Functionalized Silica Aerogels for Advanced Drug Carrier Systems

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Abstract

Because of their high surface area, open pore structure and their biocompatibility aerogels were shown to be an ideal candidate for drug delivery systems. This work aims to enhance the loading of drugs in silica aerogels by means of surface functionalization of the carrier, and to investigate the influence of surface functional group on the release rate of the loaded drug in aqueous media. Aminogroups were taken as an example of functional groups. Different approaches were followed to control the surface functionalization: pretreatment of the gel before the drying step, or a post treatment of the aerogels. The obtained amino-functionalized aerogels were characterized by CHNS and BET analysis, and UV-spectroscopy. It has been shown that the functionalized silica aerogel maintain the same structural properties as the origin aerogels. For the first time transparent amino-modified aerogels with a high surface area up to 1000 m^2/g were obtained. These aerogels were loaded with drugs by adsorption from supercritical CO_2. With increasing the concentration of the aminogroups on aerogels surface the amount of the loaded drug was increased. The reason is that the modified aerogels offers more active adsorption sites for the drug substance to be adsorbed on the modified surfaces. Furthermore functionalized aerogels show promising results in controlling the release rate of the drug compared to that of crystalline active drug substances. Aerogels functionalization opens the possibilities to design a drug carrier for a specific active drug substance, as well as to control the release of that drug in the released media.

Keywords: Aerogels; Aminogroups; Functionalization; Drug carrier; Supercritical CO_2

1. Introduction

Aerogels are a class of ceramic materials with a superior properties, with 15 entries in Guinness Book of Records for properties such as lowest density solid, best insulator and highest surface area per unit volume of any solid, up to 3000 m^2/g. Aerogels are a fascinating material to be investigated in different and wide applications [1-4], starting from space engineering, thermal insulation [5], ultra high-density capacitors [6], solar-energy collectors, Cherenkov detector [7], waste treatment [8], drug delivery and targeting systems [9-11] and many others [12-14].

Silica aerogels have an open cell structure composed of primary particles usually less than 10 nm in size connected to each other forming a 3-D network with a porosity in the mesopore range ~ 20-50 nm [15, 16]. Silica aerogels are produced by the sol-gel process, in which the chemicals containing silica undergoes a chemical reaction which leads to the formation of an internal three-dimensional network. During this time the viscosity of the reaction mixture increases, the solution forms a gel which becomes more stable by the so called aging. To produce an aerogel the solvent inside the gel network should be substituted by air. By means of supercritical extraction the drying is achieved without phase change, hence no capillary forces will be present and the internal network will be maintained [17].

Because of its biocompatibility, open pore structure and high surface area silica aerogel was approved to be an ideal drug carrier [9], Smirnova et al. have shown that using aerogel as a drug carrier enhance the solubility of poorly soluble active drug substances in aqueous solution [10], furthermore the dissolution rate of the poorly soluble drug in aqueous media was highly increased [19],

Since the active drug substances have different functional group, it is possible to enhance their loading as well as the release rate by implementing special functional groups on the surface of the drug carrier by means of functionalization. Depending on the drug properties and functional group it is possible to make the drug carrier more hydrophobic or more hydrophilic,

In this work the functionalization of silica aerogel with aminogroups was successfully achieved using different techniques, each of them has its own application and advantages, afterward the loading and the release behavior of ketoprofen as a model drug were studied.

2. Experimental Part

Materials:

Carbon dioxide with a purity of 99.9% was supplied by AGA Gas GmbH, Hamburg. Ketoprofen (racemic mixture) was purchased from Chemische Fabrik Kreussler & Co. GmbH, Wiesbaden. Tetramethoxysilane (TMOS) with a purity of 98%, (3-Aminopropyl)trimethoxysilane (APTMS) 97% and Acetonitrile 99.8% were purchased from Fluka Germany, methanol 99.5%, hydrochloric acid 30% and ammonia hydroxide 25% were purchased from Merk Germany. All chemical were used as they provided without any further processing.

Aerogel Production

Silica aerogel were produced following the two step sol-gel process [21]. In the first step tetramethylorthosilicate (TMOS), methanol, water, and hydrochloric acid were mixed together with a molar ratio:

1 mol TMOS: 2:4 mol MeOH: 1:3 mol $H2O$:10^{-5} mol HCl.

The mixture was stirred at room temperature for 30 min. after that additional water and ammonia solution were added, to obtain the following molar ratio:

1 mol TMOS: 2:4 mol MeOH: 4 mol H2O: 10^{-5} mol HCl: 10^{-2} mol N H_4OH.

Then the mixture was diluted with acetonitrile to obtain the desired density of the aerogel and stirred for further 3 min. afterward the solution were poured into a cylindrical mould to be aged over night, to obtain aerogel the aged gel was then dried using CO_2 at supercritical conditions for 24 hours.

Functionalization Methods

Aerogel functionalization with aminogroups was achieved through different approaches. Depending on the stage of functionalization it is possible to differentiate two main routes of functionalization: (a) the functionalization of the produced aerogel by mean of gas phase reaction, and (b) functionalization of the gel before the drying step.

