Characterization of functionalized calcium carbonate as a new pharmaceutical excipient

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Tanja Stirnimann

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Prof. Dr. Jörg Huwyler
Prof. Dr. Kurt Hersberger

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Prof. Dr. Jörg Schibler
Dekan

Dedicated to my mother, my sister, and my fiancé

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Abbreviations

API active pharmaceutical ingredient

BCS biopharmaceutical classification system

CPP critical process parameter

CQA critical quality attribute

FCC functionalized calcium carbonate

FDA Food and Drug Administration

IPEC International Pharmaceutical Excipients Council

MCC microcrystalline cellulose

MUPS multiple unit pellet system

ODT orally dispersible tablet

PAT process analytical technology

PhEur European Pharmacopeia

QbD Quality by Design

QTPP quality target product profile

SMCC Silicified microcrystalline cellulose

UHT ultra hard tablet

Summary

Excipients are indispensable functional components, which are used to develop innovative, robust, and reproducible formulations with good patient compliance due to optimized plasma concentrations and less side effects. Nowadays, new excipients have to show a multifunctionality in order to be used for unique applications that are not feasible with existing excipients. This multifunctionality can be achieved by co-processing excipients, where undesirable properties of an excipient are masked, favorable attributes are retained, and new properties supplement the substance.

The main aim of this thesis was to map the applicability of such a co-processed novel excipient, FCC, in the field of pharmaceutical technology.

The results of the mechanistic study showed that the attributes of FCC present a striking success in the field of excipient research. FCC-based tablet formulations had mechanical properties equal or superior to those of conventionally used excipients such as microcrystalline cellulose (MCC), mannitol, or calcium carbonate. FCC tablets with high tensile strength and high porosity were obtained already at low compressive pressures. The key factor for the outstanding performance of FCC was the lamellar structure of the particle, which formed a porous meshwork (intraparticle porosity), resulting in a high specific surface area available for particle bonding.
The limitations of poor flowability and high bulk density of FCC powder during direct compression were overcome by granulation. FCC granules prepared by roller compaction showed excellent flowability and reduced bulk volume, whereas all the outstanding properties of the powder, such as compactability and compressibility, were preserved. The dry granulation process converted FCC into a suitable form for scale-up processes on high-throughput tablet presses. Roller compaction is the process of choice if porosity and high surface area of FCC particles have to be preserved during granulation process.

On the examplary model of direct compressed ODTs, the applicability of FCC was investigated. ODTs containing FCC were produced by direct compression. Owing to the lamellar structure, FCC was able to overcome the limitation of insufficient hardness during the production of highly porous ODTs. These findings could revolutionize the production of ODTs and hence open up new vistas. To protect the valuable findings, a patent was applied for the production of ODTs made of FCC.

The characterization of co-processed FCC revealed a promising new pharmaceutical excipient with a broad range of applicability. Applicability of FCC seems to be of particular interest for formulations that are characterized by high porosity, high tensile strength, or both. This is the case, amongst others, for ODTs, carriers, adsorbents, floating tablets, effervescent tablets, controlled-released formulations, ultra hard tablet (UHT), and cushioning agents.

Chapter 1

Introduction

1.1 Pharmaceutical excipients

Excipients were already used in the ancient Greece to produce salves and ointments made of natural materials [1]. The function of the excipients was to convert the active pharmaceutical ingredient (API) in a form that was convenient for the patient [2]. That time, people did not pay a lot of attention to the excipients and considered them as inert. A turning point came in the year 1937. A chemist decided to mix the toxicologically untested excipient diethylene glycol with sulfonamide antibiotics that had a bad taste. The result was a blue colored elixir with a sweet taste. After taking this elixir, over 100 children died and several hundreds became ill. The reason was the toxicity of the excipient, leading to kidney failure. As a consequence, a law was enacted in 1938 that regulates the responsibility of the manufacturer for drug safety [3–5].
The situation has changed again since 1970. New technologies enabled the investigation of excipients with respect to solid state of materials. Therefore, regulatory authorities increased qualitative requirements. Amongst others, this led to to the International Conference on Harmonization where people from the United States, Japan, and Europe worked on a harmonization of the standards [6]. Furthermore, the first edition of the reference book "Handbook of Pharmaceutical Excipients" was published in 1986 [7].

1.1.1 Definitions

Different definitions exist for the word *excipient*, depending on the source. The International Pharmaceutical Excipients Council (IPEC) for example defines *excipient* as follows [8]:

> *"Pharmaceutical excipients are substances other than the API which have been appropriately evaluated for safety and are intentionally included in a drug delivery system."*

In contrast, the definition of the European Pharmacopeia (PhEur) is shorter but contains some examples [9]:

> *"Excipient (auxiliary substance): Any constituent of a medicinal product that is not an active substance. Adjuvants, stabilizers, antimicrobial preservatives, diluents, antioxidants, for example, are excipients."*

The PhEur does neither mention anything about safety of the excipient, nor about the intentionally addition of it into the formulation. The latter could imply that contaminations and impurities are defined as excipients [10].

1.1.2 Function of excipients

As mentioned above, in the past excipients were considered as inert. Nowadays, excipients are treated as functional components of the formulations [6,11]. In the following sections, a selection of functions are presented to give an overview over the broad field of application of excipients. From now on the focus is on the use of excipients for tablet formulations.

Dosing: Some APIs, such as paracetamol, are taken in amounts up to 1 gram per dose. In contrast, there are active substances such as digoxin that are taken in very small amounts of 0.125 mg per dose [12]. Excipients allow to compact tablets with convenient sizes and shapes, regardless of the API content. The tablet press enables a consistent volumetric dosing of the required amount of powder used for one tablet [1].

Palatability: The success of a formulation on the market depends strongly on the palatability of a formulation. Taste, smell, and swallowability are parameters that influence the palatability. Excipients serve, for example, to mask a bitter tasting API or to disintegrate a tablet already in the mouth to reduce swallowing problems [1, 6, 13].

Controlled release: Excipients are used to control the release of a dosage form. Different excipients cover the whole spectra; from very fast dispersible tablets (drug release in the range of seconds) to sustained release formulations (drug release over several hours) [14, 15]. The release pattern determines the frequency of dosing and thus influences patient compliance.

Stability: Stability of APIs is an important prerequisite to achieve the expected plasma concentrations. Excipients can, for example, help to hold up the desired polymorphic form of the API. Another example is the protection of acidic degradation of an API in the stomach with an enteric coating [16].

Bioavailability: Oral administration of drugs is by far the most widely used route of administration. However, some drugs such as peptides and proteins, still need to be administered by the parenteral route. These drugs are limited by low bioavailability, for example due to presystemic enzymatic degradation, and poor permeability through the intestinal membrane [17].
Drugs can be classified according to the biopharmaceutical classification system (BCS) as shown in Figure 1.1. The system divides the APIs into 4 classes according to low or high solubility and low or high permeability [18]. APIs which belong to the BCS class I possess all the prerequisites for a high bioavailability, namely high solubility and high permeability. All the other APIs from BCS classes II-IV have either low permeability, low solubility, or both, resulting in reduced bioavailabil-

ity. Excipients can help to overcome these limitations and to make these challenging APIs available for oral administration. Numerous excipients are used to increase the solubility of APIs, such as polyethylene glycol, cyclodextrin, and glycerin [19]. In order to overcome the limitation of low permeability, innovative delivery systems are needed. Such an innovative approach is for example the chitosan nanoparticle-mediated oral delivery of insulin [17, 20].
Beside the fact that excipients can be used to overcome the limitation of low solubility and low permeability, they can also have an influence on the gastrointestinal motility themselves. Excipients, such as mannitol and other sugar alcohols, are often used to sweeten a formulation or as a diluent. Sugar alcohols can reduce the transition time of a formulation in the gastrointestinal tract and hence, reduce the bioavailability of BCS class III drugs with high solubility and low permeability [16].

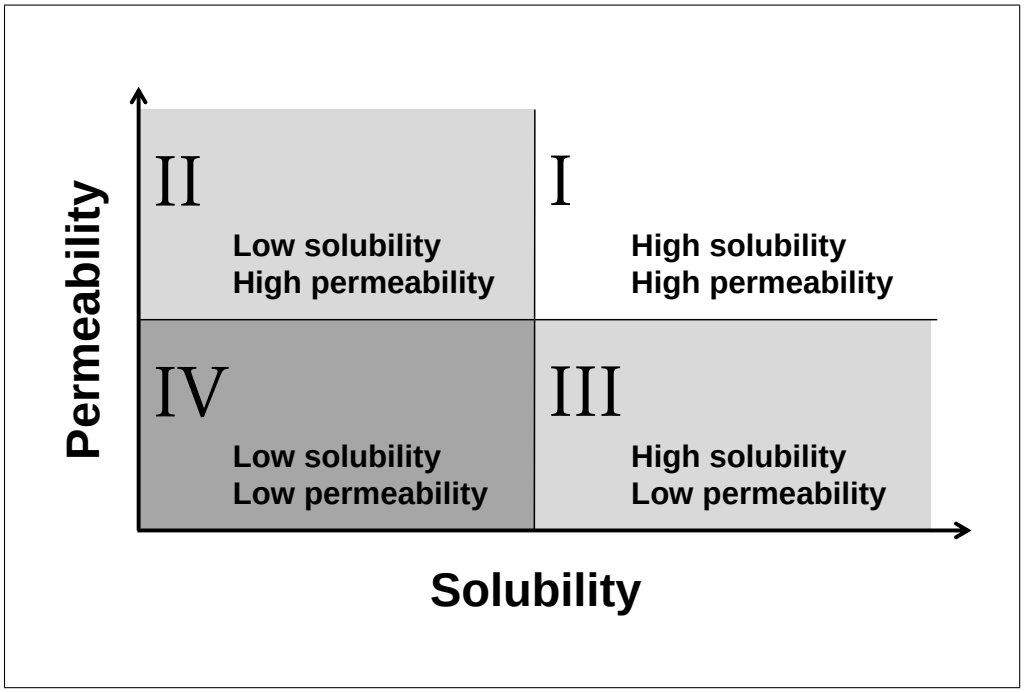

Figure 1.1: BCS of APIs based on their solubility and permeability. APIs in BCS class I show the prerequisites for high bioavailability. Bioavailability of APIs in BCS class II and III is either affected by low solubility or low permeability. APIs in BCS class IV show lowest bioavailability due to low solubility and low permeability [18].

Side effects: A selective use of excipients can improve a certain release profile that peaks in the plasma can be avoided and thus, side effects are reduced [1].

To sum up, excipients help to develop innovative, robust, and reproducible formulations with good patient compliance due to optimized plasma concentrations and less side effects.

1.1.3 Categorization of excipients

Three different types of excipients are discriminated, namely standard excipients, mixed excipients and co-processed excipients. In the following sections, the three different types are presented and illustrated with some examples [8].

Standard excipients

Standard excipients are substances, that neither belong to the mixed excipients, nor to the co-processed excipients. Standard excipients can be compendial or non-compendial. Beside the substance itself, residual processing aids or additives and concomitant components can coexist [8]. Examples for standard excipients are microcrystalline cellulose, UICEL, and crospovidone, which are presented now more detailed.

MCC (e.g. MCC Sanaq®, Avicel® PH, Vivapur®): Cellulose is the fibrous material of plants. Cellulose shows an amorphous and a crystalline part. The latter consists of two polymorphic forms, cellulose I and cellulose II [7]. To extract MCC out of cellulose, the cellulose has to undergo a hydrolysis with a strong mineral acid in form of an aqueous solution. Afterwards, the product is filtrated to purify it and the aqueous slurry is spray dried. The result is MCC as porous particles with different particle sizes, depending on the grade [21]. MCC shows the polymorphic form of cellulose I, which corresponds to the native cellulose lattice. Within the cellulose I form, a parallel arrangement of the chains is observed. This results in a higher degree of crystallinity compared to the cellulose II form [22]. The degree of crystallinity is important due to the fact that properties such as compactability and flowability are affected [6]. MCC is used as a binder and diluent for direct compression as well as for wet granulation [7]. MCC is a popular excipient, especially due to the fact that it shows excellent compactability and compressibility. Nevertheless, flowability of MCC is only moderate [23, 24].

UICEL (e.g. MCC Sanaq® burst): The name UICEL is the abbreviation of University of Iowa Cellulose. At this university, the substance was produced and investigated for the first time. The basic raw material for this excipient is the same as for MCC, namely cellulose. To obtain UICEL, the cellulose goes through a mercerization process, where it is soaked in a sodium hydroxide solution. Afterwards, it is precipitated with ethyl alcohol and subsequently neutralized with water. In a last process step, the powder is dried. In contrast to MCC, UICEL consists of the polymorphic form of cellulose II. This results in properties that make UICEL an effective disintegrant. In addition, the excipient is still a good filler and binder. The better taste compared to other cellulose types in combination with good binding and disintegration properties make the UICEL a promising excipient to produce orally dispersible tablets [21, 25].

Crospovidone (e.g. Kollidon® CL): Crospovidone is produced over several chemical reaction steps out of acetylene and formaldehyde. Among other things, crospovidone is used as a tablet disinte-

grant in the concentration of 2-5%. The function of crospovidone as a disintegrant bases upon the high capillary activity and hydration capacity [7].

Mixed excipients

Mixed excipients are two or more standard excipients that are physically mixed for a short duration by a low- to medium-shear process. During this process, the substances are not allowed to change chemically. Examples for mixed excipients are flavor and color blends [3, 7].

Co-processed excipients

Co-processed excipients are two or more standard excipients, whose properties are physically modified without changing the chemical properties significantly. The same result cannot be achieved by a physical mixture of the substances [8]. Particle engineering plays an important role in co-processing of excipients. In general, solid substances consist of three levels, namely a molecular level, a particle level, and a bulk level. These three levels are connected and a change on one level does influence the other levels. On the molecular level, the arrangement of the molecules in the crystal lattice is regulated and does therefore give information about polymorphism and amorphous state of a substance. The particle level determines the properties of the individual particles, such as size, surface area, shape, and porosity. The bulk level reflects the interaction of the particles that can be measured with the help of flowability, compressibility, and dilution potential.
During the co-processing step, one excipient is incorporated into the particle structure of another excipient. The processes used are for example spray drying, melt extrusion, or high shear granulation. With this procedure, a multifunctionality can be achieved by masking the undesirable properties of an excipient, retaining the favorable attributes, and supplementing a substance with new properties.
It seems that co-processed excipients are the excipients of the future due to the fact that they can be used for unique applications that are not feasible with existing excipients due to problems with performance or consistency. Furthermore, co-processed excipients can be produced by meeting the needs of quality by design [3, 9, 26]. What quality by design is, will be discussed later on. In the following sections, two examples of co-processed excipients are shown.

Silicified microcrystalline cellulose (SMCC)(ProSolv® SMCC): SMCC consists of MCC and 2% (w/w) of colloidal silicon dioxide. It is obtained out of a suspension of MCC and colloidal silicon dioxide that is co-dried. The colloidal silicon dioxide binds physically on the surface and inside the SMCC particles. SMCC is used as a diluent in tablet production. The co-processing of the two excipients yielded in improved flow properties of SMCC compared to MCC. Furthermore, SMCC showed improved compaction properties in direct compression, as well as after wet granulation compared to MCC [7, 24, 27, 28].

Ludipress®: Ludipress® is a combination of 93% lactose monohydrate (filler), 3.5% polyvinylpyrrolidone (binder), and 3.5% crospovidone (disintegrant). Lactose monohydrate is a natural disaccharide that is obtained from milk. Polyvinylpyrrolidone and crospovidone are both obtained with chemical reactions out of acetylene and formaldehyde. The excipient Ludipress® is produced with the help of a fluidized bed process. Ludipress® shows added advantages such as excellent flowability due to sphericity and smooth surface of particles. Furthermore, the hygroscopicity is lower. Beside the improved properties in comparison to lactose monohydrate, there is still a need for a glidant [7, 29–31].

1.1.4 Need for new excipients

Even nowadays there are manifold reasons for new excipients. One reason are new technologies that allow tablet production with high-speed tablet presses. Such machines can produce up to 1.5-2.0 millions of tablets per hour. The powder has to meet a lot of requirements to be compacted with such a press, such as good flowability, good compressibility, and low moisture sensitivity. There is a demand for a binder that fulfills all these criteria. [3, 29]. Another reason is the need for excipients to formulate new, innovative APIs, such as peptides. In general, there is a need for elaborated excipients that can be used for modified release formulations and new therapeutic systems [6]. The problems with low solubility and low permeability (BCS class II-IV) represent an omnipresent need for new excipients [3].

The possibility to engineer particles on request by co-processing two or more existing excipients or to develop a new chemical entity leads to the question how an ideal excipient is defined. In the first instance, this clearly depends on the tablet formulation that should be designed. The following points should be kept in mind by working on an ideal excipient [6]:

- Toxicologically and pharmacologically inactive
- Physically and chemically inert versus the drug
- Compatible with other formulation components
- Good flowability
- High compressibility
- Inexpensive
- Worldwide available from different suppliers
- Reproducible to minimize batch to batch variability
- Well characterized

The itemization discloses that it is challenging to work on a novel excipient that can fulfill all these requirements.

1.2 Further processing of excipients

The easiest way to produce a tablet out of an API and excipients is the direct compression. To do so, the powder blend has to meet some requirements. If the requirements are not met, another process step has to be included, namely the granulation. Granulation can be split into wet granulation and dry granulation. Before 1950, tablets were mainly produced by wet granulation. Nowadays there is a clear trend towards direct compression of tablets. The development of new and co-processed excipients as well as advanced tablet presses may be responsible for this trend due to the fact that more excipients can fulfill the requirements for direct compression [23, 29]. Due to the fact that a lot of new APIs are chemically sensitive, there is another trend from wet granulation to dry granulation. The liquid and the heat during the drying process after wet granulation stress the fragile APIs. Moreover, a lot of new APIs have a low bulk density that can be increased more effective by dry granulation than by wet granulation [32].

1.2.1 Direct compression

Direct compression is featured by advantages. It is a short and effective process that is at the same time cost efficient. The API and the excipient have simply to be blended and compacted. Furthermore, the process is suitable for heat- and moisture sensitive APIs [33]. Nevertheless, there are some issues that limit the application range of direct compression. Formulations with very high or very low API content are challenging for direct compression [33, 34]. For formulations with a low API content, a homogeneous distribution of the drug in the powder blend has to be ensured. Segregation, for example, is a problem that can occur due to differences in particle sizes, densities, and flow properties [35]. Static charges are another problem and may lead to a powder blend with nonuniform API distribution [36]. All these problems lead finally to a nonuniform distribution of the API in the tablet formulation. Another problem is observed if the API doses are very high; the low amount of excipients is not able anymore to compensate the poor compressibility of the API, resulting in a bad tablet quality [33, 34]. Furthermore, the raw materials should be characterized by a good flowability. A good flowability is indispensable to receive a consistent tablet weight, and hence a uniform distribution of the API in the tablet [37]. Another limitation for direct compression is a low bulk density of the powder. In this case the required volume of powder to produce a tablet with a certain amount of API can be higher than the volume of the die, or the resulting tablet is very thin [34, 38].
Different types of excipients can be used for direct compression, including lubricants, disintegrants, binders, and fillers. The binder holds everything together within a tablet and therefore plays an important role during direct compaction. The binder, as well as the filler (especially if used in large amounts), is ideally characterized by a good flowability and compactibility. The excipients have to be chosen carefully by considering the properties of the API, such as particle size, shape,

brittleness, and elasticity [38].

1.2.2 Granulation

If raw materials are limited by above mentioned issues, they have to be granulated. Due to an additional process step, the production of the formulation needs more time and more costs incur. Furthermore, there is a loss of product due to the fact that the granulation process consists of several steps; granulation, drying, milling, and sieving [33].
The granulation serves to produce powders with a desired flowability (enlargement and densification of small powder particles) and reduces the amount of dust. Furthermore, powders with a narrow particle size distribution are produced to overcome the problem of segregation during tableting [33, 39].
If the amount of API in a formulation is very high, the API can be granulated alone and later on added to the powder blend with the excipients. In case of a low API content it makes more sense to granulate the API together with the excipients to reduce the risk of segregation. Nevertheless, the procedure has to be evaluated for each formulation separately by considering the properties of the raw materials [33, 34].

Dry granulation

Dry granulation is sub-divided into slugging and roller compaction. By slugging, the powder is compacted with the help of a compression machine into a slug, similar to a large tablet. Nowadays, slugging is replaced by roller compaction. Reasons for the substitution of slugging by roller compaction were the low throughput per hour, poor process control and that it was not a continuous process [39].
The roller compaction process has the advantage that heat- and moisture sensitive drugs can be processed with this method [40]. Even poor flowing raw materials are suitable for roller compaction due to a feeding system that brings the powder to the rolls [41]. A disadvantage of the dry granulation process is the loss of reworkability, meaning that tensile strength of the tablet is reduced after compacting the granules in a tablet in comparison to powder. In general, plastic deforming materials are more affected by the problem of reworkability [42, 43]. Another negative issue during roller compaction is the production of fines. A study showed that this problem can be controlled with different roll surfaces (e.g. convex instead of smooth) [44]. Numerous studies were performed in the past to show the influence of roll speed, roll pressure, and feeding screw speed on the granule properties and consequently on the tablet properties [45–48].
By selecting suitable excipients during roller compaction the processibility of a powder mixture can be improved by balancing the poor physical properties of the API. Similar to direct compression, binders and fillers belong to the most important excipients used for roller compaction. Fillers are responsible for good ribbon and granule quality by balancing the plasticity/elasticity/brittleness

of the API. Binders play an important role during the agglomeration process of the API and the excipients. Polyvinylpyrrolidone and cellulose derivatives are examples for binders commonly used for dry granulation [49].

Wet granulation

Wet granulation was, and most probably still is, the most common way of granulation. Different types of wet granulation exist, namely fluidized-bed granulation and high-shear granulation. The process is chosen depending on the required properties of the granules. Fluid-bed granulation is a low-shear process where granules with a low density are obtained. The high-shear granulation results in denser granules due to the fact that more shear (mechanical force) is applied [34].
During the wet granulation process, a solution (either aqueous or solvent based) is pumped into the machine. In most of the cases, a binder that later on forms the powder agglomerates (granules),is dissolved in the solution. The wet granulation process is a critical unit operation at which the particle size distribution during granulation is depending on the liquid addition. Since years, researchers are looking for the end-point during wet granulation. The power consumption profile during a wet granulation can be divided into different phases, however, there is no clear scientific end-point [50, 51].
After the granulation process, the granules have to be dried. This process is critical in view of the fact that the moisture content of the granules has an impact on the compaction behavior of the granules. Overdried granules result in a high fine fraction after milling, which in turn is responsible for weight variations due to bad flowability. Furthermore, overdried particles can cause capping and lamination. On the other side, if the granules are too wet during tableting, the powder can stick on the tooling [34].

1.3 Quality by Design

Four different components play an important role during the pharmaceutical development, namely the API, the excipient(s), the process, and the interaction of these three components [1]. It is obvious, that these components are decisive responsible for product quality. In 1992, Juran published a book where he presented his idea of Quality by Design (QbD). He was of the mind that the quality is projectable [52]. Some years later, the Food and Drug Administration (FDA) introduced a guidance for the industry due to the fact that they noticed that, although a lot of tests were performed, the quality did not improve. Therefore, they suggested that "quality should be built in by design" [53].
In general, QbD means for the pharmaceutical development industry that they understand their products and the processes involved to obtain a certain product. The FDA recommends to consider at least the subsequent mentioned points.

In a first step during pharmaceutical development, the *quality target product profile (QTPP)* has to be defined. The quality, safety, and efficacy are in the spotlight of QTPP. Related questions to be answered can for example concern the intended use, dosage form, dosage strength, and the drug release out of the dosage form. In a next step, potential *critical quality attribute (CQA)* of the drug product have to be pinpointed. This allows later on a study and control of product characteristics that impacted the quality of the product. The CQAs have to be within a defined limit that they can meet the pre-estimated QTPP. According to the desired quality, the drug substance and excipients are selected based on their CQAs. The drug product is afterwards produced with an adequate manufacturing process. The *critical process parameter (CPP)* such as for example mixing speed or temperature are measured. Finally, the FDA recommends an appropriate control strategy to measure if the products and processes are consistent and show the desired quality. The focus of the control should not only be on the final product but also on the in-process control and on the intermediate products [53].

Figure 1.2 visualizes how the pharmaceutical unit operations (in black boxes), process parameters, and quality attributes are connected. Figure 1.2 and the above mentioned procedure are only recommendations and are not complemented. Depending on the drug product and the manufacturing process, the QbD can be extended arbitrarily. A critical consideration is helpful for determine the factors / parameter that should be measured. During the repetition of a process it makes for example sense to check the operating parameters. Sometimes (for example during a scale-up process) it pays out to measure the material attributes of the output instead of observing the operating parameters. In this case the critical material attributes should be considered as a control strategy and not the operating parameters due to the fact that they are going to change by using another machine [54].

A helpful tool during the QbD process is the PAT. Leuenberger for example used PAT years before the term QbD came into play. That time, Leuenberger developed a device to measure the power consumption during a wet granulation process. He observed, that the statistical variances between the batches were reduced with respect to granule size distribution if the power consumption profile was identical among the batches [25]. PAT requires to collect information during a process. This information are studied and the gained knowledge should help to control and monitor the process to ensure desired product quality [54, 55]. With this respect, PAT is a tool for a better understanding of the process.

Yu predicted that the knowledge about mechanical properties of the drug and excipients are going to become more important in the future [56]. The mechanical properties play an important role within a solid dosage form. Different methods were presented in the past to gain such knowledge about mechanical properties [57].

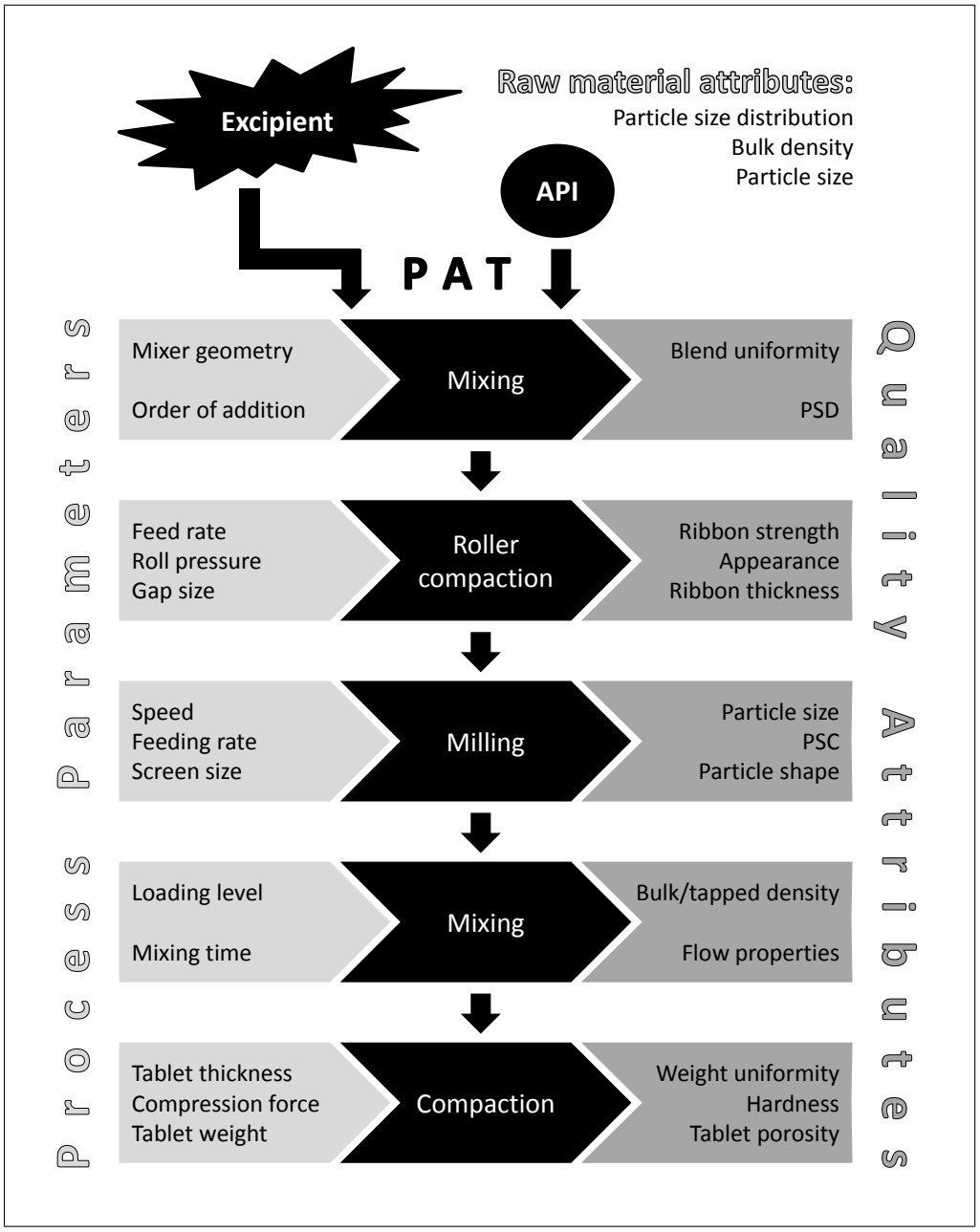

Figure 1.2: Quality by design. The API and the excipients are characterized by raw material attributes. During the processing of this powder blend, PAT is a helpful tool for a better understanding of the process. The collected information during a process has to be connected to the resulting quality attributes. The gained knowledge allows to control and monitor the process that desired product quality can be ensured [54–56].

