Understanding controlled drug release from mesoporous silicates: Theory and experiment

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ABSTRACT

Based on the results of carefully designed experiments upgraded with appropriate theoretical modeling, we present clear evidence that the release curves from mesoporous materials are significantly affected by drug–matrix interactions. In experimental curves, these interactions are manifested as a non-convergence at long times and an inverse dependence of release kinetics on pore size. Neither of these phenomena is expected in non-interacting systems. Although both phenomena have, rather sporadically, been observed in previous research, they have not been explained in terms of a general and consistent theoretical model. The concept is demonstrated on a model drug indomethacin embedded into SBA-15 and MCM-41 porous silicates. The experimental release curves agree exceptionally well with theoretical predictions in the case of significant drug–wall attractions. The latter are described using a 2D Fokker–Planck equation. One could say that the interactions affect the relative cross-section of pores where the local flux has a non-vanishing axial component and in turn control the effective transfer of drug into bulk solution. Finally, we identify the critical parameters determining the pore size dependence of release kinetics and construct a dynamic phase diagram of the various resulting transport regimes.

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1. Introduction

To enhance the biological efficiency of drug delivery systems, it is often highly desired to accurately control the rate at which drug molecules are delivered into the bloodstream or even to a specific binding site. This way, one not only decreases the administration frequency but also minimizes possible side effects. The kinetics of drug transport into the bloodstream can be manipulated by adjusting the rate at which drug molecules are released from the formulation. Devices that enable such a manipulation are commonly referred to as controlled delivery systems. Among others, ordered mesoporous silicates have emerged as very promising materials for tunable drug delivery [1–9], as they can either enhance [10] or slow down [11,12] release kinetics simply by modifying their structural (for example pore size) or surface properties (for example surface polarity). It has been shown on several occasions that one can alter the release kinetics in a controllable manner by adjusting the pore size of mesoporous materials [1,2,6,13]. More specifically, it has been found, that upon reduction of pore size the release from mesoporous silicates becomes slower. The prevailing opinion is that this effect is caused by the so-called ‘spatially hindered’ diffusion (as opposed to ‘free’ diffusion), which, in turn, is i.e. spatially obstructed molecular diffusion resulting in a depleted effective release from the porous matrix which is supposed to be diffusion controlled. One of the physical phenomena that could be associated with this hindrance is the so-called subdiffusion or single-file diffusion [14,15], which occurs in crowded media or in the presence of tight spatial confinement. However, for subdiffusion to occur in the case of drug molecules in mesopores, the diffusing molecules would have to be forced to arrange into a single file. The pore size of mesoporous silicates (typically lying between 3 and 20 nm) is, however, not small enough to enforce subdiffusion. Namely, the normal character of diffusion is not affected as long as two molecules are able to pass one another regardless of inter-particle and particle–wall interactions [16]. In mesopores two drug molecules are always allowed to pass one another. Meanwhile, Knudsen diffusion, which is believed to be the dominant transport mechanism of gasses in mesoporous materials [17], is not relevant in the present case, since the mean free path in a solution is significantly smaller than the pore size. What is more, we have shown recently in a theoretical study [18], that in the absence of anomalous diffusion and particle–wall attractions, a reduction of pore size in fact enhances the effective release kinetics.

As shown in our recent study, the experimentally determined pore size dependence of release from mesoporous matrices can only be reproduced in a theoretical description by including sufficiently strong attractions to pore walls. The same study also reveals a highly...
non-trivial relation between the local transport inside the pores and the total drug transfer rate into the bulk solution [19]. This implicitly suggests that attractions to walls play an essential and fundamental role in drug release from mesoporous matrices, regardless of whether they are functionalized or not. Namely, van der Waals (vdW) interactions between drug molecules and pore walls are always present, irrespective of surface functionalization. Meanwhile, the experimentally observed depleted release from surface-functionalized materials as compared to non-functionalized but with the same pore size was attributed to attractions between the drug and the chemically modified pore walls [see for example 11,12]. Taking into account the essential and general role of drug–wall attractions it is possible to derive a unified picture of drug release from mesoporous matrices [20].

