Oral dosage form development of mesoporous silica for enhanced release of poorly soluble compounds

Monica Vialpando
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>Ac-Di-Sol® (croscarmellose sodium)</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the Curve</td>
</tr>
<tr>
<td>BJH</td>
<td>Barrett-Joyner-Halenda</td>
</tr>
<tr>
<td>COK-12</td>
<td>Centrum voor Oppervlaktechemie en Katalyse no. 12</td>
</tr>
<tr>
<td>DMS</td>
<td>Disordered Mesoporous Silica</td>
</tr>
<tr>
<td>DSC</td>
<td>Differential Scanning Calorimetry</td>
</tr>
<tr>
<td>MAS NMR</td>
<td>Magic Angle Spinning Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>MCM-41</td>
<td>Mobil Composition of Material no. 41</td>
</tr>
<tr>
<td>MCC</td>
<td>Microcrystalline Cellulose</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>HPMC</td>
<td>Hydroxypropyl Methyl Cellulose</td>
</tr>
<tr>
<td>KJS</td>
<td>Kruk-Jeroniec-Sayari</td>
</tr>
<tr>
<td>OMS</td>
<td>Ordered Mesoporous Silica</td>
</tr>
<tr>
<td>PTFE</td>
<td>Polytetrafluoroethylene</td>
</tr>
<tr>
<td>PDR</td>
<td>Premature Drug Release</td>
</tr>
<tr>
<td>PVP</td>
<td>Polyvinylpyrrolidone</td>
</tr>
<tr>
<td>RH</td>
<td>Relative Humidity</td>
</tr>
<tr>
<td>SBA-15</td>
<td>Santa Barbara Amorphous no. 15</td>
</tr>
<tr>
<td>SEM</td>
<td>Scanning Electron Microscopy</td>
</tr>
<tr>
<td>SAXS</td>
<td>Small Angle X-ray Scattering</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SLS</td>
<td>Sodium Lauryl Sulfate</td>
</tr>
<tr>
<td>SGF</td>
<td>Simulated Gastric Fluid</td>
</tr>
<tr>
<td>TEM</td>
<td>Transmission Electron Microscopy</td>
</tr>
<tr>
<td>T_g</td>
<td>Glass Transition Temperature</td>
</tr>
<tr>
<td>T_m</td>
<td>Melting Temperature</td>
</tr>
<tr>
<td>XRPD</td>
<td>X-ray Powder Diffraction</td>
</tr>
</tbody>
</table>
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Chapter 1

Introduction

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Introduction

Oral drug delivery is undoubtedly the most attractive and extensively used approach to deliver drugs into the systemic circulatory system. Making up roughly 80% of the marketed products worldwide, this route of administration improves patient compliance, safety, and lower production costs [1]. However, achieving sufficient oral bioavailability can be challenging due to first pass metabolism and efflux mechanisms. Oral bioavailability is a measure of the rate and extent to which a drug reaches the systemic circulation. In order to sufficiently achieve this, the active pharmaceutical ingredient (API) must undergo critical steps in order to obtain the desired therapeutic effect. Prior to absorption into the systemic circulatory system, disintegration of drug product and solubilization of the API must occur. Here, the compound’s solubility plays a critical role. If the drug were not in solution in the stomach, gastric emptying would then expose it to the small intestine, where the solid drug could then dissolve in the presence of the small intestinal fluid.

Achieving adequate solubility is a growing challenge due to the increase in use of combinatorial chemistry approaches and advancements in high-throughput screening strategies. While the number of potent lipophilic/hydrophobic drug candidates increases, so does the number of low aqueous soluble compounds. Poor solubility in the gastrointestinal fluids typically leads to low and variable drug absorption. This in turn, decreases the therapeutic efficiency. Currently, 60% of new chemical entities are reported as poorly soluble [2]. This does not only complicate development and slow down regulatory pathways, but also hinders the ultimate goal of achieving a robust commercial product.

1.1 Biopharmaceutics Classification System (BCS)

Amidon et al. first introduced the BCS system with the objective to correlate in vitro release and permeability results to in vivo oral bioavailability, which categorizes a compound into one of four classes (Figure 1-1) [3]. This classification system addresses solubility, intestinal permeability, and dissolution rate; factors that affect the rate and extent of oral drug absorption. A compound is considered to have high solubility when the maximum dose is soluble in 250 ml over the pH range of 1.0 to 7.5 (Class I & III). Otherwise, it is considered poorly soluble (Class II & IV). The permeability classification is the direct assessment of human intestinal drug absorption. Compounds are considered highly permeable when the extent of intestinal absorption is greater than 90% (Class I & II). Otherwise, it is considered poorly permeable (Class III & IV).
1.1.1 BCS class II model compounds

The structure and physicochemical properties of selected model compounds, itraconazole (weakly basic), fenofibrate (neutral), ibuprofen and naproxen (weakly acidic) are provided in Table 1-1.

Table 1-1. Structure and physicochemical properties of selected poorly water-soluble compounds. Adapted from [4].

<table>
<thead>
<tr>
<th></th>
<th>Itraconazole</th>
<th>Fenofibrate</th>
<th>Naproxen</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td><img src="image1.png" alt="Itraconazole Structure" /></td>
<td><img src="image2.png" alt="Fenofibrate Structure" /></td>
<td><img src="image3.png" alt="Naproxen Structure" /></td>
<td><img src="image4.png" alt="Ibuprofen Structure" /></td>
</tr>
<tr>
<td><strong>Molecular Weight (g/mol)</strong></td>
<td>705.64</td>
<td>360.83</td>
<td>230.26</td>
<td>206.28</td>
</tr>
<tr>
<td><strong>Molar Volume (cm³/mol)</strong></td>
<td>507.3</td>
<td>306.4</td>
<td>192.2</td>
<td>200.3</td>
</tr>
<tr>
<td><strong>Solubility_{water} (mg/mL)</strong></td>
<td>(1 \times 10^{-9})</td>
<td>0.80</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>(T_m / T_g {^{(°C)}})</td>
<td>168 / 59</td>
<td>81 / -16</td>
<td>158 / 6</td>
<td>76 / -30</td>
</tr>
<tr>
<td><strong>pK_{a})</strong></td>
<td>1.5 &amp; 3.7</td>
<td>Neutral</td>
<td>4.2</td>
<td>4.9</td>
</tr>
</tbody>
</table>

1.1.1.1 Itraconazole (ITZ)

Itraconazole belongs to the triazole group of antifungal agents against dermatophytes, candida, cryptococcus and pityrosporum [5]. It is a weak base containing four basic nitrogen atoms. As shown in Table 1-1, it has pKa values of 1.5 and 3.7 belonging to the triazole and piperazine moiety, respectively. The other two nitrogen atoms do not protonate in the pH range of 2-10. Crystalline ITZ exhibits a high lattice energy, which results in a low aqueous solubility of 1 ng/mL at pH 7 and 4.
µg/mL at pH 1 [6]. Differential scanning calorimetry was used to identify the melting transition at 168 °C. Glassy ITZ is identified by its T_g of 59 °C and two other endothermic transitions. Upon heating, the first is observed at 74 °C due to molecular rotational restriction and the second at 90 °C is caused by the transition from chiral nematic mesophase to an isotropic liquid [7]. For oral administration, the marketed product, Sporanox®, is available as either a capsule or solution. The capsule is a solid dispersion prepared by dissolving ITZ with HPMC and coated onto sugar spheres. Because ITZ is pH dependent, a decreased oral bioavailability is observed when gastric acidity is low [8]. Therefore, the oral solution was developed as an alternative for patients who suffer from achlorhydria or hypochlorhydria. This formulation utilizes itraconazole in hydroxypropyl-β-cyclodextrin to increase the solubility, independent of pH [9].

1.1.1.2 Fenofibrate (FNF)

Fenofibrate is the most commonly used fibrate worldwide for patients who suffer from cardiovascular disease [10]. It improves cholesterol levels by decreasing low-density (LDL) lipoprotein and very-low-density (VLDL) lipoprotein levels while increasing high-density lipoprotein (HDL) [11]. After oral administration, it is rapidly converted into fenofibric acid through hydrolysis of the ester bond [12]. The lipid-modifying properties of fibrates are attributed to the selective activation of nuclear transcription factor peroxisome proliferated-activated receptor alpha [13]. It lacks strong intermolecular interactions such as hydrogen bonding and undergoes rapid crystallization from its amorphous form [14]. A major drawback is due to its low bioavailability when taken under fasted conditions. While this was originally improved with the micronized capsule formulation, the nanoparticle tablet formulation, TriCor®, was developed to improve bioavailability independent of food and fat content.

1.1.1.3 Naproxen (NAP) and Ibuprofen (IBU)

Naproxen and ibuprofen are both non-steroidal anti-inflammatory drugs (NSAID) used to treat pain, inflammation and fever. These acidic compounds contain a carboxyl moiety with a pKa of 4.2 and 4.9 for NAP and IBU, respectively. Because weakly acidic drugs such as NAP and IBU exhibit low solubility in the stomach but high solubility in the proximal portion of the small intestine, the possibility of extending the BCS biowaver has been considered [15]. However, follow-up investigations from different groups recommended that the biowaver should not be applied to naproxen or ibuprofen because it fails to predict changes in in vivo rate of absorption, which is related to the therapeutic effect [16, 17].

These NSAIDs work by inhibiting the cyclooxygenase (COX) enzyme, which converts arachidonic acid to prostaglandin H2. Prostaglandins are crucial in body temperature regulation and smooth muscle tissue. They are nonselective COX inhibitors, in that they inhibit two isoforms of
cyclooxygenase, COX-1 and COX-2. The inhibition of COX-1 is responsible for unwanted effects in the gastrointestinal tract [18]. However, the extent of gastric damage effects of NSAIDs is unclear and various compounds result in different degrees of gastric damage [19].

1.2 Solubility and dissolution

Solubility is the property of a solute to dissolve and form a homogeneous solution of the solute in the solvent. The term, solubility, is more accurately defined as equilibrium solubility, which does not define the kinetics of solution formation. Because the rate of absorption plays a critical role in achieving the desired therapeutic effect, the kinetics of the API passing into solution, referred to as dissolution, makes it a determining factor. The intrinsic dissolution rate is described by the modified Noyes-Whitney Equation (Eqn. 1-1), which relates the dissolution rate of solids to the properties of the solid and the dissolution medium [20].

\[
\frac{dm}{dt} = \frac{DA}{h} (C_s - C)
\]

This illustrates that the dissolution rate is dependent on the diffusion coefficient \( (D) \) of the drug through an aqueous diffusion layer with a thickness \( (h) \), surface area available for dissolution \( (A) \), the drug concentration \( (C) \), and the saturation solubility of the drug in solution at the solid surface \( (C_s) \). Because the diffusion coefficient is a molecular property, formulation strategies are ineffective in enhancing the dissolution rate. The aqueous diffusion layer can be manipulated by decreasing the particle size. Therefore, formulation strategies aim towards either increasing the surface area or altering the solubility to enhance dissolution.

1.2.1 Formulation strategies to improve drug solubility

An illustration of the most commonly used formulation strategies is provided in Figure 1-2 and an overview of the various strategies is discussed in the following sections.

Figure 1-2. Illustration of common strategies used to address low drug solubility [21].
Introduction

1.2.1.1 Particle size reduction

Decreasing the particle size increases the surface area and therefore, improves the dissolution rate and absorption. This is achieved by obtaining either micro- or nanoparticles, which are on average 2-5 μm or 200-500 nm, respectively [22, 23]. They are prepared either by the ‘top-down’ or ‘bottom-up’ processing method. The top-down procedure is the preferred approach whereby larger particles are often reduced in size by milling [24, 25]. For bottom-up, the API is precipitated from solution. One drawback with this approach is that the nucleation rate and crystal size can be difficult to control [26].

Due to their much smaller particle size, nanoparticles result in a higher increase in surface area and hence, higher dissolution rate. As described by the Oswal-Freundlich equation (Eqn. 1-2), their solubility is further enhanced due to the increased particle curvature, where \( C_{s,r} \) and \( C_{s,\infty} \) are the solubilities of a nanoparticle with radius, \( r \), and a very large particle, respectively, \( \gamma \) the interfacial tension between the solid surface and the surrounding medium, \( V_m \) the molar volume of the compound, \( R \) the universal gas constant and \( T \) is the absolute temperature [27]. One main disadvantage is that they are susceptible to aggregation and therefore, creating a suspension with stabilizers is necessary to prevent this.

\[
\ln \frac{C_{s,r}}{C_{s,\infty}} = \frac{2\gamma V_m}{rRT}
\]

Eqn. 1-2.

1.2.1.2 Solubility modification

Altering the solubility is usually favored due to the greater range in formulation strategies available. The most common approach to enhance solubility is to disrupt the crystal structure to formulate the amorphous form. Because the amorphous state lacks long-range order, it results in a higher internal energy compared to its crystalline counterpart. Therefore, it is unstable and will revert back to its stable and lower soluble form [28]. A solid dispersion is an example of such an approach. This strategy aims to create a molecular dispersion of the poorly soluble compound in an inert carrier, typically an organic polymer. The drug is released in its supersaturated state as individual molecules or fine colloidal particles when the carrier is exposed to aqueous media. [29-31]. Solid dispersions are either prepared by means of fusion and solvent methods such as melt extrusion and spray drying, respectively [31].

The simplest approach involves the use of pH adjustment and co-solvents. Altering the pH is the most common method for solubilizing weak acids/bases. Co-solvents are water miscible organic compounds used to alter the properties of an aqueous system by reducing the polarity. They interfere with the strong hydrogen bonding interactions of water to inhibit the “squeezing out” effect [32].

Cyclodextrins are oligosaccharides comprised of α-D-(1→4)-linked glycosyl units, which vary in number. The most common are 6, 7, and 8 glucose molecules corresponding to α-, β-, γ-cyclodextrin, respectively. The hydrophilic outer layer and hydrophobic cavity enables a complexation
by partially including the hydrophobic drug molecule leading to altered physicochemical properties such as increased solubility, stability, and bioavailability [33].

Lipid based systems such as self-microemulsifying drug delivery systems (SMEDDS) are typically comprised of a surfactant, oil, and drug. Upon dilution with aqueous media and under gentle agitation, the mixture spontaneously forms a fine oil-in-water (o/w) microemulsion [34]. This technique improves absorption by presenting the dissolved drug in small droplets (5-200 nm) with a large interfacial surface area for drug absorption in the gastrointestinal tract. SMEDDS are typically prepared as liquid dosage forms administrated in soft gelatin capsules [34, 35].

Another approach is to change the composition of the crystal form through the use of co-crystals or salts. A co-crystal is a multiple component crystal in which all components are solid under ambient conditions when in their pure form. These components co-exist as a stoichiometric ratio of the target molecule or ion and the neutral molecular co-crystal former(s) [36]. Without changing the chemical composition of the API, physicochemical properties can be improved such as dissolution rate, hygroscopicity, compaction behavior, and stability [37]. One main advantage is their potential for intellectual property protection of products containing co-crystal technology [38]. Disadvantages stem from their preparation method because co-crystal screening is labor intensive and still difficult to automate [37, 39]. However, advancements towards improving high-throughput screening are recently reported [40]. Salts are widely used in oral solution and suspension formulations and can exist in many forms. The effects of salts on drug solubility can be treated like the effects of co-solvents, which forms a continuum with water [32]. The aqueous solubility of an acidic or basic drug as a function of pH dictates whether a compound will form a suitable salt [41]. However, the presence of ionizable groups does not always guarantee the formation of a suitable salt. Salts may also suffer from reductions in apparent solubility because of the presence of ions in the dissolution media that are common with the counterion used for salt formation [21].

Despite the number of formulation approaches to circumvent poor aqueous solubility, there is, unfortunately, not one tool that is suitable for all compounds. Due to the growing number of poorly soluble NCEs, scientists are led to search for new and innovative approaches to overcome this critical drug development challenge. Resulting from this is the interest in mesoporous silica as one of the more recent and burgeoning areas of drug delivery research (Figure 1-3) [42-44].
Introduction

Figure 1-3. Publications per year indexed in the ISI web of science by the topic “mesoporous silica” and “drug delivery” [45].

1.3 Enhanced release from mesoporous silica

According to the International Union of Pure and Applied Chemistry (IUPAC) nomenclature, mesopore sizes correspond to the range of 2-50 nm. Pharmaceutical mesoporous SiO₂ is typically prepared by a sol-gel process, producing either a disordered (DMS) or ordered (OMS) pore structure. The widespread attraction to these materials is attributed to their unique characteristics. Their large specific surface area and pore volume invites a high drug loading capacity and potential for drug adsorption [43]. In addition, the pore size and surface chemistry can be modified during the synthesis to fit the application needs of the user [46]. For example, the release rate is most easily controlled by the pore size, thus making the ability to control the pore diameter a key attribute [47-49]. Mellaerts et al. were the first to demonstrate the advantage of using wider mesopores to increase the release rate [48].

The enhanced release from mesoporous silica is due to constriction of individual molecules within the pores. In pharmaceutical terminology, the term “amorphous state” is often used to designate situations where the compound does not exhibit sharp x-ray diffraction peaks or a melting endotherm signal in differential scanning calorimetry (DSC), ascribed to the crystalline state. Here, the absence of crystalline fingerprints is due to the lack of intermolecular interactions between adsorbed molecules. Strictly speaking, the term “amorphous” pertains to a situation where the molecules are packed in clusters, which do not exhibit long-range order. Here, it is adopted to refer to the situation of molecules adsorbed in the confined space in the pores. The molecules, which are only slightly smaller than the pores themselves, are constricted and unable to convert to a more stable bulk phase. So long as the proportion between the compound and pore diameter remains relatively low (roughly < 20 times molecular diameter) the confined molecule is stable in its amorphous form [50]. In the presence of water, the adsorbed drug molecules are competing for the hydrophilic silica surface and are individually released in a solvated high-energy state. This results in a higher apparent solubility and release rate when compared to the crystalline state.
1.4 Early drug development history

1.4.1 Disordered mesoporous silica (DMS)

Colloidal silica gel is considered a coherent and rigid network of continuous particles. Silica powder consists of either small granules of silica gel or submicron aggregate particles. While silica gels were invented in the 1920s, significant developments of porous silica did not occur until the period of 1950-1970 [51]. During this time, the understanding of various manufacturing processes that produced silica aerogels, pyrogenic and precipitated silica were developed. The first study to utilize silica as a drug release enhancer was in 1972 with nine model compounds adsorbed onto fumed silicon dioxide [52]. In the 1980s, advancements in sol-gel chemistry introduced nanostructure silica. Here, the first reports that utilized porous silica gels (e.g., Syloid® 244), to enhance dissolution were introduced [53, 54]. Nowadays, these materials are present in wide variety of applications. In the pharmaceutical industry, they are common excipients as fillers, glidants, adsorbents, and in film coating (www.discoverysciences.com). Despite their widespread use in the pharmaceutical industry, interest in their solubility enhancing capabilities did not arise until the popularity of OMS as a drug delivery system.

1.4.2 Ordered mesoporous silica (OMS)

The first synthesized OMS, Mobile Composition of Matter (MCM-41), was in 1992 with the intention as a new family of molecular sieves [55]. Following this discovery, adaptations to the synthesis procedure were investigated to produce mesoporous silica exhibiting various types of surface and textural properties [56-58]. Due to the wide range of available OMS types, materials were applied to a variety of fields such as adsorption, chromatography, catalysis and optics [42, 59, 60]. Nearly a decade following their discovery, Vallet-Regi et al. were the first to evaluate OMS as a drug delivery carrier. Here, the authors investigated MCM-41 using ibuprofen as the model drug, which launched early development towards controlled release applications [47, 61-63]. Tozuka et al. first assessed OMS as a release enhancer by physically blending and heating salicylamide with folded sheet mesoporous material (FSM-16) [64]. Shortly thereafter, investigations regarding their solubility enhancing capabilities followed and substantially grew [48, 65].

1.5 Synthesis procedure

1.5.1 DMS synthesis procedure

Silica gel is formed from either an alkoxysilane (e.g., TEOS) or sodium silicate precursor. The alkoxysilanes undergo hydrolysis to form silanol groups. This is followed by a condensation step to form reactive siloxane bonds (Si-O-Si). Polymerization begins as these bonds begin to grow and interconnect and form chains, resulting in a sponge-like network. Due to Oswald ripening, smaller particles dissolve and attach to the surface of the larger particles until a critical size is reached. Using sodium silicate, the reaction occurs in acidified water to form silanol groups (Si-O-H), which is then
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also followed by a condensation reaction to form siloxane bonds. The growth and amount of cross-linking between the particles is dependent on pH, molar ratio of water and alkoxides, solvent type, and electrolytes. Finally, the glass-like gel is broken into granules, washed, aged, and dried to produce the highly porous material [66].

1.5.2 OMS synthesis procedure

Despite the number of studies that investigate various OMS synthesis procedures, the current production scale is still limited. As with DMS, the mesopore structure is synthesized via sol-gel synthesis but utilizes a template such as surfactant or polymeric micelles. An illustration of the supramolecular chemistry of an OMS synthesis that results in hexagonal symmetry (P6m) is shown in Figure 1-4. Following micelle formation, co-assembly occurs and micelles aggregate to form a liquid crystal phase (e.g., 2D hexagonal). Following the addition of the silica source, condensation of the silanol groups leads to the formation of the silica framework through siloxane bonds. After the silica is polymerized, the template is removed by chemical or heat treatment, leading to its porosity and narrow pore size distribution [55, 58, 67].

![Figure 1-4. General mechanistic pathway of the OMS synthesis procedure [68].](image)

The morphology and textural properties can be modified according to the use of different block copolymers, co-surfactants, co-solvents, and type of electrolytes [67, 69]. An example of this is illustrated in Figure 1-5 [69]. Also, the presence of high concentrations of silanol groups on the mesopore walls attracts chemical functionalization and tailoring of surface properties [70]. This ease of modification has a wide interest for such areas as sustained release and targeted drug delivery [43]. For immediate release purposes, functionalization is not necessary and will not be discussed here in further detail as it is beyond the scope of this work. As observed by their x-ray diffraction, OMS reveal a periodic variation of the electron density due to long range ordering of the pores [65]. Thus, they are referred to as “ordered” despite their amorphous walls.
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1.5.2.1 SBA-15 synthesis procedure

Several years following the invention of MCM-41, Zhao et al. first described Santa Barbara Amorphous (SBA-15) [58]. The structure-directing template is the triblock copolymer, Pluronic® P123, made of up polyethylene oxide (PEO) and polypropylene oxide (PPO) of the composition (PEO$_{20}$PPO$_{70}$PEO$_{20}$) and TEOS as the silica source. Synthesis of SBA-15 is necessary in an acidic environment where the silica species are positively charged and can interact with the hydrophilic PEO block of the P123 template. Here, these electrostatic interactions between the protonated silica precursor and the PEO separate the silica block copolymer mesophase from the aqueous phase which results in the ordered structure. The final SBA-15 material exhibits cylindrical pores with a uniform pore size diameter of 5 to 15 nm, specific surface area of 600 to 900 m$^2$/g, and pore volume of 0.5 to 1 cm$^3$/g [58]. Due to the P123, SBA-15 materials generally have a second intrawall porosity, micropores that are less than 2 nm in diameter. These are caused by the penetration of the hydrophilic PEO groups of the triblock copolymer chain into the silica matrix (Figure 1-6). It is also possible to tailor the micro/mesopore ratio. Furthermore, the length of these polymer chains also dictates the wall thickness.

SBA-15 is typically preferred for enhanced release due to its wider pore diameter and thicker walls. Studies show that the thicker walls of 3 to 6 nm found in SBA-15 result in superior mechanical, thermal and hydrothermal stability [71, 72]. However, stability is not only governed by wall thickness. Verlooy et al. reported that a higher degree of silicate condensation also contributes to OMS stability.
Introduction

[73]. In a recent comparison of silanol sites in commonly used OMS materials, SBA-15 resulted in the highest concentration [74].

1.5.2.2 COK-12 synthesis procedure

Centrum voor Oppervlaktechemie en Katalyse (COK-12) was first introduced in 2009 as a more environmentally friendly and economical synthesis procedure [75]. No heat or strong acids are necessary to synthesize COK-12, thereby minimizing waste and corrosion [75, 76]. Here, sodium silicate replaces TEOS as less expensive silica source. The novelty of the synthesis procedure is attributed to the citric acid and sodium citrate buffer (pH 5). Utilizing citrate enhances the hydrophobic interaction of the P123, (PEO\textsubscript{20}PPO\textsubscript{70}PEO\textsubscript{20}) triblock copolymer and the interaction between the surfactant and sodium silicate. Due to this salting out effect, ordered structures are obtained in the absence of electrostatic forces. Besides being a more ecofriendly synthesis procedure, another advantage in utilizing these cost effective and gentler conditions is the advancement towards a larger production scale synthesis process [42, 76].

As illustrated in Figure 1-7, the external morphology results in hexagonal platelets of roughly 500 nm and an internal structure that is analogous to SBA-15. The relatively neutral pH conditions of the COK-12 synthesis results in a more rapid polymerization process, thus the silica network results in a higher connectivity than SBA-15 [75].

![Figure 1-7. (left) SEM and (right) TEM micrographs of COK-12 [76].](image)

1.6 Other OMS materials

MCM-41 is the most extensively researched OMS for biomedical applications [45]. As with SBA-15 and COK-12, it contains a hexagonal structure of cylindrical pores comprised of a 1000-1500 m\textsuperscript{2}/g surface area, 0.5-1 cm\textsuperscript{3}/g pore volume but with a smaller diameter that ranges from 1.5-8 nm [47, 63, 77]. One main disadvantage is attributed to the thin pore walls of roughly 1 nm [47].

Concurrent with MCM-41 development, Inagaki et al. introduced FSM-16 [78]. The resulting hexagonally ordered material exhibits a pore diameter of 1.5-3 nm, surface area of 700-1000 m\textsuperscript{2}/g and 0.5-0.8 cm\textsuperscript{3}/g pore volume. As previously mentioned (section 1.4.2), this material was first utilized for enhanced release studies [64].

MCM-48 and SBA-16 are comprised of a 3-dimensional cubic pore symmetry belonging to
the Ia3d and Im3m space group, respectively. MCM-48 is best represented as a gyroid minimal surface [79]. The gyroid structure, which can be interpreted as two interwoven cylindrical channels, is illustrated in Figure 1-8. MCM-48 yields a similar pore size, pore volume and wall thickness as MCM-41. SBA-16 contains cage-like mesopores ranging from 5-15 nm in size. It can be described by a threefold periodic minimal surface of 1-WP (body centered, wrapped package), as illustrated in Figure 1-8 [80]. SBA-16 results in thicker walls than SBA-15 due to the longer PPO chains in Pluronic F127 compared to Pluronic P123 (Figure 1-6).

![Figure 1-8. Structure of (left) MCM-48 and (right) SBA-16 [79, 80].](image)

1.7 Drug loading methods
There are a number of ways to incorporate a compound into the mesopore structure, most often using a solvent-based approach. Ibuprofen was first loaded into OMS by means of soaking [63]. Here, a concentrated drug solution is introduced and stirred for a fixed amount of time while preventing solvent evaporation. Solvents must be selected according to their solubilization and volatility to facilitate residual solvent removal. Similar solvent parameters must also be considered for another common loading method, the incipient wetness impregnation procedure. Here, the concentrated solution of dissolved drug is taken up through capillary forces. Using cycles with solvent evaporation, the drug is loaded in different stages into the mesopores until the target drug load is achieved [65]. Charnay et al. first investigated this method and stated that the more polar solvents hamper the drug loading (Table 1-2) and therefore, affect the loading efficiency and ultimately the drug release performance. Furthermore, the drug’s solubility in the loading solvent also affects the loading efficiency [81, 82]. For example, ibuprofen is extremely soluble in ethanol (~530 mg/ml) and resulted in the highest amorphous drug load of 50% [83, 84]. This was achieved by spray drying, which has been utilized in a number of other drug loading studies [85, 86]. The use of a fluidized bed and rotavapor are also reported to successfully load indomethacin into DMS and OMS material, Syloid® 244 and MCM-41, respectively [87]. While the most appropriate solvent system readily dissolves the compound and exhibits a low vapor pressure, one foreseeable challenge with this is the development of new chemical entities that increasingly exhibit poor solubility in such inorganic solvents.
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Table 1-2. Effect of solvent properties on resulting ibuprofen drug load into MCM-41 following the incipient wetness procedure [65]. Table adapted from [88].

