CHAPTER

8

Amorphous drug stabilization using mesoporous materials

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1. Background

The use of mesoporous materials in pharmaceutical applications has received increasing attention over the last decade due to their ability to stabilize the amorphous form and enhance the oral bioavailability of poorly soluble drugs. This is also reflected in the number of recent literature reviews, of which [1–6] provide an excellent and detailed overview of the advances within the field. Rather than summarizing the field again, this chapter focuses on recent findings that point towards the importance of understanding the physical form that a drug can have upon loading onto the mesoporous materials. Once loaded into the mesopores, the drug molecules can be either adsorbed directly to the pore surface, i.e., the drug monolayer, or be present as additional amorphous drug layers that are not in direct contact with the pore surface but confined inside the pores, i.e., pore filling. With this in mind, this chapter aims to provide an overview of the key findings, current trends and perspectives in the use of mesoporous materials as amorphous drug carriers.

2. Introduction

Since the introduction of modern medicine, oral drug delivery has remained the preferred route of administration mainly due to high patient safety and compliance, and low cost of production compared to topical and parenteral administration [7]. To reach systemic circulation, the drug must dissolve in the gastrointestinal fluid before it can permeate the intestinal epithelial [8]. Therefore it is generally recognized that the rate and extent of drug absorption is controlled by the aqueous solubility and permeability of the drug [9,10].

With the introduction of combinatorial chemistry and high-throughput screening methods in the 1990s, the number of potent drug candidates is increasing. However, because these target-selective drugs are often highly hydrophobic, it is estimated that up to 90% of all small molecules in the current drug discovery pipelines have limited oral bioavailability due to poor aqueous solubility [11,12]. Therefore the development of strategies to improve the aqueous solubility of these drug candidates currently constitutes one

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of the biggest challenges for the pharmaceutical industry [13,14].

Perhaps the most promising and effective approach to increase the aqueous solubility and dissolution rate of a drug is through amorphization [15]. The amorphous form of a drug lacks the long-range molecular order of a crystal and has higher molecular mobility and free energy. As a result, less energy is required to separate the molecules in an amorphous material and ergo it has increased (apparent) aqueous solubility and dissolution rate compared to its crystalline counterpart [16]. In this regard, Wendelboe et al. showed that the apparent solubility of the nonsteroidal antiinflammatory drug (NSAID) celecoxib was increased fourfold after amorphization. This increase in apparent solubility had positive implications in rats, where the oral bioavailability of neat amorphous celecoxib was twofold higher compared to crystalline celecoxib [17]. However, due to their high free energy, neat amorphous drugs are also thermodynamically unstable and tend to nucleate and ultimately devitrify into the stable, but poorly soluble, crystal form [18–20]. Consequently, the stabilization of the amorphous form of a drug is critical for this formulation approach to succeed [21].

Different technological approaches have been demonstrated to stabilize the amorphous form of a drug, the most publicized being inclusion complexation with a cyclodextrin [22], molecular solid dispersion in a polymer [23,24], coamorphization with another small molecule [21,25], and adsorption to a mesoporous material [3,21]. All of these approaches have in common multicomponent amorphous mixtures where the addition of an excipient stabilizes the amorphous form of the drug. However, the approaches differ in the type of excipient used and the resulting mechanism of stabilization. When using cyclodextrins, the drug is incorporated into the hydrophobic cavity of the cyclodextrin, resulting in an inclusion complex. When using polymeric carriers, the drug is antiplasticized by the polymer and may additionally be dissolved in the polymer below its saturation solubility. A co-amorphous system is comprised solely of low molecular weight components, e.g., the drug and an excipient, and stabilization of the amorphous form is achieved by strong molecular interactions between both components. Lastly, mesoporous carriers offer a large surface area for drug adsorption and narrow pores that can accommodate additional amorphous drug.

Zingone et al. found that the physical stability of the anticoagulant drug warfarin was increased to >12 months through inclusion complexation with β-cyclodextrin. The *in vitro* dissolution rate and aqueous solubility of the inclusion complex was also increased 28-fold compared to crystalline warfarin, suggesting that this approach can improve the oral bioavailability [26]. Rask et al. found that the physical stability of celecoxib could be ensured through molecular solid dispersion in the polymer polyvinylpyrrolidone (PVP) and the co-polymer polyvinylpyrrolidone-*co*-vinylacetate (PVP/VA) [27]. Knopp et al. found that the apparent solubility of the same polymeric amorphous solid dispersions was increased eightfold and the oral bioavailability in rats threefold compared to crystalline celecoxib [28]. Maher et al. found that the physical stability of the atypical antipsychotic drug olanzapine was increased to >3 months through coamorphization with ascorbic acid. This formulation also improved oral bioavailability in humans compared with marketed reference products Olazine and Zyprexa [29]. In a study by Kasten et al., similar findings were demonstrated after coamorphization of the NSAID drug naproxen with the amino acid arginine [30]. However, common for these three approaches (cyclodextrin complexation, polymer dispersion, and coamorphization) is that the amorphous drug in most of the systems is physically/kinetically stabilized through reduction of molecular

mobility. This means that these systems are thermodynamically unstable and will eventually crystallize, and only a long-term stability study may reveal whether this inevitable event will occur after several months, years, or even decades [21].

