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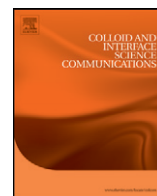


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Rapid Communication

Solvent strategies for loading and release in mesoporous silica

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ABSTRACT

A model molecule, ibuprofen, was loaded in the pores of mesoporous silica by adsorption from nonpolar solvents (liquid carbon dioxide and cyclohexane) and from a polar solvent (methanol). It was sufficient with a very low concentration of ibuprofen in the nonpolar solvents to achieve maximum loading of ibuprofen in the mesoporous particles. When using liquid carbon dioxide, the pores of the mesoporous silica particles were filled completely with ibuprofen at a lower ibuprofen concentration than similar experiments performed with cyclohexane. When methanol was used, the maximum amount of loaded ibuprofen was never achieved. Furthermore, x-ray scattering showed that all ibuprofen loaded into the mesoporous particles were in an amorphous state. Ibuprofen was released from the mesoporous particles to water within a couple of minutes, regardless of solvent used for loading. It was found that the release of ibuprofen from mesoporous silica was much faster than that of crystalline ibuprofen.

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Molecules are often loaded into vehicles to transport them to a desired position. It is advisable to have control over both the loading process and the release of the loaded molecule. One commonly applied technique is to use hydrophilic polymers to control the release of drugs from matrix formulations [1]. By this technique the release behaviour is rather uncontrolled since it depends on the swelling and erosion of the polymer. A different approach is to use mesoporous materials based on silica as the vehicle.

Mesoporous silica materials were introduced in the 1990s and many applications have been suggested for this kind of materials [2,3]. Using the mesoporous particles in delivery systems shows high potential owing to, e.g., large surface area ($>1000 \text{ m}^2/\text{g}$), narrow pore size distribution, and an open and well-defined pore system. Vallet-Regi et al. were among the first to explore mesoporous silica as potential host for drug molecules in an attempt to prolong the release of ibuprofen using MCM-41 as a carrier [4]. Ibuprofen was chosen as a model molecule because of its small size ($5 \times 12 \times 8 \text{ \AA}$) and for its fairly low water solubility. Several authors have reported on the possibility to load ibuprofen in mesoporous silica using different organic solvents [5–10].

In this communication, we have focused on loading of ibuprofen in and release from mesoporous silica of MCM-41 type. One of our aims

was to replace organic solvents with a more environmentally friendly and nontoxic alternative, i.e., liquid carbon dioxide. The major advantages using liquid carbon dioxide as a solvent are that no solvent residues are left in the material after depressurizing the system, the material is immediately dry after removal of the solvent, and that it can be used in processes at relatively low pressures [11,12].

The adsorption data from the ibuprofen loading into the mesoporous silica were determined using thermal gravimetric analysis. The adsorption data were analysed and processed using a multi-step approach [13] based on adsorption energy distribution (AED) calculations prior to the adsorption model fittings.

The release of ibuprofen from mesoporous particles has been studied earlier and the time to reach complete release of ibuprofen from the silica matrix varied from 1 h up to 70 h [6,7,9,14–16]. Since the surface tension of liquid carbon dioxide is low, ibuprofen molecules could possibly penetrate deeper into the mesoporous silica matrix than what is possible with organic solvents with higher interfacial tension [17].

Adsorption isotherms describe the relation between adsorbed and free concentrations of solute at a constant and specific temperature; see supplementary information about the models used in this study. To draw conclusions of the association equilibrium constant and monolayer saturation capacity of the adsorption process, an adsorption isotherm fitting to the adsorption data is needed. If an inappropriate adsorption isotherm model is used in the fitting, misleading assumptions

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about the adsorption process could be drawn. In this section we present an approach to reduce the risk of using a wrong model.