1.4 Special applications

Among pharmaceutical dosage forms, tablets are the most popular dosage form. They are easy and cost-efficient to produce and they can be easily self-administered by the patient. Furthermore, tablets are noninvasive in comparison to, for example, parenteralia. The API is protected from environmental conditions, the release of the API can be controlled and the dosage form is stable enough to be packed and transported. Under adequate storage conditions, tablets can be stable over years [58].
A special tablet type is the ODT, which is defined as followes by PhEur [9]:

> *"Orodispersible tablets are uncoated tablets intended to be placed in the mouth, where they disperse rapidly before being swallowed."*

According to PhEur the ODTs should disintegrate within 3 min when tested with the disintegration test using water [9]. The FDA Guidance for industry gives even a more precise definition of an ODT. According to the FDA, an ODT should disintegrate within 30 s and the tablet weight should be below 500 mg [59].

Conventional tablets can give troubles to certain patient groups, particularly to pediatrics and geriatrics due to swallowing problems. A study with 6158 tested subjects that were consulting a general practitioner found, that 26% of total tested patients complained about swallowing problems [60]. The number of patients with swallowing problems fluctuates quiet heavily between the different studies. The reasons for the swallowing problems are manifold. Swallowing problems can be caused by psychological factors (anxiety, discomfort) as well as by physical issues [61, 62]. Physical issues can for example be a reduced salivary flow (e.g. due to an anticholinergic side effect of a drug), weak muscles, neurogenic disorders, sensory deficits, and so on [61].

Due to numerous advantages, ODTs are preferred to conventional tablets [63]:

- Easy to use and convenient [64]
- Improved compliance [65, 66]
- Suitable for pediatrics [67]
- No need of water (advantageous for patients with nausea, travelers) [64]
- Rapid dissolution and onset of action [68]
- Absorbance from the mouth, pharynx, and esophagus and thus increased bioavailability by bypassing the first pass metabolism [69]

Despite the numerous advantages, ODTs are limited amongst others by insufficient hardness. To ensure a rapid disintegration, the tablets are often very porous. A high compaction force would destroy the porous structure. Furthermore, drugs with an unpleasant taste (taste-masking is very

important for acceptance of formulation) or a controlled release profile are challenging [70, 71].

In the 1990s, mono-functional excipients (e.g. cellulose derivates) were used to produce ODTs. Later on, sugars and polyols (e.g. mannitol, sucrose, xylitol, and maltodextrin) were included in the ODT formulations. Mannitol played a key role as an excipient for ODTs due to its sweet taste and cooling sensation in the mouth. Nevertheless, tablets made with mannitol showed low mechanical hardness due to bad compactability of the substance. Other researchers made use of co-processed excipients that combined for example a binder with a disintegrant. By improving the performance of an ODT, different technologies were patented to receive a product with desired hardness, disintegration time, and palatability [71].

In general, ODTs can be prepared by lyophilization or by direct compression. A choice of such technologies is presented in Table 1.1. In general, lyophilization results in a highly porous matrix that dissolves or disintegrates within seconds after contact with water due to the high surface. Due to the low mechanical stability and high friability, the lyophilisates can not be packed into "push-through"-blisters. They are sold in "peel-off"-blisters, from which the lyophilisates have to be removed carefully. In addition, the blister protects the lyophilisates from humidity. The prices for lyophilized ODTs are higher compared to direct compressed ODTs due to more complex production technology and more expensive "peel-off"-blisters. In contrast to lyophilized ODTs, direct compressed ODTs are produced with conventional tablet presses. The resulting tablets are mechanically robust and hence can be packed into cheaper "push-through"-blisters [71–73].

Another new appearance are orally dispersible films. To produce such a film, water-soluble polymers are mixed with the API. The liquid is spread on a plate and dried in an oven. The film is afterwards cut into individual doses. The high moisture sensitivity and the low doses are limiting this technology [72]. An example that is on the market in Switzerland, is the Risperidon Sandoz® Solufilm.

The fast dispersible dosage forms became even more important after the new regulation of the European Union with respect to pediatric formulations was enacted. The new regulation asks for appropriate formulations for different subgroups of children. Especially for younger children the convential tablets and capsules demonstrate a risk for choking. With fast dispersible dosage forms this risk can be avoided by offering at the same time a convenient formulation [74].

Table 1.1: Different technologies for the preparation of ODTs by direct compression and lyophilization. The table was adapted from [72, 73]

Method	**Technology**	**Preparation**	**Products**
Direct compression	Flashtab®	Taste-masked API microparticles are blended with conventional excipients, super disintegrants (e.g. crospovidone), and swelling agents (e.g. MCC).	Prevacid® Solutab (Lansoprazole)
	Orasolv®	Taste-masked API microparticles are blended with effervescent material and other excipients before everything is compacted at low pressure to maintain a high degree of porosity. Special blisters are required due to weakness of the tablets (6-25 N).	Remeron® Soltab (Mirtazapine)
	Durasolv®	Taste-masked API microparticles are blended with or without effervescent material and other excipients before everything is compacted. In contrast to the Orasolv® technology, the compaction force is higher, resulting in more robust tablets that can be packed into push-through blisters.	Zomig® oro (Zolmitriptan)
	Wowtab®	Low moldable sugars (quick dissolution) and high moldable sugars (high hardness) are granulated together to combine the advantages of theses two sugar types. A special humidity treatment follows after the compaction of the tablets.	Benadryl® fastmelt (Diphenhydramine)
Lyophilization (freeze-drying)	Zydis®	A water-soluble matrix is mixed with the API, preformed in a blister, and afterwards lyophilized. This technology is extended to protein and peptide products or oral vaccines.	Zofran® Zydis® lingual (Ondansetron)
	Lyoc®	An emulsion is prepared with the API, a lipid component, a stabilizer, a filler, and a thickening agent. The oil-in-water emulsion is freeze-dried.	Loperamide-Lyoc® (Loperamide)
	Quicksolv®	An aqueous dispersion is prepared with the API and matrix components. The dispersion is lyophilized or submerged in alcohol.	Risperidal® Quicklet® (Risperidone)

Chapter 2

Aim

FCC is a mesoporous and particulate material which had been used as a filler in paper industry. The main aim of this thesis was to investigate if this material can be used as a novel pharmaceutical excipient and to map its applicability. Three inter-related projects were defined in order to reach the main aim:

(I) Characterization of the physical properties of FCC powder, such as shape, size, porosity, and specific surface area. The intention was to compare physical properties of FCC with those of other excipients, such as ground calcium carbonate and MCC powder, in order to pinpoint possible differences.

(II) Examination of the mechanical properties of FCC, namely compactability and compressibility, in comparison to other excipients. The aim was to study the influence of the new excipient's physical properties on the behavior under mechanical stress in order to gain scientific knowledge on the influence of FCC's microstructure for future tablet developments.

(III) Investigation of the applicability of FCC on the examplary model ODT, including production optimization, such as granulation, for industrial scale-up. According to the achievable properties of ODTs made with FCC, the objective was to demonstrate a general proof-of-concept for the use of FCC in other dosage forms.

Chapter 3

Publications in peer-reviewed journals

3.1 Direct compaction of FCC

Compaction of functionalized calcium carbonate, a porous and crystalline microparticulate material with a lamellar surface

Tanja Stirnimann[1], Susanna Atria[1], Joachim Schoelkopf[2], Patrick A.C. Gane[2, 3], Rainer Alles[1], Jörg Huwyler[1], Maxim Puchkov[1]

[1] Department of Pharmaceutical Sciences, University of Basel, Switzerland
[2] Omya International AG, R&D Minerals and Surface Chemistry, Oftringen, Switzerland
[3] School of Chemical Technology, Aalto University, Finland

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Compaction of functionalized calcium carbonate, a porous and crystalline microparticulate material with a lamellar surface

Tanja Stirnimann [a], Susanna Atria [a], Joachim Schoelkopf [b], Patrick A.C. Gane [b,c], Rainer Alles [a], Jörg Huwyler [a,*], Maxim Puchkov [a]

[a] Division of Pharmaceutical Technology, Department of Pharmaceutical Sciences, University of Basel, Klingelbergstrasse 50, CH-4056 Basel, Switzerland
[b] Omya International AG, R&D Minerals and Surface Chemistry, Baslerstrasse 42, 4665 Oftringen, Switzerland
[c] Aalto University, School of Chemical Technology, P.O. Box 16300, FI-00076 Aalto, Finland

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ABSTRACT

In the present study, we aimed to characterize the compressibility and compactibility of the novel pharmaceutical excipient, functionalized calcium carbonate (FCC). We studied three FCC modifications and compared the values for compressibility and compactibility with mannitol, microcrystalline cellulose (MCC), and ground calcium carbonate (CC 330) as well as mixtures of paracetamol and MCC or FCC at drug loads of 0%, 25%, 50%, 75%, and 100% (w/w). We used Heckel analysis, modified Heckel analysis, and Leuenberger analysis to characterize the compaction and compression behavior of the mixtures. Compaction analysis of FCC showed this material to markedly differ from ground calcium carbonate, exhibiting properties, i.e. plastic deformability, similar to those of MCC. This effect was attributed to the highly lamellar structure of FCC particles whose thickness is of the order of a single crystal unit cell. According to Leuenberger parameters, we concluded that FCC-based tablet formulations had mechanical properties equal or superior to those formulated with MCC. FCC tablets with high tensile strength were obtained already at low compressive pressures. Owing to these favorable properties (i.e. marked tensile strength and porosity), FCC promises to be suitable for the preparation of solid dosage forms.

1. Introduction

In response to the introduction of the Process analytical technology Initiative by the Food and Drug Administration (FDA) and the Quality by Design (QbD) paradigm in pharmaceutical research and development, there is a need for novel, fully characterized multifunctional excipients for pharmaceutical products (FDA, 2004).

Compaction behavior, i.e. compressibility, compactibility, and pressure susceptibility, are critical criteria that need to be met to avoid issues in scale-up or stability of solid dosage forms. Performance of materials under pressure has been extensively studied, and the criteria known to account for compression and compaction behavior have been defined. These criteria are often used as composite assessment to determine the suitability of excipients for target formulations.

Compressibility of a material is the relationship between compaction pressure and tablet porosity (Leuenberger, 1982; Leuenberger and Jetzer, 1984). Several researchers suggested various equations to describe compressibility (Heckel, 1961a; Heckel, 1961b; Cooper and Eaton, 1962; Nelson et al., 1955). One of the approaches to analyze compaction behavior was proposed by Heckel. In the present work, data were analyzed according to the Heckel equation. It is a popular equation that allows to compare volume reductions among different materials under constant experimental conditions (York, 1979; Duberg and Nyström, 1986). The major advantage of the Heckel equation is the availability of a large reference dataset. This makes the Heckel equation a convenient tool for analysis and comparison of different materials. Heckel analysis assumes that the volume reduction (reduction of compact porosity) under pressure follows first-order kinetics (Heckel, 1961a; Heckel, 1961b). The reciprocal of the Heckel slope is defined as the yield pressure of the material and represents the resistance of a material to deformation (Hersey and Rees, 1971). Susceptibility of a material to pressure can be taken into account by the modified Heckel equation, which is particularly suitable for low pressure ranges (Kuentz and Leuenberger, 1999).

Powder compactibility is often assessed by plotting the crushing strength as a function of compressive pressure (Leuenberger, 1982;

* Corresponding author. Tel.: +41 61 267 15 13; fax: +41 61 267 15 16.
E-mail addresses: tanja.stirnimann@unibas.ch (T. Stirnimann), susanna.atria@stud.unibas.ch (S. Atria), joachim.schoelkopf@omya.com (J. Schoelkopf), patrick.gane@omya.com (P. A.C. Gane), rainer.alles@unibas.ch (R. Alles), joerg.huwyler@unibas.ch (Jö. Huwyler), maxim.puchkov@unibas.ch (M. Puchkov).

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Leuenberger and Jetzer, 1984). Nowadays, crushing strength is mostly replaced by tensile strength because tensile strength takes differences in tablet size into account (Fell and Newton, 1968). Jetzer et al. published an equation to calculate the compactibility and compression susceptibility. These two parameters provide information about the deformation of the material under stress and the bonding properties of the material (Jetzer et al., 1983).

The roller compaction process leads to the formation of secondary micro-hardened regions in the roller-compacted ribbons of materials, such as magnesium carbonate (Freitag et al., 2004). We assumed a similar behavior for highly lamellar materials, due to the formation of local hardening in zones consisting of interpenetrating or interlocking lamellae. According to this hypothesis, we assumed the contact surfaces to be a governing factor to achieve compacts of higher tensile strength even at lower pressures.

Functionalized calcium carbonate (FCC) is a particulate (5–15 μm in size) material with highly developed surface and internal structures. It is produced by re-precipitation of inorganic mixed salts (calcium phosphate in this case) incorporating the starting material (calcium carbonate) under controlled conditions to form microporous particles with a specific lamellar surface area of 40–80 m^2/g and a porosity of approximately 70%. In a previous study, we successfully used this substance to produce mechanically robust, orally dispersible tablets by direct compression (Stirnimann et al., 2013). In the present study, we characterized compressibility and compactibility of the novel pharmaceutical excipient FCC.

2. Materials and methods

2.1. Materials

Three different modifications of FCC (VP-OM2501 S01, VP-OM2501 S02, and VP-OM2501 S03, Omya International AG, Oftringen, Switzerland) were compared to microcrystalline cellulose (MCC SANAQ® 102, Pharmatrans Sanaq AG, Allschwil, Switzerland), calcium carbonate (PharMagnesia CC Type Natura 330, Lehmann & Voss & Co., Hamburg, Germany), and mannitol (Mannitolum Ph Eur, Hänseler AG, Herisau, Switzerland). As an active pharmaceutical ingredient, we chose paracetamol (Acetaminophen USP/Paracetamol Ph Eur Powder, Mallinckrodt, Saint Louis, MO, USA).

Hydroxypropyl methyl cellulose (HPMC) E5PLV (Colorcon Limited, Dartford Kent, UK) was used as a binder for wet granulation. Magnesium stearate (Novartis, Basel, Switzerland) was used as a lubricant for tableting. For particle-size distribution measurements, we used isopropyl myristate (Hänseler) as a dispersant. Mercury (Sigma-Aldrich, Munich, Germany) was used as a non-wetting liquid for porosimetry measurements.

2.2. Methods

2.2.1. Characterization of raw materials

Scanning electron microscopy (SEM) images were obtained using an FEI/Philips XL30 FEG instrument (Philips, Eindhoven, Netherlands). The samples were sputtered with a 40 nm gold layer by a sputter coating device (MED 020, BalTec, Balzers, Liechtenstein) before microscope imaging.

Apparent true densities of the substances were determined by helium pycnometry (Micromeritics AccuPyc 1330, Norcross, GA, USA). Before the measurement, substances were dried overnight (12–15 h) under nitrogen flow in a vacuum drying cabinet type KVTS 11 (Salvis, Oftringen, Switzerland).

Particle-size distribution was determined with the Mastersizer X long bed laser diffractometer (Malvern Instruments, Malvern, Worcestershire, UK). FCC, MCC, CC 330, and paracetamol were dispersed in isopropyl myristate and analyzed by using the small volume sample presentation unit (Malvern Instruments). For mannitol, we used a dry powder feeder (Malvern Instruments). Measurements were performed in triplicate.

A Nova 2000e (Quantachrome Instruments, Boynton Beach, FL, USA) was used to quantify the specific surface area of FCC with the five-point BET (Brunauer–Emmett–Teller) method. After degassing the samples for 12–15 h at room temperature, they were measured in duplicates with nitrogen at constant temperature (77.4 K). Mannitol, MCC, CC 330, and paracetamol were not assessed due to the limit of resolution of the instrument ($<0.01\ m^2/g$).

Pore-size distribution of the substances was determined with an Auto Pore IV 9500 mercury porosimeter (Micromeritics Instrument, Norcross, GA, USA). Low-pressure mercury intrusion ranged from 3.59 kPa to 206.64 kPa. During high-pressure mercury intrusion, the pressure ranged from 206.64 kPa to 206.78 MPa. For both high- and low-pressure intrusion, equilibration time was set to 10 s.

2.2.2. Granulation of FCC

Granulation of FCC was achieved by roller compaction (Chilsonator IR220 roller compactor, Fitzpatrick, Elmhurst, IL, USA). The roll pressure was set to 20 bars at a roll gap of 1 mm and a roll speed of 4 rpm. The speed of the horizontal feed screw was set to 25 rpm, and the vertical feed screw moved with a speed of 120 rpm. To ensure constant powder flow to the horizontal feeding screw within the powder chute, we used a stirring device of type RE162 (IKA Labortechnik, Janke & Kunkel GmbH & Co. KG, Staufen, Germany) at 35 rpm. High-shear mixer granulation of FCC was carried out with an Oystar Micromix high-shear mixer (Hüttlin GmbH, Schopfheim, Germany). The binder (HPMC E5PLV) was dissolved in distilled water using a magnetic stirrer IKAMAG® RCT (IKA Labortechnik, Janke & Kunkel Gmbh & Co. KG) to obtain a 4% (w/w) solution. The binder solution was foamed with pressurized air (approximately 8 bars) in a Tornador® Z-011 foam gun (Bendel Werkzeuge, Bad Bevensen, Germany). FCC S02 was granulated with 5% (w/w) HPMC E5PLV. The foamed binder was added to the powder at a speed of 5.3 g/min with a peristaltic pump (Vario-Pumpsystem-Antrieb, Ismatec SA, Glattbrugg, Switzerland). The impeller speed was approximately 150 rpm and the chopper speed was approximately 1500 rpm. Afterwards, the granules were dried at 60 °C in a Heraeus UT 6200 drying oven (Sorvall Heraeus Instruments, Hanau, Germany) until loss on drying (LOD) was approximately 2%. LOD was determined gravimetrically with a Mettler LP 16 infrared lamp and a Mettler PE 360 balance (Mettler Instruments, Greifensee, Switzerland).

After roller compaction and high-shear granulation, ribbons and granules were milled with a Fitz®Mill comminutor L1A (Fitzpatrick) at a speed of approximately 500 rpm. Granules were sieved for 10 min at an amplitude setting of 46 to obtain particles sized between 180 μm and 500 μm (Retsch Vibro, Schieritz & Hauenstein AG, Arlesheim, Switzerland).

2.2.3. Tablet preparation

Prior to compaction, each powder was sieved through a 1000 μm sieve to eliminate agglomerates. Powders and granules were dried overnight (12–15 h) under nitrogen flow in a vacuum drying cabinet of type KVTS 11 (Salvis).

Mixtures were prepared by blending excipients with paracetamol to obtain paracetamol contents of 25% (w/w), 50% (w/w), 75% (w/w), and 100% (w/w). Furthermore, a reference formulation without paracetamol was prepared. Powders were mixed for 10 min in a tumbling mixer (Turbula T2C, Basel, Switzerland) at 32 rpm.

All powders and granules were compressed using a Styl'One 105 mL tablet press (Medel'Pharm, Beynost, France) with 10 mm round flat tooling. Analis software version 2.01 (Medel'Pharm) was used to operate the instrument and monitor the process. Due to the highly variable porosities of the raw materials, tablets with varying porosities were obtained at defined pressure. Therefore, we decided to hold the tablet volume constant at the lowest compressive

pressure. With an electronic balance type AX204 DeltaRange (Mettler Toledo), we manually (except for the granules) weighed the necessary amount of substance to obtain a tablet with a height of 6 mm at a compressive pressure of 6.37 MPa (0.5 kN). We used this sample mass for all tablets and all formulations over the whole compressive pressure range. FCC S02 granules were compacted using a feed shoe. Table 1 shows the tablet weight for each formulation (mean ± SD of $n = 3$ measurements).

The formulations with and without paracetamol were compacted in triplicate at 10 and 16 different compressive pressures ranging from 6 MPa to 500 MPa. Compressive pressure step-up was stopped if lamination occurred below 500 MPa. Punches were manually lubricated with magnesium stearate. For the automated process, magnesium stearate (0.5%, w/w) was mixed into the granules using a tumbling mixer (Turbula T2C) for 3 min at 32 rpm. To compress the tablets, we used the minimum possible dwell time achievable on our tablet press; rise and fall of the lower punch was set to 750 ms keeping the "maintain" phase set to "0" to simulate the shortest possible dwell time.

During tablet preparation and characterization, the temperature was kept between 24 °C and 34 °C and relative humidity between 31% and 57%.

2.2.4. Tablet weight, diameter, height, and crushing force

Immediately after tablet compression, we determined the weight, diameter, and height of the tablets. The tablets ($n = 3$) were weighed on an electronic balance type AX204 DeltaRange (Mettler Toledo). Diameter and height of the tablets were determined with a micrometer screw (Mitutoyo Model CD-15CPX, Kawasaki, Japan). Before measuring the crushing force, the tablets were allowed to expand for at least 1 h. If the crushing force of the tablets was lower than 400 N, we used a tablet hardness tester (8M, Dr. Schleuniger Pharmatron, Solothurn, Switzerland) with a speed of impact 1 mm/s (default value). In case of harder tablets, the tablet crushing force was analyzed on the Styl'One 105 mL tablet press (Medel'Pharm). To this end, the height was set to 13.5 mm, and the thickness of the tablet was set to 9 mm. When the punch had reached the lowest position, we placed the tablet vertically in the die, i.e. on a cylindrical edge, and proceeded with the compression sequence. The speed of impact was 0.3 mm/s in average for all measurements performed with Styl'One tablet press. The maximum force applied was the force needed to break the tablet. Both methods yielded the same crushing force for identical tablets despite the differences in impact speed.

2.2.5. Heckel, modified Heckel, and Leuenberger analyses

Using the software package OriginPro version 8.5 (OriginLab Corporation, Northampton, MA, USA), the Heckel equation (Heckel, 1961a,b) was fitted according to equation (1):

$$\ln\left(\frac{1}{1-p}\right) = k \times \sigma + A \tag{1}$$

where ρ is the density of the tablet (g/cm^3), k is the Heckel parameter (MPa^{-1}), σ is the compressive pressure (MPa), and A is a constant. We considered all data points for compressive pressures between 50 MPa and 200 MPa.

Density (ρ) of the tablet was calculated with equation (2):

$$\rho = \frac{(m/\pi r^2 h)}{\rho_{\text{true}}} \tag{2}$$

where m is the tablet mass (g), r is the tablet radius (cm), h is the tablet height (cm), and ρ_{true} is the true density of the substance forming the skeletal structure of the porous tablet (g/cm^3).

Mean yield pressure (σ_y, MPa) was calculated according to equation (3):

$$\sigma_y = \frac{1}{k} \tag{3}$$

where k is the Heckel parameter (MPa^{-1}).

With the modified Heckel equation (Kuentz and Leuenberger, 1999), the relative critical density (ρ_{rc}) and constant (C, MPa^{-1}) were calculated according to equation (4):

$$\sigma = \frac{1}{C}\left[\rho_{\text{rc}} - \rho - (1-\rho_{\text{rc}})\ln\left(\frac{1-\rho}{1-\rho_{\text{rc}}}\right)\right] \tag{4}$$

where σ is the compressive pressure (MPa) and ρ is the relative density of the tablet. Relative critical density is a parameter that defines a rigidity threshold and indicates the pressure susceptibility, i.e. the lower the value of ρ_{rc}, the earlier the onset of probability to form a stable pharmaceutical compact. The data between 6 MPa and 200 MPa were considered for the modified Heckel analysis.

By means of the Leuenberger equation (Jetzer et al., 1983), compactibility (σ_{tmax}) and compression susceptibility (γ) were calculated using equation (5):

$$\sigma_t = \sigma_{\text{t max}} \times (1 - e^{(-\gamma \times \sigma \times \rho)}) \tag{5}$$

where σ_t is the radial tensile strength (MPa), σ_{tmax} is the tensile strength (MPa) when σ (compressive pressure) $\to \infty$ and ρ (relative density) $\to 1$, γ is the compression susceptibility (MPa^{-1}), ρ is the relative density of the tablet, and σ is the applied compressive pressure (MPa). Data points over the entire compression range used were included in the calculation.

2.2.6. Tensile strength and porosity

Tensile strength was calculated according to equation (6):

$$\sigma_t = \frac{2 \times F}{\pi \times d \times h} \tag{6}$$

where σ_t is the radial tensile strength (MPa), F is the crushing force (N), d is the tablet diameter (mm), and h is the thickness of the tablet (mm).

With the aid of Analis software 2.01 (Medel'Pharm), we calculated the porosity of the tablets in accordance with equation (7):

$$\varepsilon = \left(1 - \frac{(m/\pi r^2 \times h)}{\rho_{\text{true}}}\right) \times 100 \tag{7}$$

where ε is the porosity (%), m is the tablet weight (g), r is the radius of the tablet (cm), h is the height of the tablet (cm), and ρ_{true} is the true density of the substance (g/cm^3).

Table 1
Weight of tablets.

Formulation	Weight (mg) ± SD
Mannitol	480.94 ± 0.62
MCC	325.09 ± 0.52
CC 330	730.09 ± 0.76
FCC S01	317.07 ± 1.78
FCC S02	295.94 ± 1.79
FCC S03	314.24 ± 4.26
FCC S02 granules RC	377.03 ± 0.94
FCC S02 granules HSM	409.67 ± 1.58
100% Paracetamol	448.36 ± 1.21
75% Paracetamol + 25% MCC	389.63 ± 1.29
50% Paracetamol + 50% MCC	360.90 ± 0.92
25% Paracetamol + 75% MCC	326.01 ± 0.59
75% Paracetamol + 25% FCC S02	399.38 ± 1.81
50% Paracetamol + 50% FCC S02	360.43 ± 0.91
25% Paracetamol + 75% FCC S02	329.72 ± 0.91

CC: calcium carbonate; FCC: functionalized calcium carbonate; HSM: high-shear mixer; MCC: microcrystalline cellulose; RC: roller compaction.

2.2.7. Pore-size distribution in tablets

To determine the distribution of pore sizes, the excipients (FCC S01, FCC S02, FCC S03, CC 330, MCC, and mannitol) were compacted without magnesium stearate at 12.73 MPa, 63.66 MPa, and 127.32 MPa using a Styl'One tablet press (Medel'Pharm). The tableting procedure is detailed in Section 2.2.3.

Pore-size distribution of the tablets was determined by mercury porosimetry as described in Section 2.2.1.

Pore size distribution of FCC powders are mostly bimodal (Ridgway et al., 2006), characterizing intra- and interparticle voids. To distinguish between intraparticle and interparticle pores, the data curve of the mercury porosimetry plot (pore diameter versus pore volume) was fitted with OriginPro version 8.5 (OriginLab). Fig. 1 shows the bimodal pore size distribution of FCC and the user-defined bimodal curve fit of equation (8). Equation (8) is constructed as a sum of two log normal distributions.

$$y = y_0 + \frac{1}{2}\left[\frac{Ae^{-1/2\left(\left(\ln(x/x_c)^2\right)/w^2\right)}\sqrt{2}}{\sqrt{\pi}wx} + \frac{A_1 e^{-1/2\left(\left(\ln(x/x_{c1})^2\right)/w_1{}^2\right)}\sqrt{2}}{\sqrt{\pi}w1x}\right] \quad (8)$$

where x is the pore size (μm), y is dV/dlog D pore volume (mL/g), x_c and x_{c1} are fitting parameters indicating the maximum of distribution, and other constants are for fitting purposes only (without physical meaning).

To find the intersection point (x_i) of this bimodal curve, we solved equation (8). After fitting equation (8) to experimental data, the parameters for two distributions were determined. The intersection point (x_i) of two curves is a solution of equation (9):

$$\frac{1}{2}\frac{Ae^{-(1/2)((\ln(x/x_c)^2)/w^2)}\sqrt{2}}{\sqrt{\pi}wx} = \frac{1}{2}\frac{A_1 e^{-(1/2)((\ln(x/x_{c1})^2)/w_1{}^2)}\sqrt{2}}{\sqrt{\pi}w_1 x} \quad (9)$$

Equation (9) has two solutions (x_1 and x_2) as shown in equation (10).

$$x_1 = e^{-\frac{(\ln(x_{c1}/x_c)w_1+\sqrt{2\ln((A\times w_1)/(A_1\times w))\times w^2 w_1{}^2-2w^4\ln((A\times w_1)/(A_1\times w))+w^2\ln(x_{c1}/x_c)^2)w_1}}{w_1^2-w^2}}$$

$$x_2 = e^{-\frac{(\ln(x_{c1}/x_c)w_2+\sqrt{2\ln((A\times W_1)/(A_1\times W))\times W^2 W_1{}^2-2W^4\ln((A\times W_1)/(A_1\times W))+W^2\ln(x_{c1}/x_c)^2)W_1}}{W_1^2-W^2}} \quad (10)$$

X_i is the solution (either x_1 or x_2), which is located between x_c and x_{c1} (Figure 1).

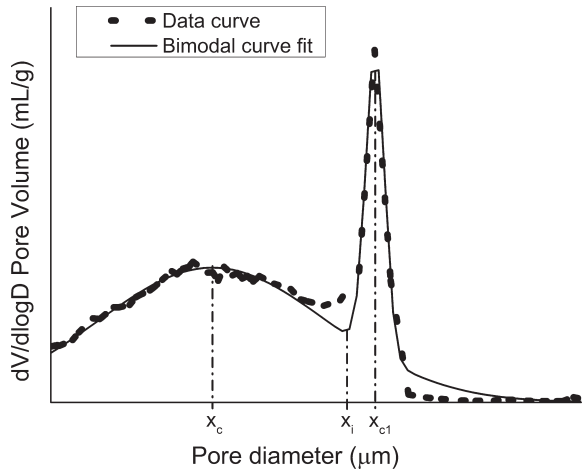

Fig. 1. Schematic representation of the bimodal curve fit.

The area under the curve (AUC) was calculated using Excel 2010 (Microsoft Corporation, Redmond, WA, USA) using the linear trapezoidal rule and the data points from the mercury porosimetry plot. All data points between zero and the intersection point (x_i) were included to calculate intraparticle AUC ($0 < x < x_i$). The values exceeding the intersection point (x_i) were used to calculate interparticle AUC ($x_i < x <$ mean median particle size). The ratio between inter- and intraparticle AUC indicated the pore distribution.