From a regulatory point of view, it is vital that a drug product meets the quality specifications at the time of release as well as during the entire shelf life. If an amorphous drug crystallizes during storage, not only will the solid-state properties of the drug change, but also the dissolution performance will change dramatically, which may influence the clinical performance and can ultimately lead to withdrawal or removal from the market [31]. Trasi et al. emphasized this challenge for the marketed product Accord 5 mg in which the immunosuppressant tacrolimus is molecularly dispersed in the polymer hydroxypropylmethylcellulose (HPMC). Even though the study did not evaluate the clinical consequences of the observation, it demonstrated that the drug crystallized rapidly when stored under open bottle stress conditions [32].

However, the inherent thermodynamic instability of amorphous drugs can be circumvented through adsorption to a mesoporous material. Due to the large surface of mesoporous materials, which provides additional surface free energy, Qian and Bogner have shown that adsorption of an amorphous drug onto the surface of a mesoporous material is thermodynamically favorable [33]. Furthermore, in 2018, Hempel et al. showed that amorphous drugs could be thermodynamically stabilized through monomolecular adsorption to the surface of mesoporous materials [34]. In addition, Vialpando et al. demonstrated that not only was the oral bioavailability of the anthelmintic drug flubendazole in rats sixfold higher when adsorbed to an ordered mesoporous silica (MS) compared to crystalline flubendazole, but also threefold higher than when the drug was formulated as an amorphous solid dispersion in HPMC [35].

Based on the foregoing, it seems that the limited oral bioavailability associated with the increasing number of poorly soluble molecules in the drug discovery pipelines can potentially be overcome. In this regard, mesoporous materials have emerged as an encouraging alternative to existing technologies. Besides the ability to thermodynamically stabilize the amorphous form of a drug, mesoporous materials also have a number of attractive features for enhancing drug dissolution, such as large surface area and pore volume, which also enables them to accommodate a relatively high drug load [3].

3. Mesoporous materials

Mesoporous materials are widely known for their versatility in scientific applications such as chromatography, chemical detection, catalysis, ion exchange, as well as for confining guest molecules (such as drugs) in their pores [2,36].

Although the first mesoporous material was synthesized in 1968 [37], the remarkable features of these products were not immediately recognized, probably due to the lack of detailed characterization at the time. This changed in 1991 when Mobil Research and Development Corporation introduced a range of ordered mesoporous materials with a pore diameter of 1.6−10 nm named Mobil Composition of Matter (MCM) [38−40]. It has been suggested that the uniformity of the pores offered new opportunities for applications in, e.g., chemical catalysis and separation. The different MCM grades vary mainly on their morphology. Probably the most widely explored mesoporous material, MCM-41, has a hexagonal pore structure, MCM-48 has a cubic pore structure, and MCM-50 has a lamellar pore structure [5].

In 1998, Zhao et al. from the University of California, Santa Barbara, synthesized mesoporous materials with a larger pore diameter of 4.6–30 nm [41,42]. These materials were named Santa Barbara Amorphous (SBA) and had superior thermal, mechanical, and chemical resistance properties compared to MCM, thus making them particularly suitable for use in catalysis. The different SBA grades also come with different morphologies, SBA-11 and SBA-16 having cubic pores and SBA-15 having hexagonal pores [5].

Ordered mesoporous materials are mainly synthesized through a sol-gel process using the liquid crystal templating mechanism. In simple terms, this involves self-assembly of a mineral precursor (metal oxide) into a framework of particles around a structure-directing amphiphilic template, usually a surfactant or a block copolymer, after which the template is removed by calcination or extraction. The structure, composition, and pore size of these materials can thus be tailored during synthesis by variation of the reaction conditions and stoichiometry, the mineral precursor, and the nature and size of the template, or by postsynthesis functionalization techniques [43,44].

Since the early developments of MCM and SBA, research efforts have been devoted to the synthesis and characterization of a large variety of different, although related, mesoporous materials of highly controlled pore size and morphology. Therefore, in the early 2000s, the International Union of Pure and Applied Chemistry recognized the need for a system of terms, whose definitions were generally accepted. Consequently, a mesoporous material was defined as an amorphous or crystalline inorganic framework of different structural arrangements and morphologies with a pore size in the range of 2–50 nm. They can be classified according to their morphology and typical examples include 2D/3D cylindrical or 3D cage-type structures with cubic, hexagonal, or lamellar pore geometry [45]. Fig. 8.1 illustrates the shape, morphology, and pore channels of three different types of MS.

