

**INVESTIGATION OF AEROGEL BASED SYSTEMS
FOR
DRUG DELIVERY**

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**Investigation of Aerogel Based Systems
for
Drug Delivery**

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*To my family &
To the memory of my grandparents*

ABSTRACT

Over the past few years, nanoporous aerogels have shown a great promise as drug delivery vehicles. In this study, inorganic and organic aerogels such as silica aerogel and alginate aerogel were investigated as drug delivery systems. Moreover, a novel layered material consisting of these two distinct aerogels was prepared for the first time by encapsulating a silica aerogel with an alginate aerogel layer. To investigate aerogels as drug delivery vehicles, different methods are utilized to load drugs into them such as the addition of the drug to the reaction mixture in one of the steps before the gel formation or by supercritical deposition to the aerogels. These techniques have disadvantages such as low solubility of pharmaceutical compounds in scCO_2 and possible reactions of pharmaceutical compounds with reactants used to form gels. An alternative technique is to load the drug after gel formation by contacting the gel with a solution of the drug. The drug diffuses into the liquid inside the pores. When this drug-loaded gel is subjected to supercritical drying, scCO_2 not only removes the solvent from the pores but also acts as an antisolvent, which causes the precipitation of the drug in the pores of the aerogel. This is similar to the gas antisolvent crystallization (GAS) process but in this case the process takes place inside the pores.

In this study, this technique was used to load paracetamol into silica and alginate aerogels with densities ranging 0.13 to 0.15 g/cm^3 and 0.055 to 0.062 g/cm^3 respectively. The initial concentration of the paracetamol-ethanol solution ranged from 0.25 M to 0.8 M. The factors affecting the amount and distribution of the drug inside the aerogel matrix were investigated. The Attenuated Total Reflectance (ATR) results indicated that the paracetamol diffused inside of the aerogel and X-ray Diffraction (XRD) analysis demonstrated that the paracetamol was in crystalline form. It was possible to control

loading by changing the concentration of the drug in the contacting solution and also by changing the pore volume of the alcogel matrix which in turn depended on the reactant concentrations. Moreover, the process enabled very high amount of loadings such as 40 wt.% for silica aerogels and 75 wt.% for alginate aerogels compared to conventional systems and also offers an advantage for aerogels as it combines two processes such as drying and loading in a single one reducing the time and the operating expenses. On the other hand, diffusion of paracetamol inside the pores was also theoretically modeled by solving partial differential equations. Experimental paracetamol uptake was shown to be in good agreement with the model predictions without any adjustable parameters.

Finally, the release of paracetamol from loaded aerogel supports in PBS buffer was investigated showing the promise of these materials as drug delivery vehicles. It was shown that native aerogels could be used as carriers for fast acting medications whereas the hybrid aerogel was suitable to achieve a retarded release profile. A mathematical model was also developed to describe the release kinetics of paracetamol from alginate aerogels comprising the swelling of the aerogel matrix, the dissolution of the drug into the pore liquid followed by its diffusion from the pores into the surrounding medium. The inclusion of these physical phenomena in the mathematical model had greatly reduced the deviations from the experimental data and resulted in good model predictions.

ÖZET

Son yıllarda nanoyapılı aerogeller ilaç taşıyıcı sistemi olarak oldukça ümit verici görülmektedir. Bu çalışmada, hem organik hem inorganik aerogeller ilaç taşıyıcı sistemleri olarak incelenmiştir. Ayrıca iki farklı aerojelden oluşan, katmanlı bir aerogel sistemi geliştirilmiştir. Katmanlı sistem inorganik silika aerogelin organik bir alginate aerogel ile kaplanmasıyla oluşturulmuştur. Nanoyapılı aerogelleri ilaç taşıyıcı sistem olarak kullanabilmek için değişik ilaç yükleme yöntemleri kullanılmaktadır. Bunlardan bazıları ilacın sentez aşamasında, jelleşmeden önce ya da süperkritik depozisyon tekniği ile aerojele yüklenmesi olarak sıralanabilir. Ancak birçok ilacın süperkritik CO₂'te çözünürlüğünün çok düşük olması ya da aerojeli yapmak için kullanılan diğer malzemelerle reaksiyona girebilecek olması bu yöntemlerin dezavantajları olarak belirtilmektedir. Alternatif bir yöntem, ilacın jelleşmeden sonra sisteme difüzyon ile yüklenmesidir. Bu şekilde ilaç yüklenmiş bir sistem süperkritik koşullarda kurutulduğu zaman, scCO₂ hem jelin içindeki sıvıyı çıkarmakta hem de antisolvent olarak hareket ederek ilacın sistemin içinde çökmesini sağlamaktadır. Bu yöntem aynı zamanda GAS yöntemi olarak bilinen metotla örtüşmektedir. Ancak bu sistemde çökeltme gözeneklerin içinde gerçekleşmektedir.

Bu çalışmada bu teknik kullanılarak silika ve alginate aerogellerin içine parasetamol yüklenmiştir. Çalışmada kullanılan silika aerogellerin yoğunluğu 0.13 ve 0.15 g/cm³ arasında değişirken alginate aerogellerin yoğunluğu 0.055 ve 0.062 g/cm³ arasında bulunmuştur. Parasetamol ile hazırlanmış çözeltinin başlangıç derişimi 0.25M ve 0.8M arasında değiştirilmiştir. Yüklenen ilaç miktarını ve ilacın sistem içindeki dağılımını etkileyen faktörler incelenmiştir. IR spektroskopisi sonuçları ilacın sistemin içine kadar yayıldığını, XRD sonuçları ise ilacın kristal yapıda olduğunu göstermiştir. Ayrıca yükleme miktarının başlangıç derişimini ve aerogelin gözenek hacmini değiştirerek kontrol edilebildiği gösterilmiştir. Bu yöntemle silika aerogeller için % 40, alginate aerogeller için

% 75 oranında yükleme yapılabilmektedir. Bu yöntemin bir başka avantajı kurutma ve ilaç yükleme aşamalarını tek yöntemle indirgeyerek zaman ve deney harcamalarını azaltabilmesidir. İlacın sisteme yüklenmesi ayrıca matematiksel olarak modellenmiş ve deneysel sonuçların model sonuçlarıyla örtüştüğü gözlemlenmiştir. İlaç yüklenmiş olan aerogeller ayrıca salım deneylerinde kullanılmıştır. Deney sonuçlarına göre ilaç yüklenmiş silika ve alginat aerogellerin çabuk etkili ilaç taşıyıcı sistemi olarak, katmanlı aerogelin ise kontrollü ilaç salım sistemi olarak kullanılabileceği öngörülmüştür. Salım kinetiği de ayrıca matematiksel olarak modellenmiştir. Modelde ilacın sisteme yayılmasının yanında, dissolüsyonu ve sistemin zaman içinde genişmesi de kullanılmıştır. Bunun sonucunda elde edilen verilerin deneysel sonuçlarla örtüştüğü görülmüştür.

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NOMENCLATURE

ρ	density
ε	porosity
PC	paracetamol
TEOS	tetraethylorthosilicate
N_A	diffusive flux of paracetamol
τ	tortuosity
scCO ₂	supercritical carbondioxide
D	diffusion coefficient
D _e	effective diffusion coefficient

Chapter 1

INTRODUCTION

Over the past few decades, research efforts were mainly directed to understand the physicochemical properties of drug molecules as well as the mechanisms of cellular uptake to achieve effective therapeutic strategies [1]. However, the treatment of some diseases like cancer involves the use of some toxic drugs which have adverse side effects and limited effectiveness because they lack the target specificity [1]. Furthermore, both pathological processes occurring in the body and the body's response to different kinds of drugs can alter the expected therapeutic effect even though required dose of the drug for a specific disease is already known. Thus, the needed amount of the drug can be different than the one which is administered.

Controlled release systems are being developed to deliver the needed amount of drug, to increase the effect of the drug in the body, to protect it from physiological degradation, to improve patient comfort and to be able to control the location where the drug is actually delivered [2]. These systems are being used to achieve a spatial and time dependent control of delivery. Additionally, economic considerations related to the reduction in the frequency and the dose of the drug and the extension of the product life are the key factors behind research efforts in this field [3].

Drug delivery systems are difficult to design as there exists various mechanisms which are involved in the release processes of drugs [2]. Various factors such as the degree

of absorption of the drug or the diffusion limitations of the drug in the medium need to be considered for effective treatment. Recently, the use of nanotechnology in drug delivery has attracted a lot of interest due to its potential for development of systems that are site specific and/or that offer time dependent controlled delivery [4]. Nanoparticles, nanocapsules or micelles as nanotechnology based drug delivery systems offer many advantages over conventional delivery systems. Furthermore, the problems associated with the delivery of a free drug such as poor solubility, tissue damage on extravasation, rapid breakdown *in vivo*, unfavorable pharmacokinetics, poor biodistribution, lack of selectivity for target tissues can be overcome by designing drug delivery vehicles via nanotechnology [2, 5]. The physicochemical properties of these nanostructured drug delivery systems are adjusted either based on the drug type or the delivery route such as nasal, transdermal or oral.

Porous materials are important components of drug delivery vehicles for the encapsulation of a variety of molecules due to their large inner surface areas, high surface to volume ratios, large pore volumes and uniform pore sizes [6-8]. Based on International Union of Pure and Applied Chemistry (IUPAC) classification, the pores of the solids are distinguished according to size: pore sizes smaller than 2 nm represent micropores, those in the range of 2 nm to 50 nm are called mesopores and those above 50 nm are denoted as macropores. The effectiveness of these porous materials for various applications such as adsorption, separation or catalysis depends on the size, shape and the volume of these pores [9]. A wide variety of micro- and mesoporous systems and the effects of their pore and surface properties on drug loading, release or matrix-drug interactions are already under investigation for sustained or controlled release applications [6, 7, 10, 11].

Aerogels as the lowest density solids with very high porosities and demonstrated biocompatibilities are attracting increased attention as components of drug delivery vehicles as evident from the increasing number of research articles and thesis studies [12-

15]. Aerogels were first synthesized in 1932 by Samuel Kistler who defined them as the materials keeping their pore and network structure intact upon exchanging their pore liquid with a gas [16]. The unique properties of these highly porous materials with open pores and high surface areas are attributed to their irregular solid structure which can be tuned through the proper selection of the preparation conditions.

Since 1960s, silica aerogels have been used in daily products with the production of Monsanto's aerogels which were used as additives for consumer products such as toothpastes or cosmetics [15]. About 60 years after their discovery by Kistler, organic aerogels were proposed for use in medical applications as diagnostic agents, artificial tissues, and specifically in drug delivery systems [17]. Since then, there has been an increasing interest for the use of inorganic or organic aerogels in the area of drug delivery.

In this study, both silica and alginate aerogels are investigated as drug delivery vehicles. Moreover, a novel layered hybrid aerogel system is prepared by encapsulating a silica aerogel with an alginate aerogel layer. For drug loading, paracetamol has been chosen as the model drug due to its high solubility in ethanol, the solvent of the system and low solubility in the supercritical carbon dioxide. Furthermore, a drug loading by diffusion model was developed to enable the prediction of the time needed for maximum amount of loading and also the distribution of the drug inside the aerogel matrix at specific time points without any adjustable parameters. Another comprehensive mathematical model including the major underlying mechanisms for drug release from a drug loaded alginate aerogel was also developed. Both models were supported with experiments and it was shown that the experimental results agreed well with the model predictions.

A general overview about aerogels, their synthesis techniques and different drug loading methods is given in chapter 2. An extensive review about studies on aerogels as drug delivery systems is also presented. Subsequently, mathematical modeling of drug loading or release mechanism is briefly reviewed.

Experimental techniques are explained in Chapter 3 including the synthesis of silica aerogel, alginate aerogel and silica aerogel encapsulated with an alginate aerogel layer. The techniques used to characterize these materials are also outlined in this chapter. Drug loading technique as well as the release method are also given.

Experimental results, derivation of the theoretical models and their results are given in Chapter 4. This includes the physical properties of the synthesized native and drug loaded aerogels, results of drug loading and drug release processes as well as the results of the developed mathematical models. A comparison between the experimental and modeling results is also included.

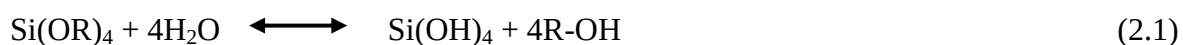
Conclusions/discussions and further insights about the future of the project are given in Chapter 5.

Chapter 2

LITERATURE REVIEW

2.1 Synthesis of Aerogels

Sol-gel polymerization is the commonly employed method used for the preparation of inorganic aerogels as shown in Figure 1 [15, 18-20]. Metal alkoxides such as tetraethylorthosilicate (TEOS) or tetramethylorthosilicate (TMOS) are the generally used chemical precursors for the synthesis of silica aerogels (Table 2.1). First, these precursors are hydrolyzed in a mixture of water and alcohol where the alkoxide groups of the precursor are replaced with hydroxyl groups as shown in Equation 2.1.



The kinetics of hydrolysis reaction can be accelerated by the addition of an acid or a base catalyst. Subsequently, Si(OH)_4 molecules go through water (Equation 2.2) and alcohol (Equation 2.3) condensation reactions forming a silica network. This step can be accelerated by the addition of a base catalyst.



Table 2.1: Commonly used reactants for the synthesis of different types of aerogels which are investigated for drug delivery applications

Aerogel Type	Precursor	Catalyst or Crosslinker	Solvent
Silica aerogel	Tetramethylorthosilicate (TMOS), Tetraethylorthosilicate (TEOS), Triethoxysilane (TriEOS), Methyltrimethoxysilane (MTMS), Sodium metasilicate (SS) and related salts, Methy silicate 51 (MS51), Polyethoxysiloxane (PEDS), Silbond H-5 (SH5)	HCl, H ₂ SO ₄ , HF, NH ₄ OH	Alcohols, acetone, ethyl acetate
Titania aerogel	Tetrabutyl orthotitanate, Titanium n-butoxide, Titanium tetraisopropoxide	HNO ₃	Ethanol, methanol, Tetrahydrofuran
Alginate aerogel	Alginic acid sodium salt	Divalent or multivalent cations and Glucono- δ -lactone	Distilled water
Starch aerogel	Potato starch, High amylose maize starch, Corn starch		Distilled water
Cellulose aerogel	Plant cellulose, bacterial cellulose	Epichlorohydrin, NaOH	N-methylmorpholine-N-oxide, calcium thiocyanate, NaOH–water solution or ionic liquids

Whey based aerogel	Whey Protein Isolate	Hydrochloric acid and sodium hydroxide	Distilled water
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The mixture finally forms a gel which is mostly constituted of SiO_2 . However, some side chains might remain unreacted (Si-OR) or partially reacted (Si-OH) at the end of the condensation reactions. These Si-OH groups render the aerogel hydrophilic and make it susceptible to water adsorption leading to structural collapse. To improve the mechanical strength of these wet gels and to finish hydrolysis and condensation reactions of unreacted precursors in the gels, they are placed in an aging solution consisting of water and alcohol. This step is necessary to obtain more compact structures which are more resistant to shrinkage and any damage. Then, the gel is subjected to solvent exchange step during which it is placed in pure solvent which is generally an alcohol to replace water and to remove any impurities remaining in the pores.

The final step is to dry this wet gel which is also called alcogel without damaging its structure. The wet gels which are dried under ambient conditions can not withstand the capillary stresses and fracture during the drying process. Therefore, alcogels are generally dried using a process called supercritical extraction. Supercritical CO_2 (scCO_2) is able to dissolve and extract the pore liquid and reduce the capillary pressure created within the pores as it does not have any surface tension. Alcogels which are dried supercritically are called aerogels whereas the ones which are dried at ambient pressure are denoted as xerogels. Supercritical drying is carried out at pressures around 100 bars and thus requires equipment which can withstand such high pressures. As a result, it is a rather costly process due to high capital costs associated with high pressure equipment; however, these costs have come down considerably over the past few years due to an increase in industrial scale scCO_2 based processes worldwide. Over the years, there have been several efforts to replace high pressure supercritical drying with low pressure drying. Among these, Smith et

al. developed a technique based on a “springback effect” to retain the properties of aerogels after ambient pressure drying involving both the modification of the surface and the strengthening of the network [21]. The patent for this technique was issued in 1996 [22]. After the solvent exchange step, the hydroxyl groups on the internal surface of the alcogels were reacted with organic substances of the form R_xMX_y where R is usually an organic group such as CH_3 , C_2H_5 ; M is Si or Al and X is a halogen which is usually Cl [22]. The replacement of hydrophilic hydroxyl groups with organic groups resulted in hydrophobic aerogels. This process was actually performed in order to modify the contact angle between the pore liquid and the pore walls during drying to reduce capillary stresses. During ambient pressure drying, a “springback” effect was observed with the re-expansion of the wet gel since neighboring surface silyl groups were chemically inert and did not interact with each other [20]. Aerogels produced using the ambient pressure drying technique are marketed under the name Lumira® (formerly Nanogel®) Aerogel by Cabot Corporation.

Other types or inorganic aerogels like titania aerogels [23] or some organic aerogels, such as resorcinol formaldehyde [24, 25] or carbon aerogels [25] are also prepared using the same sol-gel route but with different precursors.

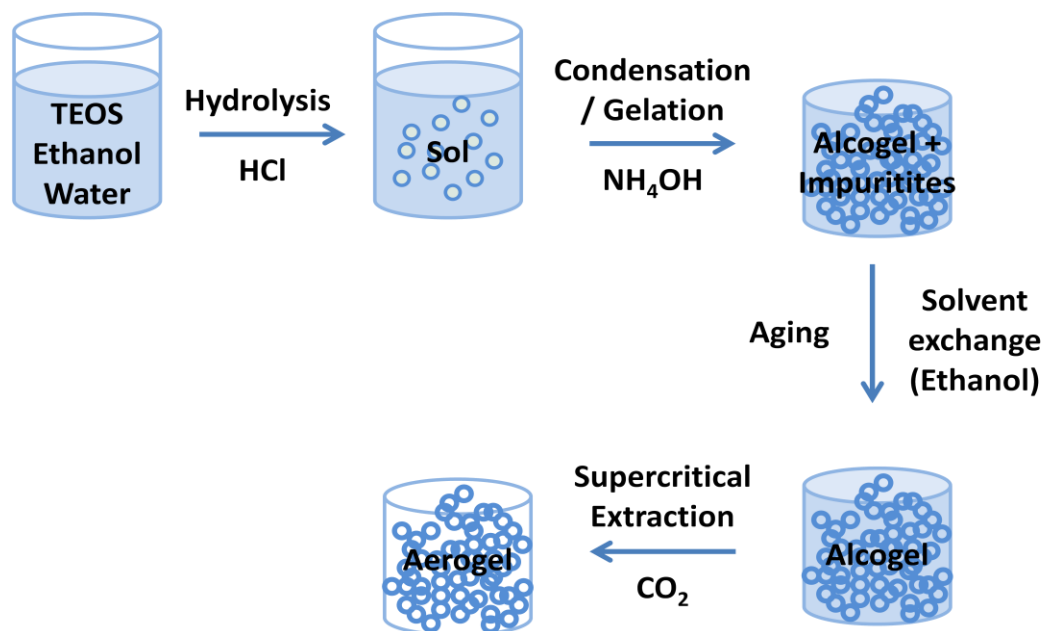


Figure 2.1: The scheme of the sol-gel polymerization method (Circles represent nanoparticles of solid component which form the 3-D network)

Organic aerogels mainly polysaccharide based ones like starch aerogels, alginate aerogels and cellulose aerogels which are promising for drug delivery applications are also synthesized in a similar manner to inorganic silica aerogels [26]. Primary step is to form a hydrogel from an aqueous starting solution triggered by a cross-linking promoter which can either have a chemical nature (chemical cross-linker) or physical nature (pH, temperature) [26]. The subsequent step which is called the aging/solvent exchange step involves the replacement of the water within the porous structure with an appropriate solvent which is usually an alcohol. The next and final step is to dry the wet gel supercritically with carbon dioxide. Although their surface areas are usually smaller than those of silica aerogels, these aerogels have still reasonably high surface areas for drug delivery applications.

Aerogels can be synthesized in any form depending on the shape of the mold in which the gelation takes place. The choice of the material of the mold is equally important

as the preparation conditions in order to obtain a crack-free monolithic aerogel. It should be chosen so that the mold would not stick to the alcogel surface allowing an easy release, and also should not interact with the sol before and after the gelation. Poco described a technique about how to obtain low density monolithic aerogels using flexible molds with flat, parallel sides [27] which facilitated their removal and thus eliminating surface irregularities. We observed that Teflon and polypropylene molds were better compared to glass molds. Similar surface groups of glass compared to silica aerogels prevent the release of alcogels from the mold. In addition, the surface of the mold should be very smooth since molds with high surface roughness leads to aerogels with increased surface irregularities.

Aerogels can be synthesized not only in monolithic form but also in the form of granules, or beads as shown in Figure 2.2 which increases their usability in various applications in the drug delivery field requiring different sizes and shapes. A simple mechanical grinding can also be used for the production of aerogel granules or powders. Aerogels which are produced by ambient pressure drying are generally in powder form. For example, Joung et al. synthesized aerogel powder via ambient pressure drying at atmospheric pressure and under vacuum at 0.08 or 0.12 atm [28]. The authors claimed that avoiding the supercritical drying step shortened the total time of the process which consisted of dissolving a water glass solution and hexamethyldisilazane (HMDS) in an organic solvent prior to gelation which was triggered by the addition of an inorganic acid to the solution. After solvent exchange, the silica hydrogel was dried and silica aerogel powders were obtained.

Such aerogel powders can be easily incorporated into already existing pharmaceutical formulations after they are loaded with drugs. Recently, the tableting properties of silica aerogels along with different silicates were investigated for their suitability as carriers for liquids or solid amorphous drugs [29]. The tabletability of the silica aerogel was found to be better than Aerosil® 200 (colloidal silica) but worse than

Neusilin ® (synthetic amorphous form of magnesium aluminometasilicate) and Florite® (calcium silicate). The hardness of the tablets obtained by the compaction of plain silica aerogels was found to be in an acceptable range.

Emulsion polymerization is another technique which can be used for the synthesis of spherical aerogel particles [30-32]. This method involves the preparation of an emulsion by mixing the sol with a suitable oil (a water in oil emulsion) followed by the gelation of the dispersed phase. Surfactants are also sometimes added to the emulsion at different concentrations. After separation of microspheres from the oil phase, supercritical drying is used to obtain the aerogel microspheres which can be either inorganic or organic. Alternatively, alginate aerogel microspheres were prepared via egg-box gelation technique [33]. Dropwise addition of the polysaccharide solution into a solution containing ions which triggered gelation, resulted in the immediate formation of a spherical gels. The details of this synthesis technique are given in section 2.4 on using organic aerogels as drug delivery systems.

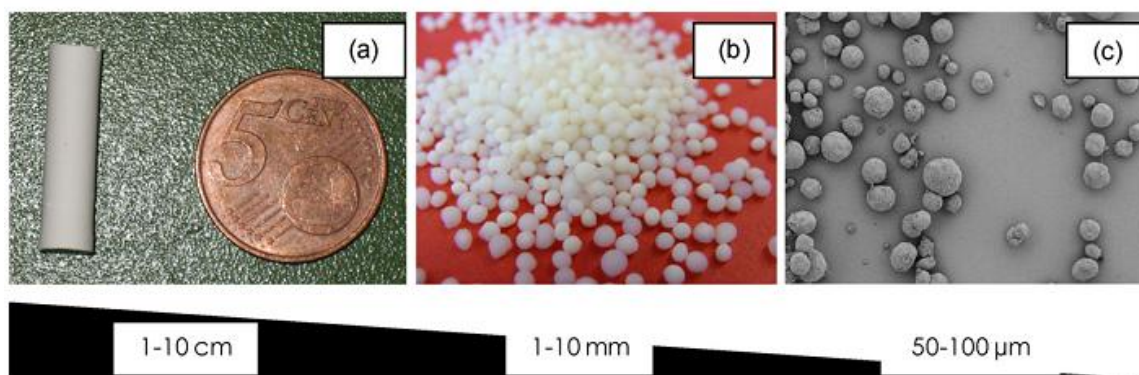


Figure 2.2: Calcium alginate aerogel samples in different forms a) monoliths b)-c) particles Reprinted from [26] with permission from Elsevier.

The possibility of controlling the nanostructure of these materials is another intriguing property. The choice of the catalyst affecting the reaction kinetics, the nature of

the solvent, and the molar ratios of the reactants are some of the important parameters to control this nanostructure. Saquing et al. have shown that increasing the organic precursor to water ratio in the sol to synthesize resorcinol formaldehyde aerogels has resulted in a reduction in the average pore size and smaller pore volume [34] which may be due to a more compact network reducing the distance between the particles. Meanwhile, using aging solutions with different concentrations and changing aging time has shown to change the porosity characteristics of aerogels [35]. More research effort should be similarly given to better analyze the effect of synthesis conditions on the porous structure of the aerogels.

2.2 Preparation of aerogel based drug delivery systems

Drug delivery vehicles based on aerogels can be prepared by different methods such as the addition of the drug during the conventional sol-gel process or during the post treatment of the synthesized aerogels as shown in Figure 3 [15]. During the sol-gel procedure, the drug can be loaded either before the gelation or during the aging steps. The addition of the drug before the gelation is an appealing way due to its simplicity and flexibility for different target compounds. With this approach, the drug molecules which are dissolved in the initial solution are expected to be trapped in the aerogel network during the gelation. Subsequent aging, solvent exchange and drying steps lead to the drug loaded aerogel.

