

Process Development for Production of Aerogels with Controlled Morphology as Potential Drug Carrier Systems

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**To my lovely wife Noura
and my kids
Ahmad & Ayham**

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Abstract

Aerogels are nanoporous materials with extremely low bulk density and high specific surface area. Usually they are produced following the sol-gel process followed by suitable solvent removal. In the past few years Aerogels have drawn an increasingly attention in different scientific and industrial applications. Because of their outstanding properties, they have been shown to be potential drug carrier systems. The aim of this work is to extend their potential in pharmaceutical applications by filling the gaps that hinder their use in some delivery routes. Three different strategies were implemented to achieve this goal: (1) in situ production of microspherical aerogel particles; (2) modifying the surface functionality of the aerogel by surface functionalization or coating; (3) and finally by producing aerogel from biodegradable organic based polymers.

Different approaches were investigated for production of microspherical aerogel particles. Combining the sol-gel process with the emulsion process followed by supercritical extraction of the solvent from the gel-oil dispersion was shown to be a potential technique for robust production of aerogel microspheres from different precursors. Aerogel microspheres with high surface area and controlled particle size distributions ranging from few microns to few millimeters were produced following the proposed process.

Controlling the dosage quantity in the drug carrier as well as obtaining a specific release mechanism of the loaded drug is of crucial importance in pharmaceutical industry. Functionalization of aerogel surface with specific functional groups that modify the adsorption capacity of the loaded drug can be step toward controlling the dosage quantity. Amino functionalization was proposed as a model functionalization for modifying the affinity of silica aerogels towards specific drugs. Different functionalization approaches were evaluated. The adsorption capacity of the functionalized aerogel was successfully modified without affecting the release properties of the aerogels.

Because of their pore structure, aerogels cannot offer a specific release profile. Applying a polymeric coating with the desired functionality on aerogel-drug formulation helps to overcome this limitation. In this work a novel process for coating of aerogels was developed in cooperation with the institute of solid process engineering and particle technology, TUHH. For the first time it was possible to coat hydrophilic aerogels with a polymeric layer. Aerogel coating in spouted bed from aqueous and melts polymers were successfully demonstrated for obtaining a pH sensitive release profile from aerogel-ibuprofen formulation.

Biodegradability is essential for many delivery routes. Nanoporous materials based on biodegradable polymers precursors are potential materials that maintains the distinguished properties of aerogel and can provide the biodegradability dimension needed for certain systems. Aerogel based on alginate was demonstrated as an example for this approach. Different processing techniques were evaluated. Microspherical alginate aerogel particles with exceptionally high surface area were produced. Applying the modification techniques developed for silica aerogels to the biodegradable aerogels offer a further possibility for different drug delivery applications.

Zusammenfassung

Aerogele sind nanoporöse Materialien mit einer extrem geringen Dichte und einer hohen spezifischen Oberfläche. Sie werden in der Regel über einen Sol-Gel-Prozess und einer anschließenden Entfernung des Lösungsmittels mittels überkritischer Extraktion hergestellt. In den letzten Jahren hat das Interesse an der Nutzung von Aerogelen für verschieden wissenschaftliche und industrielle Anwendungen stetig zugenommen. Wegen ihrer besonderen Eigenschaften sind sie prinzipiell für den Einsatz als medizinische Wirkstoffträger geeignet. Das Ziel dieser Arbeit ist das Potential der Aerogele im Bereich des pharmazeutischen Einsatzes um neue Verabreichungsrouten zu erweitern. Drei verschiedene Strategien wurden zum Erreichen dieses Ziels angewendet: (1) Die In-Situ Produktion von mikrosphärischen Aerogel-Partikeln; (2) die Modifizierung der Oberflächeneigenschaften durch Veränderung der funktionellen Gruppen oder Oberflächenbeschichtung; (3) und zuletzt den Einsatz biologisch abbaubarer, organischer Polymere für die Aerogelproduktion.

Für die Herstellung mikrosphärischer Aerogelpartikel wurden verschiedene Ansätze verfolgt. Die Kombination des Sol-Gel-Prozesses mit einem Emulgierprozess, gefolgt von einer überkritischen Extraktion des Lösungsmittels aus der Gel-Öl-Dispersion erscheint als geeignete Technik für die Produktion von Aerogel-Mikrosphären aus verschiedenen Präkursoren. Mit diesem Prozess konnten Aerogel-Mikrosphären mit hoher spezifischer Oberfläche und kontrollierter Partikelgrößenverteilung im Bereich von wenigen Mikrometern bis einigen Millimetern hergestellt werden.

Die Kontrolle über Dosierung und Abgabemechanismus eines Wirkstoffes sind von großer Bedeutung in der pharmazeutischen Industrie. Die spezifische Oberflächenfunktionalisierung von Aerogelen führt über die Modifizierung der Adsorptionskapazität zu einer besseren Kontrolle der

Wirkstoffdosierung. Für die Modifizierung der Ketoprofenbeladung von Silica-Aerogelen wurde die Funktionalisierung mit Aminogruppen vorgeschlagen. Verschiedene Funktionalisierungsansätze wurden geprüft. Die Adsorptionskapazität der funktionalisierten Aerogele wurde erfolgreich verändert ohne die Freisetzungseigenschaften des Aerogels zu beeinträchtigen.

Wegen ihrer offenen Porenstruktur lassen sich mit Aerogelen keine spezifischen Freisetzungsprofile erreichen. Diese Einschränkung lässt sich durch eine Polymer-Beschichtung von wirkstoffbeladenen Aerogelen überwinden. In dieser Arbeit wurde in Zusammenarbeit mit dem Institut für Feststoffverfahrenstechnik und Partikeltechnologie der TUHH ein neuartiger Prozess für die Beschichtung von Aerogelen entwickelt. Zum ersten Mal gelang damit die Beschichtung der hydrophilen Aerogele mit einer Polymeroberfläche. Die Beschichtung wurde in einer Strahlschicht realisiert und ermöglichte die Herstellung einer Aerogel-Ibuprofen-Formulierung mit pH-sensitivem Freisetzungsprofil.

Eine biologische Abbauarbeit [des Wirkstoffträgers] ist für viele Verabreichungsrouten essentiell. Auf biologisch abbaubaren Polymeren basierende nanoporöse Materialien vereinen die besonderen Eigenschaften der Aerogele mit der für bestimmte Systeme nötigen biologischen Abbaubarkeit. Ein Beispiel für diesen Ansatz sind Aerogele aus Alginat. Verschiedene Herstellungstechniken [zur Produktion von Alginat-Aerogelen] wurden evaluiert mit dem Ziel, mikrosphärische Alginat-Aerogelpartikel mit hohen Oberflächen zu produzieren. Dabei wurden die für Silica-Aerogele entwickelten Prozesses erfolgreich auf biologisch abbaubare Aerogele übertragen.

Introduction

Aerogels are distinguished nanoporous materials with exceptional properties. In general, they are produced using the sol-gel technology followed by removal of the solvent from the gel in a way that preserved the textural properties of the wet gel intact. The final properties of the aerogel depend mainly in the used precursors and the sol-gel process parameters.

Monolith silica aerogels were the central focus of previous research in our group. Different processing routes were investigated with a target of applying the produced aerogels in the field of pharmaceutics ([Gorle, 2009](#); [Reddy, 2005](#); [I. Smirnova, 2002](#); [Suttiruengwong, 2005](#)). Wide steps have been achieved toward extending their use as drug delivery systems including optimization of the production process and developing new possible applications of the produced monolith aerogels.

Targeting life science fields (food technology, biomedical applications, cosmetics and pharmaceutics) imply that the developed product should fulfill specific requirements to compete with the available alternatives. Silica aerogels are biocompatible, which together with their other properties make them ideal candidates for diverse life science applications. However, for tailor made drug delivery systems this is not enough, since, for many applications a control over the architecture of the produced delivery vehicles is of crucial importance.

The general objective of the presented work is to develop potential drug delivery systems based on aerogels by implementing novel processing and design strategies. Therefore, the following goals should be achieved:

- For divers applications microspherical particles are essential. Microparticles obtained from milling of aerogels monoliths are irregular in shape; this can be the limiting factor

for some delivery routes. Besides that, the flowability of drug-formulation is highly affected by the particles shape. Hence, the first goal of this work is to develop a process that enables in situ production of microspherical aerogel particles with controlled particle size distributions.

- Controlling the dosage quantity of the loaded active substance drug on aerogels is of vital importance in delivery systems. Modifying aerogel surface to meet certain loading requirements is the second goal of this work.
- Until now there are no reports regarding implementing aerogels in controlled drug release formulations. Extending the usage of aerogel in this application area is the third goal of this work.
- For many life science applications biocompatibility should be combined with biodegradability. The acquisition of biodegradable drug carrier systems that maintain the outstanding properties of silica aerogels and meet the previous mentioned design requirements is the fourth motivation of the present work.

Accordingly, the presented work is divided in to two main parts: (I) silica aerogels and (II) polysaccharide based aerogels. The first part consists of three chapters. The first chapter gives an overview of silica aerogel including production, processing and the recent achievements reported in the literature. In the second chapter, the production of silica aerogel microparticles is discussed. Different approaches are given and compared. Finally, in the last chapter, tailoring of silica aerogels by means of surface modifications is discussed. Amino functionalization of silica aerogels is applied as a model technique for modification of aerogel surface to meet specific functionality. Furthermore, coating of silica aerogel in a spouted bed is presented as a novel process that enables controlled drug delivery based on aerogels carriers.

Part II of this work is devoted for development of biodegradable nanoporous materials based on polysaccharides. In the first chapter, the state of the art in this research area is outlined. The main steps involved in this technology are discussed. Furthermore, the recent achievements in different polysaccharide based aerogel are furnished. Finally, production of aerogel microspheres based on alginate is presented in the last chapter of part II. Different proposed production approaches are discussed and evaluated in term of their potential for life science applications.

Finally this work is closed with a summary that highlight the main achievements of this work. A graphical summary of the thesis structure is shown in Fig. 1.

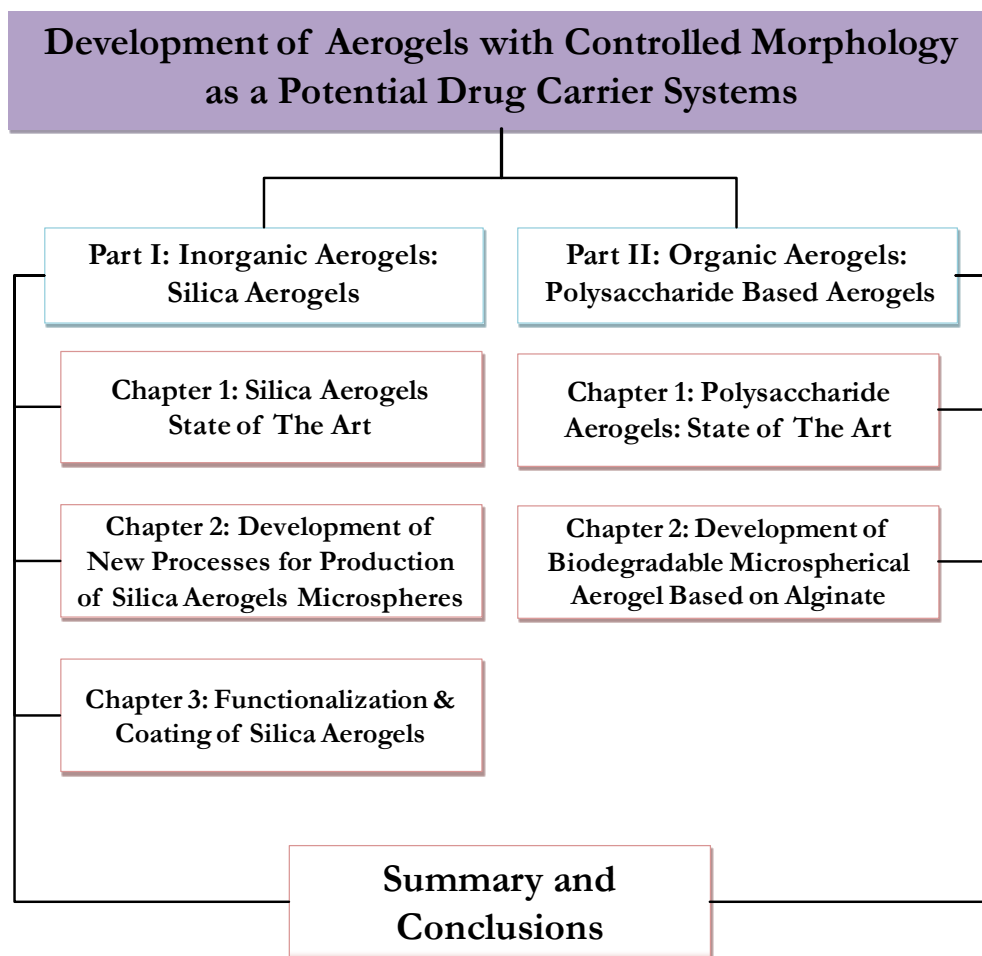


Fig. 1: Graphical presentation of the thesis structure.

Part I

Inorganic Aerogels:

Silica Aerogels

I. Inorganic Aerogels: Silica Aerogels

1 Silica Aerogel: The State of The Art

Aerogels are nanoporous materials with an open pore structure and large specific surface area. They are synthesized from a wide range of molecular precursors using the sol-gel technology and special drying methods. In the past few years, aerogels have drawn increasingly more attention in many scientific and technological fields. Due to their outstanding properties, they have been found to be ideal candidates for wide range of advanced applications. Silica aerogels are one of the most popular and investigated aerogels. Based on their isolation properties, an industrial scale production of silica aerogel is already existed for advanced isolation applications. However; isolation is only one of many possible potential applications of aerogels. Hence, more investigation should be conducted to explore aerogel properties and apply them for cut edge applications that can help in the development of mankind. This chapter provides the basic background needed for understanding the production of silica aerogel (from sol to aerogel). Finally, a review of silica aerogel applications and their future trends is given.

1.1 Sol-gel technology

Sol-gel technology describes those processes where a mixture of precursors undergoes chemical reactions forming a colloidal solution, which end up with a solid network ([Bergna & Roberts, 2006](#)). Sol-gel technology has proved to be a versatile and valuable method for production and processing of materials. Metallic, organic, inorganic and hybrid materials are examples of the precursors that can be used for this process. The end products can range from highly advanced materials to materials of general daily use. The importance of the sol-gel process arises from two main causes: 1) production of highly pure materials; 2) creation of novel valuable materials ([Sakka, 2002](#)). Fig. 2 shows a general

sketch of the main most commonly used steps in the sol-gel processes. Typical sol-gel preparation starts with mixing the precursors, f. i., metal oxides, with a hydrolysis agent, and a solvent. The precursors undergo a series of hydrolysis and polycondensation reactions, which can be catalyzed using an acidic, a basic catalysts or a combination of both (two-steps). A sol colloidal solution is eventually formed, which can be considered as a dispersion of polymers or fine particles ($\sim 1\text{-}1000$ nm) in a solvent. Further reactions result in connecting these fine particles. Eventually, the sol converts to a wet gel containing the solvent. Evaporation of the solvent from the wet gel results in a dry gel “xerogel” ([Kaufman & Avnir, 1986](#)), heating this dried gel to several hundred degrees results in dense material in form of films, fibers, particles or monoliths ([Kumar et al., 2008](#); [Lu et al., 2007](#); [Mukherjee et al., 2006](#)).

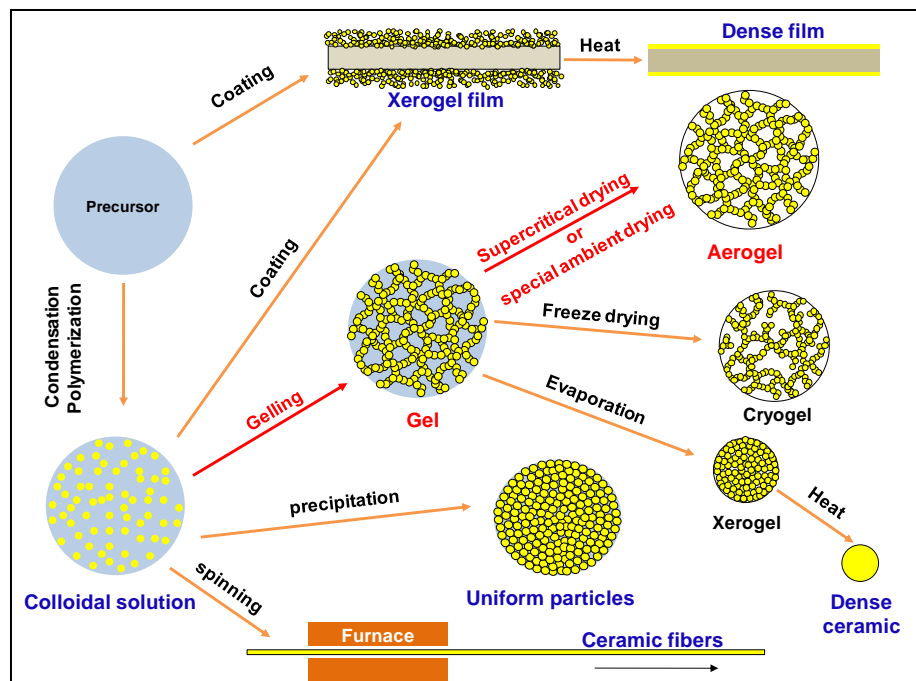


Fig. 2: General steps involved in the processing of materials using the sol-gel technology and some possible final products structure.

For a broad number of applications, the gel porous network is the key feature for their use. Hence, it is important to remove the solvent, residues and the unreacted chemicals from the

network in a way that preserved the internal textural properties of the gel. During solvent evaporation from the gel network the curvature of vapor-liquid interface changes. The curvature of the meniscus decreases with time (Fig. 3). As a result capillary forces take place. The pressure difference between the liquid and vapor phase can be given by Laplace's equation:

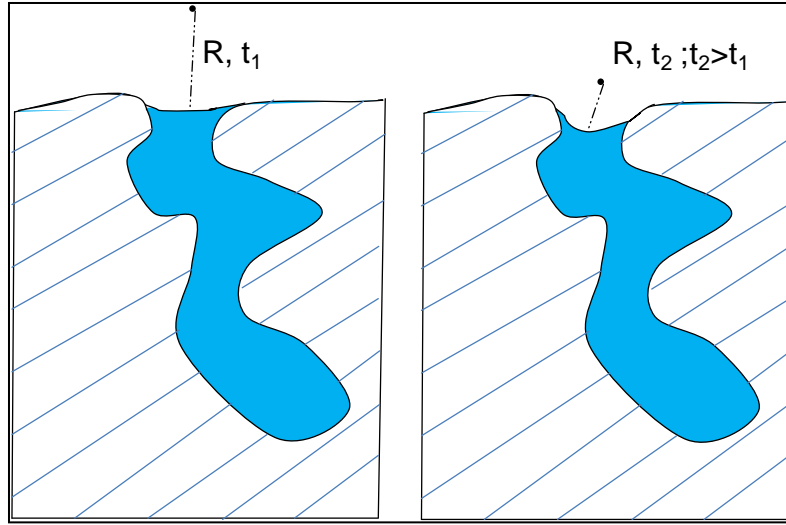


Fig. 3: Change in liquid-vapor meniscus radius as a function of drying time at the pore surface.

$$\Delta P = -\frac{\sigma \cos \theta}{R} \quad 1.1$$

Where σ is the liquid/vapor interfacial surface tension, R is the meniscus radius and θ is the contact angle at which the liquid/vapor interface meets the solid surface. Accordingly the gel structure is subject to compression stresses. Because of the high capillary pressure induced upon solvent evaporation and the fragility of the gel structure, cracks and shrinkages are obtained. Hence, a reduction of the textural properties of the dry gel will be observed.

However, it is possible to reduce the capillary pressure induced during drying by using a solvent which has a low surface tension value (equ. 1.1). Table 1 shows the interfacial surface tension of some liquids that might be used as a solvent for the gel. By means of solvent exchange it is possible to reduce the capillary forces; using solvent with lower surface tension. However, since the capillary

force depends also on the radius of the capillary, pore radius, which is in the nano-scale, the capillary forces induced by the lowest possible interfacial surface tension will be large enough to destroy the textural structure of the gel.

Table 1: The surface tension of some fluids ([Rideal, 2007](#)).

Solvent	σ [mN/m]	T [°C]
Water	72.80	20
Acetone	25.20	20
Acetonitril	29.10	20
methanol	22.61	20
n-Hexane	18.43	20
Carbon dioxide	1.16	20
Nitrogen	6.6	-183

Fig. 4 shows the capillary forces induced by different solvents as a function of the pore radius. It can be seen that the capillary forces are reduced by using solvents with lower surface tension, however, at small pore size, the capillary forces can be as large as several thousands of bars ([Weissmüller et al., 2010](#)). Furthermore, a gradient of capillary forces is induced due to the pores size distribution, resulting in inhomogeneous distribution of the forces acting on the fragile porous gel, which leads definitely to the destruction of the gel network.

Accordingly, the gel structure can be preserved only if the capillary forces emerge during drying process are avoided. This can be achieved only if the interfacial surface tension between the phases ceased. Freeze drying and supercritical extraction of the solvent from the gel are among the most intensively investigated processes to produce intact dried gel structures. Freeze drying consists of lowering the temperature of the solvent below the crystallization temperature. The solvent is then removed as a vapor by reducing the pressure (sublimation). The product of this process is usually

called a cryogel ([Jungbauer & Hahn, 2004](#); [Kumar et al., 2003](#); [Mukai et al., 2004](#); [Plieva et al., 2008](#); [Plieva et al., 2004](#); [Rey & May, 2004](#)). However, many obstacles are associated with freeze drying, among them are: the slow rate of sublimation; solvent exchange maybe required; increase of the solvent volume upon crystallization, this induces stresses directed from the crust toward inside, resulting in shrinkages and breakage of the crust layers as small particles. This phenomenon explains the fact that most of freeze drying products are powders (production of monoliths is extremely difficult).

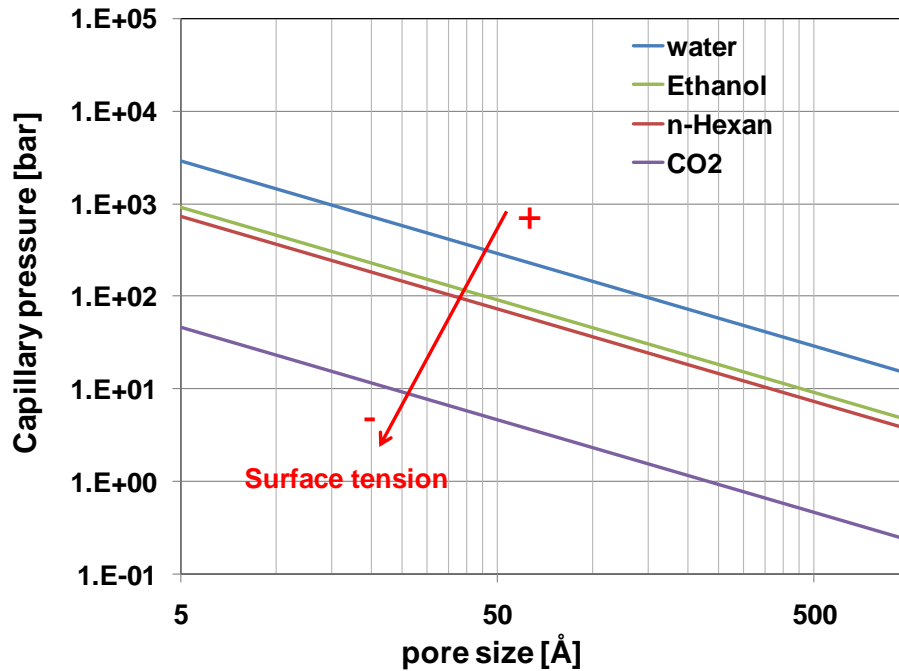


Fig. 4: Capillary pressure of different solvent at different pore sizes (assumption: θ is 0).

The other possibility to maintain the textural structure of the gel upon removal of the solvent is the supercritical drying (extraction). The resulting product of this process called aerogel.

1.2 Aerogel technology

Fig. 5 shows a class of the sol-gel technology. Here the end product of the production line called aerogel. By mean of sol-gel technology, aerogels from organic, inorganic, and hybrid precursors can

be produced. Depending on the processing steps, it is possible to produce aerogel in form of monoliths, beads and microparticles. The central focus of this work is the production of aerogels for life science application, namely drug delivery systems. To meet the needs for this approach, several factors should be taken into consideration. Among them, biocompatibility and biodegradability are the key factors in refining the potential candidates. The availability, ease of production, cost factors and the possibility to formulate the drug-aerogel in the needed form would be the second refining criteria for choosing the best possible precursors for aerogel production.

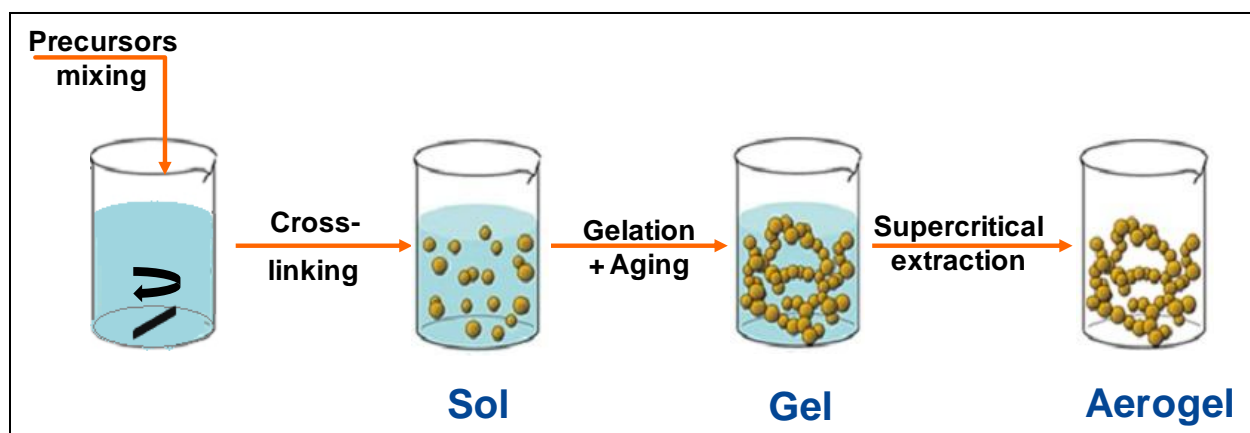


Fig. 5: Main steps in aerogel production.

1.2.1 Silica Aerogel

Among all known aerogels, silica aerogels are the most popular one (Fig. 6). They possess a wide variety of extraordinary properties; many of them are registered in the Guinness Book of Records for Properties ([Fricke & Emmerling, 1999](#)). High porosity ($\sim 99\%$), high specific surface area ($\sim 1000 \text{ m}^2/\text{g}$), low density ($\sim 0.002 \text{ g}/\text{cm}^3$), low thermal conductivity ($\sim 0.01 \text{ W}/\text{m}\cdot\text{K}$), high optical transition ($\sim 99\%$), low refractive index (~ 1.05), low dielectric constant ($\sim 1.0 - 2.0$) and low sound velocity (100 m/s) are some of their exceptional properties that make them promising candidates for many advanced applications ([Fricke & Emmerling, 1999](#); [Fricke & Reichenauer, 1986](#); [Gurav, Jung, et al., 2010](#); [Hrubesh, 1998](#); [Soleimani Dorcheh & Abbasi, 2008](#)).

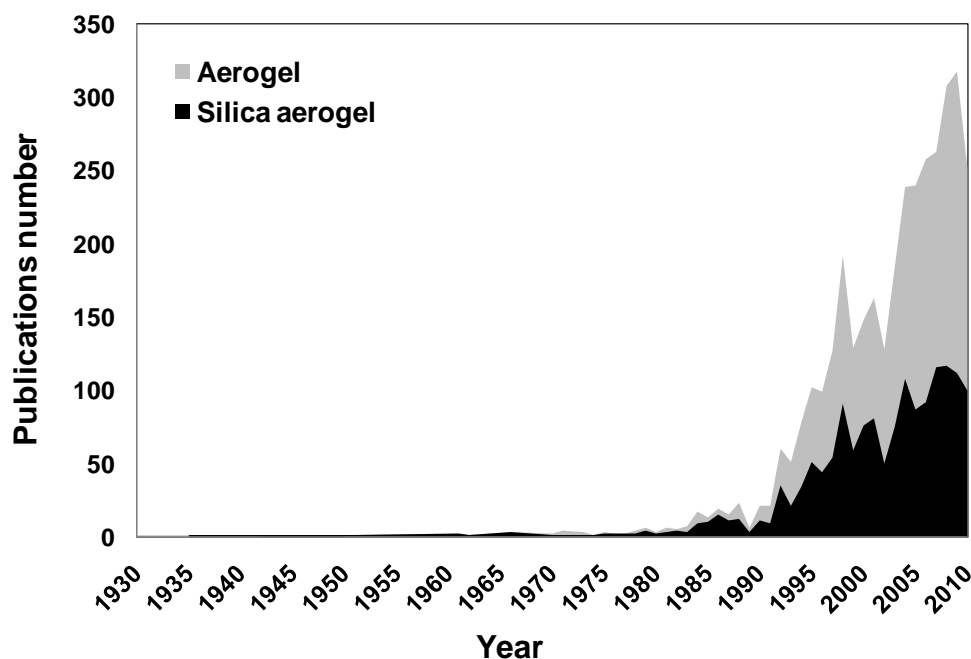


Fig. 6: Number of articles that contains silica aerogel and aerogel in their title.

Silica aerogels were first produced on 1930s, when Samuel Kistler found the way to replace the liquid inside the gel with a gas with slight shrinkage. With his new invention he was able to produce aerogel from different organic and inorganic precursors ([Kistler, 1931](#), [1932](#)). Few years later Kistler join Monsanto Corp, thereafter, the company start marketing new product called simply Aerogel. However, the production ceased on 1960 when the cheap fumed silica overtakes the applications of silica aerogel. Silica aerogel were rediscovered on 1968 when the student of Professor S. J. Teichner, used metaloxide namely TMOS and methanol to prepare the so called alcogel. Accordingly, he has encompassed the two most time consuming steps in Kistler's procedure (the gelation and the solvent exchange step)([Astier et al., 1976](#)). At this stage, several applications were proposed for using silica aerogel, yet nothing was performed. In 1974, the first Cerenkov radiation detector based on silica aerogel was developed by Cantin et al ([Cantin et al., 1974](#)). In the early 1980s, the first pilot plant for production silica aerogel was established by members of the Lund group in Sjöbo, Sweden. With a capacity of 3000 liters, TMOS gel was extracted using supercritical methanol. Supercritical

carbon dioxide was first used in 1983 when Microstructured Materials Group at Berkeley Lab found that the alcohol within a gel could be replaced by liquid carbon dioxide before supercritical drying without harming the aerogel. The first symposium on aerogel was held on 1985 in Wurzburg, Germany. Thereafter, silica aerogel have been used or considered to be used for laser application, thermal insulation, sensors, optical applications, waste management, metal's melts, electronic devices, catalyst and catalyst carriers and drug delivery systems ([Gurav, Jung, et al., 2010](#); [Soleimani Dorcheh & Abbasi, 2008](#)). Recently more groups around the world are investigating aerogel for immense applications. Hence it is necessary to understand the processing steps to produce silica aerogels to give us the tools to tailor its properties for the needed application.