Here we present clear evidence that the experimental drug release curves are significantly affected by effective interactions between the drug and the porous matrix. The finding is based on a comparison of results of carefully designed experiments and theoretical predictions of molecular transport that includes such interactions. Various cases that mimic realistic situations found in drug–matrix composites are considered and commented to prove the viability of the proposed concept. In order to control the experimental conditions as much as possible, SBA-15 and MCM-41 are prepared with average pore sizes of 9 and 3 nm respectively, having almost equal particle size and merely a 28% mismatch in mesopore volume. Indomethacin (IMC) was chosen as a model drug and loaded into mesoporous silicates. The physical properties and phase transformation of mesoscopically confined phases are described in detail in a separate study [21]. Drug release experiments are performed in pure water in five-fold replicas and the sampling performed with high frequency to minimize the statistical error. The theoretical approach is based on extensive numerical simulations of molecular transport in model 2D ordered porous matrices using the 2D Fokker–Planck equation under reflecting boundary conditions. Different types of initial drug distribution inside the pores are considered along with the importance of the amount of substance initially deposited on the external matrix surface. The experimentally determined relative time-scale dependence of release kinetics agrees qualitatively exceptionally well with the theoretical predictions and confirms the universal role of drug–wall interactions. Our results indicate consistently, that the current opinion on the mechanism of drug release from ordered mesoporous silicates needs to be extensively revised.

2. Methods

2.1. Synthesis of SBA-15 matrix

SBA-15 with the average pore size of 9 nm was prepared with a hydrothermal synthesis using Pluronic P123 (a PEG–PPO–PEG block copolymer, Aldrich) as a structure directing agent and tetraethyl orthosilicate (98% TEOS, Aldrich) as a silica precursor. First 2 g of Pluronic P123 was dissolved in a mixture of 50 g distilled water and 12 g hydrochloric acid (37% HCl, Aldrich) at 298 K under magnetic stirring. After 3 h, the Pluronic P123 solution was placed in an oil bath at 312 K and 4.25 g of TEOS was added drop-wise under vigorous stirring. After 10 min, the mixture was kept under static conditions at the same temperature for 20 h. The next day, the silica suspension was transferred into a Teflon-lined autoclave and placed in an oven for hydrothermal treatment at 373 K for 24 h. The obtained white powder was washed on a filter with distilled water to a pH 6–6.5, dried at 323 K for 24 h and calcined at 823 K for 6 h in an air flow to remove the trichlobcopolymer from the pores. The sample was denoted SBA-15. Immediately after preparation the samples were placed in an inert Ar atmosphere and kept there right until the loading process.

2.2. Synthesis of MCM-41 matrix

MCM-41 with a mean pore diameter of 3 nm was synthesized using hexadecyltrimethylammonium bromide (CTAB, Aldrich) as a structure directing agent and tetraethyl orthosilicate (98% TEOS, Aldrich) as a silica source. First, 26.7 g of ammonia solution (25% NH4OH, Merck) was mixed with 105 g of distilled water and then 500 g of CTAB was added to the solution. This mixture was placed in an oil bath under stirring and heated to a homogeneous solution. When the solution had become clear 2.35 g of TEOS was added drop-wise. After 3 h of stirring and heating at 348 K, the obtained white powder was washed on a filter with distilled water to a pH 7, dried at 323 K for 24 h and calcined at 823 K for 6 h in an air flow to remove the CTAB from the pores. The sample was denoted MCM-41. Immediately after preparation the samples were placed in an inert Ar atmosphere and kept there right until the loading process.

2.3. Drug loading

First a solution of indomethacin (γ-IMC, Sigma) in tetrahydrofuran (THF, Sigma-Aldrich) was prepared. The IMC solution with a concentration 75 mg per g THF was added drop-wise to a fine layer of calcined samples of SBA-15 and MCM-41, allowing the powder to soak the added drops. The prepared samples were then dried, first at 313 K for 24 h in a ventilation dryer and then, additionally, for 24 h at 313 K in a vacuum dryer. The first step is supposed to remove the majority of the solvent while the second step removes the residual solvent which is adsorbed more strongly to the pore walls or capillary condensed. Immediately after drying, the samples were placed in a desiccator under inert Ar atmosphere to avoid exposure to moisture and were kept under such conditions until right before the measurements. It was found that such pretreatment decisively improved the repeatability and enabled one to avoid the otherwise very prominent effects of residual loading solvent and/or water. Further details of the loading procedure are presented elsewhere [21].

2.4. Scanning (SEM) and transmission (TEM) electron microscopy

SEM micrographs were obtained by a Zeiss SupraTM 35VP Scanning Electron Microscope (SEM) operated at 1 keV. TEM analysis was performed on a 200-kV field-emission gun (FEG) microscope JEOL JEM 2100. For TEM studies a drop of an ethanol-diluted nanoparticles solution was placed on a copper grid and dried at room temperature. The specimens were additionally coated with carbon in order to prevent excessive charging and decomposition of the sample under the electron beam.