One tool to determine the heterogeneity of the adsorption process is to calculate the adsorption energy distribution (AED) [18], a continuous distribution is obtained by expansion of the Langmuir model over the energy space:

$$q^*(c) = \int_{K_{\min}}^{K_{\max}} f(\ln K_a) \theta(c, K_a) d \ln K_a \quad (1)$$

where $f(\ln K)$ is the AED, c is the concentration of free ibuprofen, K_a is the association equilibrium constant, and q^* is the amount adsorbed to the surface. K_{\min} and K_{\max} are calculated from $0.1/c_{\max}$ and $10/c_{\min}$, respectively, where c_{\max} and c_{\min} are the highest and lowest concentration, respectively, used in the adsorption isotherm determination. $\theta(c, K_a)$ is the local adsorption isotherm. In this case we use the Langmuir model as local model,

$$\theta(c, K_a) = \frac{K_a c}{1 + K_a c} \quad (2)$$

The integral of the adsorption energy distribution is the monolayer saturation capacity, q_s^* ,

$$\int f(\ln K_a) = q_s^* \quad (3)$$

The raw adsorption isotherms were analysed using a three-step approach: Scatchard plots (q^*/c vs q^*) were plotted to deduce the characteristics of the adsorption process. A linear Scatchard plot is only true for the Langmuir model. Most adsorption models, however, result in concave Scatchard plots. From concave Scatchard plots alone, it is impossible to deduce which adsorption model is most suitable [19]. In the second step, the AED is calculated. An AED will give information about how many different adsorption sites are present. Using the results from the Scatchard plots and AED makes it possible to distinguish

between heterogeneous adsorption models, such as the bi-Langmuir and the Tóth models. As data are discrete, the integrals are to be solved numerically, which was done using an expectation–maximization method [20], see supplementary information for more details. If more than one possible model is left that could describe the adsorption data, F-tests are used to deduce which model fits the data significantly best in the final step [13].

The adsorption isotherms for loading ibuprofen in mesoporous SiO₂ using three different solvents are shown in Fig. 1a. The maximum level of adsorbed amount of ibuprofen in the particles (approximately 300 mg/g) was reached when using liquid carbon dioxide or cyclohexane [21]. A lower concentration of ibuprofen in liquid carbon dioxide (approximately 7 mM) could be used to reach this level than when loading was performed in cyclohexane, which required an ibuprofen concentration of 40–50 mM. It should be noted that the solubility limit of ibuprofen in liquid carbon dioxide is 7.3 mM. In the case of using cyclohexane or methanol as the loading solvent, a plateau level in the adsorption isotherm was reached before the saturation limit of ibuprofen in the solvent. Using methanol as loading solvent allows for higher ibuprofen concentrations; in the present study up to 51 mM. In spite of this, the adsorbed amount of ibuprofen in the particles was significantly lower: Only up to 20% of the accessible pores were filled. A nonpolar solvent is required for loading of ibuprofen in mesoporous SiO₂ and when using a polar solvent there is a competition between ibuprofen and the solvent to adsorb to the adsorption sites in the SiO₂ pores [21].

To gain deeper insight about the adsorption process the adsorption isotherms were determined. In Fig. 1b, the Scatchard plots for all raw adsorption data are present. The plot for adsorption of ibuprofen using cyclohexane as solvent is concave; this indicates that the adsorption is heterogeneous from an energy perspective. The plots of the other solvents are more or less linear, indicating that the Langmuir model could be used. The AED, see Fig. 1c, for the adsorption using cyclohexane (light grey) contains two distributions, one at low energy and one at high energy. The bi-Langmuir model fitted well to these data, Fig. 1a. The predicted association equilibrium constants are $K_{a,1} = 18.3$ and