1.2.2 From sol to aerogel

Fig. 5 gives the main steps followed in silica aerogel production. As it can be seen it is possible to differentiate three main steps: 1) mixing the precursors and the formation of the sol (colloidal solution); 2) gelation of the sol solution and aging of the gel; 3) extraction of the solvent from the gel. Any aerogel production method is a derivative or a modification of the previously mentioned steps.

1.2.2.1 The sol

A sol is a colloidal suspension of tiny particles or polymers with a size range of $\sim 1\text{-}1000$ nm suspended in a liquid. Understanding the mechanisms behind the sol formation, gives the tool to master and control the gel properties and eventually, the aerogels properties.

1.2.2.1.1 Precursors

The starting point of the sol formation is the mixing of precursors. Limiting ourselves to silica aerogels, there are many possible precursors that can be used. In all cases, the used precursors should be soluble in the reaction media (solvent). Furthermore, it should be active enough to

participate in the sol formation. Amines, salts, oxides, alkoxides, complexes or mixtures of them can be used as precursors for the sol-gel process ([Al-Oweini & El-Rassy, 2010](#); [Bergna & Roberts, 2006](#); [Chandradass et al., 2008](#); [Krissanasaeranee et al., 2008](#); [Latthe et al., 2009](#); [Maamur et al., 2010a](#); [Meunier et al., 2009](#); [Son et al., 2008](#); [H. Tan et al., 2010](#); [Turova, 2002](#)).

Silicon alkoxides are the most popular precursors for the sol gel process. Among them, tetramethyl orthosilicate (TMOS) is the most commonly used. TMOS undergoes fast hydrolysis and condensation reactions leading to the fast formation of a stable gel. However, being toxic (cause blindness) and expensive, devote researchers to intensively search for alternatives. Tetraethyl orthosilicate (TEOS) is a cheaper precursor and less toxic than TMOS. Several researcher have investigated the use of TEOS for aerogel production ([Tamon et al., 1998](#); [Venkateswara Rao & Bhagat, 2004](#); [Venkateswara Rao & Kalesh, 2003](#)), still some of them claimed that aerogels based on TMOS yield higher surface area and narrower pore size distribution ([Wagh et al., 1999](#)).

The cost factor of supercritical drying step was the key motivation of finding other precursors and additives. Thus, modifying the silica gel network to enhance its hydrophobicity was proposed as a method to enable drying at ambient pressure. Hence, several additives and precursors were investigated. Adding methyltrimethoxysilane (MTMS) and methyltriethoxysilane (MTES) to TMOS or TEOS enhances their hydrophobicity ([Ingale et al., 2010](#); [Toledo-Fernández et al., 2008](#); [Venkateswara Rao et al., 2006](#)). Aerogel based on MTMS were prepared by ambient drying conditions. It has been shown that aerogels prepared by this methods show enough elasticity that allows the dried aerogel to relax after drying stresses are over. The network relaxation allows maintaining the gel network structure intact. This effect called the spring back effect ([Kanamori et al., 2009](#); [Venkateswara Rao, et al., 2006](#)). The stress of skipping supercritical drying step led to a new range of coprecursors that claimed to produce super hydrophobic gel which can be dried at

ambient conditions. Perfluoroalkylsilane (PFAS), hexamethyldisiloxane (HMDSO), hexamethyldisilazane (HMDS) and MTMS are examples of coprecursors that result in a super hydrophobic aerogel network ([Bhagat, Kim, et al., 2008](#); [D. J. Kang & Bae, 2008](#)).

Water glass or sodium silicate has proven to be a cheaper alternative for production of silica aerogels. Several researchers have investigated aerogel production based on sodium silicate with the hope to shorten the steps of commercialization of aerogels ([Bhagat, Kim, et al., 2008](#); [Chandradass, et al., 2008](#); [Sobha Rani et al., 2010](#)). The optimal production conditions were as well proposed ([Bhagat et al., 2006](#); [Bhagat, Park, et al., 2008](#); [M. I. Liu et al., 2008](#)). One of the main drawbacks of this technology is that it results in a fragile gel that needs purification before transferring it to an aerogels. However, being cheap made sodium silicate the base of most aerogel industrial scales production.

Moreover, aerogel based on the waste of some industries were proposed as a promising alternative for the expensive precursors available in the market. Aerogel from rice hull ash was produced from the waste of the rice industry ([Maamur et al., 2010b](#); [Tang & Wang, 2005](#)). Furthermore, aerogel based on oil shale ash was proposed as a process to produce silica aerogel using the waste of oil industry ([Gao et al., 2010](#)).

1.2.2.1.2 Formation of the sol (reaction mechanism)

The description of the reaction mechanism for all possible precursors is beyond the scope of this work, moreover these mechanisms can be found in some key references ([Bergna & Roberts, 2006](#); [Brinker & Scherer, 1990](#)). In this work, the description of sol formation from the most commonly used precursors is given (TMOS, TEOS and sodium silicates).

In order to prepare the sol of silica particles, silica precursors are mixed with a hydrolysis agent and a solvent. Upon reaction a silanol groups is formed, these silanol group connect to each other forming a siloxane bridge (Si–O–Si). Each Si molecule can make up to 4 siloxane bridges, allowing many small molecules to join together forming a giant molecules containing thousands of Si–O bridges. The assembly of these molecules forms the silica nanoparticles. The size of the assembly can goes up to few nanometers([Brinker & Scherer, 1990](#)).

Silicon alkoxide

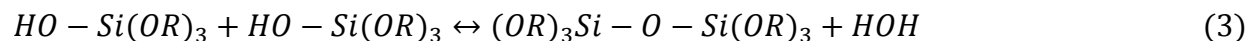
The most commonly used silicon alkoxides are TMOS and TEOS. Metal alkoxides are popular precursors because they react readily with water (hydrolysis). As a result a hydroxyl group is attached to the metal (silicon) as shown in the following reaction:



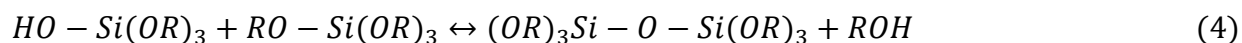
where R represent a proton or other ligand, for instance alkyl group. Depending on the presence of water molecules and the catalyst, the reaction can go towards complete hydrolysis, or stop resulting in a partially hydrolyzed alkoxide.



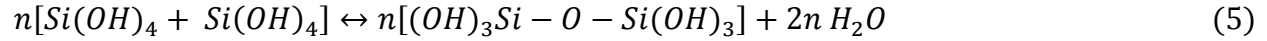
Two partially hydrolyzed molecules can be joined by the condensation reaction. This results in liberation of small molecules; water or alcohol:



or:



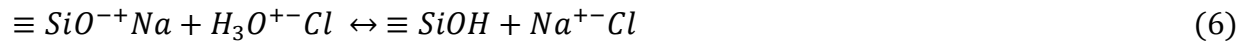
Several thousand of these reactions (reaction 3 and 4) can occur resulting in the formation of a giant molecule with a size of few nanometers by the so called polymerization reaction:



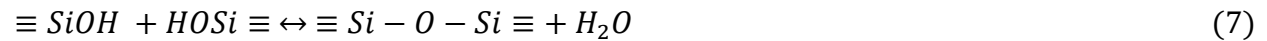
The sum of the produced nanoparticles forms the primary particles of the sol ([Brinker & Scherer, 1990](#)). It should be mention that the previous reactions can happen simultaneously, by mixing all precursors in the needed stoichiometry and catalyzed by either base or acid catalyst, and can be named as one step method ([I. Smirnova, 2002](#)). On the other hand it is possible to carry out the previous reactions in two steps where the hydrolysis and condensation can be separately accelerated by series of acid/basic catalyst ([Tillotson, 1992](#)).

Water glass (the alternative)

Water glass or sodium silicate is a cheap alternative for producing silica gel. Sodium silicate is an inexpensive white solid. Unlike silicon alkoxide, the presence of water does not initiate the hydrolysis neither the condensation. However, being basic, by the presence of an acid, like hydrochloric acid, sodium silicate tends to neutralized and the hydrolysis occurs, as a result a silanol group is formed:



After that, the hydrolyzed silicate links together forming siloxane bridges:



The chemistry after that is similar to that of silicon alkoxides. Several thousand of molecules bridge together making the nanoparticles of the sol. It should be mentioned here that some time the

heating of the sodium silicate aqueous solution is needed to initiate the hydrolysis step ([Bergna & Roberts, 2006](#)).

1.2.2.2 The gel

It is possible to say that the gel forms when the sol lose its fluidity. This mechanism can be described following different theories. The easiest explanation is that upon hydrolysis and condensation siloxane bridges between silicon molecules are built. Consequently, large number of silicon molecule interconnect forming the primary nanoparticles which form the sol. Eventually, the size of these primary particles stop to grow in size instead it agglomerate with another primary particles nearby, forming clusters of particles. It is possible to imagine that these cluster swims in the solvent. Upon collision with another cluster, it is possible to form bridges that connect these clusters together. At the moment when the last free cluster bonds with other clusters the sol lose its fluidity and a gel is formed.

The structure of the gel results from successive hydrolysis, condensation and polymerization reaction. Furthermore, reverse reactions can also take place (esterification and de-polymerization). Knowing the kinetics of these reactions provides an insight into the gel formation process and provides the tools needed to tailor the final gel properties.

Process parameters like pH, solvent type, catalyst, precursors concentrations/ratios, temperature, etc., can significantly affect the final gel/aerogel properties. These fundamental investigations have been intensively investigated by different researchers ([Brinker & Scherer, 1990](#); [Gurav, Jung, et al., 2010](#); [Moner-Girona, 2002](#); [Sakka, 2002](#); [I. Smirnova, 2002](#); [Soleimani Dorcheh & Abbasi, 2008](#)).

pH of the reaction media were found to be one of the key factors that influence the gelation process. It has been found that the hydrolysis reaction can be catalyzed using either acidic or basic catalyst. However, at low pH values a linear chain is formed with small number of crosslinking. As a result, a reversible (redispersible) soft gel is formed. Here the hydrolysis reaction occurs due to electrophilic attack on the oxygen atom of the alkoxide group. Addition of basic catalyst will enhance the condensation reactions and high density of branched crosslinking will be obtained. Here, the hydrolysis and polymerization occurs due to a nucleophilic attack on the Si ion ([Brinker & Scherer, 1990](#); [Gurav, Jung, et al., 2010](#); [Turova, 2002](#)).

1.2.2.2.1 Aging of the gel

Although gel forms when the last span cluster bonds to the 3D network, the formation of new bonds will continue. Depending on the aging process, reactant concentration, temperature, pH of the gel, solvent, etc., these reactions can last for months([Brinker & Scherer, 1990](#)). Aging is characterized by increasing the stiffness of the gel. This can be understood by knowing the three main processes involved in the aging step: (1) polymerization; (2) syneresis; (3) ripening.

Silica gel is rich in hydroxyl free groups (Si-OH), theoretically, these groups are still able to condense together forming new siloxane bonds (Si-O-Si). The more bonds forms, the more stable the gel is. This called polymerization process, it starts after mixing the precursors and can last for a very long time thereafter (see equation 5). In addition to the condensation a hydrolysis reaction may also occur (see equation 1), this provides the network with more possible site to connect and enhance its mechanical properties.

Based on these new bridges, syneresis occurs. Syneresis can be defined as the repulsion of the solvent (alcohol, water) from the pores of the gel. Consequently, shrinkages of the gel pores are expected ([Loy et al., 2005](#))(Fig. 7a). Moreover, these new bonds may occur between two flexible

chains while coming in contact, resulting in increasing the stiffness of the gel as well as extensive shrinkages (Fig. 7b).

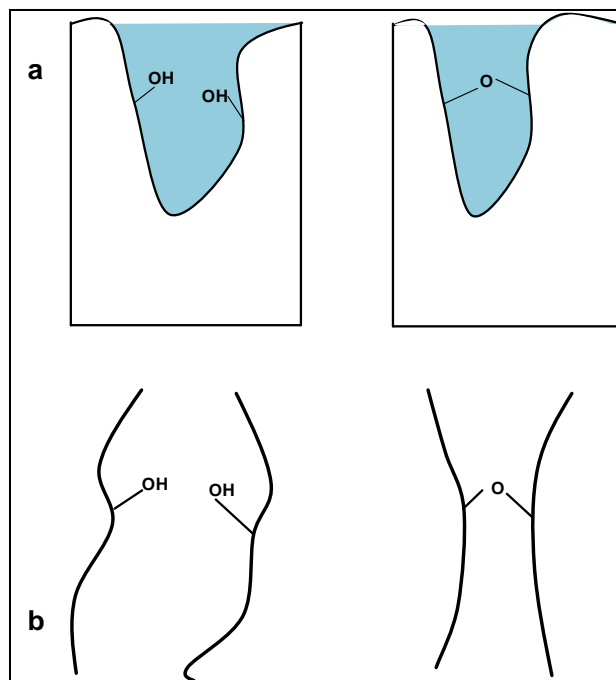


Fig. 7: Syneresis scenarios: a) bond between two neighboring molecules resulting in shrinkage upon relaxation of the new bond, b) two flexible chains may connect resulting in restriction the extent of flexibility and extensive shrinkage.

Aging of gels is necessary to give the gel the stability to withstand the drying steps before turn it into aerogel ([Strøm et al., 2007](#)). Accordingly, it is important to modify the mechanical properties of the gel by aging within acceptable time ([Einarsrud et al., 2001](#); [Strøm, et al., 2007](#); [Suh et al., 2000](#)). Different process can be used to accelerate this step, like aging on the mother solution, temperature, etc. ([Smitha et al., 2006](#); [Strøm, et al., 2007](#); [Takahashi et al., 2005](#)).

1.2.2.3 Drying of the gel

For aerogel applications, the 3D network of the gel is the product of interest, hence, it is expected to remove the solvent, residues, unreacted precursors and the byproduct from the network in a way that the 3D network preserved intact. Aerogels are usually obtained from wet gels by using

the supercritical drying technology. Supercritical drying transforms the liquid contained in the gel into a supercritical fluid. The inherent null surface tension of supercritical fluids avoids the pore collapse phenomenon in the gel structure during solvent elimination ([Brunner, 2004](#); [Sun, 2002](#)). Recently, more interests are rising to avoid the supercritical drying step and replace it by ambient drying condition. Several attempts have been conducted, mostly based on modifying the gel surface and get the benefits of spring back effect ([M. I. Liu, et al., 2008](#); [A. V. Rao et al., 2005](#)).

1.2.2.3.1 Supercritical drying technology

It is possible to differentiate two general methods in applying the supercritical principle: 1) high temperature supercritical drying (HTSCD); 2) low temperature supercritical drying (LTSCD). Table 2 shows the critical conditions of some solvents. Accordingly, methanol, ethanol and acetone follow the HTSCD fluids. Whereas, carbon dioxide, methane, ethane, propane, ethylene and propylene are among the fluids which follow the LTSCD.

Table 2: Critical conditions of some solvents.

Solvent	Critical temperature K	Critical pressure MPa	Critical density g/cm ³
Carbon dioxide (CO ₂)	304.1	7.38	0.469
Water (H ₂ O)	647.1	22.06	0.322
Methane(CH ₄)	190.4	4.60	0.162
Ethane(C ₂ H ₆)	305.3	4.87	0.203
Propane (C ₃ H ₈)	369.8	4.25	0.217
Ethylene(C ₂ H ₄)	282.4	5.04	0.215
Propylene (C ₃ H ₆)	364.9	4.60	0.232
Methanol(CH ₃ OH)	512.6	8.09	0.272
Ethanol (C ₂ H ₅ OH)	513.9	6.14	0.276
Acetone (C ₃ H ₆ O)	508.1	4.70	0.278

High temperature supercritical drying

HTSCD was first used by Kistler in 1931 for preparing the first known aerogel and still in use for silica aerogel production. Fig. 8 represent a scheme for HTSCD using methanol as an example. The procedure consists of three main steps: 1) the gel with an excess amount of methanol is placed in an autoclave. The temperature of the gel-methanol is raised slowly to prevent crossing the liquid-gas interface. Eventually the pressure of the mixture will be raised as well. When the supercritical condition is attained (the set point of drying) the process conditions are kept for some time. At these conditions, all gel liquids will transform to the supercritical condition and will be freely mobile; 2) the pressure of the system is reduced slowly and isothermally by venting the autoclave; 3) finally when the ambient pressure is attained the autoclave is cooled down to room temperature. ([Maamur & Jais, 2009](#); [Venkateswara Rao et al., 1998](#); [Yoda & Ohshima, 1999](#))

Drying the gel in organic solvent at their critical conditions can lead to a change of the gel properties due to the reactions that can occur at these conditions. Taking silica gel as an example, HTSCD produces hydrophobic silica aerogel that can withstand atmospheric moisture which is an advantage for some application. However, flammability of the organic solvent, and degradation of organic gel are some of the limitations of this process.

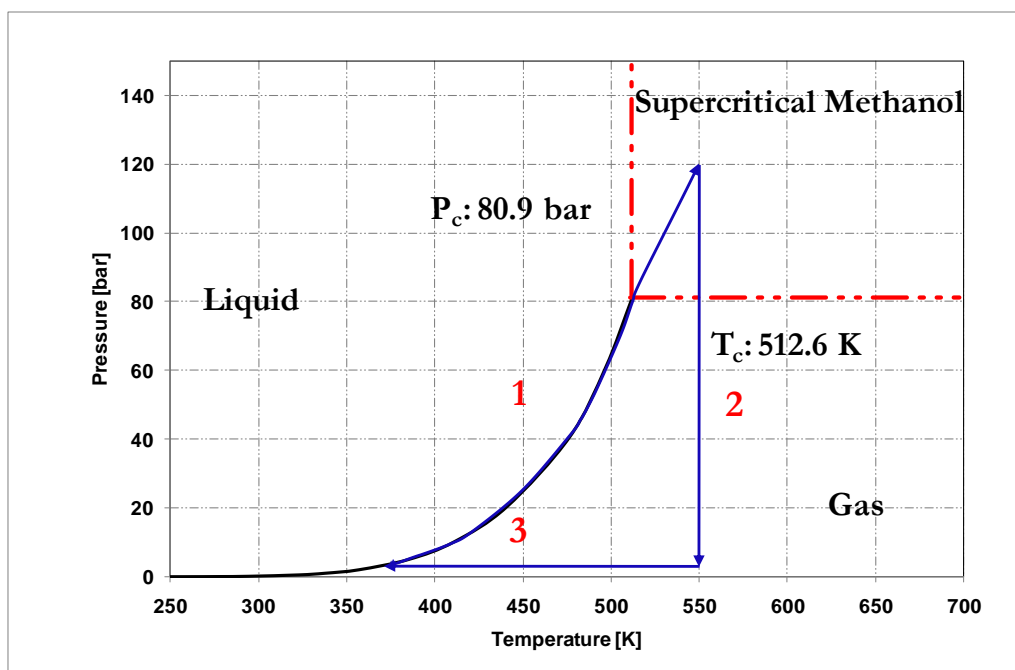


Fig. 8: Supercritical drying schema of HTSCD method, methanol as an example.

Low temperature supercritical drying

Although, many solvents can be categorized within LTSCD, carbon dioxide is the mainly used one. Flammability of other possible solvent like propane hindered their use for extraction applications. It has been extensively demonstrated that supercritical carbon dioxide extraction is suitable for the development of solvent-free products with no need for further purification steps, and fulfilling standards of quality and safety of industry (e.g., current good manufacturing practice (cGMP), Environmental Health and Safety (EHS))([Brunner, 2004](#); [MacHugh & Krukoni, 1994](#); [Sun, 2002](#)).

A typical procedure for supercritical drying with scCO_2 is sketched in Fig. 9. Briefly, the wet gel is loaded into an autoclave/extractor (E1) and put in contact with CO_2 at a pressure and temperature above its critical point. The contact regime between the gel and the supercritical fluid determines the type of supercritical drying: loading of the extractor with scCO_2 in batches (static supercritical drying) or with a continuous flow of scCO_2 throughout the process (continuous

After a certain time, the extraction process is stopped and the autoclave is depressurized. The dry product remained in the autoclave called aerogel (Fig. 10). Table 3 shows typical properties of silica aerogel.

Property	Value	Comment
Apparent density	0.002-0.5 g/cm ³	Most common density is 0.1g/cm ³ ($\rho_{\text{air}} = 0.001\text{g/cm}^3$)
Inner surface area	400-1500 m ² /g	As determined by nitrogen adsorption / desorption. (A cubic centimeter of an aerogel has about the same surface area as one soccer field)

Solid percentage in volume	0.13-15 %	Typically 5 % (95 % free space)
Mean pore diameter	~20 nm	As determined by nitrogen adsorption/desorption (varies with density)
Primary particle diameter	2-5 nm	Determined by transmission electron microscopy
Index of refraction	1.007-1.24	Very low for solid material ($n_{\text{air}} = 1.004$)
Thermal tolerance	Up to 500°C	Shrinkage begins slowly at 500 °C, increases with increasing temperature. Melting point is ~1200°C
Poisson's ratio	0.2	Independent of density, similar to dense silica. Determined using ultrasonic methods.
Young's modulus	0.1-300 MPa	Very small ($<10^4$) compared to dense silica
Tensile strength	16 kPa	For density of 0.1 g/cm ³
Fracture toughness	~ 0.8 kPa.m ^{1/2}	For density of 0.1 g/cm ³ . Determined by 3-point bending
Dielectric constant	~1.1	For density of 0.1 g/cm ³ , very low for a solid material ($k_{\text{air}} = 1$)
Acoustic impedance	10 ⁴ Kg/m ² .s	Determined using ultrasonic methods at KHz frequency.
Sound velocity through the medium	20-800 m/s	100 m/s for density of 0.07 g/cm ³ , one of the lowest velocities for a solid material
Optical property	Transmittance >90% (630nm)	Transparent-blue haze
Thermal conductivity	~ 0.02 W/mK (20 °C)	Very low thermal conductivity. 2 cm slab provides the same insulation as 30 panes of glass

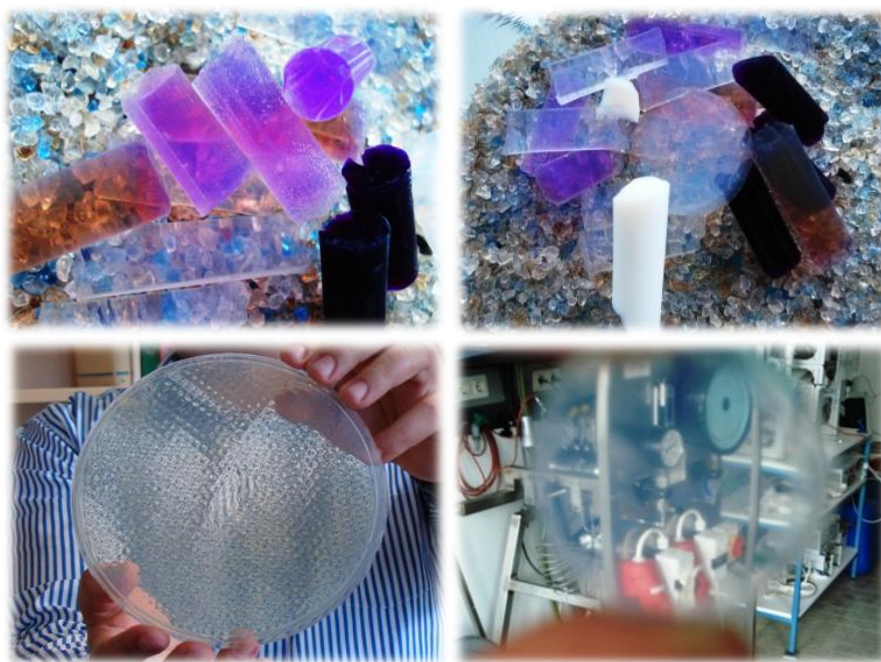


Fig. 10: Silica aerogels produced by supercritical extraction.

1.2.2.3.2 Ambient pressure drying

Supercritical drying is regarded as an expensive step that hinders commercialization of aerogel. Ambient drying of gels is considered as a promising solution for aerogel production toward economical scale production. As discussed previously, during ambient drying of the gel a meniscus is formed between the gas and liquid phases, this generates a capillary pressure able to destroy the gel structure. Accordingly, one of the proposed solutions was to avoid the presence of such menisci through preventing the presence of two phases at a time (supercritical drying). On the other hand these capillary forces can be minimized by influencing the contact angle between the solvent/vapor interface and the pore wall. This implies a modification of the gel inner surface.

Silylation is an example of silica gel surface modification. Here the OH of the Si–OH groups is replaced by Si–R group, where R is a hydrophobic group. As a result a hydrophobic gel is obtained (Fig. 11).

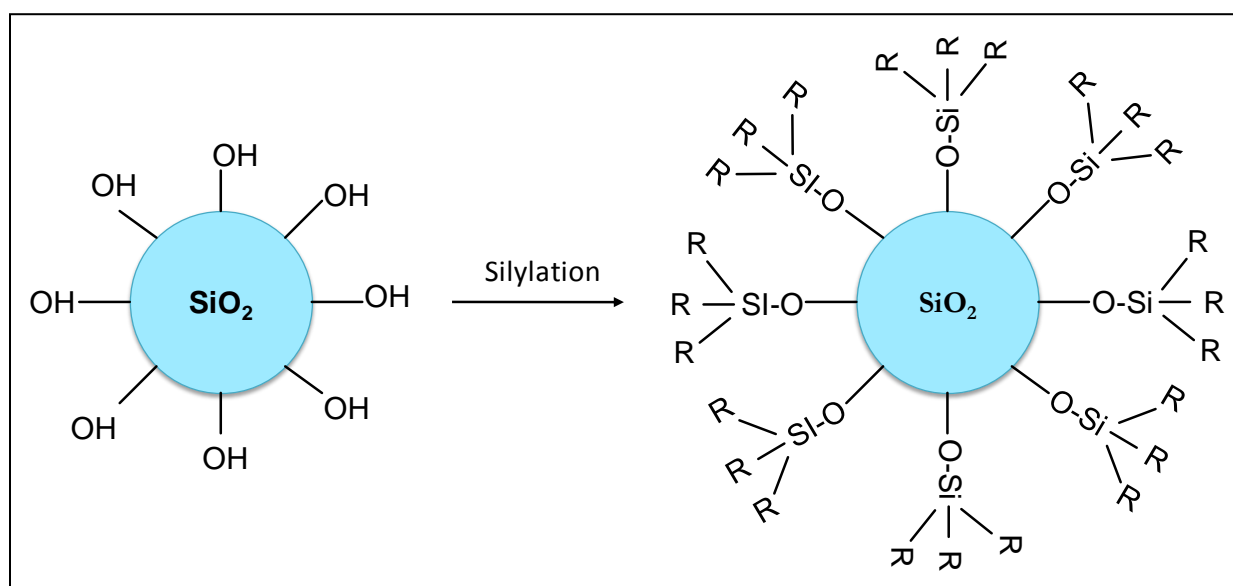


Fig. 11: Modifying silica gel surface by the silylation reaction.

Two basic methods are used to modify the silica gel: 1) using coprecursors during the sol preparation; 2) post treatment of the gel by placing it in a solution of the silating agent ([Bangi et al.](#),

[2008](#); [Venkateswara Rao et al., 2007](#)). Vinyl-Tris-(methoxydiethoxy)silane (VTMS), propyltrimethoxysilane (PTMS), propyltriethoxysilane (PTES), trimethyl(methoxy)silane (TMMS), methyl triethoxysilane (MTES), hexamethyldisilazane (HDMZ), hexamethyldisiloxane (HDMZO) and dimethyldimethoxysilane (DMDMS) are among the most popular used silating agents([Hegde et al., 2007](#); [Venkateswara Rao & Kalesh, 2003](#); [Venkateswara Rao & Pajonk, 2001](#); [Venkateswara Rao et al., 2001](#); [Wagh, et al., 1999](#); [Wagh et al., 1998](#)). Finally, before the drying step, solvent exchange takes place (using of a solvent with low surface tension). Eventually, drying can take place at ambient pressure. Improving the textural properties of the produced aerogel so that they are comparable with those of aerogel produced from the supercritical drying route would be a key development. Moreover, continuous production schemes as well as reduction of process steps (solvent exchange) are important as well ([Gurav, Rao, et al., 2010](#); [Ingale, et al., 2010](#); [Nadargi & Rao, 2009](#); [A. P. Rao & Rao, 2009](#); [A. P. Rao et al., 2008](#); [A. V. Rao et al., 2010](#); [Shewale et al., 2008](#)).

1.3 Silica aerogel applications

Fig. 12 shows a general overview of aerogel applications based on some specific properties.

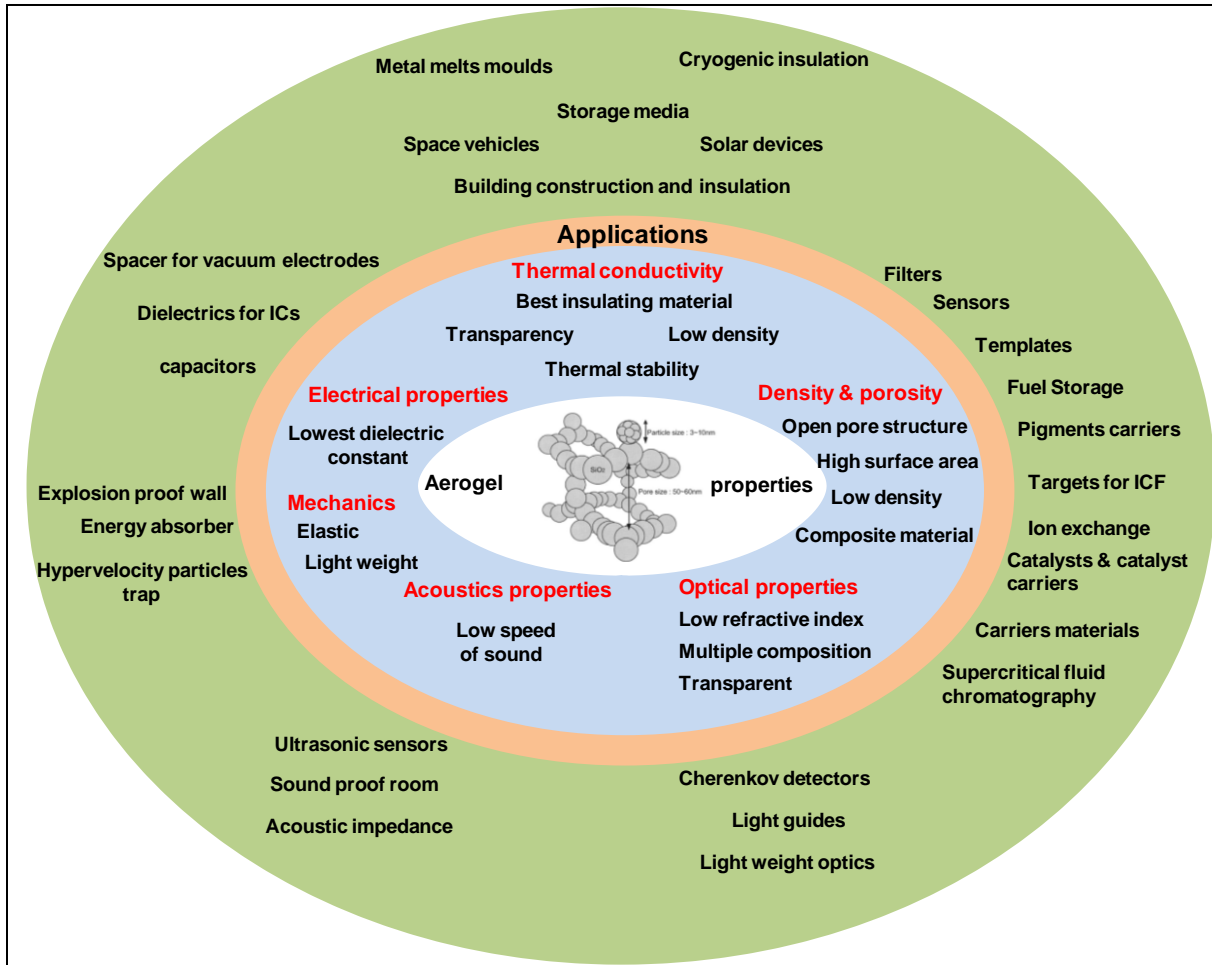


Fig. 12: General overview of aerogel applications ([Akimov, 2003](#); [Gurav, Jung, et al., 2010](#)).