3. Results

3.1. Characterization of raw materials

Fig. 2 shows SEM pictures of the three different types of FCC particles. Typically, the FCC particles consisted of thin lamellae, forming a porous meshwork. FCC S01 and FCC S02 were similar, but FCC S03 had a more compact structure of lamellae and solid inclusions.

Table 2 summarizes the apparent true densities, mean median particle sizes, specific surface areas, core voids, and stratum/interparticle voids of the substances used.

Fig. 3 presents the porosimetry plots of the raw materials in powder form. The plots of MCC, mannitol, and CC 330 showed only one peak (pore diameter above 500 nm). In contrast, the plots of FCC showed two peaks; one below a pore diameter of 500 nm and one above 500 nm. Furthermore, the porosimetry plots indicated that the three different batches of FCC exhibited a different pore size distribution below a pore diameter of 500 nm. In the range of 10 nm to 200 nm, FCC S01 showed a higher volume of larger pores (e.g. 100 nm) than of very small pores (e.g. 10 nm), whereas FCC S03 was the opposite, with a higher pore volume of very small pores apparently. Under pressure, these effects were amplified. In powder form or at very low compressive pressure (12.7 MPa), FCC S02 showed a higher volume of larger pores than of small pores. At higher compressive pressure (127.3 MPa), we observed a higher volume of very small pores than of larger pores (data not shown).

3.2. Tablet properties

3.2.1. Comparison of FCC modifications

Table 3 summarizes the values for tensile strength and porosity for the different FCC/paracetamol mixtures at two compressive pressure settings. Porosities of tablets were very similar for all FCC/paracetamol mixtures at either pressure. We observed a trend towards higher tensile strength for FCC S02, especially in the lower pressure range. Under these conditions, reliable data were obtained only with this material. Therefore, we used FCC S02 for a mechanistic follow-up study.

3.2.2. Heckel, modified Heckel, and Leuenberger analyses

Table 4 shows the Heckel, modified Heckel, and Leuenberger parameters of the tablets. Our data exhibited a high value for the goodness of fit (R^2). The Heckel values (k) for formulations without paracetamol were highest when using MCC, followed by mannitol. The carbonates (FCC and CC) showed lower Heckel values than MCC and mannitol, but FCC reached higher values than CC 330. The mean yield pressure was approximately 180 MPa for MCC and mannitol. For the carbonates, mean yield pressure ranged from 294 MPa to 513 MPa (CC 330). Fig. 4 shows a comparison of the initial non-linear part of the Heckel-plot for the different types of FCC. The curves of FCC S01 and FCC S02 were comparable whereas FCC S03 shows less non-linearity. Modified Heckel analysis showed that the values for C were smaller than those for k, but the order was the same (except within FCC). FCC exhibited the lowest critical relative density (0.125–0.154), followed by MCC (0.253), CC 330

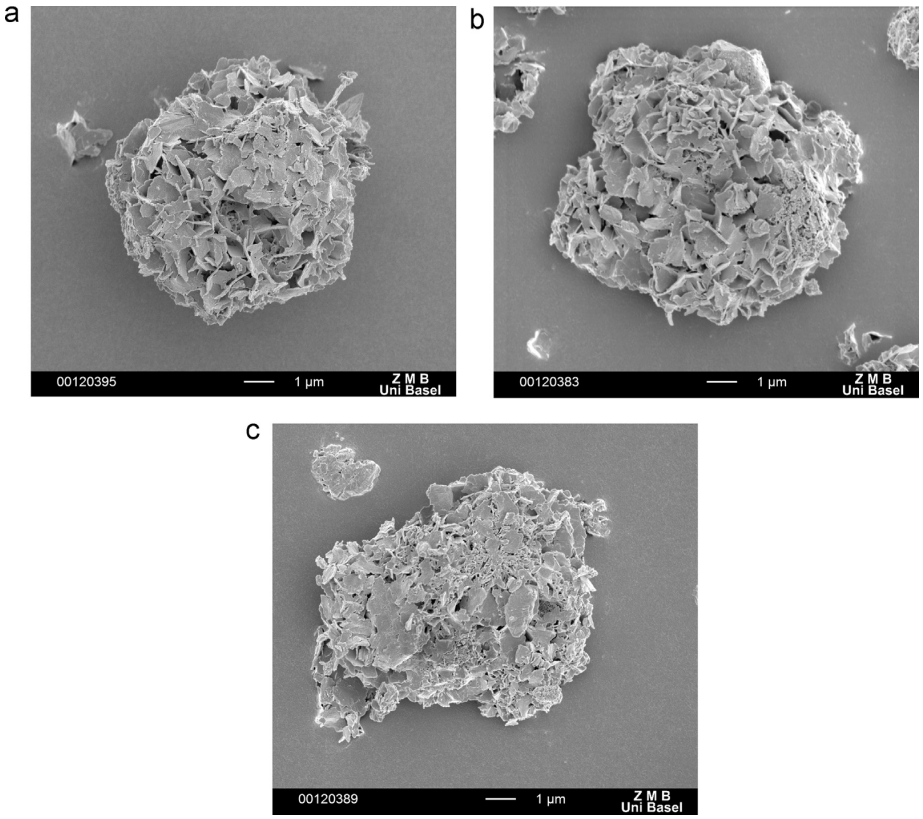

Fig. 2. (a–c) SEM pictures of (a) FCC S01, (b) FCC S02, and (c) FCC S03 (magnification: ×6702).

(0.525), and mannitol (0.594). Pure paracetamol tablets could not be compacted over the whole compression range due to lamination. Paracetamol/MCC tablets showed higher values for k and C (and therefore lower values for the mean yield pressure) than paracetamol/FCC S02 tablets. In each case, the values for C were significantly lower than the values for k. Furthermore, we observed a trend towards higher k and C values with decreasing amounts of paracetamol.

Critical relative densities of paracetamol tables formulated with either MCC or FCC S02 at identical mixing ratios were similar. The higher the amount of paracetamol in a formulation, the higher was the relative critical density of the resulting tablets.

In general, the quality of fit was better for the modified Heckel equation than for the Heckel equation.

In the Leuenberger analysis (Table 4), compactibility (σ_{tmax}) values for the formulations without paracetamol exceeded 10 for CC 330 (3.27×10^3 MPa), FCC S03 (13.92 MPa), MCC (12.40 MPa), and FCC S01 (11.88 MPa). FCC S02 achieved a compactibility value of 8.55 MPa, and mannitol showed by far the lowest value (2.77 MPa). For compression susceptibility (γ), FCC S02 showed a significantly higher value (13.38×10^{-3} MPa^{-1}) than the other materials, with MCC achieving a value of 7.56×10^{-3} MPa^{-1}, followed by FCC S01 (6.19×10^{-3} MPa^{-1}), FCC S03 (5.45×10^{-3} MPa^{-1}), mannitol (4.23×10^{-3} MPa^{-1}), and CC 330 (0.001×10^{-3} MPa^{-1}).

By adding and increasing the amount of paracetamol in a formulation, compactibility (σ_{tmax}) values decreased. For the same mixing proportions, compactibility values were not significantly different for paracetamol formulations based on either MCC or FCC S02. Compression susceptibility (γ) was significantly higher for FCC S02 formulations than for MCC formulations. The smaller the amount of paracetamol in a formulation, the higher was the value for compression susceptibility.

Table 2
Apparent true density (skeletal density), mean median particle size, specific surface area, core voids, and stratum/interparticle voids of the substances.

Substance	Apparent true density (g/cm^3)	Mean median particle size (µm) ± SD	Specific surface area (m^2/g) ± SD	Core voids (%, v/v)	Stratum and interparticle voids (%, v/v)
Mannitol	1.4849	121.31 ± 0.24	<LOD	0	100
MCC	1.5476	102.91 ± 1.22	<LOD	0	100
CC 330	2.7144	10.15 ± 0.24	<LOD	0	100
FCC S01	2.6893	14.15 ± 0.01	37.89 ± 0.04	9	91
FCC S02	2.7259	6.80 ± 0.03	56.22 ± 0.10	11	89
FCC S03	2.5054	9.19 ± 0.04	59.16 ± 0.19	9	91
Paracetamol	1.292	106.99 ± 0.32	<LOD	0	100

CC: calcium carbonate; FCC: functionalized calcium carbonate; LOD: limit of detection; MCC: microcrystalline cellulose.

Table 3
Tensile strength and porosity of paracetamol mixtures with FCC S01, FCC S02, and FCC S03.

Mixtures	Mean compressive pressure (MPa)	Tensile strength (MPa)	Porosity (%)
25% P + 75% FCC S01	7.25 ± 0.07	0.109 ± 0.005	66.12 ± 0.08
	94.33 ± 0.55	1.958 ± 0.015	40.23 ± 0.21
50% P + 50% FCC S01	7.15 ± 0.09	<LOD	55.61 ± 0.04
	93.32 ± 0.27	0.910 ± 0.012	31.97 ± 0.03
75% P + 25% FCC S01	6.99 ± 0.15	<LOD	43.91 ± 0.21
	91.98 ± 0.55	0.474 ± 0.043	24.36 ± 0.12
25% P + 75% FCC S02	7.06 ± 0.05	0.199 ± 0.010	67.52 ± 0.06
	93.24 ± 0.12	2.187 ± 0.079	40.01 ± 0.27
50% P + 50% FCC S02	6.90 ± 0.13	0.113 ± 0.006	56.54 ± 0.46
	92.08 ± 0.13	1.017 ± 0.022	31.79 ± 0.19
75% P + 25% FCC S02	7.05 ± 0.10	<LOD	43.64 ± 0.39
	92.34 ± 0.41	0.423 ± 0.007	23.46 ± 0.02
25% P + 75% FCC S03	7.19 ± 0.11	0.147 ± 0.000	64.82 ± 0.17
	93.90 ± 0.11	2.068 ± 0.079	40.54 ± 0.19
50% P + 50% FCC S03	7.18 ± 0.29	0.085 ± 0.000	53.80 ± 0.06
	92.93 ± 0.23	0.976 ± 0.036	31.80 ± 0.35
75% P + 25% FCC S03	7.16 ± 0.26	<LOD	41.68 ± 0.41
	92.38 ± 0.42	0.351 ± 0.011	23.57 ± 0.26

FCC: functionalized calcium carbonate; LOD: limit of detection; P: paracetamol.

3.2.3. Porosities and tensile strength of tablets

Fig. 5(a) shows the summative percentages of intra- and interparticle porosities as a function of compressive pressure for the formulations without paracetamol. Porosities of mannitol tablets (and in part also of MCC tablets) were much lower than the porosities of the calcium carbonate tablets. At low pressures (<10 MPa), FCC tablets had a porosity of more than 70% (v/v). At a compressive pressure of 400 MPa, porosities of CC 330 and FCC tablets were comparable (approximately 25% v/v). At the low range of compressive pressure, we observed a marked decrease of porosity for MCC tablets, and the change of porosity in response to altered compressive pressure was less marked for the other substances.

Fig. 5(b) is the correlation plot between compressive pressure and tablet porosity for the formulations with paracetamol. Depending on mixing ratios, MCC tablets showed a porosity of 40% (v/v) to 57% (v/v) at low compressive pressures. At the same pressure range, FCC S02 tablets reached porosities between 43% (v/v) and 77% (v/v). At around 240 MPa, porosity of all MCC formulations was approximately 10% (v/v). Tablets prepared with FCC S02 showed significantly higher porosities at the same pressure. At a compressive pressure of 240 MPa, tablets containing 75% paracetamol and 25% FCC S02 showed a porosity of 16.8% (v/v), tablets containing 50% paracetamol and 50% FCC S02 had a porosity of 22% (v/v), and tablets containing 25% paracetamol and 75% FCC S02 reached a porosity as high as 28% (v/v). Pure FCC S02 showed a porosity 3.5 times higher than that determined for the formulations with pure MCC at the same compressive pressure.

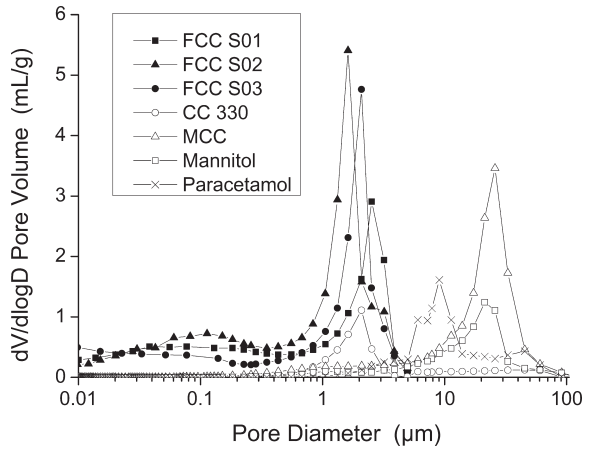

Fig. 3. Porosimetry plot of raw materials in powder form (for FCC modifications, the data points above 10 µm are not shown).

Fig. 5(c) shows the tensile strength as a function of compressive pressure for formulations without paracetamol. Mannitol and CC 330 exhibited very low tensile strength, even at high compressive pressures. Compared to CC 330, FCC reached high values for tensile strength that were similar to those of MCC. At low compressive pressures (below 100 MPa), the tensile strengths of FCC S02 and MCC were in the same range. FCC S03 was comparable to MCC at higher compressive pressures (above 200 MPa). Compressive pressure and tensile strength correlated in a linear fashion. For all FCC-based formulations, and especially for pure FCC powders, an atypical crack propagation of the tablets occurred during the crushing force measurement, i.e. the breaking pattern was more typical of a highly homogeneous, brittle material similar to porcelain. We assumed this effect to be responsible for the more variable crushing force measurements for tables formulated with FCC.

Fig. 5(d) is the correlation plot between compressive pressure and tensile strength for the mixtures with paracetamol. Below a pressure of 50 MPa, the tensile strengths of pure MCC and pure FCC S02 were comparable. Above 50 MPa, MCC tablets reached a higher tensile strength. However, below a compressive pressure of 180 MPa, all paracetamol tablets formulated with FCC S02 (independent of the mixing ratio) exhibited a tensile strength superior to that measured for MCC/paracetamol formulations. Above a compressive pressure of 180 MPa, MCC/paracetamol tablets showed a higher tensile strength than FCC S02/paracetamol tablets. In general, tensile strength increased with increasing proportions of FCC S02 or MCC.

3.2.4. Porosity and tensile strength of tablets prepared from granules

Porosity of tablets prepared from granulated material was generally lower than that of tablets formulated with FCC powder (Fig. 5a). If granules produced by roller compaction were used, porosity of the tablets was less markedly reduced than if granules produced by high-shear granulation were used, but in either case, the loss of porosity was below 10%.

In all cases, tensile strength of tablets made of roller-compacted granulates was similar to the tensile strength of tablets formulated

Table 4
Heckel, modified Heckel, and Leuenberger parameters of the tablets.

Substance	Heckel equation				Modified Heckel equation			Leuenberger equation		
	k (10^{-3} MPa^{-1}) ± SD	A ± SD	σ_y (MPa)	R^2	C (10^{-3} MPa^{-1}) ± SD	ρ_{rc} ± SD	R^2	σ_{tmax} (MPa) ± SD	γ (10^{-3} MPa^{-1}) ± SD	R^2
Mannitol	5.54 ± 0.16	1.40 ± 0.02	181	0.997	1.73 ± 0.09	0.594 ± 0.004	0.989	2.77 ± 0.28	4.23 ± 0.80	0.973
MCC	5.72 ± 0.60	1.06 ± 0.06	175	0.957	4.32 ± 0.32	0.253 ± 0.024	0.991	12.40 ± 0.28	7.56 ± 0.43	0.995
CC 330	1.95 ± 0.07	0.92 ± 0.01	513	0.995	0.31 ± 0.01	0.525 ± 0.002	0.999	3.27×10^3 ± 0.36×10^7	0.001 ± 1.113	0.943
FCC S01	2.70 ± 0.16	0.44 ± 0.02	370	0.986	1.25 ± 0.03	0.128 ± 0.004	1.000	11.88 ± 0.98	6.19 ± 0.92	0.985
FCC S02	2.63 ± 0.07	0.43 ± 0.01	380	0.997	1.22 ± 0.05	0.125 ± 0.007	0.995	8.55 ± 0.31	13.38 ± 0.98	0.995
FCC S03	3.40 ± 0.18	0.39 ± 0.01	294	0.988	1.16 ± 0.02	0.154 ± 0.002	0.999	13.92 ± 0.88	5.45 ± 0.61	0.993
25% Paracetamol + 75% MCC	6.49 ± 0.52	0.89 ± 0.07	154	0.981	3.27 ± 0.39	0.320 ± 0.038	0.994	6.35 ± 0.28	4.64 ± 0.41	0.995
50% Paracetamol + 50% MCC	6.02 ± 0.33	1.01 ± 0.02	166	0.991	2.37 ± 0.31	0.430 ± 0.033	0.993	3.35 ± 0.29	3.98 ± 0.63	0.986
75% Paracetamol + 25% MCC	5.02 ± 0.24	1.23 ± 0.04	199	0.993	1.57 ± 0.18	0.544 ± 0.021	0.995	1.61 ± 0.24	3.86 ± 1.01	0.966
25% Paracetamol + 75% FCC S02	3.09 ± 0.23	0.60 ± 0.03	324	0.984	1.05 ± 0.12	0.280 ± 0.024	0.994	4.00 ± 0.22	14.69 ± 1.92	0.990
50% Paracetamol + 50% FCC S02	3.29 ± 0.22	0.81 ± 0.03	304	0.987	0.99 ± 0.13	0.406 ± 0.023	0.993	2.09 ± 0.08	11.07 ± 0.91	0.997
75% Paracetamol + 25% FCC S02	2.72 ± 0.21	1.20 ± 0.02	368	0.983	0.71 ± 0.14	0.562 ± 0.025	0.986	0.88 ± 0.11	10.26 ± 2.58	0.973

CC: calcium carbonate; FCC: functionalized calcium carbonate; MCC: microcrystalline cellulose.

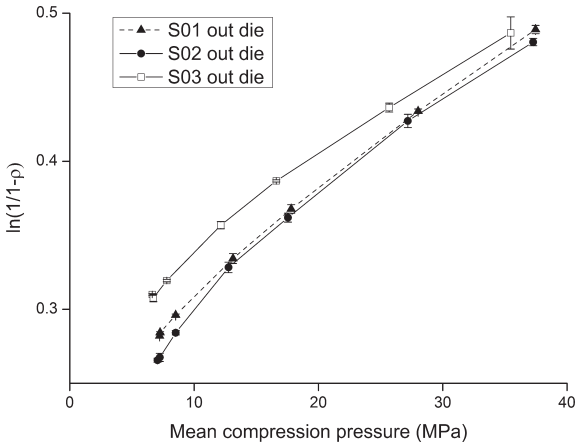

Fig. 4. Comparison of Heckel plots for FCC types in the lower pressure range (values are means ± SD; $n = 3$).

with pure FCC S02 powder. However, granulation by the high-shear mixer noticeably lowered tensile strength of the tablets (Fig. 5c).

4. Discussion

4.1. Pore volume distribution and morphology of raw materials

The bimodal distribution of pore sizes within FCC particles (see Figs. 1 and 3) for all types of FCC indicates that individual particles consist of denser cores, i.e. voids <500 nm (core voids) surrounded by a porous layer with larger pores and channels, i.e. voids >500 nm (stratum voids). The interparticle voids are also classified to be >500 nm. Clear distinction between stratum and interparticle voids is difficult. In previous investigations by Ridgway et al., these distribution patterns were classified as inter- and intraparticle voids (Ridgway et al., 2004).

Pore volume distribution and morphology of stratum voids are specific to each FCC type, resulting from specific changes in production parameters. For all other substances studied, we only detected interparticle voids, i.e. the voids between individual particles.

4.2. Tablet properties

4.2.1. Tablets without paracetamol

Heckel and modified Heckel analyses of the tablets without paracetamol showed MCC (σ_y = 175 MPa) and mannitol (σ_y = 181 MPa) to have elastic/plastic deformation behavior under pressure, whereas all carbonates were brittle. The σ_y values were significantly smaller for FCC (σ_y~350 MPa) than for CC 330 (σ_y~500 MPa), indicating the plastic behavior of FCC particles. Nevertheless, our values for mean yield pressure were rather high compared to other reports (Ilkka and Paronen, 1993; Paronen Heckel, 1986; Sonnergaard, 1999). These higher values resulted from the wider range of compressive pressure used in our study. The pressure range for plastically deforming materials was reported to be 40–135 MPa, and fragmentation occurs at a yield pressure range between 340 MPa and 430 MPa (Jain, 1999). Values determined for the relative critical density showed that FCC can be compacted into a stable tablet at a lower pressure than MCC, which is a sign of plastic deformation behavior. For mannitol and CC 330, higher pressure was needed to form robust compacts.

Using Leuenberger analysis, we showed that the compacts based on FCC S03 had the highest mechanical resistance (σ_{tmax}), followed

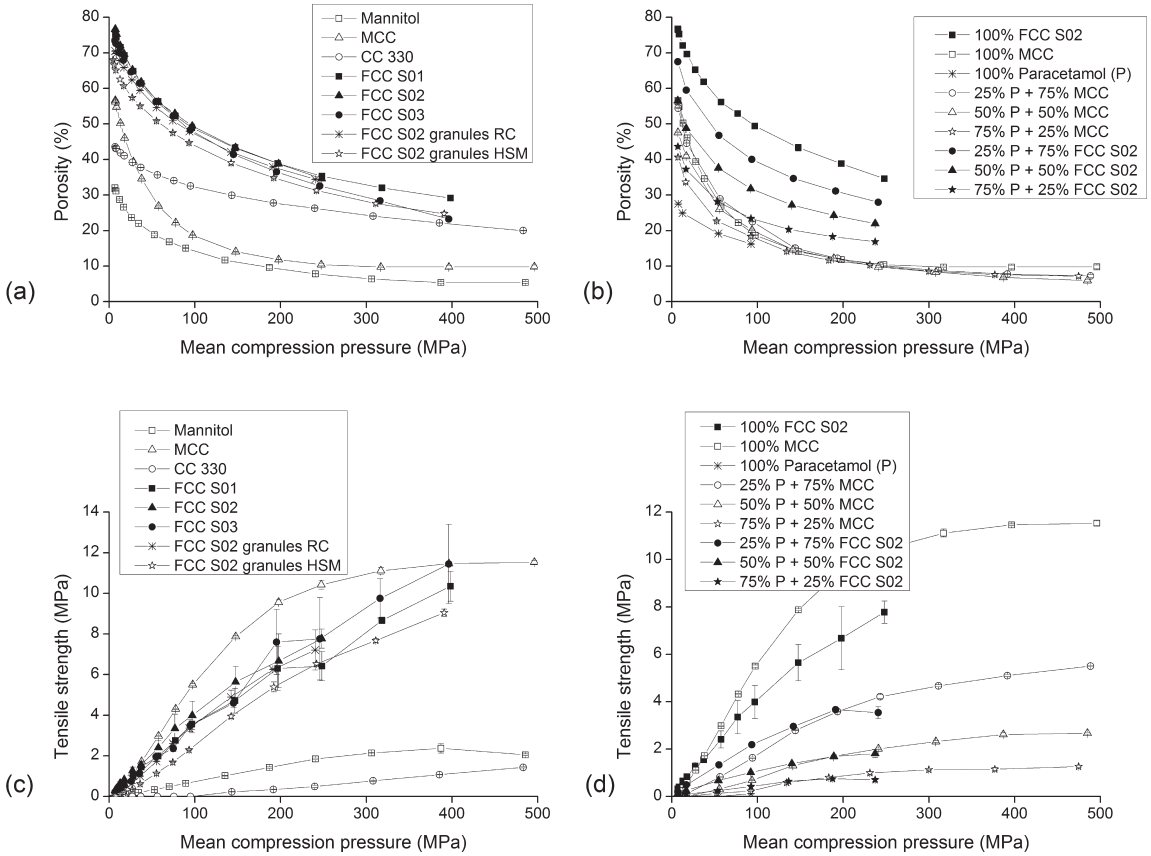

Fig. 5. Summative percentage of inter- and intraparticle porosity (v/v) (a, b) and tensile strength (c, d) of tablets compressed at different pressures.

by MCC, FCC S01, and FCC S02. These results were confirmed by the tensile strength plot (Fig. 5c). Tensile strength was comparable for MCC and FCC S03, especially above a compressive pressure of 200 MPa. Fig. 6 shows a schematic representation of FCC particles and two types of possible contact surfaces. We assumed that the particles moved closer to each other under low compressive pressure, and interlocking structures were formed between the lamellae (type I). The reasons for the differences in the non-linear part of the Heckel-plot (Fig. 4) could be due to densification by fracture of brittle lamellae followed by plastic deformation at higher compressive pressures. The initial differences of the density at 7.5 MPa for FCC S03 was attributed to less lamellae on the surface of FCC S03 particles (see Fig. 2). More spherical FCC S03 is better packed under low pressure (<20 MPa) as compared to FCC S01 or FCC S02. Under higher compressive pressure, the compact densities were similar. This indicates brittle deformation of lamellae under pressure. According to Heckel analysis (linear part), particles deform by fragmentation under higher compressive pressure, and the disruption of the particle provides a new contact surface for potential bonds (type II, Fig. 6). With FCC, we observed a stepwise increase of the tensile strength. For example, FCC S03 showed such a step at a compressive pressure between 150 MPa and 200 MPa. We assumed that the FCC S03 particles broke/collapsed more frequently than FCC S01 or FCC S02 particles at this compressive pressure. Due to the large volume of very small intraparticular pores in FCC S03 (Fig. 3), a large surface area for type II bonds would be available after particle disruption, resulting in a strong grip between the particles (Fig. 6, type II). As a consequence, tensile strength increased at higher compressive pressure. In contrast, FCC S01 and S02 showed a more extensive volume of larger pores than very small pores at low compressive pressures (Fig. 3). We speculated that under low compressive pressure, these larger pores of FCC S01 and S02 provided a markedly larger contact surface for possible bonds (type I) than did FCC S03 particles. FCC S03 exhibited a much smaller volume of large pores; hence the contact surface for possible bonds was limited under low compressive pressures.

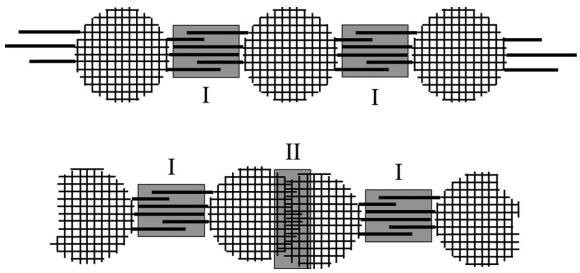

Fig. 6. Schematic representation of FCC particles and the 2 types of contact surfaces (gray). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Possible reasons for the marked tensile strength achieved with FCC could be (1) the surface texture in the stratum of FCC (rough, lamellae) and (2) the smaller size of the FCC particles. FCC particles were around 10 times smaller than MCC particles and therefore possessed a larger surface area in relation to the same volume.

Thus, the potential contact surface area of FCC is considerably larger than that associated with MCC, CC 330, or mannitol.

Leuenberger analysis revealed that compression susceptibilities (γ) varied significantly among the different substances. FCC S02 showed marked compression susceptibility with a value almost double the value for MCC, indicating that the plateau of tensile strength was reached faster than with the other substances. This finding was confirmed by the fact that FCC S02 showed capping above 250 MPa as the pressure increased. Below 50 MPa, FCC S02 yielded tablets with a high tensile strength, comparable or even superior to the tensile strength of MCC tablets (Fig. 5c).

Figs. 5a and 5c show certain limitations for MCC and mannitol at higher compressive pressures. Above 250 MPa, the tensile strength and porosity curves for MCC and mannitol started to level off and reached a plateau. FCC and CC 330 did not show such behavior at higher pressures. At 400 MPa, MCC had a porosity of only approximately 10%, in contrast to FCC and CC 330 whose porosities still exceeded 20%. This resulted in a higher volume (available for drug loading, for example), whilst maintaining high compact tensile strength. Above 400 MPa, porosities of FCC and CC 330 were comparable because the core and stratum voids of FCC broke down at these pressures.

4.2.2. Paracetamol tablets

Because paracetamol crystals are brittle (Duberg and Nyström, 1986; Prasad et al., 2001), the tablets increasingly deformed by fragmentation as paracetamol amounts were increased. The higher the proportion of paracetamol in the tablets, the higher was the critical relative density. This indicated that the compressive pressure had to be increased to obtain a robust compact.

By increasing the proportion of paracetamol in the formulations, mechanical resistance (σ_{tmax}) of the tablets decreased. Paracetamol is known to compensate mechanical stress by elastic recovery rather than by fracture or particle rearrangement (Leigh et al., 1967; Malamataris et al., 1984; Bangudu and Pilpel, 1985; Malamataris et al., 1996; Carless and Leigh, 1974). Compression susceptibility (γ) was higher for the paracetamol formulations with FCC S02 than for those with MCC. Therefore, FCC S02 produced stronger compacts even at low pressures. With lower amounts of FCC S02 in the formulation, the contact surface area to form new bonds is also decreased. Thus, to produce harder tablets, higher compaction pressure is necessary to force the FCC lamellae from the stratum into contact with other FCC particles. Compression susceptibilities of paracetamol formulations based on MCC were much more strongly influenced by increasing the paracetamol ratio than were paracetamol/FCC S02 formulations.

With respect to porosity changes upon compaction, FCC S02 was less pressure-sensitive than MCC. We assumed that the lamellar surface of FCC S02 acted as an energy dissipator to compensate the stress on pressure increase. Therefore, porosity decreased slowly by increasing the pressure.

Fig. 5(d) shows that pure MCC reached higher tensile strengths than pure FCC S02. In combination with paracetamol, FCC S02 reached a higher tensile strength in the low compressive pressure range compared to MCC. This effect supports the hypothesis that the contact surface area is a governing factor for a compact's mechanical stability. Moreover, the higher the proportion of paracetamol in a formulation, the earlier (at lower pressures) was the loss of mechanical stability, i.e. because of lamination, capping, etc.