4. Structural characterization of mesoporous materials

Characterization of the volume, pore connection, pore diameter, and specific surface area of a mesoporous matrix is essential to predict the behavior of the material, from postsynthesis evaluation to its performance in specific applications. Several characterization techniques have been proposed in the literature, but gas adsorption/desorption, X-ray powder diffraction (XRPD), and transmission electron microscopy (TEM) are routinely used to elucidate the structural and textural properties of mesoporous materials for pharmaceutical applications [50,51].

Gas (often N_2) adsorption/desorption is a method used to obtain comprehensive information on the surface area, pore volume, and pore size distribution of a porous material. The principle of this method is based on the Langmuir adsorption model that describes the amount of adsorbate (gas) that can be adsorbed to a surface as a function of pressure, assuming that the gas exhibits ideal behavior at isothermal conditions. Mesoporous materials are normally analyzed in the pressure range associated with capillary condensation, which is generally accompanied by a hysteresis loop in the adsorption–desorption isotherm [51]. This hysteresis loop is characteristic for the porous material; the height of the loop reflects the volume of the pores and the accentuation of the loop inflection reflects the pore size distribution. Consequently, the surface area and pore size distribution can be derived from the hysteresis loop by the application of procedures based on the Kelvin equation such as the Brunauer–Emmett–Teller theory [52]. Using N_2 isotherms, Zhang et al. demonstrated the formation of a monolayer of the angiotensin II receptor antagonist telmisartan on an MS material through a

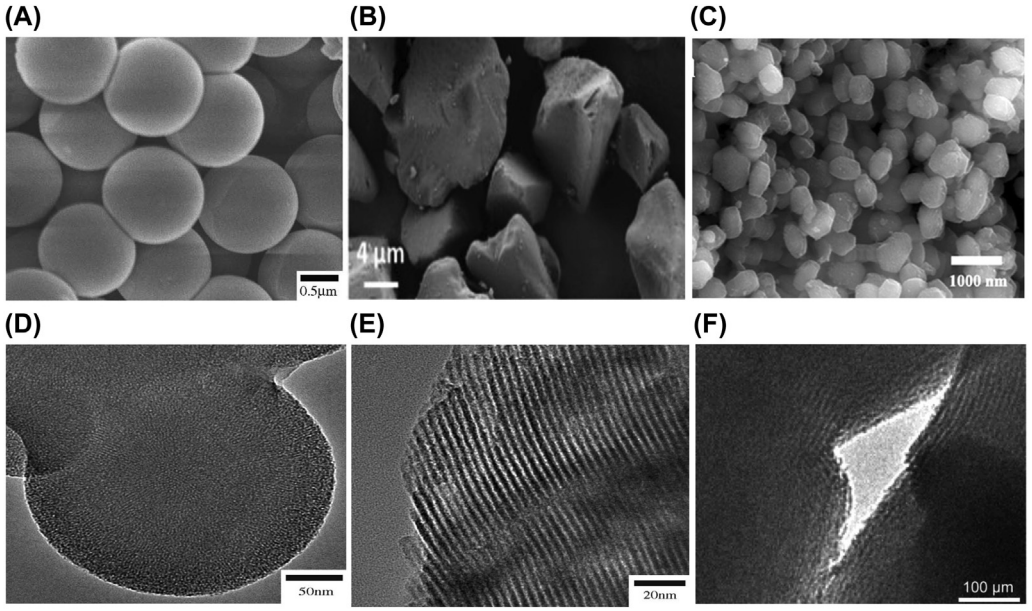

FIGURE 8.1 Scanning electron microscopy images of the mesoporous silica (A) MCM-41 [46], (B) Parteck SLC [47], and (C) SBA-15 [48], as well as transmission electron microscopy images showing the pore channels of MCM-41 (D and E) [46] and SBA-15 (F) [49]. *Adapted with permission from Qu F, Zhu G, Lin H, Zhang W, Sun J, Li S, Qiu S. A controlled release of ibuprofen by systematically tailoring the morphology of mesoporous silica materials. J Solid State Chem 2006;179:2027–2035; Pang J, Zhao L, Zhang L, Li Z, Luan Y. Folate-conjugated hybrid SBA-15 particles for targeted anticancer drug delivery. J Colloid Interface Sci 2013;395:31–39; Krajnović T, Maksimović-Ivanić D, Mijatović S, Drača D, Wolf K, Edeler D, Wessjohann L, Kaluđerović G. Drug delivery system for emodin based on mesoporous silica SBA-15. Nanomaterials 2018;8:322. Copyright 2006, 2013, 2018 Elsevier and 2018 MDPI.*

decrease in the surface area and pore volume after loading [53].