1.3.1 Aerogel for space engineering

NASA use aerogel to trap space dust particles. Because of its porous structure and low density, aerogels are able to trap space projectiles traveling with hypervelocity speed (order of km s^{-1}). This action is not possible using other materials with higher density than aerogel; upon collision and removal of these particles for analysis, severe damages and even a complete loss of the trapped particles are observed. Moreover, NASA used aerogel for thermal insulation of Mars Rover and space suits ([Burchell et al., 2008](#); [Fesmire, 2006](#); [Johnson et al., 2010](#); [N. Leventis, 2005](#)).

1.3.2 Aerogel for thermal insulation

Beside its porous structure and low density, the very low thermal conductivity of aerogel ($20 \text{ mWm}^{-1}\text{K}^{-1}$ at room temperature and for 0.1 g cm^{-3} density) makes aerogel a competitive candidate in the insulation technology. This fascinating property allows providing a sufficient insulation with a thin profile. Some products are already available on the market, although their use is still constrained because of the relatively high cost of the product. Aspen Aerogels makes an aerogel blanket called Spaceluft for Interior/exterior walls, floors, and roofs insulation. Furthermore, they produce several other products like: Pyrogel® XTF, Pyrogel® 6650, Cryogel® x201, etc. which can be used for diverse thermal insulation applications ([aspen-aerogels](#)). Moreover, Thermablok produces narrow strips containing aerogel that may be a more cost-effective way of utilizing aerogel insulation ([Bardy et al., 2007](#); [Coffman et al., 2010](#); [Thermablok](#); [S. White et al., 2010](#)).

1.3.3 Aerogel as a catalyst

Being highly porous materials with a high surface area per unit mass, aerogels are ideal candidates as catalysts or catalysts carriers. Furthermore, the possibilities to produce different composites of aerogel materials make them promising candidates for heterogeneous catalysis systems; where the reactions take place in the gas or the liquid phase ([Aravind et al., 2009](#); [L. Chen et al., 2010](#); [Lee et al., 2009](#); [Lukić et al., 2010](#); [Mejri et al., 2010](#)). Table 4 shows some examples where aerogels were used as catalysts or catalyst carriers. Older systems are reviewed in the thesis of I. Smirnova ([I. Smirnova, 2002](#)).

Table 4: Examples of using aerogel as a catalyst or catalyst carrier.

Aerogel catalyst	Reaction	Reference
Silica-titania aerogel	Transformation of 1-octene to 1,2-octanediol	(Lee et al., 2010)
Phosphate-vanadium impregnated silica-titania	Transformation of 1-octene to 1,2-octanediol	(Lee, et al., 2009)

Sulfated silica-titania aerogel (SO₄/ST)	Transformation of 1-octene to 1,2-octanediol	(Ling & Hamdan, 2008)
Silica aerogels	Transesterification of a vegetal oil with methanol	(Nassreddine et al., 2008)
Au/titania-coated silica aerogel	CO oxidation	(Tai & Tajiri, 2008)
Silica supported sulfated zirconia	n-hexane isomerization reaction	(Akkari et al., 2008)
Pt and Co doped silica aerogels	Preferential oxidation of CO in H ₂ -rich fuels	(Choi et al., 2008)
Cobalt, iron and ruthenium catalysts supported on silica aerogel	Synthesis of a variety of hydrocarbons from syngas	(Ma et al., 2007)
Ceria-doped silica aerogel	Producing hydrogen from coal-derived syngas	(Turpin et al., 2006)
Niobia-silica aerogel mixed oxide catalysts	Epoxidation of olefins with hydrogen peroxide	(Somma et al., 2006)
Iron oxide-silica aerogel	methanol partial oxidation	(C. T. Wang & Ro, 2005)
Cobalt catalysts supported on silica aerogel	Fischer-Tropsch synthesis	(Dunn et al., 2005)
Hydrophobic silica aerogel-lipase	Esterification reaction of lauric acid with 1-octanol	(El Rassy et al., 2004)
Cobalt and ruthenium catalysts supported on silica aerogel	Fischer-Tropsch synthesis	(Dunn et al., 2004)
Silica aerogel-iron oxide nanocomposites	Biginelli reaction	(Martínez et al., 2003)
Alumina/silica aerogel with zinc chloride	Alkylation catalyst	(Orlović et al., 2002)
Titania-silica aerogels	Epoxidation of isophorone with TBHP	(Müller et al., 2000)

1.3.4 Aerogel as a sensor

Since aerogels are nanoporous materials with an open and accessible pore structure and high surface area, they are potential candidates as sensors. Plata et al. have used silica aerogel as a fast sensor for detecting the change of oxygen concentration ([Plata et al., 2004](#)). Moreover, because of low density, low elasticity, and extremely low acoustic impedance, Iwamoto et al. has proposed the use of silica aerogel in a sensitive sensor for a wide range of sound frequencies, since silica aerogel

structure enables the uptake of acoustic energy from ultrasonic waves ([Iwamoto et al., 2009](#)). Furthermore, aerogels have found their way as biosensors. They have been successfully used in formulation for recognition of short human gene ([Y. K. Li et al., 2010](#)).

1.3.5 Aerogel for microelectronics

Among other outstanding properties of aerogel, holding the record in being the material with the lowest dielectrical constant makes aerogels a potential material for electronics. Introducing aerogel to electronic chips allows the reduction of the appropriate parasitic capacitance and hence an increase in response speeds. One of the challenges of this technology is to apply the thin films of aerogel onto silicon substrates with sufficient adhesion ([Gómez et al., 2002](#); [C. T. Wang & Wu, 2006](#)).

1.3.6 Aerogel as cherenkov counters

One of the promising applications that promote the development of high quality transparent silica aerogel was the use of this low density material in physics as Cherenkov detector ([Alexa et al., 1995](#); [Aschenauer et al., 2000](#); [Bourdinaud et al., 1976](#); [De Brion et al., 1981](#); [Fernandez et al., 1984](#); [Lagamba et al., 2001](#); [Sallaz-Damaz et al., 2010](#); [Tabata et al., 2010](#)). Cherenkov radiation occurs when the velocity of a charged particle (v) moving through a material with a refractive index n exceeds the velocity of light (c/n) in this material (c is the velocity of the light in the vacuum). The medium is polarized in such a way that light is emitted at an angle θ_c with respect to the momentum vector comparable to a super-sonic shock wave. The angle is given by $\cos(\theta_c) = (\beta n)^{-1}$, with $\beta = v/c$.

The selection of a transparent material with a specific refractive index as a Cherenkov radiation source, depend on the goals of the targeted experiment. Gases have the lowest values of refractive indices, whereas, solid material have the highest values. Liquids have intermediate values of refractive indices. Until aerogel were discovered, there was a gap between the refractive indices of

gases and that of liquids limiting the use of this technique in detecting particles that needs this refractive index ranges. Besides possessing this refractive index range (1.007-1.24), aerogels are solids and easy to be handled in contrast to gases and liquids. ([Akimov, 2003](#); [I. Smirnova, 2002](#)).

1.3.7 Aerogel as adsorbent

Because of their high surface area, aerogels can be an ideal filter or sorbent media. Fisher et al have reported aerogel as one of the top ten technologies that could have a major effect on pollution control and abatement in the near future. Accordingly, aerogel could be used to soak up heavy metals in runoff water from polluted industrial sites ([Fisher, 2008](#)). The versatile sol-gel technology allows the modification of aerogels structural and surface properties. Hydrophobic aerogels were found to be a competitive candidate for adsorption of oil and other organic compounds. Several attempts have been already reported to use them for cleaning oil splits from water ([Gurav, Rao, et al., 2010](#); [Quevedo et al., 2009](#); [Reynolds et al., 2001](#)). The hydrophobicity of the material enhances the adsorption capacity of organic compound and give them the strength to withstand being in liquids. The adsorption capacity of aerogel can be at least two orders of magnitude of that of activated carbon of the same mass([Akimov, 2003](#)). Sintered silica aerogels, have been reports as a host matrix for storing long life nuclear wastes and up to 10 wt.% of storage have been successfully achieved ([Woignier et al., 1998](#)). Silica aerogel/activated carbon composites were also assessed for purifying aqueous solutions from uranium ([Woignier, et al., 1998](#)). Furthermore, composites of Aerosol® 380 and hydrophobic aerogels have been reported for confining nuclear wastes ([Aravind et al., 2008](#)). Power et al. have reported the possibility of using aerogel as biofilters. Accordingly, the high surface area and porous structure of aerogel can be used as a filter to purify air from viruses and bacteria ([Power et al., 2001](#)). Composites of silica aerogels and vanadium, copper and aluminum were proposed as a heterogeneous catalysis in the car exhaust pipe for reduction of NO_x emissions from cars ([Chono et al., 2001](#); [M. Kang et al., 2009](#)). Being inert, insoluble and thermodynamically-

stable materials, aerogels can be a promising candidate for long-term storage of CO₂. Furthermore, the possibility of modifying the shape, chemistry and surface functionality of aerogels can enhance and facilitate this process ([Santos et al., 2008](#)).

1.3.8 Aerogels as an active agent carrier

Besides their high surface area, pore structure and low density, being biocompatible, makes silica aerogel an ideal candidate for a varieties of life science applications. Silica aerogel were firstly used in 1960s as an additive for cosmetics and toothpaste under the name of Monsanto's aerogels. The production has lasted for few years until silica aerogel was replaced by the cheap fumed silica. During the following decades aerogel production has been continuously improved resulting in spectacular properties and in the same time the cost factor was slowly minimized. In spite the cost factor, silica aerogel is chemically identical with fumed silica; the later has been proven to be used for pharmaceutics and food industry ([Degussa, 2001](#)), furthermore, silica aerogel characterized with higher surface area (1000 m²/g) than that of fumed silica (200 m²/g). These factors derive scientists to investigate silica aerogel as a carrier system for different active compounds. However, it should be mentioned that a complete toxicity investigations on silica aerogel are not available.

In principle, active compounds can be loaded on silica aerogel matrix following two main routes: (1) mixing the active compounds drug with the sol before the gelation takes place, followed by the drying step (Fig. 13 A); (2) post treatment of the aerogel in a way that allows the deposition of the active compound particles on aerogel surface. (Fig. 13 B).

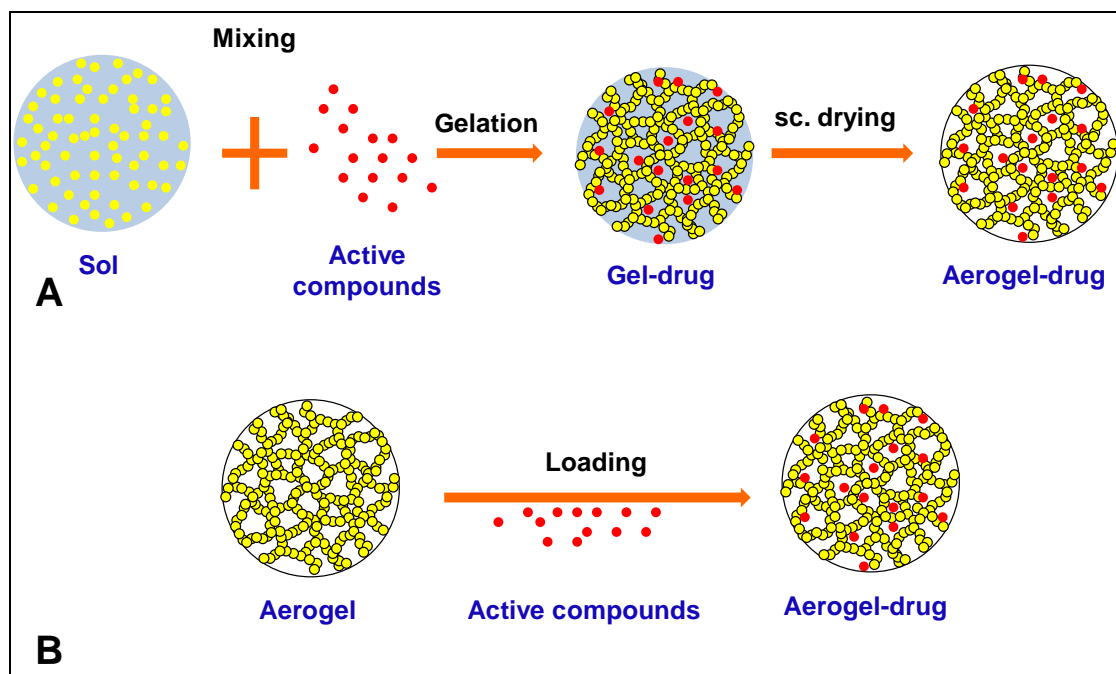


Fig. 13: Possible methods of loading aerogels with drug: A) mixing during the sol-gel process; B) adsorption from sc. CO₂ phase.

1.3.8.1 Route one

Route one characterized by the simplicity of the process. Here the active compound can be added to the sol as a liquid or powders and mixed with the sol at the molecular level. Limiting ourselves to pharmaceutical and food processes, there have been some reports that employ this technique to load aerogel with the needed active compounds. Mehling et al. have load different polysaccharide based aerogels with two different drugs namely, ibuprofen and paracetamol. Depending on the used matrix they have reported a loading of about 25 wt% for both used drugs ([Mehling et al., 2009](#)). Klug et al. have reported the possibility to encapsulate ketoprofen within PLGA gel using emulsion technology. However, they report the use of the sc.CO₂ for extraction of the organic phase of the emulsion and no reports for aerogel production was recorded ([Kluge, Fusaro, Casas, et al., 2009](#); [Kluge, Fusaro, Mazzotti, et al., 2009](#)). Several research groups have used this method or similar one to load the gel with a certain active compound. Draget et al. have reviewed the use of alginate gel for encapsulation of drugs, accordingly, beside using alginate as a

vehicles for drugs, alginate itself can be used to heal some respiratory diseases ([K. I. Draget & Taylor, 2011](#)). In order to overcome the problem of low water solubility and severe toxicity of some drugs, Li et al. has proposed a drug carrier based on chitosan. They have propose this kind of carrier to treat human ovarian cancer ([X. Li et al., 2011](#)). Many other authors have reported the usage of gel for encapsulation of different active components ([Saboktakin et al., 2010](#); [C. M. Silva, A. J. Ribeiro, D. Ferreira, et al., 2006](#); [Yang et al., 2000](#)). In principle, this is only one step before converting these formulations to aerogel-drug systems. Still, many precautions should be considered; for instance, the reactivity of the active compounds with the sol components, which may include undesired transformation. Stability of the loaded materials throughout the aerogel process is an important factor that needs to be carefully investigated. Addition of further materials to the sol-gel process can influence the gelation process and the final properties of the produced aerogel. Furthermore, it is possible to lose the active compound during the supercritical drying step by simply wash out effect.

1.3.8.2 Route two

In order to prevent the capillary forces that can partially or completely destroy the aerogel texture, route two requires the loading of the active component from the gaseous or the supercritical phase. It is known that most pharmaceutical and food active compounds are temperature sensitive materials; hence, it is possible to limit this technique to adsorption of the active compounds from sc.CO₂ or gaseous loading through allowing the gas/vapor of those volatile active compounds to pass through aerogel network. The main drawback of this process is that it required an extra processing step which can be considered as an extra cost factor. Furthermore, the use of this process implies the solubility of the active component in sc. CO₂ phase, or having a high vapor pressure to evaporate the active compound below its decomposition temperature. In 2003, Smirnova et al. have firstly demonstrated the possibility to load silica aerogels with active components by adsorption from their sc. solutions ([I. Smirnova, Arlt, W., 2003](#)). Thereafter, this process was intensively

investigated for a variety of drugs and process conditions. Investigating the drug adsorption isotherms on aerogel was proposed as a method for controlling the dosage of specific drugs on aerogel surface. Furthermore, surface hydrophobicity was shown to influence the loading of a model drug, namely ketoprofen ([I. Smirnova et al., 2003](#)). One year later, the role of aerogel in the enhancement of the dissolution rate of poorly water soluble drugs was reported, griseofulvin and ketoprofen were taken as model drugs for this investigation. It was shown that the dissolution rate of these drugs-aerogel formulations was at least five times faster than that of the crystalline drug form. The dissolution enhancement was explained by enlarged specific surface area of the drug by adsorption on silica aerogel and the immediate collapse of aerogel network upon contact with aqueous media ([I. Smirnova, Suttiruengwong, & Arlt, 2004](#); [I. Smirnova, Suttiruengwong, Seiler, et al., 2004](#)). In 2005, Smirnova et al. have shown a comparison of dissolution enhancement using different preparations. It has been reported that griseofulvin-aerogel formulation shows much better dissolution enhancement than that of micronized griseofulvin with conventional milling or rapid expansion of supercritical solution (RESS) processes. They have justified this behavior with the help of IR investigations which have shown no crystallinity structure of the drug adsorbed on aerogel, whereas those from the other preparation were crystalline, not forgetting the effects described in their previous work ([I. Smirnova, Turk, et al., 2005](#)). After that, the possibility of tailoring the drug release profile by means of surface modification was proposed. Prolong and immediate release were obtained from drug-aerogel formulation based on its hydrophobicity ([I. Smirnova, Suttiruengwong, et al., 2005](#)). New possibilities of silica aerogel in pharmaceutical industries were explored by the so called adsorptive crystallization. Here the possibility of production of micro organic particles inside aerogel pores was investigated, based on solute-aerogel interaction amorphous or crystalline state of the loaded component can be obtained ([Gorle et al., 2008](#)). The usage of silica aerogel as a drug carrier system for dermal delivery route was firstly proposed by Günther et al. Dithranol (unstable

and nearly insoluble drug) was loaded on silica aerogels. The penetration and drug availability were compared with different standard preparations using two different membrane systems to simulate human stratum corneum. Accordingly, aerogel formulation has shown a superior penetration profile over the standard ointments ([Guenther et al., 2008](#)). Thermal trigger release of volatile compounds with adjustable release temperature was proposed by Gorle et al., they have shown that the surface functionality of aerogel as well as the chemical structure of the adsorbed compounds contribute significantly in the loading-release process ([Gorle, Smirnova, & McHugh, 2009](#)). The significance of this work arises from the possibility to use such systems for storage and transportation of highly volatile chemicals with potential applications in the food, drug, flavors, and other industries. Mehling et al. have also used this technology for loading aerogel with drugs. However, they have used organic matrices as a drug carrier based on polysaccharide. Hence, they have attained the challenge of having biocompatible and biodegradable drug carrier ([Mehling, et al., 2009](#)).

Recently several groups have reported this method for the loading of drugs or active compounds on aerogels. Su et al. have investigated the adsorption of two different esters on C18-bonded silica from sc. CO₂. They have reported the effect of temperature, pressure and the solute properties on the adsorption equilibrium curves. Accordingly the main factors that affect the heat of the adsorption were found to be the density of the CO₂ and the adsorbed amount of the solute ([Su et al., 2009](#)). Miura et al. have investigated the dissolution rate of different drug formulations. They have found that adsorption of a very poorly water soluble drug (2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one (K-832)) from sc.CO₂ enhance their bio-availability. They have reported that up to ~70% of the loaded drug was released within 5 min. whereas, less than 2.5% from a physical mixture of the drug were release within 120 min ([Miura et al., 2010](#)). Murillo-Cremaes et al. have also used this method for synthesizing photo active molecules inside the pores of nanoporous materials. They have described this technology by “ship-in-a-bottle-approach”, being

a zero waste technology is one of the main advantages of this approach ([Murillo-Cremaes et al., 2010](#)).

2 *Development of New Processes for Production of Silica Aerogel Microspheres*

In this work, the development of two new technologies, namely, *in situ* preparation of silica aerogel microspheres using the emulsion technology and the modified spray drying are proposed. These techniques enable engineering of aerogels in the desired morphology and functionality. Fig. 14 shows three different techniques for processing the sol. If the sol placed on a mould and left there for aging, then the resultant product is a monolith gel with the shape of the mould. This is the most reported method for silica aerogel production (Fig. 14a) ([Al-Oweini & El-Rassy, 2010](#); [Gurav, Jung, et al., 2010](#); [I. Smirnova, 2002](#)). For wide range of applications aerogel microparticles with a specific shape are required, for instance, specific aerodynamic diameters is required for drug carriers used for inhalation route delivery systems. Crushing, milling or grinding of gel/aerogel monoliths can be the solution for producing microparticles. However, because of the fragility of gel/aerogel it is impossible to obtain specific particles shape (Fig. 15). This can be a limiting factor for many applications. Hence, in this work two new techniques were developed for *in situ* production of aerogel microparticles: (1) emulsification of the sol with an oil phase followed by supercritical extraction of oil-gel dispersion (Fig. 14b); (2) spraying the sol into an autoclave containing CO₂ at supercritical conditions through a nozzle (Fig. 14c).

2.1 *Chemicals*

The chemical needed for the production as well as characterization methods used in this work are described below.

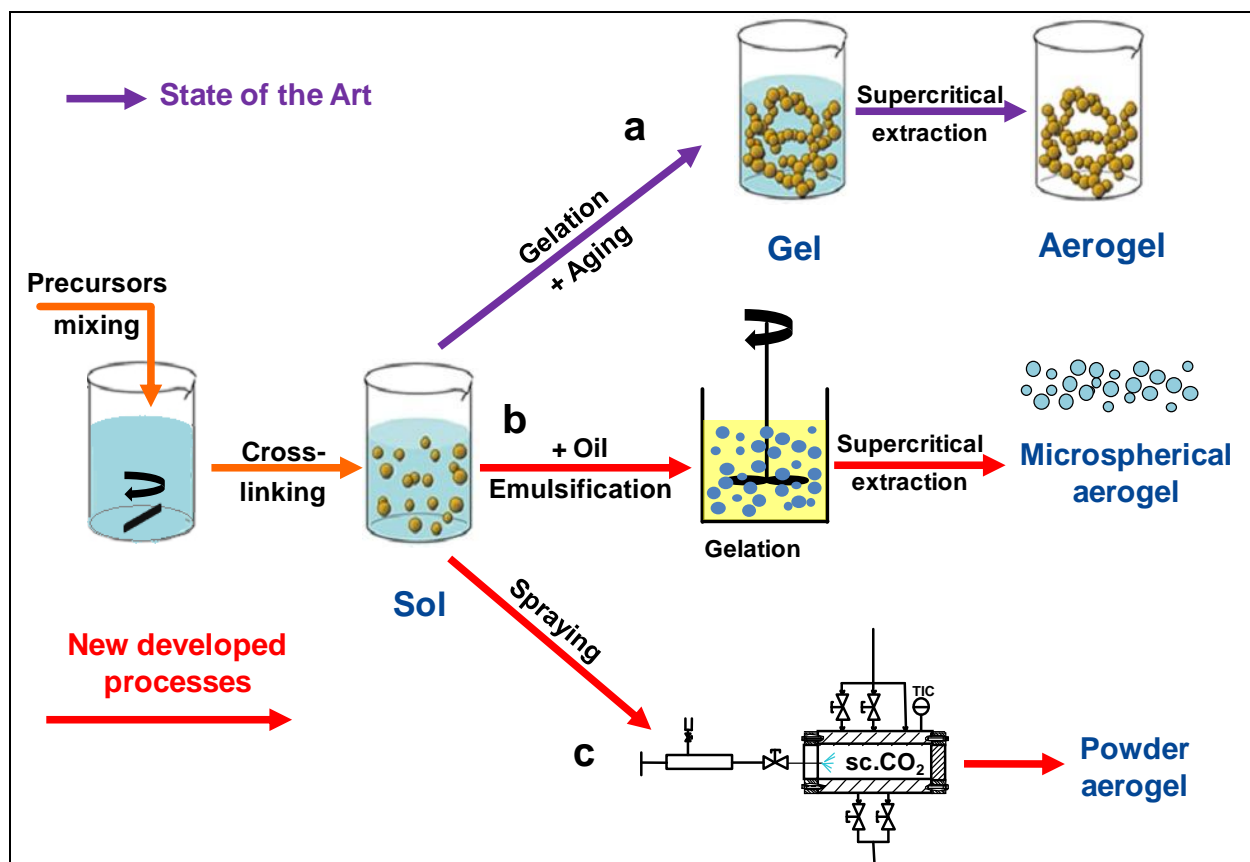


Fig. 14: Silica aerogel production methods: a) the state of art of monoliths production; b) emulsification the sol with an oil phase for production of microspheres aerogel; c) spraying the sol into an autoclave at sc.CO₂ conditions.

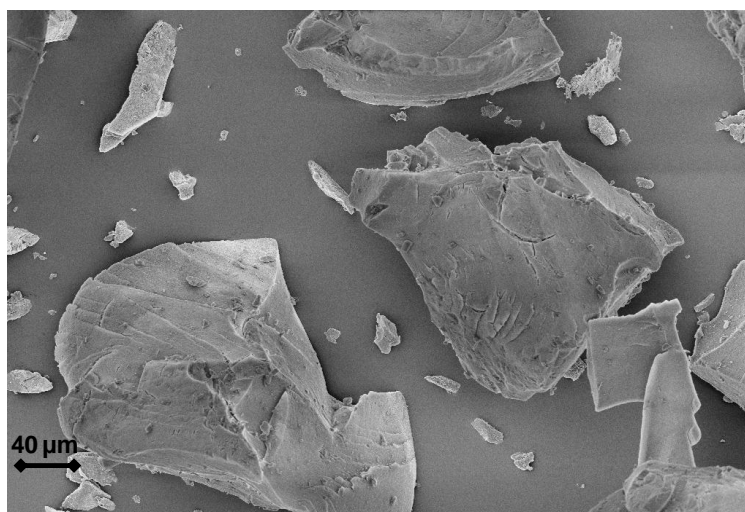


Fig. 15: Silica aerogel particles shape result from crushing aerogel monoliths using a lab mortar.

Aerogel synthesis materials: Carbon dioxide with a purity of (>99.9%) was supplied by AGA Gas GmbH, Hamburg. Tetramethoxysilane (TMOS), (APTMS) 97% and Acetonitrile (ACN) 99.8% were purchased from Fluka Germany. Ethanol 99.8%, glacial acetic acid, CaCl_2 , methanol 99.5%, ethanol (p.a.), hydrochloric acid 30% and ammonia hydroxide 25% were purchased from Merck Germany. CaCO_3 was kindly provided by Magnesia GmbH Germany. Glucono- δ -lactone (GDL) was purchased from Alfa Aesar, Germany. Paraffin oil was purchased from Carl Roth GmbH Germany. Vegetable oil was achieved from domestic shops. Na-alginate was purchased from Sigma life science, Germany.

Coating materials: Eudragit[®] L 30 D-55 was provided by Evonik, Germany. Polyethylene glycol 2000 (PEG 2000) was purchased from Fagron, Barsbüttel, Germany. Polysorbate 80 and triethyl citrate were bought from Carl Roth GmbH, Germany. glycerol monostearate was acquired from Caesar & Loretz GmbH, Germany.

Model drugs: Ketoprofen (racemic mixture) was purchased from Chemische Fabrik Kreussler & Co. GmbH. Ibuprofen (> 99%) was obtained from Fluka, Germany. Grisofolvin was achieved from Fagron, Barsbüttel, Germany.

All chemicals were used as provided without any further purification.

2.2 Characterization techniques

2.2.1 Nitrogen adsorption and desorption isotherms

Surface analyzer Nova 3200e (Quantachrom Instruments) was used to characterized the textural properties of the produced aerogels. Weighted samples correspond to 10-30 m² are pretreated under vacuum at temperature of 200°C to remove the adsorbed water. In case of functionalized and organic aerogels, pretreatment was performed at lower temperature to avoid undesired

conformation. Then, the samples are subjected to N₂ adsorption and desorption. The adsorption desorption isotherms data were analyzed using the following methods:

- Surface area: BET analytical method.
- Pore volume: filling the pores completely with liquid nitrogen at $P / P_0 = 0.99$.
- Average pore size distribution: BJH desorption method.

A detailed description of the used method and models can be found in literature ([Barrett et al., 1951](#); [Brunauer et al., 1938](#); [Condon, 2006](#); [Lowell, 2004](#)).

2.2.2 Microscopy

Aerogel particles shape and form were analyzed using light microscopy (Zeiss Microscope, Axio Scope, USA) and scanning electron microscopy (SEM) (Leo Zeiss 1530, USA).

2.2.3 Particle size distribution

The particle size distribution of the samples was determined in triplicate by laser diffraction using a dry dispersing system with a feeding air pressure of 1 bar (HELOS equipped with RODOS, Sympatec, Clausthal-Zellerfeld, Germany).

2.2.4 Elemental analysis

Elemental analysis (Euro EA elementary analyzer) is used to determine the amount of Carbon, Hydrogen, and Nitrogen (CHN). 2-3 mg of aerogel samples are burned at 1000°C in flowing oxygen. The obtained vapors containing CO₂, N₂, N_xO_y, and H₂O are analyzed using thermal conductivity detector. The amount of CHN is measured with an accuracy of ± 0.03 wt%. This method was used to quantify the amount of amino groups in the functionalized silica aerogel.

2.2.5 UV-VIS spectroscopy

Ultra Violet - Visible radiation spectrometer Evolution 300 from company Thermo Scientific was used to determine the concentration of solutes in aerogels. The aerogel samples filled with solutes are crushed, dispersed in the solvent and stirred for 1 hour. Thereafter, the solution was filtered and analyzed. In the present work three different solutes were measured using this method (Table 5).

Table 5: UV wavelength of the used organic substances.

Substance	Adsorption wave length λ
Ketoprofen	252 nm
Ibuprofen	220 nm
Griseofulvin	295 nm

2.2.6 Drug release

Drug release of the loaded aerogel was measured according to the Ph. Eur. in phosphate buffer (pH 6.8) or in HCl solution (pH 1.0) using a paddle apparatus (Sotax AT7, Allschwil, Switzerland) at 100 rpm and 37 °C. In each vessel containing 900 ml dissolution medium one sample unit corresponding to 3 mg of loaded drug was analyzed. The drug release profiles were recorded spectrophotometrically at the drug corresponding adsorption wave length (Table 5) ([Aulton, 2002](#)).

2.3 *Conventional method: monoliths as reference materials*

Silica aerogel were produced following the two step sol-gel process ([Alnaief & Smirnova, 2010a](#); [I. Smirnova, 2002](#); [Tillotson, 1992](#)). In the first step tetramethylorthosilicate (TMOS), methanol, water, and hydrochloric acid were mixed together with a molar ratio of:

1 mol TMOS: 2.4 mol MeOH: 1.3 mol H₂O:10⁻⁵ mol HCl.