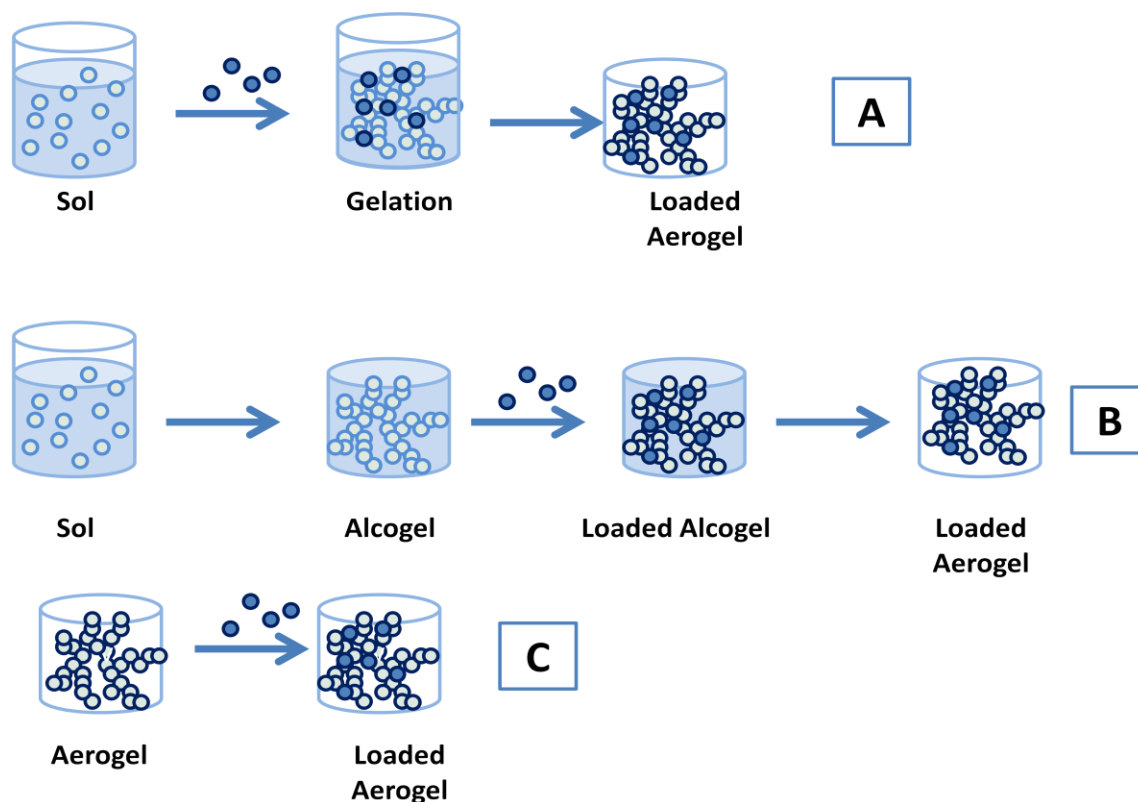


Figure 2.3: Preparation routes of drug loaded aerogels. A) Addition of the drug during the sol-gel process (before gelation) B) Addition of the drug during the sol-gel process (during aging) C) Addition of the drug through adsorption/precipitation in the already dried aerogel (Adapted from [15])

The other approach is the addition of the therapeutic agent during the aging step. The alcogel is contacted with an aging solution which contains the drug which then diffuses into the pores of the alcogel from the aging solution. This process might require a long time depending on the diffusion rate of the drug molecules into the pores of the alcogels. The diffusion rate depends on the size of the molecules, size of the pores and the initial concentration of the aging solution. The diffusion continues until the concentrations in the pore liquid and the aging solution become equal. Subsequently, alcogel containing

the drug is subjected to supercritical drying. During this stage, scCO_2 also acts like an anti-solvent reducing the solvent power of the solvent which is present in the pores. As more and more CO_2 is dissolved in the solvent, the drug starts to precipitate in the pores of the alcogel. This process continues until all of the solvent inside the pores is removed. Subsequently, the system is depressurized to obtain the drug loaded aerogel. The solvent should be selected such that the drug should be soluble in the solvent, the solvent should not damage the aerogel and the solvent should be extractable using scCO_2 .

This process is very similar to the gas anti solvent (GAS) process in which an anti solvent is added to a binary solution of a solute in a solvent to initiate a phase separation due to a decrease in the solubility of the solute [36]. The chosen antisolvent has no or little affinity for the solute but forms at least a partially miscible solution with the solvent [37]. ScCO_2 is one of the most widely investigated anti solvents. The crystallization of various drugs like paracetamol [38], griseofulvin[39] and copper indomethacin [40] via GAS process have been investigated. The crystallization thermodynamics of these drugs on aerogels during supercritical drying stage should be similar to the thermodynamics of conventional GAS process. The only difference is the fact the process occurs inside nano-sized pores. In order to control the drug loading process using this technique, a detailed knowledge of the ternary phase behavior of the system consisting of the alcohol (the solvent), the drug (the solute) and the CO_2 (the anti-solvent) should be known in advance as shown in Figure 2.4.

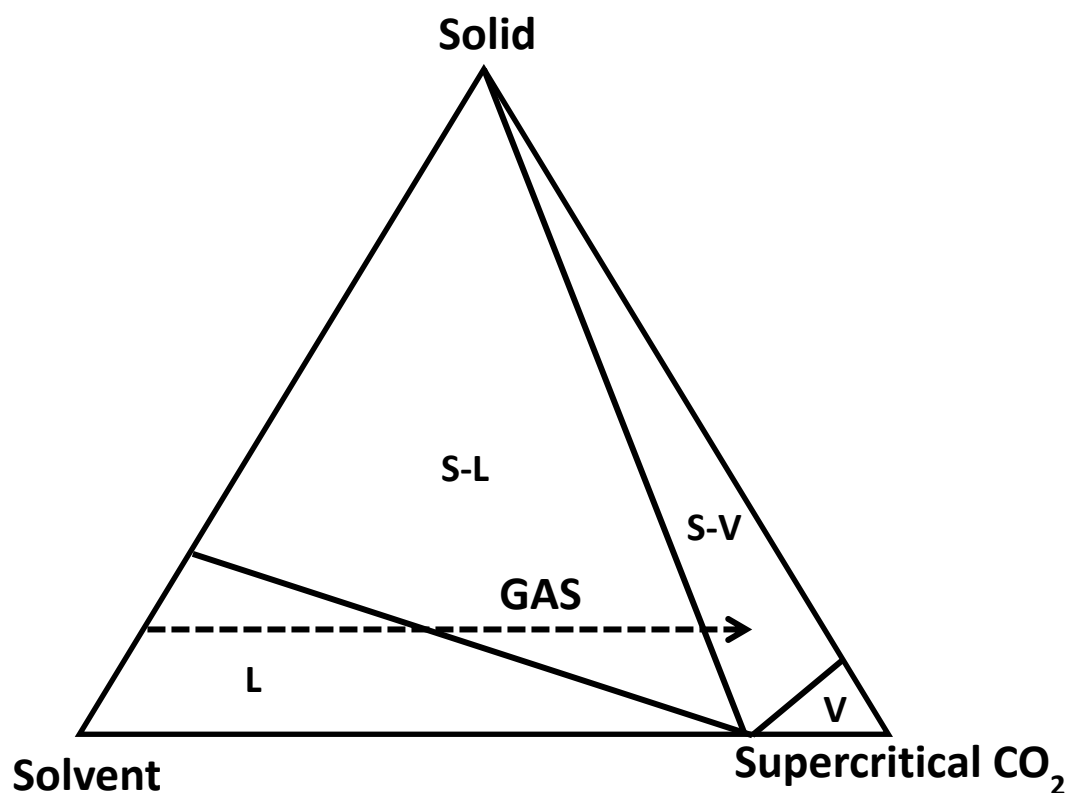


Figure 2.4: An example of the ternary phase diagram for CO₂ + solvent + solid above the mixture critical point. Adapted from [38].

As shown in the diagram for a mixture above its critical pressure, the solute forms a partially miscible mixture with the solvent and scCO₂ whereas the solvent forms a miscible mixture with scCO₂. The process starts with a liquid solution at a certain solute concentration. As the concentration of anti-solvent CO₂ increases inside the liquid phase, it causes a volumetric expansion of the system reducing the bulk density of the solution which in turn lowers the solvating power of the solvent [38]. Thus, the mixture passes from the homogeneous liquid (L) phase to a two phase solid-liquid (S-L) and the solute starts precipitating. The path then passes through a solid-vapor (S-V) region with an increasing amount of solid phase due to the decreasing amount of liquid through its extraction to

scCO₂ [37]. The solid may be in amorphous form or crystal form depending not only on the process parameters such as pressure, temperature and depressurization rate but also on the interaction of aerogel matrix with the drug molecules. Strong adsorption favors amorphous precipitates whereas weak interactions result in crystal formation [41]. The structure of the resulting drug particles is important for the kinetics of drug release. These processes require the drug to be insoluble in scCO₂ to prevent the drug from being removed from the aerogel matrix during supercritical drying with CO₂. Furthermore, the reactivity of the drug with the constituents of the sol which could in turn affect the gelation process or the final properties of the product and the stability of the drug in the matrix should as well be deeply investigated for these loading methods.

Second approach for loading the drug to the aerogel could be contacting the pure aerogel with a solution of the drug after the supercritical drying step similar to the study involving the liquid adsorption of a basic dye on silica aerogels [42]. The drug would then diffuse into the pores of the aerogel and would adsorb on the surface of the aerogel. Subsequent removal of the solvent would then lead to a drug loaded aerogel. However, this process has drawbacks for various aerogels such as silica aerogels since they are hydrophilic by nature due to their surface hydroxyl groups and rapidly collapse when immersed in liquid solutions. Therefore, a possible solution is to load the drug from the supercritical phase. However, this method requires the drug to be soluble in scCO₂. For such CO₂ soluble drugs, the loading capacity depends both on their solubility in scCO₂ and on their affinity to the aerogel surface. Thus, the structural properties of the aerogel as well as its surface properties affect the loading capacity [15]. Another advantage of using scCO₂ is that it is non toxic and is easily removed from the product only by lowering the pressure leaving no residue on the treated medium. In a pioneering study, Smirnova et al. demonstrated that aerogels can be loaded with pharmaceutical compounds by adsorption from their solutions in scCO₂ [43]. In this regard, it is crucial to know the thermodynamics

and kinetics of adsorption of drugs for the design of such processes and to control loadings. The thermodynamics of adsorption is generally described by adsorption isotherms. The adsorption isotherms of several drugs in supercritical CO₂-aerogel systems were measured in various studies [44-46]. The adsorption isotherms of most of the drugs could be represented by the Langmuir isotherm showing that the loading of the drug can be increased until the saturation point of the matrix. Kinetics of adsorption depends on a series of complex mass transfer processes such as diffusion inside the pore volume, external mass transfer and surface diffusion. Zhang et al. developed a mass transfer model based on diffusion inside the pore volume to describe the kinetics of adsorption of an organometallic compound onto carbon aerogels from supercritical solutions [47]. The same model was also applied to successfully predict the kinetics of adsorption of a platinum precursor onto resorcinol formaldehyde aerogel spheres [48]. Adsorption isotherms were represented by a modified Langmuir model and it was shown that the measured and the modeled adsorption kinetics of the platinum precursor were in a good agreement. A similar model could as well be used in order to describe the adsorption kinetics of various drugs on porous aerogels. However, determination of some important parameters such as tortuosity not by regression from experimental data but from other sources would be beneficial.

If the solubility of the chosen drug in scCO₂ is low, then the adsorbed amount does not reach the saturation level but remains low. The solubility of various drugs such as ketoprofen, nimesulfide, piroxicam [49], aspirin [50], some fat soluble vitamins [51] and many others [37] in scCO₂ can be found in literature. The solubility of the drug is not only dependent on its chemical structure but also on the pressure and the temperature of the system which is directly related to the density of the supercritical phase. Increasing density of the supercritical phase increases the solubility due to enhanced molecular interactions at higher densities [37]. The solvent power of CO₂ at lower pressures can also be increased by the addition of an entrainer to the system due to additional interactions between the drug

and the entrainer [52]. However, an additional component complicates the adsorption thermodynamics and necessitates further measurements for the new ternary system and there are no such studies in the literature. Thus, more research should be devoted to understand the phase behavior of drug-solvent-supercritical fluid mixtures and adsorption from such solutions on various aerogels.

Various studies on aerogel based drug delivery systems can be found in literature. A summary of these studies is given in Table 2.2 indicating the type of the aerogel, the drug and the loading method which is used in each study.

Table 2.2: Studies about the aerogels as drug delivery vehicles in the literature

Aerogel Type	Drug Loaded	Loading Method	Reference
Starch aerogel, alginate aerogel	Ibuprofen	Post treatment	[53]
Starch aerogel	Paracetamol	Solvent exchange	[53]
Starch aerogel	Ketoprofen	Post treatment	[31]
Silica aerogel	Ketoprofen, Miconazole	Post treatment	[44]
Silica aerogel	Ketoprofen, Griseofulvin	Post treatment	[45]
Silica aerogel	Griseofulvin	Post treatment	[46]
Silica aerogel	Diathranol	Post treatment	[54]
Silica aerogel	Ketoprofen, Miconazole, Terfenadine, Diathranol, Niclosamid, Griseofulvin	Post treatment	[55]
Silica aerogel	Triflusal	Post treatment	[56]
Silica aerogel	Ketoprofen, Miconazole, Flurbiprofen, diathranol, Griseofulvin, Ibuprofen	Post treatment	[57]

Silica aerogel	Nimesulide	Post treatment	[58, 59]
PEG hydrogel	Ketoprofen	Post treatment	[60]
coated silica aerogel			
Polymer coated silica aerogel	Ibuprofen	Post treatment	[61]
Alginate aerogel	Nicotinic acid	Gel preparation	[62]
Alginate aerogel	Ketoprofen, Ketoprofen lysinate	Gel preparation	[63]
Multi membrane alginate aerogel	Nicotinic acid	Gel preparation	[64]
Bacterial cellulose aerogels	Dexpanthenol, L-Ascorbic acid	Solvent Exchange	[65]
Whey protein based aerogel	Ketoprofen	Post treatment	[66]
Amine modified silica aerogel	Ketoprofen	Post treatment	[67]

Besides loading of the drug, its release kinetics is another critical parameter while designing drug delivery systems based on aerogels [15]. An ideal drug delivery system would deliver the drug to the location in the body which needs it and would not affect any other locations in the body. It would also release the drug at a specific time following the selected release profile. There are three types of release profiles which are usually discussed in the design of drug delivery systems [15] such as bolus release, sustained release and controlled release. The bolus release which is also known as burst/immediate release refers to the complete release of the loaded drug within a short period of time.

Although it is usually seen as a negative consequence of drug delivery applications, burst release systems can be used for carrying fast acting medications to where high initial delivery rates are desirable [68]. On the other hand, sustained release systems involves the continuous release of the loaded drug within a period of time. Controlled release systems or smart release systems could be explained by the combination of different release profiles. They are designed in such a way that they release an appropriate amount of drug when needed within a specified amount of time which could be either very short or prolonged.

As a result, the choice of aerogel type with different porous structures, the loading technique or the release medium would certainly affect the resulting release profile and thus should be selected accordingly.

2.3 Inorganic Aerogel Based Drug Delivery Systems

2.3.1 Native Silica Aerogels

Among various materials that are investigated for drug delivery, silica based materials were shown to be biocompatible [1]. Furthermore, these materials and their functionalized forms were shown to enable the controlled release of various therapeutic agents [1, 3, 69, 70].

The chemical structure of silica aerogels resembles fumed silicon dioxide which has been in use in the pharmaceutical industry for many years. The so-called product “Aerosil” was developed by a German company called Degussa and has been in the market since 1940. The clinical tests showed that this product was not harmful to the human body [71]. Orally administered Aerosil was shown to pass through the gastrointestinal track without being resorbed in detectable quantities [15]. Silica aerogel, having the same chemical structure as Aerosil is expected to have similar clinical characteristics. Silica aerogel presents even superior characteristics due to its larger surface area (around 1000 m²/g compared to around 200 m²/g) and its tunable characteristics [15].

Various patents and studies concerning the use of silica aerogels as drug delivery systems can be found in literature [43, 72]. In 2001, Schwertfeger et al. reported that silica aerogels are promising materials as carrier matrices and utilized both hydrophilic and hydrophobic aerogels as drug delivery systems [72]. The corresponding aerogels were primarily loaded with several pharmaceutically active compounds such as furosemide-sodium, penbutulol hemisulfate, methylprednisolone by adsorption from a solution of the drug until equilibrium was reached and then filtered and dried to obtain drug loaded aerogels. The final material was in powder form. Since the loading was carried out from a liquid phase after drying, some reduction in pore volume must have occurred. Nevertheless, they demonstrated that hydrophobic drugs can be incorporated into a hydrophilic aerogel and hydrophilic drugs into a hydrophobic aerogel [72].

Drug release studies have shown that high drug loadings could be achieved by using aerogels as carrier systems and it was demonstrated that the drugs adsorbed on the hydrophilic silica aerogels dissolved faster than the crystalline form of the corresponding drugs [45, 46, 54, 55]. Thus, hydrophilic aerogels were proposed for use in immediate release systems as an alternative to systems prepared by conventional micronization techniques [45]. This fast release was related to the increased surface area of the drug which was adsorbed on the silica aerogel and the disintegration of the hydrophilic aerogels when immersed in aqueous solutions. As the adsorbed drugs were no more in their crystalline form, no energy was required to destroy their crystal lattice leading to a faster dissolution [45]. Thus, the open pore structure of the hydrophilic silica aerogels allowing fast penetration of liquids inside and thereby collapsing their structure makes hydrophilic aerogels unsuitable for prolonged release but suitable for immediate release applications especially for poorly water soluble or hydrophobic drugs.

Smirnova et al. loaded hydrophilic aerogels with two model drugs which were griseofulvin and ketoprofen by adsorption from scCO_2 [45]. It was shown that maximum

loading of the drug depended on the chemical structure of the drug because of the different adsorption isotherms for the two drugs. The release rates of the drugs were five and four times higher than their crystalline forms for ketoprofen and griseofulvin, respectively. The release rate was found to be independent of the density of the hydrophilic silica aerogel since the collapse of the matrix was the key factor governing the rate. Guenther et al. utilized drug loaded hydrophilic silica aerogels as dermal drug delivery systems [54]. It was shown that the release and the penetration properties of the model drug, dithranol, were improved when it was released from the aerogel matrix. The adsorption of dithranol on silica aerogels resulted in higher flux and shorter lag times in the penetration of dithranol in two different artificial membranes and human stratum corneum compared to the suspension of the crystalline form of dithranol. Caputo et al. recently showed that the release rate of another drug, nimesulide, was also increased upon loading on hydrophilic silica aerogels by adsorption from $scCO_2$ [59]. Around 80% of nimesulide was released within the first few minutes compared to the dissolution of native crystalline drug which took about 2 hours. The kinetics of adsorption was also investigated by measuring the uptake amount of nimesulide on silica aerogels at different times. The slow adsorption kinetics was related to the low affinity of the nimesulide towards the silica aerogel and also to its low solubility in $scCO_2$. A subsequent study by the same group on nimesulide adsorption on silica aerogels involved the use of an entrainer to increase the solubility of the drug in $scCO_2$ [58]. It was shown that the uptake was six times higher when ethanol was used as the entrainer.

Along with increasing the bioavailability of low solubility drugs, the aerogel matrix has also been shown to prolong the stability of the drug. In the study of Murillo-Creanés et al., a model drug triflusal was loaded on silica aerogel monoliths and on polymethylmethacrylate (PMMA) for comparison [56]. Triflusal which was dispersed in the aerogel matrix by adsorption from the supercritical phase was relatively stable under

ambient conditions up to six months. When it was loaded on PMMA and stored under same conditions, it was gradually changed to 2-hydroxy-4-trifluoromethyl benzoic acid (HTB metabolite) which is the product of progressive hydrolysis of triflusal in water. It was suggested that the acidity provided by the aerogel matrix to the adsorbed water stabilized triflusal molecules against hydrolysis. Furthermore, it was observed that the aerogel systems exhibited a much faster release rate and 80% of the drug was released within the first few minutes.

Besides silica aerogels, there exists other inorganic aerogels like titania based aerogels. Moreover, surface functionalized titania nanoparticles with flavin mononucleotide as a fluorescent probe for intracellular imaging were also loaded with chemotherapeutic drugs, such as doxorubicin for drug delivery applications [73]. To test the potential of these materials in intracellular applications, safety and toxicological tests were also conducted. It was shown that these mesoporous nanoparticles with high surface areas such as 237 m²/g were also biocompatible.

2.3.2 Surface Functionalized Aerogels

For hydrophilic aerogels, the limitation of fast matrix erosion when placed in liquids can be overcome by replacing the surface hydroxyl groups with hydrophobic groups. Such a surface treatment procedure makes the aerogel matrix hydrophobic limiting the penetration of liquid water into the pores. Thereby, the burst release of drugs could be hindered and a controlled release could be achieved. This replacement could be achieved by several methods. One approach is to use different silica precursors in the synthesis. Using different organo-silanes such as methyltrimethoxysilane (MTMS), methyltriethoxysilane (MTES), dimethylchlorosilane (DMCS), trimethylethoxysilane (TMES), ethyltriethoxysilane (ETES) and phenyltriethoxysilane (PTES) as co-precursors, aerogels with different hydrophobicities can be obtained due to the reaction of the silyl

groups of the co-precursors with the silica network during the condensation reactions [74]. Synthesizing aerogels using directly MTMS as the precursor resulted in superhydrophobic aerogels with contact angles as high as 173° [75].

Surface modification of the aerogels can also be performed after the drying step. Since contacting the aerogels with liquid solutions containing surface modification agents disintegrates the aerogels, treatments from either vapor phase or supercritical phase can be applied. For example, the hydrophilic surface of a silica aerogel was modified via reaction with gaseous methanol in 10 hours [76]. The treatment led to extremely hydrophobic aerogels which could even float on water without being wetted for several hours [44]. Besides methanol, hexamethyldisilazane (HMDS) can also be used as a surface modification agent either in pure vapor form or as a solution in scCO_2 as shown in Figure 2.5 [77]. Aerogels with a contact angles as high as 130° could be obtained using HMDS dissolved in scCO_2 . The phase behavior of HMDS and CO_2 at high pressures was recently investigated by measuring the bubble point pressures for different compositions at different temperatures and it was found that HMDS and CO_2 forms miscible mixtures at all compositions at relatively low pressures [77]. Such data are necessary to design and develop large scale processes to modify the surfaces of aerogels.

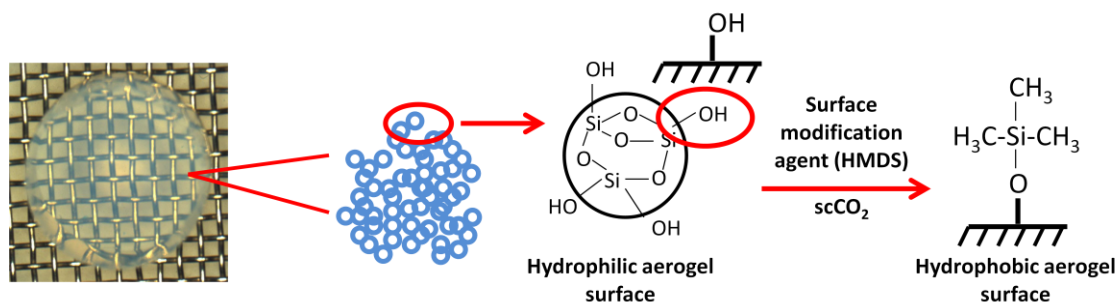


Figure 2.5: Surface functionalization with HMDS

Although hydrophobization of the surface of the aerogel matrix can retard the collapse of the aerogel matrix and thus enable prolonged release, the modification of

surface hydroxyl groups which are known as active adsorption sites might decrease the adsorption capacity of the same aerogels [15]. Therefore, a larger quantity of aerogel would be needed to load the same amount of pharmaceutical compound compared to non-functionalized aerogels.

Hydrophobic silica aerogels were synthesized and tested for controlled release applications and their release behavior was compared with hydrophilic aerogels [55, 57]. Moreover, it was also shown that the adsorption and release rates could be controlled by the density and the hydrophobicity of the aerogels. As shown in Figure 2.6, the loading of the ketoprofen on hydrophilic aerogels was greater compared to hydrophobic ones at all densities. Furthermore, the loading increased with increasing aerogel density since aerogels with higher densities had higher surface areas [57].

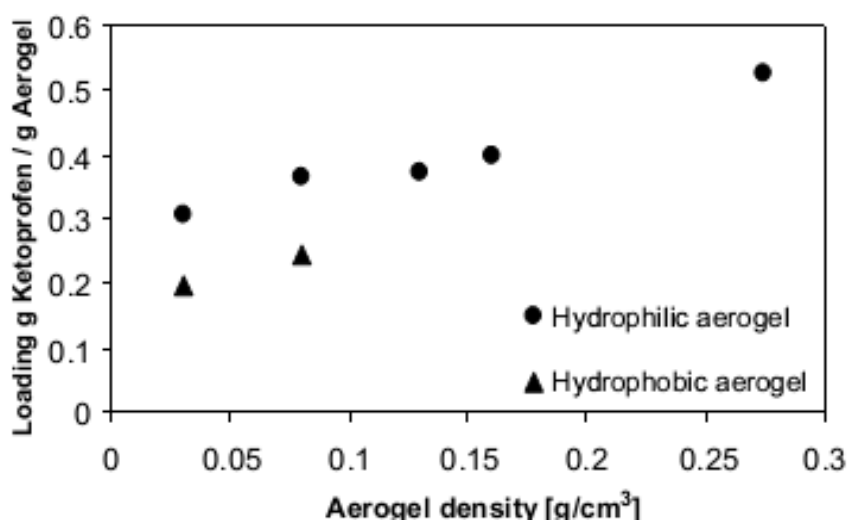


Figure 2.6: The loading of ketoprofen on silica aerogels with different densities. Reprinted from [55] with permission from Elsevier.

