Understanding the functionality of MCC Rapid as an excipient for DC - Moving towards QbD

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Dekan

To my mum and dad

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1 TABLE OF CONTENTS

2 ABBREVIATIONS

QbD: Quality by design

DC: Direct compaction

DWT: Dwell time

ER: Elastic recovery

MCC: Microcrystalline cellulose

RH: Relative humidity

DSR: Dwell time sensitivity ratio

LSR: Lubricant sensitivity ratio

Mgstr: Magnesium stearate

USP: United States Pharmacopoeia

%(w/w): Percentage per weight

FDA: Food and Drug Administration

RPM: Revolution per minute

3 SUMMARY

Excipients have a valuable role in improving processability, and stability of a pharmaceutical dosage forms. Furthermore certain excipients have a valuable role in insuring bioavailability of the drug and reducing its side effects. Therefore fundamental understanding of the excipients functionality and factors affecting its performance in a formulation will reduce the numbers of trial and error experiments. This is in agreement with the PAT initiative quality by design.

The aim of this thesis was to investigate the functionality of MCC Rapid, a new cellulose II polymorph based excipient compared to conventional microcrystalline cellulose powder (MCC). MCC Rapid is intended to be used as an excipient for direct compaction (DC). Therefore the functionality of this excipient was evaluated through testing its manufacturability compared to MCC, which is a well known excipient for DC. Parameters such as compaction pressure and dwell time of the replicated rotary tabletting press, were taken into account. Mechanical properties of both excipients were also evaluated through drug loading with a poorly compactable model drug (Paracetamol fine powder).The disintegration effect of MCC Rapid and MCC was also evaluated. Ibuprofen (IBU) a low soluble drug was used to evaluate the disintegrating behavior of MCC Rapid and MCC. Also the hydrophobic effect of Mgstr on disintegration and dissolution was investigated at various IBU/excipient loadings. X-ray measurements of MCC Rapid and MCC confirmed the different polymorphic forms and showed a lower degree of crystallinity for MCC Rapid (68%) than for MCC (78%). Moisture sorption isotherms of both substance showed that MCC Rapid was more hygroscopic than MCC. This is explained due reasons, mainly MCC Rapid has different polymorphic structure, additionally the slight difference in the amorphous part could increase hygroscopicity of the powder.

Excipients for DC have different mechanical properties, depending on many factors related to its physical characterization, such as particle size and shape, as well as deformation mechanism of powder upon compaction and the extent of bonding between these particles. In order to understand the mechanical properties of MCC Rapid and MCC at real production parameters, compactibility and compressibility were studied with the aid of Presster™, a compaction press replicator. Therefore MCC Rapid mechanical properties were compared

to MCC at dwell times (DWT) of 118.3 and 9.5 ms, respectively. In overall both excipients proved to deform plastically. Despite the fact that the speed of tabletting press often influences mechanical properties of plastic deforming materials, the calculated compressibility parameters of Heckel and modified Heckel were not changed upon the change in DWT.

Internal lubrication of Mgstr affected only slightly the compressibility of MCC Rapid, exhibiting a decrease in friction between its elongated fibers and resulted in better powder densification. According to Leuenberger equation parameters, compactibility constants of MCC Rapid showed a good compactibility behavior compared to the extraordinary compactibility properties of MCC. Although MCC exhibited higher mechanical strength than MCC Rapid, both excipients had the same compactibility behavior upon the change in DWT. Internal lubrication with Mgstr, as expected, had a negative influence on the compactibility of both excipients. MCC Rapid had a higher surface area which was the reason behind its increased lubricity compared to MCC. Friability of MCC Rapid and MCC tablets crucially dependant on tablets relative density. Tablets of both excipients at relative density of 0.55 and higher had a low tendency towards friability. Additionally, DWT showed a significant effect only at tablets prepared at relative density of 0.45.

The results of elastic recovery revealed that MCC Rapid has exhibited higher tendency to recover elastically than MCC. Both Compaction Pressure (Indirectly the relative density) and DWT had an influence on the elastic recovery on both excipients for a certain limit. MCC Rapid was more affected by the change in DWT especially at higher relative densities. In case of MCC the increase in compaction pressure and subsequently the relative density, had increased the extent of elastic recovery regardless of DWT. According to Leuenberger equation, the compactibility constants of both excipients were gradually decreasing upon loading with Paracetamol. Investigations on the effect of DWT on the compactibility showed that MCC Rapid was more sensitive towards the change in DWT. The increase in sensitivity was correlated with the increase in Paracetamol loading until 60% (w/w). Further loading of Paracetamol led to sudden decrease in DWT sensitivity for both excipients, in which Paracetamol phase was dominating the physical properties of the tablet. In order to identify the influence of drug loading on the disintegration and

dissolution rate, tablet with the same properties were produced by DC. Disintegration and dissolution of MCC tablets loaded with IBU showed a great dependence on drug concentration. As only tablets containing 70%(w/w) and 90% (w/w) of IBU has been disintegrated, and had immediate release, therefore MCC can function as disintegrant only within these ratios. When MCC was loaded with low amounts of IBU, it functioned as a matrix forming agent, and it retarded the release of IBU. MCC Rapid containing tablets had an immediate and quick disintegration at all IBU loadings, and subsequently resulted in robust and fast drug release of IBU. The disintegration of MCC Rapid is due to increased water up take due to its increased hygroscopicity. Plus the fact the MCC Rapid particles showed more tendencies to have elastic recovery. This phenomenon provided more repulsion energy between the particles during disintegration and dissolution.

Incorporation of hydrophobic lubricants is known to influence the in-vitro performance of solid dosage forms. The addition of 0.5 % (w/w) Mgstr, a hydrophobic lubricant, showed no significant effect on the performance of MCC Rapid tablets loaded with IBU. This is due to the super-disintegration behavior exhibited by MCC Rapid which can overcome the effect of hydrophobic lubricants at the studied mixing conditions. MCC tablets containing IBU showed only a significant difference in drug release only at loading of 70% and 90%, in which these tablets exhibited higher dissolution release. This unexpected behavior can be due to the fact that the binding of the particle within the tablets were weakened enough to exhibit a higher disintegration and dissolution rates. Therefore it has hindered the effect of the hydrophobic effect of Mgstr. Investigations on the functionality of MCC Rapid revealed that MCC Rapid it is able to function as a multifunctional excipient (filler, binder, and disintegrant) for DC. MCC Rapid showed to be effective at all concentrations tested in tablet formulation despite of the tabletting process parameters. Internal lubrication showed to have a greater impact on the mechanical properties more than its disintegration behavior.

4 THEORETICAL SECTION

4.1 INTRODUCTION

4.1.1 FUNCTIONS AND PERFORMANCE OF EXCIPIENTS

Tablets or hard gelatin capsules ranked on the top of the medical marketed products [1]. Ideally, such dosage forms should deliver the drug precisely with the right amount to the right site in the body of the patient. Otherwise, therapeutic effect will not take place or increased toxicity or side effects will occur. However, the drug cannot be delivered in its pure form. Thus, to achieve bioavailability of the drug or the site of action, it should be delivered as a formulation containing excipients. This formulation is responsible for its release at the proper place and also in the proper amount.

During the formulation of the drug, a lot of challenges appear concerning their physic-chemical properties, such as chemical and physical stability. Therefore we need to develop a tailored formulation for each active substance.

The definition that an excipient should be functional and inert at the same time is sometimes contradictory [2]. An excipient needs to be chemically and physically compactable with drug substances or other excipients in the same dosage form system. An excipient could exhibit polymorphism showing different crystalline structures with different physical-chemical properties, such as hygroscopicity, solubility, stability, compactibility etc., therefore different polymorphic modifications of excipients can have a different role or function [3].

To save time during drug product development, formulators frequently select wet granulation as their manufacturing process. Wet granulation is a process that is less dependent on excipient performance. However, it involves multiple manufacturing steps, which can add time and cost to the development process. Conversely, DC is becoming a preferred manufacturing process due to its economic and productivity advantages. DC requires excipients with the physical characteristics that increase flowability and compressibility of the tabletting blend. Usually, Active Pharmaceutical Ingredient (API) is incorporated with excipients such as filler, binder, disintegrant, glidants and lubricants. The physical properties of these powder mixtures are often hard to predict. Tabletting

parameters, such as equipment geometry and energy input, can add to the complexity of the process when working with multi-particulate powder systems.

These findings strongly support the requirement to insist on a formulator to understand both the excipient involved in the formulation, and the process used in manufacturing science-based approach in designing optimal and robust formulations. A robust formulation may be defined as: A formulation that is able to adapt the typical variability seen in the API, excipients, and process without the compromising manufacturing, stability, or performance of the product.

Most formulations have three components: the active pharmaceutical ingredient drug (API), the excipient(s), and the manufacturing process.

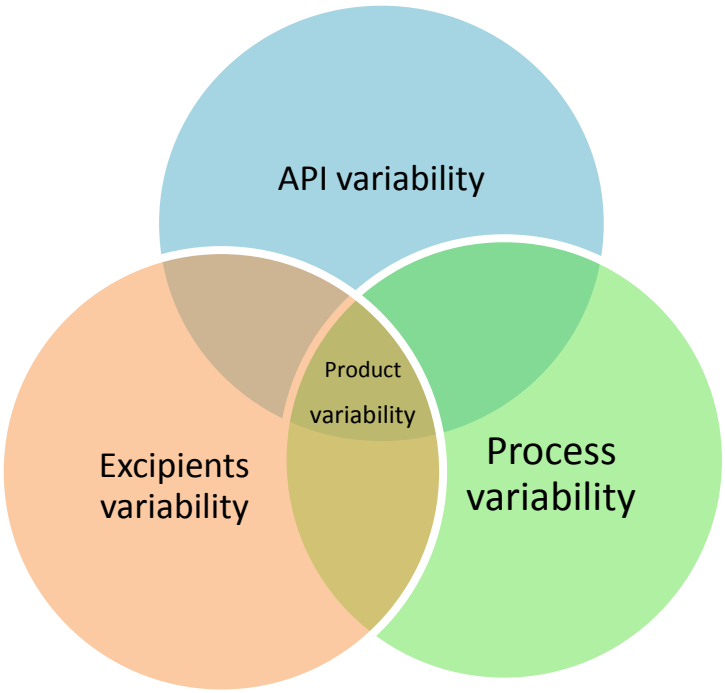


Figure 1 Sources of product variability

To understand product variability, we must understand all input variability. The variability of the API, excipients, and process parameters are obvious components of the overall variability. Nonetheless, other factors affect the manufacture, stability, or performance of the product. For example, how materials are fed into the unit process, how materials

interact together during processing, and how an operator carries out the operations which can all affect the final product attributes. Thus, for a given formulation and process, we must understand variability in the raw materials and their interactions to define the process and then demonstrate sufficient understanding of the process to define the design space for the product. We can represent this process schematically using variance as a measure of variability (Figure 1).

So to understand the functionality of a certain excipient we need to study the critical parameters affecting its manufacturability and performance. Thus, we need to take in account the manufacturing process parameters and the physical-chemical properties of the active ingredient incorporated in the formulation. All these variables should be set in one design space.

Design space (Figure 2) is the multi-dimension combination and interaction of input variables and process parameters that are demonstrated to provide assurance of end-product quality. Design space exists within the knowledge space that is formed during the development of a pharmaceutical product, the latter generated from sources extending from statistical experimental designs and first principles approaches to manufacturing experience and scale-up correlations. Manufacturing control space for production exists within the design space. The larger the design space, the more likely we will produce a robust formulation.

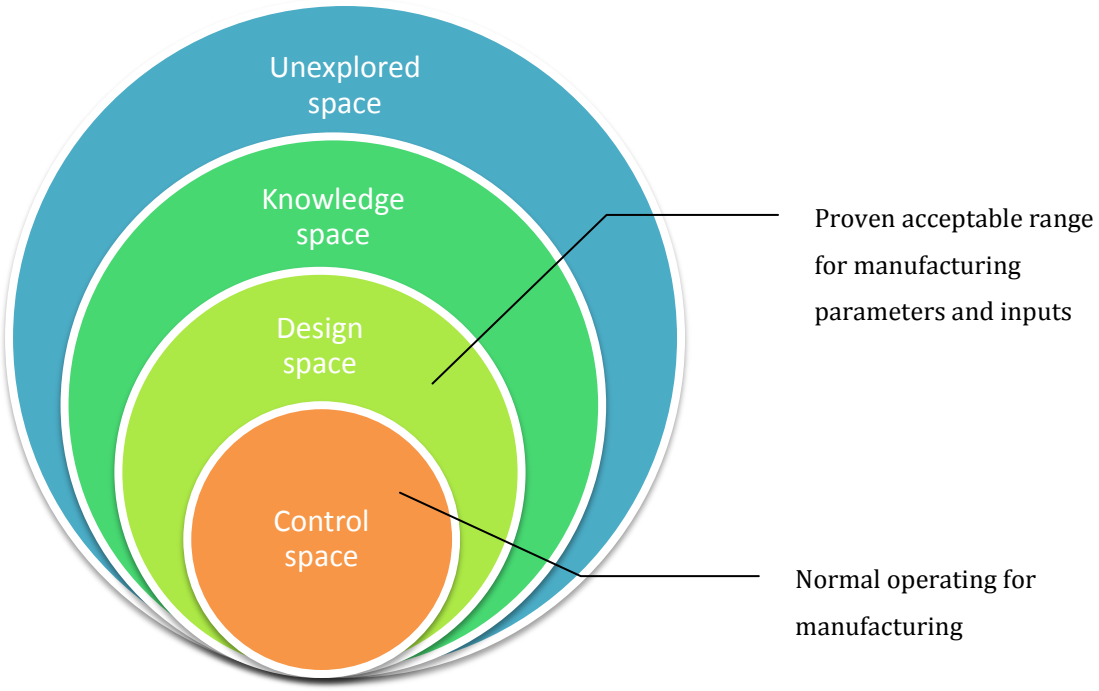


Figure 2 Concept of design space

4.1.2 CELLULOSE

Over 150 years ago, Anselme Payen discovered and isolated cellulose from green plants [4]. Several reviews have been published on cellulose research. They state that this compound is the most abundant material on the earth: it is the main constituent of plants, serving to maintain their structure, and is also present in bacteria, fungi, algae and even in animals.

Cellulose is long-chain polymeric polysaccharide carbohydrates, of beta-glucose, (Figure 3). It forms the primary structural component of green plants. The primary cell wall of green plants is made primarily of cellulose; one of the most common biopolymers on Earth Cellulose monomers (β-glucose) are linked together through ß1→4 glycosidic bonds by condensation. This is in contrast to the α 1→4 glycosidic bonds present in other carbohydrates like starch. Cellulose is a straight chain polymer: unlike starch, no coiling occurs, and the molecule adopts an extended rod-like conformation. In microfibrils, the multiple hydroxyl groups on the glucose residues hydrogen bond with each other, holding the chains firmly together and contributing to their high tensile strength.

When cellulose pulp are dispersed in 17.5% NaOH solution, where the non-solved parts of it can be removed, a white residue of pure α -cellulose after washing and pulverization is called cellulose powder, having lower degree of polymerization.

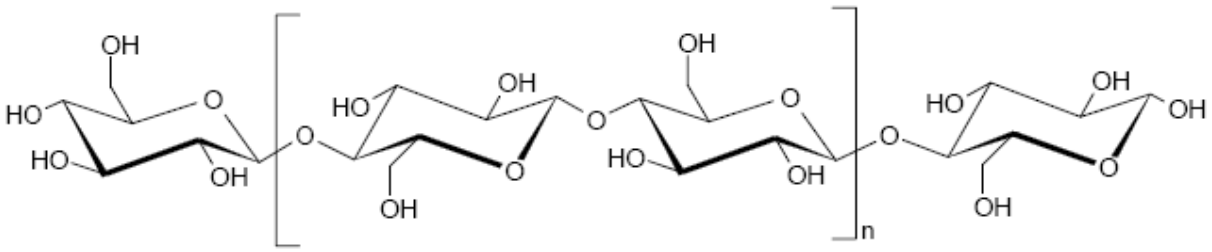


Figure 3 Molecular structure of cellulose

4.1.2.1 Polymorphism of cellulose

Cellulose exists in four major crystal modifications, Cellulose I, II, III and IV. The polymorphic forms can be inter-converted according to Figure 4 mostly by certain chemical and thermal treatments [5, 6]. Cellulose I and II are the most important forms [4].

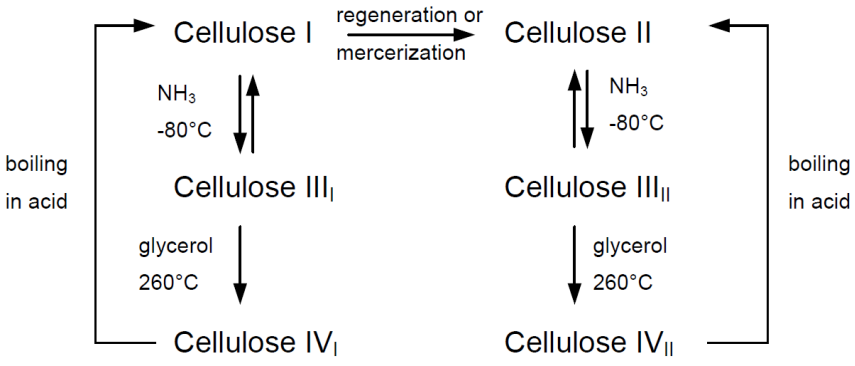


Figure 4 Inter-conversion of the polymorphs of cellulose [7]

Cellulose I, or native cellulose, is the form found in nature. Cellulose II, the second most extensively studied form, may be obtained from cellulose I by either of two processes:

1. Regeneration, which is the solubilization of cellulose I in a solvent followed by re-precipitation by dilution in water to give cellulose II
2. Mercerization, which is the process of swelling native fibers in concentrated sodium hydroxide, to yield cellulose II on removal of the swelling agent.

4.1.2.1.1 Applications of cellulose in pharmaceutical solid dosage forms

1. Cellulose I

Mainly known as Microcrystalline Cellulose (MCC), MCC is an excipient used in the formulation of tablets and capsules, and has been studied extensively during the past decades. It can be used as a binding agent, due to its excellent compaction properties. It also has uses as a disintegrant, in order to increase the biological availability of a medicine, and as a lubricant to aid in the tabletting procedure. It is also physiologically inert, odorless and tasteless, making it suitable as a diluent in order to fill out a tablet and make a more convenient and accurate dosage form.

2. Cellulose II

Cellulose II powder was developed at a lab scale at the University of Iowa, and has been investigated and employed in pharmaceutical technology. This new excipient is called UICEL. It is said to have excellent compaction properties. Cellulose based tabletting excipient that has been developed at the University of Iowa [3, 8].

Cellulose powder is treated with an aqueous solution of sodium hydroxide (5N) and precipitated with ethanol. It shows a cellulose-II-lattice and consists of a mixture of aggregated and non-aggregated fibers. It can be compressed to a tablet without any binder. The resulting tablet shows an extremely rapid disintegration time irrespective of its hardness. The ability to act as binder and as a highly effective disintegrant at the same time makes UICEL an interesting aid for direct compaction (DC).

Recently, MCC Rapid a new excipient based on cellulose II powder has been developed and produced in large scales by Pharmatrans Sanaq, Switzerland. In order to find the proper use and function of MCC Rapid, further investigations have been performed. The functionally of the new excipients has been tested to know the excipients critical parameters, that it can help the formulator to develop formulation for DC in minimum required time, based on a scientific approach. Taking into account all variables involved during developing a formulation for DC, such as physico-chemical properties of API, and process manufacturing variables.

4.2 TABLETS MANUFACTURING

The earliest reference to a dosage form resembling the tablet is to be found in tenth century Arabic medical literature. Drug particles were compressed between the ends of engraved ebony rods, force being applied by means of a hammer [9]. Nowadays, the compressed tablet is the most widely used dosage form, having advantages for both the manufacturer and the patient. Furthermore, the fact that the tablet is a dry dosage form promotes stability, and in general, tablets have shelf lives measured in years. They are also convenient to transport in bulk, since they contain relatively small proportions of excipients unlike, for example, oral liquids. From the viewpoint of the pharmacist, tablets are easy to dispense, while the patient receives a concentrated and readily transportable and consumed dosage form. Furthermore, if properly prepared, tablets provide a uniformity of dosage greater than that of most other medicines, and appropriate coating can mask unpleasant tastes and improve patient acceptance. Though most tablets are intended to for oral intake, the same basic production process, using the appropriate formulation, provides medicines for sublingual, buccal, rectal, and vaginal administration, together with lozenges, soluble, dispersible, and effervescent tablets. However, the manufacture of tablets is not simple, and far from being well understood, since only a few excipients and active ingredients that naturally have the properties which are necessary for the manufacture of tablets of satisfactory quality. Therefore, some preliminary treatment such as granulation and incorporation of excipients in the formulation is essential in many cases.

4.2.1 TABLET COMPACTION

4.2.1.1 Stages of compaction

All tablets are made by the process of compaction. Solids in the form of powder mixtures or granulation are contained in a die and a compaction pressure of several tones is applied by the mean of punches. The shape of die and punches governs the corss-sectional and longitudinal-section of the tablet, respectively. Regardless to the type of the press, eccentric or rotary tabletting machine the tablet compaction process can be divided into three stages as shown in Figure 5.

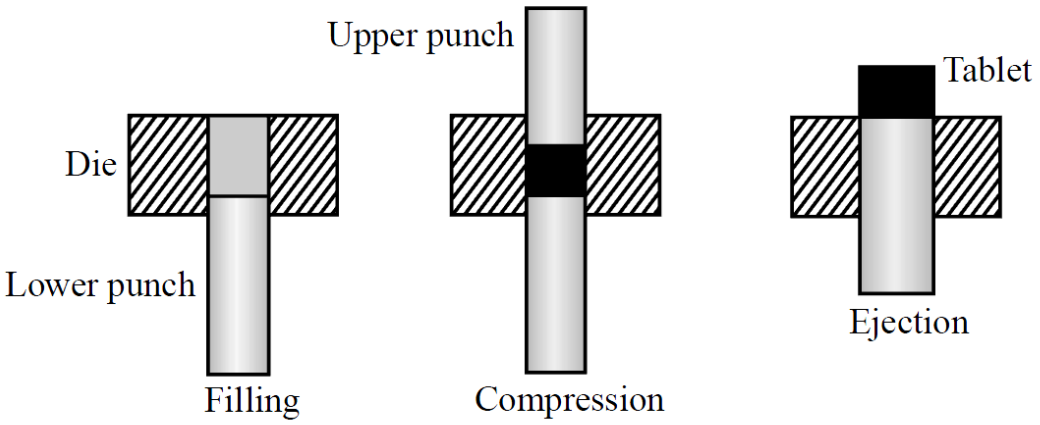


Figure 5 Cycle of operations of an eccentric tablet press

4.2.1.1.1 Stage 1 - filling

Before powder compaction, the punches fall leaving the die cavity empty. The particulate solid is filled into the die. The volume, which the powder adopts, is defined by different properties of the material such as density, particle size distribution, particle shape, surface properties and flowability, furthermore by technical reasons like the movement of the hopper or centrifugal forces in the production process. The punch touches the material and the particles start to overcome the friction force and to slide past each other to energetically convenient positions. When this densest packing is achieved the bulk density corresponds approximately to the tapped density.

4.2.1.1.2 Stage 2 - compaction

The upper punch descends, and its tip enters the die, immobilizing the particles. The distance separating the punch faces decreases, either by movement of the upper punch alone or by movement of both punches. The density of the contents in the die is increased. When the particles are close enough together, interparticulate bindings are formed causing the individual particles to aggregate, forming a tablet. The closer the distance between punches, the higher compaction pressure, causing the particles to cohere together.

As the pressure is increased, the initial particles change shape or deform and further compaction leads to some type of deformation (Figure 6). When the load is removed, some particles are able to return to original shape (elastic deformation), whilst other ones are permanently deformed (plastic deformation). The force required to initiate a plastic

deformation is noted as yield stress. Brittle particle undergo fragmentation, crashing of the original particles into smaller units. A single particle may pass through several of these stages during compaction. Some materials consolidate by a plastic deformation (microcrystalline cellulose, starch, sodium chloride), some by fragmentation (crystalline lactose, sucrose, Emcompress), but all materials posses both elastic and plastic behavior depending on the applied pressure.

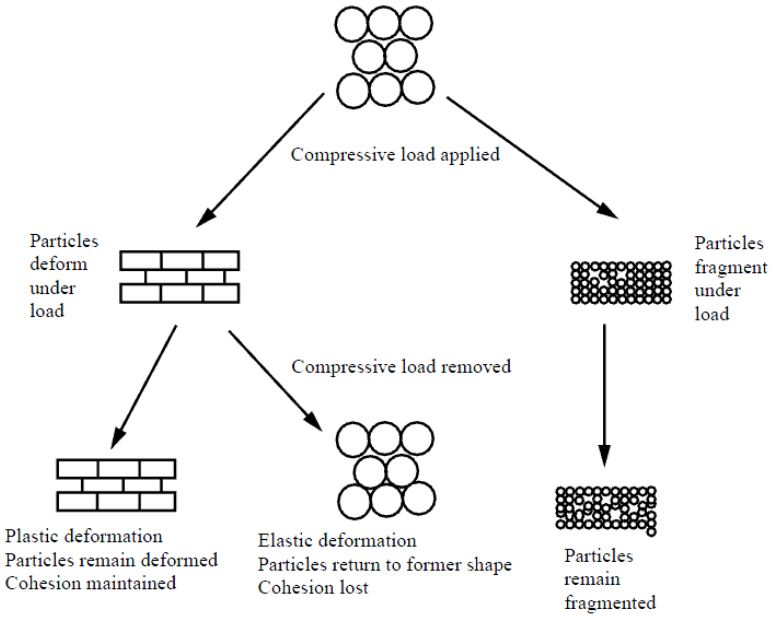


Figure 6 Plasticity, elasticity and fragmentation in a powder system after compaction [10]

4.2.1.1.3 Stage 4- ejection

Pressure applied to the tablet is removed at the moment the upper punch is withdrawn from the die. The removal of compaction pressure causes the tablets to return to their former shape depending on the material elastic properties. When tablet elastic recovery takes place, this would result in a decrease in the interparticulate contact and therefore the tensile strength of the tablet is negatively affected. Also this phenomenon induces tablet capping.

Simultaneously, upon the removal of the upper punch, the lower punch pushes the compact outside the die cavity. In which ejection takes place. Upon removal of the tablets frictional forces between the powder particle and die wall are present. Therefore, a successful ejection demands lack of adhesion-friction between the tablet and the die wall.

4.2.1.2 Bonding in tablets

Tablet strength after compaction can be explained due to the adhesive forces. These forces form, when the particles are closer. At the same time the number of contacts between particles are increasing, which is adding a positive effect concerning strengthening adhesion. There are three types of interparticular adhesion that are of significance in tablet formation [11]:

– Intermolecular forces

– Mechanical interlocking

– Material bridges

The intermolecular forces are considered most important for the mechanical strength in the tablet. Intermolecular forces denote a collective term of bonding forces, such as van der Waal forces, electrostatic forces and hydrogen bonding [12] that acts between the surfaces separated by some distance. Mechanical interlocking is dependent on the shape and the surface of the particles and their deformation during the compaction process. This mechanism is not founded on atomic interaction forces and therefore plays a minor role. Material bridges result from re-crystallization or melting and solidification. These phenomena can only appear in special cases, e.g. a partial melting or dissolution in adsorbed water. Furthermore liquid bridges, which arise from capillary condensation of water or from residual moisture after wet granulation, have a significant impact on the compaction behavior of the solid. In general, moisture increases the compact strength [13].