XRPD is one of the most widely used tools for characterizing the solid-state structural properties of a material. The principle of this method is governed by Bragg's law, describing the diffraction of a monochromatic X-ray on an atomic plane. When X-rays are directed towards a plane of crystalline material with molecules arranged in a highly ordered lattice, the X-rays will be diffracted at the same angle, which is correlated to the spacings between the plane of molecules in the lattice. The resulting diffraction pattern then represents a characteristic fingerprint for that given crystal. In contrast, if the X-rays are directed towards a plane of highly disordered amorphous material, the X-rays will be diffracted in all directions and therefore no specific diffraction pattern is observed [54]. Using this technique, Shen et al. showed that the drug ibuprofen upon adsorption to SBA-15 remained amorphous for >12 months [55].

It is not straightforward to resolve the structural properties and morphology of a mesoporous material based on XRPD data even for a relatively simple 2D structure. However, this can easily be observed by high-resolution TEM imaging if the images can be recorded along the channel direction [50]. In a TEM, a thin sample specimen is illuminated with an electron beam generated by a thermoionic source or a high-voltage accelerated gun under vacuum. When the beam passes through the specimen (transmission), the electrons will either scatter or hit a fluorescent screen at the bottom of the microscope, depending on the density of

the sample. The different intensities of the electron beams impacting the fluorescent screen will then result in a contrast image of the specimen [56]. Using TEM, Kimura et al. demonstrated the formation of square channels in a novel ordered MS denoted KSW-2 [57]. Other types of microscopy, such as scanning electron microscopy and atomic force microscopy, may also be employed, but TEM is one of the most commonly used techniques for microstructural characterization of mesoporous materials.

5. Mesoporous materials in drug delivery

Although mesoporous materials offer a range of different applications, the objective of this chapter is to give an overview of the use of mesoporous materials in oral drug delivery and particularly in the stabilization of amorphous drugs. Several mesoporous materials have been developed and used with the premise of drug delivery, including the MS grades TUD-1, COK-12, and HMM-33 [58–60]. Each of these materials has its own physical–chemical and morphological characteristics, allowing personalization of its use in drug delivery. However, to the best of our knowledge only two commercially available grades of MS, Parteck SLC from Merck Millipore and SilSol 6035 from W.R. Grace and Co., were developed specifically for oral bioavailability enhancement of poorly water-soluble drugs through amorphous drug stabilization. Besides these two grades, other commercially available mesoporous materials such as MS Aeroperl 300 from Evonik Industries and mesoporous magnesium aluminometasilicate Neusilin US2 from Fuji Chemical Industry Co. have also been studied for similar purposes [61–63].

In 1979, Yang et al. were among the first to systematically show that the dissolution of drugs can be improved by incorporating them in mesoporous material and many other researchers since followed working on this principle [64]. Subsequently, the ability of these materials to stabilize the amorphous form of a drug was investigated [3,65,66]. In 2009, Nolte et al. from Capsulation Pharma filed a patent application for the CapsMorph technology in which amorphous drugs were stabilized through deposition in sponge-like carrier matrices, i.e., mesoporous materials [67]. In a later study by Wei et al. it was shown that 30 formulations produced using this technology were still fully amorphous even after 3 years of storage [68]. Finally, the increased *in vitro* performance of MS formulations has also shown to manifest in increased bioavailability compared to commercial products in various *in vivo* models, including rats, dogs, pigs, and even humans [6]. Nevertheless, despite the active research and promising outlook, the first pharmaceutical product containing amorphous drug stabilized in a mesoporous material is still to reach the market.

6. Different forms of the loaded drug: monolayer versus pore filling

As outlined in the introduction, it has been shown that the drug monolayer, i.e., the drug directly adsorbed to the surface of the mesoporous materials, is thermodynamically favorable over the crystalline state of the drug [33]. Furthermore, additional drug layers can be loaded on top of the monolayer until the pores are completely filled if the pore diameter is large enough to accommodate more than the monolayer. The amorphous form of a drug resulting from pore filling is stabilized by a size-constrained effect, i.e., if the pore diameter is smaller than the critical crystal nuclei, the drug cannot crystallize within the pores [69]. Any drug that is not in the monolayer or constrained inside the pores does not perceive the foregoing stabilization, and hence it behaves as neat amorphous drug. The different forms in which a drug can exist once loaded onto a mesoporous material are illustrated in Fig. 8.2.

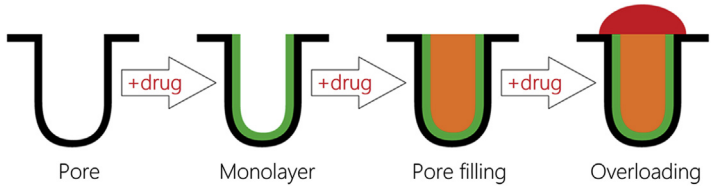

FIGURE 8.2 Schematic illustration of a single pore in a mesoporous material (*black*). Upon addition of drug, the pore surface is initially covered by drug monolayer, which is in direct contact with the pore surface (*green*; light gray in printed version). Upon further addition, the drug will start filling up the pore (*orange*; gray in printed version) and once the pores are completely filled, it will also overfill the pores (*red*; dark gray in printed version).

