Supplementary Information for *Modus operandi* of controlled release from mesoporous matrices: A theoretical prespective†

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1 On subdiffusion due to spatial confinement

Subdiffusion or single-file diffusion occurs in crowded media or in the presence of tight spatial confinement. In the particular case of diffusion in a narrow channel, the motion of an assembly of small particles can be so tightly restricted that they arrange themselves into a single file (hence the term single-file diffusion). In such a situation the longitudinal motion of each particle is hindered by its neighbors, which act as impenetrable obstacles. In this respect, inter-particle interactions can suppress Brownian motion in one dimension. However, inter-particle interactions do not affect the normal character of Brownian diffusion as long as particles are able to pass one another, no matter how closely they are confined[1]. This holds also if attracting particles cluster or condense in the potential wells[2,3]. Thus, 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. While this should hold in the case of transport in zeolites and molecular sieves, carbon nanotubes and microporous materials, the pore diameter of mesoporous materials (typically lying between 3.5 and 20 nm) is not small enough to enforce subdiffusion of drug molecules with Connolly radii below 10 Å. Without going into an involved mathematical reasoning, the assumption can be justified by considering that loading of pores with drug molecules would be drastically slower than experimentally observed and also the fact that molecules are able to crystallize in mesoporous materials at sufficiently high loading (see for example[4,5]). Namely, for crystallization to occur, a critical nucleus needs to be formed, which is established by a cooperative density fluctuation in which typically several tens to hundreds of molecules are involved. Needless to say, for this to occur unconstrained diffusion must be possible.

2 The release time

In order to asses the influence of pore size and interaction strength on transport from interacting porous matrices on a large scale as sample and clear as possible, we introduce the release time, t_φ, which expresses the time at which a fraction φ of the solute molecules is transported into the bulk solution. The latter is defined as the exterior region of a square with side $L+2\times 10\Delta$ and centered in the origin. The region of thickness 10Δ surrounding the matrix is considered as, what is usually called, *the diffusion layer*. We define t_φ implicitly as an integral of the total flux across the outer surface of the *the diffusion layer, O*:

$$-\int_0^{t_\varphi} \mathrm{d}\tau \oint_O D\left(\frac{C(\mathbf{r})}{k_BT}\nabla_{\mathbf{xy}}V(\mathbf{r})+\nabla_{\mathbf{xy}}C(\mathbf{r})\right)\cdot \mathrm{d}\mathbf{S} = \varphi\int_R C(\mathbf{r},\tau=0)\mathrm{d}^2\mathbf{r},$$

where $\mathrm{d}\mathbf{S}$ is the differential of the surface normal of *O*. In this section we consider three types of initial conditions (IC). The three types of initial conditions inherently enable us to asses the importance of (1) degree of initial local relaxation and (2) influence of the total amount of drug deposited inside the pores on drug release kinetics. The release times are computed by first solving for $C(\mathbf{r},\tau)$ and then performing the integral in Eq.S1 As an example, Fig.1 shows $t_{1/10}$ and $t_{1/2}$ ((a) and (b) respectively). Both $t_{1/10}$ and $t_{1/2}$ exhibit the same qualitative pore size dependence regardless of thy type of IC. Namely, for $q_{min} < 0.2\ k_BT$ a reduction of pore size from d_0 (black) to $2d_0/5$ (violet) both $t_{1/10}$ and $t_{1/2}$ monotonically decrease (see insets in Fig.1 (a) and (b)). Thus, the geometrical constraints imposed by the pore network in absence of significant attractions to pore walls in fact enhance large scale drug transport. This is due to 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 (for details of transport in this regime refer to[6]). For $q_{min} \geq 0.3\ k_BT$ the pore size dependence is reversed. Upon a reduction of pore size, the release rate is decreased. For $0.2 \leq q_{min} < 0.3\ k_BT$ the release rate has a non-monotonic pore size dependence (see lower inset in Fig.1 (b)). Thus, the inclusion of attractions to pore walls not only induces a depletion of release at given pore size, but in fact causes an inversion of the pore size dependence in the case of sufficiently strong attractions. Drug release kinetics from mesoporous matrices obviously do not scale trivially with pore size. Note, however, that although the large scale drug transport is depleted in the case of sufficiently strong attractions, the local fluxes inside the pore network are in fact enhanced (for a detailed discussion refer to[7]). It is only the axial component of the local flux that is severely reduced. Note also, that at given pore size and attraction strength re-