The mixture was stirred at room temperature for 30 min. Then the mixture was diluted with acetonitrile to obtain the desired density of the aerogel. After that additional water and ammonia solution were added to obtain the following molar ratio:

1 mol TMOS: 2.4 mol MeOH: 4 mol H₂O: 10⁻⁵ mol HCl: 10⁻² mol NH₄OH.

After that, the mixture was stirred for 3 minutes. For some preparation acetonitrile was replaced with acetone or ethanol. Finally, the sol was poured into cylindrical moulds to be aged over night (Fig. 14a). To obtain aerogels the aged gels were then dried for 12 hours using supercritical CO₂ at 40°C and 100 bar, the average flow rate of CO₂ was 250 Nl/h.

The effect of reaction parameters on aerogel prepared by this method was intensively investigated in the literature ([Alnaief & Smirnova, 2010a](#); [Fricke & Emmerling, 1999](#); [Gorle, et al., 2008](#); [Gorle, et al., 2009](#); [Moner-Girona, 2002](#); [I. Smirnova, 2002](#); [I. Smirnova & Arlt, 2003](#); [Soleimani Dorcheh & Abbasi, 2008](#)) and are not the scope of this work. Hence, only a general overview of aerogels produced using this method will be given.

Table 6 shows the general textural properties of silica aerogel monoliths produced following the previous described procedure. These properties based on averaging the properties of at least 10 different production batches. These aerogels were taken as a reference to evaluate aerogels produced from the new developed techniques.

Table 6: Textural properties of silica aerogel monoliths produced following the two step method.

	Surface area [m ² /g] BET method	C constant BET method	Density [g/cm ³]	Pore radius [nm]	Pore volume [cm ³ /g] BJH method
Silica aerogel	1040 ± 52	86 ± 16	0.13 ± 0.06	8.72 ± 0.56	4.57 ± 0.18

2.4 In situ production of spherical aerogel microparticles: emulsion technique

In this work emulsion-based method for production of microspherical aerogel particles with controlled particle size distribution is proposed. Emulsion formation is a well known process that would allow production of a large amount of microspherical droplets in a robust and controlled manner. Still, production of a stable gel and extraction of the solvent from the gel are challenges in aerogel production. Thus, a modification of the established emulsion process is required to overcome these challenges ([S. Freitas et al., 2005](#)). The suggested process consists of four basic steps: (1) preparation of the disperse phase by the sol-gel process; (2) emulsification of the disperse phase in a continuous phase (oil, immiscible with the first one); (3) cross linking/gelation reaction within the dispersed phase (liquid microdroplets) to form stable gel microspheres; (4) CO₂ supercritical extraction of the oil-gel dispersion to obtain the final microsphere aerogel particles. These steps are schematically presented in Fig. 16.

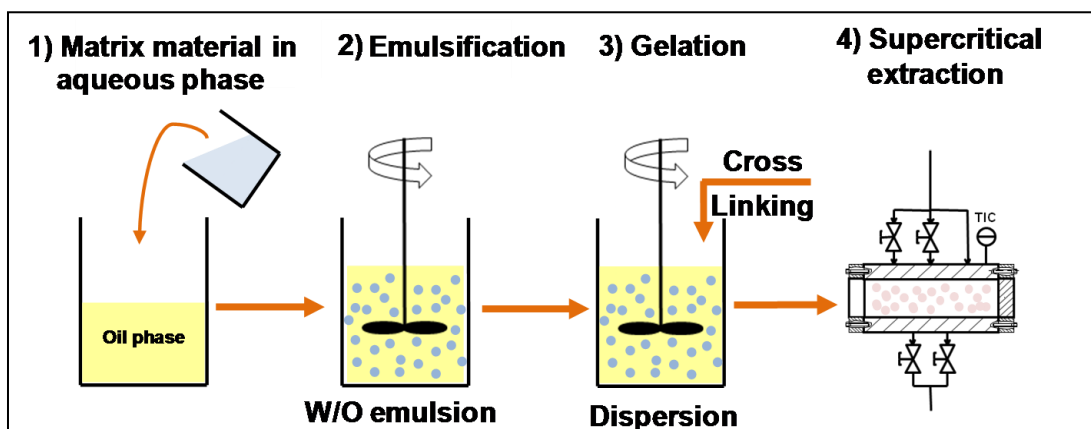


Fig. 16: Schematic overview over the four main steps in aerogel microsphere preparation by emulsion method combined with supercritical extraction.

2.4.1 Setup

It is possible to divide the setup used for this process into two main blocks: (a) the emulsification unit; (b) the sc. CO₂ drying unit.

The emulsification consists of two main parts:

- Mechanical mixer: consists of a motor (RZR 2020, Heidolph Instruments GmbH & Co. KG, ([Heidolph](#))) connected to a mixer through a shaft. The motor can deliver a rotational speed ranging from 40 to 2000 rpm. Depending on the desired power input, different types of mixers can be attached, for instance: radial, axial and marine mixer.
- Vessel: baffled or normal beakers with different sizes were used as a pot for the emulsification of the oil-sol phase.

The supercritical CO₂ drying unit consists of:

- Two cylindrical high pressure vessels (2 and 4l).
- NOVA SWISS[®] diaphragm compressor with a maximum output pressure of 1000 bar ([Spargue-products](#)).
- Tubing system connects the individual parts
- Temperature, pressure and flow gauges.

A schema of the used unit is shown in Fig. 17.

2.4.2 Procedures

2.4.2.1 Preparation of the sol phase

Silica sol was produced following the two step sol-gel process as described in section (2.3). However, instead of acetonitrile, ethanol was used to obtain the required density. After adding the second components, the mixture was mixed for further 3 min. before pouring it into an oil phase.

2.4.2.2 Emulsification of the silica sol in an oil phase

Canola oil (continuous phase) saturated with ethanol was placed in a 600 ml vessel and mixed using a stirrer with a constant stirring rate. The sol (dispersed phase) was then poured into the oil phase at once. Subsequently, droplets of the dispersed phase were formed under continuous stirring. After 20-30 min. the gelation of the dispersed phase took place. At this stage the stirring was stopped since the emulsion converted into dispersion of spherical gel particles in the oil phase. Thus the described method is different from that where CO_2 acts as antisolvent to precipitate the dispersed phase from an emulsion ([Mattea et al., 2010](#)). Furthermore, the supercritical CO_2 phase will not affect the emulsion properties ([Mattea, et al., 2010](#)), since simply at supercritical extraction stage there is no emulsion anymore, but oil-gel dispersion. Finally the gel spheres were left over night in the oil phase for aging.

2.4.2.3 Supercritical extraction of the gel-oil dispersion

A process flow diagram of the supercritical extraction is shown in Fig. 17. In a typical experiment, the gel-oil dispersion was placed into the 4 l cylindrical stainless steel vessel. Supercritical CO_2 was delivered using a high pressure diaphragm pump and was introduced from the top of the vessel at constant flow rate (100 – 200 g/min). Temperature was maintained constant at 40-50 °C using an oil heating jacket. At the outlet of the vessel sc. CO_2 loaded with solvent and oil was directed to another 2 l cylindrical stainless steel vessel (separator), where oil and solvent were separated from CO_2 . The pressure and temperature of the separator were maintained constant at 40-50 °C and 50-60 bar respectively. Solvent-lean CO_2 was then recycled to the 4 l autoclave. After 8 hours the extraction was completed. The aerogel microspheres were removed from the 4 l autoclave, whereas the solvent-oil mixture was removed from the bottom of the separator (2 l autoclave). Typically the recycled CO_2 was exchanged for fresh CO_2 at least four times during the extraction process to ensure the complete extraction of the gel. The extraction of a gel using supercritical CO_2

is a mass transfer problem in which the diffusion rate of the ethanol from the gel pores is inversely proportional to the square of the radius (cross sectional radius of the cylinder, or the radius of the sphere) (Bird et al., 2002). Thus, the extraction time needed to produce aerogels in form of microparticles is much shorter than that needed for the supercritical extraction of the same gel volume in form of monoliths.

It should be mentioned that it was also possible to separate oil from the gel phase by filtration before supercritical extraction. However, since oil is very good extractable with supercritical CO₂ (King & List, 1996), it was more convenient to skip this step and conduct the extraction for the complete oil-gel dispersion and recycle the extracted oil-ethanol mixture.

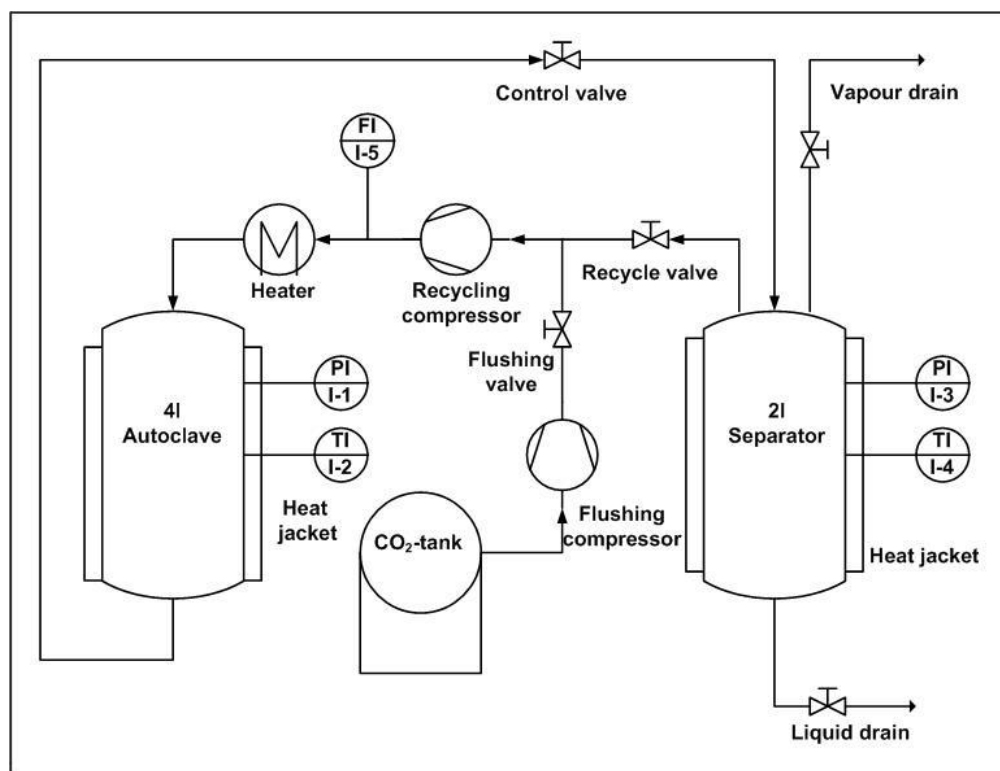


Fig. 17: Schematic diagram of the 4 L supercritical extraction unit.

2.4.3 Results and discussions

Particle shape and size distribution produced by the emulsion process depend on different parameters, these parameters can be classified to three main groups: (1) geometrical parameter, like the mixer shape and diameter; (2) physical parameters like viscosity and density; (3) process related parameter, like stirring rate ([Zlokarnik, 2001](#)). Mixer shape and speed are the easiest parameters to control the dispersion of the dispersed phase in the continuous phase. However, the minimum attainable droplet size depends on many other parameters like the viscosity of the dispersed and continuous phases, the interfacial tension between the two phases, their relative volume ratio, the size ratio of mixer to the mixing vessel, number of mixers, etc. ([S. Freitas, et al., 2005](#)).

In this work, the following parameters were investigated in order to control the final product properties: stirrer geometry, phase ratio, surfactant concentration and stirring rate.

2.4.3.1 Effect of the phase ratio (dispersed to continuous phase)

The impact of the volume ratio between the dispersed and the continuous phase on the PSD of the resulting microspheres is not fully understood. Various studies report the reduction of the mean particles size with a reduction in the volume of the continuous phase ([Jeffery et al., 1991](#)), while other studies report that no significant effect was observed ([Gabor et al., 1999](#)). In this study, four different sol:oil volume ratios were investigated, namely: 2:1, 1:1, 1:2 and 1:3, for all experiments a constant total volume (100 ml) and stirring rate (500 rpm) was used. For the sol:oil ratio of (2:1) no microspheres could be obtained. Since the sol phase is larger than the oil phase, there was no chance to get sol droplet dispersed in the oil phase. When the gelation took place the sol phase transformed to a separate continuous gel phase. For all other investigated phases volume ratios it was possible to obtain microspherical particles. It was noticed that the mean particle size increases as the oil phase increases (Table 7). Taking into consideration that the viscosity of the oil phase is about 50 cP ([Abramovic, 1998](#)), and that of aqueous phase is about 1 cP, then by increasing the oil phase ratio

the total viscosity of the system increases, consequently more energy is needed to form the same micro particles. Based on these findings, the sol:oil ratio of 1:1 was chosen for further experiments, since smaller amount of oil is preferable for further extraction.

Table 7: Particle size distribution of the aerogel microspheres as a function of water /oil phase ratio (0% surfactant, 500 rpm).

Phase ratio	w/o 1:1	w/o 1:2	w/o 1:3
Average [μm]	722 ± 15	803 ± 16	853 ± 17
D₁₀ [μm]	197 ± 24	338 ± 15	317 ± 48
D₅₀ [μm]	703 ± 16	813 ± 13	876 ± 17
D₉₀ [μm]	1255 ± 26	1243 ± 21	1345 ± 27
D₃₂ [μm]	269 ± 11	339 ± 8	368 ± 9

2.4.3.2 Particle shape and size distribution: effect of agitator shape

For the first set of experiments, a four bladed radial stirrer (diameter = 5 cm) was used to emulsify 200 ml sol-oil mixture (1:1 volume ratio) in a 600 ml vessel (9 cm internal diameter). The resulting aerogel particles were observed by light microscopy. It was noticed that for a high stirring rate (1000-1800 rpm) particles were not uniform in shape (Fig. 18 a) and some breakages were observed. However, at a lower stirring rate, 800 rpm, microspherical gel particles with the diameter between 100 and 200 μm were obtained (Fig. 18 b). Although the particles were spherical, for many applications it is beneficial to have a smaller mean particle size less than those obtained using these conditions. However, this is not possible using this kind of stirrer due to the high shear stresses applied to gel particles at the tip of the blade during mixing. Moreover, radial mixers result in such flow profile that particles collide with the vessel walls. This amplifies high collision energy which leads to the abrasion and destruction of the spherical gel particles. For this reason another type of stirrer, which allows high energy input and smooth flow pattern, namely, a two bladed axial stirrer,

was chosen. For this type of stirrer it was possible to produce spherical particles at much higher revolution speeds (up to 1800 rpm) (Fig. 18 c). To understand the different behaviors of these stirrers, the power number and the stirrer power of these two different stirrers were compared. The power number for the 4 bladed stirrer is 5 with a stirrer power of 38.8 W, whereas that of the axial stirrer was only 0.4 and 7.7 W as stirrer power, keeping all other process parameters unchanged (viscosity, density, dimensions, rpm). The values results from the two bladed axial stirrer at 1800 rpm correspond to a stirring rate of 1000 rpm of the four bladed radial stirrer ([Zlokarnik, 2001](#)). Based on these findings, all further experiments were conducted using two bladed axial stirrer.

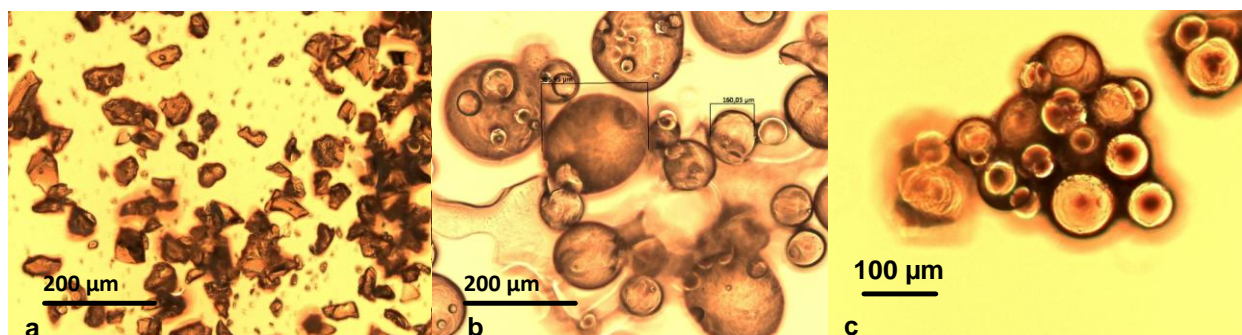


Fig. 18: Effect of stirrer type and revolution rate on the form of silica gel particles: a) 4 blade stirrer at 1800 rpm; b) 4 blade stirrer at 800 rpm; c) propeller at 1800 rpm.

2.4.3.3 Effect of stirring rate

In order to investigate the effect of the stirring, the two bladed axial stirrer (diameter = 6 cm) was used to emulsify 200 ml of system (sol:oil phases volume ratio= 1:1) with different revolution speeds. The particle size distributions (PSD) as a function of the stirring speed are determined by laser scattering analysis reported in Table 2. The mean particle diameter (D_{50}) varies from 1730 μm to 143 μm , when the stirrer revolution rate varies from 200 to 1300 rpm respectively (Table 8). Increasing the mixer speed results in a higher energy input to the system, this allows the building of larger interfacial surface area, thus the dispersed droplets become smaller, and consequently the gel microspheres will have a smaller mean size ([Yang, et al., 2000](#)). These results confirmed that the

main factor in controlling the PSD is the stirrer revolution rate ([Jung & Perrut, 2001](#); [Mateovic et al., 2002](#); [Rafati et al., 1997](#)). It can be noticed that the PSD is relatively broad in all cases. Among many other factors, viscosity of the dispersed as well as the continuous phase play a major role in controlling PSD of the emulsion process ([Yang, et al., 2000](#)). In our process, the viscosity of the continuous phase remains nearly constant (50.8 cP) throughout the experiment. However, the viscosity of the dispersed phase (sol phase) increases continuously with time until the formation of the gel particles. This might lead to the broadening of the resulting particle size distribution (Table 8).

Table 8: Particle size distribution of the aerogel microspheres as a function of the revolution speed during emulsification.

Rpm	200	300	400	500	600	800	1300
Average	1720 ± 23	1615 ± 70	996 ± 95	908 ± 32	601 ± 35	323 ± 27	155 ± 7
D₁₀ [μm]	1166 ± 6	987 ± 100	522 ± 36	495 ± 40	281 ± 60	194 ± 22	46 ± 2
D₅₀ [μm]	1729 ± 18	1645 ± 60	957 ± 80	842 ± 18	566 ± 28	310 ± 22	143 ± 2
D₉₀ [μm]	2267 ± 14	2214 ± 36	1509 ± 100	1386 ± 100	957 ± 18	494 ± 16	277 ± 14

2.4.3.4 Effect of surfactant concentration

A stabilizer (surfactant) is generally added to the continuous phase to prevent coalescence of the droplets. Increasing the surfactant concentration leads to a reduction of the interfacial surface tension, as a result smaller droplets sizes are usually produced (under the same stirring conditions)([Mittal, 2010](#); [Myers, 2006](#); [Tadros, 2005](#)). Taking into account the hydrophilic-lipophilic balance (HLB) it was found that Span® 40 (HLB 6.7) is a suitable surfactant for the used system(HLB Canola oil 7 ± 1)([G. Banker & C. Rhodes, 2002](#)). Keeping all process parameters constant, the concentration of the surfactant was varied between 0 and 10 wt% of the continuous phase (oil). It can be seen that by increasing the surfactant concentration a reduction of the mean particle size is obtained (Table 9). This is also confirmed by the decreasing the sauter diameter d_{32} ,

which indicate that larger surface area (smaller particles) is obtained from the same volume of particles at higher surfactant concentration (Table 9).

Table 9: Particle size distribution of the aerogel microspheres as a function of surfactant concentration (w/o 1:1, 500 rpm).

Surfactant concentration [wt%]	0	1	3	5	10
Average [μm]	861 ± 22	762 ± 41	733 ± 12	684 ± 28	584 ± 72
D₁₀ [μm]	233 ± 81	180 ± 32	298 ± 17	215 ± 22	169 ± 69
D₅₀ [μm]	863 ± 37	788 ± 24	736 ± 32	677 ± 37	582 ± 41
D₉₀ [μm]	1516 ± 18	1260 ± 31	1152 ± 45	1154 ± 19	988 ± 60
D₃₂ [μm]	290 ± 21	274 ± 19	294 ± 16	251 ± 15	221 ± 35

2.4.3.5 Textural properties of the aerogel microparticles

For the first set of experiments, pure vegetable oil was used as a continuous phase. It was noticed that the produced aerogel particles have relatively high densities in the range of (0.3-0.4) g/cm³. Moreover, the specific surface area of the resultant aerogels was very low (100-300) m²/g. The reason for this is that approx. 15 wt% of the ethanol used in the sol-gel process dissolves in the oil phase at 25°C and up to 25 wt% at 40°C. As a result, the gel matrix shrinks leading to a denser particles with smaller surface area. This problem was solved by saturating the oil phase with ethanol prior to the emulsification. Fig. 19 shows typical silica aerogel microspheres produced by the suggested process. The particles clearly display a spherical shape. For all samples, density, surface area, pore size and pore volume were measured. It was observed that these properties do not depend on the specific parameters of the emulsion process, but rather on the sol-gel process itself (catalysts, component ratio etc.).

The average textural properties of the produced aerogel microparticles resulting from multiple measurements ($n \geq 3$) are shown in Table 10. A typical pore size distribution is shown in Fig. 20. The average packed density of all produced aerogel microspheres is 0.07 ± 0.02 .

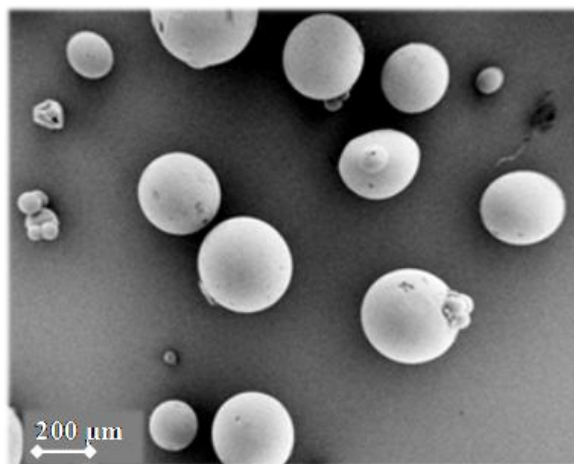


Fig. 19: SEM image of silica aerogel microspheres. Experimental conditions: (700 rpm, two bladed axial stirrer (D: 6 cm), 1:1 phase ratio).

These textural properties are comparable with those of the controlled monolithic silica aerogel samples produced using the same sol-gel procedure without emulsification step (Table 6). Thus, the proposed method allows the production of aerogels in form of spherical microparticles by supercritical extraction of dispersion, keeping the internal structural properties similar to that of the monolithic samples which represent the state of the art so far. Since this form of the aerogel is beneficial for many applications, the process can be applied for the fast production of large amount of aerogels microspheres of corresponding size.

Table 10: Internal surface characterization of aerogel microspheres produced under different parameters.

production process	BET surface area [m ² /g]	BJH pore volume [cm ³ /g]	Average pore diameter [nm]	C constant BET
monoliths silica aerogel	982 ± 54	4.13 ± 0.34	16 ± 2	95 ± 12
1:1 phase ratio	1123 ± 56	3.42 ± 0.17	16 ± 1	47 ± 3
1:2 phase ratio	1107 ± 55	-	-	41 ± 4
1:3 phase ratio	1068 ± 53	3.54 ± 0.27	15 ± 2	48 ± 3
0 wt.% span® 40	1189 ± 58	3.53 ± 0.24	15 ± 2	41 ± 2
3 wt.% span® 40	1191 ± 60	3.36 ± 0.18	16 ± 1	45 ± 3
10 wt.% span® 40	1110 ± 55	-	-	46 ± 4

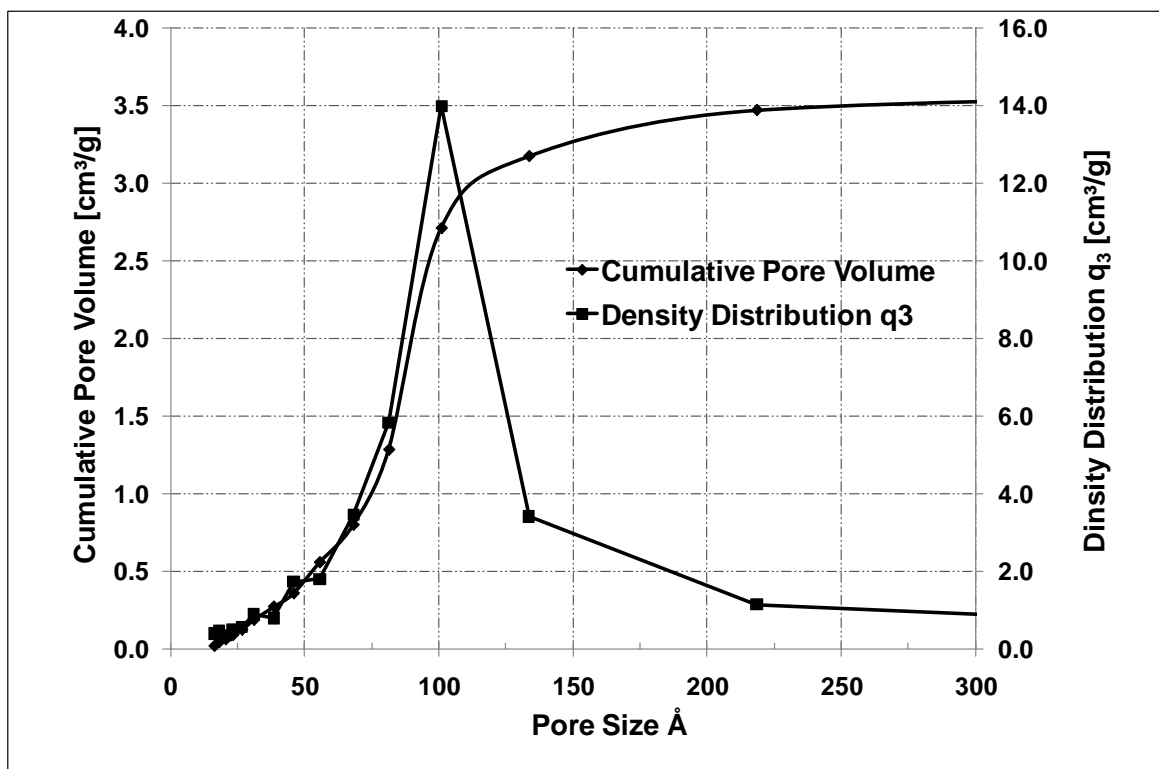


Fig. 20: Typical pore size distribution of silica aerogel microspheres.

2.4.4 Conclusions

Combining the sol-gel process with supercritical extraction of the oil-gel dispersion is proposed as a versatile method for industrially relevant production of aerogel microspheres in a robust and reproducible manner allowing shortening the extraction time in comparison to monolithic aerogels.

The process was demonstrated for silica aerogel microspheres. Stirrer shape and revolution rate were found to be the main factors that control the PSDs of the produced microspheres. Depending on the production conditions, silica aerogel microspheres with a mean diameter from 155 μm to 1.7 mm were produced. The textural properties of the aerogels (surface area, pore size) were less affected by the emulsion preparation, but rather by the composition of the sol itself and showed similar values to the corresponding monolithic aerogels. The proposed process is the best known process for mass production of microspherical silica aerogel particles without affecting their textural properties, which is not the case with the other technique presented in the literature ([Moner-Girona et al., 2003](#); [Sui et al., 2004](#)).

2.4.5 Outlook

The proposed process enables the production of microspherical aerogel particles ranging from 150 μm to few mm. However, for many applications, smaller particles are needed. Hence, it is interesting to modify the used system to cover the smaller particles region ($< 100 \mu\text{m}$). The modification can start with replacing the mechanical stirrer with a professional homogenizer system that able to evenly distribute more energy in the emulsion system. Some examples of these homogenizer are: the CML 4 laboratory mixer (1.5 to 4 l) ([symex](#)). Furthermore, the Homogenizer DISPERMAT[®] AS is suitable for being in use in the pilot plant scale ([VMA-GETZMANN](#)).

Providing an empirical equation that defines the gel particle size as a function of the process parameters can be a great aid toward commercialization aerogels. Hence, a detailed structured sensitivity analysis is required to achieve this task.

2.5 Development of spray drying process for production of silica aerogel microparticles

Smirnova et al. have reported the effect of CO₂ presence in accelerating the gelation process of silica sol ([I. Smirnova & Arlt, 2003](#)). Accordingly, silica gel based on TMOS as a precursor and using the two step method ([Tillotson, 1992](#)) was prepared with a target density of 0.03 g/cm³, with the following molar ratio:



Using the autoclave system shown in Fig. 21a, they have reported a gelation time of 21 h at 40°C, whereas, by addition of CO₂ at the same conditions, the reported gelation time was only 53 min. In order to explain this phenomenon, the authors have investigated different process parameters like temperature, CO₂ concentration, TMOS concentration, solvents, the effect of different acidic catalysis, etc. The authors have proposed this method to produce silica aerogels with low densities in the range of 0.03 – 0.1 g/cm³.

In the same period of time Moner-Girona et al. have reported two methods for production of microspherical and fiber aerogel particles using supercritical fluid technology ([Moner-Girona, et al., 2003](#)). Depending on the used solvent, two different approaches were implemented: (1) high temperature method when ethanol or acetone was used; (2) low temperature method when supercritical CO₂ was used. Since high temperature supercritical drying is out of the scope of this work, only the second method will be considered. Briefly, the authors have injected TEOS as a precursor for the sol-gel process in an autoclave at supercritical conditions. Since water cannot be used to initiate the hydrolysis reaction (almost not soluble in sc.CO₂), formic acid was injected in the autoclave as a condensation agent. Destabilizing the system by pressure reduction, result in particles precipitation. Accordingly, different process parameters were investigated namely, (40-95 °C), (100 –

150 bar) and (1 – 48 h) for temperature, pressure and residence time respectively. The authors have reported only one image of spherical particles with 1 μm particles average diameter (Fig. 14), the measured surface area was in the range of 200 – 500 m^2/g and the reported pore size distribution was in the range of 1-50 nm. Using supercritical solvent for polymerization reaction was first reported by D.A. Loy et al. ([Loy et al., 1997](#)). Accordingly, they have produced aerogel monoliths with a specific surface area of 200 - 500 m^2/g and a bi-modal pore size distribution namely, mesoporous range (100 – 121 Å) and macroporous > 500 Å. This was only possible because of the new emerged technology, at that time, of water free sol-gel polymerization reaction proposed by Sharp et al. ([Sharp, 1994](#)).

Summarizing the previous reported finding:

- CO_2 accelerate the gelation time of silica sol. (Smirnova et al.).
- CO_2 is the solvent in which the polymerization reaction will occur. Upon injection of the precursor (TMOS/TEOS), it will dissolve in the CO_2 phase and homogeneously distribute all over the autoclave (Moner-Gerona et al. and Loy et al.).
- Using CO_2 as a solvent imply the usage of condensation agent rather than water to initiate the polymerization reaction (Moner-Gerona et al. and Loy et al.).
- Gelation and drying of the produced particles/monoliths can take up to 2 days (Smirnova et al., Moner-Gerona et al. and Loy et al.).