2.5. X-ray powder diffraction (XRPD)

XRPD patterns were recorded on a PANalytical X-Pert PRO high-resolution diffractometer with 01 configuration using CuKα radiation (1.5406 Å) in the range from 0.5 to 10° 2θ, using a step of 0.017 per 100 s and separately in the range from 5 to 35° 2θ, using a step of 0.033° per 100 s under air conditions.

2.6. N2 adsorption–desorption analysis

Adsorption and desorption isotherms of nitrogen were measured on a Micromeritics ASAP 2020 volumetric adsorption analyzer at 77 K. Before the sorption analysis, the calcined samples were outgassed under vacuum for 2 h at 473 K and the loaded samples for 2 h at 333 K. The specific surface area (S_{BET}) was determined using the BET (Brunauer–Emmett–Teller) equation. The total pore volume (V_{t}) was estimated from the amount adsorbed at a relative pressure of 0.989, converting it to the volume of liquid nitrogen at 77 K. The microporosity of SBA-15 (V_{mic}) was calculated by t-plot method from...
the adsorption data. The calculation of pore size distribution (PSD) was performed by analyzing the adsorption data of N₂ isotherm using the Barrett–Joyner–Halenda (BJH) method with Halsey–Faas correction for bare calcined and loaded SBA-15, and BJH method with Halsey–Kruk–Jaroniec–Sayari correction for bare calcined and loaded MCM-41. The average pore diameter, \( d_{\text{mic}} \), corresponds to the peak value of the BJH distribution.

2.7. Quantification of loading fraction

The quantification of the relative amount of the loaded drug was carried out by means of thermogravimetric analysis (TGA) coupled with differential scanning calorimetry (DSC). Measurements were carried out between 303 and 1073 K with a heating rate of 20 K/min using a Mettler Toledo (Schwerzenbach, Switzerland) thermogravimetric analyzer model TGA/DSC 1 under a constant gas flow rate (oxygen, 50 ml/min). The initial sample mass ranged from 5 to 10 mg. The measurements were repeated three times.

The weight loss accompanying combustion of IMC was used to determine the fraction of loaded IMC (for details see Supplementary data). The weight loss due to the dehydroxylation of the surface was determined from the TGA curves of bare silicates, respectively, and subtracted from the total weight loss of the loaded samples. The temperature interval of IMC combustion was determined from the first derivative of the weight loss with respect to temperature. The absence of drug particles located outside the pores was confirmed with a combination of X-ray powder diffraction and solid-state NMR, both performed at several temperatures. Further details of the characterization procedures are given elsewhere [21].

2.8. Drug release experiments

Drug release experiments were performed in highly purified water using a standard dissolution apparatus (USP Dissolution Apparatus 1, Vankel Dissolution apparatus, model VK 7000, USA) equipped with a wire-mesh basked attached to a rotation shaft adjusted to 50 rpm at 298 K. The approach (Apparatus 1 and slow rotation) was chosen specifically to avoid the intrinsic hydrodynamic issues arising in the rotating paddle method (USP Dissolution Apparatus 2) [22], which is usually used for these sorts of experiments, and to minimize all hydrodynamic effects in general. Samples were collected in triplet replacements to minimize the statistical error. The solubility of IMC was determined from the TGA curves of bare silicates, respectively, and data). The weight loss due to the dehydroxylation of the surface was determined from the TGA curves of bare silicates, respectively, and data). The weight loss due to the dehydroxylation of the surface was determined from the TGA curves of bare silicates, respectively, and subtracted from the total weight loss of the loaded samples. The temperature interval of IMC combustion was determined from the first derivative of the weight loss with respect to temperature. The absence of drug particles located outside the pores was confirmed with a combination of X-ray powder diffraction and solid-state NMR, both performed at several temperatures. Further details of the characterization procedures are given elsewhere [21].