4.2.1.3 Tablet manufacturing by DC

Despite the fact that DC is considered to be the classical and the first method of tablet manufacturing wet granulation was the preferable method by most pharmaceutical manufacturers. Major disadvantages that retarded the interest of manufacturing tablet by DC were flowability and compactibility.

Due to the recent advances in material sciences, excipient suppliers started to produce excipients which are suitable for DC. Therefore the interest in DC method of production of tablets has been increasingly growing. This interest is due to its economical advantages (Table 1), additionally the recommendation by the FDA's PAT initiative. Manufacturing of

tablets by DC requires fewer steps when compared to wet granulation method as seen in Figure 7.

Table 1 Advantages and disadvantages of DC [14]

Advantages	Disadvantages
• Simple, thus requires fewer unit operations, shorter time, less energy is spent, reduced labor.	• Requires highly flowing materials
• Suitable for heat and/or moisture sensitive drugs	• Segregation of particles
• Enhancement of dissolution. Tablets disintegrate in their into their primary particles rather than granular aggregates	• Compactibility for poorly compactable drugs, and limitations in drug loading

Therefore process variables are much minimized, leading to easier control and simpler understanding of process parameters. A formulation for DC should be attribute three essential qualities. First the formulation must flow into the die space of the tablet press sufficiently rapidly and in a reproducible manner. This is important to avoid variation in tablet weight, and in content uniformity. Second, the particles in the formulation must cohere when compaction pressure is applied, and should remain intact after removal of the force. Third after compaction the tablet should eject without damage to either the tablet or the press.

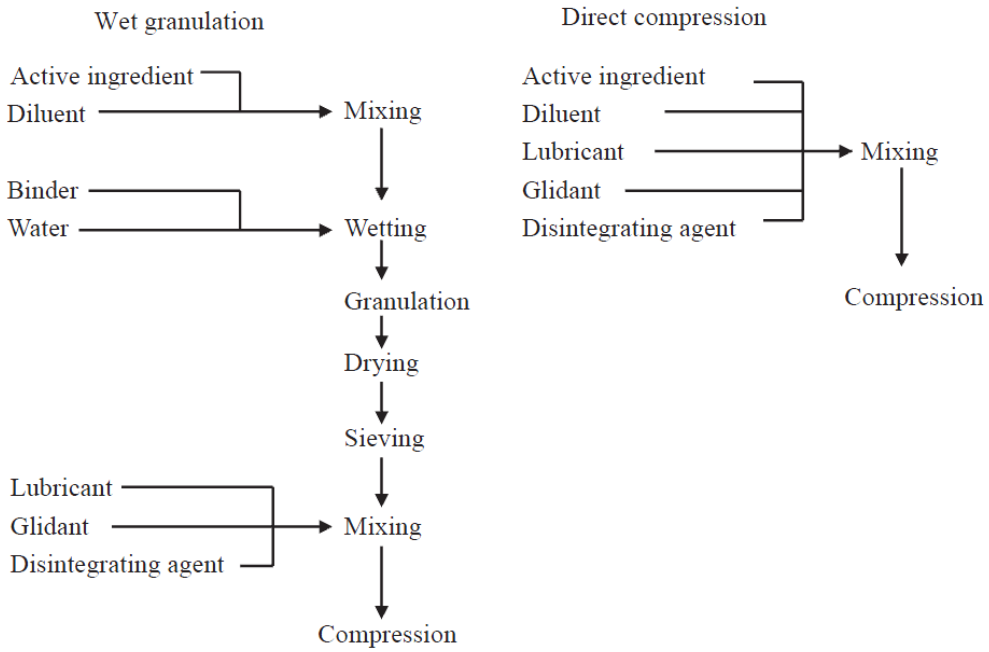


Figure 7 Comparison of the wet granulation and DC processes of tablet manufacture

Although the tabletting parameters, like speed and compaction force has proved to have an influence on the tablet characteristics. The process of DC considered being a formulation dependant. In other words little changes in physicochemical properties. Such variation can be found in batch to batch variation. This little variation in particle size distribution for instance could lead to failure in producing a tablet with acceptable qualities. When compared to the wet granulation method, the particles here, despite the batch to batch a variation are agglomerated together with a binder. Thus, Granule properties are mainly dependent on the process itself. That is the granules are manufactured in a reproducible manner despite the batch to batch variation.

4.2.1.3.1 Properties Required for DC diluent

- Flowability

Good flow is a prerequisite for any tablet formulation to ensure uniformity of tablet weight, which in turn contributes to uniformity of content.

- Ease of mixing and lack of segregation

Achievement of a homogeneous mixture of active ingredient and diluent is essential to obtain tablets with an acceptable uniformity of content of active ingredient. The main cause of segregation is differences in the particle size of components, with differences in shape and density being secondary factors.

- Compaction pressure–Tablet strength profile

This is the relationship between the compaction pressure applied to the formulation and the physical strength of the resulting tablets.

- Capacity or dilution potential

By definition, DC diluents are intended to be mixed with other ingredients. Therefore, not only should the pressure–tablet strength profile of the diluent be determined, but also should those of mixtures of the diluent with an active ingredient. The capacity of a DC diluent is the proportion of another ingredient that can be mixed with it while still obtaining tablets of acceptable quality. The definition of "acceptable" will depend on the purpose for which the tablets are required.

- The mechanism of consolidation

The effect of compaction speed on tablet quality is dependent on the consolidation mechanism. Fragmentation can be regarded as a virtually instantaneous process. Thus, solids which consolidate by fragmentation show little dependence, if any, on the speed at which the consolidation pressure is applied. Deformation on the other hand is time dependent. It takes a finite time for deformation to occur, and at high rates of punch movement, not enough time may be available for the full effect of the pressure to be exerted.

In general, addition of a lubricant such as magnesium stearate causes a reduction in tablet breaking strength. As the diluent is mixed with the lubricant, each diluent particle becomes coated with a thin film of lubricant which interferes with interparticulate bonding. However, if fragmentation is the primary method of consolidation, new surface that is uncontaminated by lubricant is continually generated, and so bonding is less affected.

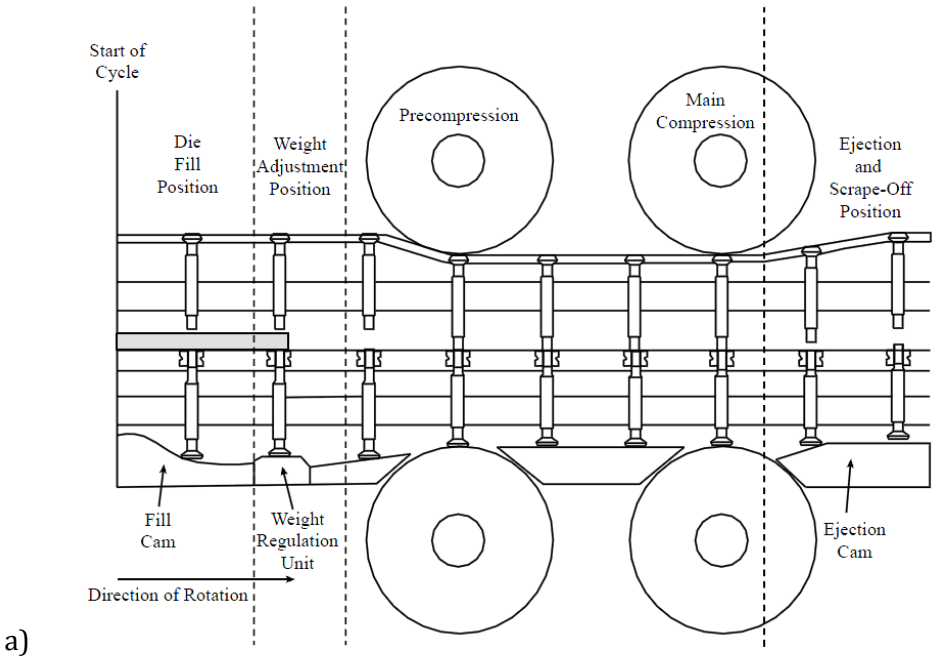
4.2.1.4 Scale-up in tabletting and the role of compaction replicators in development of tablets

According to Merriam Webster dictionary, scale-up means an increase in size according to fixed ratio. Thus, increase in batch size. In case of some pharmaceutical processes like granulation and drying, increase in output size requires increase the processing size. When it comes to tabletting, scale-up has a different aspect as the increase in batch size does not require increase in the process size, unlike the process of granulation. Scale-up of tablet depends mainly on increase of speed of the tabletting machine. The challenge comes along the process of technology transfer: how this formulation will behave when produced at production scale? Developed formulations need to sustain the changes upon tabletting on production scale. Subsequently, it should provide robustness when produced at different parameters such as compaction pressure and speed. A robust formulation in this case should sustain its mechanical properties, and avoid capping, lamination change in porosity of a tablet which can affect dissolution and consequently bioavailability. Moving into production scale requires extra trials to test the formulation and the tabletting process under the new process conditions and parameters. Thus, large amount of powders are wasted for the sake of trial and error scaling up experiments.

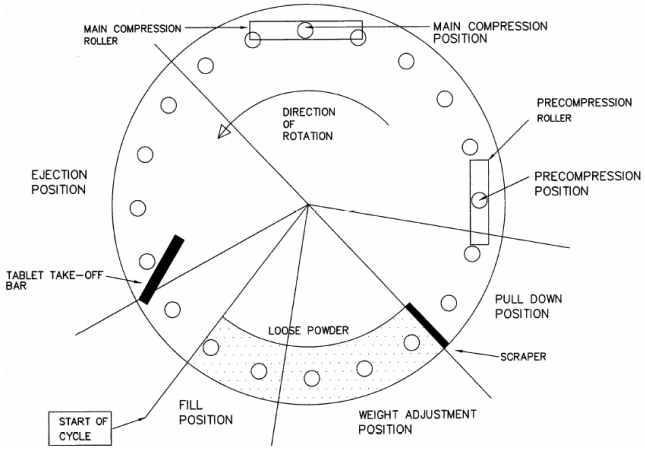
With the aid to of Dimensional Analysis approach, technology transfer becomes easier. Dimensional analysis is a method for creating dimensionless numbers that completely describe and characterize the process. Because all dimensionless numbers necessary to describe the process in similar systems must have the same numerical value [15]. When such values are matching on variant scales it ensures the success in any scale-up operation. In tabletting applications, the process scale-up involves different speeds of production in what is essentially the same unit volume (die cavity in which the compaction takes place). Thus, one of the conditions of the theory of models (similar geometric space) is met [16].

4.2.1.4.1 Presster™

Upon formulation scale-up to high-speed rotary press machines, scale-up problems can be minimized by simulation of production conditions in the formulation development lab. Potential scale-up problem can be eliminated by developing robust formulations with respect to process parameters. But, this cannot be achieved without testing in production environment, especially when a small amount of drug is provided for testing. To solve this problem, compaction simulators were designed, in a way to simulate the production conditions and facilitate the development of robust formulations. The Presster was introduced to mimic production rotary presses on a small scale. This machine can be classified as a mechanical compaction simulator. Based on a high speed single station press that is also a tablet press simulator (Figure 8). No hydraulic controls are involved, thus, it can simulate the tablet presses without the need of any artificial, theoretical or prerecorded punch displacement profiles. Punches and die are built in a carriage that moves linearly between the compaction rolls. The linear speed of the carriage is variable, powder weight and volume in-die is controlled, the distance between the rolls is adjustable which match IPT or any special tooling. All these features can guarantee the successful mechanical simulation of most tablet presses. The linear movement of the punches allows the calculation of RPM and dwell time for any press, regardless the number of stations. Pre-compaction and ejection can be included in simulation. Presster is incapable to record the artificial punch movement, simulation of the die fill and feeding at high speeds, or speed-related temperature and vibration fluctuations.



a)



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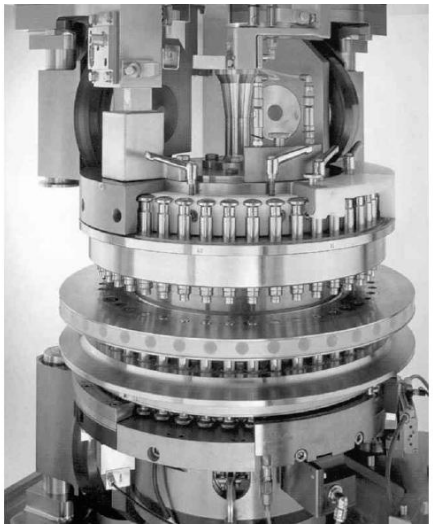


c)

Figure 8 Multi stations rotary press with pre-compression and compression stations. (a): schema view from side (b) schema view from top, (c) picture of a Fette machine [17].

Rotary press in RPM of the research and production presses has no relation, because both presses represent a different number of stations and pitch circle diameter. Matching tablet press speed (RPM) of the research and production presses has, of course, no meaning, because of different number of stations and pitch circle diameter. It is vital, therefore, to translate the speed of tabletting press in RPM into dwell time or contact time. Dwell time is defined as the time the flat portion of punch head is in contact with the compaction wheel

(time at maximum punch displacement, or time when the punch does not move in vertical direction). Effect of dwell time has been studied on pharmaceutical formulation containing plastic materials, showing an important impact on the mechanical properties [18]. Dwell time can be calculated according to the following equation (1)

$$\text{DWT(ms)} = \frac{\text{L}\cdot\text{NS}\cdot 3{,}600{,}000}{\pi\cdot\text{PCD}\cdot\text{TPH}} \quad (1)$$

Where

L=Length of a flat portion of the punch head (mm), NS=Number of stations, π= 3.14159265

PCD= Pitch circle diameter of the turret (mm), and TPH= Tablets per hour.

4.2.2 Evaluation of Mechanical properties

4.2.2.1 Powder compressibility and compactibility analysis

Tablets Mechanical properties usually are measured by test the extent of compactibility or compressibility. Compressibility is an ability of a powder to decrease in volume under pressure, and compactibility is the ability of the material to be compressed into a tablet of specified strength [19]. The behavior of powder upon compaction is not simple to understand. Therefore many equations and models were proposed to evaluate the mechanical properties of tablets [20]. Most of the equations used were based on relation between compaction pressure, density and tensile strength.

4.2.2.1.1 Heckel Equation

During tabletting, the bed porosity of the powder changes as the compaction pressure is applied. This reduction in volume or density of the compact upon application of force can be calculated using the Heckel equation (Equation 2), and is given by the mean yield pressure, σ_y

Heckel Equation:

$$\ln\left(\frac{1}{1-\rho_r}\right) = = \text{K}\cdot\sigma + \text{A} \quad (2)$$

Where, ρ_r, was the relative density at compaction pressure σ, the constant in the Heckel equation, the constants, A and K, were determined, from the slope and the intercept of the Heckel plot respectively.

The density, D_0, of the powder at the point when the applied pressure equals zero is used to describe the initial rearrangement phase densification as a result of die filing and high value indicating very dense packing. The relative densities D_a and D_0 were calculated from equations (3) and (4), respectively:

$$D_a = 1 - e^{-a} \quad (3)$$

$$D_0 = 1 - e^{-a_0} \quad (4)$$

Where a_0 represented the intercept of the line at $\sigma=0$. The difference between D_a and D_0 represented the extent of particle rearrangement (D_b). The relative density D_b, describes phase of arrangement during the initial stages of the compaction. The extent of this depends on theoretical point of densification at which particle deformation beings. The mean yield pressure (σ_y) was obtained as the reciprocal of the slope of the linear section in the curve. σ_y, is inversely related to the ability of the material to deform plastically under pressure. The Heckel plot is linear only at high pressure. According to the character of the material the linearity is noted at different pressures. There are two different approaches to obtain density-pressure profiles: “in die” and “out of die”. In the case of the first method, “in die”, dimensions of the tablets are measured during applied pressure, by evaluating punch displacement. The “out of die” method, calculates tablet volume by measuring its dimensions after compaction and relaxation.

4.2.2.1.2 Modified Heckel Equation

Due to the fact that Heckel plot shows linearity only in a region of high pressure, Leuenberger developed a modified Heckel equation which takes into consideration the relation between the pressure susceptibility and relative density of the material. The modified Heckel equation is especially suitable for low pressure range. Pressure susceptibility is in a function of porosity and compaction pressure (equation 5) [21]

$$\sigma = \frac{1}{C}\left[\rho_{rc} - \rho_r - (1 - \rho_{rc})\ln\left(\frac{1-\rho_r}{1-\rho_{rc}}\right)\right] \quad (5)$$

In the case of modified Heckel equation, the constant C, indicates deformability of powder and the constant of the critical density,ρ_{rc}, denotes the critical state where the powder mass starts to gain some rigidity or strength, at a compaction pressure close to zero.

Tablets relative density (ρ_r) and the porosity (ε), was calculated according to equations (6) and (7) respectively.

$$\rho_r = \frac{m}{\rho_t \cdot V_{tablet}} = \frac{m}{\rho_t \cdot h \cdot r^2 \cdot \pi} \quad (6)$$

$$\varepsilon = [1 - \rho_r] \quad (7)$$

Where m and V_{tablet} were the weight and volume of the tablet, respectively, and ρ_t was the true density of the powder, h is thickness and r is radius. The constant C from modified Heckel equation corresponds to constant K from Heckel equation and indicates ability of the material to deform plastically. The larger value C means that material is more plastic in character, andρ_{rc}, is the predicted tapped density for the investigated powder.

4.2.2.1.3 *Leuenberger Equation*

Based on the concept of effective contact points or bonding points across a cross-sectional area of a compact, Leuenberger and co-workers proposed that deformation hardness of a tablet can be correlated with the compressive stresses during compaction [22]. They have assumed that increasing the relative density of the compact allows more particles to come into contact and increases the deformation hardness, σ_T:

Radial tensile strength versus the multiplication of the relative density and the compaction pressure was fitted according to Leuenberger equation (8) [22]:

$$\sigma_T = \sigma_{Tmax} \cdot (1 - e^{-\gamma_t \cdot \sigma \cdot \rho_r}) \quad (8)$$

σ_{Tmax}, denotes the theoretical maximum deformation (Brinell) hardness when the number of non-bonding points is reduced to zero and the applied compressive stress, σ, is highest or infinite. A low σ_{Tmax} value shows a relatively poor compactibility, for even with high compaction stress this limiting value cannot be exceeded. The parameter γ_t specifies the rate at which the compact hardness σ builds-up with an increase in applied compaction stress and provides information about compressibility. A high value of γ_t will imply $\sigma_T = \sigma_{Tmax}$ and a sharp decrease in compact porosity may be attained with low compaction forces. A plastically deforming material will have a high value of g and a low value of σ_{Tmax} whereas the reverse is the case for brittle materials [23].

4.2.3 IN-VITRO EVALUATION OF TABLETS

4.2.3.1 Disintegration

In immediate release dosage forms, the first step toward the dissolution of drug substance is disintegration of a dosage form into its primary granules or particles (Figure 9). Disintegration increases surface of contact between formulated drug and liquid what thereby facilitates drug dissolution. Disintegration represents a limiting factor of dissolution, especially for low soluble drugs in water or in biological fluids. Thus disintegration times are often directly correlated to dissolution rate constants [24]. Disintegration involves the submersion of the dosage form into the dissolution medium or in water at approximately 37°C. Disintegration time is the time required for a dosage form to disintegrate completely. The viscosity, surface tension and penetration angle of the penetrating solution also influence the disintegration of the tablet accompanied with the mean diameter of the capillaries in the tablet, and as the mean capillary diameter alters with different compaction forces [25] it is clear that disintegration is a very important parameter to observe when changing tabletting presses or scaling up.

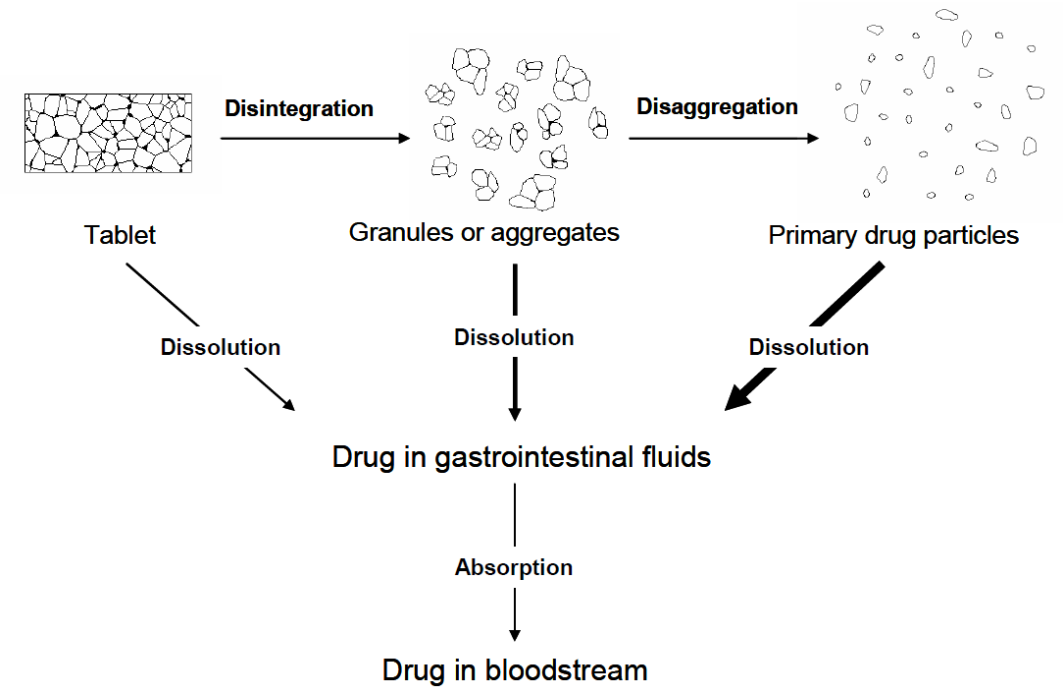


Figure 9 Dissolution of an immediate release tablet inside the body

4.2.3.1.1 Mechanism of disintegration

Although disintegrants are important components in solid dosage forms, their mechanism of action has not been clearly elucidated. The mechanisms proposed in the past include water wicking, swelling, deformation recovery, repulsion, and heat of wetting. It seems likely that no single mechanism can explain the complex behavior of the disintegrants. However, each of these proposed mechanisms provides some understanding of different aspects of disintegrant action.

4.2.3.2 Dissolution

The dissolution characteristic of a dosage form is one of the most important parameters to keep an eye on throughout development, scale-up and equipment and process changes. Dissolution is defined as the process by which a solid substance enters in the solvent to yield a solution. The process by which a solid substance dissolves is controlled by the affinity between the solid substance and the solvent. Drug absorption into systemic circulation from a solid dosage form after oral administration depends on the release of the drug substance, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. The dissolution characteristics of drugs can be influenced by different factors such as the physical characteristics of the dosage form, the wettability of the dosage unit, the penetration ability of the dissolution medium, the disintegration, disaggregation and swelling process of the dosage form a pharmaceutical tablet disintegrates into granules, and these granules disaggregate in turn into fine particles.

4.2.3.2.1 Statistical evaluation of dissolution profiles using fit factors

A simple model independent approach was proposed to compare dissolution profiles using fit factors, i.e., a difference factor (f1) and a similarity factor (f2) [26]. Fit factors were adopted by FDA Center for Drug Evaluation and Research (CDER) and the similarity factor was also adopted by the European Medicines Evaluation Agency (EMEA) Committee for Proprietary Medicinal Products (CPMP) as an assessment criterion of similarity between two in-vitro dissolution profiles [27, 28]. The difference factor (f1), as shown in equation 9, calculates the percent difference between the two curves at each time point, referred to a measure of the relative error between the two curves

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum R_t} \times 100 \quad (9)$$

Where, n is the number of time points, R_t is the dissolution value of the reference formulation at time t and T_t is the dissolution value of the test formulation at time t.

The similarity factor (f2), as shown in equation 10, is a logarithmic reciprocal square root transformation of the sum of squared error, referred to a measurement of the similarity in the percent dissolution between the curves

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (10)$$

4.2.4 PERCOLATION THEORY IN PHARMACEUTICAL TECHNOLOGY

The application of percolation theory in pharmaceutical technology has successfully, explained the behavior of complex formulation consisting of a number of multi-component drug carrier systems [29]. According to percolation theory, the tablet is consisting of clusters of particles which form a network. This theory showed a useful explanation to describe the formation of the tablet and the distribution of pores and particles within it [30]. Many tablet properties are related to the relative density of a tablet and the percolation theory relates changes in tablet properties, such as mechanical strength, to the appearance of percolation thresholds. The percolation theory has been applied to describe the compaction of both single components and binary mixtures [30-32]. For example, property changes associated with a change in the composition of a binary mixture were interpreted using this theory [31].

Carabllo et. .al applied the theory to explain release profiles from inert matrix compressed tablets [33]. Also the theory was also used to interpret water uptake, disintegration time and intrinsic dissolution rate of tablets [34, 35]. In the case of disintegration, they found that a critical concentration of disintegrant exists for which one the disintegration time reaches a minimum. In case of swelling disintegrant, disintegration time decreases with increasing the disintegrant volumetric percentage (% v/v) of the mix until a critical value (percolation threshold). After this critical amount of disintegrant, disintegration time increases again with increasing disintegrant percentage, giving a typical V-shape curve

while plotting disintegration time versus disintegrant volumetric percentage. The increase of dwell time after the critical value of disintegrant amount was interpreted as follow:

- After threshold, the excess of swollen disintegrant starts retarding the penetration of water by blocking pores within the compact.

- After the percolation threshold, the continuous cluster of material conducting water (composed of disintegrant particles and pores) starts to extend by forming dead-end arms (excess of disintegrant). The increased complexity of the network retards the penetration of water within the tablet in comparison to the continuous cluster at the percolation threshold [36].

5 AIMS OF THE STUDY

Understanding the functionality of excipients can reduce time, efforts, and maintain its proper use during formulation development. Due to the increase of interest in DC process for tablet manufacturing, new excipients have been developed and co-processed to improve performance of this tabletting method [37]. MCC Sanaq Rapid (MCC Rapid), a new cellulose II polymorph based excipient has been developed by Pharmatrans Sanaq, Switzerland. The aim was to provide an excipient which can aid as multifunctional excipient for DC method. Understanding the critical parameters that affects the manufacturability and performance of excipients is important to maintain robustness of dosage form during formulation design. Due to challenges a formulation appearing when moving from lab to scale up stage, in this study we investigated the functionality of MCC Rapid compared to well known MCC Sanaq (MCC), a cellulose I polymorph, at realistic tabletting manufacturing conditions. This was achieved using Presster™, a tabletting press replicator. Subsequently, the aim of this study includes the following issues:

- Characterization of powder properties of MCC Sanaq Rapid and MCC Sanaq.
- Influence of polymorphism, compaction dwell time and lubricant on mechanical properties of MCC Sanaq Rapid and MCC Sanaq tablets.
- Influence of incorporation of Paracetamol (a poorly compactable drug) on the manufacturability of formulation containing MCC Rapid versus MCC Sanaq, taking into account the effect of compaction dwell time.
- Influence of IBU (a low soluble drug) loading on dissolution and disintegration performance of formulation containing MCC Sanaq Rapid and MCC Sanaq.
- Influence of Magnesium stearate (hydrophobic lubricant) on disintegration and dissolution performance of MCC Sanaq Rapid formulations compared to MCC Sanaq.

And accordingly, this research will reveal more critical factors that affect the proposed multi-functionality of MCC Rapid as an excipient for DC.

