

Adsorptive Crystallization From Supercritical Solutions

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In this work crystallization of organic compounds in silica aerogels is discussed. The effect of density and surface properties of silica aerogels on crystallization of naphthalene and benzoic acid from supercritical CO₂ is investigated. It is shown that the surface properties of aerogels play a significant role in affecting the crystallization process. Loading of hydrophilic aerogel is higher compared to hydrophobic aerogel for both substances, even though both aerogels have very similar structural properties (surface area, pore size distribution, and pore volume). Both naphthalene and benzoic acid particles obtained inside the aerogel matrix are in the range of 500 nm – 2 μm depending on the crystallization conditions. It was shown that the crystallinity of the additive in aerogels is strongly influenced by the interaction of additive and aerogel surface. Naphthalene formed crystals inside the aerogel matrix whereas benzoic acid stayed amorphous. The potential of this process as “adsorptive crystallization” is discussed.

Key words: aerogels, adsorptive crystallization, supercritical carbon dioxide, crystallization.

INTRODUCTION

Crystallizing of organic substances and especially pharmaceuticals in a porous matrix is of significant importance since it gives a possibility to produce the “enveloped” organic particles. The particles formed inside the pores are less sensitive to oxidation and less reactive compared to the original microparticles. Furthermore, the agglomeration of microparticles is avoided, because the particles are separated from each other inside the pores. Crystallization process in this case is influenced by the surface properties of the porous substances. In this work we focus on the influence of the adsorptive properties of the carrier on further crystallization of organic materials from supercritical CO₂ (“adsorptive crystallization”). Silica aerogels are used as carrier materials since they are highly transparent so that the particle characterization by optical methods is enabled. Further, aerogels exhibit high thermal stability and are biocompatible.

Silica aerogel is an amorphous transparent porous substance consisting mainly of silicon oxide. It has a highly crosslinked network with a pore size ranging from 20 to 100 nm which results in a high surface area (400-1500 m²/g). The density of silica aerogels varies from 0.003 to 0.25 g/cm³ [1]. Doping of silica aerogels with different substances has attracted a great interest in the last years. Buisson et al. [2] encapsulated lipases in silica aerogels. Nanogluing of proteins in silica aerogels is reported by Wallace et. al [3]. Yoda et al. [4] suggested to use titania impregnated silica aerogels to remove VOC's from air. Adsorption of several active compounds (drugs) in silica aerogels was studied and it was shown that the resulting formulations have excellent release properties and can be successfully applied as drug delivery systems [5,6,12]. However, the loading of aerogels with several drugs by adsorption is rather small [9], which is a serious disadvantage for their application as a drug delivery system (the needed amount of the carrier is too large). To overcome this problem, we

suggest to apply crystallization (instead of adsorption) to load aerogels with active agents. If pharmaceutical compounds are crystallized inside aerogels, the resulting formulation can be applied directly as oral or dermal delivery systems similar to the drugs adsorbed on aerogels. Besides this fact, organic particles or drug particles formed inside the pores would be less sensitive to oxidation and less reactive compared to the pure drug micro- or nanoparticles. However, to the best of our knowledge no organic micro- or nanoparticles in silica aerogels were reported in the literature. In our previous work [12] we have started the investigation of naphthalene crystallization in aerogels. In this paper, adsorption and crystallization of naphthalene and benzoic acid from supercritical CO₂ in the aerogels is studied. Firstly, adsorption isotherms of the above substances at different temperatures and pressures are measured using a magnetic suspension balance (MSB) (this is our on going work). Secondly, the crystallization process is carried out: pure aerogels along with the solute are placed in an autoclave and pressurized with CO₂ to the same pressure as for the adsorption process; after a certain time, the pressure is released rapidly to initiate crystallization. The results of the adsorption experiments enable us to distinguish between the adsorbed and crystallized solute in aerogels. The effect of density and surface properties (i.e functionalized silica aerogels; -OH, -CH₃) of aerogels on crystallization under supercritical conditions for both the additives is investigated