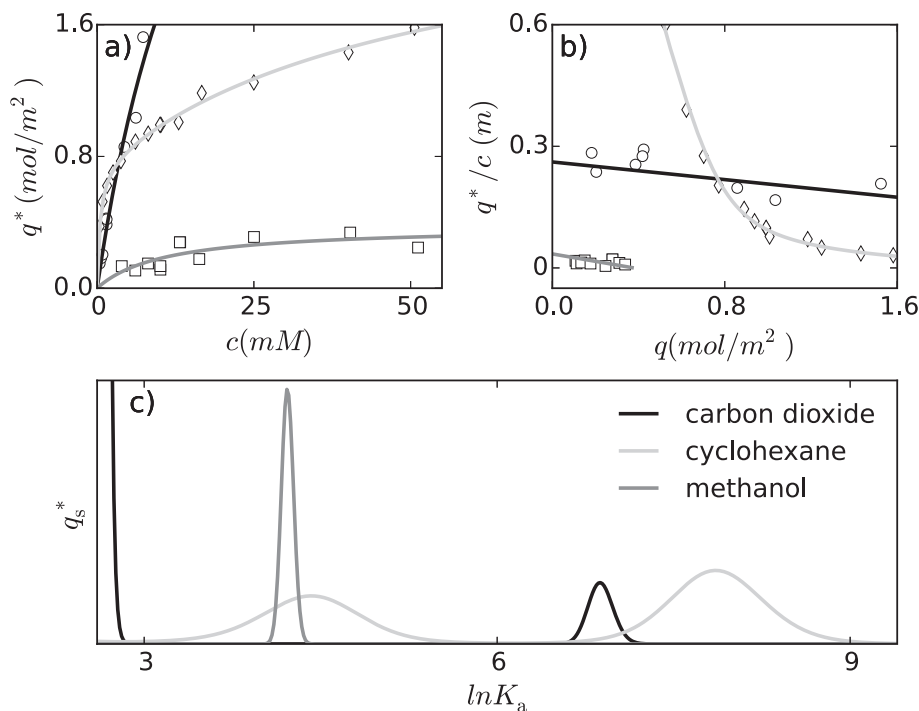


Fig. 1. a). The experimental adsorption isotherms for loading ibuprofen in mesoporous SiO₂ using three different solvents: liquid carbon dioxide (circles), cyclohexane (diamonds) and methanol (squares). The lines are adsorption isotherm model fitted to the raw data. b) The corresponding Scatchard plots for the adsorption data. c) The AED calculation result from the adsorption data. The energy space was span using 400 grid points and 150 000 iterations were used to find these solutions.

Table 1

Adsorption isotherm parameters from the model fit of ibuprofen to silica using different solvents.

Solvent	Model	$q_{s,1}^*$	$K_{a,1}$	$q_{s,2}^*$	$K_{a,2}$
CO ₂	Langmuir	4.81	54.35		
Cyclohexane	Bi-Langmuir	1.68	18.33	0.7552	2144
Methanol	Langmuir	0.38	91.47		

$K_{a,2} = 2144$, Table 1. The AED is unimodal when methanol is used, indicating that Langmuir model is a good model. Inspecting the AED of liquid carbon dioxide, one finds an unresolved low energy site. This unresolved adsorption site is probably a calculation artefact due to the noisy adsorption data, as can be observed in Fig. 1b. The predicted association equilibrium constants were determined to be 91.5 and 54.3 when using methanol and liquid carbon dioxide, respectively, Table 1. To conclude, ibuprofen adsorbs strongest to the surface when cyclohexane is used and weakest if liquid carbon dioxide is used. The estimated monolayer saturation capacities from the model fit, in order from the largest to the smallest, are 4.8, 2.4 and 0.37 mol/m² when using liquid carbon dioxide, cyclohexane and methanol, respectively. The reason for the observed steep adsorption isotherm slope of the ibuprofen adsorption using liquid carbon dioxide is mainly due to the large saturation capacity. One must also stress that due to the low solubility of ibuprofen in liquid carbon dioxide, extrapolation of the adsorption isotherm parameters is needed. Hence, they contain some errors, even though the global model prediction is good.

