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Experimental and theoretical investigation of drug loading to silica alcogels

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ABSTRACT

The loading of a model drug, paracetamol (PC), via diffusion from an ethanol solution to the pores of the silica alcogel was studied. Partial differential equation representing the mass transfer within the cylindrical silica alcogel phase was developed and solved using the finite difference method. The model enabled the prediction of the time needed for maximum amount of loading and also the distribution of the drug inside the matrix at specific time points. It was observed that the concentration in the regions closer to the surface increased rapidly contrary to concentration in the regions close to the center which increased more slowly. The uptake of paracetamol was also measured gravimetrically and these experimental data were found to be in good agreement with the model predictions without any adjustable parameters. The effects of the tortuosity of the aerogels were also investigated by simulations. It was found that the duration for the maximum amount of loading increased with increasing tortuosity values. Moreover, silica alcogels that were loaded with paracetamol were dried with supercritical CO_2 which resulted in paracetamol loaded monolithic silica aerogels. Characterization of these paracetamol loaded silica aerogels showed that paracetamol had diffused through the center of the aerogel and it had a crystal structure.

1. Introduction

Nanoporous aerogels with very large inner surface areas, high surface to volume ratios, large pore volumes and uniform pore sizes are generally synthesized via the conventional sol–gel method involving subsequent hydrolysis, condensation, gelation, aging and supercritical drying steps or via direct polymerization of organic precursors followed by solvent exchange and supercritical drying steps [1–3]. Over the past few years, aerogel based systems constitute an emerging platform for drug delivery due to their high drug loading capacities, their ability of controlled drug release, their capability to increase the bioavailability of low solubility drugs, to improve both their stability and their release kinetics [3–5]. Not only the unique properties such as very high porosities and high surface areas but also the ability to control properties by manipulation of synthesis conditions is driving the developments in this field. Moreover, the surface chemistry of the aerogels which can be modified by different surface functionalization techniques [6,7] was shown to affect the adsorption and release of the drugs. Furthermore, composite and layered aerogels provide new possibilities to achieve the targeted formulation properties [8,9].

There are several methods to incorporate drugs into aerogels such as the addition of the drug during the synthesis or during the post treatment of the synthesized gels or aerogels [5,10].

The loading during the post treatment generally implies the incorporation of the pharmaceutical compound by adsorption into the pores of the aerogels mostly from supercritical CO_2 ($scCO_2$) [10,11]. This technique is very attractive since $scCO_2$ is nontoxic, nonflammable and leaves no residue in the matrix and it can provide high mass transfer rates due the high diffusivities of drug molecules in $scCO_2$ [12,13]. Moreover, its density, viscosity and solvent power might be modified by adjusting the pressure and the temperature. However, most of the pharmaceutical compounds have limited solubilities in $scCO_2$ which restricts the use of this technique for a wide variety of drugs. It was recently suggested by Haimer et al. that this low or insolubility of many compounds in $scCO_2$ might be beneficial for their incorporation during the solvent exchange step [14]. In this approach, alcogels are contacted with a solution containing the drug to be loaded. Due to a concentration gradient of the drug in the pore liquid and the contacting solution, the drug diffuses into the liquid in the pores. The diffusion continues until the concentrations in the pore liquid and the contacting solution become equal. Subsequently, the alcogel is subjected to supercritical drying in which the pore liquid is extracted by $scCO_2$ and the loaded drug precipitates during this extraction stage due to its insolubility in $scCO_2$. This drying process is actually similar to the

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gas antisolvent crystallization (GAS) process in which $scCO_2$ acts as an antisolvent [15] to precipitate drug inside the pores. Haimer et al. have demonstrated that bacterial cellulose aerogels can be loaded with bioactive compounds via antisolvent crystallization inside the pores with $scCO_2$ [14]. They studied the loading of dexpanthenol and L-ascorbic acid from ethanol to the pores of bacterial cellulose aerogels and concluded that the loading was independent of the nature of the drug. Rueda et al. stabilized magnesium hydride in silica aerogel microparticles using the same process [16]. They loaded silica aerogel microparticles with magnesium acetate and magnesium boride which precipitated during the drying of the alcogel. Then, the product was hydrogenated to be tested as a hydrogen storage material. Ulker and Erkey also used this technique to load paracetamol into a layered aerogel system consisting of a silica aerogel core encapsulated by an alginate aerogel layer [9].