The questions now are: what will happen if a sol prepared by the normal two step method is injected into an autoclave containing CO_2 at supercritical conditions? (Combination of I. Smirnova et al. and Moner-Gerona et al. work). How fast will be the gelation and the drying time? What is the final shape of the produced particles? Which textural properties will they have?

In this part of work spraying the sol into an autoclave containing CO₂ at supercritical conditions is proposed as an alternative method for production of silica aerogel microparticles (Fig. 21). In the following sections a detail description of the used setup and the corresponding experiments and results are discussed.

2.5.1 Setup

Fig. 21 shows the setup used for this process. It can be seen that the system contains three main components:

(a) Continuous supercritical drying setup consists of:

- High pressure autoclave with a volume of 250 ml, equipped with glass windows.
- CO₂ reservoir providing a constant pressure (1).
- Gas compressor (3).
- Heat exchangers.
- Pressure gauges and flowmeter.
- Pressure piping system to connect the drying setup components.

(b) Pressure generator system consists of:

- Manual pressure generator with a capacity of 100 ml suction volume and ability to generate pressure up to 1000 bar (SITEC-Sieber Engineering AG, Switzerland).
- Two pressure valves for regulation of the inlet and outlet of the pressure generator.
- Piping system connect the output of the pressure generator to the nozzle.
- Pressure gauge.

(c) The nozzle: a simple capillary tube with an inner diameter of (0.25, 0.5) mm was mounted to a metal closure plate, which replaced one of the glass windows. The capillary tube was connected to the pressure generator system through specific fitting parts.

2.5.2 Procedure

A sol based on the TMOS was prepared with a target density of 0.08 g/cm^3 as described in section 2.3. During the preparation process, the preheated 250 ml autoclave was pressurized with CO_2 until the desired temperature and pressure were reached (150 bar and 40°C). After mixing all precursors together, the sol was placed in the pressure generator pump. The sol was pressurized to a pressure higher than that of CO_2 in the autoclave, namely 200 bar (Fig. 21b). At this moment the sol was pumped continuously into the autoclave by opening valve (17) before the nozzle (Fig. 21c). Thereafter, the valve was closed and the autoclave was mechanically shaken at constant supercritical conditions for 30 min. After that, the gel was supercritically dried for 6 hours using CO_2 at 100 bar and 40°C . The average flow rate of CO_2 was 250 Nl/h. Finally, the autoclave was vent slowly for 30 min. and the aerogels were collected and prepared for further analysis.

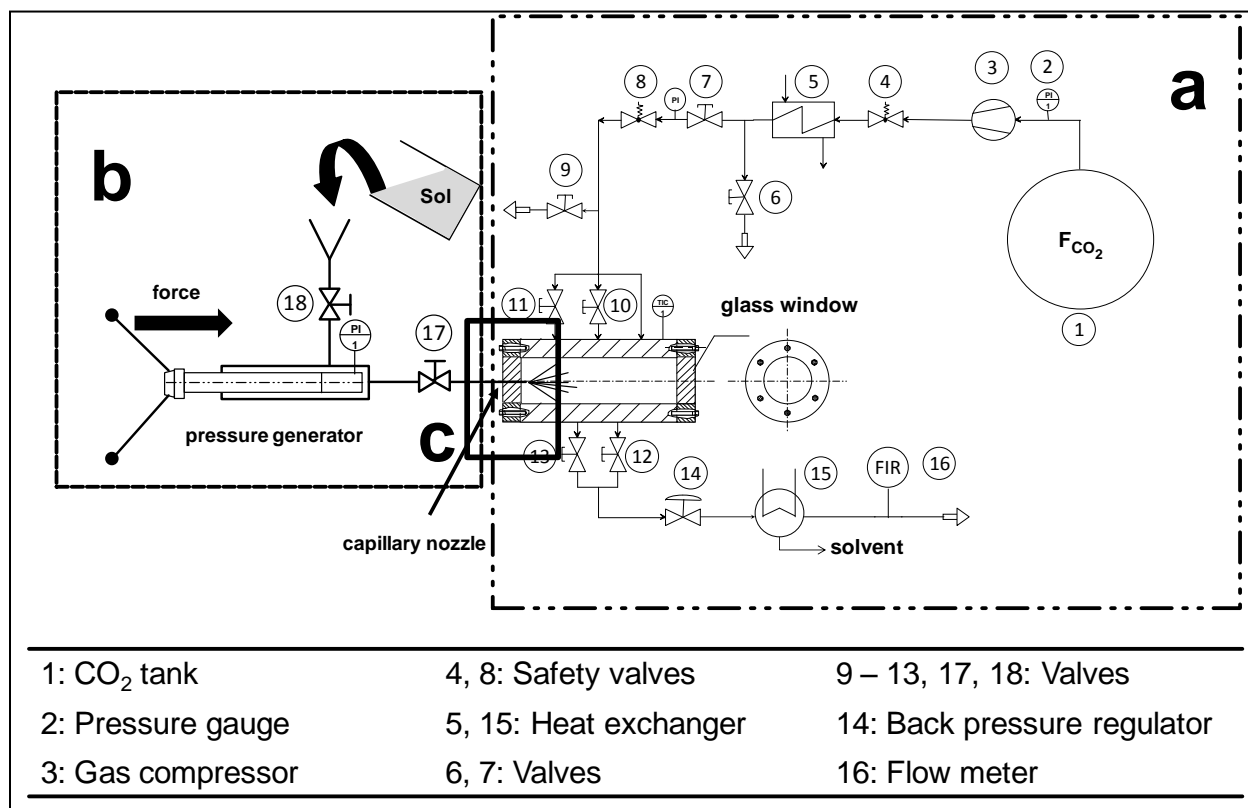


Fig. 21: Production of silica aerogel microparticles by supercritical spray drying of the sol. a: supercritical drying setup; b: pressure generator system; c: the nozzle system.

2.5.3 Results and discussions

Particles design using the described approach is a challenging task. Several interconnected factors can affect the properties of the final product. Hence, it would be beneficial to differentiate two sets of parameters: (1) the sol-gel parameters; (2) setup design and configuration. Beside the known sol-gel parameters like, precursors type and concentration, catalysis, solvent, etc., the presence of CO₂ as polymerization cosolvent plays a significant role in the sol-gel process ([L. Smirnova & Arlt, 2003](#)). The design parameters include the autoclave configuration, nozzle type and pumping system. Simple system components were used to test the applicability of the proposed approach.

2.5.3.1 Gelation time

Spraying the sol can only happen as long as no gelation takes place. It is highly important to use a sol preparation which gelify fast enough upon contact with sc.CO₂. However, slow enough to allow spraying the sol. Hence, the determination of the gelation time for different preparations is of key importance for this technique. Brinker et al. have shown that the gelation time of the two step method depends mainly on the precursor's concentration ([Brinker & Scherer, 1990](#)), which can be interpreted as the designed or target density of the final aerogel preparation. For this work, two different target densities were investigated namely, 0.1 and 0.08 g/cm³. Smaller densities were out of interest since an instantaneous gelation upon contact with CO₂ was desired. The average gelation time for the gel was determined based on at least 5 different preparations. For the gel preparation with 0.08 g/cm³ target density the gelation time was about 15 ± 3 min, whereas it was only of 5 ± 2 min for that of 0.1 g/cm³ target density. Based on these findings the gel with target density of 0.1

g/cm^3 was eliminated from being further investigated, since it gels before being sprayed in to the autoclave. Further experiments were limited to the gel with the target density of 0.08 g/cm^3 .

For the first set of experiments, acetonitrile was used as the solvent for sol-gel process. The sol was prepared with a target density of 0.08 g/cm^3 , using the two step method. After adding the chemical of the second step, the mixture was mixed for 3 min. after that, the sol was filled into the pressure generator system. Then, the procedure described in section 2.5.2 was followed.

2.5.3.2 Particles shape

Fig. 22 shows the shape of the micro particles produced by the proposed method at different magnifications. It can be seen that the produced particles are interconnected forming a coral like shape. Further magnification of the particles network, shows that the network consists of nanospherical particles interconnected at the surface due to necking formation (Fig. 23). This phenomenon was reported by Moner-Girona et al., they have reported that production of spherical particles using the polymerization in sc. CO_2 is difficult due to the agglomeration of the particles (Fig. 24). However a complete analysis or explanation of the process was not given ([Moner-Girona, et al., 2003](#)). Although the used system in their work is different than that of this work, both systems show a degree of similarity in resulting agglomerated microspherical particles (Fig. 23, Fig. 24).

Agglomeration or nicking of particles can result due the formation of bonds between several particles close to each other. To form necks or bonds, the particles should have a free active site where Si-O-Si bond can be formed, which can be a sign of incomplete condensation reactions (section 1.2.2). Furthermore, to make this kind of bonds, another active particle is needed. Hence, a possible solution would be to: 1) dilute the system (reduction of the possible interparticles collision); 2) accelerate the condensation reaction. These actions can minimize the impact of the particles agglomeration.

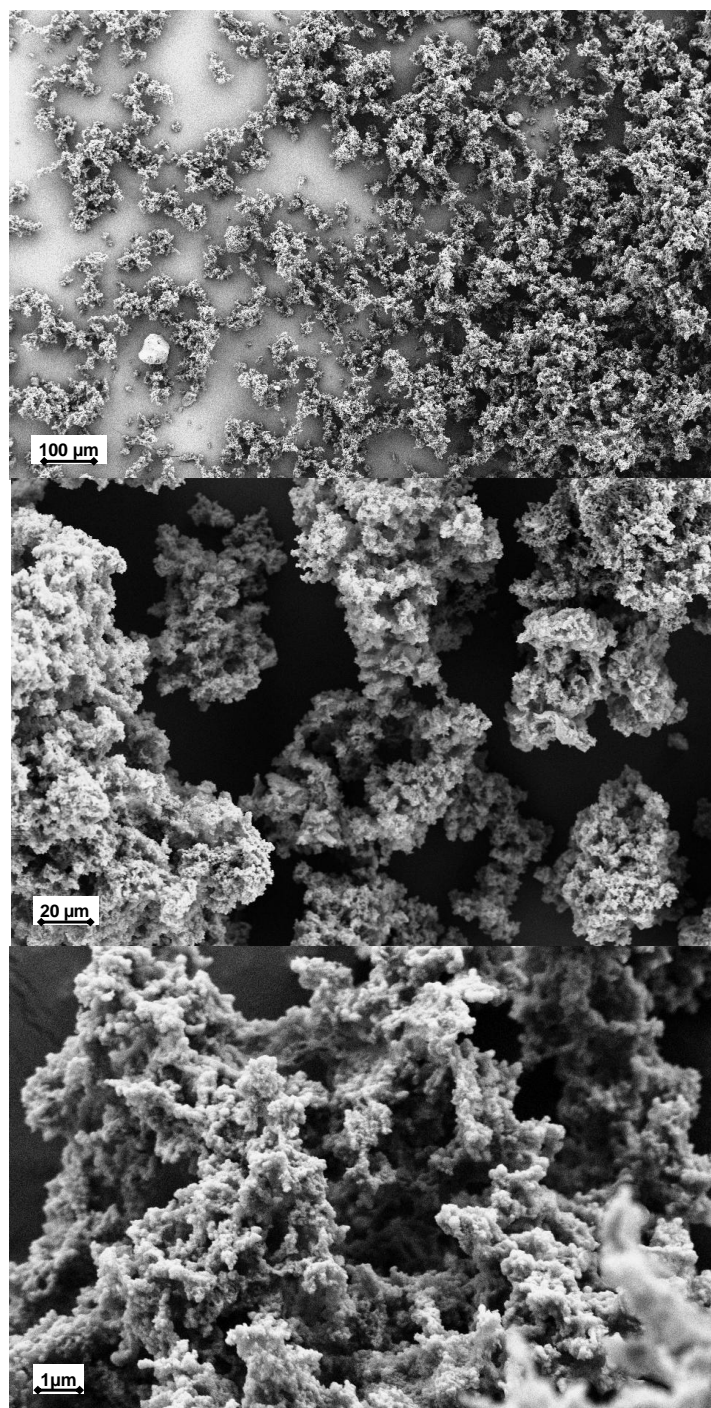


Fig. 22: Coral like shape particles produced by the modified spray drying method.

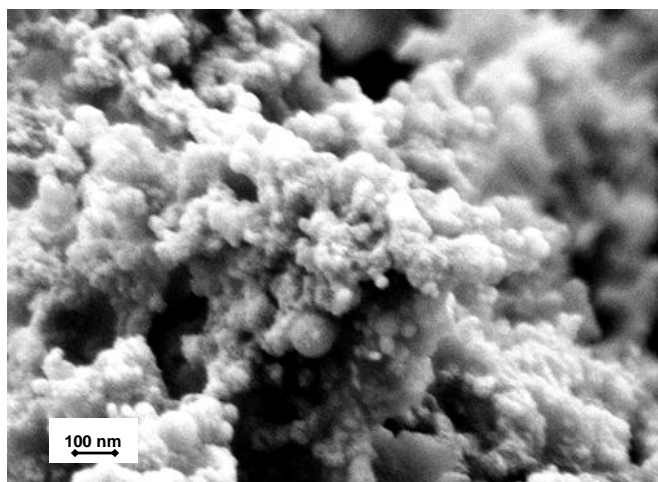


Fig. 23: Small microspherical interconnected particles forming the coral like network.

Upon spraying the sol into the autoclave, the formed particles collide with the other side of the autoclave which is only 10 cm away. Logically, many of them return to the spraying direction. Hence, most of the returning particles collide with the new sprayed droplets coming out from the nozzle. It can be assumed that the first droplets sprayed into the autoclave, have enough time to gel and form the spherical shape. However, those which collide with the returning particles will gel on their surface. As a result an agglomeration with a coral like shape will be formed. Fig. 23 can provide a proof for the proposed explanation. As it can be seen, the core spherical particles are interconnected with spherical like and non spherical particles making up the agglomerate.

The question which arise now, is it possible to solve this problem (agglomeration) by controlling the sol-gel parameter? The answer of this question can be extracted from Sui et al ([Sui, et al., 2004](#)). work. They have used similar system as that used by Moner-Gerona, however, using in situ ATR-FTIR spectroscopy allow them to provide more insight and analysis of the system. Furthermore, they have succeeded to minimize the degree of particle agglomeration (Fig. 25). According to them, the degree of agglomeration can be reduced if the rate of polymerization reaction is reduced in a way that prevents particles precipitation. Accordingly, they provided two results with the same conditions but with diluted reactant concentrations (Fig. 25 a, b).

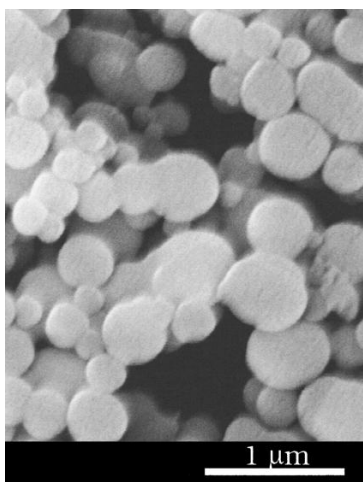


Fig. 24: Scanning electron micrograph of aerogel silica particles obtained in supercritical carbon dioxide at 50 °C, 99 bar ([Moner-Girona, et al., 2003](#)).

Thus, several approaches can be used to reduce the rate of the polymerization reaction. Changing the precursor concentration or type, lowering the reaction temperature, controlling the catalysis concentration, etc. allows the reduction of polymerization reaction rate.

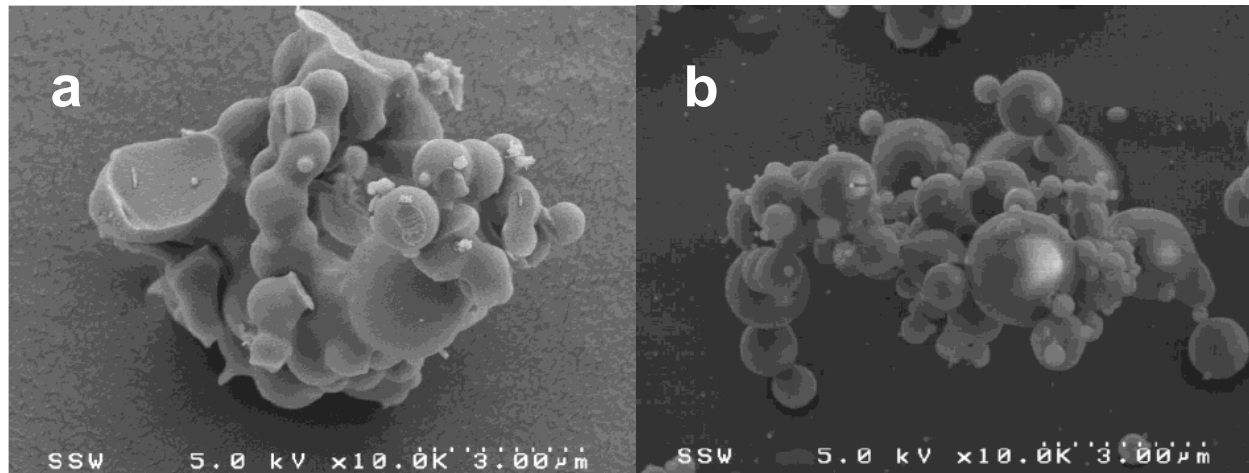


Fig. 25: SEM of silica aerogel powder. The experimental conditions are a: 1.1 mmol TEOS + 7.7 mmol 96% HCOOH; b: 0.176 mmol TEOS + 2.64 mmol 96% HCOOH. Both were conducted in 25-mL view cell, at 138 bar, 40 °C ([Sui, et al., 2004](#)).

2.5.3.3 Particle size distribution and textural properties

The average PSD of three different batches produced at the same conditions is sketched in Fig. 26. It can be seen that the PSD of the different batches is quite reproducible. Moreover, the particle

size range is $\sim 2 - 80 \mu\text{m}$ with a mean particle size of $12 \pm 4 \mu\text{m}$. The British Standards Institute has defined the span of the particles size distribution as:

$$\text{span} = \frac{(D_{90} - D_{10})}{D_{50}} \quad 2.1$$

where D_{90} , D_{10} and D_{50} are the equivalent volume diameters at 90, 10 and 50% cumulative volume, respectively ([Standards, 1993](#)). The “span” measures the width of the PSD. Accordingly, small values of the span indicate a narrow PSD. The span of the PSD of the aerogel particles produced by this method was in the range of 1.8 – 2.2 which is a sign of broad PSD. The reason behind this broadness is the same one behind the formation of the agglomerate (section 2.5.3.2).

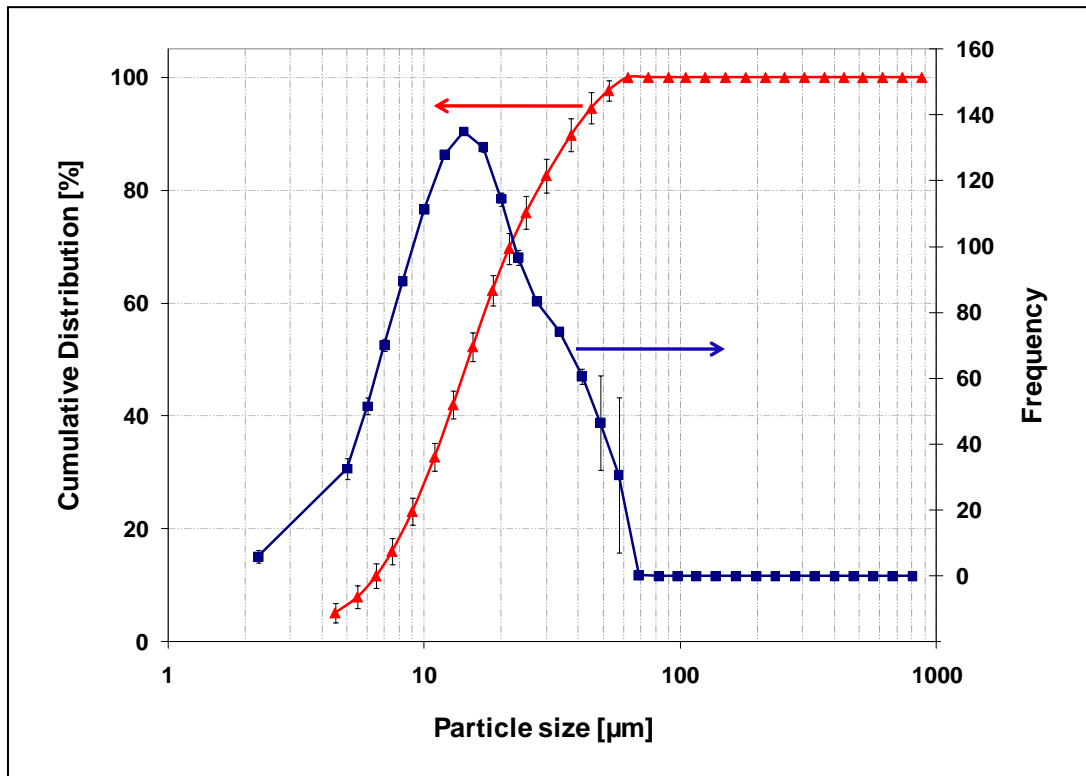


Fig. 26: PSD of the particles produced by the modified spray drying method.

Textural properties

Aerogel particles produced following the described procedure, shows comparable properties as those produced as monoliths following the classical preparation route (Table 6). Table 11 shows the textural properties of silica aerogel produced by the proposed method in comparison with those produced following the principle of polymerization in sc.CO_2 . It can be seen that the specific surface area for the produced particles in this work is at least double that of any reported values by others work ([Loy, et al., 1997](#); [Moner-Girona, et al., 2003](#); [Sharp, 1994](#); [Sui, et al., 2004](#)). The average pore radius for all preparation was almost in the same range (1.5 – 4.6 nm) except for that reported by Moner-Girona et al. However, only a range of the pore size was given, not the distribution itself. The pore radius and total pore volume of the presented preparation is smaller than that of aerogel monoliths (Table 6). One possible explanation is that upon fast gelation of the sol, the primary particles form relatively short clusters which upon connecting with another cluster produce small pores. Furthermore, qualitatively it is possible to assume a bimodal pore structure consisting of macro and meso pore size distribution (Fig. 23), this porous structure is quite similar to that reported by Loy et al. ([Loy, et al., 1997](#)).

Table 11: Average textural properties of aerogel prepared using the modified spray drying technique.

Textural properties	Surface area [m ² /g], BET Method	C constant, BET method	Density [g/cm ³]	Pore radius [nm]	Pore volume [cm ³ /g], BJH method
Aerogel/this work	1066 ± 117	278 ± 33	0.003 ± 0.001	2.54 ± 0.81	0.46 ± 0.08
(Loy, et al., 1997)	260 - 586	-	-	1.2 – 4.6	-
(Moner-Girona, et al., 2003)	200 – 600	-	-	1 – 25	-
(Sui, et al., 2004)	-	-	-	-	-
(Sharp, 1994)	200-600	-	-	1.5	-

2.5.4 Conclusions

Coral like Silica aerogel microparticles with a small agglomerate size in the range of 2 – 80 μm and up to 1120 m^2/g specific surface area were produced following the presented method. The modified spray drying technique is a mixture of the classical route of performing the SiO_2 polymerization reaction in a traditional solvent like ethanol, acetone, etc. and carrying out the polymerization using in sc.CO_2 as a solvent. The presented technique allows the reduction of the processing time of aerogel production, the complete process starting from mixing the precursors until harvesting the particles take less than 8 hours. Further modification of the process is required in order to tailor the final morphology and textural properties of the produced aerogel.

2.5.5 Outlook

Based on the given results, it is possible to say that this technique is still in the test phase. Hence, further investigation should be conducted in order to optimize the production process. Two main modification of the experimental setup should be made before any further investigation: (1) exchanging the manual pressure generator with a syringe pump equipped with a chick valve; (2) replacing the autoclave used in the setup with a longer one and mounted in the vertical direction. The first modification is extremely necessary, since with the old system it was impossible to control the amount of the injected sol. Furthermore, the absence of a check valve between the nozzle and the pump system allow CO_2 to come into contact with the sol inside the pipes and the pump volume. As a result, the sol was often gelify inside the used pump system. The modified autoclave configuration is proposed in Fig. 27. This can extremely minimize the formation of agglomerates. The length of the autoclave should be enough to allow the injected droplets to completely transfer to gel particles with minimum active reaction sites. This will prevent necking upon collisions with other particles.

Since the proposed method was still at the test phase, no special attention was paid to the nozzle design. However, nozzle type is an important design parameter that can influence the morphology and the PSD of the produced particles ([Bouchard et al., 2008](#); [Hezave & Esmacilzadeh, 2010](#); [J. Huang & Moriyoshi, 2006](#); [Matson & Smith, 1987](#); [Obrzut et al., 2007](#)). Fig. 28 shows a SEM image of the used nozzle. It can be seen that such irregular structure can be an obstacle for production of microspheres.

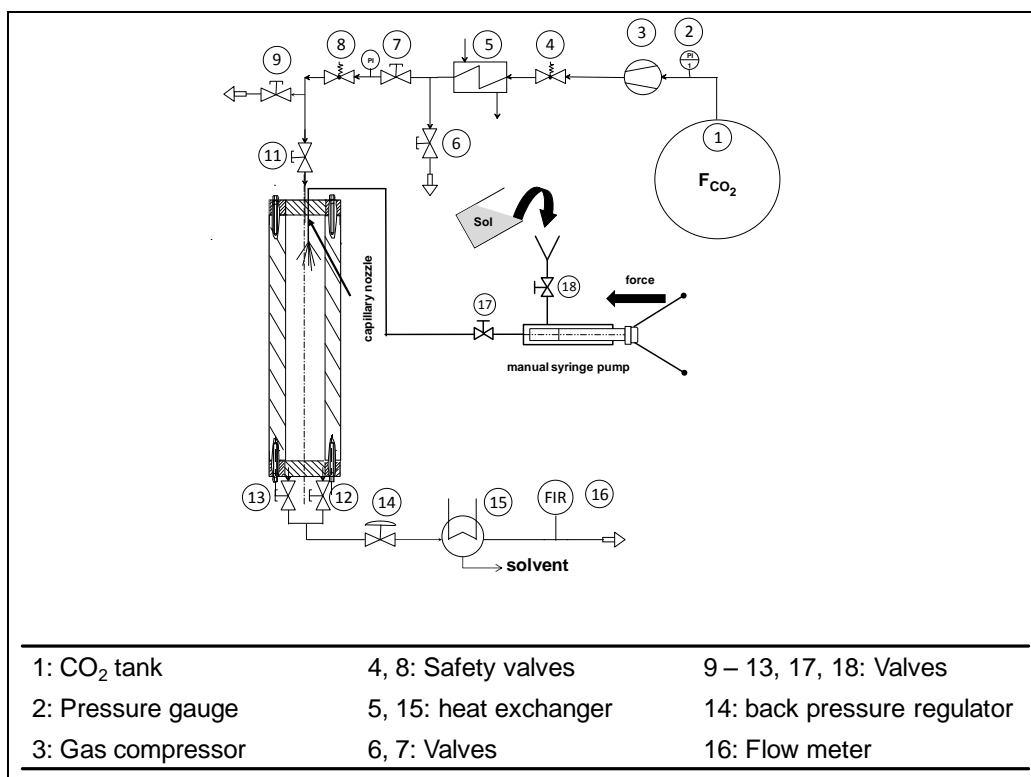


Fig. 27: Possible configuration.

The sol-gel parameters can also influence the morphology and the textural properties of the produced aerogel parameters. Loy et al. have reported that the final particles shape depends mainly on the polymerization reaction rate, accordingly slower polymerization reaction results in microspherical particles ([Loy, et al., 1997](#)).

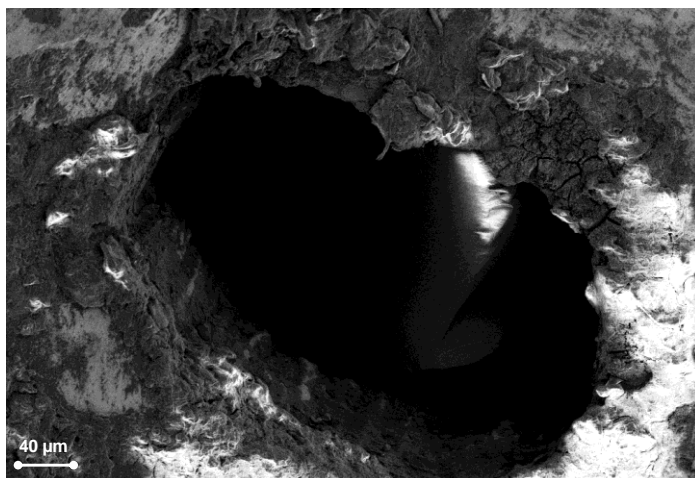


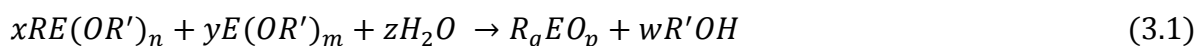
Fig. 28: Capillary pipe opening used for the spraying system.

3 *Development of Functionalization & Coating Processes for Modifying Silica Aerogels*

Modifying of aerogels is essential for some application to achieve specific functionality. Silica aerogel tailoring can start during the sol-gel process, after gelation or after obtaining the aerogel. In this work, two different processes were proposed for modifying silica aerogels properties, namely: (1) Surface functionalization of aerogels to regulate the adsorption capacity and thus the dosage quantity of the drug active agents on aerogel; (2) Applying a polymeric coating on aerogel surface with the desired functionality

3.1 *Silica aerogel functionalization*

Modification of aerogels by means of surface functionalization is a way to tune their properties for different end products. Different functional groups can be implemented into the aerogel matrix ([Schwertfeger et al., 1994](#)) by means of physical blending or via chemical reaction, which can be described by the following equation:



Varying the functional groups (R) or the metal oxide (E) or the ratio between them can result in a number of interesting hybrid materials ([Fryxell & Cao, 2007](#); [Sakka, 2005](#); [U. Schubert et al., 1995](#)). Some examples of the R groups are: alkyl-, aryl-, hydroxyl-, and aminogroups. Modification of silica aerogels with aminogroups allows to crosslink silica aerogel with di-isocyanate, which improves the mechanical properties of silica aerogels like the elasticity and the strength of the skeleton ([Capadona et al., 2006](#); [Kanamori, 2011](#); [Katti et al., 2006](#); [Meador et al., 2005](#)). Further the adsorption capacity of aerogels towards specific chemicals having affinity to aminogroups can be enhanced in this way.

However, the textural properties of the processed aerogels might change significantly due to the modification process ([Husing et al., 1999](#)).

Silica aerogels modified by amino groups were produced using different (tetraethyl orthosilicate (TEOS)/ $(\text{MeO})_3\text{Si}(\text{CH}_2)_3\text{NR}'_2$) mixtures ($\text{NR}'_2 = \text{NH}_2$ or $\text{NHCH}_2\text{CH}_2\text{NH}_2$) as precursors for the sol-gel process ([Bois et al., 2003](#); [S. Chen et al., 2009](#); [Husing, et al., 1999](#); [Yan et al., 2004](#)). The resultant aerogels exhibited a specific surface area in the range of 100 – 430 m^2/g and relative low polarity as determined from the C-constant of nitrogen adsorption desorption measurement ([Condon, 2006](#); [Husing, et al., 1999](#)). Similar approach was used for the production of aerogel monoliths starting with different mixtures of (TMOS/APTMS) for the sol-gel process. It was noticed that the resultant aerogels were white in color and have a low surface area (less than 200 m^2/g) ([Reddy, 2005](#)).