Gas Phase Functionalization (a)

To functionalize aerogel in the Gas phase the following procedure was used. A mixture of APTMS and acetonitrile was placed in the boiler. The resultant vapor was driven through the autoclave. The autoclave temperature was kept over the condensation temperature of the gaseous mixture. Aerogels were placed in inside the autoclave figure 1. A gas phase reaction was occurred upon the contact between aerogels and the gas mixture. In this stage the functional groups were bonded on the aerogel surface. After leaving the autoclave the vapor was condensed using a condenser. The resultant condensate was then recirculated to the boiler. After certain time the functionalization was stopped and aerogels were taken out for further analysis.

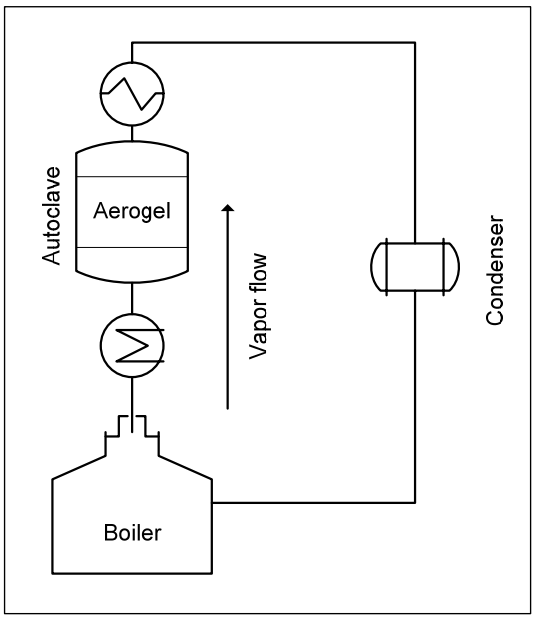

Figure 1. Schematic chart for the gas functionalization setup

Gel Functionalization (b)

Process (i)

The first method is to functionalize the gel after the aging process. Different concentrations of APTMS/acetonitrile solutions were prepared. After that the gel were placed in the functionalization solution for 24 hours at 50° C. the resultant functionalized gel was washed with acetonitrile and placed in acetonitrile bath for two hours. Afterward the gel was dried using supercritical CO_2.

Process (ii)

The second method is to functionalize the gel during the condensation step of the sol-gel process. APTMS instead of NH_4OH were used with the required concentration. Lastly the sol-gel solution gelated, aged and finally dried using supercritical CO_2.

The resultant functionalized aerogels were analyzed using elementary analysis (CHN) and BET analysis

Loading of Aerogel with Drugs

The Loading of the drug on aerogel was achieved by the following procedure. A weighed amount of the drug and aerogel wrapped in a filter paper were placed in the autoclave. After that the autoclave was sealed and heated to 40°C and CO_2 was pumped inside until a pressure of 180 bar was reached. Then the autoclave was shacked for 48 hours, finally the pressure was released and the loaded aerogel was removed. To determine the drug concentration in the sample a part of the aerogel powder was dispersed in acetonitrile. The solution was stirred for at least 60 min to ensure a complete dissolution of the drug. The concentration of both drugs in acetonitrile was determined using UV-spectrometry ($\gamma_{Ketoprofen}$=252 nm). Based on these measurements the amount of the drug in the loaded aerogel was calculated. Each experiment was repeated at least twice

3. Results and Discussions

Gas phase functionalization

The dependence of the amount of aminogroups on the reaction time was studied. The concentration of the APTMS solution was kept constant (10 wt %). The average surface area of the resulted functionalized aerogel was 872 ± 62 m²/g, with an average density = 0.11 ± 0.015 g/cm³. Figure (2) shows that the concentration of aminogroups was increased with increasing the reaction time. CHN analysis shows that increasing the reaction time from 12 to 48 hours the amount of aminogroups was increased from 1.1 to 2.95 wt%. These results were supported by loading of ketoprofen on aerogel matrix. Figure (2) shows that the depositing of ketoprofen on the aerogel matrix was enhanced from 9.7 to 21.1 wt%. This can be explained by the fact of increasing the active absorption sites available for absorption of the drug substance.

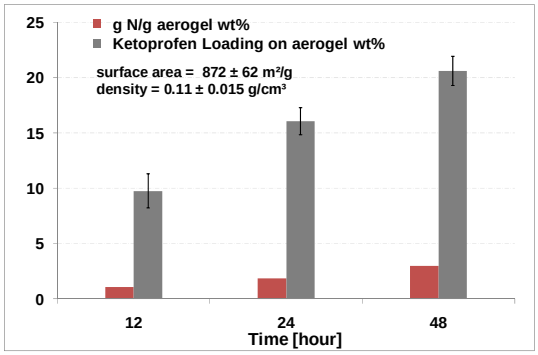

Figure 2. Effect of functionalization time on the concentration of aminogroups as well as on loading of ketoprofen in aerogel matrix