In this technique, the total uptake consists of the amount adsorbed on the surface and the amount in the pore liquid. For cases in which the adsorbed amount on the surface is more than the amount in the pore liquid, the interactions between the surface and the molecules, the concentration of the solution inside the pores and the available surface area are the important parameters governing the loading. High surface areas and strong interactions between the surface and the molecule are expected to lead to higher loadings. On the other hand, when adsorption on the surface is negligible, loading depends on the final concentration of the solution inside the pores (which in turn depends on the initial concentration of the contacting solution), the pore volume of the matrix and time of contact. Therefore, if the matrix has a high pore volume and the compound has a high solubility in the chosen solvent, very high loadings can be achieved. The time of contact is another important parameter depending on the diffusion rate of the pharmaceutical compound in the pore liquid which in turn depends on molecular diffusivity, pore properties such as the porosity and the tortuosity of the matrix and the initial concentration of the loading solution. Time considerations become especially important when preparing formulations. It is essential to know the exact time when a particular loading amount would be achieved due to stringent regulations in the pharmaceutical industry. Moreover, improving our understanding of the effects of pore properties, the type of solvent, the concentrations of loading solutions on loading amounts and times should facilitate the commercialization of these materials. Mathematical models for drug loading should enable us to investigate the effects of these factors in more detail. Moreover, mathematical models on the kinetics of drug loading can be beneficial for obtaining alcogels with different amounts of drug loading from the same batch. Even though there are some studies in the literature on mathematical modeling of drug adsorption into aerogels from supercritical CO_2 or into alcogels from aqueous solutions [17,18], there are no studies on modeling of drug loading into silica alcogels by diffusion.

In this study, the loading of paracetamol (PC) in the pores of the silica alcogel from an ethanol solution of the drug. PC was chosen as the model drug due to its high solubility in ethanol we investigated. Moreover, it is also not possible to load paracetamol by adsorption from $scCO_2$ due to its extremely low solubility in $scCO_2$. Then the loading of PC in the pores of the silica alcogels from a solution of paracetamol in ethanol was modeled and the model results were compared with experimental data. The time needed to obtain the maximum loadings, the distribution of the drug inside the porous matrix and the amount of loading at different times were predicted by the model. Good agreement was found between the theoretical results and the experimental data. In addition, paracetamol loaded alcogels were subjected to supercritical drying which led to paracetamol loaded aerogels due to the precipitation of paracetamol as a result of a gas anti solvent process occurring in the nanosized pores.

2. Materials and methods

2.1. Synthesis of silica aerogels

A two step sol–gel process consisting of consecutive hydrolysis, condensation, gelation, aging and drying steps was used to synthesize silica aerogels. Initially, an equal weight percent mixture of tetraethylorthosilicate (TEOS) (from Alfa Aesar 98% purity) and ethanol (from Merck) was prepared. Subsequently, water and then HCl (from Riedel-de Haen with 37% purity) was added to adjust the pH to 2.0 to increase the rate of hydrolysis. Afterwards, NH_4OH (from Aldrich 2.0 M in ethanol) as the condensation catalyst was added to accelerate condensation reactions leading to gelation at neutral conditions. Overall, the mole ratio of TEOS to water was 1:4, TEOS to HCl was 500:1, TEOS to ethanol was 1:4.5 and TEOS to NH_4OH was 96:1. The final concentration of TEOS in the sol was around 1.9 M. Before gelation, the sol was poured into cylindrical molds in equal volumes with the help of a micropipette. After gelation, the wet gels were taken out from their molds and placed in equivolume mixture of ethanol and water at 323 K for aging. The purpose of performing this aging step was to improve the mechanical strength of the wet gels by inducing hydrolysis and condensation reactions of unreacted TEOS remaining on the gels. After 24 h, these gels were placed in pure ethanol for 3 days. This solvent exchange step aimed to remove all impurities and water remaining in the pores. The last step was to dry alcogels at 90 bar and 313 K with $scCO_2$ to obtain native silica aerogels.

2.2. Paracetamol loading to the silica alcogels

The general strategy used to obtain paracetamol loaded aerogels is shown in Fig. 1. The silica alcogel cores which were obtained after the gelation were primarily subjected to usual aging steps as mentioned in Section 2.1. Subsequently, alcogels were contacted with an ethanol solution containing paracetamol with different molarities which caused the transfer of paracetamol into the pores of the alcogel from the loading solution under constant stirring at room temperature. Finally, the alcogel containing the drug was dried with $scCO_2$ at 313 K and 90 bar.

2.3. Characterization of silica aerogels loaded with paracetamol

IR spectra were recorded using a spectrophotometer (Thermoscientific Nicolet IS10). For analysis, no sample preparation was required. A small amount of powder obtained by crushing a small piece of aerogel was used as the sample. The crystal structure of paracetamol was confirmed with XRD analysis. XRD patterns of the samples were collected on a Bruker D2 phaser. The density of the samples was measured by simply dividing their mass by their volume which was calculated using the dimensions of the sample measured with the help of a caliper.

2.4. Release of paracetamol from silica aerogel

The release experiments of PC were conducted at 310 K under constant stirring. The release medium was phosphate buffered saline (PBS) (pH of 5.8). A PC loaded aerogel sample was placed on a wire mesh and immersed into a glass vessel containing PBS solution (40 ml). The glass vessel was covered to prevent any solvent evaporation and it was kept inside an oven at 310 K. At specific time points, 100 μl sample was taken for analysis by a UV-spectrophotometer at 242 nm due to the specific absorption of PC at this wavelength. In control samples, silica aerogels did not give any significant absorbance at 242 nm confirming that the measured absorbance was due to the presence of paracetamol only.