2.9. Model and computational methods

Porous matrices were modeled as 2-dimensional arrays of channels with diameter \( d \) and wall thickness \( a \) (see Fig. 1(a) top panel). This structure should describe well the geometry of the porous network in mesoporous silicates with hexagonal pore arrangement, such as SBA-15, MCM-41 and related materials. We denote the size of the porous matrix with \( L \) and the thickness of the surrounding buffer zone by \( L_s \). The latter is chosen to be large enough to assure that the interactions with pore walls vanish and that the concentrations never reach appreciable values at large distances from the matrix. \( L_s \) along with the total pore volume and the total pore entrance area are constant in all cases (see Fig. 1(a)). Various pore sizes are considered in the calculations (see Fig. 1(a)).

We assume that the drug molecules experience an external force due to interactions with pore walls while they move through the porous matrix. The total interaction experienced by a diffusing molecule at a given position \( r \) is equal to the sum of interactions with all molecules constituting pore walls. We model the attractive part of these effective intermolecular interactions with the attractive part of the Morse potential and the repulsive part with a hard repulsive core (see Fig. 1(b)). Thus, the local external potential is defined as

\[
V(r) = \sum_{j} \varphi_{ij} |r - \mathbf{r}_j| \phi_{ij}(r) d^2r'.
\]

where the pair potential is defined as

\[
u_{ij}(r - r') = \begin{cases} 
q_{\text{min}} \left( 2\alpha_{ij} - 2\alpha_{ij} |r - r'| \right) & \text{if } |r - r'| \geq \Delta \\
\infty & \text{otherwise.}
\end{cases}
\]
where $p(r)$ is the local density of the matrix at position $r=(x, y)$ and is equal to 1 if $r$ lies inside a pore wall and zero otherwise. $q_{\text{min}}$ and $z$ are the depth and position of the pair potential minimum, $\sigma$ describes the width of the potential well and thereby also its range and $\Delta$ is a lower cut-off distance, which will be explicitly defined later.

It was shown that although solute–solvent and solute–solid interactions significantly affect the concentration dependence of the binary diffusion coefficient, the resulting nonlinear local transport under the influence of local concentration gradients is rather independent of those interactions [18] (i.e. one may equally well describe the local and macroscopic transport by neglecting interactions and assuming a concentration independent diffusion coefficient). Thus in the model we completely neglect interactions between drug molecules and describe their motion as Brownian motion in an external potential.

Locally the concentration, $C(r)$, changes due to the local forces exerted on diffusing molecules by pore walls (the drift) and due to diffusion according to the local concentration gradient. We consider a low Reynolds number environment and isotropic mobility, $\mu$ = $D/k_BT$, and therefore assume a linear relationship between force and velocity, $\mathbf{w} = \mathbf{\Gamma} \cdot \mathbf{j}$. The dynamics of the solute concentration field are described with the 2-dimensional Fokker–Planck equation (FPE):

$$\frac{\partial C(r)}{\partial t} = D \nabla_{xy} \left( \frac{C(r)}{k_BT} \nabla_{xy} V(r) + \nabla_{xy} C(r) \right) \mathbf{\nabla}_{xy} \cdot \mathbf{j}$$

(3) where $\nabla_{xy}$ represents the 2-dimensional gradient operator, $\nabla_{xy} = \partial / \partial x \hat{x} + \partial / \partial y \hat{y}$, $D$ is the diffusion coefficient, $k_B$ is the Boltzmann constant, $T$ is the temperature, and $\mathbf{j}$ the generalized flux. Since the impenetrability conditions simply reflect the absence of an effective driving force for solute transport into the pore walls, we can replace the repulsive part of the external potential by reflecting boundary conditions for $C$ and $V$ at the walls, $\nabla_{xy} C(\mathbf{n}) = 0$ and $\nabla_{xy} V \cdot \mathbf{n} = 0$, where $\mathbf{n}$ is the unit surface normal of pore walls. All calculations are performed numerically on a square grid with spacing $\Delta$ taking $\Delta = \Delta$ and $\sigma = 1$ in Eq. (1). Further computational details and formal definitions of average potential characteristics $<V_{\text{cont}}>$ (the average potential in the center of pores) and $<V_{\text{cont}}>$ (the average contact potential) are presented elsewhere [19].

We consider various initial conditions (IC), which are most likely to be met in experimental studies (see Fig. 1(c)). The basic types of IC (I–III) represent situations, where no drug molecules are initially located on the external surface. Specifically, type I corresponds to a homogeneous concentration inside the pores, type II to a concentration proportional to the local Boltzmann factor, exp $(-V(r)/k_BT)$, and type III to a thin adlayer of equal concentration as in type I. In a separate set of calculations we additionally introduce a thin adlayer of various concentrations on the external surface of the matrix.