The drug release measurements for the resultant aerogel-ketoprofen formulations were studied following the recommendations of the International Pharmaceutical Federation (FIP). The procedures as well as the apparatus are described elsewhere [10]. Chart 3 shows the results of dissolution profiles of crystalline ketoprofen and different aerogel-ketoprofen formulations. The release of crystalline ketoprofen is much slower than that of drug –aerogel formulations: more than 70% of the loaded drug can be released on the first 30 min, 99% release can be achieved within 3 hours. This fast release of the drug from aerogel matrix can be explained by three main factors: firstly the extended specific surface area of the

loaded drug by being absorbed on aerogel, secondly, the rapid collapse of aerogel formulation upon contact with an aqueous solution, and thirdly, the amorphization of the absorbed drug inside the aerogel matrix [10]. Functionalization of the hydrophilic aerogel matrix by NH_2 groups has almost no effect on the release kinetics, since for hydrophilic aerogel the fast release of the drug in the dissolution media depends mostly on the collapse of the aerogel network upon the contact with aqueous solution. The dissolution rate can be controlled by changing the art of functionalization, for instance by adding hydrophobic functional groups.

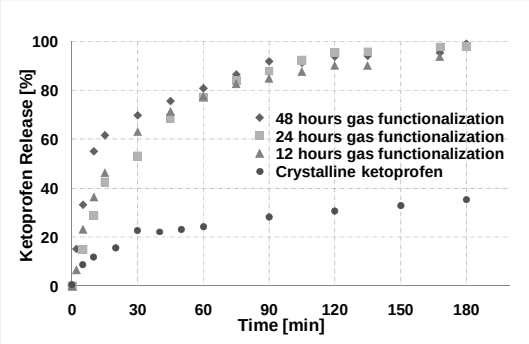

Figure 3. Dissolution profile of crystalline ketoprofen and gas functionalized aerogel-ketoprofen formulation

Liquid Phase Functionalization

The effect of the concentration of functionalization solution on the amount of NH_2 groups bound on the aerogel was studied. For the first functionalization method (i), different APTMS/Acetonitrile solutions with concentrations between 2 wt% and 6 wt% were used. The resultant CHN analysis shows that the concentrations of the aminogroups in the aerogel samples increases from 3.12 to 6.86 wt% g N/g sample. This effects consequently the loading of ketoprofen in aerogel matrix (figure 4): by changing the concentration of functionalization solution it is possible to enhance the loading of ketoprofen on aerogel matrix, since more aminogroups are present on the Aerogel.

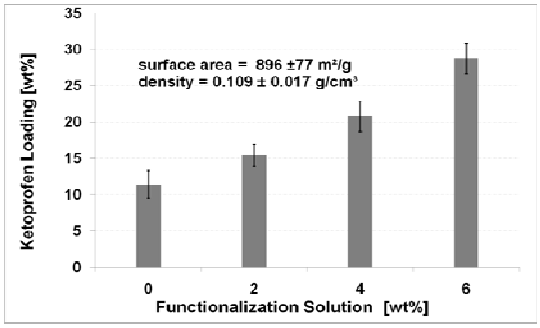

Figure 4. Effect of APTMS concentration on the loading of ketoprofen in aerogel matrix.

Figure 5 shows that the dissolution rate of loaded ketoprofen from the aerogel matrix is much higher than that of crystalline ketoprofen. The average release behavior of ketoprofen from aerogel-ketoprofen formulation was similar, this finding support our finding in the gas phase functionalization part, that hydrophilic functionalization has almost no effect on the release rate of the loaded drug. The small deviation from the average behavior was due to the difference of the specific surface area of the functionalized aerogel.

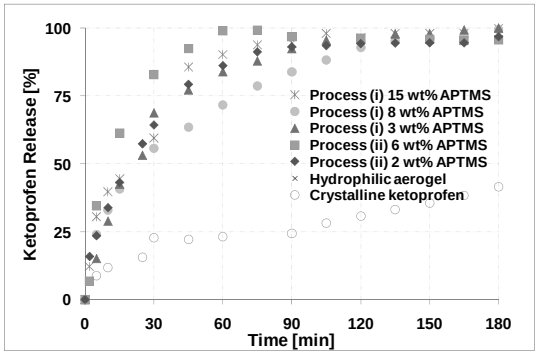

Figure 5. Dissolution profile of crystalline ketoprofen and liquid functionalized aerogel-ketoprofen formulation

4. Conclusion

Aerogel was successfully functionalized with aminogroups using different techniques. For the first time it was

possible to produce a transparent amino-functionalized aerogel with a BET surface area of 960 m²/g, which is more than two times larger than that obtained by other groups [22]. The loading of ketoprofen in the functionalized aerogel matrix was enhanced by increasing the concentration of aminogroups in the matrix. The dissolution rate of the ketoprofen-aerogel formulation was much higher of that for the crystalline ketoprofen. Increasing the hydrophilicity of aerogel has almost no effect on the dissolution rate of the loaded drug.

5. References

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