.

Table II *Mentions of most prevalent medication errors in HIC and LMIC hospitals collated with prevalence categories*

Prevalence categories / Medication error type	#1-ME Weighting = 16 points	#2-ME Weighting = 8 points	#3-ME Weighting = 4 points	#4-ME Weighting = 2 points	#5-ME Weighting = 1 point
Preparation errors	2	1	1	0	0
Wrong drug	0	0	0	1	1
Wrong dose	4	3	2	0	0
Wrong dosage form	0	0	0	0	0
Deteriorated drug / precipitated drug	0	0	0	0	0
Expired drug	0	0	0	0	0
Wrong diluent / wrong preparation technique	2	3	0	0	0
Not mixed / wrong mixed / wrong reconstitution	3	1	2	0	0
Labelling error	0	0	1	0	0
Prescription error	1	0	0	0	0
Administration errors	0	3	0	0	0
Wrong administration rate	6	3	0	0	0
Wrong administration technique / wrong administration route	2	1	1	1	1
Wrong time / wrong frequency	2	1	1	3	0
Missed dose / omitted dose	1	1	2	0	0
Unordered drug	0	1	0	1	0
Aseptic errors	1	0	0	0	1
No hand washing / no hand disinfection	0	0	0	0	0
Working Environment not cleaned or not disinfected	0	0	0	0	0
Vial / ampoule surface not swabbed	2	0	0	0	0

To identify the error types that were identified with the greatest occurrence and severity on the patient's health, the extracted most prevalent ME was weighted with 16 points, while a ME listed as the fifth most significantly observed error type was weighted with only 1 point. For each error type the weighting of the prevalence category was multiplied with the associated number of mentions in the evaluated studies. Thus a numerical point value could be obtained for every error type. Consequently, the sum of the prevalence categories' weightings could be formed for each error type and the error types were then sorted by this point system from the highest to lowest value. These accumulated points by error type and prevalence category were denoted as "Mentions of most prevalent error types (weighted)" and the error types were then numerically sorted according to their weighting from highest point score to lowest, as shown in Table III. The most prominent MEs with the highest prevalence in the investigated studies were found to be "wrong administration rate", "wrong dose", "not mixed / wrong mixed / wrong reconstitution", "wrong diluent / wrong preparation technique", and "wrong time / wrong frequency".

Errors with a lower prevalence that were listed less often were errors concerning the “wrong administration route or wrong administration technique”, “doses omitted or missed”, “prescription and labelling errors” and aseptic handling errors in general. Errors that did occur (in fewer instances) but were not highlighted by the authors as most prevalent were found to be “expired drugs” or errors associated with deteriorated drugs, “wrong dosage forms” or personal hygiene and working environment hygiene-related errors. These were identified in the respective articles as potential MEs, but were not categorized as severe and thus did not receive a point rating. However, these MEs were seen as a potential gateway for patient health concerns and were therefore kept in Table III.

Table III *Medication error types ranked by their number of occurrences and weighted according to their specified severity*

Mentions of most prevalent error types (weighted)	Medication error types
120 pts	Wrong administration rate
96 pts	Wrong dose
64 pts	Not mixed / wrong mixed / wrong reconstitution
56 pts	Wrong diluent / wrong preparation technique
50 pts	Wrong time / wrong frequency
47 pts	Wrong administration technique/route
44 pts	Preparation errors
32 pts	Missed dose / omitted dose
32 pts	Vial / ampoule surface not swabbed
24 pts	Administration errors
17 pts	Aseptic errors
16 pts	Prescription error
10 pts	Unordered drug
4 pts	Labelling error
3 pts	Wrong drug
0 pts	Wrong dosage form
0 pts	Deteriorated drug / precipitated drug
0 pts	Expired drug
0 pts	No hand washing / no hand disinfection
0 pts	Working environment not cleaned or not disinfected

3. Preparation and administration errors in intravenous drug applications

The most prominent error types that were derived from the analysis were attributed to the top-level categories of preparation and administration errors. The highest ranked error type with 120 points was identified as "wrong administration rate". In the evaluated studies, gravity-induced drip infusions, infusion pump-facilitated infusions and intravenous bolus injections were found to show a great likelihood for being the cause of a ME. The incorrect adjustment of the roller clamps, limiting the administration rate during gravity feed infusions, and omissions in verifying properly adjusted drop rates per minute, were listed as some of the infusion rate errors [37, 38]. Alternatively, administered infusions with infusion pumps displayed challenges in maintaining a continuous infusion rate, as the incorrect setup or the insufficient battery charge led to premature terminations of the infusion than programmed [39]. Furthermore, the incorrect interaction with the infusion pump interface is a potential threat to patients when safety features are bypassed and alerts are disregarded [31, 40]. Mistakes such as incorrectly programmed infusion rates—due to mistakes in typing the correct infusion rate into the infusion pump interface—were also attributed to "wrong administration rates", but occurred less frequently and were found to be more likely in normal infusion pumps than smart infusion pumps [41]. Administration rates for IV bolus injections were also observed to be higher than the rates specified and recommended by drug manufacturers, and also known to cause pain, shock, or cardiac arrest in patients [42]. These events could be avoided if the general preparation of bolus injections was substituted or supported by central intravenous additive services (CIVA) [26, 43, 44]. These services can provide injections as short intravenous infusion therapies, allowing the administration of an injection as a mini-infusion with a slower infusion rate due to the higher volume. As a result, the healthcare professional would be relieved of the necessity of remaining at the patient's bedside for 3–5 minutes to perform the administration of an IV bolus injection [26, 45].

For the error types of "wrong dose" and "not mixed / wrong mixed / wrong reconstitution", it can be assumed that these are linked and can be discussed together. While a wrong dose can be attributed to medication left in the infusion bag that was not entirely administered to the patient, it can also refer to a drug being diluted in an incorrect diluent or the use of an incorrect IV bag size with too much diluent volume. Furthermore, dosage calculations could be compromised by unit confusion when units are mistaken by similar looking units, for example mmol and ml [46, 47]. In other instances, this error was connected to the drug being insufficiently homogenized. Thus the extraction of a patient-specific volume led to the administration of a concentration that was either too low (extracted from the portion of the diluent), or too high (extracted from the portion of the undissolved drug). In the case of powdered or lyophilized drug products, it was observed that doses were extracted before complete dissolution/reconstitution was achieved, leading to the administration of insufficient drug quantities and thus an underdosing of the patient [48, 49]. Alternatively, when a viscous or highly concentrated drug is diluted and the solution is not completely homogenized, the administration of an unexpectedly high dose is possible too. Drugs that have a narrow therapeutic index might leave the patient in shock due to overdosing, while underdosing potentially compromises the positive progression of a treatment [47, 50]. Gravimetric workflow control systems and barcoding procedures were observed to reduce these types of errors. By using these approaches, the detection rate of dose deviations and the preparation of drugs with the wrong diluent could be increased by up to 74-fold.

However, the significant improvement on patients' safety requires specialized software, barcode scanners and the availability of adequate balances for the correct measurement of weight-based drug amounts [51, 52].

The use of the "wrong diluent" can interfere with the solubility of drugs or can pose compatibility issues that lead to a reduced stability or even reduced potency [26, 53]. While the term diluent refers to the liquid used for the dilution or reconstitution of the drug product, the vehicle is considered as the liquid that is used in IV bags or bolus injection syringes to administer the diluted drug product to the patients. Both terms were used interchangeably in the screened articles but should generally be differentiated to visualize the respective error in the preparation or administration. For ease of understanding, these terms were not differentiated in this article. Healthcare professionals are confronted with the task of preparing the CSP on time, but also with the need to identify the correct diluent for the respective drug without facing compatibility issues. Without prior knowledge, healthcare professionals must consult the manufacturer's package insert leaflet (PIL) or an electronic information system to obtain the information on the required correct diluent, as the information on the diluent is generally missing on prescriptions. Observations revealed that the quick preparation of the drug is at times favored over crosschecking with the PIL [26]. Charts and tables with common diluent/drug combinations or highlighted incompatibility signs on the drug container were proposed as possible safety measures to avoid drug precipitation, potency loss and/or long reconstitution times. Additionally, it was generally suggested to permanently connect the drug vials to the administration container (IV bag or syringe) during the administration and to include flag labels—labels that can be removed from the drug container and reapplied to infusion bags and syringes—to reduce potential diluent drug confusions [26].

Another major ME that was highlighted was the "wrong time" or "wrong frequency" of drug administrations. Some medications require consistent, stable, and steady-state concentrations in the plasma to achieve positive treatment outcomes in due time. If the drug preparation is applied outside of that time window, the patient can potentially suffer from an insufficient treatment, or if applied too early, from adverse drug effects due to increased drug concentrations in the plasma [26, 47, 54, 55].

4. Aseptic preparation issues in intravenous drug applications

As a general recommendation (prior to preparing medications and handling CSPs), the healthcare professional is recommended to clean the handling area, wash their hands or wear sterile gloves, disinfect the drug container by rubbing the septum for 30 seconds with rubbing alcohol and ensure that windows in the preparation area are closed [21, 22]. The assumption that the handling of drug products in HIC environments was performed with greater care concerning aseptic behaviors was disproved by some observational studies. In the studies conducted by Cousins et al., the compliance with aseptic recommendations in HIC hospital environments revealed diverse scenarios. While no hand washing prior to medication preparation was observed to be a standard in the preparation of CSPs in UK hospitals, hand washing was performed in only 5% of hospitals in Germany and was observed in France in 91% of the observations.

Moreover, the frequency of swabbing vial septa with alcohol soaked swabs also varied, with 1%, 42% and 96% of nurses in the UK, Germany and France, respectively, adhering to this aseptic procedure [26]. In a Malaysian tertiary care hospital, Ong et al. investigated the errors in medication pre-preparation, and observed that the preparation areas for IV drugs were only cleaned in 1 of 11 cases. The dedicated preparation areas (special IV trolleys) were disregarded and the preparation was performed in preparation areas with limited space and empty-undisposed drug packages. Additionally, hand washing or wearing sterile gloves was observed in only 26% of cases, and the majority of ampoules or vials (> 98%) were not rubbed with alcohol prior to withdrawal of doses or dilution procedures [45]. Similar omissions of correct aseptic drug handling were found by Tavakoli-Ardakani et al. in an Iranian teaching hospital. In 281 of 544 chemotherapy drug preparation cases, hand washing was skipped, while in 14 of those cases, body decontamination (in terms of personal disinfecting procedures) was omitted [48]. These occurrences of uncompliant drug handling procedures are not only seen in LMIC hospital settings in Iran or Malaysia, but also in HIC hospital settings, as observed in the UK, Germany and France. However, the prevalence of aseptic issues being observed after CSPs were prepared in pharmacy settings was shown to be lower compared to clinical and ward environments. This difference is most likely due to extensive training efforts and regular validations of aseptic handling skills necessary in pharmacy environments [26, 31, 56]. Nevertheless, training and provision of information brochures in clinical environments proved that compliance with hand disinfection routines and cleaning of ampoules during drug preparation could be raised significantly from a previous 55.0% and 48.7% to values of 81.3% and 75.0%, respectively. It was also observed that adherence to 30 seconds of hand rubbing procedures (with rubbing alcohol) and 30 seconds of catheter hub drying times could not be increased and would require further intensified training and greater discipline of the healthcare professionals [57]. A reduction of these errors was possible to be facilitated by pharmacist-led trainings that led to a reduction of error rates in ICUs from 64.0% to 48.9% [28]. Such training methods prove their benefit in increasing the adherence to hygiene guidelines and are therefore able to reduce nosocomial infections.

Technological approaches and solutions for complication reduced CSP handling

As described earlier, some infusions are not prepared in nursing wards but are requested to be prepared by adhering clinical pharmacies. The special environments for low particulate contamination and the recurring trainings on aseptic preparation skills provide a reliable basis for compliant CSP mixing in pharmacy settings. Preparation of CSPs is thereby connected to lower ME rates when they are prepared in a central pharmacy setting, compared to their preparation in the nursing ward [58]. In some cases however, the preparation of infusions by pharmacists is looked upon unfavorably. Compared to the instances when the preparations were prepared in the adherent clinical pharmacy setting [59], drug preparations labelled by nurses resulted in a lower likelihood of mistakes and mix-ups, as information gaps and complexity by additional transfers were reduced.. This is one of the main arguments in the ongoing discussion of which preparation approach is best suited for the reduction of MEs. In general, each setting would benefit from an automated preparation of CSPs, as this is considered the least prone to error [60-62].

A different approach to reduce preparation, administration and aseptic errors could be facilitated by using novel drug product preparation systems. More prefilled syringe systems, vial adapter systems and injector devices for the subcutaneous application of medicines are emerging and are about to take over home care for parenteral drug administrations. These administration systems allow patients to overcome the burden of visiting the clinical environment for routine intravenous therapies and instead enable them to administer their medication self-reliantly at home [63-65]. Predominantly, not all drugs can be administered in the home care setting due to their need to be administered intravenously and thus require a medical professional. Furthermore, in cases of emergencies, accidents, or during hospitalization, therapies require the administration of intravenous medicines due to faster onset, prolonged and continuous application rates, or solubility and compatibility issues concerning the route of administration. Those intravenous medicines are mainly provided as liquid solutions in glass vials or as dry powders or lyophilizates that must be reconstituted prior to administration. Due to these requirements, greater special attention is required for their preparation. With the intention to mitigate some of the analyzed MEs, different manufacturers invented and marketed several technical solutions to evade preparation and administration MEs elucidated in the articles studied above. Moreover, these generated solutions are also intended to facilitate an aseptically safe transfer of the drug into appropriate administration containers and additionally reduce the exposure of healthcare professionals to high potent active pharmaceutical ingredients (HPAPI). A collection of these marketed solutions is displayed in Table IV.

Three different connection types were found that connect either (1) vial to vial by an adapter, (2) vials to infusion bags by an adapter, or (3) powdered drug products to a diluent in one infusion bag. The Mix2Vial system from West Pharmaceutical Services Inc. is of connection type (1) and is intended to mount a diluent vial to a drug vial with a double spike adapter, which allows the immediate reconstitution of a lyophilizate drug. Prior to connection, the diluent vial septum and the drug vial septum are rubbed with an alcohol swab, followed by piercing the spike adapter into the diluent vial. The adapter diluent assembly is then inverted and pierced into the drug vial allowing the reconstitution. The assembly can then be separated for the withdrawal of the reconstituted drug by a syringe [66].

This system offers the aseptically safe and complete transfer of the reconstituted drug, but is dependent on available vacuum in the drug vial facilitating the flow of the diluent to the lyophilized drug.

Another approach for complete drug reconstitution or mix of liquid drugs into infusion bags was introduced by the vial to infusion bag adapters (2). These systems, such as the MINI-BAG Plus, the Vial2Bag Advanced™, the addEASE® binary connector, the ADD-vantage™, or the Vial-Mate, enable the healthcare professional to easily mount a drug vial onto an infusion bag. The spike adapter in the vial to infusion bag adapter systems allows the mounting of the vial by piercing through the septum of the vial and then into the infusion bag septum. By pressurizing the diluent in the infusion bag (while the vial is pointed to the bottom), the liquid flows into the drug product vial, dissolves/reconstitutes and ultimately dilutes the drug product to the correct single unit dosage. Mixing of the drug and the diluent can be performed without the necessity of reconstituting or pre-diluting the drug and transferring the drug into the infusion bag, where each step requires a new pair of syringes and cannulas that create possibilities for additional MEs [67-70]. Inverting the bag and forcing air into the vial leads to the extraction of the dissolved drug into the infusion bag. The use of such systems allows the aseptically fast and safe transfer of drugs into infusion bags with a reduced prevalence for MEs such as “wrong preparation technique” or “wrong homogenization”. As the diluted drug product must be completely transferred into the infusion bag, the drug product might eventually dissociate completely in case insufficient mixing time was attributed to the drug product during the transfer of diluent to the vial. However, it was described in the handling instructions that a loss of dose must be anticipated that can account for < 10% of the liquid drug within the drug vial [71]. Furthermore, some connection systems such as the addEASE® or the ADD-vantage™ systems are proprietary and are only to be used with the diluent infusion bags or with the drug vial containers coming from the same manufacturer, which limits the use of the connection system to only a few cases, but also limits the likelihood of using incorrect diluents [68, 70, 71]. Although these systems are capable of preparing CSPs with a reduced likelihood of MEs occurring, a preceding dose adaptation in the drug product vial needs to be performed for patient-specific dose calculations. In the case of lyophilizates used for these preparations, these adaptations can’t be made on a patient-specific basis, as the complete content of the drug product vial is used for the preparation of one CSP. These systems are thus limited in their advantageous application in dose-banding approaches when one CSP covers a broad range of different patients and no further adjustment of the dose or concentration is required.

The other connection system offers the containment of a fixed-dose medication in an infusion bag already paired with the correct diluent in an adjacent compartment. These systems are dual chamber infusion bags and pair the drug with the diluent in one system. To provide drug and diluent in one system, the DUPLEX®-, PLW® or Dual-Mix® infusion bags are therefore separated into two compartments separating the chambers by a temporary seal. The first compartment houses the drug powder or liquid drug and the second compartment houses the diluent. To combine the drug and the diluent in these systems, pressure must be applied to the diluent compartment generating a passageway by rupturing the seal that separates the compartments. Such a quick activation and preparation system ensures the complete dose dilution and ultimately complete dose administration to the patient, while the use of a wrong diluent that potentially compromises the drug potency or solubility is avoided.

Furthermore, the design allows the safe handling of drug preparations by minimizing interaction steps and exposure of the healthcare professional to the incorporated antibiotics or cytotoxic agents [72-74]. Additionally, through the introduction of nosocomial pathogens, aseptic MEs are mitigated by reducing the necessary interaction steps with the drug product and omitting the manual introduction of medicine preparations by syringe and cannula. Though these systems mitigate many MEs, other potential MEs can be anticipated for the respective designs as well. Depending on the allocation of the diluent compartment, the administration of diluent could only occur if it is adjacent to the infusion port, or pockets of undiluted powdery drug product could remain in corners and thus reduce the administered dosage, leading to the occurrence of "wrong dose" MEs. However, some of these systems also lack the flexibility of adding adjuvants or administering a dosage greater or lower than incorporated into the respective dual chamber infusion bag. This demands that the dual chamber infusion bags need to be provided in a wide dose range to effectively treat a broad range of patients. A potential approach of loading these systems with drug product systems to overcome the likelihood of undiluted powdery products remnants, along with a comparison of the stability of such systems compared to the drug product stability in vials, was discussed earlier [75, 76].

Table IV *Technical solutions for complication-reduced and faster drug preparations*

Product name	Manufacturer	Preparation system adaptor / Preparation device	Possible to use with non-proprietary drug vials?
Mix2Vial – reconstitution system and needle-free transfer device	West Pharmaceutical Services Inc. ®	Adapter to connect drug vial to diluent vial	Yes
MINI-BAG Plus	Baxter International Inc.	Diluent infusion bag with attached vial adapter to connect drug vial	Yes
Vial2Bag Advanced ™	West Pharmaceutical Services Inc. ®	Adapter to connect drug vial to diluent infusion bag	Yes
addEASE® binary connector	B.Braun Medical Inc.	Adapter to connect drug vial to diluent infusion bag	Restricted to B.Braun infusion bags
ADD-vantage™	Pfizer Hospital Products Group Inc.	Adapter to connect drug vial to diluent infusion bag	No
Vial-Mate	Baxter International Inc.	Adapter to connect drug vial to diluent infusion bag	Yes
DUPLEX® dual chamber bags	B.Braun Medical Inc.	Dual chamber infusion bag with separation between drug and diluent compartment	No
PLW® dual chamber bags	Nipro Pharma Corporation	Dual chamber infusion bag with separation between drug and diluent compartment	Yes
Dual-Mix® multi chamber bags	Technoflex SA	Dual chamber infusion bag with separation between drug and diluent compartment	Yes

Summary and Conclusion

Although training efforts in hospitals and clinical centers in the form of educational interventions, training sessions and the creation of guideline posters and calculation charts for CSP preparations were made, the gap in preparing CSPs meeting the guidelines and recommendations by USP and ASHP still exists [28, 29, 77]. Contrary to general assumptions that MEs would be more prevalent in LMICs than in HICs, it was illustrated that MEs are widespread and independent of the location of the clinic or care facility. The distribution of errors is split among those observed during the preparation, administration, and aseptic handling of CSPs, and these findings may vary depending on the clinic or potentially also on the observer.

While errors such as “wrong administration rate”, “wrong mixing and wrong reconstitution”, “wrong diluent”, “wrong preparation technique”, and “wrong time or wrong frequency” were found to be the most common, these errors are not easily distinguished from each other. The preparation of one CSP can include multiple MEs. For example, by reconstituting a drug with a wrong diluent, the prepared CSP can cause the following observed MEs: “wrong dose” because of low solubility, “wrong reconstitution” because of incompatibility with the diluent, a “prescription error” as the diluent was mistaken for another, and ultimately “wrong time” as the drug dissolved longer than expected and was administered with a delay. Several strategies to prevent these errors have been proposed but in some cases these strategies showed only limited success. The inclusion of CIVA for the preparation of mini-infusions, instead of bolus injections with long waiting periods next to the patients’ bedside, were highlighted as factors for the reduction of administration rate-related MEs. Gravimetric control systems, including barcode scanning, ensured the preparation of CSPs with the correct dosage, and also identified errors when the drug was prepared with the wrong diluent. The prevalence for CSPs administered with drug-diluent incompatibilities, or even the potential to cause harm to the patient, were thereby reduced [51, 52].

Such approaches offer relief for healthcare professionals, as the medications can be administered in a timely fashion and are ensured to be prepared according to prescription and manufacturers’ information in the PIL. Nevertheless, these approaches require special services provided by adherent clinical pharmacies or the purchase of additional equipment and software that require maintenance, care, and proper training. Another approach described to tackle reoccurring MEs is the use of novel technical solutions to facilitate the preparation of CSPs without the need to establish special services or invest in additional devices. Utilizing adapter systems can facilitate a more robust and improved aseptic transfer of drug doses and eliminate incidents of wrongly mixed CSPs. By employing proprietary systems that eliminate the preparation of drugs with the wrong diluent, incorrect mixtures with known incompatibilities can be prevented. The dual chamber infusion bag preparation systems proved to be the most beneficial in terms of avoiding the majority of the analyzed and highlighted MEs. The combination of the correct diluent with the correct drug dose in one system limits the interaction and possible exposure of the healthcare provider to the drug. In return, it also enables them to prepare the CSP next to the bedside of the patient in the absence of a special preparation area. The simple compounding step provides a fast preparation of the CSP and a subsequent immediate administration, without the prior need to compound the medication to ensure correct timing or frequency of the medication, which could risk the growth of microbial contaminants prior to administration.

We therefore propose that drug manufacturers shift their attention from the provision of drugs in vials and ampoules, and to consider the preparation of fixed-dose medications in containers that empower the users of the medications to work more efficiently and thus reduce the likelihood of errors.

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CHAPTER II

Part I: Significant reduction of lyophilization process times by using novel matrix based scaffolds

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Highlights: Lyophilizates are a promising vehicle to sustain long-term stability of proteinaceous drugs especially monoclonal antibodies. The manufacturing of such lyophilizates is however time and energy consuming and less favored over the storage of proteinaceous drugs as liquid solutions. This study evaluated the possibility to manufacture lyophilizates outside of the common production and storage container, the glass vial. Several different container formats were assessed on their ability to decrease processing times while maintaining solid state properties found in drugs lyophilized in glass vials. Ultimately, subtractive and additive manufacturing techniques were used to generate three-dimensional lattice structures i.e. scaffolds, that were able to process the lyophilized drug product outside of the final storage container. Achieving equivalent solid state properties found in glass vials, with greater batch homogeneity and a decrease of processing times by more than 50%.

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Research paper

Part I: Significant reduction of lyophilization process times by using novel matrix based scaffolds

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ABSTRACT

To improve the long-term stability of drugs with limited stability (e.g., biologicals such as monoclonal antibodies, antibody drug conjugates or peptides), some pharmaceuticals endure a lengthy and cost-intensive process called lyophilization. While the shelf life of lyophilized drugs may be prolonged compared to their liquid form, the drawbacks come in the form of intensified manufacturing, preparation, and dosing efforts. The use of glass vials as the primary container unit for lyophilized products hinders their complication-free, fast and flexible use, as they require a skilled healthcare professional and an aseptic environment in which to prepare them. The feasibility of substituting glass vials with novel container designs offering the complete transfer of the lyophilizate cake into modern administration devices, while reducing the economic footprint of the lyophilization process, was investigated. The lyophilization process of a monoclonal antibody solution was studied by assessing primary drying conditions, homogeneity of the drying process, and critical quality attributes after successful lyophilization. The creation of novel container designs utilized vacuum-forming to generate confined containers with removable bottoms and rapid prototyping, including subtractive and additive manufacturing methods, to generate porous 3D structures for drug housing. The novel container designs generated lyophilizates twice as fast and achieved a threefold faster reconstitution compared to their vial counterparts, without adaptation of the processing conditions. We conclude that the use of intermediate process containers offers significant relief for healthcare professionals in terms of reduced probability of handling errors, while drug manufacturers benefit from the accelerated processing times, increased batch homogeneity, and sustainability.

1. Introduction

Current lyophilizate manufacturing processes in glass vials are associated with long development times to generate elegant and defect-free lyophilizate cakes, long processing times for single batches, and energy inefficiency during manufacturing [1]. By freeing the lyophilizate from the container and co-locating it with the diluent or in the administration system of choice, an ease in application, a potential for fixed dose combination and a significant decrease in the probability of handling errors could be achieved [2–4]. If the process in such an intermediate system optimizes and additionally accelerates the unit operation to produce lyophilizates more economically, the application of lyophilization could perhaps be considered more regularly in the manufacturing of current drugs. This would broaden the availability of these drugs in countries and locations where their use would have been considered unfeasible due to economic constraints.

Leaving behind the established concept of using the final packaging container during the process presents attractive opportunities to work with a process-optimized container and a storage/application-optimized container. The integration of process-optimized containers leads to efficiently used processing times and reduced energy consumption. Subsequently, the transfer of the drug from the process-optimized container to the storage/application-optimized container results in extended shelf life stability and improved usability by the healthcare professional. This separation (uncoupling of process and storage/application container) could broaden the availability of drugs and promote the more frequent choice of freeze-drying as unit operation for drugs that require intravenous (IV) application.

Although the majority of containers currently used for IV drugs in which freeze-drying is performed are vials, some market-approved formulations are provided in cartridges and dual chamber syringes. Besides glass as the primary packaging material in vials, plastic compounds as

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Cyclic Olefin Copolymer (COC) and Cyclic Olefin Polymers (COP) are also slowly emerging on the market. These formats increase the design freedom, break resistance, and in combination with coating technologies, provide increasing barrier functionalities [5–7]. However, these container formats still lack the flexibility of allowing quick and effortless transfer of the incorporated drug into the infusion or injection system of choice. The vials and cartridges enclose the drug product nicely in their translucent castle, allowing optimal visual inspection, for example, but usually demand patient-specific compounding and preparation processes, and thus limit the market acceptance of lyophilizate use. In light of these limitations, a different approach emerged.

First steps for establishing a separation of process and storage/application container were taken by Werk et al., by introducing a steel cartridge as an intermediate process container for the freeze-drying step. The freeze-dried cakes manufactured in these steel cartridges are subsequently transferrable. However, the transfer was focused only on dual chamber syringes and cartridges with fill volumes limited to 1.2 ml [8]. For the production of bulk freeze dried material the use of LYOGUARD® trays is described by Gassier et al. and Hiebler et al. [9,10]. These single-use trays facilitate the preparation of several liters of freeze-dried material within one LYOGUARD® processing container, but require further processing to separate the material into the administration or final storage containers.

In this study, we addressed some of the mentioned drawbacks of lyophilization in vials by omitting the primary container and preparing a dried powder instead. The use of novel manufacturing systems, such as the Active Freeze Dryer system from Hosokawa Micron BV (Doetinchem, Netherlands) or the SprayCon and LyoMotion systems from Meridion Technologies (Müllheim, Germany), advertise that those systems facilitate the manufacturing of “homogeneous and free flowing lyophilized bulk ware” in an “efficient and cost-effective manner”. However, the loss of product in the processing vessel, difficulties in achieving accurate powder dosing, and potential release of hazardous highly potent active pharmaceuticals (HPAPI) dust, excluded these technologies from our considerations.

We approached the generation of process-optimized intermediate containers by identifying the shortcomings of the common drug product containers, such as glass and COC/COP vials. Shortcomings of the common containers include the material of construction (MOC), the limitations in fill height, the poor heat-mass transfer properties from shelf to cake, the confined sublimation surface and exhaust passage, and the restricted heat-mass transfer properties within the cake. Potential carrier-based systems were assessed in this study to facilitate high comparability to the current manufacturing process for lyophilizate vials. Container designs utilizing vacuum-forming to generate confined containers with removable bottoms and rapid prototyping were used to generate such carrier-based systems. These designs included subtractive and additive manufacturing methods. Subtractive manufacturing refers to the removal of matter from a solid piece of material to form a specific three-dimensional structure, while the term additive manufacturing refers to procedures in which fine layers upon layers are stacked or manufactured on each other achieving the same outcome. Structures prepared by additive manufacturing allow the manufacturing of intricate inner geometries that are not achievable by subtractive methods. Our focus was to investigate such carrier-based systems and to elucidate ways of facilitating larger drug product volume transfers compared to the preparations in steel cartridges.

In light of the limitations and drawbacks associated with the preparation of current lyophilization applications, the aim of this study was to investigate the substitution of glass vials as lyophilization containers. We hypothesize that an intermediate process container system optimized for the freeze-drying process could facilitate freeze-drying outside the common vial format. This would increase the flexibility of incorporating the freeze-dried cake into a variety of final primary packaging systems. Through the introduction of differently designed container concepts, the optimization of the freeze-drying process and the transfer of a lyophilization cake into a final storage/application container should be enabled. By designing container formats that facilitate efficient freeze-drying operations with less occupation times, homogeneous products with less rejects, and a strategy of introducing the exact dose of prepared drug product into the final application container of choice, these economic benefits could advocate for a much broader application of freeze-drying.

2. Materials and methods

2.1. Containers

The first criterion to establish an intermediate container, dimensioned as the standard 20R glass and COC vial, included the design change from a vial to a thin walled polyethylene terephthalate container. In doing so, the containers provided a reduced headspace volume, thin walls, and a bottom with reduced thickness. The radial dimensions chosen for these containers were matched with those of the 20R glass vial. Such intermediate processing containers were manufactured from thin walled polyethylene terephthalate and offered a polypropylene (PP) film or aluminum (alu) foil that could be removed by peeling the foil at the bottom (hence twPETC PP or twPETC alu), depicted in Fig. 1. After processing, peeling the foil/film allowed the extraction of the lyophilizate cake. Conduction of the heat from the shelf took place via the transparent PP film or the aluminum foil at the bottom. By using these flexible films or foils, the accessible conduction surface at the bottom could theoretically be increased from 1.83 cm^2 for vials to 6.99 cm^2 for twPETCs. Furthermore, the thickness of the bottom layer in contact with product and shelf could be reduced from 0.85 ± 0.15 mm (glass) to 0.110 mm or 0.033 mm for the PP film or aluminum foil, respectively. The accessible conduction surface responsible for the heat transfer was determined by staining the bottom surface of the vials and twPETCs with an ink pad and measuring the received imprint after pressing the container on a sheet of paper on a flat surface, a procedure that has been described previously [11]. The imprints were measured before and after freezing to evaluate changes in the conduction surface occurring during freezing. Water vapor removal in the twPETCs was enabled via the 20 mm wide opening on the top of these containers. The twPET-containers with PP films had the tendency to bulge and reduce the conduction surface, while the aluminum foil versions maintained their flat surface.

The next design concept considered the delicate and brittle structure of the lyophilizate cake and the potential loss of product during transfer into the final container. The design of the next intermediate container was therefore changed from a confining container with a limiting perimeter to a container with a matrix, depicted in Fig. 1. This strengthened the drug product cake by its porous structure. The dimensions chosen for these porous structures were matched to the dimensions occupied by filling 10 ml of water in a 20R vial and adapting the inner geometry to allow the structures to be filled with 9.0 ml of liquid plus extra space for expansion during freezing. The porous structures were designed to increase the available sublimation surface from a planar circular layer on the top of the frozen product solution in vials to a cylindrical sublimation surface on the outside of the porous structures. Furthermore, the porous structures were designed to also improve the heat and mass transfer during lyophilization. These structures were first created by subtractive manufacturing (computerized numerical control lathing, generating CNC scaffolds). This method achieved high porosities but with a simple geometry. By utilizing additive manufacturing techniques (selective laser sintering/melting, generating SLS scaffolds), the inner geometry of the porous structures could be changed to more intricate designs, while maintaining high porosity. The MOC in these porous structures was varied and chosen to consist of a plastic and alloy-like stainless steel or aluminum. This was done to assess the conduction of supplied heat to the inner core of the lyophilizate cake by use of different materials. These porous structures

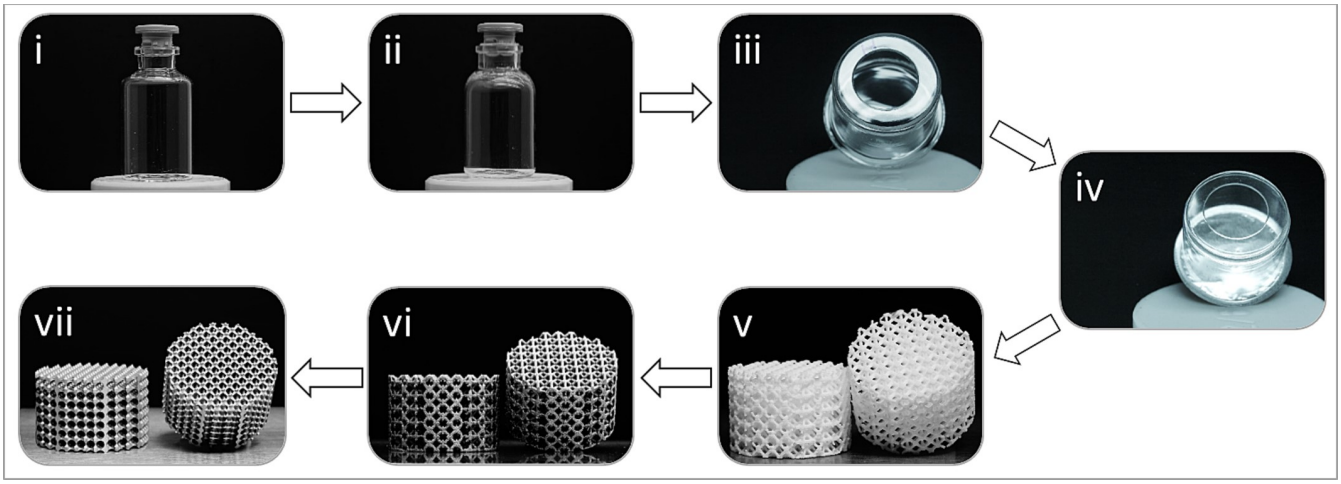

Fig. 1. Container designs intended for freeze-drying experiments suited to receive, incorporate, and hold 9.0 ml of liquid drug product. (i) 20R Schott Fiolax glass vial, (ii) 20R Medicopack COC vial, (iii) twPETC PP container, (iv) twPETC alu container, v) SLS nylon scaffold, (vi) SLS SS scaffold, and (vii) CNC alu scaffold.

increased the sublimation surface from a previous 6.74 cm^2 circular planar surface in glass vials (determined by the inner diameter of the 20R glass vial) to a 25.9 cm^2 cylindrical surface in porous structures.

2.1.1. Vials

Fiolax® glass vials 20R (Schott, Müllheim, Germany) were filled with 9.0 ml of mAb1 formulation and partially stoppered with 20 mm Lyo-stoppers D777-1 (DAIKYO Seiko Ltd., Tokyo, Japan) before freeze-drying.

Clear vials COC 20R (MedicoPack A/S, Langeskov, Denmark) were filled with 9.0 ml of mAb1 formulation and partially stoppered with 20 mm Lyo-stoppers D777-1 (DAIKYO Seiko Ltd., Tokyo, Japan) before freeze-drying.

2.1.2. Thin-walled polyethylene-terephthalate containers (twPETCs)

The twPETCs were manufactured by vacuum-forming. VIVAK® polyethylene terephthalate glycol (PET-G) films (Vink Schweiz GmbH, Dietikon, Switzerland) of 0.5 mm thickness were used to prepare the PET containers. The PET-G material was chosen as a MOC for its transparent appearance, the manufacturability in the vacuum forming process, and potential sterilization suitability. The dimensions of the twPETCs were predefined to resemble the inner diameters of a 20R Schott Fiolax® glass vial. The vacuum-formed twPETCs were separated from the residual PET-G film material using a hollow punch with a wider diameter than the twPETC container. This created a 1 mm rim around the bottom orifice. Another orifice was punched into the top part of the twPETC to allow the subsequent filling of drug product into the container. Either a translucent Clear Heat Seal film or an aluminum heat seal foil (4titude Limited, Wotton, UK) was welded onto the rim of the bottom part, later in contact with the shelves. Films and foils were welded onto the twPETCs by heat sealing. The twPETCs were filled with 9.0 ml of mAb1 formulation before freeze-drying.

2.1.3. Porous structures/scaffolds

2.1.3.1. Scaffold structures by subtractive manufacturing. A structural design was rendered that accommodates the drug product solution in a matrix. A solid EN AW-6082 T6 aluminum rod (Metall Service Menziken, Menziken, Switzerland) of Ø 30 mm was used as a source material to generate the scaffold structures. The interconnected pores were generated by drilling bores into the rod using a Kern MMP CNC lathing machine (Kern Mikrotechnik GmbH, Murnau, Germany). Bores were drilled from the x-, y-, and z-axes to generate pores extending from the top to the bottom and to the lateral boundaries. To remove the porous structure from the rod, the resulting structure was then lathed with the CNC machine. Resulting structures were anodized in a post process operation to passivate the surface. These structures also refer to the group of porous structures, alloy structures or solely as CNC alu scaffolds.

Scaffolds prepared in this manner were equally equipped with a perimeter for filling, received the formulation via dispensing, and handled prior to the primary drying, similarly to the structures prepared by additive manufacturing.

2.1.3.2. Scaffold structures by additive manufacturing. A second, more dense structural design was rendered to accommodate the drug product solution. Two different materials and manufacturing methods were applied to generate these structures, resulting in two separate structures. The porous structures were prepared from Nylon PA 2200 powder (eos GmbH, Kreiling, Germany) by SLS in a FORMIGA P 110 printer (eos GmbH, Kreiling, Germany). The nature of the PA 2200 compound used in this study allowed a fast prototyping, good flexibility accompanied by high mechanical strength, and is considered a biocompatible compound. The same dense structure was also prepared from 316L/1.4404 stainless steel powder (Carpenter Technology Corp., Philadelphia, PA, USA) by SLM in a Concept Laser M2 cusing printer (GE Additive, Cincinnati, OH, USA).

A perimeter was required to allow complete loading of the structures without leakage of solution. Two different sized Parafilm® M sealing film squares (Heathrow Scientific LLC, Vernon Hills, IL, USA) were used to wrap the scaffolds at the base and at the lateral surrounding, excluding the area at the top. A volume of 9.0 ml mAb1 formulation was then dispensed from the top into the porous structures. Gentle agitation was used to remove entrapped air bubbles. Prior to the start of the primary drying step and after complete freezing, the scaffolds were freed of their perimeter and placed back on the shelf.

The MOC, dimensions, and properties of the designed containers are listed in Table 1.

2.2. Materials and formulations

A model monoclonal antibody, mAb1, (IgG1, 148 kDa, isoelectric point ~ 8.7) was formulated at a concentration of 10 mg/ml in 20 mM histidine/histidine-HCL buffer (Ajinomoto, Tokyo, Japan) at pH 5.5 with 80.0 mg/ml sucrose (Ferro Pfanstiehl Inc, Waukegan, IL, USA) and 0.02 % Polysorbate 20 (Croda International, Snaith, UK). The formulation was sterile filtered through a hydrophilic 0.22 μm PVDF filter membrane (Merck Millipore, Burlington, MA, USA).

Table 1
List of container designs with their material information, dimensions, and specific physical properties.

Container identifier	Container variant	Material of construction	Manufacturer	Subgroups of containers	Dimensions H×Ø	Conduction & sublimation surface	Thermal conductivity k & specific heat capacity c_{sp}
20R Glass Vial	Confined container	Borosilicate glass	Schott AG	–	58.0 mm × 31.5 mm vial shape	1.83 cm^2 6.74 cm^2	k = 0.9–1.2 W/(m·K) @90 °C [20] c_{sp}(borosilicate glass) = 0.42–0.84 J/g•K [20]
20R COC Vial	Confined container	Cyclic olefin copolymer	Medicopack	–	55.0 mm × 29.8 mm vial shape	0.78 cm^2 6.32 cm^2	k = 0.12–0.15 W/(m·K) @20 °C [21]
twPETC PP/ twPETC alu	Confined container	0.5 mm Polyethylene terephthalate G	Internal prototyping workshop	PP foil seal of 0.110 mm/aluminum foil seal of 0.033 mm	25.4 mm × 30.8 mm conical shape	6.99 cm^2 6.99 cm^2	k = 0.249 W/(m·K) [22]/ k = 15–180 W/(m·K) @20 °C [23]
SLS nylon scaffold	Porous scaffold structure	PA2200 based on Polyamid 12	Internal prototyping workshop	–	20.3 mm × 29.7 mm cylindrical shape	6.91 cm^2 25.85 cm^2	$k_{vertical\ layer}$ = 0.144 W/(m·K) & $k_{horiziontal\ layer}$ = 0.127 W/(m·K) c_{sp} (PA2200) = 2.35 J/g•K [24]
SLS SS scaffold	Porous scaffold structure	Stainless steel EN 1.4404	Irpd AG	–	20.0 mm × 30.1 mm cylindrical shape	7.10 cm^2 26.00 cm^2	k = 15 W/(m·K) @20 °C c_{sp} (1.4404) = 0.500 J/g•K [25]
CNC alu scaffold	Porous scaffold structure	Aluminum EN AW-6082	Internal prototyping workshop	–	20.0 mm × 30.0 mm cylindrical shape	7.05 cm^2 25.91 cm^2	k = 170–180 W/(m·K) @23 °C c_{sp} (EN AW-6082) = 0.890 J/g•K [23]

2.3. Freeze-drying

Lyophilization and temperature measurements of the solutions were performed in one lyophilizer and with two temperature measuring systems. The freeze-dryer of choice was a 0.5 m^2 TR01 Lyophilizer (HOF Sonderanlagenbau GmbH, Lohra, Germany) consisting of three loading shelves. The lyophilizer was operated and monitored with the LyoCom III Software (HOF Sonderanlagenbau GmbH, Lohra, Germany). Samples within the lyophilizer were monitored by a TLAB.transfer and 16 wireless temperature probes Type TL18 (Tempris GmbH, Holzkirchen, Germany). The TLAB.transfer and its wireless temperature probes were operated and monitored with the TDS Tempris DataServer software (Tempris GmbH, Holzkirchen, Germany). Samples requiring the use of thin wired probes were equipped with thin wire thermocouples type T (Messmatik AG, Rheinfelden, Switzerland). Data was logged with an external temperature logger TC-Log8 USB T (Messmatik AG, Rheinfelden, Switzerland).