2 EXPERIMENTAL

Synthesis of silica aerogels and surface modification of silica aerogels

Silica aerogels are produced by using a two step sol-gel process [7]. The preparation of gels in detail is described elsewhere [12]. The gel is aged for 12 hrs and then the pore liquid is extracted by supercritical CO₂ (40°C, 100 bar). The aerogels obtained are hydrophilic due to unreacted -OH groups on the surface. The densities of cylindrical aerogels (0.6mm X 20mm) are measured by weighing the samples of the known volume. The surface area, pore size, and pore volume of samples are analyzed by nitrogen adsorption (BET, Nova 3000e). Hydroxyl groups on the surface of hydrophilic silica aerogels are esterified by the method of Lee et. al [8]. Hydrophilic silica aerogels are placed in a reactor and heated up to 180°C. Methanol or Trimethylmethoxysilane vapor passes through the reactor for 42-48 hrs. The time of the reaction is regulated by the desired amount of O-CH₃ groups as showed in [9]. Hydrophobic aerogels obtained in this way float on water without being wetted for several hours. The amount of O-CH₃ groups is measured by the elementary analysis (CHN).

Crystallization experiments

Experimental setup

The 557 cm³ view cell is connected to a circulating pump to maintain a proper mixing of solutes. The pressure and temperature are registered by the data acquisition program Labview 7.0. The details of the experimental setup are given elsewhere [12].

In a typical experiment the required amount of the solute is placed along with the silica aerogels in the view cell and heated to the target temperature within the accuracy of ± 1°C. CO₂ is added up to the desired pressure (110-220 bar) and these conditions are kept for 12 hrs

to reach the equilibrium. Then, the pressure is released either gradually or stepwise with different release rate.

The amount of solute in aerogels is analyzed by UV spectrometry (Perkin Elmer Lambda 600 model). For this, loaded aerogels are powdered and dispersed in toluene. The solution is stirred for 2 hrs, filtered and analyzed at $\lambda_{\text{naphthalene}} = 287.8 \text{ nm}$ and $\lambda_{\text{Benzoic Acid}} = 272 \text{ nm}$.

Loaded samples are characterized by X-Ray diffraction (XRD) and differential scanning calorimeter (DSC) measurements.

3 RESULTS

Hydrophilic aerogels were synthesized and a part of them were hydrophobized as described above. An advantage of the hydrophobization of aerogels by the gas phase reaction (post-treatment of hydrophilic aerogels) is the fact that the pore size distribution and surface area do not change significantly during this process. It gives the possibility to study the influence of the functional groups on the crystallization by comparing of hydrophilic and hydrophobic samples having the same structural properties.

It is expected that the size of naphthalene or benzoic acid particles formed inside the aerogel depends on aerogel's properties and on the pressure release rate since the nucleation process and particle growth are driven by supersaturation inside the pores. It is known that a higher supersaturation is needed to initiate the nucleation in small pores in comparison to bulk solutions [10]. Analogous to crystallization in gels, heterogeneous nucleation is likely to take place in aerogels [11].

The minimum temperature of the SLG curve for binary mixture of naphthalene and CO_2 is between $58\text{-}62^\circ\text{C}$ and in the case of benzoic acid is $65\text{-}68^\circ\text{C}$, therefore temperatures between 58°C for naphthalene and 65°C for benzoic acid were chosen for the experiments. Crystallization was performed at different conditions and typical aerogel samples loaded with naphthalene from the saturated solutions are shown in Figure 1. The particle size decreases with increasing release rate. Naphthalene crystals in the range of $500 \text{ nm} - 2 \text{ mm}$ were obtained inside the aerogel matrix depending on the crystallization conditions.

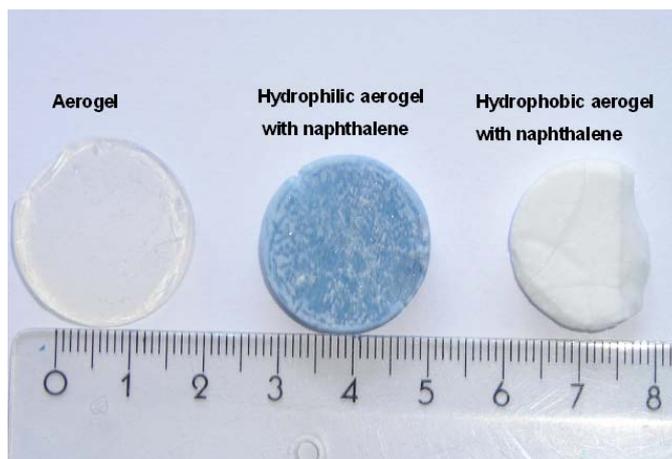


Figure 1. Aerogel samples after crystallization in comparison to the initial aerogel. Crystallization conditions: 58°C , 220 bar, 16 wt% of bulk naphthalene in CO_2 , $\rho_{\text{aerogel}} = 0.155 \text{ g/cm}^3$.