6 MATERIALS AND METHODS

6.1 MATERIALS

In this study two polymorphic forms of cellulose were used. MCC Rapid in the form of Cellulose II (lot no.: 126-T03) and MCC Sanaq 102 G in the form cellulose I (Lot no.: 240358). Both excipients were provided from Pharmatrans Sanaq, Switzerland. The drug models used were Ibuprofen (lot no.:29-163-900), and Paracetamol fine powder (lot no.:01272103) kindly provided by Glatt GmbH, Germany and Rhodia, Lyon, France respectively. Magnesium stearate (lot no.: 84808), kindly provided by Novartis Pharma, Switzerland. All other chemical used in this study were analytical grade.

6.2 METHODS

6.2.1 POWDER CHARACTERIZATION

6.2.1.1 Storage

All starting materials were stored at room temperature for at least 48 hours prior to characterization, mixing and compaction.

6.2.1.2 X-Ray Diffraction

X-ray powder diffraction profiles were taken at room temperature using Siemens X-ray diffractometer D5005 (Siemens Inc. Germany) with Ni filtered CuK radiation (voltage 40kV, 40 mA). The measurement was ranged from 2 to 40°2θ at a detection step of 0.02° and a scan rate of 0.5°/min. Data were collected using EVA software for windows.

6.2.1.2.1 Crystallinity

The crystallinity index of MCC Rapid and MCC was calculated according to following equations:

$$\mathrm{CrI} = \frac{I_{002} - I_{18^\circ}}{I_{002}} \qquad (11)$$

$$\mathrm{CrI} = \frac{I_{10\bar{1}} - I_{16^\circ}}{I_{10\bar{1}}} \qquad (12)$$

Where, CrI is the crystallinity index, I_{002} and $I_{10\bar{1}}$ are the overall intensity of the peak at 2θ about 22° for MCC, and MCC, respectively. I_{18° and I_{16° are the intensities of the baseline at 2θ about 16° for MCC Rapid and 18◦ for MCC, respectively [38].

6.2.1.3 Particle Size Distribution

Particle size analyzer based on laser scattering (MasterSizer X Long Bed, Malvern Instruments, UK) was used to determine the particle size distribution. The measurement was performed with dry analysis method using the Manual Dry Powder Feeder, and dispersion produced by air at pressure of 3 bars (Malvern Instruments, UK). Data analysis of the results and the apparatus system was operated using MasterSizer X (software version 2.19, Malvern Instruments, UK).

6.2.1.4 Scanning Electron Microscopy

Images were taken using a scanning electron microscope Philips XL30 ESEM, (Philips, Eindhoven, Netherlands). Prior to analysis, powder samples were mounted on aluminum holders, and sputtered with gold. Images were taken at acceleration voltage between 3 and 5 kV.

6.2.1.5 True, bulk and tapped density

True density of materials was determined using the helium gas displacement pycnometer AccuPyc 1330 (Micromeritics Instrument Corporation, USA) with a nominal cell volume of 10 ml.

Bulk and Tapped density measurements were performed according to the European Pharmacopoeia method using the apparatus; Type STAV 2003, Engelsmann AG, Ludwigshafen, Germany.

6.2.1.6 Hausner factor and Carr's Index

Hausner factor and Carr's index were calculated according to equations (13) and (14) respectively.

$$\text{Hausner ratio} = \frac{\text{Tap density}}{\text{Bulk density}} \tag{13}$$

$$\text{Carr}'\text{s index} = \frac{\text{Tap density} - \text{Bulk density}}{\text{Tap density}} \cdot 100 \tag{14}$$

6.2.1.7 Moisture sorption isotherms

To evaluate moisture sorption of materials, samples were stored over phosphorus Pentoxide (0% RH) for 14 days and subsequently stored over different saturated salt solutions as given in Table 2. Moisture desorption behavior was measured by storing the samples first over water for 14 days, and then stored over the same series of salt solutions used in the sorption process [39].

Table 2 Saturated salt solution and their corresponding relative humidity at room temperature

Saturated Solution	$LiCl \cdot H_2O$	$CaCl_2$	$MgCl_2 \cdot H_2O$	K_2CO_3	$Mg(NO_3)_2 \cdot 6H_2O$	NaCl	H_2O
RH%	11.6	28.8	32.8	44	53.4	75.5	100

6.2.1.7.1 Loss on drying

Residual moisture content was determined using an infrared balance Mettler Toledo type LP 16M (Mettler Instrument, Naenikon Uster, Swtizerland). Samples of approximately 1 g were heated up at 105°C for 20 minutes and the loss of moisture was measured in percent by weight.

6.2.2 PREPARATION OF TABLETS

The and powder behavior upon compaction was studied through the physical characterization of tablets after manufacturing; using a compaction replicator Presster™, Metropolitan Computing Corp., NJ, USA. In order to simulate the compaction of the investigated excipients and formulation behavior under the industrial production condition of a rotary tablet press (Korsch® PH336). Tabletting process, tooling and tablet weight used for all experiments are presented in Table 3.

Table 3 Compaction parameters for Presster™

Simulated Press	**Korsch PH 336**	
Stations	36 stations	
Die diameter	10 mm (Flat face punches)	
Tablet Weight	250 mg	
Powder feeding	Manual	
Speed parameters		
Desired Speeds [RPM]	5 RPM	62 RPM
Tablets Per Hour	10,800	134,000
Desired DWT	118.3 ms	9.5 ms

6.2.2.1 Preparation of tablets for compressibility and compactibility analysis

To study the effect of DWT on parameters of Heckel, modified Heckel, and Leuenberger equations, tablets were prepared according to the same parameter above. Mgstr 0.5 (w/w) was added to the powder and mixed in a tabula mixer for 5 minutes before tabletting. Rotational speed of the mixer was kept constant.

6.2.2.2 Preparation of tablets to study the effect of drug loading and DWT on compactibility

To study the influence of DWT on powder dilution capacity, compressibility and compactibility, MCC Rapid and MCC powders were mixed for 7 min with Paracetamol at different ratios, as provided in Table 4 All tablets were compacted under the applied compaction pressure in the range of 20-300 MPa at DWT of 118.3 and 9.5 ms. At each compaction pressure 5 tablets were produced.

Table 4 Binary mixtures containing MCC or MCC Rapid loaded with Paracetamol

Composition	**% (w/w)**				
Paracetamol	0	20	40	60	80
MCC	100	80	60	40	20
MCC Rapid	100	80	60	40	20

6.2.2.3 Preparation of tablets for evaluation of elastic recovery and friability investigations

For each batch the gap between the punches was adjusted to achieve predetermined relative densities of 0.75, 0.65, 0.55 and 0.45. At each relative density, tablets were compacted at two different DWT. After tabletting Elastic recovery as well as friability of the tablets was also studied.

6.2.2.4 Preparation of IBU tablets for evaluation of in-vitro performance

To study the effect of MCC Rapid and MCC used as disintegrants, IBU was chosen to be a model drug due to its low soluble property. Tablets containing different ratios of IBU were compacted as summarized in Table 5 and the porosities were kept constant at the minimum level of 10-12% (n=6). To achieve this porosity, the gap between the punches was adjusted to the corresponding values and DWT was set at 118.3 ms. the effect of internal and external lubrication was also studied.

Table 5 Composition of IBU tablets containing MCC or MCC Rapid used as disintegrants and Mgstr used as a lubricant

Drug Model %(w/w)	**Disintegrant** %(w/w)		**Lubricant** %(w/w)
IBU	MCC	MCC Rapid	Mgstr
10	90	-	0.5 External Lubrication
	-	90	0.5 External Lubrication
30	70	-	0.5 External Lubrication
	-	70	0.5 External Lubrication
50	50	-	0.5 External Lubrication
	-	50	0.5 External Lubrication
70	70	-	0.5 External Lubrication
	-	70	0.5 External Lubrication
90	90	-	0.5 External Lubrication
	-	90	0.5 External Lubrication

6.2.3 EVALUATION OF MECHANICAL PROPERTIES

6.2.3.1 Powder compressibility and compactibility analysis

6.2.3.1.1 Heckel and modified Heckel Equations

Due to possible changes in powder densification properties, upon addition of lubricants as well as the change in DWT, compressibility of MCC Rapid and MCC was investigated. Tablets were prepared as described in the part of preparation of tablets (section 6.2.2). The analysis was performed with "out of die" method Thickness of tablets was measured 48 h after manufacturing with thickness gage (Digital caliper).

Compaction properties of tablets prepared by DC at two different DWT (118.3 and 9.5 ms), compared to lubricated ones. The parameters K and A of Heckel, and C and ρ_{rc} of modified Heckel equation, were used to compare the compaction behavior of the materials. Reciprocal value of the slope K of the linear region of the Heckel plot, mean yield pressure ρ_y can be as well used as a measure of materials ability to deform plastically.

6.2.3.1.2 Radial tensile strength

Using a tablet hardness tester (8M- Dr. Schleuniger Pharmatron AG, Switzerland), crushing strength was measured and calculated the radial tensile strength of cylindrical compacts according to equation (16)

$$\sigma_T = \frac{2 \cdot F}{\pi \cdot D \cdot T} \qquad (16)$$

Where, σ_T is the tensile strength, F is crushing force, D is the diameter of the tablet, and T is the thickness of the tablet. Five tablets were tested and the average was reported.

6.2.3.1.3 Leuenberger Equation

Compactibility and compressibility of the powder systems containing MCC Rapid and MCC were also investigated using Leuenberger equation. Tablets were prepared as described in the part of preparation of tablets (section 6.2.2). Relative density, tensile strength and compaction pressure values were calculated as explained in tablet manufacturing chapter (section 4.2.2) and fitted in the Leuenberger equation. All factors such as DWT, lubrication, and drug loading we studied after the calculation of both the compactibility (σ_{Tmax}) and compressibility (γ_t) constants.

6.2.3.2 Lubricant Sensitivity

Lubricant sensitivity ratio (LSR %) was calculated after internal and external lubrication of the produced tablets according to the equation below.

$$LSR\% = \frac{\sigma_{Tmax\ U} - \sigma_{Tmax\ L}}{\sigma_{Tmax\ U}} \cdot 100 \quad (17)$$

Where, $\sigma_{Tmax\ U}$ is the compactibility index for the externally lubricated powder, and $\sigma_{Tmax\ L}$ is of powder with internal and external lubricating, respectively. Both constants were obtained through the fitting of Leuenberger equation as described in the previous section.

6.2.3.3 Elastic Recovery

Elastic recovery (ER) was calculated according to equation (18) based on the difference in the out of die and in-die relative densities. Analysis was performed for MCC Rapid and MCC at different DWT, with respect to the tablets relative densities.

$$ER\ \% = \frac{\rho_{r\ (out\ of\ die)} - \rho_{r(\ in\text{-}die)}}{\rho_{r\ (out\ of\ die)}} \cdot 100 \quad (18)$$

6.2.3.4 Friability

Friability was measured according to the standard friability test Ph.Eur.5, using a friability tester (Erweka TAP, ERWEKA, USA) at the rotation speed of 25 revolutions per minute for 100 revolutions. Tablets with the total weight of not less than 6.5 g were tested for each batch. Furthermore, friability testing was extended to 200, 300, 500, 1000 and 2000 revolutions. The tablet samples were carefully cleaned with a brush and accurately weighed before and after spinning. Friability was obtained from the percentages of weight loss after spinning.

6.2.3.5 Effect of Paracetamol loading and DWT on mechanical properties

To study the effects of Paracetamol loading and DWT on the tablet properties, Leuenberger equation and dilution potential method were applied.

6.2.3.5.1 Effect of DWT on Leuenberger equation parameters

The effect of DWT sensitivity was studied in binary mixtures containing Paracetamol. The percentage of DWT was calculated according to the following equation:

$$DWT\ \% = \frac{\sigma_{Tmax\ L} - \sigma_{Tmax\ S}}{\sigma_{Tmax\ L}} \cdot 100 \quad (19)$$

Where, σ_{Tmax} L is the compactibility constant of the formulation at long DWT (118.3 ms) andσ_{Tmax} S, is the compactibility constant of the formulation at short DWT (9.5 ms)

6.2.3.5.2 Effect of DWT on dilution capacity of MCC Rapid and MCC

By definition, DC diluents are intended to be mixed with other ingredients. Therefore, not only should the pressure–tablet strength profile of the diluents be determined, but also should those of mixtures of the diluent (MCC Rapid or MCC) with an active ingredient. The capacity of a DC diluent is the proportion of another ingredient that can be mixed with it while still obtaining tablets of acceptable quality. The definition of "acceptable" will depend on the purpose for which the tablets are required.

The magnitude of the effect that a given active ingredient will have on tablet properties will clearly depend on the tabletting properties of that substance. If it is also capable of DC, then the effect will not be great. If, however, it is a substance that is difficult to compress into tablets, then it will cause a marked deterioration in tablet quality when mixed with the diluent. Therefore, for a reliable test of capacity, the DC diluent should be mixed with a "standard" substance and tabletted under standardized conditions. The pressure–strength profiles of the mixtures can then be constructed. Paracetamol have been used as standard.

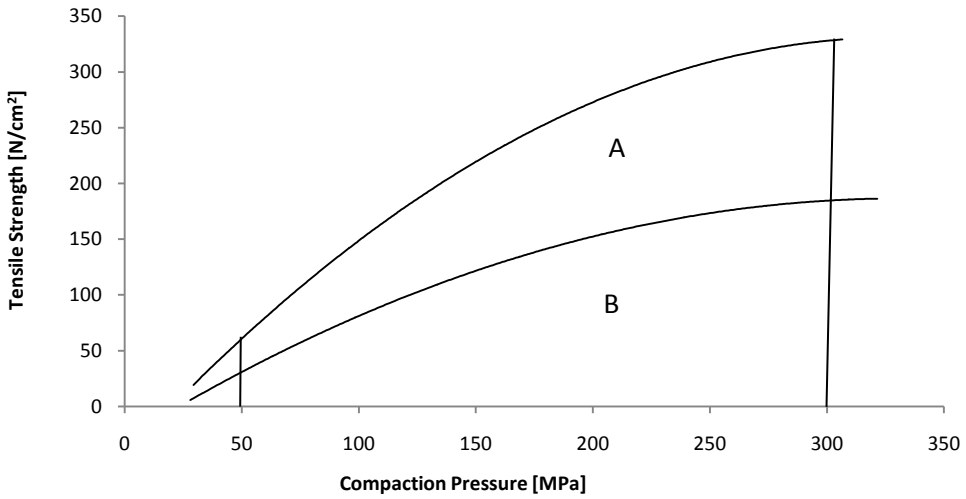


Figure 10 Calculation of dilution capacity according to the method proposed by Habib Y et.al. [40]

The powder behavior upon compaction was studied through the physical characterization of tablets after manufacturing. Tensile strength was calculated according to equation (14). Accordingly, all radial tensile strength of binary mixtures was plotted versus compaction pressure and the Points were fitted into a quadratic polynomial equation. The area under the plotted curves (AUC) was calculated using the trapezium method as shown in Figure 10. Using the method proposed by Habib et. al. and Minchom et. al. [40, 41]. The AUC of each mixture (B) was divided by the AUC of each pure excipient (A), to give a value known as work potential or area ratio. All ratios were plotted against the %(w/w) of Paracetamol for each excipient. Linear regression and back extrapolation to zero area ratios gave the values of dilution capacity.

6.2.4 EVALUATION OF DISINTEGRATION AND DISSOLUTION RATES

Disintegration behavior of MCC Rapid in respect to relative density was studied, taking in account the internal lubrication of Mgstr. Also disintegration and dissolution rates were investigated. Both excipients were loaded with IBU at different concentrations. Taking in account the influence of Mgstr. IBU is a water poorly soluble drug that may extend disintegration time. Besides, Mgstr is well-known to prolong disintegration time due to the hydrophobic film which coats the particles during powder mixing.

6.2.4.1 Disintegration

Disintegration time was measured immediately after tablet production according to the Ph.Eur. 5 using a disintegration apparatus Sotax DT3 (Sotax AG, Basel, Switzerland) (n=6). Statistical evaluation of disintegration data was analyzed using T-test (Microsoft Excel 2007).

6.2.4.2 Dissolution

The dissolution was performed after tablet production (n=6), using a dissolution apparatus (Sotax AT7, Sotax AG, Basel), equipped with an automatically sampling unit. The dissolution procedure was performed with a USP Paddle method (according to the dissolution criteria of IBU tablet USP 31). The speed of the paddles was set to a constant speed of 50 RPM. The dissolution medium was phosphate buffer pH 7.2 (900 ml, 37±1 C°). The concentration of IBU was quantified with a UV spectrophotometer (Lambda 25)

PerkinElmer, Inc. Fullerton, USA) at the maximum wavelength of 264 nm (λ_{max}) compared to the calibration curve of IBU in the same medium.

6.2.4.2.1 Statistical evaluation of dissolution profiles using fit factors

The difference factor (f1) and the similarity factor (f2) were calculated as discussed in theoretical part (section 4.2.3.2.1). The dissolution profiles of IBU tablets containing Mgstr were compared to the same formulations containing no Mgstr. All tablets were produced according to the method in section6.2.2.4.

7 RESULTS AND DISCUSSION

7.1 CHARACTERIZATION

7.1.1 POWDER CHARACTERIZATION

7.1.1.1 X-ray diffraction

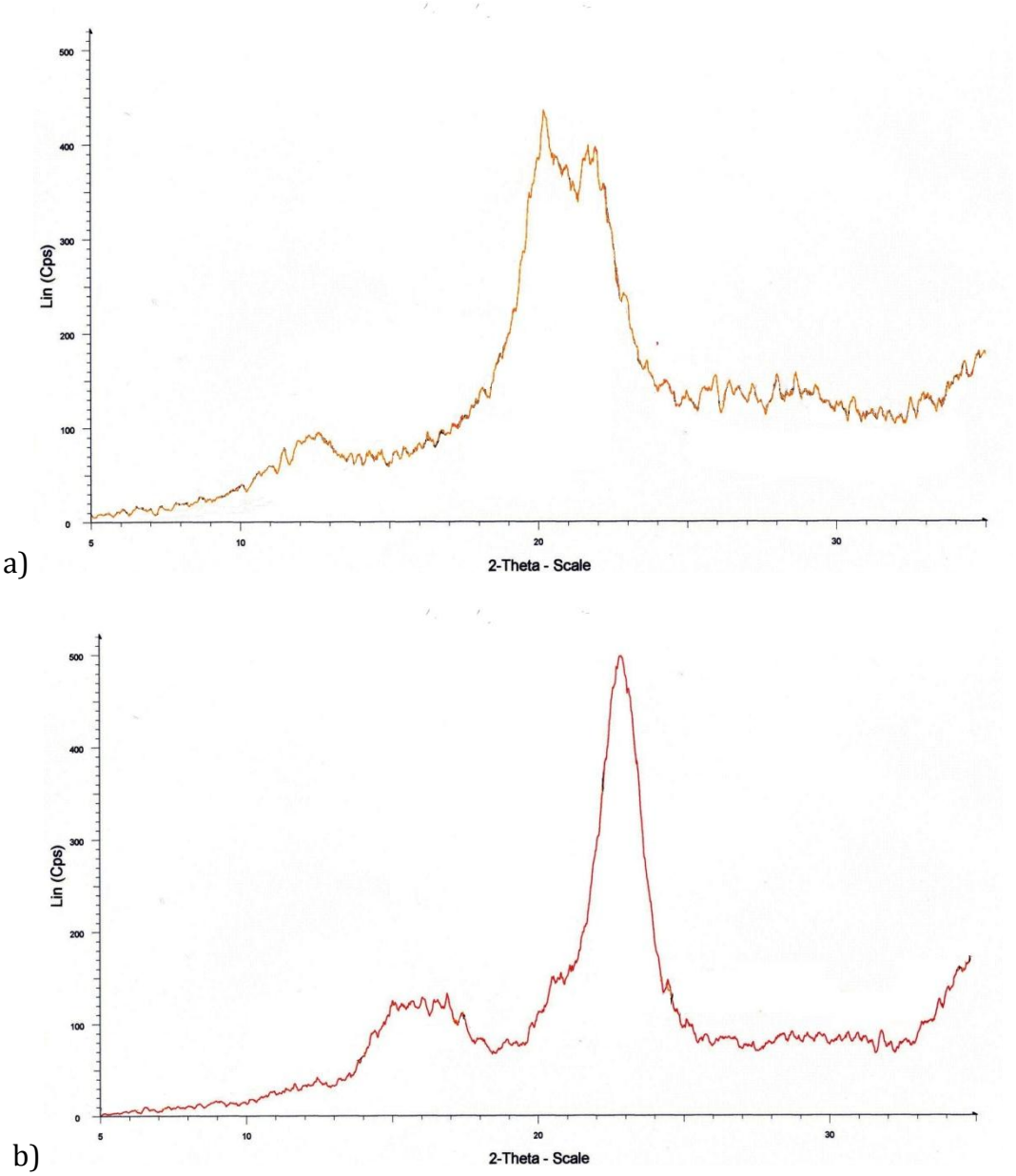


Figure 11 Powder X-ray diffractograms: a) MCC Rapid b) MCC

The X-ray spectrum of MCC Rapid and MCC samples shows that each sample has different diffractograms (Figure 11). MCC Rapid diffraction peaks appear at about 12°, 20°, and 22°

2θ, which indicate the presence of the cellulose II lattice. In contrast MCC shows the distinct peaks at about 15, 17, 23°2θ which indicates and confirm the presence of Cellulose I lattice [42].

7.1.1.1.1 Crystallinity

Intensity of the peaks of MCC Rapid at 20° and 22° were 360 and 330 respectively. Compared to MCC intensity of the peak at 23 which was 500, showing that MCC is more crystalline than MCC Rapid. Crystallinity index calculated according to the equation values showed in Table 6 was higher in MCC than MCC Rapid by 10% [43]. This shows that the MCC Rapid is not only dominated by Cellulose II crystals, also it is less crystalline than MCC.

Table 6 Degree of crystallinity of MCC Rapid and MCC

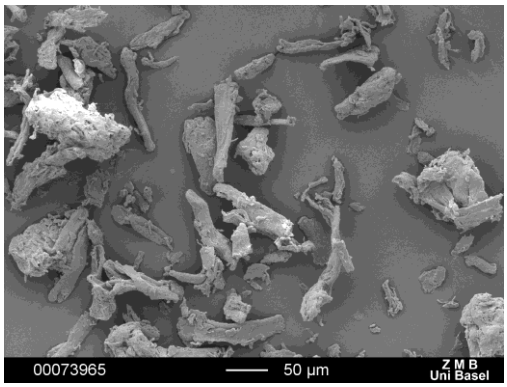
Substance	Crystallinity Index (%)
MCC Rapid	68%
MCC	78%

The difference in polymorphism and crystallinity is due to the drastic chemical treatment needed to prepare cellulose II powders [3].

7.1.1.2 Scanning Electron Microscopy

SEM photographs (Figure 12) of MCC Rapid and MCC show the same degree of agglomeration, whereas MCC Rapid showed different particle morphology, obviously due to the difference in polymorphism. MCC Rapid had more elongated fibers and more regularity in particle shape than MCC. In both types of powder, the crystal habit was hardly distinguished from the fiber shapes or surface texture. This is due to the irregular agglomeration of particles and the mixed composition of crystalline and amorphous cellulose.

MCC



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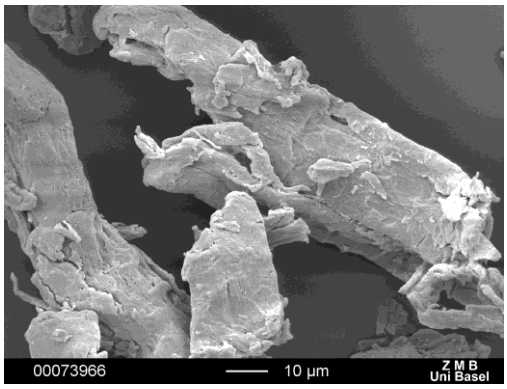

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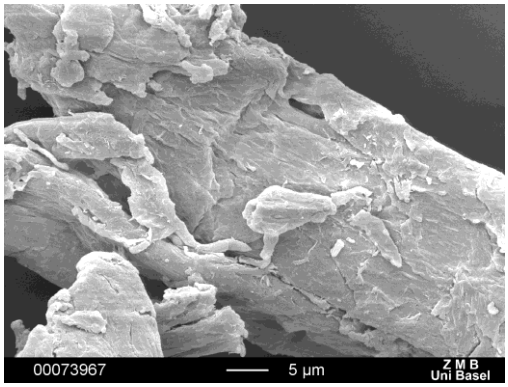

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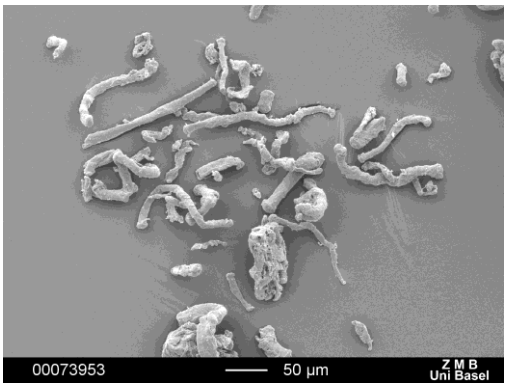
MCC Rapid



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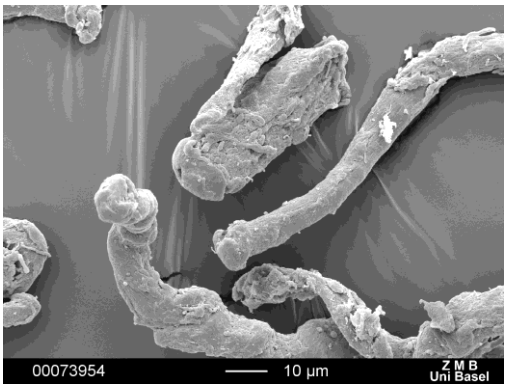

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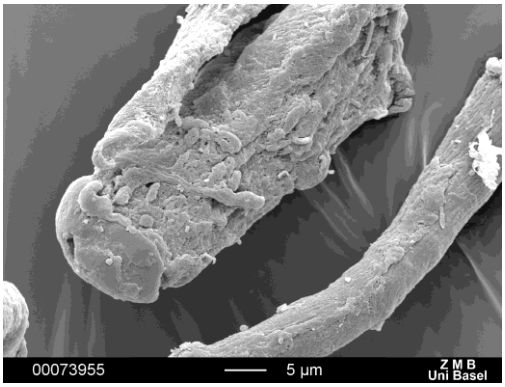

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Figure 12 SEM photographs of MCC and MCC Rapid at different magnifications

7.1.1.3 Particle size distribution measurement

Table 7 presents volume mean and median diameters of MCC Rapid and MCC size distribution. Particle size distribution was measured using laser scattering. In this technique the laser beam is reflected according to the volume occupied by the particles in the dispersion phase, therefore the shape of the particle influences the measured particle size. So, this method it does not give accurate information on the fibrous particles dimensions of MCC Rapid and MCC. MCC Rapid has relatively larger mean values, and smaller median particle size than MCC. Therefore this difference will influence flow ability of powder, mechanical strength, and disintegration of tablets [44-47].Many tablet characteristics depend particle size distribution. Flow ability of powder, mechanical strength, and disintegration of tablets. The larger particle size distribution results in the better tabletting properties in favor of MCC, as larger surface area will result in more contact points between the particles themselves. Concerning flowability, the difference in particle size distribution between both excipients came in favor of MCC Rapid. This is because the particles difference between mean and median particle size, compared to MCC. High difference in particle size leads to increase segregation in between particles, but here it is not the case as both have relatively small particle size. The major reason behind the difference in particle size is that both excipients are prepared using different methods, which is not only affecting particle size distribution but also other physical characters will be discussed further.