In another study which compared the hydrophilic and hydrophobic silica aerogels as drug delivery vehicles, it was again suggested that the reduction in the available effective surface area due to less OH sites had resulted in lower drug loading amounts for the

hydrophobic aerogels [57]. Furthermore, hydrophobic aerogels were shown to be suitable for the prolonged release of drugs since their release mechanism is governed by diffusion rather than collapse of the network integrity. The burst release of the drug which was adsorbed on the surface was followed by its slow diffusion from the pores which allowed the control over the release to some extent as shown in Figure 2.7. Thus, it was concluded that the release kinetics could be controlled by changing the hydrophobicity and the density of aerogels [57].

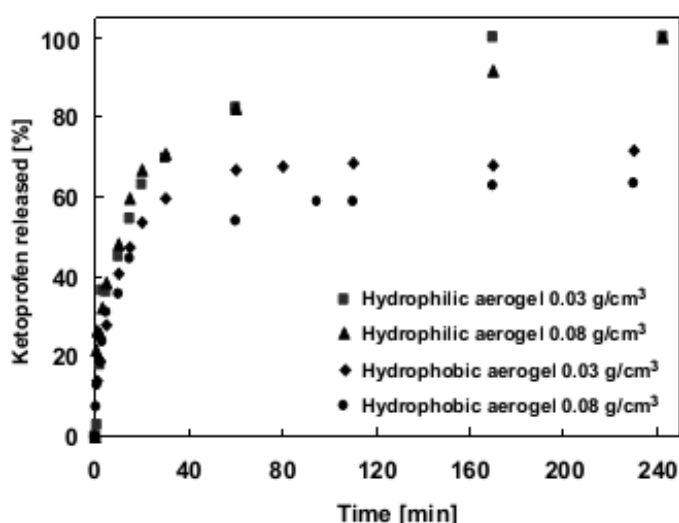


Figure 2.7: The release of ketoprofen from hydrophilic and hydrophobic aerogels with different densities in 0.1N HCl at 37 °C. Reprinted from [55] with permission from Elsevier.

The surface of the silica aerogels can also be modified with amine groups which can be incorporated from either gas phase or liquid phase [67]. To functionalize from the liquid phase, the wet gel can either be prepared with 3-(aminopropyl)-trimethoxysilane (APTMS) as the catalyst or it can be placed in an aging solution containing APTMS. For the gas phase functionalization, the pure aerogel can be contacted with the vapor of APTMS solution. Functionalization from the gas phase was found to preserve the pore

properties of the native aerogel; however, the concentration of the surface amino groups was found to be lower compared to liquid phase modification. Overall, the drug loading capacity was increased using both methods owing to the strong interactions of amino groups with acidic groups of the model drug, ketoprofen. Moreover, the amino functionalization did not retard the release rate of ketoprofen. As the functionalized aerogels were also hydrophilic, the release was also thought to be dependent on the collapse of the aerogel matrix. It was shown that 70 % of the adsorbed drug was released within the first 30 minutes for all formulations used in the study.

2.3.3 Silica Aerogels for the encapsulation of biomolecules

Protein drugs are increasingly becoming key components of modern medical care. Four of the top fifteen U.S. pharmaceutical products by sales in 2008 were protein drugs [78]. The studies which demonstrated the potential of aerogels for drug delivery suggest the suitability of these porous materials for the encapsulation of protein or enzymes [15].

An enzyme within a host material, (a supported enzyme) is more desirable than free enzymes for various applications such as biocatalysis since it is easier to remove the supported enzyme from the reaction media and separate it from the reaction products [79]. However, the encapsulation should change neither the stability nor the activity of the enzyme. Sol-gel techniques were used to encapsulate various enzymes [80] and it was shown that enzymes usually retained their catalytic activity and were protected from degradation within their silica cages. Due to a porous structure enabling the spreading of the enzyme on a large surface area, silica aerogels were shown to be suitable hosts for the encapsulation of various biomolecules such as enzymes or proteins without deteriorating their properties [79, 81, 82]. For example, the biocatalytic activity of an aerogel encapsulated lipase for transesterification reactions was studied [82]. It was shown that the enzyme was well dispersed in the aerogel matrix which prevented its agglomeration.

Moreover, the catalytic activity of the lipase was higher in supercritically dried aerogels compared to ambient pressure dried xerogels [79] which was attributed to the highly porous structure of the aerogel which enabled the enzyme to be flexible in its host matrix. For instance, the specific pore volumes of the synthesized aerogels were shown to be around 2 cm³/g compared to xerogels with 0.5 cm³/g giving a higher area for the enzymes to be more flexible. Recently, it was also shown that a protein, cytochrome c could be trapped in an aerogel matrix using a nanogluing approach [83, 84]. Proteins were added together with silver or gold nanoparticles to the sol just before the gelation leading to the spontaneous formation of loosely multilayered superstructures of proteins. The use of supercritical drying then resulted in protein-noble metal-aerogel composites. These protein-metal superstructures displayed rapid gas phase recognition of nitric oxide while entrapped in the aerogel network and remained active for weeks at room temperature [83]. Since not all proteins might be able to form superstructures with metal nanoparticles, the researchers also investigated the stability of the same protein, cytochrome c, in the aerogel matrix without nanogluing it to a noble metal [84]. Although the superstructure was found to be only slightly more stable than the protein alone, it was revealed that proteins preserved most of their structural integrity and responded to nitric oxide without the presence of metal nanoparticles. These studies indicate the potential of the encapsulation of proteins within aerogel matrices which could also serve as a basis for the development of aerogels as protein delivery vehicles.

2.3.4 Composite Aerogels

Composite materials are always attractive due to the combination of diverse functionalities in one entity. It is thereby possible to suppress the disadvantages of one material with superior properties of another. Thus, in the pharmaceutical field, composite aerogels might be an alternative choice as drug delivery vehicles. Polymers are promising

candidates as secondary materials since there are a variety of polymers which are already used in the medical field. The addition of polymer into the aerogel matrix may improve the mechanical properties of the overall composite retarding its collapse and thereby prolonging the drug release. It may also be possible to replace supercritical drying by air drying if the network has sufficient strength. In addition, any change in surface properties could favor the adsorption of some drugs by increasing the interaction between the drug and the surface of the aerogel matrix. The organic entity can also interfere with the network formation with possible formation of macro or micropores due to settlement of organic part into different locations. The presence of diverse sized pores could enable the loading of different sized drugs.

Several methods have been already developed to synthesize silica aerogel polymer composites for a wide variety of applications other than drug delivery. Co-condensation reactions with organically substituted precursor or polymers [85], attachment of styrene [86], isocyanates [87, 88] or epoxides [89] to the modified amine ends of the aerogel surface or liquid phase modifications without using any additional substance but with direct addition of the monomer in the initial solution [90, 91] are some methods which were used for preparation of the composites. Supercritical fluid deposition [92-94] has also been attracting increased attention as a post synthesis modification techniques. Although the materials prepared in these studies were not intended for use in drug delivery applications, the same preparation techniques could be used to obtain suitable materials for pharmaceutical applications.

Sabri et al. investigated the short and long term biocompatibility of polyurea crosslinked silica aerogel composite implants in a Sprague-Dawley rat model [95]. The tissues surrounding the implants or the distant organs did not show any noticeable systemic reaction or immune response. Although this study was carried out with a small number of animals, the results suggest these polyurea based silica aerogels could be useful as drug

delivery vehicles. It was suggested that the nanoporous and three dimensional surface structure of the aerogel limited and prevented its movement by forming anchoring sites with nearby tissues eliminating the need for sutures and thus increasing patient comfort. In vivo experiments suggested that further investigations should be carried out to better understand the interaction between the aerogel implant and the living tissue.

2.4 Organic Aerogel Based Drug Delivery Systems

Even though silica aerogels have interesting and unique properties, they are not biodegradable which may complicate in vivo applications and limit their use for some drug delivery applications. As it was already shown that controlled drug release kinetics and biomolecule entrapment while maintaining its biological functionality can be achieved with these aerogels, more research should be devoted to this area for further development. Alternatively, organic aerogels mostly based on polysaccharides possess several beneficial characteristics of inorganic aerogels such as high surface areas and porous structures and they are also biodegradable. Meanwhile, the biodegradability of these organic aerogels should also be investigated in vivo case by case. Several patents have been already published showing that organic aerogels could be loaded with pharmaceutical compounds. In 1995, Berge et al. has shown that resorcinol formaldehyde aerogels could be loaded with testosterone adipate and 5-fluorouracil via the aforementioned methods in Section 2.2 [17]. Lee et al. loaded organic aerogels based on transacetylation of derivatized mannitol and trehalose with methadone, naltrexone or insulin as the model drugs by contacting the alcogels with a solution of the drug before the supercritical drying step [96]. The resulting powder was found to have a very low density which in turn could enable its application as an aerosol for inhalation. The authors claimed that the aerogel powder containing therapeutic agent had particle size in the range of 0.5 to 10 microns as a result of a milling

process which would permit them to reach the alveoli of a human subject's lungs upon inhalation.

Biodegradable starch is an abundant, edible, nontoxic and low cost polysaccharide which is composed mainly of amylose and amylopectin, the relative proportions of which are dependent upon the starch source [26]. In synthesis of starch aerogels, the first step is to swell the starch by placing it in an aqueous solution [26]. While heating, the starch dissolves and gelation occurs with the destruction of granular structure. Upon cooling and aging, starch hydrogel is formed following the partial reorganization and the crystallization of the polysaccharide structure. The hydrogel is then subjected to solvent exchange with an alcohol followed by supercritical drying resulting in a starch aerogel. The amylase amount and the temperature at which gelation occurs are parameters governing the hydrogel and thus the aerogel structure.

Mehling et al. loaded paracetamol and ibuprofen as model drugs on starch aerogels and investigated their release in 0.2 M phosphate buffer at a pH of 7.2 and at 37 °C [53]. Different kinds of starch, potato starch and modified starch (Eurylon 7) were used to prepare starch aerogels. Owing to high solubility of paracetamol in ethanol, the loading was performed during the solvent exchange step and loadings as high as 25 % by weight was obtained. SEM images of those aerogels which are drug loaded and drug free are given in Figure 9. The average pore size of the potato starch aerogel (around 7.2 nm) was higher than that of the Eurylon 7 (around 1.9 nm) based aerogel. SEM image of the paracetamol loaded potato starch aerogel indicates the presence of some paracetamol in crystalline form due to the possible crystallization of paracetamol inside the pores during the supercritical drying step as explained previously. On the other hand, ibuprofen which was loaded by adsorption from a solution of scCO₂ was found to be in amorphous form. Similar amounts of loading could be achieved for both drugs using the two methods. The specific surface area and the pore size were seen as the major factors affecting the loading. Higher surface

areas resulted in higher drug loading. Furthermore, smaller pore sizes led to increased loading due to capillary forces holding the drug molecules inside. It was shown that the release kinetics were dependent on the structure of the matrix along with the properties of the model drugs. Since paracetamol was highly soluble at given pH, its dissolution was faster than ibuprofen for all matrices. However, the release rate of ibuprofen which was adsorbed from scCO₂ and had a lower solubility than paracetamol was highly dependent on the kind of matrix. The rate was higher with fast collapsing matrices such as Eurylon 7 and hydrophilic silica aerogel and lower with more stable matrices such as potato starch aerogel.

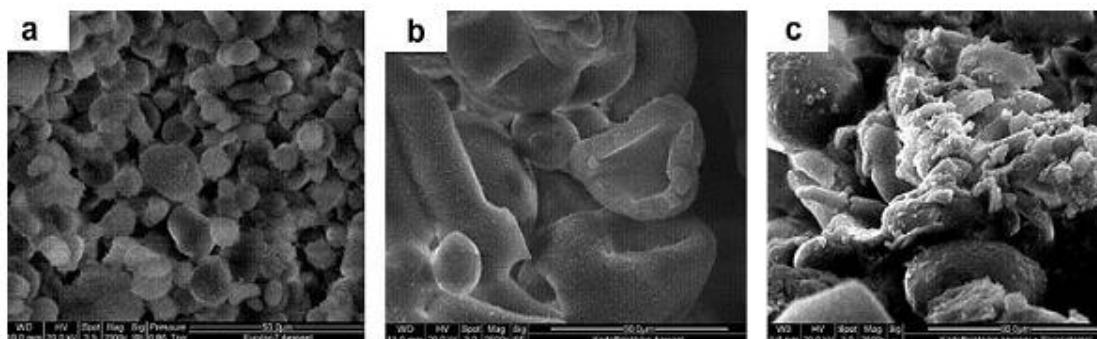


Figure 2.8: SEM pictures of starch based aerogels with 2500 fold magnification, a) Eurylon 7 based aerogel, b) potato starch aerogel, c) paracetamol loaded potato starch aerogel. Reprinted from [53] with permission from Elsevier.

The loading capacity of corn starch aerogel microspheres was investigated using the model drug ketoprofen and the loading capacity of these organic aerogels with surface areas ranging from 34 m²/g to 120 m²/g was found to be in the same range of silica aerogels with higher surface areas (around 1000 m²/g) [31]. The loading was given as 1.1x10⁻³g/m² corresponding to 15.8 % by weight [31] compared to the loading in the silica aerogel matrix which was reported as 2.8-3.8x10⁻⁴ g/m² corresponding to around 30 % by weight [55]. The effect of the oil to starch ratio, surfactant amount and the gelation

temperature on the physical properties of the starch aerogels were also investigated. The maximum loading capacity was found to be dependent on the density, the surface area and the pore size. Lower densities with high porosities and high surface areas were shown to enhance the loading of the active compound.

The importance of the operating conditions of the supercritical drying process on the physical properties such as density, surface area and pore size was demonstrated in a very recent study on starch aerogel microspheres [97]. It was shown that long drying times were detrimental in preserving the porosity of starch aerogels. This was attributed to the local distortions and collapses in the aerogel structure by extraction of structural water from the starch aerogel network by scCO_2 [98]. Microspheres prepared using a shorter supercritical drying period had desirable properties. The time dependent loading of the ketoprofen on starch aerogels resulted in a specific loading capacity of almost one order of magnitude higher than that obtained for silica aerogels as a matrix [55]. The release of the ketoprofen was shown to follow Korsmeyer-Peppas release model involving both the diffusion of the active ingredient and the matrix erosion processes [97].

Another polysaccharide, alginate, was also used to prepare aerogels which were then investigated as drug delivery vehicles. Alginate which is an abundant polysaccharide is used as a host material for several biologically active materials in various applications [99, 100]. The chemical structure of alginate consists of a copolymer of 1,4-linked- β -D-mannuronic acid (M) and α -L-guluronic acid (G) [99-101]. Divalent cations such as Ca^{+2} are usually used to trigger the gelation of the alginate following the “egg-box” gelation model mechanism [33]. The addition of the alginate solution to the cation source solution (diffusion method) [102] or the controlled addition of the cation (the cross-linking ion) to the polysaccharide solution (internal setting method) [103] can induce the gelation of the alginate.

Mehling et al. prepared Na-alginate aerogels and loaded them with ibuprofen with the post-treatment method [53]. It was observed that the release of the drug from alginate aerogels was quite fast due to the high affinity of alginate for water and more efficient transport of the drug to the surrounding medium due to the large pores of the aerogel with an average pore radius around 11.7 nm. In another study concerning alginate aerogels, the effect of preparation conditions on the properties of the aerogels and on the release of a model drug, nicotinic acid were investigated [62]. It was shown that the initial alginate concentration enabled control over the drug release. Increasing the alginate concentration resulted in more compact aerogels with a higher degree of cross-linking retarding the release of the drug. More compact structures exhibited less shrinkage and thus higher pore volumes. Furthermore, it was also observed that loading of the drug during the gel synthesis decreased shrinkage of the gels during the solvent exchange step.

Monodisperse alginate particles with a porous structure were synthesized using a prilling process [63]. An alginate solution containing ketoprofen as the model drug was sprayed into an aqueous or ethanolic CaCl_2 gelling bath through a nozzle. The resulting alginate beads were either supercritically or air/oven dried. Since the loading of the drug was performed prior to drying, the loadings of drugs that are soluble in scCO_2 were lower compared to air dried samples due to extraction of the drug by scCO_2 during drying. The porous structure resulting from scCO_2 drying enhanced the dissolution of the drug and also allowed the modulation of the release rate of the drug. It was shown that performing the cross-linking in aqueous CaCl_2 solutions resulted in the amorphous form of the drug compared to crystal clusters of ketoprofen obtained when the cross-linking was performed in ethanol.

Cellulose aerogels which are another type of organic aerogels are prepared either by freeze or supercritical drying of dissolved cellulose nanofibrils and nanowhiskers [15, 104, 105]. They have very similar properties compared to silica and other organic aerogels [65].

In addition to plant cellulose, bacterial cellulose is another interesting source due to its high purity, molecular weight, fiber strength and degree of hydration and has already a 3D framework [106]. Ultra-lightweight cellulose aerogels were prepared from purified bacterial cellulose as the starting material which was produced by the gram-negative bacterium *Gluconacetobacter xylinum*. The cultivated bacterial cellulose was briefly boiled, treated with NaOH and then washed with deionized water for neutralization. Resulting hydrogels were also subjected to solvent exchange step prior drying. The use of supercritical drying conserved the dimensional stability of the materials leading to very small amounts of shrinkage [106]. Haimmer et al. studied the loading of dexpanthenol and L-ascorbic acid on bacterial cellulose matrices via precipitation from ethanolic solutions by supercritical carbon dioxide [65]. It was shown that the drug loading was independent of the nature of the drug contrary to the release profile which was dependent on the type of the loaded substance. The release rate was also shown to be dependent on the thickness of the bacterial cellulose matrix due to the fact that the release was found to be driven by diffusion only. The release kinetics could be successfully predicted using a mathematical model taking into account both the solvent diffusion into the pores and the solute diffusion out of the pores. Successful predictions confirmed that no specific interaction existed between the drugs and cellulose matrix.

Betz et al. prepared a novel whey protein-based aerogel for drug delivery applications [66]. Previously, it had been shown that water insoluble whey based hydrogels were suitable for the encapsulation of drugs [107, 108]. The use of supercritical drying rather than freeze drying as the final step in the preparation of these materials resulted in the formation of biopolymer based aerogel structures. The covalent disulfide bonds within these materials prevented the collapse of the aerogel structure when placed in aqueous media and led to a pH dependent swelling behavior upon rehydration. the release of the drug was shown to be dependent mostly on diffusion. As shown in Figure 2.9, the release

of ketoprofen was retarded when it was encapsulated in aerogels compared to its pure form. The higher dissolution rate of ketoprofen at pH 6.8 was attributed to its higher solubility at neutral pH conditions.

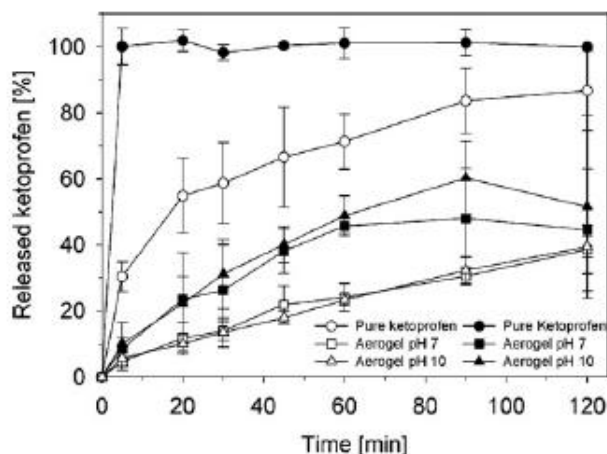


Figure 2.9: The release of ketoprofen from whey protein based aerogels generated from precursory hydrogels at pH 7 and pH 10. (open white symbols represent pH 1.2 and closed black symbols represent pH 6.8). Reprinted from [66] with permission from Elsevier.

2.5 Layered Aerogels as Drug Delivery Systems

Our immune system is ready to attack any unknown substance which is introduced into the body, thus the designed drug delivery vehicles should have their own protective layer or they should mimic the already recognized substances. In addition, the application of some systems like hydrophilic aerogels which collapse when placed in aqueous solutions can be extended by covering them with protective layers. These layers may not only protect the core material but also regulate the release of the drug which is a desirable aspect in drug delivery applications. It was shown that such stealth properties can be incorporated to nanostructured drug carriers by proper design of the density, thickness and hydrophilicity of the coatings [109]. For example, Chen et al. prepared an armor from poly(butyl methacrylate) latex particles around polymer vesicles which were prepared from poly(n-

butyl methacrylate)-b-(N,N-dimethylaminoethyl methacrylate) block copolymers which could enable the control of the overall rigidity of the polymer vesicles [110]. In addition, it was proposed that this armor could be an effective tool to vary the permeability and thus control the release of the drugs. The polymer vesicles were also coated with a stealth supracolloidal armor which was prepared from a mixture of ethyl acrylate and methacrylic acid. The partial dissolution of this armor upon pH change could be exploited for drug delivery. The same strategy could also be applied to suitable aerogel systems to provide protection and also a controlled release.

Another advantage of using a multi-layered system could be to obtain a sequential release of different drugs for combined therapeutic effect [111]. The loading of two or more different drugs on different layers can also prevent the encounter of these drugs which lose their effectiveness when they interact. The design of multi-layers with different hydrophobicity levels could provide a controlled and prolonged release of a drug with subsequent collapse of successive layers and also control of the diffusion through the layers. The use of hydrophilic core with a hydrophobic coating, vice versa, or combining hydrophilic and hydrophobic cores in the same device could enable the delivery of hydrophilic and hydrophobic drugs by the same drug delivery vehicle [112]. Furthermore, stimuli sensitive layers might lead to target specific delivery, enabling release of different drugs at different physiological conditions [113]. For example, different layers could be designed such that each layer would be sensitive to a different pH value. Thus, this layered system could release different drugs at different pH conditions in the body.

Different methods are already established to design layered materials. Suitable techniques which should neither damage nor collapse the porous structure have to be developed not to affect the high pore volumes and surface areas of porous aerogels. Layer by layer (LbL) assembly technique involving the deposition of positively and negatively charged species is a common method which is also applied to coat diverse biomedically

relevant substrates [70]. The ability of achieving high drug loading within the film layer and conformal coating complex geometries with micro- to nanometer scales are attracting features of LbL systems [70]. Meanwhile, spray LbL assembly technique enables the manipulation of the LbL film deposition on porous media and scaffolds with respect to the final degree of pore coverage and film morphology [114]. Shukla et al. have shown that the microstructure of porous gelatin sponges was conserved after the spray LbL process [70]. Thus, established technologies as well as innovative systems should be tested and developed to obtain more complex layered systems suitable for aerogels in drug delivery applications.

One similar approach was adopted by Giray et al. [60] to prolong the release of drugs from hydrophilic silica aerogels by coating them with a PEG based hydrogel layer which had been previously used to produce nano-carriers with stealth properties [109]. To form this composite (Figure 2.10), synthesized silica alcogels were primarily loaded with Eosin-Y as the photoinitiator prior to drying. The surface of Eosin-Y loaded alcogels were rendered hydrophobic using HMDS as the surface modification agent and scCO_2 as the solvent. Subsequently, hydrophilic or hydrophobic aerogels were placed in PEG diacrylate prepolymer solution and photopolymerization was performed using visible light (514 nm) leading to a PEG hydrogel coated aerogel as shown in Figure 2.10. The composite was then loaded with ketoprofen to test its potential as a drug delivery system. It was shown that both drug loading capacity and drug release profiles can be tuned by altering the hydrophobicity of aerogels and the concentration of PEG in hydrogel coating affecting the crosslink density.

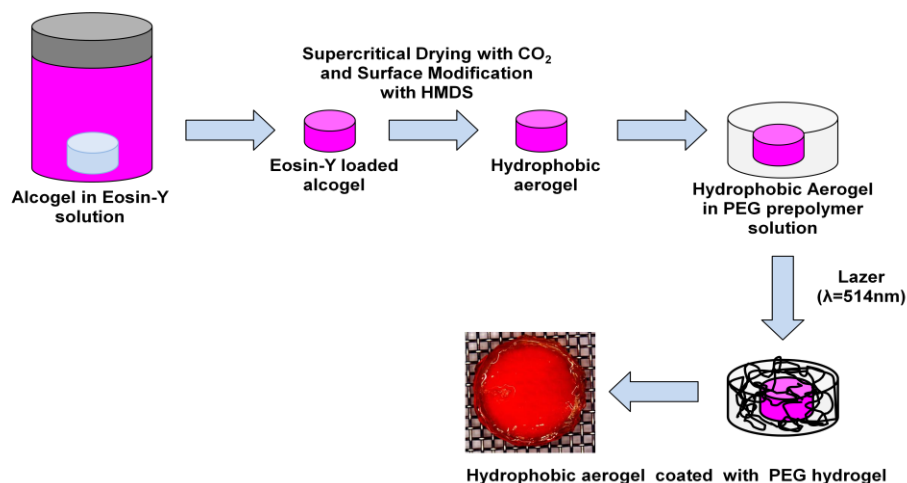


Figure 2.10: The procedure for the preparation of PEG hydrogel coated silica aerogels. Adapted from [60].

Following a similar approach, a novel process for coating of aerogel particles with polymeric materials using a spouted bed technology was recently developed [61]. The process was carried out in a slit-shaped spouted fluidized bed with a horizontal gas inlet and an adjustable gas supply. The polymers were sprayed as an aqueous suspension or melts over the aerogels. This technology was applied to silica aerogel particles which were previously loaded with ibuprofen as a model drug. Aerogel particles were firstly coated with PEG 2000 as the protection layer and then with a pH sensitive polymer Eudragit® L resulting in double layer coating. It was shown that the polymeric coating allowed a pH controlled release due to the variation of the stability of the polymer with pH. As Eudragit® L is soluble at pH values above 5.5 the coating did not affect the release rate of ibuprofen at neutral pH conditions. However, the polymeric coating was shown to reduce the release to as low as % 20 compared to almost % 94 within 2 hours at very low pH values such as 1.