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Dielectric Constant at 25°C</th>
<th>Dipole Moment</th>
<th>Ibuprofen Adsorption (mg/mg SBA-15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexane</td>
<td>1.88</td>
<td>0.08</td>
<td>4.3</td>
</tr>
<tr>
<td>Ethanol</td>
<td>24.5</td>
<td>1.69</td>
<td>0.18</td>
</tr>
<tr>
<td>Dimethylacetamide</td>
<td>37.8</td>
<td>3.82</td>
<td>0.025</td>
</tr>
<tr>
<td>Dimethylsulfoxide</td>
<td>46.7</td>
<td>3.96</td>
<td>0.047</td>
</tr>
<tr>
<td>Water</td>
<td>78.5</td>
<td>1.85</td>
<td>n/a</td>
</tr>
</tbody>
</table>

While there are less reports of drug loading in the absence of organic solvent, these offer a more environmentally friendly and economic alternative. There is growing interest in the use of supercritical CO₂ due to its high dissolution capacity, low toxicity and low environmental impact [11, 89, 90]. Other common solvent-free approaches include mechanical activation such as co-milling [91-93] or vapor phase-mediated loading [94-96]. The melt method involves a physical mixture of API and silica that is then heated above the drug’s melting point. This is then followed by vortexing to load the API into the pores [97].

In a comparison study of three different drug loading methods, Mellaerts et al. investigated the location of ibuprofen and itraconazole in SBA-15 by means of N₂ physisorption, thermogravimetric analysis (TGA), DSC, diffuse-reflectance UV, and X-ray photoelectron spectroscopy (XPS). Here, the authors conclude that the effectiveness of the loading method is strongly compound dependent, which ultimately also affects the drug release (Figure 1-9) [97]. These data emphasize the great need for extensive research regarding the compound dependency of intrapore molecular organization and release kinetics depending on the drug loading method.

![Diagram showing physical state of itraconazole and ibuprofen in SBA-15 following three different drug loading methods](image)

Figure 1-9. Physical state of itraconazole and ibuprofen in SBA-15 following three different drug loading methods [97].

1.8 Confinement effects

The dynamics of a molecule in the mesopores is a balance between confinement and surface effects. As previously mentioned, when the molecule is only slightly smaller than the pores themselves, it is constricted and unable to convert to a more stable bulk phase. So long as the proportion between the
compound and pore diameter remains relatively low, an individual confined molecule is stable [98]. Should a compound crystallize in a larger pore, confinement effects will typically result in $T_m$ depression [99]. The Gibbs-Thomson equation (Eqn. 1-3) describes how melting point depression is inversely proportional to the pore size of a radius, $R$, in equation 1-3:

\[
\Delta T_m = T_{mb} - T_m = \frac{2T_m(\gamma_w - \gamma_{wl})v}{R \Delta_h \Delta_i}
\]

where $T_{mb}$ and $T_m$ represent melting transition temperature of the bulk material and the material confined in the pores, respectively; $\gamma_w$ and $\gamma_{wl}$ are the wall-solid and wall-liquid excess free energies (interfacial tensions), $v$ is the molar volume of the liquid and $\Delta_i \Delta_h$ is the molar enthalpy of melting [100]. With respect to the bulk phase, the temperature is lowered if the pore wall prefers the liquid phase to the solid phase and vice versa. In a study by Jackson and McKenna, a linear relationship was determined between the melting point depression and the reciprocal diameter using seven organic materials loaded into porous adsorbents (controlled pore glasses), ranging from 4 to 73 nm in diameter (Figure 1-10) [99].

![Image of Figure 1-10](image-url)

**Figure 1-10.** Experimental values of $\Delta T_m$ plotted as a function of the reciprocal pore diameter for (○) cis-decalin, (●) trans-decalin, (◇) cyclohexane, (Δ) benzene, (▲) chlorobenzene, (♦) naphthalene, and (□) heptane [99].

Assessing the compounds behavior confined in the mesopores has mainly been limited to ibuprofen. In an earlier study conducted at room temperature, $^1$H, $^{13}$C, and $^{29}$Si solid-state NMR were used to determine that ibuprofen exhibited extreme mobility in MCM-41 and did not exist in the amorphous or crystalline state. Ibuprofen was most mobile the largest pore size of 11.6 nm where it was able to crystallize [101]. In a recent study by Brás et al., the authors assess ibuprofen in SBA-15 over a broad temperature range using dielectric relaxation spectroscopy. Here, two families of molecules with different molecular mobility were identified. Mobility was higher in the pore center compared to the adsorbed molecule, where weak H-bond interaction with the silanol groups takes place [102].
1.9 Surface chemistry effects

The surface chemical properties are mainly governed by the presence of abundant silanol groups [103]. The interaction of these carriers with the guest molecules would be via weak interactions such as van der Waals forces or hydrogen bonds. For example, the carboxyl moiety of IBU is assumed to either link with the silanol groups on the surface or form IBU dimers, as illustrated in Figure 1-11 [102, 103].

![Figure 1-11. IBU linkage to silanol groups via hydrogen bonding (left) or physisorbed dimer at the surface (right) [103].](image)

In a study by Mellaerts et al., the authors report that the release of ITZ loaded SBA-15 was enhanced following 52% and 97%RH storage. $^{29}$Si NMR data revealed a reduction in $Q^4$ configuration and an increase in $Q^2$ and $Q^3$ (Figure 1-12). The authors conclude that SBA-15 undergoes gradual hydroxylation, leading an increased hydrophilicity and enhanced release [104].

![Figure 1-12. Illustration of –O-Si linkage of an Si atom [88].](image)

Shenderovich et al. assessed the hydrogen bond interaction of pyridine with the silanol groups of MCM-41 and SBA-15 [105]. Using a combination of various solid state NMR techniques, SBA-15 resulted in a higher degree of inner surface roughness. This was determined from Si(OH)$_2$ groups associated with surface defects by silanol groups pointing into the pore center and into other direction of space, including the pore axes. These surface roughness defects contained isolated and interacting Si-OH groups as well as germinal Si(OH)$_2$ groups, resulting in an isotropic molecular reorientation of pyridine (Figure 1-13). MCM-41 displayed isolated surface Si-OH groups, resulting in an anisotropic pyridine reorientation.
1.10 Release kinetics

One advantage of OMS is that the uniform pore structure allows for better control of the drug loading and release kinetics [49]. Moreover, theoretical prediction models are mainly developed for simple pore geometries such as the OMS cylindrical design and therefore, more effective in correlating experimental results [98]. Upon contact with the aqueous release medium, water penetrates the pores and the adsorbed hydrophobic drug is displaced from the hydrophilic silica surface and transported by way of Fickian diffusion, most commonly described with the Higuchi equation. The amount of drug release (Q) per unit of exposed area varies with the square root of time (t) as described by Eqn. 1-4:

\[ Q = k_h \sqrt{t} \]  
\[ \text{Eqn. 1-4} \]

The release rate constant \((k_h)\) is dependent on factors such as porosity, the drug’s solubility in the release medium, the initial drug load, and the diffusion coefficient of the drug molecules in the medium [61, 106, 107]. Consideration that this model is adequate for describing release of molecules that are uniformly distributed throughout the porous matrix should be kept in mind. A more extensive approach to characterize the release kinetics is with the Korsmeyer-Peppas model described in Eqn. 1-5:

\[ kt^n = \frac{M_t}{M_o} \]  
\[ \text{Eqn. 1-5} \]

where \(M_t\) and \(M_o\) represent the cumulative mass of drug released at time \(t\) and at infinite time, respectively. The proportionality constant, \(k\), and the release index, \(n\), are mechanism specific. Fickian diffusion is determined when \(n = 0.5\) [107].
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1.11 Biocompatibility and toxicity
In 2009, the Scientific Panel on Food Additives and Nutrient Sources added to Food delivered a scientific opinion on silicon dioxide for nutritional purposes to food supplements by request of the European Food Safety Authority. It was concluded that the use of silicon dioxide up to 1500 mg SiO$_2$/day added to food supplements is of no safety concern [108]. Furthermore, according to both European and US pharmacopeia, hydrated silica is an accepted material in pharmaceutical formulations. Based on chemical composition, mesoporous materials qualify as hydrated silica, albeit with a unique pore structure. The results mentioned suggest the safety of silica for oral administration. However, due to their porosity and high surface area, mesoporous silica can absorb and interact in different ways than their nonporous counterparts [109]. Klose et al. reported that micron sized particles are unlikely to cross most biological barriers, whereas nanosized particles may become absorbed in the gastrointestinal tract [110]. While there is a growing interest in the potential of their cytotoxicity, their overall cytotoxic response is presently not well understood. Moreover, due to the complex gastrointestinal system, reaching agreement between in vitro and in vivo results is often difficult [111].

Using the Caco-2 cell culture systems, Zhang et al. reported that cellular uptake was highly size, concentration, and time dependent based on results of SBA-15 and nanoparticles ranging from 20 to 90 nm in size [112]. Heikkilä et al. studied the cytotoxic effect of both MCM-41 and SBA-15 using Caco-2 cells by adding 0.2-4 mg/ml of OMS to a well plate containing 2-3 x 10$^5$ cells/well designed to assume a 200 mg dose of OMS several times a day [113]. A major cause of cytotoxicity was determined from particles that were less than 5 µm, which inflicted physical damage on the cell membrane and/or initiated apoptotic signaling after cellular uptake. Kupferschmidt et al. evaluated in vivo toxicity in rats following oral administration of nanoporous folic acid template material (NFM-1) and anionic surfactant template mesoporous silica (AMS-6) material. The spherical shape AMS-6 and rod shape NFM-1 differ in size of 230 nm and 2.2 µm, respectively. It was reported that no change in bodyweight or other clinical symptoms were observed following single-step administration. Also, no maximum tolerable dose was reached following 1200 mg/kg doses for seven consecutive days [109].

Moreover, functionalization of the particle surface can be engineered to modulate the interaction with biological systems [114]. In a study using MCM-41 as a bioactive material for bone reconstruction, Vallet-Regi et al. compared pure MCM-41 to that of phosphorous doped MCM-41, revealing that bioactivity greatly improved even with small amounts of phosphor [115].

1.12 Mesoporous silica tablet development
Despite the growing interest in mesoporous silica as a drug delivery carrier, research in assessing their mechanical behavior is limited. In an early study, seven different OMS materials were characterized following compression to 296 MPa. The authors reported that the specific surface area and mesopore volume decreases, whereas the pore diameter remained unaffected [71]. These results indicate that
some pores are blocked or that less stable pores completely collapse while some pores remain unaffected. Furthermore, the authors attribute the superior mechanical stability of SBA-15 to its thicker pore walls. Another study reported that following tableting, the dissolution rate and permeability of indomethacin (IMC)-loaded thermally oxidized mesoporous silica microparticles (TOPSi) decreased with increasing ratio of the TOPSi-IMC particles in the formulation. The authors attributed this to deformation of pore structure following compression [116]. Limnel et al. reported no damage to the Syloid® 244 pore structure following compression and fast release properties maintained. However, it should be noted that the formulation contained only 25 wt. % silica [87].

The Heckel equation is commonly used to characterize the deformation process of powder blends (Eqn. 1-6).

$$\ln \left( \frac{1}{1-D} \right) = A + KP$$

It is based on the assumption that the material behaves analogous to a first-order reaction where $P$ is the pressure, $D$ is the relative density of the compact, and $K$ and $A$ are constants [117]. The yield pressure value is obtained by calculating 1/slope. A high slope and thus, low yield pressure represents a high degree of plastic deformation [118].

In a recent study by Hentzschel et al., the authors utilize Heckel plots to assess the tablet properties of silica aerogel, Neusilin® US2 (magnesium aluminometasilica), Florite® (calcium silicate), and Aerosil® 200 (colloidal silica). Figure 1-14 illustrates the results in which plastic deformation decreased with increasing silica concentration [119]. It was also reported that Aerosil® and Florite® resulted in poor flowability due to cohesive forces from their smaller particle size of 17 μm and 33 μm, respectively.

![Figure 1-14. Influence of the silica concentration on the mean yield pressure of the Avicel®/silica powder blends [119].](image)

All studies involving mesoporous silica tablets were prepared by physical mixtures and directly compressed [87, 119, 120]. To the best of our knowledge, there is only one report that
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involves processing of OMS for oral dosage form development [121]. In this study, the authors manufacture pellets with carbamazepine loaded SBA-15 by extrusion/spheronization (Table 1-3). However, the formulation comprised of only 25% wt. loaded silica that resulted in a low drug load [121].

MCC is one of the most often used substance for direct compression (Figure 1-15). Its various roles range from a filler, disintegrant, flow aid, and dry binder to produce hard tablets at low compression forces. Several different grades are available, which vary in particle size, moisture, flow etc. [122]. PH-101 contains a typical particle size of 50 μm and is arguably the most widely used for direct compression (Figure 1-15).

Figure 1-15. Structural formula of MCC (left) and SEM micrograph of PH-101 (right) [122].

Takeuchi et al. reported that tablet disintegration was the rate-limiting step for drug release of indomethacin from DMS, Sylysia® 350 [85]. Here, the authors selected low-substituted hydroxypropylcellulose and pre-gelatinized starch as disintegrants. The role of a disintegrant is to break up the compacted tablet into particles of the API and excipients. Factors contributing to disintegrant action include: swelling, capillary action, strain recovery, expansion of entrapped air, and deformation or breaking of physicochemical bonds [123]. Although MCC and partially pre-gelatinized starch are frequently used in formulations for compaction and disintegration, the three super disintegrants preferred today are croscarmellose sodium (Ac-Di-Sol®), sodium starch glycolate (Explotab®), and crospovidone NF (Figure 1-16).

Figure 1-16. The chemical structure of (left) croscarmellose sodium, www.fcm.com, (middle) sodium starch glycolate, and (right) crospovidone [122].

Croscarmellose sodium is an internally cross-linked sodium carboxymethylcellulose. The cross-linking makes it insoluble, while allowing the material to swell and absorb many times its weight in water. Furthermore, it exhibits good binding and compression properties. Sodium starch
glycolate is a sodium salt of a carboxymethyl ether of starch [122]. A polymerization process results in a cross-linked insoluble polyvinylpyrrolidone, crospovidone [124]. In a study that utilized high-speed video imaging of disintegration mechanisms of the three super disintegrants concluded that the disintegration behavior of compacts containing crospovidone was attributed to shape-memory characteristics (Figure 1-17) [123]. This was attributed to the absence of free hydroxyl groups and lower water binding capacity [123, 125].

**Figure 1-17.** Schematic of (a) starch and cellulose based disintegrants and (b) crospovidone. (I) Free disintegrant particles before compression, (II) compacted disintegrant particles, and (III) compacted disintegrant particles following exposure to water [123].

Due to the large particle size difference between silica microparticles and standard tableting excipients (e.g., MCC), particle segregation is likely to occur with physical mixtures and will result in dose content uniformity issues [126]. As previously reported, the small particle size of mesoporous silica contributes to the poor flow behavior [127]. While their abundance of silanol groups, large specific surface area and porosity are attractive from a development perspective; these features attribute to low bulk density and hygroscopicity, which pose a challenge from tableting perspective. Therefore, the lack of down-stream process understanding of mesoporous silica to improve powder flow, compression and compaction properties while maximizing the dose, necessary for an oral dosage form was the driving force of this research.

### 1.13 Granulation

Granulation is an industrial process defined as any process in which small particles are gathered into larger, permanent masses where the original particle can still be identified [128]. Granulation is used in numerous applications such as cosmetics, detergents, fertilizers, and pharmaceutical manufacturing. Reasons for granulating a pharmaceutical compound include: increase density, drug content uniformity and shelf life, enhance compressibility and powder flow, reduce dustiness and improve product appearance [129]. Table 1-3 lists an overview of various agglomeration methods used in the pharmaceutical industry.
Table 1-3. Granulation methods employed in the pharmaceutical industry. Adapted from [129].

<table>
<thead>
<tr>
<th>Method</th>
<th>Granule Density</th>
<th>Scale of Operation</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous high-shear,</td>
<td>High</td>
<td>&lt;50 tons/hr,</td>
<td>Handles very cohesive materials well</td>
</tr>
<tr>
<td>Batch high-shear</td>
<td></td>
<td>&lt;500 kg/hr</td>
<td></td>
</tr>
<tr>
<td>Fluidized bed</td>
<td>Low</td>
<td>100-900 kg (batch),</td>
<td>Easy to scale, difficult for cohesive powders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;50 tons/hr (contin.)</td>
<td></td>
</tr>
<tr>
<td>Centrifugal granulator</td>
<td>Medium-High</td>
<td>&lt;200 kg/batch</td>
<td>Powder layering and coating applications</td>
</tr>
<tr>
<td>Spray-drying</td>
<td>Low</td>
<td></td>
<td>Wide range of morphology</td>
</tr>
<tr>
<td>Extrusion,</td>
<td>High-very high</td>
<td>&lt;5 ton/hr,</td>
<td>Narrow size distribution, sensitive to powder flow and mechanical properties</td>
</tr>
<tr>
<td>Roll press</td>
<td></td>
<td>&lt;50 tons/hr</td>
<td></td>
</tr>
</tbody>
</table>

This thesis focuses on batch high-shear granulation. Here, the meltable or liquid binder can be added in either wet (binder dissolved in a granulating liquid) or a dry state [130]. The current preference is the latter, which blends the polymeric binder and other ingredients in the dry state, followed by the addition of heat or liquid (e.g., water) [129]. A high-shear granulating system consists of a mixing bowl equipped with impeller blades that rotate either in a horizontal or vertical direction at speeds of 100-1000 rpm. A chopper is often employed to control the maximum size of granules and operates at typical speeds of 1000-5000 rpm [129]. An illustration of this design is provided in Figure 1-18. One challenge faced with high-shear granulation is a phenomenon referred to as overgranulation. It is defined as the inability of granules to be compressed into intact tablets. This can occur when process conditions result in overly agglomerated material [129].

![Figure 1-18](image_url)  
*Figure 1-18. Overview of high-shear granulation processes design adapted from [129].*

As illustrated in Figure 1-19, the granulation process is categorized into three main processing steps, which typically occur simultaneously: (1) wetting & nucleation, (2) consolidation & growth, (3) breaking & attrition.
1.13.1.1 Wetting & nucleation
During the first step, the binder comes into contact with the powder bed and is distributed throughout the powder, resulting in the formation of small nuclei. This is strongly influenced by the spray rate, binder distribution, and mechanical mixing. Furthermore, the spreading coefficient and contact angle of the binder also play an important role [128].

1.13.1.2 Consolidation & growth
Consolidation occurs when granules collide with other granules and begin to grow. It includes the coalescence of existing granules as well as the layering of fine powder onto previously formed granules. Newitt and Conway-Jones were the first to describe different states of liquid bridging necessary for granule growth. Figure 1-20 illustrates the four liquid saturation stages. The transition from pendular to the funicular state occurs at roughly 20-25% liquid saturation. Capillary state occurs when liquid saturation is around 80%. In the droplet state, the agglomerate is overly saturated with the occurrence of surface liquid [131].

The static strength of the pendular liquid bridge, which is mainly responsible for granule formation, is dictated by the capillary suction pressure and interfacial surface tension. The Laplace-Young equation (Eqn. 1-7) is used to determine the capillary suction pressure ($\Delta P_{cap}$) where $\gamma_{lv}$ is the liquid surface tension, $r$ is the bridge curvature from the two principal radii, as shown in Figure 1-21.

\[
\Delta P_{cap} = \frac{2\gamma_{lv}}{r} = \gamma_{lv} \left(\frac{1}{r_1} - \frac{1}{r_2}\right) = \gamma_{lv} \left(\frac{\frac{r}{[1+\frac{r}{r_2}]}^{1/2} - \frac{1}{[r(1+\frac{r}{r_2})]^{1/2}}}{[1+\frac{r}{r_2}]}^{1/2}\right)
\]
Introduction

Figure 1-21. Static liquid bridge illustrated in the \(x-r\) plane between particles with radius, \(a\). The principal radii are denoted by \(r_1\) and \(r_2\). The angle between the tangent plane to the spheres and the fluid surface is equal to the fluid contact angle \(\theta\), the bridge height at \(x = 0\) is \(h\), and the half-filling angle is \(\phi\) [128].

1.13.1.3 Breaking & attrition

Breakage of wet granules can occur during granulation impact and attrition of dried granules can occur during product handling [128]. Several studies report that increasing the mixing intensity reduces the final mean granule size [132, 133]. The Stokes deformation number \((St_{de})\) is used to predict granule breakage. As described in Eqn. 1-8, it is defined as the ratio between the external kinetic energy and the energy dissipated by the liquid bonds between the particles, where \(U_c\) is the collision velocity in the granulator, \(\rho_g\) and \(Y_g\) are the granule density and dynamic yield stress, respectively. Therefore, granules will break if they cannot withstand the shear and impaction forces [134].

Eqn. 1-8

\[
St_{def} = \frac{\rho_g U_c^2}{2Y_g}
\]

Attrition or fracture of the granules following granulation is undesirable. Fracture toughness, \(K_c\), is defined as stress distribution in the body just before fracture (Eqn. 1-11).

Eqn. 1-11

\[
K_c = Y\sigma_f\sqrt{\pi(c+\delta_c)} \quad \text{with} \quad \delta_c \sim r_p
\]

Here, \(\sigma_f\) is the applied fracture stress, \(c\) in the crack length of the crack in the body, \(Y\) is a calibration factor that accounts for different body geometries (Figure 1-22), \(r_p\) is the process zone size that is treated as an effective increase in crack length \(\delta_c\) [135]. As shown in Figure 1-22, the tensile stress concentrates near the crack tip, which is much higher than the applied stress that leads to local yielding near the crack tip (the process zone). The process zone size is a measure of the yield stress of the material in comparison to its brittleness. Yielding within the process zone may take place either plastically or by diffuse microcracking [128].
Introduction

1.13.2 Granulation binders

During granulation, the binder’s role is to provide an adhesive network, necessary for particle size enlargement. They are also a key component in dictating the resulting granule properties. Binders are usually comprised of sugars and natural or synthetic polymers. Compared to polymers, sugars (e.g., dextrose, sucrose) are less frequently used as granulation binders. Natural binders include starch, pregelatinized starch, and gelatin. Synthetic polymers are often the binder of choice for granulation. Examples of these include polyvinylpyrrolidone (PVP), hydroxypropyl methyl cellulose (HPMC), and polyethylene glycol (PEG) which were utilized in this work.

1.13.2.1 Polyvinylpyrrolidone (PVP)

PVP (Figure 1-16) is one of the most commonly used binders. The soluble grades are obtained by free-radical polymerization in water or isopropanol, yielding a chain structure of PVP [124]. It is characterized by its K-value, obtained from the Fikentscher equation, which is a function of its average molecular weight, degree of polymerization, and intrinsic viscosity. Compared to other binders, PVP is extremely hygroscopic and can deliquesce at high RH.

1.13.2.2 Hydroxypropyl methyl cellulose (HPMC)

HPMC (Figure 1-24) is available in several grades, which vary in extent of substitution and chain length. Grades are distinguished by a four-digit number (e.g., HPMC 2910), where the first two refer to the approximate percentage of the methoxy groups (OCH₃) and the last two to the hydroxypropoxy groups (OCH₂CH(OH)CH₃) [122]. HPMC is soluble in cold water and forms a viscous colloidal solution. HPMC typically becomes a gel when the water content reaches 70-80% [136, 137]. Due to their supramolecular/ordered structures, a significant amount of water is required to break its intermolecular hydrogen bonding for it to be hydrated (Figure 1-24).
Introduction

![Figure 1-24. Structural formula of HPMC where R is H, CH₃, or CH₃CH(OH)CH₂ [122].](image)

1.13.2.3 Poloxamer

Poloxamers (Pluronic®) are a group of widely used surface active compounds. They are an ABA type block copolymer consisting of a central hydrophobic PPO block in between two hydrophilic PEO blocks (Figure 1-25). They are prepared by reacting propylene oxide with propylene glycol to form polyoxypropylene glycol, followed by ethylene oxide [122]. Due to possible combinations of different block combinations, a variety of molecular weights and properties are available. A three-digit number designates the type of poloxamer (e.g., Poloxamer 188). The first two multiplied by 100 give the approximate molecular weight of the polyoxypropylene core. The last digit multiplied by 10 gives the percentage of hydrophilic PEO content. Poloxamers are stable and are less toxic compared to other surfactants [138]. For oral administration, they are typically used as wetting agents. Poloxamer 188 is selected as a suitable binder for melt granulation due to its surface activity and low melting temperature [139].

![Figure 1-25. Structural formula of poloxamer [122].](image)
Chapter 2

Objectives

Solid oral dosage forms are the preferred route of administration and are a promising approach to deliver mesoporous silica as a release enhancer for poorly soluble compounds. However, tableting of mesoporous silica is a major challenge due to their poor compression and compaction properties. Moreover, their hygroscopic nature is a drawback in terms of tablet behavior as well as decreasing powder flow. The low bulk density, small particle size, and particle shape also contribute to their poor flow behavior. These aforementioned challenges motivate this research to assess the down-stream processability of mesoporous silica for the development of an oral dosage form. Investigations in doing so are divided into four main studies:

1) Assess changes to the structure and release behavior following compression of non-loaded and itraconazole loaded OMS materials, SBA-15 and COK-12.
2) Determine the risk of premature drug release from COK-12 during wet granulation using poorly soluble compounds itraconazole, fenofibrate, ibuprofen, and naproxen.
3) Compare agglomerates of ordered (COK-12) and disordered (Syloid® 244) mesoporous silica loaded with itraconazole prepared using two methods: melt and steam granulation prepared in a high-shear mixer.
4) Steam granulation process parameters screening using a factorial design approach with itraconazole loaded into Syloid® 244.
Chapter 3

Evaluation of ordered mesoporous silica as a carrier for poorly soluble drugs:
Influence of pressure on the structure and drug release

Results described in this chapter are published in the following article:
3.1. Abstract
Ordered mesoporous silica materials are considered a promising drug delivery system for the dissolution enhancement of poorly soluble compounds. The purpose of the present work is to determine structural and behavioral changes of compressed ordered mesoporous silica material necessary for the development of an immediate-release oral-dosage formulation. Two types of ordered mesoporous silica materials (SBA-15 and COK-12) were subjected to pressures both in and beyond the tableting region and characterized by nitrogen physisorption, scanning and transmission electron microscopy, small-angle x-ray scattering, and differential scanning calorimetry. Itraconazole was used as the poorly soluble model drug and the release process with respect to pressure was determined in vitro. The resulting decreased drug release due to increased pressure was recovered by incorporating a plastically deforming material such as microcrystalline cellulose in combination with croscarmellose sodium. These findings further elucidate the understanding of their structural behavior for the advancement as a drug delivery carrier.

3.2. Introduction
Since their discovery in 1992 by the Mobil Corporation (Princeton, New Jersey, USA), highly ordered mesoporous silica materials (OMS) have attracted substantial interest for a broad range of applications such as catalysis, nonlinear optics, and molecular adsorption. More recently, interest in development as an oral drug delivery system is rapidly growing [55, 107, 140-142]. These materials display an array of uniform mesopores of 2-50 nm in diameter. OMS exhibit good hydrothermal and chemical stability [73, 143]. The large pore volume (ca. 1 ml/g) in combination with the large specific surface area (ca. 700 m²/g) of these OMS materials results in a high drug-loading capacity. In addition, the tunable pore size and surface chemistry can be modified during synthesis, to fit the application needs of the user [46, 144].

Vallet-Regi et al. first evaluated this novel drug delivery approach as a slow release oral formulation. Following this, Charnay et al. investigated its use as a dissolution enhancer of poorly soluble compounds with ibuprofen and later Mellaerts et al. with itraconazole [48, 63, 65]. Poor aqueous solubility leads to incomplete dissolution throughout the gastrointestinal (GI) tract, resulting in low and variable bioavailability. During the mid-1990s, it was reported that roughly 40% of new drug candidates failed during development due to poor bioavailability, with numbers increasing due to developments in high-throughput screening strategies [145, 146]. Therefore, advancement in innovative approaches to overcome this important formulation challenge is critically needed, making the development of this drug delivery method highly desirable.