Given the different mechanism of amorphous stabilization (monolayer vs. pore filling) or lack of stabilization (overfilling), it is therefore crucial to know how much drug can be loaded as a monolayer, i.e., the monolayer loading capacity (MLC), and for pore filling, i.e., the pore filling capacity (PFC).

In 2018, Hempel et al. developed a differential scanning calorimetry (DSC)-based method, which allows for reliable determination of the maximum MLC of drugs with good or moderate glass-forming ability [34]. Briefly, the method is based on a heat/cool/heat protocol, where an excess of drug is melted and mixed with the mesoporous materials *in situ*. The melt is allowed to fuse into the pores and subsequently the excess amorphous drug that did not adsorb to the pore surface (i.e., everything above the MLC) is quantified via the change in heat capacity (ΔC_p) over the glass transition temperature (T_g). The method takes advantage of the monolayer not contributing to the T_g and ΔC_p signal in the DSC thermograms. Consequently, since ΔC_p decreases as a function of the amount of excess amorphous drug, the MLC of the drug in the mesoporous matrix can be obtained by extrapolating ΔC_p to zero (Fig. 8.3).

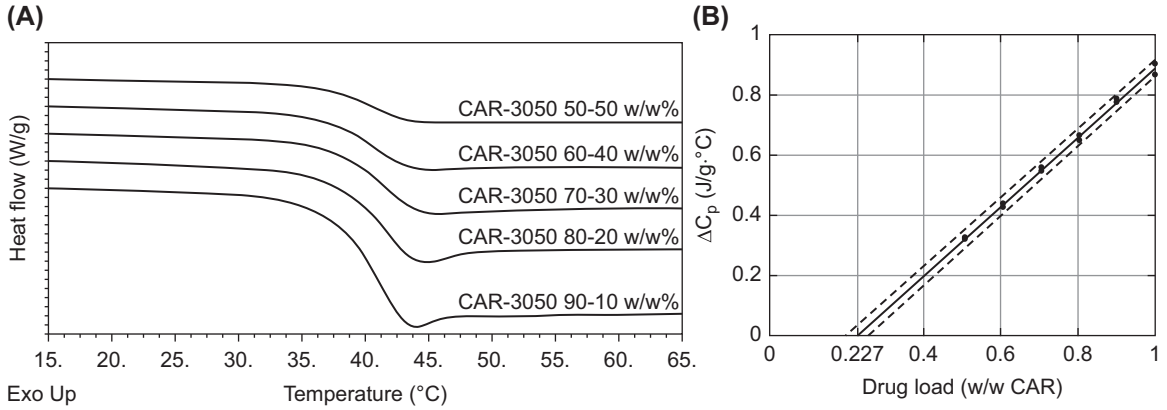

FIGURE 8.3 (A) Differential scanning calorimetry thermograms of carvedilol and the mesoporous silica Syloid 3050 at drug loadings from 50% to 90% (w/w), i.e., above the monolayer loading capacity (MLC). The glass transition temperature (T_g) is indicative of an amorphous carvedilol fraction and the change in heat capacity (ΔC_p) is proportional to the amount of amorphous carvedilol. (B) Linear extrapolation of the ΔC_p values as a function of carvedilol loading. The *x*-intercept indicates the MLC as 22.7% (w/w). *Reprinted with permission from Hempel N-J, Brede K, Olesen NE, Genina N, Knopp MM, Löbmann K. A fast and reliable DSC-based method to determine the loading capacity in mesoporous silica. Int J Pharm 2018;544:153–157. Copyright 2018 Elsevier.*

Based on this method, Bavnhøj et al. investigated the correlation between the MS textural properties (surface area, pore volume, and pore size) and their ability to load drugs with different amorphous densities [70]. In this regard, the authors introduced a theoretical means to estimate the MLC (Eq. 8.1), i.e., *tMLC*:

$$tMLC\ (wt\%) = \frac{\frac{A_{MS} \cdot M_{w(drug)}}{A_{drug} \cdot N_A}}{1 + \frac{A_{MS} \cdot M_{w(drug)}}{A_{drug} \cdot N_A}} \cdot 100\% \tag{8.1}$$

where A_{MS} is the surface area of the MS, $M_{W(drug)}$ is the molecular weight of the drug, A_{drug} is the minimal projection (surface) area of the drug assuming that the drug molecules are densely packing themselves on the pore surface, and N_A is the Avogadro constant. Furthermore, Bavnhøj et al. also introduced a theoretical means to estimate the theoretical PFC (Eq. 8.2), i.e., *tPFC* [70]:

$$tPFC = \frac{V_{MS\ pore} \cdot \rho_{drug}}{1 + V_{MS\ pore} \cdot \rho_{drug}} \cdot 100\% \tag{8.2}$$

where $V_{MS\ pore}$ is the pore volume of the MS and ρ_{drug} is the amorphous density of the drug.