The vials were placed in a predetermined hexagonal pattern with specific locations for the filled samples to achieve a configuration as uniform as possible among all samples. This setup was previously described by Tang et al. [12]. A layer of six empty dummy vials and a second layer consisting of 12 vials surrounded each probed sample. This setup ensured that convection and conduction were maintained while avoiding atypical radiation effects. Thermal influence of other filled vials was avoided by not placing product-filled vials directly adjacent to probed samples. In the second layer of dummy vials, four vials were also filled with the formulation and were arranged above, below, right, and left of the probed vial. Filled edge-vials did not meet these criteria and were therefore only used to enable this specific configuration for the probed samples in the inner area of the shelf. The vial and new container formats were evaluated by being rotated in their lyophilizer position to avoid a position-based bias regarding their drying behavior.

To assess if the drying by lyophilization could be performed in the container designs, the ensemble of containers was filled with the model formulation and freeze-dried according to the freeze-drying recipe in Table 2. This configuration was applied equally to all containers. The lyophilization recipe was selected based on the hypothesis that this would suit all intermediate processing containers.

2.3.1. Differential scanning calorimetry

Differential scanning calorimetry measurements were performed on a Discovery DSC (TA Instruments Inc., New Castle, DE, USA) to determine the glass transition temperature of the maximally freeze concentrated solution (T_g') of the used formulation. The determination of T_g' was performed with 20 µl of formulation sample hermetically sealed in Tzero Aluminum Pans. The recipe used for the testing included a freezing ramp of 10.0 °C/min to −50.0 °C, followed by an isothermal hold of 5.0 min, and a subsequent heating ramp of 10.0 °C/min to 25.0 °C. The T_g' was determined in triplicate at the midpoint of the glass transition temperature and reported as the mean ± standard deviation.

2.4. Primary drying endpoint determination

Determination of the primary drying endpoint can be approached by various means and techniques, e.g. pressure-dependent-, spectroscopic-, or product temperature-specialized techniques [13–15]. In our

Table 2
Overview of the non-adjusted generic freeze-drying parameters employed for the lyophilization runs. Individual product temperatures T_p within the designed containers were measured with thin wire probes or wireless probes.

Parameters		Loading	Freezing	Primary Drying	Secondary Drying	Cycle End
Temperature Shelf Ts	[°C]	+5	−35	−10	+25	+5
Temperature Condenser	[°C]	–	–	−80	−80	−80
Ramp Rate	[°C/min]	–	−0.3	+0.2	+0.2	–
Hold time	[min]	60	180	3360	480	–
Pressure	[mTorr]	ambient	ambient	100	100	500

investigations we employed individual product temperature testing as the endpoint determination method of choice. This was because of the limited number of samples and the use of various containers per run. The endpoint determination for the primary drying step could be performed by measuring the individual product temperature (T_p), either by thin wire probes or by wireless temperature probes. The endpoint determination was described as the timepoint when the T_p exceeded the shelf temperature (T_s) or when T_p was equivalent to T_s [16]. The distinct configuration of the intermediate container designs and materials had to be taken into consideration when determining the endpoint of the primary drying. While the twPETCs exceeded the T_s and then attained a constant temperature with minimal change, the porous structures exhibited a relatively early constant temperature, although not exceeding the T_s at that point. Thus, the endpoint determination needed to be approached differently for the novel container designs.

To measure the temperature of the last drying fraction within the lyophilized cake, thin wire probes were inserted into the containers and installed at the last fraction of ice, touching the container material. Probes in confined containers (glass vials, COC vials, and twPETCs) were located in the center bottom. For the investigation of the last drying fraction within porous scaffold structures (SLS nylon, SLS SS, and CNC alu scaffolds), a heat mapping experiment was conducted in which the structures were simultaneously probed with three temperature probes to determine the last fraction of ice of drying in the vertical axis. In doing so, the last point of sublimation within the scaffold structure could be determined to be the area in the center core. Follow up characterizations were thus performed by installing the thin wire probes in the center core of the porous structures.

Primary drying endpoints for vials and twPETCs were determined by means of thermocouples placed at the bottom center of the vial to evaluate the last fraction of ice subliming. They were defined as the timepoint when the thermocouple temperature within the confining containers exceeded the T_s [17]. Primary drying endpoints for porous structures were determined when the thermocouple temperature within the structure achieved a plateau phase close to the T_s. More specifically, the temperature at a specific timepoint during the drying was averaged with five temperature values both before and after the specific timepoint. The standard deviation was calculated for this averaged timepoint and plotted with the temperature curve against the duration (data not shown). When the individual temperature curve transitioned into the plateau phase, the averaged SD declined and approached values < 0.05. This low SD was observed during the steady state and thus used as a threshold to specify the endpoint of primary drying within these structures. The timepoint when the plotted SD curve intersected the threshold value was specified as the primary drying endpoint for this individual porous structure.

2.5. Solid state properties

Typical solid state properties (SSPs) for lyophilizates comprise reconstitution time, appearance of the freeze-dried cake, appearance of the reconstituted solution, and residual moisture. These SSPs can be assessed by solid state characterizations and are frequently determined to investigate the quality of lyophilizates and their respective freeze-drying process. In our investigations, the aim was to deliver an intermediate container design capable of being transferred into other final packaging systems for immediate use. These designs must achieve SSPs comparable to lyophilizate cakes generated in vials. As such, the following SSPs were evaluated for the novel intermediate container designs: reconstitution time, residual moisture, and cake appearance.

2.5.1. Reconstitution time

The lyophilizates in vials were reconstituted by injecting 9.0 ml water for injection through the stopper onto the inner glass wall of the vial.

Porous structures with embedded lyophilizate cake were transferred individually after lyophilization into a nitrogen-flushed wide mouth amber packer with Teflon faced foamed PE lined PP cap (DWK Life Sciences LLC, Milville, NJ, USA), hereafter referred to as amber jar. A single scaffold was withdrawn and transferred into a 20 ml glass beaker. Reconstitution was performed by injecting 9.0 ml of water for injection onto the porous structures.

Reconstitution times were determined with a stopwatch. For both the vials and the porous structures, the timing started after completed injection. Homogenization in both cases was achieved by gentle swirling every 30 s. Timing stopped when the solutions and pores inside the porous structures were visibly free of solid residues.

2.5.2. Residual moisture

Residual moisture levels were determined using a C30 Coulometric Karl Fischer titrator (Mettler Toledo, Greifensee, Switzerland). The vial with lyophilized cake was weighed before reconstitution and reconstituted with 10.0 ml of dry methanol, vortexed, and allowed to dissolve for 1 h before Karl Fischer titration. A non-turbid aliquot of the supernatant was extracted with a 5 ml plastic syringe and injected into the measuring cell. It was then titrated against standardized KF reagent. The vials and stopper were rinsed with water and ethanol and heat dried at 120 °C for 20 min. The cake weight was then obtained by reweighing the empty vial and stopper.

The residual moisture levels in the porous structures were determined by injecting 10 ml dry methanol onto the porous structure within an amber jar. The amber jar was then vortexed and the cake within the porous structure was allowed to dissolve for 1 h before Karl Fischer titration. An aliquot of the supernatant was extracted with a 5 ml BD syringe and injected into the measuring cell where it was titrated against a standardized KF reagent. The amber jar, respective cap, and porous structure were thoroughly rinsed with water and ethanol and then dried at 120 °C for 20 min in order to determine the embedded cake weight.

2.5.3. Cake appearance

The quality of the freeze-dried products was determined by visual appearance of the cakes within the glass and COC vials, and twPETCs. As the inner structures were not accessible by visual appearance evaluations, the appearance of the lyophilized cakes was evaluated by micro computed tomography (μCT). This was done in addition to the standard visual inspection. The visual inspection is only suitable for the outer dimensions of the cake, while μCT data also visualize the inner geometries of the cake and matrix.

2.5.3.1. Micro computed tomography (μCT) evaluations. Inner cake structure of the lyophilized material was determined by μCT measurements. These were performed based on a method recently developed by Haeuser et al. [18,19]. Lyophilizate cakes within glass vials were analyzed without sample preparation. Porous scaffolds were transferred into twPETC alu containers under dry nitrogen conditions and kept under these conditions until initiation of the measurement. A SkyScan 1272 X-ray microtomograph (Bruker Corp., Billerica, MA, USA) was used to acquire the images of the lyophilizate cakes. For the investigations of cakes within glass vials, the settings in Table 3 were applied. For all container designs, the cakes were investigated by rotating the container for a complete 360° rotation with a step size of 0.1°. The 3D visualizations of the cake tomograms were reconstructed with the 3D.SUITE software (Bruker Corp., Billerica, MA, USA).

3. Results

During the evaluation of the results, the entirety of each sample group was tested by statistical methods, such as Tukey's method of outlier detection and the Student's *t*-test, to ensure data integrity and good comparability among the lyophilization runs and characterizations

Table 3
Applied measurement parameters for μCT evaluation of the different intermediate container designs.

Parameters		Glass vials	SLS nylon scaffolds	SLS SS scaffolds	CNC alu scaffolds
Acceleration voltage	[kV]	60	40	100	60
Beam current	[μA]	166	250	100	166
Ramp exposure time	[s]	3025	1069	5315	3024
Image averaging	[frames per projection]	4	4	4	4
Filter		Aluminum 0.5 mm	–	Copper 0.11 mm	Copper 0.11 mm

of the solid state properties.

3.1. Heat and mass flow characterization of the different container designs

The primary drying durations for each container design are depicted in Fig. 2. Primary drying of 9.0 ml mAb1 formulation in generic 20R glass vials was completed within a mean of 26.7 h. Broad variability of sublimation time during the lyophilization runs was observed, as shown by the interquartile range (IQR) of 5.2 h. The COC containers achieved comparable mean drying durations of 26.5 h, with a narrower IQR of 2.1 h, drying similarly to glass vials but with a higher homogeneity, as shown by the lower IQR. The twPETC PP and twPETC alu containers reduced the mean drying duration by 13.1 % and 37.5 % to durations of 23.2 h and 16.7 h, respectively, while displaying narrower IQR values of 2.9 h and 2.2 h, respectively, similarly to the ones observed in COC vials. The porous structures exhibited similar or faster primary drying rates. While the SLS nylon scaffolds dried the drug product on average within 28.3 h and with an IQR of 3.1 h, the SLS SS and CNC alu scaffolds reduced the drying durations by 50.9 % and 34.9 % to 13.1 h and 17.4 h, respectively. Moreover, the IQRs in the SLS SS and CNC alu scaffolds were reduced to 1.2 h and 1.5 h, respectively.

As all container designs were distributed evenly on the shelf within the lyophilization runs and rotated in their positioning between the runs, a position-specific bias of drying duration can be excluded.

Drying of the individual containers was recorded and is depicted in Fig. 3. The individual containers measured with temperature probes were arranged in a hexagonal pattern with empty dummy vials surrounding the probed sample, thereby diminishing the impact of adjacent container radiation by shielding. The temperature was recorded where the last ice fraction is determined to dry. For confined containers, this is in the center bottom and for porous structures in the center middle. The T_p curves during primary drying of COC vials, twPETCs with PP foil, twPETCs with aluminum foil and within porous structures, were compared to their equivalently filled glass vial counterparts. The start of the primary drying was initiated by pulling vacuum. The T_p initially dropped because of the onset of sublimation. Subsequently, the T_p increased due to the energy transferred by the heated shelves and then transitioned into a rather constant temperature curve (steady state). Following the steady state, the T_p transitioned into a steep slope before approximating the T_s, indicating the depletion of ice to be sublimed and therewith the primary drying endpoint. After reaching the endpoint, the individual temperature curves transitioned to a flat curve. Glass vials of four lyophilization runs dried at different rates and reached their endpoints between 21.3 h and 35.0 h. This was visible as a high inter- and intra-batch heterogeneity. The steady state period (after the initial ascent of the temperature ramp) displayed a relatively high temperature close to the T_g' of the formulation. The T_g' for the model antibody

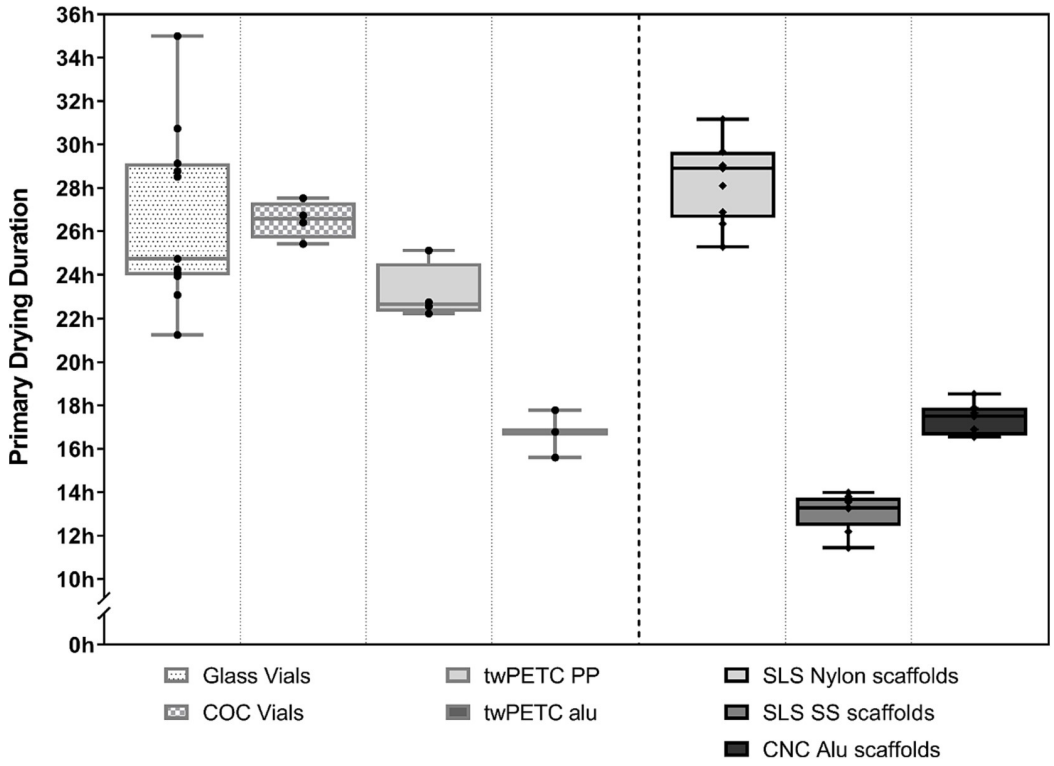

Fig. 2. Primary drying durations of the confined containers (left of dashed vertical line) and the porous structures (right of dashed vertical line). Average drying durations for the containers: Glass vials 26.7 h (N = 11, P = 0.05; CI: 24.0–29.4), COC vials 26.5 h (N = 4, P = 0.05; CI: 25.1–27.9), twPETCs PP 23.2 h (N = 4, P = 0.05; CI: 21.1–25.3), twPETCs alu 16.7 h (N = 3, P = 0.05; CI: 14.0–19.4), SLS nylon scaffolds 28.3 h (N = 9, P = 0.05; CI: 26.9–29.8), SLS stainless steel scaffolds 13.1 h (N = 8, P = 0.05; CI: 12.4–13.8) and CNC alu scaffolds 17.4 h (N = 7, P = 0.05; CI: 16.7–18.1).

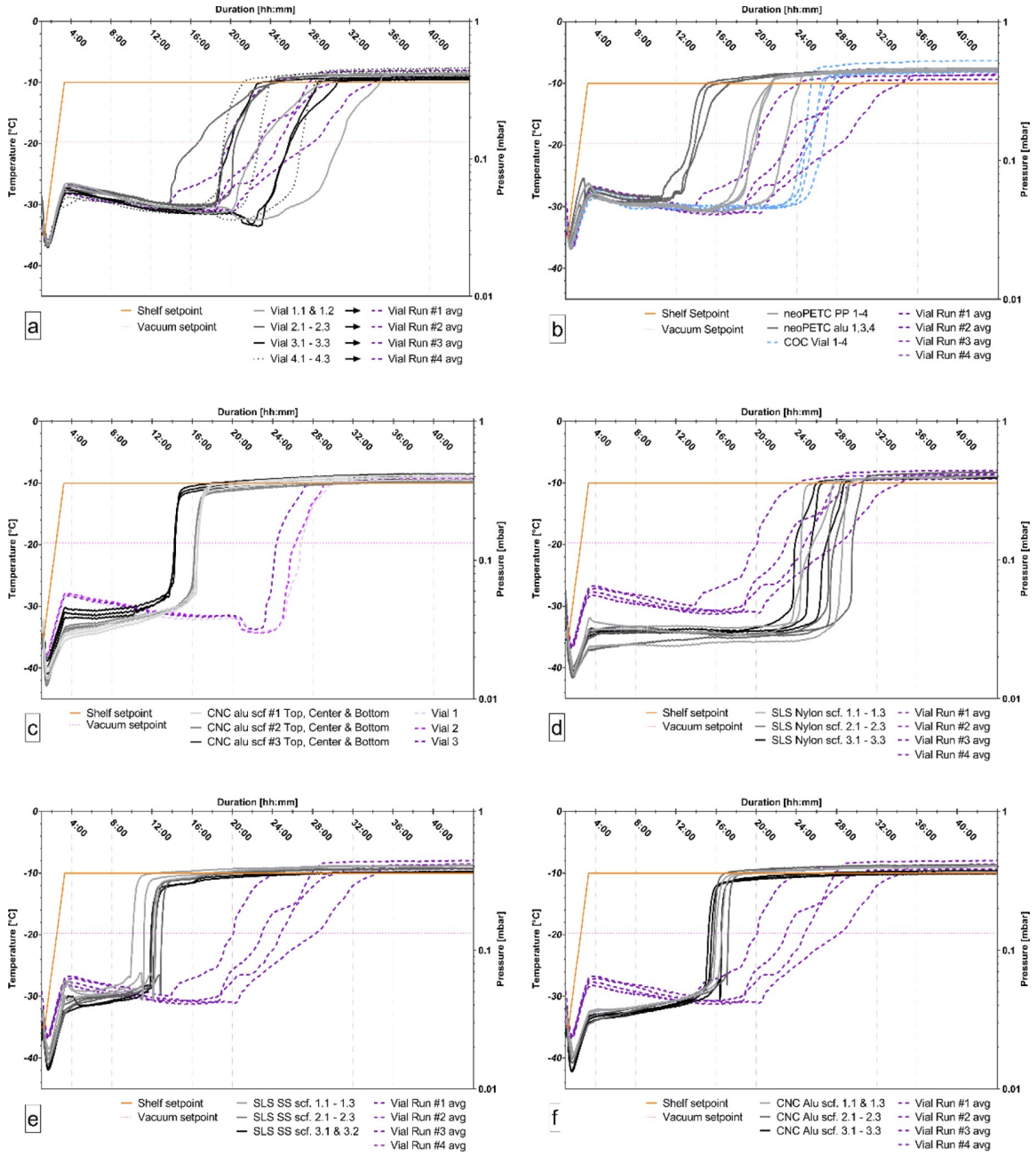

Fig. 3. Primary drying kinetics in different container designs determined by thin wire probes and wireless probes within lyophilized cakes. Lyophilization runs were performed according to the recipe depicted in Table 2 and compared to averaged vial temperature curves, as purple dashed curves. Individual temperature curves of the distinct containers are plotted against the respective shelf temperature and vacuum setpoint. The number of performed runs = N. Depicted are: (a) glass vial curves [N = 4], (b) twPETC PP, twPETC alu and COC vial curves [N = 3], (c) heat mapping within CNC alu scaffolds with vials at comparable positions on shelf [N = 1], (d) SLS nylon scaffold curves [N = 3], (e) SLS SS scaffold curves [N = 3], and (f) CNC alu scaffold curves [N = 3].

solution was determined to be −33.3 ± 0.2 °C.

Equal lyophilization conditions led to different sublimation parameters. Low sublimation rates were connected to high product temperatures displayed in the drying of glass vials, potentially increasing the possibility for collapse. The lyophilizates within the COC vials dried within 25.4 h and 27.5 h. In the twPETC containers, the drying duration was dependent on the bottom foil/film used. While the twPETC alu versions dried within 15.6 h to 17.8 h, the twPETC PP versions required between 22.2 h and 25.1 h. All designed porous structures were evaluated simultaneously in three lyophilization runs, but were rotated in their shelf arrangement to minimize the possible influence of choke flow or atypical radiation effects on one specific container format. The additive manufactured SLS nylon scaffolds dried their drug product between 25.3 h and 31.2 h. Equally shaped SLS SS scaffolds dried their drug product load between 11.4 h and 14.0 h. The CNC alu scaffolds prepared by subtractive manufacturing dried their drug product between 16.6 h and 18.5 h. Compared to all confined containers, the porous structures transitioned from the steady state period to the endpoint of drying with a steeper and less variable product temperature slope.

Generally, the drastically increased surface area of the porous structures led to a higher sublimation rate and subsequently lower product temperatures during the steady state of primary drying. Moreover, lyophilization in vials was performed above the T_g', while drying of

the porous structures was performed below the T_g', affecting the possibility for collapse.

3.2. Assessment of container designs by ability to meet desired solid state properties

The intermediate container designs were investigated on their ability to release the lyophilized cake by reconstitution. Fig. 4 illustrates the comparison of the reconstitution times of glass vials and porous structures. The reconstitution of the lyophilized cakes in porous structures took approximately 48.8 % less time on average than in glass vials. The endpoint of reconstitution time was considered complete when the horizontal passageway pores of scaffold structures were visibly free of lyophilized cake, and when no remaining particulate matter was visible in the solution. In all examinations, the solution was clear and free of undissolved matter.

Residual moisture values of lyophilized cakes measured in glass vials averaged 2.61 %, approximately 23.3 % lower than those of the group of porous structures. CNC alu scaffolds demonstrated higher residual moisture values than their glass vial counterparts, averaging 3.21 %, but the variability of the entrapped moisture was lower among the samples evaluated for three lyophilization runs. SLS printed structures with the same matrix structure among the two versions but built from different source materials displayed equal residual moisture and similar variability levels, averaging 3.20–3.24 %.

Cake structures within glass vials and SLS nylon scaffolds were evaluated by visual inspection and by μCT. Images of cake slices and cross-sections are depicted in Fig. 5. The structures within CNC alu and SLS SS scaffolds could not be analyzed, as the energy necessary to investigate the cores of these alloy structures exceeded the contrast limits necessary for the detection of the lyophilizate cake structures. Thus, a visualization of alloy matrix structures and lyophilizate cake could not be achieved. Cakes within glass vials or embedded in porous structures were reconstructed and sliced from top to bottom by the 3D. SUITE software. Larger z-values indicated layers on top of the lyophilized cakes, while smaller z-values referred to bottom layers that were closer to the lyophilizer shelf. The lyophilized cakes in glass vials showed a consistent cake structure through the vertical z-axis (I and III in Fig. 5).

The top slices displayed cake structures with slightly wider pores than in the core or bottom of the cake. While the bottom slices displayed minor cracks, dents on the outside perimeter of the lyophilizate cake, and micro collapse structures at the edges of the cake were observed at Z = 615 and Z = 803. The micro collapse structures can be differentiated from the porous cake structures by their bright appearance on the edge of the lyophilized cake. Areas with higher density appear brighter in μCT images, while areas without matter (e.g., dents, cracks, holes, bigger pores that are less dense or hollow) appear as black or dark grey. The cake structure within the SLS nylon scaffold (II and IV in Fig. 5) was streaked by the matrix structure of the scaffold shown in bright grey and displayed an inhomogeneous cake structure along the z-axis. The top slice of the lyophilizate cake displayed large structural conical cavities interconnected with the lower layers. These conical cavities in the center of the scaffold extended several layers vertically to the bottom of the scaffold. Moreover, some radial perpendicular pores were observed in the outer perimeter of the scaffolds.

Pores seen in the upper and middle layers of the scaffold displayed larger diameters compared to the fine pores visible at the bottom of the SLS nylon scaffold that were in contact with the lyophilizer shelf. The middle sections at Z = 1219 and Z = 878 displayed a constant decrease in pore size. In addition to the cake structure observed in glass vials, the cake structure at the bottom layers in the SLS nylon scaffold exhibited minor cracks, and although smaller, were more abundant. In contrast to the glass vial, the cake in the porous scaffold was free of collapse structures. An additional morphology next to the ice structures in the core of the SLS nylon scaffold was spotted in the center around the matrix structure. The morphology in the core of the cross-section, which is also visible in slice Z = 1219, is different than that of the cake structures. This is apparent by the contrast difference and resembles the matrix structure, although less dense. A second morphology in dark grey was observed in the right third of the cross-section surface in the SLS nylon scaffolds, representing an entrapped air bubble.

Visual inspection of the cakes within the glass vials and porous structures displayed minor cosmetic defects for both container designs. The following properties were common for all cakes found at the perimeter of the porous structures: no flakes or chipped product loss, coarse product lamellas indicating larger ice structures, and no dents. Minor cracks were visible in the two alloy versions of the SLS SS scaffold and the CNC alu scaffolds. Moreover, tiny holes were visible in the outer perimeter of the alloy scaffolds located in the top layers, likely corresponding to air bubbles not removed during the filling operation. Lyophilized cakes in vials displayed a homogeneous cake structure and minor shrinkage after lyophilization. The main finding in vials was the presence of dents in all lyophilized cakes, located at the bottom.

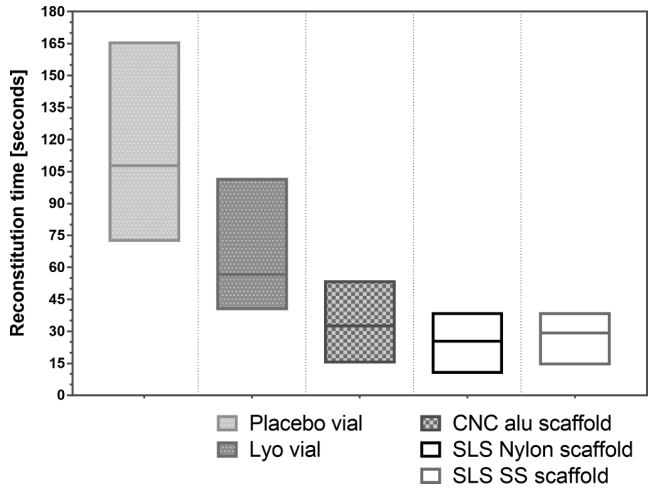

Fig. 4. Reconstitution time of lyophilizate cakes within glass vials and porous structures [N = 6 per container]. Mean, minimum, and maximum values depicted as inner line and outer lines in the floating boxes, respectively. Glass vials Mean = 56.6 s, SD = 25.7 s; SLS nylon scaffolds Mean = 25.3 s, SD = 10.9 s; SLS SS scaffolds Mean = 29.2 s, SD = 10.9 s; CNC alu scaffolds Mean = 32.5 s, SD = 12.8 s.

4. Discussion

Due to the demographic change, a continuous rise in mortality rates connected to non-communicable diseases (NCD) has been observed, from which 41 million people perish each year. This figure is equivalent to 71 % of all global deaths [20]. Prominent illnesses listed under NCDs include cancer, diabetes, cardiovascular and respiratory diseases, and many of the applied therapies rely increasingly on the administration of parenteral drugs [21,22]. Many of those parenteral therapies are currently prepared from liquid drug products that are administered intravenously, either as a single bolus injection or as a continuous drip infusion. In some cases, a powder or lyophilized drug needs to be dissolved and reconstituted to generate a drug product that can be dosed for these IV indications. However, the preparation of these dry products in vials is associated with multiple complications, including numerous handling steps, potential for contamination, exposure to the HPAPI, and time consuming dose calculations. The preparation is also considered a labor-intensive process in the clinical environment [23–27]. Next to potentially long reconstitution times, special attention must be given to the correct diluent choice, the failure-free application of closed system transfer devices (if used), proper reconstitution volume, and adequate

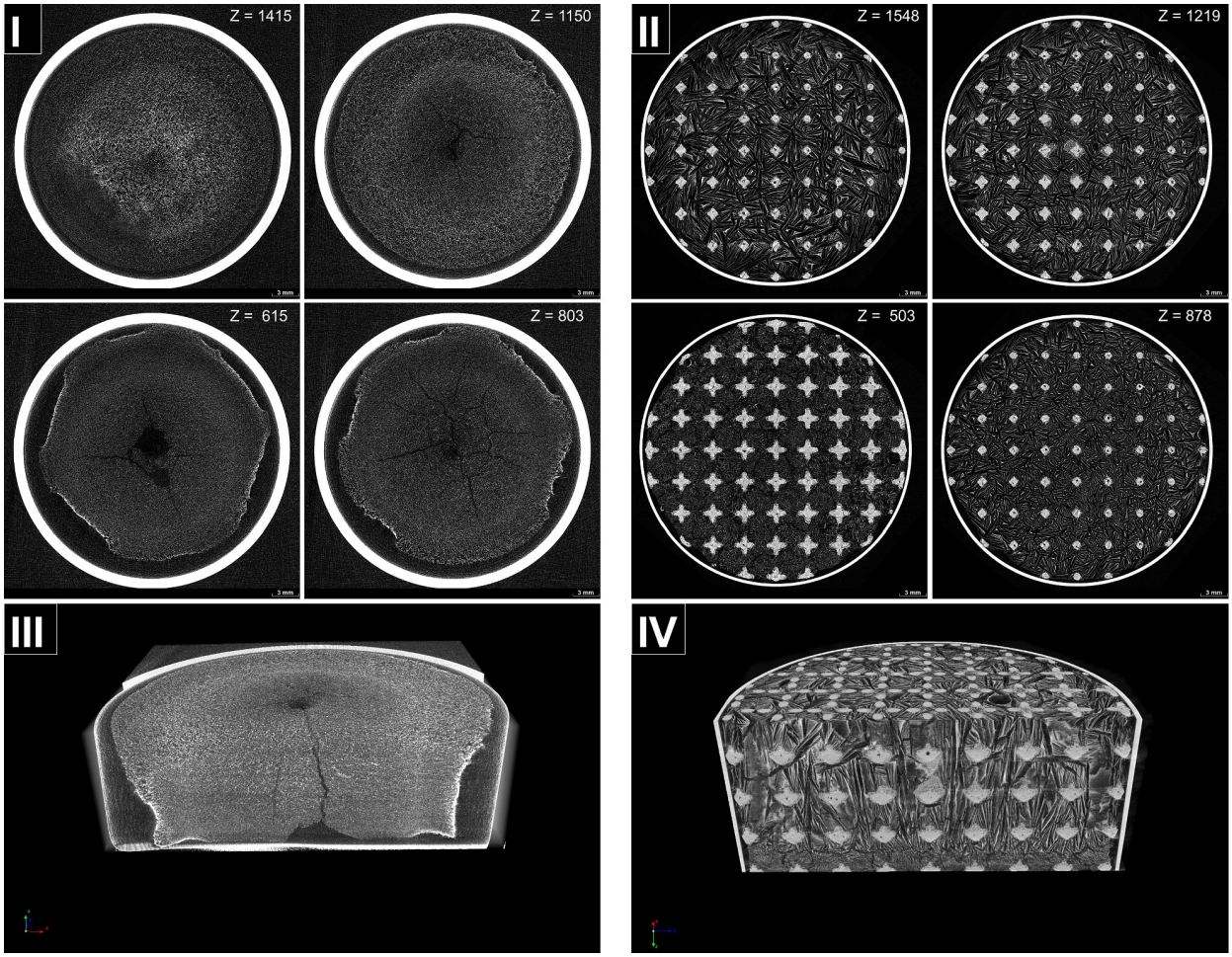

Fig. 5. Micro computed tomography slices of lyophilized cake structures within glass vials (I) and SLS nylon scaffolds (II). The structures were sliced from the top to the bottom. High z-values indicate slices at the top and low z-values at the bottom of the lyophilized cake structures. Vertical cross-sections of the lyophilized cake in glass vials in (III) and of a lyophilized cake in SLS nylon scaffolds in (IV).

mixing. Finally, the exposure to HPAPIs must also be avoided to protect the well-being of healthcare professionals [25–29]. After reconstitution, the solution must be transferred aseptically in a timely manner to the administration device of choice. An incorrectly executed transfer step constitutes a microbial threat to the product and/or a hazardous threat to the healthcare professional.

Despite the challenges, freeze-dried products exhibit a range of benefits. For example, the process allows the gentle desiccation of delicate active pharmaceuticals (API) such as biologicals. This leads to improved product stability during storage, while facilitating easy and lightweight shipping without the risk of agitation-induced denaturation. Additionally, the introduction of novel excipients for storage at elevated temperatures broadens the possibilities to store these drugs in the absence of a maintained cold chain, thereby opening the door for wider distribution in countries faced with temperature control limitations [30]. However, it is unlikely that these benefits of lyophilizates will take effect if the current distribution is also dependent on the use of glass vials and the associated rigid and complex preparation steps involved in the reconstitution process.

A collection of different container designs was created as intermediate container units for the freeze-drying of drug products and the flexible transfer of the resulting cakes into final containers or medical devices. This exercise was performed to overcome the limitations when drug products are lyophilized in vials and to assess if lyophilization occurs equivalently fast and homogeneously in these containers. In a second step, these containers were evaluated on their ability to successfully generate lyophilized cakes with comparable solid state properties. These properties include visual cake appearance, residual moisture content, reconstitution time, and inner cake structure found in glass vials. The widely used glass vial in the 20R format was used as the reference, comparing the obtained cakes in the newly designed containers to those obtained in the newly designed intermediate containers.

4.1. Heat- and mass flow-related characterization of the intermediate container designs in comparison with glass vials

The drying heterogeneity in a container design was observed to be comparably narrow or to vary significantly, depending on the container design and the MOC (Fig. 2). A strong dependency on these parameters can also be identified for the heat-mass-flux. Although the COC and twPETC PP formats did not dry the formulation significantly faster than the glass vial counterparts, the variability for the drying duration among the new container formats was less. Though the accessible conduction surface was increased in the twPETC PP containers, no major acceleration of the drying process could be observed. A probable explanation for this observation was found at the bottom of the freeze-dried twPETCs. During freezing of the formulation, the flexible PP film wrinkled, preventing the container surface from maintaining even contact with the shelf, leading to an inconsistent heat flux from shelf to cake. By changing the film from PP to an aluminum foil, the twPETC alu formats circumvented the wrinkling. This observation was reproduced by measuring the contact surface of filled twPETCs with PP film and aluminum foil

before and after freezing (data not shown).

Compared to the PP film, the aluminum foil could be sealed to the twPETC bottom with a higher tension after completed sealing, which enabled the twPETC alu formats to maintain a planar contact surface between shelf and product at any temperature. The tensioned foil ensured that the entire conduction surface could mediate a higher and consistent heat flux from shelf to the drug product over the course of lyophilization. This adjustment shortened the primary drying duration by 10 h compared to the glass vial. Containers that dried the frozen cake without a confinement (SLS nylon, SLS SS, and CNC alu scaffolds) also displayed a strong dependency on the MOC used. While the SLS scaffolds made from nylon dried the formulation at an equal rate as the glass vials, the SLS scaffolds with the same structure but prepared from stainless steel, cut the primary drying duration by more than 50 % to 13.1 h. Additionally, the use of alloys with higher thermal conductivities than glass or plastic reduce the heterogeneity of the individual temperature curves during drying by facilitating a more homogeneous distribution of the heat in the individual product cakes [8]. While the SLS nylon scaffolds share the same matrix structure as the SLS SS scaffold, the drying endpoints are distributed less evenly within the nylon variant. This shows that the material used is more influential on the increased homogeneity than the container geometry.

While the T_p in the confined containers exceeded the T_s when the primary drying was finished, the porous structures only approximated the T_s and transitioned into a flat curve. T_p curves of the three horizontal layers examined in CNC alu scaffolds exhibited that a good distribution of the supplied heat was found among the bottom, center and top of the porous structure, as shown in Fig. 3c. CNC alu scaffold #3 and glass vial #3 (see Fig. 3c), both being closest to the Makrolon® door of the freeze-dryer, experienced additional radiation heat. This resulted in faster drying than their counterparts, visible by their earlier product temperature increase after the steady state. However, it can also be seen for this design that the heat is distributed evenly within the entire cake, supporting the observation that the received heat is also distributed evenly throughout the matrix structure. Examining the three different porous structures, their drying behavior is different to that observed in glass vials or other confined containers. The primary drying duration in the alloy versions of the porous structures is shorter than that in the plastic version of the porous structure. As discussed by Pikal et al., the increase of the product temperature by 1 °C during primary drying decreases the primary drying duration potentially by 13 % [31]. Employing more aggressive freeze-drying recipes with higher primary drying temperatures could in this setup lead to a further reduction of primary drying times, while reducing energy consumption.

Followed by the steady state, a steep transition towards the shelf temperature can be seen in all porous structures, independent of the material used. For some SLS SS and CNC alu scaffolds, a drop in temperature can be seen at the end of the steady state period shortly before the ascent to T_s. This observation can be explained by the high conductivity and heat capacity of the materials and the exact positioning of the thin wire probes in the last drying fraction of the ice. Heat capacity and conductivity of the materials lead to a burst sublimation of the small remaining fraction of the ice, which explains the steep temperature drop at the end of the sublimation phase. When the last fraction of ice is sublimed within the porous structure, the surrounding material supplies extensive heat compared to the small volume of this fraction. This is visible by the local T_p maximum prior to the temperature drop. This amount of energy supplied is facilitated by the thermal conductivity and specific heat capacity of the respective material, along with the mass of the matrix structure that supplies the energy. The stored energy is then consumed in less than six minutes for the sublimation of ice in this last fraction. Through this process, cooling of the area around the thin wire probe occurs, leading to the drop in temperature prior to the ascent. As the thermal conductivity of the SLS nylon scaffolds is lower than the thermal conductivity of the SLS SS and CNC alu scaffolds, this behavior was not observed in those structures.

An additional finding for the porous structures is the steep temperature drop of the T_p curves at the beginning of the lyophilization when the activation of the vacuum pump initiates the primary drying. While the accessible surface for the initial ice removal in vials and twPETCs is only 6.7 cm^2, the porous structures can account for an approximately fourfold larger surface of ~ 26 cm^2. This indicates that the amount of ice on the cylindrical sublimation surface is more accessible and thus more easily removed than the same amount of ice located in the circular planar sublimation surface in confined containers. This drastically increases the sublimation speed in porous structures. By pulling vacuum, the great amount of ice transformed to water vapor leads to a more pronounced consumption of sublimation energy in the porous structures, which is displayed by a stronger drop of temperature within those structures. This greater consumption of sublimation energy accounts for a difference of 4 K between confined containers and porous structures.

The continuously rising product temperature is an indicator for ongoing ice removal, although the slope of the temperature curve varies depending on the container format and material used. Glass vials in Fig. 3a and the COC vials in Fig. 3b maintain a descending steady state for durations of 14 h to 27 h and the twPETCs in Fig. 3b illustrate shorter durations of only 7 h or 15 h next to the similarly descending steady state. The porous structures manufactured from alloys, however, display an ascending ramp during the steady state, lasting between 8 h and 12 h. The SLS nylon scaffolds display an almost horizontal steady state progression in comparison. The drying above the glass transition temperature of the maximally freeze concentrated solution T_g' or even above the collapse temperature T_c is known to negatively affect the cake appearance and can lead to a negative effect on drug product stability of lyophilizates by forming collapse structures that are subject to rejection during visual inspection [32,33]. As the majority of the primary drying time of the confined containers took place while the frozen solution is in the range of the T_g', one can assume that the resulting cakes might display collapse structures.

In comparison, the porous structures, like the SLS nylon and CNC alu scaffolds, dried the formulation at lower temperatures, and only briefly exceeded the T_g' just before ascending to the shelf temperature finishing the primary drying. The generic lyo recipe was chosen as a borderline recipe with the potential to impose partial collapse in containers that provide unfavorable drying prerequisites, being on the edge of processability. Lyophilizate cakes in glass vials revealed micro collapse structures when evaluated by μCT measurements. These structures proved that the drying of mAb1 was performed at shelf setpoints and vacuum levels leading to product temperatures close to those seen in meltback formation (for this combination of formulation and container format). This observation of micro collapse can potentially be linked to the declining product temperature trend during primary drying. This was seen in all confined containers but was not observed in the porous structures.

SLS SS structures, which dried the formulation at higher temperatures, would require further investigations to clarify if collapse structures were formed during the primary drying. Based on the elevated product temperature exceeding T_g', micro collapse structures could be assumed, but could be discounted by the increasing product temperature trend during primary drying. Noteworthy, Pikal et al. investigated the formation of collapse structures and linked the occurrence to the sublimation rate. In their investigations, they found that collapse is partially arrested by the increase in viscosity and viscous flow, the effect of which is more pronounced with a greater sublimation rate [34]. Accordingly, it can be assumed that collapse-structures are not likely to be observed in the alloy scaffolds. The individual product temperatures among the alloy structures in c, e, and f in Fig. 3 ascended in a less variable manner towards the shelf temperature, which is also visible in the smaller standard deviations in Fig. 2. This drying behavior can again be explained by the increased thermal conductivity of the alloy materials, facilitating an

equal distribution of heat throughout the cake supplied by the shelf. SLS nylon scaffolds in Fig. 3d showed a slightly narrower distribution of the individual temperature curves compared to glass vials, but lacked the extraordinary thermal conduction properties of alloys, as expected.