Table 7 Particle size distribution for MCC Rapid and MCC (n=5)

	MCC Rapid	MCC
Mean [μm] ± SD	37.40 ± 1.24	31.42 ± 0.16
Median [μm] ± SD	87.67 ± 4.37	112.01 ± 0.26

7.1.1.4 True, bulk and tapped densities

From Table 8, true density values shows that MCC Rapid has lower true density values. Many factors can influence cellulose powders density and its measurement. These factors vary between the type of cellulose polymorph, crystallinity and water content [48]. Evaluation of powder densification behavior upon tapping was performed through

calculating Hausner ratio [49] and Carr's compressibility index [50, 51] for both powders. According to Hausner ratio, MCC Rapid and MCC gave passable and fair flow characteristics, respectively. The result was consistent with the lower Carr's compressibility index of MCC Rapid than MCC, showing that MCC exhibits higher compressibility than MCC Rapid. This can be explained by morphology of MCC Rapid which more elongated particles are visualized. These long particles obviously lead to poor flowability of the powder. Additionally, the higher true density value of MCC is in favor to increase its compressibility index and Hausner ratio compared to MCC Rapid.

Table 8 Powder characterization for MCC Rapid and MCC (n=3)

	MCC Rapid	**MCC**
Densities		
True density [g cm^{-3}] ± SD	1.5 ± 0.01	1.55 ± 0.01
Bulk density [g/ml] ± SD	0.284 ± 0.010	0.345 ± 0.010
Tap density [g/ml] ± SD	0.38 ± 0.024	0.43 ± 0.003
Porosity (%) ± SD	62% ± 0.8	58% ± 0.64
Hausner ratio ± SD	1.34 ± 0.05 (Passable)	1.23 ± 0.024 (Fair)
Carr index ± SD	25 ± 2.93 (Passable)	18.85 ± 1.62 (Fair)
Water Content at Room RH ± SD	8.4% (w/w) ± 1.5	6% (w/w) ± 0.8

7.1.1.5 Moisture Sorption isotherms

Water content can be an issue for tablet's physical and chemical stability. Hygroscopic excipients could be useful to absorb water away from water sensitive drugs such as Acetylsalicylic acid [7], thus, it can improve chemical stability due to hydrolysis chemical reactions. On the other hand, increased water sorption could affect the physical characters such as tensile strength and disintegration of the tablets after production [52, 53].

Moisture sorption isotherms are illustrated in Figure 13

Figure 13 showing that both MCC Rapid and MCC are classified as slightly hygroscopic materials. Additionally, both materials showed the sorption characteristics following a classic profile of type II isotherm according to the classification of hygroscopicity of

excipients [54], where a wide hysteresis between the adsorption and desorption curve is remarkable.

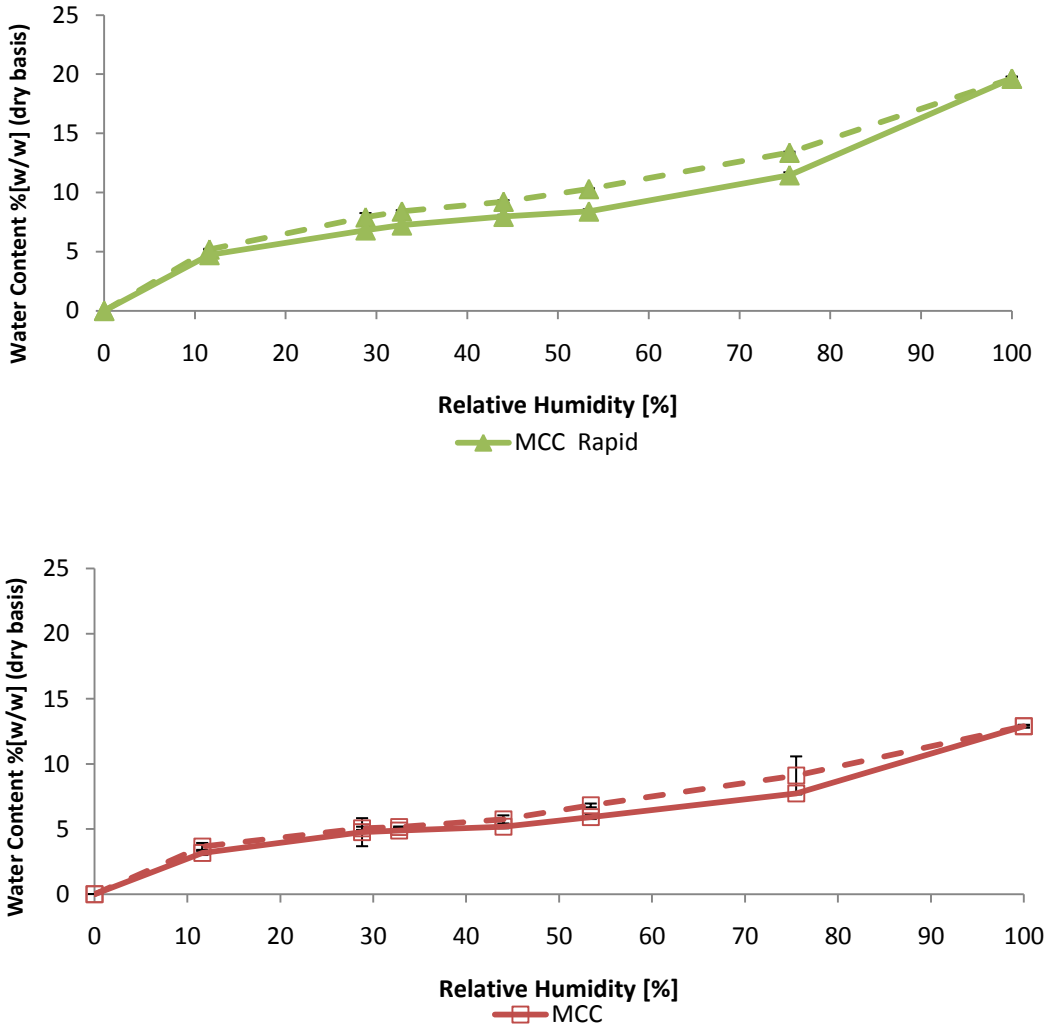


Figure 13 moisture sorption isotherms of MCC RAPID AND MCC. Continuous lines represent sorption and dashed lines represent desorption.

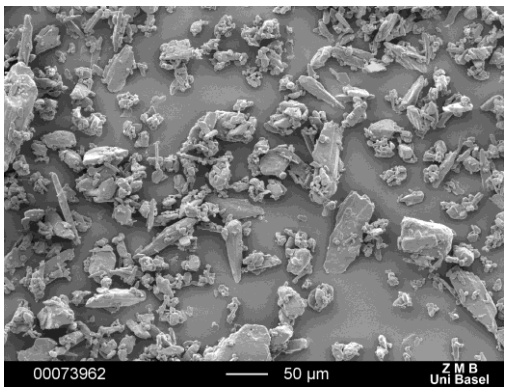
MCC Rapid showed higher hygroscopic properties, indicating that it has higher water uptake capacity than MCC. As reported earlier that non-crystalline and the disordered regions are responsible for accommodation of moisture in the bulk of cellulose [4, 55, 56], broader hysteresis arising between the adsorption and desorption curves could refer to the presence of higher amorphous fraction in MCC Rapid [57]. The reasons behind the

occurrence of the hysteresis of isotherms, is explained by the capillary moisture condensation phenomenon [58, 59].

For MCC Rapid and MCC kept at the room condition with relative humidity of 45%, moisture contents of MCC Rapid and MCC were 8 and 5.7 % (w/w) respectively [60, 61]. As moisture exerts its effect directly by changing the surface properties as well as increasing the cohesiveness of the cellulose powder, it certainly affects the flowability of the powder. Thus, the increased moisture content in MCC Rapid powder is considered as one of the factors that negatively affects Hausner ratio and Carr's index. Moreover, water content in the powder also has an important role in compactibility of a powder system. Water molecules on the surface of the powder increases hydrogen bonding, thus, improving compactibility [62] In this case we can conclude that the change in compaction behavior of MCC Rapid could be less robust than MCC. As the water content is more affected upon the change of relative humidity, as MCC Rapid tended to obtain water molecules much more than MCC. Therefore the water content value could be crucial and need to be optimized prior to tabletting, especially if the wet granulation was method of manufacturing.

7.1.2 CHARACTERIZATION OF DRUG MODELS

Paracetamol powder



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IBU powder

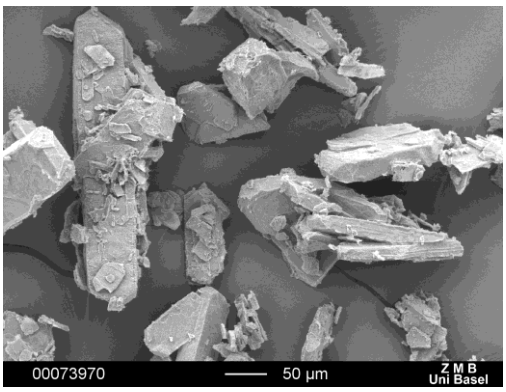

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Figure 14 SEM Photographs of drugs models

Table 9 True density and mean particle size for model drugs (n=5)

Drug Models	True density [g cm^{-3}] ± SD	Mean particle size [μm] ± SD
Paracetamol	1.26 ± 0.02	40 ± 3.2
IBU	1.1 ± 0.06	308 ± 2.2

The drug models, Paracetamol and IBU powder were examined for the morphology by SEM, as shown in Paracetamol exhibits relatively small particles compared to IBU Figure 14. Plus both drugs do not exhibit any fibrous structure. True density values in Table 9 showed that both have much lower densities than MCC and MCC Rapid. Therefore both drugs will reduce the total density excipient drug in binary mixtures, and consequently the tabletting properties will of the whole formulation will be affected. Also it can reduce the flowability the binary mixtures, which can have important consequences on the process of DC related to tablets weight and content uniformity. The Mean particle size of the active ingredients has great role in controlling the drug release. The smaller the particles are, the higher the surface area exposed to the drug release media.

7.2 Evaluation of mechanical properties of MCC Rapid and MCC

7.2.1 Compressibility according to Heckel and Modified Heckel equations

MCC Rapid and MCC powder are compacted at the different compaction pressures. Physical properties of the tablets were examined including, diameter, out-of-die thickness and calculated relative tablet density for the analysis of compressibility with Heckel and modified Heckel equations. The lists of corresponding constants are summarized in Table 10 and Table 11 for Heckel equation and modified Heckel equations, respectively. The fitting of density and compaction pressure in the modified Heckel plot included the nonlinear part which Heckel plot cannot precisely analyze this region (Figure 15). The fitting with the modified Heckel plot resulted in higher correlation coefficients (R^2) values, proving that the modified Heckel equation can cover both the linear and the nonlinear part of the whole relative density versus compaction pressure profile. During compaction phases, the change of the tablets relative density in the early compaction stages tends to be nonlinear especially in case of plastic materials. Thus, the linear fitting of Heckel equation (Figure 16) leads to decrease the correlation coefficient especially at low pressure values. Figure 16 illustrates Heckel plots of all formulations. The effect MCC Rapid and MCC at the same compaction pressure are observed in Figure 16 (a) and (B) which MCC Rapid gave the lower intercept, showing that MCC Rapid can be compacted at the lower pressure. The effect of DWT on individual material is not profound, as shown in Figure 16 (c) and (d). However, the effect of lubrication on the tablets compacted at high speed (DWT 9.5 ms) is noticeable in case of MCC Rapid tablets (Figure 16 (e) and (f)). The slop of MCC Rapid tablets with lubrication is decreased, showing the reduced plasticity of the powder.

Table 10 Modified Heckel equation parameters

Excipient	Lubrication	DWT (ms)	ρ_{cr}	C [$10^{-3} \cdot Mpa^{-1}$]	R^2
MCC	External	118.3	0.28	4.1	0.99
	External	9.5	0.32	3.5	0.996
	Internal	9.5	0.3	3.9	0.989
MCC Rapid	External	118.3	0.22	4.3	0.998
	External	9.5	0.25	3.7	0.99
	Internal	9.5	0.18	5.9	0.997

Table 11 Heckel equation parameters

Excipient	Lubrication	DWT (ms)	A	K [$10^{-3} \cdot MPa^{-1}$]	σ_y [MPa^{-1}]	R^2	A_0	D_A	D_0	D_B
MCC	External	118.3	0.71	9.3	107.5	0.96	0.63	0.51	0.465	0.043
	External	9.5	0.74	9.0	111.1	0.98	0.65	0.53	0.476	0.047
	Internal	9.5	0.71	9.4	106.4	0.96	0.54	0.51	0.416	0.093
MCC Rapid	External	118.3	0.61	9.2	108.7	0.98	0.49	0.46	0.387	0.068
	External	9.5	0.61	9.0	111.1	0.98	0.47	0.46	0.376	0.079
	Internal	9.5	0.61	11.0	90.9	0.98	0.47	0.51	0.415	0.096

7.2.1.1 Effect of DWT and internal lubrication on ρ_{cr} and D_B D_a D_0

From Table 10, the critical density, ρ_{cr}, derived from modified Heckel equation, for both MCC Rapid and MCC were slightly increased upon the decrease in the DWT, showing that the force transmission at the high tabletting speed is less than at the low speed which consequently the powder would have less ability to be compacted at zero pressure.

In case of internal and external lubrication, both MCC Rapid and MCC compacted at the 9.5 ms DWT gave a slight decrease in the critical density, showing that lubricated powders have the ability to form a compact at zero pressure better than the externally lubricated ones.

Regarding to Heckel equation and corresponding parameters reported in Table 10, the initial density D_a of MCC was higher than MCC Rapid, and in both cases D_0 was independent from the decrease of DWT or addition of lubricant. Values of D_b, which describes the extent of particle rearrangement, were slightly increased with the increase of speed or the addition of lubricant.

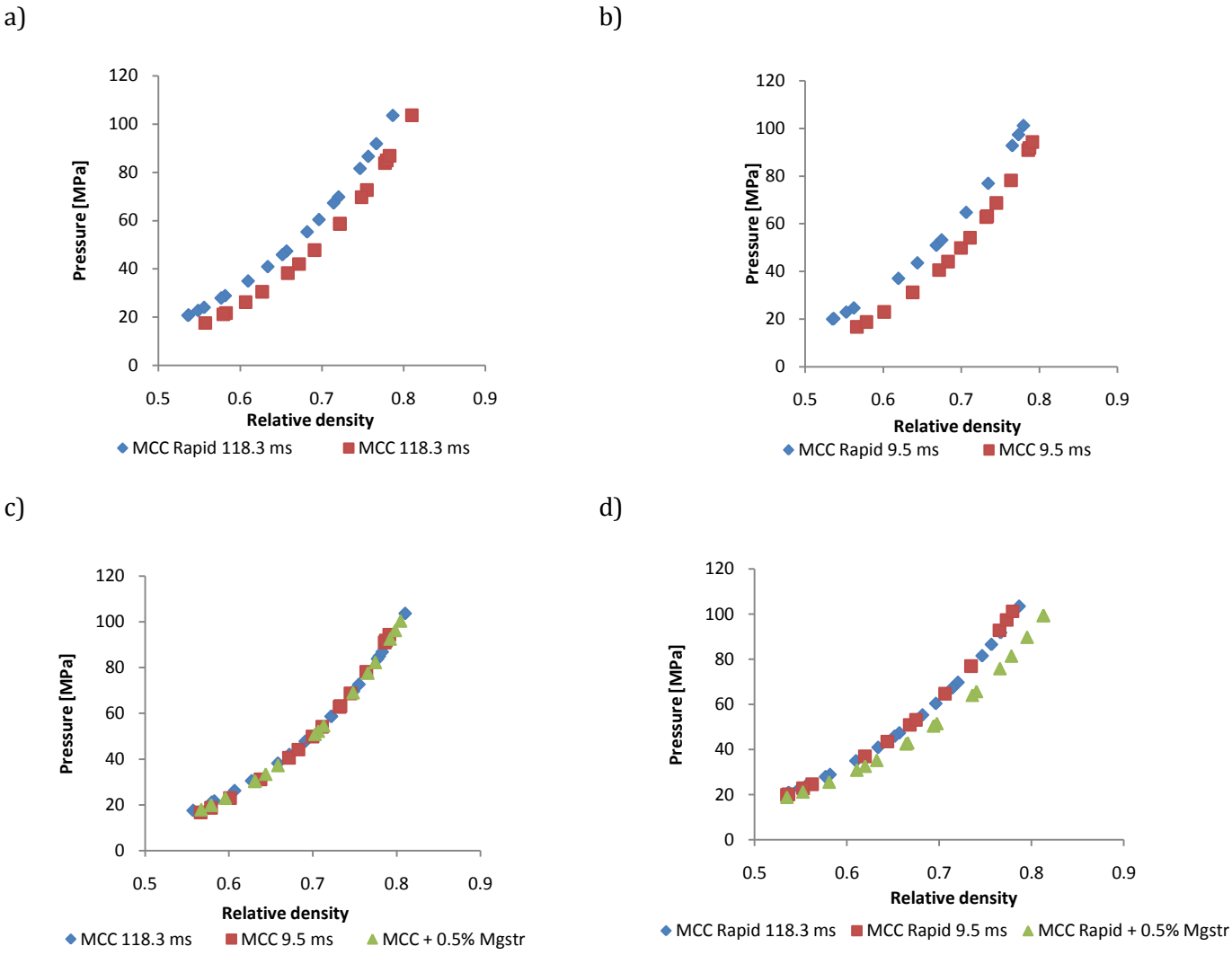


Figure 15 Modified Heckel plots for MCC Rapid and MCC at different DWT, and for both externally and internally lubricated powders.

7.2.1.2 Effect of DWT and internal lubrication on C and K

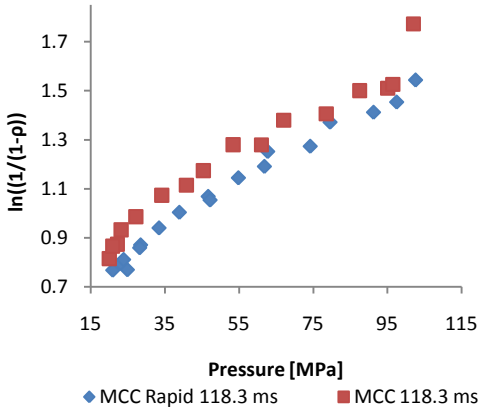
With respect to modified Heckel and Heckel equations, the constants, C and K, represent plasticity of the compacted powder. The higher the constant values the more plastic the material is. From Table 11 and Table 10, values of K and C constants for MCC Rapid and MCC in all tests at different DWT and with external and internal lubrication are in the range of plastic deforming materials [63]. A slight decrease in plasticity has been observed with the decrease of DWT which is common found in plastic deforming materials [64]. Although, in previous study, it was found that cellulose II powder behaves less plastically than cellulose I [8], the result in this study does not present such a significant difference. This is because

many factors can influence the compressibility of the materials, such as, speed of punch, particle shape and size, working conditions and the range of compaction pressure involved in the fitting [65, 66].

Lubricated powders at the same DWT showed increased values of the constant C and K which came in agreement with other studies [67]. The yield pressure values, inversely related to constant K showing that lubrication with Mgstr has increased the compressibility of both materials, but it had more impact on MCC Rapid than MCC. It is interesting to note that lubrication with Mgstr has increased the compressibility of both MCC Rapid and MCC, but it has more impact on MCC Rapid than MCC. This slight change in plasticity of the powders upon compaction can be due to the change of the initial bulk density in the die cavity due to the lubrication [68].

Significant decrease in the constants C and K values with the addition of Mgstr in both MCC Rapid and MCC shows that Mgstr has improved densification of the elongated fibrous particles, thus increases their bulk and tapped densities. This finding shows that the lubrication can improve compressibility of MCC Rapid.

a)



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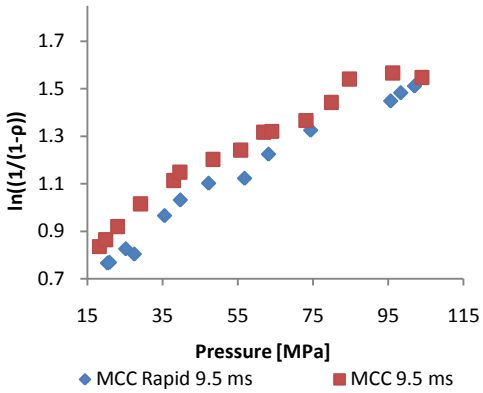

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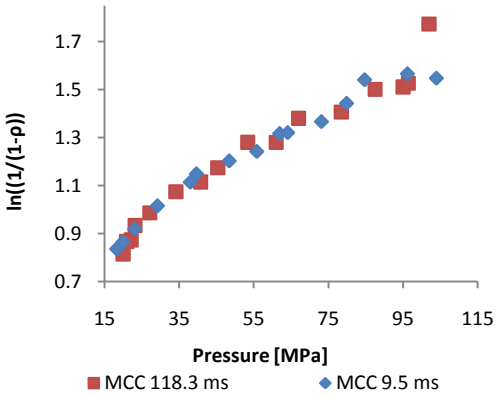

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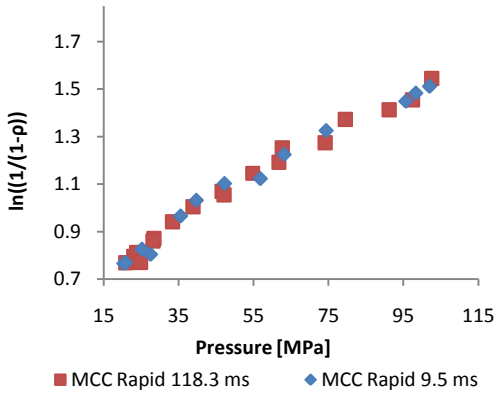

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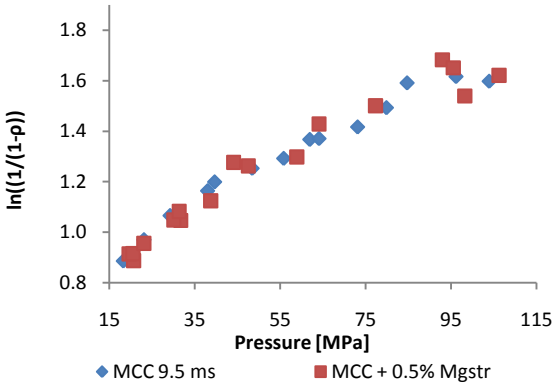


f)

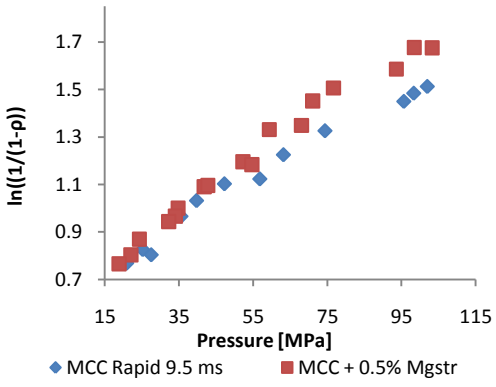


Figure 16 Heckel plots for MCC Rapid and MCC at different DWT, and for both externally and internally lubricated powders.

7.2.2 LEUENBERGER EQUATION

7.2.2.1 Effect of Speed and lubrication on Leuenberger parameters

Through the application of Leuenberger equation, the relation between the type of excipient, DWT, and method of lubrication on compactibility and compressibility of powder systems was observed.

Data in Table 12 show the effect of DWT on the Leuenberger equation constants, both the compactibility (σ_{ymax}) and the susceptibility (γ_t) constants.

Table 12 Leuenberger equation parameters after the fitting of radial tensile strength values

Excipient	Lubrication	DWT (ms)	σ_{ymax} [MPa]	γ_t [$10^{-3} \cdot MPa^{-1}$]	R^2
MCC	External	118.3	12.95±0.21	8.78±0.32	0.998
	External	9.5	12.82±0.36	7.88±0.86	0.998
	Internal	9.5	8.84±0.27	11.24±0.41	0.996
MCC Rapid	External	118.3	9.21±0.94	7.78 ±1.13	0.991
	External	9.5	8.56±0.18	6.46±0.43	0.998
	Internal	9.5	5.4±0.46	11.4±0.3	0.996

The values of Compressibility constant for MCC Rapid and MCC were 7.78 and 8.78 at DWT of 118.5 7.78 and 7.88 at 9.5 respectively. Despite the slight differences in the compressibility constants values, MCC Rapid compressibility behaviour showed to be close to the plastically deforming MCC [63] regardless the compaction DWT times.

In previous study, the compressibility of cellulose I and cellulose II were also evaluated. It was found that cellulose II was less compressible than cellulose I, which does not come in agreement with our finding. This is due to the fact that it was used a narrower particle size distribution (75-105 μm) [8]. The importance of particle size was investigated in studies showing that the densification of the plastic deforming materials could vary depending on the particle size distribution [45, 69-71]. Additionally, other factors such speed, type of the tabletting machine and compaction pressure range were also different, which certainly had could influence the compressibility of the plastic deforming materials [66, 67].

The DWT plays an important role in powder consolidation and densification. The higher the DWT is the more the compact between the punches is exposed to that specific force. Plastic

materials, depending on its elastic extent, tend to retain it particle shape after compaction leading to expansion in the tablet shape. The degree of expansion or elastic recovery is depends on the elastic properties of the material itself. Thus, higher DWT will give the particles more chance to arrange themselves by increasing the bonding points within the tablet [72, 73]. Comparing the compressibility constants of MCC Rapid to MCC, the difference in DWT was insignificant for both excipients at range of the used DWT, showing that the compressibility of the placebo tablets made from MCC Rapid or MCC was robust within the used compaction parameters. C.K Tye et al. [74] found that the effect of DWT was more influencing the porosity of the produced tablets only at DWT time higher than 20 sec. They studied the effect of DWT on compressibility of MCC between the range 8ms-90s, and it was found that DWT had an effect on the compressibility of the MCC mainly when tablets were produced at 20 and 90 seconds respectively.

Internal Lubrication of powders, showed a slight increase in the value of the constant γt, presenting improved densification behavior. This came with agreement with study in which [67, 75] and found that Mgstr concentration and mixing time has slightly decreased the values of the yield strength and kawakita constants after mixing with MCC. This slight increase in compressibility is obviously due the increased initial packing powder in the die cavity, which was also related to bulk and tapped densities of the lubricated

Powder [68, 76].

The DWT plays an important role in powder consolidation and densification. The more DWT the more the compact between the punches is exposed to that specific force. Plastic materials, depending on its elastic extent, tend to retain it particle shape after compaction leading to expansion in the tablet shape. The degree of expansion or elastic recovery is depends on the elastic properties of the material itself. Thus, higher DWT will give the particles more chance to arrange themselves by increasing the bonding points within the tablet [72, 73, 77].