We consider a wide range of strengths of solute–wall attractions, ranging from a complete absence of solute–wall attractions ($q_{\text{min}} = 0$) to $q_{\text{min}} = 0.5 k_BT$ (see Fig. 1(b)). A total of $600 \cdot 10^{12}$ integration steps are performed with increment $\Delta t$ taking $\Delta t = 0.2$.

The release kinetics are quantified by means of the release time defined as the time in which a fraction $\varphi$ of drug is transported into the bulk solution (for details see Supporting information) and is obtained simply by integration of the total flux across the outer surface of the so-called diffusion layer, $O$:

$$\int_0^t \int_0^{\Delta r} j(r, \tau) \cdot dS = \varphi \int_0^t C(r, \tau = 0) d^2r$$

(4) where $dS$ is the differential of the surface normal of $O$.

3. Results and discussion

SEM images of the obtained calcined mesoporous silica show well-defined polyhedral particles without intergrowth aggregation for both SBA-15 and MCM-41. For both samples the sizes of mesoporous silica particles range from 400 nm to 1000 nm with an average size around 600 nm (see Fig. 2). In both cases TEM images clearly show hexagonal arrangements of the porous system and the uniformity of the cylindrical pores (Fig. 2 inset). The average pore diameter of the silicates observed from TEM images is in good agreement with XRPD (Fig. 3) patterns and $N_2$ sorption measurements (Fig. 4). In conjunction with TEM images, a high degree of order in the pore arrangement is also observed from XRPD patterns (Fig. 3) exhibiting three well resolved peaks, which are assigned to reflections from the (100), (110) and (200) planes of a hexagonal well ordered structure with $p6mm$ space group.

Equal particle size of SBA-15 and MCM-41 silicates is particularly important, since it allows a direct comparison of experimentally determined release kinetics with theoretical predictions, where we kept the particle size fixed in all calculations.

The $N_2$ adsorption–desorption isotherms (shown in Fig. 4) are found to be of type IV sorption isotherms according to the IUPAC classification. They exhibit well-defined H1 hysteresis loops which are typical for SBA-15 and MCM-41 silicates. The presence of H1 hysteresis type confirms that they have open-ended cylindrical mesopores. The fact that both isotherms have hysteresis loops with sharp adsorption–desorption branches indicates a narrow pore size distribution in both silicates. The corresponding pore size distributions are shown in Fig. 4 and specific surface areas, pore volumes and average pore diameters are given Table 1.

Note that the discrepancy in total pore volume between SBA-15 and MCM-41 is only around 28%, which in principle should allow us to make direct qualitative comparison with theoretical predictions. As expected, the specific surface area and the total pore volume decrease significantly upon drug loading. This suggests that majority of the
nanometer channels of the silicates are still open, although a portion of the voids are filled with drug. The IMC molecules embedded inside the pores do not fully occupy the available space, such that there is still some space for $N_2$ adsorption. The effect of drug loading is also nicely seen in the pore size distributions (Fig. 4). Note that in the case of SBA-15, the average pore size decreases upon loading, which suggest that beside fully loaded pore segments, one also finds regions of thin adlayers. From the diffraction patterns one observes that the hexagonal pore arrangement is not disrupted upon drug loading. Furthermore, the positions of the (110) and (200) peaks are shifted slightly towards larger $2\theta$ values upon drug loading in the case of SBA-15 which is in agreement with the change in the average pore diameter. Meanwhile, the diffraction patterns at $2\theta \text{= } 10^\circ$ exhibit no peaks corresponding to crystalline IMC particles located outside the pores (see Fig. 3), which suggest that the vast majority of IMC is accommodated inside the pores.

In the case of SBA-15 at small pore diameters, the tail in the pore size distribution corresponding to traces of micropores, vanishes upon loading which in turn suggests either filling of the micropores or alternatively an extensively obstructed access to the micropores, for example, due to the presence of a drug particle. The effects of drug loading are quantified in Table 1. The relative fraction of loaded IMC, as determined from TGA/DSC (for details see Supplementary data), is 32% in SBA-15 and 33% in MCM-41. Thus, according to the results both model systems are sufficiently similar to allow a direct qualitative comparison between experimental results of drug release kinetics with theoretical predictions.