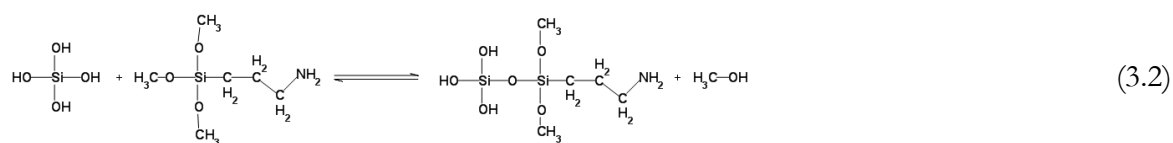
In this work, aerogel modification by means of surface functionalization is suggested as a versatile approach for adjusting the dosage quantity of certain drug active agents in aerogel. Aminogroups were chosen as a model functional group and two different functionalization processes were developed. The amino-functionalized aerogels were characterized by CHN and BET analysis. The drug loading extents as well as the drug release profiles were obtained using UV-spectroscopy.

3.1.1 Procedures

Aerogel functionalization with aminogroups was conducted by two different processes: (a) the functionalization of the dry silica aerogel by reaction in the gas phase; (b) functionalization of the gel before the drying step (during the sol-gel process or after gelation).

3.1.1.1 Gas phase functionalization (a)

The scheme of the gas functionalization is shown in Fig. 29. Aerogels were placed inside an autoclave (100 ml) at 200°C, APTMS/acetonitril solution (10 wt %) was placed in the boiler and evaporated. The vapor passed through the autoclave and upon contact with aerogels the following



reaction occurred:

After leaving the autoclave the vapor was condensed and circulated to the boiler. After certain time the reaction was stopped and aerogels were taken out for further analysis.

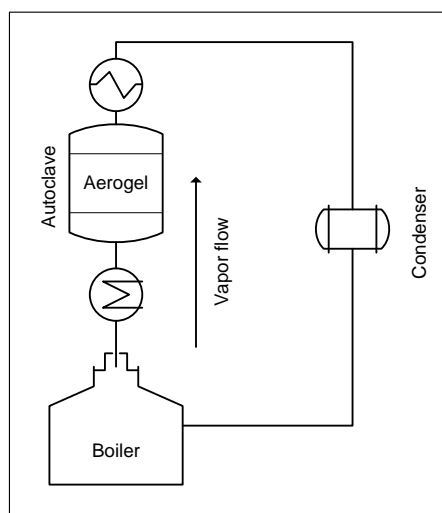


Fig. 29: Schematic chart for the gas functionalization setup.

3.1.1.2 Liquid phase functionalization (b)

Process (i)

In this method functionalization of the gel takes place directly after the aging process. The wet gel was placed in APTMS/acetonitrile solutions of different concentrations for 24 hours at 50° C. The resulting functionalized gel was shortly washed with acetonitrile and placed in acetonitrile bath for two hours. Finally the gel was dried using supercritical CO₂.

Process (ii)

The second method is to functionalize the gel during the condensation step of the sol-gel process. Here APTMS is used as the catalyst instead of NH₄OH. The resulting gels were aged for 24 hours and finally, dried using supercritical CO₂.

3.1.1.3 Loading of aerogel with drugs

A weighed amount of the drug and aerogel, each wrapped in a filter paper were placed in the autoclave. After that the autoclave was sealed, heated to 40°C and CO₂ was pumped inside until a pressure of 180 bar was reached. Then the autoclave was shaken for 48 hours under constant conditions. Finally, the pressure was released and the loaded aerogel was removed. The drug loading were determined using UV-spectrometry as described previously.

3.1.2 Results and discussion

3.1.2.1 Effect of functionalization art on the textural properties and the functionalization extent of aerogels

Gas phase functionalization:

Silica aerogels were functionalized by post treatment with APTMS vapor as described previously (section 3.1.1.1). Table 12 shows the average textural properties of the functionalized silica aerogel in comparison to that of the reference sample (section 2.3). No significant changes in the textural

properties were observed. Moreover, the transparency of silica aerogel was not affected by amino-functionalization (Fig. 30).

Table 12: Average* textural properties of modified aerogels.

	Surface area [m ² /g] BET method	C constant BET method	Density [g/cm ³]	Pore radius [nm]	Pore volume [cm ³ /g] BJH method
Control sample aerogel	1040 ± 52	86 ± 8	0.13 ± 0.02	8.72 ± 0.56	4.57 ± 0.18
Gas phase functionalization	975 ± 40	104 ± 11	0.13 ± 0.03	7.16 ± 0.61	4.86 ± 0.34
Process (i)	872 ± 63	114 ± 15	0.14 ± 0.04	11.48 ± 0.67	3.45 ± 0.16
Process (ii)	950 ± 61	132 ± 9	0.14 ± 0.02	8.17 ± 0.28	4.31 ± 0.21

* Each value based at least on three aerogel samples.

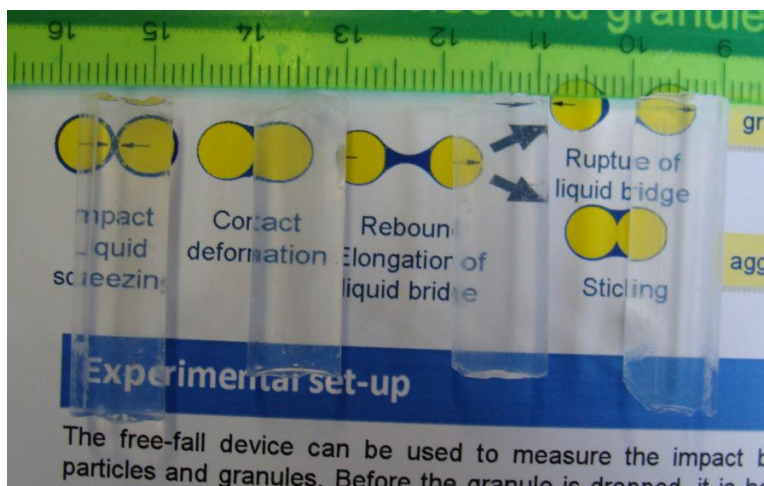


Fig. 30: Effect of amino-functionalization on the appearance of silica aerogels. From right to left; normal silica aerogel, gas functionalized silica aerogel, liquid functionalized silica aerogel process (ii), liquid functionalization silica aerogel process (i).

The effect of functionalization time on the final concentration of aminogroups bonded to the aerogel's surface was studied. The concentration of the APTMS solution was kept constant at 10 wt%. Multiple samples were removed from the reactor (autoclave) after the desired reaction time was reached. The functionalized aerogel samples were analyzed using elemental analysis to quantify the amount of bonded aminogroups (Fig. 31). Further, their textural properties as a function of the bonded aminogroups were compared (Table 13). As it can be seen, by increasing the reaction time from 12 to 48 hours the amount of aminogroups bonded to aerogel's surface increased from 1.06 to

2.98 wt% (0.77 to 2.18 $\mu\text{mol NH}_2/\text{m}^2$). Nevertheless, the textural properties of the modified aerogels were almost similar to that of the reference sample.

Table 13: Silica aerogel textural properties as a function of aminogroups concentration.

	Surface area [m^2/g] BET method	Density [g/cm^3]	Pore radius [nm]	Pore volume [cm^3/g] BJH method
Gas phase functionalization				
NH_2 wt%				
1.06	1014 ± 40	0.130 ± 0.015	6.81 ± 1.19	5.12 ± 0.63
1.87	975 ± 39	0.097 ± 0.022	7.89 ± 0.74	4.52 ± 0.87
2.98	934 ± 37	0.118 ± 0.014	6.71 ± 0.82	4.71 ± 0.45
Process (i)				
NH_2 wt%				
3.12	945 ± 38	0.131 ± 0.017	12.21 ± 1.12	3.29 ± 0.68
4.74	841 ± 34	0.098 ± 0.021	10.89 ± 1.43	3.61 ± 0.74
6.86	829 ± 33	0.183 ± 0.009	11.34 ± 0.95	3.45 ± 0.60
Process (ii)				
NH_2 wt%				
2.87	1005 ± 40	0.120 ± 0.011	8.41 ± 1.05	4.53 ± 0.65
5.21	875 ± 35	0.162 ± 0.017	8.25 ± 1.34	4.19 ± 0.43
6.91	960 ± 38	0.134 ± 0.010	7.85 ± 0.78	4.21 ± 0.83

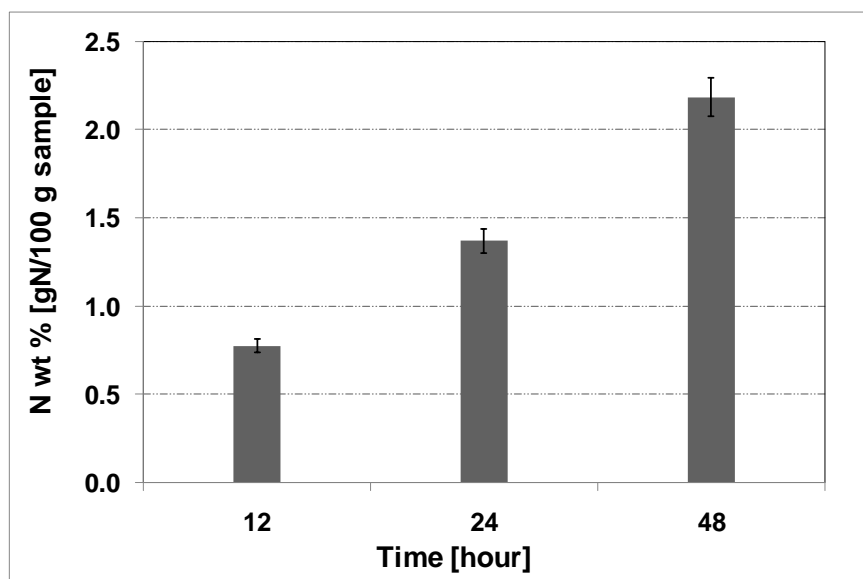


Fig. 31: The effect of functionalization time on the concentration of aminogroups.

Liquid phase functionalization:

Functionalization involving the reaction in the wet gel or the sol-gel process itself is expected to influence the textural properties of the resulted aerogels more than that of the gas phase process presented previously.

The textural properties of the silica aerogels modified by liquid functionalization method (process i and ii) are shown in Table 12 and Table 13. In comparison to unmodified samples, aerogels with smaller surface area ($872 \text{ m}^2/\text{g}$), higher density ($0.14 \text{ g}/\text{cm}^3$), larger pore radius (11.48 nm) and smaller pore volume ($3.45 \text{ cm}^3/\text{g}$) were produced by this process. On the other hand, aerogels obtained from process (ii) were less affected by the functionalization process. The average textural properties of those aerogels were: $950 \text{ m}^2/\text{g}$, $0.14 \text{ g}/\text{cm}^3$, 8.17 nm and $4.31 \text{ cm}^3/\text{g}$ for surface area, density, pore radius and pore volume respectively.

The effect of the functionalization solution concentration on the final amount of NH_2 groups bounded on the aerogel surface was investigated. For process (i) the concentration of APTMS in the APTMS/Acetonitrile mixture was varied between 2 wt.% and 6 wt.%. In case of process (ii) the amounts of APTMS added during the condensation step was varied between 2 wt.% to 8 wt. %. Accordingly, the resulting concentration of aminogroups bonded to aerogel surface increased from 3.12 to 6.86 wt% g N/g sample for process i and from 2.87 to 6.92 wt% g N/g sample for process ii (Fig. 32).

Post-treatment of the aerogels by gas phase functionalization seems to be the most suitable method if the original structural properties of the aerogel should be maintained. This is expected since during this type of functionalization, dried aerogels are only in contact with the vapor, hence, no vapor can condense in the pores (high temperature $\sim 180^\circ\text{C}$), thus, no capillary forces can take place and aerogel textural properties will be maintained. However the concentration of aminogroups bounded to the surface (Fig. 31) is lower than that achieved by gel functionalization in liquid

solutions (Fig. 32). This can be due to the temperature gradient within the aerogel as well as the transport hindrances in gas-solid reaction, which directly affects the functionalization process (Bird, et al., 2002).

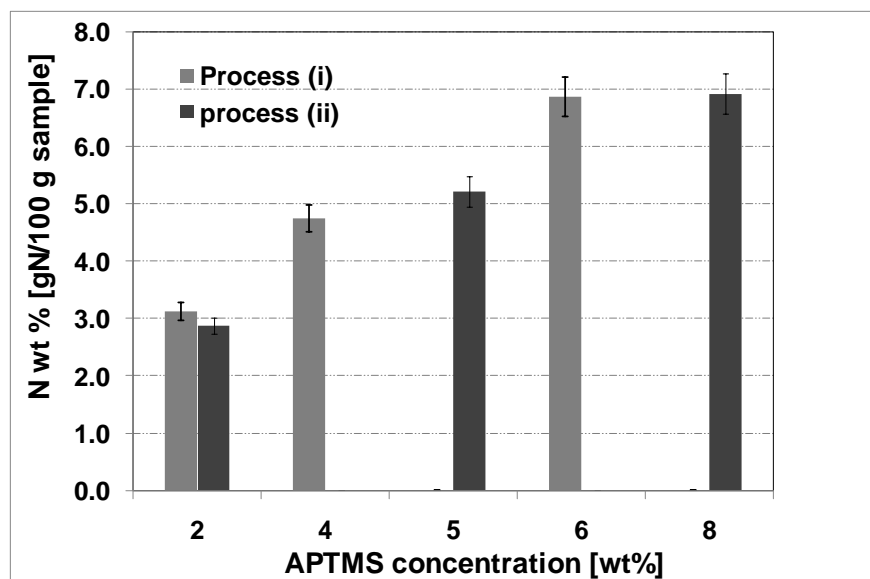


Fig. 32: Effect of APTMS concentration on the concentration of aminogroups on aerogel surface (liquid phase functionalization).

In case of liquid phase functionalization more significant structural changes were observed. In process (i), the gel was functionalized by submersing it in the APTMS/acetonitrile solution at 50°C. During this process further condensation and esterification reactions can happen (almost all water was consumed during the building of the gel network; hence, esterification reaction will be favorable). Therefore internal gel network is changed in term of pore size, density surface area, etc (Table 13).

In process (ii) functionalization occurs during the condensation step of the described sol-gel process. Here APTMS participates in the building of the gel itself. Because of the basic properties of the APTMS it acts as a catalyst for the condensation step. Hence, when the concentration of the APTMS exceeds a certain level, the condensation reaction can be too fast and the building of a

stable internal network of the gel (Si-O-Si) will be prevented. As a result, aerogels exhibit low specific surface area and a loss in transparency after the drying. This fact was reported by several scientific groups. Bois et al reported the effect of ((aminopropyl)-Triethoxysilane) APTES to TMOS ratio (r) in the hydrolysis step of the sol-gel process. A reduction of the surface area from 662 to 358 m^2/g with increasing of r from 0 to 0.5 was observed ([Bois, et al., 2003](#)). Gelation by co-condensation of $\text{Si}(\text{OEt})_4$ and aminopropyl-triethoxysilane and [amino-ethylamino]-propyltrimethoxysilane results in aerogels with specific area of 200-300 m^2/g ([U. Schubert, et al., 1995](#)).

In both functionalization arts, gas and liquid phase functionalization, it can be assumed that the organic functional groups condense in the last stage of the network forming. Therefore, the functional groups must be located on the surface of the SiO_2 primary particles and have good accessibility for further reactions. This can be proven by comparing the C-constant values obtained from the BET measurement, which can be a sign of the polarity of the surface ([Condon, 2006](#)). Typical value for unmodified aerogels is 120 ([Husing, et al., 1999](#)). The C values for the amino modified aerogels obtained in this work varies from 104 to 132 depending on the functionalization method (Table 12). This indicates an increase of the surface polarity, which in this case can be only a result of the presence of active accessible NH_2 groups on the aerogel surface. Hüsing et al. reported that the C values obtained for their amino-functionalized aerogels indicate that they are unpolar ($C < 50$). The suggested explanation was that the amino groups build intra- and intermolecular hydrogen bonds (to the surface silanol groups or among each other) and the nitrogen molecules therefore get in contact with the unpolar propylene spacer ([Husing, et al., 1999](#)). Furthermore, the functionalization extent can be indirectly proven by investigating the change of the adsorption properties.

Controlling the extent of aminogroups functionalization depends mainly on the nature of the used process. For instance, in case of gas phase functionalization, the amount of aminogroups can be adjusted by controlling the reaction time as shown in Fig. 31. However, long reactions times can have a negative economical impact on aerogel functionalization process. Hence, only a limited aminogroups concentration can be obtained (< 3 wt.%).

In case of liquid phase functionalization, for process (i) the concentration of aminogroups can be controlled by the concentration of APTMS/ACN solution (Fig. 32). Here the aminogroup concentration on aerogel surface can reach up to 7 wt.%. It has been noticed that further increase of APTMS concentration gives no further significant effects on the concentration of surface aminogroups. Bios et. al. reported a maximum value of 4.7 wt.%, however the resultant surface area was $317 \text{ m}^2/\text{g}$ ([Bois, et al., 2003](#)). For other publications ([Husing, et al., 1999](#); [Reddy, 2005](#); [Yan, et al., 2004](#)) only the initial concentrations of the functionalization agent (amino group source) were given, no final concentrations of amino-groups on the aerogel were given.

In case of process (ii) the concentration of APTMS added to the system during the condensation step of the sol-gel process can be varied from 1.0 to 8.0 wt%. High concentrations of aminogroups (up to 6.7 wt%) can be reached. From the literature it is known, that even higher values are possible ([Husing, et al., 1999](#)), however, the trade off will be a lower surface area and a loss of the transparency as discussed above.

3.1.2.2 Loading and release properties of the functionalized aerogels

The presence of amino functional groups on aerogel surface regarded as an attractive adsorption sites for ketoprofen (due to the presence of carboxylic group), thus, an increase of the loading extent is expected (Fig. 33 and Fig. 34). It can be seen that ketoprofen loading increases from 9.7 to 21.1 wt% by increasing the concentration of aminogroups from 0.77 to $2.18 \text{ } \mu\text{mol NH}_2/\text{m}^2$ on aerogel

surface for gas functionalization (Fig. 33). Further increase of amino group concentration on aerogel surface results on a higher ketoprofen loading, up to 32 wt% at $\sim 5.5 \mu\text{mol NH}_2/\text{m}^2$ were achieved in the case of liquid phase functionalization (Fig. 34).

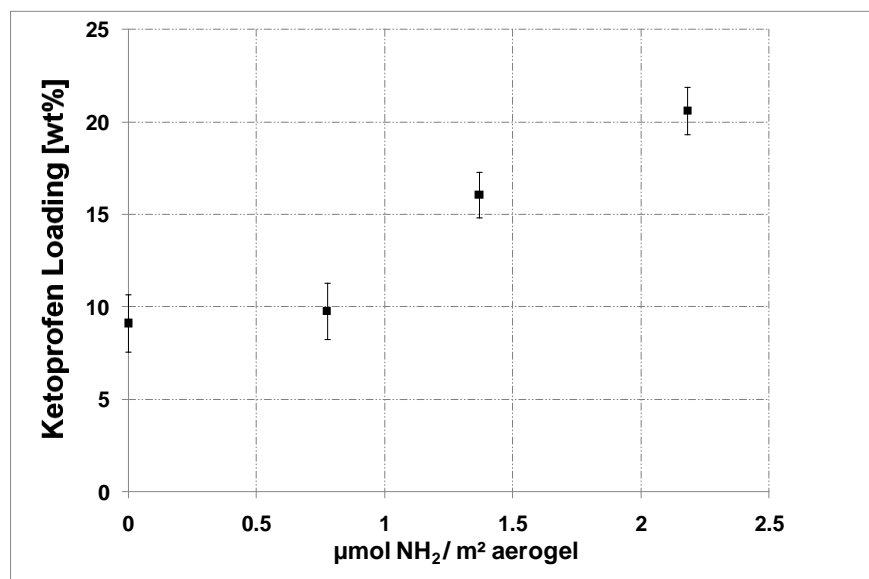


Fig. 33: Effect of aminogroups concentration on the loading of ketoprofen (gas phase functionalization).

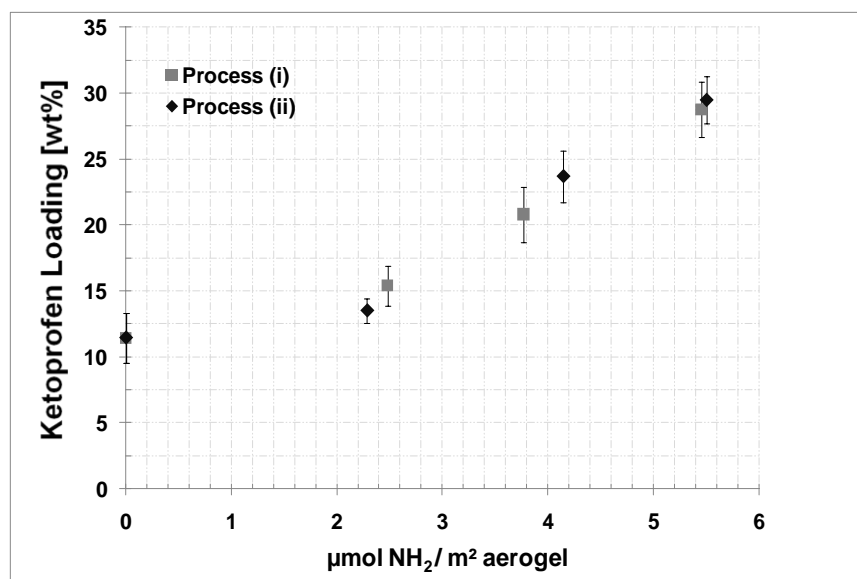


Fig. 34: Effect of aminogroups concentration on the loading of ketoprofen (liquid phase functionalization).

Finally the impact of functionalization on the release rate of ketoprofen from these aerogels was investigated. Fig. 35 and Fig. 36 show the dissolution profiles of crystalline ketoprofen and different

aerogel-ketoprofen formulations. The release of the loaded ketoprofen from all drug–aerogel formulations is very fast: more than 70% of the loaded drug can be released in the first 30 min. 99 wt% release can be achieved within 3 hours. Functionalization of the aerogel matrix by NH_2 groups has almost no effect on the release kinetics. Since aerogels obtained by this functionalization process maintains their hydrophilicity. Hence, the collapse of the aerogel network upon the contact with an aqueous solution will not be affected and a fast release of the drug can be preserved.

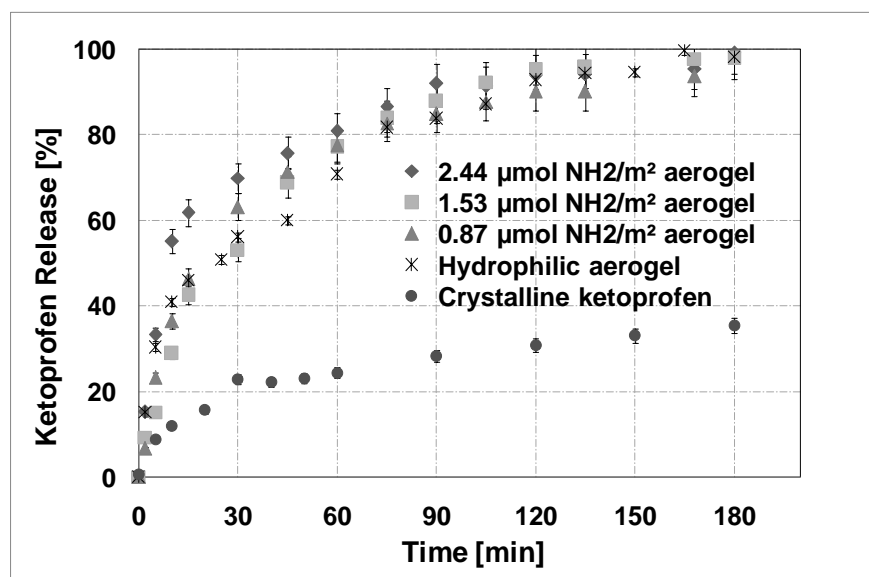


Fig. 35: Dissolution profiles ketoprofen from gas functionalized aerogels.

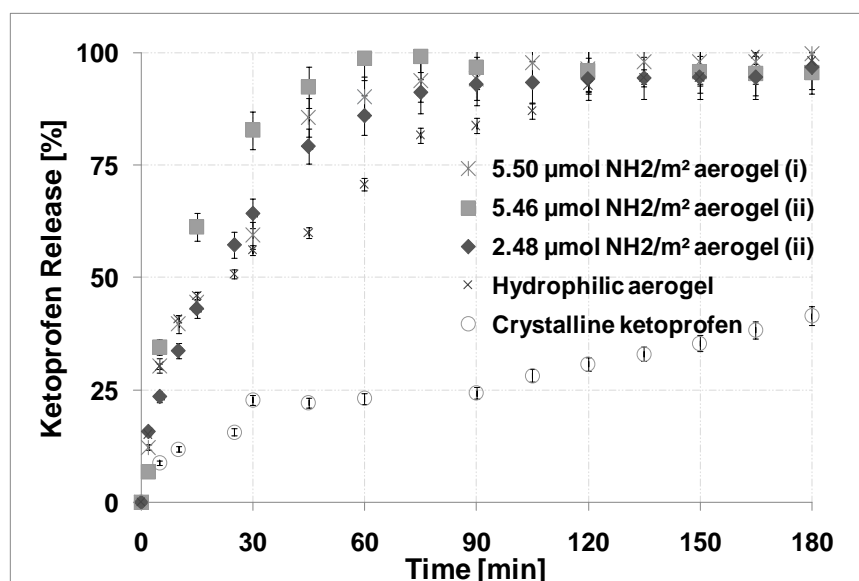


Fig. 36: Dissolution profiles of ketoprofen from amino functionalized aerogel-ketoprofen formulations, Liquid phase functionalization (processes i and ii).

Small differences can be rather ascribed to the difference of the specific surface area of the functionalized aerogel. Therefore, it is possible to conclude that the functionalization allows us to increase the adsorption capacity of aerogel matrices without influencing their release characteristics significantly.

3.1.3 Conclusions

Changing the nature of the surface functional groups is a versatile tool that allows producing functional hybrid materials with a high potential for advanced applications. Amino functionalization was proposed as a method for modifying the adsorption properties of silica aerogels. Different approaches for silica aerogels functionalization were compared. For the first time transparent amino functionalized silica aerogels with a high specific surface area of 800–1040 m²/g and high amino content, up to 7 wt%, were produced. Functionalization of aerogels allows controlling their dosage capacity toward specific drugs and enhances their potential as drug carriers. Drug release characteristics from aerogel were not affected by the addition of the aminogroups on aerogel surface. A fast release comparable to that of hydrophilic silica aerogels was achieved. This approach of modifying silica aerogel can be considered as a promising process that allows tailoring of silica aerogel properties to the needed application.

3.1.4 Outlook

Aerogels functionalization is a powerful tool for manipulating their surface properties to the targeted application. Hence, it is necessary to extend this approach for different functional group types; hydrophilic, hydrophobic and combination of both. Beside the CHN analysis it would be useful to include further characterization techniques like TGA, solid NMR and IR spectroscopy; this can give more insight to the process and allows optimization of the used technique. In the present

work, the functionalization was limited to silica aerogels; however it would be interesting to extend this technique to the organic aerogels like alginate, starch, pectin, etc. and compare the functionalization efficiency with that of inorganic aerogels. Aerogel functionalization was proposed to enhance the adsorption capacity of drugs on aerogels, nevertheless, this method can be used for different applications like adsorption and storing of CO₂, nuclear wastes, VOC, bio filters, etc.

3.2 Aerogel coating for controlled drug release applications

The limitation of aerogels (especially hydrophilic ones) in a number of applications is their open-pore structure, allowing the penetration of liquids therein resulting in destruction of their textural properties. Upon contact with gastrointestinal tract fluids, a large capillary force is induced that lead to destroying the aerogel network, hence, a fast drug release from the aerogel-drug formulation is obtained ([Guenther, et al., 2008](#); [I. Smirnova, et al., 2003](#); [I. Smirnova, et al., 2004](#)). This release phenomenon is the main limitation that prevents aerogel from being in use for controlled drug release. Hence, it is necessary to protect this porous structure from being in direct contact with the gastrointestinal tract fluid until it reaches the desired release target. Applying a functional polymeric layer on aerogel surface is a promising technique that enables the usage of aerogel for controlled drug release technology as well as many new ranges of applications ([Gurav, Jung, et al., 2010](#); [Omer et al., 2007](#); [Plawsky et al., 2010](#)).

Different experimental equipments and methods for the coating of solid particles are known. According to the principle of the particle movement, they can be categorized into two main groups; mechanical and fluidized beds methods. The mechanical methods, for instance, rotating drums, based on mechanically transformation of the motion to the particles. Hence, high cohesion forces are generated during the process which can destroy the fragile aerogel particles. Fluidized beds are characterized by an intensive mass and heat transfer between the gas stream and the solid phase, which turn with an efficient drying or coating process ([Bhagat, Park, et al., 2008](#)). Despite the advantages of coating in fluidized bed, coating of aerogel is a challenging task. Firstly, aqueous coating with polymeric materials in a fluidized bed is commonly used ([D. Liu et al., 2006](#)). Depending on the surface wettability, aerogel textural will be partially or fully destroyed upon contact with aqueous dispersions, since large capillary forces will be induced. Therefore, it is

necessary to minimize the contact time with aqueous solution. Another solution would be coating from a polymer melt, since the penetration of the melt inside aerogel pores is generally far less than that of aqueous dispersions. Coating using polymers melt can be used either as the end-coating or as a protection layer before an aqueous coating. Secondly, the extreme low density ($< 0.1 \text{ g/cm}^3$) of aerogels prevents fluidizing them in conventional bubbling fluidized beds. Hence, the solution would be a fluidized bed in which a stable fluidization regime at low process flow rate can be maintained. Such flow behavior can be utilized by spouted beds.

A spouted bed is an apparatus that allows solid granulates to come in contact with a fluid. Usually, a jet of the fluids is introduced from the bottom of the apparatus which can be a conical or a cylindrical vessel containing the solid material. At a certain conditions the fluid jet can penetrate the solid granulate creating a spouted zone, fountain above the spout and annulus surrounding the spout. The circulation of the particles within the spout, fountain and the annulus is the most important characteristic of the spouted bed. This flow behavior allows spouted beds to be used for fluidizing:

- Particles with wide particle distributions.
- Rough and very cohesive particles.
- Very small or very large particle size.
- Non spherical and irregular particles shape.

In general spouted beds offer a superior mixing between the solid dispersed phase and the process fluid phase. Hence, an intensive heat and mass transfer between the gas phase and the solid phase can be obtained yielding nearly isothermal conditions ([Gryczka et al., 2009](#); [Gryczka et al., 2008](#)). Therefore, spouted beds have been intensively investigate for diverse range of applications

like drying ([Pereira et al., 2010](#); [San José et al., 2010](#)), combustion ([López et al., 2010](#); [Lopez et al., 2009](#); [Olazar et al., 2008](#); [Olazar et al., 2000](#)), coating ([Behzadi et al., 2008](#); [Borini et al., 2009](#); [Kfuri & Freitas, 2005](#); [Takei et al., 2009](#)) and many other applications ([Cui & Grace, 2008](#); [Mlotek et al., 2009](#); [Olazar et al., 2003](#); [Shirvanian & Calo, 2005](#); [Song & Watkinson, 2000](#)).