The pore structure of OMS is the key attribute to improving the dissolution rate of poorly soluble drugs. Because the pores are only a few times larger than drug molecules, the drug is confined and unable to crystallize [50]. In this form, compounds exhibit higher dissolution rates when compared
to their crystalline state, especially when the solubility is limited by high lattice energy [147, 148]. This, in turn, increases oral bioavailability, as shown by Mellaerts et al. [149]. Investigations of OMS for oral delivery have included assessments of drug loading methods, parameters affecting release, evaluation of physiochemical diverse compounds, and physicochemical stability. Textural and structural properties of OMS have also been assessed based on their drug loading and release behavior [97, 104, 150, 151]. However, there is a significant lack in our understanding of how the pressure used to make solid dosage forms such as tablets affects the performance of these materials. Ghedini et al. evaluated the response of MCM-41, SBA-15, and silica gel to pressure, but only one applied pressure value was used and their assessment was limited to a slow release formulation [120]. No development has yet been made for immediate release of poorly soluble drugs.

For this study, SBA-15 and COK-12 were selected as model OMS materials. Of the two materials, SBA-15 is the most extensively studied and was first described by Zhao et al. [58]. Their distinctly different synthesis procedures result in structural similarity with different silicate connectivity in the pore walls. Both display a hexagonally-ordered two-dimensional array of uniform sized cylindrical pores of 4 to 13 nm, along with complementary micropores of less than 2 nm inside the pore wall. Their typical pore volume and specific surface area range from 0.8 to 1.2 ml/g and 600 to 1000 m²/g, respectively [58, 75]. Itraconazole (ITZ), a class II drug based on the Biopharmaceutical Classification System, is selected as our model compound. This well characterized antifungal agent has a high lattice energy and a low aqueous solubility of 1 ng/ml at pH 7 and 4 µg/ml at pH 1 [7].

The objective of this study was to characterize the structure and performance of OMS as a function of pressure. To determine the effect of the drug, comparisons are made between drug-loaded and non-loaded OMS. Pressures of 72 and 120 MPa were selected to reflect the applicable tableting pressure range. Moreover, higher pressures of 240, 360, and 480 MPa were selected to evaluate extreme scenarios. We hypothesize that compression compromises the pore structure, which, in turn, would affect the itraconazole release behavior. Also, by adding a plastically deformable material prior to compression, the compression energy can be dissipated and thus, reducing the extent of structural damage. To test this hypothesis, the release kinetics is evaluated with respect to structural and porosity changes. The effect of various concentrations of the plastically deforming material, microcrystalline cellulose (MCC), on the release behavior of the material was determined with and without the presence of a model disintegrant, croscarmellose sodium (Ac-Di-Sol®; FMC, Little Cork, Ireland). Characterization techniques include true, bulk, and tapped density measurements, determination of nitrogen adsorption isotherms, small-angle x-ray scattering (SAXS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), modulated differential scanning calorimetry (MDSC), high performance liquid chromatography (HPLC), and particle sizing by laser diffraction.
3.3. Materials and Methods

3.3.1 Synthesis procedure

SBA-15 was synthesized according to the procedure described by Kosuge et al. [67]. Here, 24 g of Pluronic P123® ethylene oxide (EO)-propylene oxide (PO) triblock copolymer (EO$_{20}$PO$_{70}$EO$_{20}$) (BASF, Ludwigshafen, Germany) was dissolved in 240 g of 2 M HCl under stirring. Next, 50.4 g of tetraethylorthosilicate (TEOS; Acros, 98%, Geel, Belgium) was diluted in 120 g of deionized H$_2$O. This TEOS mixture was then added drop-wise to the acidic Pluronic® solution under vigorous stirring at 37 °C. After 5 min, the mixture remained at 37 °C static synthesis conditions for 24 h. Afterwards, the mixture temperature was increased to 90 °C for an additional 48 h. Subsequently, the mixture was cooled to room temperature, vacuum filtered over a 110 mm paper filter (Whatman Schleicher and Schuell, Dassel, Germany), washed with deionized H$_2$O and dried. Finally, it was heated at 1°C/min to 550 °C, and calcined for 8 h under ambient pressure to remove the Pluronic P123® from the pores of the silica material.

COK-12 was synthesized according to the procedure described by Jammaer et al. [75]. Here, 4.0 g of Pluronic P123® was dissolved in 107.5 g deionized H$_2$O under stirring following the addition of 3.684 g citric acid monohydrate (Riedel-de Haen, Seelze, Germany) and 2.540 g trisodium citrate (UCB, Brussels, Belgium). The resulting surfactant solution was stirred for 24 h. Next, 10.6 g of sodium silicate solution (10% NaOH, 27% SiO$_2$, Merck, Darmstadt, Germany) was diluted with 30.0 g of water and added to the surfactant solution. The pH was measured prior to and after the sodium silicate addition using a Mettler Toledo, InLab®Expert Pro pH electrode (Zaventem, Belgium). The final mixture was stirred for 5 min at 175 rpm with a mechanical stirrer and kept at room temperature under static synthesis conditions for 24 h. The synthesized material was then filtered, dried at 80 °C, and calcined in two steps: 8 hours at 300 °C and 8 hours at 500 °C with a 1°C/min heating rate.

3.3.2 He pycnometry

A Beckman model 930 (Sucliffe, Belgium) gas helium pycnometer was used to measure true particle density. Samples were analyzed after immediate removal from a 40 °C vacuum oven (Heraeus, Liederkerke, Belgium) at a reduced pressure of 1 mbar. The reported density value is the mean of three measurements.

3.3.3 Tapped density

Tapped density was measured using a J. Engelsman (Ludwigshaven, Germany) jolting volumeter. The 1 mm sieved samples were analyzed after immediate removal from a 105 °C oven (Binder, Germany). Thirty-five milliliters was then poured into a 50 ml graduated cylinder. Samples were subjected to successive sets of 500, 750 and 1250 taps at 240 taps/min until a volume difference of less than 2% was achieved between sets. Reported values for bulk and tapped density are the mean of three measurements.
3.3.4 Particle size distribution analysis
A Malvern Mastersizer™ (Hoeilaart, Belgium) was used to assess particle size distribution of the starting material with laser scattering using a He-Ne laser (633 nm). All samples were suspended in water and treated with ultrasound prior to the analysis. Calculations were performed using the Mie theory. Reported values are the average of three replicates.

3.3.5 Drug loading
Itraconazole (Janssen Pharmaceutica, Beerse, Belgium) was loaded into the silica material using the incipient wetness procedure [65]. Using this approach, the drug is infused into the pores through capillary forces. A solution of 50 mg/ml of itraconazole in methylene chloride was used to load the drug into the silica. The target drug load was 20% (w/w). The damp material was then placed in a 40 °C vacuum oven (Heraeus, Liederkerke, Belgium) at a reduced pressure of 1 mbar for a minimum of 24 h to remove any residual methylene chloride.

3.3.6 Compression
Compression experiments were carried out on pure silica, silica loaded with itraconazole, and mixtures of loaded silica with microcrystalline cellulose (Avicel®; FMC, Little Island, Cork, Ireland) prepared with and without croscarmellose sodium (Ac-Di-Sol®; FMC, Little Island, Cork, Ireland). Homogeneous samples were prepared by geometric dilutions and mixed again after pouring into a 13 mm die (Perkin Elmer, England) with a spatula immediately prior to compression. A Rodac RQPBA15 (Sittard, the Netherlands) press was used to manually subject the material to specific pressures of 72, 120, 240, 360, and 480 MPa for 10 s. The resulting sample was then ground using a mortar and pestle prior to further analysis.

3.3.7 N₂ adsorption-desorption isotherms
Nitrogen adsorption isotherms of all silica materials were measured at -196 °C using a Micrometrics Tristar II 3020-apparatus (Brussels, Belgium). Samples were pre-treated overnight at respectively, 110 °C and 250 °C for drug loaded and non-loaded silica, under a nitrogen flush. The pore volume and the surface area were calculated using the t-plot method of Jaroniec and Kruk [152]. The mesopore size distribution was derived from the adsorption branches of the nitrogen isotherms using the Kruk-Jeroniec-Sayari (KJS) model. The KJS model was developed specifically for hexagonal mesopores and was used in this study instead of the traditional Barrett-Joyner-Halenda (BJH) model, which underestimates pore size [153, 154].
Influence of Pressure

3.3.8 Modulated differential scanning calorimetry (MDSC)
A DSC 2920 (TA Instruments, Brussels, Belgium) was used to assess the physical state of ITZ. Each loaded OMS sample (4-8 mg) was heated from 30 °C to 180 °C at a rate of 2°C/min with a ± 0.212 °C amplitude every 40 s. All experiments were performed in open aluminum pans (TA Instruments) using dry nitrogen at a flow rate of 50 ml/min. Indium was as used to calibrate the temperature and enthalpic response. Sapphire was used to calibrate for heat capacity. Samples were analyzed in duplicate.

3.3.9 High-performance liquid chromatography (HPLC) assay
Drug content and release were quantified using an HPLC system consisting of a LaChrom® L-7100 HPLC pump, an autosampler model L-7200 equipped with a 100 µl loop, a UV detector model L-7420, and an Interface D-7000. UV signals were monitored at 260 nm and peaks were integrated using the D-7000 HSM software (Merck, Darmstadt, Germany). The mobile phase consisted of acetonitrile/0.01N tetrabutyl ammonium hydrogen sulfate (50/50, v/v), which was filtered through a 0.45 µm polytetrafluoroethylene (PTFE) membrane and degassed prior to use. A Chromolith® RP-18E 100 x 4.6 mm column (Merck, Darmstadt, Germany) was used at a flow rate of 1.5 ml/min and a 20 µl injection volume. For each sample, three replicates were analyzed at room temperature. The standard curves were linear over the concentration range of 0.1-300 µg/ml.

3.3.10 In vitro drug release
The in vitro drug release assessment was performed in simulated gastric fluid (SGF) and 0.5 wt.% sodium lauryl sulfate (SLS) at pH 1.2 (sink conditions). Experiments were performed in 10 ml test tubes using a rotary mixer (Labinco, Breda, The Netherlands) at 65 rpm containing 0.8 ± 0.1 mg of drug. At specific time-points (5, 10, 15, 30, and 60 min), samples were collected and filtered through a 0.45 µm PTFE membrane prior to HPLC analysis. All release samples were measured in triplicate.

3.3.11 Scanning electron microscopy (SEM)
Morphology was assessed using SEM. Images were taken with a Philips SEM XL30 FEG instrument (Philips, Eindhoven, the Netherlands) in high vacuum mode. All samples were gold-coated to imaging at room temperature.

3.3.12 Transmission electron microscopy (TEM)
TEM images were obtained using a Philips CM200 FEG (Philips, Eindhoven, the Netherlands) microscope with a field emission gun at a 200 kV operation. Each sample was prepared at room temperature by placing a small amount of the powder on a copper TEM grid, which was coated with a lacy carbon film.
### 3.3.13 Small-angle x-ray scattering (SAXS)

SAXS patterns of powder samples placed between two pieces of Scotch® tape (3M, Diegem, Belgium) were measured in vacuum at room temperature (25 °C) with a SAXSess mc2 instrument (Anton Paar GmbH, Graz, Austria), using line-collimated CuKα radiation (0.154 nm) and an image plate detector. The scattering of Scotch® tape was subtracted as background. Background subtraction and correction for instrumental broadening was performed using the SAXSquant software (Anton Paar GmbH).

### 3.4. Results and Discussion

Table 3-1 summarizes the pharmaceutically relevant powder parameters of the non-loaded OMS materials. Tapped density measurements were performed to assess compressibility and flowability of the OMS materials. The Hausner Ratio and Carr Index values were determined using Eqn. 3-1 and 3-2, respectively, wherein \( \rho_B \) and \( \rho_T \) represent bulk and tapped density, respectively.

\[
H = \frac{\rho_T}{\rho_B}
\]

\[
C = 100 \left(1 - \frac{\rho_B}{\rho_T}\right)
\]

From a practical perspective, powders with a Carr index of at least 23 and Hausner ratio of at least 1.5 are characterized as poorly flowing powders [155, 156]. The high values obtained indicate that both materials exhibit poor compressibility and flowability properties, a challenge for tablet development. While the 0.094 g/cm³ bulk density of COK-12 is slightly higher than that of 0.092 g/cm³ for SBA-15, the resulting Carr Index of 34.29 and Hausner Ratio of 1.52 are lower, indicating a better flowing material.

<table>
<thead>
<tr>
<th>OMS</th>
<th>( \rho_{\text{bulk}} ) (g/cm³)</th>
<th>( \rho_{\text{tapped}} ) (g/cm³)</th>
<th>( \rho_{\text{true}} ) (g/cm³)</th>
<th>Carr Index</th>
<th>Hausner Ratio</th>
<th>PSD (µm)</th>
<th>D (v,0.50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBA-15</td>
<td>0.092 ± 0.006</td>
<td>0.163 ± 0.013</td>
<td>1.8 ± 0.06</td>
<td>43.8 ± 3.3</td>
<td>1.8 ± 0.1</td>
<td>13.8 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>COK-12</td>
<td>0.094 ± 0.003</td>
<td>0.144 ± 0.005</td>
<td>2.0 ± 0.03</td>
<td>34.3 ± 2.9</td>
<td>1.5 ± 0.1</td>
<td>19.0 ± 0.1</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3-1.** Bulk Powder Properties of Ordered Mesoporous Silica (OMS)

The SEM and TEM images of loaded COK-12 compressed to 0 and 480 MPa are shown in Figure 3-1. Comparable to SBA-15, the morphology of non-compressed COK-12 consists of smaller particles (<1 µm) which are covalently linked, forming larger randomly oriented conglomerates, as seen in Figure 3-1a [149]. The material subjected to 480 MPa no longer exhibits these well-defined separate submicron particles. However, Figure 3-1b reveals that the overall morphology of the larger aggregates remains intact. The TEM image in Figure 3-1c clearly displays the well-defined hexagonal honeycomb-like pore structure of the non-compressed COK-12. Following compression to 480 MPa,
Influence of Pressure

small pieces of the individual particles are broken off from the surface and no longer exhibit contrast of pores, indicating heavy damage with applied pressure, as shown in Figure 3-1d. However, intact pores can still be observed despite the extreme pressure applied.

![Figure 3-1. Micrographs of COK-12 loaded ITZ (a) SEM of non-compressed, (b) SEM after 480 MPa compression, (c) TEM of non-compressed, and (d) TEM after 480 MPa compression.](image)

The porosity and surface area obtained from the t-plot analysis of the nitrogen adsorption isotherms of both materials are listed in Table 3-2. The parent COK-12 and SBA-15 materials display very similar values for the pore volume and the specific surface area. Structural deterioration is caused by increasing pressure, as observed by the overall decrease in specific surface area and volume in both non-loaded and loaded materials. Compared to the changes in specific surface area and volume, the KJS pore diameter size is weakly affected. Cassiers et al. previously also reported similar findings [71]. While it appears that the KJS pore size diameter remains relatively unaffected, the decrease difference in pore volume and surface area support their claim in which some pores may be blocked due to partial collapse of pores and that less resistant pores completely collapse due to compression, whereas some pores still remain unaffected, as observed in our TEM analysis. The collapse of larger pores into smaller ones results in the overall micropore volume increase with pressure, while the mesopore volume decreases. No microporosity for the loaded material could be detected, which is likely due to the ITZ molecules loaded inside the micropores [97].
Table 3-2. Textural Properties of Pure and Loaded Mesoporous Silica Materials (OMS) as Determined by N\textsubscript{2} physisorption and Small-Angle X-ray Scattering (SAXS).

<table>
<thead>
<tr>
<th>OMS</th>
<th>Pressure (MPa)</th>
<th>Pore Diameter (nm)</th>
<th>Wall Thickness (nm)</th>
<th>S\textsubscript{me} (m\textsuperscript{2}/g)</th>
<th>V\textsubscript{me} (ml/g)</th>
<th>V\textsubscript{mi} (ml/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBA-15</td>
<td>0</td>
<td>8.1</td>
<td>2.9</td>
<td>618</td>
<td>1.048</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>8.1</td>
<td>2.9</td>
<td>562</td>
<td>0.920</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>8.1</td>
<td>2.9</td>
<td>621</td>
<td>0.994</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>240</td>
<td>8.1</td>
<td>2.9</td>
<td>565</td>
<td>0.840</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>360</td>
<td>8.0</td>
<td>3.0</td>
<td>529</td>
<td>0.731</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>480</td>
<td>7.8</td>
<td>3.3</td>
<td>487</td>
<td>0.618</td>
<td>0.020</td>
</tr>
<tr>
<td>COK-12</td>
<td>0</td>
<td>9.1</td>
<td>3.0</td>
<td>652</td>
<td>1.054</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>9.0</td>
<td>3.1</td>
<td>554</td>
<td>0.912</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>8.9</td>
<td>3.2</td>
<td>534</td>
<td>0.851</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>240</td>
<td>8.6</td>
<td>3.5</td>
<td>500</td>
<td>0.750</td>
<td>0.020</td>
</tr>
<tr>
<td></td>
<td>360</td>
<td>8.4</td>
<td>3.7</td>
<td>498</td>
<td>0.711</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>480</td>
<td>8.1</td>
<td>4.0</td>
<td>445</td>
<td>0.551</td>
<td>0.027</td>
</tr>
<tr>
<td>Loaded SBA-15</td>
<td>0</td>
<td>7.8</td>
<td>3.3</td>
<td>360</td>
<td>0.740</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>7.8</td>
<td>3.2</td>
<td>289</td>
<td>0.590</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>7.7</td>
<td>3.3</td>
<td>274</td>
<td>0.546</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>240</td>
<td>7.8</td>
<td>3.2</td>
<td>257</td>
<td>0.510</td>
<td>-</td>
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<tr>
<td></td>
<td>360</td>
<td>7.7</td>
<td>3.3</td>
<td>231</td>
<td>0.425</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>480</td>
<td>7.9</td>
<td>3.1</td>
<td>203</td>
<td>0.346</td>
<td>-</td>
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<tr>
<td>Loaded COK-12</td>
<td>0</td>
<td>8.7</td>
<td>3.4</td>
<td>334</td>
<td>0.664</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>8.7</td>
<td>3.4</td>
<td>296</td>
<td>0.594</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>8.6</td>
<td>3.5</td>
<td>280</td>
<td>0.564</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>240</td>
<td>8.4</td>
<td>3.7</td>
<td>256</td>
<td>0.513</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>360</td>
<td>8.2</td>
<td>3.9</td>
<td>226</td>
<td>0.421</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>480</td>
<td>8.0</td>
<td>4.0</td>
<td>203</td>
<td>0.362</td>
<td>-</td>
</tr>
</tbody>
</table>

S\textsubscript{me}, mesopore surface area; V\textsubscript{me}, mesopore volume; V\textsubscript{mi}, micropore volume.
Influence of Pressure

From the intense reflection of the (100) diffraction measured by SAXS, the unit cell ($a = 2d_{100}/\sqrt{3}$) is determined. The KJS pore diameter ($D_p$) wall was calculated using Eqn. 3-3, where $t$ represents the statistical film thickness, $p/p^*$ is the capillary condensation step on the adsorption isotherm, and the best-fit parameters of $a$, $b$, and $c$ are 1.15, 0.87, and 0.27, respectively.

Eqn. 3-3

$$p = -\frac{a}{\log\left(\frac{p}{p^*}\right)} + 2t + c$$

The wall thickness is the difference between the unit cell ($a$) and $D_p$. These results indicate that wall thickness increases with increasing compression, further supporting the claim that some pores are completely collapsing. The greater wall thickness of the non-compressed-loaded material compared to the non-loaded, is due to the itraconazole molecules depositing on the mesopore walls [97].

In comparing the resistance to compaction of loaded materials, Figure 3-2 displays SAXS results of loaded SBA-15 and COK-12 at 0, 72, and 120 MPa pressures. Neither material displays a shift in $d$-spacing. However, peak broadening is observed for SBA-15 at 72 MPa due to reduced pore ordering, distortion or pore shape, and/or a decreased domain size. Peak broadening was not observed in loaded COK-12 until 240 MPa (data not shown). The thicker wall in COK-12 and the higher condensation degree of the silicate framework determined by $^{29}$Si Magic Angle Spinning Nuclear Magnetic Resonance (MAS NMR) causes this material to be more robust [75]. No significant difference between samples compressed at the same pressure was observed based on SAXS analysis (data not shown).

![Figure 3-2. SAXS patterns of loaded SBA-15 (left) and COK-12 (right) compressed to (□) 0 MPa, (◊) 72 MPa, and (○) 120 MPa.](image)

The nitrogen adsorption-desorption isotherm differences with respect to pressure of non-loaded and loaded COK-12 at 0, 72, and 120 MPa are illustrated in Figure 3-3. The isotherms are typical type IV according to the International Union of Pure and Applied Chemistry classification for mesoporous materials. The overall decrease in volume of nitrogen adsorbed is due to itraconazole filling the pores.
Influence of Pressure

Based on the larger decrease in pore volume, the non-loaded material reveals a greater sensitivity to pressure. Elongation of the hysteresis loop at roughly 0.45 relative pressure in the region prior to condensation is observed in the compressed samples, indicating changes to the uniform pore structure due to partial and/or full pore collapse. In contrast, the loaded material maintains its overall hysteresis loop shape with only a slight decrease in volume adsorbed with increased pressure. Therefore, the drug serves as a structural support during compression. These observations are also consistent with SBA-15 findings (data not shown).

**Figure 3-3.** Nitrogen adsorption/desorption isotherms of COK-12 non-loaded (left) and loaded (right) samples compressed at (□) 0 MPa, (◊) 72 MPa, and (○) 120 MPa.

Following drug loading, the physical state of ITZ was determined using MDSC. Pure, crystalline ITZ melts at 168 °C, whereas glassy ITZ displays a glass transition at 59 °C along with two other endothermic transitions. The first is observed at 74 °C due to molecular rotational restriction and the second at 90 °C caused by a transition from an isotropic liquid to a chiral nematic mesophase [7]. Because of the state of the loaded drug, no glass transition, bulk or depressed melting temperature could be detected for either SBA-15 or COK-12, as shown in Figure 3-4a and 3-4b, confirming successful loading into the pores. Furthermore, MDSC was also used to verify that the drug molecules remain in the pores following compression at 480 MPa due to the absence of a melting peak and/or glass transition.

**Figure 3-4.** MDSC thermograms of (a) reversing heat flow and (b) total heat flow of ITZ in (i) SBA-15, (ii) COK-12, (iii) SBA-15 and compressed to 480 MPa, and (iv) COK-12 and compressed to 480 MPa.
Influence of Pressure

The drug contents of non-compressed SBA-15 and COK-12 were 19.1 ± 0.2 (wt.%) and 18.1 ± 0.2 (wt.%), respectively, as measured by HPLC. Using a manual press, these samples were then subjected to pressures of 72, 120, 240, 360, or 480 MPa. Following compression, each sample was ground with a mortar and pestle prior to the release experiments. Figure 3-5 reveals an overall decrease in drug release with increased pressure for both materials, due to reduction in pore size and volume [71]. Partial and/or total pore collapse would block the drug inside the pore system, therefore reducing drug release. Dissolution results are consistent with the SAXS findings in which SBA-15 displays greater sensitivity to compression than COK-12. Release with SBA-15 is faster than crystalline itraconazole up to 240 MPa, as seen in Figure 3-5a. In contrast, all compressed COK-12 samples resulted in a greater percent released compared to that of crystalline itraconazole in Figure 3-5b. When compared to the non-compressed, the percent release at 60 min of SBA-15 decreased approximately 39% following 480 MPa compression. At 60 min, COK-12 decreased roughly 25% following 480 MPa, due to the larger pore sizes of COK-12 before and after compression.

![Figure 3-5](image)

**Figure 3-5.** (a) Release profiles of ITZ loaded in SBA-15 and (b) COK-12 compressed at (●) 0 MPa, (○) 72 MPa, (♦) 120 MPa, (◇) 240 MPa, (■) 360 MPa, and (□) 480 MPa, and (—) crystalline ITZ in SGF + 0.5 % wt. SLS (n = 3, mean ± sd).

Microcrystalline cellulose is a standard tableting excipient often used as a filler, flow aid, and/or dry binder. Because it plastically deforms, our hypothesis is that it would aid in dissipating the compression energy and therefore, protect the silica and improve the release behavior following compression. To test this, various amounts of MCC (30, 50 and 70% (w/w) were added to the OMS prior to compression to 120 MPa. Figure 3-6a illustrates the drug release from COK-12 at each mixture before and after compression. In the presence of MCC, compression leads to a difference in drug release compared to non-compressed MCC containing COK-12. However, compared to drug release after compression of the loaded COK-12 without MCC (Figure 3-5), the release is much higher when compression was performed in the presence of MCC. Following compression, increasing the amount of MCC from 30% to 70% leads to faster release, but after 60 min, approximately 80% of ITZ was released, independent of the amount of MCC added. Similar findings were also observed with
SBA-15. These results support our hypothesis that the plastically deforming MCC displays a mechanical buffering effect that counteracts the pore collapse after compression. Full recovery of drug release could, however, not be achieved within 60 min. This was attributed to poor disintegration of the compacted particles.

Therefore, to further improve drug release, croscarmellose sodium (AC) was added to the COK-12/MCC mixture prior to compression. On the basis of its ability to swell and absorb water beyond its weight, AC was used to help break up the ground compacted particles. Samples made up of COK-12, MCC and AC were prepared in the following ratio: (COK-12/MCC/AC; w/w/w) 66.5/28.4/5.1, 47.4/47.6/5, and 28.5/66.7/4.8. The addition of AC further improved the release following compression, as shown in Figure 3-6b. The mixture of 28.5/66.7/4.8 showed no release difference before and after compression. The non-compressed sample released 79.5 ± 4.0 and 80.5 ± 3.5 at 5 and 60 min, respectively. Following compression to 120 MPa, release results are 72.2 ± 4.2 and 82.2 ± 1.1 at 5 and 60 min, respectively. Similar results were obtained for SBA-15 where no release difference following compression was achieved with the SBA-15/MCC/AC composition of 28.5/66.5/5.0. These results indicate that the role of MCC is dual. Due to plastic deformation, it can act as a mechanical buffer and dissipate the compression energy, thereby counteracting the pore collapse, which is responsible for decreased drug release. On the other hand, addition of MCC leads to compacted particles, which poorly disintegrate and need a disintegrant to obtain adequate drug release.

Figure 3-6 (a) Release profiles of itraconazole from COK-12/MCC mixtures in SGF + 0.5 % wt. SLS (n = 3, mean ± sd). The amount of MCC is 30% (■/□), 50% (◊), and 70% (●/○). Filled and empty symbols refer to compression at 0 and 120 MPa, respectively. (b) Release profiles of itraconazole from COK-12/MCC/AC MCC mixtures in SGF + 0.5 % wt. SLS (n = 3, mean ± sd). The composition of the mixtures is (COK-12/MCC/AC, w/w/w) 66.5/28.4/5.1 (■/□), 47.4/47.6/5 (◊/○), and 28.5/66.7/4.8 (●/○). Filled and empty symbols refer to compression at 0 and 120 MPa, respectively.

3.5. Conclusions
Compression of the ordered mesoporous silica materials, SBA-15 and COK-12, results in decreasing pore volume and surface area with increasing pressure. This is due to partial structural failure of some pores, outer pores completely collapsing and walls breaking off, and some pores remaining intact. The non-loaded material had less resistance to compaction, indicating that the drug molecules loaded in the
Influence of Pressure

pore system serve as a structural support and hence, buffer the impact of the applied pressure. The overall reduction in porosity results in an overall decrease in drug release. Because of its slightly thicker walls and higher condensation degree of the silicate framework, COK-12 is more resistant to compaction, as shown in the drug release profiles and the SAXS patterns. The addition of MCC before compression of drug loaded OMS materials resulted in a partial recovery of drug release due to energy dissipation as a consequence of plastic deformation of MCC. However, poor disintegration of the compacted OMS particles made the addition of a disintegrant like AC necessary to fully recover drug release.