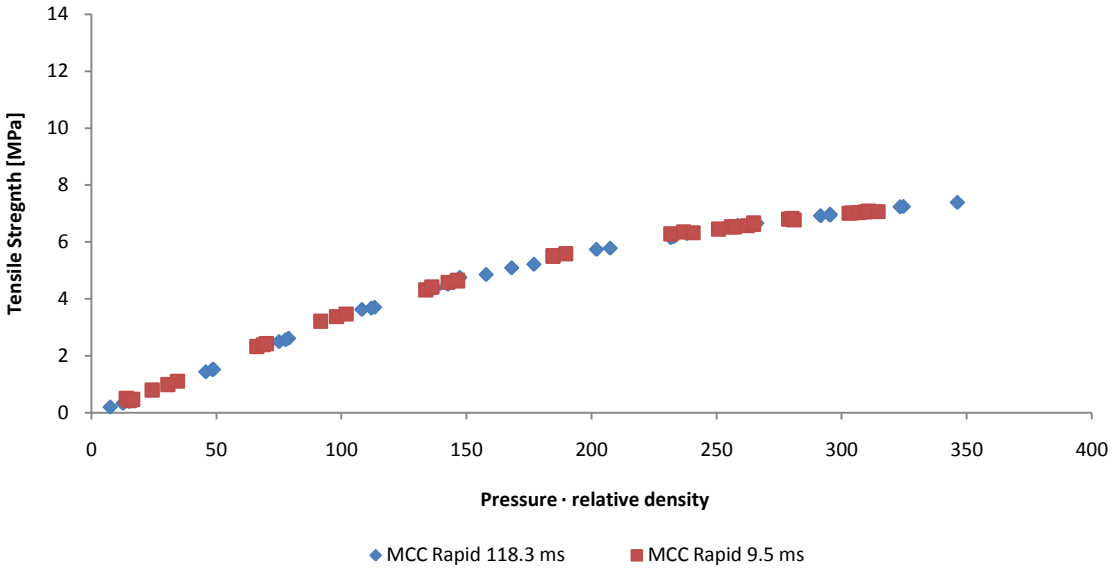


Figure 17 Comparison of the fitted tensile strength into Leuenberger equation of MCC Rapid at DWT of 118.3 and 9.5 ms

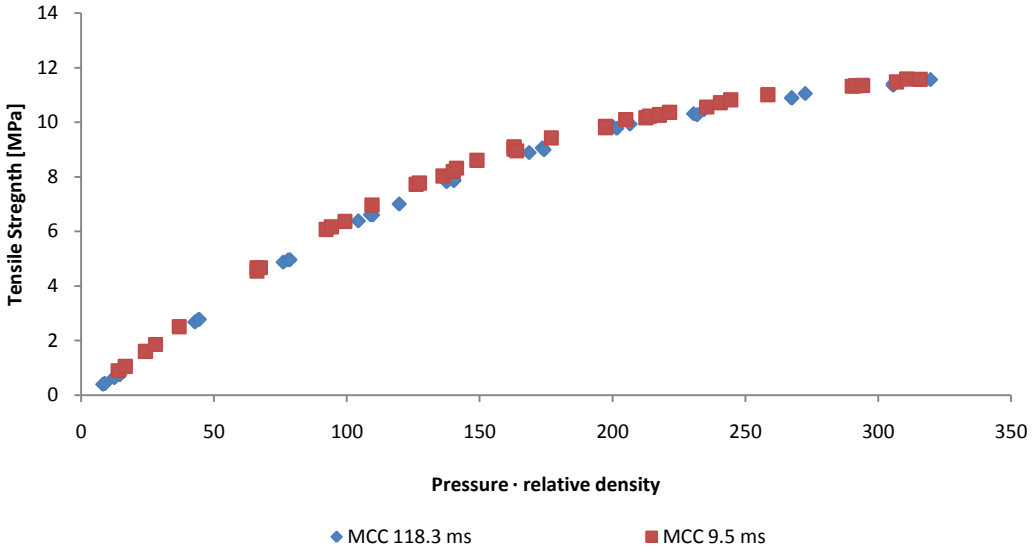


Figure 18 Comparison of the fitted tensile strength into Leuenberger equation of MCC at DWT of 118.3 and 9.5 ms

Although it has been reported that MCC is sensitive to compaction speed, leading to reduction of tensile strength [72], visually, through Figure 17 and Figure 18 MCC Rapid and MCC, respectively, the effect of DWT on both MCC Rapid and MCC was not important, also both Leuenberger parameters were slightly affected by DWT (Table 12). These findings

confirm that both excipients had decreased the degree of the mechanical property changes upon the change of DWT.

Figure 19 denotes that MCC exhibits high ability of forming rigid compacts more than MCC Rapid at the same DWT. Values of MCC Rapid show a good strength of 9.21 and 8.56 MPa at DWT of 118.3 and 9.5ms respectively in comparison to other excipients, including, PEG, lactose α-monohydrate, Starch 1500®, PVC, Eudragit reported previously at 3.3, 1.0, 5.3, 1.13 and 1.02 MPa, respectively [78, 79].

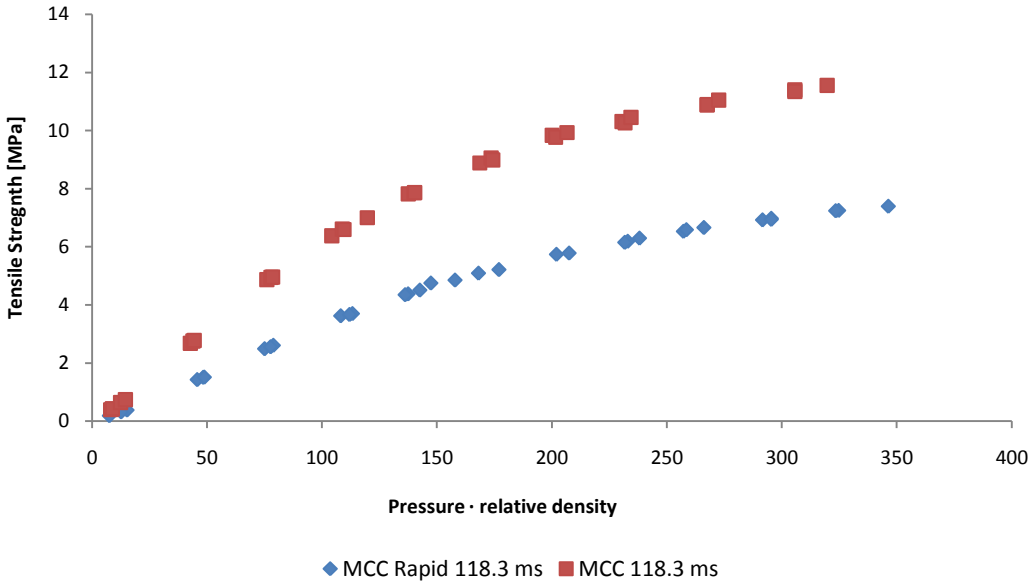


Figure 19 Comparison of the fitted tensile strength into Leuenberger equation for MCC Rapid and MCC at DWT of 118.3 ms

MCC Rapid when compared to MCC it has shown a decreased compactibility properties. Despite of the fact that particle shape and size distribution, water content, and crystallinity are all in favor to give MCC Rapid better compactibility [47], the hydrogen bond formation between the particles of both excipients tends to be more dependent on the fibers polymorphic type rather than other investigated physicochemical properties.

On the basis of the lubricating effect, internal lubrication of dry powders has a negative impact on tensile strength of the tablets presented as the reduced Leuenberger compactibility constant, $\sigma_{ymax,}$ (Table 12). The main reason behind the decrease in the mechanical strength is due to the formation of lubricant film around the powder particle.

This film prevents the formation of excipient-excipient bonding, and substitutes with lubricant-lubricant bonding which are much weaker [80]. This phenomenon of lubricant sensitivity is mainly occurring in plastic deforming materials [67]. In case of materials that deform by fragmentation it does break the lubricant film around its particle and can form excipient-excipient bonding [81].

Figure 20 and Figure 21 illustrated the influence of internal lubrication with Mgstr on the compactibility profiles of MCC Rapid and MCC. Obviously, the effect of lubricant started to have a noticeable impact on compactibility of both MCC Rapid and MCC at around 100 MPa and above, in which at point the compaction phase has entered from the plastic deforming into the strain hardening. Therefore, lower lubricant sensitivity can be achieved when tablets are prepared at lower compaction forces.

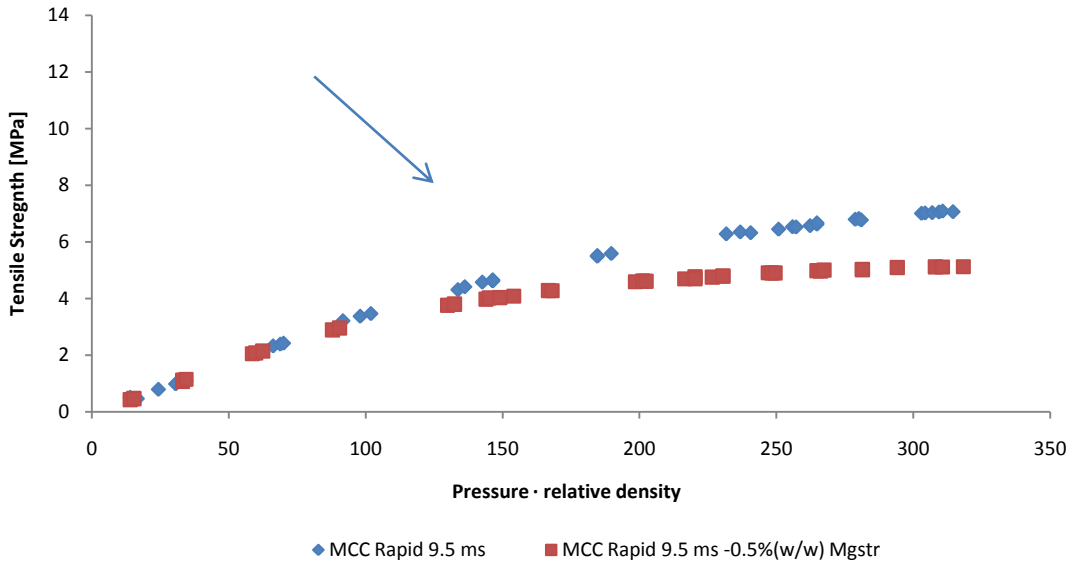


Figure 20 A comparison of the fitted tensile strength into Leuenberger equation of MCC Rapid and MCC Rapid 0.5%(w/w) Mgstr at DWT of 9.5 ms

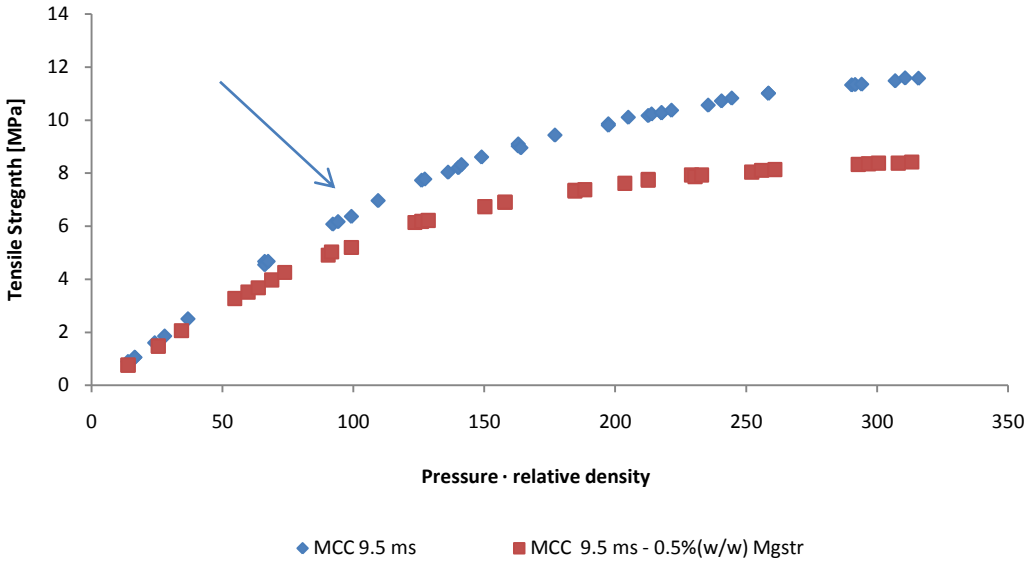


Figure 21 A comparison of the fitted tensile strength into Leuenberger equation of MCC and MCC 0.5%(w/w) Mgstr at DWT of 9.5 ms

The lubricant sensitivity for both investigated excipients is more pronounced in the region where the compaction phase changes from plastic deformation to strain hardening. Therefore, through Leuenberger equation graphical fitting, the lubricant sensitivity of a MCC and MCC Rapid has been estimated more accurately.

According to the traditional sensitivity ratio interpretation [82], to calculate the lubricant sensitivity ratio we need to obtain two crushing strength points, one for the lubricated and the other for none or less lubricated powder at same compaction pressure. Thus it gives a false indication on the lubricity of a certain powder. Because this method does not cover a wide all crushing strengths over a certain compaction range. As discussed before, the lubricant sensitivity appears after the plastic deformation phase in case of plastic deforming materials. Therefore to have a better overview on the lubricant sensitivity, over a wider range of pressures for both excipients, we substituted the crushing strength values in the traditional lubricant sensitivity equation with the compactibility constant, $\sigma_{ymax.}$

Table 13 Lubricant sensitivity ratio of MCC Rapid and MCC

Excipient	Lubricant sensitivity ratio (%)
MCC Rapid	**41.3**
MCC	**31**

Results presented in Table 13 showed lubricants sensitivity ratio according to the new method (equation 17) showed that is MCC Rapid was slightly more sensitive towards Mgstr than MCC. Difference in the lubricant sensitivity ratio is mainly due to the high surface area exhibited by MCC Rapid, therefore increasing lubricity of the excipient [83].

7.2.3 FRIABILITY

We tested the effects of density and DWT on the friability and mechanical resistance of the tablets resulting from wear due to shocks and attrition using standard method in US pharmacopeia. MCC Rapid and MCC tablets were prepared at specific relative densities and different DWT, i.e. Tablets were compacted in cylindrical shape which generally gives a high tendency to be damaged under attrition, compared to other tablet shapes such as concave or capsule shaped tablets. Figure 22, shows that weight loss markedly depends on the relative density. These results came in agreement with results of I.C. Sinka et al. [84]. At a relative density above 0.55, in which the tablets start to build up more rigid compacts, the loss in weight was less than 1%, for both excipients at both DWT.

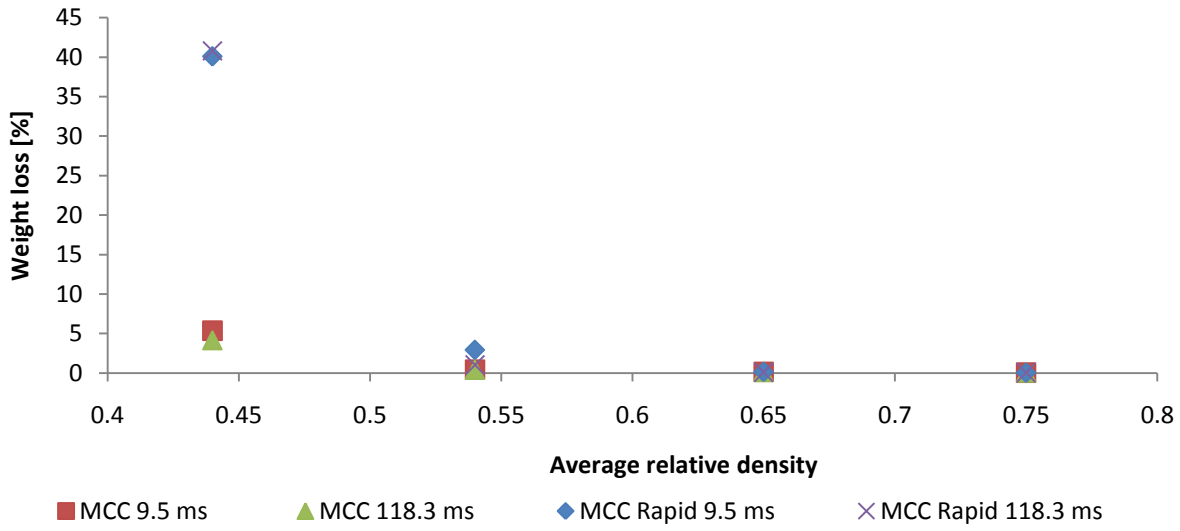
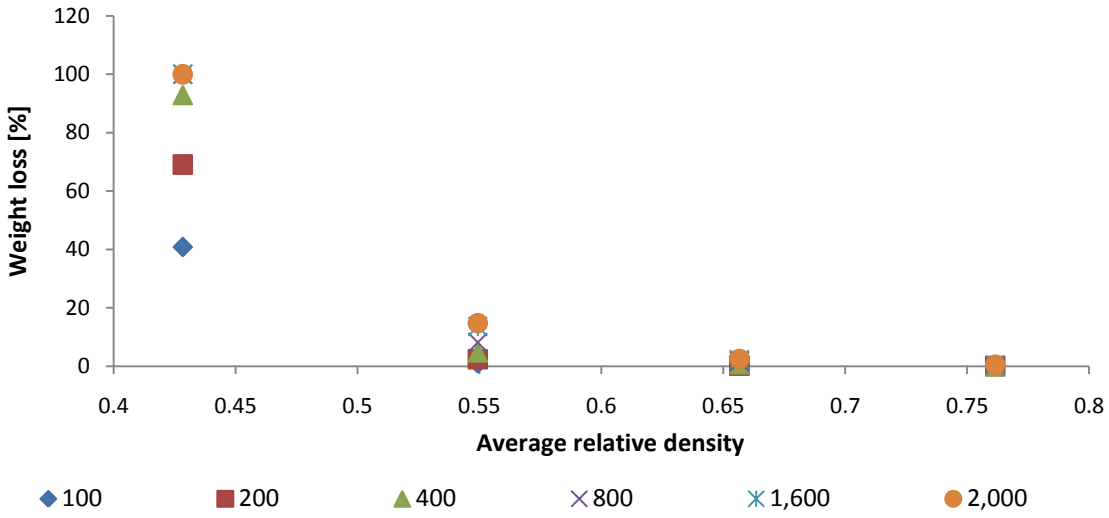


Figure 22 Friability of tablets made of MCC Rapid and MCC at DWT of 118.3 and 9.5 ms

According to percolation theory, tablets exhibits two percolation threshold during its formation. The first one appears when the particle in a powder bed are de-aerated and rearranged in forming an infinite cluster (tapped density state). At further compaction forces at higher relative densities of the tablets, the pore network may no longer form an infinite cluster. Thus, a second percolation threshold appears. In this case we could notice the second percolation threshold around the relative density of 0.55 and reflected on the tablet's physical properties [22, 85].

MCC exhibited lower friability at all relative densities even at the low relative densities in particular, compared to MCC Rapid. The DWT had a slight effect on the friability of MCC, but an increased weight loss was noticeable in case of MCC Rapid at relative density lower than 0.55. This result shows that MCC tablets have superior interparticulate bonding than MCC Rapid. To study these effects in the extreme condition, the friability measurement was extended to the revolution range of 100-2,000 rpm. The result is shown in Figure 23 and Figure 24 .



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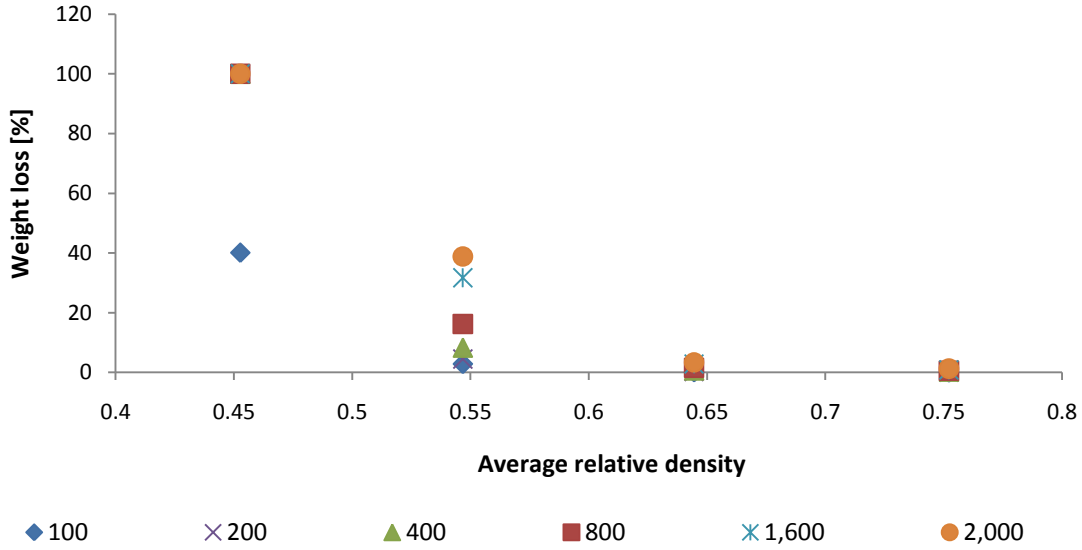
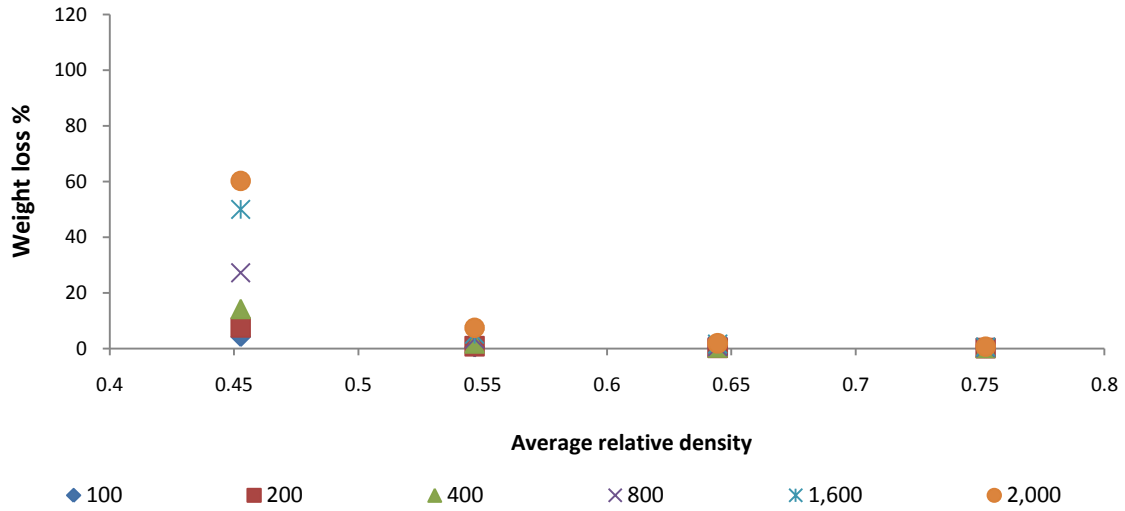


b)

Figure 23 Weight loss of tablets after extended friability measurement at the revolution range of 100-2,000 rpm, a) MCC Rapid at DWT= 118.3 ms, b) MCC Rapid at DWT=9.5 ms

After extended friability measurements, both excipients showed the same behavior where weight loss was apparently reduced at the relative density of 0.55. The influence of DWT was noticed only at extended friability measurement.



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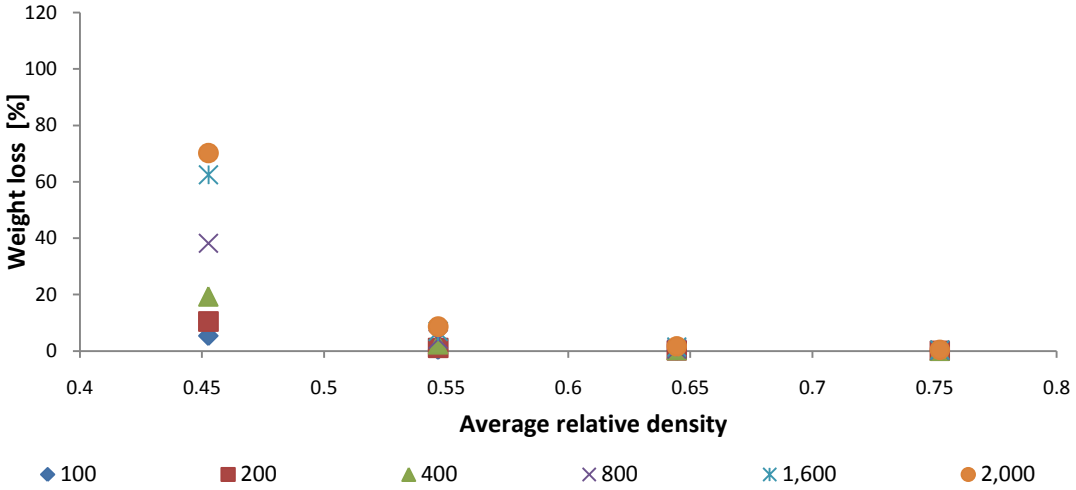


b)

Figure 24 Weight loss of tablets after extended friability measurement at the revolution range of 100-2,000 rpm, a) MCC at DWT= 118.3 ms, b) MCC at DWT=9.5 ms

Generally, the lower the density was the more the friability was influenced by DWT. Additionally; MCC Rapid was more friable than MCC at relative density of 0.45 and below.

Compactibility of both excipients was discussed before. MCC better compaction properties than MCC Rapid as discussed before showing better binding properties between the particles. This excellent binding property of MCC upon compaction explains its good rigidity during friability.

7.2.4 ELASTIC RECOVERY

Elastic recovery (ER) is a typical behavior of plastic deforming materials, including microcrystalline cellulose [8]. Figure 25 presents elastic recovery of both excipients at various relative densities and DWT after compaction.

MCC had less elastic recovery than MCC Rapid at all DWT and densities. The ER values of MCC Rapid were approximately two times more than MCC, showing a greater ability of MCC Rapid to recover elastically. Besides higher elastic recovery, increasing density by mean of compaction force had no significant effect on the elastic recovery. In contrast, MCC tablets exhibited a significant increase in the elastic recovery with the increased density.

DWT had significant effect on MCC Rapid especially at higher relative densities. Tabletting at short DWT apparently increased elastic recovery whereas tablet density did not (significantly) change at longer DWT. On the other hand, in case of MCC, short DWT slightly increased elastic recovery regardless of tablet density. Therefore the elastic energy was higher when materials were compacted at higher compaction speed where short DWT was achievable. The elevated elastic recovery for MCC Rapid compared to MCC, is one of the factors explaining why MCC Rapid is less compactable than MCC. The increase of ER upon the increase of force or decrease of DWT is typical for plastic and viscoelastic materials [72, 86]. AS discussed before we have found that MCC Rapid and MCC are plastic materials, therefore, the observed elastic recovery was expected and confirms that the compaction behavior for both excipients is time-dependent.

The lower elastic recovery of MCC tablets reflects higher inter-particulate bonding of MCC particles than MCC Rapid. The bonding of microcrystalline cellulose particles are commonly reported as hydrogen bonding interaction [87]. It can be taken into account that the difference in interparticulate bonding between MCC and MCC rapid is due to the difference in their polymorphism.