The experimental results of drug release experiments are given in Fig. 5. IMC is known to be very poorly soluble in water and its dissolution rate in water is consequently also very slow. From the shape of the release profile we can assume that the wetting of IMC particles by the water interface is poor, which results in a time lag before significant dissolution occurs. On the other hand, the release from both MCM-41 + IMC and SBA-15 + IMC is significantly faster, which is a consequence of the absence of wetting problems (no time lag) and the geometrically enhanced diffusion currents from the porous network. The latter was explained in detail elsewhere [18].
Furthermore, at all times the release is faster from SBA-15, the matrix with larger pores, which is in agreement with the findings of Horcajada et al. [2] and Izquierdo-Barba et al. [3], who attributed this effect to ‘constraints of the diffusion process’. Release profiles form SBA-15 and MCM-41 do not converge to a common value and are also not expected to do so asymptotically. In fact we checked this experimentally by measuring concentrations after 2 and 5 days (points not shown) and found that the SBA-15 profile converges asymptotically to a value of about 0.44 and from MCM-41 to a value around 0.39 (see Fig. 5(a)). The asymptotic fractions of released IMC correspond to 35.2 and 31.2% of the solubility of IMC in the medium, respectively. A comparison of experimental profiles is meaningful only if the size and morphology of particles with different pore sizes are similar, as pointed out earlier by Qu et al. [6]. This condition is certainly met in the present case, while in the literature this is often not the case. Furthermore, the observation that profiles do not converge agrees completely with the existing literature where the conditions of similar particle size and morphology are met [2,3]. The release was found to be even slower in the case of surface-functionalized matrices having a more hydrophobic surface [3], which was ascribed to an enhanced adsorption affinity. Even though it was not specifically addressed by the authors, they also found a lower asymptotic fraction of released drug. Recently, Mellaerts et al. [24] investigated the molecular organization of hydrophobic guest molecules in SBA-15 using a combination of spectroscopic methods. They found that the presence of co-adsorbed water significantly affects the interactions of guest molecules with pore walls and thereby alters the adsorption, aggregation and migration behavior of guest molecules with respect to dry samples.

The behavior observed in Fig. 5, as well as similar observations in the literature [2], is unexpected on the basis of the conventional picture about the drug release from pores of matrices. In particular, these observations cannot be explained by means of the geometrical influence of pore size on diffusion inside and from the pores. Namely, the equilibrium steady state of a diffusive system is always a homogeneous concentration distribution. Accordingly, the asymptotic total fraction of drug released depends only on the volume into which the drug diffuses. Since in a typical experiment, the volume of the medium is constant and the volume of the porous particles is negligible with respect to the volume of the release medium, the asymptotic fraction of released drug would have to be independent of the pore size. This is, however, not the case. Furthermore, we have shown that the kinetics of diffusion controlled release from porous matrices are in fact faster in the case of smaller pores [18]. A theoretical prediction of the corresponding release profiles from 2D porous matrices assuming $q_{\min} = 0$ is given in the inset in Fig. 5. There are two important differences between the experimental results and the usual theoretical predictions, namely, the lack of convergence of the experimental profiles, and the reversed order of the pore size dependence of release kinetics.

As we show in the following section, the unexpected lack of convergence of measured release profiles along with all the discrepancies between experimental results and theoretical predictions of the pore size dependence of drug release are removed if we assume that drug–wall attractions play an essential role in release from mesoporous materials, regardless of whether they are functionalized or not.

3.1. Explanation of experimental observations

First we summarize the main theoretical findings, which are presented in detail elsewhere [18–20]. The local relaxation process towards a transient local quasi-equilibrium state of the concentration distribution inside the pores is several orders of magnitude faster than the effective macroscopic drug release from the matrix. This means that the local and large-scale transport are essentially decoupled. The large-scale release follows an effective diffusion equation with an effective diffusion coefficient (which reflects both the geometrical effect and the effect of interactions with walls) only for asymptotically large times. This effective diffusion coefficient is not a measure of the actual Brownian motion of molecules inside the pores, but is a result of spatial averaging of local fluxes over larger scales. We term the dynamical regime in the absence of attractions to pore walls the geometrically controlled release, since the geometry of the porous network determines the local as well as the large-scale transport. In this, geometrically controlled, regime a reduction of pore size accelerates the release kinetics from the porous matrix. The mechanism leading to this effect is the enhancement of the local flux component along the pores, which is mediated by the fact that the available volume outside the matrix can be filled more effectively if there are more sources (pore-openings) present at the surface. The volume per unit pore-opening area in which the molecules can flow by means of lateral diffusion is larger in the case of smaller pores. The general effect of progressively stronger attractions to pore walls is readily observed in Fig. 6.