Contrary to the expectation that the porous structure with the greatest thermal conductivity and specific heat capacity—the CNC alu scaffolds—would dry the formulation faster than its counterparts, the SLS SS scaffolds were shown to be superior in this regard by taking on average 4.3 h less time to dry the formulation. This difference in drying speed could be explained by the following equation (Eq. (1)) for stored heat based on specific heat capacity:

$$Q = m \times c_{sp} \times \Delta T \quad (1)$$

In Eq. (1), Q represents the amount of heat, m is the mass of the substrate, c_{sp} is the specific heat capacity, and ΔT is the temperature difference. In our calculations, the mass and specific heat capacities listed in Table 1 were used for each container design. The mean weight for the respective porous structures differed between the scaffold structures. Where an SLS nylon scaffold weighed on average 3.022 g, a CNC alu scaffold 7.810 g, and the SLS SS scaffold 30.563 g. The stored heat supplied to the formulation when the temperature of the scaffold matrix decreased by 1 K accounted for 7.10 J for SLS nylon scaffolds, 6.95 J for CNC alu scaffolds and 15.28 J for the SLS SS scaffolds. Compared to stainless steel, the thermal conductivity coefficient k and the specific heat capacity c_{sp} for aluminum were more than 10-fold and almost twice as high, respectively (Table 1). However, due to the greater mass of the SLS SS scaffolds and the lower thermal conductivity, more stored heat Q was retained within the matrix structure. This stored heat could then be released to the frozen or partially frozen formulation to perform the phase transition. This led to faster processing times, as more heat was available to transform solid ice to water vapor. The lower thermal conductivity but greater mass of the stainless steel scaffolds guaranteed a prolonged delivery of energy necessary for the sublimation of ice within the core of the structure, while the lightweight aluminum dissipated the heat to the environment.

Though both porous alloy structures provided great conduction surfaces for the cake to receive heat, the inner surface dimensions and material surface structures differed between the additive- (SLS SS scaffolds) and subtractive- (CNC alu scaffolds) manufactured structures. This difference may have influenced the drying behavior. Another potential reason for the weaker performance observed in the CNC alu scaffolds could be found in the passivation of the aluminum surface by anodization. The levels of thermal conductivity shrink by a factor of more than 110 (180 W/(mK) to $<$ 1.6 W/(mK)) when changing the contact surface from pure aluminum to aluminum oxide [35]. Depending on the layer thickness, this decreased thermal conductivity could contribute to drying durations being higher than expected.

In addition to the thermal properties of the materials, the formed ice structures also influenced the mass flux of the sublimed ice to water vapor. As investigated by Rambhatla et al., the product resistance is inversely correlated with the sublimation rate, with high sublimation rates corresponding to low product resistance, and vice versa [36]. While the cake structure within glass vials was highly porous, delicate, and almost homogeneous throughout, the pore structures found in SLS nylon scaffolds were more diverse. Pores in the upper layers of the structure were coarser and wider in diameter and streaked axially through the cake towards the bottom, where they decreased in size. Moreover, these product structures appeared to be connected, and tunneled the scaffold from bottom to top, as displayed in μCT panels II and IV in Fig. 5. These conical cavities can act as chimneys for the water vapor, formed in the lower and center layers, to evade the cake without the need to traverse the dense and highly porous cake usually found in vials [37,38]. As the ice crystal structure was generated during nucleation and freezing, the product structure can be understood as a template of the formed ice. The generation of large ice crystals is usually only achieved by the application of annealing methods subsequent to the nucleation event, which facilitate ice crystal growth at temperatures above the T_g' and below the nucleation temperature [38–40]. The increased ice crystal size was correlated with larger pores and resulted in accelerated drying with less product resistance and higher homogeneity among the containers distributed over the shelf. However, this was only the case if the heat supply towards the sublimation front was ensured.

Although the SLS nylon scaffolds offered large internal pores, the low drying temperature and low thermal conductivity are likely an explanation for the comparably slow propagation of the drying [38,40–42]. Without a continuous and sufficient supply of heat, the sublimation process can only progress with reduced velocity. The thermal conductivity of nylon in comparison to the other porous structures made from aluminum or stainless steel was missing the high conductivity.

The standardized applied methods generated equally fast or faster drying progressions in the intermediate container designs. Both the change of the container to a porous structure and the utilization of MOCs with a high thermal conductivity showed their beneficial impact on the reduction of the drying duration and increase of homogeneity during drying. As the lyophilization recipe was not adjusted to the specific containers, the potential of each container design was not fully exploited. By adjusting drying parameters more specifically to porous scaffolds, the process times could largely benefit from the use of these matrices. Utilizing the big conical crevices formed axially in the cake as chimneys to release the sublimed water, and the good thermal conductivity of the containers, drying with high sublimation rates could be facilitated around the T_g' to avoid collapse structures.

4.2. Assessment of drug product solid state properties in different container designs

The porous structures, including the SLS nylon, SLS SS, and CNC alu scaffolds, were the only intermediate container designs included in further evaluations. Further evaluation of COC vials and twPETC containers was discontinued. Although the drying durations in the COC vials and twPETC containers could be shortened and an increase in homogeneity of drying was observed, their further use was precluded by the following observations: the generation of powder during extraction of the cake, leakage propensity at the bottom of the sealing, and the necessity to alter the lyophilization recipe to generate cakes without collapse. Furthermore, the visual appearance of the cakes in these confined containers lacked the qualities expected of properly dried lyophilizates [32,43].These qualities included the absence of elegant and homogeneous cake structures, while they also displayed non-uniform cake textures, crown formation, and collapse (data not shown). The obtained lyophilization cakes from the mAb1 formulation were evaluated according to the solid state properties of reconstitution time, residual moisture levels, and cake appearance.

4.2.1. Reconstitution time

The reconstitution times displayed in Fig. 4 are all well within a range expected from lyophilized products with a low solid content. Although all reconstitutions were finished relatively rapidly on the scale of seconds, it took approximately 57 s to reconstitute the full cake in the glass vials. The SLS nylon scaffolds achieved complete reconstitution in less than half the time. The reconstitution times for SLS SS and CNC alu scaffolds are marginally longer, but also in the range of 30 s. The effective reconstitution times of these scaffolds can be attributed to the increased accessible surface provided by the matrix structure. It can also be hypothesized that the additional surface area provided by the coarse product structure embedded in the matrix of the scaffolds played an important role. To assess the extent of the accelerated reconstitution by using porous structures, more challenging formulations must be evaluated. These formulations demand more time for cake solvation or confront the structures with a high density lyophilizate cake. A formulation with a higher protein content, or excipients that require more time

for dissolution, potentially defy the hypothesis of advantageous reconstitution using these novel containers.

The wide conical crevices found in the top layers of the SLS nylon scaffold (II and IV in Fig. 5) allow the diluent to wet the lyophilized cake more easily and consequently access the remaining cake structures inside the porous structures faster. The wider pore diameter allows the liquid to take advantage of the capillarity and penetrate the cake more easily. This is in contrast to the highly dense cake with its numerous small pores found in the glass vial, which counteract the permeation of the reconstitution media [44]. Although these wide conical crevices are visible in the SLS nylon scaffolds, only assumptions can be made that these cake structures also exist in the alloy versions of the porous structures. This is because of the different choice of material and associated material properties (i.e., thermal conductivity, heat capacity, and specific density), which could lead to a different nucleation and freezing pattern. This difference could result in a different pore size distribution and cake resistance. Nevertheless, the cake resistance found in these structures appeared to be low enough, as the structures were able to dry the formulations homogeneously, and in less time, compared to their SLS nylon scaffold counterparts. Unfortunately, the distinct cake structures could not be elucidated through μCT investigations. This was because contrast ratios between lyophilized cake and alloy structure were distributed to the disadvantage of the lyophilizate cake. As the intensity of the μCT had to be increased to penetrate the high material density of the MOC used for the alloy scaffolds, the comparably low material density of the lyophilized cake could not be resolved and was thus not visible during the analysis.

4.2.2. Residual moisture

Another investigated SSP for the characterization of lyophilizate quality was the residual moisture. Generally, the residual moisture for IgG formulations is expected to be rather low, with values<3 % [45,46]. It is known that some products require even lower levels of residual moisture, although over-drying has also been described to negatively affect the long term stability of freeze dried products [46–48]. Although the lyophilizer was flushed with dry nitrogen during extraction, the transfer of the porous structures into the intermediate storage containers, i.e., amber jars, could not be performed in a completely moisture-deprived environment. For this reason, we hypothesize that the porous structures were exposed to surrounding moisture. To obtain unaffected residual moisture values for the lyophilizates in glass vials, the related vials were automatically stoppered at the end of the lyophilization run. This difference in extraction can account for additional moisture absorbed by the dry cake within the porous scaffolds.

If assumed that the freeze-dried cakes achieved equal residual moisture levels after secondary drying, the porous scaffolds absorbed an additional 0.6 % residual moisture. This excess can not only be attributed to the different extraction method, but also needs to be correlated to the inner structure of the matrix and the secondary drying. Although all containers behaved similarly in secondary drying with overlapping individual temperature curves, a difference in residual moisture was apparent. A possible explanation was found in the μCT slices of the SLS nylon scaffold.

Aside from the coarse cake structure in the SLS nylon scaffold, another observation was made in the center of the scaffolds visible in the core of the scaffold in II (slice Z / 1219) and IV in Fig. 5. In the center area of the scaffold, a morphology with different contrast and appearance was visible. It was less bright than the matrix, but brighter than the cake, covering the matrix of the scaffold structure. After reconstitution and cleaning of the scaffold, the morphology was still visible in μCT images (data not shown). The morphology was retraced to be compacted and trapped source material powder arising from the manufacturing process of the SLS nylon scaffolds. This trapped powder formed a dense pocket within and around the matrix structure that was permeable for the liquid formulation, but likely created a resistance barrier for the water vapor. We hypothesize that these dense pockets with entrapped product solution confronted the remaining capillary water that was about to desorb with increased cake resistance. The trapped water vapor was thereby not able to escape the densely packed powder pockets during the freeze-drying process and remained there until reconstitution for residual moisture measurements was performed.

The product cakes were measured swiftly after the extraction, consistently for each lyophilization run. As the amount of entrapped source material differed between the SLS nylon scaffolds, the variability in residual moisture could be explained by this. Similarly prepared SLS SS scaffolds, which were also designed with the same inner matrix geometry, could have experienced the same phenomenon of source material entrapment and therefore exhibited the high and variable amounts of residual moisture. As the CNC alu scaffolds were prepared by subtractive manufacturing methods, no powder pockets could be formed. However, the low variability of residual moisture found in the CNC alu scaffolds and the high variability in the SLS scaffolds could be correlated with the different manufacturing methods and inner geometries of the container designs.

4.2.3. Cake appearance

The final investigated SSP was cake appearance. To support the visual cake appearance investigations, the lyophilized cakes within the glass vials and the porous structures were examined by μCT measurements to obtain additional information of the cake structure within the matrix. Visual appearance of the cakes contained in the porous structures displayed minor to no visual defects. The appearance of small cracks can be correlated with the fast drying propagations of the scaffolds and the relaxation of the cake matrix upon removal of the unfrozen water fractions [32]. It could be hypothesized that the extension of the matrix structure upon increase of shelf temperature could also lead to cracks in the cake structure. However, the thermal expansion of the matrix would only account for some 20–30 μm of extension within the alloy versions, and around 100 μm in the SLS nylon scaffolds. Although the thermal expansion of the SLS nylon structures is greater, the observed cake structures did not exhibit cracks on the perimeter. Some cracks were visible only internally in the dense cake regions in the bottom layers, supporting the hypothesis that the removal of unfrozen water found in highly porous capillaries led to the formation of these cracks, and not the thermal expansion of the matrix structure. The observed holes on the perimeter of the porous structures, and visible in the μCT cross-section within the SLS nylon scaffold, are likely connected to the filling process of the scaffolds.

The tight perimeter and matrix structure with the cavities and pores hinder the escape of potentially introduced air bubbles. Although the structures were agitated prior to loading, the removal of all air bubbles was apparently insufficient, and these were retained during the nucleation process. The air bubbles are only generated by the filling procedure and there is no other known impact on other SSPs. The formulation lyophilized in glass vials, on the other hand, displayed more obvious cosmetic defects as dents and shrinkage. While the dents do not regularly account for a reject, the observation of micro collapse structures at the edge of the dents could influence the reconstitution time, compromise the stability of the drug during long-term storage, and suggest a poor control of the process [49,50]. However, the negative effects of micro collapse are not entirely known, but are in general not considered as a reason for rejection [32,51,52].

The observation of cake shrinkage as another cosmetic defect within the glass vial is not commonly considered a critical defect. Several studies summarized the underlying physics, indicating only the mechanical properties of the cake being altered and not the incorporated product [32]. As the individual product temperatures indicated that drying occurred above and around the T_g' within glass vials, the occurrence of shrinkage can be retraced to this event. The remaining ice located at the bottom center of the cake at the end of primary drying is faced with the highly porous and dense cake structure surrounding it. For the remaining water vapor, the path through the top layers of the

cake is connected with great resistance: As such, a less resistant path along the open interface between the glass perimeter and cake edge is favored by the water vapor [53].

5. Conclusion

In terms of energy and time consumption, the primary drying step represents the largest share in the unit operation of lyophilization. As such, a reduction of primary drying and the application of more aggressive lyophilization protocols reduce costs and increase the frequency of manufacturing line occupancy.

The established freeze-drying process in the final containers is limited by conduction between the shelf and product, conduction within the product cake, small sublimation surface, high cake resistance, a generally slow primary drying velocity, and batch heterogeneity. Some of these limitations were addressed by omitting the primary container and preparing a dried powder instead. In our approach, we tackled the bottlenecks with the generation of a flexible intermediate container by also omitting the perimeter, and utilizing novel manufacturing methods to generate porous structures that were able to house the lyophilizate, while accelerating the primary drying and generating more homogeneous lyophilizates.

These porous structures produced elegant cakes with intricate inner cake structures and shortened reconstitution times, meeting expected SSPs set by the lyophilizate cakes prepared in 20R glass vials. Although higher residual moisture values were observed for these structures, they can be attributed to the extraction of the porous structures in a humid environment. They can additionally be linked to the use of a generic freeze-drying recipe that was not adapted to the needs of the formulation and the thermal properties of the container designs. Patel et al. suggest that the ultimate objective of the freeze-drying process is to achieve consistent batch to batch homogeneity, which in turn refers to a consistent product temperature history of all the samples distributed over the shelf [54]. Summarizing that this ultimate goal is virtually achieved, but requires minor process streamlining, this technology of using an intermediate container design could broaden the application of lyophilization in the industry. It would provide an attractive and lean process with a twofold processing time acceleration and a sustainability advantage due to lower energy consumptions through the use of more aggressive lyophilization cycles.

While excellent lyophilization prerequisites are now offered by these porous structures, their use in application devices, such as infusion bags or drug device combinations, still needs to be investigated. This would be a useful area of future research. The combination of next generation porous structure lyophilizates coupled with the incorporation of novel excipients and adapted one-step freeze-drying protocols, introduced by Chang et al and further described by Haeuser et al. and Pansare et al. [19,30,55,56], could advocate for a broader application of lyophilization. By making the lyophilization process economically favorable and the drugs resistant to higher process and storage temperatures, the purchase and distribution of much needed drugs in low- and middle income countries with missing cold chains and low economic power, appears entirely feasible.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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CHAPTER III

Part II: Matrix based scaffold lyophilization facilitates processing as a prerequisite for an innovative packaging system

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Highlights: Lyophilized drug products are commonly stored in glass vials and require an aseptic environment and accurate handling to compound the drug product with the correct diluent into a sterile intravenous infusion. This study investigated if the combined storage of a lyophilized drug product in the vicinity of the diluent is feasible and comparable to the stability of drug product stored in glass vials. Lyophilized drug products were therefore prepared in novel intermediate processing containers (i.e. scaffold structures) and transferred into two differently designed dual chamber bags. During an accelerated stability study, drug products as liquid and as lyophilizate in glass vials were challenged against lyophilized drug products in dual chamber bags. The results showed, that the storage is highly dependent on the material choice of the dual chamber bag. Limiting the transfer of water vapor towards the drug product by use of temporary aluminum shielding and intricate chamber separations led to stability results comparable to the storage of lyophilizates stored in glass vials. This presentation of lyophilizates in dual chamber bags would thus allow the immediate and aseptically safe preparation of intravenous infusions while allowing the storage of the drug product with the associated diluent.

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Research paper

Part II: Matrix based scaffold lyophilization facilitates processing as a prerequisite for an innovative packaging system

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ABSTRACT

On large manufacturing lines, the fill finish process of drugs is generally accomplished by filling vials and syringes with their respective deliverable doses. Glass as a final container provides excellent protection of the drug product because of its chemical inertia, gas impermeability and relative robustness. However, due to potential needle stitch issues, diluent mix ups, or the required use of complex closed system transfer devices, lyophilizate vials present a significant challenge for healthcare professionals during the correct preparation of intravenous (IV) infusions. A more suitable container could potentially minimize such shortfalls during the preparation of IV infusions. Our investigations aimed at assessing if a novel medication system, consisting of an infusion bag separated into individual dry product and liquid diluent chambers, could facilitate the storage of a lyophilized product equivalently to the current standard, a vial. By incorporating an intermediate process container into two different dual chamber bags (DCB), the stability of a model monoclonal antibody formulation (mAb) was studied. The DCBs were evaluated over a 24-week period against their liquid and lyophilized dosage form equivalents in glass vials. Their stability was assessed through investigations into protein stability, residual moisture uptake of the dry products and permeability of the foil and film materials. It could be demonstrated that the stability of the incorporated drug is highly dependent on the container configuration. Ultimately it could be shown that the storage of lyophilizates is equally possible in DCBs as it is in vials, while being stored next to the diluent within the administration device.

1. Introduction

The lack of medicinal infrastructure, a temperature-controlled supply chain, aseptic compounding environments, and economic power, present significant challenges for effectively supplying drugs to patients in low- and middle-income countries (LMIC). Of the 53 drugs newly approved in 2020, 16 are categorized as biological targets (monoclonal antibodies (mAb), peptides, and oligonucleotides), and used for the treatment of cancers, autoimmune diseases, and Ebola infections [1]. The majority of these biologic drugs are formulated as liquid solutions that require a cold chain and refrigerated storage with careful transport. Out of these 16, only 5 are prepared as dry drug powders—lyophilizates—that are usually less prone to deterioration during shipping [1]. By storing such biologics, like proteins, in a liquid form, enhanced aggregation can occur, induced by shear and interfacial stress from agitation, which can have a negative influence on drug product quality attributes, and can induce adverse events by acting immunogenic [2–5]. Additionally, physicochemical degradation, e.g. by glycation, hydrolysis, or oxidation, can be induced by storage or transport at elevated temperatures, or by decomposition of formulation components over time [6–11]. Any relevant change in potency and safety of the drug should be avoided. Thus, in some real-world situations, lyophilized drugs have certain advantages over liquid formulations.

Despite the advantages of supplying drugs in a dry state, challenges do exist. Although the stability of these drugs may be prolonged, their preparation suffers from increased complexity, including the need to select the proper diluent for reconstitution, reconstitute the dry formulation to the correct concentration, achieve full reconstitution without undetected powder remnants, and homogenize the reconstituted solution cautiously enough to avoid interfacial stress [5,12,13]. Additionally, the lack of aseptic compounding areas available for the transfer of the homogenized drug product solutions into infusion bags present difficulties for safely preparing an intravenous (IV) solution, while

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keeping the healthcare professional safe from exposure to the drug. This scenario introduces another level of difficulty in LMIC. Ideally, an innovative packaging system for the dry drug product with the correct diluent in the adjacency would allow the alleviated transport, storage, and easier preparation of drugs in any environment. Such systems do exist, and a system similar to the ready-to-use total parenteral nutrition (TPN) system could provide such alleviations.

TPN systems consist of a large infusion bag separated into multiple chambers (2 to 3 compartments), with each chamber housing a separate solution. This solution could be the lipid emulsion, the amino acids solution, or the electrolytes with dextrose [14–16]. These solutions would deteriorate rapidly by interacting with each other if stored as a mixture, but when separated, remain stable for up to 24 months [15]. Prior to administration, the TPN bags are activated by creating a passageway between the individual chambers. Suppliers offer different approaches to generate passageways combining the chambers, for example by removing a divider between the chambers or by applying pressure to rupture an internal seam separating the chambers. These TPN systems offer the amenity of preparing such solutions in the absence of a sterile environment, correct composition, and easy handling and storage.

Only a few systems have been developed to provide drugs in such separated infusion bag systems. Marketed examples include dual chamber bag (DCB) systems, such as the B. Braun DUPLEX®, the Nipro PLW®, Otsuka Antibiotic Kit solution® or the Technoflex DUAL-MIX® systems [17–20]. In a previous study submitted for publication, the generation of an intermediate process container based on the embedding of the liquid formulation into a porous structure was introduced [21]. Based on the findings for successful lyophilization and complete transfer of the generated lyophilized cake into the storage container of choice without product loss, the technique was considered an effective method to fill dual chamber bag systems with a lyophilized drug product. However, given the lack of published data on the stability of freeze-dried drugs within such dual chamber bags, the present novel study provides a basis for considering such systems as a viable and beneficial alternative to lyophilized drug product presentations in vials.

The aim of this study was to elucidate if DCBs are suitable for the storage of lyophilized drug products. Of particular interest was to evaluate the suitability of a diluent being stored in close proximity to the hygroscopic material, and further to compare if storage under elevated temperature conditions would be possible. To evaluate the suitability of lyophilizates in novel preparation and administration devices, we characterized the stability of a model mAb under different storage conditions. The focus of our interest was the suitability of these lyophilizates in different containers.

A delicate mAb was formulated, embedded into porous structures, and stored in two different DCBs. The goal involved comparing the stability of the new housing for the same formulation, with the storage of the same formulation either in its lyophilized form or as a liquid solution in glass vials. The filled containers were exposed to different storage conditions to assess their stability in an accelerated manner and to eventually evaluate and rate their potential in environments without consistent cold chain storage.

2. Materials and methods

2.1. Materials and formulations

A model monoclonal antibody, mAb1, (IgG1, 148 kDa, isoelectrical point ~ 8.7) was formulated at a concentration of 10 mg/ml in 20 mM histidine/histidine-HCl buffer (Ajinomoto, Tokyo, Japan) at pH 5.5 with 80 mg/ml sucrose (Ferro Pfanstiehl Inc, Waukegan, IL, USA) and 0.02 % Polysorbate 20 (Croda International, Snaith, UK). The formulation was sterile filtered through a hydrophilic 0.22 μm PVDF filter membrane (Merck Millipore, Burlington, MA, USA). The preparation methodology has been described previously [21].

Saline solution for the filling of the dual chamber bags was extracted from NaCl 0.9 % Ecobags (B. Braun Melsungen AG, Melsungen, Germany).

2.2. Containers

2.2.1. Vials and SLS nylon scaffolds

Fiolax® glass vials 20 ml (Schott, Müllheim, Germany) were filled with 9.0 ml of mAb1 formulation and partially stoppered with 20 mm Lyo-stoppers D777-1 (Daikyo Seiko, ltd., Tokyo, Japan) before freeze-drying. For liquid versions of the mAb1 formulation, Fiolax® glass vials were filled with 9.0 ml and stoppered with 20 mm Serum-stoppers D777-1 (Daikyo Seiko, ltd., Tokyo, Japan).

A porous structural matrix design was rendered as an intermediate process container to accommodate the drug product solution. It was prepared from Nylon PA 2200 powder (eos GmbH, Kreiling, Germany) by selective laser sintering (SLS) in an FORMIGA P 110 printer (eos GmbH, Kreiling, Germany). The PA 2200 compound allowed a fast prototyping, good flexibility, and high mechanical strength. It is also considered a biocompatible compound. These structures are hereafter referred to as SLS nylon scaffolds.

Loading of the scaffolds required a perimeter to allow complete loading of the structures without leakage of the mAb1 formulation. Parafilm® M sealing film squares (Heathrow Scientific LLC, Vernon Hills, IL, USA) of two sizes were used to wrap the scaffolds at the base and at the lateral surrounding; the top was not wrapped. A volume of 9.0 ml liquid formulation was then dispensed from the top into the porous matrix. Gentle agitation was applied to remove entrapped air bubbles. Prior to the start of the primary drying step and after complete freezing, the scaffolds were freed of their perimeter. After removal of the perimeter, scaffolds were returned to their position on the freeze-dryer shelf for continuation of the drying process.

2.2.2. Dual chamber bags version I and version II

Infusion bags with two separated compartments were acquired, with the chambers of each bag divided by a temporary separator. Dual chamber bag version 1 (DCB I) was a Hemedis MIB500.2 K multi-chamber bag (Hemedis GmbH, Weissenborn/Erzgebirge, Germany) consisting of two different sized chambers separated by a metal sleeve and a rubber rod. The single infusion bag made from high quality ethylene–vinyl acetate was separated by a seal into a compartment with a volume of 500 ml and a second compartment with a volume of 100 ml. The seal between the two compartments was created by placing the infusion bag into the C-shaped metal sleeve and pressing the rubber rod onto the infusion bag placed within the metal sleeve. The design of the seal with the rubber rod fitted into the C-shaped metal sleeve ensured a consistent pressure on the bag, separating it into two compartments: a diluent and a product compartment. The generation of a passageway between the two compartments was achieved by removing the rubber strip within the metal sleeve.

Dual chamber bag version 2 (DCB II) was a dual chamber bag consisting of two different sized compartments separated by a weld seam (Nipro Corporation, Osaka, Japan). The larger diluent compartment was made from one single film material, while the smaller product compartment consisted of a film and a foil material, one translucent and the other non-translucent aluminized plastic. The translucent product chamber film was additionally equipped with a removable aluminum foil cover. DCB II provided openings for each of the diluent and product compartments on the long side of the bag. The generation of an open passageway between the two compartments was achieved by applying force on the diluent compartment, leading to a rupture of the weld seam between the two compartments.

For both DCB versions, the large compartment was established as the diluent chamber and filled with 50 ml of saline solution, either via the Luer-Lock connector (DCB I) or via the opening on the long side (DCB II). The second compartment of DCB I was accessed by creating an opening in the top short side and inserting the SLS nylon scaffold containing the

lyophilized drug product (DP). The SLS nylon scaffold containing the DP was added to the second compartment of DCB II by inserting it via the long side opening. The compartments of each DCB were then sealed by welding the openings with a SAROSEAL IZ300DS long nose plier and a SAROSEAL 120 GE pulse generator (Saropack GmbH, Lörrach, Germany). Parallel double weld seams were generated to ensure reliable seal and barrier properties. All filling and welding operations were performed in a glovebox under dry nitrogen conditions to ensure that no additional moisture uptake occurred. The preparation, filling, and closure process is illustrated in Fig. 1.

Fig. 2 displays a side by side comparison of the two DCBs.

2.3. Freeze-drying

Lyophilization of the solutions within the 20R glass vials and the SLS nylon scaffolds was performed in a 0.5 m^2 TR01 Lyophilizer (HOF Sonderanlagenbau GmbH, Lohra, Germany). Two of the three loading shelves for the lyophilization of the glass vials and scaffolds were used. The lyophilizer was operated and monitored with the LyoCom III Software (HOF Sonderanlagenbau GmbH, Lohra, Germany). The vials containing the mAb1 formulation were placed in a predetermined hexagonal pattern in the center of the shelf surrounded by empty vials at the edge, which served as atypical radiation shielding. SLS nylon scaffolds were also placed in a hexagonal pattern, separated by several millimeters from the other scaffolds, and were also surrounded by empty vials.

For the lyophilization, all vials and scaffolds were loaded into the lyophilizer on two pre-cooled shelves at 5 °C and were kept there for 1 h for temperature equilibration. Subsequently, the samples were frozen to −35 °C with a ramp of −0.3 °C/min and kept at −35 °C for 3 h. Prior to initiation of primary drying, the porous scaffolds were unwrapped from their confinement and returned to their specified shelf position. The primary drying step was initiated by pulling vacuum to 100 mTorr and increasing the shelf temperature to −10 °C with a ramp of + 0.2 °C/min. Samples were kept for 56 h at these conditions. The secondary drying started by increasing the shelf temperature to + 25 °C with a ramp of + 0.2 °C/min, while keeping the 100 mTorr of vacuum. Samples were kept for 8 h at these conditions. Stoppering was performed at + 5 °C and a pressure of 500 mTorr. These conditions were maintained until extraction of the samples could be performed. During the entire primary and secondary drying and until extraction, the condenser temperature was kept at −80 °C. Lyophilized SLS nylon scaffolds were extracted and placed into a wide neck Duran® laboratory jar (DWK Life Sciences LLC, Millville, NJ, USA), flushed with dry nitrogen, and kept until filling into dual chamber bags could be performed.

2.4. Assessment of product quality attributes during 24-week stability protocol

Lyophilizate vials and SLS nylon cakes within DCBs I and II were reconstituted by the procedures described in Section 2.4.5. Aliquots from each container at each time point were subjected to the analytical methods described below.

2.4.1. Storage conditions for protein stability investigations

Lyophilized and liquid samples were subjected to three different storage conditions after preparation. Samples were stored for a total of 24 weeks at 2–8 °C (refrigerated conditions), 25 °C/60 % relative humidity (r.H.) (ambient conditions), and 40 °C/75 % r.H. (accelerated conditions). Samples were measured after compounding (t0) and removed from these conditions after four weeks (t4w), eight weeks (t8w), 12 weeks (t12w), and 24 weeks (t24w) of storage.

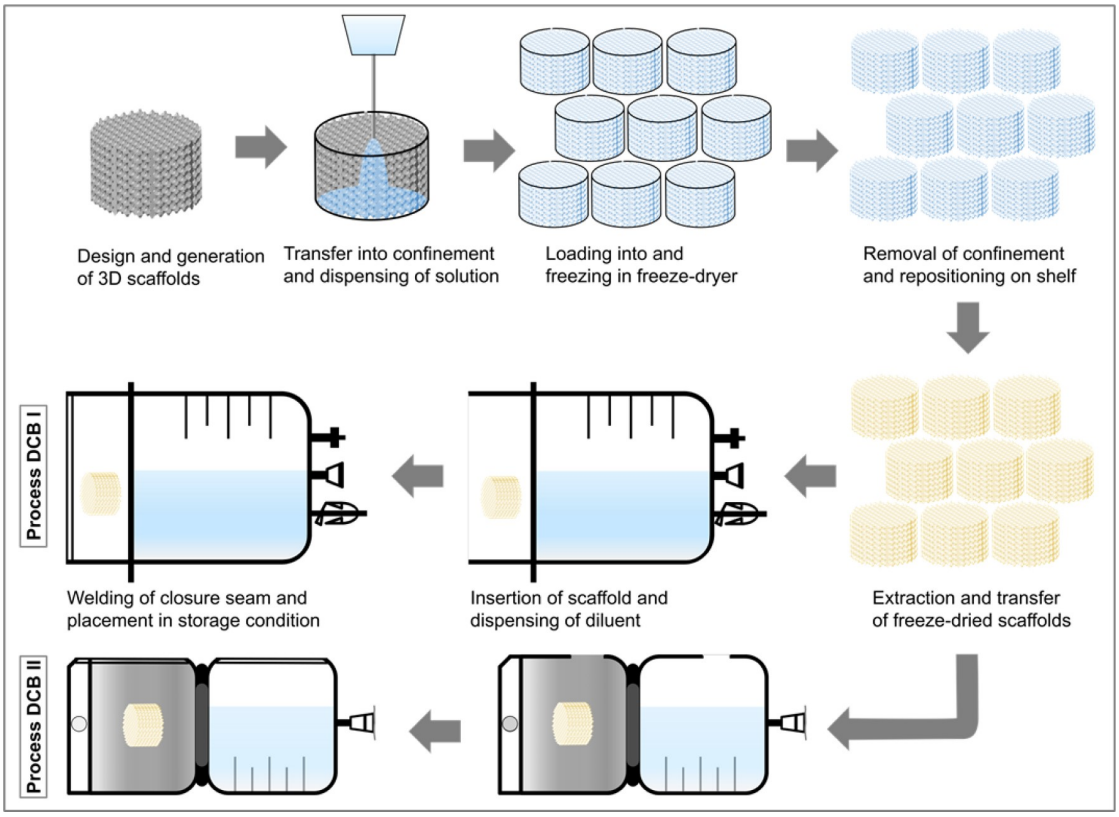

Fig. 1. Process visualization of scaffold generation, dispensing of DP solution into 3D scaffold within perimeter, preparation in lyophilizer, transfer into dual chamber bags and finishing by sealing; respective processes shown for DCB I and DCB II.

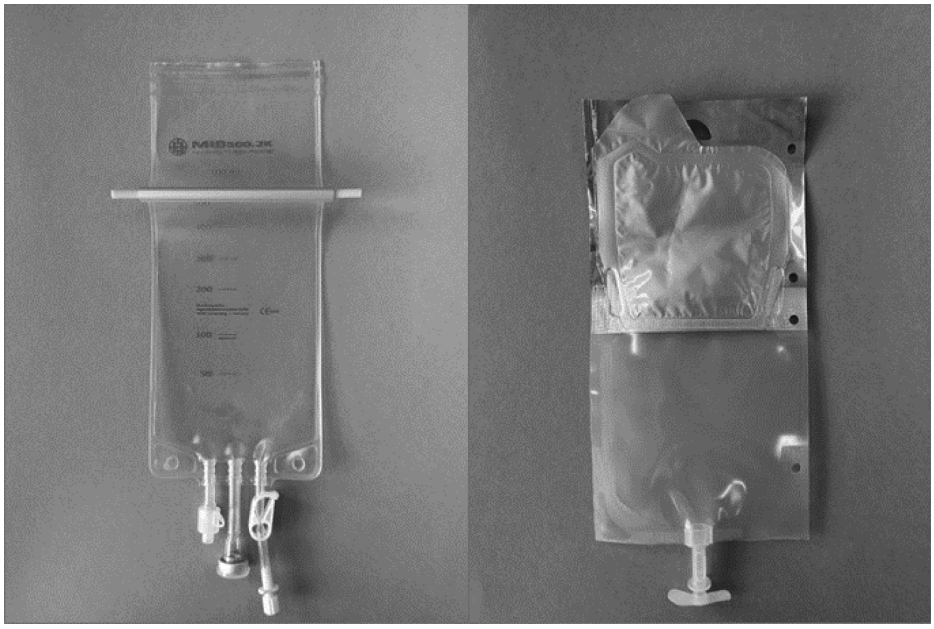

Fig. 2. Side by side comparison of the two dual chamber bag versions DCB I (left) and DCB II (right). The product containing compartment is located at the top and the diluent containing compartment at the bottom of the illustration. Both compartments are separated by a temporary separator.

2.4.2. Cake appearance

The quality of the freeze-dried products was determined qualitatively by visual cake appearance. The quality of the cakes within the vials and DCBs was determined on the basis of their visually perceived change experienced during their respective storage periods and conditions compared to their initial characteristics.

2.4.3. Residual moisture

Residual moisture (RM) levels were determined using a C30 Coulometric Karl Fischer (KF) titrator (Mettler Toledo, Greifensee, Switzerland). The lyophilized vial was weighed before reconstitution and the contents reconstituted by adding 10 ml dry methanol and vortexing for 2 min. A hold time of 1 h was added to allow extraction of the water before titration. An aliquot of the supernatant was removed with a 5 ml disposable plastic syringe and injected into the measuring cell where it was titrated against a standardized KF reagent. Following titration, vials and stoppers were thoroughly rinsed with water and ethanol and heat dried at 120 °C for 20 min. The cake weight was then obtained by reweighing the dry empty vial and stopper.

The RM levels in the SLS nylon scaffolds within the DCBs were determined by removing the scaffolds from the DCBs and transferring them into nitrogen-flushed wide mouth amber packers with Teflon-faced foamed polyethylene lined polypropylene caps (DWK Life Sciences LLC, Millville, NJ, USA), hereafter referred to as amber jar. The lyophilized cakes within the SLS nylon scaffolds were then reconstituted by adding 20 ml dry methanol to the amber jar and vortexing for 2 min. For equivalent submersion of the scaffold in the amber jar (aligned to the RM determination of dried cakes in vials), the volume of dry methanol was adjusted from 10 ml to 20 ml. A hold time of 1 h was applied to allow extraction of the water before KF titration. An aliquot of the supernatant was removed with a 5 ml disposable siliconized Luer-Lock plastic syringe and injected into the measuring cell where it was titrated against a standardized KF reagent. After titration, the amber jar, respective cap, and SLS nylon scaffold were thoroughly rinsed with water and ethanol, then dried at 120 °C for 20 min. These were then weighed to obtain the cake weight contained in the SLS nylon scaffold.

2.4.4. Osmolality

Osmolality of the diluent within the diluent chamber of the DCBs was evaluated by an Osmomat O30 freezing point osmometer (Gonotec GmbH, Berlin, Germany). Samples from the diluent chambers remaining from the RM evaluations were used for the osmolality determinations at each timepoint. The diluent in the diluent chambers was homogenized by inverting the bag 10 times to ensure that an aliquot of 1 ml could be extracted. For the osmolality determination, triplicate 50 µl subsamples of that aliquot were analyzed and the result reported as a mean value.

2.4.5. Product recovery upon reconstitution

Product recovery was measured after reconstituting the lyophilizates within the vials and DCBs. Lyophilizate vial samples were reconstituted at each timepoint by injecting 9.0 ml of saline solution through the stopper onto the inner wall of the vial. Gentle swirling was performed until full reconstitution without visible cake remnants was achieved.

Reconstitution for SLS nylon scaffolds in the DCBs was achieved by activating the DCB. To combine the diluent and DP chambers, reconstitution was initiated by pulling the rubber strip or applying force to the liquid chamber for DCB I and DCB II, respectively. Following homogenization by inverting the bag 10 times and squeezing the solution back and forth, an aliquot of 6.0 ml of the mixture was extracted through the port of the DCB.

Protein concentration after successful reconstitution (post-reconstitution) was different for samples in vials than for those in DCBs. Reconstitution in vials led to a protein concentration of approximately 10 mg/mL, while the reconstitution in the DCBs led to a post-reconstitution protein concentration of approximately 1.8 mg/mL. The concentration of mAb1 was determined at a wavelength (λ) of 280 nm with a NanoDrop One microvolume UV–vis spectrophotometer (Thermo Fischer Scientific Inc., Waltham, MA, USA). Samples were blanked against the saline solution and measured in triplicate. Results were reported as a mean $\pm$ standard deviation. With the mean concentration and the measured concentration of the reconstituted solution at t0, the theoretical drug content recovery was determined. The obtained concentration upon activation at each timepoint was divided by the initial concentration and reported in percent as drug content recovery.

2.4.6. Subvisible and visible particle analysis

Subvisible particle analysis was performed with light obscuration measurements. According to USP ⟨787⟩ and Ph.Eur. 2.9.19

requirements, the number and size distributions were recorded with a HIAC 9703 + liquid particle counter (Skan, Allschwil, Switzerland) [22,23]. Prior to each sample measurement, the system was rinsed with deionized water, followed by 0.5 ml of sample solution. Four aliquots of 0.2 ml were then analyzed and detected particles were classified into categories of ≥ 2 μm, ≥ 5 μm, ≥ 10 μm, and ≥ 25 μm. The first run was discarded as a flushing of the system and the second to fourth runs were reported as the mean number of cumulative particles per ml ± standard deviation.

Visible particles of the reconstituted formulations were analyzed by visual inspection according to Ph. Eur. 2.9.20. in front of a black and white background [24]. The presence of visible particles was reported as (1) "practically free from particles", (2) "with few particles", or (3) "with many particles".

2.4.7. Size-Exclusion chromatography

Monomer stability of mAb1 was determined by size-exclusion chromatography (*SEC*) using either an Alliance 2695 or an Alliance e2695 HPLC instrument (Waters Corporation, Milford, MA, USA) equipped with a 2487 or 2489 UV/visible detector (Waters Corporation, Milford, MA, USA), respectively. The column oven temperature was adjusted to 25 °C and the autosampler temperature to 5 °C. Samples in vials (liquid and post-reconstitution) and reconstituted samples in DCBs were injected undiluted, while reference samples were diluted to approximately 10 μg/μl. A load of 150 μg of mAb1 was then injected for all samples on a TSK-Gel 3000SWXl, 7.8 × 300 mm column (Tosoh Bioscience, Stuttgart, Germany). Samples were eluted over 30 min with 0.2 M K_2HPO_4/KH_2PO_4 and 0.25 M KCl mobile phase at pH 7.0 and a flow rate of 0.5 ml/min. Sample signals were detected by UV absorbance at λ = 280 nm. Monomer content determinations and follow-up data processing were performed with Empower 3 Chromatography Data System software (Waters Corporation, Milford, MA, USA). Peak areas were reported as a percentage of the total peak area.

2.4.8. Ion-Exchange chromatography

Changes of molecular charge heterogeneity in mAb1 were determined by ion-exchange chromatography (IEC). An Alliance 2695 or an Alliance e2695 HPLC instrument (Waters Corporation, Milford, MA, USA) equipped with a 2487 or 2489 UV/visible detector (Waters Corporation, Milford, MA, USA), respectively, were used in combination with a MabPac™ SCX-10, 4.0 × 250 mm column (Thermo Fischer Scientific Inc., Waltham, MA, USA). The column was pre-equilibrated at a flow rate of 0.8 ml/min with a mixture of 99 % solvent A (20 mM ACES, pH 7.60) and 1 % solvent B (20 mM ACES and 200 mM NaCl, pH 7.60). Sample preparation included the buffer exchange from saline conditions to solvent A by use of Amicon Ultra 0.5 Centrifugal filter units (Merck Millipore, Burlington, MA, USA), the dilution of samples to 1 mg/ml, and addition of 1 % w/w carboxypeptidase B. The mixtures were then incubated at 37 °C for 20 min. Samples were stored in the autosampler at 10 °C until analysis.

The following gradient was applied for the injection of 100 μg of sample: after 3 min post-injection, a step gradient elution from 1 to 47 % solvent B for 40 min, followed by an increase from 47 to 100 % solvent B within 1 min and a hold for 6 min, then an immediate return to 99 % solvent A for the remainder of the 60 min. The gradient was performed at a flow rate of 0.8 ml/min. Samples were detected by UV absorbance at λ = 280 nm and main peak, acidic, and basic species were reported as a percentage of the total peak area. The Empower 3 Chromatography Data System software (Waters Corporation, Milford, MA, USA) was utilized for evaluation and reporting.