The authors found that the experimental MLC is generally directly proportional to the available surface area of the MS, i.e., with increasing surface area higher MLCs can be obtained. In addition, the experimental MLC values obtained from the aforementioned DSC method were in good agreement with the *tMLC* calculated from Eq. (8.1). However, since Eq. (8.1) assumes that drug molecules are able to cover the entire surface of the mesoporous material, deviations between the experimentally obtained MLC and the *tMLC* were observed for one MS grade because of its small pore size. In this care, the pore diameter was too narrow and the space within the pores was insufficient to (1) accommodate two molecules on opposing pore sides allowing the formation of a "perfect" monolayer, and/or (2) limit their access to the entire available surface area. Rather than forming a perfect monolayer, the narrow pores are filled up by the drug molecules and one molecule may also occupy opposing sites of the pore walls. Hence, for this MS grade, the experimentally obtained MLC was in agreement with the prediction based on Eq. (8.2), which in turn suggested that Eq. (8.2) can be used to estimate the PFC of a given mesoporous material. Fig. 8.4

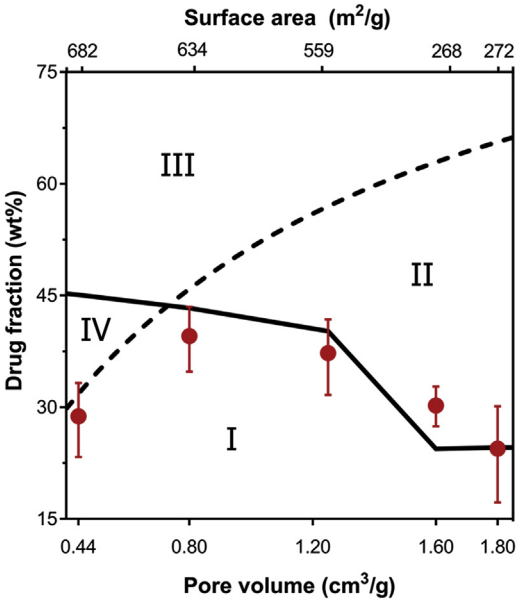

FIGURE 8.4 Experimentally determined monolayer loading capacity (MLC) (*red dots*; gray in printed version) values for the nonsteroidal antiinflammatory drug paracetamol in different mesoporous silica grades (Sylysia) with varying surface areas and pore volumes. The *solid and dotted lines* represent the *tMLC* and *tPFC*, respectively. The graph can be divided into four zones: Zone I represents drug loadings below the MLC. The drug loadings in Zone II are those resulting from the pore filling. In Zone III, the pores are overloaded. The pores are also overloaded in Zone IV, but the full potential of a perfect monolayer is not fulfilled since the pores are too small. *Adapted with permission from Bavnhøj CG, Knopp MM, Madsen CM, Löbmann K. The role interplay between mesoporous silica pore volume and surface area and their effect on drug loading capacity. Int J Pharm 2019;X:100008. Copyright 2019 Elsevier.*

summarizes the correlation of the MLC and PFC and their dependency on the available surface area and pore volume of the mesoporous material.

7. Drug loading techniques

7.1 Solvent-based loading

Currently, the majority of methods to load drug molecules onto mesoporous carriers use organic solvents in which the drug is dissolved. Probably the most rudimental technique is the solvent immersion method [71], where a mesoporous carrier is added to a solution of known drug concentration in a volatile solvent. The system is kept under agitation for a predetermined time to allow the drug to adsorb to the surface of the carrier, and finally the solvent is removed using filtration and drying. Using this method, the polarity of the solvent and affinity of the drug to the solvent and carrier surfaces have an influence on drug-loading efficiency [72,73]. In this regard, it has been shown that the use of solvents with high polarity, such as dimethylacetamide, may result in low drug loading, whereas the use of solvents with low polarity, such as hexane, results in relatively high drug loading [72,73]. Since the solvent will also interact with the surface of the mesoporous carriers, it is in competition with drug to bind to the surface and hence the polarity of the solvent and affinity to the surface of the mesoporous carrier are crucial for successful drug loading using this technique. Given the adsorption of the drug to the surface of the carrier from solution, it is likely that only drug loadings below the MLC can be achieved using this method.

Another frequently used and simple solvent-based loading technique is the incipient impregnation method, which is based on the use of a concentrated drug solution in a volatile solvent, which is sprayed onto the dry mesoporous carrier. The solution is adsorbed into the pores by capillary forces and the solvent can then be removed by heating. By repeating this procedure several times, much higher drug loadings can be achieved compared to the solvent immersion method [3,74], potentially also above the MLC. Other commonly used organic solvent-based methods such as the solvent drying method [58,75] or spray drying [76,77] have also been reported.

Since a loading technique based on organic solvents requires the careful removal of all residual solvents to ensure that the final system can be considered safe and nontoxic, applications of supercritical carbon dioxide (CO_2) have been investigated for solvent-based drug loading onto mesoporous carriers [78,79]. Similar to the foregoing methods, the drug is dissolved in supercritical CO_2 (7.37 MPa, 31.2°C), allowed to penetrate the porous matrix, and subsequently the solvent is removed by depressurizing the system. However, drug loading using supercritical CO_2 is still less frequently used compared to other methods, given that it is more complex and requires specially designed equipment [80].