One could argue that the different solvents used would differ in capability to disperse the silica particles. Given that the mesoporous particles are highly porous, however, the absorption of ibuprofen will reach completeness, regardless of solvent. In order to determine the degree of pore filling of ibuprofen in mesoporous SiO₂, the BET surface area was measured. For a sample with the maximum level of adsorbed amount of ibuprofen in the particles (302 mg/g, liquid carbon dioxide was used as a loading solvent), the measured BET surface area was 62 m²/g. This value should be compared with the BET surface area of the empty mesoporous silica material with a value of 1106 m²/g [22]. Hence, there was a significant reduction in empty SiO₂ pores after the adsorption of ibuprofen but still 6% of the area of the pores was accessible for N₂ adsorption even after loading. The considerable decrease in BET surface area shows that a substantial amount of ibuprofen has entered into the SiO₂ pores. Furthermore, it was confirmed by XRPD analysis that ibuprofen was not deposited on the surface of the mesoporous particles.

In addition to filling the pores of SiO₂ completely with ibuprofen, it has previously been shown that the ibuprofen molecules in the narrow SiO₂-pores cannot crystallize since roughly only a monolayer can occupy the pores [23]. The noncrystalline nature of ibuprofen in mesoporous SiO₂ was confirmed with XRPD, see Fig. 2. Mesoporous SiO₂ has three peaks in the low 2θ-range, while crystalline ibuprofen has several peaks in the measured 2θ-range. When ibuprofen was adsorbed in mesoporous SiO₂, all peaks from crystalline ibuprofen disappeared. This was independent on the loading solvent since no peaks of ibuprofen were observed when using liquid carbon dioxide, cyclohexane or methanol as loading solvent. For all the presented XRPD patterns of ibuprofen in mesoporous SiO₂ using different solvents in Fig. 2, samples containing the maximum achieved adsorbed amount of ibuprofen in SiO₂ for each solvent were analysed.

The release profile of ibuprofen from mesoporous SiO₂ in water is shown in Fig. 3 with an initial content of 1.8 mg ibuprofen when loaded from the apolar solvents, while the content was 0.4 mg when methanol was used as solvent. The percentage of ibuprofen release was calculated from normalizing the absorbance value with the equilibrium absorbance value after 24 h of release in water.

From the release experiments, it can be concluded that ibuprofen was released to water very fast. Already after 25–40 s, 50% of all ibuprofen in

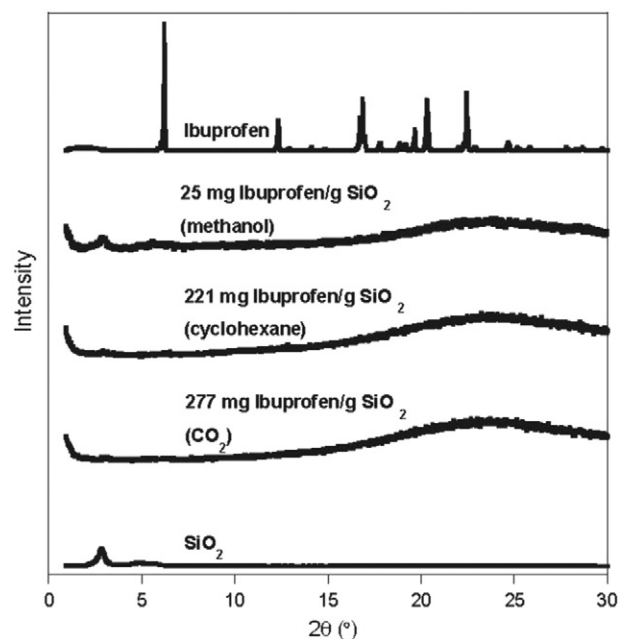


Fig. 2. XRPD patterns for mesoporous SiO₂ and ibuprofen loaded in mesoporous SiO₂ using three different solvents. The XRPD pattern for ibuprofen is also included as a reference.

the particles have been released to and dissolved in the water and after 200 s 90% of all ibuprofen are released to the solution. There are no differences in the release profiles that are indicating that the loading solvent should have any effect on the release, since the time to reach 50% release is more or less similar for all three solvents. One should keep in mind that the ibuprofen loading was significantly lower using methanol as solvent, yielding larger relative errors in the measurements.