2.4.9. Water vapor ingress

Water vapor transmission rates (WVTR) were investigated for the DCB films and foil and the respective compartment separators. To determine the WVTR through the film and foil material, an Aquatran Model 2 (Mocon Inc., Brooklyn Park, MN, USA) WVTR instrument was used. The tight seal between the measurement chambers and the films was supported by an adhesive aluminum foil that mitigated any potential cross-diffusion. The films and foil were measured at 25 °C/60 % r.H. and 40 °C/100 % r.H.

The water vapor permeability of the separator between the two compartments was tested by an inverse-gravimetrical approach. The diluent compartment was filled with 50 ml of saline solution and the product compartment with a cellulose pouch filled with 10 g Supelco® silica gel with indicator (Merck KGaA, Darmstadt, Germany). The DCBs were placed in nitrogen-flushed desiccators filled with Supelco® silica gel and stored for up to 12 weeks at 25 °C and 0 % r.H. The moisture transfer into the product chamber was determined gravimetrically by comparing the weight of the cellulose pouch filled with silica gel with the initial weight. Orthogonally, the osmolality of the saline solution within the diluent chamber was assessed as described in Section 2.4.4.

3. Results

3.1. Product stability assessment of mAb1 and primary packaging suitability by purity and physicochemical analysis methods

3.1.1. Physical stability

The physical stability of the mAb1 formulation, stored in glass vials as liquid or lyophilized formulations and as lyophilized scaffolds in DCB I and DCB II containers, was assessed by *SEC*. The stability behavior of the mAb1 formulation stored in these containers at the different conditions is illustrated in Fig. 3. Samples stored under refrigerated conditions (2–8 °C) displayed equal stability over the entire course of the stability evaluation without loss of monomer. Under ambient conditions (25 °C/60 % r.H.), samples stored as liquid vials and as lyophilized scaffolds in DCB I containers displayed depletion of the monomer species of 1.6 area% and 8.4 area%, respectively. Samples stored as lyophilizate vials and as lyophilized scaffolds in DCB II containers remained stable. Under accelerated storage conditions (40 °C/75 % r.H.), samples as lyophilizate vials and in DCB II remained stable and did not display depletion of the monomer species, whereas significant loss of the monomer species of 47.7 area% was observed in DCB I samples. The depletion in liquid vials was less pronounced with a loss of 9.8 area%.

3.1.2. Chemical stability

Analysis of the chemical stability of the mAb1 formulation in the respective containers by IEC displayed no degradation under refrigerated conditions and similar stability among all container formats (Fig. 4**a**). Stability of mAb1 in lyophilizate vials and in lyophilizate cakes within SLS nylon scaffolds in DCB II stored under ambient conditions was confirmed over the course of 12 weeks. However, a slightly smaller main peak area was observed for DCB II samples after 24 weeks, which accounted for 1.6 area% less than that of the lyophilized vials. Under ambient conditions, the main peak levels in DCB II and lyophilizate vials were comparable to the values obtained during refrigerated storage.

Stability of mAb1 in liquid vials and in DCB I under ambient conditions was detectibly lower, exhibited by the significant depletion of main peak in DCB I that commenced immediately after the initiation of storage, along with the delayed but continuous depletion of mAb1 in the liquid vials (Fig. 4**b**). The loss of main peak under ambient conditions averaged 8.7 area% and 18.7 area% over 24 weeks in liquid vials and DCB I samples, respectively. Under accelerated storage conditions of increased temperature and r.H., the contents of all storage containers displayed a loss of mAb1 main peak area to varying extents (Fig. 4**c**). While lyophilizate vials and DCB II samples exhibited a similar pattern of moderate degradation, which resulted in smaller peak areas after 24 weeks of 4.0 % and 5.0 %, respectively, the main peak within DCB I samples had completely degraded after 8 weeks of storage. Interestingly, more than half of the main peak area was already lost after 4 weeks of storage. Significant instability of mAb1 in liquid vials was observed already after 4 weeks of storage at 40 °C/75 % r.H. After 12 weeks of

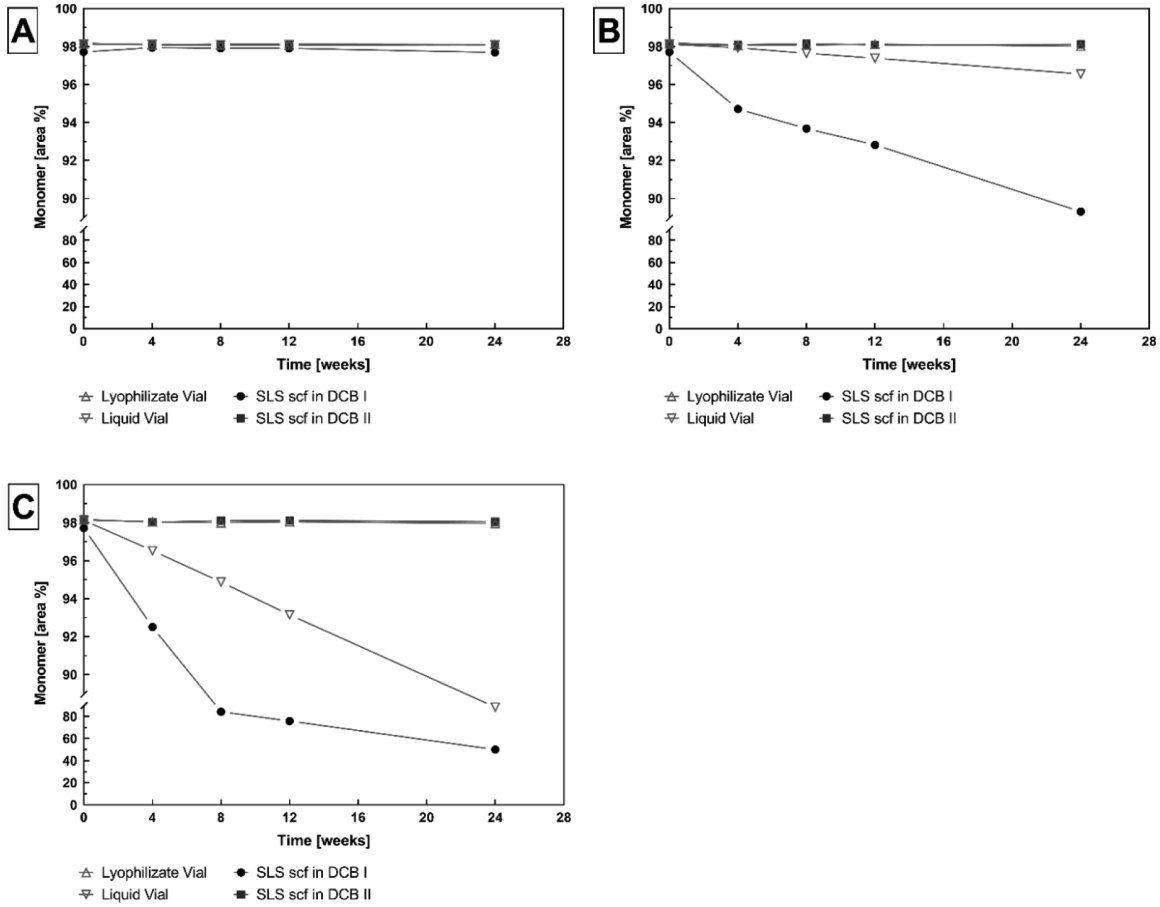

Fig. 3. Stability of the mAb1 formulations in different container formats during storage over 24 weeks under three different storage conditions. Physical stability of liquid and lyophilized mAb1 formulation in vials and lyophilized mAb1 formulation in SLS nylon scaffolds in both DCB I and DCB II; evaluated by size exclusion chromatography. Storage condition of 2–8 °C in [A], 25 °C/60 % r.H. in [B], and 40 °C/75 % r.H. in [C].

storage, less than half of the main peak area remained. Although the degradation rate stabilized somewhat after 12 weeks of storage, an overall main peak loss of 40.2 area% after 24 weeks was observed.

3.1.3. Visible and subvisible particles

The physicochemical stability of the samples was assessed via visible and subvisible particle investigations. The samples containing the SLS nylon scaffolds displayed high visible particle counts of many visible particles. Additionally, such high particle counts were also found in all subvisible particle size classes (≥2 μm, ≥ 5 μm, ≥ 10 μm, and ≥ 25 μm). It could be confirmed with unloaded scaffold structures, that these particles originated from the manufacturing process of the SLS nylon scaffolds. As a consequence, the exact identification of particles potentially being formed during the stability study was inhibited. The results of visible and subvisible particle identification are therefore not shown.

3.1.4. Moisture content

Moisture content of the samples was determined by KF titration. The progression of moisture increase in the freeze-dried samples is portrayed in Fig. 5. Lyophilizate vials stored under all conditions consistently displayed the lowest RM content, followed by the SLS nylon scaffolds in DCB II. The SLS nylon scaffolds in DCB I displayed the highest RM content. Both lyophilized vials and DBC II performed similarly in their RM behavior over time, while the DCB I containers showed a minor but consistent uptake of water during the assessed time frame.

No trend for RM increase in lyophilizate vials was visible under both refrigerated and ambient conditions. RM content fluctuated between 1.9 % and 2.6 % w/w, with similar RM content observed under both conditions. This deviation in RM was potentially due to the method variability of the KF titration. Under accelerated conditions, a 1.1 % gain of moisture in lyophilizate vials was observed, from an initial value of 2.0 % to 3.1 % over the course of 24 weeks. The slightly lower RM content after 12 weeks could be due to insufficient drying of the primary packaging material and therefore higher tare weight of the emptied and rinsed primary packaging weight. Thus, a consistently lower RM value could be achieved for the lyophilized vials at this timepoint. A repetition of the measurement was not possible due to limited material availability.

SLS nylon scaffolds in DCB II started with higher RM values than the lyophilizate vials, accounting for 3.2 %. No gain in moisture was observed during storage under refrigerated conditions, with RM levels remaining essentially stable over the 24-week storage period. However, although RM content remained stable under ambient conditions, a minor increase in mean moisture content was observed for all timepoints (other than t0) during storage under ambient conditions compared with the refrigerated samples. Under accelerated conditions, a continuous moisture gain in SLS nylon scaffolds within DCB II samples was observed, accounting for an increase of 1.3 % over the course of 24 weeks.

The SLS nylon scaffolds within DCB I samples consistently displayed much greater RM than their lyophilizate vial and DCB II counterparts, accounting for more than twice the amount found in DCB II samples when comparing the initial RM values under all three storage conditions. After evaluation of the initial samples, the SLS nylon scaffolds of the subsequent DCB I samples under all storage conditions exhibited either completely or partially transformed dry cakes. Cakes embedded in

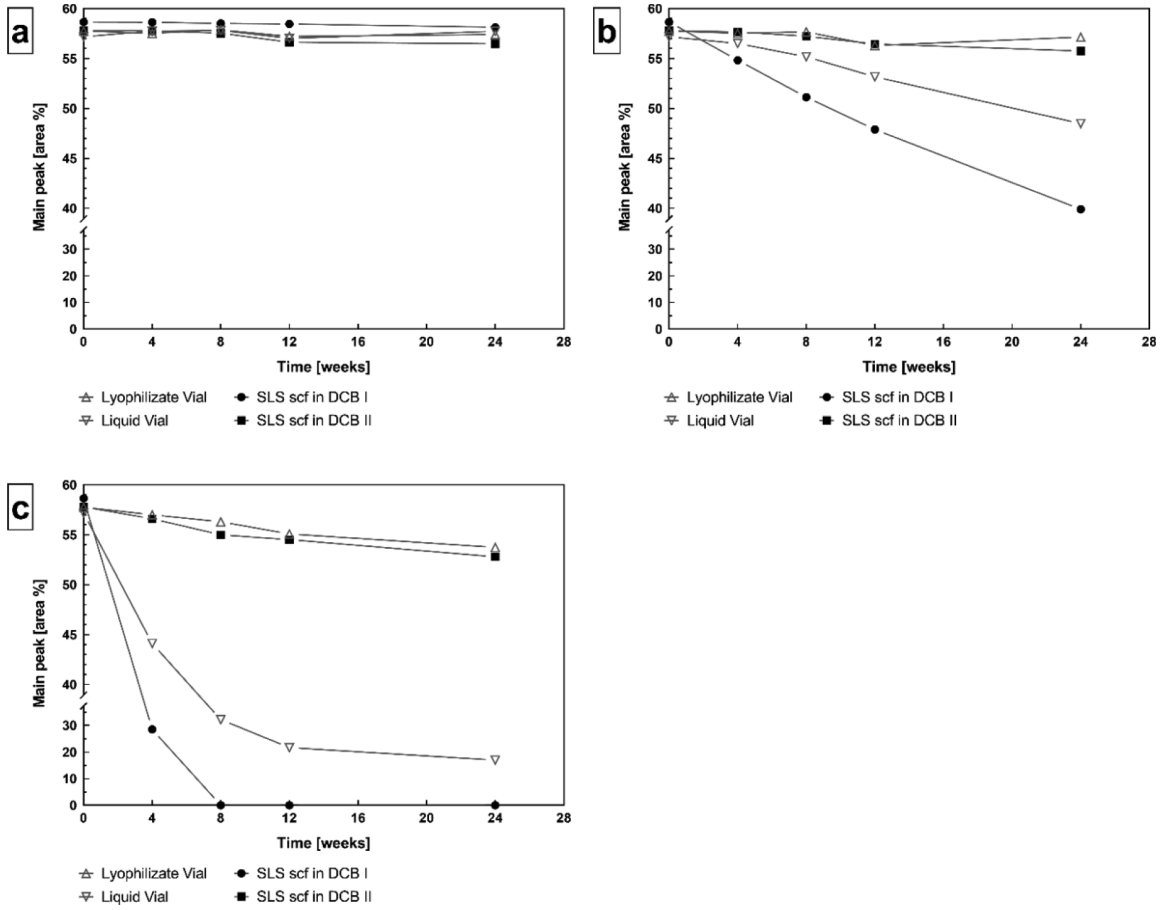

Fig. 4. Stability of the mAb1 formulations in different container formats during storage over 24 weeks under three different storage conditions. Chemical stability of liquid and lyophilized mAb1 formulation in vials and lyophilized mAb1 formulation in SLS nylon scaffolds in both DCB I and DCB II; evaluated by ion exchange chromatography. Storage condition of 2–8 °C in [a], 25 °C/60 % r.H. in [b], and 40 °C/75 % r.H. in [c].

SLS nylon scaffolds changed their appearance to rewetted cakes or viscous-liquid embedded in the scaffold matrix. RM values for DCB I samples (after the initial t0 samples) stored under refrigerated conditions were found in a range of 18.4 % to 23.8 %, while samples stored under ambient conditions ranged from 5.0 % to 5.9 %. RM values for samples stored under accelerated conditions ranged from 6.2 % to 10.3 %.

For SLS nylon scaffolds, the fluctuations in RM could be influenced by the extraction of the SLS nylon scaffolds from the lyophilizer and from the DCBs.

3.2. Investigations into primary packaging properties of the dual chamber bags

3.2.1. Drug content recovery

The drug content recovery of the mAb1 formulation was determined after activation of the dual chamber bags and following reconstitution of the scaffolds within the DCBs (Fig. 6).

For DCB I samples stored under refrigerated conditions, the entire drug content could be recovered at each timepoint. Under ambient and accelerated conditions, a greater drug content recovery was observed during the 24-week assessment compared to the initially recovered amount, accounting for an increase of 15 % and 196 %, respectively, in relation to the initial samples. The increase in drug content recovery was consistent and continuous.

Concentrations of mAb1 measured in DCB II samples revealed that the drug content could be recovered consistently in all samples stored under all conditions. However, a minor increase in the measured concentration—and thus drug content recovery—was observed in all samples stored for 24 weeks.

3.2.2. Osmolality

The diluent compartment of the DCBs (removed during the RM assessment from a related sample) was investigated for the content's osmolality (Fig. 6).

In parallel with the increased drug content recovery, an increase in the osmolality of the diluent was observed for DCB I samples. Under refrigerated conditions, a minor increase in the osmolality of the diluent was observed over time. Samples stored for 24 weeks under ambient conditions experienced an increase in osmolality of 16.9 %, to 332 mOsm/kg, while saline osmolality of samples stored under accelerated conditions increased by 46.8 %, to 417 mOsm/kg, compared to the initial value of 284 mOsm/kg.

In DCB II, osmolality remained essentially stable under all storage conditions at all timepoints. Only under accelerated storage conditions after 24 weeks of storage was a minor but significant increase of 5.0 % observed. For each timepoint, the osmolality of a saline solution from B. Braun bags was measured as a reference.

3.2.3. Water vapor transmission rate

The permeability of the film and foil material used in the DCBs and the seal separating the compartments were assessed by WVTR methods and inverse-gravimetric testing. WVTR measurements were recorded under ambient conditions of 25 °C/60 % r.H. and accelerated conditions of 40 °C/100 % r.H. (Fig. 7**i**). WVTR of the film material used in DCB I (film material covering the DP and diluent on both sides) resulted in an

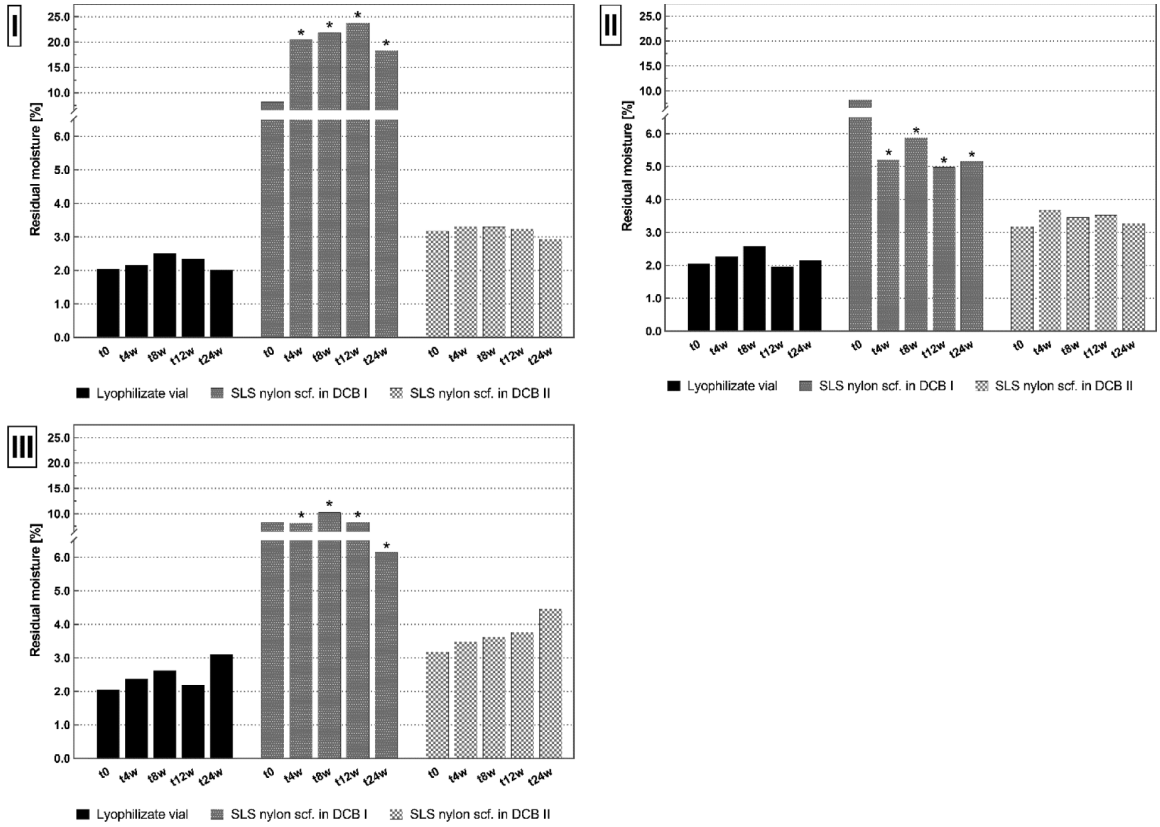

Fig. 5. Residual moisture evaluations of the lyophilized structures in their respective containers during storage over the course of 24 weeks. Storage condition of 2–8 °C in [I], 25 °C/60 % r.H. in [II], and 40 °C/75 % r.H. in [III]. Asterisks (*) refer to samples that displayed a rewetted cake or viscous-liquid cake transformation.

average of 1.29×10^{-2} g/(m^2·day) and 5.69×10^{-2} g/(m^2·day) for ambient and accelerated conditions, respectively.

In DCB II, a WVTR value for the aluminized multilayer plastic film covering one side of the DP chamber could not be obtained successfully. The preparation of the film material failed with several different attempts, as cross-diffusion alongside the film layer hindered the controlled analysis of WVTR values through the film. For the translucent film covering the other side of the DP chamber of DCB II, the WVTR averaged 2.06×10^{-1} g/(m^2·day) and 3.48×10^{-1} g/(m^2·day) under ambient and accelerated conditions, respectively. The film wrapping both sides of the diluent chamber in DCB II averaged 1.04×10^{-3} g/(m^2·day) and 3.31×10^{-3} g/(m^2·day) for ambient and accelerated storage conditions, respectively. The removable aluminum foil cover attached to the translucent film of the DP chamber in DCB II samples averaged 3.31×10^{-4} g/(m^2·day) and is referred to as a negative control sample. A comparison with measurements of other available aluminum foils showed similar WVTR values (data not shown).

The WVTR through the respective seals of DCB I and DCB II was determined by the weight increase of Supelco® silica gel over the course of 12 weeks stored at 25 °C and 0 % r.H. After 12 weeks, 0.229 g of water vapor had migrated from the diluent chamber to the DP chamber in DCB I. In DCB II samples, the weight increase was 0.021 g over the same time period. Thus, the seal in DCB I displayed a permeability of 2.73×10^{-3} g/(seal·day) and the seal of DCB II a permeability of 2.50×10^{-4} g/(seal·day) (Fig. 7**ii**).

4. Discussion

Nowadays, high-income countries ensure the preparation of IV medications by well-trained healthcare professionals, aseptic compounding, and in preparation areas meeting all the conditions predefined by health authorities. These aseptic preparation areas and cleanrooms are equipped with a variety of materials, devices and disposables, and medicines are stored, supplied, and delivered under the guarantee of consistent cold chain retention [25]. However, this well-equipped environment is not representative of LMIC, where a lack in prevention of microbial contamination measures, personal protective equipment, diagnostic capacity and access to drugs, and handling related materials is widespread [26–28]. The stability of liquid drug products, especially biologicals, is easily compromised by their inherent susceptibility to form aggregates. By changing the liquid drug formulation to a dry lyophilized form, impacts of these conditions can be mitigated and the stability increased [29,30]. However, lyophilizates present drawbacks, with most of them related to intensive and time-consuming preparation efforts prior to administration. Nevertheless, their advantage of prolonging the shelf life and easing shipping advocates for their broader use.

4.1. Physical and chemical storage stability of mAb 1 stored in vials and DCBs

Storage conditions evaluated for both the liquid and dry formulations suggested that storage as a freeze-dried product is favorable from a stability perspective. However, this is only valid as long as the dry product remains in a dry state. Under refrigerated conditions, all container formats stored the mAb1 formulation sufficiently and maintained drug product stability. However, when the liquid and dry formulations were stored under ICH conditions of 25 °C/60 % r.H. and 40 °C/75 % r.H., the influence of the container for protecting the dry format became more relevant than their actual physical liquid or dry product state.

While the lyophilized glass vial maintained physical stability of the contained mAb1 formulation at ~ 98.0 % under elevated (ambient or accelerated) conditions, the formulation stored in the liquid state was

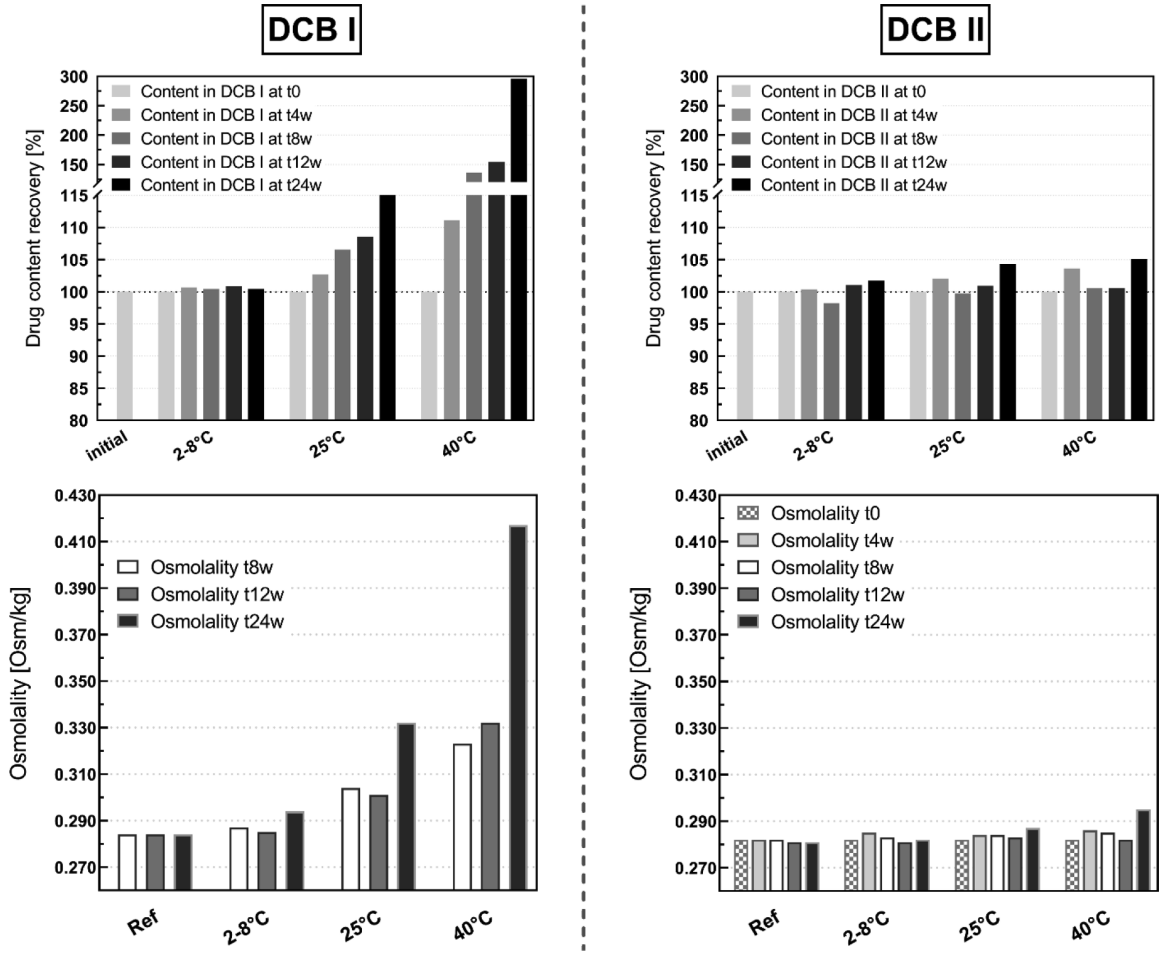

Fig. 6. Dosage recovery analysis upon reconstitution of lyophilized cakes in DCBs and osmolality evaluation of diluent. Left side shows content recovery and osmolality measurements conducted with DCB I samples; right side shows content recovery and osmolality measurements conducted with DCB II samples.

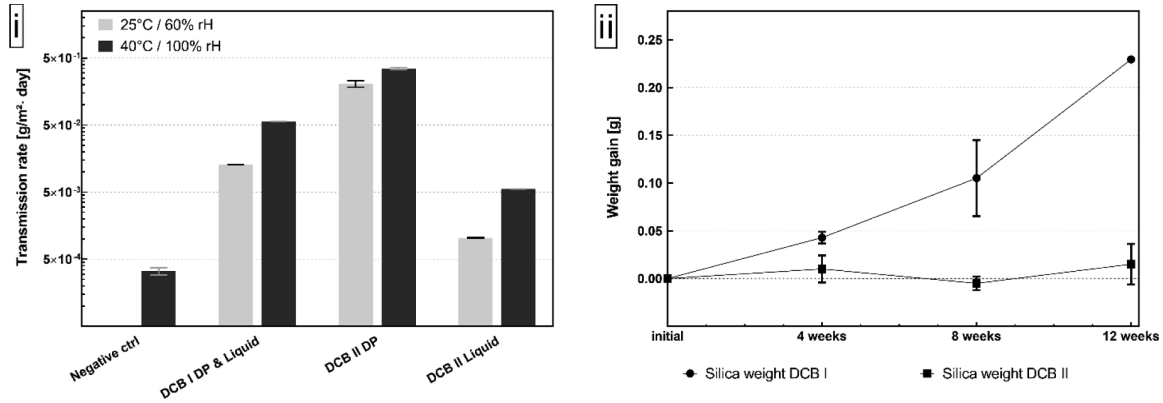

Fig. 7. Water vapor transmission rate evaluations of used foil materials in DCBs I and II under ambient (25 °C/60 % r.H.) and accelerated (40 °C/100 % r.H.) conditions in [i]. Permeability of the respective chamber separation seal used in the DCBs I and II to separate DP from diluent chamber; assessed by reverted gravimetric testing (at 25 °C/0% r.H.) in [ii].

only able to store the monomer under ambient conditions for four weeks until the onset of degradation was observed. The liquid state favors aggregation kinetics due to its different physical state, in which the individual mAbs have a greater space of motion and can transition more easily into a partially unfolded state in which hydrophobic residues are observed. These partially unfolded hydrophobic residues have the tendency to attract other hydrophobic residues and allow the individual mAbs to aggregate [31–33]. This higher occurrence of partially unfolded mAbs in this environment allows for a faster onset of high molecular weight species (HMWS) formation, compared to the dry environment found in the lyophilized vial. In the lyophilized vial, the unfolding of the mAbs is delayed, and due to the vitrified environment, individual mAbs are hindered from interaction with other mAbs. Although the onset of degradation occurred already after four weeks under ambient

conditions, the depletion rate in the liquid formulation was comparably slow in relation to DCB I samples, with 96.6 % monomer remaining after 24 weeks. Under accelerated conditions, 40 °C, the depletion rate of the monomer in the liquid vials was greater after 24 weeks, with the remaining monomer accounting for less than 90 %.

For all three storage conditions, all samples stored in DCB II demonstrated equivalent mAb1 stability to that observed in the lyophilized vials. These observations indicate that the stability of mAb1 was not compromised by the lyophilization in the scaffold structures contained within DCB II. The same DCB II samples analyzed by IEC on the chemical denaturation of mAb1 demonstrated similar degradation rates as the samples in the lyophilized vials over the course of the study. This was further illustrated when the samples were incubated under accelerated conditions. The main peak was conserved at levels of 53.7 % in the lyophilizate vials and 52.8 % in DCB II, thereby supporting the assumption that storage of lyophilized mAb1 embedded in scaffolds in DCB II is equivalent to storage of lyophilizates in vials.

DCB I was not capable of providing the same protective environment as DCB II. DCB I versions facilitated greater depletion of the main peak than samples stored in the liquid form. Under ambient conditions, samples in DCB I displayed a consistent depletion of the main peak to levels of 39.9 % after 24 weeks of storage. Under accelerated conditions, the degradation rate increased to such an extent that the main peak was indistinguishable from the other peaks after 8 weeks of storage. The subsequent analysis revealed the complete decomposition of the main peak into subspecies that were not separable with the applied analytical method. Compared to the liquid vial, which was expected to provide the least stable environment for the storage of mAb1, DCB I provided an even less stable storage environment, despite being freeze-dried.

4.2. Physicochemical characteristics of lyophilized cakes stored in vials and DCBs

As it was observed in the visual inspection of the DCB I containers, the lyophilized scaffold structures experienced major rewetting and thus a partial reconstitution process of the molecule, leading to a high protein concentration solution. This high concentration leads to a closer environment of potentially partially unfolded mAbs that now have a higher likelihood of attracting other partially unfolded mAb counterparts to undergo aggregate formation. Aggregation is not the only possible degradation pathway found in high concentration protein solutions, as many chemical reactions can also be found as deamidation, oxidation or peptide bond hydrolysis reactions leading to fragmented mAb species. These reactions occur in the presence of water, as they are hydrolytically driven, and attend to a kinetic that follows a lower order concentration dependency.

Insufficiencies in product protection were also observed in the visual appearance of the DP cake embedded in the SLS nylon scaffolds stored in the DCB I version. Although the lyophilizate cakes in vials and the lyophilizate scaffolds in DCB II samples remained intact, whitish in appearance, and presented a dry cake structure over the course of 24 weeks, the DP embedded in lyophilizate scaffolds within DCB I containers displayed none of those characteristics. After 4 weeks of storage and at later timepoints, cakes under all storage conditions displayed a rewetted cake, or a viscous-liquid-like appearance. The lyophilized cakes experienced a phase transition from dry to viscous-liquid as moisture from the adjacent diluent chamber and from the environment permeated into the DP chamber, either through the seal or film material. The phenomenon of rewetting or the formation of viscous-liquid within DCB I was also observed during RM evaluations.

Already in the initial samples, high RM values were observed, while being stored only for one day under refrigerated conditions, post filling, and sealing of the bag. Samples stored under refrigerated conditions exhibited RM values exceeding 20 %. This phenomenon of initially high RM values could potentially be explained by additional moisture that was trapped and incorporated during the handling and sealing of the DCB I containers before RM testing of the material was performed. Although, RM levels were elevated in DCB I samples stored under refrigerated conditions, the monomer purity results showed no difference compared to the other tested formats. During long term storage under ambient and accelerated storage conditions, the dry cake that was previously possible to reconstitute changed to a high viscous-liquid protein solution that remained attached to the scaffold structure. Consequently, it is unclear if the entire moisture content was tangible for the RM evaluations, as the viscous liquid trapped within the scaffolds could not be dissolved in the KF solvent and thus might not be entirely captured by it. It can be assumed that the RM values observed for DCB I samples after the initial timepoint were impeded by the formation of rewetted cakes and viscous-liquid and thus represent a distorted RM level not representative of the moisture captured within the viscous-liquid.

The greater amount of moisture found in DCB I samples stored under accelerated conditions compared to samples stored under ambient conditions might be related to the greater permeability of the film materials and the greater penetrability of the sealing at higher temperatures. Furthermore, the higher temperature conditions allowed a higher saturated vapor pressure in the product chamber, facilitating a greater amount of adsorbed moisture to the viscous-liquid surface. As the surface of the freeze-dried material was already in a viscous-liquid state from the t4w timepoint onwards, no change in the moisture could have been detected as the vapor pressure was potentially already saturated in those samples [34].

Contrary to the observations within vials and DCB II samples, a visible gain in moisture over time was not perceived under ambient conditions in DCB I samples, while a minor increase was observed under accelerated conditions. The refrigerated and rewetted samples in DCB I maintained a RM content around 21 %, ambient stored viscous-liquid samples around 5.4 %, and viscous-liquid samples under accelerated conditions around 8.3 %. Rewetted or viscous-liquid-like samples appeared to promote/facilitate a moisture saturation level with a respective saturated vapor pressure for each condition, after which no further increase in moisture could be detected. It is hypothesized that the viscous-liquid-like mAb1 formulation found in ambient and accelerated samples is a less protective environment for the mAb, as the process of rewetting and partial reconstitution of the cake in a small volume generates a high concentration formulation from the dry cake. The increased amount of water found in this formulation thereby acts as a plasticizer, increasing the local mobility of the protein and thus favoring aggregation and chemical denaturation [35–37]. Furthermore, this makes short-range protein–protein interactions increasingly likely and favors subsequent degradation mechanisms due to stronger intermolecular interactions and the greater likelihood of self-association events [38–41].

After storage for 8 weeks under accelerated conditions, distinct brownish discoloration of the embedded lyophilizate cake in DCB I was visible, indicating that a Maillard reaction between the amine groups of mAb1 amino acids and the carbonyl group of a reducing sugar occurred (data not shown). Although sucrose was incorporated as a non-reducing excipient, the cleavage of it to its subunits of glucose and fructose is known to occur when sucrose-containing samples are stored at elevated temperatures and in formulations with a low pH [42,43], as in our case at 40 °C with pH 5.5. The cleaved glucose or fructose molecules were likely interacting as reducing sugars with the amine groups of mAb1, leading to the brown discoloration of the cake and also possible glycation of side chains [44–46]. This chemical degradation mechanism is dependent on available excess moisture and low pH conditions, and is favored by elevated temperature [47]. No further characterization of the discolored samples was performed, indicating that only assumptions on the exact degradation products and degradation processes can be made.

4.3. Primary packaging assessment and influence on mAb1 storage stability

The novel container formats proved their suitability for storing a lyophilized mAb under refrigerated conditions, although at higher temperatures and humidities, the DCB I version demonstrated insufficiencies through the increase in moisture transfer to the DP chamber. As revealed during product stability evaluations, the rewetting of samples was identified as a key challenge, severely affecting the physical and chemical stability of mAb1. However, the increase in drug product content recovery that was identified in DCB I samples under ambient and accelerated conditions raised the question as to whether moisture transmission was unidirectional.

Through additional investigations into the adjacent saline compartment by osmolality measurements, the occurrence of evaporation and up-concentration of the saline solution could be verified. Subsequently, a water vapor transmission method and an inverse-gravimetrical setup were applied to investigate the extent of this evaporation and migration events. The applied WVTR measurements illustrated the high permeability of the film material used within DCB I containers that facilitated the rewetting and evaporation events under ambient and accelerated conditions. Although the DCB I film displayed a comparably high transmission rate of $\sim 5.0 \times 10^{-2}$ g/(m^2·day), the DCB II DP chamber film revealed a 6-fold higher transmission rate under accelerated conditions. This observation raised the question of why no rewetting events were visible in this container format. Based on the other deployed materials in this container, the dry drug product experienced consistent protection.

The DCB II DP chamber is enclosed on one side by an aluminized multilayer plastic film, while the associated chamber film is additionally masked by a temporary aluminum foil cover that is laminated to the seal region of the bag. These characteristics increase the protective properties of the DCB II DP chamber to such an extent that moisture transfer is hardly possible [48,49]. This application of aluminized multilayer plastic film and a temporary aluminum foil cover thus serve as a safe housing for the dry lyophilizate to maintain its stability, even when exposed to high temperature and humidity conditions (ICH conditions 25 °C/60 % r.H. and 40 °C/75 % r.H.). The diluent chamber in DCB II containers was also found superior to the foil material utilized in DCB I containers. The film material enclosing the diluent chamber of DCB II provides a 10-fold lower transmission rate of $\sim 5.0 \times 10^{-3}$ g/(m^2·day) compared to the film used in DCB I containers. This protects the diluent from pronounced evaporation and maintains the initial diluent osmolality level and volume upon reconstitution.

In the case of DCB I, the seal separates a single infusion bag into two chambers by applying a C-shaped metallic sleeve on one side of the bag, inserting the infusion bag into the crevice of the sleeve, and pressing a rubber rod from the opposing side into the crevice. This design applies a constant physical pressure on both sides of the infusion bag to divide the chambers. The separation seal is thus composed of a sandwich design of a C-shaped metal sleeve, infusion bag and rubber rod. Alternatively, the seal in DCB II separates the passageway between the chambers by fusing the opposing inner layers partially together, creating a frangible seal between the two opposing sheets of the bag. The strength of the seam is thereby dependent on the fusing method (e.g. ultrasonic welding or heat welding), the applied force, and introduced temperature/energy. Balancing these attributes generates a strong seal that allows the activation when intended, but also maintains separation during transport. By applying pressure to the inner seam of the diluent chamber, the passageway is generated when the partially fused layers are ruptured, allowing the drug to be dissolved.

Regarding the two separation seal technologies, it can be assumed that an open passageway, temporarily closed by pressing the opposing infusion bag sides together from the outside, is less likely to prevent gas molecules from entering the adjacent chamber than is a passageway division where the opposing film sides are superficially fused to each other. Inverse gravimetrical moisture transfer investigations into the separation seals support this assumption and showed that the separation seals in DCB II containers cut the moisture transfer per day to less than a tenth of that found in DCB I containers. The separation seal of the DCB I containers allowed enhanced permeation of moisture from the diluent chamber towards the DP chamber, making the storage of a lyophilized product in close proximity to a diluent in this setup very challenging. Taking these assessments into account, the initially observed high RM values in the DCB I t0 samples could be attributed to the high permeability of the film material and of the seal technology used for these containers. Together with the applied protective properties of the DP chamber, the DCB II container is almost capable of offering the same barrier properties to moisture ingress as those found in lyophilized vials, making DCB II a very promising alternative or complement to the already well-established lyophilized vial option.

5. Conclusion

It is well known that dry powder or lyophilizate dosage forms provide better stability attributes for delicate drugs such as antibiotics, antivenoms, or most prominently, delicate proteins as monoclonal antibodies that do not maintain stability in their liquid form. The use of lyophilizates in modern dosage forms is, however, inhibited by their intensive handling requirements, along with the need for sterile environments and laminar air flow boxes, highly trained users for proper lyophilized drug preparation, and disposables of all sorts [50–53]. Moreover, the primary packaging container of choice used by drug manufacturers to supply lyophilizates complicates the routine and fast preparation of IV solutions by requiring the preparation from glass or plastic vials. This complication is due to a lack of alternatives that would otherwise expand the use of lyophilizates with their enhanced stability and storage attributes. To investigate potential options to address this lack of alternatives, novel DCBs filled with 3D printed structures to contain the lyophilizates were studied with a model mAb and stored for 24 weeks under three different conditions. The two DCBs were assessed against liquid and lyophilizate vials to investigate if such previously unstudied container formats could achieve equivalent drug stability preservation, and to identify which characteristics of these containers most significantly influence the stability of the drug product.