4.2.3. Porosity and tensile strength of tablets prepared from granules

Over the entire range of compressive pressure, the tablets made from the roller-compacted FCC S02 granules showed higher porosities and higher tensile strengths than the tablets formulated with FCC S02 granules produced by the high-shear process. The reason for this was that roller-compacted FCC S02 granules possessed a large surface area allowing a strong grip between particles and the formation of stronger tablets already at lower pressures. Furthermore, the high shear forces in the mixer partially destroyed the stratum lamellae of FCC S02 and thus reduced the contact area. Granulation by roller compaction of FCC particles improved the flowability (data not shown) and retained the marked mechanical strength of the resulting FCC tablets. This property is unique to FCC, as a loss of tablet strength with other materials after roller-compaction granulation has been reported for all available excipients, including MCC.

5. Conclusion

The term FCC encompasses a family of new pharmaceutical excipients consisting of particles with a matrix of thin lamellae that form a porous meshwork. Differently produced FCC showed different pore types, namely the core voids that were surrounded by stratum voids. Upon compaction, numerous changes are observed, both on the microscopic and mesoscopic (particulate) size range. In particular, FCC can be compacted into tablets with high tensile strength at compressive pressures which are much lower than those needed for the compaction of other excipients such as mannitol or cellulose. This phenomenon can be attributed to interlocking of surface lamellae between FCC particles. We assume that the lamellar structure, and hence, the larger surface area of FCC, is the main origin of these extraordinary properties.

Inter- and intraparticle voids can accommodate drugs of interest such as paracetamol, offering interesting opportunities for drug delivery. The porosity of FCC containing tablets subjected to a compressive pressure of 100 MPa can reach values up to 60%, whereas tablets containing cellulose or mannitol only have 20% void volume.

FCC granules can be prepared by roller compaction or high shear granulation. Roller compaction had no significant impact on FCC tablet properties. Due to the high porosity, water penetrates FCC rapidly by capillary forces, leading to a fast disintegration of FCC tablets. This phenomenon can be exploited for the preparation of orally dispersible tablets (Stirnimann et al., 2013). Although FCC is a brittle substance, it showed mechanical properties (e.g. tensile strength and porosity) equal or superior to those of plastically deforming microcrystalline cellulose. We therefore anticipate FCC to have a considerable potential in pharmaceutical research and development.

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3.2 Roller compaction of FCC

Roller compaction of functionalized calcium carbonate (FCC): Improved powder properties at retained compactibility

Tanja Stirnimann[1], Joachim Schoelkopf[2], Patrick A.C. Gane[2, 3], Jörg Huwyler[1], Maxim Puchkov[1]

[1] Department of Pharmaceutical Sciences, University of Basel, Switzerland
[2] Omya International AG, R&D Minerals and Surface Chemistry, Oftringen, Switzerland
[3] School of Chemical Technology, Aalto University, Finland

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Roller compaction of functionalized calcium carbonate (FCC): improved powder properties at retained compactibility

Abstract

Purpose: The aim of the present study was to investigate the influence of roller compaction on the tableting properties of functionalized calcium carbonate (FCC) and its formulations.

Methods: We compared FCC with Avicel as well as mixtures of these excipients in combination with paracetamol at drug loads of 0%, 24.75%, 49.50%, 74.25%, and 100% (w/w). Granules were roller-compacted at 5 bar and 20 bar roll pressures. Compactibility was analyzed after tableting the granules at a compressive pressure of 6 MPa to 500 MPa.

Results: FCC granules showed better flowability than Avicel granules. In the low pressure range (< 100 MPa), the loss of compactibility due to dry granulation was marginal for FCC. Over 100 MPa compressive pressure, dry granulation increased the compressibility of FCC granules in comparison to FCC powder. Mixtures with FCC and paracetamol yielded significantly higher tensile strengths over the whole pressure range than mixtures with Avicel and paracetamol (except for the formulation with 74.25% (w/w) drug load). Mercury porosimetry showed that intraparticle pore structure of the FCC powder within the granules was affected neither by the roller compaction process nor by the subsequent tableting process.

Conclusions: This study showed that FCC is a suitable excipient for dry granulation due to easily-producible ribbons and retained compactibiliy properties after roller compaction.

Keywords

Dry granulation, tensile strength, functionalized calcium carbonate (FCC), lamellar structure, high surface, flowability, pore structure

1. Introduction

Roller compaction is a dry granulation method where agglomerates (ribbons) are formed. The transition from powder particles to a larger granulate entity reduces interparticle cohesiveness, resulting in a better flowability and improved uniformity of content. Roller compaction is a continuous process. It can handle high drug loading and prevents segregation. The fact that no liquid has to be added makes roller compaction a convenient method to granulate moisture and heat sensitive drugs. During the roller compaction process, particles bind to each other due to surface contacts. In the feeding zone of a roller compactor the particles rearrange before deformation, fragmentation, and bonding takes place (1). The type of bonding between particles, namely due to van der Waals interaction, e.g. interlocking forces and solid bridges, depends on the material properties (compressibility, deformation, fragmentation) (2).

Drawbacks of conventional roller compaction processes are reduced compactibility and dissolution issues. Compactibility can be described by plotting the crushing strength (nowadays crushing strength is often replaced by tensile strength) as a function of compressive pressures (3,4). Compactibility provides information about the bonding properties of a material (5). Malkowska and Khan observed for the first time that roller compaction has a negative influence on the tablet tensile strength in comparison to direct compression (6). Sun and Himmelspach studied the mechanism for the loss of compactibility of microcrystalline cellulose (MCC). They found that granule size enlargement was responsible for reduced compactibility of MCC due to decreased surface area (7). Patel et al. showed that the loss of compactibility for MCC is a combination of the work-hardening phenomenon and size enlargement, whereas the granule-hardening affects tensile strength more than granule size enlargement (8). Bultman showed that multiple compaction of pure microcrystalline cellulose could reduce the amount of fines, increases flow properties and improves size distribution. Furthermore, he found that each compression step irreversibly reduces some of the limited binding potential of MCC (9). In general, fine particles show better compactibility than coarse particles depending also on the size distribution characteristics of the particles. Nevertheless, the compaction properties of brittle materials are less affected by the particle size of the granules compared to plastic materials. Plastic materials characteristically display a reduced surface area available for bonding. During the fragmentation of brittle materials new surfaces are created, serving as new bonding regions. This effect was shown by Wu and Sun. They performed studies on brittle granules made of spray-dried lactose monohydrate, anhydrous dibasic calcium phosphate, and mannitol. Their study concluded that compactibility of brittle granules prepared with roller compaction are insensitive to granule size (10).

The effect of available surface for bonding is one of the most important factors for roller compacted ribbons, i.e. granule strength. Based on this main assumption, functionalized calcium carbonate (FCC)

as a material with highly developed and large specific surface (> 60 m²/g) is a material of interest for formulations developed with roller compactors.

The petal structure of FCC surface was described by Stirnimann et al. (11) and implies that the lamellae are very thin (in the range of a few nanometers), which assumes potentially high flexibility, similar to that displayed by nacre (12); hence, an ability to maintain a high contact surface after initial mechanical deformation (roller compaction). Therefore, it is possible to assume that FCC will not lose its high compactibility properties after initial deformation under roller compaction.

The aim of the present study was to investigate the influence of roller compaction on the tableting properties of FCC and formulations containing it.

2. Materials and methods

2.1 Materials

Functionalized calcium carbonate (FCC), type S02, (VP-OM2501 S02, Omya International AG, Switzerland) was compared to microcrystalline cellulose (Avicel® PH 102, FMC BioPolymer, Ireland). Paracetamol was chosen as a model drug (Acetaminophen USP / Paracetamol Ph Eur Powder, Mallinckrodt, USA) used in the role of active pharmaceutical ingredient. Sodium stearyl fumarate (SSF, LubriSanaq®, Pharmatrans Sanaq AG, Switzerland) was used as an inner phase lubricant during roller compaction, whereas magnesium stearate (MgSt, Sandoz, Switzerland) was used as an outer phase lubricant during tableting. Mercury (Sigma-Aldrich, Germany) was used for pressure intrusion porosimetry measurements as a non-wetting liquid.

2.2 Methods

2.2.1 Roller compaction and milling

Before roller compaction, each powder was sieved through a 1 000 µm sieve to destroy agglomerates. Excipients were blended with paracetamol to obtain relative paracetamol contents of 24.75% (w/w), 49.50% (w/w), 74.25% (w/w), and 99% (w/w). In addition, reference formulations without paracetamol were prepared. For comparative reasons, all the formulations contained 1% of sodium stearyl fumarate as an inner lubricant. The lubrication was necessary for the roller compaction process of paracetamol, due to sticking problems. We mixed the powders for 10 min in a tumbling mixer (Turbula T2C, Willy A. Bachofen AG, Switzerland) at 32 rpm. Granulation was performed with a Fitzpatrick® Chilsonator IR220 roller compactor (The Fitzpatrick Company, USA). Pressure was set either to 5 bar or to 20 bar. The feed rate and the roll speed were adjusted to obtain a ribbon thickness of 0.6 mm. After roller compaction the ribbons were milled with a FitzMill® L1A (The Fitzpatrick Company, USA) at 500 rpm.

2.2.2 Screening

A screening was performed to find the formulations of interest. For each formulation 10 g of the respective ribbon were put on a sieve with 500 µm mesh size. The sieve was shaken for 10 minutes with the help of a vibrating sieve tower (Vibro Retsch, Switzerland) at a shaking displacement of 1.5 mm. The remaining fraction (*RF*) was calculated with the help of equation (1):

$$RF\% = 100 - \left(\frac{(m_{\mathrm{tot}} - m_{res}) \times 100}{m_{tot}}\right) \quad (1)$$

where m_{tot} is the total mass applied initially on the sieve (g) and m_{res} is the residual amount on the sieve (g) after 10 minutes of shaking.

Formulations with a remaining fraction of more than 60% were considered as robust enough for the tableting process.

2.2.3 Granule analysis

To determine the fine fraction obtained with the roller compaction process, the product of the roller compaction process (ribbons including fines) was collected, weighed (m_{tot}), and afterwards sieved through a sieve with 180 µm mesh size as described in section 2.2.2.

The fine fraction (*FF*) was calculated with the help of equation (2):

$$FF\% = \frac{(m_{\mathrm{tot}} - m_{\mathrm{res}}) \times 100}{m_{\mathrm{tot}}} \quad (2)$$

where m_{tot} is the mass applied initially on the sieve (g) and m_{res} is the residual amount on the sieve (g) after 10 minutes of shaking.

The particle size distribution analysis was performed with a vibrating sieve tower. The sieving tower was shaken for 10 minutes at a shaking displacement of 1.5 mm. We used steel wire screens (Vibro Retsch, Germany) with mesh sizes of 180 µm, 250 µm, 355 µm, 500 µm, and 710 µm. The amount of powder remaining on each sieve was weighed. Granules with a size of less than 180 µm or more than 710 µm were excluded.

Flowability as well as bulk and tapped density were measured for selected granular fractions according to Ph Eur (13). For the flowability measurement a Mettler PM460 balance (Mettler Toledo, Switzerland) was used. Three different openings (5 mm, 7 mm, and 9 mm) were chosen. Bulk and tapped density were measured with a STAV 2003 volumeter (J. Engelsmann, Germany). The Hausner ratio (tapped density/bulk density) was calculated according to Ph Eur (13).

2.2.4 Tablet preparation

For the tablet preparation, all granules with a size between 180 µm and 710 µm (14) were used. The granules were dried overnight (12-15 h) under nitrogen flow in a vacuum drying cabinet of type KVTS 11 (Salvis, Switzerland) before they were mixed in a tumbling mixer (Turbula T2C, Willy A. Bachofen AG, Switzerland) for 10 minutes at 32 rpm. The granules were compressed with a 10 mm round, flat tooling, using a Styl'One 105 ml tablet press (Medel'Pharm, France). The tablet press was instrumented with the Analis software version 2.01 (Medel'Pharm, France). During compaction, tablet volume was kept constant at the lowest compressive pressure due to highly variable porosities of the raw materials. The punch gap was adjusted for each formulation to obtain a tablet height of 6 mm at a compressive pressure of 6.37 MPa (0.50 kN). The punch gap was kept constant over the whole compressive pressure range for each formulation. The formulations were compacted in triplicate at 10 different compressive pressures, ranging from 6 MPa to 500 MPa. If lamination occurred below 500 MPa, further increase of the compressive pressure was halted. Punches and die were manually lubricated with magnesium stearate. Tablets were compressed at minimum possible dwell time by setting the rise and fall of the lower punch to 750 ms and the "maintain" phase to 0 ms.

Temperature and relative humidity during tablet preparation and analysis were between 22.3°C and 25.9°C, and 28.5% and 50.0%, respectively.

2.2.5 Tablet analysis (weight, diameter, height, crushing force, tensile strength, and friability)

Tablet weight, diameter, height, and crushing force were measured in triplicate directly after tablet compression. Weight was determined with a Delta Range AX204 balance (Mettler Toledo, Switzerland). Diameter and height were measured with a micrometer screw of type CD-15CPX (Mitutoyo, Japan). Crushing forces below 400 N were measured with a tablet hardness tester (8M, Dr. Schleuniger Pharmatron, Switzerland) at a speed of impact of 1 mm/s. Harder tablets (> 400 N) were tested with the Styl'One tablet press (Medel'Pharm, France) as described in the previous study (11).

Tensile strength was calculated with equation (3):

$$\sigma_t = \frac{2F}{\pi d h} \quad (3)$$

where σ_t is the radial tensile strength (MPa), *F* is the crushing force (N), *d* is the tablet diameter (mm), and *h* is the tablet thickness (mm).

Friability of tablets compressed at 100 MPa was measured with a drum (Erweka, Germany) according to Ph Eur (13).

2.2.6 Heckel and modified Heckel equation

With the help of the software OriginPro version 8.5 (OriginLab Corporation, USA), the Heckel expression (15,16) was fitted according to equation (4):

$$\ln\left(\frac{1}{1-\rho}\right) = k\sigma + \mathrm{A} \tag{4}$$

where ρ is the tablet density (g/cm^3), *k* is the Heckel parameter (MPa^{-1}), σ is the compressive pressure (MPa), and A is a constant. We considered 4 data points between 50 MPa and 200 MPa for the Heckel analysis.

The density (ρ) was calculated according to equation (5):

$$\rho = \frac{(m/\pi r^2 h)}{\rho_{\mathrm{true}}} \tag{5}$$

where *m* is the tablet mass (g), *r* is the tablet radius (cm), h is the tablet height (cm), and ρ_{true} is the true density of the skeletal forming substance within the porous tablet (g/cm^3).

Mean yield pressure (σ_y, MPa) was calculated with equation (6):

$$\sigma_{\mathrm{y}} = \frac{1}{k} \tag{6}$$

where *k* is the Heckel parameter (MPa^{-1}).

The modified Heckel equation (17) was fitted according to equation (7):

$$\sigma = \frac{1}{\mathrm{C}}\left[\rho_{\mathrm{rc}} - \rho - (1-\rho_{\mathrm{rc}})\ln\left(\frac{1-\rho}{1-\rho_{\mathrm{rc}}}\right)\right] \tag{7}$$

where σ is the compressive pressure (MPa), C is a constant (MPa^{-1}), ρ_{rc} is the relative critical density, and ρ is the relative density of the tablet. For the modified Heckel analysis 6 data points between 5 MPa and 200 MPa were considered.

2.2.7 Pore size distribution in tablets

To measure the pore size distribution, tablets were prepared as described in section 2.2.4. The analysis was performed with an Auto Pore IV 9500 mercury porosimeter (Micromeritics, USA). Low-pressure and high-pressure mercury intrusion ranged from 3.59 kPa to 206.64 kPa and from 206.78 kPa to 206.78 MPa, respectively. Equilibration time was set to 10 s over the whole pressure range.

3. Results and Discussion

3.1 Screening

A screening process was aimed to find the formulations of interest for further studies, namely compaction studies. For tableting, the granules have to show certain rigidity for further processing. In our setup, the fine fraction (< 500 µm) gave us a hint of the rigidity of a ribbon. A screening with 18 formulations yielded 10 formulations of interest because they all showed a remaining fraction (> 500 µm) of more than 60% (w/w). This means that only 40% of the solid (in the form of ribbons) was collapsed into fines with a size of less than 500 µm after shaking for 10 minutes.

FCC with SSF showed a very high remaining fraction (approx. 90%) during roller compaction, independent of the applied roll pressure (the value for the remaining fraction for granules prepared at 20 bar is within the standard deviation of the value for 5 bar). This result showed that rigid ribbons made of FCC could be roller-compacted even at low pressures (5 bar). In general we observed higher remaining fractions; thus, more rigid ribbons for the powder blends that were roller compacted at higher pressure (20 bar). This effect was more pronounced for mixtures containing Avicel. We assumed that the particles were packed denser at higher pressures, resulting in stronger interparticle bonds due to more surface contacts and therefore, more rigid ribbons. Avicel with SSF admixtures processed at 5 bar roll pressure showed only 10% (w/w) remaining fraction, which is a sign of very fragile ribbon. We assumed that, in contrast to FCC, the pressure of 5 bar was not enough for Avicel to form a sufficient number of interparticle bonds. At 20 bar the Avicel and SSF powder blend did not enter the compression region and resulted in the failure within the feeding zone of the roller compactor.

For the drug loads over 50% (w/w), the remaining fraction was inferior and, therefore, the ribbons were weakest. It is well known, that paracetamol crystals are brittle (18,19); however, during tableting paracetamol compensates mechanical stress by elastic recovery (20–24). We assume that the elastic recovery of paracetamol is responsible for weakening the ribbons at higher paracetamol contents.

3.2 Granule properties

Table 1 shows the fine fraction during roller compaction for all the formulations of interest. Again we supposed a negative influence of paracetamol on the rigidity of Avicel ribbons. We assumed that Avicel was not able to compensate the effect of elastic recovery caused by paracetamol, especially at high drug loads. FCC mixtures showed a 50% reduction of the fine fraction after increasing compressive pressure during roller compaction from 5 bar to 20 bar. We consider that the particles moved closer together at

higher pressure and formed a higher number of interparticle bonds. Comparable to Avicel, we observed a trend for higher fine fractions for FCC by increasing the amount of paracetamol in the mixtures. The amount of fines could be reduced by further process optimization, for example by changing the profile of the rolls.

By employing roller compaction of FCC it was possible to increase the flowability of FCC significantly and, hence, overcome the limitations of the poor flowability of FCC in powder form (11,24). With respect to flowability, table 1 shows that granules obtained at 5 bar were significantly slower flowing than the ones obtained at 20 bar. A possible reason was the denser packing at 20 bar and a smoother surface with less outstanding lamellae (reduced cohesiveness). FCC in combination with SSF showed fastest flowability (8.51 g/s through an opening of 9 mm). At the same drug load and at the same compressive pressure during roller compaction, the FCC mixtures were always faster than the Avicel mixtures. Possible reasons are different particle shapes, different particle sizes, different particle size distributions, and a smoother surface texture. The particle size distribution of Avicel showed that the mixture mainly contained fines and very coarse granules (data not shown). We assumed that this distribution was responsible for slower flow, especially due to the fines which hindered the flowability due to increased cohesiveness. Furthermore, we assumed that the high mass fraction of coarse particles in the FCC mixtures accelerated the flowability because they were heavier than the smaller ones. Our observations are in agreement with Liu et al., who showed better flowability for powder with narrow particle size distribution. Among powders with narrow size distribution they also observed a faster flow for larger particles (26). For the openings between 9 mm to 7 mm the flow rate was reduced by factors ranging from 1.7 to 1.8. From the opening 7 mm to 5 mm the speed of the particles was reduced by the factors 2.4 to 2.6.

Table 1 shows that 5 bar compacted granules showed lower densities compared to granules compacted at 20 bar due to a looser packing derived from the lower applied pressure during roller compaction. In general, densities for FCC mixtures were always higher compared to Avicel mixtures. The Hausner ratio lay between 1.04 and 1.11 for all the mixtures, meaning that the consolidation during tapping was minimal. It is noted that the Hausner ratio became smaller by increasing the amount of paracetamol. A possible reason is the structure and smooth surface texture of paracetamol, which did not allow rearrangement after the initial packing. Lamellae of FCC and the fibers of Avicel can interlock and prevent the particles from forming a dense packing. The higher the amount of paracetamol in the formulation, the smaller the interlocking effects of Avicel and FCC, hence the reduction of the Hausner ratio.

3.3 Tablet properties

Table 1 presents the resulting tablet weights for different formulations. Granules roller-compacted at 5 bar yielded lighter tablets than the granules at 20 bar due to less densification during roller compaction. Among paracetamol mixtures processed at 20 bar, the FCC-paracetamol mixtures produced heavier tablets compared to Avicel-paracetamol mixtures at the same drug-excipient ratio due to higher FCC bulk density (ca. 0.64 g/cm^3) compared to Avicel (ca. 0.57 g/cm^3).

Table 1: Granule and tablet properties. "x" is indicating that no tablet was obtained at 100 MPa (not stable enough / lamination). "Fail" means that the sample failed the test due to broken tablets.

Mixtures	Fine fraction (%)	Flowability (g/s)			Bulk density (g/ml)	Tapped density (g/ml)	Hausner ratio	Tablet weight (mg)	Friability at 100 MPa (%)
		5 mm	7 mm	9 mm					
99% FCC + 1% SSF_5bar	12	5.10 ± 0.05	2.93 ± 0.06	1.19 ± 0.01	0.53	0.56	1.06	350.1 ± 2.6	0.24
99% FCC + 1% SSF_20bar	6	8.51 ± 0.02	4.72 ± 0.01	1.91 ± 0.01	0.79	0.82	1.04	462.6 ± 4.2	0.73
74.25% FCC + 24.75% P + 1% SSF_5bar	21	5.52 ± 0.04	3.09 ± 0.00	1.27 ± 0.02	0.55	0.58	1.06	371.4 ± 2.9	0.56
74.25% FCC + 24.75% P + 1% SSF_20bar	10	7.54 ± 0.02	4.19 ± 0.01	1.68 ± 0.02	0.66	0.73	1.11	436.7 ± 3.7	1.13
49.50% FCC + 49.50% P + 1% SSF_20bar	30	7.02 ± 0.05	3.85 ± 0.02	1.56 ± 0.01	0.63	0.68	1.07	442.0 ± 4.3	1.76
24.75% FCC + 74.25% P + 1% SSF_20bar	29	7.17 ± 0.02	3.96 ± 0.00	1.58 ± 0.02	0.64	0.68	1.05	435.2 ± 2.7	x
74.25% Avicel + 24.75% P + 1% SSF_20bar	8	5.98 ± 0.04	3.44 ± 0.02	1.41 ± 0.00	0.55	0.60	1.10	375.6 ± 3.4	Fail
49.50% Avicel + 49.50% P + 1% SSF_20bar	17	6.13 ± 0.02	3.41 ± 0.01	1.33 ± 0.01	0.56	0.61	1.09	383.5 ± 6.5	6.71
24.75% Avicel + 74.25% P + 1% SSF_20bar	45	6.19 ± 0.02	3.54 ± 0.03	1.39 ± 0.02	0.61	0.64	1.04	394.9 ± 4.2	Fail
99% P + 1% SSF_20bar	55	6.39 ± 0.06	3.57 ± 0.02	1.49 ± 0.01	0.63	0.68	1.07	448.7 ± 2.1	x

Table 1 shows that the tablet friability was considerably lower for FCC-paracetamol mixtures than for Avicel–paracetamol blends. Among the Avicel formulations, friability could only be measured for the tablets with 49.50% drug load. We assumed that the elastic properties of paracetamol could not be compensated by Avicel and, as a result, the tablets did not show enough physical strength to pass the friability test. Friability values for FCC with admixtures of SSF (independent of pressure applied during roller compaction) and FCC in combination with a low drug load (roller compacted at 5 bar) were below 1%. Interestingly, the FCC granules obtained at 5 bar produced tablets with significantly lower friability than the ones compressed at 20 bar. This phenomenon is explained in Figure 1.

Figure 1 shows the tablet tensile strengths as a function of compressive pressures. Up to 250 MPa pressure, the tensile strength increased almost linearly for all formulations at increasing compressive pressure. At the same compressive pressure within the low pressure range (enlargement inside Figure 1), the tablet tensile strength was higher for compacts prepared from powders, followed by compacts from granules roller-compacted at 5 bar, and, finally, tablets made from granules compacted at 20 bar. In other words, the friability is dependent on the tablet tensile strength, which is a function of surface available for contacts. The higher the pressure during roller compaction, the denser is the packing of the particles and the higher the loss of surface area.

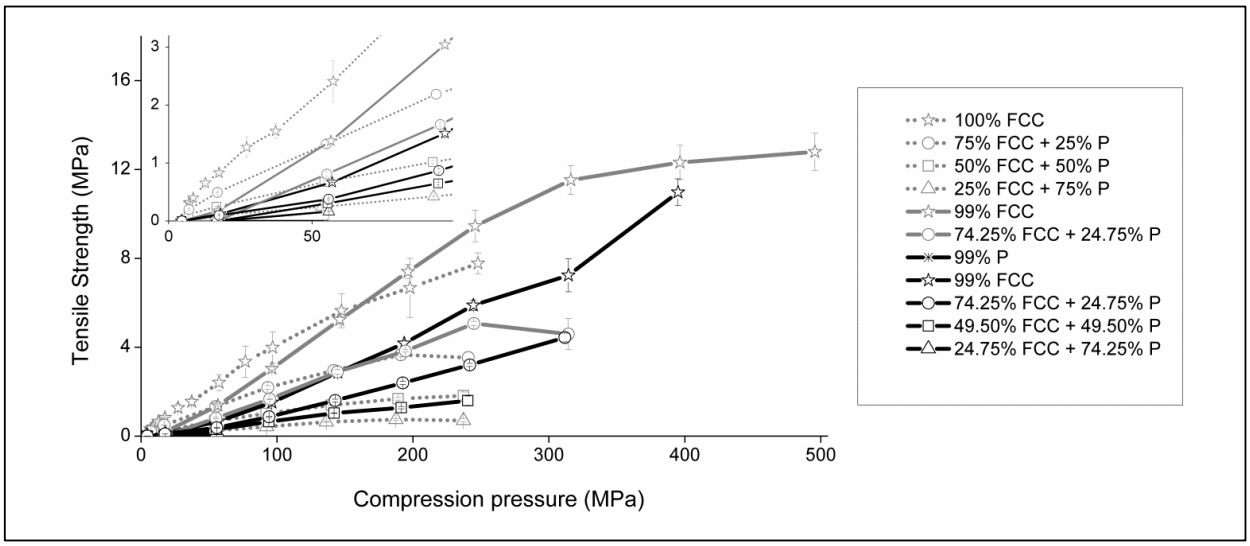

Figure 1: Tensile strength of FCC based tablet formulations as a function of compressive pressure. Tablets contained varying amounts of paracetamol (P) and were prepared using FCC powder (dotted lines) or FCC granules obtained by roller compaction at 5 bar (gray solid line) or 20 bar (black solid line). All granules contained 1% sodium stearyl fumarate. Values are means ± SD of *n*=3 experiments. Insert: magnification of the low compressive pressure range up to 100 MPa

However, this statement is not entirely supported by the tensile strength results at higher compressive pressures (> 200 MPa), where the tensile strengths of tablets made from 5 bar granules were higher than the ones made from powder. This can be explained by the fact that SSF admixture to the FCC reduces the lamellar contact area by forming contact obstacles.

At very high pressures (~ 400 MPa), tensile strength of tablets made of 5 bar granules and 20 bar granules were comparable. At such stresses, the granules (and also the particles within a granule) could break and, hence, provide additional surface area for bond-making contacts (12). The effect of increasing tensile strength due to particle breaking, we already observed in a previous study (11). For granules compressed at 20 bar, more compressive pressure was necessary to break the particles, in

contrast to granules obtained at 5 bar. In contrast to tablets made of powder blends, the risk for tablet lamination was reduced at higher compressive pressures using FCC granules. This observation can be best explained by the fact that during the roller compaction process, a packing and densification of FCC particles takes place, which facilitate the rearrangement and packing of the granules later during tableting in contrast to the bulky powder. In such a case the roller-compaction process acts as a pre-compression stage during tableting for FCC-based formulations.

The positive effect of high specific surface on the stability of tablets is supported by tablet tensile strength results for FCC-paracetamol and Avicel-paracetamol mixtures.

Figure 2 shows the tensile strength as a function of compressive pressure for paracetamol mixtures with FCC and Avicel. The mixtures with FCC reached much higher tensile strength values than the mixtures of Avicel and paracetamol, except the formulation with 24.75% FCC. For the mixture with 74.25% paracetamol, FCC reached the maximal tensile strength (0.16 MPa) already at 50 MPa. The Avicel formulation with the same drug load reached this value after 150 MPa compressive pressure was applied. The Avicel formulation with 74.25% drug load reached a 3.4 times higher tensile strength than FCC in combination with paracetamol, but needed 10 times more pressure to reach this value. We suppose that the lamellar surface of FCC is responsible for the high values of tensile strength even at lower pressures. At higher drug load, FCC showed superior properties compared to Avicel, especially in the lower pressure range. Paracetamol is known to be a difficult substance for tableting due to the fact that it compensates mechanical stress by elastic recovery (20–24). Therefore, we assume similar behavior as shown for FCC in this study not only for combinations with paracetamol but also in combination with other drugs.