3.6. Acknowledgements

Financial support for this study was made possible by the Flemish Government through long term funding to J.A. Martens (Methusalem). A. Aerts acknowledges the Flemish Fund for Scientific Research (FWO) for a postdoctoral fellowship. At the Physical Metallurgy and Materials Engineering Section (KU Leuven), we thank Prof. M. Seo for operating TEM and R. De Vos for performing SEM experiments.
Chapter 4

Risk assessment of premature drug release during wet granulation of ordered mesoporous silica material loaded with poorly soluble compounds itraconazole, fenofibrate, naproxen, and ibuprofen

Results described in this chapter are published in the following article:
Wet Granulation Risk Assessment

4.1 Abstract
In this study, the potential of wet granulation of ordered mesoporous silica (OMS) material was evaluated to assess the risk of premature drug release during processing and to improve the bulk powder flow properties and compactibility for the development of an immediate release oral dosage form. The poorly water-soluble model compounds, itraconazole, fenofibrate, naproxen, and ibuprofen were loaded into the model OMS, COK-12, and granulated using a polyvinylpyrrolidone (PVP) binder solution. Preliminary assessments were made with itraconazole loaded COK-12 to study the effects of the initial drug load, binder concentration, binder addition rate, and granulation temperature on premature drug release. Comparison to pure COK-12 revealed particle size enlargement and enhanced powder flow based on Carr Index and Hausner Ratio results. Following compression to 120 MPa, the compactibility of the granulated material also improved when compared to the untreated COK-12. In vitro release of itraconazole from the compressed granulated material was assessed with and without the disintegrant, croscarmellose sodium. Incorporation of 2.4 wt.% croscarmellose sodium prior to compression successfully recovered the slight release loss following compression. To assess premature drug release, developments made with itraconazole loaded COK-12 were applied to loaded fenofibrate, naproxen, and ibuprofen. Results from modulated differential scanning calorimetry (MDSC) indicated that the risk of premature drug release during wet granulation was primarily compound dependent. These findings highlight challenges in preparation for a successful manufacturing process of OMS based formulations.

4.2 Introduction
Ordered mesoporous silica (OMS) materials were originally developed with the application as molecular sieves [55]. Due to their unique pore structure, they emerged into a variety of applications prior to their evaluation as a novel drug delivery system for controlled release [63]. Shortly thereafter, their capability to enhance the release of poorly soluble drugs was also discovered [64, 65]. Mellaerts et al. first correlated increased release rate from OMS with an increase in bioavailability and demonstrated a performance comparable to that of a marketed product [149]. Due to the growing interest in this novel drug delivery technique, there have been numerous studies to aid its advancement and elucidate their mechanism of action, which are summarized in various reviews [68, 88, 107]. While these findings benefit our understanding of factors such as how the pore structure affects drug release, little is known on their manufacturability as an oral dosage form.

According to the International Union of Pure and Applied Chemistry (IUPAC), the term mesopore is given to a pore size ranging from 2 to 50 nm in diameter. Their large specific pore volume (ca. 1 cm³/g) and surface area (ca. 1000 m²/g) can accommodate high drug loads. Through simple synthesis modifications, key parameters such as pore size can easily be adjusted [46, 144]. Several studies have shown that increasing the pore diameter enhances the release rate and vice versa [47-49]. Also, due to their uniform pore size, the drug is released in a controlled manner. When exposed to
water, the adsorbed drug molecules compete for the hydrophilic silica surface and are released from the pores. So long as the pore channel is less than about 20 times the diameter of the molecular size, the drug is confined and unable to crystallize [50].

As determined by scanning electron microscopy (SEM), the OMS morphology consists of 0.2-1 µm single particles, which consist of randomly oriented blocks forming larger covalently, linked aggregates [149]. These irregularly shaped particles will cause mechanical interlocking, leading to their poor flow behavior. Van der Waals’ and electrostatic forces cause adhesion and cohesion due to their small particle size. It was shown that their low bulk density contributes to their categorization as very poor flowing material based on their high Carr Index (>32) and Hausner Ratio (>1.5) values [155-157]. While an oral dosage form is the preferred route of administration, their inadequate powder flow properties pose a critical challenge from a tableting perspective.

Due to their poor intrinsic compaction properties, a plastically deforming excipient is necessary to protect the pore structure and form strong bonds necessary for a desirable tablet [157]. However, careful consideration to their tablet manufacturing process must be made to ensure that the least amount of excipients are involved in order to maintain their potential as a high drug load carrier and thus, reducing costs and pill burden. Due to their morphological structure and poor flow, physical mixtures are not recommended due to risk of particle segregation and dose inhomogeneity. No investigation has yet been made for granulation development.

Granulation is primarily used to prepare powders for tableting and is defined as any process in which small particles are gathered into larger, permanent masses where the original particle can still be identified [128]. Granulated material results in reduced dustiness. Thus, minimizes loss and inhalation risks, improves dose content uniformity, and optimizes tablet properties. Therefore, the aim was to investigate wet granulation to assess the risk of premature drug release from the pores during processing and the potential to improve powder flow and compactibility. COK-12 was the selected model OMS material due to its thicker walls and higher degree of silica condensation, which results in its greater resistance to compression [75, 157]. Polyvinylpyrrolidone (PVP) was selected as the binding agent due to its widespread use as a binder in wet granulation.

Our hypothesis is that wet granulation is a suitable technique to improve powder flow and compactibility of OMS. However, careful considerations of the process parameters must be made to avoid premature drug release from the pores during the granulation step. Evaluation of four poorly water soluble compounds, itraconazole (ITZ), fenofibrate (FNF), naproxen (NAP), and ibuprofen (IBU) revealed that the risk of premature drug release during granulation is primarily compound dependent. Using ITZ loaded COK-12 for primary assessments, various concentrations of binder in solution, type of solvent, and flow rate addition was assessed. A correlation between improved compactibility and processing temperature was also established. Furthermore, powder flow of the agglomerated material improved based on Carr Index and Hausner Ratio results.
4.3 Materials and Methods

4.3.1 Model Compounds

Table 4-1 lists the physicochemical properties of the selected Class II compounds from the Biopharmaceutical Classification System. Itraconazole (Janssen Pharmaceutica, Beerse, Belgium) belongs to the triazole group of antifungal agents against histoplasmosis, blastomycosis, and onchomycosis [7]. Fenofibrate (Indis, Aartselaar, Belgium) improves cholesterol levels by decreasing low-density (LDL) lipoprotein and very-low-density (VLDL) lipoprotein levels while increasing high-density lipoprotein (HDL) [11]. Naproxen (Certa Ltd, Braine-l’Alleud, Belgium) and ibuprofen (Fagron NV, Waregem, Belgium) are both non-steroidal anti-inflammatory drugs.

Table 4-1. Physicochemical properties and granulation parameters of model compounds

<table>
<thead>
<tr>
<th>Structure</th>
<th>Itraconazole (ITZ)</th>
<th>Fenofibrate (FNF)</th>
<th>Naproxen (NAP)</th>
<th>Ibuprofen (IBU)</th>
</tr>
</thead>
</table>
| Molecular Weight (g/mol)
| 705.64 | 360.83 | 230.26 | 206.28 |
| Molar Volume (cm³/mol)
| 507.3 | 306.4 | 192.2 | 200.3 |
| H-Bond Donors
| 0 | 0 | 1 | 1 |
| H-Bond Acceptors
| 11 | 4 | 3 | 2 |
| Solubility<sub>water</sub> (mg/ml)<sup>b</sup>
| 1x10⁻⁹ [7] | 0.8 [158] | 0.025 [159] | 0.02 [160] |
| Solubility<sub>ethanol</sub> (mg/ml)
| 0.21<sup>c</sup> | 43 [161] | 57 [83] | 528 [83] |
| T<sub>m</sub> (°C)
| T<sub>g</sub> (°C)
| pK<sub>a</sub>
| 3.7 [97] | Neutral [164] | 4.2 [165] | 4.9 [160] |
| Initial Drug Load (wt.%) | 22.2 ± 0.3 | 23.2 ± 0.1 | 17.9 ± 0.1 | 20.5 ± 0.1 |
| Granulation Temperature (°C)
| 50 & 75 | 65 | 75 | 65 |

a) ChemSketch
b) Solubility at 25 °C
c) Internal data
4.3.2 Synthesis procedure

COK-12 was synthesized according to the procedure described by Jammaer et al. [75]. Here, 4.0 g of Pluronic P123® (BASF, Ludwigshaven, Germany) was dissolved in 107.5 g deionized water under stirring following the addition of 3.7 g citric acid monohydrate (Riedel-de Haen, Seelze, Germany) and 2.5 g trisodium citrate (UCB, Brussels, Belgium). The resulting surfactant solution was stirred for 24 h. Next, 10.4 g of sodium silicate solution (10% NaOH, 27% SiO₂, Merck, Darmstadt, Germany) was diluted with 30.0 g of water and added to the surfactant solution. The pH was measured prior to and after the sodium silicate addition using a Mettler Toledo, InLab®Expert Pro pH electrode (Zaventem, Belgium). The final mixture was stirred for 5 min at 175 rpm with a mechanical stirrer and kept at room temperature under static synthesis conditions for 24 h. The synthesized material was then filtered, dried at 80 °C and calcined in two steps: 8 h at 300 °C and 8 h at 500 °C with a 1°C/min heating rate.

4.3.3 N₂ adsorption-desorption isotherms

Nitrogen adsorption isotherms of all silica materials were determined at -196 °C using a Micrometrics Tristar II 3020-apparatus (Brussels, Belgium). Samples were pre-treated overnight at respectively, 110 °C and 250 °C for itraconazole loaded and non-loaded OMS, under nitrogen flush. The pore volume and the surface area was calculated using the t-plot method of Jaroniec and Kruk [152]. The mesopore size distribution of each sample was derived from the adsorption branch of its nitrogen isotherm using the Barret-Joyner-Halenda (BJH) model [166]. Samples were analyzed as n = 1.

4.3.4 Drug loading

All compounds were loaded into COK-12 using the incipient wetness impregnation procedure, which infuses the drug into the pores through capillary forces [65]. Loading solutions were prepared as follows: 50 mg/ml in dichloromethane (J.T. Baker, Deventer, the Netherlands) for itraconazole and fenofibrate, 100 mg/ml in dichloromethane for ibuprofen, and 50 mg/ml in acetone (CL-Chemlab NV, Zedelgem, Belgium) for naproxen. The target drug load was 20% (w/w). The damp material was then placed in a 40 °C vacuum oven (Heraeus, Liederkerke, Belgium) at a reduced pressure of 100 mbar for a minimum of 24 h to remove any residual solvent.

4.3.5 Wet granulation

Wet granulation feasibility was performed in a 10 ml beaker containing 300 mg of loaded COK-12 with a 10 mm stir bar. Samples to be analyzed for powder flow, compression, and compaction were prepared using a 50 ml beaker containing 2000 mg of loaded COK-12 with a 25 mm stir bar. All experiments were continuously stirred at 250 rpm on a stir plate, which was also used to heat the samples to the desired temperature. A specified amount of PVP K25 (BASF, Ludwigshafen, Germany) solution was added to COK-12 with a calibrated pipette every minute until the desired theoretical
concentration of PVP was achieved. The resulting sample was then placed in a 40 °C vacuum oven at a reduced pressure of 100 mbar for a minimum of 24 h.

4.3.6 Compression
A 250 ± 0.5 mg sample was poured into a 13 mm die (Perkin Elmer, Buckinghamshire, England) with a spatula immediately prior to compression. Tablets were analyzed as \( n = 3 \pm \) the standard deviation (sd). A Rodac RQPBA15 (Sittard, the Netherlands) was used to manually subject the material to a pressure of 120 MPa for 10 s, an applied pressure relevant to tableting. After compression, the tablet thickness was measured using a Lorentzen & Wettre instrument 141 type 1-1 (AB Lorentzen & Wettre, Stockholm, Sweden) and tablet hardness with a Schleuniger instrument model 2E/205 (Dr. K. Schleuniger, Zürich, Switzerland). Prior to further analysis, the resulting tablet was then ground using a mortar and pestle to compare starting powder with compressed powder.

4.3.7 Modulated differential scanning calorimetry (MDSC)
A DSC Q2000 (TA Instruments, Brussels, Belgium) was used to assess the solid state of each model compound. Each loaded 4-8 mg OMS sample was analyzed in two cycles. The first cycle was to investigate the enthalpy of melting by heating from 25 °C to above the melting temperature (T_m) at a rate of 20°C/min. During the second cycle, the glassy material was assessed by quench cooling to below the glass transition temperature (T_g) and modulating at 2°C/min heating rate with an amplitude of ±0.212 °C every 40 s to a temperature above the T_m. All experiments were performed in crimped aluminum pans (TA Instruments, Brussels, Belgium) using dry nitrogen at a flow rate of 50 ml/min. Indium was as used to calibrate the temperature and enthalpic response. Sapphire was used to calibrate the heat capacity. Analysis was performed \( n = 4 \) and \( n = 6 \) for samples showing no thermal event and a thermal event, respectively.

4.3.8 High performance liquid chromatography (HPLC) assay
Drug content and release were quantified using an HPLC system consisting of a LaChrom® L-7100 HPLC pump, an autosampler model L-7200 equipped with a 100 µl loop, a UV detector model L-7420 (Merck, Darmstadt, Germany) was set at 260 nm for itraconazole, 290 nm for fenofibrate, 270 nm for naproxen and 220 nm for ibuprofen. The peaks were integrated using an interface D-7000 and using the D-7000 HSM software (Merck, Darmstadt, Germany). A Chromolith® RP-18E 100 x 4.6 mm (Merck, Darmstadt, Germany) was the selected column. For itraconazole, the mobile phase consisted of (50/50, v/v) acetonitrile/0.01N tetrabutyl ammonium hydrogen sulfate. The selected mobile phase for fenofibrate was (80/20, v/v) methanol/50 mM sodium acetate (pH 3.5). The pH was measured using a WTW 330i pH meter (Weinheim, Germany). Both itraconazole and fenofibrate were analyzed using a 1.5 ml/min flow rate and a 20 µl injection volume. For naproxen, the mobile phase consisted of (70/30, v/v) methanol/25 mM sodium acetate (pH 3.5) and for ibuprofen, (40/60, v/v)
acetonitrile/0.01 M sodium phosphate (pH 5.5). Both naproxen and ibuprofen were analyzed using a 1 ml/min flow rate and a 10 µl injection volume. Each sample was analyzed as $n = 3 \pm \text{sd}$ at room temperature. All solvents were filtered through a 0.45 µm polytetrafluoroethylene (PTFE) membrane and degassed prior to use. All standard curves were linear over the concentration range of 0.1-150 µg/ml.

4.3.9 In vitro drug release

In vitro drug release of itraconazole was assessed in simulated gastric fluid (SGF) + 0.5 wt.% sodium lauryl sulfate (SLS) at pH 1.2. Experiments were performed in 10 ml test tubes using a rotary mixer (Labinco, Breda, the Netherlands) at 65 rpm containing 0.8 ± 0.1 mg of drug (sink conditions). At specific time-points (5, 10, 15, 30, and 60 minutes), samples were collected and filtered through a 0.45 µm PTFE membrane prior to HPLC analysis. All release samples were measured in triplicate.

4.3.10 Scanning Electron Microscopy (SEM)

The morphology was qualitatively evaluated using SEM. Images were taken with a Philips SEM XL30 FEG instrument (Philips, Eindhoven, the Netherlands) in high vacuum mode. All samples were gold-coated at room temperature prior to imaging. Each sample was analyzed as $n = 1$.

4.3.11 Tapped density

Tapped density was measured using a J. Engelsman (Ludwigshaven, Germany) jolting volumeter. The 750 µm sieved samples were analyzed after immediate removal from a 40 ºC vacuum oven at a reduced pressure of 100 mbar. Thirty-five milliliters of the untreated COK-12 or 11-14 ml of the granulated material were then poured into a 50 ml graduated cylinder. The volume of the granulated material measured was less due to sample availability. Samples were subjected to successive sets of 500, 750 and 1250 taps at 240 taps/min until a volume difference of < 2% was achieved between sets. Reported values for bulk and tapped density are the means for $n = 3 \pm \text{sd}$.

4.3.12 Viscosity

An SV-10 sensor unit (A&D Co., Japan) connected to an SV-10 Vibro Viscometer (A&D Co., Japan) was used to measure the viscosity of the binder solution. A water bath was used to heat the 50 ml sample from room temperature to 25, 50 or 75 ºC and measured every 10 s. Results were processed with the RSVisco version 1.10 software (A&D Co., Japan). Reported values are means for $n = 15 \pm \text{sd}$.

4.3.13 Stability

Samples were placed in storage conditions to investigate whether drug would displace from the mesopores during storage. ITZ loaded COK-12 treated with either pure milli-Q H2O or ethanol (EtOH) were stored in desiccators at 0%RH using phosphorous pentoxide (Acros, Geel, Belgium) in either a
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25 °C (Type B50, Memmert Analis, Schwabach, Germany) or a 60 °C oven (Type B500, Memmert Analis, Schwabach, Germany). A saturated solution of potassium iodide (RPL, Leuven, Belgium) was used to prepare the 25°C/69%RH storage conditions.

4.3.14 PVP quantification

A Hewlett Packard 8452A (Diegem, Belgium) Diode array spectrophotometer UV/Vis was used to quantitatively determine PVP by photometry from a complex of PVP and Iodine (Acros, Geel, Belgium). The standard curve was linear over the concentration range of 0-225 µg/ml. Each sample was analyzed $n = 3 \pm sd$ at 470 nm wavelength [124].

4.4 Results and Discussion

An overview of the physicochemical properties and granulation parameters are shown in Table 4-1. The model compounds were selected for their differences in molecular volume, hydrogen bond donors/acceptors, and solubility. Following drug loading and granulation, MDSC was used to determine the compound’s physical state. According to the Gibbs-Thomson equation, a molecule’s behavior is significantly altered when in a confined space. As seen in Eqn. 1-3 for open cylindrical pores of radius, $R$, the melting point depression is inversely proportional to the pore size. Successful loading and no premature drug release during granulation was confirmed when no glass transition, bulk or depressed melting point was observed. The broad endothermal event observed in some thermograms (Figures 4-1, 4-3 & 4-8) is due to the evaporation of water upon initial heating during the first DSC cycle.

PVP is a synthetic polymer that consists of a linear chain of 1-vinyl 2-pyrrolidone groups, which can vary in degree of polymerization. A binder’s ability to construct strong granules is dependent on the binder itself and its distribution in the granulate. PVP K25 was selected for its adequate viscosity, which allows it to spread more efficiently across the silica surface, thus improving homogeneity and granule strength. Another function is to form a hydrophilic film over the COK-12 surface, which improves wettability and therefore, release rate. The binder increases the particle size by joining two or more particles together through mobile liquid bridges, held by capillary and viscous forces until more permanent bonds are formed following drying or sintering [128]. This increased particle size, improves flowability and compactibility, which leads to improvements in dose uniformity and tablet properties.

The three main processes in determining wet granulation behavior are wetting and nucleation; consolidation and growth; breakage and attrition [167, 168]. These parameters need to be sufficiently understood prior to any theoretical predictions can be made on formulation properties, equipment, or operating conditions [128]. The lack of predictive behavior of the granulation process has complicated the development of suitable models, and consequently, the granulation process is often considered to require a trial-and-error approach [169]. A primary concern during wet granulation of OMS was to
achieve a balance of maintaining the OMS as dry as possible to avoid premature drug extraction yet wetting the material enough to form liquid bridges necessary for agglomeration. While H₂O is often the solvent of choice, EtOH was also investigated due to its lower boiling point of 78 °C.

4.4.1 Assessments with itraconazole loaded COK-12

The influence of binder addition rate on ITZ release was determined by adding 20, 50, or 100 µl of 5% binder solution (w/v) in H₂O to drug loaded COK-12 every min until a final concentration of 14 wt.% PVP was achieved. As seen in Figure 4-1, these samples showed no thermal event besides the evaporation of adsorbed H₂O and indicate that ITZ was not extracted from the pores during the granulation step.

![Graph](https://via.placeholder.com/150)

**Figure 4-1.** DSC thermograms of ITZ loaded COK-12 treated with 5% w/v PVP at (a) 20 µl/min, (b) 50 µl/min, (c) 100 µl/min.

Their *in vitro* release behavior before and after 120 MPa compression is shown in Figure 4-2. Prior to compression, no significant difference is observed between samples. Following compression, the release rate increases with decreasing binder addition rate. The chances of localized overwetting decrease by reducing the binder addition rate, which results in a more homogeneous and thin layer distribution of the binder liquid. The 100 µl/min addition rate resulted in excessively large agglomerates due to localized over wetting and inhomogeneous distribution of PVP. These results are consistent with previous findings in which Holm reported that inhomogeneous liquid distribution might result in the formation of over wetted lumps [170]. This was not observed with the 50 µl/min rate, which therefore was selected for all further experiments.
Wet Granulation Risk Assessment

Figure 4-2. In vitro drug release of ITZ from granulated PVP/COK-12 (13/77, w/w) prepared at (●/○) 20 µl/min, (■/□) 50 µl/min and (Δ/▲) 100 µl/min in SGF + 0.5% wt. SLS (n = 3, mean ± sd). Filled and empty symbols refer to compression at 0 and 120 MPa, respectively.

The solid-state of granulates prepared with 5% and 10% (w/v) PVP in H₂O binder solution is shown in Figure 4-3. A PVP concentration of 20% (w/w) in the granulate was prepared at room temperature by adding 50 µl/min of binding solution to 300 mg of ITZ loaded COK-12. In order to add the same amount of PVP to COK-12, 1500 µl and 750 µl of solvent need to be added for 5% and 10% w/v, respectively. Based on the enthalpy of melting, 1.52 ± 0.5% of ITZ was released during the granulation step from the sample prepared with the 5% (w/v) solution. Due to the lack of premature drug release observed with the 10% (w/v) binder solution sample, this concentration was selected for all future developmental studies.

Figure 4-3. DSC thermograms of ITZ loaded COK-12 treated with (a) 10% w/v PVP and (b) 5% w/v PVP in water binder solution.

Binder viscosity is recognized as an important parameter in controlling granulation behavior [171]. Increasing the binder concentration would increase the viscosity, reduce the spreading of binder, which could lead to localized overwetting and increase the chances of premature drug release. Therefore, increasing the binder concentration above 10% (w/v) was not investigated. Previous reports show that the viscosity of the PVP solution is a function of the PVP concentration and inversely proportional to its temperature [172]. Table 4-2 lists the measured viscosity as a function of temperature for both 1/9 (w/v) PVP/H₂O and 1/9 (w/v) PVP/EtOH. Due to the decreased viscosity of
the binder solution with increased granulation temperature, the influence of granulation temperature on tablet properties and in vitro drug release was investigated. While the PVP/EtOH binder solution results in a lower viscosity, H₂O was selected due to its more common use as a binder solvent.

Table 4-2. Viscosity of PVP binder solutions measured at various temperatures (n = 15 ± sd).

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>1/9 (w/v) PVP/H₂O</th>
<th>1/9 (w/v) PVP/Ethanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viscosity (mPa·s)</td>
<td>5.00 ± 0.01</td>
<td>4.51 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>50.57 ± 0.08</td>
<td>2.00 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>23.77 ± 0.02</td>
<td>3.40 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>75.01 ± 0.07</td>
<td>2.51 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>24.74 ± 0.13</td>
<td>1.26 ± 0.00</td>
</tr>
<tr>
<td></td>
<td>49.88 ± 0.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75.45 ± 0.18</td>
<td></td>
</tr>
</tbody>
</table>

Table 4-3 compares the tablet properties, Carr Index and Hausner Ratio results of the granulated material (1/4, w/w, PVP/COK-12) to that of the untreated COK-12. From a practical perspective, powders with a Carr Index >32 and Hausner Ratio >1.5 are characterized as very poor flowing powders [155, 156]. Regardless of granulation temperature, both materials displayed a substantial decrease in both Carr Index and Hausner Ratio values when compared to untreated COK-12. Based on these results, increasing the temperature from 50 °C to 75 °C does not appear to further improve the flow. However, increasing the granulation temperature did increase the tablet hardness. The weaker 50 °C granulated tablets are most likely a result of poor distribution of binder upon processing. Compared to the 75 °C samples, this temperature gave rise to overly large particles stemming from localized over wetting.

Table 4-3. The influence of granulation temperature and the addition of Ac-Di-Sol® (AC) on the compactibility and flow properties of 20% wt. itraconazole loaded COK-12 compared to the untreated COK-12 material granulated with PVP/H₂O (1/9, w/v) binder solution.

<table>
<thead>
<tr>
<th></th>
<th>Thickness</th>
<th>Hardness (kp)</th>
<th>Carr Index</th>
<th>Hausner Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loaded COK-12</td>
<td>2.855 ± 0.038</td>
<td>0.0 ± 0.0</td>
<td>36.7 ± 0.8</td>
<td>1.58 ± 0.02</td>
</tr>
<tr>
<td>PVP/COK-12 (1/4, w/w) @ 50°C</td>
<td>2.531 ± 0.002</td>
<td>0.0 ± 0.0</td>
<td>23.7 ± 3.6</td>
<td>1.31 ± 0.06</td>
</tr>
<tr>
<td>PVP/COK-12 (1/4, w/w) @ 75°C</td>
<td>2.354 ± 0.023</td>
<td>6.0 ± 1.7</td>
<td>25.7 ± 1.3</td>
<td>1.31 ± 0.02</td>
</tr>
<tr>
<td>PVP/COK-12/AC (24.4/73.2/2.4, w/w/w) @ 50°C</td>
<td>2.396 ± 0.055</td>
<td>2.2 ± 2.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PVP/COK-12/AC (24.4/73.2/2.4, w/w/w) @ 75°C</td>
<td>2.281 ± 0.061</td>
<td>5.3 ± 0.6</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Along with microcrystalline cellulose, the disintegrant, croscarmellose sodium, Ac-Di-Sol® (AC), has been shown to compensate for the release loss following compression of compacted OMS particles [157]. Therefore, a 2.4 wt.% of AC was added as a physical mixture prior to compression. This resulted in a slight decrease in tablet thickness for both granulation temperature samples but had less effect on the tablet hardness. For the 50 °C granulated sample, a hardness value obtained with AC ranged from 0 to 4.4 kp. AC decreased the variability of the 75 °C granulated samples which ranged from 5 to 6 kp compared to the granulate only of 4 to 7 kp. The sample granulated at 75 °C was
selected for further investigations. Due to insufficient sample, tapped density experiments necessary to calculate Carr Index and Hausner Ratio values were not measured with samples containing AC.

It has been previously reported that applying pressure to OMS results in decreased pore volume and surface area which contributes to a reduced drug release rate [157]. The changes in porosity following compression, as measured by N₂ physisorption, are shown in Table 4-4. Compared to the non-loaded COK-12, the lack of micropores detected and overall decrease in pore volume, surface area, and pore diameter is due to the successful loading of ITZ inside the micropores and along the mesopore walls [97]. Following compression to 120 MPa, the overall pore volume and surface area of COK-12 decreased. Previous results show that only a slight decrease in pore diameter following compression is observed [71, 157]. These results are consistent with only a slight change of 0.1 nm in pore diameter. Following granulation, the decrease in pore diameter from 7.5 to 7.3 nm is due to partial pore blockage of PVP. As with untreated COK-12, an overall decrease in volume and surface area is observed following compression. However, the decrease in pore diameter from 7.3 to 6.8 nm is most likely due to further spreading of PVP across the COK-12 particles upon compression and, therefore, additional pore blockage.