Attractions to walls cause accumulation of the drug at the pore walls, which can be understood as a multilayer adsorption process. As mentioned earlier, the relaxation towards this transient quasi-equilibrium state is very fast and leads to a local distribution, which is proportional to the Boltzmann factor, $\exp(-V(r)/k_BT)$. Thus, the transient concentration difference between the center of the pores and the adlayer at pore walls depends on the potential difference. The external potential directly at pore walls is almost independent of pore size, while the potential in the center of pores is less favorable in larger pores (see Fig. 1(b)), which means that the aforementioned concentration difference is larger in larger pores. The local dynamics depend on the local forces (the drift component $\mu r(r) = -\mu q(r)V(r)$) and the local concentration gradient. The net effect is a larger total local flux, but with a smaller axial component (i.e. a larger component towards the pore walls). Since only the axial component contributes to large-scale release, the effective release kinetics become depleted. The relative cross-section of pores, where the local flux has a nonzero axial component is larger in smaller pores. The geometrical effect and the effect of interactions oppose

<table>
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<th>Sample</th>
<th>$S_{\text{BET}}$ [m$^2$/g]</th>
<th>$V_{\text{mic}}$ [cm$^3$/g]</th>
<th>$V_{\text{p}}$ [cm$^3$/g]</th>
<th>$t_{\text{diss}}$ [min]</th>
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<td>9.2</td>
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<tr>
<td>MCM-41</td>
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<td>0.776</td>
<td>/</td>
<td>3.1</td>
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<tr>
<td>SBA-15 + IMC</td>
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<td>0.929</td>
<td>0.002</td>
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<td>MCM-41 + IMC</td>
<td>224</td>
<td>0.2024</td>
<td>/</td>
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**Table 1** Specific surface area, total and micropore volumes and pore diameter of prepared mesoporous silicates.

**Fig. 5.** Experimentally determined drug release profiles. The horizontal dotted lines correspond to asymptotic release fractions after 5 days (7200 min). Inset: Theoretically predicted release profiles in the case of a diffusion controlled release.
each other. We termed the regime, where effects of attractions to walls dominate, the interaction controlled release. In this regime, a reduction of pore size slows down the effective release kinetics. In the intermediate mixed regime, a small reduction of pore size accelerates the release kinetics, while a further reduction results in a slower release. The release kinetics (the rate of change of the fraction of released solute) are insensitive to the degree of local relaxation as well as to the total loading fraction (i.e., the release profiles evolving from types I, II and III boundary conditions are essentially the same).

The predicted release profiles within the geometry controlled regime ($q_{\text{min}} = 0$) and the interaction controlled regime ($q_{\text{min}} = 0.4k_BT$) are shown in Fig. 7(a)—dotted lines. Note that the release profiles corresponding to different pore sizes converge to a common asymptotic value within the geometry controlled regime, while in the interaction controlled regime the asymptotic fraction released is larger in the case of larger pore size. The latter is in complete agreement with the experimental observations.

The picture changes somewhat if a significant amount of the drug is initially located on the external surface of the matrix particle (see Fig. 7(a)—full lines). If initially the drug is located exclusively on the external matrix surface (i.e., empty pores), the release occurs as a desorption process and is faster in the case of larger pores, regardless of the strength of attraction to walls. The mechanism is exactly the same as the one leading to faster release from smaller pores in the absence of attractions to pore walls, but with the direction of the fluxes reversed. Conveniently, we call the regime that is dominated by desorption, the desorption controlled release. As before, the difference in asymptotic fractions released is observed only in the presence of interactions.

The two relevant parameters, determining the pore size dependence of release kinetics are thus the strength of attraction to pore walls and the relative fraction of drug initially located on the external surface. In fact, they determine an interesting dynamic phase diagram, which can be constructed by performing numerous calculations with increasing relative amounts of drug on the external surface. Specifically, we consider type III IC with gradually increasing concentration in the
external surface adlayer and the result is shown in Fig. 7(b). In our representation, we chose to describe the relative amount of drug on the external surface in terms of the ratio of concentrations in the adlayers on external and internal matrix surfaces.

Since the ratio external:internal surface area is typically very low in the case of mesoporous silicates, one can expect that the desorption controlled regime will be relevant only for extremely small particles with large pore size and low porosity.