Veronovski et al. used a multi step sol-gel process to prepare alginate aerogels with multi-layers [64]. The spherical alginate aerogels were prepared by dropwise addition of

the alginate solution to a CaCl_2 solution. Subsequently, the wet alginate alcogels were washed with pure water and then immersed in a second alginate solution leading to the development of the second alginate layer. Repeating this process resulted in spherical multi-layer alginate aerogel. It was shown that the model drug nicotinic acid's loading was increased and its release was prolonged by adding more layers around the core. While 75% of the drug was released in 5 minutes from the native alginate core, only 50% of the drug was released in 1 hour when using alginate aerogel with 8 layers as shown in Figure 2.11. Higher drug loadings were achieved by covering each layer with nicotinic acid which in turn resulted in even more extended release like the release of 50 % of the drug within 4 hours.

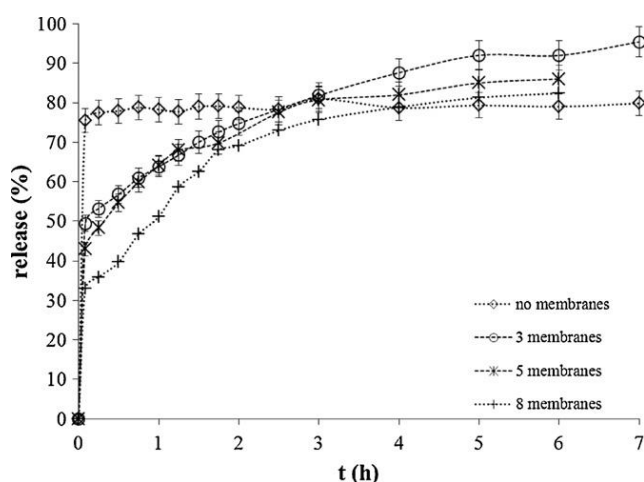


Figure 2.11: The release kinetics of nicotinic acid from spherical multilayer alginate aerogels with different number of layers. Reprinted from [64] with permission from Elsevier.

2.6 Mathematical Modeling in Drug Delivery

Development of mathematical models for drug delivery systems to predict the kinetics of drug loading and drug release is very important for a variety of reasons. Modeling gives insights about the mass transport and chemical processes occurring in the

drug delivery systems along with the effect of the design parameters such as geometry, and loading amount [115]. Optimization of these models is expected to improve the efficiency and easiness of drug delivery systems. Good estimates for different composition, geometry and preparation procedure of various types of systems will shorten the time required for experimental studies saving time and reducing costs. The models should also consider the desired administration method, the dose of the drug and the release profile.

Over the years, various mathematical models were developed to describe the drug release mechanisms. Takeru Higuchi who is known as the father of modeling of drug delivery developed the famous Higuchi equation describing drug release from an ointment base in 1961 as shown in equation 2.4 [116].

$$M_t = k\sqrt{t} \quad (2.4)$$

where $k = A\sqrt{(2C_iDC_s)}$, A is the surface area of the film which is exposed to the skin, D is the diffusion coefficient, C_i is the initial concentration of the drug and C_s is the drug solubility.

The major advantage of this equation is its simplicity [117]. However, several assumptions must be fulfilled for good predictions. An initial concentration of the drug higher than its solubility, the choice of a thin film with negligible edge effects as the device geometry, no swelling or degradation processes, constant diffusion coefficient for the drug were given as some of the assumptions for the development of this model [117].

Since then, variety of empirical/semi empirical or mechanistic mathematical models were developed [117]. Empirical/semi empirical models are mostly descriptive models which provide no or limited insight into drug release mechanisms. Although these models have a low predictive power, they can be used to compare different drug release profiles using specific parameters [118]. On the other hand, mechanistic theories are based on actual physicochemical phenomena such as diffusion, dissolution, swelling, erosion,

precipitation and/or degradation [115, 118]. These models provide information about the system specific parameters giving insight about the underlying drug release mechanisms. These realistic models allow the quantitative prediction of the effects of preparation conditions and processing parameters on the resulting kinetics of the drug release. Accordingly required preparation conditions, size, shape and composition of the system to achieve the desired properties become theoretically predictable.

2.6.1 Mechanistic Theories

Based on the literature, the major phenomena governing the drug transport are diffusion which is the mixing process by molecular motion [119], swelling referring the water uptake of the system resulting in an increase in its volume and erosion meaning the loss of material from the bulk [2, 120]. The properties of the carrier material such as hydrophilicity or biodegradability along with the properties of the drug such as the solubility or the bioavailability are important and have a large impact on the drug delivery mechanism. Accordingly, mathematical models should be developed using specific equations that describe the actual physical situation. Many existing models for drug delivery are based on diffusion equations since diffusion seems to be playing the central role in drug delivery applications as it is almost always involved in the control of drug release from a carrier [121, 122]. Mass transfer of drug molecules in the carrier or from the carrier to the outside medium are described by Fick's Law of diffusion (for one dimensional diffusion in planar geometry) if the drug transport is purely diffusion controlled (Equation 2.5).

$$N_A = -D_A \frac{\partial C_A}{\partial x} \quad (2.5)$$

Additionally, Fick's second law is used to determine the change in the concentration with respect to time as shown in equation 2.6:

$$\frac{\partial C_A}{\partial t} = -D_A \frac{\partial^2 C_A}{\partial x^2} \quad (2.6)$$

where C_A is the concentration of species A inside the carrier, N_A is the diffusive flux of species A, D_A is the diffusion coefficient, x is the direction and t is the time.

Similar equations can be developed for thick slabs, cylindrical devices or spherical matrices. For each different type of drug delivery system, different initial and boundary conditions need to be used [122]. The initial drug distribution in the carrier is specified with the initial conditions whereas the potential movement of the specific boundaries (shrinking or swelling) or the symmetry within the system are given with the boundary conditions. Either analytical or numerical solutions are then derived depending on the complexity and the number of these equations.

On the other hand, there are cases where the concentration of the loaded drug is much higher than its solubility in the surrounding medium. In this case, the reduction in the amount of drug due to the release will be compensated by dissolution of the adsorbed/precipitated drug inside the carrier. Consequently, the drug concentration in the carrier will remain constant (saturated) until the concentration of the solid drug drop below the saturation limit [118]. As a result, the dissolution process describing the transformation of the solid drug into its dissolved state is also included in the models as shown in equation 2.7:

$$\frac{\partial C_A}{\partial t} = -D_A \nabla C_A + S \quad (2.7)$$

where S is a source term which takes into account the dissolution of the drug increasing the amount of dissolved drug inside the carrier.

The source term can also be given as a reduction in the concentration of the solid drug and can be modeled as:

$$\frac{\partial S}{\partial t} = k_d A (C_s - C_A) \quad (2.8)$$

where k_d is the dissolution rate constant and C_s is the solubility of the species in the medium and A is the average surface area of the drug . Thus, the final system of equation can be given as:

$$\frac{\partial C_A}{\partial t} = -D_A \frac{\partial^2 C_A}{\partial x^2} + k_d A (C_s - C_A) \quad (2.9)$$

If the swelling of the carrier material is of importance for the control of drug transport, the transition of the carrier molecules from their glassy to the rubbery state have to be taken into account [123]. Due to swelling, the diffusion pathways of the drug molecules would increase leading to reduce concentration gradients and thus slower rates of drug transport [118]. However, in a fully swollen matrix, the diffusion coefficient would be similar to that in a solution which would lead to a increased diffusion rate and thus increased rates of drug transport. Therefore, the dominant effect would modify the rate of drug transport.

The last major mechanism affecting the rate of drug transport is the degradation or the erosion process which are also referred as the cleavage of the chains into oligomers and monomers and the loss of material from the bulk, respectively. There are mainly two types of erosion processes which are the bulk erosion and the surface erosion. If the penetration of the dissolution medium is faster than the cleavage of the chains, then the entire system is degraded resulting in a bulk erosion. However, if the degradation is limited to the outer layers, erosion primarily affects the surface but not the inner layers which would result in a surface erosion process.

2.6.2 Empirical or Semi-Empirical Models:

Empirical or semi empirical models are generally used to compare different release profiles [118]. Under specific conditions, semi empirical models might be realistic to a certain extent giving an indication of underlying mechanism for drug transport.

An empirical model which is frequently used is the Peppas equation of power law which is given by the equation 2.10 [118, 124]:

$$\frac{M_t}{M_0} = kt^n \quad (2.10)$$

where M_t and M_0 are the absolute cumulative amount of drug released at time t and at infinity respectively, k is a constant incorporating structural and geometric characteristics of the system, n is the release exponent indicating the mechanism of the release only if the underlying assumptions of the model are fulfilled. It was already shown that a release exponent equal to 0.5 will give the Higuchi equation. However, a value greater than 0.5 up to 1 which indicates a swelling controlled release will suggest a anomalous transport mechanism involving different types of phenomena such as diffusion and swelling.

Afterwards, Hoffenberg came up with a new approach involving the degradable systems [118, 124]. The model represented a quantitative description of drug release from degradable systems exhibiting a release rate which is proportional to the surface area of the carrier.

$$\frac{M_t}{M_0} = 1 - \left(1 - \frac{k_0 t}{C_0 a}\right)^n \quad (2.11)$$

where k_0 is rate constant representing all the mass transfer processes that are involved in the drug release (they are assumed to add up to a single zero order process), C_0 is the uniform initial drug concentration within the system and a is the radius of the sphere of the

cylinder, or the half thickness of the of a slab, n is a shape factor (1 for slab geometry, 2 for cylinder and 3 for spheres).

Hixson and Crowell derived another model in order to account for the effect of changing surface area and diameter of particles during dissolution based on the fact that the area of the particle is proportional to the cubic root of its volume [124].

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}t \quad (2.12)$$

where Q_0 is the initial amount of drug in the carrier, Q_t is the amount remaining at time t and K_{HC} is the Hixson-Crowell cube root dissolution rate constant.

Furthermore, Cooney developed a more detailed model for spheres and cylinders undergoing surface erosion [118]. He also considered one single zero order kinetics process which was confined to the surface of the drug delivery system.

$$f = \frac{(D_0 - 2Kt)^2 + 2(D_0 - 2Kt)(L_0 - 2Kt)}{D_0^2 + 2D_0L_0} \quad (2.13)$$

where K is a constant, D_0 and L_0 are the initial diameter and length of the cylinder, respectively and t is the time.

Although aerogels emerge as promising candidates for drug delivery, there are hardly any studies on modeling of drug release from aerogels. Developing these models could actually help to understand physical phenomena occurring inside the systems. There are different mathematical models which are already derived to describe the drug release from hydrogels [125], HPMC matrices [123] and polymeric matrices [126]. However, there is no study describing the drug release from aerogel matrices considering all underlying mechanisms during the release. Moreover, mathematical models on the kinetics of drug loading can also be beneficial to enable 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. They can also be used for obtaining carriers with different drug loading amounts from the same batch. Even though there are some studies in the literature on mathematical modeling of drug adsorption into aerogels from supercritical CO₂ or into alcogels from aqueous solutions [127, 128], there are again no studies on modeling of drug loading into silica alcogels by diffusion.

Chapter 3

EXPERIMENTAL METHODS and CHARACTERIZATION TECHNIQUES

3.1 Materials

Tetraethylorthosilicate (TEOS) (from Alfa Aesar 98% purity), ethanol (from Merck), HCl (from Riedel-de Haen with 37% purity and NH_4OH (from Aldrich 2.0 M in ethanol) were used for the synthesis of silica aerogels. Alginic acid sodium salt from brown algae (from Sigma Aldrich, >2000cp of a %2 solution), CaCl_2 (From Sigma Aldrich, anhydrous, granular) were used for the synthesis of alginate aerogels. Phosphate-buffered saline (PBS) tablets were purchased from Amresco (Solon, Ohio).

3.2 Synthesis of aerogels

3.2.1 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 TEOS and ethanol was prepared. Subsequently, water and then HCl was added to adjust the pH to 2.0 to increase the rate of hydrolysis. Afterwards, NH_4OH as the condensation catalyst was added to accelerate condensation reactions leading to gelation at neutral conditions. Overall, the final concentration of TEOS in the sol was around 1.9 M (Table 3.1). 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 a mixture of ethanol and water in equal volumes at 323 K

for aging step. 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 hours, 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 scCO₂ to obtain native silica aerogels as explained in Section 3.2.4.

Table 3.1: The amounts of reactants used in a typical synthesis of silica aerogel

Reactants	Amounts used in the synthesis
TEOS	3 g.
H ₂ O	1.02 g.
EtOH	3 g.
HCl in EtOH (0.048M)	0.5 ml
NH ₄ OH in EtOH (0.2M)	0.8 ml

3.2.2 Synthesis of Alginate Aerogels

To prepare alginate aerogels, the alginate source was dissolved in water to obtain %1.5 (or %0.5, %1 and %2) by weight solution. Another solution was prepared with the gelation trigger, CaCl₂ with the final concentration of 0.2 M. The wet gels were prepared either by diffusion or by internal settling method. In the internal settling method, the alginate solution was poured into the CaCl₂ solution continuously from a burette. Alginate gel drops formed immediately as soon as the alginate solution touched the CaCl₂ solution. The dimensions of the spherical alginate wet gels were dependent on the device which was used to pour the alginate solution. The bigger is the mouth of the device, the bigger is the final dimension. The spherical alginate gels which were obtained in this study had a diameter of around 3.4 mm. These alginate alcogels were left for 10 minutes in the CaCl₂

solution for ripening and then separated from the cationic solution and washed with distilled water. Then they were successively subjected to a series of ethanol-water aging solutions of increasing ethanol concentration (10, 30, 50, 70, 90 and 100% ethanol) during at least 30 minutes each. Then, the alcogels were dried with scCO_2 at 90 bar and 313 K as explained in Section 3.2.4.

Table 3.2: The amounts of reactants used in the synthesis of silica aerogel

Reactants	Amounts used in the synthesis
Na-alginate	0.5, 1, 1.5, 2 wt. % alginate in H_2O
CaCl_2	0.02, 0.2, 2 M CaCl_2

3.2.3 Synthesis of Silica Aerogels Encapsulated with Alginate Aerogels

Initially, an equal weight percent mixture of TEOS and ethanol was prepared. Afterwards, CaCl_2 solution and then HCl was added to adjust the pH to 2.0 where the rate of hydrolysis of the silica precursor is sufficiently high to complete hydrolysis within 45 minutes. After hydrolysis, NH_4OH as the condensation catalyst was added to accelerate condensation reactions leading to gelation at neutral conditions. The typical CaCl_2 concentrations in the final solutions ranged from 0.02 to 0.2 M. Just before gelation, the solution was poured into cylindrical molds. Later, the wet gels were taken out from their molds and placed in Na-alginate solution. The concentration of the Na-alginate in distilled water was varied between 0.5 wt. % and 1.5 wt. %. The diffusion of Ca^{2+} ions from the porous silica alcogel structure through the alginate solution resulted in the formation of an alginate layer around the silica alcogel core. The resulting layered aerogel structure was then subjected to successive aging steps prior to supercritical drying. The samples were then successively placed in a series of ethanol-water baths with increasing alcohol concentrations (10, 30, 50, 70, 90 and 100). The reason of using this kind of aging was to prevent the structural changes which could have occurred if 100% ethanol was immediately

added. These solvent exchange steps aimed to remove all the impurities and replace water remaining in the pores. The last step was to dry layered alcogels at 90 bar and 313 K as explained in Section 3.2.4.

3.2.4 Supercritical Drying

The synthesized alcogels were subjected to the supercritical extraction method in order to extract the liquid from the pores. The alcogels were dried using Applied Separations Speed SFE unit (tubular vessel, volume=26 ml). This supercritical extraction unit consists of a high pressure vessel in an oven for heating purposes, a pump to pressurize the system, a carbon dioxide cylinder, a cooler, a rotameter and a temperature control unit for the extraction vessel and the expansion valve.

Temperature of the extraction vessel was set to 313 K and the vessel was preheated to the extraction temperature before beginning the drying process. Then the system was pressurized very fast with carbon dioxide until the desired operating pressure of 90 bar was reached. After the process whose duration depended mainly on the volume of the alcogels, the vessel was depressurized slowly to obtain dried aerogels.

3.3 Drug Loading

The general strategy used to obtain paracetamol loaded aerogels is shown in Figure 3.1. The silica alcogel cores which were obtained after gelation were primarily subjected to usual aging steps as mentioned in Section 3.2.1. 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. PC was chosen as the model drug due to its high solubility in ethanol. Moreover, it is also not possible to load paracetamol by adsorption

from scCO_2 due to its extremely low solubility in scCO_2 . Finally, the alcogel containing the drug was dried with scCO_2 at 313K and 90 bars.

To load silica alcogels encapsulated with alginate aerogel layers with paracetamol, a different procedure was followed. The silica alcogel core was primarily loaded with paracetamol following the procedure above which was then immersed in a 0.2 M CaCl_2 solution. Subsequently, the silica alcogel was placed in Na-alginate solution for the layer formation. Without any aging step, the drug loaded layered aerogel was dried using scCO_2 at 313K and 90 bar. The aim of omitting aging steps was to minimize the drug loss which could occur due to the diffusion of paracetamol (which has a high solubility in ethanol) to the ethanol during aging and solvent exchange steps.

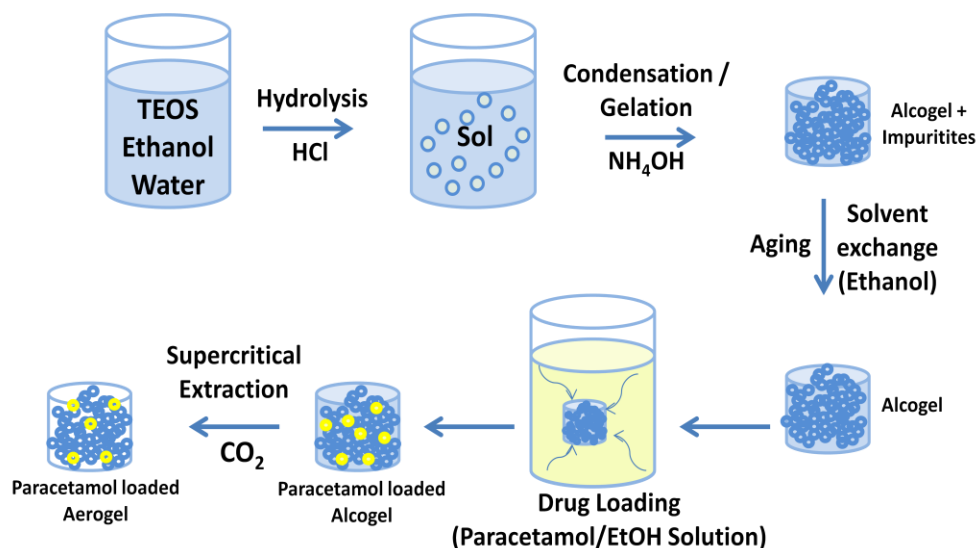


Figure 3.1: The procedure for the preparation of paracetamol loaded silica aerogels

3.3.1 Determination of the amount of drug loading

After the loading procedure, the amount of loaded drug should also be determined for corresponding release experiments. Measuring the change in the concentration of the initial solution to measure the uptake of paracetamol was not found to be feasible as the

initial concentration remained almost constant throughout the experiment. It may be possible to determine the PC uptake gravimetrically after the supercritical drying process but some drug loss may occur during this step which can lead to errors in loading amounts. We utilized another technique to determine the paracetamol uptake of alcogels which takes advantage of the very low vapor pressure of paracetamol. The alcogels loaded with paracetamol were placed in the oven. After the evaporation of the solvent, only solid silica and loaded PC was left. The weight of solid silica was determined in another experiment by evaporating the solvent from the silica alcogels which were synthesized in the same batch and measuring the weight of the remaining solid. Then, the weight belonging to PC only could be calculated by subtracting the weight of this sample from the weight of the sample consisting of solid silica and PC.

To perform this gravimetric experiment, the silica alcogels were prepared using the procedure given in Section 3.2.1. After the aging and solvent exchange steps ensuring that only ethanol is present inside the pores, alcogels were placed on a wire mesh in the paracetamol-ethanol solution which was stirred constantly as shown in Figure 3.3. At specific time points, 3 alcogels loaded with paracetamol were taken out from the loading solution and placed in oven at 50°C for at least 3 days together with a native silica alcogel. Additionally, pure paracetamol was also kept at the same conditions to record any change in its mass; however, its mass did not change throughout the drying process as expected because of its very low vapor pressure. After evaporation of all the ethanol, all alcogels turned into powder as expected. The weight of the samples was measured each day until the weight did not change anymore. The weight of samples obtained from native silica alcogels were subtracted from the weight PC loaded alcogels to determine the amount of paracetamol which was loaded inside the pores of the alcogel by diffusion.

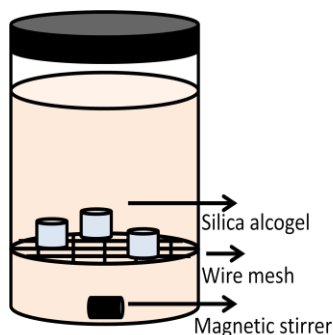


Figure 3.2: The experimental set-up for loading paracetamol to the silica alcogel

3.4 Drug Release

The release experiments of PC were conducted at 310 K under constant stirring. The release medium was phosphate buffered saline (PBS). pH of the PBS solution was adjusted to 5.8 with 6 M HCl solution. A PC loaded aerogel sample was placed on a wire mesh and immersed into a glass vessel containing freshly prepared 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 μ l sample was taken for analysis by a UV-spectrophotometer at 242 nm due to the specific absorption of PC at this wavelength. 100 μ l fresh PBS solution was simultaneously added in the release medium to keep the total volume constant through the experiment. In control samples, aerogels did not give any significant absorbance at 242 nm confirming that the measured absorbance should be the result of paracetamol only. The concentration of paracetamol was estimated using the calibration curve of paracetamol in PBS solution (pH:5.8). The percent release was calculated by equation 3.1.

$$\% \text{ release} = \frac{C_{PC} V_{sol}}{m_t} \times 100 \quad (3.1)$$

where C_{PC} is the concentration of PC at the sample solution, V_{sol} is the volume of the release medium and m_t is the total amount of paracetamol loading.

3.5 Characterization techniques

The density of the samples was determined by simply dividing the final mass by the final volume. The dimensions of the alcogels and aerogels were determined with the help of a caliper.

For the swelling studies of alginate aerogels, a weighted amount of aerogel sample free of paracetamol was immersed in 40 ml PBS solution (pH 5.8). At selected times, samples were taken from the solution, dried with filter paper and weighted. Their radius was also measured with caliper for use in the theoretical release model. Three parallel measurements were performed for each time. The swelling ratio (SR) was calculated as:

$$SR = \frac{m_{sw}-m_i}{m_i} \quad (3.2)$$

where m_{sw} is the mass of the swollen sample and m_i is the mass of the initial (non swollen) sample.

The average pore size and the specific surface area along with the micropore area were determined by N₂ physisorption (Micromeritics ASAP 2020). The samples were primarily degassed at 573 K (for silica aerogels) or 353 K (alginate aerogels) for 1 day prior to measurement to remove any impurities or solvent remaining in the pores. After determining the exact weight of the degassed sample, pore analysis was conducted using 60-point N₂ adsorption/desorption isotherms with a relative pressure (P/P_0) ranging from 10^{-7} to 1 (which required at least 24 h of continuous operation). The pore size distribution of the samples was determined using the Barret, Joyner and Halenda (BJH) method. The desorption branch of the isotherm was chosen for the pore size analysis since the desorption process is thermodynamically stable and is usually chosen for the analysis of mesoporous materials which show a type II adsorption isotherm.

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.

XRD patterns of the samples were collected on a Bruker D8 ADVANCE Diffractometer (Cu-K α ; 1.54018 Å) using focused beam with Goebel mirror and equipped with a Vantec detector or a Bruker D2 phaser.

The pore structure was also analyzed with Zeiss Ultra Plus Field Emission Scanning Electron Microscope after gold coating (~5 nm).

3.6 Cell Viability Tests

Cell viability of the synthesized native aerogels was investigated using a human fibroblast cell line. For these experiments, 1.5 and 2 wt % alginate aerogels were synthesized along with native silica aerogels (diameter: 0.4 cm) and silica aerogels encapsulated with alginate aerogels. Cells were initially cultured at 37 °C with 5% CO₂ in an incubator and maintained in DMEM supplemented with 1% penicillin/streptomycin, 2 mM L-glutamine and 10% FBS [129]. BJ fibroblasts (5000 cells per well of a 96 well plate, plated in triplicate) were exposed to 1.3 mg and 1.5 mg of 1.5 wt. % and 2 wt. % alginate aerogels respectively. Simultaneously, BJ fibroblasts (25000 cells per well of a 24 well plate, plated in triplicate) were exposed to 9.5mg and 10 mg of silica aerogel and silica aerogel encapsulated with an alginate aerogel layer respectively using cell culture plate inserts (Millicell-Pcf, Merck,MA). The gels were then placed in the incubator and viability was measured at days 1 and 4 using CellTiter-Glo Luminescent Cell Viability Assay (Promega, Madison, WI). Results are reported as relative percentage change in ATP with each group internally normalized to the respective control group.

Chapter 4

RESULTS AND DISCUSSION

4.1 Characterization of Aerogels

4.1.1 Native aerogels

The final properties of the synthesized silica and alginate aerogels and a short summary about their production routes is given in Table 4.1.