Samples in the DCB I containers displayed consistent and rapid mAb1 degradation, facilitated by enhanced moisture uptake, leading to the transformation of the dry cake into a high concentration, viscous liquid. DCB II containers, on the other hand, were capable of maintaining a dry product over the entire duration of the study, even after exposure to increased temperature and humidity. Despite the benefit of safe and fast handling of these novel container systems, further evaluation should be performed under real-world conditions in a clinical LMIC setup or similar, to confirm that they indeed offer the intended benefit of complication-reduced and fast compounding of IV solutions for patients in need. Although the relatively short time frame of this characterization is not equivalent to performing exhaustive shelf-life and expiration date estimations, the application of accelerated conditions can certainly provide a reliable foundation for non-Arrhenius degradation behavior [30,54]. However, based on the findings of this study, the successful implementation of lyophilizates into such novel container formats with the proper configuration appears entirely feasible.

By providing ease of use and safe handling, while crucially preserving stability of the drug product, the introduction of such novel containers could promote the broader use of lyophilizates, even in challenging environments such as countries with a lack of refrigerated supply chain options.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

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DISCUSSION

In the presented dissertation a novel form of intermediate primary packaging container has been introduced that allows the flexible and complete transfer of a freeze-dried drug product. The intended use case for such flexible lyophilizate cakes, is the transfer into application devices that allow safe handling of high-potent active pharmaceutical ingredients and the complication-reduced preparation. The use of additive- and subtractive manufacturing methods allowed the generation of porous structures that were used to embed liquid drug product formulations and lyophilize them in a timely manner. These structures were introduced into dual chamber bags for stability evaluations and compared against the general dosage forms in form of liquid- and lyophilized product vials. In the following paragraphs the achieved results are discussed and framed into a bigger picture.

Investigations into medication errors

During hospitalization patients rely on the experience and knowledge of healthcare professionals like nurses, clinicians, practitioners and clinical pharmacists. A relationship of trust between patient and healthcare professional is important to allow a positive treatment outcome. Without trust every interaction of the healthcare professional is contested that potentially mitigates the correct and timely treatment, however in some situations these doubts on the treatment are justified. Unintentional medication errors occur daily, causing low therapy progression, infliction of unnecessary pain or entail some serious consequences as nosocomial infections with methicillin-resistant Staphylococcus aureus or patient death. To assess the most prevalent medication errors we analyzed and extracted the most significant and frequently highlighted medication errors (ME). As medication errors occur worldwide we analyzed the prevalence of MEs in low- and middle income countries (LMIC) and in high income countries (HIC) in intensive care units, tertiary care units and teaching hospitals. The assumption that less MEs or less severe MEs were likely in HIC settings was disproved. In both settings the authors observed less severe MEs as labelling errors that lacked the time of preparation or significant MEs as microbial contamination that led to the decease of two patients [1, 2]. Based on the most frequent mentions of the authors and their highlighting which ME was accounted for the most deviations in the dealings of compounded sterile preparations (CSPs), the five most prevalent MEs were extracted and discussed. The ME which was mentioned with the highest frequency and entitled with greatest significance was the “wrong administration rate”. Condensed, the administration with a too high or too low rate was owed to the wrong placement of the roller clamp in gravity feed infusions, the incorrect programming of the infusion pump, incorrect setup or insufficient charge of the infusion pump, or the administration of bolus injections in less time than described by hospital policy and drug manufacturer information [1, 3-11]. Following the other most prevalent incidents were assessed to be “wrong dose”, “not mixed / wrong mixed / wrong reconstituted”, “wrong diluent / wrong preparation technique”, and completed by “wrong time / wrong frequency”. The ME of “wrong dose” can be referred to observations in which the prepared dose was not administered entirely

as a portion of the dose remained in the infusion bag or to calculation based errors with unit confusions. The omission of applying the entire dose, was either due to incorrect setup of the infusion pumps which terminated the infusion early or to the incorrect withdrawal of drug by volumetric measures and not verifying the amount by gravimetric measures [7, 12-17]. CSPs that were found to be "not mixed / wrong mixed / wrong reconstituted" illustrated reduced concentrations or insufficiently homogenized preparations. In those, portions were either extracted from poorly dissociated powder drug preparations or in liquid dilutions in which portions were extracted from insufficiently diluted solutions that were found to contain greater drug concentrations. In both cases the patients experienced adverse side effects either in the long term, as the drug preparation were below their therapeutic index and did not achieve a remedy of the underlying conditions. Or the effects were experienced rapidly, when the administered drug was exceeding the therapeutic index and induced a shock in the patients. Wrong reconstitution of the drug was attributed to long waiting periods for the drug to be dissociated, potential precipitation upon storage, or incompatibility of the drug with the diluent itself [18-22]. While the wrong diluent was also mentioned in connection to the wrong preparation technique this referred to the decrease in potency due to incompatibility reactions with the drug vehicle (infusion bag or syringe). Incorrect preparation techniques accounted for CSPs that were agitated or prepared and left at the incorrect storage condition e.g. refrigerated, though drug manufacturer information and hospital policy advised to avoid this behavior. Leading to interfacial stress induced aggregation or precipitation of solutes within the dilutions [1, 16, 19, 20, 23, 24]. Mistakes observed concerning the "wrong time / wrong frequency" were related to the delayed or premature administration of CSPs or the administration of an additional dose which was already administered. Either of these incidents potentially inflict reduced serum concentrations of the drug or elevated levels leading to adverse drug events [2, 5, 13, 25].

Aseptic handling challenges during medication preparation

Beside preparation and administration errors also errors in the aseptic handling were observed that potentially compromise the treatment success of the patient by induce prolonged hospitalization due to infections. Common omissions of aseptic handling include the lack of hand washing and disinfection, the covering of hands in sterile gloves, the cleaning of the preparation area and the swabbing of the septum prior dose extraction [6, 26, 27]. Evidence for reduced aseptic care like lack of hand washing and disinfection were found in both hospitals settings. In the UK, Germany and the Netherlands, but also in Iran, Malaysia, and Northern and Eastern African countries observations were made that insufficient attention was allocated to these tasks [1, 28, 29]. A frequently observed complication was omission of swabbing the vial septum for 30 seconds. Even though importance was highlighted in trainings and events of nosocomial infections were described, continued violation of that directive was observed. In discussions with healthcare professionals this was explained by the long waiting periods that must be tolerated, while other duties and patient treatments were cumulating. These maintained violations illustrate that training measures are only effective to a certain extent.

As possible strategies to counter complications relating to "wrong administration rate" the use of central intravenous additive services (CIVA) were mentioned. A service that is preparing bolus injections as mini-infusion therapies for a correct slow administration of the CSP during the

prescribed duration of 3-5 minutes. By employing the CIVA approach healthcare professionals could administer the CSP and can omit the administration period next to the bedside of the patient and focus on other duties. Complications of "wrong dose" were approached by use of gravimetrical workflow systems and the use of barcoding to also reduce the incidents of "wrong diluent" MEs. By use of a gravimetrical workflow systems pre- and post-preparation weighing the infusion bag—the error rates were reduced by 74-fold [16, 17]. Moreover, confusion of unit conversion (leading to wrong dosages) and complications regarding wrong reconstitution were mitigated by introduction of conversion charts and posters within wards and preparation rooms. For "wrong frequency" challenges the inclusion of flag labels—removable labels able to be transferred from CSPs to other containers or patient records—as introduced that are likely to diminish the administration of additional doses by visualizing that a label from a former dose is attached to the patient record.

Gap assessment of current drug container omissions

Several complications were observed that are potentially critical to patient health, but are avertible by introduction of evasion methods as gravimetrical workflow systems, trainings sessions and CIVA services. However, not many clinics are capable to procure and maintain new devices and software or initiate services that add up to the preparation fees. Many of the observed challenges can be retraced to the use of vials and ampoules. Incomplete transfer of the dose by premature transfer of the insufficiently diluted powder or the missing information which diluent is required for the drug dilution were potential tripwires for the correct preparation of CSPs. Other approaches to avert these MEs are likely to be found in technical solutions. Therefore, the elaborated most prevalent MEs were associated with already marketed devices, adapters and preparation systems. Some of these systems like the ADD-vantage™ and the addEASE® binary connector allow the mixture of a drug product vial only with the correct diluent avoiding the use of wrong diluents or compounding of wrong doses. Systems like the MINI-BAG Plus, the Vial2Bag Advanced or the Vial-Mate system enable the transfer of the entire drug powder into the infusion bag, thus giving the drug more time to dissociate properly prior administration. These systems thereby eliminate the complications of "wrong dose", "wrong diluent / wrong preparation technique" and potentially also "not mixed / wrong mixed / wrong reconstitution". However, attention needs to be given to appropriate connection of these adapter systems and the complete transfer of the dose to the infusion bags, as a reduced dose transfer was reported for the addEASE® binary connector system [30]. Additionally, special care is required when systems are mounted to each other, as tilted objects and high force during mounting of the drug vial and adapter system can cause vial breakage injuries or unintentional exposure to the incorporated drug [31]. A remaining complication is presented by aseptic handling, these systems still require the 30 seconds swabbing duration prior assembly. This challenge was not tackled by these adapter systems and remained a complication for the correct aseptic handling of CSP preparation. Another preparation system for CSPs that was discussed, relates to a combination device that incorporates the diluent and the drug of choice in one system—a dual chamber infusion bag—and potentially mitigates the prevalence for aseptic handling complications. The generation of a product that combines the drug and the diluent permanently in one system enables the healthcare professional to prepare the CSP with reduced likelihood for MEs like "not mixed / wrong mixing /wrong reconstitution" and high likelihood for

complete prevention of “wrong dose”, “wrong diluent” and “wrong administration rate”. The DUPLEX®, PLW® and Dual-Mix® dual chamber bags offer the drug in one chamber of an infusion bag, while the other adjacent chamber is filled with the correct diluent. Both chambers are separated from each other by a seal which is ruptured during the activation process and allows the diluent to recover and dissociate the adjacent powder. Although, some designs illustrate a potential threat for drug recovery, as the diluent chamber is allocated next to the infusion port. In case of an unsuccessful or insufficient rupture of the separation seal the drug powder is potentially not dissociated and the patient receives either no dose or only a fraction.

Aim and use case for a flexible lyophilizate cake

The elaborated complications found in medication preparation, the absence of ready to use administration devices for safer and easier medication preparation and the further growing landscape of vials and ampoules displayed the need for a technology that facilitates the transfer of dried product into more ready to use administration devices. Liquid products for the preparation of CSPs are convenient to dose and require rarely preparation prior handling. Further, they are the major dosage form in the growing sector of non-communicable disease (NCD) treatment and are there applied for the therapy of diabetes, cancer, cardiovascular diseases and respiratory diseases. The treatment of these NCDs is increasingly relying on immunotherapy, a form of medication which engages the disease by use of specialized and targeted biological drugs that attract the immune cells of the patient, substitute a missing endogenous protein or suppress the expression of a mistranslated proteins. Targeted biologics like antibodies, antibody-drug-conjugates, and oligonucleotides are highly selective compounds based on proteins or DNA and RNA fragments and are intended to fight multiple cancer subtypes or interact with genetic diseases. Their foundation of being manufactured by amino acid chains and nucleotide chains make them susceptible to degradation and aggregation, which decrease their potency and potentially induce immunogenic adverse reactions. These degradation processes are catalyzed by the presence of water and elevated temperatures, which facilitate hydrolysis and oxidation reactions within the protein chains. The presence of a liquid-air interface in liquid formulations is as well characterized as a potential source of degradation products, due to agitation induced aggregates and particle formation, potency loss and immunogenic reactions can be expected. A solution for these degradation pathways poses the desiccation of the liquid formulation into a dry dosage form. However, drying the liquid formulation at elevated temperature to remove the excess liquid degrades the proteins and leaves them without potency. A method to maintain the potency—equally to levels in liquid formulations—is the application of freeze-drying or lyophilization. This process gently desiccates the moisture by sublimation and desorption under vacuum conditions, while the liquid formulation is kept frozen. Therefore, a freeze-dryer freezes the liquid formulation in the vials and applies vacuum to facilitate the transformation of water ice to water vapor. The water vapor is collected on a condenser that attracts the gaseous moisture by providing a cooler surface for deposition as water ice. Sublimation is a process that requires heat for its continuation and this heat is delivered by the shelves, on which the vials are positioned. After successful drying the vials are closed to ensure the maintenance of a dry environment for the product. The received dry formulation, often referred to as freeze-dried or lyophilized cake, is in its dry state safe from agitation induced aggregation, less likely to develop hydrolyzed subspecies and allows long term

storage without fear of being a growth medium for microbes due to the absence of moisture. These lyophilized cakes can be shipped easily, due to their lower weight and reduced propensity for agitation stress. However, they come with their own set of drawbacks as the necessity to return the dry formulation into a solution (reconstitution), the use of the correct diluent to reconstitute, and potential long reconstitution times of several minutes or even hours. Described in the **INTRODUCTION** these drawbacks were observed to be responsible for many ME and account for reconstitution-, dose and preparation technique errors. As lyophilizates are almost exclusively delivered in vials, these drawbacks maintain and the hurdles of removing of the lyophilizate cake out of the vial into another container for improved preparation or administration are significant. Cake loss, ingress of moisture and issues in dosing are only a few complications. The full potential of a lyophilized drug could be exploited, when stored next to the correct diluent in an administration device that is beneficially ready to use. For small volumes these systems are available as dual chamber syringes, which provide a lyophilized drug in a glass barrel separated from the diluent by another stopper. Upon activation a passageway is used to connect drug and liquid prior application, allowing the reconstitution of the drug. These dual chamber syringe systems, however require a substantial amount of energy to prepare these lyophilized cakes in syringe containers, as efficient heat transfer for the sublimation of the excess water is hindered by the container design and its distance to receive the heat from the shelf. The preparation of a flexible lyophilizate cake that could be transferred post processing into the syringe barrel, would advocate for expanded use cases of these ready to use dual chamber syringes. Applying such a technology for systems that require larger dosages could enable the generation of ready to use infusions capable to circumvent the preparation and - administration errors elaborated in the **INTRODUCTION** and facilitate the aseptic delivery of immunotherapies to patients that are struggling with NCDs.

Improvement and reconsideration of confining containers to allow flexible lyophilizate transfer

To identify drawbacks of the current container formats freeze-drying studies with glass and plastic vials—plastic vials manufactured from cyclic-olefin-copolymer (COC)—were conducted. The use of the widely used 20 ml vial format by drug manufacturers to supply their compounds, was the reason for our evaluations to rely on this format. The confined character of these vial shaped containers limited the possible extraction of lyophilized cakes as a whole and manufacturing of lyophilizates within these containers is known to generate rejects based on insufficient drying and potential collapse of lyophilizate cake structure. Therefore design adaptations were made to facilitate the extraction the cake and allow the potential transfer into administration devices of choice. Described in **CHAPTER I** first prototypes were designed with similar inner dimensions as the 20 ml vials, prepared by vacuum forming of thin polyethylene-terephthalate G (PET) sheets. Hollow PET cups or –containers with thin walls (twPETC) were formed that offer a removable foil at the bottom and an opening on the opposite end were custom made to house the drug during filling and lyophilization. The bottoms of the PETCs were either sealed by a PP plastic foil or an aluminum foil and thus generated twPETC PP or twPETC alu containers. Subsequent to the freeze-drying operation, the removable foil was peeled away to allow the extraction of the cake. During these preliminary investigations, limitations in the preparation and extractability of the cakes were

identified. A propensity for leakage during filling and post filling during residence in the freeze-dryer was identified, hindering the complete dose recovery and being a significant hurdle for a robust and clean preparation process without possible drug exposure. Moreover, the container formats lacked the ability to free the entire cake without remnants on the perimeter and on the removable foil limiting the application if dose recovery in this formats is limited. The stability and robustness of the extracted lyophilizate cakes were also identified as critical limitations, as the brittle cakes were too delicate to be handled post extraction and generated dust particles, chips of lyophilized cake, and breakage into larger pieces.

The transition from a confining container generating a brittle and delicate cake, to a design that allows the lyophilized cakes to be handled without loss of product was therefore aimed for. Incorporating of the liquid drug into a porous matrix and freeze drying the formulation within, allowed the generation of a freely transferable lyophilizate cake. The matrix structures offered a robust housing for the dried material eliminating the loss of product or the chipping and breakage experienced by handling the lyophilizate cakes extracted from PETCs. These porous structures were generated by additive – or subtractive manufacturing methods that facilitate the design of intricate geometries for drug housing and expelling. With these methods three prototypes of porous structures were generated. Two porous structures, or scaffolds, were generated with the same design by additive manufacturing procedures but prepared by use of biocompatible nylon or stainless steel source material. These porous structures were referred to as SLS nylon scaffolds and SLS SS scaffolds. Additional porous structures were generated by subtractive manufacturing methods; prepared from aluminum and referred to CNC alu scaffolds. The entirety of porous structure were able to house the drug product appropriately in their container structure and allowed leakage free filling and extractability from the freeze-dryer.

Thermal characterization of container formats

As freeze-drying is characterized by long drying periods requiring several days to finish one batch—the primary drying step accounting for the majority of that duration—the determination of the endpoint of such dryings needs to be evaluated in prior studies to avoid excessive energy consumption and manufacturing line occupancy. The endpoint determination can be performed by multiple approaches e.g. comparative pressure measurements, H_2O monitoring by tunable diode laser absorption spectroscopy, pressure rise tests by manometric temperature measurements or product temperature measurements by use of thermocouples [32, 33]. When a small development batch of a liquid product is lyophilized, the introduction of thermocouples for lyophilization progress mapping are preferred over other methods. Thereby the progression of the sublimation over lyophilization cycle can be recorded within the frozen material. A temperature increase indicates the progression of the drying and the endpoint of the drying can be approximated when the thermocouple records the intersection of the product temperature with the shelf temperature. The recorded temperature curves indicate whether the process is progressing slowly or quickly, or if the process is compromised by factors like shelf load overfill, too high product resistance or additional atypical radiation effects. To characterize the drying of the novel designs (including PETCs and scaffold structures) the containers were compared to the standard vial containers made from glass and COC. All containers were filled with the same amount of a model antibody formulation (mAb1 formulation), equipped with thermocouples to record the

drying progression and dried with a generic freeze-drying recipe. While glass vials and COC vials finished the drying of the mAb1 formulation within ~27 h and displayed a broad range of vials that dried the formulation faster and slower than their average, the novel containers in contrary were able to significantly reduce the drying times and dry the samples with less heterogeneity. Reductions of the mean drying time by more than 37.5 % were achieved for twPETC alu containers, reductions of 34.8 % were observed for CNC alu scaffolds and SLS SS scaffolds finished the drying in less than 50.9 % of the time. Other containers as twPETC PP were observed to dry the formulation faster but with less significant reductions in drying duration. SLS nylon scaffolds illustrated prolonged drying times, compared to glass vials, but were able to decrease the heterogeneity of the individual drying curves slightly. The two porous structures manufactured from stainless steel and aluminum (alloy scaffolds) and the twPETC alu containers exhibited significant decrease in heterogeneity by displaying a narrow distribution of the individual temperature curves. Compared to vials it was observed, that the temperature of the scaffolds at the end of the primary drying approximated to the shelf temperature in a plateau, instead of intersecting with the shelf temperature. Therefore characterizations of the containers were extended to determine the progression of drying within these porous structures. For this reason CNC alu scaffolds were equipped with three vertically aligned thermocouples in the bottom, the center, and the top thirds of the structure. Subsequently these structures were filled and lyophilized to monitor the progression of the sublimation front. Sublimation progression in vials is confirmed to dry the frozen cake from the top to the bottom, with the last ice to be dried located at the center bottom [32]. To accurately determine the end point during drying in vials, thermocouples were therefore positioned at this location. A different drying progression as known from vials was observed. Instead of drying from the top to the bottom, the sublimation front was found to shrink from the outside perimeter of the scaffolds towards the lower center of the scaffolds. The thermocouple in the top of the scaffold achieved a stable temperature plateau close to the shelf temperature first, but closely followed by the center and bottom thermocouple temperatures, indicating a radial drying progression from the outside towards the inside. As the alloy scaffolds were dried in several lyophilization runs and differently positioned in each, the narrow distribution of the individual temperature curves is remarkable and leads to the assumption that the ultimate objective of freeze-drying—a consistent batch to batch homogeneity—was met [34]. Although the drying was finished comparably fast, the full potential of the porous structures was not fully elucidated, as the applied drying recipe was generic and not fitted to the individual container properties. Exemplarily, the alloy scaffolds displayed an ascending steady state prior achieving the plateau close to the shelf temperature, while SLS nylon scaffolds maintained a horizontal steady state and vials displayed a descending steady state. This implies that the ratio of energy transfer into the lyophilized cake and energy consumption by sublimation is dependent on the used material. As the temperature increases slightly in alloy scaffolds, it can be suggested that the sublimation rate can be increased by applying more aggressive lyophilization cycles. As the ratio between energy input and sublimation rate was even in SLS nylon scaffolds it can be reasonably assumed that the generic recipe was suited for the drying of the formulation within these porous structures.

Assessment of Critical Quality Attributes achievement

Although the drying behavior in porous scaffolds displayed a striking homogeneity and in case for the alloy scaffolds a significant reduction in primary drying time as well, this approach is only barely suited to determine the quality of the received lyophilisates. Therefore the received embedded lyophilizate cakes and the lyophilizate cakes in glass vials were analyzed on their ability to meet several Critical Quality Attributes (CQAs). These CQAs include the achievements to reconstitute the embedded lyophilized cake material, achieve low residual moisture contents, and display satisfying cake appearance supported by µCT investigations. The achievement of CQAs was successful if the values were consistent with or better than the captured results in vials. The twPETC container designs were discontinued in these assessments as the continued leakage, cake appearance and cake transfer complications were seen as a major hurdle for further investigations and applications [35, 36]. Cake appearance in all scaffolds structures was found to satisfy the attributes of a lyophilized cake, however minor cosmetic defects were found. Besides minor cracks in the alloy scaffolds, some tiny holes were visible in the outer perimeter of the porous structures retraceable to confined air bubbles during filling. Although, the lyophilized cake displayed a tightly embedded coarse cake structure with lamellas indicating larger ice structures during freezing, further no flakes or chipped product losses were observed. Vials lyophilized in the same freeze-drying cycles presented also satisfying cake appearance with homogeneous cake structure, but presented more differentiable cosmetic defects. Minor shrinkage and the formation of dents at the bottom were seen in the lyophilized cakes. Despite these cosmetics defects the lyophilized cakes sufficed the requirements and did not exhibit collapse or meltback structures [36]. The visual cake appearance was supported by µCT images captured of the embedded cakes within the SLS nylon structure and the lyophilized cake within glass vials. Evaluations of alloy structures were unsuccessful, as the applied power to invade the matrix structure were too high to visualize contrast differences between cake and matrix. The investigated cake appearance within SLS nylon scaffolds revealed a coarse pored lamellar structure within the matrix that streaks from the top to the bottom and tapers towards the bottom into a fine pored care and dense cake structure. The large pores visible in the cake structure are the template of the frozen ice and thus visualize a growth of ice crystal during the freezing process. Surprisingly these crystals appear like annealed structures that were probably generated during the freezing process of the formulation within the matrix structure. It can be assumed that the matrix structure supplied additional heat during the freezing process and thus led to growth of crystal structures prior reaching the final freezing temperature. Further analysis displayed that the SLS nylon scaffolds probably entrapped residual source material in the cavities of the intricate designs, these were visible in the rinsed and cleaned structures recaptured when a repetition µCT scan was performed. These dense pockets were capable to incorporate lyophilized material and thus present a potential shortfall for complete moisture removal and dose recovery. Vials revealed cracks and homogenous cake structures throughout the vertical axis of the cake, but displayed minor collapse at the border of the dents found at the bottom as well that could potentially affect long term storage of the drug [37, 38]. These dense structures are known to be formed in sucrose formulations with low protein concentrations [39]. During reconstitution time measurements, all cakes were reconstituted without visible remaining powder remnants within less than 2 minutes, which is an acceptable duration for formulations with comparatively low protein concentrations [40-43]. The increased surface area presented by porous scaffolds, was beneficial for reducing the reconstitution time during dissolution. Similar mean reconstitution

times were achieved in all the porous scaffolds, which averaged a 48.8 % shorter reconstitution time than found in lyophilized cakes within glass vials. The reduced reconstitution time was potentially affected by big lamellar pores identified during the µCT scans. Regarding the residual moisture evaluations the porous structures revealed higher residual moisture levels than their vial counterpart. Explanations for these increased moisture contents are potentially found in the handling of the structures during extraction from the freeze-dryer. While the vials were stoppered after the successful lyophilization, the scaffolds were extracted and subjected to the humidity in the handling area in front of the lyophilizer. As investigated with µCT the increased moisture could partially stem from the dense source material pockets that entrapped lyophilized formulation; high cake resistance in these pockets and their location in the center of the matrix, have potentially exacerbated the desorption and exit of the residual moisture amounts. The elevated residual moisture amounts in porous structures must be investigated further, to ensure that a modified process of extraction, or a fitted lyophilization recipe can accomplish the achievement of this important CQA. Nevertheless slightly higher residual moisture levels are known to increase the stability of the incorporated drug, while over-drying was studied to have an adverse effect, however this is drug specific attribute and needs to be evaluated case by case [44-46]

Generation of an Instant Infusion Lyo Kit

With the technology available to prepare flexible lyophilized cakes the next step of transferring these into novel administration devices was approached by evaluating the transferability of porous structures. These evaluations were discussed in **CHAPTER II**. Therefore two dual chamber infusion bags (DCBs) were acquired that offer the separation of the administration device in two compartments; one for the diluent and the other for the drug product. These DCB versions DCB I and DCB II were different in their foil material and their separation seal. DCB I offered a single infusion bag that was separated into two chambers by an external separator rubber rod and a metal sleeve arranging the separation seal in a sandwich-like design. The sandwich-like seal consisted of the infusion bag placed within the metal sleeve and the rubber strip pressed into the metal sleeve. With the infusion bag placed between metal sleeve and rubber strip, the single infusion bag was separated into two compartments, a diluent and a product compartment. The DCB II container consisted of two different sized compartments that were separated by a weld seam. The product intended compartment was manufactured from two different foil materials, one aluminized-plastic foil and one translucent foil that was additionally covered by a removable aluminum foil cover. The activation of the individual DCBs was performed either by removing the separation rod from the metal sleeve for DCB I containers, or by applying pressure onto the diluent chamber rupturing the frangible seal to generate a passageway for reconstitution.

Transferability of the lyophilizate cake container format

Lyophilized drug product was prepared in porous scaffold structures and as the manufacturing of the SLS nylon scaffolds was rapidly feasible and the used nylon polymer known to be biocompatible these structures were favored for this stability study [47]. Unknown effects of the CNC alu scaffolds and SLS SS scaffolds were considered to be likely, therefore the nylon polymer variant was preferred. Lyophilized drug product scaffold were generated according to the description in

 and stored until inclusion under nitrogen atmosphere. The DCBI containers were dissected to allow the incorporation of the drug housing porous structures, while DCB II containers offered two filling ports for the transfer of the porous scaffolds and the diluent. The transfer of the porous scaffold was achieved in a glove box which was purged with dried nitrogen gas for 24 h. The individual porous scaffold were thereby transferred with their complete drug load into the respective DCB. The saline solution was either inserted by the luer lock port at the bottom of DCB I container or by the filling port of DCB II containers. After successful filling of the drug and the diluent the open filling ports were sealed with a long nose plier. A parallel double weld was generated to ensure a tight closure of the DCBs minimizing potential cross-diffusion of moisture into or outside the bag compartments and to avoid unintentional rupture of the weld during preparation of the CSPs.

Stability comparison between common formats and DCBs

To assess the stability of the respective drug products stored in DCBs the containers were compared to the general drug product storage in lyophilizate vials and liquid drug vials. In all containers the exact same formulation of mAb1 was incorporated, and porous structures were lyophilized in the same freeze-drying run as the liquid vials to avoid process deviations among two lyophilization runs. The generated samples were then stored under different conditions to evaluate their stability behavior. At recommended refrigerated storage conditions of 2-8 °C and at ambient and accelerated storage conditions of 25 °C / 60% r.H. and 40°C / 75% r.H., respectively. Elevated conditions were applied to simulate the long-term storage at refrigerated conditions and to obtain non-Arrhenius degradation behaviors [48, 49]. Samples were pulled over the course of 24 weeks and quantitatively analyzed on their physical- and chemical degradation by use of size exclusion chromatography to investigate generation of aggregates and ion exchange chromatography to investigate oxidation and hydrolysis events. Residual moisture testing was also performed by Karl Fischer titration to evaluate the moisture content progression. Qualitative analysis of the samples was performed by visual cake appearance.
At refrigerated conditions all samples in the different containers maintained stability of the protein over the course of 24 weeks. At ambient conditions the onset of degradation in liquid vials was visible that began after 4 weeks of storage. For DCB I containers the stability declined at ambient conditions rapidly both in terms of physical deterioration and chemical deterioration. At accelerated conditions the protein stability analyzed by IEC was undistinguishable from the deteriorated protein species after a storage of 8 weeks. The corresponding samples analyzed by SEC were separable from the high and low molecular weight species, but the stability declined below values of 40 area%. Liquid vials stored at this condition, however remained comparably stable and displayed a loss of monomer accounting for 18.7 area%. Nevertheless, also enhanced chemical degradation was displayed in liquid vials as the main peak area declined below levels of 18% from former 58%. In contrast to the findings in DCB I and liquid vial containers, the stability of mAb1 in lyophilizate vials was as expected. No degradation or depletion in SEC and IEC results were observed at ambient conditions. Only minor chemical degradation of mAb1 was found in IEC samples after the storage over 24 weeks at accelerated conditions. No significant degradation was found for lyophilizate vials analyzed by SEC. The most surprising results were achieved in the DCB II containers, as their stability progression was found to be alike the one displayed in lyophilizate

vials. Although, the lyophilized mAb1 formulation was stored adjacent to the liquid compartment and stored at ambient and accelerated conditions, degradation patterns observed during IEC analysis showed only minor degradation of the main peak compared to the lyophilizate vials. In SEC results no significant difference was observed compared to lyophilizate vials. The mentioned observations were matched with qualitative visual appearance evaluations. While lyophilizate vials and porous structures in DCB II containers remained unchanged over the course of 24 weeks at all conditions, severe degradation of the lyophilizate cakes embedded in porous structures of DCB I container were perceived. Transformation of the former dry lyophilized cakes within the porous structures materialized after 4 weeks of storage in DCB I containers in all storage conditions. This transformation was perceived as a change from a dry drug product cake to a rewetted cake that ultimately changed to a syrup embedded into the porous matrix. Additionally, at elevated conditions (ambient and accelerated conditions) a discoloration of the white cake to a brown syrup materialized. Indicating that a potential Maillard reaction of the cleaved sucrose molecules with the amine groups of the amino acids of mAb1 occurred. Sucrose is known to undergo a non-enzymatic cleavage into its subunits fructose and glucose under acidic conditions, elevated temperature and time [50-52]. The cleaved subunits were assumed to interact with the protein leading to the perceived discoloration, however, without further characterization by orthogonal methods as LC-ESI-MS or boronate affinity chromatography no concrete determination of the discoloration can be made [53, 54]. Residual moisture investigations were unsuccessful in determining the moisture increase in DCB I samples and presented only comparably high residual moisture values over the course of 24 weeks. As the residual moisture values remained relatively stable over the progression of the study, we assume that the rewetted and syrup-like samples promote or facilitate a moisture saturation level at each condition. This saturation levels was kept constant during the duration of the study and inhibited further moisture uptake. In contrary it could be also possible that more moisture was accumulated in the samples but the Karl Fischer method with methanol was unsuited to dissolve or capture the incorporated water from the syrup-like formulation. This syrup-like formulation appears to be the reason for the severely reduced main peak area in IEC results. As the high concentrated mAb1 formulation formed in this syrup-like environment potentially enhanced the local mobility of the protein aggregation and chemical denaturation were favored [55-57]. This enhanced local mobility is likely to facilitate short-range protein-protein interactions and favors subsequent degradation pathways. Probably caused by stronger intermolecular interactions and greater likelihood of self-association events [58-61]. However, not only the DCB I samples were subjected to a gain in residual moisture also lyophilizate vials and DCB II samples accumulated additional moisture over the course of the study. Noteworthy, this increase in residual moisture materialized only in samples that were stored at accelerated conditions and not in refrigerated or ambient stored samples. A potential conjecture of minor residual moisture gain in DCB II samples, can be assumed at ambient stored samples, but an additional timepoint is missing to confirm this hypothesis.

Identification of moisture income and prevention strategies

As moisture ingress was evident in the DCB I and II samples by residual moisture testing, water vapor moisture transfer investigations into the main income route were conducted. However, not only moisture income into the product was observed, but also moisture evaporation. During the

stability testing of the samples, the product recovery within the DCBs was investigated to confirm that the complete reconstitution of the dose is feasible over the course of the study. Therefore the concentration of the dose was measured and an increase of dose recovery was detected after 4 weeks of storage at ambient and accelerated conditions in DCB I containers. A possible leak was ruled out, as refrigerated samples were otherwise the only samples unaffected from this incident. Following, the diluents were analyzed on osmolality and an increase in osmolality could be detected for the incorporated saline solution. As with the increased residual moisture the increase in osmolality was primarily observed in DCB I containers stored at ambient and accelerated conditions.

The gas permeability in terms of water vapor transmission rate, was therefore investigated for the different foil materials utilized in the generation of the DCBs at ambient and at accelerated conditions. It was thereby detected that the used ethylene-vinyl acetate material of DCB I containers is highly permeable for water vapor. The transmission was measured for both directions and thus allows the ingress of moisture to the dry product and the evaporation of moisture from the diluent chamber. The diluent foil used in DCB II containers provided a tighter barrier for the water vapor and displayed a 10-fold lower transmission rate as measured in DCB I containers. Although, the DCB II translucent product foil was derived as the most permeable foil material observed to let 16-fold more vapor (at ambient conditions) pass through its barrier than the foil of DCB I, the attached temporary aluminum foil cover and the aluminized plastic foil on the opposite end of the product chamber compensate the high permeability. By covering the dry drug product from two ends with an almost impermeable aluminum barrier foil, the product stored in DCB II containers is housed in a remarkably safe environment, cutting the moisture ingress via the foil material to a level less than 172-fold of the DCB I container.

To account for the probable moisture ingress via the seal, a reverse gravimetrical approach was applied to measure the moisture uptake of incorporate silica gel in the absence of moisture in the surrounding environment. Therefore only the adjacent diluent compartment was filled with saline solution and the DCBs were stored in desiccator filled with additional orange gel and overlaid with dry nitrogen. The moisture transmission via the separation seals was thus investigated for both different DCBs and was determined to be almost 11-fold higher for the DCB I container than for the DCB II container. This demonstrates the superiority of heat-, ultrasonic or alike generated separation over the external separation by pressurizing a passageway.

CONCLUSIONS AND OUTLOOK

This dissertation elucidated a potential alternative of IV infusion therapy to the common approach of compounded sterile preparations (CSP) from ampoules and vials. The aim of the thesis was to identify a medication system that allows the fast preparation of an IV infusion with limited opportunities for preparation errors and aseptic complications. To facilitate easy transport and broad applicability the medication system should rely on the preparation of CSPs with lyophilized compounds.

We demonstrated that the embedding of a lyophilizate into a porous matrix accelerates freeze-drying processing times and allows the combination with dual chamber bags for complication-reduced preparation of CSP while sustaining drug storage stability.

In a first step, the expected most prevalent medication errors in LMIC and HIC hospital settings were extracted and consolidated to visualize the gap the current preparation process is facing. By analyzing the most prevalent errors and their reasons for occurrence, we were able to link them to possible technical evasion strategies. A solution that was found to circumnavigate the most errors effectively was found in the technology of dual chamber bags. This technology is capable to generate CSPs without the opportunities for wrong dose calculations, incorrect diluent use or wrong administration rates. Further, it enables healthcare professionals to prepare these CSPs at the bedside of the patient, without special preparation areas to ensure sterility and cautionary measures to avoid exposure. Nevertheless, the technology is currently limited to the use of antibiotics that can be transferred only by powder dosing into the dual chamber bag drug-compartments and require specialized facilities to contain the exposure to antineoplastic dust. Drugs that are incompatible with preparation as powders and need gentler desiccation procedures to maintain their stability—like antibodies, ADCs or oligonucleotides—lack the opportunity to be transferred in such medication systems.

Therefore we investigated possible alternatives for drug powder transfer and focused on the preparation by lyophilization. As most of the biological targets are manufactured and stored in glass vials, the first approach was to adapt the container to facilitate a complete extraction of a lyophilized cake. The generated twPETC cups that resembled vials, but were equipped with a removable bottom displayed good lyophilization properties of a mAb formulation in terms of processing speed but poor extractability, cake appearance and susceptibility for leakage. Extracted cakes suffered from chipping and breakage upon handling and were thus lacking the qualities necessary for a transfer into dual chamber bags. The transition from a confining container, to a container offering a strong and supporting inner matrix structure allowed the generation of flexible lyophilizate cakes. The by additive- and subtractive manufacturing generated structures from biocompatible nylon, stainless steel or aluminum embedded the incorporated drug within their porous structure. During lyophilization they demonstrated remarkable reductions in processing times while promoting a consistent inter batch homogeneity. The extracted porous structures housed their drug product safely within their matrix and allowed complete and stable collection of the incorporated dose when a diluent was added. Nevertheless, some shortfalls were experienced like insufficient removal of residual moisture or additional uptake during extraction from the freeze-dryer.

Moreover, dense pockets of source material entrapping moisture and thereby potential powder residues that could result in the identification of visible particles in the prepared CSP.
Based on the promising results of generating a flexible lyophilization cake, the transfer into medication systems like dual chamber bags was approached, to study the feasibility and the long term stability of a degradation susceptible biological drug under three storage conditions. Two dual chamber bags with different physical characteristics were employed to investigate the stability of the mAb1 formulation embedded in the porous structures. Over the course of 24 weeks the DCBs were challenged against mAb1 as liquid and lyophilized dosage form in glass vials and were found to demonstrate both inferior or equivalent storage and stabilization properties. On one hand DCB I containers without an additional aluminum barrier and with a sandwich-like separation seal between the individual diluent and drug product chambers demonstrated inferior stability than the liquid vial counterpart. The DCB II containers on the other hand highlighted, that the inclusion of a temporary aluminum foil cover, the use of an aluminized plastic foil and the separation seal based on a weld seam can promote similar stability retention in DCBs as observed in lyophilizate vials. The root cause for the accelerated degradation in DCB I containers and the lack of such accelerated rates in DCB II containers, was determined to be inflicted or prevented by the used foil material and separation seal.

The concept of generating a flexible lyophilizate cake as an intermediate container for the transfer of freeze-dried drugs was realized and in combination with a dual chamber bag as a storage system the stability retention of a delicate drug product was proven. With these tools the broad usage for the preparation of CSPs in a complication-reduced manner seems achievable. Healthcare professionals and ultimately patients could benefit from such an Instant Infusion Lyo Kit (IIK) and its broad application, as the most prevalent medication errors like “wrong dose”, “wrong preparation technique”, “wrong diluent” and the complications concerning aseptic handling would be evaded. Nevertheless, the IIK could benefit from some further refinements, to increase the affordability and the potential likelihood to be applied. Investigations targeted to improve the intricate design of the porous structures could facilitate more efficient removal and less entrapment of moisture. Additionally, the utilization of thermodynamic modelling of heat flows in different materials could be employed, to identify and link the most suited source material for the porous structure. These could be also aligned to the drying behavior and properties of the considered formulation. By enhancing the thermodynamic properties of the porous structure and adjusting the material choice to the formulation requirements, the establishing of an IIK-platform technology could be possible, allowing a variety of different compounds to be incorporated into such a design. In terms of formulation, the incorporation of hydroxypropyl-betacyclodextrin (HPBCD) as an excipient for the formulation of delicate biologics could not only take advantage from the elevated temperature storage capacities of this additive, but also make use of the application of aggressive freeze-drying cycles that reduced the lyophilization procedure to a single-step process [39, 62]. The gain in a more efficient lyophilization process and shortened manufacturing line occupancy—eventually resulting in a smaller economic footprint—could advocate for the increased availability and affordability of highly required medicines in low and middle income countries.

The current investigations to substitute the calculation of required dose from data based on age, metabolism, and body surface area, by the use of dose banding approaches could reduce the amount of IIK species to only a few that cover a specific range of patient groups [63, 64].
When combining these future concepts with the inclusion of snakebite-antivenins, the availability of such emergency medicines could be enhanced and thus save more lives. Therefore IIKs with antivenin combinations must be distributed at strategic points in in sub-Saharan and southeast-Asian countries to facilitate immediate and easy access.
With these IIKs as a platform a complication-reduced and aseptically compliant preparation of CSPs can be envisioned wherever emergencies happen or common therapies are necessary.

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PATENT APPLICATIONS

During the dissertation, four patent applications were submitted and successfully published with the following titles:

WO 2020/0109194 A1 – LYOPHILISATE CONTAINER AND INFUSION KIT

WO 2020/0109195 A1 – MANUFACTURING A FLEXIBLE CONTAINER

WO 2021/213992 A1 – METHOD OF GENERATING A DRIED DRUG FORMULATION

WO 2022/0038273 A1 – LYOPHILISATE RETAINER, METHOD OF MANUFACTURING THEREOF AND PROCEDURE OF DRYING A SUBSTRATE

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(54) Title: LYOPHILISATE CONTAINER AND INFUSION KIT

(57) Abstract: A lyophilisate container (39) comprising a compartment; a wall (3119, 3129) limiting the compartment; and a lyophilisate arranged inside the compartment. At least a portion of the wall (3119, 3129) is semipermeable allowing vapour permeation in one direction out of the compartment through the wall (3119, 3129) and preventing vapour permeation in an opposite direction into the compartment through the wall (3119, 3129).

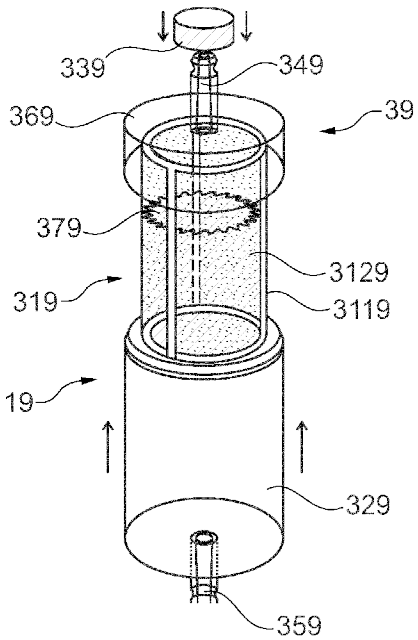

Fig. 6

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[Continued on next page]

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

DESCRIPTION

Title

LYOPHILISATE CONTAINER AND INFUSION KIT

Technical Field

[0001] The present invention relates to lyophilisate containers, infusion kits having such lyophilisate containers, methods of preparing such lyophilisate containers and use of such lyophilisate containers.