7.2 Solvent-free loading

In the past few years, there have been increasing reports of solvent-free loading techniques to avoid the use of large quantities of organic solvent, their subsequent removal, and the risk of potentially toxic solvent residuals in the product. A very simple means of loading a mesoporous carrier with a drug is by melting the crystalline drug in the presence of the carrier [81]. The molten drug can then simply fuse into the pores by capillary forces. As outlined

earlier, this approach was utilized for the determination of the MLC and PFC [34,70]; however, it can in theory also be used to obtain different degrees of drug loading, both below or above the MLC and PLC. To upscale the melt loading, Hoashi et al. and Genina et al. investigated hot melt extrusion of MS in the presence of drugs [82,83]. Both studies, however, showed limitations, since either high drug loadings (50 wt%), potentially above the MLC, were required to make the extrusion process feasible given that the MS remains solid during the process [82], or the addition of a processing polymer was necessary [83]. In the latter, the authors observed that the drug in addition to its loading onto the MS also dissolved to some degree in the polymer phase, hence distributing itself between the MS and polymer. Furthermore, any loading based on melting requires the thermal stability of the drug during processing at elevated temperatures.

It has also been shown that loading of a compound onto mesoporous carriers can be achieved through the gas phase in a closed system. For example, compounds with very high vapor pressure, such as the organic synthesis precursor naphthalene, sublimates from the crystalline phase and adsorbs onto the MS surface [33]. Given that this process was spontaneous, the authors calculated the thermodynamics of amorphization and were able to show that the adsorbed naphthalene molecules in the monolayer have a lower free energy than in crystalline naphthalene. In other words, the drug monolayer is thermodynamically more favorable than the crystalline form. Since this process requires a compound to have a very high vapor pressure, it may not be applicable to actual drug molecules. However, the study also showed that the adsorption process can be facilitated through physical contact for the two drugs ibuprofen and diflunisal (having a lower vapor pressure than naphthalene) and the mesoporous material. Similarly, other studies showed that amorphization through adsorption onto mesoporous surfaces can be achieved by simple mixing processes. Here, it could be shown that the physical contact [84,85], reduced pressure [84–86], increased temperature [84–86], mixing time [84,87], drug particle size [87], and the right drug-to-MS ratio [87] (most likely $\leq$MLC) influence the kinetics of this process. When intensifying the contact between the drug and the carrier, e.g., using vibrational ball milling, the kinetics of this process are even faster [88].

8. Performance of drug-loaded mesoporous materials

8.1 Physical stability

As outlined earlier, mesoporous materials have been introduced to stabilize the amorphous form of a drug. Since the monolayer is in a thermodynamically more favorable form [33], drug loadings at or below the MLC should in theory also be thermodynamically stable. On the contrary, excess amorphous drug inside the pores (above MLC but below PFC) is stabilized by the small pore diameter of the pores, which physically restrains a crystallization of the drug inside the pore. This fraction of the drug, being the pure amorphous form of the drug with a T_g, is, however, not thermodynamically stable because its crystalline form represents the lowest energy state.

Hempel et al. investigated the physical stability of the four drugs below, at, and above the MLC (but below PFC) in four different types of mesoporous carriers with a range of different properties [34]. The authors found that during the 12 weeks of accelerated storage (at 40°C

and 75% relative humidity), the majority of samples prepared above the MLC showed signs of recrystallization, whereas all the samples prepared below the MLC remained amorphous. These findings suggest that indeed the drug in the monolayer is stable, whereas the confined amorphous excess drug will eventually crystallize. Nevertheless, confinement of the drug inside the pores and the size constraint effect did increase the physical stability of the amorphous drugs, since the neat amorphous drugs (without carrier) crystallize within a short time after preparation. With that, overloading the mesoporous carriers above the MLC will only be feasible if the confinement of the drug offers sufficient stabilization over the shelf life of the drug. Furthermore, overloading above the PFC should be avoided since a drug phase outside of the mesoporous carriers, being either crystalline or amorphous, may result in physical instability and negatively interfere with drug dissolution performance and ultimately oral bioavailability.

Hence, knowledge of the MLC and PFC of a given drug and a given mesoporous carrier are crucial to understand the stability and performance of any investigated drug−mesoporous carrier system. Unfortunately, most of the published work did not enclose information about the exact nature of the investigated drug loading, i.e., below, at, or above MLC or PFC, which impedes proper interpretation and comparison of many of these findings.