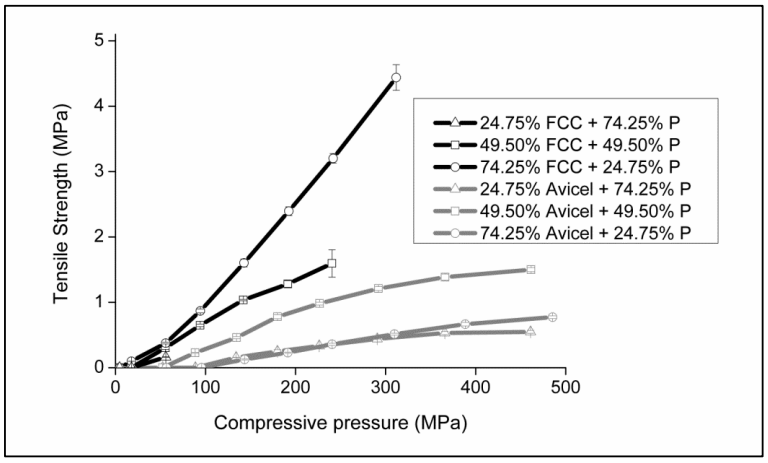

Figure 2: Compaction of granules containing mixtures of paracetamol (P) and FCC or Avicel. Comparison of tensile strength of tablets as a function of compressive pressure. All formulations were granulated at 20 bar and contained 1% sodium stearyl fumarate. Values are means ± SD of *n*=3 experiments.

Table 2 shows the values for the Heckel and modified Heckel analysis. The higher the pressures during roller compaction, the lower the values for the Heckel parameter (*k*) for the tablets. A low value for "*k*"

indicates higher pressure is needed to obtain a stable tablet at the same tensile strength. The values for relative critical density (ρ_{rc}), i.e. the tablet density at which the stable compacts can be first formed, supported the results from the Heckel analysis. The differences between the powder and 5 bar granules were much smaller than the differences between the 5 and 20 bar granules.

Table 2: Heckel and modified Heckel parameters. The values for mixtures containing Avicel and paracetamol are not shown because some values were missing for the fitting in the chosen pressure range. *) indicates that these data were already pubished (11)

Substances	Heckel equation				Modified Heckel equation		
	$k(10^{-3}$ MPa$^{-1})$ ± SD	A ± SD	σ_y (MPa)	R^2	$C(10^{-3}$ MPa$^{-1})$ ± SD	ρ_{rc} ± SD	R^2
100% FCC powder	2.61 ± 0.15	0.44 ± 0.02	383	0.990	1.006 ± 0.064	0.160 ± 0.014	0.998004
99% FCC + 1%SSF_5bar	2.43 ± 0.15	0.43 ± 0.02	412	0.989	0.767 ± 0.031	0.193 ± 0.008	0.999036
99% FCC + 1%SSF_20bar	2.13 ± 0.08	0.55 ± 0.01	469	0.996	0.525 ± 0.029	0.303 ± 0.008	0.998171
75% FCC + 25% P powder *)	2.97 ± 0.28	0.62 ± 0.04	336	0.974	1.051 ± 0.122	0.280 ± 0.024	0.994061
74.25% FCC + 24.75% P +1% SSF_5bar	2.82 ± 0.13	0.58 ± 0.02	354	0.994	0.891 ± 0.021	0.285 ± 0.004	0.999704
74.25% FCC + 24.75% P +1% SSF_20bar	2.29 ± 0.09	0.69 ± 0.01	437	0.995	0.549 ± 0.018	0.380 ± 0.004	0.999448
50% FCC + 50% P powder *)	3.23 ± 0.32	0.83 ± 0.04	309	0.972	0.985 ± 0.127	0.406 ± 0.023	0.993015
49.5% FCC + 49.5% P +1% SSF_20bar	2.46 ± 0.21	0.95 ± 0.03	406	0.979	0.507 ± 0.043	0.509 ± 0.010	0.996791
25% FCC + 25% P powder *)	3.19 ± 0.42	1.13 ± 0.05	313	0.951	0.708 ± 0.137	0.562 ± 0.025	0.98597
24.75% FCC + 74.25% P +1% SSF_20bar	nd	nd	nd	nd	nd	nd	nd

3.4 Mercury porosimetry

Figure 3 shows a mercury porosimetry plot of the pore size distributions of FCC tablets made with powder and granulates. The tablets were compressed at three different compressive pressures. By increasing the compressive pressure, the characteristic peaks were shifted to smaller pore diameters (Figure 3) as a result of FCC densification and collapsing of lamellae on the surface of particles. The plots of tablets compressed at the same compressive pressure were almost congruent, for all types of the primary material (powder or granules). The only noted difference is the higher pore volume of granules at larger pore diameters compared to powders. We assumed that the voids between granules were larger after rearrangement and compression than the voids between powder particles. The effect was more pronounced at lower compressive pressures due to a lesser densification and, thus, to a greater likelihood of void volume preservation. The intraparticular structure of FCC (pores with a diameter of less than 0.02 µm) was affected neither by the roller compaction process, nor by tableting.

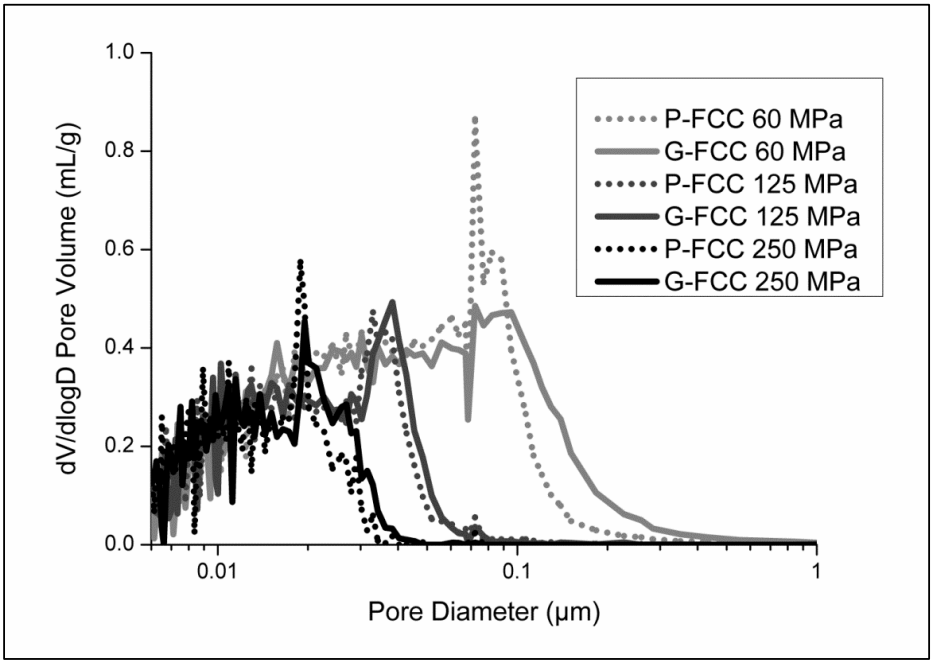

Figure 3: Porosity of FCC after compaction. Comparison of compacted FCC powder (P-FCC) or FCC granules (G-FCC). G-FCC was granulated at 5 bar. Mercury porosimetry was used to analyze the pore size distribution of FCC at increasing compaction pressures. Values are means of *n*=2 measurements.

Conclusion

Roller compaction of FCC revealed rigid ribbons at a low fine fraction, even at low pressures during roller compaction. The resulting granules made of FCC and a model drug showed better flowabilities than Avicel based formulations. We could show that the loss of compressibility for FCC in the low pressure range below 100 MPa was marginal. Over 100 MPa compressive pressure, which is a commonly used pressure for industrial production, the granulation had a significant positive effect on the compressibility compared to tablets made of FCC powder only. We conclude that pre-densification during roller compaction led to a more homogenous stress distribution during tableting with granules. In addition, tablets composed of granulated FCC and the model drug showed significantly higher tensile strengths over the whole pressure range than Avicel based formulations. Thus, granulated formulations of FCC have superior properties with respect to flowability and compressiblity as compared to Avicel or non-granulated FCC formulations.

The intraparticular structure of FCC, i.e. mesoporous voids with a pore diameter in the range of 2 to 50 nm, was affected neither by roller compaction, nor by tableting. This result indicates that neither the flexible lamellar structure nor the high surface area of FCC are affected by roller compaction. We conclude that granulation does not interfere with drug loading of FCC.

FCC powder has a poor flowability limiting its use in pharmaceutical production. This problem can be overcome by dry granulation using roller compaction. This offers the possibility to process the novel pharmaceutical excipient FCC on high speed rotary tablet presses and to make it accessible for industrial large scale production.

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3.3 Power consumption as a function of particle configuration

Analysis of power consumption profiles during wet granulation as a function of particle configuration

Tanja Stirnimann[1], Hans Leuenberger[2, 3], Jörg Huwyler[1], Maxim Puchkov[1]

[1] Department of Pharmaceutical Sciences, University of Basel, Switzerland
[2] CINCAP GmbH, Pfeffingen, Switzerland
[3] IFIIP GmbH, Pfeffingen, Switzerland

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Analysis of power consumption profiles during wet granulation as a function of particle configuration

Abstract

Purpose: The aim of this study was to investigate the appearance of liquid bridges of different configurations, which result in stepwise increase of the power consumption profile during a wet granulation.

Methods: Spherical Fujicalin particles were used as model particles. Fujicalin particles were granulated in a high-shear mixer by the addition of three different binder concentrations (10%, 15%, and 20% Kollidon 25). The experimentally obtained results were compared with the calculated wetting ratios at different granulation phases.

Results: It was possible to interpret the stepwise increase of the torque signal in a typical power consumption profile by different geometrical arrangements of the spherical particles depending on the liquid content. The calculated regions of bridge configuration changes were detected on the experimental power consumption profiles.

Conclusions: Our findings confirm that, during liquid addition to a powder bed, the critical concentration of liquid is influencing not the powder system as a whole (e.g., classical single percolation concentration or percolation threshold) but first changes granular composition, followed by alteration of overall system properties. The proposed new method to determine the bridge configuration changes will be helpful for further understanding of the granulation process and for calculating potential critical phases during large scale trials.

Keywords

Excipients, contact angle, granulation, powder technology, mathematical model, liquid bridge morphologies, high-shear mixer, granulation phases

1. Introduction

1.1 Background

Wet granulation in a high-shear mixer is a widely-used pharmaceutical unit operation to produce granules for further processing, such as tableting. Granulation is a critical process step in pharmaceutical research, development, and production.

In the past, there were several attempts made to control the agglomeration process in a high-shear mixer with the help of power consumption recording. It is possible to monitor during high-shear granulation the mixer power consumption as a function of the added granulation liquid [1]. In such case, the granulation liquid has to be added slowly and continuously to the powder bed that is stirred by an impeller and a chopper. The adhesion force between the particles during the agglomeration process cannot be measured directly; however, it can be assessed by the power consumption analysis. Figure 1 shows that the granulation process can be divided into five phases according to Leuenberger. In a first phase, an initial and slow wetting of the powder mixture takes place and the internal micro-pores are filled with the binder liquid. In phase II, the first pendular bridges between particles are formed and the powder particles agglomerate. Further agglomeration, simultaneous kneading, and compacting of the powder occur in phase III. This phase can be characterized by a balance between liquid bridges in pendular and funicular states. This is the phase of interest for pharmaceutical applications as the granules obtained within this phase are mostly desired. Afterwards, in phase IV and V, an irreversible, or catastrophic, over-wetting takes place. The system changes into a suspension due to the excess of water [1–3]. The end point of the granulation depends on the formulation, the process parameters, the desired final granule size distribution, and so on. Detection of the granulation end-point remains a very complex, yet very important task for process engineers.

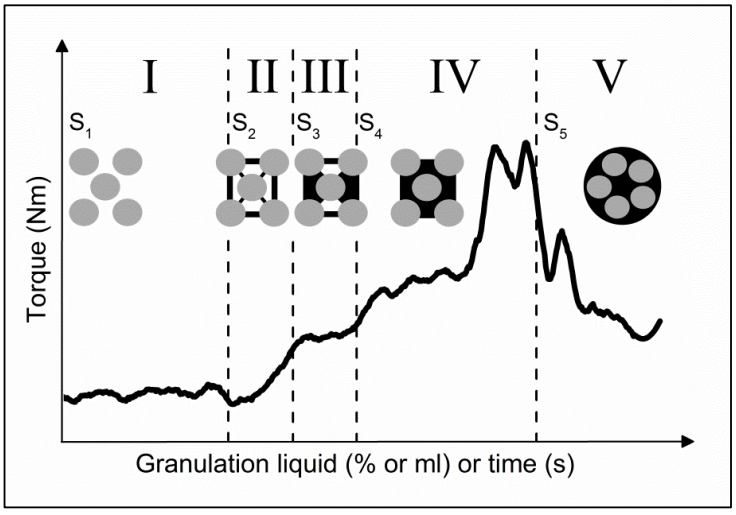


Figure 1: Schematic representation of the different stages during wet granulation in a high-shear mixer. Dry state (phase I), pendular state (phase II & III, individual liquid bridges (black) are formed at the contact points of the particles (grey)), funicular state (phase II-III, individual liquid bridges start to merge, more than two particles can be linked), capillary state (phase IV, cavities between the particles are fully saturated with liquid), and droplet state (phase V, particles are suspended in the liquid) [1,2].

Scheel et al. have shown that within a wetting ratio (W) of 1-16% (v/v), defined as liquid volume divided by the total sample volume, the amount of liquid added to a sand pile has almost no influence on the mechanical properties of the pile [4,5]. At the same time it could be shown that above W ~ 2.5% (v/v) and a half-filling angle (φ, Figure 2) beyond $\pi/6$ (=30°C) the cohesive forces between the particles do not grow anymore (because the pressure inside the liquid levels off) and as a result the capillary bridges (pendular state) start to merge, i.e. following a transition to a funicular state. With the help of x-ray microtomography it was possible to show that by increasing the liquid content, the liquid bridges (capillary bridges) merge first to trimers, then to pentamers and finally to filled tetrahedras until a wet cluster is formed that finally turns into a slurry [4–7]. The x-ray microtomography experiments on the wet sand pile for spherical equally-sized particles show that above W ~ 11% (v/v) almost all particles in the powder bed are connected by one large, percolating cluster that contains about 90% of the liquid [5]. Interestingly, the wetting ratio (W) during high-shear granulation is often around 10% (v/v) for initial start of phase II, as reported previously [8,9].

1.2 Theoretical considerations for new analysis of power consumption profile

As it was shown in the work of Scheel et al.[5], the bridge geometries are not changing monotonously with increase of moisture content for a simple, equisized spherical test system. This finding is very important to reconsider classical view on liquid bridge formation between two or more solid spheres, if those spheres are part of very large population. Interestingly, the transition from one bridge geometry to another is not happening continuously for systems with large number of interacting particles.

Scheel et al.[5] have experimentally determined the prevalent configurations at different wetting ranges, i.e. bi-, tri-, tetra-, penta- and heptamers. Thus, existence of major agglomerate configurations at certain liquid concentration range assumes that individual volume of each bridge configuration stays same. In the same work of Scheel et al., the bridge volumes of different configurations were determined experimentally (in voxels) for glass beads with the help of X-ray imaging. We summarized the number of voxels necessary to build each bridge configuration and used them to calculate the volume multiplication factor: capillary bridge (CB) is 1; trimer is 4; pentamer is 8; tetrahedra is 12 unit volumes.

The main theoretical assumption of this study is that same geometrical transitions could be observed on a power consumption profile during wet granulation. In such case it is possible to calculate the amounts of liquid added where the bridge configuration change is expected, using the single bridge volume and the corresponding multiplication factor.

If the liquid addition rate is fixed during the granulation process, the time to transition can be calculated.

In order to carry out the necessary calculations we assumed the powder bed is composed of spherical, equisized particles of non-soluble material with hydrophilic surface. We attempted to calculate the single capillary bridge volume and liquid necessary to reach specific agglomerate configuration for 3 different concentrations of the binder polymers.

Kepler conjecture

The closest packing of equally sized spheres in a three-dimensional space can reach a maximum density of 0.74048 [10,11]. If the spheres are randomly packed, density decreases to around 0.64 [12]. However, this packing efficiency is valid for spherical, equally-sized particles only. Another important parameter is the size of the particles used. For highly poly-disperse powder the packing efficiency is heavily changing and is related to Apollonian packing problem [13]. In order to leverage such effects the application of single-size fractions of the powders is advantageous.

Capillary liquid bridge

Calculation of a liquid bridge volume for different particle geometries and materials in contact is well documented [14,15]. Figure 2 shows a schematic representation of two particles connected with a liquid bridge.

In the following steps the calculation of a liquid bridge volume between two particles is shown. The radii of the liquid bridge curvature (ρ_1 and ρ_2) can be calculated according to the geometrical analysis by equation 1 and 2:

$$\rho_1 = \frac{s_i + r_i(1-cos\varphi_i)}{\cos(\varphi_i+\theta)}, \quad (1)$$

$$\rho_2 = r_i sin\varphi_i - \rho_1[1-\sin(\varphi_i+\theta)], \quad (2)$$

where s_i indicates half of the distance from one particle (i) to another (h), r_i is the radius of the particle (i), φ_i is half of the filling angle of particle (i) in radians, and θ is the contact angle in radians between the particle and the binder liquid.

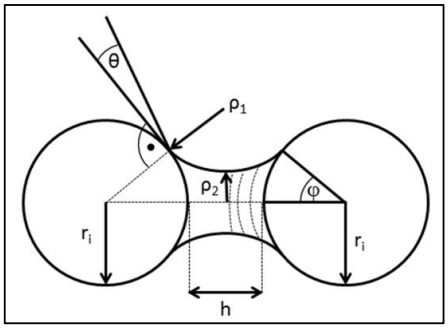


Figure 2: Schematic representation of a liquid bridge between two particles. In our model, the distance h between two particles (i) with radius r_i was zero. The half-filling angle φ_i was 15 degrees [16], the contact angle θ was determined experimentally, and ρ_1 and ρ_2 are the radii of the liquid bridge curvature that can be calculated [15].

The volume of the liquid bridge (V_l) between two particles can be calculated according to Pietsch and Rumpf [14] with equation 3:

$$V_l = 2\pi\left\{[\rho_1^2 + (\rho_1 + \rho_2)^2]\rho_1 cos(\varphi + \theta) - \frac{\rho_1^3 cos^3(\varphi+\theta)}{3} - \rho_1^2(\rho_1+\rho_2)\left[cos(\varphi + \theta) * sin(\varphi + \theta) * \left(\frac{\pi}{2} - \varphi - \theta\right) - \frac{r_i^3}{3}(2 + cos\varphi)(1 - cos\varphi)^2\right]\right\} \quad (3)$$

In case of particle size polydispersity the proposed concept is valid, however, the values for packing efficiency and bridge volumes will not be the same.

1.3 Aim

The aim of this study was to investigate the appearance of liquid bridges of different configurations, which result in stepwise increase of the power consumption profile during a wet granulation. The power consumption profiles were analyzed as a function of liquid bridge volumes of specific configuration, bridge and particle configurations, and contact properties between the liquid and the pseudo-spherical particles as a model system. The calculated theoretical concentrations with changing bridge geometries were compared to the experimentally determined data.

2. Materials and Methods

2.1 Materials

Fujicalin® as a powder model for spherical particles was from Fuji Chemical Industry, Japan. Kollidon® 25 (BASF, Germany) was used together with demineralized water as a binder. Isopropyl myristate was used as a dispersant for the particle size measurement. To determine the contact angle with the help of Washburn method, n-Hexane (VWR International, Belgium) was used as a non-polar liquid with contact angle around 0°.

2.2 Methods

2.2.1 Characterization of Fujicalin

Fujicalin is a granulated form of calcium phosphate dibasic anhydrous with spherical and smooth particles of 120 µm in diameter. The granules can be used for direct compression due to exceptional flow and compression properties[17]. Shape and surface of Fujicalin were studied with a scanning electron microscope by using the FEI/Philips XL30 FEG apparatus (Philips, Netherlands). Before the measurement, the samples were sputtered with a 20 nm gold layer by a sputter coating machine (MED 020, BalTec, Liechtenstein).

Particle size distribution of Fujicalin was measured with a Mastersizer X long bed laser diffractometer (Malvern Instruments, UK). Fujicalin was dispersed in isopropyl myristate and analyzed with the help of the small volume sample presentation unit (Malvern Instruments, UK). The measurement was carried out in triplicate. The mean value of median particle diameter is shown with its standard deviation.

Loss on drying (LOD) was measured gravimetrically for 10 minutes with an infrared lamp Mettler LP 16 and a Mettler PE 360 balance (Mettler Instruments, Switzerland).

2.2.2 Characterization of binder solution

To measure the density (n=3) of the binder liquid, the Kollidon 25 solution was filled into a volumetric flask (V = 250 ml) and the weight was measured with a Mettler PB3002-L balance (Mettler Toledo, Switzerland). Density was calculated according to equation 4:

$$\rho = \frac{m}{V} \quad (4)$$

where ρ is the density (g/ml), m is the mass (g), and V is the volume (ml).

Viscosity of the binder solution was measured with a capillary viscometer (SI Analytics GmbH, Germany) according to the Ph.Eur. capillary viscometer method [18]. The measurements for all binder concentrations were performed in triplicate. Viscosity was calculated according to equation 5:

$$\mu = k \cdot \rho \cdot t \quad (5)$$

where μ is the dynamic viscosity (mPa·s), k is the constant of the apparatus (mm^2/s^2), ρ is the density of the binder solution (g/ml), and t is the flow time of the sample (s).

Surface tension, contact angle, and speed of liquid uptake (n=3) were measured with a tensiometer K100MK2 (Krüss GmbH, Germany). Surface tension was detected according to du Nouy ring method. Contact angle and speed of water uptake were measured with the sorption method with the help of laboratory desktop software 3.1 (Krüss GmbH, Germany).

2.2.3 High shear granulation of Fujicalin particles

One liter of Fujicalin was put into the Oystar Micromix high shear mixer (Hüttlin GmbH, Germany). The mass of particles was calculated according to equation 6:

$$m = \rho_{tapped} \cdot V \quad (6)$$

where m is the total mass of Fujicalin (g), ρ_{tapped} is the tapped density (g/ml) measured according to Ph.Eur. [18], and V is the total volume of the sample in the vessel (ml). Impeller speed was set to 150 rpm and chopper speed was adjusted to 1500 rpm. Kollidon 25 was added as a 10%, 15%, and 20% (w/w) solution at a spray rate of 11.3 ± 0.3 g/min (Vario-Pumpsystem, Ismatec SA, Switzerland). Impeller speed, chopper speed, torque, and temperature were registered with the data recording software version 1.10 (Hüttlin GmbH, Germany) during the granulation process. Granulation was stopped after formation of big lumps (> 10 mm in diameter).

2.2.4 Calculation of required binder amount for granulation

Liquid bridge volume

The volume of the liquid bridge between two granulated particles was calculated according to equation 1, 2, and 3 (chapter 1.2 “Theoretical considerations”). The volume in equation 3 is strongly dependent of the contact angle (θ) and the half-filling angle (φ). In case of contact angle we experimentally measured this parameter; however, for the half-filling angle the experimental observations were limited. In the work of Gröger [16] the half-filling angle was simulated (with respect to the minimum separating distance h) versus dimensionless tensile force of the liquid and expresses a maximum in the range of 15 degrees [16]. We used this value (φ_i = 15°) as a constant to calculate the volume of the single liquid bridge throughout this study.

Parameter s_i from equation 1 was set to 0, meaning that the particles touch each other. We assumed that the particles are ideal spheres with shape factor of 1 and that no liquid sorption into the particles takes place. Furthermore, we assumed that the surface tension and contact angle of the granulation liquid are constant over the change of process parameters, i.e. temperature; and are invariant to concentration change due to evaporation. We also assumed that φ_i is constant for all three concentrations of binder liquid.

Calculation of wetting ratio (W)

Scheel et al. have shown that one particle can build maximum 6 bridges before the liquid starts to coalescence and a trimer structure is obtained [5]. The amount of liquid needed to build a network through the granulation vessel where every particle builds 6 liquid bridges is shown in equations 7-12. In a first step the volume of one particle was calculated according to equation 7:

$$V_{Particle} = \frac{4}{3}\pi r^3 \tag{7}$$

where $V_{Particle}$ is the volume of one particle (mm^3) and r is the radius of a particle (mm).

With the help of equation 8 we determined the volume of solids in the high shear mixer:

$$V_{Solid} = V \cdot 0.64 \tag{8}$$

where V_{Solid} is the volume of solids in the high shear mixer (mm^3), V is the volume of the particles from equation 6 ($V=1 \cdot 10^6$ mm^3), and 0.64 is the value for Kepler conjecture for randomly packed spheres [12].

The number of particles ($N_{Particles}$) in the high shear mixer was calculated with equation 9:

$$N_{Particles} = V_{Solid} : V_{Particle} \tag{9}$$

The wetting ratio (W), defined as liquid volume divided by the total sample volume was calculated with equation 10:

$$W = (N_{Particles} \cdot V_l \cdot 6)/V \quad (10)$$

where V_l is the volume of one liquid bridge (ml) between two particles (equation 3), number 6 is related to the maximum number of bridges one particle can build [5], and V is the total volume of the sample in the vessel from equation 6 (V=1000ml).

2.2.5 Evaluation of torque profiles

To evaluate the torque profiles and to determine the first transition from phase I to phase II a user-defined double linear curve fit was used. Equation 11 shows the two linear equations from the user-defined double linear curve fit. The equations were fitted with OriginPro version 8.5 (OriginLab Corporation, USA). Figure 3 shows a schematic representation of the user-defined double linear curve fit.

$$T_a = T_0 + k_0 * t_a \quad \text{if } t_a < t$$

$$T_b = T_1 + k_1 * t_b \quad \text{if } t_b \geq t \quad (11)$$

where T is the torque (Nm), t is the time (min), and k is the slope of the linear curve (Nm/min). The point where T_a=T_b is the intersection point of these two linear curves and hence the point of interest. The intersection point (t) was calculated according to equation 12.

$$t = \frac{T_0 - T_1}{k_1 - k_0} \quad (12)$$

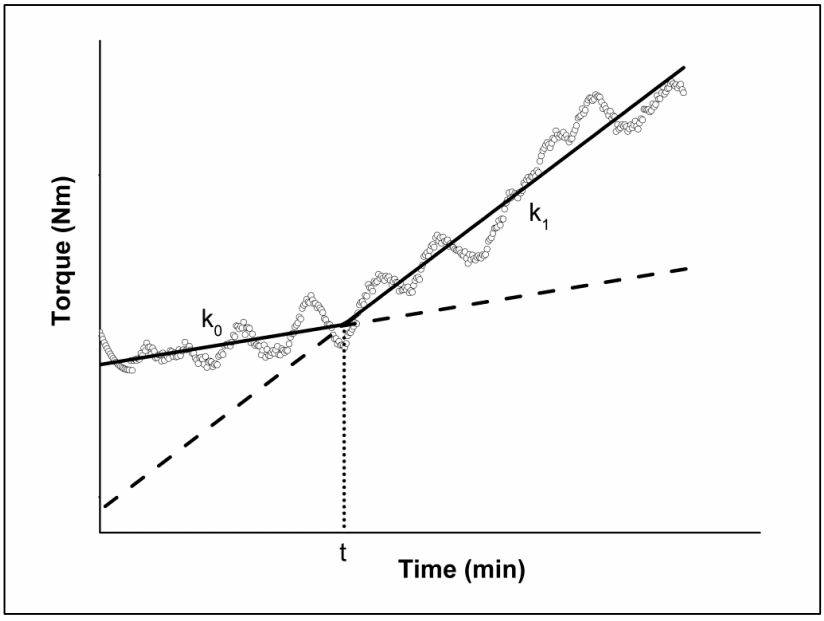


Figure 3: Schematic presentation of a user-defined double linear curve fit. The intersection point (t) indicates the start of the granulation process and hence the transition from phase I to phase II.

2.2.6 Particle size distribution analysis

To determine the particle size distribution during granulation, we stopped the granulation processes at certain time points (5 to 25 minutes, in 5 minutes intervals). The granules were dried in a Heraeus UT6200 oven (Heraeus, Germany) to a residual moisture content of 2.0 ± 0.6 %. We used a vibrating sieve tower (Vibro Retsch, Switzerland) to perform the particle size distribution analysis. The sieving tower was shaken for 10 minutes at a shaking displacement of 1.5 mm. We used steel wire screens (Vibro Retsch, Germany) with mesh sizes 90 µm, 125 µm, 180 µm, 250 µm, 355 µm, 500 µm, 710 µm, 1 mm, 1.4 mm, 2 mm, 2.8 mm, and 4 mm. The amount of powder remained on each sieve was weighted.

3. Results and Discussion

3.1 Characterization of Fujicalin

Figure 4 shows two scanning electron microscope (SEM) images of Fujicalin at different magnifications. The particles were spherical with a narrow particle size distribution. Fujicalin had a median particle size of 117.37 ± 0.07 µm.

During LOD measurement there was no change in weight (LOD=0%).

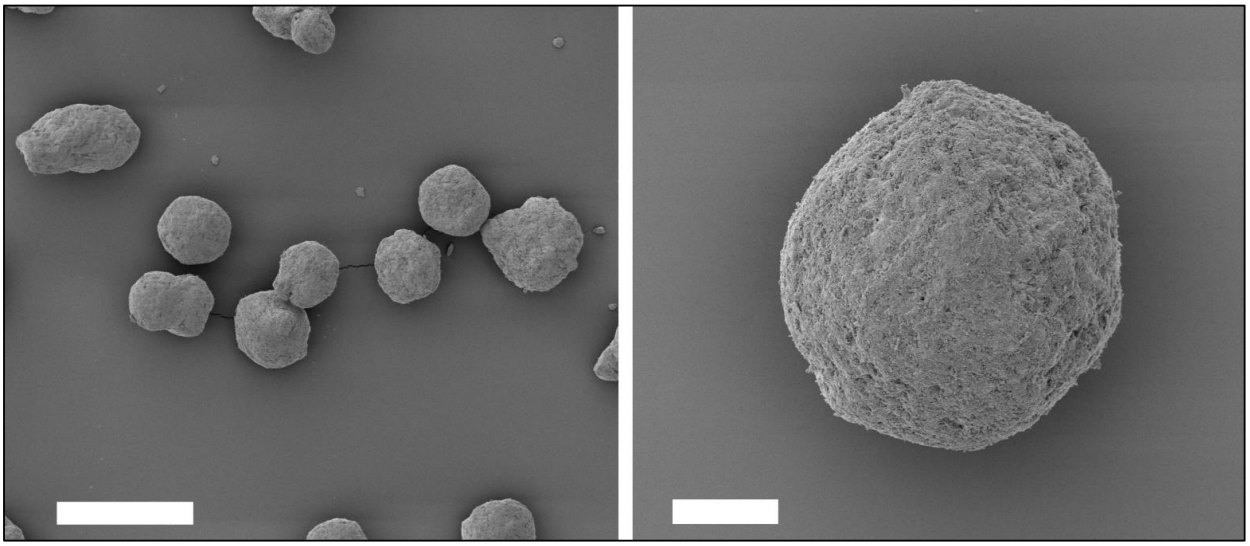


Figure 4: Electron micrographs of Fujicalin at two different magnifications. Left image: scale bar = 300 µm. Right image: scale bar = 50 µm.