An interesting effect has been observed during the crystallization of naphthalene in hydrophilic aerogels. When the pressure release was performed slowly, transparent aerogels

filled with white naphthalene particles were obtained. However, after the fast stepwise pressure release, hydrophilic aerogels exhibit a blue color after the crystallization. This effect is reproducible and the hydrophilic samples stay blue in color for several weeks. The corresponding samples are shown in figure 1. Several reasons could explain this fact. Firstly, different light scattering of the aerogel samples could occur due to the difference in particle size of naphthalene. Secondly, interactions between naphthalene and the aerogel matrix could vary due to the presence of different functional groups (OH and OR). The different arrangement of naphthalene molecules on silica aerogel surface could occur as well.

To prove this, DSC experiments with these samples were performed (results not shown). Pure naphthalene shows an endothermic peak typical for crystalline substances at 80.1°C (T_m of pure naphthalene = 80-81°C). In case of naphthalene implemented in the pores of silica aerogels, similar endothermic peak is observed confirming the crystalline state. Crystallinity was additionally proven by XRD analysis (not shown here). However, the melting point is shifted to 60.8°C in the hydrophilic aerogels and to 63.8°C in hydrophobic ones. Larger melting point depression in case of hydrophilic aerogels indicates either the smaller particle size or the stronger interaction of naphthalene with the matrix. The loading of aerogels with naphthalene at different experimental conditions was determined. In loaded aerogels samples both adsorbed and crystallized naphthalene should be present.

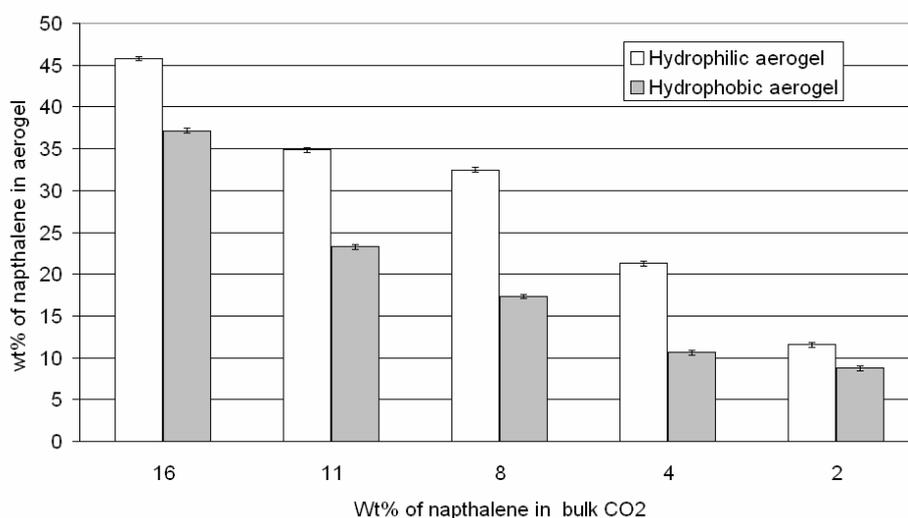


Figure 2: Loading of naphthalene on silica aerogels for varying initial naphthalene concentration in bulk CO₂ for a fixed aerogel density of 0.212 g/cm³, conditions: T = 58°C, P = 210-110 bar [12].

The experimental method used in this work (extraction with an organic solvent) allows to detect the overall loading (adsorbed + crystallized naphthalene) only.

The dependence of aerogel loading on the bulk concentration of naphthalene in CO₂ is shown in figure 2. Rather high loadings (up to 45 wt%) have been achieved.