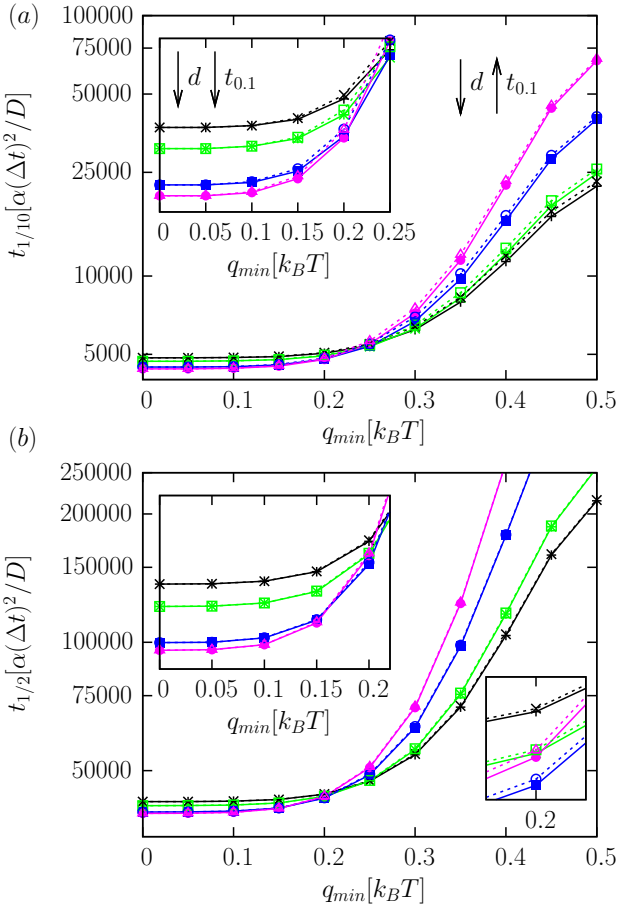

Fig. 1 (*a*) $t_{1/10}$ and (*b*) $t_{1/2}$ in the case of d_0 (black), $4d_0/5$ (green), $d_0/2$ (blue) and $2d_0/5$ (violet) as a function of q_{min}. Full lines correspond to type *I* IC, dashed lines to type *II* and dotted to type *III* IC. The colors denoting pore sizes will be used throughout the entire paper.

lease kinetics are almost completely independent on the initial concentration distribution inside the pores, which is usually thought to be very important.

3 Characteristics of the external potential

The potential is most attractive directly at the walls inside the pores and vanishes outside the matrix already at a distance of 10Δ away from the surface. It scales linearly with q_{min}. The depth of $V(\mathbf{r})$ inside the pores increases with decreasing pore size. This means that in the steady state at given q_{min} the concentration inside the matrix will be larger in the case of smaller pores and therefore the asymptotic total fraction of released substance will decrease with decreasing pore size. Locally, the steady state concentration will depart significantly from a homogeneous distribution everywhere where $\tilde{V} \leq -1$. The dynamics are influenced by the local forces (see the force field in Fig.2 (b)) which are, in contrast to the potential, strongest at the outer pore walls and are oriented in the direction normal to the surface. Inside the pores, the normal component of the force in the center of pores vanishes by symmetry and the axial component reduces to zero at app. 10Δ away from the pore entrance. The magnitude of the local forces at given pore size scales linearly with q_{min}. The characteristics of the external potential at given pore size and q_{min}, which should roughly capture the essential features that influence large scale transport, are the average contact potential, $\langle V_{cont}\rangle$,the average normal force at contact with pore walls, $\langle F_n\rangle$, the average external potential in the center of pores, $\langle V_{cent}\rangle$. Explicitly, we define them as follows.