<table>
<thead>
<tr>
<th></th>
<th>Pore Diameter (nm)</th>
<th>Mesopore Surface Area (m²/g)</th>
<th>Mesopore Volume (cm³/g)</th>
<th>Micropore Volume (cm³/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COK-12</td>
<td>8.0</td>
<td>934</td>
<td>0.646</td>
<td>0.013</td>
</tr>
<tr>
<td>Loaded COK-12</td>
<td>7.5</td>
<td>574</td>
<td>0.352</td>
<td>-</td>
</tr>
<tr>
<td>Loaded COK-12 (120 MPa)</td>
<td>7.4</td>
<td>525</td>
<td>0.384</td>
<td>-</td>
</tr>
<tr>
<td>PVP/COK-12</td>
<td>7.3</td>
<td>473</td>
<td>0.348</td>
<td>-</td>
</tr>
<tr>
<td>PVP/COK-12 (120 MPa)</td>
<td>6.8</td>
<td>373</td>
<td>0.291</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 4-4 displays ITZ release before and after compression of the 75 °C granulated sample described in Table 4-3 with comparison to crystalline ITZ. Following compression to 120 MPa, results show a slight decrease in release up to 30 min. The addition of 2.4 wt.% AC was successful in achieving full release recovery following compression. It has been previously shown that full release recovery was achieved with a physical mixture containing 28.5% COK-12 [157]. Here, wet granulation was able to achieve this with the high COK-12 concentration of 73.2%.
Figure 4-4. Release profiles of ITZ from (●/○) 1/4, PVP/COK-12, w/w and (▲/Δ) 24.4/73.2/2.4 (w/w/w) PVP/COK-12/AC of samples granulated with 1/9, (w/v) PVP/H₂O compared to (■) crystalline ITZ in SGF + 0.5% wt. SLS (n = 3, mean ± sd). Filled and empty symbols refer to compression at 0 and 120 MPa, respectively.

A morphological comparison of granulates prepared from the optimized parameters (1/9, w/v, PVP/H₂O at 75 °C) to the untreated COK-12 are shown in Figure 4-5. COK-12 has been described as silica platelets with short channels crossing a uniform plate thickness of ca. 250 nm [76]. Compared to COK-12, wet granulation displays an overall increase in particle size and smoothing of the particle surface by filling the platelet voids with PVP. This observation correlates well with the improved powder flow shown in Table 4-3.

To investigate whether further release occurred during storage, a 20 wt.% ITZ loaded COK-12 sample was treated with either pure milli-Q H₂O or EtOH at a 50 µl/min rate for 30 min. Samples were then stored in conditions of 25°C/0%RH, 60°C/0%RH (t = 20, 60 & 120 days) and 25°C/69%RH (t = 10, 40 & 90 days). As determined by the enthalpy of fusion, no additional drug release was observed for both H₂O and EtOH treated samples for each time-point (data not shown).

Figure 4-5. SEM comparison of (a and b) COK-12 and (c and d) 1/4 (w/w) PVP/COK-12.
4.4.2 Compound comparison

Following assessments with ITZ, a compound comparison study was performed to determine whether premature drug release is compound dependent. Figure 4-6 displays the thermograms of pure COK-12 and loaded material wherein no thermal event is observed. Thus, indicating successful drug loading into the pores.

![Figure 4-6. MDSC thermograms of (a) pure, (b) ITZ, (c) NAP, (d) FNF, and (e) IBU loaded COK-12 material.](image)

The target PVP concentration for all compound comparison experiments was 25% (w/w). ITZ and NAP were granulated at 75 °C. Due to the lower T_m of IBU and FNF (Table 4-1), granulation temperature was reduced to 65 °C. The MDSC results (cycle 2) following granulation with 10% PVP binder solution with either H_2O or EtOH are shown in Figure 4-7. Regardless of binder solution used, no thermal event was observed for NAP, IBU, or FNF.

![Figure 4-7. MDSC thermograms of loaded (a) NAP, (b) FNF, and (c) IBU following granulation with either 1/9, (w/v) PVP/H_2O (solid line) or 1/9, (w/v) PVP/EtOH (dashed line).](image)

Using NAP loaded COK-12, the influence of solubility on premature drug release was investigated. The pH of 1/9 (w/v) PVP/H_2O was 3.6. NAP is a weak acid with a pK_a of 4.2 (Table 4-1) and therefore, is mainly in the un-ionized form at pH 3.6. Using sodium hydroxide (BDH, Poole England), two binder solutions of 1/9 (w/v) PVP/H_2O were prepared with the pH adjusted to either 6 or 8. Following the same granulation conditions as in the original experiment, no thermal event was observed (data not shown).
Regardless of binder solution, an endothermal event corresponding to the T\text{m}\ of ITZ (Table 4-1) was observed following granulation (Figure 4-8) during the initial heating of 20°C/min. It has been previously reported that higher drug loadings result in higher percentage release rate due to the covering of less energetically favorable sites [48]. Therefore, the effect of initial drug loading on premature drug release was investigated. ITZ granulation experiment conditions were repeated with a varying drug load of either 4.6 ± 0.0, 9.0 ± 0.0, 13.4 ± 0.1, or 15.8 ± 0.0 compared to the original of 22.2 ± 0.3 wt.% ITZ. Figure 4-8 (left) reveals that drug release did not occur with 1/9 (w/v) PVP/H\textsubscript{2}O until 9.2% loading, whereas Figure 4-8 (right) did not reveal a melting endotherm until 15.8% ITZ following granulation with 1/9 (w/v) PVP/EtOH. While results indicate that premature drug release does occur at lower drug loads for H\textsubscript{2}O as binder solution, the percent drug release was higher for EtOH as compared to H\textsubscript{2}O. Based on the enthalpy of fusion (J/g), the 15.8% drug loaded sample resulted in 3.5 ± 1.8% and 7.2 ± 1.3% and the 22.3% drug loaded sample resulted in 5.9 ± 2.0% and 15.4 ± 2.0% wt. ITZ release for H\textsubscript{2}O and EtOH binder solution, respectively.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{DSC_thermograms}
\caption{DSC thermograms of COK-12 loaded ITZ granulated with (left) 1/9 (w/v) PVP/H\textsubscript{2}O and (right) 1/9 (w/v) PVP/EtOH with initial wt.% ITZ loading of (i) 4.6, (ii) 9.2, (iii) 13.4, (iv) 15.8, and (22.2).}
\end{figure}

In the case of ITZ granulation experiments, the resulting thermal event was attributed to the API crystalline form. Glassy ITZ is identified by its T\text{g} of 59°C and two other endothermic transitions at 75°C and 90°C [7]. These were not observed, indicating that ITZ crystallized following premature extraction. COK-12 exhibits a higher affinity for H\textsubscript{2}O than EtOH, which could explain the premature drug release observed at lower initial drug loads (Figure 4-8). ITZ displayed the most pronounced premature drug release likely due to its large molar volume and absence of hydrogen-bond donors (Table 4-1). While slight premature drug release did occur, the granules still exhibited an enhanced release rate when compared to the crystalline form (Figure 4-4) and comparable to the loaded non-compressed material where premature drug release had not yet occurred. Furthermore, samples were stable following storage conditions.

Based on these results, a compound’s solubility in the binder solution can be eliminated as a factor contributing to premature drug release, as previously described with NAP. Also in example of ITZ, which has the lowest solubility in EtOH (Table 4-1), yet it was the ITZ sample granulated with 1/9 (w/v) PVP/EtOH that displayed the greatest amount of premature drug release. One explanation
for the absence of drug release during processing could be attributed to the carboxyl group of IBU and NAP binding to the silanol groups on the COK-12 surface.

There is currently a lack in understanding regarding the factors which affect drug loading efficiency, the compounds position in the pores, and release following different loading methods [68]. Mellaerts et al. investigated three OMS loading procedures on itraconazole and ibuprofen and concluded that the effectiveness of drug loading is strongly compound dependent [97]. This, in turn, is also expected to affect the chances of premature drug release and as shown here, is also compound dependent.

4.5 Conclusions
It is demonstrated that wet granulation can successfully improve the powder flow and compactibility by increasing the particle size, bulk density, and smoothing of the surface of COK-12 ordered mesoporous silica material. To achieve this, the OMS cannot be overly wetted due to the possibility of the molecule prematurely extracting from the pores. On the other hand, the OMS must be moistened enough to form liquid bridges necessary for agglomeration. The risk of premature drug extracting during granulation is also compound dependent. Decreasing the initial drug load of the material and binder solution addition rate or increasing the granulation temperature and binder solution concentration can reduce this risk.

The optimized parameters developed with ITZ loaded COK-12 reveal that the loss in the drug release rate following 120 MPa compression was fully recovered by incorporating croscarmellose sodium to break apart the compacted granulates. This resulted in no release difference before and after compression. These results elucidate important parameters to consider for preparation of a successful scaled-up manufacturing process of a dosage form based on ordered mesoporous silica carrier material.

4.6 Acknowledgements
Financial support for this study was made possible by the Flemish Government through long-term funding to J.A. Martens (Methusalem). Floris Backhuijs acknowledges the Erasmus scholarship of Ministerie van Onderwijs, Cultuur en Wetenschap (MOCW), Flanders. We would like to thank FORMAC Pharmaceuticals NV for use of their N₂ physisorption instrument.
Chapter 5

Agglomeration of mesoporous silica prepared by melt and steam granulation. Part I:
A comparison between ordered and disordered mesoporous silica

Results described in this chapter are in press as the following article:
Vialpando M, Albertini, B, Passerini, N, Bergers, D, Rombaut P, Martens JA, Van den Mooter G.
Agglomeration of mesoporous silica prepared by melt and steam granulation. Part I: A comparison
between ordered and disordered mesoporous silica. DOI:10.1002/jps.23700
Ordered and Disordered Mesopore Comparison

5.1 Abstract
The objective of this study was to compare agglomeration by melt and steam granulation of ordered, COK-12, and disordered, Syloid® 244 FP (244), mesoporous silica material. Poloxamer 188 (P188) and Polyvinylpyrrolidone K25 were chosen as binders for melt and steam granulation, respectively. The poorly water-soluble compound, itraconazole (ITZ) was selected for the development of an immediate release oral dosage form. Steam granulation resulted in the largest granules, however the slowest in vitro release rate. Compression behavior and tablet properties of steam-granulated material prepared with COK-12 and 244 were similar, while 244 melt-granulated material performed slightly better. As determined by x-ray powder diffraction (XRPD), melt granulation resulted in the most ITZ to extract from the pores during processing. However, enhanced release rate was still maintained when compared to the crystalline form. Moreover, no additional drug extraction was observed following 6 months storage at 25°C/60%RH and 40°C/75%RH. P188 diffraction peaks are present in 244 melt-granulated material, but disappeared due to degradation following 1 week storage in 40°C/75%RH conditions. Moreover, DSC analysis indicated that degradation of P188 already occurs during the granulation process itself. Based on these results, steam granulation with PVP is the preferred method over melt granulation with P188.

5.2 Introduction
There is growing awareness in drug development regarding the number of new chemical entities (NCE) that exhibit poor aqueous solubility [146, 173]. Low solubility leads to decreased therapeutic efficacy due to incomplete and/or variable drug absorption, when oral absorption is limited by solubility dissolution rate. It was recently reported that 54% of NCE now belong to Class II in the Biopharmaceutics Classification System (BCS), where oral absorption is limited by solubility [2]. It is therefore necessary for scientists to continue to search for new and creative approaches to overcome this critical drug development challenge. One quickly emerging technique involves use of mesoporous silica as a carrier for the enhanced release of poorly water-soluble drugs [43, 68, 88].

As defined by the International Union of Pure and Applied Chemistry (IUPAC), mesopore sizes correspond to the range of 2-50 nm. The unique honeycomb-like structure of ordered mesoporous silica (OMS) is comprised of a high pore volume and large specific surface area of roughly 1 cm³/g and 800 m²/g, respectively. This provides for high drug loading capacity and potential for drug adsorption [103]. While disordered silica is a common pharmaceutical excipient, there is a gaining interest in its role as a drug delivery carrier [87, 119, 174]. This commercially available material is accessible in a wide range of pore sizes and bulk powder properties. However, the uniform pore size of the OMS structure allows for better control of the drug loading and release kinetics [49]. Moreover, theoretical prediction models are mainly developed for simple pore geometries such as the OMS cylindrical design and therefore, more effective in correlating experimental results [98]. Despite
the number of studies that investigate OMS for enhanced release, few compare the physicochemical differences between ordered and disordered mesoporous silica [87, 174].

Based on improved patient compliance, safety and lower production costs, an oral dosage form is the preferred route of administration. However, characteristics of mesoporous silica create a major challenge for tableting. Their hygroscopic nature, low bulk density, small particle size, and irregular particle shape are drawbacks in contributing to their poor powder flow behavior [157]. One solution to overcome these issues is to agglomerate particles through granulation. This technique is commonly used to prepare powders for tableting and is defined as any process in which small particles are gathered into larger, permanent masses where the original particle can still be identified [128]. The classic granulation approach, wet granulation, was recently reported to improve the flow properties and tablet behavior of OMS material, COK-12 [4]. However, it was also demonstrated that when COK-12 became overly wetted, the risk of extracting the molecule from the pores increased, referred to as premature drug release (PDR). Should this occur during processing, the compound could crystallize into its stable but lower soluble form.

The usefulness of granulation techniques able to reduce or avoid the employment of water during the process is considered. Because applied pressure to OMS material can damage the pore structure and in turn, hinder the release rate, dry granulation was not considered [157]. Therefore, the objective of this study was to evaluate melt (MG) and steam (SG) granulation as approaches to avoid or minimize the amount of solvent used during granulation to reduce the risk of premature drug release. Our hypothesis is that agglomeration with steam or by melting is a more suitable method than the traditional wet granulation for the processing of mesoporous silica. Steam granulation involves the use of steam as granulating medium instead of liquid water. Previous studies show that, compared to traditional wet granulation, steam granulation results in a 50% reduction of water and reduced processing time [175, 176]. Melt granulation is a process in which pharmaceutical powders are efficiently agglomerated by the use of a substance, which melts at relatively low temperature (50-80°C). The molten substance acts like a liquid binder and the dry granules are obtained as the molten binder solidifies upon cooling [139, 177]. In this paper, we evaluate the granulation behavior and physicochemical properties of granules from ordered and disordered mesoporous silica: COK-12 and Syloid® 244 (244), respectively, using melt and steam granulation. In a follow-up study (chapter 6), we assess steam granulation process parameters using a factorial design approach. Previous results involving four poorly water-soluble compounds reveal that the risk PDR from COK-12 was compound dependent [4]. Because itraconazole (ITZ) exhibited the greatest PDR, it was again selected as the poorly soluble model compound for this study. Due to its low melting temperature and surface activity, Poloxamer 188 (P188) was selected as the melt granulation binder. Polyvinylpyrrolidone K25 (PVP) was chosen for steam granulation due to its widespread use as a wet granulation binder and previous results obtained with COK-12 in chapter 4 [4].
Ordered and Disordered Mesopore Comparison

5.3 Materials and Methods

5.3.1 Mesoporous silica
Disordered 244 FP was kindly provided by Grace Davison & Co. (Lokeren, Belgium) and used as received. COK-12 was synthesized according to the procedure described by Jammaer et al. [75]. Here, 4.0 g of Pluronic P123® (BASF, Ludwigshaven, Germany) was dissolved in 107.5 g deionized water under stirring following the addition of 3.7 g citric acid monohydrate (Riedel-de Haen, Seelze, Germany) and 2.5 g trisodium citrate (UCB, Brussels, Belgium). The resulting surfactant solution was stirred for 24 h. Next, 10.4 g of sodium silicate solution (10% NaOH, 27% SiO₂, Merck, Darmstadt, Germany) was diluted with 30.0 g of water and added to the surfactant solution. The pH was measured prior to and after the sodium silicate addition using a Mettler Toledo, InLab® Expert Pro pH electrode (Zaventem, Belgium). The final mixture was stirred for 5 min at 175 rpm with a mechanical stirrer and kept at room temperature under static synthesis conditions for 24 h. The synthesized material was then filtered, dried at 80 °C and calcined in two steps: 8 hours at 300 °C and 8 h at 500 °C with a 1°C/min heating rate.

5.3.2 Excipients
Microcrystalline cellulose (MCC; Avicel® PH 101) and croscarmellose sodium (AC; Ac-Di-Sol®) were purchased from FMC (Little Island, Cork, Ireland). Micronized Poloxamer 188 (P188; Lutrol® micro 68) and Polyvinylpyrrolidone K25 (PVP; Kollidon® 25) were obtained from BASF (Ludwigshafen, Germany) and magnesium stearate from Sigma-Aldrich (Diegem, Belgium). Lactose 200 (Pharmatose® 200mesh) was purchased from DFE pharma (Goch, Germany).

5.3.3 Drug Loading
A target drug load of 20% (w/w) was prepared using a 50 mg/ml solution of itraconazole (Janssen Pharmaceutica, Beerse, Belgium) in dichloromethane (J.T. Baker, Deventer, The Netherlands). Itraconazole was loaded using the incipient wetness procedure [65]. The damp material was then placed in a 40 °C vacuum oven (Heraeus, Liederkerke, Belgium) at a reduced pressure of 100 mbar for a minimum of 24 h to remove any residual solvent. The actual drug loading obtained was 17.3 ± 0.9 and 17.9 ± 0.1% (w/w) for 244 and COK-12, respectively.

5.3.4 Granulation
Both melt and steam-granulated material were prepared in Rotolab® (Zanchetta, Lucca, Italy) laboratory scale high-shear mixer in 100 g batches, which contains a hermetically sealed 2 liter thermostatic vessel equipped with a three-blade impeller and product temperature probe. A tiny flux of air was injected into the bowl to avoid any entrapping of solid. Prior to COK-12 granulation, process development and formulation screening studies were performed using disordered silica gel, Syloid® 244 (244).
5.3.4.1 Steam granulation

As previously described by Cavallari et al., steam was produced in a small electric boiler that was calibrated at 3.5 atm \([176]\). An enclosed polyethylene bottle (Thermo Scientific, Erembodegem-Aalst) was attached to the thermostated line to avoid droplets from feeding into the vessel. During agglomeration, the vessel was kept at a constant 70 °C to avoid excess condensation. The steam was introduced through a 6x4 mm Rilsan® tube (Arkema, Pennsylvania, USA), which was located 5 mm above the impeller. Each actuation supplied a steady flow of 0.82 g/sec for 5 s on and 30 s off. Thirty actuations were necessary to introduce a target amount of 80 g steam to the powder due to condensed steam collected in the polyethylene bottle. To dry the steam-granulated material, a vacuum (25-40 mbar) was applied for 30 min to the vessel while continuously tilting. Granules were then placed in a 40 °C oven (Friocell; MMM Medcenter, Milano, Italy) for at least 24 h. The phases and main process parameters are summarized in Table 5-1.

Table 5-1. Overview of granulation parameters for melt (MG) and steam (SG) granulation.

<table>
<thead>
<tr>
<th>Step</th>
<th>Time (min)</th>
<th>Impeller (rpm)</th>
<th>Jacket Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MG</td>
<td>SG</td>
<td>MG</td>
</tr>
<tr>
<td>Mixing</td>
<td>10</td>
<td>10</td>
<td>120</td>
</tr>
<tr>
<td>Granulation</td>
<td>25</td>
<td>21.5(^a)</td>
<td>&lt; 400</td>
</tr>
<tr>
<td>Drying</td>
<td>-</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Cooling</td>
<td>10</td>
<td>-</td>
<td>120(^c)</td>
</tr>
</tbody>
</table>

\(^a\)steam added 5 s every 35 sec; \(^b\)10 s on every 20 s; \(^c\)10 s every 50 s

5.3.4.2 Melt granulation

The melt-granulated material was preparing using the *in situ* procedure. The powders (silica, P188 and MCC) were mixed for 10 min, using an impeller speed of 120 rpm. The heating jacket was then heated up to 85 °C and the impeller speed was increased up to 400 rpm to utilize shear forces as an aid in melting the P188. During this granulation phase, the target product temperature was set to 62 °C and maintained for at least 5 min to ensure thorough distribution of P188, which melts at 52 °C \([139]\). After 25 min, the granulation end point was reached. Finally the cooling phase was performed utilizing the bowl tilt system and setting an automatic impeller cycle at 120 rpm for 10 min. The phases and the main process parameters are summarized in Table 5-1. Detailed granulation parameters for the granule formulations selected for development and batch reproducibility are provided in Table 5-2.
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Table 5.2. COK-12 and 244 melt granulation parameters of formulations selected for detailed analysis and reproducibility assessment.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Impeller Speed (rpm)</th>
<th>Jacket Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Silica/Poloxamer 188/Microcrystalline Cellulose (w/w/w)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/3/1 (n=1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>125</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>200</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>300</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>300</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>300</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>350</td>
<td>85</td>
</tr>
<tr>
<td>5/3.5/1.5 (n=1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>125</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>200</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>300</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>300</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>300</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>350</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>400</td>
<td>85</td>
</tr>
<tr>
<td>67.5/27.5/5 (n=3)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.5</td>
<td>125</td>
<td>80</td>
</tr>
<tr>
<td>7.5</td>
<td>150</td>
<td>80</td>
</tr>
<tr>
<td>7.5</td>
<td>175</td>
<td>85</td>
</tr>
<tr>
<td>7.5</td>
<td>200</td>
<td>85</td>
</tr>
<tr>
<td>3.75</td>
<td>250</td>
<td>90</td>
</tr>
<tr>
<td>7.5</td>
<td>350</td>
<td>90</td>
</tr>
<tr>
<td>3.75</td>
<td>350</td>
<td>90</td>
</tr>
</tbody>
</table>

*244 only

5.3.5 X-ray powder diffraction (XRPD)

The solid state of ITZ in melt and steam-granulated samples was determined by XRPD in reflection mode using a X’Pert PRO diffractometer (PANalytical, Almelo, The Netherlands). To investigate relative crystallinity, samples were measured at room temperature by scanning from 10 to 30 °2θ with a 0.017° step size every 400 s using CuKα radiation (0.154 nm). The area under the curve (AUC) obtained from the 17.5°, 18°, 20.5° and 27° 2θ peaks were selected to estimate the relative crystallinity by comparing the AUC values of crystalline ITZ to the granulated material using the X’Pert High Score Plus version 2.2a (PANalytical) software. Reported values are the means for n = 3 ± sd.

5.3.6 Small angle x-ray scattering (SAXS)

SAXS was used to evaluate the COK-12 unit cell dimensions before and after granulation. Powder samples were placed in a capillary and measured in vacuum at room temperature with a SAXSess mc2
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instrument (Anton Paar GmbH, Graz, Austria) using line-collimated CuKα radiation (0.154 nm) and an image plate detector. Background subtraction and correction for instrumental broadening were performed using the SAXSquant software (Anton Paar GmbH).

5.3.7 Electron Microscopy

5.3.7.1 Scanning Electron Microscopy
The morphology was qualitatively evaluated using scanning electron microscopy (SEM). Images were taken with a Philips SEM XL30 FEG instrument (Philips, Eindhoven, The Netherlands) in high vacuum mode. All samples were gold-coated at room temperature prior to imaging.

5.3.7.2 Transmission Electron Microscopy
Transmission electron microscopy (TEM) images were obtained using a Philips CM200 FEG (Philips, Eindhoven, The Netherlands) microscope with a field emission gun operating at 200 kV. Each sample was prepared at room temperature by placing a small amount of powder on a copper TEM grid, which was coated with a lacey carbon film.

5.3.8 High Performance Liquid Chromatography
Drug content and release were quantified using an HPLC system consisting of a LaChrom® L-7100 HPLC pump and an auto sampler model L-7200 equipped with a 100 µl loop. The UV detector model L-7420 (Merck, Darmstadt, Germany) was set to 260 nm. Peaks were integrated using an interface D-7000 and using the D-7000 HSM software (Merck, Darmstadt, Germany). The mobile phase consisted of (50/50, v/v) acetonitrile/0.01N tetrabutyl ammonium hydrogen sulfate using a 1.5 ml/min flow rate and a 20 µl injection volume through a Chromolith® RP-18E 100 x 4.6 mm (Merck, Darmstadt, Germany) column. All solvents were filtered through a 0.45 µm polytetrafluoroethylene (PTFE) membrane and degassed prior to use. Each sample was analyzed (n = 3 ± sd) at room temperature and all standard curves were linear over the concentration range of 0.1-150 µg/ml.

5.3.9 N₂ adsorption-desorption isotherms
Nitrogen isotherms were determined at -196 °C with a Micrometrics Tristar II 3020-apparatus (Brussels, Belgium). Prior to analysis, samples were pre-treated overnight under nitrogen flush at 40 °C and 110 °C for granulated and loaded mesoporous silica, respectively. Pore volume and surface area were determined using the t-plot method [152]. The pore size distribution was derived from the adsorption branch of its nitrogen isotherm using the Barret-Joyner-Halenda (BJH) model [166].

5.3.10 Particle size by laser diffraction
The Sympatec® (Clausthal-Zellerfeld, Germany) RODOS instrument was used to measure the primary particle size of the granules by laser diffraction using the Fraunhofer model. Results were
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analyzed using WINDOX 5 version 5.7.2.0 software with range combination module. Each sample was measured in duplicate.

5.3.11 Powder flow
Carr Index values were determined from tapped density results obtained using an Erweka D-63150 (Heusenstamm, Germany) jolting volumeter. Samples were analyzed following removal from a 40 °C oven (Friocell; MMM Medcenter, Milano, Italy) and the loss on drying (Top Ray 160; Bel Engineers, Monza, Italy) was measured immediately prior to testing to ensure the water content was less than 2%. Fifty milliliters of powder was analyzed in a 100 ml graduated cylinder. Samples were subjected to successive sets of 500, 750 and 1250 taps at 250 taps/min until a volume difference of less than 2% was achieved between sets. Reported values are the means for \( n = 5 \pm s.d. \)

Flow function curves were obtained using the Brookfield® Powder Flow Tester (Harlow, England), which measures the major principal consolidation stress as a function of unconfined yield failure strength. Samples were filled into the 230 cm\(^3\) trough immediately following removal from a 40 °C oven. Results are from \( n = 1 \) for COK-12 and melt-granulated material. Due to the amount of volume needed for flow function measurements, not all granules could be analyzed. All others samples were measured as \( n = 3 \) and results were evaluated using the Powder Flow Pro software version 1.2.

5.3.12 Stability
COK-12 and 244 melt-granulated materials were stored in desiccators at 25°C/60%RH (Type B50, Analis, Gent, Belgium) and 40°C/75%RH (ICH 256, Analis) using a saturated salt solution of sodium bromide (Merck; Darmstadt, Germany) and sodium chloride (Sigma-Aldrich, Steinheim, Germany), respectively. In vitro release was assessed at \( t = 0 \) and 6 months. At specific time-points of \( t = 1 \) week, 1 month, 3 month and 6 months, samples were analyzed by XRPD to determine the relative percent crystallinity. The stability of pure poloxamer 188 (P188) was evaluated after storage for 1 week at 40°C/75%RH.

5.3.13 Differential Scanning Calorimetry (DSC)
The solid state of Poloxamer 188 and melt-granulated material was assessed before and after 40°C/75%RH storage conditions using a DSC Q2000 (TA instruments, Brussels, Belgium) by heating from 25 °C to 80 °C at a rate of 20°C/min. All experiments were performed in aluminum pans (TA Instruments) using dry nitrogen at a flow rate of 50 ml/min. Indium was as used to calibrate the temperature and enthalpic response. Analysis was performed in triplicate for each sample.

5.3.14 He Pycnometry
A Beckman model 930 (Suarlee, Belgium) helium pycnometer was used to measure true particle density. Samples were analyzed after immediate removal from a 40 °C vacuum oven (Heraeus,
Liederkerke, Belgium) at a reduced pressure of 100 mbar. The reported density value is the mean of $n = 3 \pm$ standard deviation (sd).

5.3.15 Tableting
Granulates and physical mixtures containing 10% wt. Ac-Di-Sol® (AC) were manually filled into a 7 mm die Korsch single-punch tablet press (Berlin, Germany) using a vibrating feeder. The die was lubricated using 0.05% (w/v) magnesium stearate in acetone (Acros, Geel, Belgium). A W+W electronic signal memory recorder (Basel, Switzerland) was used to record the measurement and data was processed with in-house developed software. Tablet weights were adjusted to contain 14 ± 0.14 mg ITZ. After compression, tablet thickness was determined using a Lorentzen & Wettre instrument 141 type 1-1 (AB Lorentzen & Wettre, Stockholm, Sweden) and tablet hardness with a Schleuniger 6D tablet tester (Dr. K. Schleuniger, Zürich, Switzerland). Reported values are the means of $n = 6 \pm$ sd. A Rodac RQPBA15 (Sittard, The Netherlands) was used to compress the pure silica to 72 MPa for 10 s. The resulting sample was then ground using a mortar and pestle prior to further analysis.