3.2 Characterization of binder solution

Table 1 shows that the three different concentrations of Kollidon 25 binder solution were different in their physical properties. The more concentrated the solution was, the higher was the density and viscosity. With the speed of liquid uptake it was directly the opposite; the higher concentrated the binder solution was, the slower was the liquid uptake. The 15% (w/w) binder solution showed the highest value for surface tension and for contact angle. The lowest value for the contact angle was measured for the 20% (w/w) binder solution and the 10% (w/w) binder solution showed the lowest value for the surface tension.

Table 1: Physical properties of the binder solutions. Values are means ± SD of n=3 experiments.

Property	10% (w/w) Kollidon 25	15% (w/w) Kollidon 25	20% (w/w) Kollidon 25
Density (g/ml)	1.02 ± 0.00	1.03 ± 0.00	1.04 ± 0.00
Viscosity (mPa·s)	5.1 ± 0.0	11.2 ± 0.0	22.2 ± 0.1
Surface tension (mN/m)	55.79 ± 1.12	64.72 ± 0.07	60.99 ± 0.13
Contact angle (°)	54.11 ± 1.00	55.66 ± 0.95	49.91 ± 1.73
Speed of liquid uptake (mg/s)	281.3 ± 3.4	202.6 ± 2.5	150.6 ± 2.7

3.3 High shear granulation of Fujicalin

Figure 5 shows four different morphologies of liquid bridges as described by Scheel et al. [5]. In our study we calculated the volume of a liquid bridge between two particles with the equation of Pietsch and Rumpf [14]. This equation is based on the assumption that the liquid bridge has the shape of a capillary bridge (cb), as shown in Figure 5a. Scheel et al. have published the volumes (voxels) of the different morphologies of the liquid bridges. With respect to their results, a trimer (tr) contains 4 times the volume of a capillary bridge (cb), a pentamer (pt) contains 8 times the volume of a capillary bridge, and the tetrahedra (th) contains 12 times the volume of a capillary bridge [5].

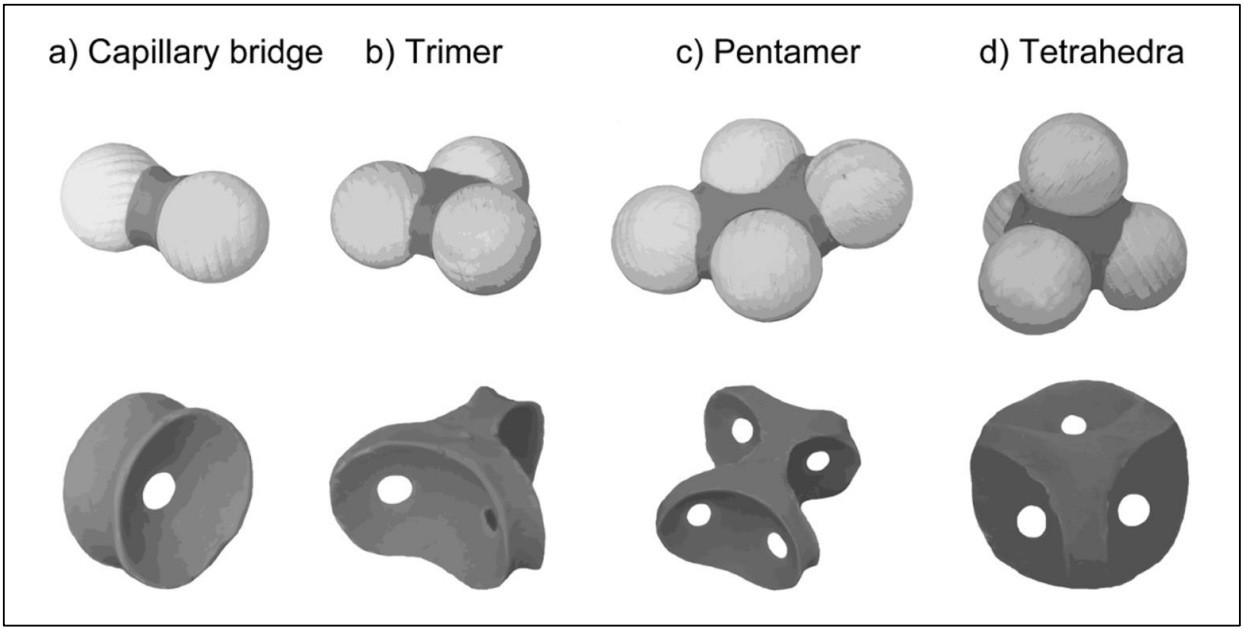


Figure 5: Schematic illustration of liquid morphologies. Arrangement of particles are characterized by 1, 3, 5, and 6 contact points between the particles [5]

Based on these findings, we calculated the wetting ratios (W) for the different liquid morphologies as shown in Table 2. Therefore, equation 10 was slightly modified by multiplying the liquid volume (V_l) with the factor mentioned above (e.g. factor 4 for a trimer structure). For a case of 6 liquid bridges per particle the value for W_{cb} yielded between 2.08% and 2.46% for the different binder concentrations, which is in a good agreement with the results of Scheel et al., i.e. 2.5% [5]. Figure 6 shows the torque profiles for the Fujicalin granulation with different binder concentrations. The data points for W_{cb} ~ 2.3% are located at the very beginning of the granulation process.

For W_{tr} we obtained between 8.31% and 9.85%, depending on the concentration of the binder solution. We observed that W_{tr} was the granulation start-point, i.e. the point when the granular formulation starts, meaning that the torque was increasing for the first time (Figure 6) at this data point. Although the initial increase of the torque at this moment was faint, we assumed that this event will be significantly amplified by increased scale of production. The results from the fitting of the double linear curve fit revealed similar results; the intersection point was found at 12% ± 0.1%. Scheel et al. [5] reported that about 90% of the liquid belongs to one cluster at W = 9%. Based on our results we assumed that the formation of capillary bridges within the powder bed could not be detected by the torque sensor in the high-shear mixer. At W ~ 10%, the liquid bridges transformed from the capillary bridge structure to trimer structures. The network of the trimers seemed to be more stable and, therefore, resulted in an increase of torque.

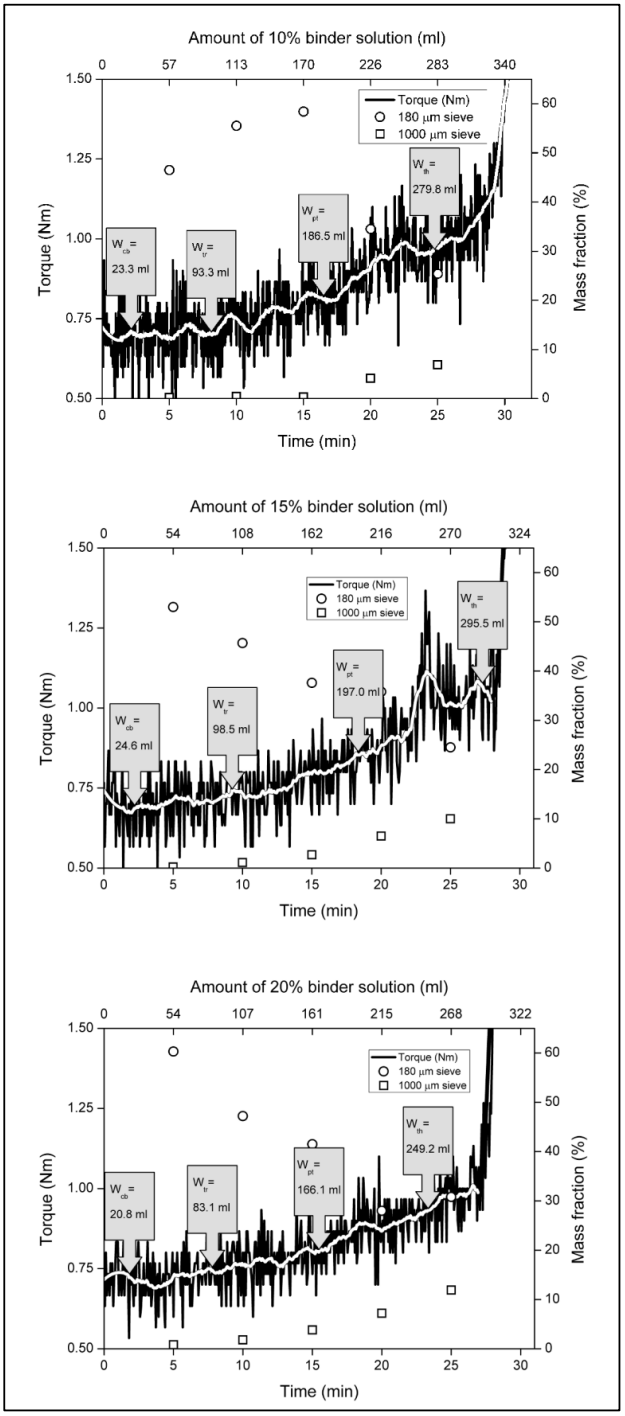
For W_{pt} we received values between 16.61% and 19.70% for the different binder solutions. At this point, phase II ended up and phase III was reached.

W_{th} was found to be between 24.92% and 29.55%, depending on the used binder liquid. In contrast to the trimer and pentamer structure, the tetrahedral structure can be considered as most efficient packing and is normally more stable. This was the reason, why the tetrahedral structure was more robust and the torque increased significantly because a lot of force was needed to destroy a network of dense packed tetrahedras.

Table 2: Wetting ratios (W) of different liquid morphologies for the different binder concentrations. Values are means ± SD of n=3 experiments.

Liquid morphologies	10% (w/w) Kollidon 25	15% (w/w) Kollidon 25	20% (w/w) Kollidon 25
W_{cb} with 1 V_l (%)	2.33 ± 0.07	2.46 ± 0.09	2.08 ± 0.08
W_{tr} with 4 V_l (%)	9.33 ± 0.30	9.85 ± 0.37	8.31 ± 0.34
W_{pt} with 8 V_l (%)	18.65 ± 0.59	19.70 ± 0.73	16.61 ± 0.67
W_{th} with 12 V_l (%)	27.98 ± 0.89	29.55 ± 1.10	24.92 ± 1.01

The particle size distribution analysis supported our findings. We observed a bimodal particle size distribution with maxima at 180 µm and 1000 µm. Figure 6a shows that during the high-shear granulation



of Fujicalin with the 10% Kollidon 25 binder solution, the 1000 µm sieve fraction started to increase shortly before W_{pt} was reached and at the same time the 180 µm sieve fraction decreased significantly, indicating the formation of agglomerates. Based on these findings we propose the granulation end-point to be between W_{pt} and W_{th}.

In general we observed that the higher the viscosity of the binder solution, the later was the onset of the different phases in the power consumption profile. Based on the results shown in Table 1, the speed of liquid uptake into the powder bed was significantly slower for the higher concentrated binder solution compared to the less viscous binder liquid. We concluded, that highly viscous binder liquids have to be sprayed slower to distribute homogenously within the granulation vessel than less concentrated binder liquids. In case there is not sufficient time given to the viscous liquid to thoroughly distribute within the granulation vessel, the geometrical transitions from *cb* to *th* will happen all at once. The result will be a power consumption profile with one peak, which will indicate the point of no return.

Figure 6: Theoretical predictions and experimental torque profiles. Torque profiles and particle size distribution during Fujicalin high-shear granulation with 10% (w/w), 15% (w/w), and 20% (w/w) Kollidon 25 binder solution (top to bottom). The white curve is a smoothed version of the measured torque curve. The grey boxes with the arrows indicate the different phases during the granulation and were obtained by calculation.

3.4 Applicability of proposed method to other particles geometry

Application of the proposed method to formulations with more complex particle geometries is theoretically possible; however, it has to be adapted. We consider several typical cases which could be found also co-existent with each other: spherical particles with different diameters, porous particles, non-spherical particles, and particles which are changing their sizes during granulation.

As a separate scenario the changes of the contact angle could be considered; moreover, it is one of the likeliest phenomena which co-exist together with other effects. The consequence of all of the above-mentioned effects is the change in particle-particle bridge geometries and liquid bridge volumes, consequently. In the case when bridge volume for a prevalent transitional geometry (e.g., pentamer or tetrahedron) changes, the multiplication factor will become different to the values used in this study. Indeed, these multiplication factors can be determined experimentally with the same method used by Scheel et al.[5].

With respect to theoretical adaptations of the proposed model to the case of different particle radii, the equation of a liquid bridge volume can be adapted. In such case, the equations 1 and 2 will account for different particle radii and the cubed radius in equation 3 can be averaged. Despite a relative simplicity of such corrective approach it has an important limitation. In case of different interacting particle radii, the more complex agglomerates such as trimers or pentamers, will have different geometries; thus, result in different or slightly different bridge volumes and, consequently, into different multiplication factors.

In case of particles with high intraparticle porosity, such as FCC [19,20], the granulation liquid will be first absorbed to saturation before any agglomeration effects will take place. However, for such cases the contact angle between particles will be different to the contact angle of liquid to a solid material. It has to be kept in mind that particles with closed or very narrow pores (10-100nm) will not absorb granulation liquid significantly; thus, the porosity of such particles can be neglected.

The complexity of the task rises for heterogeneous geometries of the granulated powder beds. In case of spherical interacting particles the simple liquid particles have rotational symmetry; for more complex or mixed geometries such symmetry will not hold, making analytical solutions for bridge volume very difficult. In such a case, the numerical simulation of the liquid bridge geometry for static configurations is necessary. A simple and convincing approach is given in [21].

The case of changing particle diameters during granulation liquid addition due to solubilizing of the solid material represents one of the most complex cases during wet granulation and can only be taken into an account in numeric simulation.

4. Conclusion

Analysis of power consumption profiles during granulation suggests that formation of liquid bridges between particles is a sequential and ordered process. Spherical particles are aligned in specific geometrical arrangements at increasing liquid content. The higher the available amount of liquid, the more stable the configuration of the resulting agglomerate is, however, further increase in granulation liquid will result in an instability of current configuration and leads to further configuration change as long as inter-granular pores are not fully saturated with liquid. Transitions between states are induced by addition of liquid and assumed to affect all particles simultaneously throughout the powder bed (Figure 7). These stepwise changes in geometrical arrangement of the spherical particles can be described by mathematical models. Thus, it is possible to predict the process end-point during granulation. We think that proposed theoretical considerations can be used in optimization of existing numerical models of agglomeration, which will find its use in the assessment and further development of the granulation methods and will lead to a development of more robust pharmaceutical formulations.

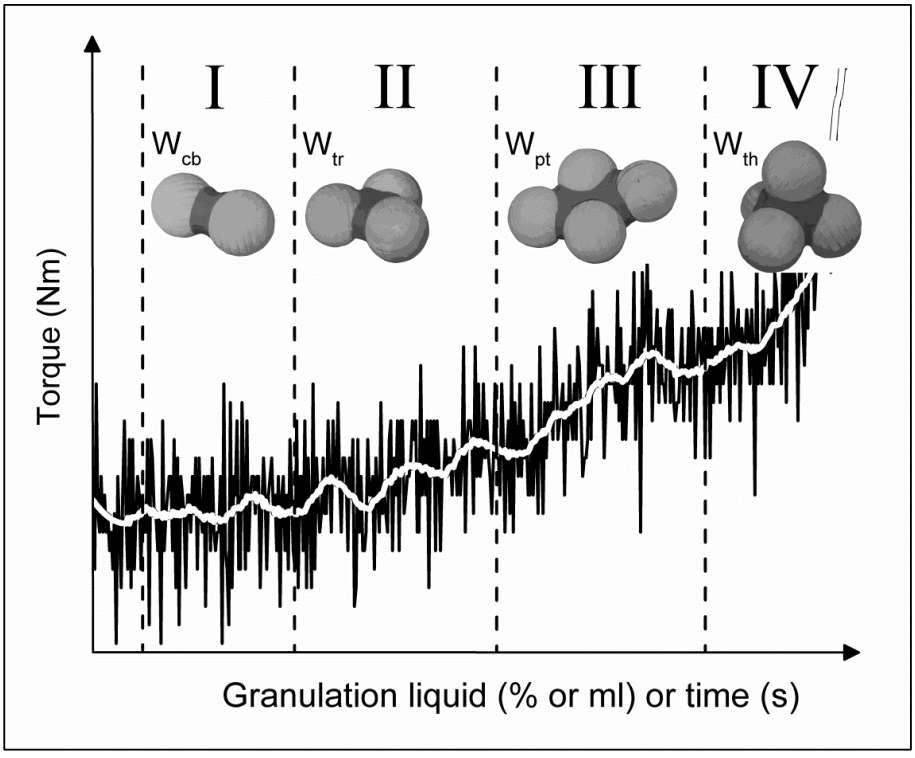


Figure 7: New interpretation of power consumption profiles during wet granulation. The different stages during a granulation process are characterized by the formation of distinct geometries of particles and liquid bridges and are a function of the total amount of liquid present in the system.

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3.4 Applicability of FCC as an ODT

Functionalized calcium carbonate as a novel pharmaceutical excipient for the preparation of orally dispersible tablets

Tanja Stirnimann[1], Nicola Di Maiuta[2], Daniel E. Gerard[2], Rainer Alles[1], Jörg Huwyler[1], Maxim Puchkov[1]

[1] Department of Pharmaceutical Sciences, University of Basel, Switzerland

[2] Omya International AG, R&D Minerals and Surface Chemistry, Oftringen, Switzerland

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RESEARCH PAPER

Functionalized Calcium Carbonate as a Novel Pharmaceutical Excipient for the Preparation of Orally Dispersible Tablets

Tanja Stirnimann • Nicola Di Maiuta • Daniel E. Gerard • Rainer Alles • Jörg Huwyler • Maxim Puchkov

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ABSTRACT

Purpose To overcome the limitation of insufficient hardness during the production of rapidly disintegrating orally dispersible tablets (ODTs). Furthermore, we investigated the properties and usefulness of functionalized calcium carbonate (FCC) as a new pharmaceutical excipient for the production of ODTs.

Methods A highly sensitive tensiometer-based method was developed to measure kinetics of weight loss during tablet disintegration. With this method we were able to determine the residence time of tablets placed on a basket immersed into a test medium. The shapes of tensiometer plots allowed us to categorize substances into four different types of disintegration.

Results At the same volume and hardness, the tablet formulations with FCC showed a significantly higher porosity (over 60%) than all other formulations. Residence time depended mainly on the tablet composition rather than on porosity. When combined with disintegrants, FCC formulations exhibited favorable disintegration properties, comparable to those of the marketed drug risperidone oro (disintegration time ca. 10 s).

Conclusions Oral dosage forms - based on the new pharmaceutical excipient FCC - can be designed to have a short disintegration time combined with good mechanical strength. Due to these properties, FCC can be used for the preparation of ODTs.

KEY WORDS disintegration · ODT · porosity · residence time · tensiometer

T. Stirnimann · R. Alles · J. Huwyler · M. Puchkov (✉)
Department of Pharmaceutical Science
Division of Pharmaceutical Technology
University Basel, Klingelbergstrasse 50
4056 Basel, Switzerland
e-mail: maxim.puchkov@unibas.ch

N. Di Maiuta · D. E. Gerard
Omya Development AG, R&D Microbiology, Baslerstrasse 42
CH4665 Oftringen, Switzerland

INTRODUCTION

Orally dispersible/disintegrating tablets (ODTs) constitute a solid, single-unit dosage form which instantaneously disperses/dissolves in the saliva (1). ODTs can be prepared by different techniques, such as freeze drying (2,3), moulding (4), spray drying (5), and mass extrusion (6). Depending on the technique, the final form dissolves very rapidly (5–15 s), but may be associated with low mechanical strength, high production costs, low drug content, or limited stability (7). The easiest technique to prepare ODTs is by direct compression. With conventional equipment, a limited number of process steps, and commonly available excipients, ODTs containing large amount of active ingredients can be produced at low costs. However, disintegration capacity of ODTs produced by this technique is limited by the size and hardness of the tablets (8,9). Increased compression force applied during tableting leads to harder tablets thus increasing disintegration time (10). Consequently, ODTs with optimal disintegration properties are often small and/or have a low hardness and higher friability (8).

In accordance with the European Pharmacopeia, ODTs should disintegrate within 3 min when tested with the conventional disintegration apparatus (11). The American Food and Drug Administration (FDA) requires an *in-vitro* disintegration time of approximately 30 s or less (12,13). The disadvantage of the conventional disintegration apparatus is poor discrimination among rapidly disintegrating tablets (14). Furthermore, the volume of the test medium (900 ml) is relatively large, compared with the volume of saliva in the mouth cavity (less than 6 ml) (15). Several techniques have been proposed to measure the disintegration time of ODTs (14,16–23). For example, one research group used the force measurement detection to analyze the forces developed during the disintegration process due to water absorption (24). In our current work, we adapted the standard liquid

absorption measurement by means of a tensiometer (25) to accurately determine tablet disintegration time and mimic disintegration in the patient's mouth cavity. This method employs the microbalance of the tensiometer to detect kinetics of weight loss during tablet disintegration. In addition, the proposed method provides quantitative information on dispersion kinetics, i.e., speed; ability to readily disperse in small volumes of liquid (e.g., teaspoon); and to detect formation of big swollen lumps.

Disintegration time of an ODT depends on the porosity of the tablet. The rate of water uptake increases with higher porosity of the ODT. Thus, disintegration rate increases because of faster wetting of the tablet (26). On the other hand, higher porosity of the ODT affects the hardness of the resulting tablets hence compromising further processing of formulations. Consequently, an ideal ODT combines two controversial properties, i.e., higher porosity and higher hardness. An excipient with combined functionality (highly porous and providing strong grip between particles) has been identified in paper industry.

Ridgway *et al.* modified a natural ground calcium carbonate to enhance porosity up to 60% (*v*/*v*) and enlarge the surface area. This functionalized calcium carbonate (FCC) absorbs water at a faster rate and is able to absorb 10 times more fluid than conventional calcium carbonate (27).

The manufacturing process of FCC shows some similarities to the production of precipitated calcium carbonate, an established pharmaceutical excipient. Both substances are produced by decomposition, once in aqueous solution (precipitated calcium carbonate) and once under acidic conditions (FCC). The different conditions and different concentrations lead to different shapes and different particle size distributions of the particles (28,29).

The aim of the current work was to investigate the properties and usefulness of FCC as a new pharmaceutical excipient in the production of ODTs. Performance of FCC was compared to that of other commonly used excipients such as microcrystalline cellulose (MCC 102 and MCC burst), and FlowLac (fillers) and AcDiSol, VivaStar, and Kollidon CL as disintegrants.

MATERIALS AND METHODS

Materials

FCC (VP-220976 S02, Omya, Switzerland), directly compressible calcium carbonate (Barcroft™ CS90, SPI Pharma, Germany), calcium carbonate (PharMagnesia CC Type Natur 120, Lehmann & Voss & Co., Germany), microcrystalline cellulose (MCC SANAQ® 102, Pharmatrans Sanaq AG, Switzerland), and lactose monohydrate (FlowLac® 100, Meggle, Germany) were used as fillers. As disintegrating agents, modified cellulose gum (Ac-Di-Sol®, FMC, USA), insoluble, cross-linked polyvinylpyrrolidone (Kollidon® CL, BASF, Germany) and sodium starch glycolate (Vivastar®, JRS, Germany) were selected. A special kind of microcrystalline cellulose (MCC SANAQ® burst, Pharmatrans Sanaq AG, Switzerland) was used both as filler and disintegrant. The market ODT formulation, Risperidone-Mepha® 0.5 oro tablets, was used as a reference of a market.

Isopropyl myristate (Hänseler AG, Switzerland) was chosen as a dispersant for particle size distribution measurements.

Methods

Characterization of FCC

The true density of FCC was determined by helium pycnometry (Micromeritics AccuPyc 1,330, USA).

Scanning electron microscopy (SEM) images were obtained using the FEI/Philips XL30 FEG apparatus (Philips, Netherlands). Before measurements, the samples were sputtered with a 40 nm gold layer by a sputter coating machine (MED 020, BalTec, Liechtenstein).

Pore size distribution of FCC was determined with a mercury porosimeter (AutoPore IV 9,500, Micromeritics Instrument, USA). Low-pressure mercury intrusion ranged from 3.59 kPa to 206.64 kPa. During high-pressure mercury intrusion, the pressure ranged from 206.64 kPa to 206.78 MPa. For both high- and low-pressure intrusion, equilibration time was 10 s.

To measure the specific surface area, Nova 2000e (Quantachrome Instruments, USA) was used with the five-point BET (Brunauer, Emmett, Teller) method. After degassing the samples for 12 h at room temperature, the samples were measured with nitrogen at constant temperature (77.4 K). The measurement was performed in duplicate.

Particle size distribution was determined with the Mastersizer X long bed (Malvern Instruments, UK). For MCC 102, MCC burst, FlowLac, Barcroft, AcDiSol and VivaStar, the dry powder feeder (Malvern) was used. These measurements were performed in triplicate. Kollidon and FCC were dispersed in isopropyl myristate and then analyzed (in duplicate) by using the small volume sample presentation unit (Malvern). The medians of the particle diameter and their standard deviations are shown.

Tablet Preparation

All powders and formulations were mixed by using a tumbling mixer (Turbula T2C, Switzerland) for 10 min at 32 rpm. The tablets were compressed by a single punch press (Korsch EK0, Berlin) with 11 mm round flat tooling. The punch gap was adjusted to compact 500 mg of FCC powder into a tablet with a hardness of 100 N. The resulting tablet had a height of

5.30 mm. This setting for the punch gap was kept constant for all other mixtures. The target hardness of 100 N was obtained by changing the mass of the compacts. The powder was introduced manually into the die. After compacting, the tablets were stored in closed glass bottles in the room at 24±2°C and at 40±5% relative humidity (measured values) for 30 days to allow enough time for expansion.

We did not use any lubricant in order to avoid potential influence of the lubricant distribution on the properties of FCC in combination with a disintegrant. Due to manual tableting, the speed of compaction was slower than with an automated process, i.e. using hopper. The lower compression speed caused less friction; hence the tablets were not damaged during ejection.

We could obtain the same tablet hardness with 0.5% magnesium stearate. In order to exclude potential influence of lubricants, we compressed 300 mg S02 powder at 4 kN. For the tablets without magnesium stearate, we obtained a hardness of 124±8 N, whereas the tablets with magnesium stearate showed a hardness of 126±5 N.

The concentration of the disintegrant was kept constant and comprises of 3% w/w in accordance to general recommendations (30). Our focus was set on the comparison of different filler excipients (e.g. FCC) on the disintegration behavior in presence of different disintegrants. In addition, our earlier experience in application of the percolation theory to the tablet disintegration and water uptake has revealed that the percolation threshold is located at 3%*v*/*v* for AcDiSol (31). This value could be corroborated by computer-based simulations of the percolation thresholds carried out by Garboczi *et al.* (32). In accordance with these results the optimal theoretical value lays in the area of 3% *v*/*v* for elongated particles with aspect ratio approx. 20.

Tablet Characterization

To determine the mean tablet weight, tablets ($n=13$) were weighted on an electronic balance (Mettler Toledo, type XS204 DeltaRange, Switzerland). Tablet diameter ($n=13$) was measured with a micrometer screw (Mitutoyo Model CD-15CPX, Japan), and tablet thickness ($n=13$) was determined with a dial indicator (Compac type 532G, Switzerland). Friability was measured by an ERWEKA (type TA200, Germany). The hardness of the tablets ($n=3$) was checked with a hardness tester (Tablet tester 8 M, Switzerland). To determine the true densities, a helium pycnometer was used (Micromeritics AccuPyc 1,330, USA). Porosity ε (%) of the tablets was calculated with the Eq. 1, as follows:

$$\varepsilon = \left(1 - \frac{\frac{\mathrm{m}}{\rho}}{\pi \cdot \mathrm{r}^2 \cdot \mathrm{h}}\right) \cdot 100 \qquad (1)$$

where m is the tablet weight (g), ρ the true density of the powder mixture (g/cm^3), r the radius of the tablet (cm), and h the height of the tablet (cm).

Method for Characterization of Disintegration and Dispersion Kinetics

To characterize disintegration and dispersion kinetics of the tablets ($n=3$, for FCC without disintegrants $n=2$) a tensiometer (Krüss Processor Tensiometer K100MK2, Germany) was used. The experimental setup was composed of a special metal-wire basket (Fig. 1a) which was attached to the microbalance of the tensiometer with four nickel wires. For the measurement of small tablets (such as risperidone oro tablets), the mesh size was reduced by a nickel wire to a size of 4 mm × 4.5 mm. As shown in Fig. 1b, the basket was immersed to a defined depth (12 mm) into a beaker. The beaker was filled up to the edge with distilled water. The beaker was heated (37°C ±1°C) by the surrounding thermostatic water bath.