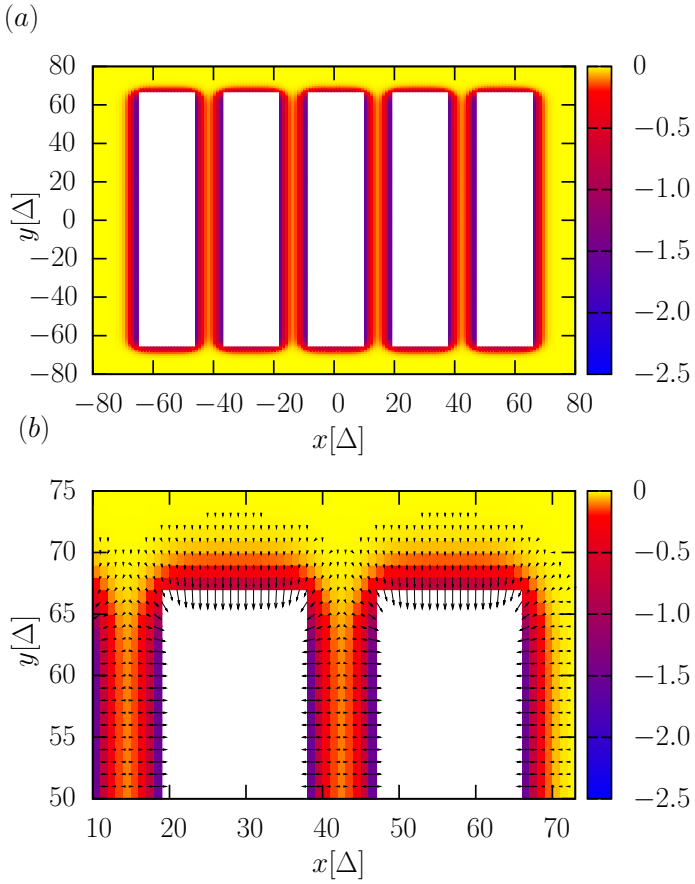

Fig. 2 (*a*) $\tilde{V}(\mathbf{r})$ in the case of largest pore size (d_0) and $q_{min} = 0.4$; (*b*) magnification of $\tilde{V}(\mathbf{r})$ with superimposed $\nabla_{\mathbf{xy}}\tilde{V}(\mathbf{r})$. The position of each vector corresponds to its origin.

If we denote the the position vector of the k-th wall facet along its contour ℓ by $\mathbf{r}_w^k(\ell) = (x_w^k(\ell), y_w^k(\ell))$, than the average of the local potential, $V(\mathbf{r})$, and local force along the surface normal, $F_n(\mathbf{r}) = \nabla_{\mathbf{xy}}V(\mathbf{r})\cdot\hat{\mathbf{n}}$ over all positions adjacent to pore walls (in discrete terms this corresponds to a distance Δ from

the wall) is given by:

$$\langle V_{cont}\rangle = \frac{\sum_{k=1}^{N_w}\iint d^2\mathbf{r}d\ell\delta(|\mathbf{r}-\mathbf{r}_w^k(\ell)|-\Delta)(1-\rho(\mathbf{r}))V(\mathbf{r})}{\sum_{k=1}^{N_w}\iint d^2\mathbf{r}d\ell\delta(|\mathbf{r}-\mathbf{r}_w^k(\ell)|-\Delta)(1-\rho(\mathbf{r}))} \quad \text{(S3.1)}$$