5.3.16 In Vitro Drug Release
Experiments were performed in 500 ml of simulated gastric fluid (SGF) + 0.5% wt. sodium lauryl sulfate (SLS) at 37 °C using an SR8 Plus dissolution apparatus (Hanson Research, Oosterhout, The Netherlands) containing a rotating paddle set to 100 rpm. At specific time-points, 4 ml samples were collected and filtered through a 0.45 µm PTFE membrane prior to HPLC analysis. Four milliliters of fresh pre-warmed (37 °C) release medium was then added. Each sample was analyzed as $n = 3 \pm$ sd.

5.3.17 Statistical Analysis
A 2-tailed unpaired t-test was used to evaluate differences in density, powder flow and tablet properties between 244 and COK-12 starting and granulated material. Results were evaluated using Office Excel 2007 and considered significant when $p < 0.05$.

6.3.5 Results and Discussion
5.4.1 Granulation process
Evaluation of process parameters and formulation screening studies were investigated with 244. An overview and comparison between the selected melt and steam granulation process parameters are described in Table 5-1. Detailed melt granulation process parameters for the selected formulations for development and repeatability are provided in Table 5-2. The steam granulation process was more straightforward in that 3, 10, and 17 steam actuations were administered during a rotation impeller speed of 120, 150, and 180 rpm, respectively. Also, gentler processing conditions were maintained when compared to the melt experiments, albeit with a longer processing time. The formulation
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containing 6/3/1 (244/PVP/MCC, w/w/w) was selected for COK-12 granulation and the actual amount of steam administered was 88 g and 78 g for 244 and COK-12, respectively. For melt granulated material, the formulations containing 6/3/1 and 5/3.5/1.5 (244/P188/MCC, w/w/w) were selected for COK-12 granulation based on their physicochemical properties, discussed in later sections. Good reproducibility was observed with both melt and steam granulation. The reproducibility results for melt-granulated samples are listed in Table 5-3.

Table 5-3. Repeatability results of melt granulated material containing 67.5/27.5/5 (244/P188/MCC, w/w/w). Results are the average of n = replicates ± standard deviation (sd).

<table>
<thead>
<tr>
<th>Replicate</th>
<th>Granule Size Fraction &gt; 10 µm (n=2)</th>
<th>Bulk Density ± sd (cm³/g) (n=5)</th>
<th>Carr Index ± sd (n=5)</th>
<th>Crystallinity ± sd (%) (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.25</td>
<td>0.16 ± 0.01</td>
<td>20.25 ± 2.40</td>
<td>6.0 ± 0.3</td>
</tr>
<tr>
<td>2</td>
<td>11.09</td>
<td>0.16 ± 0.00</td>
<td>20.80 ± 2.17</td>
<td>5.1 ± 0.6</td>
</tr>
<tr>
<td>3</td>
<td>12.13</td>
<td>0.16 ± 0.01</td>
<td>23.00 ± 1.00</td>
<td>4.4 ± 0.4</td>
</tr>
<tr>
<td>Average</td>
<td>11.80</td>
<td>0.16</td>
<td>21.35</td>
<td>5.2</td>
</tr>
<tr>
<td>SD</td>
<td>0.60</td>
<td>0.00</td>
<td>1.46</td>
<td>0.8</td>
</tr>
<tr>
<td>%RSD</td>
<td>5.40</td>
<td>1.45</td>
<td>6.82</td>
<td>15.5</td>
</tr>
</tbody>
</table>

Because the D₅₀ value of 244 starting material is roughly 3 µm (Grace Davison specifications), the fraction of granules > 10 µm was selected to determine the extent of particle size enlargement, as measured by laser diffraction. Due to precision of the method, the average of two replicates is reported. Detailed discussion regarding steam granulation reproducibility is provided in chapter 6.

Figure 5-1. TEM micrographs of (a) 244, (c) COK-12; SEM micrographs of (b) 244, (c) MG: 244/P188/MCC (d) SG: 244/PVP/MCC (f) COK-12, (g) MG: COK-12/P188/MCC (d) SG: COK-12/PVP/MCC. Granulate compositions are 6/3/1, w/w/w.
The morphological differences between 244 and COK-12 are illustrated in Figure 5-1. The TEM image of 244 (Figure 5-1a) reveals their disordered pore network, which varies in pore size. As observed in Figure 5-1e, TEM results of COK-12 clearly display parallel and cylindrical pores of uniform size. The SEM micrographs illustrate the external morphology of the silica material, melt and steam granulates consisting of silica/binder/MCC (6/3/1, w/w/w). In comparing Figure 5-1b and 5-1f, 244 exhibits a much smaller particle size compared to COK-12, which is also confirmed by laser diffraction in Figure 5-2. However, COK-12 is made up of smaller particles, which are covalently linked to form a larger conglomerated unit. Based on these images, it appears that the COK-12 particle size did not greatly increase following granulation (Figures 5-1g and 5-1h). However, filling of the voids within these smaller particles is clearly observed, which contributes to the increase in bulk density (Table 5-4). While melt-granulated material prepared from 244 displays an increase in particle size (Figures 5-1c and 5-1d), this is mainly due to MCC, as shown from the bimodal particle size distribution in Figure 5-2. Unlike 244 granules, COK-12 resulted in a unimodal distribution. The largest granules were obtained by steam granulation in both 244 and COK-12 samples, based on the samples prepared with 30 wt.% binder.

Figure 5-2. Particle size distribution of MCC, silica starting material, and granules prepared with 244 (left) and COK-12 (right). Granule compositions expressed as silica/binder/MCC (w/w/w).

While the silica walls are amorphous, periodic variations in electron density of OMS give rise to diffraction patterns. Therefore, SAXS was used to determine whether damage to the unit cell occurred following granulation (data not shown). Compared to COK-12 starting material, no peak shift or broadening was observed following melt or steam granulation and the unit cell remained at 12.5 nm. Due to the disordered pore network, 244 was not analyzed by SAXS.

5.4.2 Flow properties

Compared to loaded COK-12, loaded 244 resulted in an overall lower Carr Index, indicating better flow behavior (Table 5-4). For each sample type (e.g, MG, SG), the bulk density and Carr Index results between 244 and COK-12 were considered statistically significant. Upon pouring of COK-12 for tapped density experiments, it is likely that mechanical interlocking caused by the irregular shape of COK-12 leads to more voids than from pouring of the more spherical 244. Following tapping, there
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is a greater reduction in volume, which leads to the higher Carr Index value of loaded COK-12. Following granulation, the bulk density is mainly increased from filling of these voids (Figures 5-1 and 5-2), resulting in the decreased Carr Index value. The bimodal distribution of granules prepared with 244 (Figure 5-2) result in better packing efficiency in the cylinder, leading to the higher bulk density for melt and steam-granulated material. Suzuki et al. reported similar results in that inter-particle friction of irregularly shaped particles was much stronger than for more spherical particles. It was also shown that void fraction decreases with increasing particle size distribution [178].

Table 5-4. Textural and bulk powder properties of ITZ loaded 244 and COK-12, steam (SG) and melt (MG) granulated material.

<table>
<thead>
<tr>
<th></th>
<th>$\rho_{\text{bulk}} \pm \text{sd}$ (g/cm$^3$)</th>
<th>Carr Index $\pm \text{sd}$</th>
<th>$S_{\text{me}}$ (m$^2$/g)</th>
<th>$V_{\text{me}}$ (cm$^3$/g)</th>
<th>$D_{p}$ (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loaded 244</td>
<td>0.07 ± 0.00</td>
<td>27.8 ± 1.9</td>
<td>207</td>
<td>0.90</td>
<td>21.8</td>
</tr>
<tr>
<td>SG: 244/PVP/MCC, 6/3/1</td>
<td>0.38 ± 0.00</td>
<td>16.7 ± 1.2</td>
<td>92</td>
<td>0.36</td>
<td>17.1</td>
</tr>
<tr>
<td>MG: 244/P188/MCC, 6/3/1</td>
<td>0.20 ± 0.00</td>
<td>16.1 ± 1.9</td>
<td>129</td>
<td>0.65</td>
<td>23.4</td>
</tr>
<tr>
<td>MG: 244/P188/MCC, 5/3.5/1.5</td>
<td>0.24 ± 0.00</td>
<td>12.8 ± 1.0</td>
<td>86</td>
<td>0.45</td>
<td>23.0</td>
</tr>
<tr>
<td>Loaded COK-12</td>
<td>0.10 ± 0.00</td>
<td>36.7 ± 0.8</td>
<td>334</td>
<td>0.66</td>
<td>8.1</td>
</tr>
<tr>
<td>SG: COK-12/PVP/MCC, 6/3/1</td>
<td>0.18 ± 0.00</td>
<td>30.0 ± 0.0</td>
<td>158</td>
<td>0.31</td>
<td>7.2</td>
</tr>
<tr>
<td>MG: COK-12/P188/MCC, 6/3/1</td>
<td>0.16 ± 0.00</td>
<td>26.3 ± 2.5</td>
<td>84</td>
<td>0.18</td>
<td>5.9</td>
</tr>
<tr>
<td>MG: COK-12/P188/MCC, 5/3.5/1.5</td>
<td>0.18 ± 0.00</td>
<td>27.3 ± 2.1</td>
<td>39</td>
<td>0.09</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Bulk density ($\rho_{\text{bulk}}$), Mesopore surface area ($S_{\text{me}}$), Mesopore volume ($V_{\text{me}}$), Pore diameter ($D_{p}$) Granule compositions expressed at w/w/w.

Because powder flow is influenced by many factors such as bulk density, particle size, size distribution, shape, moisture content etc., inconsistencies between methods are known to occur [179]. In the present study, we observed that flowability determined from powder rheology measurements was opposite from that obtained from tapped density measurements (Figure 5-3). The flow function test determines the yield limit by measuring the consolidation stress followed by the failure strength. The yield limit represents the shear stress, which is required to initiate flow (failure) as a function of normal stress. When shear forces are exerted on COK-12, the particles will most likely rearrange to fill their voids and thus, initiate flow at lower stresses. Because the voids are mostly filled in COK-12 granules, more stress is needed to initiate flow. Therefore based on the flow function results, COK-12 granules result in poorer flow properties than loaded COK-12 itself. In the case of 244 granules, more efficient packing is achieved based on the bimodal and hence, longer distribution as shown in Figure 5-2, resulting in COK-12 granules exhibiting a higher flow function slope. To investigate the inconsistency between powder flow results, the well-characterized poor and good flowing excipients, lactose and MCC, were selected for analysis. Carr Index values for lactose and MCC resulted in 31.7 ± 1.5 and 26.1 ± 1.4, respectively. These results are in agreement with flow function curves shown in Figure 5-3.
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Figure 5.3. Flow function curves of COK12 and 244 starting material, MG: silica/P188/MCC, 5/3.5/1.5 (w/w/w), MCC, and lactose.

5.3.12 Granule solid-state properties and stability

XRPD was used to determine the effect of premature drug release following melt or steam granulation. Figures 5-4a and 5-4b display the diffraction patterns of 244 and COK-12 samples, respectively, along with crystalline ITZ, P188, and MCC. The presence of sharp diffraction peaks designates crystallinity, as shown with crystalline ITZ. Therefore, it is clear that granulation using steam results in less premature drug release than by melting. Samples containing silica/P188/MCC (5/3.5/1.5, w/w/w) resulted in the highest percent crystallinity of 4.7 ± 0.2% and 4.4 ± 0.2% for 244 and COK-12, respectively. We previously showed that a compound’s solubility in the binder does not affect the risk of premature drug release [4]. Therefore, a plausible explanation for the difference between melt and steam-granulated material could be due to the hydrophilicity of P188, which results in a stronger affinity to the silanol groups and thus, displaces the drug. Another possible explanation could be due to the gentler processing conditions (180 vs. 400 rpm) required with steam. Here, we observe that the amount of P188 has an influence on PDR. Using 244 melt-granulated samples, the average PDR from n=4 samples containing 20% or 35% wt. P188 resulted in 2.2 ± 0.5% and 5.1 ± 0.5% crystallinity, respectively. Due to the synthesis scale of COK-12, only 244 was used to investigate this. These hypotheses have been further investigated and are discussed in chapter 6 where it is revealed that the binder properties themselves also play a major role in PDR.

Figure 5-4. XRPD diffraction patterns of (i) silica/P188/MCC, 5/3.5/1.5, (ii) silica/P188/MCC, 6/3/1, (iii) silica/PVP/MCC, 6/3/1, (iv) P188 (v) MCC, and (vi) crystalline ITZ. Granule compositions expressed as w/w/w and granules prepared from 244 and COK-12 illustrated in (a) and (b), respectively.
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Another interesting observation is the presence of the 19° and 23° 2theta peaks attributed to P188 in melt granulated 244 samples, which are not observed in COK-12 samples. It is reported that the peak around 19° is associated with the polyethylene oxide (120) series plane and interlayer spacing of 4.5Å while 23°2theta is the (032) series plane diffraction with an interlayer spacing of 3.8-4.0Å [180]. Pore diameter evaluation (Figure 5-5) reveals that the smaller pores of 244 are filled first, most likely due to stronger capillary forces. Because COK-12 exhibits a much smaller pore diameter, more P188 is driven into the pores during processing. This hypothesis is further supported by the mesopore volume results, shown in Table 5-4. Based on the difference in volume following granulation, 244 pores result in a larger volume than COK-12. Furthermore, the smaller pore size of COK-12 could also be more effective at inhibiting P188 crystallization [50].

Figure 5-5. BJH determined pore diameter distribution of loaded silica and granules prepared with 244 (left) and COK-12 (right). Granule compositions are silica/binder/MCC (w/w/w).

As previously stated, melt granulated samples containing silica/P188/MCC (5/3.5/1.5, w/w/w) resulted in the highest percent crystallinity and were therefore selected for stability assessments. Figure 5-6 displays the diffraction patterns of granules prepared with COK-12 and 244 following t = 1 week and t = 6 months storage at 25°C/60%RH and 40°C/75%RH. Following 1 week storage in 40°C/75%RH, the 19° and 23° 2theta peaks attributed to P188 disappear in the 244 granules but remain present following storage in 25°C/60%RH up to 6 months. Previous reports state that P188 undergoes degradation in 40°C/75%RH conditions. Here, the author concludes that the propylene oxide block degrades faster due to the formation of formic and acetic acid observed over time [181]. To investigate this, the pH of 1/9 (w/v) P188/H₂O before and after 1 week of storage in 40°C/75%RH was measured using a WTW 330i pH meter (Weinheim, Germany) and resulted in a decrease from 6.8 to 5.4, respectively.
Ordered and Disordered Mesopore Comparison

Figure 5-6. XRPD diffraction patterns of 244/P188/MCC (5/3.5/1.5, w/w/w) following 1 week storage at (a) 25°C/60%RH and (b) 40°C/75%RH; following 6 months storage in (c) 25°C/60%RH and (d) 40°C/75%RH; COK-12/P188/MCC (5/3.5/1.5, w/w/w) following 1 week storage in (e) 25°C/60%RH and (f) 40°C/75%RH; following 6 months storage in (g) 25°C/60%RH and (h) 40°C/75%RH.

DSC thermograms of P188 in Figure 5-7 reveal the melting temperature ($T_m$) peak at ~ 52 °C. Following 1 week in 40°C/75%RH conditions, the formation of a double peak occurs. Moreover, a double endothermal peak in melt-granulated samples is also present, albeit shifted to slightly lower temperatures with 244 granules. These results indicate that degradation of the P188 occurs during the granulation process itself. The decrease in temperature observed in 244 granules may be due to a $T_m$ depression of the confined molecule compared to the $T_m$ of the bulk, described by the Gibbs-Thompson equation [182]. Crystalline ITZ melts at 168 °C and displays a glass transition around 59 °C. Furthermore, two other endothermic transitions occur at 74 °C and 90 °C in the glassy state. Therefore, the thermal events observed in the granules are not attributed to extracted ITZ [7]. Based on the P188 degradation, steam granulation was selected as the preferred method for this study. However, analysis of another binder (e.g., Gelucire® 50/13) and/or drug combination could alter this conclusion.

Figure 5-7. DSC thermograms of (left) pure P188 (a) $t = 0$ and (b) following $t = 1$ week 40°C/75%RH; (right) MG: silica/P188/MCC 5/3.5/1.5 (w/w/w) at $t = 0$ (a) COK-12 and (b) 244, following $t = 6$ months 40°C/75%RH (c) COK-12 and (d) 244.
Ordered and Disordered Mesopore Comparison

There was no difference in percent crystallinity at each time-point for all samples and no difference in diffraction patterns observed with COK-12 granules (Figure 5-6). The release profiles in Figure 5-8 reveal only slight changes following storage between granules containing COK-12 and 244. Compared to ITZ-loaded silica, the release rate from granules (t = 0) is enhanced due to the presence of excipients. Linnell et al. also reported this observation with PVP K30 but attributed it to precipitation inhibition [87]. Here, these samples are tested in sink conditions and increased release is likely due to enhanced wettability and/or surface activity of P188. Release profiles of 244 granules (left) show that the rate is slightly enhanced following storage, whereas the rate from COK-12 samples (right) is slightly decreased. There are conflicting reports as to whether storage conditions enhance or delay the release of ITZ from mesopores. Mellaerts et al., reported faster release from OMS material, SBA-15, following storage due to gradual hydroxylation. This led to the increase in hydrophilicity and drug release [104]. Kinnari et al. observed a slight decrease in release rate from 244 following 3 months storage (40°C/70%RH) [174]. It is known that many factors (i.e., drug loading method) can contribute to the release rate and therefore, may be due to differences in the position of ITZ and/or the P188 inside and/or outside the pores [68, 97]. However, most notable is that only slight changes to the release rate are observed and that it remains greatly enhanced when compared to the crystalline form, despite the occurrence of premature drug release and P188 degradation from stressed storage conditions.

Figure 5-8. Release of (+) crystalline ITZ, (■) ITZ-loaded silica, ITZ from (●) t=0 of silica/P188/MCC (5/3.5/1.5, w/w/w), and following t=6 months storage conditions in (♦) 25°C/60%RH and (▲) 40°C/75%RH in SGF + 0.5 wt.% SLS (n = 3, mean ± sd).

5.4.4 Properties of compressed granules

Compression behavior was analyzed using the Heckel equation (Eqn. 1-6). These results, along with the resulting tablet properties of granules and granules mixed with 10% wt. Ac-Di-Sol® (AC) are provided in Table 5-5. Elastic recovery was determined based on the change between the minimum thickness measured at maximum compression force (Force_max) and the resulting tablet thickness. Granules prepared from 244 resulted in an overall lower elastic recovery than COK-12, indicating stronger bond formation upon compression. Furthermore, larger differences between COK-12 and 244 are observed for granules prepared by melting.
Table 5-5. Tablet properties of granulated material with and without the presence of 10% wt. Ac-Di-Sol (AC).

<table>
<thead>
<tr>
<th>Silica</th>
<th>Thickness (mm)</th>
<th>Hardness* (kp)</th>
<th>Force&lt;sub&gt;max&lt;/sub&gt; (N)</th>
<th>Elastic Recovery (%)</th>
<th>Yield Pressure (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steam Granulation: Silica/PVP/MCC (6/3/1, w/w/w)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>244</td>
<td>1.42 ± 0.01</td>
<td>3.4 ± 0.1</td>
<td>8507 ± 302</td>
<td>14.3 ± 0.9</td>
<td>112.8 ± 3.6</td>
</tr>
<tr>
<td>244 + AC</td>
<td>1.50 ± 0.01*</td>
<td>4.3 ± 1.0</td>
<td>9787 ± 530</td>
<td>14.5 ± 0.9</td>
<td>113.7 ± 3.9*</td>
</tr>
<tr>
<td>COK-12</td>
<td>1.52 ± 0.03</td>
<td>3.5 ± 0.4</td>
<td>7560 ± 290</td>
<td>21.2 ± 2.6</td>
<td>123.3 ± 3.7</td>
</tr>
<tr>
<td>COK-12 + AC</td>
<td>1.53 ± 0.01*</td>
<td>3.8 ± 0.4</td>
<td>7507 ± 178</td>
<td>18.12 ± 1.2</td>
<td>119.7 ± 5.4*</td>
</tr>
<tr>
<td>Melt Granulation: Silica/P188/MCC (6/3/1, w/w/w)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>244</td>
<td>1.42 ± 0.01</td>
<td>2.4 ± 0.4</td>
<td>6387 ± 288</td>
<td>21.8 ± 0.6</td>
<td>63.2 ± 1.7</td>
</tr>
<tr>
<td>244 + AC</td>
<td>1.44 ± 0.00</td>
<td>2.9 ± 0.5</td>
<td>7867 ± 334</td>
<td>20.8 ± 0.7</td>
<td>64.6 ± 1.7</td>
</tr>
<tr>
<td>COK-12</td>
<td>1.09 ± 0.00</td>
<td>0.7 ± 0.3</td>
<td>18947 ± 1052</td>
<td>39.7± 7.0</td>
<td>126.0 ± 4.1</td>
</tr>
<tr>
<td>COK-12 + AC</td>
<td>1.04 ± 0.02</td>
<td>2.9 ± 0.7</td>
<td>20400 ± 530</td>
<td>33.6 ± 4.6</td>
<td>115.8 ± 2.4</td>
</tr>
<tr>
<td>Melt Granulation: Silica/P188/MCC (5/3.5/1.5, w/w/w)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>244</td>
<td>1.61 ± 0.00</td>
<td>0.8 ± 0.1</td>
<td>2440 ± 280</td>
<td>17.7 ± 0.3</td>
<td>30.2 ± 3.6</td>
</tr>
<tr>
<td>244 + AC</td>
<td>1.44 ± 0.04</td>
<td>3.3 ± 1.0</td>
<td>5087 ± 954</td>
<td>15.9 ± 0.8</td>
<td>37.3 ± 3.3</td>
</tr>
<tr>
<td>COK-12</td>
<td>1.57 ± 0.03</td>
<td>0.8 ± 0.3</td>
<td>18707 ± 1407</td>
<td>54.7 ± 4.2</td>
<td>64.3 ± 5.3</td>
</tr>
<tr>
<td>COK-12 + AC</td>
<td>1.52 ± 0.01</td>
<td>3.1 ± 0.3</td>
<td>7267 ± 356</td>
<td>18.8 ± 0.5</td>
<td>42.5 ± 1.1</td>
</tr>
</tbody>
</table>

* no significant difference between 244 and COK-12 samples. Hardness value for silica/P188/MCC (6/3/1, w/w/w) as exception where p < 0.05.

Granules were physically mixed with croscarmellose sodium (AC) based on previous findings in that a disintegrant was necessary to disintegrate the compacted mesoporous silica particles [85, 157]. For 244 granules mixed with AC, similar hardness values as COK-12 were obtained, but with a lower compression force. Due to fracture upon ejection, increasing the force to improve the hardness of tablets from COK-12 melt-granulated material alone was not achievable.

A comparison of the release rates from the tablets containing 10% wt. AC described in Table 5-5 is illustrated in Figure 5-9. Compared to the starting granules, both agglomeration techniques result in a decrease in release rate following compression, likely due to damage of the pore structure [157]. Because previous results show that this can be corrected with the use of excipients, our objective here was to assess release rate differences between disordered 244 and ordered COK-12 [157]. The smaller granule size (Figure 5-2) and/or surface active properties of P188 in 244 melt-granulated material is likely the cause of the faster release rate of ITZ than those prepared with steam. Furthermore, more external ITZ is present in melt-granulated material, which does not require time to diffuse out of the pores.
Ordered and Disordered Mesopore Comparison

![Graph showing release of ITZ from different formulations](image)

**Figure 5-9.** Release of ITZ from (●/○) SG: silica/PVP/MCC, 6/3/1, (♦/◊) MG: silica/P188/MCC, 6/3/1 and (▲/∆) MG: silica/P188/MCC, 5/3.5/3.5 in SGF + 0.5 wt.% SLS (n = 3, mean ± sd). Filled and empty symbols refer to granules and tablets, respectively. Granule compositions expressed as w/w/w.

On the basis of a smaller decrease in pore volume, nitrogen physisorption results in Figure 5-10 demonstrate that pure COK-12 results in a greater mechanical strength than 244. This is also reflected by the overall slightly higher release rate of tablets prepared with COK-12 than the 244 counterpart and is most notable with steam-granulated material. Therefore, the amount of required excipients necessary to protect the pore structure upon compression is expected to be less when formulating with COK-12. Compared to the tablets, the release rate of COK-12 steam-granulated material is lower (<60 min) due to the granules initially floating on top of the vessel.

![Graph showing nitrogen adsorption/desorption isotherms](image)

**Figure 5-10.** Nitrogen adsorption/desorption isotherms of (■/□) COK-12 and (●/○) 244. Filled and empty symbols refer to compression at 0 and 72 MPa, respectively. COK-12 results adapted from [157].

5.5 Conclusions

It was demonstrated that mesoporous silica can be processed by melt or steam granulation with little or no premature drug release. We assess the difference in granulation behavior and granule properties of disordered 244 and ordered COK-12 mesoporous silica material using P188 and PVP as binders for melt and steam agglomeration, respectively. Itraconazole was selected as the poorly soluble model...
compound for the development of an immediate release oral dosage form. Granules prepared with steam resulted in the overall largest granule size. All 244 granules resulted in a bimodal granule size distribution. XRPD results show that Bragg peaks associated with crystalline ITZ were most prevalent in melt-granulated samples. Melt granulated material from 244 also exhibited diffraction peaks of P188, which were not observed in COK-12. Compression and compaction properties between the two silica materials also differed that resulted in melt-granulated material from 244 in slightly better tablet behavior. Following 6 months storage in 25°C/60%RH and 40°C/75%RH, no additional increase in crystallinity was determined. Due to the greater increase in granule size enlargement and less PDR, steam granulation with PVP is the preferred method for processing mesoporous silica over melt granulation with P188.

5.6 Acknowledgements

This study was made possible by the Flemish Government long-term funding (Methusalem) to J.A. Martens and the Flemish Fund for Scientific Research (FWO) for short-term research abroad. We would also like to thank Formac Pharmaceuticals for use of their nitrogen physisorption instrument, Prof. Maria Seo for providing the TEM images and Stef Kerkhofs for assistance with SAXS measurements.
Agglomeration of mesoporous silica prepared by melt and steam granulation. Part II: Screening of steam granulation process parameters using a factorial design

Results described in this chapter are in press as the following article:
Steam Granulation

6.1 Abstract
The objectives of this study were to identify the key process parameters during steam granulation of disordered mesoporous silica material Syloid® 244 FP (244) and to compare two different binders: polyvinylpyrrolidone (PVP) K25 and hydroxypropylmethyl cellulose (HPMC). Itraconazole (ITZ) was selected as model compound for the development of an oral dosage form for enhanced release. Six factors: binder content, steam amount, mixing time, impeller speed, spray pause time, and filler content were investigated using a two-level quarter-fraction factorial design of experiment (DOE) for each binder type. As experimental responses, characteristics correlating to both granules and tablets were selected. Granules prepared from PVP resulted in an overall higher bulk density, granule size, increased flow properties and better compression and compaction behavior. While granulation with PVP resulted in the most ITZ to extract from the pores during processing, the premature drug release was less than 5%. Centerpoint replicates of granules prepared with HPMC were highly variable. The results of the DOE indicate that the risk of extracting the drug from the pores during processing is governed both by the process parameters and the binder properties.

6.2 Introduction
Interest in mesoporous silica as a release enhancer of poorly soluble compounds is one of the more recent and burgeoning areas of drug delivery research [43, 44, 68]. Several studies report that mesoporous silica exhibit poor powder flow behavior, attributed to small particle size, low bulk density and hygroscopicity [119, 121, 157]. From an oral dosage form development perspective, these pose critical challenges such as particle segregation issues and handling difficulties. Moreover, compression of these materials leads to structural damage, which hinders their release performance [116, 157]. One approach to improve these poor tableting characteristics is through granulation, which is commonly used in the pharmaceutical industry to increase bulk density, dose content uniformity and shelf life, enhance compressibility and powder flow, reduce dustiness and improve product appearance [129]. It was demonstrated that the use of excess solvent during mesoporous silica processing could result in premature drug release (PDR). It is hypothesized that PDR is a result of capillary forces pulling the solvent into the pores and displacing the drug [4]. Dry granulation is not considered because the use of pressure could result in structural damage and affect the release behavior [116, 157].