In our previous work, it was shown that only 4-5 wt% of naphthalene could be adsorbed in hydrophilic silica aerogels [13]. As expected, the loading increases with the increasing naphthalene concentration, but in all cases hydrophilic aerogels exhibit higher loading than

hydrophobic ones. Hence crystallization process is influenced by the prior adsorption we term it as “adsorptive crystallization”.

Benzoic acid crystallization in aerogels

Similar to naphthalene experiments, benzoic acid loading is carried out at 65°C (SLG-minimum is 65-68°C for binary mixture of CO₂ and benzoic acid). Figure 3 shows the aerogel loading at different bulk concentration of benzoic acid in CO₂. The maximum loading of 25% is achieved. Hydrophilic aerogels have higher loading compared to hydrophobic aerogels. The effect of surface functional groups influenced more significantly compared with the case of naphthalene. Hydroxyl group of benzoic acid has stronger interactions with hydroxyl groups of aerogel surface, resulting in a hydrogen bonding. Hydrophobic aerogel having less or few active hydroxyl groups on the surface cannot have less interaction which results in a smaller loading.

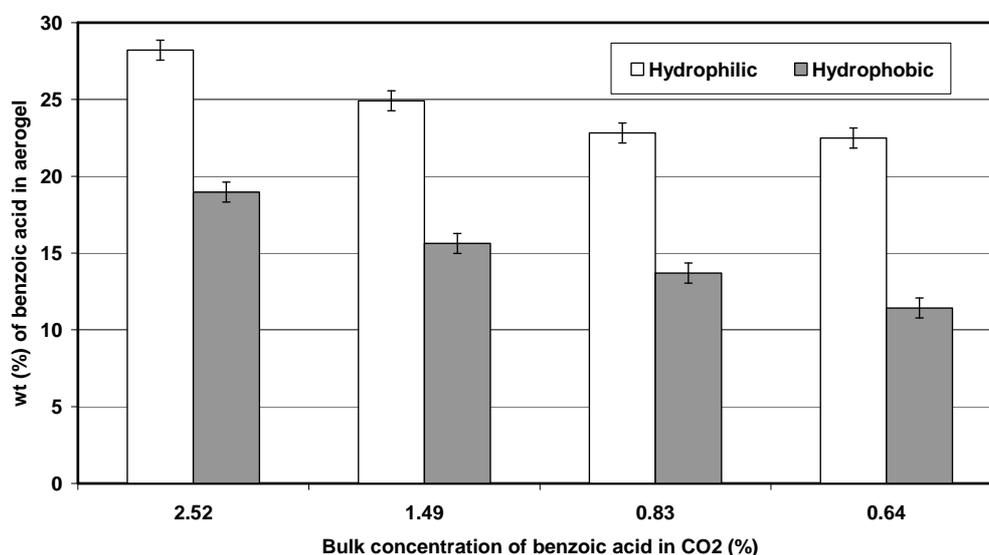


Figure 3: Wt % of benzoic acid in silica aerogels for varying bulk concentration of benzoic acid concentration in CO₂ for a fixed aerogel density of 0.10 g/cm³; T = 65°C.

To understand the influence of surface functional groups on the loading, hydrophilic aerogel were hydrophobized with different percentage of -CH₃ groups and loaded with benzoic acid. Figure 4 shows the influence of the degree of hydrophobization on the benzoic acid concentration in aerogels with different bulk densities. The loading decreases with increasing amount of -CH₃ groups. Hence, the amount of loading can be tailored based on the amount of functional groups on the surface of silica aerogels.