Table 4.1 Summary of the synthesis of aerogels and their final properties

	Silica Aerogel	Alginate Aerogel
Synthesis Method	Two step sol-gel synthesis	Ionic cross-linking
Synthesis Conditions	Room temperature and pressure	Room temperature and pressure
Synthesis Duration	Gel Formation: 1 hour Solvent Exchange: 3 days Sc-Drying: ~5 hours	Gel Formation: Instantly Solvent Exchange: 2 days Sc-Drying: ~3 hours
Reactants	TEOS, H ₂ O, EtOH, HCl, NH ₄ OH (amounts given in Table 3.1)	Na-Alginate, CaCl ₂ , H ₂ O (amounts given in Table 3.2)
Final Composition	SiO ₂ with some unreacted reactants if any	Na-alginate chains linked with Ca ²⁺ ions

Pore Properties	Mesoporous, surface areas up to 950 m ² /g	Mesoporous, surface areas up to 400 m ² /g
Final Properties	Transparent, hydrophilic, fragile, monolith in cylindrical shape	White, hydrophilic, flexible, monolith in spherical shape

Synthesized aerogels were characterized by various techniques as explained in Chapter 3. The density of the pure silica aerogels ranged from 0.13 to 0.15 g/cm³ whereas the density of the alginate aerogels with 1.5 wt % alginate ranged from 0.055 g/cm³ to 0.062 g/cm³. According to BET results, both aerogel types had high surface areas and pore sizes ranging in the nanometer scale. XRD results indicated that the aerogels were amorphous which also help to easily distinguish crystalline paracetamol inside the matrix. The IR spectra of native silica and native alginate aerogels are shown in Figure 4.1, which are later used for investigating the presence of the drug molecules inside the aerogel matrices.

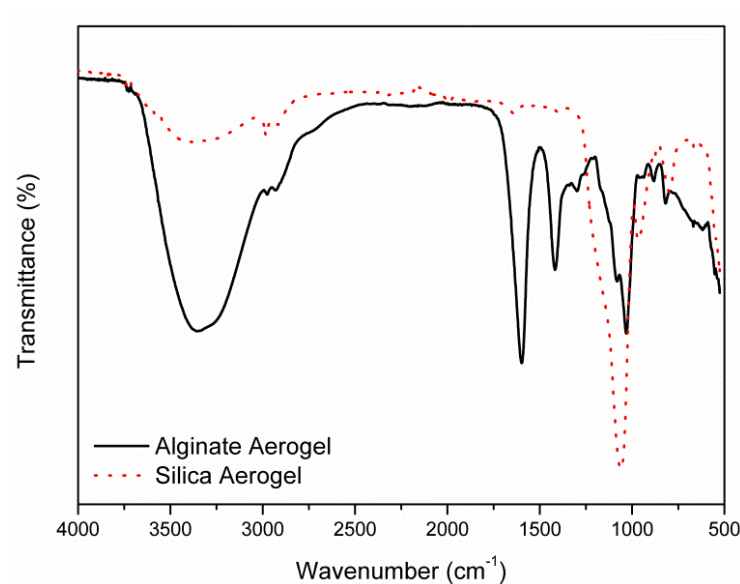


Figure 4.1: IR Spectra of silica aerogel and alginate aerogel

The swelling of the alginate aerogels was studied as it is considered an essential factor affecting the release behavior. The radii of the aerogels were measured with the help of a caliper as explained in Section 3.5. The alginate aerogels primarily shrank as soon as they are immersed in the release medium as shown in Figure 4.2. Afterwards, swelling started and the radius of the aerogels increased almost 1.5 fold within the time interval needed for the release of paracetamol (Figure 4.3). This corresponds for 1.5 wt. % alginate aerogels to a swelling ratio as high as 70% as shown in Figure 4.4. As a result of the reduction in the strength of the crosslinks between alginate chains due to the pH of the medium, aerogel matrix swells increasing the distance between the chains. Moreover, its swelling resulted in longer distances for loaded molecules to diffuse in order to reach the release medium. Thus, the swelling might lower the release rate.

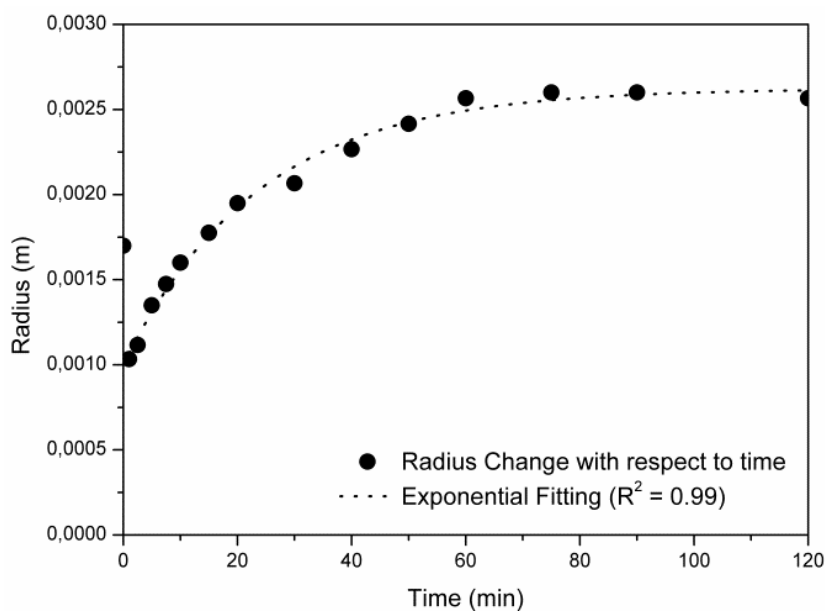


Figure 4.2: The change in the radius of alginate aerogel with respect to time when placed in the release medium

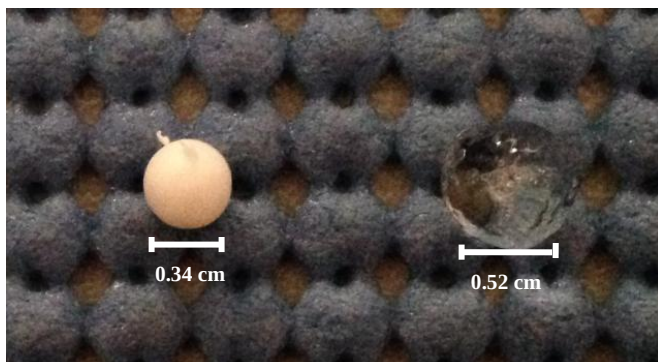


Figure 4.3: Photos of paracetamol loaded alginate aerogel and swollen alginate hydrogel after the release of paracetamol.

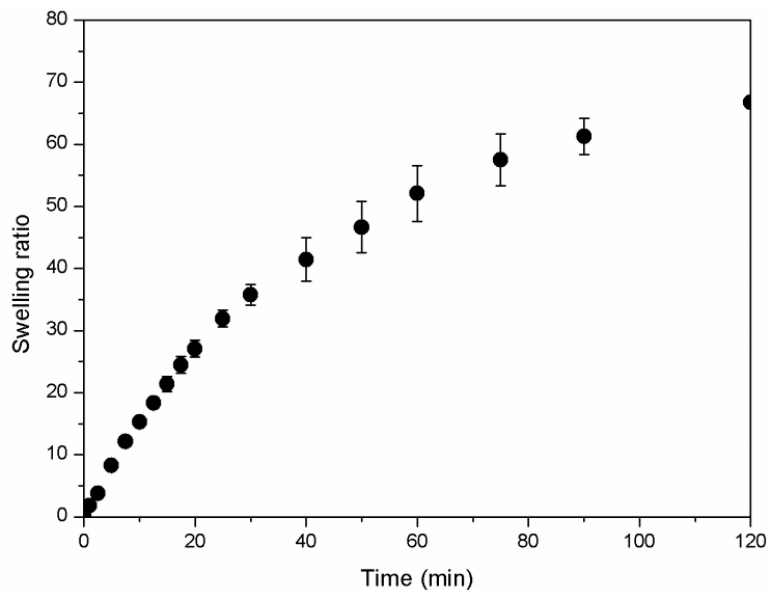


Figure 4.4: Swelling ratio of alginate aerogels (1.5 wt. %)

4.1.2 Silica aerogels encapsulated with alginate aerogel layers

Silica alcogels were successfully encapsulated with alginate hydrogels and then supercritically dried to obtain silica aerogels with alginate aerogel layers as shown in Figure 4.5. It was observed that the alginate aerogel layer could protect the silica aerogel core when immersed in the release medium in which hydrophilic silica aerogel totally

disintegrated into very small pieces. Based on the preliminary drug release experiments using these layered aerogels, it was also seen that the release rate was slightly retarded (Section 4.4).



Figure 4.5: Photos of a silica aerogel (left) and a silica aerogel encapsulated with an alginate aerogel layer (right)

The pore properties of those hybrid aerogels was investigated both by BET and SEM analyses. N_2 physisorption results as shown in Figures 4.6A and 4.6B indicated that the formation of an alginate layer around the silica aerogel did not significantly affect the pore characteristics of the silica aerogel. The small reduction in its surface area (which is usually around $\sim 950\text{-}1000\text{ m}^2/\text{g}$) could be related to its volume shrinkage during the layer formation due to the absence of the conventional first aging step which strengthens the network. In addition, the surface area of alginate aerogel layers was sufficiently high indicative of high loading capacities. Furthermore, the difference in pore sizes could be used to enable the control over the loading and release of different sized, especially large biomolecules.

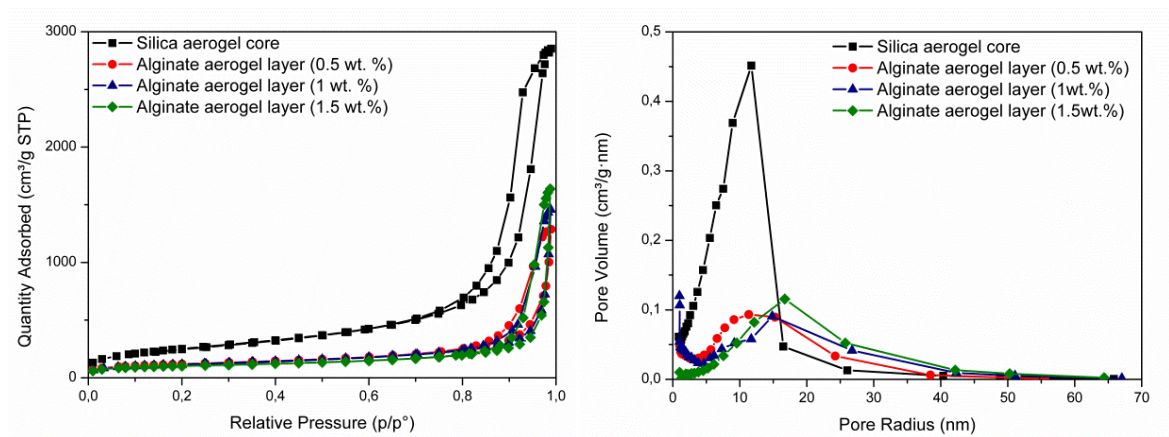


Figure 4.6: A) Adsorption Isotherms of N₂ on Alginate Aerogel Layers and Silica aerogel Core. B) The pore size distribution of different alginate layers and silica aerogel core.

As shown in Table 4.2, the surface areas of alginate layers which were prepared with different concentrations ranging from 0.5 g of alginate per 100 grams of water to 1.5 g of alginate per 100 grams of water were found to be similar [130, 131] and even higher [132] compared to the values in the literature for alginate aerogels. Veronovski et al. showed that increasing the concentration of the alginate solution resulted in a higher degree of cross-linking leading to more compact and stable gels [130] which should indicate the reason of higher pore sizes for the highest alginate concentration. This can perhaps be attributed to a higher degree of cross-linking which enables a higher resistance to shrinkage during supercritical drying due to the higher strength of the solid network.

Table 4.2: BET Results for silica aerogel core and alginate aerogel layers with different concentrations

Sample	BET Surface area (m ² /g)	Desorption average pore radius (BJH) (nm)
Silica aerogel core	905	8,0
Alginate aerogel layer (%1.5w/w)	345	16,5
Alginate aerogel layer (%1w/w)	400	11,7
Alginate aerogel layer (%0.5w/w)	407	10,3

As shown in Figure 4.6B, alginate layers had wide pore size distributions. This can also be seen from the SEM images of the alginate layers which were prepared using solutions with different percentages of Na-alginate in water as shown in Figure 4.7A, B and C. SEM images also indicate that the alginate aerogel layers have a fibrous cross-linked structure with different sized pores. From the average pore size and specific surface area data, the alginate aerogel layers can be considered to be mesoporous with a small fraction of microporosity compared to the silica aerogel which has lower micropore volume.

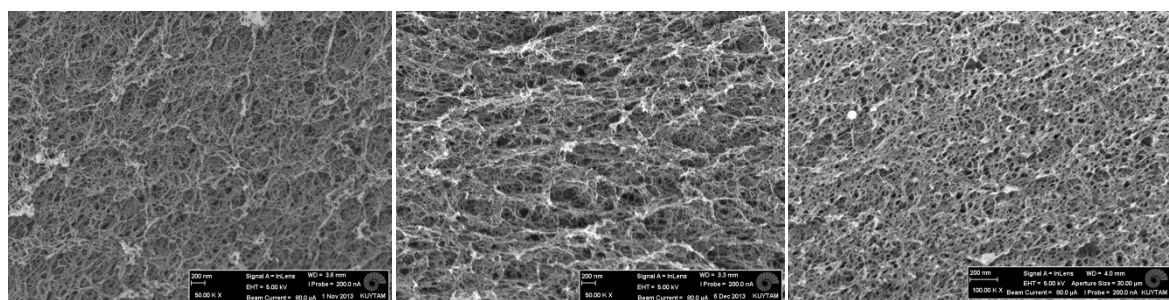


Figure 4.7: SEM image of alginate layers. A) 0.5 wt. %, B) 1 wt. %, C) 1.5 wt%.

The thickness of the alginate layer could also be changed by changing the parameters such as the concentration of the alginate in water and the concentration of the CaCl_2 in the initial solution. As shown in Figure 4.8, the layer got thicker with increasing

crosslinking time and increasing CaCl_2 concentration in the pores of the silica alcogel due to the existence of more free divalent cations. The change in Ca^{2+} ion concentration in the silica alcogel core with a diameter of 1.13cm changed the time required for the growth of the alginate layer to a certain thickness.

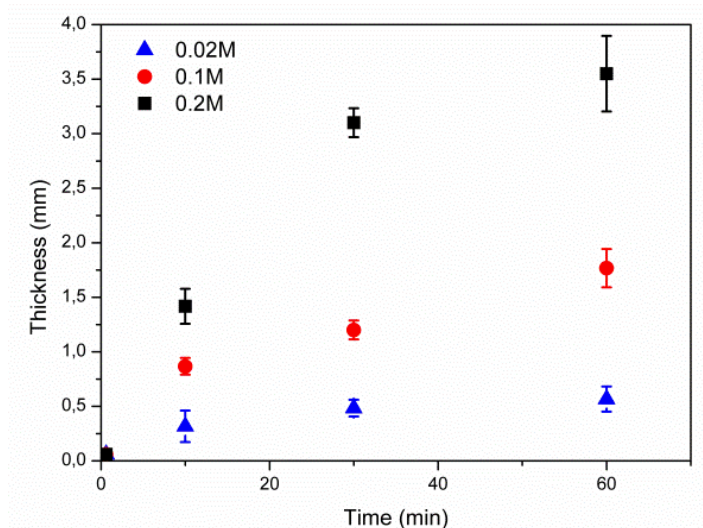


Figure 4.8: The change in the thickness of the alginate layer with time using different CaCl_2 concentrations (0.5 wt. % alginate)

The thickness reached almost 4 mm in 60 minutes for the highest CaCl_2 concentration versus 0.5 mm for the lowest CaCl_2 concentration for experiments carried out using the same composition of alginate solution. The rate of layer growth was reduced after 60 minutes which can be attributed to the reduced rate of diffusion of Ca^{2+} ions through the silica alcogel and then the newly formed alginate hydrogel layer. As seen in Figure 4.9, there was a linear correlation between the concentration of Ca^{2+} ions and the thickness of the alginate layer at a certain time for a fixed alginate concentration. As the initial CaCl_2 concentration increased, the alginate layer was found to be thicker at a constant alginate concentration due to the existence of more free divalent cations. Moreover, as the alginate concentration was increased, the growth of the layer was shown

to be reduced at a constant CaCl_2 concentration due to the formation of more cross links creating a tighter layer. This linear relation enables the selection of the appropriate concentration for a desired thickness over a specified time period.

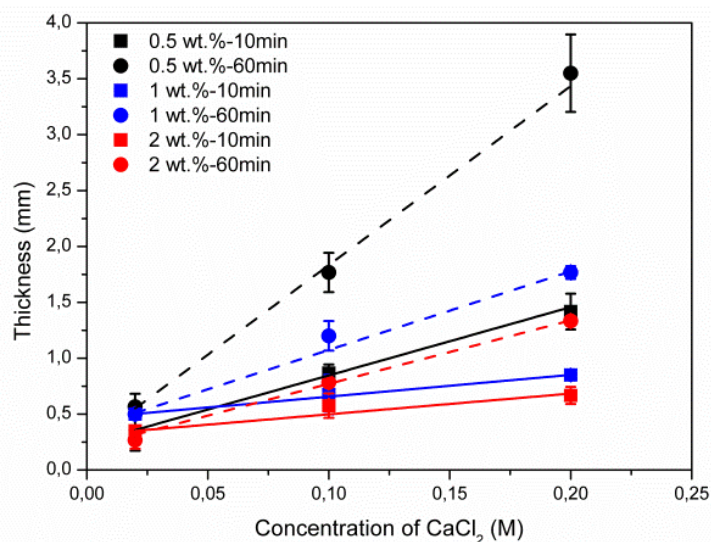


Figure 4. 9: The thickness of the alginate layer versus CaCl_2 concentration (10 min and 60 min)

4.2 Drug Loading

In this study, algogels were 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 diffused into the liquid in the pores. The diffusion continued until the concentrations in the pore liquid and the contacting solution became equal.

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 which depends 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.

4.2.1 Mathematical Modeling of Drug Loading by Diffusion

Besides experiments, the loading of paracetamol was also mathematically modeled. The model was expected to enable the prediction of the required duration for the maximum or a specified amount of loading. Furthermore, the prediction of the drug distribution inside the carrier matrix was also anticipated.

In the model, the mass transport of drug molecules inside the gel was only based on diffusion. Mass transfer from the loading solution to the liquid inside the pores of the alcogel was described by a partial differential equation along with appropriate boundary conditions. Two dimensional diffusion of paracetamol through axial and radial directions in the pores of the alcogel was modeled based on the Fick's second law. External mass transfer by convection was neglected due to the constant stirring conditions. Furthermore, adsorption of paracetamol to the alcogel surface was not considered since the adsorbed amount was much smaller than the amount in the liquid inside the pores (Section 4.2.2). Thus, the mass transfer was assumed to occur only by diffusion inside the pores of the silica alcogel. Moreover, as the volume of the loading bath was far greater (approximately

70 times greater) than the pore volume of alcogels, the concentration of PC in the bath was assumed to be constant throughout the loading process.

The mass balance in a differential volume element in the alcogel for the mass transfer of paracetamol is given by:

$$N_{A,r}2\pi r\Delta z - N_{A,r+\Delta r}2\pi r\Delta z + N_{A,z}2\pi r\Delta r - N_{A,z+\Delta z}2\pi r\Delta r = \frac{\partial C_A}{\partial t}2\pi r\Delta r\Delta z \quad (4.1)$$

where z and r represent the direction that diffusion occurs in the gel where $N_{A,r}$ (given as $N_{A,r} = -D_e \frac{dC_A}{dr}$) is the diffusive flux in r direction and $N_{A,z}$ (given as $N_{A,z} = -D_e \frac{dC_A}{dz}$) is diffusive flux in z direction.

The partial differential equation obtained from this mass balance in a differential volume element in the alcogel is given by:

$$\frac{\partial C_A}{\partial t} = \frac{\partial}{\partial z} \left(D_e \frac{\partial C_A}{\partial z} \right) + \frac{1}{r} \frac{\partial}{\partial r} \left(r D_e \frac{\partial C_A}{\partial r} \right) \quad (4.2)$$

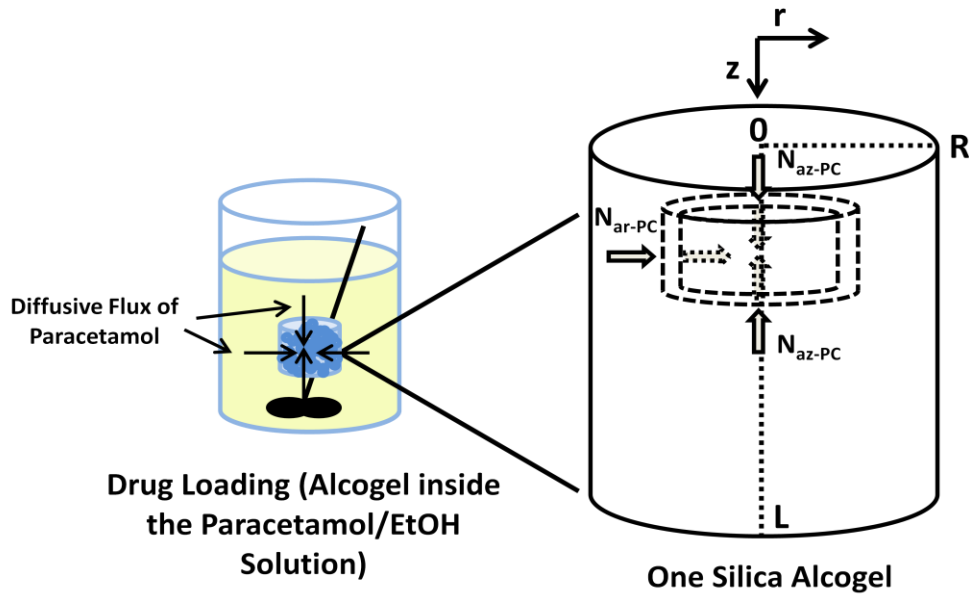


Figure 4.10: The control volume element

where C_A is concentration of paracetamol in the pores of the alcogel (mol/L), D_e is effective diffusion coefficient (m^2/s) of paracetamol in ethanol inside the pores, R is radius of the alcogel (m), t is time (s), L is the length of the alcogel (m).

Diffusion coefficient of paracetamol in ethanol was calculated using Wilke-Chang equation (Equation 4.3) for diffusion in liquids which is usually used to estimate the diffusion coefficients of low molecular weight solutes in dilute solutions which is suitable for our solute/solvent pair. The value for diffusion coefficient was calculated as $8.3 \times 10^{-10} m^2/s$. Then, the effective diffusion coefficient, D_e was calculated as $7.28 \times 10^{-10} m^2/s$ via equation 4.4.

$$D = 7.4 \times 10^{-8} \frac{\sqrt{\varphi_B MW_B T}}{\mu V_A^{0.6}} \quad (4.3)$$

where φ_B is the association parameter for the solvent, T is the absolute temperature, μ is the viscosity of the solution and V_A is the molar volume of the solute.

$$D_e = \frac{D_e \varepsilon}{\tau} \quad (4.4)$$

where ε is the porosity of the alcogels which was calculated with equation 4.5 and τ is the tortuosity of the alcogels given by “ $1/\varepsilon$ ”.

$$\varepsilon = \frac{\rho_{silica} - \rho_{aerogel}}{\rho_{silica}} \quad (4.5)$$

where ρ_{silica} is the density of pure silica ($\sim 2.19 g/cm^3$) and $\rho_{aerogel}$ is the density of the aerogel.

The initial and boundary conditions are given by:

$t=0, C_A(r,z,0) = 0$ (The concentration in the alcogel is zero at the beginning)

$t>0, C_A(R,0,t) = C_s$

$C_A(R,L,t) = C_s$ (The concentration at the external surface of the alcogel is constant as the concentration of the loading bath is assumed to be constant during the process.)

$$t > 0, \frac{\partial C_A}{\partial r}(0, z, t) = 0 \text{ due to symmetry}$$

where C_s is the surface concentration (mol/L) which was taken as the initial concentration in the loading solution.

Finite difference method was used to solve the representative equations. The differential equation and the boundary conditions were approximated by a point-wise discretization scheme which was divided into equal parts with increments of Δr and Δz in the r and z directions, respectively. The values of Δr and Δz were selected from the region giving stable results. Solutions obtained using Δr and Δz outside of this region resulted in unstable concentration profiles as shown in Appendix D. Transformed discretized equations as shown in Appendix A at each nodal point were used to obtain a set of algebraic equations involving the unknown values at the grid points. Then the algebraic equations were solved with Matlab and the concentration profiles as a function of position and time were obtained. Furthermore, the amount of loaded paracetamol was calculated by the summation of the amount of PC in each volume element as given by:

$$\text{Amount loaded (mol)} = \sum_i C_i \times \Delta V_i \quad (4.6)$$

where C_i is the average concentration in each volume element, ΔV_i is the volume of each volume element (V_{pore}/i) and i is the total number of volume elements. Since ΔV_i is identical for each element, it can be taken out of the summation. Then, by dividing the sum of C_i 's by the number of elements, we actually find an average concentration for the total pore volume. Then, the amount of PC loaded can be calculated by equation 4.7.

$$m_{PC \text{ loaded}} = C_{PC,avg} \times V_{pore} \times MW_{PC} \times 10^3 \quad (4.7)$$

where $C_{PC,avg}$ is the final average concentration of paracetamol inside the pores of the alcogel (mol/L), V_{pore} is the pore volume of the alcogel represented by “ $V_{total} \times \varepsilon$ ” (L), and MW_{PC} (g/mol) is the molecular weight of the paracetamol.