3.2. Further indications of interaction controlled release

Obviously, a faster release from larger pores is established if (i) drug molecules experience a significant attraction to pore walls or (ii) there is no significant attraction with pore walls but, rather, a significant amount of the drug was initially located on the external surface of the matrix particles of SBA-15 and MCM-41. Although (ii) is rather unlikely, since the external surface of both SBA-15 and MCM-41 is extremely small compared to the internal surface inside the porous network, no definite conclusions can be drawn immediately from Fig. 7(a). However, in the absence of Drug–wall attractions the curves evolving from IC with an additional surface adlayer (full black and green lines) converge to a common asymptotic value. This is expected, since the equilibrium steady state corresponds to a homogeneous concentration distribution, where the final concentration depends only on the total amount of the drug and the volume of the solution. On the other hand, in the presence of Drug–wall attractions the steady state solution is inhomogeneous and proportional to the local Boltzmann factor. This in turn means that a certain amount of the drug is not expected to be released. Since the local Boltzmann factor and hence the steady state solution depends on the pore size (the external potential due to attractions with pore walls is more attractive in smaller pores) a lower asymptotic value of the pore size (the external potential due to attractions with pore walls is Boltzmann factor and hence the steady state solution depends on the amount of the drug is not expected to be released. Since the local Boltzmann factor and hence the steady state solution depends on the pore size and porosity.

Figure 8 illustrates the behavior on various time and length scales. On the other hand, since only the large length-scale behavior is probed in drug release experiments, it is interesting to look at the macroscopic dynamics on different time scales. This is trivially achieved by simply plotting the release profiles on a logarithmic time scale. To be able to do so, the sampling frequency was chosen to be very high at short times. The results are shown in Fig. 8.

By comparing Fig. 8(a) and (b) we see that the characteristic behavior on various time scales in experimental profiles agrees very well with theoretical predictions. Note that on a logarithmic timescale the experimental profiles for different pore sizes are parallel (but not linear) at long times (see Fig. 8(a)), which agrees exceptionally well with the theoretical predictions in the case of significant attractions to pore walls shown in Fig. 8(b) (black and green lines). The latter holds irrespective of whether there is initially an external adlayer or not. On the other hand, in the absence of Drug–wall attractions (inset in Fig. 8(b)), the curves correspond to different pore sizes first diverge at short times and afterwards converge at long times and are at no time parallel. The convergence in the latter case is a consequence of a homogeneous steady state distribution in the absence of Drug–wall attractions. The value of total drug released depends on the total pore volume and total internal pore wall area. The quantitative discrepancy in the experimentally measured and theoretically predicted total fraction of released drug is simply a consequence of the fact that the total internal pore wall area with respect to total pore volume and particle size in the model is much smaller than in the case of SBA-15 and MCM-41. For obvious reasons a simulation of real size matrices is simply infeasible.

On hand of all aforementioned evidence, we may conclude with high confidence, that the release from mesoporous silicates is interaction controlled. This holds true not only for surface-functionalized materials but holds in general. It has to be stressed here, that all presented results hold also in case of different pore arrangement, various ranges of Drug–wall attractions and over a wider range of pore sizes [19].

4. Conclusion

A combination of carefully designed experimental results and appropriate theoretical modeling has given clear evidence, that release curves are significantly affected by interactions between drug and matrix. The phenomenon is observed as a non-convergence of release profiles at long times but also as a reversed dependence of release kinetics on pore size if compared to the kinetics expected in non-interacting systems. Both phenomena have been observed, rather sporadically, in selected previous works but there has been a lack of appropriate quantitative explanation. By contrast, we showed that the experimentally determined release profiles and the relative
time-scale dependence of release kinetics from prepared model SBA-15 and MCM-41 particles agree exceptionally well with theoretical predictions in the case of significant drug–wall attractions. We also showed that the drug–wall attractions may be the main reason for the commonly observed dependence of drug release kinetics on pore size; namely, these attractions crucially determine the local fluxes inside the porous network and, consequently, also the effective large-scale release. The interactions to walls of pores inherently affect the relative cross-section of pores, where the local flux has a non-vanishing axial component. This way, the effective transfer of drug into bulk solution is also affected. The parameters that govern in general the pore size dependence of release kinetics are the strength of attraction to walls and the fraction of drug initially located on the external surface. The resulting phase diagram reveals a variety of different regimes of release kinetics. Our findings might have a profound influence on the design of drug delivery systems based on mesoporous materials.

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Appendix A. Supplementary data

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References