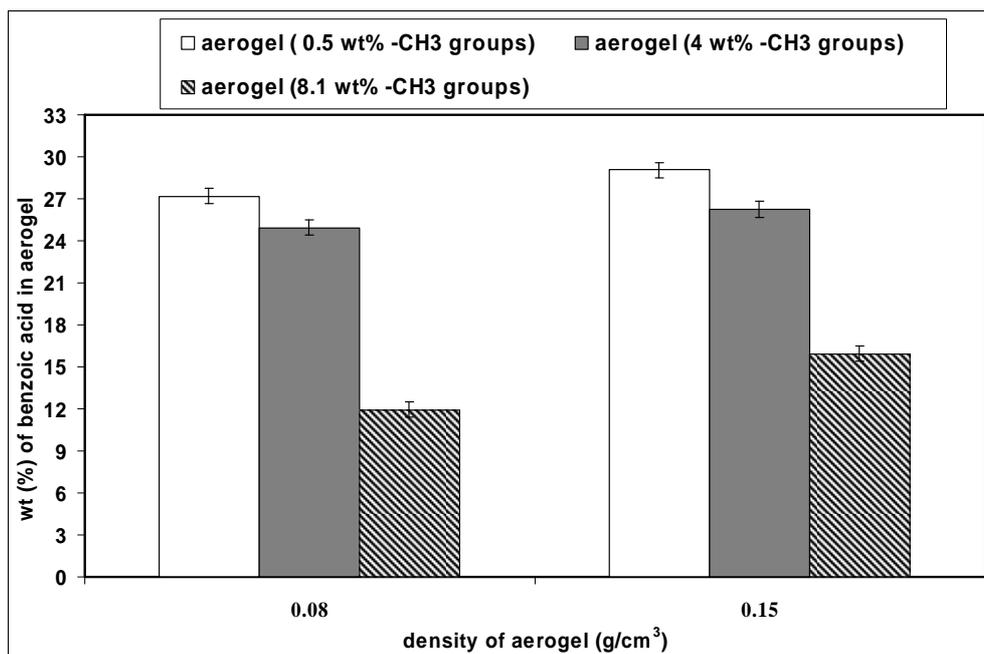


Figure 4: Wt % of benzoic acid in silica aerogels of different degree of hydrophobization: 0% to ~ 8 wt% of carbon. (Conditions: P = 195 bar, T = 63.5°C, time of loading = 24 hrs, bulk concentration of benzoic acid in CO₂ = ~2.3 wt %; Stepwise pressure release: a) 140-90 bar: fast release b) 90-1 bar: slow release

An interesting result is observed from DSC and XRD results in case of benzoic acid. It is observed that the benzoic acid in the pores of both hydrophilic and hydrophobic aerogels is amorphous in nature (DSC curves not shown here). Contrary to naphthalene, no crystalline structures were observed. This might be due strong interactions of benzoic acid with hydroxyl groups of silica aerogels, which prevent the adsorbed benzoic acid to crystallize, it stays rather in amorphous form. These finding can have potential application in pharmaceuticals, since the bioavailability is enhanced when the drug is amorphous. Hence, even the state of substance (crystallinity or amorphous nature) can be controlled based on the functional groups of the carrier. To further elucidate this phenomena, crystallization of another solute (octocasane) was studied. Octocasane is fully saturated alkane, so it is likely to have no strong interactions with the aerogel surface. So we expect that it would readily form crystals in the pores of aerogels. Even the amount crystallized should be almost same in hydrophilic and hydrophobic aerogels. This expectation was also confirmed experimentally. Even very small amount of octocasane (loading of 1.5 wt%) exhibit crystalline structure being loaded in aerogels. Hence, the crystallinity in the pores of carrier is function of both functional groups of the additive as well as the amount and type of functional groups on the surface of the porous carrier (in this case aerogel).

4 CONCLUSIONS

Crystallization of naphthalene, benzoic acid and octocasane in silica aerogels from supercritical CO₂ solution was studied. Maximal loadings achieved were as 55 wt% of naphthalene and 31 wt% of benzoic acid and 1.5 wt% of octocasane. The loading itself and the

properties of the resulting microparticles are influenced by the structural and surface properties of silica aerogels, in particular by their adsorption capacity. Strong interactions with hydrophilic aerogels lead to more effective particle formation in their pores. Not only the amount of loading but also the crystallinity of the loaded substances is strongly influenced by interaction with the surface functional groups. Substances which exhibit stronger interactions with aerogels tend to form amorphous particles inside the pores, whereas those having less interactions will rather form crystals. Hence, the crystallization process is influenced by a prior adsorption on the surface of the aerogels (adsorptive crystallization). This process could be used to form amorphous or crystalline drug particles in aerogels to produce effective pharmaceutical formulations.

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