4.2.2 Modeling Results and Comparison with Experimental Data

Primarily, the hypothesis of negligible adsorption was tested based on the mass balance given by equation 4.8.

$$m_{ads} + m_{pore} + m_{bath} = m_{initial} \quad (4.8)$$

where m_{ads} is the amount of drug which is adsorbed on the alcogel, m_{pore} is the amount of drug which is inside the pore liquid, m_{bath} is the amount of drug which remains in the loading bath and $m_{initial}$ is the initial amount of drug which was used to prepare the initial solution.

The equation can be expressed more explicitly by equation 4.9:

$$m_{ads} + C_{eq}V_{pore}MW_{PC} + C_{eq}V_{bath}MW_{PC} = C_{in}V_{bath}MW_{PC} \quad (4.9)$$

where C_{eq} is the final equilibrium concentration in the pores and in the bath after the loading, V_{pore} is the volume of the pores, V_{bath} is the volume of the bath, C_{in} is the initial concentration of the loading bath and MW_{PC} is the molecular weight of paracetamol.

In our experiments, the total amount of paracetamol loaded to the alcogel (which was determined gravimetrically as explained in Experimental section) consists of PC adsorbed on the surface and also PC inside the pore liquid ($m_{ads} + m_{pore}$). Then, C_{eq} was calculated using Eq. 4.9 since V_{bath} and C_{in} are known. Then, the amount of paracetamol which was in the pore liquid was calculated by multiplying this equilibrium concentration with pore volume. Then, the amount adsorbed on the surface was calculated by using Eq.

4.8 and compared with the amount in the pore liquid. The adsorbed mass in all cases was substantially lower than the amount in the pore liquid showing that adsorption on the surface can be neglected.

Figures 4.11 and 4.12 show the change in the drug concentration as a function of time and position for initial concentrations of paracetamol in ethanol of 0.5 M and 0.8 M, respectively as predicted by the model. As shown in Figures 4.11 and 4.12, the concentration of the drug increases rapidly in regions closer to the surface whereas the concentration close to the center of the alcogel increases more slowly. Since the diffusion of paracetamol was from both the top and the bottom of the alcogel, a symmetric profile was obtained around $r=0$ axis as seen in Figures 4.11b and 4.12b. The loading rate decreased as the loading progressed which might be attributed to a reduced concentration gradient. It was observed that equilibrium is reached in about 5 hours with concentrations in the pore liquid and contacting the solution becoming equal.

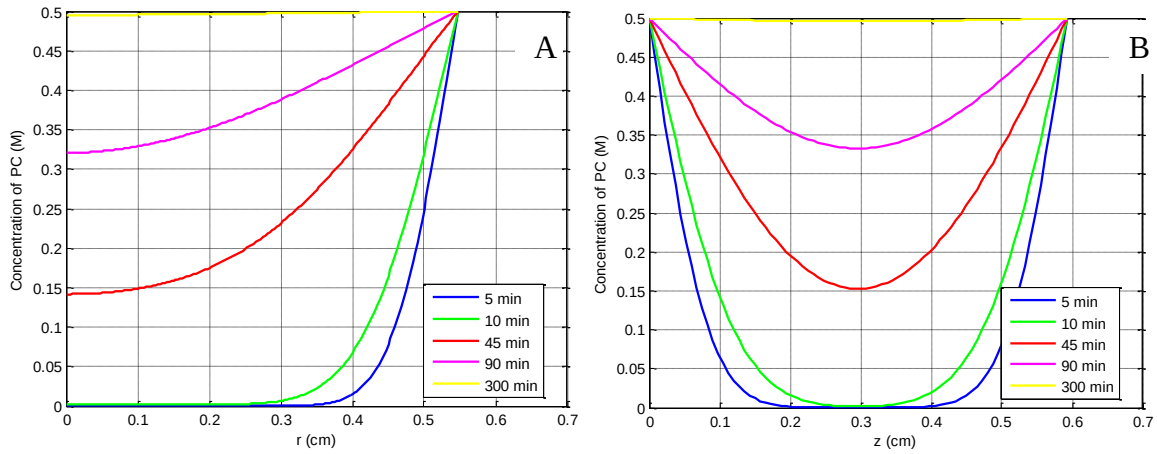


Figure 4.11: A) The concentration profile of paracetamol inside the alcogel with respect to r direction at $z=0.3$ cm B) The concentration profile of paracetamol inside the alcogel with respect to z direction at $r=0.125$ cm ($C_s=0.5$ M, alcogel with a radius of 0.54 cm and height of 0.6 cm, $\rho_{\text{alcogel}} = 0.135 \text{ g/cm}^3$)

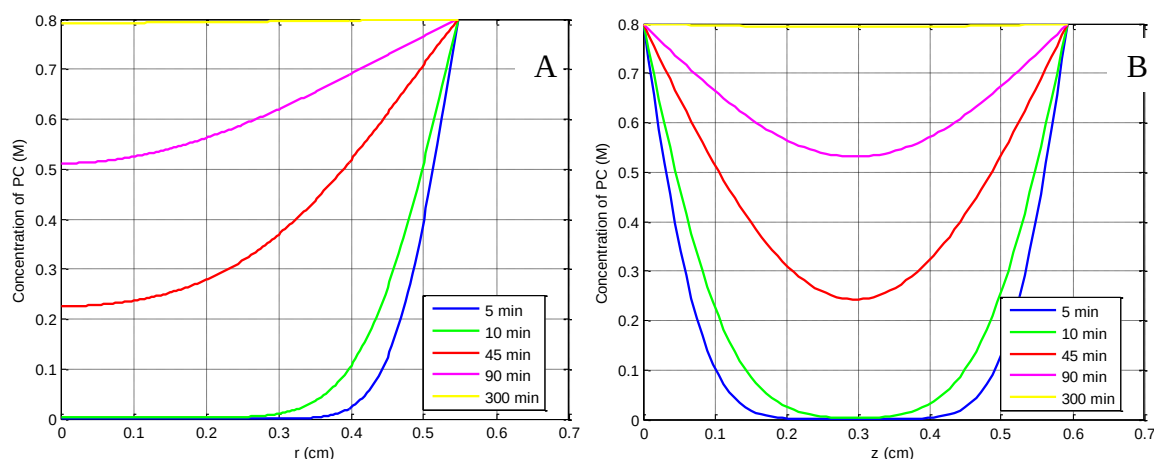


Figure 4.12: A) The concentration profile of paracetamol inside the alcogel with respect to r direction at $z=0.3$ cm B) The concentration profile of paracetamol inside the alcogel with respect to z direction at $r=0.125$ cm ($C_s=0.8$ M, alcogel with a radius of 0.54 cm and height of 0.6 cm, $\rho_{\text{alcogel}} = 0.139$ g/cm³)

Using the concentration profile in the alcogel obtained in the simulations, the amount of paracetamol in the pores of the silica alcogel was calculated theoretically as explained previously. Then, the experimental data were compared with those theoretical results to test the validity of the model. As shown in Figure 4.13 and 4.14 representing the amount of loading of the drug as a function of time and the change in the weight percent of the paracetamol inside the silica matrix, the model predictions agree well with the experimental data with model predictions slightly higher than experimental uptake values. These slight deviations might perhaps be attributed to the assumption that the alcogel disc is a perfect cylinder. Actually, the real alcogel disc volume is slightly lower because it has a small concave meniscus slightly reducing its volume. In addition, the assumption that all pores are open and could be filled with paracetamol solution may lead to higher loading amounts in simulations. However, a small fraction of pores might be closed or disrupted as

a result of simultaneous hydrolysis and condensation reactions, reducing the amount of expected total loading.

Moreover, as shown in Figures 4.13 and 4.14, the loading amounts can be controlled by changing the initial concentration of the loading solution as expected. Using a 0.8 M solution, loading as high as 40 wt. % could be achieved. This can even be increased further by increasing the concentration of the initial solution. The maximum loading can be obtained using a saturated solution. The solubility of paracetamol in pure ethanol is 1.21 moles/l [133] and therefore it should be possible to reach loadings as high as 56 wt% for an aerogel which has a density of 0.135 g/cm³. The combination of high pore volume of aerogels and high solubility of drugs in organic solvents coupled with supercritical drying lead to matrices with very high drug loadings which is quite difficult to achieve with other loading methods and matrix combinations [127, 134-136].

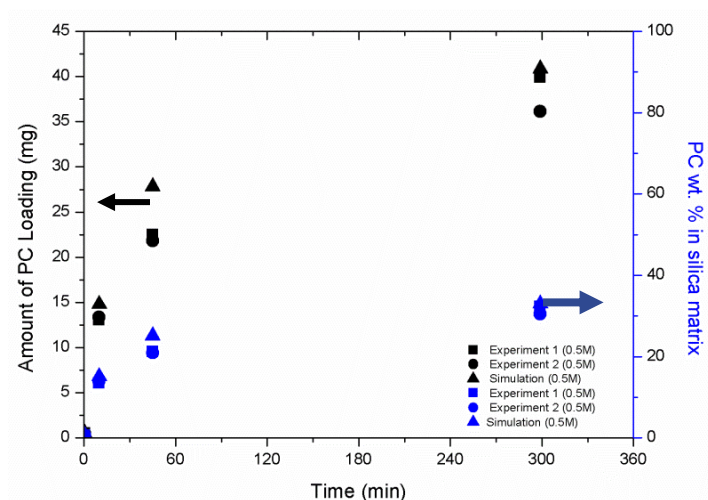


Figure 4.13: The amount of PC loading and weight percent of PC in silica matrix as a function of time for an initial concentration of 0.5 M. (Aerogels with a radius of 0.54 cm and height of 0.6 cm, $\rho_{\text{aerogel}} = 0.135 \text{ g/cm}^3$)

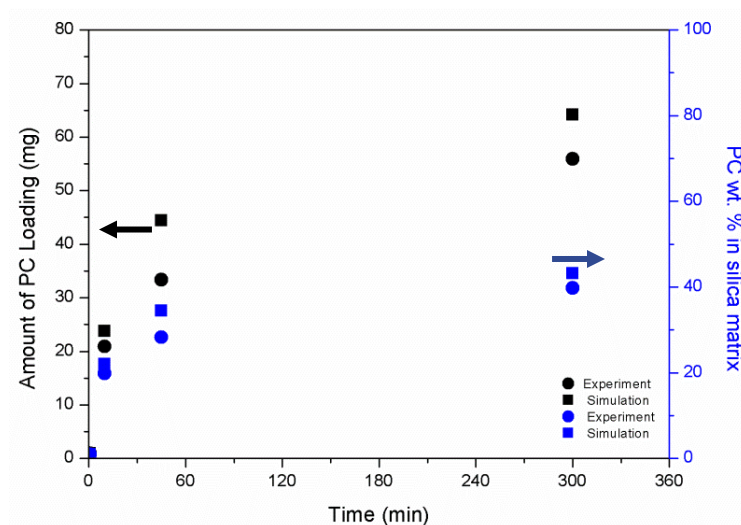


Figure 4. 14: The amount of PC loading and weight percent of PC in silica matrix as a function of time for an initial concentration of 0.8 M. (Alcogel with a radius of 0.54cm and height of 0.6 cm, $\rho_{\text{aerogel}} = 0.139 \text{ g/cm}^3$)

Furthermore, the loading from an ethanol solution was shown to reduce the time needed for drug loading which is usually in the order of 1-2 days in case of loading drug from supercritical phase due to factors such as longer times needed for the dissolution of the drug in the absence of stirring, the lower concentration of the drug in the initial scCO_2 solution due to low solubilities of the drug in scCO_2 and longer times to reach adsorption equilibrium [44, 134, 137]. In addition, the number of drugs which have appreciable solubility in scCO_2 is limited. Besides, the loading from supercritical phase requires higher temperatures and pressures than the ones which are actually needed for supercritical drying due to the solubility issues. Thus, the method which was used in this study could be advantageous as it can be applied to more pharmaceutical compounds in more suitable pressure and temperature conditions.

4.2.2.1 Effect of density (porosity) and tortuosity on the rate of loading

The porosity of the aerogel, which is directly related to its density, affects both the effective diffusion coefficient and the total amount of loading. As the porosity of the aerogel increased, the effective diffusion coefficient also increased resulting in faster diffusion. Moreover, an increased porosity meaning a higher pore volume would lead to the storage of more paracetamol inside and also enable an easier pathway for paracetamol to diffuse inside the pores. Thus, it is essential to produce aerogels with low densities to have high porosities and thus high amount of loadings.

As shown in Figure 4.15, increasing tortuosity values (which were selected in the range of values that were used for different aerogels) resulted in slower diffusion rates increasing the total loading duration. A greater tortuosity value indicates a more tortuous network retarding the diffusion of the substance inside the matrix which in turn increases the duration for the maximum amount of loading. The significant difference which arises as tortuosity value increases greatly indicates the importance of this parameter.

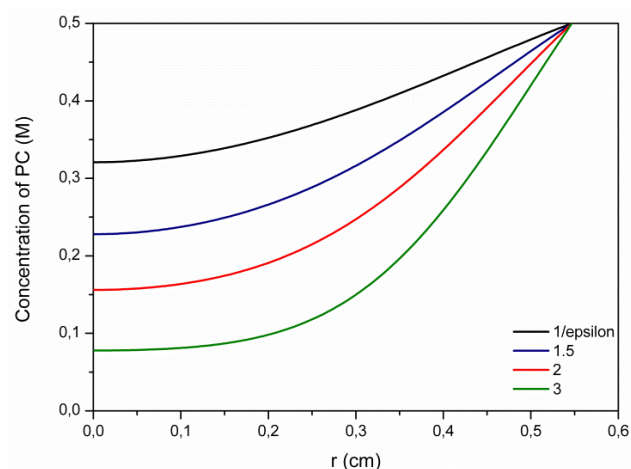


Figure 4.15: The concentration profile of paracetamol inside the aerogel with respect to r direction at $z=0.3\text{cm}$ at $t=90\text{ min}$ ($C_s=0.8\text{M}$, aerogel with a radius of 0.54 cm and height of 0.6 cm , $\rho_{\text{aerogel}} = 0.139\text{ g/cm}^3$, with different tortuosity values)

Furthermore, fitting the proposed model to experimental loading data could enable one to determine the tortuosity of the alcogels which are used in the experiments. There are hardly any data in the literature on the tortuosities of aerogels. In some studies, the tortuosity value was reported to be in the range of (1-6) including the calculated tortuosity value for this study [138-141] .

4.3 Supercritical Drying and PC Loaded Aerogels

After loading alcogels with the model drug, they were subjected to supercritical drying to obtain paracetamol loaded aerogels. Supercritical drying during which the pore liquid was extracted by scCO_2 also caused the precipitation of the drug due to its insolubility in scCO_2 . This drying process was actually similar to the gas antisolvent crystallization (GAS) process in which scCO_2 acts as an antisolvent to precipitate drug inside the pores. The ability of using this technique inside of the pores permitted a novel and facile approach to load substances into aerogels. Moreover, the process enabled higher amount of loadings and also offered an advantage for aerogels as it combined two processes such as drying and loading in a single one reducing the time and the expenses.

On the other hand, supercritical drying is known to be a crucial step in the aerogel synthesis. As shown in Figure 4.16, the samples which were not dried with scCO_2 were not able to retain their monolithic structures. Cracks appeared on their surface even after 5 minutes as shown in Figure 4.17A and B. Moreover, peaks belonging to the crystalline PC were not observed for the sample which was dried in the oven based on XRD analysis (See section 4.3.1, Figure 4.19). As the sample was more transparent compared to other 2 samples, it was suggested that the amount of PC was so low that it was not detectable by XRD analysis. Depending on the amount of drug loading, the samples were shown to be homogeneously (Figure 4.16) or partially loaded (image not shown). As shown in XRD

analysis, different drying techniques have resulted in distinct crystal structures based on the shifts of the XRD peaks (Figure 4.19).



Figure 4.16: Comparison of 3 drying methods: (from left to right) Supercritical drying, oven drying at 50°C, ambient pressure drying

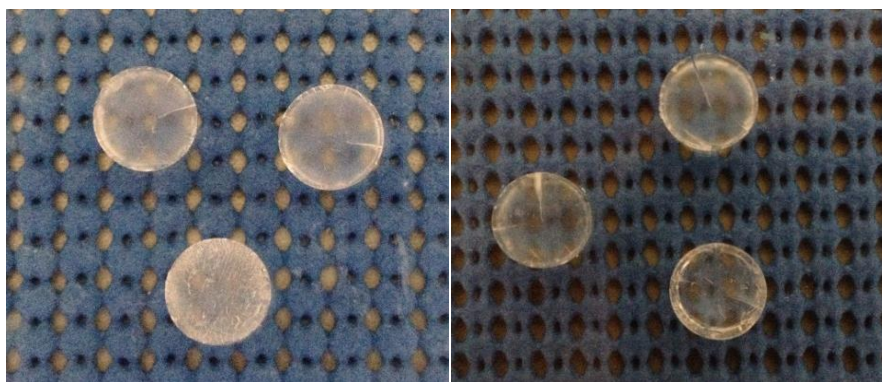


Figure 4.17: Photos of paracetamol loaded silica xerogels 5 minutes after the beginning of drying via A) ambient pressure B) in oven at 50°C

4.3.1 Characterization of PC Loaded Aerogels

Supercritical drying of the PC loaded alcogels resulted in monolithic aerogels with different amount of PC loadings. As shown in Table 4.3, the loading of PC was affected by the initial concentration of the PC solution in which silica alcogels were immersed. An increased initial concentration resulted in an increased density for the same sample volume indicating a higher drug loading as expected. Moreover, the use of a higher initial

concentration also resulted in a homogeneous dispersion of the drug in the matrix at the end of the drying. Conversely, a low initial concentration such as 0.25 M resulted in a loading only on the surface of the aerogel matrix. This loading was mostly similar to a PC coating rather than a homogeneous distribution of the drug inside the matrix. This was related to the diffusion of paracetamol inside the pore liquid until it reaches the saturation concentration in the ethanol-CO₂ mixture and begins to precipitate. When the concentration of loaded paracetamol was low inside the pores, paracetamol molecules had more time to diffuse before precipitating.

Table 4.3: Density of the PC loaded silica aerogel samples

Initial PC Concentration in the loading solution	Average Density (g/cm ³)
0.25M	0.160±0.003
0.5 M	0.184±0.005
0.75 M	0.229±0.010

After supercritical drying, monolithic aerogels which were loaded with PC was subjected to IR and XRD analysis as seen in Figures 4.18 and 4.19. As shown in IR spectra, the peaks belonging to pure paracetamol were also visible in the PC loaded samples indicating that PC should be intact in the aerogel matrix. Furthermore, the intensity of the peaks which was taken from the inside of the loaded aerogel was sufficiently high which indicated that paracetamol diffused to the center of the alcogel.

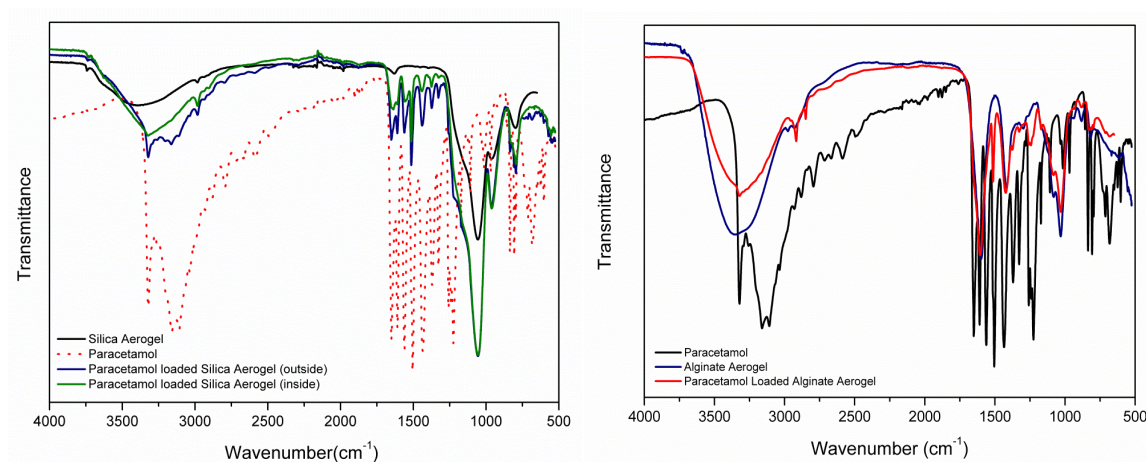


Figure 4.18 A) IR Spectra of silica aerogel, paracetamol and silica aerogel loaded with paracetamol. B) IR Spectra of alginate aerogel, paracetamol and alginate aerogel loaded with paracetamol.

Moreover, the crystallinity of the PC was observed from the XRD data as seen in Figure 4.20. When the XRD spectrum was analyzed, the intensity of the peaks was higher for an initial solution of 0.75 M compared to 0.5 M. However, the peaks for the samples prepared with lowest concentration of 0.25 M were not easily distinguishable in the spectra.

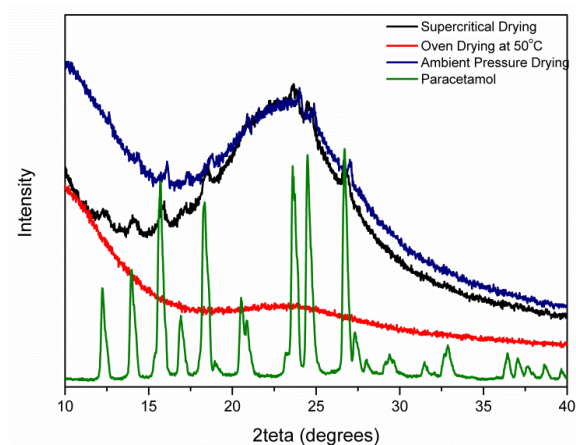


Figure 4.19: XRD spectra of paracetamol loaded silica aerogels dried with different methods

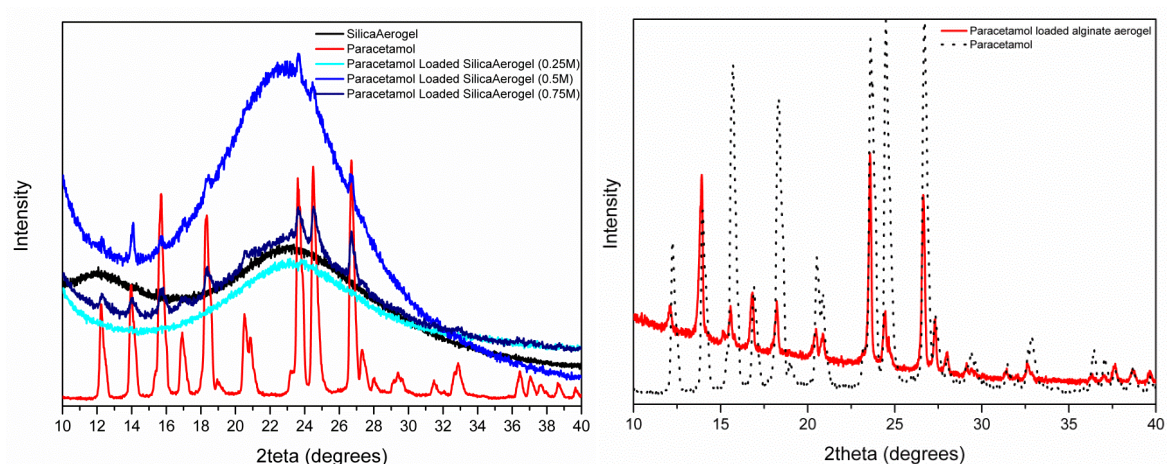


Figure 4.20: A) XRD spectra of silica aerogel, paracetamol and silica aerogel loaded with paracetamol with different initial concentrations. B) XRD spectra of paracetamol and alginate aerogel loaded with paracetamol.

4.4 Drug Release

The release experiments were performed using a PBS medium (pH 5.8). The drug loaded aerogels were placed on a wire mesh to prevent their contact with the magnetic stirring bar which could physically damage the aerogels causing a different release behavior. Then the aerogels were immersed in a glass vial filled with the fresh release medium. Subsequently, the release experiments of PC were conducted at 37°C under constant stirring. Different stirring rates were tested in order to show the effect of the rate of stirring on the release kinetics as shown in Figure 4.21. The experiments were then conducted using the range of the stirring rate that has no effect on the rate of drug release to eliminate convective mass transfer.

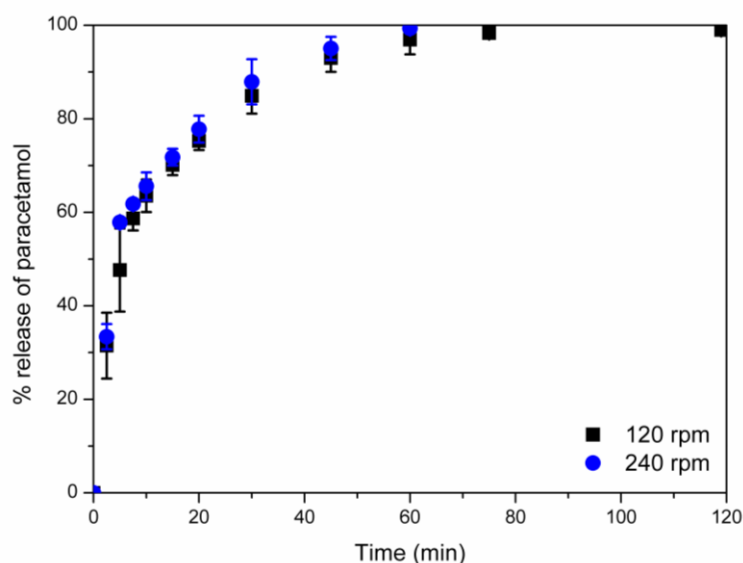


Figure 4.21: The comparison of different stirring rates on the kinetics of release rate

During release experiments, hydrophilic silica aerogel collapsed when placed inside the release medium with the instant penetration of the liquid in its pores since it cannot withstand the capillary pressure created inside the pores. Thus, initially a burst release was observed. However, the integrity of the PC loaded silica aerogels endured longer times with increasing amount of PC loading which can be attributed to the presence of PC inside the hydrophilic matrix keeping it intact. In the case of silica aerogel, the release of paracetamol is mainly governed by its diffusion from the pores of the matrix coupled with the dissolution of the precipitated excess drug. Even if the matrix is degraded, the diffusion continues from the pores of the smaller pieces.