In this work a novel process for coating of silica aerogel particles in a spouted bed apparatus was developed in cooperation with the Institute of Solids Process Engineering and Particle Technology, TUHH, Hamburg.

A sketch of the main steps involved in this process is shown in Fig. 37. The complete process consists of 4 main steps: 1) preparation of silica aerogel microspheres; 2) loading of the model drug by adsorption from the supercritical CO₂ phase; 3) applying the coating polymer using a spouted bed; 4) drug release measurements to assess the quality of the coating.

A number of experiments were conducted to obtain the best operating parameters for aerogels coating process. One polymer layer coating as well as multipolymer layers coating was investigated. pH sensitive release was chosen as a model controlled release mechanism. Eudragit[®] L was chosen as a pH sensitive coating polymer in the aqueous suspension form. PEG 2000 melt was used as a protection layer between the liquid suspension and the porous aerogel surface. Since PEG 2000 is highly water-soluble modified drug release profile is solely caused by the Eudragit[®] L coating layer.

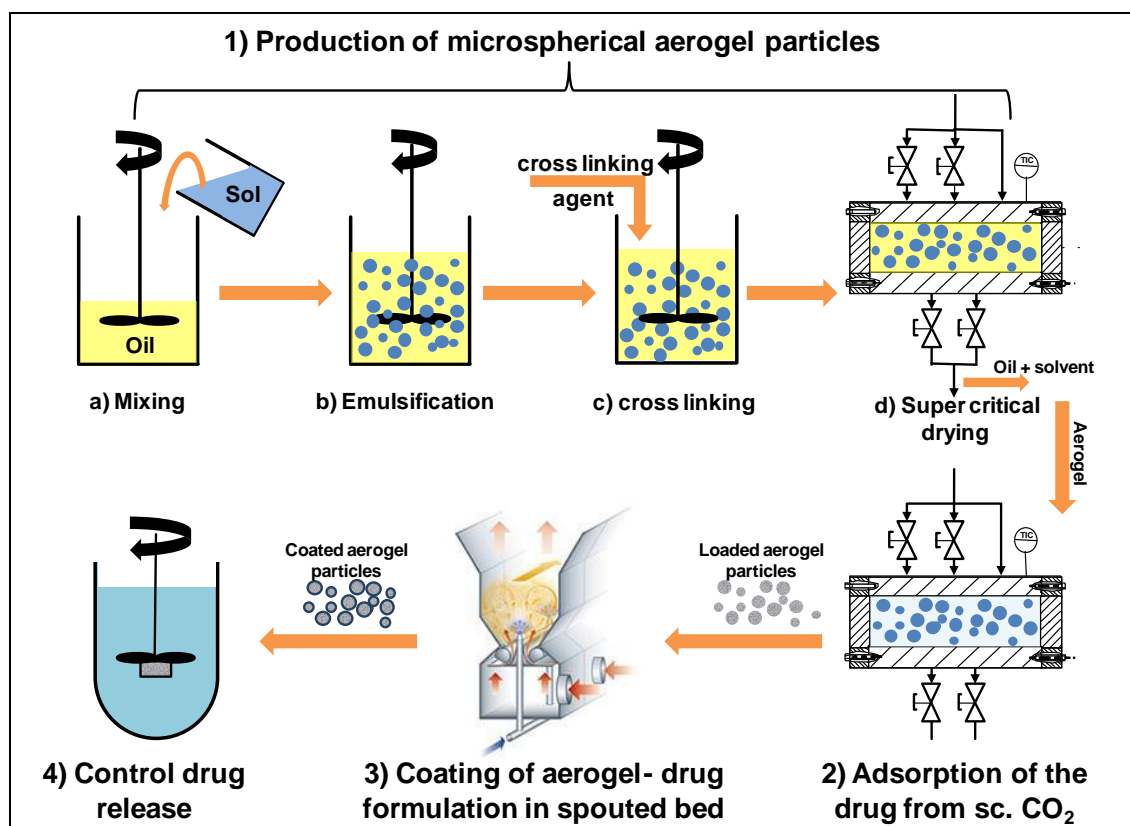


Fig. 37: General steps involved in aerogel coating technology.

3.2.1 Procedures and preparation methods

Silica aerogel microspheres were prepared as discussed in chapter 1.1 of this work. The microspheres were loaded with ibuprofen following the procedure described in section 3.1.1.3.

3.2.1.1 Preparation of the Eudragit® L spray suspension

For preparation of 1000 ml of the Eudragit® L suspension, 10.4 g Polysorbate 80, 17.1 g triethyl citrate, and 8.5 g glycerol monostearate were mixed with 158 g distilled hot water (70 °C) using Ultra Turrax. After that 236 g distilled water at the room temperature (~ 20 °C) was added to the hot mixture and stirred using a magnetic stirrer until the temperature of the mixture cooled down to the room temperature. Then, the mixture was poured into a beaker containing 570 g of Eudragit® L

3.2.1.2 Coating in spouted bed

To perform the coating of the aerogels an experimental spouted bed apparatus was used, which is shown in Fig. 38. This apparatus allows the operation under batch conditions. The spouted bed apparatus consists of a cylindrical freeboard (diameter of 630 mm and height of 500 mm). It is connected through a conical part with a prismatic fluidization chamber with two horizontal gas inlets and adjustable gas supply.

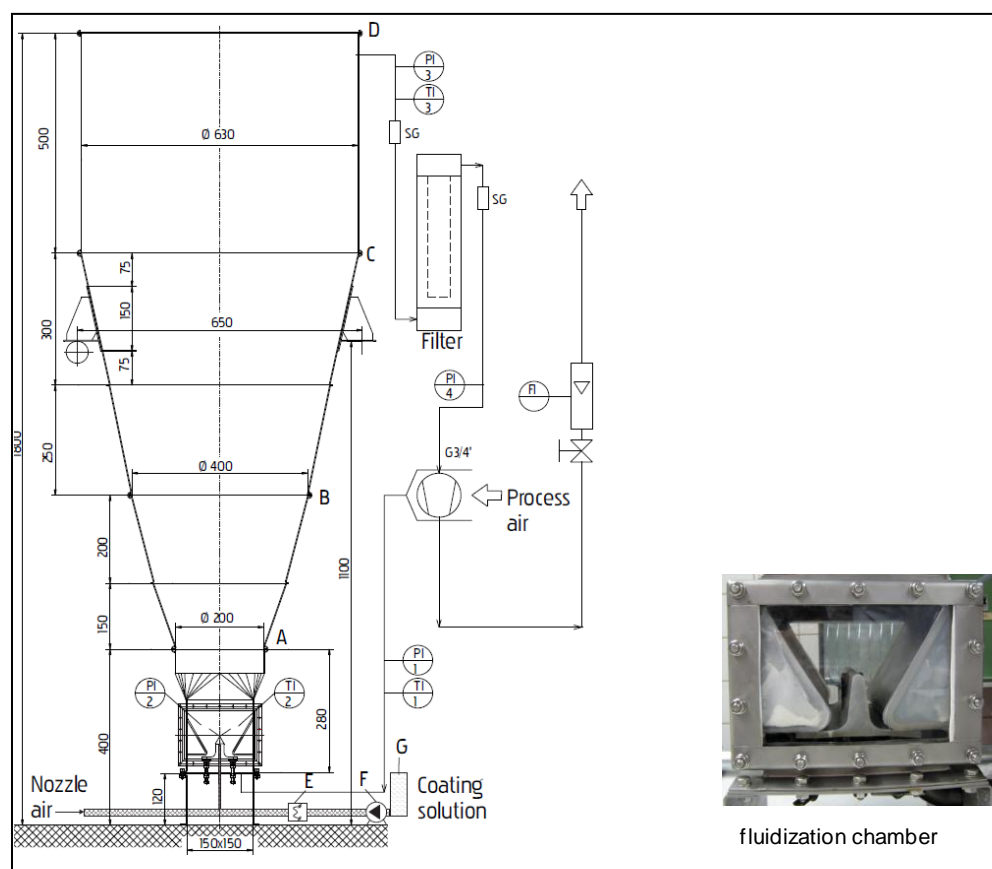


Fig. 38: Schematic representation of experimental spouted bed apparatus for the coating of aerogels, [scheme provided by SPE].

The process air was introduced to the fluidization chamber from the bottom through flat slots. The velocity of the inlet air can be varied by changing the height of these slots. The air blower can deliver a maximum flow rate of 160 m³/h. The fine control of the process mass flow rate occurs with the help of a frequency converter of the blower. The process air can be heated up to a temperature of 100 °C using a 500 W heater.

A suspension or a melt of the coating material was placed in a vessel and heated up to a given temperature. Using a peristaltic pump, the coating suspension was transported in a hose with a constant mass flow rate and atomized into the fluidized bed through a two-component nozzle. To maintain constant temperature of PEG melt during the transportation, the jacket of the hose was heated with circulating hot water. Furthermore, a heating cartridge (350 W) was installed on the nozzle to heat it up to the melt temperature. The air temperature before, after and inside the bed were controlled. Moreover, the temperatures of the feed, the nozzle and the pressure drop across the fluidized bed were recorded. Glass windows were installed at the front and the back sides of the fluidized chamber. This enables the observation of the flow behavior of the particles in the bed using a high-speed camera. The exhaust gas pass through a fabric filter to separate small overspray and attrition particles entrained with the gas.

The advantages of this set-up for the coating processes are the ordered circulating motion of the particles through separated spraying and drying zones and high rotation, which provide a homogenous layering. Moreover, short residence time of the particles in the spray zone and high shear forces in the area of the spouts is obtained resulting in reducing aerogel particles agglomeration.

3.2.2 Results and discussion

3.2.2.1 Coating with Eudragit® L suspension

Aqueous suspension of pH sensitive polymer, Eudragit® L, was used for the coating of aerogel in order to evaluate the possibility of observing controlled drug release profile. The flow rate of the coating suspension and the nozzle air directly influence the size distribution of the droplets which is an important parameter of the coating process. Small droplets result in forming more homogeneous and thinner layers of the coating. The particle size distributions (PSDs) of the droplets atomizing by the used two-component nozzle were obtained with the help of a laser diffraction spectrometer. For the comparison, both Eudragit suspension and pure water were injected through the nozzle. Fig. 39 A shows the PSDs of the water droplets as a function of the air flow rate at constant liquid flow rate (12 g/min). It can be seen that the droplet size decreases with increasing the air flow rate. The viscosity of Eudragit suspension (3-10 mPa·s; at 20°C, provided by the supplier) is higher than that of water (~1 mPa·s at 20°C), therefore, increasing the air flow rate of air has smaller effect on the Eudragit PSDs in comparison to that of water, still the behavior of both was similar (Fig. 39 B).

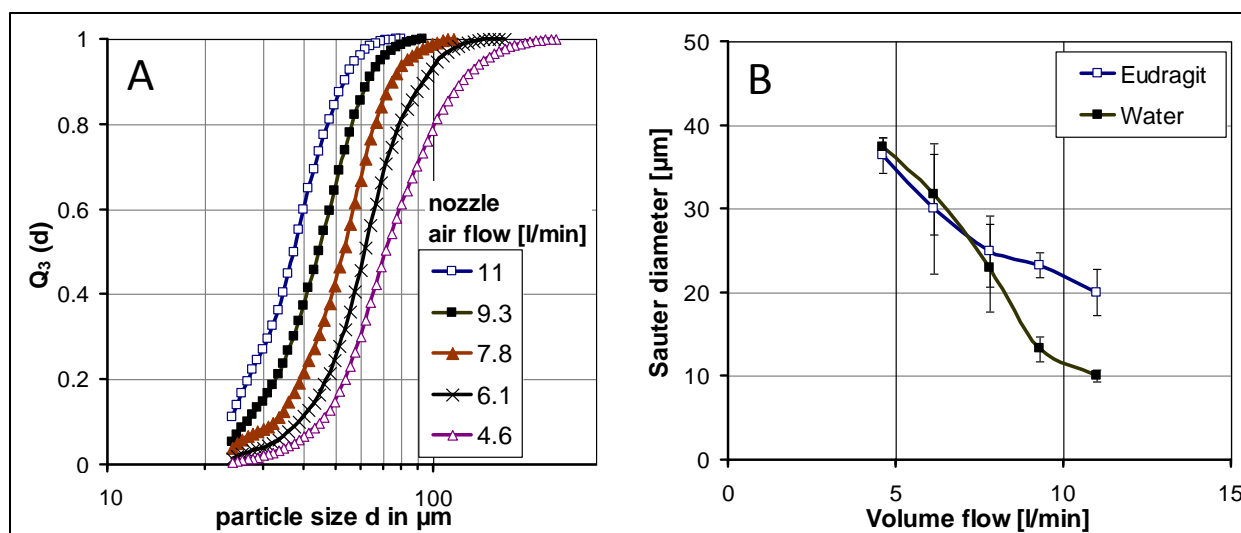


Fig. 39: Influence of the nozzle air flow rate on: A - the particle size distribution of the water droplets; B - the Sauter diameter of the Eudragit® L and water.

The size of the droplets also depends on the gas-liquid mass ratio. According to Mörl et al. this ratio must be between one and four to produce the droplets with a size smaller than 50 μm ([Mörl et al., 2007](#)). The size of the Eudragit droplets must be small enough to form a homogeneous layer and to reduce the drying time of the coated particles. Therefore, for the next coating experiments, the maximum possible air flow rate of this nozzle in the range of 15-20 l/min was used. The suspension flow rate corresponds to the liquid-air mass flow in the range of 1.1-1.4 l/min.

For the first set of experiments Eudragit[®] L suspension was used to coat silica aerogel particles. It was noticed that aerogel microspheres show high shrinkages during the coating process. Fig. 40 shows the PSD of a batch of 60 g aerogel particles at different coating amount of the Eudragit[®] L suspension. It can be noticed that after spraying of 50 g of the coating suspension a dramatic reduction of the PSD was observed; d_{50} was reduced from 670 μm to 165 μm . Thereafter, particles growth was observed. However, at this stage the textural properties of the aerogel were already destroyed. Coating hydrophilic aerogel particles with a low viscous suspension like Eudragit[®] L (3-10 mPa·s) allows the wicking into the porous structure of aerogel particles (Fig. 41), consequently, large capillary forces were induced in the nanopores of the aerogel. As a result a destruction of the porous structure expressed by the shrinkage of the microparticles was observed.

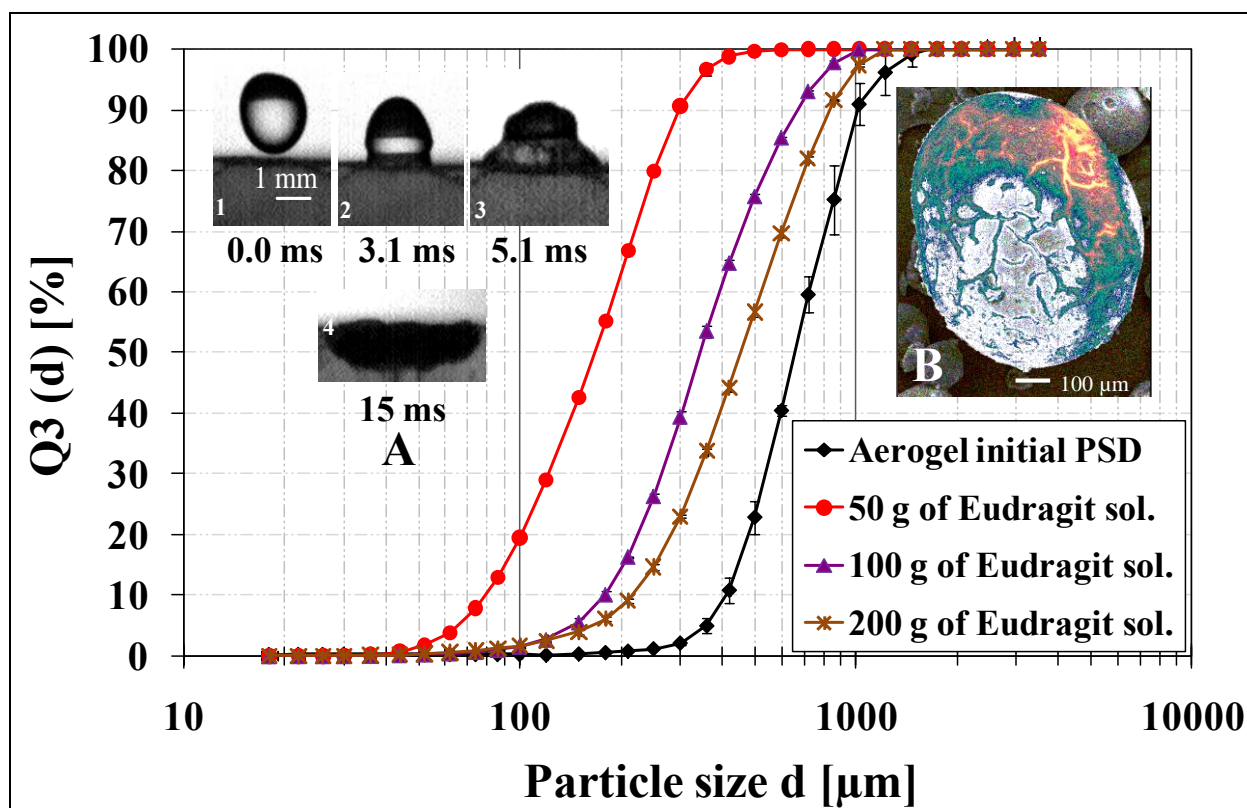


Fig. 40: Shrinkage and growth of the aerogel particles during the coating with aqueous Eudragit®L.

This process was monitored with a high-speed camera with an image rate of $18600 \text{ frames} \cdot \text{s}^{-1}$. Fig. 40 A shows the impact of a water droplet on a flat aerogel surface. At the first moment of contact droplet shape shows different curvatures. The curvature of the droplet bottom characterized the three phase contact with a dynamic contact angle in the range of $40^\circ - 50^\circ$. In the case of Eudragit suspension, the obtained wetting angle is in range of $35^\circ - 45^\circ$. The shape of the droplet changes dynamically during its penetration. Within short time (15 ms) the droplet penetrates into the aerogel resulting in a massive destruction of the aerogel structure. The SEM image of the coated aerogel shows the typical concave curvature of the coating layer (Fig. 41). Accordingly, it is impossible to coat hydrophilic silica aerogel with an aqueous polymeric suspension without destroying its network structure.

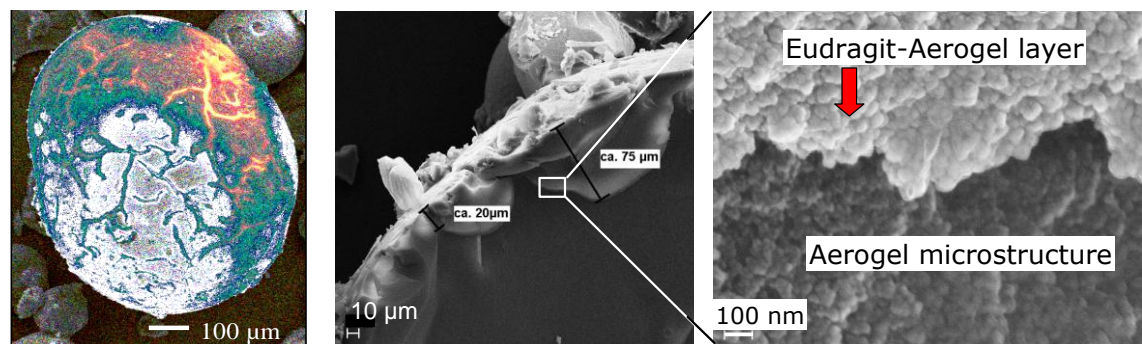


Fig. 41: Aerogel particle coated in spouted bed apparatus with Eudragit® L suspensions (left) and the cross section area of the layer (middle and right).

However, once the Eudragit® L coating droplets dried on the aerogel surface, a kind of protection layer is formed, consequently, the PSD shift to right while increasing the sprayed amount of the suspension, as an indication of the growth (Fig. 40). This observation was the guidance to the fact that a protection layer on hydrophilic aerogel surface is needed to enable the coating with an aqueous suspension. Polymer melts are promising candidates for this task. Because of their viscosity they can't penetrate easily into aerogels pores. Furthermore, they can be solidified on aerogel surface very fast. Hence, coating with two materials was carried out. Firstly PEG 2000 (as a melt) was used to form the protection layer. Thereafter, the Eudragit® L suspension was sprayed over the pre-coated aerogel particles.

3.2.2.2 Double coating of aerogel particles

Table 14 shows the operation conditions used for coating of the aerogel with two layers in the spouted bed. 50 g of the protection layer (PEG 2000, viscosity 200-250 mPa s ([Vlasenko et al., 1980](#))) was sprayed at 80°C with a constant mass flow of 20 g/min over 60 g of aerogel particles. Thereafter, 200 g of Eudragit® L suspension was sprayed at 25 °C and constant injected mass flow of 10 g/min. The bed temperature was maintained constant at ~ 50°C to allow the drying of the Eudragit layer on the solid layer of the PEG 2000. The process air mass flow was increased gradually since the mass of the aerogel particles was increased while coating. During the coating with melt of

PEG the agglomeration of the particles can be observed. At a bed temperature close to the melting point of the injected polymer, in this case (50 °C), the viscous liquid on aerogel particles can bridge the impacting particles. On the other hand at lower temperature the small droplets can harden before arriving particle surface. The growth of the PEG layer on the surface of the particles and agglomeration in the spouted bed were investigated varying the temperature of the process air i.e. the bed temperature. For these experiments the methylcellulose particles as a model material (with initial mass of 100 g) were used. 30 g of the PEG was injected in the bed with a mass flow of 4.3 g/min. The experiments were performed at three different temperatures. The particle size distribution of the coated particles was measured using a laser diffraction spectrometer. The obtained layer thickness is given in Table 15. It can be seen that by increasing the temperature the layer thickness remains nearly constant and the mass fraction of the agglomerates increases. Hence, for the aerogel coating experiment, PEG was injected at a bed temperature of 30° to minimize the probability of agglomeration.

Fig. 42 shows a cross sectional image of one aerogel particle coated with two layers. It is possible to differentiate two layers; one is the protection layer (PEG 2000) and the second is the Eudragit® L layer. In order to confirm this statement the drug release profile was measured.

Table 14: Average process parameters for aerogel coating.

Parameter	PEG 2000	Eudragit® L
process air mass flow rate in m ³ /h	25-40	25-40
bed temperature in °C	30	50
mass flow rate of the coating fluid in g/min	15	8-10
injected mass of the coating fluid in g	50	200
temperature of the coating fluid in °C	95	25

flow rate of the nozzle air in l/min	15-18	15-20
temperature of the nozzle in °C	80	45

Table 15: Influence of the bed temperature on the thickness of PEG layer and agglomeration ratio.

Bed temperature in °C	Layer thickness [μm]	Mass fraction of the agglomerates [mass-%]
35	35 ± 3.2	13.4 ± 1.1
30	30 ± 2.9	8.4 ± 0.5
27	33 ± 2.0	5.9 ± 0.2

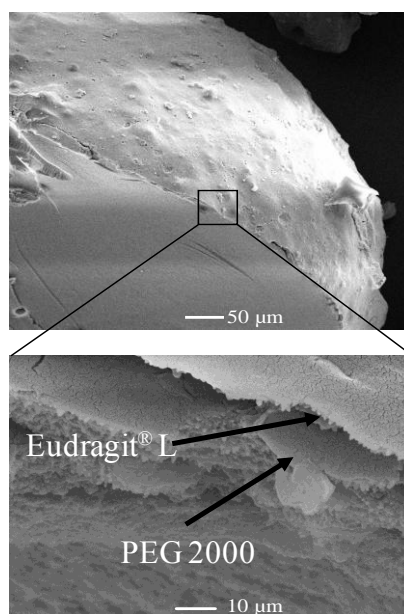


Fig. 42: images of the cross section area of a silica aerogel particle coated with two layers.

3.2.2.3 pH sensitive drug release

Fig. 43 shows the dissolution rate of ibuprofen from coated aerogels at different pH values in comparison with that of uncoated silica aerogels. It is clear that the release profile of ibuprofen-loaded aerogels can be modified by coating with Eudragit® L. At low pH value (1.0) ibuprofen loaded-aerogels released almost 94 % of the drug within 120 min, whereas coating of the aerogels with Eudragit® L enabled a reduction of the release to less than 20 % within 120 min. Eudragit® L is

an anionic polymer that is usually used to develop a pH controlled drug release or rather gastric resistance ([Gupta et al., 2001](#); [O. S. Silva et al., 2006](#)). Since the release profile of ibuprofen was modified at lower pH value, this gives a clear indication that the drug-loaded aerogel was successfully coated using the developed process. However, the presence of some intact layers on some aerogel particles can be the reason behind the released Ibuprofen amount at this pH value. As Eudragit® L is soluble at pH values above 5.5, the applied coating does not affect the release profile of ibuprofen at pH value 7.2. It can be seen that the release profile of coated ibuprofen-loaded aerogel is comparable with that from uncoated ibuprofen-loaded aerogel (Fig. 43). Depending on the coating properties (type of polymer, thickness, number, etc.) it is possible to provide specific release mechanism of pharmaceuticals (thermal, pH-sensitive or enzyme triggered release) from aerogels.

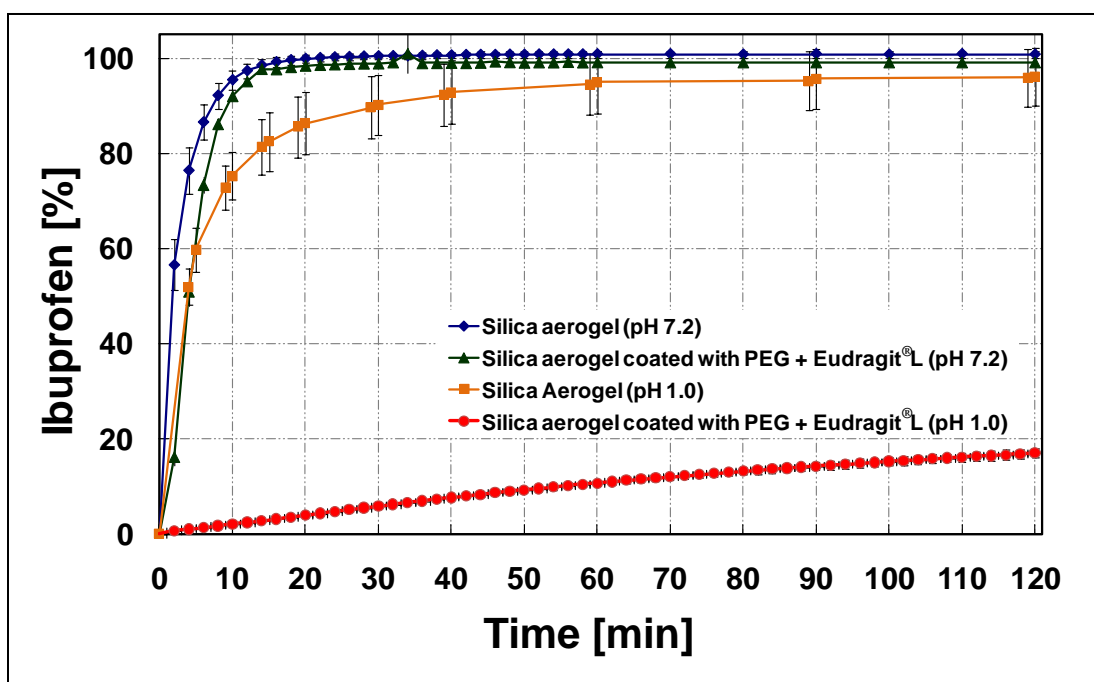


Fig. 43: Drug release profiles of ibuprofen-loaded silica aerogel microspheres at different pH values.

3.2.3 *Conclusions*

A novel process for coating of hydrophilic silica aerogel particles is proposed as a versatile method to enable controlled drug release from aerogels. This process was successfully demonstrated for pH controlled release of Ibuprofen. Spouted bed apparatus enables the stable fluidization and effective coating of light, brittle and cohesive aerogel microparticles without their agglomeration and breakage. The coating experiments with the aqueous Eudragit® L suspension showed the shrinking and breakage of aerogel due to very fast penetration of the aqueous suspension into the hydrophilic porous structure (milliseconds) leading to a destruction of its textural properties. To produce an intact Eudragit® layer and avert the shrinking of the aerogel the particles can be coated with a melt as protection material. Coating of aerogel is a versatile process that can extend the functionality of aerogels for new applications. Beside pharmaceutical industry, coated aerogel can be used for those applications where aerogels need to be isolated from the external environment to maintain their properties. A large market for this application would be the insulation based on aerogels.

3.2.4 *Outlook*

Coating of aerogels is a novel technique that expands their potential for new range of applications. Hence, optimization of the process is of highly importance. Firstly, some setup modifications are needed to allow continuous coating of the used polymers. Furthermore, a dual coating nozzles from top and bottom of the apparatus would be advantageous for multi layers coating problems. Controlling of the temperature at different coating zones is very critical parameter for the coating process, thus, it is required to modify the setup accordingly. During coating of aerogels an increase of their density is observed, as a result the process air introduced to the setup should be increases to compensate this effect. Although manual operation can resolve this problem,

it is recommended to adjust the setup in a way that enables automatic controlling of the fluidization process. Applying different functional polymers on aerogels should be further investigated for different controlled release mechanisms, for instance, temperature, enzymatic, delay, etc. modeling of the process using some simulation tools is a versatile approach to go insight the developed process. This can allow optimization and modification of process parameters and units. Eventually, this would be the first step toward developing of new process in which production and coating of aerogel can occurs in different zones of the same fluidized bed. This is a challenging task that required fundamental and advanced knowledge of aerogel and the fluidized bed technologies.

Part II

Organic Aerogels:

Polysaccharide Based Aerogels

II. Polysaccharide Based Aerogels

Beside all unique properties of silica aerogels, the biodegradability quest for many delivery routes can limit their application significantly. Hence, the last part of this work was focused in implementing the developed processes for silica aerogel to produce aerogel materials based on biodegradable polymers. In the following chapters polysaccharides based aerogels were investigated as a potential example that can combine the beneficial properties of silica aerogels with the biodegradability.

4 Polysaccharide Aerogels: The State of The Art

The use of natural polysaccharides and derivatives are especially attractive because of their non-toxicity, stability, availability and renewability ([H. J. Huang et al., 2006](#); [Malafaya et al., 2007](#)). Moreover, the usual biodegradability and biocompatibility of these natural polymers, coupled with their capability to chemical modification confers them ideal properties for drug release tuning ([K. I. Draget & Taylor, 2011](#); [Mehling, et al., 2009](#); [Robitzer et al., 2011](#)).

The broad portfolio of bio-based polysaccharides allows their use in pharmaceutical products with different routes of applications, target organs and/or drug delivery profiles (Table 16) ([Domb & Kost, 1997](#); [Dumitriu, 2005](#)). They can be used as solid matrices in different forms, such as monoliths, beads, micro- or nanoparticles to incorporate drugs. In this respect, the drug loading amount will be largely influenced by the chemical structure of the matrix, the porosity and the surface area of the polysaccharide-based matrix ([K. I. Draget & Taylor, 2011](#); [N Leventis et al., 2010](#); [Mehling, et al., 2009](#); [Robitzer, et al., 2011](#)). Surface modification of the matrix can also dramatically influence the release profile and the bioavailability of the loaded drug ([Almodóvar & Kipper, 2011](#);

[Alnaief & Smirnova, 2010a](#); [Andrade et al., 2010](#); [Gorle, Smirnova, & Arlt, 2009](#); [Jiang et al., 2010](#); [Ping et al., 2010](#); [Singh et al., 2010](#)).