$$\langle F_n\rangle = \frac{\sum_{k=1}^{N_w}\iint d^2\mathbf{r}d\ell\delta(|\mathbf{r}-\mathbf{r}_w^k(\ell)|-\Delta)(1-\rho(\mathbf{r}))\nabla_{\mathbf{xy}}V(\mathbf{r})\cdot\hat{\mathbf{n}}_k}{\sum_{k=1}^{N_w}\iint d^2\mathbf{r}d\ell\delta(|\mathbf{r}-\mathbf{r}_w^k(\ell)|-\Delta)(1-\rho(\mathbf{r}))}, \quad \text{(S3.2)}$$

where the sum runs over all N_w wall facets and the δ-function projects out all points adjacent to pore walls. As for the average contact quantities, we define the position vector of the center of the k-th pore along its contour ℓ by $\mathbf{r}_c^k(\ell) = (x_c^k(\ell), y_c^k(\ell))$. Then the average external potential in the center of pores is given by:

$$\langle V_{cent}\rangle = \frac{\sum_{k=1}^{N_c}\iint d^2\mathbf{r}d\ell\delta(\mathbf{r}-\mathbf{r}_c^k(\ell))(1-\rho(\mathbf{r}))V(\mathbf{r})}{\sum_{k=1}^{N_c}\iint d^2\mathbf{r}d\ell\delta(\mathbf{r}-\mathbf{r}_c^k(\ell))(1-\rho(\mathbf{r}))} \quad \text{(S3.3)}$$

4 Introduction of drug molecules on the external matrix surface

Significant amounts of drug deposited initially on the external matrix surface can change the pore size dependence of release kinetics. As an illustration of the importance of the fraction of molecules deposited initially on the external matrix surface, Fig.3 displays $t_{1/2}$ with and without a surface adlayer in the case of type *I* IC (Fig.3(a)) and type *III* IC (Fig.3(b)). In the latter, the fraction represented by molecules on the external surface is much larger. As a results of a desorption controlled release mechanism the results in (b) display a monotonic pore size dependence irrespective of q_{min}. Note that for large q_{min}, the results with a surface adlayer converge to those of zero initial surface concentration, which suggests that for sufficiently strong attraction the mechanism is always interaction controlled.

5 Evolution of the fraction of solute released with respect to pore size, IC and attraction strength to pore walls

The fraction of molecules released as a function of time is shown in Fig.4. Note that the release kinetics at given pore size and q_{min} are completely independent on the initial distribution inside the matrix if initially there is no external adlayer (compare dotted lines: blue versus black and red versus green). In the case when there exists initially an external adlayer, the internal distribution is important only in terms of the total amount of matter deposited inside the matrix and thereby also the fraction of matter on the external surface. This can be seen directly by comparing full and dotted lines corresponding to type *III* IC for different pore sizes and recalling that the internal surface, and therefore the total amount of matter adsorbed initially, is larger in the case of smaller pores. Namely, the difference between curves for type *III* IC corresponding to an existence of an initial external adlayer and absence of it decreases with decreasing pore size. Note further, that in general this difference is smaller in the case of stronger attractions. One also observes, that in absence of strong attractions, the desorption time scale is an order of magnitude shorter that the timescale of release from the porous network. The desorption kinetics are decreased in case of stronger attractions. Based on all these findings, we may conclude, that the pore size, attraction strength and the fraction of matter deposited initially on the external surface are parameters, which determine the release kinetics. The internal distribution, however, is irrelevant.