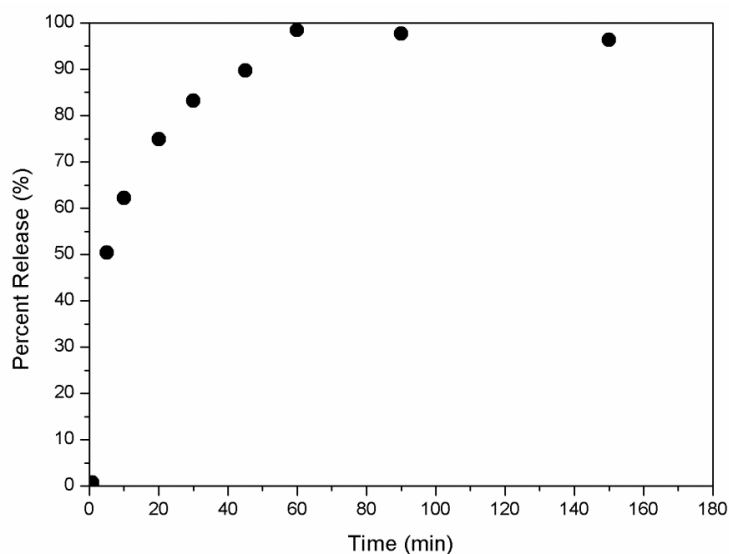


Figure 4.22: The release of PC from silica aerogel in PBS buffer (pH:5.8), $C_{in} = 0.5$ M.

In order to show the effect of an alginate aerogel layer around the silica aerogel on the release kinetics, the release of paracetamol from a native silica aerogel and silica aerogels encapsulated with alginate aerogel layer was also compared in PBS buffer (pH: 5.8) at the same conditions. The alginate aerogel layer prevented the fast collapse of the silica aerogel when contacted with the release medium, swelled with time, and thus reduced the burst drug release and thereby slightly retarded the drug release as shown in Figure 4.23. As the thickness of the alginate aerogel layer was only around 1-2 mm, the release was not significantly affected but comparably slowed down indicating that these hybrid aerogels are promising as drug delivery systems to achieve retarded drug release rates. Increasing the concentration of the alginate in the initial solution and increasing the thickness of the layer are expected to result in a slower release.

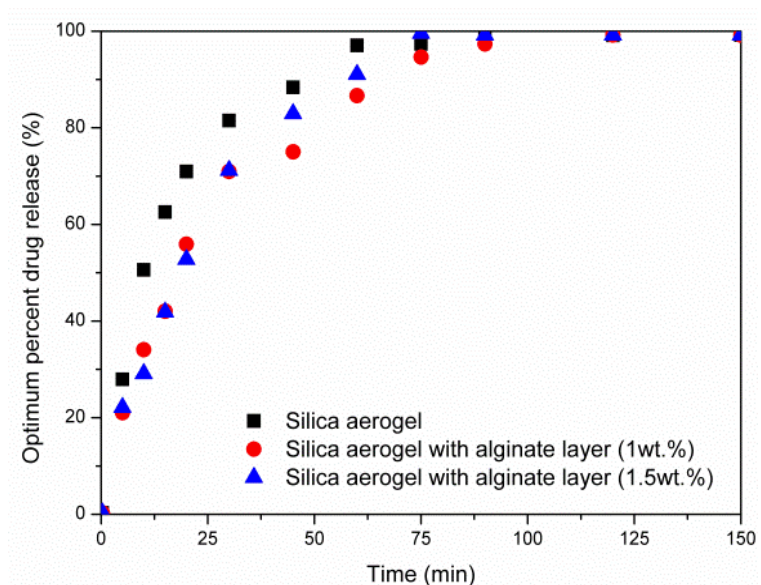


Figure 4. 23: Comparison of paracetamol release in PBS buffer (pH:5.8) from native silica aerogel and silica aerogel encapsulated with alginate aerogel layer with different weight percents.

For the alginate aerogels, the drug release profile was similar to silica aerogels . Due to the flexibility of the alginate chains as it was also observed for hybrid aerogels, alginate aerogels did not degrade when immersed in the release medium. Besides, they primarily shrank and then slowly swelled as shown in Figure 4.24. As a result, a burst release was initially seen followed by a slower drug release rate.

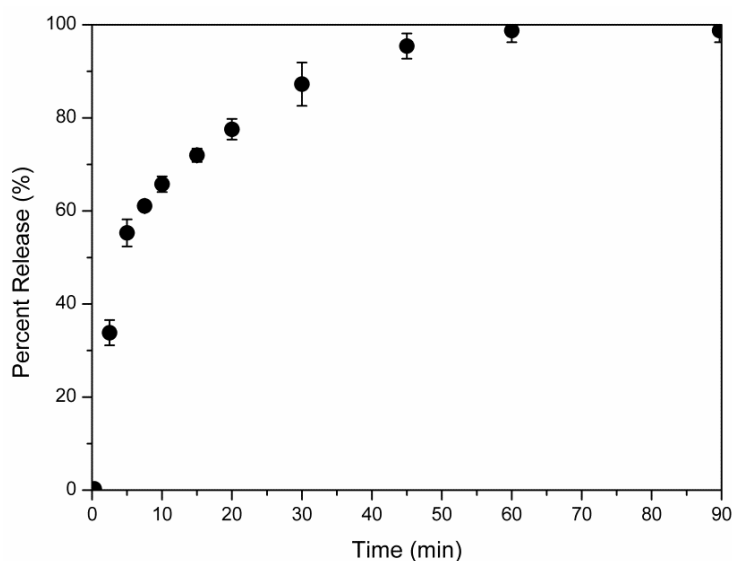


Figure 4.24: The release of PC from alginate aerogel in PBS buffer (pH:5.8), $C_{in} = 0.5M$.

4.4.1 Mathematical Modeling of Drug Release

A model was developed to describe the release from a spherical porous alginate aerogel loaded with paracetamol. Mass transfer from the pores of this drug loaded aerogel to the surrounding solution was described by partial differential equations along with appropriate boundary conditions. The underlying mechanisms of the release process were be the dissolution and the diffusion of the drug and the swelling of the matrix. All these physical phenomena were incorporated in the mathematical model.

One dimensional diffusion of paracetamol through radial direction inside the pores of the spherical alginate aerogel was modeled based on Fick's second law. External mass transfer by convection was neglected due to the constant stirring conditions. The matrix was assumed to be instantly wetted with the release medium dissolving some of the solid drug and causing all pores to be filled with a saturated paracetamol solution at the beginning. The initial drug distribution inside the matrix was taken as homogeneous and the same everywhere. The results of the swelling tests were also incorporated to the model

by modifying the radius in r-direction based on the experimental swelling data and changing the boundary conditions accordingly. Since the amount of the loaded drug was greater than its solubility at the release conditions, the presence of solid drug present inside the pores was also taken into account. Consequently, the dissolution of the drug was also considered in the model. Therefore, drug was assumed to be in dissolved or solid state which were described by $C(r,t)$, and $S(r,t)$, the concentration of dissolved drug in the pores and the concentration of the solid drug in the pores respectively.

The mass balance in a differential volume element in the spherical aerogel for the mass transfer of paracetamol is given by:

$$N_{A,r}4\pi r^2 - N_{A,r+\Delta r}4\pi r^2 - \frac{\partial S}{\partial t}4\pi r^2\Delta r = \frac{\partial C_A}{\partial t}4\pi r^2\Delta r \quad (4.10)$$

where r represent the direction that diffusion occurs in the gel and $N_{A,r}$ (given as $N_{A,r} = -D_e \frac{dC_A}{dr}$) is the diffusive flux in r direction.

The partial differential equation obtained from this mass balance in a differential volume element in the alcogel is given by:

$$\frac{\partial C_A}{\partial t} = D_e \frac{\partial^2 C_A}{\partial r^2} + \frac{2}{r} D_e \left(\frac{\partial C_A}{\partial r} \right) - \frac{\partial S}{\partial t} \quad (4.11)$$

$$\frac{\partial S}{\partial t} = -k' \left(\frac{S}{S_0} \right)^{\frac{2}{3}} (C_s - C_A) \quad (4.12)$$

where C_A is concentration of dissolved paracetamol in the pores of the alcogel (mol/L), S is the concentration of solid paracetamol inside the pores (mol/L), S_0 is the initial concentration of the solid paracetamol (mol/L), C_s is the saturation concentration of paracetamol in PBS (mol/L), D_e is effective diffusion coefficient (m^2/s) of paracetamol in PBS inside the pores, R is radius of the alcogel (m), t is time (s).

Equation 4.11 is the one dimensional diffusion equation in r direction for a spherical geometry with an additional term resulting from the drug dissolution [142]. Equation 4.12 is a reformulated Noyes-Whitney equation which assumes that the surface area of the non-dissolved drug particles is proportional to the volume to the power $2/3$. This assumption was already applied for different cases to describe the dissolution of dispersed materials [143]. It is valid as long as solid drug is present in the pores. When all solid drug molecules are dissolved, the term should be excluded to end up with a one dimensional diffusion equation only [142].

Diffusion coefficient of paracetamol in PBS was found using Wilke-Chang equation (Equation 4.3) for diffusion in liquids which is usually used to estimate the diffusion coefficients of low molecular weight solutes in dilute solutions which is suitable for our solute/solvent pair. The value for diffusion coefficient was calculated as $1.28 \times 10^{-9} \text{ m}^2/\text{s}$. Then, the effective diffusion coefficient was calculated as $1.20 \times 10^{-9} \text{ m}^2/\text{s}$ via equation 4.13. The effective diffusion coefficient was also calculated based on the experimental data and was found as $1.77 \times 10^{-9} \text{ m}^2/\text{s}$ which was close to the value found by the Wilke-Chang Equation (Appendix E). As the matrix swells, its dimensions change. Therefore, the diffusion coefficient might also change correspondingly. Since the aerogel matrix had already a very high porosity, the diffusion coefficient should not be significantly affected because of the swelling and thus was taken as constant in the model and calculated using:

$$D_e = \frac{D \times \varepsilon}{\tau} \quad (4.13)$$

where D is the diffusion coefficient (m^2/s), ε is the porosity of the alcogels which was calculated with equation 4.14 and τ is the tortuosity of the alcogels given by “ $1/\varepsilon$ ”.

$$\varepsilon = \frac{\rho_{\text{alginate}} - \rho_{\text{aerogel}}}{\rho_{\text{alginate}}} \quad (4.14)$$

where ρ_{alginate} is the density of alginic acid ($\sim 1.6 \text{ g/cm}^3$) and ρ_{aerogel} is the density of the aerogel.

The initial and boundary conditions are given by:

$t=0, C_A(r,0) = C_{\text{sat}}$ (Initially, the concentration in the alcogel is at the saturation concentration)

$S_A(r,0) = S_s$ (Initially, the concentration of solid drug in the alcogel is constant)

$t>0, C_A(R(t),t) = 0$

$S_A(R(t),t) = 0$ (The concentration at the external surface of the alcogel is zero due to the sink conditions.)

$t>0, \frac{\partial C_A}{\partial r}(0,t) = 0$ due to symmetry

where C_{sat} is the saturation concentration (mol/L) which was taken as the initial concentration of the dissolved drug inside the pores.

The release process starts with the penetration of the release medium into the pores of the aerogel due to capillary effect [123]. Once the pores are filled with liquid, the drug dissolves instantaneously leading to a saturated drug solution in the pores and starts to diffuse outside of the matrix. Solid drug remaining in the pores is not available for diffusion but replenishes the solution and keep the solution concentration in the pores at the saturation level until all of it is dissolved. Simultaneously, the diameter of the matrix also slowly increase due to swelling. As the diffusion progresses, the concentration of the solid drug is reduced to a critical concentration which might correspond to the adsorbed drug molecules forming a monolayer. This small amount could be estimated based on the surface area of the matrix and the size of the drug as shown in Equation 4.15.

$$m_{\text{ads}} = \left(\frac{SA_{\text{aero}} \times m_{\text{aer}}}{PA_{\text{PC}} \times N_A} \right) MW_{\text{PC}} \quad (4.15)$$

where m_{ads} is the maximum amount of adsorbed paracetamol molecules (g), SA_{aero} is the surface of the aerogel (m^2/g), m_{aer} is the mass of the native aerogel which is loaded with paracetamol (g), PA_{PC} is the projected area of a paracetamol molecule (m^2), N_A is the avogadro's number and MW_{PC} is the molecular weight of the paracetamol (g/mol).

However, the calculated value represents the maximum amount of paracetamol which might be adsorbed on the aerogel. As the loading is performed from an ethanol solution of the paracetamol, actually this amount can be not reached. Nevertheless, even if the amount could be negligible compared with the total amount of drug loading, it might retard the release through the end of the release process. This effect was also included in the model with a change in the dissolution rate constant.

Finite difference method was used to solve the representative equations. The differential equations and the boundary conditions were approximated by a point-wise discretization scheme which was divided into equal parts with increments of Δr in the r direction. The value of Δr was selected from the region which gave stable results. Runs outside of this region resulted in unstable concentration profiles as shown in Appendix D. Transformed discretized equations (as shown in Appendix A) at each nodal point were used to obtain a set of algebraic equations involving the unknown values at the grid points. Then the algebraic equations were solved with Matlab and the concentration profiles as a function of position and time were obtained. Furthermore, the amount of paracetamol which was released was calculated using the summation of the amount of PC in each volume element as given by equation 4.5 and the initial amount of loading.

Several assumptions were made while developing the theoretical model. The transport of the drug and its dissolution rate were described by the Fick's second law and Noyes-Whitney equation, respectively. The effective diffusion coefficient was assumed to be independent of the concentration. The initial drug distribution inside the matrix was taken as homogeneous and the same everywhere. However, the concentration of the drug

should be slightly larger closer to the outside surface. The penetration rate of the release medium was accepted to be faster than the diffusion of the drug. Thus, initially all pores were assumed to be completely filled with the release medium and solid drug was immediately dissolved to form a saturated solution in the pores. Moreover, the dissolution rate constant was adjusted with the experimental data. It was chosen in such a range that it does not significantly affect the release profile. Finally, perfect sink conditions were maintained throughout the process as the change in the concentration of the release medium was negligible.

To validate our model with appropriate experiments, the amount of drug which was released was determined in order to enable a comparison between the model predictions and experiments. Thus, the change in the concentration of the release medium was monitored through the experiment and the amount of drug which was released was calculated at specified time points.

4.4.2 Modeling Results and Comparison with Experimental Data

The release kinetics of paracetamol from alginate aerogels based on the mathematical model was compared with the experimental data. It was shown that although diffusion may be the dominant process, other effects such as the dissolution of the solid drug, the swelling of the matrix and the desorption process can not be neglected to achieve good agreement with model predictions.

Primarily, it was assumed that all pores were filled with a saturated solution of paracetamol neglecting the presence of an non-dissolved drug for the theoretical model. As a result, the total amount of drug release reached only 25-30% of the total amount of drug loading (Figure 4.25, Stage 1). Therefore, the non-dissolved drug was also taken into account. In that case, as the concentration in the pores can not exceed the saturation concentration, the dissolution of the solid drug was included. As a result, the total amount

of drug release matched with the total amount of drug loading. Consequently, swelling of the alginate aerogel was also included in the model (Figure 4.25, Stage 2). However, the rate of drug release was still higher than the experimental release rate. Thus, to even reduce the rate of drug release more, the dissolution rate of the solid drug which was represented by k' , was decreased after reaching a critical concentration as explained in Section 4.4.1 (Figure 4.25, Stage 3). As a result, a similar release behavior was obtained when compared with the experimental data. However, the predicted release rate was still higher. Finally, the tortuosity of the aerogel was modified by comparing the experimental data with model predictions. The tortuosity was increased to retard the release indicating that the diffusion pathway of the paracetamol might be more tortuous slowing its movement. In conclusion, the deviations of the model predictions from the experimental data were significantly reduced and a good agreement was obtained as shown in Figure 4.26.

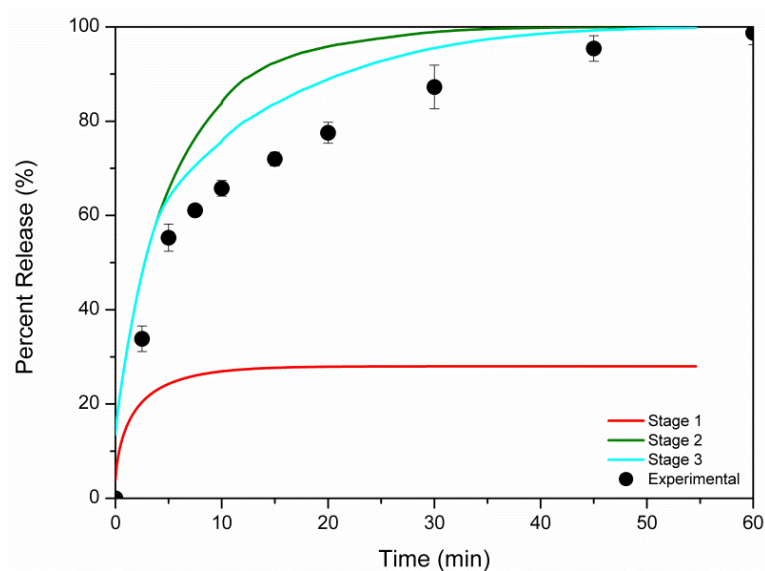


Figure 4. 25: Comparison of experimental release profile with model predictions

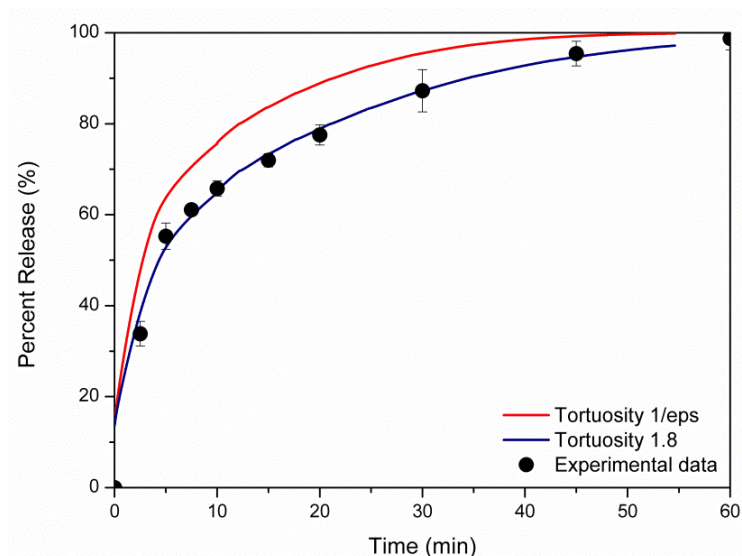


Figure 4. 26: Effect of tortuosity on the model predictions

The dissolution rate constant was also modified in order to see the effect of increasing dissolution rate constant on the release kinetics. As shown in Figure 4.27, the release rate did not significantly change when the k' value was increased up to 10 fold ($k'3$). Thus, the selected value was in a suitable range.

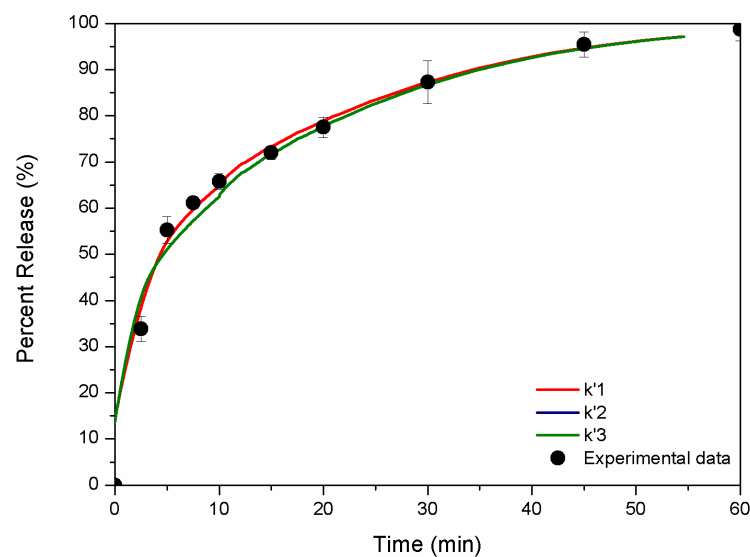


Figure 4. 27: The effect of increasing k' value on the model predictions

The concentration change with respect to r at various times is given in Figure 4.26. As shown in the figure, the concentration at the beginning of the release process is relatively high. Only the points closer to the surface of the aerogel had some reduced concentrations due to the diffusion process. As expected, the concentrations closer to the center decreased slowly as the distance for diffusion is the longest. The effect of the increase in the radius due to swelling can also be seen in Figure 4.28. The concentration profile was calculated based on the new radius values accordingly.

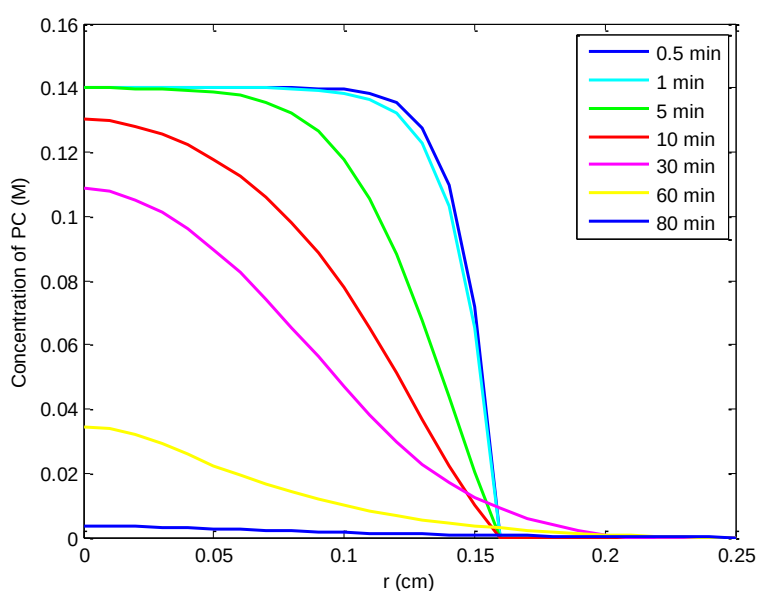


Figure 4. 28: Change in the concentration of dissolved drug with respect to radius at specified time points.

The model could be further modified by using concentration dependent diffusion coefficients as well as different dissolution profiles rather than Noyes-Whitney equation if necessary. The mathematical model can also be adjusted for different geometries such as cylindrical devices or planar sheets.

4.5 Results of cell viability tests

The cell viability tests showed that all of the investigated aerogel types were non-toxic to human fibroblasts cells. At day 1, they slightly reduced the viability which can be explained by fibroblast cells trying to get used to the new environment. Later, at day 4, it was seen that the viability was restored for silica aerogels and it was even higher for native alginate aerogels and silica aerogels encapsulated with alginate aerogels. It can be concluded that fibroblasts might be using alginate which is a natural polysaccharide for growing and thus increasing their viability. Thus, encapsulating silica aerogels or other materials with alginate aerogel layers can protect the cells from the core material.

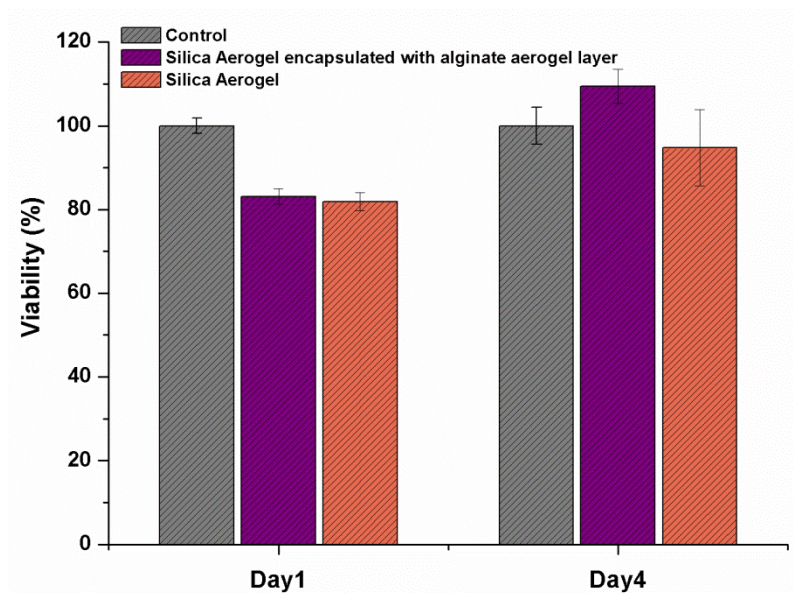


Figure 4.29: Viability of human dermal fibroblasts with native silica aerogels and silica aerogels encapsulated with alginate aerogel layers.