8.2 Dissolution and *in vivo* performance

Because the drug in the loaded mesoporous carriers is amorphous, it will show a higher (apparent) solubility and faster dissolution [16]. When the drug is loaded as a monolayer, the large surface area of the mesoporous carriers covered with a single drug layer as well as the drug being in the amorphous form certainly contribute to very fast drug release from such a system [71]. Since the affinity of the solvent to the surface of the mesoporous carriers highly affects the drug loading achieved during the solvent immersion method [72,73] (see earlier), the high affinity of water to the polar surface of most mesoporous carriers will also easily replace the drug and further facilitate a fast drug release. It has also been shown that the pore geometry can influence the kinetics of the drug release. For example, Che et al. showed that the longer pores of the MS SBA-15LP resulted in a comparatively slower drug release than MS SBA-15 with shorter pores [89]. In another study, the larger pores of Syloid 244FP showed a faster drug release than the narrower pores of MCM-41 [90], most likely by being more easily accessible for the dissolution medium. The higher solubility and faster dissolution from drug-loaded mesoporous carriers is also reflected in their *in vivo* performance. For example, Xia et al. showed a 4.6-fold and 4.1-fold increase in C_{max} and AUC_{0-8h}, respectively, for the antiretroviral drug atazanavir when loaded onto a mesoporous carrier compared its crystalline control group in rats [91]. In another study, the oral bioavailability in rats of the drug flubendazole was sixfold higher when loaded onto MS compared to the crystalline drug [35]. Furthermore, Bukara et al. showed that a drug-loaded MS formulation also showed improved oral bioavailability for fenofibrate in a clinical study compared to the marketed formulation Lipanthyl [92]. In particular, a reduction of the drug load by 50% resulted in a similar *in vivo* performance compared to the control group with Lipanthyl (Fig. 8.5).

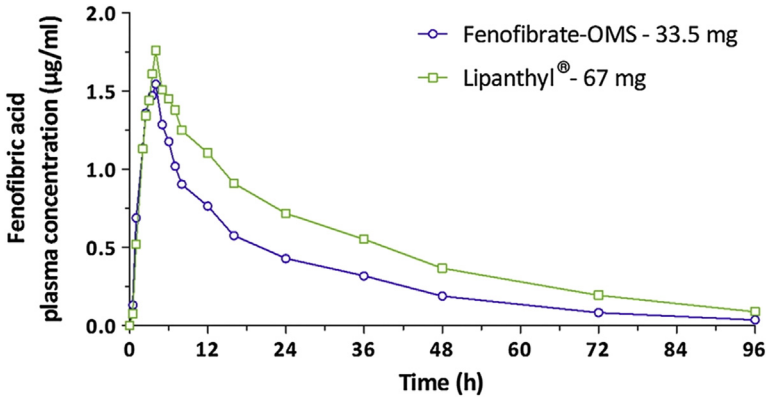

FIGURE 8.5 Comparison of the plasma concentration (mean value, $n = 12$) versus time profiles obtained from fenofibrate-loaded ordered mesoporous silica (fenofibrate-OMS) containing 33.5 mg of drug as well as the marketed formulation containing 67 mg of micronized fenofibrate (Lipanthyl). *Adapted with permission from Bukara K, Schueller L, Rosier J, Martens MA, Daems T, Verheyden L, Eelen S, Van Speybroeck M, Libanati C, Martens JA. Ordered mesoporous silica to enhance the bioavailability of poorly water-soluble drugs: proof of concept in man. Eur J Pharm Biopharm 2016;108:220–225. Copyright 2019 Elsevier.*

9. Conclusion

The potential of mesoporous carriers to overcome the issues related to poorly soluble drugs is promising. The research field is very active, and many studies are published showing the benefits of using mesoporous carriers to increase amorphous drug stability, solubility, and oral bioavailability. Nevertheless, most of the published work lacks concrete information on the physical form in which the drug is loaded onto the carriers, i.e., whether the investigated loadings are below, at, or above the MLC or PFC. As outlined earlier, this type of information is crucial to ensure the physical stability and dissolution performance of these systems, but also to gain a better fundamental understanding of how these systems work. A lack of knowledge of the MLC and PFC potentially means, e.g., that it is unclear whether the applied loading method fully utilizes the maximum degree of drug loading, which offers enough physical stability. In other words, the applied loading methods may result in drug loadings that are potentially lower than the maximum achievable MLC. Hence, the full potential of the mesoporous materials may not be realized. On the other hand, the applied loading methods may result in a drug loading above the MLC or even above the PFC. As outlined earlier, drug loadings above the MLC but below the PFC are potentially prone to show recrystallization and one must ensure that the amorphous stabilization by confinement is sufficient for the shelf life of the system. With the recent advances outlined earlier, it will be interesting to see the field develop in view of the importance of the degree of drug loading and the two physical forms of the loaded drug, i.e., in the monolayer or as confined amorphous drug. The formulation scientist will then be able to choose the ideal mesoporous carrier properties (surface area, pore size, and pore volume) as well as loading method for each given drug molecule. From this knowledge, it is possible to develop formulations that present physical–chemical properties that ensure storage stability and consistent performance in an oral drug delivery application.

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