References

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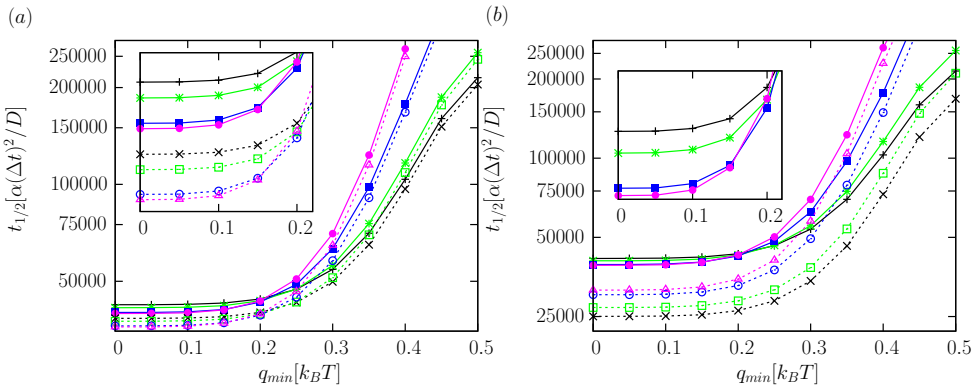

Fig. 3 (a) $t_{1/2}$ in the case a homogeneous initial concentration distribution inside the pores with an additional adlayer of equal concentration on the external surface (dotted lines) and without the external adlayer (full lines); (b) $t_{1/2}$ in case of the initial internal adlayer (full lines) and with an additional adlayer of equal concentration on the external surface (dotted lines). As before, the colors denote the pore size.

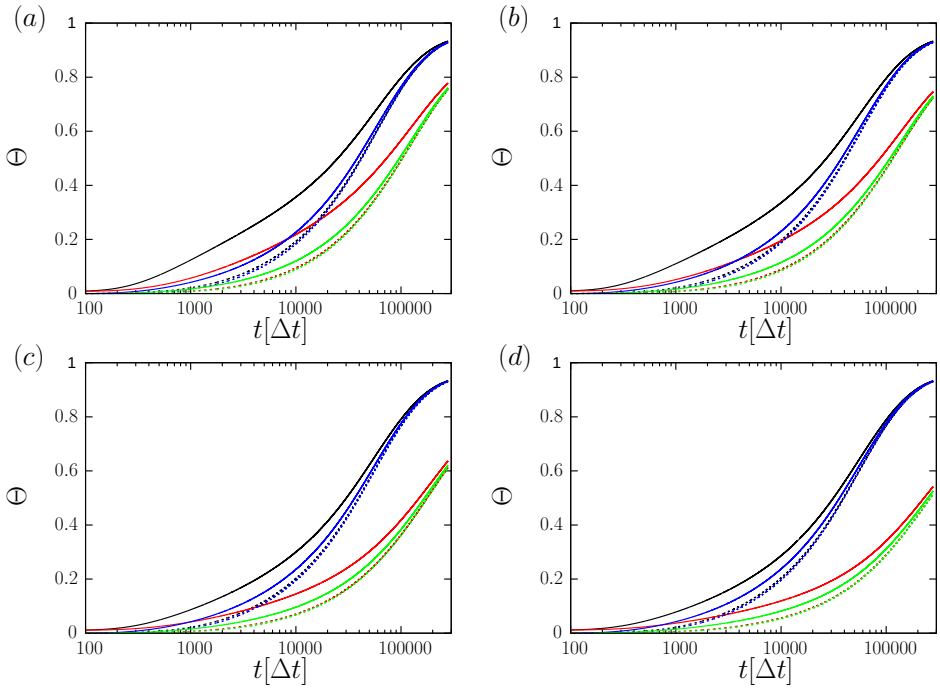

Fig. 4 Evolution of Θ as a function of pore size and q_{min}: (a) $d = d_0$, (b) $d = 4d_0/5$, (c) $d = d_0/2$ and (d) $d = 2d_0/5$. The internal IC used are type *I* (blue-$q_{min} = 0$ and green lines-$q_{min} = 0.4k_BT$) and type *III* (black-$q_{min} = 0$ and red lines-$q_{min} = 0.4k_BT$). Full lines correspond to to an additional initial surface adlayer, while dotted lines are a results of a zero initial concentration on the external matrix surface.