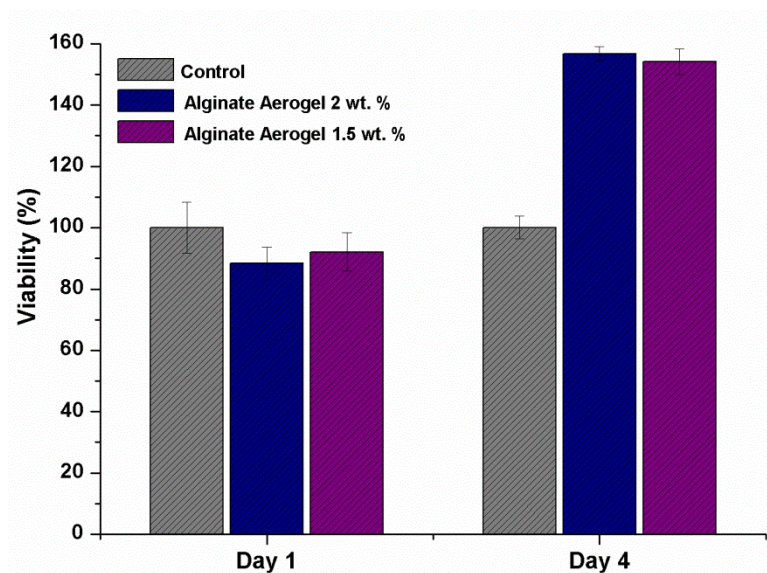


Figure 4.30: Viability of human dermal fibroblasts with alginate aerogels 2 wt. % and 1.5 wt. %.

Chapter 5

CONCLUSION AND FUTURE WORK

Over the past few decades, research efforts in the area of drug delivery have been more and more directed towards nanoporous materials. In this study, both inorganic and organic aerogels such as silica aerogel and alginate aerogel were investigated as drug delivery vehicles. Moreover, a novel layered material consisting of these two distinct aerogels was prepared for the first time by encapsulating a silica aerogel with an alginate aerogel layer. Final aerogel samples had high surface areas such as 950 m²/g and 400 m²/g for silica and alginate aerogels respectively. Furthermore, all samples were mesoporous up to 97% porosity with very low densities.

To test the samples as drug delivery vehicles, paracetamol was chosen as the model drug due to its high solubility in ethanol and no/limited solubility in scCO₂. Then, synthesized alcogels were successfully loaded by contacting them with a solution of PC in ethanol. Loadings as high as 40 wt. % for silica aerogels and 75 wt.% for alginate aerogels were obtained. It was shown that the loading amounts could be controlled by changing the initial concentration of the loading solution. Moreover, it can be concluded that the maximum loading can be obtained using a saturated solution. The loading of the paracetamol was further investigated by simulations. Partial differential equation representing the diffusion in the system was developed and solved using finite difference method. The weight percent of the paracetamol in the silica alcogel matrix was found to be

in good agreement with model predictions. Developed 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 without any adjustable parameters. The model predictions might as well show what time is required for loading samples with different dimensions. The model can also be further modified to be used for different matrices and also for different drugs.

The use of supercritical drying after drug loading resulted in precipitation of the paracetamol in the pores of the aerogels similar to a gas anti solvent process. It was shown that high drug loadings can be achieved via this method inside the pores while keeping the monolithic structure and the porous characteristics intact. Gas antisolvent processes have certainly a bright future especially for drug delivery systems as they allow producing particles to a great flexibility for a variety of compounds. Furthermore, the ability of using this technique inside the pores permits a novel and facile approach to load substances into aerogels which are becoming increasingly important in various fields. The process also enables high amount of loadings and also offers an advantage for aerogels as it combines two processes such as drying and loading in a single one reducing the time and the expenses.

There is an increasing research on aerogels as drug delivery systems, thus different release profiles have been already achieved with various aerogel types. In this study, it was shown that aerogels can be used for both fast acting or retarded release agents. Rapid degradation of the silica aerogel matrix or fast release of the drug loaded on the surface leading to a burst release can actually be useful for fast acting medications since a higher percent of the loaded drug will be released in a short duration. Furthermore, the remaining drug will continue to be slowly released by diffusion from the pores to keep the drug level in the desired range. On the other hand, the synthesized hybrid aerogels might be used for a retarded drug release. As the alginate aerogel layer would reduce the burst release, it would

decrease the rate of drug release. The ability of changing the porous structure of the alginate aerogel layer and its thickness as desired would result in a controlled release rate. Furthermore, the layers were not only expected to protect the core and to retard the release of the drug but also to be used as a delivery device capable of carrying different molecules at the same time for sequential release.

To further understand the underlying mechanisms of the drug release from swelling alginate aerogels, another theoretical model was developed. The release model was based on the diffusion and the dissolution of the drug, the swelling of the matrix and the desorption of the drug from the matrix. The dissolution rate constant, the tortuosity of the matrix were adjusted to improve the theoretical prediction. Current model is quite suitable for further development and for the incorporation of other physical phenomena if any. Consequently, the model could be used for any other drug and different carriers which might behave differently in a release medium.

Overall, this dissertation contributes to understanding of the use of aerogels as drug delivery agents showing that both inorganic and organic aerogels present a huge potential in the field of drug delivery. The intended loading or release of the active ingredients which are also dependent on the structural properties can be modified by tailoring the synthesis conditions. Taking into account the increasing importance of aerogels in a variety of application areas, their use in drug delivery can be expected to grow in the coming years. Besides, developed theoretical models are expected to reduce the required experimental work which would further increase the importance of these materials and lead to their more frequent use in the bionanotechnology field.

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APPENDIX A:

$$\frac{\partial^2 f}{\partial x^2}(i, k) = \frac{f(i+1, k) - 2f(i, k) + f(i-1, k)}{dx^2}$$

$$\frac{\partial f}{\partial x}(i, k) = \frac{f(i+1, k) - f(i-1, k)}{2dx}$$

$$\frac{\partial f}{\partial t}(i, k) = \frac{f(i, k+1) - f(i, k)}{dt}$$

APPENDIX B: Matlab Code for Loading Paracetamol inside of a cylindrical silica**alcogel**

```

>Loading to a cylindrical aerogel (r & z directions)
%Finite Difference Method

clear all,close all, clc

%Physical Properties of Paracetamol
density = 0.135;
porosity = (2.19-density)/2.19;
eps = porosity; % porosity
tort = 1/eps; % tortuosity
%tort =1.5; % changing tortuosity
Te = 22; % temperature in celcius
MW = 46.07; % molecular weight of the solvent
S = 1.5; % parameter
T = Te + 273.15; % temperature in kelvin
mu = 1.242; %viscosity in cp
MV = 119.98; % molar volume of the solute in cm3/mol
D = (7.4*10^-8)*(sqrt(MW*S))*T/(mu*(MV^0.6)); %Wilke Chang in cm2/s
D = D*10^-4; % Diffusion coefficient in m2/s
Dp = D*eps/tort; %Effective Diffusion Coefficient

t(1)=0; %initial time
tfinal=2700; % final time point
dt=0.2;
t=t(1):dt:(tfinal);
L= 0.0064; % Length of the material (m)
Da=0.0108; % Diameter in meter
r=Da/2; % Radius in meter
dt=0.2; % mesh in time
dr=0.000036; %mesh in r direction
dz=0.00008; %mesh in z direction
numr=r/dr;
numt=t/dt;
numz=round(L/(dz));

C=zeros(numr,numz,length(t)); % C inside alcogel is initially zero

% INITIAL CONDITIONS
% Surface of the alcogel is directly in contact with the PC solution so
% that the concentration is 0.5 and does not change
C(numr, :, :)=0.5;
C(:, 1, :)=0.5;
C(:, numz, :)=0.5;

```

```

for k=1:length(t)

    t(k+1)=t(k)+dt;

    for i=1:numr-1
        for j=2:numz-1

            if (i==numr) % Center of the alcogel in r direction
                C(numr,1:numz,k)=0.5;

            elseif (i==1) % Surface of the alcogel in r direction
                C(1,:,k)=(-C(3,:,k)+4*C(2,:,k))/3;
                %C(1,1:numz,k) = C(i+1,:,k);
            elseif (j==1) % Top surface of the alcogel in z direction
                C(1:numr,1,k) = 0.5;

            elseif (j==numz) % Bottom surface of the alcogel in z direction

                C(1:numr,numz,k)= 0.5;

            else

                % Inside of the alcogel except the surface points
                C(i,j,k+1)= C(i,j,k) + (Dp.*dt./(dr.^2)).*(C(i+1,j,k)-
                2.*C(i,j,k)+C(i-1,j,k))+(Dp.*dt./(r*2*dr)).*(C(i+1,j,k)-C(i-1,j,k))+
                (Dp.*dt./(dz.^2)).*(C(i,j+1,k)-2.*C(i,j,k)+C(i,j-1,k));
            end
        end
    end
end
%Final concentrations (final time point) at all points, 2D
AA = C(:,: ,k);
for m=1:numr
    M(m) = mean(AA(m,:));
end
avg = mean(M);

sum = 0;
part = zeros(numr,numz);
volume = 0;
for i=1:numr
    for j=1:numz
        part(i,j)= AA(i,j).*(dz.*dr).*(10^3)*pi*r*eps;
        vol = dz.*dr.*(10^3)*pi*r;
    end
end

```

```

    volume = volume + vol;
    sum = sum + part(i,j); % number of moles
end
end
mass = sum*151.163*1000; %amount of paracetamol inside of the alcogel
(mg)
avgmass = avg*volume*eps*151.163*1000;

s= C(1:numr,1:numz,1500)';
m= C(1:numr,1:numz,3000)';
n= C(1:numr,1:numz,13500)';
a= C(1:numr,1:numz,90000)';
aa=C(1:numr,1:numz,27000)';
rr =(0:dr:(numr-1)*dr)*100;
figure(1)
plot(rr,  s(40,:),'r','linewidth',2); xlabel('r(cm)'); ylabel(
'Concentration of PC (M)');
hold on
grid
plot(rr,  m(40,:),'g','linewidth',2); xlabel('r (cm)'); ylabel(
'Concentration of PC (M)');
plot(rr,  n(40,:),'r','linewidth',2); xlabel('r (cm)'); ylabel(
'Concentration of PC (M)');
plot(rr,  aa(40,:),'m','linewidth',2); xlabel('r (cm)'); ylabel(
'Concentration of PC (M)');
plot(rr,  a(40,:),'y','linewidth',2); xlabel('r (cm)'); ylabel(
'Concentration of PC (M)');
legend('5 min','10 min','45 min','90 min','300 min','Location','best');

zz =(0:dz:(numz-1)*dz)*100;
figure(2)
plot(zz,  s(:,40),'r','linewidth',2); xlabel('z(cm)'); ylabel(
'Concentration of PC (M)');
hold on
grid
plot(zz,  m(:,40),'g','linewidth',2); xlabel('z (cm)'); ylabel(
'Concentration of PC (M)');
plot(zz,  n(:,40),'r','linewidth',2); xlabel('z (cm)'); ylabel(
'Concentration of PC (M)');
plot(zz,  aa(:,40),'m','linewidth',2); xlabel('z (cm)'); ylabel(
'Concentration of PC (M)');
plot(zz,  a(:,40),'y','linewidth',2); xlabel('z (cm)'); ylabel(
'Concentration of PC (M)');
legend('5 min','10 min','45 min','90 min','300 min','Location','best');

```

APPENDIX C: Matlab Code for Drug Release from a spherical alginate aerogel

```

%Release from a spherical aerogel (only r-direction)
%Finite Difference Method

clear all,close all, clc
%Physical Properties of Paracetamol
density = 0.055;
porosity = (1.6-density)/1.6;
eps = porosity; % porosity
tort = 1/eps; % tortuosity
%tort = 1.8; %BEST ONE
Te = 37; % temperature in celcius
MW = 18.02; % molecular weight of the solvent
S = 2.6; % parameter
T = Te + 273.15; % temperature in kelvin
mu = 0.692; %viscosity in cp
MV = 119.98; % molar volume of the solute in cm3/mol
D = (7.4*10^-8)*(sqrt(MW*S))*T/(mu*(MV^0.6)); %Wilke Chang in cm2/s
D = D*10^-4; % Diffusion coefficient in m2/s
Dp = D*eps/tort; %Effective Diffusion Coefficient

t(1)=0; %initial time
tfinal=24; % final time point
dt=0.001;
t=0:dt:(tfinal);
TotalLoading = 0.5;
kd=0.05;
%kd=0.05; %BEST ONE
Csat = 0.14; % saturation concentration at experimental conditions
S0 = TotalLoading-Csat; % concentration of the solid drug inside the
pores

Da=0.0034; % Diameter in meter
r=Da/2; % Radius in meter
dt=0.2;
dr=0.0001;

volume_aer = (0.0017^3)*(4/3)*3.14; %volume in m3
numr=r/dr;
num_t=t/dt; %mesh in time

C=zeros(round(numr),length(t))*Csat;% C inside alcogel is initially zero
S=zeros(round(numr),length(t))*S0;% C of solid drug inside alcogel is
initially constant
%C(1,:)=0.14;
C(:,1)=Csat; % Initially, the pores are filled with saturated solution

```

```

S(:,1)=S0; % Initially, solid drug is also present in the pores
% C(1:5,1)=0.05; %% If the initial concentration was not homogeneous
% C(5:10,1)=0.1;
% C(10:numr,1)=0.14;
C(numr,:)=0; % For sink conditions
j=1;
rx= 0.0015;
rad(1) = dr; % Initial radius for volume calculations
total_amount=zeros(length(t)); % To calculate the amount of dissolved
drug
total_solid=zeros(length(t)); % To calculate the amount of solid drug

for k=1:length(t)

    t(k+1)=t(k)+dt;

    for i=1:numr

        % Volume calculations for each shell
        rad(i+1)= dr.*(i+1);
        Vol(1,k) = ((rad(1).^3)*4/3*pi);
        Vol(i+1,k) = ((rad(i+1).^3)*4/3*pi)-((rad(i).^3)*4/3*pi);

        if (i==1) % center

            C(i,k+1) = (-C(i+2,k)+4*C(i+1,k))/3;
            S(i,k+1) = (-S(i+2,k)+4*S(i+1,k))/3;

            if S(i,k)-0.0000001 <= 0 % if no solid drug is present set S
to zero
                S(i,k) = 0;
            end

            elseif (i==numr) % concentration is always zero at the surface of
the aerogel
                C(numr,k) = 0;
                S(numr,k) = 0;

            else %inside alcogel

                C(i,k+1)= C(i,k) + (Dp*dt./(dr^2)).*(C(i+1,k)-
2*C(i,k)+C(i-1,k))+Dp*2*dt./(r*dr).*(C(i+1,k)-C(i-1,k))+kd*dt.*(Csat-
C(i,k)).*((S(i,k)./S0).^(2/3));
                S(i,k+1)= S(i,k) - kd*dt.*(Csat-
C(i,k)).*((S(i,k)./S0).^(2/3));

```

```

        if S(i,k+1)-0.000001 <= 0% if no solid drug is present set S
to zero
            S(i,k+1) = 0;
        end

        if S(i,k+1)-0.000001 <= 0% if the amount of solid drug is
low, dissolution rate cst is lowered
            kd = 0.005;
        end

    end % end of if statement

    amount_inside(i,k) = C(i,k).*Vol(i,k)*1000*151.169*1000; % amount
of dissolved drug in the pores
    solid_inside(i,k) = S(i,k).*Vol(i,k)*1000*151.169*1000; % amount
of solid drug in the pores

end % end of for loop for numr

if (t(k)/60)-10 <= 0 % if there is no swelling

    Q(k)=sum(amount_inside(1:numr,k)); % Total amount of
dissolved drug inside the pores
    Solid(k)=sum(solid_inside(1:numr,k)); % Total amount of solid
drug inside the pores
    R(k)=(Csat+S0)*(volume_aer*eps*1000*151.169*1000)-
(Q(k)+Solid(k)); % Amount of drug that is released
    percent(k)=R(k)/(0.5*(volume_aer*eps*1000*151.169*1000))*100;
% Percent of released drug

else %(t(k)/60) > 1 % swelling starts

    if (rx-0.0026) < 0 % If swelling continues !
        rx = -0.00162*exp(-(t(k)/60)/23.68763)+0.00262;% calculation
of new r for the next time step
        radius(k) = rx; % to check radius change through the process
        numrx = numr;% store the old number
        numr = round(rx./dr); % calculate a new numr

        if numrx < numr

            Q(k)=sum(amount_inside(1:numrx,k)); % Amount of dissolved
drug inside the pores
            Solid(k)=sum(solid_inside(1:numrx,k)); % Amount of solid
drug inside the pores

```

```

        R(k)=(Csat+S0)*(volume_aer*eps*1000*151.169*1000)-
        (Q(k)+Solid(k)); % Amount of drug that is released

percent(k)=R(k)/(0.5*(volume_aer*eps*1000*151.169*1000))*100; % Percent
of released drug

        C(numrx:numr,k+1)= 0; % swollen parts have no dissolved
drug inside
        S(numrx:numr,k+1)= 0; % swollen parts have no solid drug
inside

        elseif numrx==numr

                Q(k)=sum(amount_inside(1:numrx,k)); % Amount of dissolved
drug inside the pores
                Solid(k)=sum(solid_inside(1:numrx,k)); % Amount of solid
drug inside the pores
                R(k)=(Csat+S0)*(volume_aer*eps*1000*151.169*1000)-
                (Q(k)+Solid(k)); % Amount of drug that is released

percent(k)=R(k)/(0.5*(volume_aer*eps*1000*151.169*1000))*100; % Percent
of released drug

        else

                Q(k)=sum(amount_inside(1:numrx,k)); % Amount of dissolved
drug inside the pores
                Solid(k)=sum(solid_inside(1:numrx,k)); % Amount of solid
drug inside the pores
                R(k)=(Csat+S0)*(volume_aer*eps*1000*151.169*1000)-
                (Q(k)+Solid(k)); % Amount of drug that is released

percent(k)=R(k)/(0.5*(volume_aer*eps*1000*151.169*1000))*100; % Percent
of released drug

                C(numr:numrx,k+1)=0;
                S(numr:numrx,k+1)= 0;
        end
    end
end
%
end

figure(1) % Change in the concentration of dissolved paracetamol
plot(t/60,C(2,:), 'k', 'linewidth',2)
grid
ylabel('C (Concentration of paracetamol in the alcogel, mol/L)');
```

```

xlabel('time(min)');
hold on
plot(t/60,C(5,:), 'g', 'linewidth',2)
plot(t/60,C(8,:), 'm', 'linewidth',2)
plot(t/60,C(15,:), 'b', 'linewidth',2)
legend('C(0.02cm)', 'C(0.05cm)', 'C(0.08cm)', 'C(0.15cm)')

figure(2) % Change in the concentration of solid paracetamol
plot(t/60,S(2,:), 'k', 'linewidth',2)
hold on
grid
plot(t/60,S(5,:), 'g', 'linewidth',2)
plot(t/60,S(15,:), 'b', 'linewidth',2)
ylabel('S(Concentration of solid paracetamol in the alcogel, mol/L)');
xlabel('time(min)');
legend('S(0.02cm)', 'S(0.05cm)', 'S(0.15cm)')
s= C(1:numr,50)';
mm=C(1:numr,200)';
m= C(1:numr,5000)';
n= C(1:numr,9000)';
a= C(1:numr,15000)';
aa=C(1:numr,24000)';
rr =(0:dr:(numr-1)*dr)*100;

figure(3) % concentration of dissolved paracetamol with respect to radius
plot(rr, s(1,:), 'linewidth',2); xlabel('r(cm)'); ylabel('Concentration of dissolved PC (M)');
hold on
grid
plot(rr, mm(1,:), 'c', 'linewidth',2); xlabel('r (cm)'); ylabel('Concentration of dissolved PC (M)');
plot(rr, m(1,:), 'g', 'linewidth',2); xlabel('r (cm)'); ylabel('Concentration of dissolved PC (M)');
plot(rr, n(1,:), 'r', 'linewidth',2); xlabel('r (cm)'); ylabel('Concentration of PC (M)');
plot(rr, a(1,:), 'm', 'linewidth',2); xlabel('r (cm)'); ylabel('Concentration of PC (M)');
plot(rr, aa(1,:), 'y', 'linewidth',2); xlabel('r (cm)'); ylabel('Concentration of PC (M)');
legend('0.16 min', '0.66 min', '16 min', '29 min', '49 min', '79 min')
figure(4) % percent release of paracetamol

timerelease = t(1,1:24001);
plot(timerelease/60,percent, 'k', 'linewidth',2)% legend('5 min', '10 min', '45 min', '90 min', '300 min', 'Location', 'best');
grid
hold on

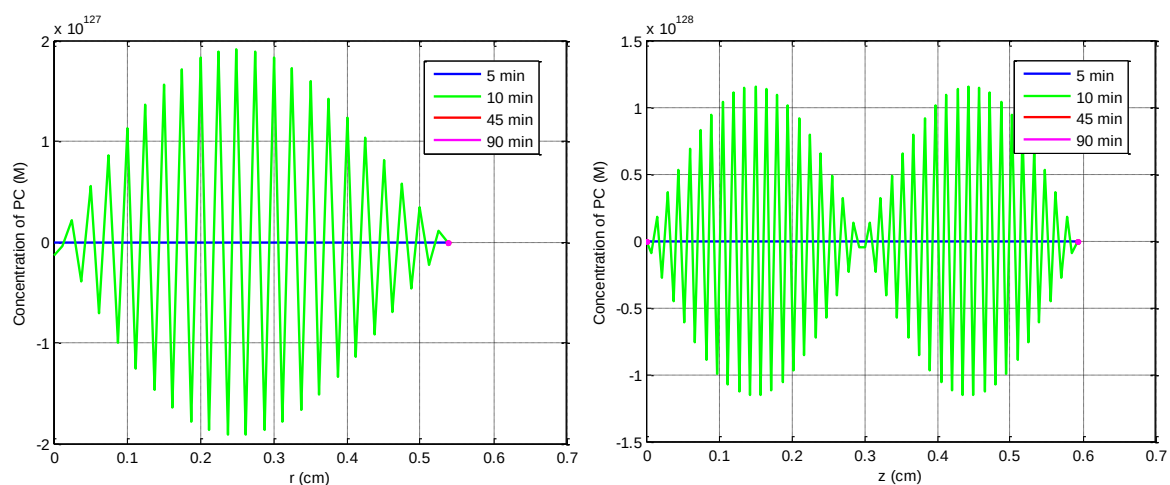
```

```
exptime=[0 2.5 5 7.5 10 15 20 30 45 60];  
exprelease=[0 33.83706324 55.2827699 61.07112215 65.75101852 71.96513853  
77.54678988 87.24923391 95.42093561 98.74247729];  
plot(exptime, exprelease,'bo','linewidth',2)  
legend('model prediction','experimental')  
xlabel('Time (min)'),ylabel('Percent Release (%)')
```

APPENDIX D: Example graphs which were obtained in the unstable regions

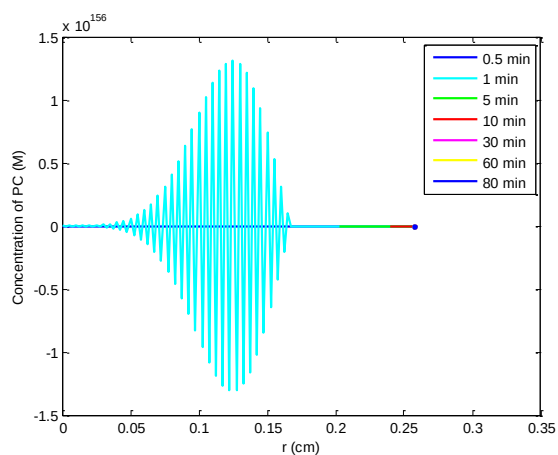
Loading Model

The concentration profile of paracetamol inside the alcogel with respect to r direction at $z=0.3$ cm and the concentration profile of paracetamol inside the alcogel with respect to z direction at $r=0.125$ cm



Release Model

Change in the concentration of dissolved drug with respect to radius at specified time points.



APPENDIX E: Calculation of the Experimental Diffusion Coefficient Based on the Experimental Data

The effective diffusion coefficient was also calculated based on the Equation A1 [60].

$$\frac{M_i}{M_{total}} \cong 2 \frac{\sqrt{D_e t}}{\sqrt{\pi} \delta^2} \quad (A1)$$

where M_i and M_{total} are the released concentrations of the drug at time i and at time infinity respectively. D_e is the effective diffusion coefficient, t is the time and δ is the half of the diameter of the aerogel.

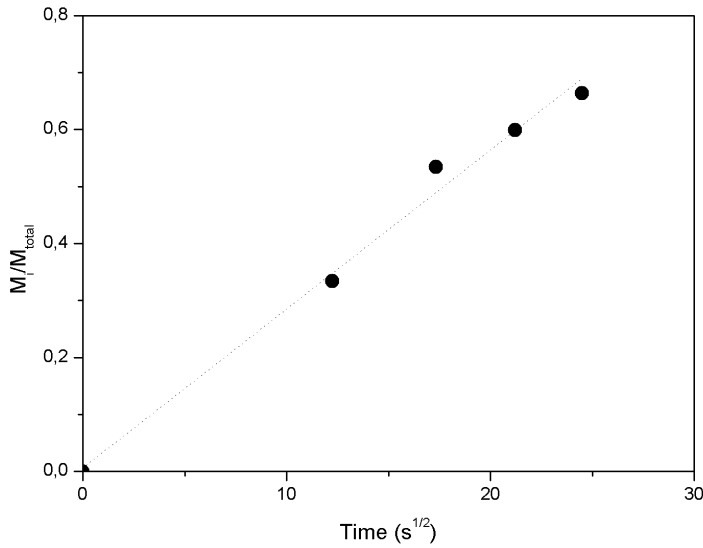


Figure A 1: Fractional Release of Paracetamol in the region representing %60 of drug release. ($R^2=0.98$)

VITA

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