It has been shown that the amorphous state of the drug molecule in bulk has a higher dissolution rate in comparison to the crystalline form [24]. Hence, one would expect that ibuprofen loaded into the mesoporous silica particles would show a faster dissolution rate as compared to the crystalline ibuprofen. A comparison was made by comparing dissolution rates for a set of samples containing an equal mass of ibuprofen, but differing in structure. The results are presented in Fig. 3. A commercial product,

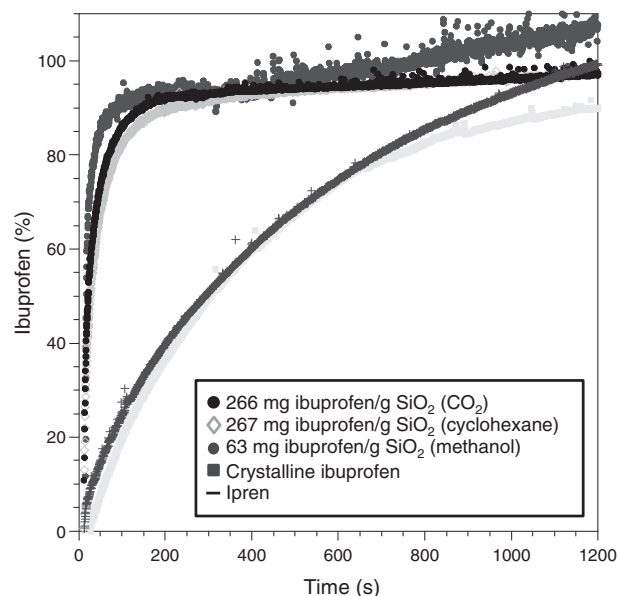


Fig. 3. Release profiles of ibuprofen from mesoporous SiO₂, crystalline ibuprofen and Ipren into water.

Ipren, is also included in the study. The initial release from the particles is much faster, even though complete release requires approximately the same time for all samples. One should keep in mind, as the particle size of the crystalline Ipren ibuprofen reference material ($D[4,3] = 112 \mu\text{m}$) was much larger in comparison to the ibuprofen-loaded in mesoporous SiO_2 particles ($D[4,3] = 9 \mu\text{m}$), that one possible reason for the more rapid dissolution could be the larger exposed ibuprofen area.

We have demonstrated that very low concentrations of ibuprofen in a nonpolar solvent, i.e., liquid carbon dioxide or cyclohexane, are enough to load the pores of mesoporous silica particles almost completely. The thermodynamic process for increase of ibuprofen in the pores is probably driven by formation of favourable hydrogen bonds between the SiO_2 and the ibuprofen [21,25]. Interestingly, the solvent that required the lowest concentration of dissolved ibuprofen to reach maximum loading of ibuprofen in the mesoporous particles was liquid carbon dioxide. This is most certainly due to the saturation capacity from model fittings, Table 1. The capacity for liquid carbon dioxide is about two times higher than that for cyclohexane and about ten times higher than for methanol. This is promising, as liquid carbon dioxide is a so-called “green solvent”. Carbon dioxide in the supercritical region has already been considered as an interesting candidate for replacing organic solvents in different pharmaceutical applications, such as controlled preparation of drug particles by using methods where supercritical carbon dioxide is either a solvent or an anti-solvent [12]. It is also shown that the large ibuprofen area in mesoporous silica yields a very fast initial release as compared to crystalline ibuprofen or from Ipren.

The Supplementary Information to this letter includes a detailed experimental section.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.colcom.2015.01.001>.

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