Weight loss *versus* time was recorded by the tensiometer software. Figure 1c shows a schematic representation of this plot. The tablet was placed manually on the basket immersed in the water. With the aid of the tensiometer software, the mass was plotted against the time. The time point at which the tablet reached the basket and disintegration induced by water absorption started was indicated as t_0. At this stage, the weight was increased due to water uptake. This was reflected as weight increase on the profiles. The weight decrease was explained as tablet disintegration upon water uptake. The end of tablet disintegration was indicated by the leveling off of the profile. This event was referenced as t_1. The difference between t_1 and t_0 (t_1-t_0) was the tablet residence time on the basket. Residence time is a measure of disintegration time and is a good indicator of the time needed to disperse the tablet in the mouth cavity or on a spoon. To determine t_0 and t_1, the two linear equations were fitted with OriginPro version 8.5 (OriginLab Corporation, USA). A user-defined double linear curve fit was programmed with Eq. 2.

$$m_{\text{absorption}} = m_0 + k_0 \cdot \mathrm{t} \qquad t < t_c$$

$$m_{\text{elimination}} = m_0 + k_0 \cdot t_c + k_1(\mathrm{t} - \mathrm{t_c}) t \geq t_c \qquad (2)$$

where m is the weight (g) and t is the time (s).

If m_a and m_e are set equal to 0 and Eq. 2 is solved for t, the following equations are obtained:

$$t_0 = \frac{-m_0}{k_0}$$

$$t_1 = t_c - \frac{m_{0+} k_0 . t_c}{k_1}$$

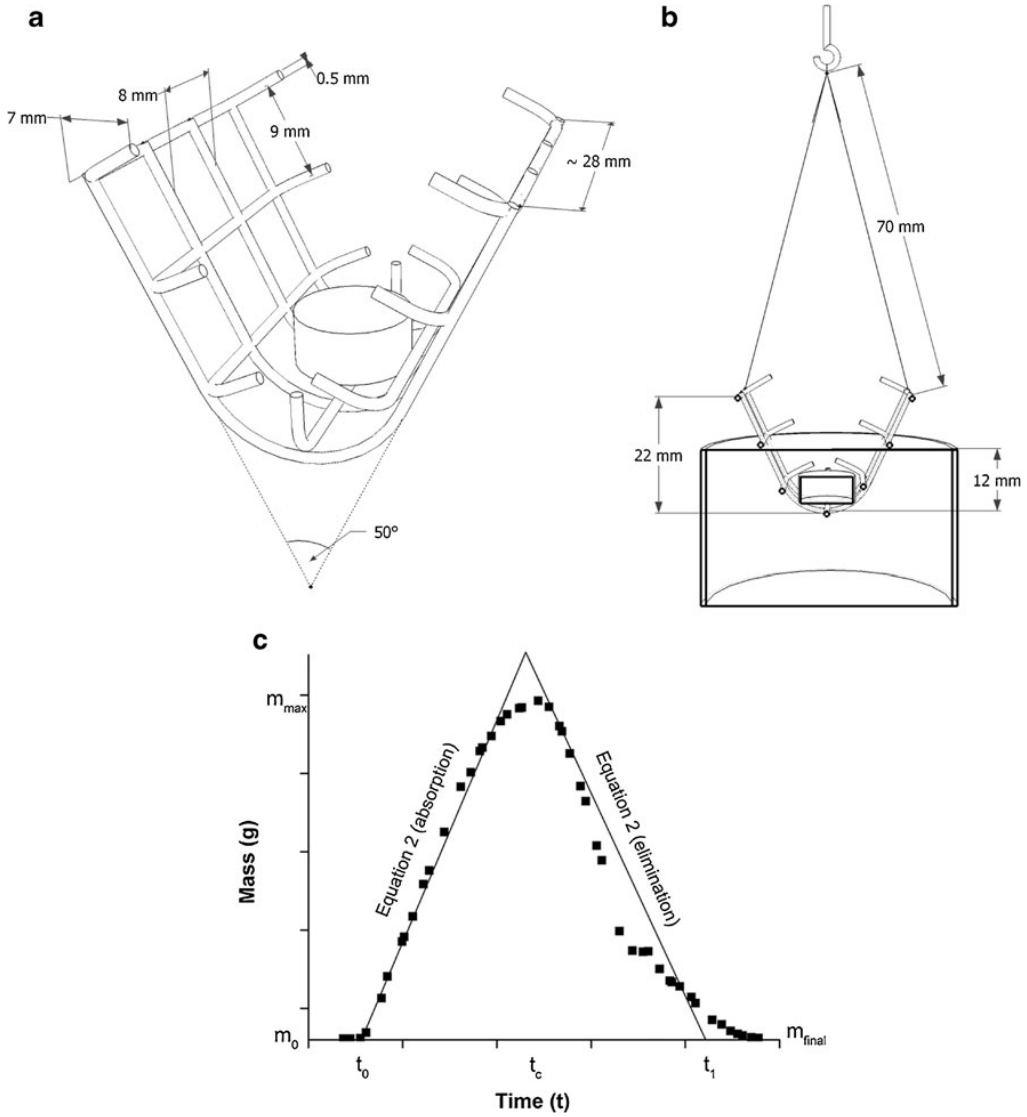

Fig. 1 (**a**) Schematic representation of the basket. (**b**) Schematic representation of the experimental setup for measuring the residence time. (**c**) Schematic representation of the mass *versus* time plot from the tensiometer software.

To calculate the residence time, Eq. 3 was used.

$$\Delta t = t_1 - t_0 = t_c - \frac{m_0 + k_0 . t_c}{k_1} - \frac{-m_0}{k_0} \quad (3)$$

In addition to the residence time, the disintegration degree was calculated with Eq. 4:

$$n = \left(1 - \frac{m_{final}}{m_{max}}\right) \cdot 100 \quad (4)$$

where n is the disintegration degree (%) and m is the weight (g). For m_{max} the weight at time point t_c was used, and m_{final} is the weight at leveling off of the profile (Fig. 1c).

Kinetics of Water Absorption (Tensiometer)

Water absorption capacity of the tablets ($n=3$) for each lot was measured with a tensiometer (Krüss Processor Tensiometer K100MK2, Germany) in a water bath (37°C ± 1°C). The tablet was placed in a glass tablet holder with a ceramic filter bottom. With the help of the software, time was plotted against mass gain. The slope of this function indicated the speed of water absorption, and the saturation level corresponded to the relative amount of absorbed water. To calculate the slope, the values for the time points between 6 and 9 s were taken into account. OriginPro version 8.5

(OriginLab Corporation, USA) was used for curve fitting and the evaluation of tensiometer plots.

RESULTS

Properties of Fillers (F) and Disintegrants (D)

Figure 2a-c shows SEM pictures of FCC at different magnifications. The size of the FCC particles was around 7 µm. The particles showed a multitude of thin lamellae that formed a porous meshwork. Figure 2d illustrates the mercury porosimetry plot of FCC.

Table I shows the true densities and medians of the particle diameter of the used substances. With the BET method a specific surface area of 62.14 ± 0.19 m^2/g was measured for the FCC particles.

Evaluation of Tablet Properties

Table II lists the properties of the tablets. At the same volume and hardness (100 N), the tablets with FCC and MCC 102 were the lightest (around 500 mg). By comparison, CS90 tablets were approx. 1.7 times heavier (approx. 840 mg) than the tablets consisting of FCC and MCC 102. Friability was 1.0% to 1.7% for all tablets except the formulations with MCC 102, where a friability of approx. 0.5% was reached. Although volume and hardness of the tablets were kept constant, porosity of the tablets varied strongly between the different tablet formulations. Tablet formulations with FCC had a porosity of over 60% whereas the MCC 102-based tablets exhibited a porosity of only 40% at the same weight. With porosities of about 25% and 35%, the tablets consisting of FlowLac and MCC burst were less porous than MCC 102 tablets. Formulations with CS90 had a porosity of approx. 35% and weighed approx. 840 mg.

Calcium carbonate Natur 120 was not suitable for the preparation of tablets with the desired properties. The target hardness (100 N) was not reached due to capping of the tablets.

Table III shows the residence times and disintegration degrees obtained after a double linear curve fit of tensiometer weight *versus* time plots (Fig. 1).

In addition, Table III indicates the speed of water absorption and amount of absorbed water after 90 s. Some formulations with FCC, MCC 102, and MCC burst reached a water absorption speed of more than 50 mg/s. Only MCC 102 and MCC burst formulations absorbed water at a speed of more than 100 mg/s. The formulations with MCC burst showed the highest absolute amount of absorbed water.

As pointed out above, an ODT should disintegrate within 3 min if tested with the standard disintegration test according to the European Pharmacopeia (11). Figure 3 illustrates the influence of tablet composition on residence time. The horizontal line indicates a residence time of 3 min. With the fillers FCC and FlowLac, three formulations in each case had a residence time of less than 3 min. In comparison with FlowLac, the FCC formulations had a significantly shorter residence time. FCC formulations showed

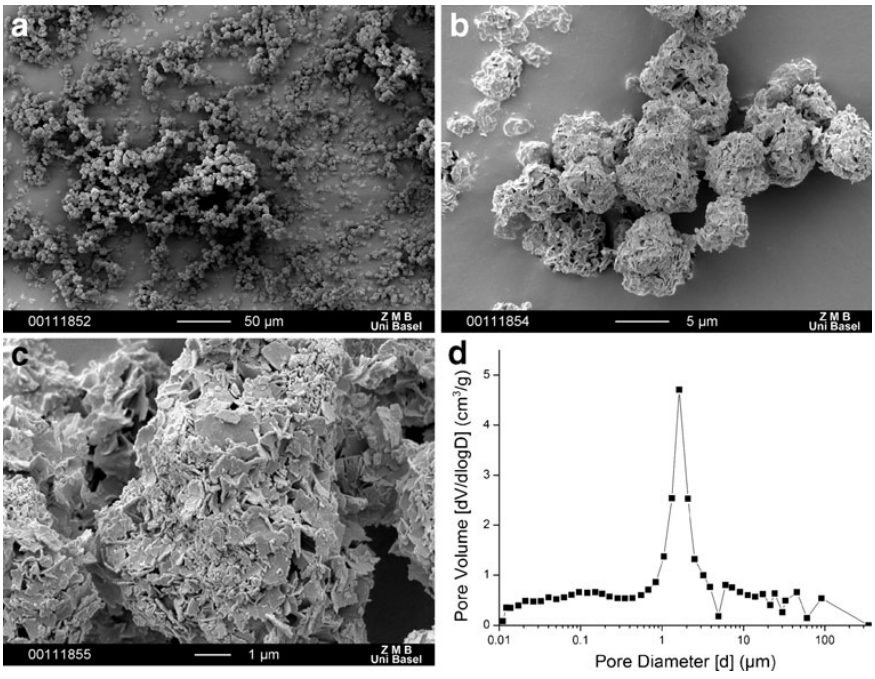

Fig. 2 (**a-c**) SEM pictures of FCC (magnifications: (**a**) x 300, (**b**) x 3,000, and (**c**) x 10,000). (**d**) Mercury porosimetry plot of FCC.

Table I True Density and Median Particle Diameter of the Substances (Where F Stands for Function as Filler and D Stands for Disintegrant)

Substance	Function in a formulation	True density (g/cm^3)	Median particle diameter (μm) ± SD
FCC	F	2.7382	7.28 ± 0.05
Barcroft CS90	F	2.5233	163.52 ± 10.00
MCC 102	F	1.5583	120.65 ± 1.31
FlowLac	F	1.5412	150.37 ± 2.19
MCC burst	F + D	1.5337	64.04 ± 0.14
AcDiSol	D	1.5996	43.74 ± 0.06
VivaStar	D	1.4778	41.20 ± 0.12
Kollidon CL	D	1.2374	91.64 ± 0.81

fast disintegration comparable to that of MCC burst and MCC 102 formulations. It is important to note that FCC formulations compared well with the reference tablets, risperidone oro. On the other hand, it has to be kept in mind that FCC had to be used in combination with a disintegrant to trigger the fast dispersion. For all tablets with a residence time below 3 min, a disintegration degree between 85% and 100% was calculated. Nevertheless, Table III shows that not all of the tablet formulations had residence times below 3 min. We marked the residence time values as ∞ if calculated residence time (Δt) indicated that water absorption was not followed by tablet disintegration.

DISCUSSION

Tensiometer Method

The present work describes a novel strategy for the design of orally dispersible tablets (ODT). Functionalized calcium carbonate (FCC) was used as the main pharmaceutical excipient for ODTs, which are characterized by a very short disintegration time (i.e. <10 s). This rapid process is a challenge, in that conventional disintegration protocols according to the European Pharmacopeia cannot be used. This standard method relies on a vertically moving sample holder. This leads to forced disintegration of tablets due to mechanical stress. For example, formulations containing spray dried calcium carbonate (i.e. the Barcroft formulations), did not disintegrate in an unstirred solution. Upon agitation only, tablet fragments are dislocated from the tablet surface. FlowLac based formulations

Table II Tablet Properties

Tablet formulation	Diameter (mm) ($n = 13$)	Thickness (mm) ($n = 13$)	Weight (mg) ± SD ($n = 13$)	Hardness (N) ± SD ($n = 3$)	Friability (%) ($n = 1$)	Porosity (%)
FCC	11.02 ± 0.01	5.30 ± 0.02	499.4 ± 2.9	117.3 ± 15.0	1.06	64
FCC + 3% AcDiSol®	11.03 ± 0.01	5.41 ± 0.01	498.9 ± 1.9	99.7 ± 9.6	1.32	64
FCC + 3% Viva Star®	11.01 ± 0.01	5.36 ± 0.05	502.3 ± 0.8	107.0 ± 3.5	1.67	64
FCC + 3% Kollidon® CL	11.02 ± 0.01	5.14 ± 0.01	499.2 ± 1.0	116.7 ± 19.2	1.18	62
FCC + 3% MCC burst	11.03 ± 0.01	5.20 ± 0.09	500.8 ± 1.6	111.7 ± 21.1	1.10	63
Barcroft™ CS90	11.07 ± 0.00	5.47 ± 0.01	851.7 ± 1.4	95.3 ± 1.2	1.12	36
Barcroft™ CS90 + 3% AcDiSol®	11.08 ± 0.00	5.58 ± 0.01	845.3 ± 1.2	88.3 ± 2.5	1.25	37
Barcroft™ CS90 + 3% Viva Star®	11.08 ± 0.01	5.50 ± 0.01	845.9 ± 1.3	94.7 ± 2.9	1.14	36
Barcroft™ CS90 + 3% Kollidon® CL	11.07 ± 0.00	5.51 ± 0.01	833.0 ± 1.5	98.3 ± 3.8	1.12	37
Barcroft™ CS90 + 3% MCC burst	11.06 ± 0.00	5.49 ± 0.01	836.9 ± 1.1	95.7 ± 0.6	1.20	36
FlowLac®	11.05 ± 0.01	5.32 ± 0.01	594.4 ± 2.7	88.3 ± 3.2	1.46	24
FlowLac® + 3% AcDiSol®	11.06 ± 0.01	5.33 ± 0.01	593.3 ± 1.3	86.3 ± 2.1	1.28	25
FlowLac® + 3% Viva Star®	11.06 ± 0.00	5.34 ± 0.01	598.7 ± 0.8	88.3 ± 5.0	1.40	24
FlowLac® + 3% Kollidon® CL	11.06 ± 0.00	5.35 ± 0.02	595.0 ± 1.2	89.3 ± 3.2	1.50	24
FlowLac® + 3% MCC burst	11.06 ± 0.01	5.34 ± 0.01	605.4 ± 2.7	97.3 ± 7.8	1.16	23
MCC 102	11.06 ± 0.01	5.53 ± 0.02	489.0 ± 3.6	93.0 ± 7.5	0.54	41
MCC 102 + 3% AcDiSol®	11.06 ± 0.01	5.55 ± 0.02	494.0 ± 2.8	93.3 ± 2.1	0.38	41
MCC 102 + 3% Viva Star®	11.07 ± 0.01	5.54 ± 0.03	498.3 ± 2.3	96.0 ± 1.0	0.51	40
MCC 102 + 3% Kollidon® CL	11.06 ± 0.01	5.55 ± 0.02	487.9 ± 1.8	98.3 ± 3.5	0.48	41
MCC 102 + 3% MCC burst	11.07 ± 0.01	5.54 ± 0.02	493.6 ± 2.0	92.3 ± 3.5	0.59	41
MCC burst	11.10 ± 0.01	5.83 ± 0.03	566.6 ± 2.9	88.7 ± 3.8	1.52	34
MCC burst + 3% AcDiSol®	11.09 ± 0.01	5.75 ± 0.03	563.3 ± 1.9	94.0 ± 3.5	1.38	34
MCC burst + 3% Viva Star®	11.08 ± 0.01	5.84 ± 0.02	573.8 ± 1.8	90.0 ± 0.0	1.64	33
MCC burst + 3% Kollidon® CL	11.10 ± 0.01	5.82 ± 0.02	566.5 ± 1.3	86.7 ± 3.8	1.53	34

Table III Calculated Parameters for Residence Time, Disintegration Degree, and Kinetic of Water Absorption

Tablet formulation	Residence time (s)	Disintegration degree (%)	Disintegration type (I-IV)	Amount of absorbed water after 90 s (g)	Speed of water absorption (mg/s)
FCC	∞	0	II	0.189 ± 0.011	4.5 ± 0.33
FCC + 3% AcDiSol®	8.92	100	I	1.232 ± 0.018	80.4 ± 2.69
FCC + 3% Viva Star®	11.94	100	I	1.599 ± 0.055	86.8 ± 3.95
FCC + 3% Kollidon® CL	9.53	100	I	0.816 ± 0.007	37.9 ± 0.92
FCC + 3% MCC burst	4858.26	2	II	0.229 ± 0.008	4.9 ± 0.54
Barcroft™ CS90	∞	0	II	0.115 ± 0.013	0.7 ± 0.09
Barcroft™ CS90 + 3% AcDiSol®	7703.4	4.7	II	0.080 ± 0.033	1.9 ± 0.05
Barcroft™ CS90 + 3% Viva Star®	197.68	100	III	0.263 ± 0.015	5.9 ± 0.29
Barcroft™ CS90 + 3% Kollidon® CL	∞	0	II	0.074 ± 0.037	1.6 ± 0.24
Barcroft™ CS90 + 3% MCC burst	∞	0	II	0.113 ± 0.021	1.1 ± 0.19
FlowLac®	61.92	100	III	0.311 ± 0.044	5.4 ± 2.06
FlowLac® + 3% AcDiSol®	127.85	100	III	0.322 ± 0.016	5.5 ± 0.29
FlowLac® + 3% Viva Star®	194.2	100	III	0.667 ± 0.026	16.2 ± 1.64
FlowLac® + 3% Kollidon® CL	65.09	100	III	0.375 ± 0.017	9.8 ± 0.33
FlowLac® + 3% MCC burst	64.57	85	III	0.344 ± 0.045	9.1 ± 0.95
MCC 102	∞	0	II	0.807 ± 0.040	79.2 ± 17.95
MCC 102 + 3% AcDiSol®	1681.78	47.2	IV	1.306 ± 0.017	82.3 ± 13.61
MCC 102 + 3% Viva Star®	9.65	99.1	I	1.840 ± 0.050	152.9 ± 27.09
MCC 102 + 3% Kollidon® CL	∞	0	IV	0.877 ± 0.016	70.1 ± 15.83
MCC 102 + 3% MCC burst	∞	0	II	0.847 ± 0.044	71.0 ± 12.97
MCC burst	∞	0	IV	1.741 ± 0.059	96.6 ± 5.63
MCC burst + 3% AcDiSol®	5.92	96.3	I	1.864 ± 0.052	70.9 ± 3.22
MCC burst + 3% Viva Star®	10.4	100	I	2.347 ± 0.034	98.1 ± 4.64
MCC burst + 3% Kollidon® CL	∞	0	IV	1.826 ± 0.054	104.9 ± 13.24
Risperidone oro	17.26	100	I	-	-

have a similar behavior in that tablets are fractured by agitation. However, this "accelerated" or "forced" disintegration does not reflect the intended use of our ODT formulations. Here, disintegration in unstirred liquid (i.e. in a spoon prior to oral administration) is needed. We were therefore forced to develop our own disintegration method. As expected, the disintegration time for most formulations was shorter for the standard method as compared to our tensiometer method. In particular, MCC based formulations swell only and do not disintegrate if not agitated. An additional advantage of our tensiometer based method is its ability to monitor rapid disintegration processes with very high precision. In addition, a slight modification of the experimental setup allows for quantification of the absorbed amount of water. Thereby, the type, volume, and temperature of fluid can be varied.

FCC as a New Pharmaceutical Excipient for the Production of ODTs

Comparison between FCC and Barcroft showed considerable differences in the porosity. FCC-containing formulations (with disintegrants) showed the best results. Formulations combining FCC with a disintegrant disintegrated/dispersed within a few seconds. Thereby, the mode of action of the different disintegrants had no significant influence on the residence time. Furthermore, all formulations of FCC combined with disintegrants belonged to the disintegration type I and showed a disintegration degree of 100%. We successfully produced tablets with marked porosity and high hardness.

Properties of FCC

Several studies have demonstrated that porosity has a surprisingly low impact on the disintegration behavior of FCC. Figure 4 correlates speed of water absorption and the absorbed amount of water after 90 s for FCC combined with different excipients. Speed of water absorption and absorbed amount of water after 90 s for each formulation were influenced by the disintegrants only.

For FCC as well as all other excipients, no correlation could be shown between the tablet weight and disintegration degree (Table II and III). Disintegration degree was only dependent on the composition of the tablet formulations. Residence time also depended on the tablet composition and

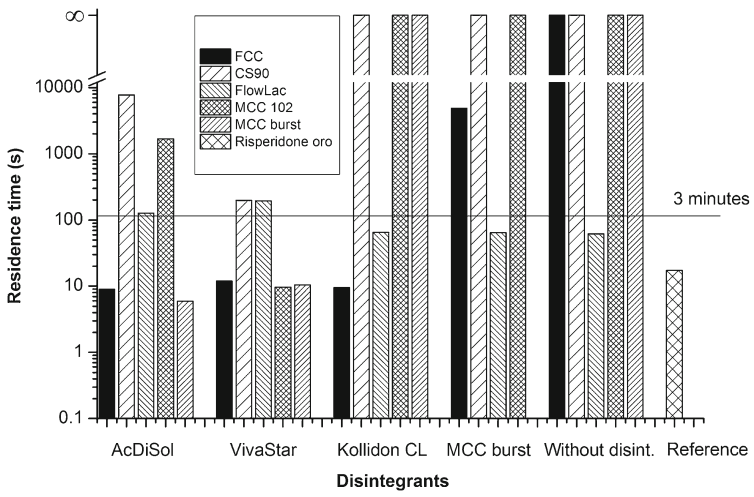

Fig. 3 Influence of tablet composition on residence time.

was not affected by the porosity or weight of the tablets. This latter finding was surprising since it has been suggested recently that porosity might be an important property of ODTs (26). Again, the combination of filler and disintegrants seems to be the decisive factor, which appears to be a unique property of FCC. All other excipients studied did not show such a linear correlation (data not shown). This result suggests that the speed of water absorption is modulated by disintegrants. In the case of FCC, water absorption is a prerequisite for disintegration since pure FCC neither absorbs water nor disintegrates. Thus, the choice of a specific disintegrant is not a critical factor.

From the percolation theory point of view, disintegration occurs above critical concentrations (threshold) of the disintegrant (33). In our study, all formulations had disintegrant concentrations close to the theoretically predicted critical value, i.e., approx. 3% (*v*/*v*). At these concentrations, the rate of disintegration is mostly governed by the type of disintegrant rather than by tablet porosity (33).

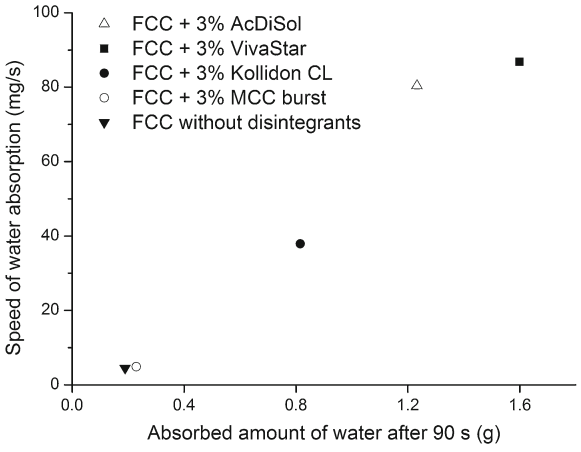

Fig. 4 Correlation plot between speed of water absorption and absorbed amount of water after 90 s.

Definition of Disintegration Patterns

We were able to distinguish four typical disintegration patterns (Table III and Fig. 5).

First, excipients such as FCC and the commercial reference, ODT formulation of risperidone oro, showed a classical disintegration pattern. Initially, absorption of water is faster than disintegration (increase in mass). After reaching a peak, the tablet continuously dispersed (decrease in mass) into very small particles. This desirable property has been termed disintegration type I. In sharp contrast, non-modified calcium carbonate particles (Barcroft) did not disintegrate. This profile was characterized by fast initial water absorption only. After saturating the pores with water, the speed of the water absorption declined continuously. Some formulations reached a plateau, whereas other formulations were still able to absorb more water, forming a large swollen lump. This profile was defined as disintegration type II. FlowLac was a typical representative of disintegration type III, which was characterized by nonuniformity in the disintegration phase caused by larger fragments falling off the tablet and then through the mesh. These parts needed some more time on the bottom of the beaker to disperse completely. We could not establish whether the fragments that had come loose were still dry on the inside. Finally, cellulose-based excipients (i.e., MCC 102 and MCC burst) combined properties of type I and type II disintegration patterns: initial phase of swelling followed by partial disintegration. This profile termed disintegration type IV.

Owing to the new and very sensitive tensiometer method, ODTs could be categorized based on their disintegration profiles (Table III).

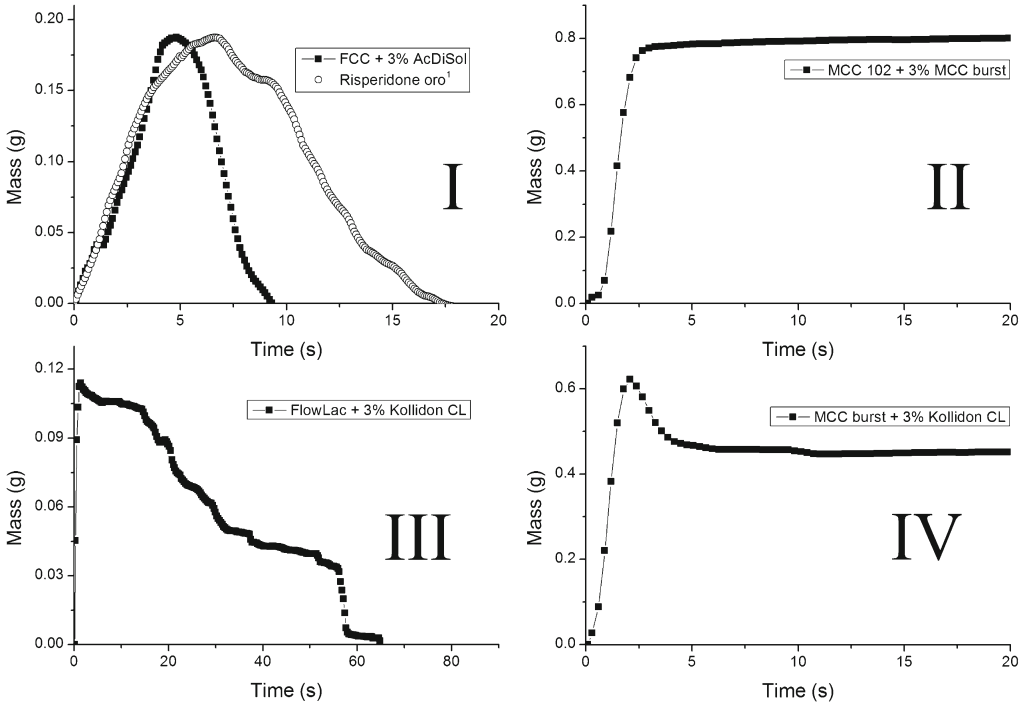

Fig. 5 Tensiometer plots for 4 types of disintegration kinetics (mass *versus* time). Re-normalized curve (with mass maximum at 0.0223 g).

Quantitative Model for Residence Time

Disintegration profiles can be evaluated using a user-defined double linear curve fit model. In the majority of cases, the values of residence time determined from the tensiometer plot (Fig. 5) agreed well with the calculated values in Table III. Quantitative evaluation for profiles of type III was difficult due to the larger parts of the tablets that had fallen through the basket mesh (i.e., without dispersing/disintegrating), hence shortening the residence time. Another limitation of the model was the discrepancy between measured and calculated values for residence time for a few formulations that showed an exponential function within the tensiometer plot.

It should be emphasized, that disintegration of tablets is a complex process. Figure 1c shows a disintegration profile, which is characterized by a series of sequential events. In a first step, the tablet was wetted by the medium, followed by medium absorbance and disintegration. Thus, the tablet mass increased until equilibrium was reached between liquid sorption and mass decrease due to disintegration. Afterwards, the disintegration predominated the water sorption resulting in a net loss of mass.

In many instances (Fig. 5), the disintegration pattern is more complex. For example, some materials first soak up liquid very fast and subsequently start to disintegrate by heterogeneous fractionation. Other materials like FCC soak up water at moderate speeds, leading to continuous disintegration and loss of mass.

Several mathematical models can be used to describe these processes. For example, the concurrent effects could be modeled by the system of two differential equations (here combined into one equation):

$$\frac{d}{dt}m(t) = M_0 e^{-k_a t} - k_e m(t);$$

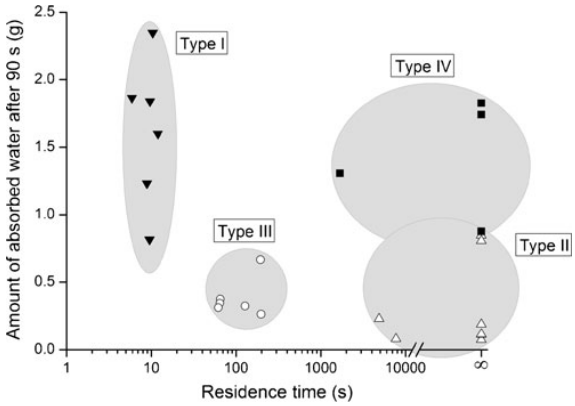

Fig. 6 Correlation plot between the amount of absorbed water after 90 s and residence time for the different disintegration types.

where m(t) is mass detected by tensiometer, t is the time, M_0 is compact mass in the test media, and K_a and K_e are the absorption and disintegration speed constants, respectively.