Background Art

[0002] In many chemical, pharmaceutical, nutritional and other applications substances are provided in a dry form. Thereby, in order to achieve a long shelf life, it is often aimed to have the substances as dry as possible. In this context, it is known to lyophilize or freeze dry the substances. Particularly, where it is necessary or beneficial to gently drying the substances, e.g. without heating them in an inappropriate manner, lyophilisation often is preferred.

[0003] For example, in many medical applications, pharmaceuticals or drug substances are to be, e.g., orally, parenterally, intravenously or subcutaneously, administered in liquid form. As an example, for intravenous administration it is known to use infusion bags which can be hanged on a support and continuously drop a liquid drug substance or a drug diluent mixture through an infusion needle into a patient. However, in connection with liquid drug substances, many pharmaceuticals and particularly biopharmaceuticals cannot be stored and supplied for an appropriate duration in liquid form since they commonly are unstable in that form. More specifically, many antibiotics or other biological drugs are unstable in liquid form such that their quality cannot be maintained as liquid. In particular, stress caused by shaking, microbiological growth, aggregation or the like may compromise the drugs. As mentioned, it is however known to supply the drug in a dry form, such as in a powder or

the like, in which they are essentially more stable and robust compared to the liquid form. The dry drug formulation is then reconstituted or dissolved shortly before administration.

[0004] To achieve or maintain appropriate hygienic and quality standards the substances are often carefully lyophilised in specific conditions such as an aseptic environment. Thereby, the substances are usually lyophilised in specific containers from which they are transferred to other containers or packages for storage and supply. Shortly before being applied or administered the substances are then reconstituted. Typically, such procedure is rather elaborate and prone to mistakes. When transferring the substances, there may be a risk of loss or contamination. This can be of particular importance when the substances, such as highly potent drug substances, are provided at comparably small amounts and/or when precise amounts have to be handled. Also, this might endanger caregivers or clinicians when they need to prepare high potent drug substances and might get in contact with those. Usually comparably large efforts are made to protect the ones that need to prepare the drug substances for patients, for example by use of laminar air flow, isolator boxes, gloves over gloves and protective sleeves. Furthermore, particularly on an industrial level, preparation can be comparably inefficient. For example, typically the time required for lyophilisation is comparably high for different reasons.

[0005] Still further, when pharmaceuticals or drug substances are involved, the persons handling the substances can be confronted with comparably high demands. Therefore, such applications are often prone to mistakes particularly when comparably low skilled or low educated persons are involved. For example, when administration in an infusion bag is aimed, the preparation of the drug substance including its reconstitution and provision in the infusion bag is of utmost importance to assure an appropriate treatment. Particularly, where highly potent drug substances are involved the treatment by infusion may be inappropriate if it cannot be assured that the preparation is performed appropriately, such as it is often the case in rather low and middle income countries where appropriate clinical environments with aseptic conditions and/or laminar air flow are scarce. Also, in application where the speed of preparation is crucial such as in emergency situations, the known preparation of highly potent drug substances often is not appropriately efficient.

[0006] Therefore, there is a need for a system or process allowing an efficient life cycle of a consumable lyophilisate starting from its preparation and ending at its administration.

Disclosure of the Invention

[0007] According to the invention this need is settled by a lyophilisate container as it is defined by the features of independent claim 1, by an infusion kit as it is defined by the features of independent claim 13, by a method of preparing a lyophilisate container as it is defined by the features of independent claim 15, and by a use of lyophilisation container as it is defined by the features of independent claim 16. Preferred embodiments are subject of the dependent claims.

[0008] In one aspect, the invention is a lyophilisate container comprising a compartment, a wall limiting the compartment, and a lyophilisate arranged inside the compartment. At least a portion of the wall is semipermeable allowing vapour permeation in one direction out of the compartment through the wall and preventing vapour permeation in an opposite direction into the compartment through the wall.

[0009] Lyophilisation in the context of the present invention is a low temperature dehydration process, which involves freezing a substrate, lowering pressure and then removing ice by sublimation and desorption. The result from lyophilisation is the lyophilisate. Lyophilisation is also referred to as freeze drying. Lyophilisation can cover bulk freeze drying, which may produce lyophilized powders, microspheres, or spray drying.

[0010] The lyophilisate can, e.g., be a nutritional or dietary substance intended to be consumed by a person by drinking, eating or the like. It can also be an analytical substance or a substance to be used in a chemical process. However, preferably the lyophilisate is a lyophilised drug formulation, particularly, a highly potent drug formulation which can comprise a biological compound such as a monoclonal antibody, an antibody drug conjugate, an antibody fragment, a locked nucleic acid (LNA), gene vectors, virus like particles, or the like. Advantageously, the lyophilisate has a moisture range of less than about 3%, i.e. a water activity of less than about 0.05.

[0011] The term “drug” as used herein relates to a therapeutically active agent, also commonly called active pharmaceutical ingredient (API), as well as to a combination of

plural such therapeutically active substances. The term also encompasses diagnostic or imaging agents, like for example contrast agents (e.g. MRI contrast agents), tracers (e.g. PET tracers) and hormones, that need to be administered in liquid form to the patient.

[0012] The term "drug formulation" as used herein relates to a single drug as defined above or a plurality of such drugs mixed or formulated. For example, besides the drug, a drug formulation may additionally comprise an excipient and/or other auxiliary ingredients. When being a dry drug formulation, the lyophilisate can be a solid, a semisolid or a powderous drug formulation.

[0013] The term "drug substance" as used herein relates to a drug formulation as defined above in a form that is suitable for administration to the patient. Thereby, the drug substance can be the pure drug formulation or a drug formulation reconstituted, diluted or dissolved in an administrable form. A particularly preferred drug substance in the context of the invention is a solution, in particular a solution for oral, parenteral intrathecal or ophthalmic administration, injection or infusion.

[0014] The term "drug product" as used herein relates to a finished end product comprising a drug substance or a plurality of drug substances. In particular, a drug product may be a ready to use product having the drug substance in an appropriate dosage and/or in an appropriate form for administration. For example, a drug product may include a handling or storage device such as a flexible container.

[0015] The term "potency" used in connection with the drug formulation can be a measure of drug activity expressed in terms of the amount required to produce an effect of given intensity. Thus, the terms "high potency", "highly potent" or similar can relate to a formulation or substance which is active at comparably small amounts or dosages. In other words, a highly potent drug formulation can evoke a given response at comparably low concentration, while a drug formulation of lower potency can evoke the same response only at higher concentrations. The potency may depend on both the affinity and efficacy of the drug formulation. Thereby, such drug formulations or substances can be particularly problematic since comparably small variations in dosing or comparably small contaminations can be comparably effective.

[0016] In numbers, a highly potent drug formulation can be defined as a drug formulation having a biological activity at approximately 15 micrograms (µg) per kilogram (kg) of body weight or below in humans. This is equivalent to a therapeutic dose at approximately 1 milligrams (mg) or below in humans. The highly potent drug formulation can thus be defined as a drug having an inhalative Acceptable Daily Exposure (ADE) value of 1.5 µg/d or less, translating into an Indicative Occupational Exposure Limit (IOEL) value of 0.15 µg/m^3. In particular, the highly potent drug formulation can be a class 3B drug or the like. When used with highly potent drug formulations to be administered by infusion, the method according to the invention can be particularly beneficial.

[0017] The term "compartment" in connection with the invention relates to any suitable interior in which the lyophilisate can be positioned or stored. It is or, at least, can be tightly closed such that the lyophilisate is protected from humidity, mechanical stress and contamination. The compartment can be formed by a soft, flexible, elastic or rigid structure of the container.

[0018] The term "wall" in connection with the structure forming the compartment can relate to any soft, hard, flexible or rigid structure suitable to form the compartment. It can be a single piece construction or a composition of plural differing parts. The wall can be semipermeable by being made of semipermeable material, by having a section of a semipermeable material or by a similar construction.

[0019] By providing the wall to be at least partially semipermeable to vapour and particularly to water vapour, it can be achieved that the final generation of the lyophilisate by freeze drying can be performed inside the container it will be supplied and, eventually, used with for administration. More specifically, the original drug formulation to be lyophilised can be positioned inside the container which is closed afterwards and then exposed to conditions inducing lyophilisation. During lyophilisation, the water or other vapour can escape the container through the wall. Thereby, it can be beneficial to have an as large portion of the wall to be semipermeable in order to achieve a highly efficient and fast lyophilisation.

[0020] By allowing lyophilisation inside the compartment, the container according to the invention achieves a reduction of the number and complexity of steps involved in preparation of the lyophilisate and its administration. Further, safety can be increased

by reducing the risk of exposing the lyophilisate such that a high quality of the lyophilisate can efficiently be achieved.

[0021] Moreover, since the wall is only permeable for vapour from the inside to the outside but not from the outside to the inside, the lyophilisate inside the compartment can be well protected. This allows a secure storage and preservation of the lyophilisate until its administration. If desired, the wall allows an aseptic preservation of the lyophilisate inside the compartment.

[0022] Furthermore, the container also allows to protect caregivers or clinicians when they need to prepare high potent drugs. A desired reduction of exposure can easily be achieved and large efforts made for protection can be prevented or at least reduced. Thus, the container according to the invention allows for providing an efficient life cycle of the lyophilisate starting from its lyophilisation and ending at its administration.

[0023] Preferably, the wall of the container comprises a semipermeable membrane which is vapour permeable in the one direction and vapour tight in the other direction. The semipermeable membrane can have various different attributes. It can be pierceable, heat conductive, UV-tight, water vapour impermeable/selectively impermeable or combine plural of those or other attributes. Such membrane efficiently allows for achieving semipermeability of the wall. Moreover, the lyophilisate inside the compartment can efficiently and safely be administered. For example, the membrane can be pierced in order to provide a liquid into the compartment for dissolving the lyophilisate before administration. Additionally, the membrane can be used for filtering the lyophilisate solution which may result in a particulate free and pure liquid or solution to be administered.

[0024] Preferably, the wall comprises a frame structure, by means of which the semipermeable membrane is spanned and/or held. Such frame structure and membrane combination allows for providing the container in a predefined shape which may be adapted in accordance with the lyophilisate and its intended application or administration. In particular, the frame structure can provide for giving a certain stability and the membrane can provide the function of semipermeability

[0025] In a preferred embodiment, the lyophilisate container comprises an outer encasing and an inner encasing positioned inside the outer encasing, wherein the wall

is a portion of the inner encasing. The outer encasing as well as the inner encasing can be essentially cylindrical, for example. In particular, the inner encasing can have a diameter which sufficiently smaller than a diameter of the outer encasing such that an appropriate room or volume is provided between the inner and outer encasings.

[0026] Having two encasings positioned inside each other and arranging the wall in the inner encasing allows for providing a comparably large area of the wall to be semipermeable and, anyway, to have a comparably robust container protecting the lyophilisate. Such large semipermeable area allows for efficient lyophilisation. Also, it allows for efficiently filtering a solution created by dissolving the lyophilisate inside the compartment.

[0027] More specifically, the inner encasing can have the frame structure spanning the semipermeable membrane. Thereby, the frame structure can be formed by a preferably flattened upper ring portion, a preferably flattened lower ring portion and a plurality of bars extending between the upper and the lower ring portions. The semipermeable membrane is spanned into the windows created by the upper and lower ring portions and the bars.

[0028] The used semipermeable membrane in the wall of the inner encasing can guide vapour either from the inside of the inner encasing to the outside and restricting the permeation of vapour to the inside of the inner encasing, or it can be attached reversed such that it allows water vapour to permeate from the outer barrier into the inside of the inner encasing but not from the inner encasing towards its outside.

[0029] The inner encasing and eventually also the outer encasing can be housed beneath a lid that is connected to the encasing(s), e.g., irreversibly. The lid, which may be part of the inner encasing unit, may join thus the inner encasing to the outer encasing. In the centre of the lid covering the inner encasing, a coupler can be embodied which is hollow and allows the transfer of substances into the inner encasing or out of it, respectively. This coupler can be part of the lid and designed to be closed by a removable and tight cap that protects the lyophilisate inside the container from environmental impairment or the leak of lyophilisate out of the container. Such coupler can not only be found on the lid that is connected to the inner encasing but it may also be found on the other end of the container on the bottom of the outer encasing. These couplers can house barriers as diaphragms or septa that need to be punctured by a

needle or thorn. Yet, the coupler passage can be hollow as well, to facilitate a substance transfer without a restricting barrier.

[0030] The coupler on the lid of the inner encasing can be intended to be jointed to a flexible container, or to a pouch, bag, bottle, or other container. The identical coupler at the outer encasing can be used to attach the container to an empty other container, pouch, bag, or bottle to collect the dissolved lyophilisate, solution or drug substance which is freshly prepared or needs to be transferred. The coupler on the lid of the inner encasing and/or the coupler at the outer encasing can be connected to a container, pouch, bag, or bottle by a flexible tube. This flexible tube can provide another identical coupler that is the respective counterpart to the couplers on the lid or bottom of the container, respectively. By such a connection via a tube, a protected transfer from flexible container, pouch, bag, bottle or other container to the product containing container or vice versa can be ensured.

[0031] The outer encasing surrounding the inner encasing, which may comprise the comparably delicate frame structure and membrane, protects the housed lyophilisate also from degradation by permeation of water-vapour or oxygen, of UV-radiation and from excessive mechanical stress.

[0032] For bonding the inner encasing and the outer encasing several techniques can be applied. For example, threaded coupling, thrust coupling, snap or press-fit, adhesive bonding, ultrasonic welding, ultrasonic staking, electromagnetic welding or similar techniques that achieve hermetic and strong bonding but avoid quality impairment.

[0033] More specifically, in a variant of the preferred embodiment of the container, the compartment for the lyophilisate is arranged in between the outer encasing and the inner encasing. There at least a portion of the wall is oriented to allow vapour permeation in the one direction from the compartment to the inner encasing through the wall and to prevent vapour permeation in the opposite direction from the inner encasing to the compartment through the wall.

[0034] In such variant, the compartment is positioned in a space formed in between the outer and inner encasings. Thereby, the lyophilisate can be filled and/or generated by filling the outer encasing with the desired substance solution before the inner frame is plugged or positioned into it. After filling, further product optimizations or product

protection steps can take place, particularly including lyophilisation to remove excess liquid. Also, the container inside can be flushed with inert gas, the container can be evacuated to remove undesired gases, or other techniques prolonging and ensuring the stability and efficacy of incorporated substances or drugs can be applied. The lyophilisation and flushing or evacuation optimizations are intended to take place when the outer encasing and the inner encasing are associated to each other already. Thereby, the wall allows for permeation of water vapour out of the outer encasing through the inner encasing. If the inner encasing is provided with the frame structure mentioned above, in this variant, the membrane advantageously is arranged around the inner encasing. Like this, it can be achieved that only the membrane is in contact with the lyophilisate or any component used for generating or reconstituting it and not any portion of the frame structure.

[0035] In another variant of the preferred embodiment of the container, the compartment is arranged in the inner encasing, and there at least a portion of the wall is oriented to allow vapour permeation in the one direction. The vapour is intended to flow from the inner compartment to the space between the outer encasing and the inner encasing through the wall and to prevent vapour permeation in the opposite direction from the space between the outer encasing and the inner encasing towards the inner compartment through the wall.

[0036] Thereby, the lyophilisate can be filled and/or generated inside the inner encasing by filling the inner encasing with a solution upfront marriage of the inner encasing and the outer encasing. After the filling, the optimizations mentioned above can be performed at least including lyophilisation to remove excess liquid. The optimization may be performed when the inner encasing is in the outer encasing or when being positioned outside of it. If the inner encasing is provided with the frame structure mentioned above, in this other variant, the membrane advantageously is arranged within the inner encasing covering the frame structure. Like this, it can be achieved that only the membrane is in contact with the lyophilisate or any component used for generating or reconstituting it and not any portion of the frame structure.

[0037] In all variants of the preferred embodiment of the container, the outer encasing or the inner encasing preferably has a conical lateral area. Thereby, the term “lateral area” can relate to a surface or area of the outer or inner encasing which surrounds the outer or inner encasing. It can be the final outer area or surface of the container.

[0038] By having such a conical area, it can be achieved that plural encasings are arranged side by side, wherein there still is some free space between them. More specifically, in the variant where the compartment is between the outer and inner encasings, the outer encasing advantageously has the conical lateral area. In the other variant where the compartment is inside the inner encasing, the inner encasing advantageously has the conical lateral area. This allows for efficiently circulating heat and/or cold around the encasings and for efficiently removing sublimed water vapour from the walls of the containers next to each other, e.g., when being placed on a lyophilisation shelve. Like this, a particularly beneficial temperature transfer and water vapour removal can be achieved which allows for increasing the efficiency of lyophilisation inside the container. Particularly, on an industrial level where it is desired to prepare a comparably high number of containers in parallel, this can be highly beneficial.

[0039] In another preferred embodiment, the lyophilisate container comprises a rigid body having a hole opening at one end side of the body and extending from the one end side of the body or container body to the other end side of the container body, wherein the hole forms the compartment and the semipermeable membrane attached to the container body thereby closing the hole at the one end side of the container body. The hole can also end in a second opening at the other end side of the body. In such embodiments, the hole is a through-hole. Alternatively, the hole can be closed at the other end side such that it is a blind hole.

[0040] Such container can allow for providing a particularly robust and at the same time simple construction. By covering the inside forming the compartment with the membrane, an efficient lyophilisation can be performed inside the container. Also such semipermeable membrane covering the hole can efficiently be used to filter a solution created by dissolving the lyophilisate inside the compartment.

[0041] The rigid body or container body can be made of any suitable plastic or other material. It can be manufactured in a blow fill and seal, deep draw moulding or other process. More specifically, such container can be manufactured by punching a cylindrical hole into the a top part of a formed deep draw mould that is then covered and welded to a semipermeable membrane or porous foil facilitating the evaporation of water out of the compartment and protecting the inside of the moulded form from permeation of water.

[0042] The container or container body can further be manufactured by turning the deep draw moulded container body upside down, such that the punched opening is directed towards the ground and the open bottom end is facing upwards. The semipermeable membrane can then be attached to the inside of the body or container body beneath the punched hole. Subsequently to the placing and welding of the membrane to the punched opening, the body or container body is filled with the desired raw substance. This means that the opening on the bottom or bottom side of the body is used for filling while it is directed upwards. The lyophilisation or freeze drying to remove excess liquid can be performed before or, particularly, after the container is closed.

[0043] Advantageously, the rigid body or container body is essentially cylindrical or hollow cylindrical. The term “essentially cylindrical” also covers forms slightly deviating from a geometrical cylinder. In particular, a cylinder being conical to a certain extent may still be essentially cylindrical. E.g., a conical cylinder having a sidewall slanted to a maximum of about 5°, about 3° or about 2° can still be essentially cylindrical. Also, the sidewall of the tubular cartridge may differ to a certain extent from a geometrical straight shape. The tubular cartridge can be embodied as a hollow cylinder wherein the open end is located at one end of the cylinder.

[0044] When the hole is a through-hole also having an opening on the other end side of the body or container body, the other end side can also be provided with a semipermeable membrane. However, preferably, the lyophilisate container comprises a non-permeable foil having a high thermal conductivity, the foil being attached to the body or container body thereby closing the through-hole at the other end side of the body or container body. The term “high thermal conductivity” can relate to a property of the non-permeable foil allowing an efficient heat or cold transfer into the compartment. Particularly, the thermal conductivity of the non-permeable foil can be high compared to the thermal conductivity of the body.

[0045] More specifically, during manufacturing of the container or container body, the opening at a bottom end or other end side may be closed with the non-permeable foil. The foil can be a pierceable or peelable foil. The attached peelable foil allows the storage of the lyophilisate in the container until a transfer of the lyophilisate into another container or a direct reconstitution thereof is intended. Thereto the foil can be removed from the container by peeling. Alternatively, the pierceable foil can facilitate the

dissolution of the lyophilisate, e.g., by a needle set attached to the container and forcing liquid into it.

[0046] The removal of the dissolved lyophilisate can be performed on the end side provided with the semipermeable membrane. Therefore, a connector can be attached facilitating the linkage of an empty container that collects the freshly prepared solution and readies it for transport. In particular, the dissolved solution can be filtered via the semipermeable membrane achieving a particulate free solution, e.g., administrable for parenteral applications when transferred into the collector container.

[0047] Preferably, the body or container body has a conical lateral area. The lateral area of the body or container body can be the outer surface of the body or container body. The conical lateral area can also be embodied over a portion of the body only such that it has straight and conical sections. As mentioned above, even when the lateral area is conical, i.e. being completely widening or having widening section(s), it can still be essentially cylindrical since its main appearance can still be as a cylinder.

[0048] In use, the end side of the body having the smaller outer diameter can be the upper end side. The end side of the body with the larger outer diameter can be the lower end side. By positioning the body on the lower end side it can stand comparably stably.

[0049] Similar as described above, by such a conical area it can be achieved that plural containers or container bodies are arranged side by side, wherein still there is some free space between them. This allows for efficiently circulating heat and/or cold around the container. Like this, a particularly high temperature transfer can be achieved which allows for increasing the efficiency of lyophilisation inside the container. Particularly, on an industrial level where it is desired to prepare a comparably high number of containers in parallel, this can be beneficial.

[0050] In still another preferred embodiment, the lyophilisate container is a pad-like structure, wherein the compartment is formed in between two sheets and at least one of the two sheets is the wall, i.e. at least partially is semipermeable. The pad-like structure can be a pouch or cushion-shaped element which has the two sheets forming an interior in which the compartment is formed. In order to form a pad-like structure the two sheets can be connected along their edges, e.g., by forming respective seal seams along the

edges. The two sheets can be two separate or separable units as well as one unit folded to form the two neighbouring sheets. The two sheets can be made of any suitable plastic, metallic, composite or other material which advantageously is flexible. Advantageously, the pad-like structure is made in a blow fill and seal process. The pad-like structure could be generated also by deep mould drawing similar to the process of the manufacturing of blister foils. The notches could then be filled, frozen and then sealed with a semipermeable membrane, or filled, sealed with a semipermeable foil or the like and then transferred into a freeze dryer.

[0051] Such pad like structure allows for providing a comparably simple construction having a comparably large semipermeable area. Like this, an efficient lyophilisation inside the compartment can be performed. Also, when being prepared before administration the lyophilisate can efficiently be reconstituted and, eventually, filtered through the semipermeable portion of the wall. For example, for providing a diluent into the compartment, one of the sheets can be pierced or ruptured.

[0052] In another aspect, the invention is an infusion kit comprising a lyophilisate as described above, a lyophilised drug formulation positioned in the lyophilisate container and a flexible container having a first compartment filled with a reconstitution liquid and a port.

[0053] The reconstitution liquid can be any liquid suitable to reconstitute the lyophilised drug formulation. It can particularly be a diluent such as a physiological solution such as a sodium chloride (NaCl) solution, a sucrose solution, an aqueous dextrose or any other similar solution. The NaCl solution can, e.g., be a 0.9% NaCl solution. The sucrose solution can, e.g., be a 5% sucrose solution. The aqueous dextrose can, e.g., be a 10% dextrose solution.

[0054] The term “flexible” as used in connection with the material or the container can relate to a comparably soft material which is not shape stable. Particularly, such material does usually not keep its shape when being differently positioned or oriented. Typical flexible materials are foils and particularly plastic foils or foil like structures such as tight meshes or the like.

[0055] The flexible container can be manufactured as follows: The first compartment of the flexible container is formed out of a flexible sheet-like material. The reconstitution

liquid is filled into the first compartment of the flexible container and the first compartment is sealed. The flexible container can particularly be manufactured within a side fill and seal or a blow fill and seal process.

[0056] The term “sheet-like” as used in connection with the material the flexible container can be made of relates to a flat typically essentially even substrate having a thickness which is considerably smaller than its length and width. In particular, the sheet-like material can be a foil or a similar structure.

[0057] The sheet-like material can be a sheet-like single plastic, composite, plastic blend or multilayer plastic. It can be altered in its surface properties to improve extractability, to reduce or exclude gas permeation and leaching of additives and/or to simplify sealing. The sheet-like material needs to be compatible with its intended purpose such as compatible with parenteral or oral solutions, nonreactive when chemicals are stored in the flexible container and/or aligned to required guidelines applicable to the drug substance, e.g., the guidelines of the Unites States Food and Drug Administration (FDA) or the guidelines of the European Medicines Agency (EMA).

[0058] The term “sealing” as used herein relates to a process or step of attaching two or more elements or portions of an element to each other such that a gas, a liquid or another fluid cannot pass the attached portions. In embodiments where the flexible sheet-like material is a foil and particularly a plastic foil, the sealing can be provided by applying a predefined temperature and/or pressure at a particular location of the foil. Thereby, the foil can be coated with an adhesive which activates its adhesive properties by application of temperature and/or pressure. Alternatively or additionally, the sealing can involve ultrasound-, high frequency- and or radio frequency welding. In particular, sealing can involve creating seal seams. The seal seams can be embodied as firm seals and/or frangible seal.

[0059] The first compartment of the flexible container can be sized to have a volume in a range of about 20 ml to about 2’000 ml.

[0060] The flexible container can consist of two identical sheet-like materials or of two different sheet-like materials. For example, one sheet-like material may be transparent while the other one may be aluminized to reduce the ingress of water vapour or oxygen.

[0061] The port can be of any kind suitable for the intended application of the kit. For example, a port can be or comprise a long cylindrical opening or a septum that enables withdrawal of liquid while assuring protection from unintended spilling. These withdrawal ports are usually found in infusion bags, septum bottles, or squeeze pouches for nutrition. The ports can be placed between the open layers or sheets of the flexible container prior sealing them, or can be attached after the layers or sheets were sealed with each other. Other ports can be attached in the proximity of the port or on the opposing border of the flexible container. Also, ports can be placed into the edges of a vertical line or seam seal directed from top to bottom. To facilitate the attachment of ports on the lateral edges of the flexible sheets forming the flexible container, punctures in the sheet can be required where ports can be placed prior the final welding of the flexible container takes place. The port/ports within the flexible container can manage the connectability to other containers or to devices used for administering or provision of the content of the flexible container.

[0062] In addition to the port, other ports can be attached in the proximity of the port or on the opposing border of the flexible container. Also, ports can be placed into the edges of a vertical line or seam seal directed from top to bottom. To facilitate the attachment of ports on the lateral edges of the flexible sheets forming the flexible container, punctures in the sheet can be required where ports can be placed prior the final welding of the container takes place. The port/ports within the flexible container can manage the connectability to other containers or to devices used for administering or provision of the content of the flexible container.

[0063] The kit allows for providing a ready to use system such as an infusion system having all components required for administration of the drug formulation by infusion. In particular, the flexible container can be an infusion bag.

[0064] It is also possible to provide multiple lyophilisate containers in the kit together with one single flexible container. Like this, a practitioner can be given the option to adjust the dosage by dissolving an appropriate amount of lyophilisates. Also, the administration of combination drug substances that can't be stored together but need to be administered or applied in parallel can be achieved. Furthermore, a stepwise activation of a process can be realised. For connecting the plural lyophilisate containers together, it can, e.g., be provided with an adapter or an intermediate piece. The final combination can then be similarly connected to the flexible container.

[0065] In a preferred embodiment, the flexible container comprises a second compartment separated from the first compartment by a frangible seal and the lyophilisate container is arranged inside the second compartment of the flexible container.

[0066] Such multiple compartments can be manufactured by – in addition to the steps mentioned above - forming a second compartment of the container out of the flexible sheet-like material and filling a lyophilisate container into the second compartment. The frangible seal can be embodied to open when the first compartment is, e.g. manually, compressed.

[0067] Any number of compartments can be positioned anywhere in the container. For example, for allowing a particularly efficient filling, the compartments can all extent to one side edge of the container such that the compartments may be filled from one side only. Or, for achieving a safe application of the container such as a particular sequence of activation, the compartments can be distributed in the container such as on opposite side edges thereof.

[0068] The term “frangible seal” relates to a connection of the two opposing flexible sheets in the flexible sheet-like material which can be released, broken or ruptured when compressing a compartment adjacent to the frangible seal. Frangible seals can also be referred to a peelable seal, non-permanent weak seal or breakable seal.

[0069] Similar as the first compartment, also the second compartment can have a volume in a range of about 20 ml to about 2’000 ml.

[0070] Specifically, forming the first and second compartments can be embodied by positioning two foils or sheets at each other and then sealing the two foils along the edges of the foils or at any other appropriate portion. Alternatively or additionally, one single foil or sheet can be folded in a suitable manner and then sealed along the edges of the foil or at any other appropriate portion. In the end the container can be a bag or bag-like device such as an infusion bag, a pouch or similar.

[0071] Such multi compartment flexible container allows for providing a closed ready to use system which can conveniently and quickly be prepared prior administration without risking any contamination or loss of the drug substance. In particular, prior administration the seal between the first and second compartments can be opened by

manually compressing the first compartment. Then the liquid or diluent can be provided into the lyophilisate container. For that purpose the lyophilisate container can be broken or ruptured, e.g., by manually compressing it. Or, the structure can be provided in the second compartment allowing for opening, cutting, piercing or breaking the lyophilisate container. Or, the lyophilisate container can be coupled to the frangible seal such that when opening the frangible seal, the lyophilisate container is opened as well.

[0072] In an other preferred embodiment, the lyophilisate container is embodied in the port of the flexible container. Like this, it can be achieved that when providing the liquid out of the port it dissolves the lyophilisate and forms a solution to be administered, e.g., by infusion.

[0073] In still another preferred embodiment, the port has a first mounting structure and the lyophilisate container has a corresponding second mounting structure such that the lyophilisate container is mountable to the flexible container to expel the liquid through the lyophilisate container. Again, this allows for providing the liquid out of the port such that it dissolves the lyophilisate and forms a solution to be administered, e.g., by infusion.

[0074] In a further other aspect, the invention is a method of preparing a lyophilisate container as described above. The method comprises the steps of: (i) positioning a moist substance inside a compartment of the container limited by a wall limiting the compartment, wherein at least a portion of the wall is semipermeable allowing vapour permeation in one direction out of the inside of the compartment through the wall and preventing vapour permeation in an opposite direction into the inside of the compartment through the wall; (ii) closing the compartment of the container; and (iii) lyophilising the moist substance in the compartment such that vapour permeates out of the inside of the compartment through the wall.

[0075] The moist substance can be a solution of the substance, a semisolid, a pasty substance or a solid substance. In particular, not only liquid solutions can be filled into the compartment, it is also possible to include pre-processed materials in the means of syrups, granulates, microtablets, spray freeze-dried powders, free flowing pre-lyophilized spheres, active pre-lyophilized dry powder or differently manufactured substances.

[0076] Such method allows for efficiently preparing the lyophilisate container also on an industrial level. Moreover, such method can be applied in a variety of fields such as in nutrition, pharmacy and others.

[0077] In still a further other aspect, the invention is a use of a lyophilisate container as described above. The use comprises the steps of reconstituting the lyophilisate of the lyophilisate container in a liquid inside the compartment of the lyophilisate container, and filtering the liquid solution comprising the reconstituted lyophilisate through the wall of the compartment.

[0078] Such in-container reconstitution allows for a particularly protected and safe preparation of the solution to be administered. The filtering of the prepared solution through the wall and particularly its semipermeable portion allows for providing a clean particulate free solution as it is beneficial, e.g., in medical applications such as in administration by infusion.

[0079] As mentioned, the invention in all aspects is designed to be used in the fields of nutrition, chemistry and diagnostics but primarily intended for medical or pharmaceutical applications.

Brief Description of the Drawings

[0080] The lyophilisate container according to the invention, the kit according to the invention, the method of preparing a lyophilisate container according to the invention and the use according to the invention are described in more detail herein below by way of an exemplary embodiment and with reference to the attached drawings, in which:

Fig. 1 shows a perspective view of a first embodiment of a kit according to the invention having a first embodiment of a lyophilisate container according to the invention;

Fig. 2 shows a perspective view of a second embodiment of a kit according to the invention having a second embodiment of a lyophilisate container according to the invention;

Fig. 3 shows a perspective view of a third embodiment of a kit according to the invention having a third embodiment of a lyophilisate container according to the invention;

Fig. 4 shows a perspective view of a fourth embodiment of a kit according to the invention having a fourth embodiment of a lyophilisate container according to the invention;

Fig. 5 shows a perspective view of some components of a fifth embodiment of a kit according to the invention having a fifth embodiment of a lyophilisate container according to the invention;

Fig. 6 shows an exploded perspective view of some components of a sixth embodiment of a kit according to the invention having a sixth embodiment of a lyophilisate container according to the invention; and

Fig. 7 shows the kit of Fig. 6 while a lyophilisate is reconstituted and transferred from one compartment of a flexible container to another one.

Description of Embodiments

[0081] In the following description certain terms are used for reasons of convenience and are not intended to limit the invention. The terms “right”, “left”, “up”, “down”, “under“ and “above“ refer to directions in the figures. The terminology comprises the explicitly mentioned terms as well as their derivations and terms with a similar meaning. Also, spatially relative terms, such as "beneath", "below", "lower", "above", "upper", "proximal", "distal", and the like, may be used to describe one element's or feature's relationship to another element or feature as illustrated in the figures. These spatially relative terms are intended to encompass different positions and orientations of the devices in use or operation in addition to the position and orientation shown in the figures. For example, if a device in the figures is turned over, elements described as "below" or "beneath" other elements or features would then be "above" or "over" the other elements or features. Thus, the exemplary term "below" can encompass both positions and orientations of above and below. The devices may be otherwise oriented (rotated 90 degrees or at other orientations), and the spatially relative descriptors used herein interpreted accordingly. Likewise, descriptions of movement along and around various axes include various special device positions and orientations.

[0082] To avoid repetition in the figures and the descriptions of the various aspects and illustrative embodiments, it should be understood that many features are common to many aspects and embodiments. Omission of an aspect from a description or figure does not imply that the aspect is missing from embodiments that incorporate that aspect. Instead, the aspect may have been omitted for clarity and to avoid prolix

description. In this context, the following applies to the rest of this description: If, in order to clarify the drawings, a figure contains reference signs which are not explained in the directly associated part of the description, then it is referred to previous or following description sections. Further, for reason of lucidity, if in a drawing not all features of a part are provided with reference signs it is referred to other drawings showing the same part. Like numbers in two or more figures represent the same or similar elements.

[0083] Fig. 1 shows a first embodiment of a kit 1 according to the invention which includes a flexible container in the form of an infusion bag 2 and a lyophilisate container 3 according to the invention. The infusion bag 2 has a first compartment 21 housing a liquid diluent 24. Inside the first compartment 21 the lyophilisate container 3 is positioned, which houses a highly potent lyophilized drug formulation 34 as lyophilisate. In a front section, the flexible container 2 has an outlet compartment 25 separated from the first compartment by a frangible seal 22. The compartments 21, 25 are formed in two sheets of a flexible plastic material by providing firm seals along the edges and the frangible seal 22 in an appropriate manner. In particular, the first compartment 25 is formed by firm seals at the outer edges of the sheets and the frangible seal 22. The outlet compartment 25 is formed by a front firm seal and the frangible seal 22 at its back end. Centrally in the front firm seal a port 23 is mounted which is in fluid connection with the outlet compartment 25. The port 23 is embodied to be connected to a structure or device for intravenous administration.

[0084] The lyophilisate container 3 has an essentially cylindrical rigid body 31 through which an axial through-hole extends. At a bottom end, the through-hole is closed by a non-permeable or tight foil 33. At about the upper end of the through-hole, a semipermeable membrane 32 closes the through-hole. Thus, a compartment is formed inside the through-hole between the foil 33 and the membrane 32, in which the lyophilized drug substance is arranged.

[0085] In use of the infusion bag 2, a user manually opens the compartment of the lyophilisate container 3. This can, e.g., be done by pushing on the foil 31 until it breaks. Or, it can be done by squeezing the container 3 or flexible container 2 such that an increase in distance between membrane 32 and the foil 33 is achieved and the membrane 32 and foil 33 are peeled off the container 3. Then the diluent 24 streams into the compartment and dissolves the drug formulation 34 such that a drug solution is obtained. The dissolving of the drug formulation 34 can be assisted by the user shaking

the infusion bag 1 in case that the drug substance is not prone to shaking movements. Then the user compresses the first compartment 21 such that the pressure inside the first compartment 21 rises. Caused by this pressure rise, the frangible seal 22 ruptures such that the first compartment 21 and the outlet compartment 25 form a common compartment. The infusion bag 1 is then hanged port 23 down on a support and an intravenous device is attached to the port 23. Thereby, the infusion bag 1 is changed to a single compartment infusion bag and can be applied as known in the art.

[0086] In Fig. 2 a second embodiment of a kit 10 according to the invention which includes a flexible container in the form of an infusion bag 20 and a lyophilisate container 30 according to the invention is shown. The infusion bag 20 has a first compartment 210 housing a liquid diluent 250, a second compartment 220 housing the lyophilisate container 30 in which a highly potent lyophilized drug formulation 350 as lyophilisate is positioned, and an outlet compartment 260 in a front section of the flexible container 20. The first compartment 210, the second compartment 220 and the outlet compartment 260 are separated from each other by frangible seals 230. The compartments 210, 220, 260 are formed in two sheets of a flexible plastic material by providing firm seals along their edges and the frangible seals 230 in an appropriate manner. Centrally in the front firm seal a port 240 is mounted which is in fluid connection with the outlet compartment 260. The port 240 is embodied to be connected to a structure or device for intravenous administration.

[0087] The lyophilisate container 30 has an essentially cylindrical rigid body 310 through which an axial through-hole extends. At a bottom end, the through-hole is closed by a non-permeable or tight foil 330. At a top end the through-hole is closed by a semipermeable membrane 320. Thus, a compartment is formed inside the through-hole between the foil 330 and the membrane 320, in which the lyophilized drug substance is arranged. Furthermore, a thorn 340 is positioned at the upper sheet inside the second compartment.

[0088] In use of the kit 10, a user manually opens the compartment of the lyophilisate container 30 by pressing the thorn 340 into the foil 310. Then the user manually compresses the first compartment 210 of the infusion bag 20 such that the frangible seal between the first and second compartments 210, 220 opens. The diluent 250 streams into the second compartment 220 and dissolves the drug formulation 350 inside the compartment of the lyophilisate container 30 such that a drug solution is

obtained. The dissolving of the drug formulation 350 can be assisted by the user shaking the infusion bag 10 in case that the drug substance is not prone to shaking movements. Then the user compresses the second compartment 220 such that the right frangible seal 230 ruptures and the first compartment 210, the second compartment 220 and the outlet compartment 260 together form a common compartment. The infusion bag 10 is then hanged port 240 down on a support and an intravenous device is attached to the port 240. Thereby, the infusion bag 10 is changed to a single compartment infusion bag and can be applied as known in the art.

[0089] Fig. 3 shows a third embodiment of a kit 16 according to the invention which includes a flexible container in the form of an infusion bag 26 and a lyophilisate container 36 according to the invention. The infusion bag 26 has a first compartment 216 housing a liquid diluent 236. The first compartment 216 is generated by sealing two sheets of a flexible plastic material at their peripheral edges. In particular, firm seal seams are established along the edges.

[0090] In a front section of the flexible container 26 a lyophilisate container 36 is placed in a receiver plug 226, which is in fluid connection with the first compartment 216. The lyophilisate container 36 has a cylindrical shape and is dimensioned corresponding to the receiver plug 226. In particular, the lyophilisate container 36 is dimensioned to suit into the receiver plug 226. More specifically, it is inserted to a certain extent into the receiver plug 226 close to a separating barrier 246. At its bottom end it is closed by a non-permeable peelable foil 336. In between the foil 336 and a pointy tapered thorn 316 a lyophilisate compartment 246 is formed which houses a highly potent lyophilized drug formulation 326 as lyophilisate.

[0091] In use of the infusion bag 26, a user manually pushes the lyophilisate container 36 into the port 226. Thereby, the thorn 316 of the lyophilisate container 36 ruptures the membrane 246 such that the diluent flows into the compartment 326 of the lyophilisate container 36. Thereby, the drug formulation 326 is reconstituted and a drug solution is generated inside the infusion bag 26. After ensuring that the solution is completely mixed, the port 256 is connected to an intravenous device. Thereby, the infusion bag 26 can be applied as a known single compartment infusion bag.

[0092] In Fig. 4 a fourth embodiment of a kit 17 according to the invention which includes a flexible container in the form of an infusion bag 27 and a lyophilisate

container 37 according to the invention is shown. The infusion bag 27 has a first compartment 217 housing a liquid diluent 237, a second compartment 227 with a receiver plug 257. The first compartment 217 and the second compartment 227 are separated from each other by a frangible seal 267. Otherwise, the compartments 217, 227 are formed in two sheets of a flexible plastic material by providing firm seals along the edges and the frangible seal 267 in an appropriate manner. Centrally, a port 247 is provided to the first compartment 217 which is in selective fluid connection with the first compartment 217. The port 247 is embodied to be connected to a structure or device for intravenous administration.

[0093] In use, the lyophilisate container 37 is plugged into the receiver plug 257 and opened towards the second compartment 227. By this insertion the lyophilisate container 37 and the compartment 227 create a through-hole that enables the connection of those two. Then, the user compresses the first compartment 217 such that the frangible seal 267 opens and one single common compartment is generated. Then the diluent is mixed with a drug formulation 317 initially located inside the lyophilisate container 37 such that a drug solution is generated inside the common compartment.

[0094] All seals involved in the embodiments of flexible containers described herein can be obtained by a process or step of attaching two or more elements or portions of a flexible sheet-like material such that a gas, a liquid or another fluid cannot pass the attached portions. In embodiments where the flexible sheet-like material is a foil and particularly a plastic foil, the sealing can be provided by applying a predefined temperature/energy and/or pressure at a particular location of the foil. Thereby, the foil can be coated with an adhesive which is thermo- and or pressure-activatable. Alternatively or additionally, the sealing can involve ultrasound-, high frequency- and or radio frequency welding. In order to generate firm seals and frangible seals the temperature/energy and/or pressure can be adjusted such that the aimed properties result.