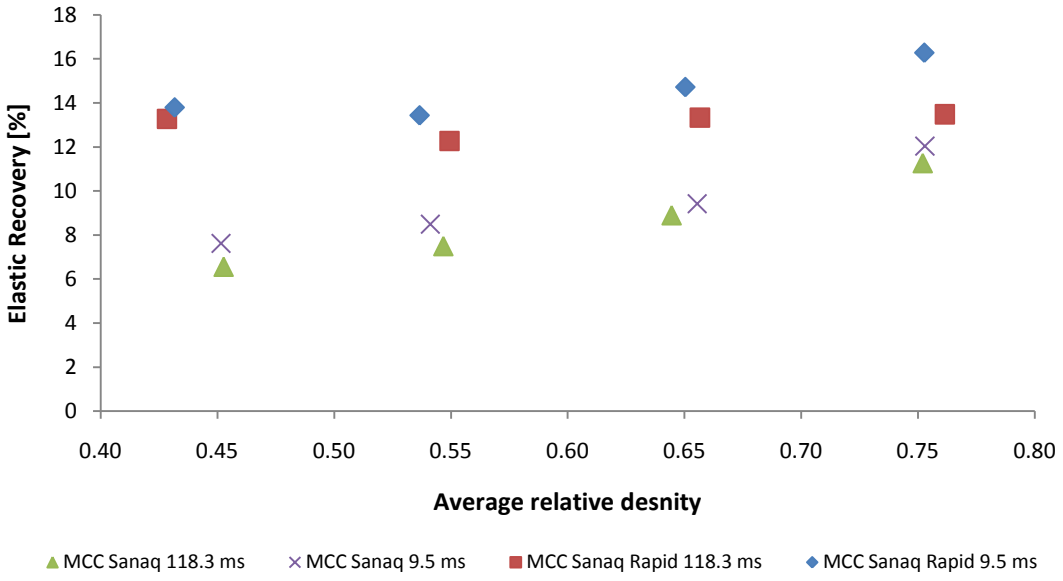


Figure 25 Elastic recovery for MCC Rapid and MCC at various relative densities and DWT at 118.3 ms and 9.5 ms

Elastic recovery, considered to be one of the crucial factors causing capping and lamination, thus to keep the robustness of the tablets, it is important to minimize the release of mechanical energy stored in the tablet after compaction by decreasing the tabletting speed., Moreover, compaction force should be optimized during tabletting process, especially when highly elastic materials are involved in the formulations [88].

7.2.5 Effect of Paracetamol loading and DWT on mechanical properties

Limitations in drug loading of excipients can make the DC of large-dose, poorly compactable drugs impractical. Poorly compactable drugs such as Paracetamol fine powder, and ascorbic acid was employed as drug models in many studies [2]. Many models have been developed, based on percolation theory, to predict the minimum required concentration of excipient to build up a tablet consisting of poorly and good compactable components [7, 89].

In this section we have evaluated the compaction behavior of MCC Rapid and MCC upon loading with Paracetamol as a brittle and poorly compactable material at the same time [90]. The influence of Paracetamol loading, and DWT of tabletting machine at 118.3 and 9.5 ms, was investigated through the application of Leuenberger equation. Measurement of dilution capacity according to the method proposed by Minchom et al. [41] was also used.

MCC Rapid and MCC were mixed in binary mixtures. Each mixture was consisting of MCC Rapid or MCC with Paracetamol in the ranges 0-80% (w/w) DWT was adjusted at 118.3 and 9.5 ms.

7.2.5.1 Compactibility of binary mixtures according to Leuenberger equation

Leuenberger Equation has been widely applied in evaluation of compressibility and compactibility of binary mixture. And here it has been used not only to evaluate influence of loading of poorly compactable drug on Leuenberger equation parameters, but also the DWT.

Tensile strength values were fitted into Leuenberger equation as shown in Figure 26. All parameters for all binary mixtures of both excipients were calculated and reported in Table 14. All results fitted well with Leuenberger equation with the coefficient of determination (R^2) more than 0.97.

Accordingly, MCC Rapid and MCC behaved in the same way of plastic deformation, as the tablet tensile strength was increasing gradually upon increase in compaction pressure. Compactibility constant, σ_{ymax}, was decreasing with the increase of Paracetamol loading Figure 26. Additionally, the compactibility of the binary mixtures containing MCC and Paracetamol was superior to the mixtures of MCC Rapid and Paracetamol mixtures at all Paracetamol loading.

The effects of drug loading and DWT on compactibility by mean of compactibility constant, σ_{ymax}, are presented in Figure 27. The difference in the compactibility behavior especially after Paracetamol loading has been observed. One might expect that percolation thresholds after loading the excipients with Paracetamol. According to percolation theory, a percolation threshold can be distinguished in the behavior of mixtures under compaction. In Figure 27, percolation thresholds were noticed at Paracetamol loading of 20% (w/w) and 60% (w/w).

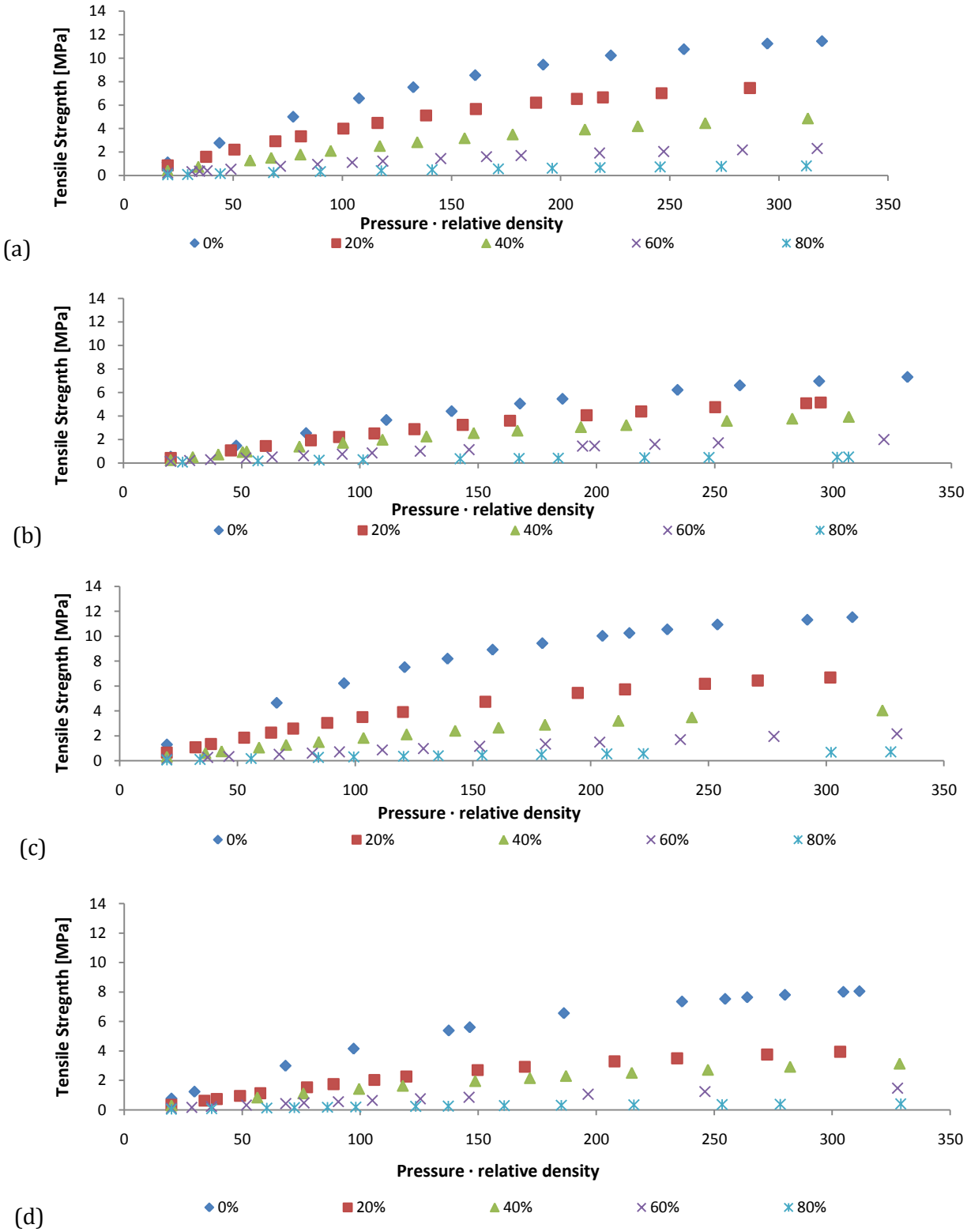


Figure 26 Tensile Strength profiles of MCC and MCC Rapid loaded with Paracetamol at DWT of 118.3 ms and 9.5 ms. Tensile strength and density values were fitted into Leuenberger equation [91].

(a) MCC/Paracetamol (118.3 ms DWT),(b) MCC Rapid/Paracetamol (118.3 ms DWT),

(c) MCC/Paracetamol (9.5ms DWT), (d) MCC Rapid/Paracetamol (9.5 ms DWT)

Table 14 Leuenberger equation parameters for MCC Rapid and MCC. Taking in account Paracetamol loading at DWT of 9.5 and 118.3 ms (n=3)

Paracetamol loading % (w/w)	Excipient	DWT (ms)	σ_{ymax} [10^{-3} · MPa]	γ_t · [10^{-3} · MPa^{-1}]	R^2
0	MCC	118.3	12.95±0.21	8.78±0.32	0.998
		9.5	12.82±0.36	7.88±0.86	0.998
	MCC Rapid	118.3	9.21±0.94	7.78 ±1.13	0.991
		9.5	8.56±0.18	6.46±0.43	0.998
20	MCC	118.3	8.70±0.23	7.87±0.41	0.999
		9.5	8.40±0.71	6.43 ±0.82	0.992
	MCC Rapid	118.3	6.5±0.071	5.81 ±0.25	0.997
		9.5	5.65±0.15	5.4 ±0.22	0.995
40	MCC	118.3	6.43±0.23	5.1±0.33	0.998
		9.5	5.76±0.28	4.62±0.32	0.991
	MCC Rapid	118.3	5.23±0.82	4.45±1.09	0.995
		9.5	4.43±0.24	4.72±0.29	0.993
60	MCC	118.3	4.3±0.2	3.41±0.74	0.995
		9.5	3.86±0.32	2.68±0.27	0.994
	MCC Rapid	118.3	2.879±0.34	4.23±1.06	0.993
		9.5	2.27±0.66	4.76±0.92	0.99
80	MCC	118.3	0.99±0.09	6.39±0.59	0.997
		9.5	0.92±0.12	5.2±0.79	0.976
	MCC Rapid	118.3	0.56±0.07	8.84±2.44	0.989
		9.5	0.47±0.063	7.2±1.42	0.981

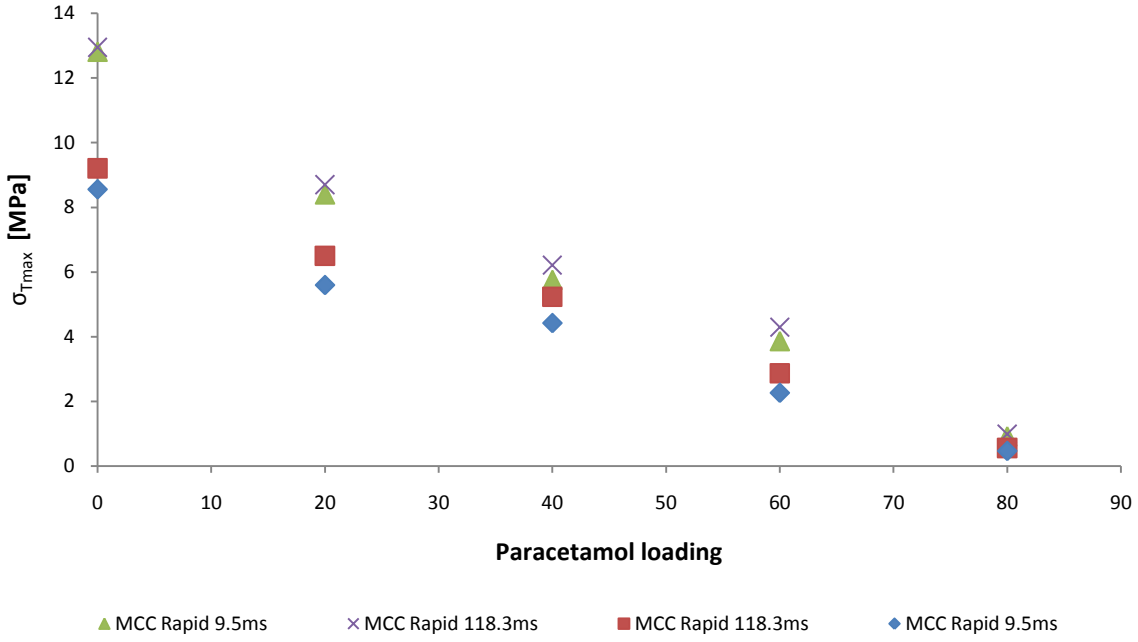


Figure 27 The effect of DWT on the relationships between the compactibility (σ_{Tmax}) and mixture compositions: (a) MCC /Paracetamol and (b) MCC Rapid/Paracetamol

Also the effect of DWT was visually observed; showing a decrease in compactibility behavior of both when after applying DWT of 9.5 ms. influence of DWT was more pronounced between 20-60% (w/w) of Paracetamol loading. The percentage of the decrease in compactibility constant, σ_{Tmax}, of the loaded excipients after decreasing DWT were plotted against the Paracetamol loading, as shown in

MCC Rapid was slightly more sensitive than MCC towards the change in DWT at all drug loadings. Add to that, the DWT sensitivity was increasing with the increase of Paracetamol loading until it reached 60% (w/w), a sudden drop in DWT sensitivity was observed. Thereby, a percolation threshold of Paracetamol loading in MCC and MCC Rapid tablet was noticed.

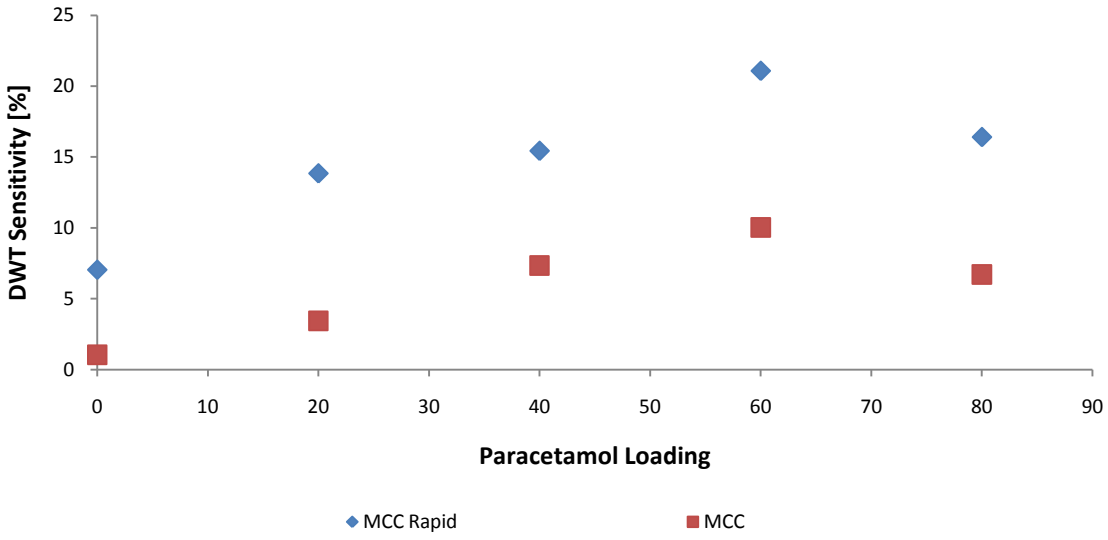
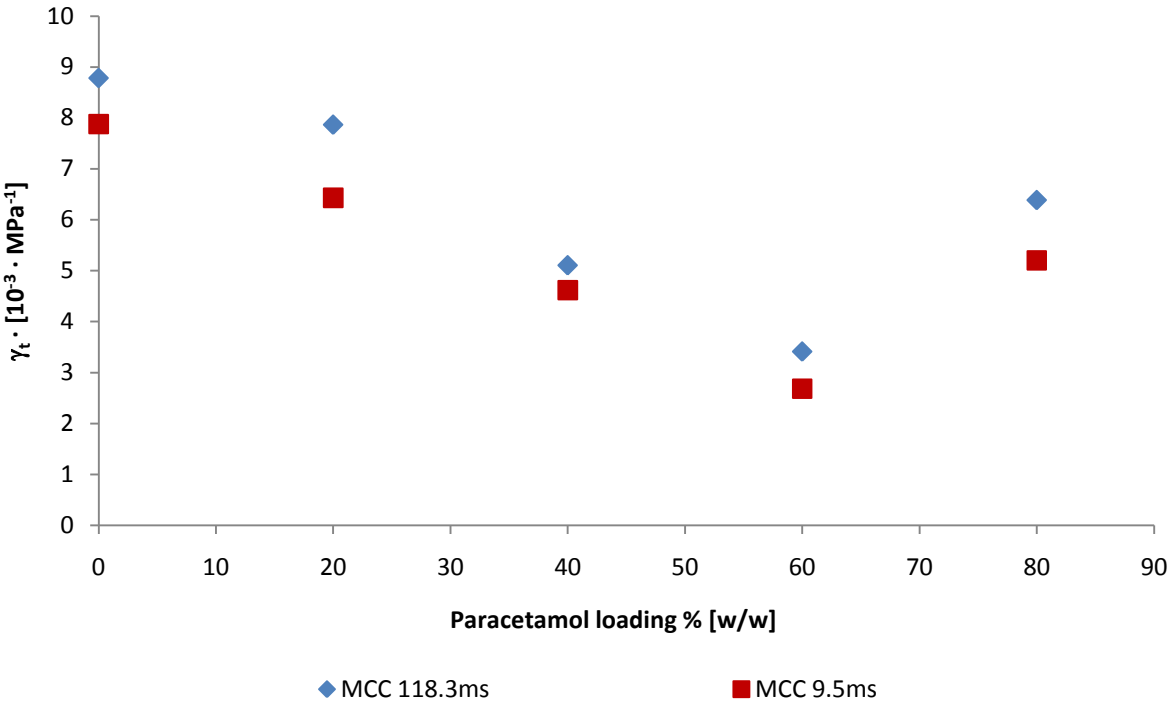


Figure 28 Influence of Paracetamol loading on the DWT sensitivity of MCC and MCC Rapid tablets and mixture compositions

The excipients in this case are considered to be the binding part of the system which builds the tablet, and Paracetamol, as a poorly compactable drug, acts as the destructive part in the tablet. With the increase of the Paracetamol loading, the destructing part, starts percolating it dominates the whole phase at higher concentrations, leading to a decline in the tensile strength [32]. Between 0-20% (w/w) of Paracetamol loading, the excipient properties were dominating the phase. The second phase in which the property of both the excipient and Paracetamol are dominating the tablet properties. Until Paracetamol loading of 60% (w/w) a third phase has been formed in which Paracetamol properties are dominating the tablet properties.

Sensitivity towards DWT has been observed increasing sharply upon Paracetamol loading 20-60% (w/w) that is DWT sensitivity is increased in the second phase between the lower and upper percolation thresholds.



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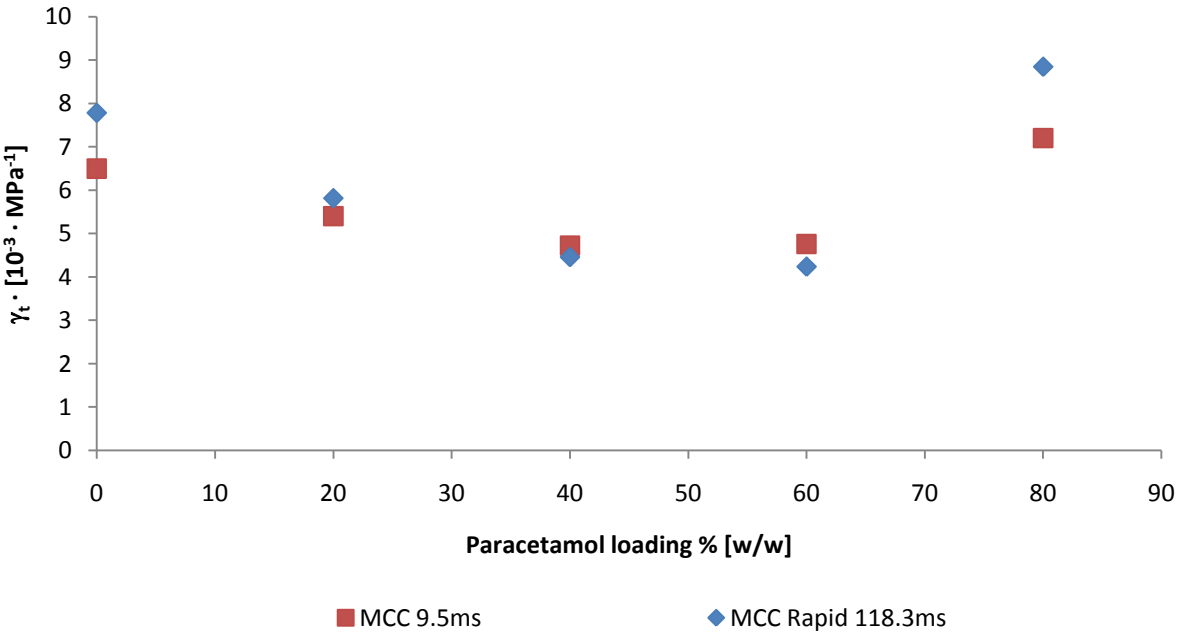
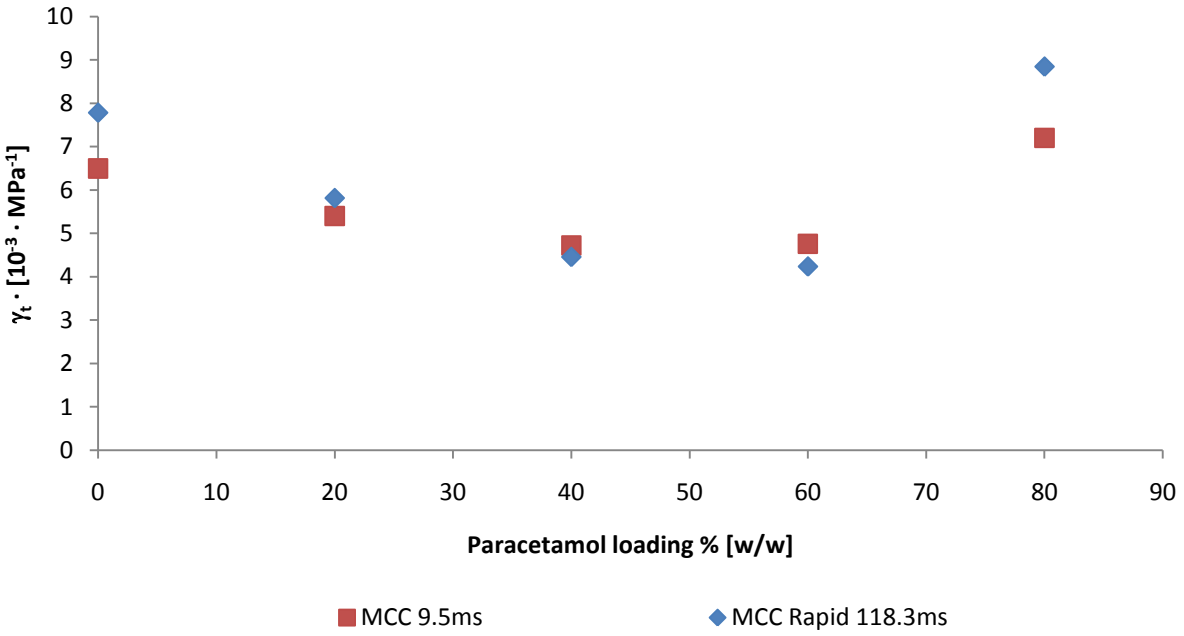


b)

Figure 29 Effect of DWT on compressiblity constant(γ_t) and mixture compositions: A) MCC /Paracetamol b) MCC Rapid/Paracetamol



b)

Figure 29 shows the relationship between the compaction susceptibility, γ_t, and Paracetamol loading of excipients, MCC Rapid and MCC at DWT of 118.3 and 9.5 ms. Percolation thresholds were also observed in both excipients. The upper percolation threshold was observed at Paracetamol loading of 20% (w/w) and the lower percolation threshold was noticed at 60% (w/w). However, in case of MCC the critical Paracetamol loadings at each percolation threshold were more pronounced than those in MCC Rapid. The Influence of DWT on the excipients was more significant in case of MCC Rapid.

The more the excipient was loaded, the less the compressibility constant was yield. The decreased compressibility reached the percolation threshold where a change in the powder consolidation behavior was occurred. In the phase were Paracetamol starts percolating the excipient phase, both the adhesive bonding start to dominate the tablet structure, leading to decrease in the compressibility constant, γ_t . When the third phase starts to take place after Paracetamol loading of 60 %(w/w) the cohesive bonding is back, but within the Paracetamol particles itself, thus it led to sudden shift in the compressibility constant, γ_t. The effect of DWT on compressibility was remarkable in case of MCC Rapid as the values of

compressibility constant were increased with the decrease of DWT. However, DWT had no significant influence on compressibility of MCC.

The interaction occurred in the binary mixtures used for all results mentioned above, were a result of changes in the tabletting mechanical properties controlled by different type of bonding. Compactibility and compressibility profiles upon loading into can be divided into three phases. Each phase represent a different type of bonding. The first phase was mainly due to cohesive bonding, between the excipient particles themselves. The second phase is due to the adhesive boding between the excipient and Paracetamol particles, and the third phase is consisting mainly from cohesive bonding between only Paracetamol particles. When two powder materials of brittle fracture property are mixed together or a single brittle powder material is mixed with another plastic deformation material to form compacts, one can expect to observe at least one percolation threshold to occur at a certain concentration of the mixtures [92]. This interaction can either be an increase or decrease in the tensile strength of the tablets. This is also made possible due to the gradual changes of the bonding properties in the tablets throughout the mixture compositions. Changes in shapes and sizes of brittle fracture particles and their interactions in terms of intermolecular forces with other materials of similar or different deformation properties after compaction and the possible presence of solid bridges and mechanical interlocking between particles may contribute to such phenomenon [79].

In case of the compactibility profiles, the poorly compactable properties of Paracetamol was dominating it brittle behavior. Thus the interaction was only found during measuring the sensitivity of these bonding towards DWT.

The increased sensitivity in DWT in the second phase at 20-60% (w/w) Paracetamol loading for both excipients shows that compactibility of both excipients is sensitive. It is clear that the adhesive bonding between Paracetamol and the excipients are more sensitive than the cohesive bonding dominating the first and second phases. With the increase of Paracetamol loading in the second phase, the adhesive bonding between the excipient and Paracetamol particles is also increasing. Obviously, these adhesive bonding is considerably weaker and more sensitive than the cohesive bonding among a component (either Paracetamol or the excipient) particles itself. The adhesive bonding reached its maximum

only when Paracetamol has completely percolated into the excipients phase, in which the contact between the different particles is equal, thus, at 60% (w/w) the highest DWT sensitivity has been noticed.

In the compressibility profiles, the interactions were more obvious, due to the fact that the compressibility is more depending on the mechanism of deformation of a material than strength of bonding between its particles. As explained before the compactibility and compressibility profiles upon loading into three phases. Each phase represent a different type of bonding. The first phase was mainly due to cohesive bonding, between the excipient particles themselves. The second phase is due to the adhesive boding between the excipient and Paracetamol particles, and the third phase is consisting mainly from cohesive bonding between Paracetamol [91].

Maximum interaction was observed in which all powder mixtures showed a minimum compressibility value as a result of the equilibrium between cohesive and interparticulate bonding of two different deforming materials. MCC and MCC Rapid, as mentioned previously, showed a plastic characteristic and elastic recovery to a certain degree, added to the well known high elasticity of Paracetamol particles and its shape combined with the particles of MCC and MCC Rapid. This would contribute in the decrease of compressibility constant, γ_t, at the percolation threshold at 60% (w/w) [79, 93].