Melt granulation is a solvent free process in which pharmaceutical powders are agglomerated with a binder, which melts at a relatively low temperature [139, 177]. Upon cooling, dry granules are obtained as the molten binder solidifies. Steam granulation is a slight modification to wet granulation, but requires less water and shorter processing time [175, 176]. Furthermore, the diffusivity rate of binders into the powder bed is also higher. We demonstrated in chapter 5 that both melt and steam granulation are capable of processing mesoporous silica with little or no PDR [183]. However, x-ray powder diffraction (XRPD) results show that PDR of itraconazole (ITZ) was most prevalent in melt-
granulated samples and that degradation of the binder, Poloxamer 188, occurred during the process itself. Also, steam granulation with polyvinylpyrrolidone K25 (PVP) resulted in the overall largest granules. Comparison between disordered, Syloid® 244 FP (244), and ordered, COK-12, mesoporous silica granulation behavior and granule properties revealed that while 244 resulted in a bimodal granule size distribution, it also exhibited lower elastic recovery and yield pressure during compression. Based on our findings in chapter 5, the aim of the present study was to optimize steam granulation process variables using 244 loaded with ITZ and identify the key attributes that contribute to PDR and process parameters resulting in the overall most desirable granule characteristics. Due to the synthesis scale of COK-12, Syloid® 244 was selected as the model mesoporous silica material.

While reports show that binder properties (e.g., viscosity) have an effect on the resulting granule properties, no evaluation has yet been made with steam granulation and/or mesoporous silica [184-186]. Therefore, hydroxypropylmethyl cellulose 2910 (HPMC) and PVP were selected to assess differences in granulation behavior and resulting granule properties. For each binder, a two-level quarter-fraction factorial design was selected to investigate six factors: binder content, steam amount, mixing time, impeller speed, spray pause time, and filler content and six responses: granule size, bulk density, flow properties, PDR, tablet properties, and in vitro release were assessed.

6.3 Materials and Methods

6.3.1 Materials
Disordered Syloid® 244 FP was kindly provided by Grace Davison & Co. (Lokeren, Belgium) and used as received. Microcrystalline cellulose (MCC; Avicel® PH 101) and croscarmellose sodium (AC; Ac-Di-Sol®) were purchased from FMC (Little Island, Cork, Ireland). Polyvinylpyrrolidone K25 (PVP; Kollidon® 25) was obtained from BASF (Ludwigshafen, Germany), hydroxypropyl methyl cellulose 2910 (HPMC; Methocel®) from Colorcon (Idstein, Germany) and magnesium stearate from Sigma-Aldrich (Diegem, Belgium).

6.3.2 Drug Loading
A target drug load of 20% (w/w) was prepared using a 50 mg/mL solution of itraconazole (Janssen Pharmaceutica, Beerse, Belgium) in dichloromethane (J.T. Baker, Deventer, The Netherlands). Itraconazole was loaded using the incipient wetness procedure [65]. The damp material was then placed in a 40 °C vacuum oven (Heraeus, Liederkerke, Belgium) at a reduced pressure of 100 mbar for a minimum of 24 h to remove any residual solvent. The actual drug loading obtained was 18.4 ± 0.2%.

6.3.3 Steam Granulation
All granules were prepared in Rotolab® (Zanchetta, Lucca, Italy) laboratory scale high-shear mixer in 100 g batches. As previously described by Cavallari et al., steam was produced in a small electric boiler that was calibrated at 3.5 atm [176]. The 2 liter hermetically sealed thermostatic vessel is
Steam Granulation

equipped with a three-blade impeller and product temperature probe. A tiny flux of air was injected into the bowl to avoid any entrapping of solid. An enclosed polyethylene bottle (Thermo Scientific, Erembodegem-Aalst) was attached to the thermostated line to avoid droplets from feeding into the vessel. During agglomeration, the vessel was kept at a constant 70 °C. The steam was introduced through a 6x4 mm Rilsan® tube (Arkema, Pennsylvania, USA), which was located 5 mm above the impeller. Each actuation supplied a steady flow of 0.82 g/sec for 5 s on and either 30, 45, or 60 s off according to the experimental design (Table 6-1). To dry the steam-granulated material, a vacuum (25-40 mbar) was applied for 45 min to the 70 °C vessel, which was continuously tilting. The impeller speed was set to 120 rpm for 10 s on 20 s off. Granules were then placed in a 40 °C oven (Friocell; MMM Medcenter, Milano, Italy) for at least 24 hrs.

Table 6-1. Two-level quarter-fraction factorial experimental design.

<table>
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<tr>
<th>Experiment</th>
<th>Steam</th>
<th>Mixing Time</th>
<th>Binder</th>
<th>Microcrystalline Cellulose</th>
<th>Impeller Speed</th>
<th>Spray Pause Time</th>
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</tr>
</tbody>
</table>

6.3.4 Factors

This study selected a two-level quarter-fraction factorial design to screen six factors in a feasible number of experiments [187]. Table 6-1 lists the experimental design conducted with both PVP and HPMC as binders. To minimize uncontrolled influences on estimated factor effects, experiments were executed in random order. For clarity, they are sorted by standard order. A total of five batches were also carried out at centerpoint levels as first, last, and every 5th experiment. Therefore, a total of 42 granulation trials were performed. The experimental parameters from investigated factors listed in Table 6-1 along with the mid-level controls are provided in Table 6-2.
Table 6-2. Parameters of investigated factors.

<table>
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<tr>
<th>Factors</th>
<th>Level 0</th>
<th>Level -1</th>
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<tr>
<td>Mixing Time (min)</td>
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<td>10</td>
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<tr>
<td>Binder (g)</td>
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<td>35</td>
</tr>
<tr>
<td>Microcrystalline Cellulose (g)</td>
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<td>10</td>
</tr>
<tr>
<td>Impeller Speed (rpm)</td>
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<td>150</td>
<td>180</td>
</tr>
<tr>
<td>Spray Pause Time (sec)</td>
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<td>45</td>
<td>60</td>
</tr>
</tbody>
</table>

6.3.5 X-ray Powder Diffraction (XRPD)

The solid state of ITZ following drug loading and steam granulation was determined by XRPD in reflection mode using an X’Pert PRO diffractometer (PANalytical, Almelo, The Netherlands). To investigate relative crystallinity, samples were measured at room temperature by scanning from 10 to 30°2theta with a 0.017° step size every 400 seconds using CuKα radiation (0.154 nm). The area under the curve (AUC) obtained from the 20.5° 2theta peaks were selected to estimate the relative crystallinity by comparing the AUC values of crystalline ITZ to the granulated material using the X’Pert High Score Plus version 2.2a (PANalytical) software. Reported values are the means for n = 3 ± standard deviation (sd).

6.3.6 High Performance Liquid Chromatography (HPLC) Assay

Drug content and release were quantified using an HPLC system consisting of a LaChrom® L-7100 HPLC pump and an auto sampler model L-7200 equipped with a 100 µl loop. The UV detector model L-7420 (Merck, Darmstadt, Germany) was set to 260 nm. Peaks were integrated using an interface D-7000 and using the D-7000 HSM software (Merck, Darmstadt, Germany). The mobile phase consisted of (50/50, v/v) acetonitrile/0.01N tetrabutyl ammonium hydrogen sulfate using a 1.5 ml/min flow rate and a 20 µl injection volume through a Chromolith® RP-18E 100 x 4.6 mm (Merck, Darmstadt, Germany) column. All solvents were filtered through a 0.45 µm polytetrafluoroethylene (PTFE) membrane and degassed prior to use. Each sample was analyzed (n = 3 ± sd) at room temperature and all standard curves were linear over the concentration range of 0.1-150 µg/ml.

6.3.7 Particle size by laser diffraction

The Sympatec® (Clausthal-Zellerfeld, Germany) RODOS instrument was used to measure the particle size of the granules by laser diffraction using the Fraunhofer model. Results were analyzed using WINDOX 5 version 5.7.2.0 software with range combination module. Each sample was measured in duplicate.
Steam Granulation

6.3.8 Powder Flow
Carr Index values were determined from tapped density results obtained using an Erweka D-63150 (Heusenstamm, Germany) jolting volumeter. Samples were analyzed following removal from a 40 °C oven (Friocell; MMM Medcenter, Milano, Italy) and the loss on drying (Top Ray 160; Bel Engineers, Monza, Italy) was measured immediately prior to testing to ensure the water content was below 2%. Fifty milliliters of powder was analyzed in a 100 ml graduated cylinder. Samples were subjected to successive sets of 500, 750 and 1250 taps at 250 taps/min until a volume difference of less than 2% was achieved between sets. Reported values are the means for \( n = 5 \pm sd \).

6.3.9 Surface Tension
The surface tension was measured with a Wilhelmy balance (KSV Instruments Ltd., Wormerveer, The Netherlands) with a 2 cm wide platina plate. The plate was introduced in to a binders/water (1/9, w/w) solution and measurements were taken at room temperature.

6.3.10 He Pycnometry
A Beckman model 930 (Suarlee, Belgium) helium pycnometer was used to measure true particle density. Samples were analyzed after immediate removal from a 40 °C vacuum oven (Heraeus, Liederkerke, Belgium) at a reduced pressure of 100 mbar. The reported density value is the mean of \( n = 3 \pm sd \).

6.3.11 Tableting
Granulates and physical mixtures containing extragranular Ac-Di-Sol® (AC) and/or microcrystalline cellulose (MCC) were manually filled into a 7 mm die Korsch single-punch tablet press (Berlin, Germany) using a vibrating feeder. The die was lubricated using 0.05% (w/v) magnesium stearate in acetone (Acros, Geel, Belgium). A W+W electronic signal memory recorder (Basel, Switzerland) was used to record the measurement and data was processed with in-house developed software. Tablet weights were adjusted to contain 21 ± 0.2 mg ITZ and tableting parameters were adapted to obtain a target hardness of 4 kp (actual 4.07 ± 0.23 kp). After compression, tablet thickness was determined using a Lorentzen & Wettre instrument 141 type 1-1 (AB Lorentzen & Wettre, Stockholm, Sweden) and tablet hardness with a Schleuniger 6D tablet tester (Dr. K. Schleuniger, Zürich, Switzerland). Reported values are the means of \( n = 6 \pm sd \).

6.3.12 In Vitro Drug Release
Experiments were performed in 500 ml of simulated gastric fluid (SGF) + 0.5% wt. sodium lauryl sulfate (SLS) at 37 °C using an SR8 Plus dissolution apparatus (Hanson Research, Oosterhout, The Netherlands) containing a rotating paddle set to 100 rpm. At specific time-points, 4 ml samples were
collected and filtered through a 0.45 µm PTFE membrane prior to HPLC analysis. Four milliliters of
fresh pre-warmed (37 °C) release medium was then added. Each sample was analyzed as \( n = 3 \pm \text{sd} \).

6.4 Results and Discussion

6.4.1 Selection of factors and responses

Due to the very high adsorptive capacity of 244 in water, the amount of steam added was designed to
cover a wide range. Previous results determined that mesoporous silica had to be sufficiently
moistened to form liquid bridges necessary for agglomeration. However, the material cannot be overly
wetted due to the possibility of PDR [4]. Therefore, it was hypothesized that PDR would be more
prevalent in granules prepared with 180 g of steam. The influence of time between steam actuations
(spray pause time) was assessed as a factor to avoid overwetting and reduce the risk of PDR.

Chapter 5 reveals that steam granulated material 244/PVP/MCC (6/3/1, w/w/w) resulted in a
bimodal distribution (Figure 5-2). The first was at around 3 µm, which is associated with \( D_{50} \) particle
size of 244 starting material (Grace Davidson specifications). The second, a broad distribution
revealed a \( D_{50} \) value around 200 µm, associated with the granulated material. While a bimodal
distribution is inevitable, it is expected to decrease with increasing processing time to support binder
dispersion and the occurrence of particle-particle contact [188]. Therefore, mixing time prior to the
addition of steam was investigated to determine whether this would aid in creating a homogeneous
distribution. Increasing the impeller speed can result in more fines but also create denser granules.
Therefore, the influence of shear forces was also evaluated [128].

The binder is a key attribute in dictating the granulation behavior and granule properties [136].
The two structurally distinct polymers, PVP and HPMC, were selected for evaluation. PVP is a linear
chain polymer comprised of 1-vinyl-2-pyrrolidone. The cellulosic binder, HPMC, contains methyl and
hydroxypropyl groups that contribute to its surface activity. It was reported that the residual hydrogen
bonds in HPMC prevent water from interacting with the hydroxyl groups, leading to excess water
necessary to form a gel, whereas PVP readily turned into a solution following water adsorption [136].
Therefore, these influences, along with binder and MCC concentration were selected for this
evaluation. Because it is hypothesized that PDR occurs when capillary forces pull the binder into the
 pores and displaces the drug, this was expected to increase with increasing binder concentration.

Table 6-3 lists the responses and the analytical methods used for their evaluation. Because the
\( D_{50} \) value of 244 starting material is roughly 3 µm, the fraction of granules > 10 µm was selected to
determine the extent of particle size enlargement, as measured by laser diffraction. Due to precision of
the method, the average of two replicates is reported. All granules resulted in a bimodal distribution
(results not shown). Therefore, the mixing time prior to the addition of steam did not appear to
influence this, based on the times selected in this design. When a compound is successfully loaded into
the pores, it is adsorbed onto the walls where it lacks intermolecular interactions between other
adsorbed molecules. Therefore, no crystalline fingerprint (Bragg peaks) is observed when analyzed by
Steam Granulation

XRPD. Premature drug release is identified by the presence of diffraction peaks associated with the crystalline material. Therefore, the extent of PDR is evaluated by the percent crystallinity.

<table>
<thead>
<tr>
<th>Table 6-3. Responses and corresponding analytical methods.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
</tr>
<tr>
<td>Granule size</td>
</tr>
<tr>
<td>Bulk Density (g/cm³)</td>
</tr>
<tr>
<td>Flow properties</td>
</tr>
<tr>
<td>Premature drug release (PDR)</td>
</tr>
<tr>
<td>Tablet properties</td>
</tr>
<tr>
<td><em>In vitro</em> release</td>
</tr>
</tbody>
</table>

As the final dosage form, response variables correlated to tablets were also examined. Compression and compaction properties were assessed based on maximum force, elastic recovery, and yield pressure results obtained from Heckel and energy plots. The percent ITZ release at 10 and 60 min were selected to evaluate release kinetics of tableted samples.

6.4.2 *Control (Centerpoint) Responses*

A tabular summary of the responses from the control experiments with both PVP and HPMC granulated material is listed in Table 6-4. For all responses, material granulated with PVP shows an overall lower variability than HPMC. This variability could be inherently due to the differences in binder properties themselves. Because PVP is more spherical than HPMC, this may lead to better mixing throughout the powder bed and therefore, better distribution and control of granule growth [184]. Moreover, Li et al. reported that PVP undergoes transition from glass to rubber-solution state at lower relative percent humidity than HPMC, which is necessary for granule formation [136]. For granulating with 244, the hygroscopicity of PVP is a disadvantage based on the presence of crystallinity observed in all control samples. Upon contact with water, HPMC begins to swell and forms a gel. Therefore, the risk of HPMC entering the pores is decreased; despite the lower surface tension value of roughly 43 mN/m as compared to 64 mN/m for PVP.
Table 6-4. Response results from centerpoint (control) experiments. Results are the average of \( n = \) replicates ± standard deviation (sd).

<table>
<thead>
<tr>
<th>Control Experiment</th>
<th>Fraction of Granules &gt;10 μm ((n=2))</th>
<th>Bulk Density ± sd ((g/cm^3)) ((n=5))</th>
<th>Carr Index ± sd ((n=5))</th>
<th>Crystallinity ± sd ((%)) ((n=3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>45.48 ± 0.349 ± 0.001</td>
<td>21.80 ± 0.45</td>
<td>2.74 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>40.08 ± 0.318 ± 0.008</td>
<td>22.60 ± 1.34</td>
<td>3.01 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>40.08 ± 0.353 ± 0.009</td>
<td>23.40 ± 2.19</td>
<td>3.60 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>44.00 ± 0.346 ± 0.005</td>
<td>23.00 ± 1.41</td>
<td>3.62 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>42.56 ± 0.325 ± 0.008</td>
<td>22.40 ± 2.41</td>
<td>1.51 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>42.44 ± 0.34</td>
<td>22.64 ± 2.9</td>
<td>2.90 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>2.39</td>
<td>0.02</td>
<td>0.61 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>%RSD</td>
<td>5.63</td>
<td>4.63</td>
<td>29.79 ± 2.7</td>
<td></td>
</tr>
<tr>
<td>HPMC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22.92 ± 0.221 ± 0.120</td>
<td>21.60 ± 1.82</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>55.41 ± 0.359 ± 0.015</td>
<td>17.40 ± 1.67</td>
<td>3.1 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>31.24 ± 0.283 ± 0.017</td>
<td>25.42 ± 2.68</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>18.24 ± 0.222 ± 0.006</td>
<td>22.20 ± 1.64</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>25.30 ± 0.249 ± 0.008</td>
<td>21.20 ± 0.84</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>30.62 ± 0.27</td>
<td>21.56 ± 2.5</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>14.63</td>
<td>0.66</td>
<td>2.86 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>%RSD</td>
<td>47.77</td>
<td>21.52</td>
<td>13.27 ± 2.7</td>
<td></td>
</tr>
</tbody>
</table>

6.4.3 Desirability Scale

Tables 6-5 and 6-6 list the experimental design response results of 244 granulated with PVP and HPMC, respectively. Granule growth appears to be most dictated by a high PVP and MCC concentration (e.g., experiments 13 and 15), which also translates to increased bulk density. Bulk density and Carr Index values were determined from tapped density experiments. However, Carr Index results do not appear to follow this trend. In the case of experiment 4, both PVP and HPMC resulted in the lowest Carr Index value and contain the overall highest silica content. As opposed to Table 6-5, it does not appear that a high HPMC and MCC concentration dictate granule growth. However, concrete interpretation from these results cannot be made due to the variability in the control results (Table 6-4).
Table 6-5. Response results of granules prepared with PVP. *Indicates overgranulation. Results are average of $n$ replicates ± standard deviation (sd).

<table>
<thead>
<tr>
<th>Control Experiment</th>
<th>Fraction of Granules $&gt;10$ μm ($n=2$)</th>
<th>Bulk Density ± sd (g/cm$^3$) ($n=5$)</th>
<th>Carr Index ± sd ($n=5$)</th>
<th>Crystallinity ± sd (%) ($n=3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.55</td>
<td>0.213 ± 0.009</td>
<td>23.20 ± 2.68</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>29.73</td>
<td>0.264 ± 0.017</td>
<td>21.60 ± 2.07</td>
<td>4.56 ± 0.1</td>
</tr>
<tr>
<td>3</td>
<td>22.13</td>
<td>0.252 ± 0.009</td>
<td>23.80 ± 2.77</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>38.72</td>
<td>0.367 ± 0.002</td>
<td>14.00 ± 0.00</td>
<td>3.9 ± 0.8</td>
</tr>
<tr>
<td>5</td>
<td>43.88</td>
<td>0.345 ± 0.001</td>
<td>22.40 ± 2.61</td>
<td>0.78 ± 0.1</td>
</tr>
<tr>
<td>6*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>41.89</td>
<td>0.329 ± 0.004</td>
<td>23.40 ± 2.19</td>
<td>0.54 ± 0.1</td>
</tr>
<tr>
<td>8*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>35.99</td>
<td>0.291 ± 0.001</td>
<td>22.20 ± 0.45</td>
<td>1.38 ± 0.2</td>
</tr>
<tr>
<td>10*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>29.46</td>
<td>0.269 ± 0.007</td>
<td>20.20 ± 1.79</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>40.78</td>
<td>0.318 ± 0.002</td>
<td>22.20 ± 0.45</td>
<td>4.09 ± 0.2</td>
</tr>
<tr>
<td>13</td>
<td>49.68</td>
<td>0.365 ± 0.004</td>
<td>20.00 ± 1.41</td>
<td>-</td>
</tr>
<tr>
<td>14*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>58.84</td>
<td>0.406 ± 0.005</td>
<td>17.80 ± 1.79</td>
<td>1.63 ± 0.5</td>
</tr>
<tr>
<td>16*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

For granules prepared with PVP, 5 out of the 8 experiments prepared with 180 g steam resulted in overgranulation. The remaining 3 resulted in the highest amount of PDR (~ 4%). While 4 out of 8 samples prepared with 80 g of steam did result in PDR, the amount of crystallinity detected was less than 2%. Table 6-6 lists the design results of 244 granulated with HPMC. Here, 3 out of the 8 experiments performed with 180 g steam resulted in overgranulation. With the exception of one control experiment, all samples resulting in PDR were prepared with 180 g of steam. This further supports our hypothesis that increasing the amount of steam increases the risk of PDR. Moreover, as discussed in section 6.4.2, the binder properties themselves also play a role. Based on the results from PVP, it does not appear that the amount of binder affects the extent of PDR. In fact, 4 out of the 7 experiments that resulted in PDR were prepared with the lower PVP concentration of 20 g (Table 2). For HPMC, all 3 experiments resulting in PDR were also prepared with 20 g binder. Therefore, PDR is dictated more by steam addition than amount of binder.
Table 6-6. Response results of granules prepared with HPMC. *Indicates overgranulation. Results are average of \( n = \) replicates ± standard deviation (sd).

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Fraction of Granules ( &gt;10 \mu m ) (( n=2 ))</th>
<th>Bulk Density ± sd (g/cm(^3)) (( n=5 ))</th>
<th>Carr Index ± sd (( n=5 ))</th>
<th>Crystallinity ± sd (%)(( n=3 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28.28 ± 0.208 (0.003)</td>
<td>0.208 ± 0.015 (0.005)</td>
<td>25.07 ± 2.77</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>26.02 ± 0.197 (0.015)</td>
<td>23.20 ± 1.79 (0.005)</td>
<td>24.00 ± 1.67</td>
<td>1.6 ± 0.1</td>
</tr>
<tr>
<td>3</td>
<td>18.40 ± 0.197 (0.005)</td>
<td>0.216 ± 0.005 (0.001)</td>
<td>23.32 ± 3.29</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>64.21 ± 0.483 (0.021)</td>
<td>10.60 ± 1.67 (0.005)</td>
<td>6.4 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>18.39 ± 0.216 (0.005)</td>
<td>23.32 ± 3.29 (0.005)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>6*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>36.60 ± 0.247 (0.001)</td>
<td>25.60 ± 2.29 (0.005)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>8*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>20.65 ± 0.232 (0.012)</td>
<td>25.20 ± 3.03 (0.005)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>43.83 ± 0.291 (0.009)</td>
<td>21.00 ± 2.24 (0.005)</td>
<td>0.8 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>19.88 ± 0.216 (0.008)</td>
<td>23.15 ± 3.02 (0.005)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>22.97 ± 0.213 (0.002)</td>
<td>24.00 ± 2.35 (0.005)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>22.90 ± 0.218 (0.005)</td>
<td>27.00 ± 1.58 (0.005)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>28.54 ± 0.264 (0.011)</td>
<td>23.60 ± 2.97 (0.005)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>23.97 ± 0.245 (0.003)</td>
<td>25.60 ± 0.89 (0.005)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>16*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

As shown in Tables 6-5 and 6-6, some experiments resulted in overgranulation. Consequently, the factor effects could not be calculated due to missing responses. For the remaining experiments, a global desirability (D) value was calculated according to Derringer’s approach [189]. The global D value is the geometric mean of the individual desirabilities (d\(_i\)) of the combined responses. The d\(_i\) values were obtained after a linear transformation of the responses to a scale from 0 to 1. Using this approach, comparisons can be made between different experiments on the same scale. Table 6-7 lists the transformations for the granules prepared with HPMC and PVP.
Table 6-7. Linear transformation from responses of granules and tablets prepared with PVP and HPMC.

<table>
<thead>
<tr>
<th>Response</th>
<th>Extremes</th>
<th>Transformation equation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( d_i = 0 )</td>
<td>( d_i = 1 )</td>
</tr>
<tr>
<td><strong>Granules</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fraction &gt; 10 μm</td>
<td>17</td>
<td>65</td>
</tr>
<tr>
<td>Bulk Density (g/cm(^3))</td>
<td>0.19</td>
<td>0.48</td>
</tr>
<tr>
<td>Carr Index</td>
<td>27.1</td>
<td>10.5</td>
</tr>
<tr>
<td><strong>Tablets</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum Force (N)</td>
<td>10500</td>
<td>6200</td>
</tr>
<tr>
<td>Elastic Recovery (%)</td>
<td>29</td>
<td>13</td>
</tr>
<tr>
<td>Yield Pressure (MPa)</td>
<td>176</td>
<td>142</td>
</tr>
<tr>
<td>Release at 10 min (%)</td>
<td>0</td>
<td>65</td>
</tr>
<tr>
<td>Release at 60 min (%)</td>
<td>0</td>
<td>96</td>
</tr>
</tbody>
</table>

Figure 6-1 illustrates the resulting D-values of the granules from each experiment. With the exception of experiments 1 and 4, the desirability value is higher for granules prepared with PVP. Because experiments 10 and 14 resulted in overgranulation for PVP but not HPMC, no D-value associated with PVP is listed. Experiment 4 and 15 resulted in the overall highest D-value for HPMC and PVP, respectively. For PVP, experiment 4 had the second highest D-value and contains the high silica content of 80% wt., as compared to 55% wt. for experiment 15. Experiment 4 was selected for tableting and in vitro release testing, despite resulting in PDR. Experiment 3, prepared with 80 g steam, also contains 80% wt. silica but no PDR. While the overall D-value is low, it was also selected to determine whether desirable tablet properties and in vitro release could still be obtained with the use of excipients. Therefore, various amounts of MCC and/or AC were added to assess their influence.

Figure 6-1. D-values for granules prepared with PVP and HPMC. Experiment number corresponds to these described in Table 6-1. Experiments 8 and 16 are not reported due to overgranulation with both binders.
Table 6-8. Tablet properties of granulated material prepared with PVP and HPMC with and without the presence of extragranular microcrystalline cellulose (MCC) and/or Ac-Di-Sol (AC).