[0095] Fig. 5 shows a fifth embodiment of a kit 18 according to the invention which includes a flexible container in the form of an infusion bag, a tube 28 and a pad 38 as a lyophilisate container according to the invention. The tube 28 has a lower collecting compartment 218 and an upper flushing portion 228. In the flushing portion 228 there is a receptacle slit 238. The pad 38 comprises an upper flexible sheet 318 and a lower

flexible sheet 328 as wall which are attached to each other by peripheral seal seams along the edges. The lower flexible sheet 328 comprises a semipermeable membrane allowing vapour permeation out of the compartment. Between the sheets 318, 328 a compartment is formed in which a lyophilized drug formulation 338 is arranged as lyophilisate.

[0096] In use, the pad 38 is introduced into the slit 238 and the upper sheet 318 is pierced or stripped. Then a diluent is flushed from the flushing portion 228 through the pad 38 which dissolves the drug formulation 338. The solution is then filtered through the semipermeable membrane of the lower sheet 328 and gathered in the collecting compartment 218. As the need may, an additional pad having the same drug formulation can then be processed the same way to adjust a dosage of the drug formulation in the solution gathered in the collecting compartment 218 and/or an additional pad having another substance can be processed the same way to generate a combined drug formulation solution in the collecting compartment 218. The lower end of the tube 28 is provided with a connector or port to be coupled to an infusion bag or the like.

[0097] In Fig. 6 a sixth embodiment of a kit 19 according to the invention which includes a flexible container in the form of an infusion bag and a lyophilisate container 39 according to the invention is shown. The lyophilisate container 39 has a cylindrical inner encasing 319 and a cylindrical outer encasing 329. The inner encasing 319 consists of a frame structure 3119 by means of which a semipermeable membrane 3129 is spanned. Thereby, the semipermeable membrane 3129 covers the interior of the frame structure 3119. In particular, the frame structure 3119 is embodied with a flattened top ring, a flattened bottom ring and vertical bars extending between and connecting the rings. Furthermore, the bottom ring is equipped with a transparent and heat conducting foil such that a compartment is generated in the inner encasing 319 in which a lyophilized highly potent drug formulation 379 is positioned as lyophilisate and such that a visual control as well as an improved heat transfer can take place. By the positioning of the membrane 3119 the drug formulation 379 is only in contact with the membrane 3119 but not with the frame structure 3129. The top ring is open such that the interior of the inner encasing 319 is accessible top down. The semipermeable membrane 3129 is oriented such that vapour can escape from the inside of the inner

encasing 319 but permeation of vapour to the inside of the inner encasing 319 is restricted or prevented.

[0098] The outer encasing 329 consists of a rigid cylinder having a bottom and an open upper end side. The inner encasing 319 is coaxially plugged into the outer encasing 329. The inner and outer encasings 319, 329 are dimensioned in a way that there is a free room or volume between the inner encasing 319 and the outer encasing 329.

[0099] The inner and outer encasings 319, 329 are coupled to each other by an outer lid 369. Further, there is an inner lid 339 provided to the inner encasing 319 that in its centre is connected to a top coupler 349. The top coupler is hollow and allows the transfer of substances into the inner encasing 319. At the bottom of the outer encasing 329 a bottom coupler 359 is provided.

[00100] In preparation of the lyophilisate container 39, the drug formulation 379 is lyophilized inside the inner encasing 319. Thereby, vapour escapes through the membrane 3129 and also possibly through the top coupler 349. More specifically, since the overall area of the membranes 3129 is comparably large and due to the close contact between the drug formulation 379 and a freeze drying shelve, an efficient lyophilisation can be achieved.

[00101] As shown in Fig. 7, in use, the lyophilisate container 39 is plugged to an infusion bag 29 as flexible container by means of the top coupler 349 and its bottom coupler 359. More specifically, the infusion bag 29 has a first compartment 219 filled with a diluent 239 and a second compartment 229. The diluent 239 is provided from the first compartment 219 via a first tube and the top coupler 349 into the inner encasing 319, where the drug formulation 379 is dissolved. The created drug solution 249 is then filtered through the membrane 3129 into the room between the inner encasing 319 and the outer encasing 329. From there it is provided through the bottom coupler 359 and a second tube 269 into the second compartment 229 of the infusion bag 29 where it is collected.

[00102] In an alternative use, multiple containers 39 are coupled in a sequence to the infusion bag. Thereby, the containers can be filled with the same drug formulation 379

to adjust the dosage within the drug solution or with a different drug formulation to be mixed with the drug formulation 329.

[00103] This description and the accompanying drawings that illustrate aspects and embodiments of the present invention should not be taken as limiting-the claims defining the protected invention. In other words, while the invention has been illustrated and described in detail in the drawings and foregoing description, such illustration and description are to be considered illustrative or exemplary and not restrictive. Various mechanical, compositional, structural, electrical, and operational changes may be made without departing from the spirit and scope of this description and the claims. In some instances, well-known circuits, structures and techniques have not been shown in detail in order not to obscure the invention. Thus, it will be understood that changes and modifications may be made by those of ordinary skill within the scope and spirit of the following claims. In particular, the present invention covers further embodiments with any combination of features from different embodiments described above and below. For example, whereas most examples described above are involving a drug formulation it is possible to operate the invention as well in non pharmaceutical applications such as in nutrition, chemical processes, analytical methods or similar.

[00104] The disclosure also covers all further features shown in the Figs. individually although they may not have been described in the afore or following description. Also, single alternatives of the embodiments described in the figures and the description and single alternatives of features thereof can be disclaimed from the subject matter of the invention or from disclosed subject matter. The disclosure comprises subject matter consisting of the features defined in the claims or the exemplary embodiments as well as subject matter comprising said features.

[00105] Furthermore, in the claims the word "comprising" does not exclude other elements or steps, and the indefinite article "a" or "an" does not exclude a plurality. A single unit or step may fulfil the functions of several features recited in the claims. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. The terms “essentially”, “about”, “approximately” and the like in connection with an attribute or a value particularly also define exactly the attribute or exactly the value, respectively. The term “about” in the context of a given numerate value or range refers to a value or range that is, e.g., within 20%, within 10%, within 5%, or within 2% of the given value or

range. Components described as coupled or connected may be electrically or mechanically directly coupled, or they may be indirectly coupled via one or more intermediate components. Any reference signs in the claims should not be construed as limiting the scope.

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CLAIMS

Claim 1: A lyophilisate container (3; 30; 36; 37; 38; 39) comprising

a compartment;

a wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129) limiting the compartment; and

a lyophilisate (34; 350; 326; 317; 338; 379) arranged inside the compartment,

wherein at least a portion of the wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129) is semipermeable allowing vapour permeation in one direction out of the compartment through the wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129) and preventing vapour permeation in an opposite direction into the compartment through the wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129).

Claim 2: The lyophilisate container (3; 30; 36; 37; 38; 39) of claim 1, wherein the wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129) comprises a semipermeable membrane which is vapour permeable in the one direction and vapour tight in the other direction.

Claim 3: The lyophilisate container (3; 30; 36; 37; 38; 39) of claim 2, wherein the wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129) comprises a frame structure (3119) by means of which the semipermeable membrane is spanned.

Claim 4: The lyophilisate container (3; 30; 36; 37; 38; 39) of any one of the preceding claims, comprising an outer encasing (329) and an inner encasing (319) positioned inside the outer encasing (329), wherein the wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129) is a portion of the inner encasing (319).

Claim 5: The lyophilisate container (3; 30; 36; 37; 38; 39) of claim 4, wherein the compartment is arranged in between the outer encasing (329) and the inner encasing (319), and the at least a portion of the wall (31, 32, 33; 310, 320, 330;

336; 318, 328; 3119, 3129) is oriented to allow vapour permeation in the one direction from the compartment to the inner encasing (319) through the wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129) and to prevent vapour permeation in the opposite direction from the inner encasing (319) to the compartment through the wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129).

Claim 6: The lyophilisate container (3; 30; 36; 37; 38; 39) of claim 4, wherein the compartment is arranged in the inner encasing (319), and the at least a portion of the wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129) is oriented to allow vapour permeation in the one direction from the compartment to between the outer encasing (329) and the inner encasing (319) through the wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129) and to prevent vapour permeation in the opposite direction from between the outer encasing (329) and the inner encasing (319) to the compartment through the wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129).

Claim 7: The lyophilisate container (3; 30; 36; 37; 38; 39) of any one of claims 4 to 6, wherein the outer encasing (329) or the inner encasing (319) has a conical lateral area.

Claim 8: The lyophilisate container (3; 30; 36; 37; 38; 39) of claim 2 or 3, comprising a rigid body (31; 310) having a hole opening at one end side of the body and extending from the one end side of the body to the an other end side of the body, wherein the hole forms the compartment and the semipermeable membrane is attached to the body (31; 310) thereby closing the hole at the one end side of the body (31; 310).

Claim 9: The lyophilisate container (3; 30; 36; 37; 38; 39) of claim 8, comprising a non-permeable foil (33; 330; 336) having a high thermal conductivity, wherein the foil is attached to the body (31; 310) thereby closing the through-hole at the other end side of the body (31; 310).

Claim 10: The lyophilisate container (3; 30; 36; 37; 38; 39) of claim 8 or 9, wherein the body (31; 310 has a conical lateral area.

Claim 11: The lyophilisate container (3; 30; 36; 37; 38; 39) of any one of claims 1 to 3, being a pad-like structure, wherein the compartment is formed in between two sheets (318, 328) and at least one of the two sheets is the wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129).

Claim 12: The lyophilisate container (3; 30; 36; 37; 38; 39) of any one of the preceding claims, wherein the lyophilisate (34; 350; 326; 317; 338; 379) is a lyophilised drug formulation, in particular, the lyophilisate (34; 350; 326; 317; 338; 379) is a highly potent drug formulation, wherein, more particularly, the lyophilised drug formulation comprises a biological component.

Claim 13: An infusion kit comprising a lyophilisate container (3; 30; 36; 37; 38; 39) according to any one of the preceding claims, a lyophilised drug formulation positioned in the lyophilisate container (3; 30; 36; 37; 38; 39) and a flexible container (2; 20; 26; 27) having a first compartment (21; 216; 217; 219) filled with a reconstitution liquid and a port (23; 240; 226; 256; 247), in particular, the flexible container comprises a second compartment (220; 229) separated from the first compartment (21; 216; 217; 219) by a frangible seal (230) and the lyophilisate container (3; 30; 36; 37; 38; 39) is arranged inside the second compartment (220; 229) of the flexible container (2; 20; 26; 27), more particular, the lyophilisate container (3; 30; 36; 37; 38; 39) is embodied in the port (23; 240; 226; 256; 247) of the flexible container (2; 20; 26; 27).

Claim 14: The infusion kit of claim 13, wherein the port has a first mounting structure and the lyophilisate container (3; 30; 36; 37; 38; 39) has a corresponding second mounting structure such that the lyophilisate container (3; 30; 36; 37; 38; 39) is mountable to the flexible container (2; 20; 26; 27) to expel the liquid through the lyophilisate container (3; 30; 36; 37; 38; 39).

Claim 15: A method of preparing a lyophilisate container (3; 30; 36; 37; 38; 39) according to any one of claims 1 to 12, comprising

positioning a moist substance inside a compartment of the lyophilisate container (3; 30; 36; 37; 38; 39) limited by a wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129) limiting the compartment, wherein at least a portion of the wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129) is semipermeable

allowing vapour permeation in one direction out of the inside of the compartment through the wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129) and preventing vapour permeation in an opposite direction into the inside of the compartment through the wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129);

closing the compartment of the lyophilisate container (3; 30; 36; 37; 38; 39); and

lyophilising the moist substance in the compartment such that vapour permeates out of the inside of the compartment through the wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129).

Claim 16: Use of a lyophilisate container (3; 30; 36; 37; 38; 39) according to any one of claims 1 to 12, comprising reconstituting the lyophilisate (34; 350; 326; 317; 338; 379) of the lyophilisate container (3; 30; 36; 37; 38; 39) in a liquid inside the compartment of the lyophilisate container (3; 30; 36; 37; 38; 39), and filtering the liquid solution comprising the reconstituted lyophilisate (34; 350; 326; 317; 338; 379) through the wall (31, 32, 33; 310, 320, 330; 336; 318, 328; 3119, 3129) of the compartment.

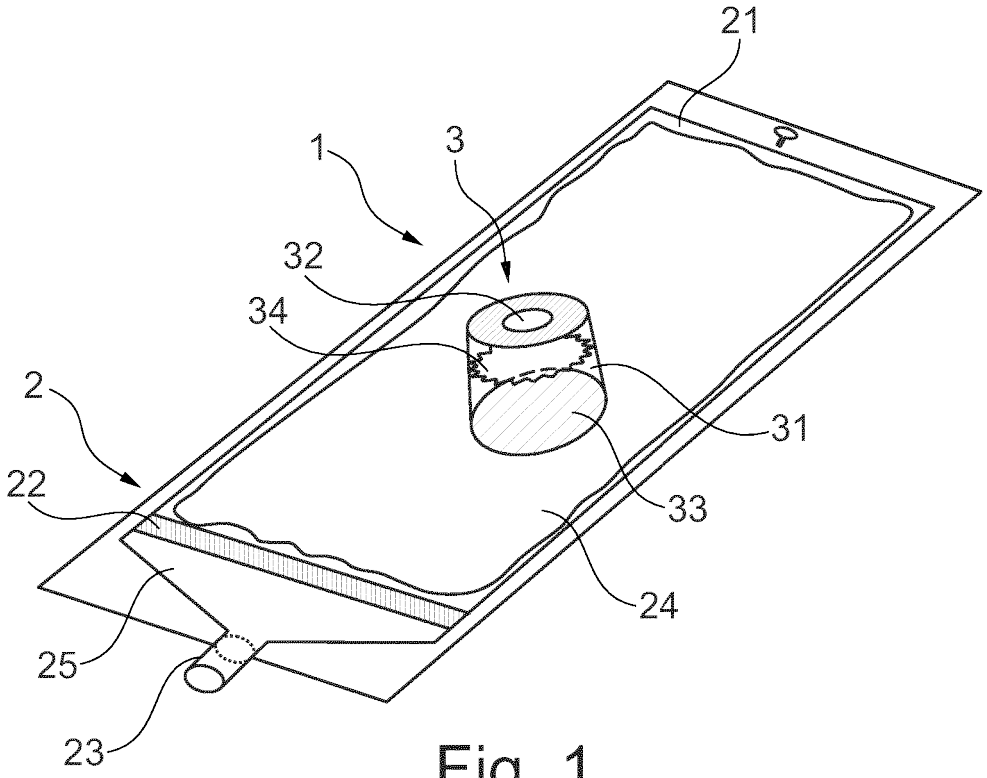
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Fig. 1

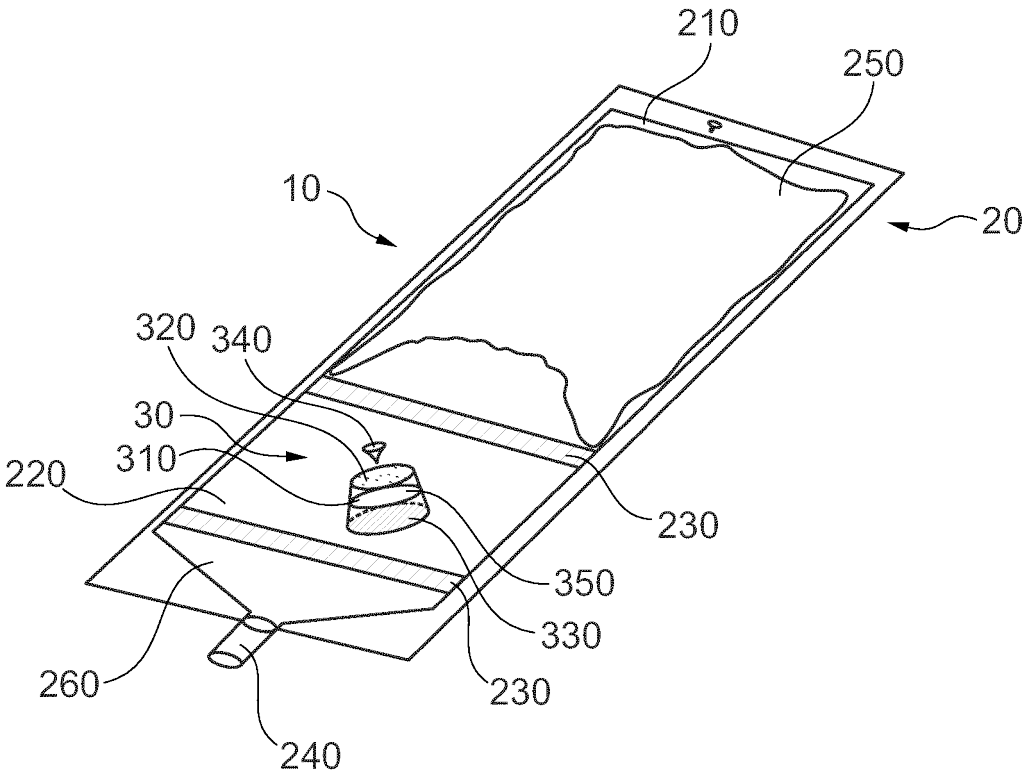
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Fig. 2

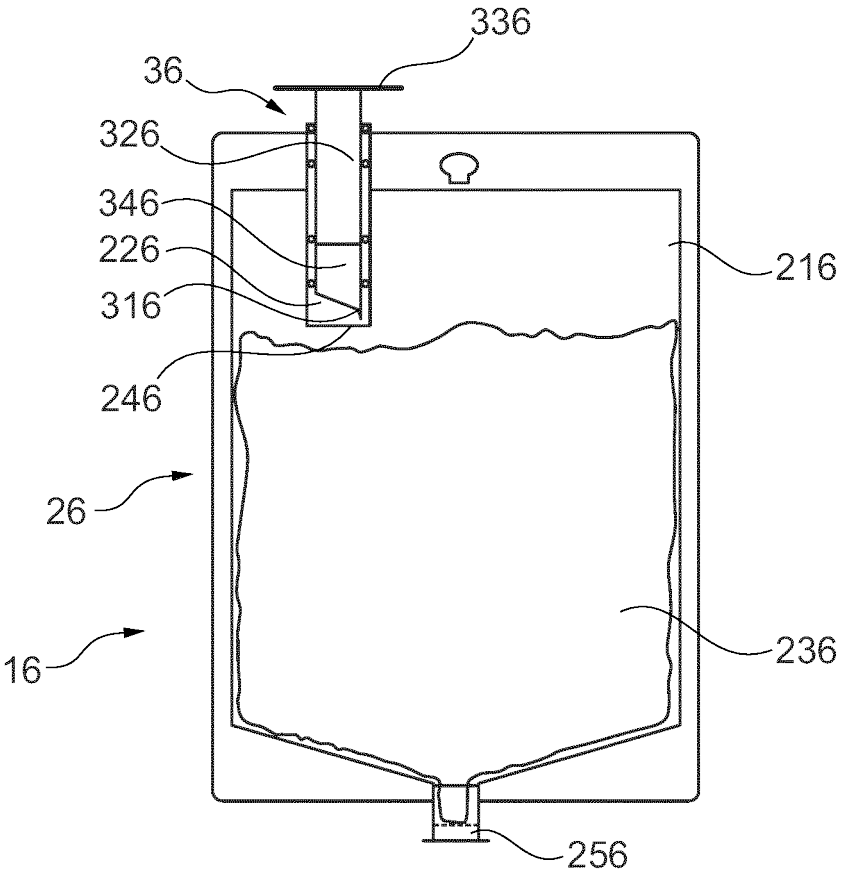
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Fig. 3

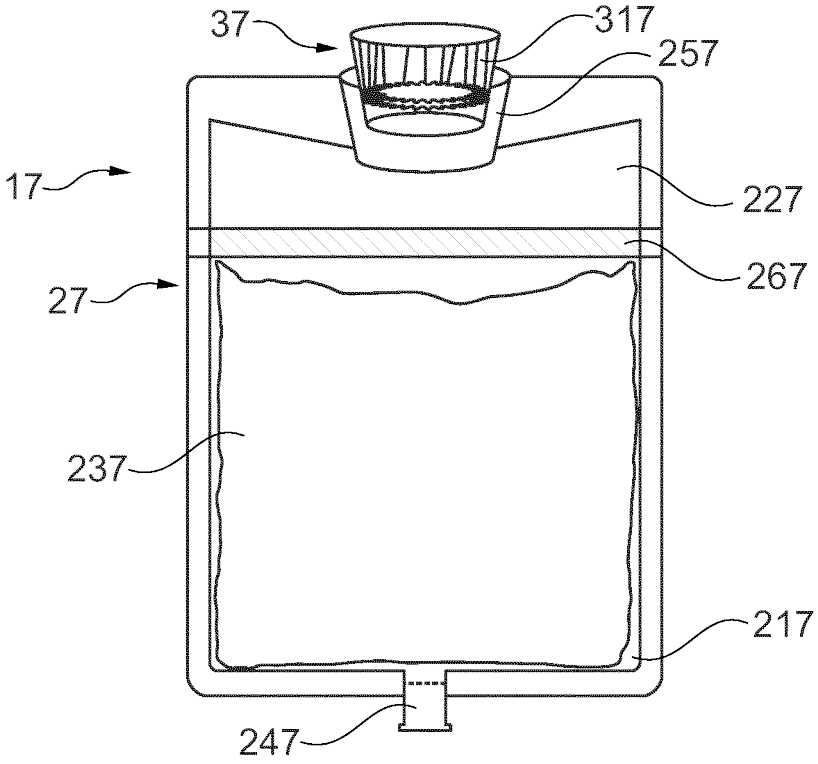
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Fig. 4

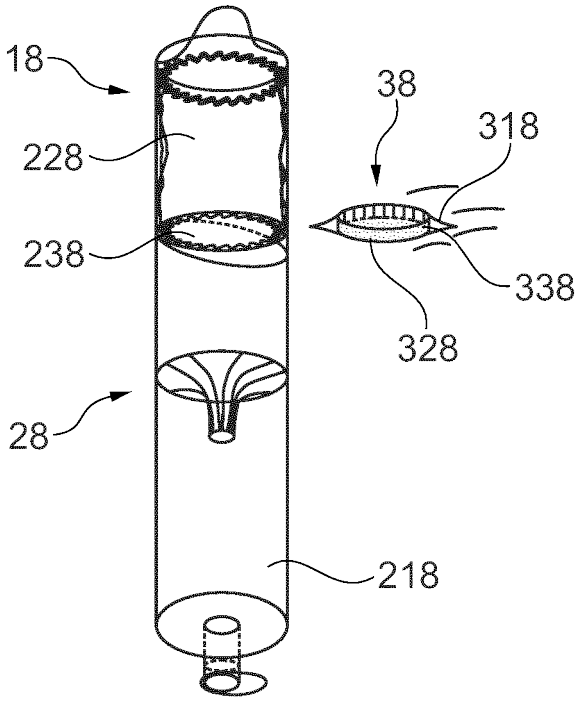
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Fig. 5

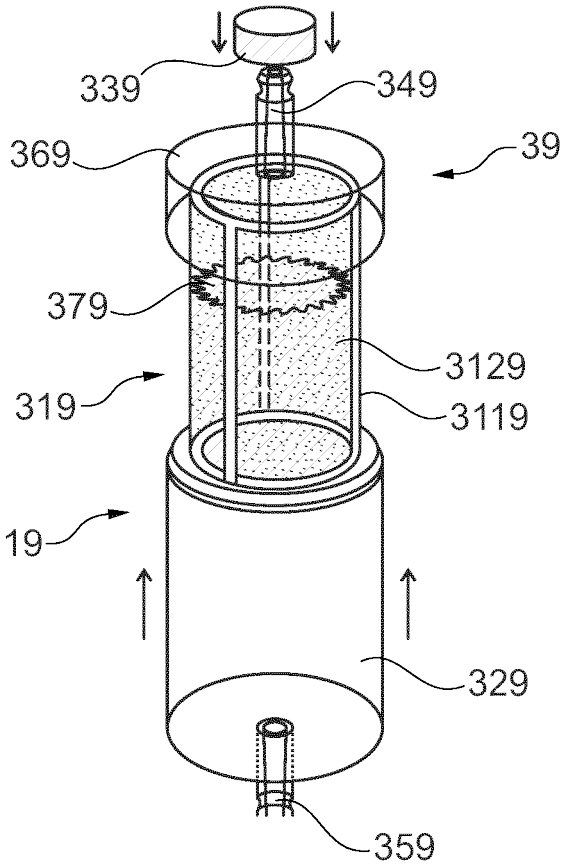
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Fig. 6

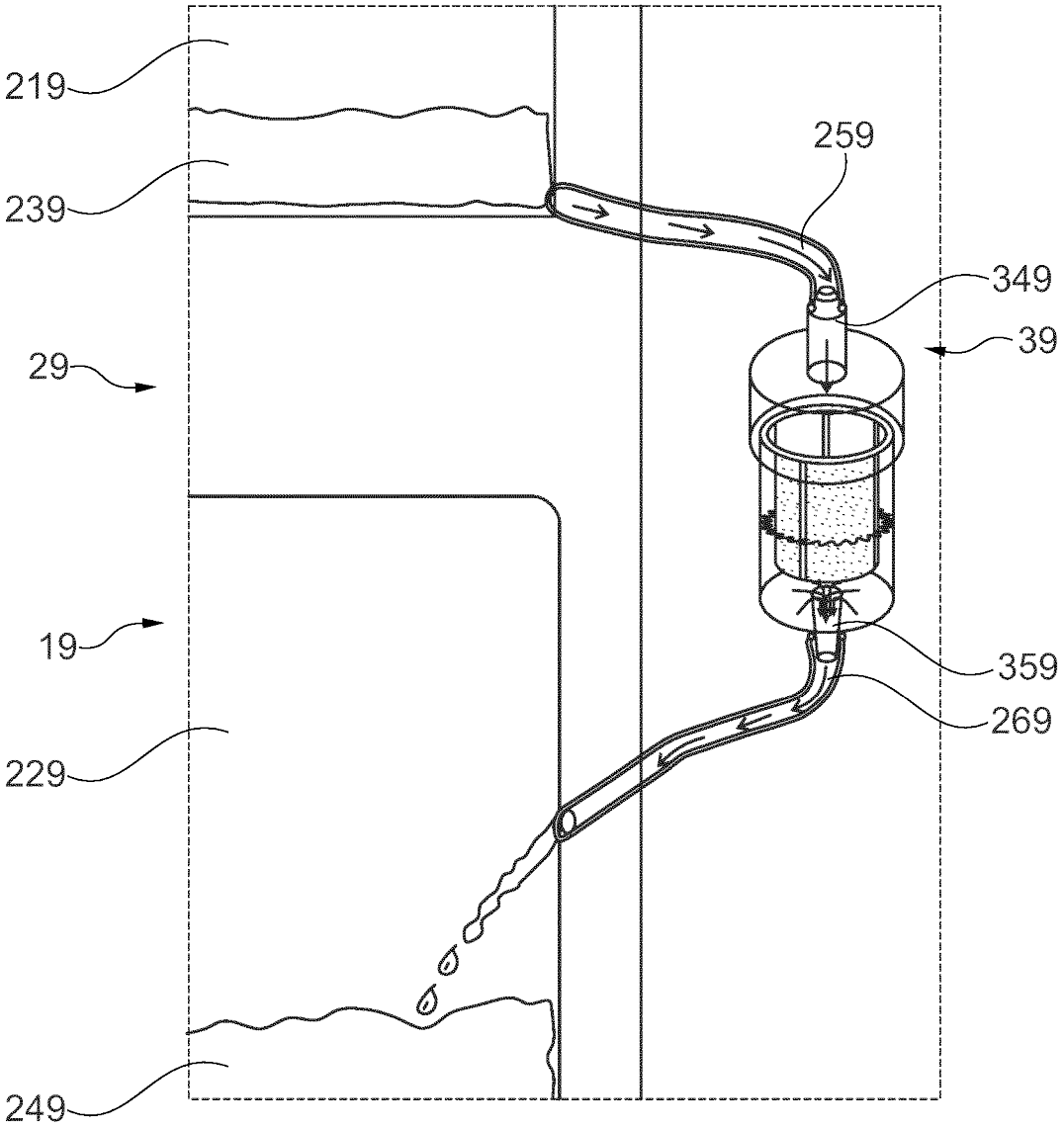

Fig. 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/082340

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61J1/10 A61J1/16 A61J1/20
ADD. A61J1/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/186183 A1 (DEANGELO JOSEPH [US] ET AL) 25 August 2005 (2005-08-25)	1,2,4-7, 11,12, 15,16
Y	paragraph [0002] paragraph [0025] paragraph [0052] - paragraph [0053] paragraph [0057] paragraph [0064] figures 1-3	3

Y	US 2015/158652 A1 (ROOT HOWARD [US] ET AL) 11 June 2015 (2015-06-11) paragraph [0066] - paragraph [0068] figure 7	3

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 February 2020	25/02/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schiffmann, Rudolf

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/158973 A2 (AKTIVPAK INC [US]; GENOSAR AMIR [US]) 22 November 2012 (2012-11-22) page 25 - page 63 figures 1-34	1
A	US 2009/107001 A1 (MCCARTHY SIMON J [US]) 30 April 2009 (2009-04-30) the whole document	1-7,11, 12,15,16
X	US 5 522 155 A (JONES C BRADFORD [US]) 4 June 1996 (1996-06-04) column 1, line 12 - line 32 column 3, line 30 - column 4, line 31 column 5, line 8 - line 15 figures 1, 5-7, 13	8-10
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1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2019/082340

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-16

   lyophilisate container

1.1. claims: 1-7, 11, 12, 15, 16

   lyophilisate container compartment wall which is semipermeable for vapour

1.2. claims: 8-10

   rigid body for lyophilisate container

1.3. claims: 13, 14

   infusion kit comprising a flexible container having two compartments separated by a frangible seal

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2019/082340

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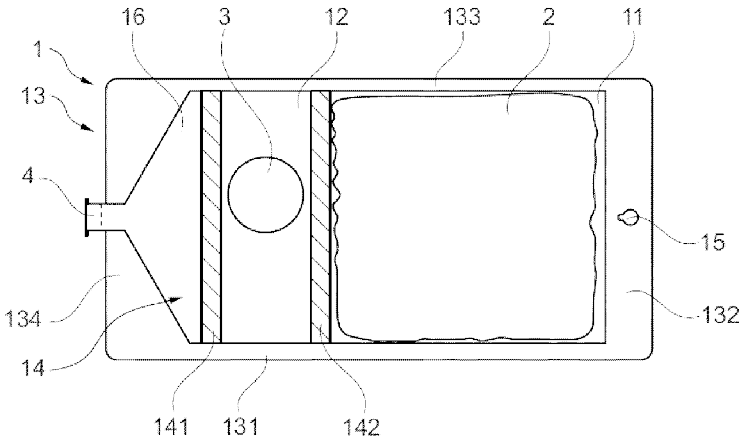

Fig. 2

(57) Abstract: A method of manufacturing a flexible container (1) housing a drug substance, comprises: forming a first compartment (11) of the container (1) out of a flexible sheet-like material, filling a liquid (2) into the first compartment (11) of the container (1), sealing the first compartment (11), forming a second compartment (12) of the container (1) out of the flexible sheet-like material, filling a dry drug formulation (3) into the second compartment (12), and sealing the second compartment (12). The method further involves lyophilizing the drug formulation inside a tubular cartridge such that the dry drug formulation (3) is generated and held in the tubular cartridge, wherein filling the dry drug formulation (3) into the second compartment (12) comprises: introducing the tubular cartridge holding the dry drug formulation (3) through an opening of the second compartment (12) of the container (1) such that an open end of the tubular cartridge is positioned distant from the opening of the second compartment (12), providing the dry drug formulation (3) out of the open end of the tubular cartridge into the second compartment (12), and withdrawing the tubular cartridge out of the opening of the second compartment (12) of the container (1). The first compartment (11) is separated from the second compartment (12) by a frangible seal (14) which opens when the first compartment (11) is compressed.

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[Continued on next page]

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

DESCRIPTION

Title

MANUFACTURING A FLEXIBLE CONTAINER

Technical Field

[0001] The present invention relates to a method of manufacturing a flexible container housing a drug substance according to the preamble of independent claim 1. Such methods comprising the steps of (i) forming a first compartment of the container out of a flexible sheet-like material, (ii) filling a liquid into the first compartment of the container, (iii) sealing the first compartment, (iv) forming a second compartment of the container out of the flexible sheet-like material, (v) filling a dry drug formulation into the second compartment, and (vi) sealing the second compartment, can provide the drug substance in a securely storable and conveniently applicable form, particularly for parenteral or intravenous administration.

Background Art

[0002] In many medical applications, pharmaceuticals or drug substances are provided in liquid form. Thereby, it can be advantageous to orally, parenterally, intravenously or subcutaneously administer the liquid drug substance. The drug substance has to be stored and supplied in a sterile fashion. Therefore, the drug substances are typically provided in appropriate containers. For example, for intravenous administration it is known to use infusion bags which can be hanged on a support and continuously drop the liquid drug substance or a drug diluent mixture through an infusion needle into a patient.

[0003] However, in connection with liquid drug substances, many pharmaceuticals and particularly biopharmaceuticals cannot be stored and supplied for an appropriate duration in liquid form since they commonly are unstable in that form. For example, many antibiotics or other biological drugs are unstable in liquid form such that their

quality cannot be maintained as liquid. In particular, stress caused by shaking, microbiological growth, aggregation or the like may compromise the drugs. In this context, it is known to supply the drug in a dry form, such as in a powder or the like, in which they are essentially more stable and robust compared to its liquid form. The dry drug formulation is then reconstituted or dissolved shortly before administration.

[0004] In the context of infusion bags, EP 1 364 638 A1 describes a flexible container with two compartments. In particular, an infusion bag made of two inter-sealed sheets is shown having one compartment filled with a liquid diluent and another compartment filled with a dry drug formulation. The two compartments are separated by a peelable seal which can be ruptured by applying a pressure on one of the compartments. Like this, an operator can mix the dry drug product with the diluent in a sterile fashion shortly before administration after manually pressing one of the compartments such the peelable seal ruptures and transferring the liquid to the dry drug product.

[0005] However, even though two compartment flexible containers known in the art often are beneficial in medical applications, they typically are not suitable for highly potent lyophilized drug formulations. In particular, usually the drug compartment is filled via an opening between the sheets and then this compartment is sealed. In such known filling processes often some drug formulation escapes the compartment during filling or is captured in the seal in between the sheets when closing the opening. Particularly, when lyophilized drug products which usually are cake-shaped are involved, filling the compartment of a flexible container can be difficult. Moreover, since highly potent drugs are usually provided at comparably small dosages, loss of small amounts of the drug can affect the treatment, already.

[0006] Therefore, also in infusion applications, highly potent lyophilized substances are today commonly provided in vials. Before administration they are dissolved by adding the diluent and then the dissolved drug formulation is transferred into an infusion bag. However, such administration may be comparably dangerous during preparation, involves a comparably high amount of steps which may be time consuming, may require an appropriate infrastructure, generates comparably delicate waste and is comparably prone to misuse or other issues affecting the quality of the medical treatment. Particularly, if comparably poorly specialised persons are involved or the environment does not allow appropriate application, such as it often the case in rather low and middle income countries, the treatment by infusion may be inappropriate.

[0007] Therefore, there is a need for a method of efficiently and safely manufacturing a flexible container, which allows the provision of a highly potent drug formulation together with a suitable diluent or constituent.

Disclosure of the Invention

[0008] According to the invention this need is settled by a method as it is defined by the features of independent claim 1. Preferred embodiments are subject of the dependent claims.

[0009] In particular, the invention is a method of manufacturing a flexible container housing a drug substance. This method comprises the steps of: forming a first compartment of the container out of a flexible sheet-like material; filling a liquid into the first compartment of the container; sealing the first compartment; forming a second compartment of the container out of the flexible sheet-like material; filling a dry drug formulation into the second compartment. Thereby, typically before filling into the second compartment, the drug formulation is lyophilised inside a tubular cartridge such that the dry drug formulation is generated and held in the tubular cartridge. More specifically, filling the dry drug formulation into the second compartment comprises: introducing the tubular cartridge holding the dry drug formulation through an opening of the second compartment of the container such that an open end of the tubular cartridge is positioned distant from the opening of the second compartment; providing the dry drug formulation out of the open end of the tubular cartridge into the second compartment; and withdrawing the tubular cartridge out of the opening of the second compartment of the container. The first compartment is separated from the second compartment by a frangible seal which opens when the first compartment is compressed.

[0010] The sequence of the steps involved in the method according to the invention can be different than listed hereinbefore. In particular, it is possible to first filling the second compartment and then filling the first compartment, vice versa, or to fill both compartments simultaneously. Advantageously, all or plural compartments are created prior to filling them in order to reduce the risk of product transfer. Also, as an alternative to performing one step after the other, some steps of the method can be executed in parallel, simultaneously or in one unified step. For example, the steps of filling the first and second compartments can be performed in parallel. Or, the steps of sealing the first

and second compartments can be unified in one single step in which both compartments are sealed at the same time.

[0011] Filling of the first and second compartments can be performed from any side best suiting to the overall process. For example, the first compartment can be filled from a side, which is then sealed by the frangible seal separating the first and second compartments. Or, both compartments can be filled from a lateral side of the container either one after the other or simultaneously, which lateral side is the firmly sealed after the compartments are filled.

[0012] The liquid involved in the method can particularly be a reconstituent such as a diluent, i.e. a liquid suitable for diluting the dry drug formulation when being mixed. Such diluent can be a physiological solution such as a sodium chloride (NaCl) solution, a sucrose solution, an aqueous dextrose or any other similar solution. The NaCl solution can, e.g., be a 0.9% NaCl solution. The sucrose solution can, e.g., be a 5% sucrose solution. The aqueous dextrose can, e.g., be a 10% dextrose solution.

[0013] The term "drug" as used herein relates to a therapeutically active agent, also commonly called active pharmaceutical ingredient (API), as well as to a combination of plural such therapeutically active substances. The term also encompasses diagnostic or imaging agents, like for example contrast agents (e.g. MRI contrast agents), tracers (e.g. PET tracers) and hormones, that need to be administered in liquid form to the patient.

[0014] The term "drug formulation" as used herein relates to a single drug as defined above or a plurality of such drugs mixed or formulated. For example, besides the drug, a drug formulation may additionally comprise an excipient and/or other auxiliary ingredients.

[0015] The term "dry drug formulation" relates to a solid drug formulation as it typically results from lyophilizing, i.e. a lyophilisate. It can also relate to or comprise a semisolid or powderous drug substance. When being held in the tubular cartridge, the dry drug formulation can have a shape of the interior volume of the cartridge or a section thereof. After being transferred into the second compartment of the container, it can still have the same shape or it can disaggregate, e.g., into a powder or fractioned structure.

[0016] The term "drug substance" as used herein relates to a drug formulation as defined above in a form that is suitable for administration to the patient. Thereby, the drug substance can be the pure drug formulation or a drug formulation reconstituted, diluted or dissolved in an administrable form. A particularly preferred drug substance in the context of the invention is a solution, in particular a solution for oral, parenteral, intrathecal or ophthalmic administration, injection or infusion.

[0017] The term "drug product" as used herein relates to a finished end product comprising a drug substance or a plurality of drug substances. In particular, a drug product may be a ready to use product having the drug substance in an appropriate dosage and/or in an appropriate form for administration. For example, a drug product may include a handling or storage device such as a flexible container.

[0018] Lyophilisation in the context of the present invention is a low temperature dehydration process, which involves freezing the substrate, i.e. the drug formulation, lowering pressure and then removing ice by sublimation and desorption. The result from lyophilisation is the lyophilisate. Lyophilisation is also referred to as freeze-drying. When being lyophilised inside the cartridge, the drug formulation can be held by friction or a similar mechanism inside the tubular cartridge. Lyophilisation can cover bulk freeze drying, which may produce lyophilized microspheres, or spray drying.

[0019] The term "flexible" as used in connection with the material or the container can relate to a comparably soft material which is not shape stable. Particularly, such material does usually not keep its shape when being differently positioned or oriented. Typical flexible materials are foils and particularly plastic foils or foil like structures such as tight meshes or the like.

[0020] The term "sheet-like" as used in connection with the material the container is made of relates to a flat typically essentially even substrate having a thickness which is considerably smaller than its length and width. In particular, the sheet-like material can be a foil or a similar structure.

[0021] The sheet-like material can be a sheet-like single plastic, composite, plastic blend or multilayer plastic. It can be altered in its surface properties to improve extractability, to reduce or exclude gas permeation and leaching of additives and/or to simplify sealing. The sheet-like material needs to be compatible with its intended

purpose such as compatible with parenteral or oral solutions, nonreactive when chemicals are stored in the container and/or aligned to required guidelines applicable to the drug substance, e.g., the guidelines of the Unites States Food and Drug Administration (FDA) or the guidelines of the European Medicines Agency (EMA).

[0022] The term "sealing" as used herein relates to a process or step of attaching two or more elements or portions of an element to each other such that a gas, a liquid or another fluid cannot pass the attached portions. In embodiments where the flexible sheet-like material is a foil and particularly a plastic foil, the sealing can be provided by applying a predefined temperature and/or pressure at a particular location of the foil. Thereby, the foil can be coated with an adhesive which is thermo- and or pressure-activatable. Alternatively or additionally, the sealing can involve ultrasound-, high frequency- and or radio frequency welding. In particular, sealing can involve creating seal seams. The seal seam can be embodied as firm seals and/or frangible seal. The term "frangible seal" relates to a connection in the flexible sheet-like material which can be released, broken or ruptured when compressing a compartment adjacent to the frangible seal. Frangible seals can also be referred to a peelable seal, non-permanent weak seals or breakable seal.

[0023] Specifically, forming the first and second compartments can be embodied by positioning two foils or sheets at each other and then sealing the two foils along the edges of the foils or at any other appropriate portion. Alternatively or additionally, one single foil or sheet can be folded in a suitable manner and then sealed along the edges of the foil or at any other appropriate portion. The compartments can be sized for the filling of 20 ml up to 2'000 ml. In the end the container can be a bag or bag-like device such as an infusion bag, a pouch or similar.