The higher the compressibility constant is, the sooner the plateau of the tensile strength will be achieved, if accompanied with a low σ_{Tmax}, which is typical behavior for brittle materials. Therefore, it has been noticed a relatively higher compressibility constant value at Paracetamol loading of 80% (w/w). At this point Paracetamol started to coat around the excipients particles, thus, Paracetamol-Paracetamol bonding starts to take place upon compaction, dominating the physical property of the tablets [31], and due to its brittle property the constant value was elevated [19]. In conclusion, the interaction due to bonding between two different deforming materials, led to decrease in compressibility at loading of 60% (w/w). This decrease in compressibility was due to the increase in elastic recovery. Therefore due to the increased elastic recovery at this Paracetamol loading the compactibility constants were more sensitive towards the change in DWT.

7.2.5.2 Dilution capacity

Tensile strength profiles of all powder mixtures is presented in Figure 30 showing that increasing drug concentration reduced tensile strength of the powder compacts.

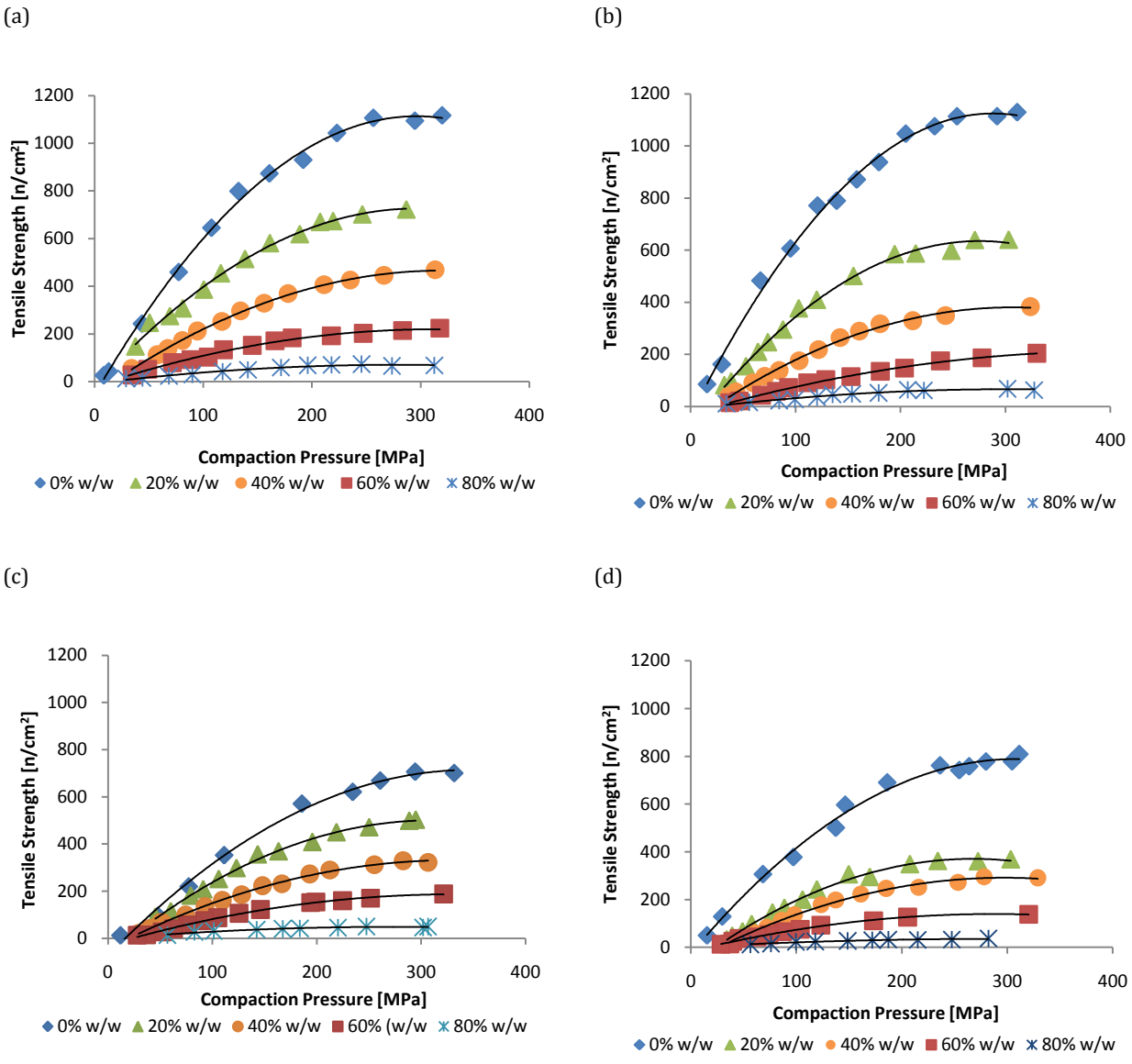
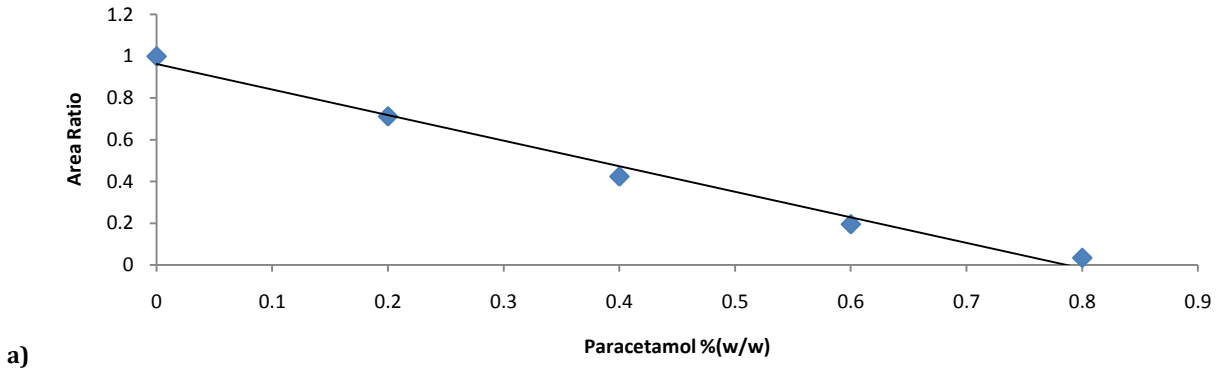
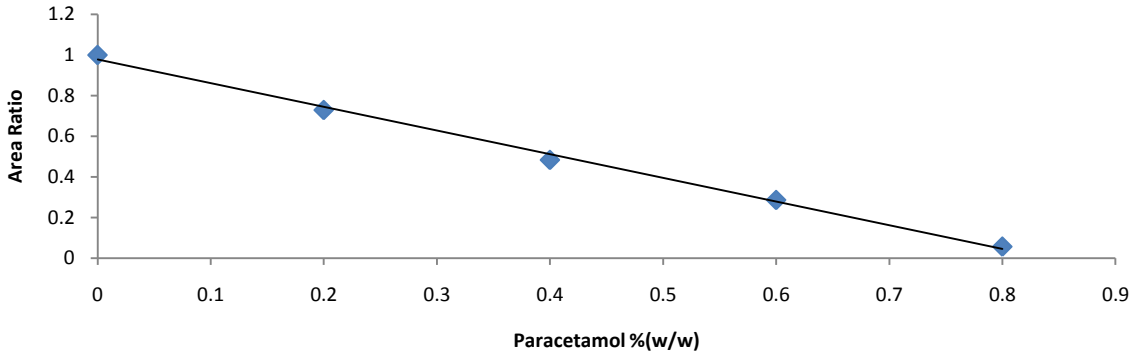


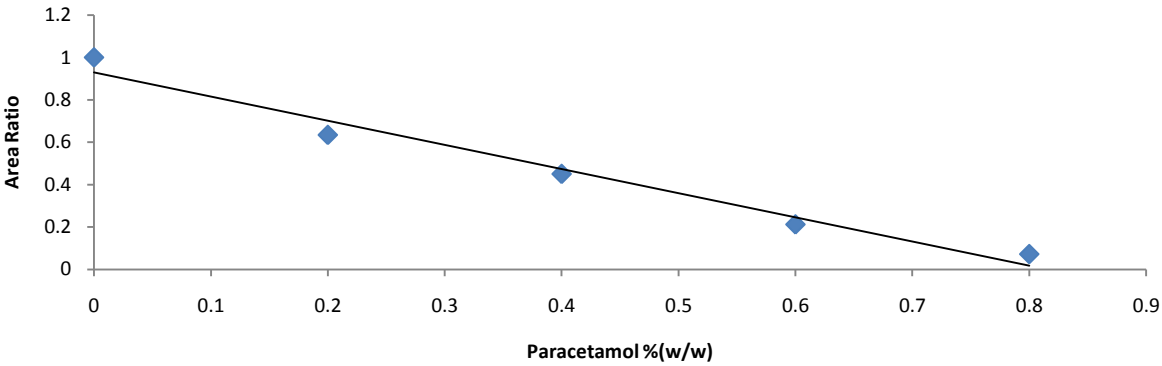
Figure 30 Compaction profiles MCC Rapid and MCC at various Paracetamol loading at different DWT, (a)MCC 118.3 ms (b)MCC 9.5 ms (c) MCC Rapid 118.3 (d)MCC Rapid 9.5 ms



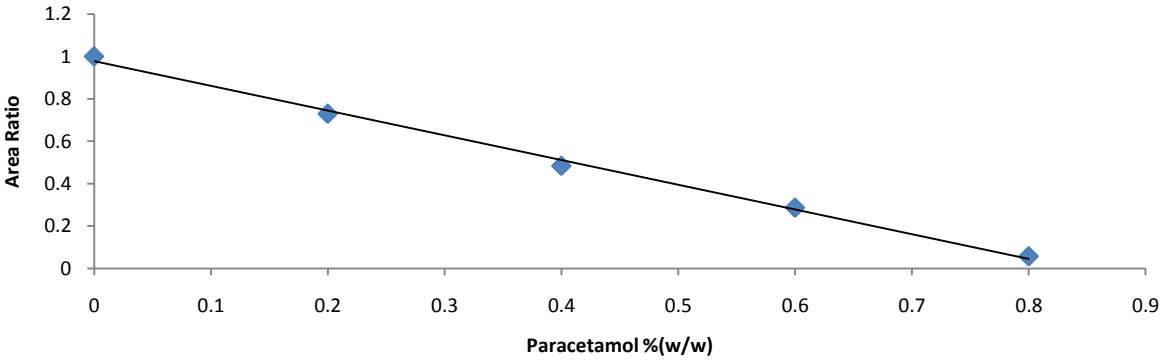
a)



b)



c)



d)

Figure 31 Work potential vs. % (w/w) Paracetamol for all binary mixtures at different DWT (a)MCC Rapid 9.5 ms DWT, (b) MCC Rapid 118.3 ms DWT (c) MCC 118.3 ms DWT (d) MCC 9.5 ms DWT

Both MCC Rapid and MCC are considered plastic materials, thus the curvature and gradual decrease of tensile strength profiles upon Paracetamol loading was expected, considering Paracetamol poorly compactable material at the same time. Subsequently, the measured AUC obtained by the fitted quadratic equation between the compaction limits is decreased.

To find the work potential of the excipient, we normalized the AUC of each binary mixture of the excipient and Paracetamol by the AUC of the original excipient. The plots of work potential, as the area ratio, against % (w/w) Paracetamol gave a linear relationship as shown in Figure 31. Regression and back extrapolation to the work potential of zero were analyzed for the dilution capacity and listed in Table 15. This dilution capacity value reflects the minimum amount of a specific excipient to form a tablet with poorly compactable drug incorporation.

Both excipients showed relatively high dilution capacity compared to the dilution capacity reported by others (65%) [40, 41]. This difference can be explained based on the different pressure ranges and extrapolation techniques applied. In this study, the fitting range reached up to 80% (w/w) Paracetamol, which gave higher back extrapolated values at zero work potential besides the fact that tabletting conditions and methods were not identical.

Table 15 Dilution Capacity of MCC Rapid and MCC at different DWT

Excipient	DWT (ms)	Dilution Capacity [%]
MCC Rapid	118.3	84
	9.5	79
MCC	118.3	82
	9.5	81

Excipients showed slight difference in dilution capacity at DWT of 118.3 ms. Dilution capacity of MCC Rapid was more influenced by compaction speed, showing a decrease around 5% at DWT of 9.5 ms, compared to 1% in case of MCC. This means that MCC Rapid can hold lower amount of Paracetamol at shorter DWT. Moreover, Paracetamol is well known to have high elastic energy which is not used for bonding but stored as deformation energy under stress. The release of this stored energy at the end of a compaction cycle allows the particles to return to their original shape and so rupture weak

particle-particle bonds, thus, decreasing compactibility [94, 95]. Therefore more energy is required to form the tablets at shorter DWT and overcome the increased cohesiveness of particles that occurs at higher compaction speed [96].

The time-dependent consolidation of the powder mixtures of Paracetamol and plastic excipients influences the tensile strength of their tablets. Therefore sufficient time required for stress relaxation and plastic deformation is not available at shorter DWT. In other words the materials become more elastic at higher compaction speeds, and subsequently the tensile strength becomes lower [18].

7.3 *EVALUATION OF IN-VITRO PERFORMANCE*

7.3.1 DISINTEGRATION RESULTS

Disintegration is considered to be a limiting step in case of tablets designed for immediate release. In immediate release tablets, the tablets usually are disintegrated into smaller particles, leading to increase in surface area around the drug particles. Therefore disintegration has a great impact on the dissolution properties tablets. The formulations have been tailored in a way we can test the disintegration behavior at different concentrations. In a different set of experiments we tested the effect of mixing with Mgstr, a hydrophobic lubricant.

To minimize the influence of porosity, tablets were prepared at the minimum porosity of 10-13%. The increase in porosity affects the capillary network inside the tablet, thus, affecting water penetration behavior [36], consequently water uptake and disintegration of the tablets.

7.3.1.1 Influence of drug loading on IBU tablets disintegration

Overall, MCC Rapid showed a robust disintegration behavior despite IBU loading, as shown in Figure 32. Additionally, all tablets disintegrated in less than 26 seconds, exhibiting an extraordinary super-disintegrating property. In contrast, MCC tablets exhibited a fast disintegration, only at the drug loading higher than 50% (w/w) as shown in Figure 33. The effect of drug loading was more pronounced than disintegration profiles of tablets containing MCC Rapid. A curvature, showing optimum disintegration times at IBU loading between 50 – 90 % (w/w). That is we can conclude at the point where MCC lost its domination on in tablet phase, the disintegration of tablets was improved showing that the MCC properties as a disintegrant are week.

The performance of super-disintegrants in many cases is concentration dependent. For disintegrants such as starch 1500, in which a critical concentration is observed exhibiting a v-shaped disintegration profile which shows typical (V) shaped disintegration profile because of the swelling properties of the disintegrant[34-36]. In case of Ac-Di-Sol for it was found that the critical concentration of this super-disintegrant lies around 3% (v/v) also due to its swelling disintegration properties [97]. In this study MCC and MCC Rapid as disintegrant showed no obvious critical concentration this is due to the fact the MCC Rapid

disintegration mechanism is mainly depending on the "wiking" or diffusion effect of water. Therefore the higher concentration of the disintegrant or filler, the higher the affinity towards water is. Thus, no branching within network of pores inside the tablet that leads to suppress the disintegration performance.

MCC Rapid showed an elevated moisture isotherms and showed higher hygroscopicity than MCC, showing higher affinity towards water and consequently increased water uptake. Water uptake has an important role in tablet disintegration [98, 99]. The high water uptake rate of the MCC Rapid tablets leads to breakage of the hydrogen bonding among particles Caused by hydrostatic pressure inside the tablet, this mechanism of disintegration is considered mainly as wicking. MCC Rapid has proved to exhibit a very low degree of swelling, which has no role in the tablets disintegration mechanism [7]. Mechanism of disintegration by repulsion is also proposed. MCC Rapid tablets upon compaction showed a great extent of elasticity. Therefore upon the breakage of the hydrogen bonding between the particles due to water uptake, the particles have a great tendency to retain its shape. This reformation of the shape leads to repel the particle from each other thus enhancing disintegration as seen in photos in Table 17.

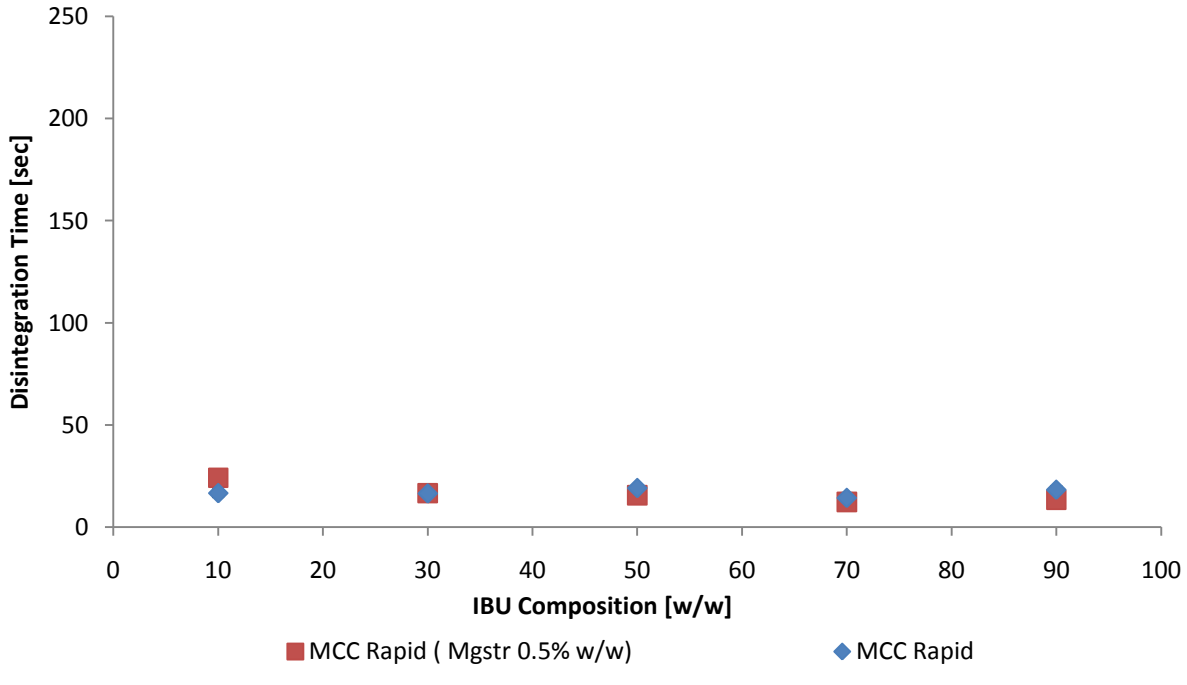


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Figure 32 **Disintegration profile showing the effect of IBU and Mgstr on MCC Rapid disintegration behaviors IBU tablets containing MCC Rapid at various IBU loading.**

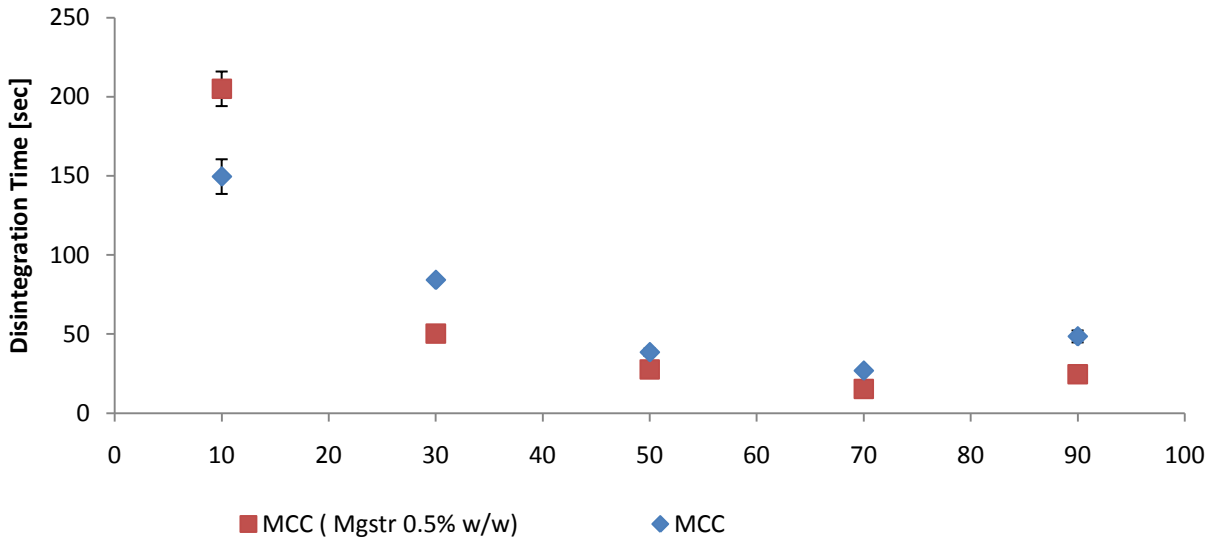


Figure 33 Disintegration profile showing the effect of IBU and Mgstr on MCC disintegration behaviors IBU tablets containing MCC at various IBU loading.

7.3.1.2 Influence of Mgstr on IBU tablets disintegration

Hydrophobic lubricants induce a negative effect on the disintegration of tablets [100], especially those tablets containing fillers which disintegrate by dissolving or dissolution. Also a greater impact has been noticed in the case of tablet containing a poorly soluble drug. During mixing with lubricants, a lubricant starts to coat the particles and form hydrophobic layer which delays the wetting of particles and consequently water uptake and disintegration time [80].

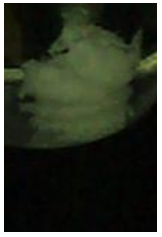
Table 16 Disintegration times of IBU/MCC Rapid, IBU/MCC at different loading internally and externally lubricated.

	Disintegration [sec]			
	MCC		MCC Rapid	
IBU % (w/w)	Internal*	External	Internal*	External
10	205±11	149.5±10.9	26.3±17.6	16.7±1.9
30	50.3± 1.2	84.2±2	16.7±1.9	16.5 ±1.0
50	27.67± 2.3	38.5±4.9	15.7±3.8	19.1±1.3
70	15.3 ±0.8	26.8±1.6	12.3±2.8	14.3±2.5
90	24.7 ±3.8	48.5±4.8	13.3±1.9	18.3±1.9

***mixed with 0.5% (w/w) Mgstr for 5 min**

Table 16 summarized the disintegration times of IBU tablets comparing formulations containing MCC and MCC Rapid. Comparing the method of lubrication we found that IBU tablets containing MCC mixed with magnesium stearate, had a significant influence on MCC formulations ($P<0.05$). The negative effect on the disintegration times was only observed at MCC tablets containing IBU 10% (w/w). On further IBU loadings (50-90% w/w) Mgstr had insignificant effect and even lower disintegration times than those containing Mgstr. Additionally Mgstr had no significant effect on the disintegration of MCC Rapid tablet ($P>0.05$) over the whole range of densities (Figure 34). This confirms the results above showing the insignificance of lubrication with Mgstr on MCC Rapid tablets. Also it shows that there is critical relative density in which a higher disintegration times are exhibited.

Table 17 Snap shots showing disintegration of MCC and MCC Rapid tablets prepared at lowest possible relative density (0.88). No agitation was included, and media was distilled water.

Time Interval [sec]	**2**	**4**	**6**	**8**	**10**
MCC Rapid					
Time Interval [sec]	**2**	**4**	**6**	**8**	**10**
MCC					
Time Interval [sec]	**12**	**14**	**16**	**18**	**20**
MCC Rapid					
Time Interval [sec]	**12**	**14**	**16**	**18**	**20**
MCC					

This shows that the extent to sensitivity towards Mgstr can be related excipient loading that is hydrophilic properties of MCC Rapid and MCC at high loading is more affected. Upon drug loading with IBU, the total true density of the mixture has been reduced. Therefore both bulk density and flowability was affected by IBU loading negatively. The increase of bulk density and indirectly the powder flowability have proved to increase lubricant sensitivity due to increased agitation of powder during mixing [76].

Additionally Mgstr had no significant effect on the disintegration of MCC Rapid tablet ($P>0.05$) over the whole range of densities (Figure 34). This confirms the results above showing the insignificance of lubrication with Mgstr on MCC Rapid tablets. Also it shows that there is critical relative density in which a higher disintegration times are exhibited.

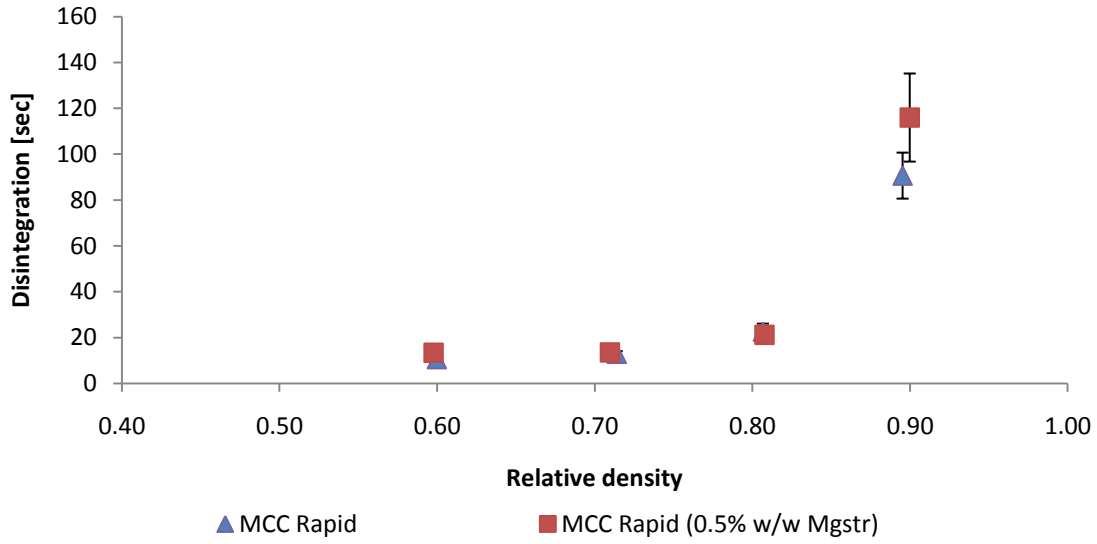


Figure 34 Effect of lubricant on MCC Rapid at different predetermined densities.

7.3.1.3 Relation between tensile strength and disintegration of IBU tablets

Tensile strength of a tablet shows the extent of how strong the particles are bonded together. Usually, increase in tablet tensile strength lead to increase of disintegration time.