However, the obtained model – although it's good illustrative properties – does not produce fits of experimental data of sufficient quality. The reason for this is that the disintegration behavior is not monotonous on the whole disintegration timeline. For example, the lactose-based formulations were disintegrating by losing larger pieces of mass, hence producing "step-wise" profiles. Such profiles produce poor fitting of the exponential equations, hence we had to discard this approach. In order to take into account such inhomogeneous effects the differential model should be modified or substituted by another, – perhaps, discrete – model.

An alternative polynomial fit of the curves was not favorable due to a potential risk of over fitting.

For this publication we used a simplified linear model, which gave best results in all encountered situations. Utilizing this approach, we can determine the residence time of the pharmaceutical compact on the tensiometer sample basket.

Optimal Type I Disintegration of FCC

Figure 6 shows a correlation plot between the amount of absorbed water after 90 s and residence time for the different disintegration types. Due to very long or even unlimited residence time, disintegration type II and type IV were of no interest for the production of ODTs. Although the majority of formulations of disintegration type III had a residence time below 3 min, type III was limited by nonuniform disintegration. Disintegration type I showed the shortest residence time and was therefore the most appropriate for producing ODTs. Within type I, the formulations are better the shorter the residence time and the lower the amount of absorbed water after 90 s. The absorbed amount of water is important with respect to patient compliance in the clinical setting. We assume that a pleasant mouth feel can be achieved with tablets dispersing in small amounts of saliva. If more saliva is absorbed by the ODT, patient's mouth feels dry, and swallowing of the tablet becomes difficult. Therefore, we conclude that FCC-based formulations were the best. When combined with disintegrants, FCC formulations showed a disintegration pattern of type I, comparable to that of the market reference drug, risperidone oro.

CONCLUSION

ODTs are designed to disperse within seconds. The prerequisite for reliable classification and quantification of disintegration properties of ODTs is the availability of a fast analytical method.

In order to compare ODT tablet formulations containing FCC, we introduced a new method to characterize the disintegration/dispersion kinetics and swelling properties of ODTs. With this method we were able to detect the exact amount of absorbed water after 90 s, speed of water absorption, and residence time of a tablet placed on a basket immersed into water with a single instrument.

We conclude that FCC has the required properties to produce ODTs, such as a fast disintegration, and sufficient mechanical strength. To fulfill the requirements for a short disintegration time, the FCC formulations have to contain superdisintegrants. The FCC formulations absorbed smallest amount of water, which would enhance patient compliance in the clinical setting.

FCC is a new pharmaceutical excipient, which can be used to assist in the preparation of orally dispersible tablets. ODTs prepared using FCC as main excipient are characterized by a short disintegration time and high mechanical strength. Thus, drug delivery to the buccal cavity or upper esophageal regions can be achieved. The oral sensation after ingesting FCC particles is expected to be favorable since particles with a particle size below 15 μm are not felt in the mouth (34). Further experiments are required to study the friability and flowability of FCC particles being a prerequisite for large scale production.

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Chapter 4

Discussion

FCC is a co-processed excipient, invented by the company OMYA® Development AG in Oftringen, Switzerland. The excipient is produced by re-crystallization of inorganic mixed salts such as calcium phosphate, incorporating the starting material calcium carbonate under controlled conditions to form micro- to mesoporous particles [75]. Originally the particles were designed to be used in the paper industry, more precisely in the field of inkjet printing technology. The unique structure of FCC was successfully used to load water-based ink into the pores [76].
In the context of this thesis, FCC was used in the field of pharmaceutical technology for the first time. Even though FCC and ground calcium carbonate have the same main constituent, they revealed very different physical properties. The two main differences between FCC particles and ground calcium carbonate are the high volume of intraparticle porosity of FCC and the significantly higher specific surface area of FCC due to the lamellar structure of the FCC particles.

4.1 Lamellar structure as a key factor

The mechanical study of FCC showed that the special physical attributes of FCC particles result in tablets with high tensile strength and high porosity at compressive pressures that are much lower than those needed for other excipients. It was assumed that the lamellar structure of the particles, and hence, the large specific surface area of FCC are the main reasons for these exceptional properties. On closer inspection it was realized that the available specific surface area is governed by the pore size distribution of intraparticle pores. Although the three FCC types showed similar shape and size, they differed in intraparticle porosity and hence in tensile strength of the tablets. Based on the results it was speculated that a higher pore volume of larger pores (pore diameter of approximately 100 nm) resulted in tablets with higher tensile strength at compressive pressures below 150 MPa compared to particles with a lower pore volume of large pores. Above a compressive pressure of 150 MPa, the particles with a higher pore volume of very small pores (around 10 nm) yielded in tablets with higher tensile strength compared to particles with lower pore volume of very small pores. Based on these findings, it is recommended to use FCC S01 and S02 at compressive pressures below 150 MPa to produce tablets with highest possible tensile strength. At compressive pressures above 150 MPa it is recommended to use FCC S03 for the same purpose. With respect to QbD, the intraparticle pore size distribution of FCC particles seems to be a critical material attribute. A shift in the pore size distribution of FCC particles is assumed to be reflected in the

tensile strength profile of the resulting tablets.

4.2 Granulation of FCC

To overcome the limitations of low bulk volume and poor flowability of FCC during direct compression, the powder was granulated. Two different methods were used for granulation, namely high shear granulation (wet granulation) and roller compaction (dry granulation).

Wet granulation

The tensile strength of tablets produced by high shear granulation was reduced in comparison to tablets produced with FCC powder or roller compacted FCC granules. It was assumed that the high shear forces in the mixer partially destroyed the stratum lamellae of FCC S02 and thus reduced the contact area, resulting in lower values for tensile strength.
In general, it was challenging to control the high-shear granulation process due to the fact that FCC particles are porous, show an irregular shape, and the particles have a broad particle size distribution. Therefore, another set of experiments was performed with Fujicalin, a model substance for spherical particles with a small particle size distribution. With these particles it was possible to show that torque increase during wet granulation is a function of geometrical arrangements of the spherical particles in the powder bed at increasing liquid content.
The findings with Fujicalin could not be directly transferred to FCC. In contrast to Fujicalin, FCC particles are characterized by an irregular shape and the particle size distribution is broad. Although Fujicalin has intraparticle pores, they do not absorb liquid. For FCC particles the situation is different. It is expected, that during the wet granulation process of FCC, these intraparticle pores are (partially) filled before the agglomeration process of the particles can take place. On one hand filling of the pores needs more time for the process (first of all to fill the pores and later on to dry them) and a higher amount of binder solution. On the other hand, the binder can plug the pores and hence reduce the porosity. Furthermore, the attached binder on the surface of FCC particles could prevent the particles to come together as close as possible that Van der Waals forces can be built. Another point that should be kept in mind is the lamellar structure of FCC. At a certain pressure / mechanical impact the lamellae could no longer withstand the impact and start to collapse / interlock. The wet granulation of FCC has to be considered as a dynamic process, where not only the shape of the particles is changing, but also the porosity and the saturation of the pores. To develop a model that takes into consideration all of the mentioned points, remains a challenge. For certain formulations, the above mentioned properties of FCC may be advantageous. An example for such a formulation is a matrix system that is built by embedding the API within the FCC particles. Collapsing and interlocking of particles could create a connected matrix system. As discussed for the high-shear granulation, it is expected that fluidized-bed granulation

will show similar problems with respect to plugged pores due to binder solution. In contrast to the high densification during high shear granulation, it is expected that the granules obtained with a fluidized bed process show marginal densification. Further investigations are necessary to prove these assumptions.

Dry granulation

Roller compactors are equipped with a feeding system that allows processing of poor flowable materials, such as FCC. With the help of the feeding screws, the powder is forced down to the rolls. In case of FCC, the bulk volume is reduced dramatically during the roller compaction. This densification takes mainly place in the nip-region, the area between the rolls where the reduction in gap width occurs. To deliver enough powder to the nip region, the feeding screws have to rotate at a high speed during roller compaction of FCC powder. For a scale-up process it is recommended to consider a vacuum-deaeration system that results in a predensification of the FCC powder.
As already mentioned in the introduction (see "1.2.2 Granulation"), dry granulation is usually connected to two main challenges, namely the loss of reworkability and the production of fines. Granulated FCC powder showed improved powder properties at retained compactibility. Also the intraparticle porosity was unaffected by the roller compaction process. These results indicate, that the loss of reworkability is no issue for FCC. With respect to the production of fines, FCC and Avicel formulations showed similar results. By modifying the surface of the rolls (knurled rolls), the amount of fines can be further decreased, which solves the issues of fines.
If the porosity and high surface area of FCC particles have to be preserved during the granulation process, dry granulation will be the process of choice. Based on the performed studies, roller compaction is expected to be the most efficient way to produce granules with a good flowability and high bulk density out of FCC. The obtained granules can be used for direct compression and are suitable for scale-up processes.

4.3 Applicability of FCC as an ODT

In the context of this thesis, ODTs containing FCC were produced by direct compression. In comparison to other excipients, FCC was able to overcome the limitation of insufficient hardness during the production of highly porous ODTs. This innovative finding was related to the lamellar structure of FCC. In addition, direct compressed ODTs made with FCC are much more time- and cost efficient than ODTs produced by, for example, the lyophilization method. In comparison to other direct compressed ODTs, in particular Risperidone oro, FCC showed considerably better performance including higher tensile strength and faster disintegration time. To protect the valuable findings, a patent was applied for the production of ODTs made of FCC [77].

For this thesis, ODTs were prepared manually by direct compaction of FCC powder with 3% of

disintegrant. Figure 4.1 gives an overview of how FCC can be used in the future to produce ODTs. The recommendations are based on the knowledge gained from FCC in the context of this thesis.

For the first approach (I), FCC is blended with the disintegrant and the API, followed by a direct compaction of the powder mixture. This method is limited by the poor flowability and high bulk density of FCC, which makes the automated industrial application impossible.
Approaches II-IV show how these limitations can be overcome by roller compaction. For the second approach (II), FCC is blended with the disintegrant and the API and afterwards roller compacted. This approach is especially recommended if the amount of API in the formulation is very high or very low and hence could result in a segregation of the mixture. Subsequently the granules are compacted into tablets. This approach is preferable due to the fact that the most uniform distribution of the different components (API, FCC, and disintegrant) will be reached within a tablet, compared to the other approaches.
A third approach (III) could be a "ready-to-mix" approach, depending on which granules consisting of FCC and disintegrant can be produced in advance. A better mouth feel due to the disintegration of the granules into smaller powder particles is the result of FCC granules containing disintegrant. Later on these "ready-to-mix"-granules can be blended with an arbitrary API. For a successful production it has to be ensured that the size of the granules and of the API are in the same range in order to prevent segregation. If segregation is an issue, the second approach is more preferable. In case of a high API load, an extragranular addition of disintegrant has to be considered. A high API load could disconnect the infinite network of the disintegrant within the tablet, resulting in an incomplete disintegration. It has to be determined experimentally if an extragranular addition of disintegrant is favorable. In a final step, the powder blend consisting of granules and powder, is finally compacted into tablets.
The fourth approach (IV) is only shown for completeness and does not have a practical relevance. For this approach, FCC powder is roller compacted prior to blending it with the other components. The FCC granules are blended with the disintegrant and the API and afterwards the mixture is compacted into a tablet. Adding the disintegrant after the granulation step involves the risk of an incomplete disintegration of the tablet and especially of the FCC granules. In this case, there is no possibility for the disintegrant to form the infinite network through the tablet that is needed for a complete disintegration. An incomplete disintegration does not only change the pharmacokinetic properties of the formulation, but also results in larger particles on the tongue and hence a bad mouth-feel of the formulation.

For scale-up and industrial production of ODTs made with FCC, a granulation step is necessary in order to increase the flowability of FCC particles. Wet granulation is no option to produce granules for an ODT formulation due to the fact that the disintegrant lost its property of swelling after the first contact with water (in this case during the granulation). Instead, roller compaction is

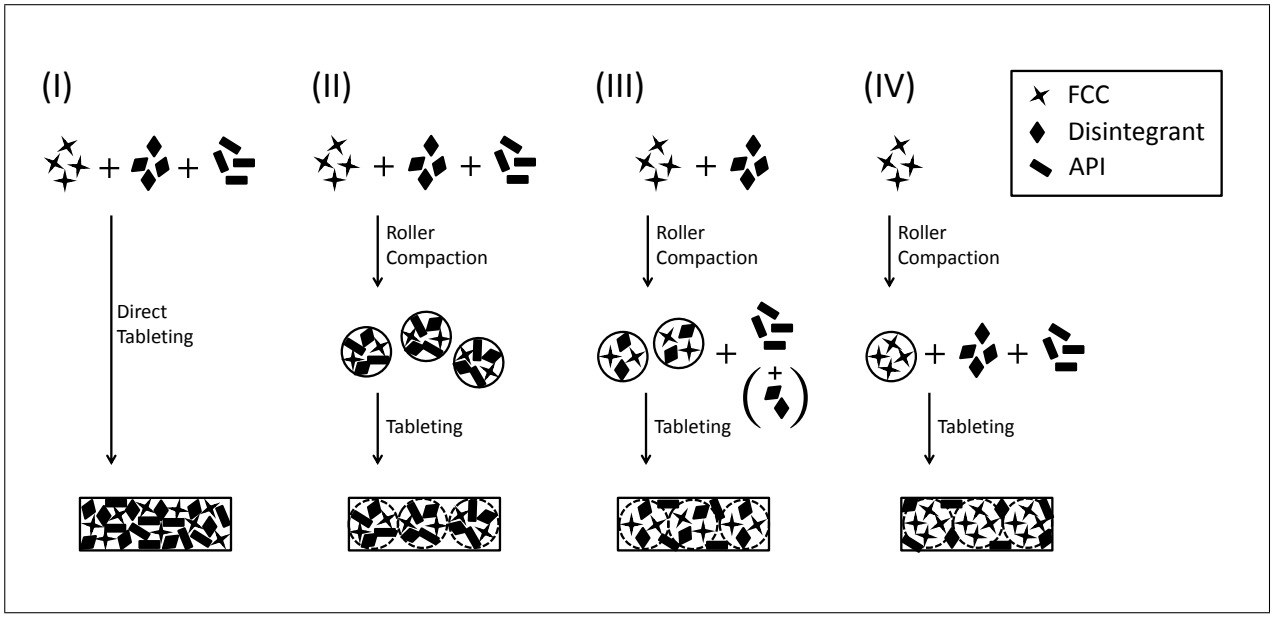

Figure 4.1: Four different approaches to produce ODTs containing FCC are shown. Approach (I) is limited by the poor flowability and high bulk density of FCC powder. These limitations were overcome by a roller compaction process (approaches II-IV). Most uniform distribution of the individual components within a tablet is expected for the approach (II). For that reason, approach (II) would be the most recommendable way to produce ODTs containing FCC. The approach (III) is a "ready-to-mix" approach where FCC granules contain disintegrant to improve patient compliance with a better mouth feel. Tablets prepared by approach (IV) bear the risk of incomplete tablet disintegration and hence, changed pharmacokinetics and reduced patient compliance due to bad mouth-feel.

the process of choice, due to the fact that high porosity and compactability are retained and the properties of the disintegrant are preserved during the dry granulation process. In summary, it is recommended to follow the second approach (II) shown in Figure 4.1 to produce ODTs made with FCC. This approach offers the most uniform distribution of the different tablet components within the tablet and hence guarantees a fast and continuous disintegration of the tablet.

Chapter 5

Conclusion and Outlook

The characterization of co-processed FCC revealed a promising new pharmaceutical excipient with a broad application spectrum. The mechanistic study showed that tablets with high tensile strength and high porosity can be obtained even at low compressive pressures. In comparison to conventionally used excipients such as MCC, mannitol, or calcium carbonate, the attributes of FCC present a striking success in the field of excipient research. The key factor for the outstanding performance of FCC and its multifunctionality is the lamellar structure of the particle, which forms a porous meshwork (intraparticle porosity), resulting in a high specific surface area. To overcome the limitations of poor flowability and high bulk density of FCC powder during direct compression, FCC powder was roller compacted (dry granulated). The granules obtained by roller compaction showed excellent flowability and reduced bulk volume, whereas all the outstanding properties of the powder, such as compactability and compressibility, were preserved. With the dry granulation process, the new excipient was converted into a suitable form for scale-up processes on high-throughput rotary tablet presses.

With the conventional disintegration test described in PhEur [9] it was not possible to measure the disintegration time of ODTs containing FCC. For this purpose, a highly sensitive tensiometer-based method was proposed. The new method did not only measure disintegration time, but also kinetics of weight loss during tablet disintegration was measured.

Application outlook of FCC as a pharmaceutical excipient

FCC particles showed a porosity of approximately 70% (v/v) and a specific surface area of approximately 60 m^2/g. This huge empty space and surface within the particle can be used manifold. Subsequently, three prospective application fields are highlighted.

Carrier: The unique structure of FCC with lamellae and thus high porosity makes the particles interesting as a carrier. Preisig et al. [78] showed, that the intraparticle pores of FCC can be loaded with APIs. The achieved drug load was 40% (w/w), in which the API was mainly deposited in the stratum voids (outer part of intraparticle pores). Furthermore, Preisig et al. [78] compared the drug release out of a drug-loaded FCC particle with the release out of a FCC-drug mixture. They found that drug release of a poorly water-soluble drug was accelerated by loading it into FCC particles. This effect has been explained by the fact that the API is distributed over a large specific surface area that stands in direct contact to the dissolution media.

Adsorbent for liquids: The high intraparticle porosity of FCC can not only be used as a drug delivery system, but also as an absorbent for various liquids. As already discussed in this thesis, the water uptake into a FCC powder bed is remarkably fast. Amongst others, FCC particles could be used instead of talc in powder formulations to treat weeping wounds. The capillary action provided by the special alignment of the lamellae could dry the wound by absorbing the liquid into the FCC particles.

Adsorbent for particles: FCC and active coal (charcoal) share the characteristic of having a high specific surface area. Active coal shows an activated (modified) surface that allows binding toxins in the intestinal tract. Therefore, active coal is indicated as an antidote after intoxication or to treat acute diarrhea. Similar surface modifications as for active coal should be feasible for FCC in order to bind on specific substances in the intestinal tract.

With respect to solid dosage forms, the applicability of FCC seems to be of particular interest for formulations that are characterized by high porosity, high tensile strength, or both. Subsequently, some examples of such formulations are provided.

ODTs: Conventional ODTs usually show a high porosity that is limited by low tensile strength of the tablet. Excipients for ODT formulations are distinguished by two critical properties. The first one, a disintegration time of a few seconds, is of pharmacological interest and improves the compliance. The second, a high tensile strength of the tablet, is of interest with respect to packing the tablet into a blister. A successful ODT formulation needs to have a high porosity that allows the liquid to penetrate through the tablet within seconds and a high tensile strength that the end product can be packed into a push-through blister. ODTs containing FCC were able to overcome the limitation of insufficient hardness and showed a disintegration time of less than 10 seconds at the same time. The high tensile strength of ODTs prepared from FCC allows producing ODTs with break lines. This feature does not yet exist on the market due to insufficient hardness of direct compressed ODTs. With respect to the requirements of the European Union that state a need for age-related tablet formulations, FCC could facilitate the formulation work. With the introduction of ODTs with break lines it could be possible that the dose of one tablet covers the need of different age groups. As an example, parents of a one-year-old child could break the ODT in quarters and dispense one of these pieces in the feeding bottle to the child. For a five-years-old, the parents could administer three-fourths of the same dosage form by placing the tablet in the mouth of the child. These findings of high tensile strength and high porosity could revolutionize the production of ODTs in the future.

Floating tablets: The requirements for the excipient to produce ODTs and floating tablets are the same, namely high porosity and at the same time high tensile strength. Eberle et al. showed that the intraparticle porosity of FCC particles can be used to produce floating tablets. To achieve floating behavior, the density of the tablet has to be smaller than the density of the gastric fluid.

At the same time, the high specific surface area provides sufficient contact area between particles, resulting in a mechanically robust formulation with high tensile strength of the tablets.

Effervescent tablets: A marginal effervescing effect was observed during the disintegration of ODTs consisting of FCC. The principle of an effervescent tablet is based upon a chemical reaction. Effervescing tablets often contain sodium bicarbonate and citric acid. After the tablet comes in contact with water, carbon dioxide is released, resulting in an effervescing effect. Similar effect could be achieved by mixing FCC with an acid, such as citric acid. In addition, a disintegrant could be added to guarantee complete disintegration of the tablet. The advantage of using FCC to produce effervescent tablets could be the capillary action that is provided by the unique structure of FCC, resulting in a fast disintegration of the tablet. In addition, FCC particles can be used as a carrier to increase the solubility of poorly water-soluble APIs by spreading the API over the high specific surface area of FCC particles. FCC based effervescent tablets could be an alternative to conventional effervescent tablets containing sodium. The use of sodium is controversially discussed due to the fact that a study associated the use of sodium for effervescent tablets with cardiovascular events [79].

Release-controller: If the challenge of drug loading into the core of FCC particles could be overcome, FCC could be used to design the whole range of release profiles; from immediate release to sustained release formulations. An ODT formulation is an example for an immediate release formulation. A sustained release profile (repository-effect) could be achieved by loading the core pores of the particles. Depending on the used API, the dissolution of the API out of the pores could result in a sustained release profile. The two approaches could also be combined to obtain a formulation with an initial boost of drug that is afterwards kept constant (steady-state) by sustained drug release out of the inner FCC pores.

Ultra hard tablets: Crushing of sustained release formulations that results in an immediate drug release is an approach commonly used by drug addicts. Amongst others, such abuses were observed for opiate formulations. The company Grünenthal invented a tablet with a hardness over 500N that can no longer be crushed especially for this purpose [80]. As it has already been shown in this thesis, the compaction of FCC resulted in very hard tablets. The reason for this extraordinary high hardness was the high surface area that provided innumerable contact points for strong bindings. Therefore, FCC could be a promising basic excipient for the production of UHTs. While the Grünenthal technology involves a cost- and time-intensive hot-melt extrusion process, FCC UHTs are direct compactable. For that purpose, FCC granules can be mixed with other excipients, if necessary, followed by a direct compaction process.

Cushioning agent: The production of a multiple unit pellet system (MUPS) is a critical process. During the tableting process, the pellets are embedded within an excipient matrix. With the existing excipients on the market, the pressure during tableting has to be adjusted carefully in order to

avoid breaking the pellets as a result of too high pressure. On the other hand, the tablet requires a certain pressure in order to reach the required mechanical robustness. Finding the appropriate pressure is a challenging task with conventional excipients. Based on the findings in this thesis, FCC could overcome these limitations by acting as a cushioning agent. Even at low compressive pressure, FCC formed tablets with high tensile strength due to the high specific surface area available for binding. In addition, this could result in a higher load of pellets.

The near future of FCC - The way on the market

Based on the results of our group, FCC will be introduced into the market of pharmaceutical excipients in the year 2015. At present, an industrial partner is setting up production facilities and is preparing the registration. It is planned to register FCC under the brand name "Omyapharm" as shown in Figure 5.1 [81]. Hopefully, FCC will find, due to its exceptional properties, widespread use in the pharmaceutical industry in the years to come.

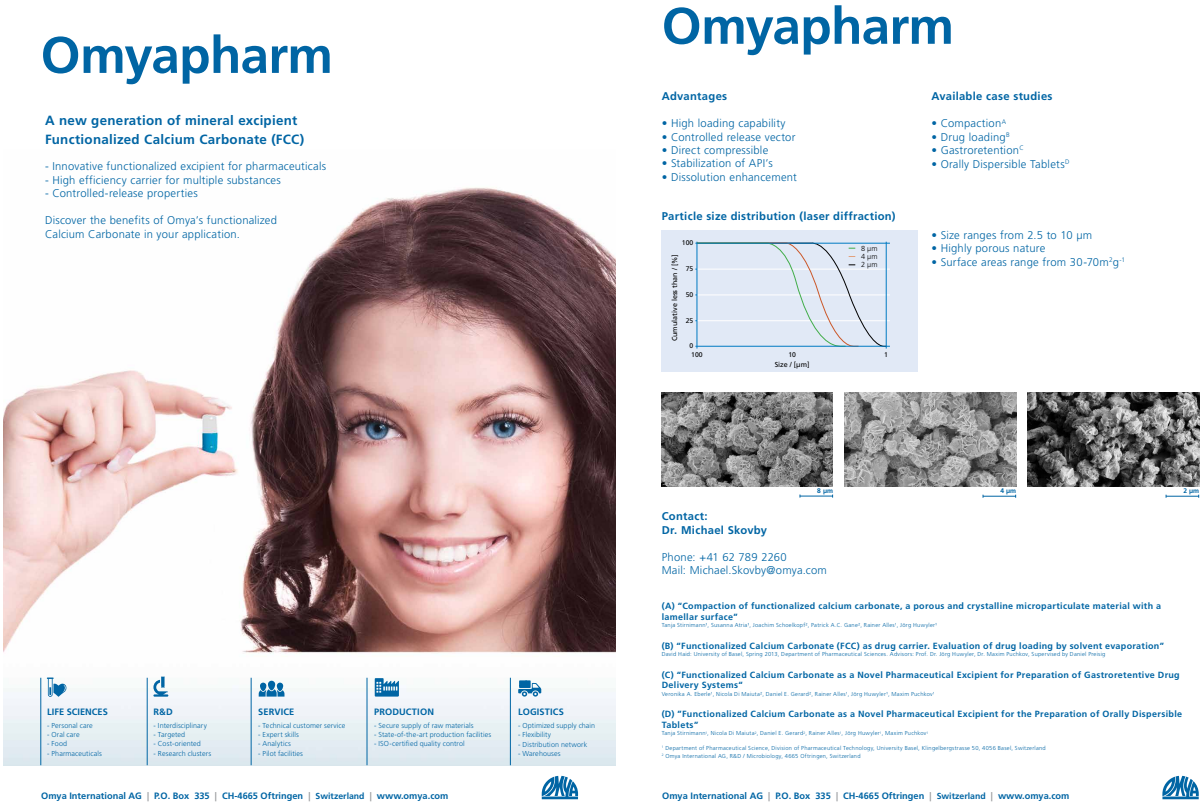

Figure 5.1: Brochure presented at the Excipient Fest Europe in Amsterdam in June 2014 to announce the introduction of the novel pharmaceutical excipient into the market [81]

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Appendix

Curriculum vitae

Curriculum Vitae

Personal information

Name	Tanja Stirnimann
Date of birth	July 2nd 1987
Native place	Ruswil (LU), Switzerland
Marital status	single
Nationality	Switzerland

Current activity

10.2011 – 10.2014 **PhD thesis** (100%), Pharmaceutical Technology (solid dosage forms), Prof. Dr. Jörg Huwyler, University of Basel, Switzerland

- Characterization of functionalized calcium carbonate as a new pharmaceutical excipient (compaction study, granulation, orally dispersible tablets)
- Supervision of a master student (dry and wet granulation)
- Supervision of solid dosage form practical for bachelor students (granulation with high shear mixer and fluidized bed, pellet layering with bottom spray coating, tablet compaction, drum coating, capsule production, analysis according to Ph.Eur.)
- Oral and poster presentation in front of national and international committees
    - Swiss Pharma Science Day, 2012/2014
    - 5th EuPFI Conference Barcelona, 2013
    - Excipient Fest Amsterdam, 2014

02.2012 – 10.2014 Pharmacist, Stern Apotheke, Basel, Switzerland

- Pharmaceutical customer support and customer consulting
- Prepare galenicals according to a prescription

Education

08.2009 – 09.2011 **MSc in Pharmacy and Swiss federal pharmacist diploma**, University of Basel, Switzerland.

01.2010 – 06.2010 **Master thesis**, University of Basel and Inselspital Bern, Switzerland

- Sodium Thiosulfate: Development of an enteric coated solid dosage form and investigation of the oral bioavailability

08.2006 – 07.2009	**BSc in Pharmaceutical Sciences**, University of Basel, Switzerland
08.2000 – 06.2006	**Matura**, focus on biology and chemistry, Kantonsschule Willisau, Switzerland

Languages

German	native speaker
English	fluent, oral and written (team language, presentations, writing of scientific publications)
French	basic knowledge

IT knowledge

Microsoft office	Word, Excel, PowerPoint (advanced skills)
Data analysis & graphing	Origin (basic knowledge)
Document preparation system	LaTeX (basic knowledge)

Voluntary activities

01.2014	Project management training at the University of Basel (2 days)
11.2013	Founder of webpage “femalescientists.unibas.ch” (portraying women with background in natural sciences)
08.2008 – 08.2010	Student representative in education committee, University of Basel
08.2008 – 08.2009	Organization committee for a student conference (1 week) in Grindelwald for 180 students (sponsoring, invitation of speakers, timetable, organization of social events, networking)

Interests

Photography (in particular nature and time exposure), cooking and eating with friends, fitness

Publications

- Stirnimann, T., Maiuta, N.D., Gerard, D.E., Alles, R., Huwyler, J., Puchkov, M., 2013. Functionalized Calcium Carbonate as a Novel Pharmaceutical Excipient for the Preparation of Orally Dispersible Tablets. Pharm. Res. 30, 1915-1925.
- Stirnimann, T., Atria, S., Schoelkopf, J., Gane, P.A.C., Alles, R., Huwyler, J., Puchkov, M., 2014. Compaction of functionalized calcium carbonate, a porous and crystalline microparticulate material with a lamellar surface. Int. J. Pharm. 466, 266–275.