<table>
<thead>
<tr>
<th>Extragranular Excipients (wt. %)</th>
<th>Thickness (mm)</th>
<th>Hardness (kp)</th>
<th>Force$_{\text{max}}$ (N)</th>
<th>Elastic Recovery (%)</th>
<th>Yield Pressure (MPa)</th>
<th>% Release @ 10 min</th>
<th>% Release @ 60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experiment 3: 244/PVP, (8/2, w/w) 80 g steam</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) n/a</td>
<td>1.91 ± 0.04</td>
<td>4.08 ± 0.44</td>
<td>7193 ± 400</td>
<td>18.87 ± 2.55</td>
<td>155.13 ± 8.19</td>
<td>1.3 ± 0.1</td>
<td>2.3 ± 0.1</td>
</tr>
<tr>
<td>2) 10% MCC</td>
<td>2.07 ± 0.02</td>
<td>3.83 ± 0.58</td>
<td>6526 ± 266</td>
<td>16.36 ± 0.29</td>
<td>145.53 ± 4.27</td>
<td>1.2 ± 0.2</td>
<td>2.3 ± 0.6</td>
</tr>
<tr>
<td>3) 10% AC</td>
<td>2.06 ± 0.01</td>
<td>3.90 ± 0.42</td>
<td>6744 ± 151</td>
<td>17.39 ± 0.46</td>
<td>150.86 ± 2.01</td>
<td>7.3 ± 1.1</td>
<td>28.7 ± 0.2</td>
</tr>
<tr>
<td>4) 5% MCC, 5% AC</td>
<td>1.93 ± 0.01</td>
<td>4.25 ± 0.55</td>
<td>7080 ± 255</td>
<td>17.53 ± 0.65</td>
<td>143.57 ± 4.18</td>
<td>6.4 ± 5.9</td>
<td>9.9 ± 2.3</td>
</tr>
<tr>
<td>5) 10% MCC, 10% AC</td>
<td>2.20 ± 0.01</td>
<td>4.28 ± 0.49</td>
<td>6864 ± 195</td>
<td>15.77 ± 0.54</td>
<td>147.24 ± 2.29</td>
<td>18.8 ± 1.6</td>
<td>40.4 ± 2.0</td>
</tr>
<tr>
<td><strong>Experiment 4: 244/PVP, (8/2, w/w) 180 g steam</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) n/a</td>
<td>2.25 ± 0.01</td>
<td>3.88 ± 0.59</td>
<td>6270 ± 421</td>
<td>13.69 ± 0.74</td>
<td>175.63 ± 3.88</td>
<td>1.3 ± 0.1</td>
<td>2.5 ± 0.1</td>
</tr>
<tr>
<td>2) 10% MCC</td>
<td>2.35 ± 0.01</td>
<td>3.97 ± 0.38</td>
<td>6610 ± 256</td>
<td>13.87 ± 0.28</td>
<td>168.65 ± 3.11</td>
<td>1.2 ± 0.2</td>
<td>2.4 ± 0.6</td>
</tr>
<tr>
<td>3) 10% AC</td>
<td>2.27 ± 0.01</td>
<td>4.00 ± 0.35</td>
<td>7280 ± 210</td>
<td>14.53 ± 0.44</td>
<td>172.94 ± 3.19</td>
<td>53.4 ± 1.5</td>
<td>89.3 ± 3.0</td>
</tr>
<tr>
<td>4) 5% MCC, 5% AC</td>
<td>2.27 ± 0.01</td>
<td>4.17 ± 0.62</td>
<td>7060 ± 466</td>
<td>14.52 ± 0.47</td>
<td>169.82 ± 7.79</td>
<td>42.2 ± 4.8</td>
<td>80.5 ± 2.9</td>
</tr>
<tr>
<td>5) 10% MCC, 10% AC</td>
<td>2.63 ± 0.01</td>
<td>4.15 ± 0.36</td>
<td>6780 ± 335</td>
<td>13.32 ± 0.27</td>
<td>167.74 ± 3.88</td>
<td>53.4 ± 1.5</td>
<td>85.9 ± 3.2</td>
</tr>
<tr>
<td><strong>Experiment 3: 244/HPMC, (8/2, w/w) 80 g steam</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) n/a</td>
<td>1.65 ± 0.03</td>
<td>3.75 ± 0.42</td>
<td>9280 ± 608</td>
<td>23.77 ± 0.82</td>
<td>164.61 ± 4.07</td>
<td>5.5 ± 4.5</td>
<td>10.3 ± 2.8</td>
</tr>
<tr>
<td>2) 10% MCC</td>
<td>1.73 ± 0.03</td>
<td>3.90 ± 0.63</td>
<td>9470 ± 685</td>
<td>23.65 ± 0.95</td>
<td>153.06 ± 4.27</td>
<td>3.7 ± 0.7</td>
<td>24.5 ± 0.8</td>
</tr>
<tr>
<td>3) 10% AC</td>
<td>1.81 ± 0.01</td>
<td>4.48 ± 0.20</td>
<td>10416 ± 376</td>
<td>23.85 ± 1.69</td>
<td>169.59 ± 4.18</td>
<td>52.1 ± 16.2</td>
<td>85.1 ± 3.4</td>
</tr>
<tr>
<td>4) 5% MCC, 5% AC</td>
<td>1.70 ± 0.02</td>
<td>4.56 ± 0.48</td>
<td>9744 ± 366</td>
<td>22.99 ± 0.61</td>
<td>152.11 ± 3.69</td>
<td>46.2 ± 1.7</td>
<td>67.0 ± 3.3</td>
</tr>
<tr>
<td>5) 10% MCC, 10% AC</td>
<td>1.74 ± 0.02</td>
<td>3.64 ± 0.29</td>
<td>10348 ± 175</td>
<td>23.45 ± 1.39</td>
<td>163.11 ± 4.07</td>
<td>55.8 ± 1.0</td>
<td>84.0 ± 1.4</td>
</tr>
<tr>
<td><strong>Experiment 4: 244/HPMC, (8/2, w/w) 180 g steam</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) n/a</td>
<td>2.49 ± 0.01</td>
<td>4.13 ± 0.21</td>
<td>7980 ± 312</td>
<td>28.95 ± 1.15</td>
<td>169.32 ± 2.96</td>
<td>4.5 ± 4.0</td>
<td>10.2 ± 1.8</td>
</tr>
<tr>
<td>2) 10% MCC</td>
<td>2.63 ± 0.00</td>
<td>4.00 ± 0.17</td>
<td>7740 ± 208</td>
<td>21.68 ± 0.09</td>
<td>170.86 ± 5.33</td>
<td>5.5 ± 0.7</td>
<td>15.2 ± 0.8</td>
</tr>
<tr>
<td>3) 10% AC</td>
<td>2.45 ± 0.01</td>
<td>4.07 ± 0.35</td>
<td>8740 ± 489</td>
<td>22.68 ± 0.97</td>
<td>165.85 ± 1.31</td>
<td>61.7 ± 1.4</td>
<td>95.9 ± 0.4</td>
</tr>
<tr>
<td>4) 5% MCC, 5% AC</td>
<td>2.27 ± 0.01</td>
<td>4.17 ± 0.62</td>
<td>7060 ± 466</td>
<td>22.98 ± 0.79</td>
<td>169.82 ± 7.79</td>
<td>54.8 ± 2.0</td>
<td>89.1 ± 1.0</td>
</tr>
<tr>
<td>5) 10% MCC, 10% AC</td>
<td>2.91 ± 0.00</td>
<td>4.23 ± 0.21</td>
<td>7420 ± 35</td>
<td>18.80 ± 0.14</td>
<td>154.13 ± 0.80</td>
<td>62.6 ± 1.4</td>
<td>92.3 ± 4.5</td>
</tr>
</tbody>
</table>

Five different tablet formulations were evaluated. Their composition and all responses along with their in vitro release results are provided in Table 6-8. Granules prepared with PVP resulted in overall better compression and compaction properties. For both PVP and HPMC granulated material, the yield pressure and tablet thickness was less for granules prepared with 80 g steam (experiment 3). Granules prepared with PVP also exhibited a lower elastic recovery than their HPMC counterparts. The transformation criteria are listed in Table 6-7 and the resulting D-values for the tablets are depicted in Figure 6-2.
Steam Granulation

As expected, there is an overall trend of increasing D-value with increasing extragranular excipients. Based on the D-value, the addition of AC is more critical than MCC for improving the tablet properties (formulations 2 & 3). As compared to experiment 3, all tablets prepared with AC resulted in a higher D-value for experiment 4, observed in both PVP and HPMC. The importance of AC is also illustrated by the *in vitro* release profiles in Figure 6-3. Here, the tablets that resulted in a similar release profile to that of the uncompressed granules all contained AC (PVP experiment 3 as exception). This is consistent with our previous findings and those reported from other labs [85, 157]. Tablets prepared with 180 g steam (experiment 4) exhibited a faster drug release profile than those prepared with 80 g (experiment 3). It should be noted that despite the presence of PDR in experiment 4, an overall enhanced release behavior is still maintained and better than experiment 3 where PDR was not observed. While granules prepared with PVP resulted in overall larger D-values (Figure 6-1), the release from tablets prepared with HPMC was slightly higher than with PVP and is most notable with experiment 3 (Figure 6-3d). The slower initial release (< 30 min) of formulation 1 (Figure 6-3b) is due to the granules initially floating on top of the vessel. This observation was also reported in chapter 5 (Figure 5-9) but does not occur with experiment 3 where a faster release profile is observed (Figure 6-3a) [183].
6.5 Conclusions

A two level quarter-fraction factorial experimental design was successfully implemented to evaluate the key process variables during steam granulation of disordered Syloid® 244 loaded with itraconazole. Also, the granulation behavior and physicochemical properties of samples prepared with PVP and HPMC are compared. Based on the control experiment results, granulation with HPMC was found to be more variable. PVP granulated material resulted in overall better granule properties but resulting tablets exhibited slightly slower in vitro release performance. Granules prepared with PVP also resulted in more premature drug release. Therefore, it is concluded that this is not only dictated by the amount of steam used during the granulation experiment but also the nature of the binder itself. While PDR was present, the amount of itraconazole extracted from the pores was less than 5\% and did not appear to affect the release performance.

6.6 Acknowledgements

This study was made possible by the Flemish Government long-term funding (Methusalem) to J.A. Martens and the Flemish Fund for Scientific Research (FWO) for short-term research abroad. We also want to thank Tom Verwijlen for assistance with surface tension analysis.
Chapter 7

Discussion

The use of mesoporous silica to improve the solubility of poorly soluble compounds is among the fastest growing newcomers to the pharmaceutical field. Along with these exciting new challenges are also many unanswered scientific and technological questions. This research focused on their downstream processability for development as an oral dosage form. The following sections discuss the major contributions towards achieving these dissertation research objectives and based on these findings, highlight the key considerations for future and scale-up development.

7.1 Textural and powder characteristics pertinent to granulation and tableting

7.1.1 Mechanical strength

Thorough physicochemical understanding is crucial for selection of the most appropriate mesoporous silica material. This work evaluated the mechanical strength and manufacturability of three model mesoporous silica materials: 1. COK-12 (OMS), 2. SBA-15 (OMS), and 3. Syloid® 244 (DMS). While COK-12 and SBA-15 are structurally similar, it was determined that selecting an OMS material with thicker walls and/or higher degree of silicate condensation is crucial for improving the mechanical strength. While SBA-15 was more sensitive to compression, we show that proper formulation selection can improve this limitation, based on the results from physical mixtures.

As discussed in chapter 3, in vitro release rate decreases with increasing applied pressure. One main objective during our in vitro release studies was to obtain an equivalent profile to that of the non-compressed material. However from an in vivo perspective, this may not be advantageous. Because the drug is released in a supersaturated state, precipitation to the more stable but lower soluble form can occur, resulting in decreased drug absorption. Van Speybroeck et al. illustrated enhanced absorption of fenofibrate by decreasing the rate of supersaturation [49]. Therefore, a decrease in release rate following tableting may actually improve absorption for molecules that are more prone to precipitation.

7.1.2 Particle size, size distribution, and morphology

Selecting a silica material of a smaller particle size will likely hinder the ease of development. If tablets are prepared from physical mixtures, large differences between the particle size of the silica and excipients will result in segregation issues and dose content inhomogeneity. The importance of processing mesoporous silica was demonstrated for the first time in chapter 4, not only to circumvent this issue but also to improve powder flow and decrease the amount of required excipients. In vitro
Discussion

release performance of processed OMS material was equivalent to physical mixtures but contained roughly 70% less excipient.

The importance of particle size also plays a role with granulation. The starting $D_{50}$ value of Syloid® 244 (244) and COK-12 are roughly 3 μm and 14 μm, respectively. In chapter 5, all granules prepared with 244 resulted in a bimodal size distribution, whereas all COK-12 samples were unimodal and processed under the same conditions. In chapter 6, we attempt to decrease the granule size distribution of 244 by increasing the mixing and processing time with limited success. From a tableting perspective, the increase in granule size distribution appeared to improve the compressibility. As granules are poured into the tableting die, more voids are filled with the smaller granules. More particle-particle contact occurs and increases the availability for bond formation upon compression. Results in chapter 6 show that tablets of similar hardness were obtained, but granules prepared with 244 required a lower compression force.

Particle size and size distribution, along with morphology, also play a crucial role in powder flow behavior. For fine particles (< 20 μm), van der Waals attraction is the predominant interaction force between solid surfaces, resulting in adhesion and/or cohesion. As the particle size increases, these forces decrease and powder flow is increased. As described in chapter 3, the morphology of SBA-15 and COK-12 is comprised of smaller particles that are covalently linked to form a larger conglomerated unit. This corrugated surface results in mechanical interlocking, contributing to poor flow. OMS flow properties are compared with DMS in chapter 5. Syloid® 244 exhibits a smoother surface and smaller particle size than COK-12. These morphological differences contributed to conflicting findings amongst different powder flow measurements. Because powder flow is influenced by many factors such as bulk density, particle size, size distribution, shape, moisture content etc., inconsistencies between methods are known to occur. Therefore, a great emphasis should be placed on understanding different powder flow measurements (e.g., static and dynamic) and their limitations to various particle sizes and morphologies. Along with the material characteristic, the process mechanism of interest should also be kept in mind. In light of this, selecting a mesoporous silica material with a smoother surface is also expected to result in a more even binder distribution around the particle and/or granule.

7.1.3 Pore structure

Our research also illustrated the importance of pore size and structure during the granulation process. Due to stronger capillary forces, smaller pores found in 244 are first filled with binder during granulation (chapter 5). While our results show that pore size differences did not appear to affect the risk of extracting the drug from the pores during processing, the likelihood of this should not be completely ruled out. Also, several studies illustrate the advantage of using ordered pores for better control of the drug loading and release kinetics [47-49, 61]. Therefore, the same theory could be applied towards controlling the binder distribution in the pores during granulation.
Because the OMS production scale is still limited, DMS materials such as Syloid® 244 offer a more economical alternative. However, current theoretical prediction models are mainly developed for simple pore geometries such as the COK-12 cylindrical design and therefore, more effective in correlating experimental results. As the OMS synthesis technology evolves towards larger production scales, development costs associated with trial and error experiments are expected to be less with OMS and eventually, may surpass the cost differences of the materials themselves.

7.2 Evaluation of agglomeration processes
As discussed in section 1.12, all prior studies involving mesoporous silica tablets were prepared from physical mixtures. Here, reports of decreased release loss following tableting were consistent unless a high amount of excipient was incorporated [87, 116, 119]. The majority of this research involved the exploration of various manufacturing processes to improve the processability while maximizing the final dose. Early investigations indicated granulation as the favorable route. Our observations from various granulation processes are highlighted in this section.

7.2.1 Agglomeration with liquid binders
As discussed in chapter 4, the classic method to prepare powders for tableting, wet granulation, was first considered. This feasibility study demonstrated that granulation was a suitable approach but careful considerations to the process parameters are necessary. Agglomeration only occurred when the COK-12 was sufficiently moistened to form liquid bridges (pendular state). On the other hand, when COK-12 became overly wetted, the molecule extracted from the pores during processing, referred to as premature drug release (PDR). This is believed to occur when capillary forces pull the solvent into the pores and displaces the drug. Compared to H₂O/PVP binder solutions, this observation was more predominant in samples prepared with ethanol/PVP. Therefore, the standard wet granulation approach is not the most ideal system for mesoporous silica.

Interestingly, a compound’s solubility in the binder liquid does not increase the chance of PDR. Itraconazole was the only molecule that resulted in PDR, which was attributed to the lack of hydrogen bond donors and large molar volume. Prior to this study, a major attraction towards OMS development was based on the understanding that this approach was suitable for a wide range of physicochemical diverse molecules. While this idea is still applicable, additional process considerations are necessary when trying to formulate an API with similar characteristics.

The use of steam as a granulating medium instead of liquid water was evaluated in chapters 5 and 6. Compared to wet granulation, previous reports stated that granulating with steam required a significant reduction of water and also reduced the total processing time [176, 190]. A major finding from these investigations revealed that PDR is not only governed by the amount of solvent used, but more so by the properties of the binders themselves. As with the wet granulation feasibility study in
Discussion

chapter 4, certain process variables (e.g., amount of steam, steam addition rate) need to be kept in consideration when granulating with steam in order to avoid PDR.

7.2.1 *Solvent free agglomeration*

Melt granulation was considered as an alternative technique to avoid the employment of liquid during processing. Here, the molten substance acts like a liquid binder and the dry granules are obtained as the molten binder solidifies upon cooling. During the steam and melt granulation comparison study (chapter 5), all melt-granulated material resulted in PDR in both COK-12 and 244. In contrast to steam granulation, increasing the binder concentration increased the amount of PDR. Solid-state analysis indicated that degradation of the melt granulation binder, Poloxamer188, already occurs during the granulation process itself. Despite these observations, enhanced *in vitro* release rate was still maintained when compared to the crystalline form. Moreover, no additional drug extraction was observed following 6 months storage in stressed conditions of 40°C/75%RH. These results emphasize the importance of proper binder selection to successfully eliminate the risk of premature drug release.

Dry granulation (e.g., roller compaction) was not considered for a number of reasons. The primary argument against this was to avoid subjecting the mesoporous silica material to additional compression forces. Here, the material is compressed during pressure compaction and again during tableting. Based on results from chapter 3, this can contribute to structural damage and in turn, significantly hinder the release rate and/or increase the amount of required excipients. Furthermore, roller compaction and slugging generate a considerable amount of dust. Based on the particle size and nature of mesoporous silica, this can considerably jeopardize inhalation safety.

7.3 *Binder characteristics associated with premature drug release*

Based on our current findings, it is difficult to pinpoint the exact binder properties that contribute to premature drug release. Nor would these binder characteristics be applicable to all agglomeration processes and binder addition methods. During melt granulation, there was a clear trend that increasing the binder content increased the amount of PDR. Because Poloxamer 188 was the only binder investigated, it is difficult to determine the properties contributing to this. One hypothesis involves the combination of low viscosity and hydrophilicity, which results in an affinity to the silanol groups and thus, displaces the drug.

During wet granulation investigation, the binder was added as a solution, whereas steam was added to the dry mixture. In spite of these differences, our results suggest that viscosity plays a significant role when agglomerating with liquids. In chapter 4, we determine that the viscosity of ethanol/PVP was lower than H₂O/PVP at three different temperatures. Here, samples prepared with ethanol/PVP exhibited the most PDR. During steam granulation (chapter 6), result differences between PVP and HPMC were compared. PVP is known for being very hygroscopic whereas HPMC swells in the presence of water. Moreover, it is insoluble in hot water. Therefore, granules prepared with PVP
Discussion

exhibited more granule growth attributed to, or at least in part, it’s lower viscosity. However, PVP granulated material also exhibited the most premature drug release. Also, it is hypothesized that binders with a lower surface tension would be more likely to enter the pores during processing. However in chapter 6, HPMC resulted in a lower value than PVP despite its slightly surface active properties.

7.4 Future perspectives

The major area of exploration of down-stream processing involves elucidation of the PDR mechanism. As discussed in section 1.7, more polar drug loading solutions hamper the final drug load due to competitive interactions between the solvent and drug molecules with the silica surface. This was not investigated but should also be considered as a parameter that could influence PDR. There is also a need to understand if any differences in PDR occur when the binder is added as a dry mix or liquid. While our results indicate that viscosity plays a role in PDR, more research is required to make these observations conclusive. Due to compression forces during processing, our hypothesis was that dry granulation is not the most suitable for agglomerating mesoporous silica. However, knowledge in this area is greatly lacking. Applied forces typically range from 3-7 MPa, which is significantly below the lowest applied pressure of 72 MPa discussed in chapter 3 [129]. Moreover, most of the processes explored in this research are not ideal for heat labile compounds. For such instances, dry granulation could be a better alternative.

It is known that a molecules behavior in the pores is compound and drug loading dependent [97]. To date, most studies that investigate the behavior under confinement are mainly limited to a number of compounds (with conflicting observations). In separate studies, two populations of naphthalene and ibuprofen were identified using $^1$H NMR and dielectric relaxation spectroscopy, respectively [102, 191]. For naphthalene, less mobility was identified in the center of the pores whereas the opposite was reported for ibuprofen. Understanding the root cause of compound/drug loading dependency and confinement behavior is likely the rate-limiting step towards understanding why PDR is compound dependent. While it has been roughly 10 years since the interest in mesoporous silica as a solubility enhancer first began, it will likely involve additional years of development milestones before the first product is introduced to the market. Despite the factors that still require clarification and analysis, this approach has the potential to become a very powerful tool in overcoming the critical development challenges associated with poorly soluble compounds.
Chapter 8

Summary

The interest in mesoporous silica as a drug release enhancer for poorly soluble drugs is one of the more recent and burgeoning areas of drug development research. While their abundance of silanol groups, large specific surface area and porosity are attractive from a development perspective; these features attribute to low bulk density and hygroscopicity, resulting in undesirable tablet properties. Because oral drug delivery is undoubtedly the most attractive and extensively used approach to administer drugs, the objective of this research was to assess the down-stream processability of mesoporous silica for the development of an immediate release solid oral dosage form.

First, assessments in structure and release behavior following compression of itraconazole loaded and non-loaded ordered mesoporous silica (OMS) materials SBA-15 and COK-12 were evaluated. Due to the thicker pore walls and a higher degree of silicate condensation, COK-12 was more resistant to compression than SBA-15. This material strength translated into superior in vitro release behavior following compression. Based on these findings, COK-12 was the OMS selected for further investigations.

Granulation was identified as a necessary step to improve OMS powder flow, compression and compaction properties required for tableting. The classic approach, wet granulation, was investigated as a feasibility study using polyvinylpyrrolidone (PVP) to determine the risk of extracting the drug out of the pores during processing. This phenomenon, referred to as premature drug release (PDR), was determined as dependent on both compound and processing conditions. Four poorly water-soluble compounds were selected for this investigation: itraconazole (weakly basic), fenofibrate (neutral) and naproxen and ibuprofen (weakly acidic). Due to the lack of hydrogen bond donors and large molar volume, itraconazole was identified as the highest risk for premature drug release.

The usefulness of granulation techniques able to reduce or avoid the employment of water during the process was considered. Therefore, agglomeration with steam and melting were considered as a more suitable alternative to wet granulation. All granulates were prepared in a laboratory-scale high-shear mixer. In this two part study, we first assess the difference in granulation behavior and granule properties of disordered mesoporous silica (DMS) and OMS material, Syloid® 244 and COK-12, respectively. Granules prepared with PVP from steam resulted in the overall largest size but slowest in vitro drug release.

PDR was most prevalent in melt-granulated samples. However, no additional drug extraction was observed following 6 months storage at 25°C/60%RH and 40°C/75%RH. In vitro release following storage slightly increased and decreased for 244 and COK-12 melt-granulated material,
Summary

respectively. Analysis of the melt granulation binder, Poloxamer 188, indicated that degradation already occurs during the granulation process itself. Compressibility between the two silica materials differed, in which granulated material from DMS resulted as the best performers.

Chapter 6 identifies the key the process variables using a quarter-fraction factorial design with six factors at two levels and compares various physicochemical properties of steam-granulated 244 prepared with PVP and HPMC from six responses. Results show that granules prepared from PVP resulted in an overall higher bulk density, granule size, increased flow properties and better compression and compaction behavior. However, PDR was most prevalent with PVP. These analyses indicate the risk of extracting the drug from the pores during processing is not only governed by the amount of solvent used but more so by the binder properties. Due to poor binder distribution, results from granules prepared with HPMC were more variable but resulted in superior in vitro release behavior.

These studies elucidate the understanding of mesoporous silica structural and release behavior following compression for the advancement as a drug delivery carrier. Furthermore, factors that increase the risk of unwanted drug extraction during mesoporous silica material are identified. The key process parameters are also identified that potentially will play a significant role for preparation for a successful scaled-up manufacturing process.
Hoofdstuk 8

Samenvatting

Het gebruik van mesoporeuze silica om de geneesmiddelvrijstelling van slecht oplosbare farmaca te verhogen heeft een grote interesse gewekt in de geneesmiddelenontwikkeling. Hoewel de hoge concentratie aan silanolgroepen, het grote specifiek oppervlak en porositeit van het materiaal voordelig zijn m.b.t. de ontwikkeling van slecht oplosbare farmaca, zullen deze eigenschappen ook bijdragen tot lage bulkdichte en hygroscopiciteit, wat bijvoorbeeld zal resulteren in slechte tableteereigenschappen. Aangezien orale toediening van geneesmiddelen ontegensprekelijk de meest attractieve en meest gebruikte toedieningswijze is, was de doelstelling van dit onderzoeksproject om de haalbaarheid te bestuderen van de processeerbaarheid van mesoporeuze silica tot vaste orale doseringen voor onmiddellijke geneesmiddelenvrijstelling.

In een eerste deel werd de structuur en het vrijstellingsgedrag na compressie van mesoporeuze silica (OMS) en SBA-15 beladen met itraconazole bestudeerd. COK-12 bleek meer resistent tegen compressie dan SBA-15 omwille van de dikkere poriewanden en een hogere graad van silicaatcondensatie. Deze materiaaleigenschappen werden vertaald in superieure in vitro geneesmiddelenfrijstelling na compressie. Op basis van deze data werd besloten om COK-12 te selecteren voor verder onderzoek.

Granulatie was een noodzakelijke stap om de vloeit-, compressie-, en compactie-eigenschappen van OMS te verbeteren. Natte granulatie met polyvinylpyrrolidone (PVP) als binder werd bestudeerd om het risico na te gaan van extractie van het geneesmiddel uit de poriën tijdens het granulatieproces. Vroegtijdige vrijstelling van het geneesmiddel uit de poriën tijdens het granulatieproces was afhankelijk van zowel het geneesmiddel ook de procescondities. Vier slecht water oplosbare geneesmiddelen werden voor deze studie geselecteerd: itraconazole (zwak basische eigenschappen), fenofibraat (neutrale stof) en naproxen en ibuprofen (beide zwak zure geneesmiddelen). Itraconazole bleek het meest gevoelig voor extractie uit de poriën tijdens het proces omwille van de afwezigheid van waterstofbrugdonoren en het grote molaire volume van dit geneesmiddel.

In een volgende stap werden granulatieprocessen bestudeerd die minder of geen granulatievloeistof (water) nodig hebben. Aldus werden stoom- en smeltgranulatie bestudeerd. De granulaten werden in een laboratoriumschema high shear menger geproduceerd. In het eerste deel van deze tweeledige studie werd het verschil in granulatiegedrag en granulaateigenschappen onderzocht van granulaten op basis van ongeordende en geordende mesoporeuze silica, t.t.z., Syloid 244 en COK-
Samenvatting

12. Granulaten die werden geproduceerd met PVP als binder resulteerden in materialen met globaal de grootste afmeting maar de laagste *in vitro* geneesmiddelenvrijstelling.

Extractie van het geneesmiddel uit de poriën was het meest uitgesproken bij smeltgranulatie. Echter, na 6 maand bewaring van deze granulaten bij 25°C/60%RH en 40°C/75%RH was er geen verdere toename in geneesmiddelextractie. Na bewaring van de granulaten werd een verhoging en een verlaging van de geneesmiddelenvrijstelling waargenomen voor Syloid 244 en COK-12, respectievelijk. Er werd eveneens vastgesteld dat de binder in het smeltgranulatieproces, Poloxamer 188, degradeerde tijdens het granulatieproces. De comprimeerbaarheid van de twee silicametrialen was verschillend, waarbij het gegranuleerde Syloid 244 de beste eigenschappen vertoonde.

In hoofdstuk 6 worden de belangrijkste procesparameters voor stoomgranulatie met Syloid 244 en PVP of HPMC als binder geïdentificeerd en worden verschillende fysicochemische eigenschappen van deze materialen vergeleken. Voor deze studie werd een vierde factoriele design met zes factoren op twee niveaus uitgevoerd. Granulaten met PVP als binder hadden een hogere bulkdichtheid en granulegrootte, verbeterde vloei-, compressie-, en compactie-eigenschappen. Echter, met deze binder werd ook de hoogste extractie van het geneesmiddel tijdens het granulatieproces vastgesteld. De resultaten van de studies tonen aan dat niet enkel de hoeveelheid solvent die tijdens het granulatieproces wordt gebruikt bijdraagt tot extractie van het geneesmiddel uit de poriën, maar evenzeer de binder. Granulaten bereid met HPMC als binder waren meer performant met betrekking tot geneesmiddelenvrijzetting, doch de granulaateigenschappen waren minder herhaalbaar omwille van minder goede distributie van de binder.

Het onderzoek beschreven in deze thesis draagt bij tot het begrijpen van de structuur van mesoporeuze silica en de geneesmiddelenvrijstellingseigenschappen na compressie van dit materiaal. Deze kennis is noodzakelijk om mesoporeuze silica uiteindelijk tot een volwaardige carrier in farmhouseformuleringen te brengen. Verder werden belangrijke factoren geïdentificeerd die oorzaak kunnen zijn voor extractie van een geneesmiddel uit de poriën tijdens een granulatieproces. Tenslotte werden in dit onderzoek procesparameters geïdentificeerd die een belangrijke rol kunnen spelen tijdens een opgeschaald productieproces.
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• Method development and validation for high-throughput screening of polymorph and salt forms
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Curriculum Vitae

Nektar Therapeutics; Research Associate II           Dec 2003 - May 2007
- Laboratory and equipment owner/manager
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- Package design (WVTR) and shelf-life prediction modeling
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