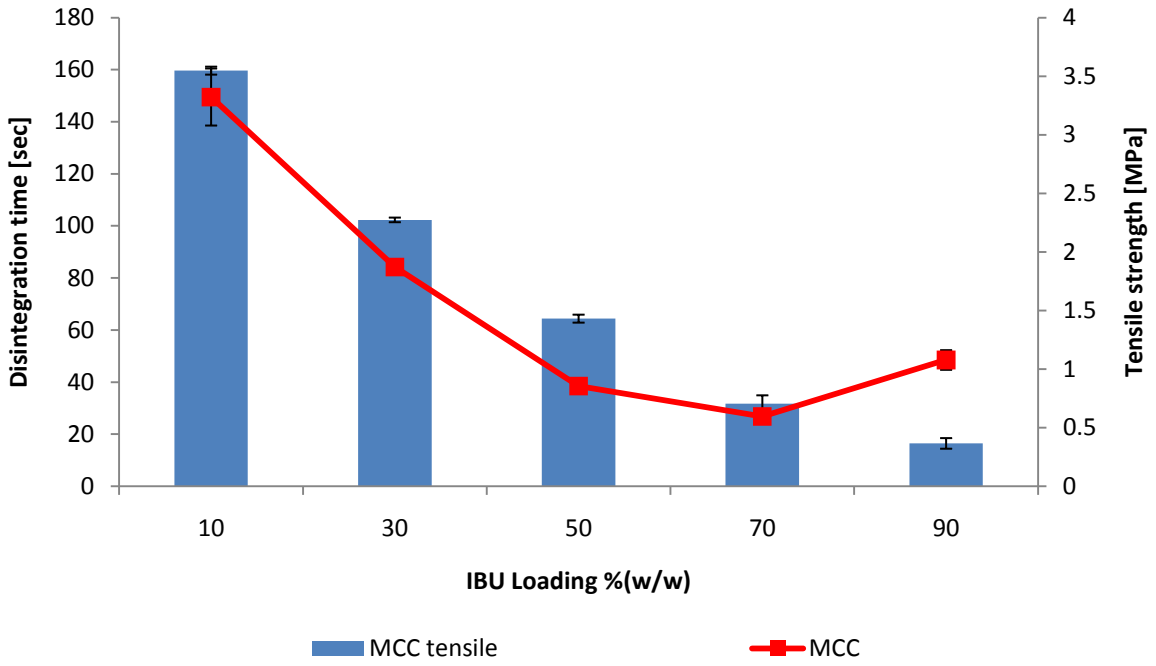


Figure 35 represents both the disintegration and tensile strength of MCC tablets loaded with IBU. A correlation between disintegration time and tensile strength was observed in case of IBU tablets containing MCC as filler. The higher the IBU loading is, the lower the tablet tensile strength. MCC as a filler is considered to be one of the best compactable excipients. This excellent compactibility and tabletability of MCC due to the high ability of bonding formation between the particles of MCC tablets, leading to a negative effect on the disintegration behavior.

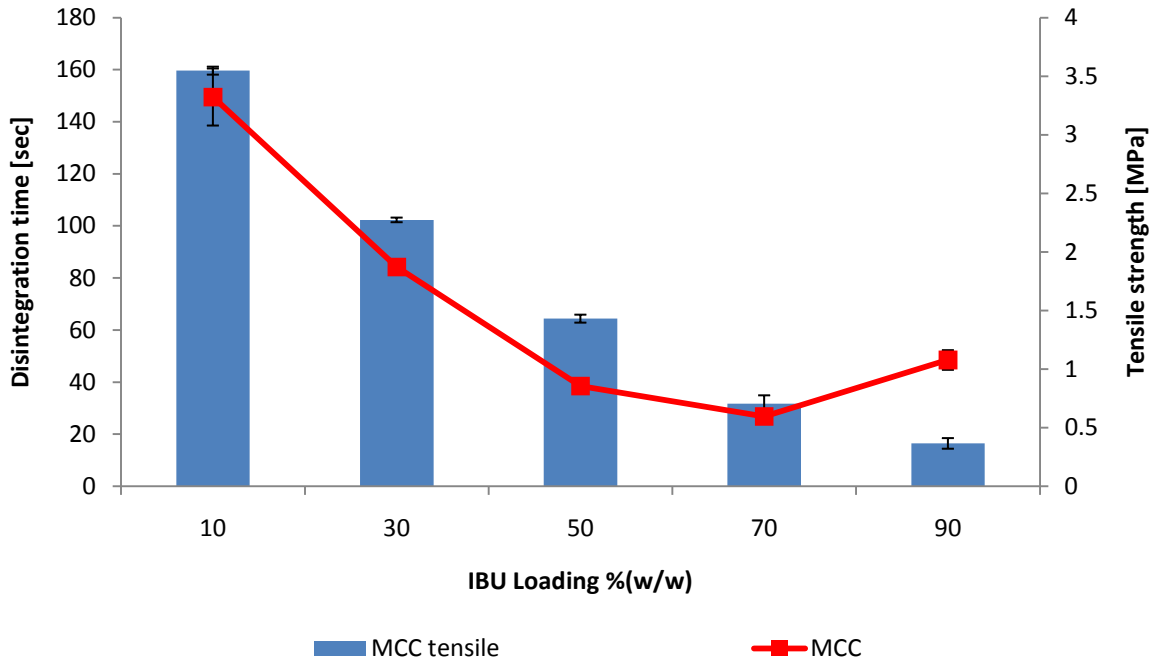


Figure 35 Disintegration and Tensile profiles of MCC tablets loaded with IBU at various loading

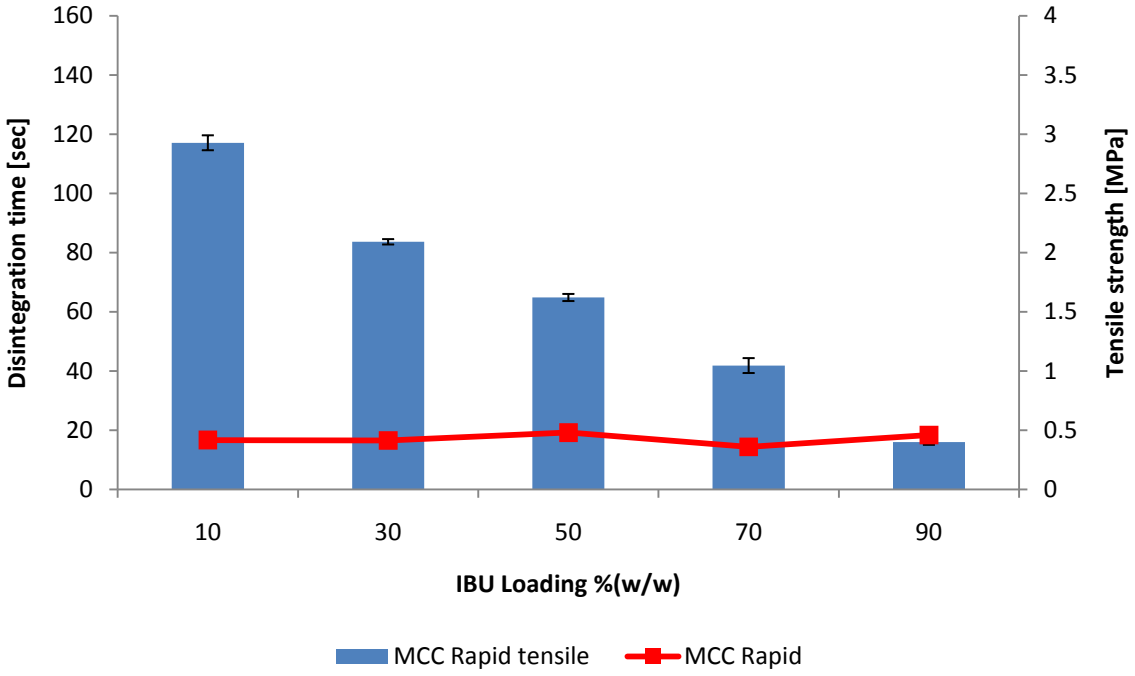


Figure 36 Disintegration and Tensile profiles of MCC Rapid tablets loaded with IBU at various loading

A correlation between disintegration time and tensile strength was observed in case of IBU tablets containing MCC as filler. The higher the MCC concentration that higher the tensile

strength and disintegration time. Figure 36, shows the relationship between tensile strength, disintegration and drug loading of tablets containing MCC Rapid. The disintegration behavior neither was in correlation with IBU load nor with tensile strength.

MCC Rapid containing tablets, as showed in Figure 36 independence from both IBU loading and tensile strength. From the relation between the drug loading, tensile strength and disintegration times for excipients, it is obvious that the decreased disintegration times at high IBU loading is mainly due to the decreased tensile strength. Therefore the bonding between the particles within the compact is poor which make the tablet rupture easier.

DISSOLUTION RESULTS

Dissolution is an essential tool to evaluate drug release from a dosage form which gives an overview of the drug release in the biological system of the gastro intestinal tract.

In this study, the effect of MCC and MCC Rapid on the dissolution performance of IBU was evaluated. IBU is classified as class II (poorly soluble and highly permeable drug) according to Biopharmaceutical Classification System [101]. IBU loading and the hydrophobic effect of Mgstr were also taken into account.

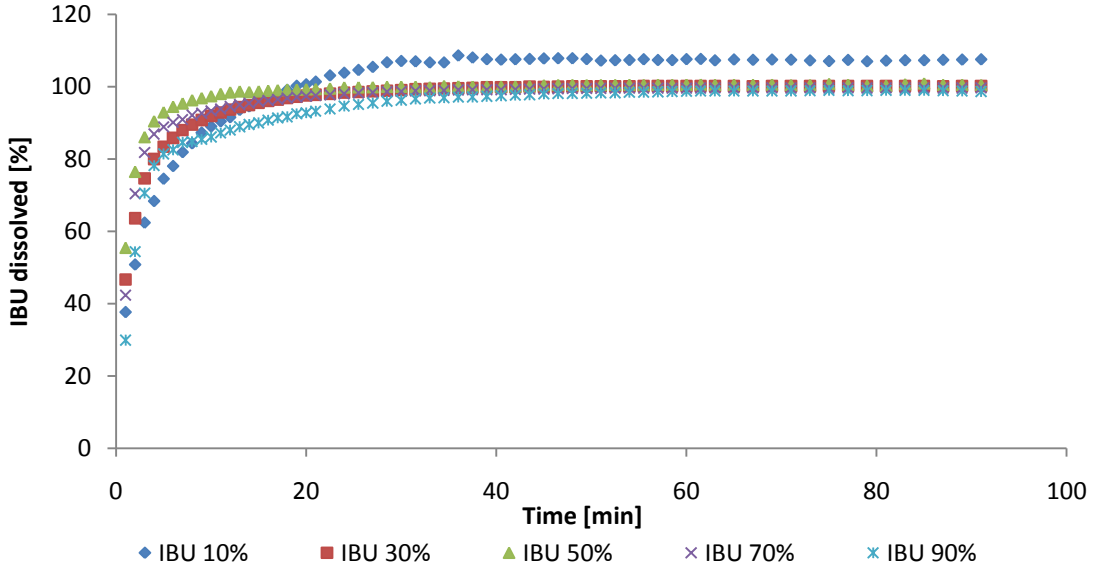


Figure 37 Dissolution profiles of IBU tablets containing MCC Rapid at different ratios

7.3.1.4 Influence of drug loading on IBU tablets dissolution

Dissolution profiles of IBU tablets containing MCC Rapid at different ratios are shown in Figure 37. IBU tablets containing MCC Rapid showed an enhanced release rate where drug release was almost complete at 15 min regardless of IBU loading. On the contrary, IBU tablets containing MCC was affected by drug loading and needed more than 1 hour to complete the drug release in cases of drug loading up to 50% (Figure 38).

Testing the excipient over various loading of drug gives a clue about its functionality at different concentrations. The formulations containing MCC Rapid exhibited a robust and quick dissolution. Critical concentrations of the disintegrant were not noticed, due to the extraordinary disintegration behavior over all IBU loading (as discussed in the section before). IBU tablets containing MCC were dramatically affected by the drug loading. In general, the higher the drug loading was, the more the drug was released. The difference in the dissolution behavior upon drug loading shows that MCC functionality is changing upon the change of its concentration. At low IBU loading, MCC forms an intact matrix around IBU particles which controlled the drug release whereas at high IBU loading above 50% (w/w) the disintegration of the tablets was pronounced, thus enhanced the dissolution profiles.

This is due to the fact that MCC at high IBU does not form a complete network that can dominate the tablet properties (as discussed before in section 7.3.1.1). The effect of MCC ratio on the dissolution behavior is in agreement with other studies, in which the same phenomenon was observed in MCC tablets containing Theophylline [102].

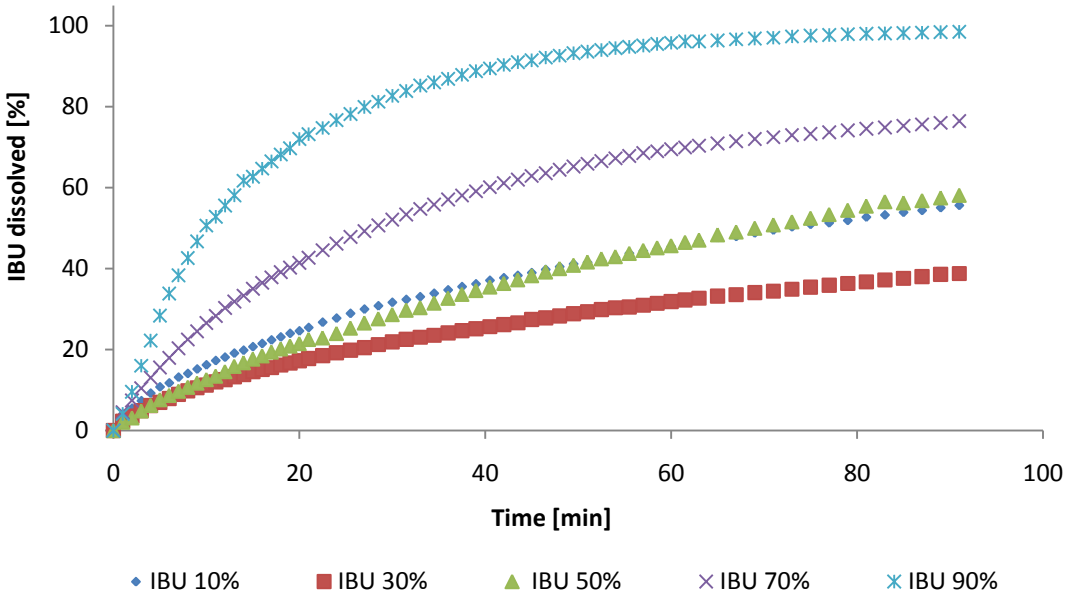


Figure 38 Dissolution profiles of IBU tablets containing MCC at different ratios.

During dissolution, it was noticed that all IBU tablets at 10% (w/w) loading particularly showed, splitting of the tablet into two parts. Therefore, the surface area of drug release was higher which leads to relatively elevated drug release, equal to tablets at IBU loading of 30% (w/w). This phenomenon of tablet splitting during dissolution and disintegration is due to the difference in porosity distribution in the tablet [103], and therefore the water uptake can be higher in some parts of the tablets than the other parts, functioning as a driving force to break the tablet. Release rate was gradually increased at 50% IBU loading and markedly increased at 70 and 90% IBU loading.

Focusing on the profiles of MCC Rapid, a critical concentration of disintegrant was not remarkable. This means, that a critical concentration of the disintegrant could lie above 90% (w/w) of drug load where the amount of MCC Rapid as less as 10 %(w/w) is effective for the disintegrating effect. Increasing amount of MCC Rapid up to 90% (w/w) in order to be applied as tablet filler also does not influence the drug release. This promising property of MCC Rapid is useful in the tablet formulations of poorly soluble active compounds. On the other hand, in case of the tablets containing MCC, the effect of IBU loading showed a pronounced critical concentration. The fast drug release of IBU loading at more than 70% (w/w) and above can be rationalized with the percolation theory [85].

Accordingly, MCC in this case have been considered as dissolution limiting excipient, and the upper and lower percolation threshold according the dissolution profiles between 10 and 70% (w/w).

It is evident that tablet formulations containing MCC are not robust as the dissolution rate significantly depends on the drug loading, in comparison to MCC Rapid formulations.

7.3.1.5 Influence of Mgstr on IBU tablets dissolution

Generally, addition of lubricants can cause the increase in hydrophobicity of the powder mixture, thus decreases water uptake of the tablet formulations. This effect leads to a delay in drug release, especially in case of poorly soluble drugs [104].

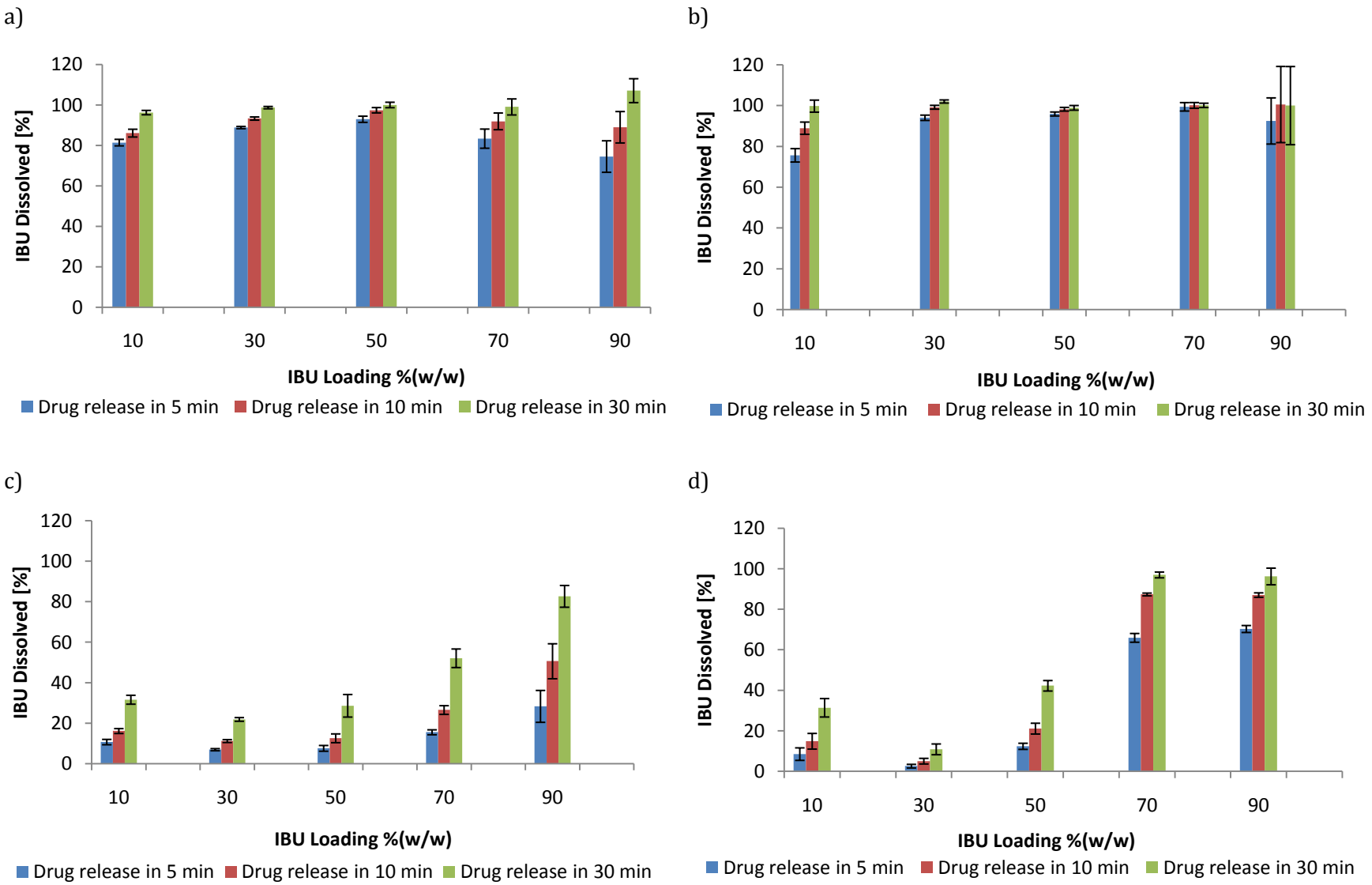


Figure 39 Effect of drug loading, lubricants, and type of excipient on the IBU release. a) MCC Rapid, b) MCC Rapid 0.5% (w/w) Mgstr, c) MCC, d) MCC 0.5% (w/w) Mgstr

8 CONCLUSION

Preparation of tablets using DC depended mainly on the tablet formulation itself, rather than tabletting process. Unlike other methods, such as wet and dry granulation in which the process have a bigger impact on tablet physical properties. Therefore testing manufacturability and In-vitro performance within the limits of design space we tailored for this study, has given more information about critical points concerning the process parameters or formulation variables.

The different in type of polymorphism was clearly distinguished using X-Ray. Also this method was useful in detection the polymorphic form and its crystallinity. Thus it can help us to relate and understand the powder properties for each excipient further on. X-ray diffractgrams had confirmed that MCC Rapid is a cellulose II lattice, whereas MCC showed cellulose I lattice. MCC Rapid had slightly lower crystallinity than MCC. Therefore we the properties exhibited by both excipients mainly are due to the crystalline form.

Difference in polymorphic type and in crystallinity, has resulted in a significant difference in powder characteristics. Moisture sorption isotherms showed that MCC Rapid is more hygroscopic than MCC. This is due to the difference in polymorphism or due to reduced crystallinity. Particle shape of MCC Rapid was more elongated than MCC. This elongated fibers decreased the bulk density properties of MCC Rapid. Consequently, according to Carr's and Hausner index the flowability is negatively affected too.

According to Heckel analysis, the constant K showed that compressibility of both excipients was close to each other, and they exhibited a plastic flow upon compaction. Although the difference between the DWT was more than 10 folds, DWT revealed to have insignificant effect on the extent of plastic deformation for MCC Rapid and MCC. After mixing with Mgstr, MCC Rapid densification properties were increased, and values of K were slightly elevated. Showing a slight increase in plasticity compared to MCC Rapid containing no Mgstr. Plastic properties of MCC was not influenced after mixing with Mgstr. Fitting with modified Heckel equation confirmed the finding of Heckel equation on the plasticity of both excipients, at all

conditions and parameters. Hence, the DWT parameter and internal lubrication with Mgstr did not have a significant effect on compressibility of both materials.

According to Leuenberger equation, MCC Rapid had lower compactibility constant values than MCC. Despite this difference of compactibility MCC Rapid is considered to have improved compactibility when compared to the compactibility constants found in the literature [19]. Despite the fact that plastic materials are affected by the change of the tabletting press speed, Compactibility of MCC Rapid and MCC were not significantly affected by the change of DWT. Internal lubrication with Mgstr compactibility significantly decrease compactibility for both excipients. Mgstr usually has a negative effect on the bonding between the plastic deforming particles. Sensitivity towards Mgstr was much more pronounced in case of MCC Rapid than MCC. The reasons behind the increased sensitivity of MCC Rapid due to two main reasons: 1) MCC Rapid has more tendency to form lubricant film during mixing around its particles. This can be related to components surface area, and degree of flowability. 2) MCC Rapid in overall showed decreased bonding properties compared to MCC. Therefore it can be more affected by the internal lubrication with Mgstr. From these findings, we can conclude that lubrication with small amount of Mgstr can dramatically affect mechanical strength of both compacts. DWT as a process parameter had the least effect on placebo tablets. Measuring Lubricant sensitivity ratio, by calculating the ratio of the compactibility constant between the lubricated and non-lubricated powders was successful to give an overview on lubricant sensitivity, not only at one compaction pressure, but also over a wide range of compaction pressures.

MCC Rapid tablets were more fragile towards attrition and abrasion during friability testing. This was expected due to the extraordinary bonding properties of MCC tablets. Relative density influenced the friability of tablet. A critical relative density equal to 0.55 has been observed. Below this point extreme deterioration of tablets had occurred. Shorter DWT hardly affected the friability of MCC tablets. Extended friability measurements showed that MCC Rapid tablet were sensitive towards the change of DWT.

The influence of DWT on elastic recovery of MCC Rapid was more noticed than for MCC. Generally MCC Rapid showed higher elastic recovery properties than MCC. Obviously the

difference in polymorphic form has attributed to this behavior. Also increase in elastic recovery had attributed negatively on the compactibility properties of MCC Rapid.

After loading MCC Rapid and MCC with Paracetamol, the dilution capacity at DWT of 118.3 ms of both excipients were relatively close. At shorter DWT of 9.5 ms, MCC Rapid showed decreased dilution capacity. Therefore, MCC Rapid loaded with Paracetamol was less robust upon the decrease of DWT. Effect of loading MCC Rapid and MCC with Paracetamol on the compactibility and compressibility constants of Leuenberger was studied. Compactibility constants were gradually decreasing upon the increase of the drug load of both excipients. Generally, MCC compactibility constants were superior to MCC Rapid. Only a high loading of Paracetamol for both excipients started to have closer constant properties. Eventually, at these loadings Paracetamol started to dominate the physical characteristics of the tablets. After calculation of the DWT sensitivity ratio loading MCC Rapid with Paracetamol resulted in increased sensitivity towards shorter DWT. compared to MCC-Paracetamol mixtures. A gradual increase in DWT sensitivity was pronounced between the Paracetamol-excipient mixtures started at Paracetamol loading 20% and reached its highest DWT sensitivity at 60%. Suddenly it was followed by a drop. This behavior is explained due to percolation theory. The Compressibility constant of Leuenberger equation was also affected by Paracetamol. A gradual decrease in compressibility values were noticed upon loading. After 60% (w/w) of Paracetamol loading, a sudden increase in the compressibility values was observed. Also this can be attributed due to percolation theory. DWT had affected the compressibility constant of mixtures containing MCC Rapid. Compressibility constants of mixtures containing MCC was less affected. This finding shows that the Paracetamol formulations at 60% (w/w) drug loading are the least robust formulations, regardless the used excipient. That is at this drug loading problems related to the tablet mechanical properties during scale up are expected.

Despite the lubrication with Mgstr and drug loading, IBU tablets containing MCC Rapid, showed extraordinary and robust disintegration behavior. This super-disintegration effect of MCC Rapid has also reflected on IBU release. Thereby, dissolution profiles showed a quick and robust drug release. Insignificant effect of Mgstr was noticed.

IBU tablets containing MCC exhibited higher disintegration times. IBU loading has critically affected the disintegration behavior of the tablets. MCC did not function as disintegrant at all mixtures. That is MCC could maintain a continuous non-dissolving, non-swelling matrix at IBU loadings below 70% (w/w). At 70 % (w/w) and above IBU has dominated the phase, and MCC had no more continuous network therefore the retarding effect of MCC was reduced. MCC disintegration behavior was correlated with the tensile strength profiles. The higher the tensile strength resulted in a higher disintegration time, unlike MCC Rapid tablets which showed independence from tensile strength values. Internal lubrication has significantly affected the drug release of IBU tablets. At low IBU loading the tablets had a slight sensitivity towards Mgstr in which disintegration time was negatively affected. At high IBU loading, after the addition of Mgstr tablets showed a dramatic decrease in tensile strength due to the poorly compactable properties of the drug. Showing values of tensile strength around 0.5 MPa. And due to this weakness in the tablet structure, IBU tablets were easily disintegrated therefore, exhibiting immediate release which was less influenced by Mgstr.

MCC Rapid maintained good mechanical robustness, despite the changes in the simulated tabletting press speed. Despite the drug loading and the hydrophobic effect of Mgstr disintegration and dissolution rates were fast and robust, which makes it an excellent disintegrant. This makes MCC Rapid an attractive multifunctional excipient which could maintain its properties as binder despite the change of the simulated rotary press speed. Additionally MCC Rapid its function as a disintegrant was not hindered by the influence of the low soluble drug IBU loading or by the hydrophobic effects of Mgstr. This robustness in MCC Rapid multi-functionality will reduce the number of involved excipients, thus, reducing physical and chemical interactions. Leading to more predicted tablets formulation, therefore time and efforts while designing a formulation for DC for are reduced.

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