[0024] Compressing the first compartment can be achieved, e.g., by applying a pressure to the first compartment. In particular, in use of the container the first compartment can be manually compressed such that the frangible seal opens and the liquid is transferred from the first compartment into the second compartment. Thereby, the seals of the container other than the frangible seal can stay tightly closed.

[0025] The term "positioned distant" in connection with the open end of the tubular cartridge and the opening of the second compartment relates to an arrangement in which the opening is not contacting the open end of the tubular cartridge. In particular,

whereas the opening of the second compartment may be contacting the outer cartridge, the open end is not in contact or directly adjoining the opening. More specifically, the distance between the open end of the cartridge and the opening of the compartment is sufficient to prevent any drug formulation to be located in or at the opening or even outside the second compartment after removal of the cartridge and during the opening of the second compartment is sealed. Like this, it can be achieved that no drug formulation gets outside the packaging, that drug formulation is located in the sealing such that the sealing of the second compartment is weakened, and that the amount of drug formulation or the dosage of the drug substance can be precisely determined.

[0026] The tubular cartridge typically is made of an essentially rigid material. It can particularly have a comparably high thermal conductivity and, more specifically, a thermal conductivity which is higher than the thermal conductivity of glass. The thermal conductivity of glass can be 1.05 W/mK at 25°C. The inside of the tubular cartridge can be coated with a friction reducing coating or friction reducing layer facilitating the complete withdrawal of drug formulation.

[0027] The method according to the invention allows to efficiently and safely manufacture a flexible container such as an infusion bag providing a sensible drug substance. In particular, the manufactured container can house a highly potent drug formulation and a suitable diluent separated from the drug formulation during supply. Before administration the drug formulation can conveniently be reconstituted by mixing the liquid with the dry drug formulation. More specifically, the liquid can be provided from the first compartment to the second compartment by manually compressing the first compartment. Like this, the pressure inside the first compartments increase, the frangible seal breaks and opens, and the liquid flows into the second compartment. Such easy preparation of the drug substance can be executed by comparably low trained or low skilled persons. The risk of misuse can considerably be lowered. Also, preparation time, human error, e.g. by product identification, preparation, dosage, etc., probability or waste generation can be considerably low in comparison to the known methods.

[0028] As mentioned, the drug formulation preferably is a high potency drug formulation. It can particularly comprise a biological component such as a monoclonal antibody, an antibody drug conjugate, an antibody fragment, a locked nucleic acid (LNA) or the like. The term “potency” in this context can be a measure of drug activity

expressed in terms of the amount required to produce an effect of given intensity. Thus, the terms "high potency", "highly potent" or similar can relate to a formulation or substance which is active at comparably small amounts or dosages. In other words, a highly potent drug formulation can evoke a given response at comparably low concentration, while a drug formulation of lower potency can evoke the same response only at higher concentrations. The potency may depend on both the affinity and efficacy of the drug formulation. Thereby, such drug formulations or substances can be particularly problematic since comparably small variations in dosing or comparably small contaminations can be comparably effective.

[0029] In numbers, a highly potent drug formulation can be defined as a drug formulation having a biological activity at approximately 15 micrograms (µg) per kilogram (kg) of body weight or below in humans. This is equivalent to a therapeutic dose at approximately 1 milligrams (mg) or below in humans. The highly potent drug formulation can thus be defined as a drug having an inhalative Acceptable Daily Exposure (ADE) value of 1.5 µg/d or less, translating into an Indicative Occupational Exposure Limit (IOEL) value of 0.15 µg/m^3. In particular, the highly potent drug formulation can be a class 3B drug or the like. When used with highly potent drug formulations to be administered by infusion, the method according to the invention can be particularly beneficial.

[0030] Preferably, the liquid in the first compartment comprises a solvent for solving the dry drug formulation. The solvent can be a diluent or a similar liquid. By solving the drug formulation, it can be administered in a particularly suitable form at a specific dosage.

[0031] Preferably, the tubular cartridge is essentially cylindrical. The term "essentially cylindrical" can relate to forms slightly deviating from a geometrical cylinder. In particular, a cylinder being conical to a certain extent may still be essentially cylindrical. E.g., a conical cylinder having a sidewall slanted to a maximum of about 5°, about 3° or about 2° can still be essentially cylindrical. Also, the sidewall of the tubular cartridge may differ to a certain extent from a geometrical straight shape. The tubular cartridge can be embodied as a hollow cylinder wherein the open end is located at one end of the cylinder.

[0032] Preferably, the tubular cartridge has a conical shape widening towards the open end of the tubular cartridge. The conical shape of the cartridge can also be embodied over a portion of it only such that it has straight and conical sections. Such partial conical shape allows for the tubular cartridge still being essentially cylindrical. As mentioned above, even when the tubular cartridge is conical, i.e. being completely widening or having a widening section, it can still be essentially cylindrical since its main appearance can still be as a cylinder. In particular, the tubular cartridge can be slightly conical, i.e. widening to a comparably small extent only. Such tubular cartridge allows for efficiently providing the dry drug formulation. In particular, since the cartridge widens, the dry drug substance can loose its hold inside the cartridge when being forwarded and exit out of the open end. For example, the dry drug formulation can be pushed for releasing it from the cartridge and then, due to the conical shape, it is not hindered or held by the rest of the cartridge such that a more or less complete provision of the dry drug substance can efficiently be achieved.

[0033] Preferably an inner wall of the tubular cartridge is coated with a friction reducing material. Like this, the provision of the dry drug formulation out of the open end can be comparably efficient. It allows for reducing a residual portion of the drug formulation in the tubular cartridge.

[0034] Preferably, providing the dry drug formulation out of the open end of the tubular cartridge into the second compartment comprises forwarding a plunger through the tubular cartridge towards the open end such that the dry drug formulation is pushed out of the open end of the cartridge. This allows for an efficient provision of the drug formulation with comparable simple means.

[0035] Preferably, forming the first compartment of the container comprises sealing the flexible sheet-like material such that a firm seal is generated which does not open when the first compartment is compressed. Like this, the first compartment and also the complete container can be safely sealed or closed towards the outside of the container. Only, within the container between the compartments the frangible seal(s) allows for being opened without damaging the container.

[0036] Thereby, the firm seal preferably is generated by sealing the flexible sheet-like material at first conditions and the frangible seal is generated by sealing the flexible sheet-like material at second conditions different from the first conditions. For examples,

the conditions can comprise an energy such as heat, ultrasound or the like, and/or pressure which is/are lower in the first conditions than in the second conditions.

[0037] Preferably, the second compartment has an opposite end at a maximum distance to the opening of the second compartment, and the dry drug formulation is provided out of the open end of the tubular cartridge into the second compartment near the opposite end of the second compartment. The term "near" in this connection can relate to a position at or close to the opposite end. In particular, it can relate to a position closer to the opposite end than to the opening. In particular, the tubular cartridge can be entered through the opening to a comparably large extent into the second compartment before providing the dry drug formulation. Like this, the risk of any residual drug formulation at the opening of the second compartment or even outside the container can considerably be lowered.

[0038] Advantageously, the container is equipped with a port. Such port can be attached after the sheet-like material is sealed. However, preferably, forming the second compartment of the container comprises sealing the port to the flexible sheet-like material such that a content of the second compartment can be expelled through the port. The port can be of any kind suitable for the intended application of the container. It can be a spout, a septum enabling withdrawal of liquid while preventing unintended spilling, or an adapter for being connected to another element such as an infusion tube or the like. For example, the port can be or comprise a long cylindrical opening or a septum that enables withdrawal of liquid while assuring protection from unintended spilling. These withdrawal supports are usually found in infusion bags, septum bottles, or squeeze pouches for nutrition. Advantageously, the port is made of a comparably rigid material which essentially keeps its shape when being sealed to the sheet-like material. Furthermore, additional elements like stoppers, septa or diaphragms can be sealed in the material, typically during a final welding step. Such a port allows for conveniently administering the drug substance, e.g. in an aseptic manner, after being prepared inside the container. In particular, the port allows for embodying the container to be suitable for a specific type of administration such as infusion. In addition to the port, other ports can be attached in the proximity of the port or on the opposing border of the flexible container. Also, ports can be placed into the edges of a vertical line or seam seal directed from top to bottom. To facilitate the attachment of ports on the lateral edges of the flexible sheets forming the flexible container, punctures in the sheet

can be required where ports can be placed prior the final welding of the container takes place. The port/ports within the flexible container can manage the connectability to other containers or to devices used for administering or provision of the content of the flexible container.

[0039] In a preferred embodiment, the method further comprises: forming a third compartment of the container out of the flexible sheet-like material; lyophilizing a further drug formulation inside a further tubular cartridge such that the dry further drug formulation is generated and held in the further tubular cartridge; filling the dry further drug formulation into the third compartment by introducing the further tubular cartridge holding the dry further drug formulation through an opening of the third compartment of the container such that an open end of the further tubular cartridge is positioned distant from the opening of the third compartment, providing the dry further drug formulation out of the open end of the further tubular cartridge into the third compartment, and withdrawing the further tubular cartridge out of the opening of the third compartment of the container; and sealing the third compartment.

[0040] The third compartment can be separated from the first compartment and/or the second compartment by a frangible seal which opens when the respective compartment is compressed. Further, the container can have an additional compartment filled with the liquid or another liquid and separated from the third compartment by a frangible seal. The other liquid can also be a reconstituent as the liquid of the first compartment. It can also be a liquid drug or a similar substance.

[0041] The further drug formulation can be the same as the drug formulation. In such embodiments, the two or more compartments of containing the same drug formulation can be used to adapt a dosage of the drug substance before administration. In particular, as the need may be, the drug formulation of an appropriate number of compartments can be solved before administration such that the overall dosage can be set.

[0042] The further drug formulation can also be different from the drug formulation. For example, the further drug formulation can be required for a specific treatment in addition to the drug formulation but not suitable to be stored together with the drug formulation. In such a case, by providing plural individual compartments, the plural drug formulations

can be mixed shortly before administration in one of the drug substance compartments, in a common compartment or in an empty compartment, e.g., positioned in between.

[0043] In some embodiments, the container can be equipped with a plurality of additional compartments each filled with a predefined amount of the drug formulation or with another drug formulation to be mixed with the drug substance before administration. Also, the container can have one or more additional compartments which are empty. Such compartment allows for (pre-)mixing before administration.

[0044] The compartments can be positioned anywhere in the container. For example, for allowing a particularly efficient filling, the compartments can all extent to one side edge of the container such that the compartments may be filled from one side only. Or, for achieving a safe application of the container such as a particular sequence of activation, the compartments can be distributed in the container such as on opposite side edges thereof.

[0045] As mentioned above, the container preferably is an infusion bag. Such infusion bags allow for a particularly efficient intravenous administration of the drug substance over a specific period.

[0046] Preferably, the method comprises a visual inspection of the first compartment and the second compartment for particulate matter, which is performed after sealing the first compartment and the second compartment. Such visual inspection can be implemented automatically by an appropriate device or by a person. It allows for maintaining high quality standard as it is required for pharmaceutical products. For example, such visual inspection allows for ensuring the reference standard 788 of the United States Pharmacopeia (USP).

[0047] Thereby, the first compartment and the second compartment and, eventually, any further compartments, preferably are at least partially or completely transparent. Such transparent compartments allow for an efficient visual inspection.

[0048] Preferably, the method is implemented in a blow fill and seal (BFS) process. Generally, BFS relates to a manufacturing technique used to produce liquid-filled containers. It is widely considered to be the superior form of aseptic processing by various medicine regulatory agencies including the U.S. Food and Drug Administration (FDA) in the packaging of pharmaceutical and healthcare products. The basic concept

of BFS is that a container is formed, filled, and sealed in a continuous process without human intervention, in a sterile enclosed area inside a machine. Therefore, this technique can be used to aseptically manufacture sterile pharmaceutical liquid dosage forms. BFS may reduce personnel intervention making it a more robust method for the aseptic preparation of sterile drug substances. Thus, such process allows for a particularly efficient manufacture of the container in a quality sufficient to be a drug product.

Brief Description of the Drawings

[0049] The method according to the invention and the thereby manufactured flexible containers are described in more detail herein below by way of exemplary embodiments and with reference to the attached drawings, in which:

Fig. 1 shows a flow scheme of a first embodiment of a method of manufacturing a flexible container according to the invention;

Fig. 2 shows a flexible container manufactured by the method of Fig. 1;

Fig. 3 shows a flow scheme of a second embodiment of a method of manufacturing a flexible container according to the invention;

Fig. 4 shows a flexible container manufactured by the method of Fig. 3;

Fig. 5 shows a tubular cartridge as it can be used in the first method of Fig. 1 or in the second method of Fig. 3 before lyophilization;

Fig. 6 shows the tubular cartridge of Fig. 5 after lyophilization.

Description of Embodiments

[0050] In the following description certain terms are used for reasons of convenience and are not intended to limit the invention. The terms “right”, “left”, “up”, “down”, “under“ and “above“ refer to directions in the figures. The terminology comprises the explicitly mentioned terms as well as their derivations and terms with a similar meaning. Also, spatially relative terms, such as "beneath", "below", "lower", "above", "upper", "proximal", "distal", and the like, may be used to describe one element's or feature's relationship to another element or feature as illustrated in the figures. These spatially relative terms are intended to encompass different positions and orientations of the devices in use or operation in addition to the position and orientation shown in the figures. For example, if a device in the figures is turned over, elements described as "below" or "beneath" other elements or features would then be "above" or "over" the

other elements or features. Thus, the exemplary term "below" can encompass both positions and orientations of above and below. The devices may be otherwise oriented (rotated 90 degrees or at other orientations), and the spatially relative descriptors used herein interpreted accordingly. Likewise, descriptions of movement along and around various axes include various special device positions and orientations.

[0051] To avoid repetition in the figures and the descriptions of the various aspects and illustrative embodiments, it should be understood that many features are common to many aspects and embodiments. Omission of an aspect from a description or figure does not imply that the aspect is missing from embodiments that incorporate that aspect. Instead, the aspect may have been omitted for clarity and to avoid prolix description. In this context, the following applies to the rest of this description: If, in order to clarify the drawings, a figure contains reference signs which are not explained in the directly associated part of the description, then it is referred to previous or following description sections. Further, for reason of lucidity, if in a drawing not all features of a part are provided with reference signs it is referred to other drawings showing the same part. Like numbers in two or more figures represent the same or similar elements.

[0052] Fig. 1 shows a first embodiment of a method of manufacturing an infusion bag as a flexible container housing a drug substance according to the invention. The method is embodied in a side fill and seal process or in a blow fill and seal (BFS) process in an at least partially aseptic environment. It comprises a step A in which two rectangular sheets of flexible plastic foil are arranged with their surfaces contacting each other as flexible sheet-like material. Thereby, the at least one of the sheets of foil is coated with an adhesive which is thermo- and pressure-activatable, wherein the coated surface of the sheets contacts the surface of the other sheet.

[0053] In a step B, two edges of the composition of the two sheets are pressurized at a first pressure and heated at a first temperature such that the sheets are bonded and sealed together at their edges. In particular, the first temperature and pressure are adjusted such that the seals generated in step B are firm seals. In a step C, a second pressure and a second temperature are applied which are lower than the first pressure and temperature, respectively. More specifically, the second temperature and pressure are applied such that two frangible seals are generated. By the two firm seals and the two frangible seals, a first compartment and a second compartment are formed between the sheets, which are separated from each other by one of the frangible seals. The first

compartment extends over about half of the two sheets. The first and second compartment are open towards the same longitudinal side of the container. In a step D a diluent is filled in liquid form into the first compartment.

[0054] Preferably in parallel to any of steps A to D, a dry drug formulation is prepared. Thereby, in a step E_i a highly potent biopharmaceutical drug formulation is positioned inside a tubular cartridge. In a step E_{ii}, the drug formulation is lyophilized inside the tubular cartridge in a way that the dry drug formulation is generated and held in the tubular cartridge. Then the lyophilized or dry drug formulation is filled into the second compartment by, in a step E_{iii}, introducing the tubular cartridge holding the dry drug formulation through an opening established by the open edges of the two sheets into the second compartment such that an open end of the tubular cartridge is positioned near an end of the second compartment opposite to the opening or compartment opening. Filling of the dry drug formulation further comprises a step E_{iv} of providing the content of the tubular cartridge by advancing a plunger through it, and a step E_v of withdrawing the tubular cartridge out of the opening of the second compartment as well as out of the container.

[0055] Following step E_{iv}, the first and second compartments are closed or sealed. In particular, in a step F the open side edge of the container is pressurized to the first pressure and heated to the first temperature such that the first and second compartments are closed by a firm seal. Then in a step G a rigid port is positioned between the non-sealed fourth edges of the two sheets. In a step H, these fourth edges are pressurized at the first pressure and heated at the first temperature such that the sheets are bonded and sealed together at their fourth edges. Thereby, a firm seal is established at the fourth edges. Alternatively, the rigid port can also be mounted in step B above.

[0056] In Fig. 2 a first embodiment of a flexible container according to the invention in the form of an infusion bag 1 is shown as it results from the method described above in connection with Fig. 1. The infusion bag 1 has a first compartment 11 housing a liquid diluent 2, a second compartment 12 housing a highly potent lyophilized drug formulation 3 and an outlet compartment 16. The compartments 11, 12, 16 are formed by generating firm seals 13 and frangible seals 14 in two sheets of a flexible plastic material in an appropriate manner. In particular, the first compartment 11 is formed by a lower longitudinal firm seal 131 extending along the infusion bag, a back firm seal 132,

an upper longitudinal firm seal 133 and a right frangible seal 142. The second compartment 12 is formed by the lower longitudinal seal 131, the right frangible seal 142, the upper longitudinal seal 133 and a left frangible seal 141. The outlet compartment 16 is formed by a front firm seal 134 and the left frangible seal 141.

[0057] Centrally in the front firm seal 134 a port 4 is mounted which is in fluid connection with the outlet compartment 16. The port 4 is embodied to be connected to a structure or device for intravenous administration. In the back firm seal 132 a hole 15 is provided for hanging the infusion bag 1 on an appropriate support.

[0058] In use of the infusion bag 1, a user manually compresses the first compartment 11 such that the pressure inside the first compartment 11 is raised. Caused by this pressure raise, the right frangible seal 142 ruptures such that the first compartment 11 and the second compartments 12 form a common compartment. In the common compartment, the diluent 2 and the lyophilized drug formulation 3 are then mixed. Such mixing can be assisted by manually shaking the infusion bag 1. Thereby, the lyophilized drug is diluted and a solution is generated as drug substance. The infusion bag 1 is then hanged port 4 down on the support and an intravenous device is attached to the port 4. Now, the left frangible seal 141 is raptured by manually applying a pressure to the common compartment. Thereby, the infusion bag 1 is changed to a single compartment infusion bag and can be applied as known in the art.

[0059] Fig. 3 shows a second embodiment of a method of manufacturing an infusion bag as a flexible container housing a drug substance according to the invention. The method is embodied in a side fill and seal process or in a blow fill and seal (BFS) process in an at least partially aseptic environment. The method of Fig. 3 comprises generally the same steps as the method described above in connection with Fig. 1. Thus, for aspects not described in the following, it is referred to the description relating to Fig. 1 above.

[0060] In contrast to the method of Fig. 1, in step B, firm seals are provided in the two sheets by appropriately pressurizing and heating the two sheets such that a first compartment, a third compartment and a fourth compartment are created. The two sheets are also pressurized and heated at lower pressure and temperature such that the third and fourth compartments are closed towards the first compartment by frangible seals. At the end of step B, the first compartment is open towards a front end as well as

the third and fourth compartments are open towards opposing lateral ends of the two sheets.

[0061] Further, in contrast to the method of Fig. 1, the method of Fig. 3 repeats steps E and F. More specifically, by repeatedly or parallely performing steps E_i and E_{ii} plural tubular cartridges of two different sizes holding a lyophilized highly potent biopharmaceutical drug formulation are provided. Then the lyophilized dry drug formulation is filled into the second, third and forth compartments by, in a step E_{iii}, introducing the tubular cartridges holding the dry drug formulation through respective openings of the second, third and fourth compartments. Then, in a step E_{iv} the content of the tubular cartridges is forwarded into the respective compartments, and in a step E_v the tubular cartridges are withdrawn out of the openings of the second, third and fourth compartments and out of the container.

[0062] Following step E, the second, third and fourth compartments are closed or sealed in a step F. In particular, the second pressure and the second temperature are applied such that a second frangible seal is generated closing the second compartment. Further, the first pressure and the first temperature are applied such that firm seals are generated closing the third and fourth compartments.

[0063] In Fig. 4 a second embodiment of a flexible container according to the invention in the form of an infusion bag 10 is shown as it results from the method described above in connection with Fig. 3. The infusion bag 10 has a first compartment 110 housing a liquid diluent 20, a second compartment 120 housing two large portions of a highly potent lyophilized drug formulation 310, a third compartment 160 housing one small portion of the highly potent lyophilized drug formulation 320, a fourth compartment 170 housing two small portions of the highly potent lyophilized drug formulation 330, and an outlet compartment 180.

[0064] The compartments 110, 120, 160, 170, 180 are formed by generating firm seals 130 and frangible seals 140 in an appropriate manner. In particular, a lower longitudinal firm seal 1310 extending along the infusion bag 10, a back firm seal 1320, an upper longitudinal firm seal 1330 and a front firm seal 1340 are generated. The first compartment 110 is separated from the second compartment 120 by right frangible seal 1410, from the third compartment 160 by an upper non-continuous frangible seal 1430, and from the fourth compartment 170 by a lower non-continuous frangible seal 1440.

The second compartment 120 is separated from the outlet compartment by a left frangible seal 1420.

[0065] Centrally in the front firm seal 1340 a port 40 is mounted which is in fluid connection with the outlet compartment 180. The port 40 is embodied to be connected to a structure or device for intravenous administration. In the back firm seal 1320 a hole 150 is provided for hanging the infusion bag 10 on an appropriate support.

[0066] In use of the infusion bag 10, a practitioner manually presses the first compartment 110 such that the pressure inside the first compartment 110 raises. Caused by this pressure raise, the right frangible seal 1410 ruptures such that the first compartment 110 and the second compartment 120 together form a common compartment. As the need may be, the dosage is adjusted by additionally rupturing the upper non-continuous frangible seal 1430 and/or the lower non-continuous frangible seal 1440. Like this, any or none of the small portions of the highly potent lyophilized drug formulation 320, 330 can be added to the common compartment. In the common compartment, the diluent 20 and the lyophilized drug formulation 30 are mixed. Thereby, the lyophilized drug is diluted and a solution is generated as final drug substance. After being visually inspected for proper mixing and absence of any visual particles, an intravenous device is attached to the port 40 and the left frangible seal 1420 is raptured by manually applying a pressure to the common compartment. Then, the infusion bag 10 is hanged port 40 down on the support.

[0067] In Fig. 5 a tubular cartridge 5 as it can be used in a method according to the invention is shown. The tubular cartridge 5 has a hollow and essentially cylindrical body 51 made of a material having a high thermal conductivity. Towards its lower end, the body 51 widens such that it comprises a conical section. Into the conical section of the body 51 a stopper 52 is provided for tightening the interior of the body 51. Inside the interior above the stopper 52 a liquid drug formulation is positioned.

[0068] The drug formulation is then lyophilized inside the tubular cartridge 5 such that a dry drug formulation 39 is generated as shown in Fig. 6. and held in the tubular cartridge. Before, filling the lyophilized or dry drug formulation 39 into a compartment of a flexible container the stopper 52 is removed. The dry drug formulation 39 is still held inside the body 51 by friction. The conical section of the body allows on one hand an efficient manipulation of the stopper 52 and on the other hand an efficient transfer of the

dry drug formulation out of the tubular cartridge 5. By using the tubular cartridge 5, it can be assured that the dry drug formulation 39 is provided inside the interior of the compartment distant from an edge thereof. Like this, contamination of the edge to be sealed or even loss of dry drug formulation out of the compartment can be prevented.

[0069] This description and the accompanying drawings that illustrate aspects and embodiments of the present invention should not be taken as limiting-the claims defining the protected invention. In other words, while the invention has been illustrated and described in detail in the drawings and foregoing description, such illustration and description are to be considered illustrative or exemplary and not restrictive. Various mechanical, compositional, structural, electrical, and operational changes may be made without departing from the spirit and scope of this description and the claims. In some instances, well-known circuits, structures and techniques have not been shown in detail in order not to obscure the invention. Thus, it will be understood that changes and modifications may be made by those of ordinary skill within the scope and spirit of the following claims. In particular, the present invention covers further embodiments with any combination of features from different embodiments described above and below.

[0070] The disclosure also covers all further features shown in the Figs. individually although they may not have been described in the afore or following description. Also, single alternatives of the embodiments described in the figures and the description and single alternatives of features thereof can be disclaimed from the subject matter of the invention or from disclosed subject matter. The disclosure comprises subject matter consisting of the features defined in the claims or the exemplary embodiments as well as subject matter comprising said features.

[0071] Furthermore, in the claims the word "comprising" does not exclude other elements or steps, and the indefinite article "a" or "an" does not exclude a plurality. A single unit or step may fulfil the functions of several features recited in the claims. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. The terms “essentially”, “about”, “approximately” and the like in connection with an attribute or a value particularly also define exactly the attribute or exactly the value, respectively. The term “about” in the context of a given numerate value or range refers to a value or range that is, e.g., within 20%, within 10%, within 5%, or within 2% of the given value or range. Components described as coupled or connected may be electrically or

mechanically directly coupled, or they may be indirectly coupled via one or more intermediate components. Any reference signs in the claims should not be construed as limiting the scope.

CLAIMS

Claim 1: A method of manufacturing a flexible container (1; 10) housing a drug substance, the method comprising:

forming a first compartment (11; 110) of the container (1; 10) out of a flexible sheet-like material,

filling a liquid (2; 20) into the first compartment (11; 110) of the container (1; 10),

sealing the first compartment (11; 110),

forming a second compartment (12; 120) of the container (1; 10) out of the flexible sheet-like material,

filling a dry drug formulation (3; 310, 320, 330) into the second compartment (12; 120), and

sealing the second compartment (12; 120),

characterized by comprising

lyophilizing the drug formulation inside a tubular cartridge (5) such that the dry drug formulation (3; 310, 320, 330) is generated and held in the tubular cartridge (5),

wherein filling the dry drug formulation (3; 310, 320, 330) into the second compartment (12; 120) comprises

introducing the tubular cartridge (5) holding the dry drug formulation (3; 310, 320, 330) through an opening of the second compartment (12; 120) of the container (1; 10) such that an open end of the tubular cartridge (5) is positioned distant from the opening of the second compartment (12; 120),

providing the dry drug formulation (3; 310, 320, 330) out of the open end of the tubular cartridge (5) into the second compartment (12; 120), and

withdrawing the tubular cartridge (5) out of the opening of the second compartment (12; 120) of the container (1; 10), and

wherein the first compartment (11; 110) is separated from the second compartment (12; 120) by a frangible seal (14; 140) which opens when the first compartment (11; 110) is compressed.

Claim 2: The method of claim 1, wherein the drug formulation is a high potency drug formulation preferably comprising a biological component.

Claim 3: The method of claim 1 or 2, wherein the liquid (2; 20) comprises a solvent for solving the dry drug formulation (3; 310, 320, 330).

Claim 4: The method of any one of the preceding claims, wherein the tubular cartridge (5) has a conical shape widening towards the open end of the tubular cartridge (5).

Claim 5: The method of any one of claims 1 to 3, wherein the tubular cartridge (5) is essentially cylindrical.

Claim 6: The method of any one of the preceding claims, wherein an inner wall of the tubular cartridge (5) is coated with a friction reducing material.

Claim 7: The method of any one of the preceding claims, wherein providing the dry drug formulation (3; 310, 320, 330) out of the open end of the tubular cartridge (5) into the second compartment (12; 120) comprises forwarding a plunger through the tubular cartridge (5) towards the open end such that the dry drug formulation (3; 310, 320, 330) is pushed out of the open end of the cartridge.

Claim 8: The method of any one of the preceding claims, wherein forming the first compartment (11; 110) of the container (1; 10) comprises sealing the flexible sheet-like material such that a firm seal (13; 130) is generated which does not open when the first compartment (11; 110) is compressed.

Claim 9: The method of claim 8, wherein the firm seal (13; 130) is generated by sealing the flexible sheet-like material at first conditions and the frangible seal (14; 140) is generated by sealing the flexible sheet-like material at second conditions different from the first conditions.

Claim 10: The method of any one of the preceding claims, wherein the second compartment (12; 120) has an opposite end at a maximum distance to the opening of the second compartment (12; 120), and the dry drug formulation (3; 310, 320, 330) is provided out of the open end of the tubular cartridge (5) into the second compartment (12; 120) near the opposite end of the second compartment (12; 120).

Claim 11: The method of any one of the preceding claims, wherein forming the second compartment (12; 120) of the container (1; 10) comprises sealing a port to the flexible sheet-like material such that a content of the second compartment (12; 120) can be expelled through the port.

Claim 12: The method of any one of the preceding claims, further comprising

forming a third compartment (160, 170) of the container (1; 10) out of the flexible sheet-like material,

lyophilizing a further drug formulation inside a further tubular cartridge (5) such that the dry further drug formulation is generated and held in the further tubular cartridge (5),

filling the dry further drug formulation into the third compartment (160, 170) by

introducing the further tubular cartridge (5) holding the dry further drug formulation through an opening of the third compartment (160, 170) of the container (1; 10) such that an open end of the further tubular cartridge (5) is positioned distant from the opening of the third compartment (160, 170),

providing the dry further drug formulation out of the open end of the further tubular cartridge (5) into the third compartment (160, 170), and

withdrawing the further tubular cartridge (5) out of the opening of the third compartment (160, 170) of the container (1; 10), and

sealing the third compartment (160, 170).

Claim 13: The method of any one of the preceding claims, wherein the container (1; 10) is an infusion bag (1; 10).

Claim 14: The method of any one of the preceding claims, comprising visually inspecting the first compartment (11; 110) and the second compartment (12; 120) for particulate matter, after sealing the first compartment (11; 110) and the second compartment (12; 120).

Claim 15: The method of claim 14, wherein the first compartment (11; 110) and the second compartment (12; 120) are at least partially transparent.

Claim 16: The method of any one of the preceding claims, implemented in a blow fill and seal process.

DRAWINGS

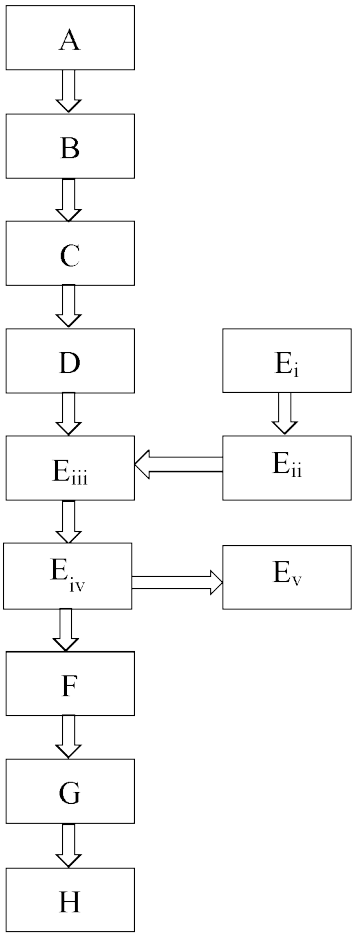

Fig. 1

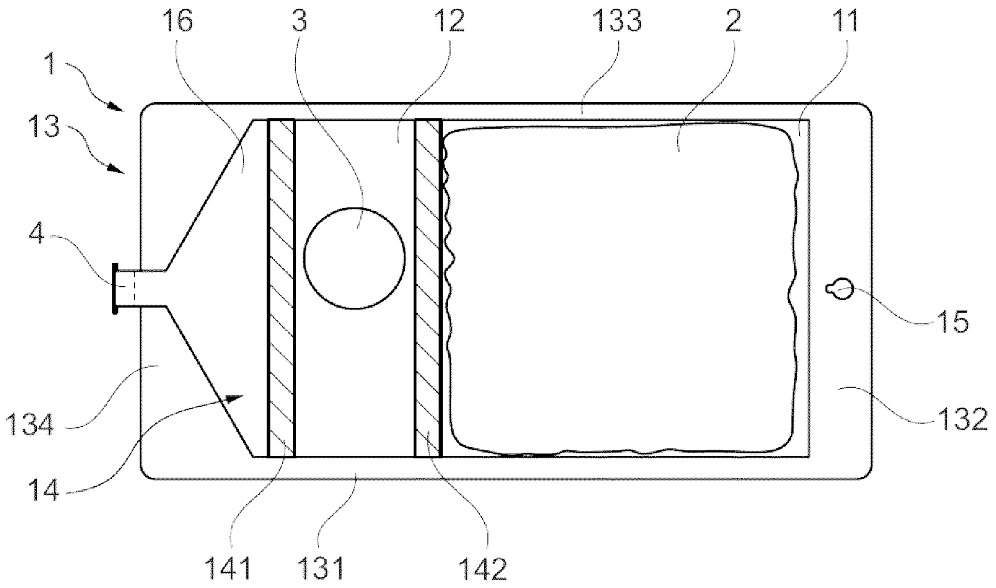
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Fig. 2

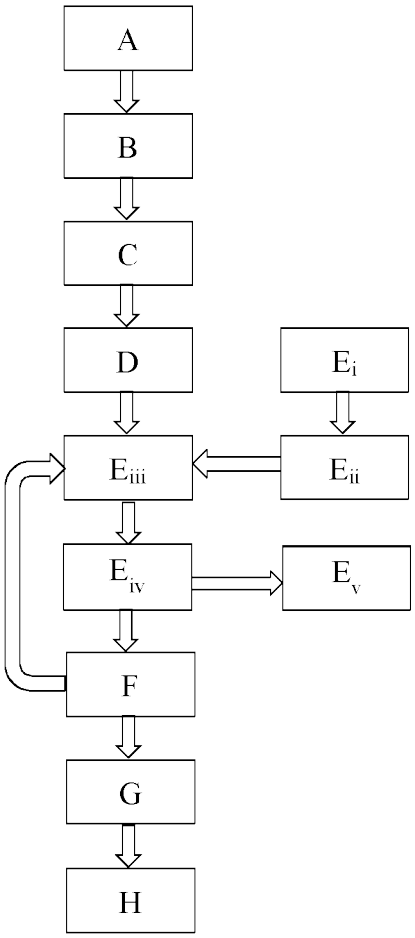
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Fig. 3

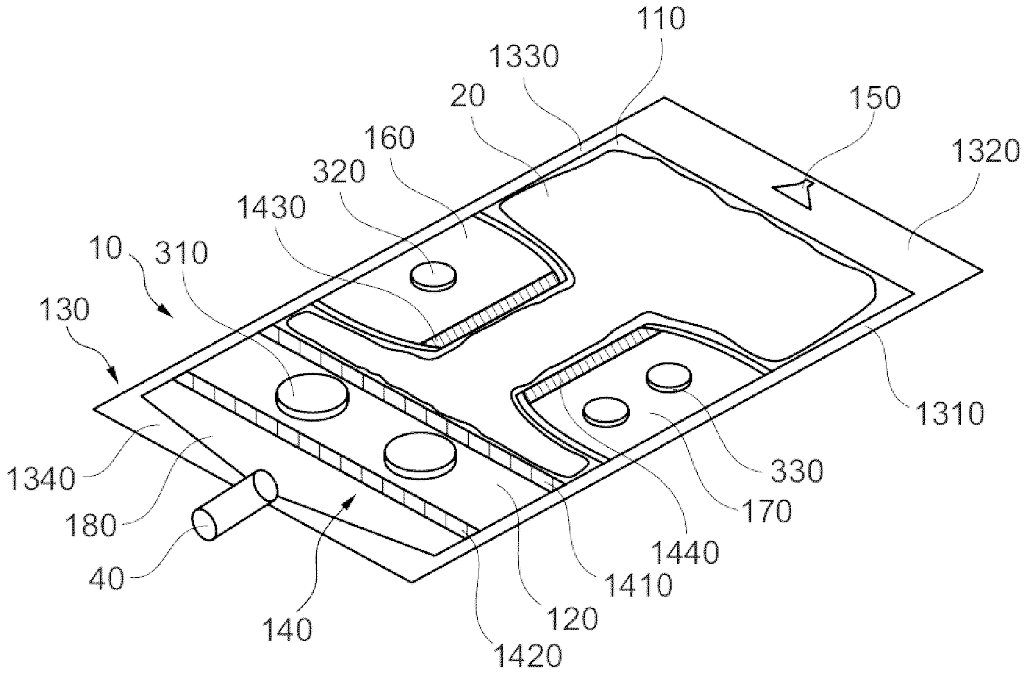

Fig. 4

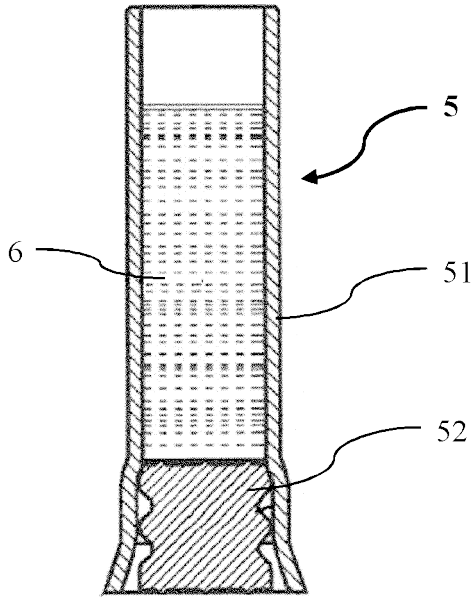

Fig. 5

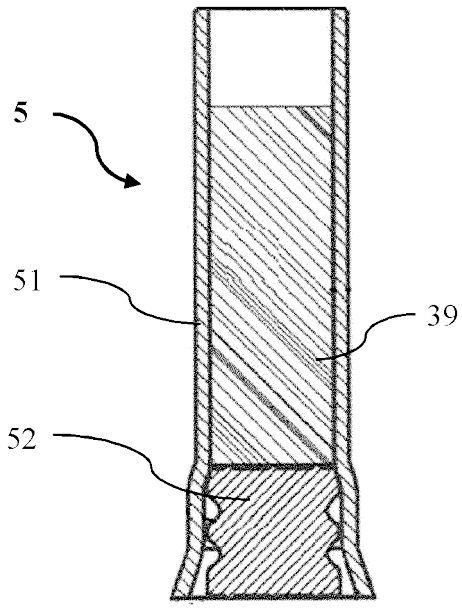

Fig. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/082342

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61J1/10 A61J1/14 A61J1/20
ADD. A61J1/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2009/223080 A1 (MCCARTHY SIMON J [US] ET AL) 10 September 2009 (2009-09-10) paragraph [0002] paragraph [0108] - paragraph [0160] figures 1-21 -----	1-11, 13-16 12
Y	EP 1 364 638 A2 (BRAUN MEDICAL INC [US]) 26 November 2003 (2003-11-26) cited in the application paragraph [0157] - paragraph [0162] figures 16-19 -----	12
A	US 2015/107195 A1 (TSAKAS SPYRIDON EDOUARD [US] ET AL) 23 April 2015 (2015-04-23) the whole document ----- -/--	1-16

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 February 2020	25/02/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schiffmann, Rudolf

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/082342

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003/175313 A1 (GARREC DOROTHEE LE [CA] ET AL) 18 September 2003 (2003-09-18) the whole document	1-16
A	US 9 931 458 B1 (DI NARO ANTONIO FRANCESCO [CH]) 3 April 2018 (2018-04-03) the whole document	1-16

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2019/082342

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Information on patent family members

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PERSONAL PROFILE

I am a pharmaceutical scientist with a penchant for tricky challenges, passionate about elucidating the root cause and tackling them with innovative solutions.

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Daniel Kullmann

SKILLS SUMMARY

- Lyophilization / Freeze-Drying
- Physico-chemical analysis of biologics
- Filing of IND submissions
- Sterile manufacturing & GMP
- Microsoft Office suite, Empower, Graphpad Prism, Zoom, JMP, etc
- Patent application drafting
- Meeting facilitator - Loop approach

LANGUAGES

- German
- English
- French

LEISURE

DR. DANIEL KULLMANN

ASSOCIATE PRINICIPAL SCIENTIST AT LONZA DRUG PRODUCT SERVICES

PROFESSIONAL EXPERIENCE

Associate Principal Scientist in Formulation Development
Lonza AG | June 2021 - present

- Development of biopharmaceutical drug product formulations for intravenous and subcutaneous applications
- Project management and coordination of project sub-teams

Industrial PhD student
F. Hoffmann - La Roche / Uni Basel | May 2017 - May 2021

- Coordination, conduction and execution of innovation projects
- Supervision and mentoring of interns

Internship
F. Hoffmann - La Roche / Uni Basel | Jan 2017 - Mai 2017

- Investigations into excipient crystallization propagation and influence of impurity spiking on crystal growth

Internship
F.Hoffmann - La Roche | Nov 2015 - Mai 2016

- Implementation of a novel crystallization method on lab scale
- Characterization of biologic and non-biologic parenteral formulations by spectroscopic and physico-chemical analytical methods
- Diafiltration, formulation and filling of biological drugs

Student employee
LMU Munich | Nov 2014 - Aug 2015

- Formulation development and release analytics for an intrauterine device for mares

ACADEMIC EDUCATION

University Basel - Division Pharmaceutical Technology
Doctorate in Pharmaceutical technology | Mai 2017 - May 2021

- PhD studies in collaboration with F. Hoffmann - La Roche on "Aseptically safe and fast administration of freeze dried drug products: Applications for emergency cases and tropical diseases" supervised by Prof. J. Huwyler

Ludwig Maximilians University Munich
Master of Science in Pharmaceutical Sciences | Oct 2014 - Dec 2016

- Masterthesis in collaboration with F. Hoffmann - La Roche on "Investigations into trehalose crystallization during frozen storage at lab scale" supervised by Prof. W. Friess

Ludwig Maximilians University Munich
Bachelor of Science in Pharmaceutical Sciences | Oct 2011 - Oct 2014

- Bachelorthesis in collaboration with NanoTemper on "Using microscale Thermophoresis (MST) and Intrinsic Fluorescence for Thermal Protein Unfolding and Aggregation Measurements" supervised by Prof. G. Winter

Basel, 11.05.2023