Table 16: Classification of polysaccharides used for drug delivery systems ([Beneke et al., 2009](#); [Domb & Kost, 1997](#)).

Polysaccharide class	Some examples of drug carriers
Natural	Agar, alginate, carrageenan, cellulose, gellan gum, hyaluronic acid, pectin, starch, xanthan gum
Semi-synthetic	Modified cellulose, chitosan

S.S. Kistler firstly described in 1931 the preparation of aerogels from polysaccharides (gelatin, agar, nitrocellulose and cellulose) and opens up the challenge with the statement “we see no reason why this list may not be extended indefinitely”([Kistler, 1931](#)). Kistler’s work also contributed to the open discussion at the time on the structure of gels (solid solution, emulsion or two-phase solid-liquid structure) ([Kistler, 1931, 1932](#)). Since then, many efforts have been focused on aerogel production from organic and polysaccharide-based precursors ([Alnaief et al., 2011](#); [Heinrich et al., 1995](#); [Mehling, et al., 2009](#); [Pekala et al., 1995](#); [Quignard et al., 2008](#); [Robitzer, et al., 2011](#); [Ulrich Schubert et al., 1994](#); [Wu et al., 1996](#)). However, research on these aerogels addressed to biotechnological and pharmaceutical applications has only been recently started. Namely, organic aerogels from FDA (U. S. Food and Drug Administration)- and EMEA (European Medicines Agency)-approved bio-based polysaccharides can afford the challenge of acting as a biocompatible plus biodegradable delivery system for the dosage of drugs. The solid form of the resulting aerogel will influence the application route, for instance, the aerodynamic diameter of an aerogel particle should not exceed 5 microns for the inhalation delivery route. Alternatively, this class of obtained aerogel materials can also meet the performance criteria for other emerging niche markets, e.g., cosmetic, food and biotechnological industry ([Benvegnu & Sassi, 2010](#); [Desbrieres et al., 2010](#); [E. Freitas et al., 2011](#); [Futrakul et al., 2010](#); [Renard et al., 2006](#)).

Finally, research on aerogel matrices composed of two or more additional phases (hybrid aerogels), one component being a polysaccharide, is also a current topic under investigation ([El Kadib et al., 2008](#); [Molvinger et al., 2004](#)). The use of these dissimilar components in a single aerogel matrix will result in novel and outstanding physicochemical properties of the aerogel. The resulting aerogel properties are the consequence of the synergistic combination of the characteristics of each individual precursor. These materials can encompass the intrinsic properties of aerogels (high porosity and surface area) with the mechanical properties of inorganic components and the functionality and biodegradability of biopolymers ([Hoshi et al., 2010](#); [Kanamori, 2011](#); [Ramadan et al., 2010](#)).

In the following, the state-of-art of preparation of polysaccharide-based aerogels will be summarized, paying special attention to the different processing methods used. Fundamentals and variables of the materials processing routes as well as examples of aerogel systems currently reported in literature for biomedical applications will be outlined.

4.1 From sol to aerogel

The processing steps needed for the production of polysaccharide-based aerogels are summarized in Fig. 44 and will be individually studied in sections 4.1.1 to 4.1.3. Although they differ on the implementation approach (formulation specifications and operating requirements), these three processing steps are commonly found for the production of aerogel from inorganic (e.g., silica, titania, zirconia, alumina) and organic (e.g., resorcinol-formaldehyde, carbon, polysaccharides, polylactic acid) origin ([Kickelbick et al., 2000](#); [Pekala, et al., 1995](#); [Ulrich Schubert, et al., 1994](#)). Briefly, polysaccharide aerogel processing starts with the formation of a gel from an aqueous solution, i.e., hydrogel (section 4.1.1). Gel formation from a solution is induced by a cross-linker promoter that can be of chemical (e.g., crosslinker compound) or physical (e.g., temperature) origin.

The next step is the replacement of the water present in the gel structure by a solvent (alcohol) to lead to an alcogel (Section 4.1.2). This step can be skipped in some cases if the gel is already processed as an alcogel instead of as a hydrogel. Finally, the alcohol (usually ethanol) is extracted from the gel by supercritical carbon dioxide-assisted drying and the aerogel end material is obtained.

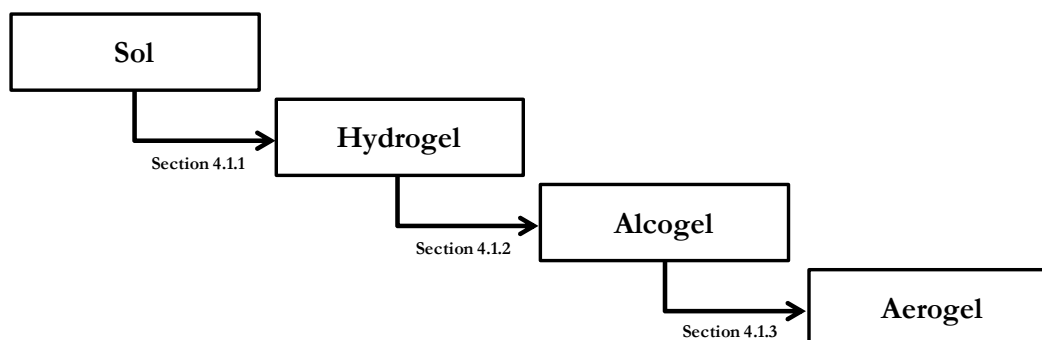


Fig. 44: Processing steps used for the production of polysaccharide-based aerogels.

4.1.1 Gel preparation

Hydrogel formation, i.e., gel swollen by water or by an aqueous solution, from polysaccharide precursors is the most common starting material. Alternatively, polysaccharide-based lyogels in organic solvents have been reported in literature as precursor for the production of aerogels (e.g., cellulose gel in N-methylmorpholine-N-oxide solvent) ([Gavillon & Budtova, 2008](#); [Innerlohinger et al., 2006](#); [Liebner et al., 2009](#)). The proper selection of the hydrogel formulation, e.g., precursor content, functional groups of the precursor, pH, cross-linker content and viscosity, is crucial to obtain high-performance bio-based aerogels. Gelation temperature and aging time may also be key process parameters for hydrogel formation ([Laurienzo, 2010](#); [Maiti et al., 2010](#); [Oh et al., 2010](#); [Park et al., 2010](#); [Quignard, et al., 2008](#); [Robitzer, et al., 2011](#); [R. J. White et al., 2008](#)). Different approaches can be found in literature for the preparation of hydrogels from polysaccharides ([Farahnaky et al., 2008](#); [Favaro et al., 2008](#); [Park, et al., 2010](#); [Phillips & Williams, 2005](#); [Rodriguez-Tenreiro et al., 2006](#); [G. H. Wang & Zhang, 2007](#)). The three-dimensional structure of the gel is

mainly governed by the degree of crosslinking between the polysaccharide chains. The resulting gel can be denoted as a chemical or physical hydrogel depending on the nature of the chain crosslinking ([Omidian & Park, 2008](#); [Park, et al., 2010](#); [Phillips & Williams, 2005](#)). A physical hydrogel is referred to a reversible crosslink between polymeric chains through weak forces, e.g., hydrogen bonding, ionic interactions or complexes. Inorganic salts ($\text{Ca}(\text{SCN})_2 \cdot 4\text{H}_2\text{O}$, CaCl_2 , CaCO_3 , CaSO_4 , NaCl , KCl , etc) can be added to promote ionic bondings ([Jin et al., 2004](#)). For some polysaccharides, the choice of either monovalent or divalent/multivalent cations will infer the formation of soluble salts or gels, respectively ([Quignard, et al., 2008](#)). In chemical hydrogels, the crosslinking of polysaccharides chains is strengthened by covalent bonding formation assisted by coupling agents or cross-linker promoters. Ethyleneglycol, diglycidylether, glutaric acid, sucrose and glutaraldehyde are among the biocompatible chemical cross linkers reported in literature for hydrogels ([Rodriguez-Tenreiro, et al., 2006](#)). The surface area and total pore volume of the resulting aerogel usually increase with the cross-linker content up to a content value where this trend can be reversed. Moreover, fast cross-linking kinetics could lead to non-homogeneous gel morphology ([Alnaief, et al., 2011](#)). Therefore, the choice of the cross-linker and its concentration should be a compromise between aerogel stability and the required open porosity and homogeneity ([Park, et al., 2010](#); [Phillips & Williams, 2005](#)).

4.1.2 Solvent exchange

Prior to the supercritical drying, a solvent exchange is needed because of the low solubility of water to supercritical carbon dioxide (scCO_2) ([Diamond & Akinfiev, 2003](#)). A thorough replacement of water is necessary as the presence of even small amounts of water can cause a dramatic change in the initially highly porous polysaccharide network upon supercritical drying ([Liebner, et al., 2009](#)). The displacement of water using a solvent with high solubility in CO_2 , commonly alcohol or acetone

([C. J. Chang et al., 1997](#); [Stievano & Elvassore, 2005](#)), followed by the removal of this alcohol/acetone using scCO_2 is the typical method for supercritical drying of the gels. The choice of these solvents for water replacement attends to the requirements of (a) not dissolving the gel structure, (b) being completely soluble with the solvent which precedes them (water), and (c) accepted for manufacturing of pharmaceuticals. In some cases, swollen gels show resistance to recompression upon solvent exchange, independently of the liquid solvent within the gel structure. Nevertheless, special attention should be paid in other cases to the main role the solvent exchange step plays in the shrinkage of polysaccharide-based aerogels, since this phenomenon essentially takes place in this processing step ([Mehling, et al., 2009](#); [Quignard, et al., 2008](#); [Valentin et al., 2005](#)). Gel shrinkage was observed to be mitigated in some cases by using multistage water-ethanol concentration steps for the solvent exchange ([Mehling, et al., 2009](#); [Robitzer et al., 2008a](#)). A significant reduction in gel shrinkage was also observed in water-to-acetone solvent exchange when using low temperatures (253 K) likely due to slower mass transfer kinetics or substitution at stable gel conditions ([Cardea et al., 2010](#)). In a different approach, Brown et al. carried out the supercritical drying directly from the hydrogel without the solvent exchange step using ethanol as a co-solvent for scCO_2 to improve the solubility of water in the drying medium and thus accelerating the drying process, but the resulting gels exhibited extensive shrinkage ([Brown et al., 2010](#)).

4.1.3 Gel drying

One major problem for the preparation of the aerogels is to eliminate the liquid solvent from the gel avoiding the collapse of the already existing nanoporous structure with the subsequent shrinkage and cracking of the dried gel. Traditional drying procedures, e.g., air drying, are not able to preserve the gel structure (Fig. 45) ([Kistler, 1931](#)). Hence, supercritical drying is necessary to obtain aerogels, otherwise gels with low open porosity will be obtained using other techniques ([Jungbauer & Hahn,](#)

2004; [Kumar, et al., 2003](#); [Mukai, et al., 2004](#); [Plieva, et al., 2008](#); [Plieva, et al., 2004](#); [Rey & May, 2004](#)). Gel drying is discussed in section (1.2.2.3).

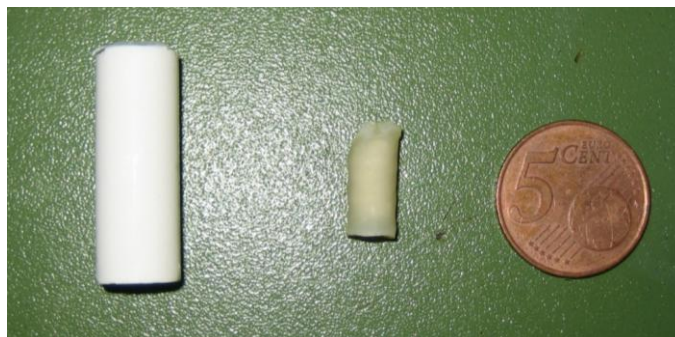


Fig. 45: Effect of gel drying method: Gel monoliths of corn starch dried of the same dimensions dried under supercritical drying (aerogel) and under air drying (xerogel).

4.2 Polysaccharide based aerogels

In the following subsections, some of the main polysaccharides based aerogels are briefly reviewed.

4.2.1 Starch aerogel

Starch is a polysaccharide present in the leaves, seeds and tubers of many vegetables (e.g., potato, corn, wheat, tapioca) in the form of granules. The two main components of starch are polymers of glucose: amylose and amylopectine. The relative proportion of these components varies as a function of the starch source and influences the crystallinity and molecular order of the polysaccharide ([Blazek et al., 2009](#); [P. Chen et al., 2011](#); [Ellis et al., 1998](#); [Jenkins & Donald, 1995](#); [Noda et al., 2005](#)). Starch undergoes gelation in a three-step thermally assisted hydration-plasticisation of the polysaccharide network. i) In the first step, *swelling* takes place by adsorption of water in the hydrophilic starch granules. Minimum water content, above the water binding capacity of starch, is needed for gelatinization to occur ([Wootton & Bamunuarachchi, 1979](#)). ii) Afterwards, *gelatinization* is observed when the starch solution is heated, leading to the leaching of amylose

molecules, irreversible physical changes and the destruction of the granule structure. In case remnants of the original granular structure are still present in the starch gel, lower surface areas in the resulting aerogel will be obtained ([Mehling, et al., 2009](#)). iii) Finally, in the so-called *retrogradation* step, the starch hydrogel structure is formed upon cooling and aging, followed by the reorganization and the partial recrystallization of the polysaccharide structure. Amylose content and gelatinization temperature are the main process parameters influencing the gel formation ([Barker, 2010](#); [Robin J. White et al., 2008](#)). Amylose molecules are detached from the starch granules during gelatinization and, upon retrogradation, they reassociate and deposit on the amylopectin scaffold, forming a porous network responsible of the mesoporosity of the starch gel. Moreover, the higher the amylose content is, the faster the retrogradation rate will occur. High gelatinization temperatures promote amylose release from the granules, however, above a certain value, an increase in the crystallinity, rigidity and density of the resulting aerogel will take place ([Mehling, et al., 2009](#); [White, et al., 2008](#)). Fast heating rates decreases the enthalpy of gelatinization as well as extends the range of temperatures with gelatinization endotherms ([Wootton & Bamunuarachchi, 1979](#)). During retrogradation, low cooling temperatures are prone to reach higher surface areas of the gel since the nucleation rate is favored (number of crystals) with respect to crystallization rate (crystal growth) ([Hoover et al., 1994](#)). Water-to-ethanol solvent exchange in starch gels is needed to avoid the collapse of the pore structure and, in the case of starch gel particles, to avoid the coalescence ([Glenn et al., 2010](#)). Solvent exchange to ethanol of starch gels leads to a more extensive shrinkage when gelatinization takes place at lower temperatures, as well as with a decreasing content in amylase ([Mehling, et al., 2009](#)). Upon supercritical drying, starch aerogels from different types of starch (potato: $\rho \approx 0.46 \text{ g/cm}^3$; $S_a = 72 \text{ m}^2/\text{g}$; $V_p = 0.47 \text{ cm}^3/\text{g}$; corn (Eurylon 7): $\rho \approx 0.34 \text{ g/cm}^3$; $S_a = 90 \text{ m}^2/\text{g}$; $V_{\text{meso}} = 0.37 \text{ cm}^3/\text{g}$) can be obtained ([Mehling, et al., 2009](#)).

4.2.2 Agar

Agar is a phycocolloid consists of agarose and agaropectin in variable proportions. Agar gelation occurs due to its agarose content. At temperature above 85 °C, agarose exists as a disordered ‘random coil’ which upon cooling forms a strong gel, adopting an ordered double helix state. Different helices bond together forming junction zones with hydrogen bonds. These interactions end up with the formation of a three-dimensional network capable of immobilizing water molecules. Agar gel has an enormous potential in applications in food industry, biotechnology and for tissue engineering ([Phillips & Williams, 2005](#)).

Brown et al. have reported the production of agar aerogels as monoliths. Accordingly, they have used sucrose solutions (1-10 % w/v) to dissolve agar powder (1-2 % w/v). The solution was the boiled for 2 min. to insure complete dissolution. After that the solution was poured into moulds and left to cool down to the room temperature. After that the authors have performed the drying using sc.CO₂ or ethanol modified sc.CO₂. The results were compared with ambient drying and freeze drying. Accordingly, after 130 min drying using ethanol modified sc CO₂ at 3l/min flow rate, aerogels were obtained, whereas, it took almost 180 min. using pure CO₂. Even though, both techniques result in extensive shrinkages. The authors have reported a voidage of 48% and 68% for pure and modified CO₂ drying respectively. The obtained voidage using freez drying were 76%. Unfortunately no textural properties were given ([Brown, et al., 2010](#)).

Robitzer et al have reported the production of agar as beads. 2% w/v agar was added to deionized water and boiled rapidly using microwave oven. The solution was then cooled by adding it drop wisely to cold water using a syringe. To obtain aerogels the beads were subject to successive ethanol-water solvent exchange at step of 10, 30, 50, 70 and 100%. Finally the ethanol was replaced with CO₂ using supercritical drying. The reported textural properties were: 0.89, 0.3 cm³/g, 35 nm

and 320 m²/g for void fraction, pore volume, pore size and specific surface area respectively ([Robitzer, et al., 2011](#)).

4.2.3 *Gelatin*

Gelatin is translucent, colorless solid substance that is derived from the parent protein collagen by processes that destroy the secondary and higher structures with varying degrees of hydrolysis of the polypeptide backbone ([Phillips & Williams, 2005](#)). Upon heating to temperatures above 35–40°C gelatins in solutions behave as random coils, however, on cooling the solution aggregation occurs and at concentrations above about 1%, depending on the quality of the gelatin and pH, a clear, transparent gel will form. Hence, it is commonly used as a gelling agent in food, pharmaceuticals and cosmetic industry. S. Kistler was the first to report preparing aerogel out of gelatin, accordingly, gelatin was modified with formaldehyde and the gel was prepared from 20 % modified gelatin to alcohol. After that, alcohol was exchanged with propane at successive steps. Propane was removed at 105°C. the reported aerogel was white, strong, hard, brittle and completely opaque ([Kistler, 1931, 1932](#)). Thereafter, there were no reports of gelatin aerogels. However, new reports that describe the production of nanoporous material based on gelatin appeared recently. Accordingly, gelatin solution was prepared as microspheres using the emulsion and crosslinked with chemical crosslinker. The prepared microspheres were porous with a continuous porous structure ([Nilsson, 2003](#)). Moreover, Kang et al. reported the production of gelatin based nanoporous material suitable for tissue engineering. In this method, 3 wt.% gelatin solution was added to 2wt.% glutaraldehyde aqueous solution to make a final gelatin concentration of 0.2 wt.%. The solution was then poured into a

moulds and left to gel for 12h, thereafter the gel was freeze dried. The resultant porous material was white, porous material with a large macro pore size (45 – 250 μm) ([H.-W. Kang et al., 1999](#)).

4.2.4 Pectin

Pectin, a waste biomass polysaccharide from the primary cell walls of terrestrial plants, can undergo gelation by either thermal or acidic treatment. Gel formation is caused by hydrogen bonding between free carboxyl groups on the pectin molecules and also between the hydroxyl groups of neighboring molecules. The choice of the gelation mechanism as well as the pectin source significantly influences the resulting gel nanostructure ([Sriamornsak, 2003](#); [Thakur et al., 1997](#)). The different pectin varieties mainly differ in the galacturonic acid/methyl esterified acid content leading to different intensities of hydrogen-bonding networks and degrees of chain alignment. Acidic gelation promotes the hydrolysis of the methyl esters inducing a pectin structure predominantly composed of galacturonic acid ([White et al., 2009](#)). In some cases, pectins require the presence of divalent cations (usually Ca^{2+}) for proper gel formation through ‘egg-box’ gelation model mechanism ([Grant et al., 1973](#); [Phillips & Williams, 2005](#)). The presence of sugar (10-20 wt. %) may also contribute to the decrease of syneresis of the gel, as well as to confer firmness to the gel ([Christensen, 1986](#)). After solvent exchange of the gel with ethanol, the supercritical drying of pectin gels yields aerogels with high surface areas and porosity for both thermal and acidic gelation mechanisms. By thermal gelation, aerogels in the form of powder were obtained ($\rho \approx 0.20 \text{ g/cm}^3$; $S_a = 485 \text{ m}^2/\text{g}$; $V_{\text{meso}} = 3.62 \text{ cm}^3/\text{g}$) ([R. J. White, V. L. Budarin, et al., 2010](#)). In contrast, the acidic gelation led to a strong gel yielding low density monoliths ($\rho \approx 0.07 \text{ g/cm}^3$; $S_a = 200 \text{ m}^2/\text{g}$; $V_{\text{meso}} = 0.38 \text{ cm}^3/\text{g}$) ([White, et al., 2010](#)). Finally, the use of pectin aerogels as soft templates allows the preparation of low density carbon aerogels ($\rho \approx 0.27 \text{ g/cm}^3$; $S_a = 298 \text{ m}^2/\text{g}$; $V_{\text{meso}} = 0.97 \text{ cm}^3/\text{g}$) by

thermal carbonization with no need of acid catalyst addition, due to the inherent acidity of this polysaccharide ([White, et al., 2010](#)).

4.3 Drug release assessment

Polysaccharides are being intensively investigated as potential candidates for drug delivery systems in different formulations. Namely, polysaccharide-based aerogels accomplish the biodegradability that silica aerogel lacks and represent a drug carrier in a dry form susceptible to be charged with high loadings of active compound. Therefore, their performance for drug delivery and biomedical systems is being a current topic under investigation ([Alnaief, et al., 2011](#); [K. I. Draget & Taylor, 2011](#); [Park, et al., 2010](#); [Robitzer, et al., 2011](#)). As in the case of inorganic aerogels, the maximum drug loading capacity of polysaccharide-based aerogels (starch) is mainly governed by the surface area of the aerogel ([Mehling, et al., 2009](#)). The specific loading of the drug within the polysaccharide based matrices ($1\text{--}4 \times 10^{-3} \text{ g/m}^2$ for ibuprofen ([Mehling, et al., 2009](#))) are in the range of the values obtained for silica aerogels. The release profile of the drug-loaded organic aerogels was observed to be influenced with the crystalline form of the drug within the matrix. The drug loading of the gels during the solvent exchange step leads to drug deposition in the crystalline form. As a result, the release profiles of hydrophilic drugs (paracetamol) from organic aerogels (starch from potato and corn origin) loaded during solvent exchange were similar to that of crystalline paracetamol. On the contrary, drug (ibuprofen) on the amorphous form was obtained by means of supercritical fluid-assisted drug loading on organic aerogels. Faster dissolution rates than of crystalline drug were obtained for some drug-loaded organic aerogels (corn starch and alginate). Finally, the release of drugs adsorbed on aerogels is also strongly influenced by the nature of the matrix and the textural properties of the aerogel. The mechanical properties and porous structure of

the aerogel matrix influence the rate of backbone collapse and the mass transport profile of the drug, respectively ([Mehling, et al., 2009](#)).

The performance of polysaccharide-based aerogels as carriers can be improved by using hybrid aerogels composed of inorganic and organic (polysaccharide) components. The accessibility of functional groups of some polysaccharides, f.i., amino groups in chitosan, to the adsorption of chemical species can be enhanced by preparing a hybrid aerogel. Improved accessibility to the amino group was obtained for silica-chitosan (80:20 w/w) hybrid aerogel system by texture tuning if both components were homogeneously distributed throughout the sample ([Molvinger, et al., 2004](#)). First studies of chitosan-silica aerogels as drug delivery systems were carried out, showing 17 wt% gentamicin encapsulated within the hybrid aerogel ([Miao et al., 2006](#)). These aerogels passed cytotoxicity tests with very little cell damage ([Ayers & Hunt, 2001](#)). A significant decrease of gel shrinkage during solvent exchange was observed for chitosan gels when processed as chitosan-titania gels ([El Kadib, et al., 2008](#)). Moreover, the resulting chitosan-titania hybrid aerogel after supercritical drying showed improved textural properties (surface area, total pore volume), mechanical stability against acidic (0.1 N acetic acid) and basic solutions (0.1 N NaOH) and enhanced catalytic activity, not attained by aerogels from each individual component of the hybrid material.

4.4 Polysaccharide aerogel morphologies

Polysaccharide-based aerogels are usually obtained in the form of monoliths (Table 17). Gels take the shape of the mould where gelation takes place. The shape of the gels is preserved in the monolithic aerogel after supercritical drying (Fig. 46), although the dimensions could diminish because of shrinkage upon syneresis ([Park, et al., 2010](#); [Phillips & Williams, 2005](#)).

On the other hand, a large surface area of the drug allows a fast dissolution rate of the drug and its absorption in the body. The specific surface area of the drug may be increased by particle micronization and/or by increasing the surface area through adsorption of a drug onto a carrier with a large surface area. Therefore, drug carriers are preferred in a microparticulate aerogel form for certain pharmaceutical applications so that both approaches can be accomplished to get a fast drug release ([N Leventis, et al., 2010](#)).

Table 17: Examples of the main polysaccharide based aerogel systems in the literature.

Natural compounds	Size	Literature
Chitosan	Aerogel (monolith)	(X. Chang et al., 2008)
Agar gel	Aerogel (monolith)	
Starch	Aerogel (monolith)	(Brown, et al., 2010)
Ca-alginate	Aerogel (monolith)	
Ca-alginate	Aerogel (microspheres)	(Mehling, et al., 2009)
Chitosan	Aerogel (monolith)	
Cellulose	Aerogel (monolith)	(Alnaief, et al., 2011)
Ca-alginate	Aerogel (2 mm beads)	
Carrageenan	Aerogel (1.2 mm beads)	(Cardea, et al., 2010)
Chitosan	Aerogel (150 microns beads)	
Ca-alginate	Aerogel (1.2 mm beads)	(Jin, et al., 2004)
Cellulose	Aerogel (monolith)	
Gelatin	Aerogel (monolith)	(Quignard, et al., 2008)
Agar	Aerogel (monolith)	
Nitrocellulose	Aerogel (monolith)	(Valentin et al., 2006b)
cellulose	Aerogel (monolith)	
Alginic acid	Aerogel (monolith)	(C. Tan et al., 2001)
		(R. J. White, C. Antonio, et al., 2010)

Micronization can be obtained by applying some destructive techniques like milling, however, the melting points of the biopolymers and the generation of hot-spot during the operation can be the hindrance of this approach. Other manufacturing option is to process the aerogels in the form of beads (in the millimeter to centimeter range). The usual processing approach is the dropping of a solution containing the polysaccharide aerogel precursor by means of syringe/nozzle into a solution containing the gelling promoter agent. The subsequent supercritical drying of the gel leads to the

aerogel formation (Fig. 46b) ([Quignard, et al., 2008](#)). The size of the beads obtained by this method is mainly controlled by the orifice diameter of the syringe/nozzle used during the gel formation. This method is also conventionally used for the immobilization in gels of molecules of biological interest for several life science applications, biocatalysis, drug delivery, etc, ([Cao, 2005](#); [Martinsen et al., 1992](#)). Finally, a modification of the process using pulsed electric fields for the atomization of the aqueous precursor solution through the nozzle was recently reported for alginate gel beads ([Zhao et al., 2007](#)). This technique leads to microsized beads in the range of 10 to 412 microns depending on the voltage applied.

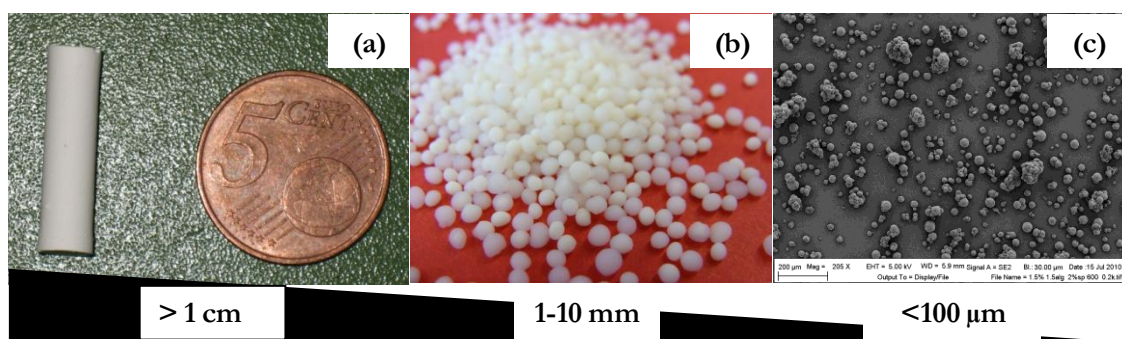


Fig. 46: Calcium-alginate aerogel obtained in different forms: (a) Monoliths, (b) beads and (c) microparticles([Alnaief, et al., 2011](#)).

In this work, the emulsion technique developed for production of silica aerogels was extended to polysaccharides based aerogels. The process was modified to meet the requirements for production of microspherical aerogel particles with high surface area. In the following chapter the production of alginate based aerogels microspheres is given as an example for the possibility of extending the emulsion process to the polysaccharide based aerogels.

5 *Development of Biodegradable Microspherical Aerogel Based on Alginate*

Alginate is a natural polysaccharide polymer, found in great abundance in brown seaweeds. Because of non-toxicity, biodegradability and accessibility, alginate has been used in food industry, pharmaceuticals and medicine ([Domb & Kost, 1997](#); [Dumitriu, 2005](#); [Phillips & Williams, 2000](#); [Walter, 1998](#)). Alginate consists of a linear copolymer composed of 1,4-linked- β -D-mannuronic acid (M) and α -L-guluronic acid (G) residues of varying composition and sequence (Fig. 47). The presence of the carboxylate group within G blocks rings bears a global negative charge at pH 7 usually compensated by sodium cations. Adding divalent ions like Ca^{2+} induces the cross-linking of the polymer and thus the formation of a gel ([Rehm, 2009](#)). This property was explained by the so-called “egg-box” model, Fig. 47, suggesting a possible binding site for Ca^{2+} in a single alginate chain ([Phillips & Williams, 2000](#); [Rehm, 2009](#)). Gelling of alginate depends mainly on the strength, number and length of cross-linking; hence, the composition and the sequence of G and M residues are the main properties of alginate, which influence the mechanical properties of the produced gel ([K. I. Draget et al., 1989](#); [Dumitriu, 2005](#); [Rehm, 2009](#)). Generally two fundamental methods are used to induce gelation of the alginate solution: 1) the diffusion method; 2) the internal setting method. In case of the diffusion method the cross-linking ion diffuses from a large reservoir into an alginate solution ([Trens et al., 2007](#); [Valentin et al., 2006a](#); [Valentin, et al., 2005](#)). Internal setting method differs from the former one by control release of the cross-linking ion which is already dispersed as an inert source within the alginate solution. Usually control release of the ion can be performed by pH control or by limiting solubility of the ion salt ([Mehling, et al., 2009](#); [Phillips & Williams, 2000](#); [C. M. Silva, A. J. Ribeiro, I. V. Figueiredo, et al., 2006](#)). The feasibility of producing highly porous structures, based on alginate, by supercritical drying with CO_2 has been reported ([Horga et al., 2007](#); [Mehling, et al., 2009](#); [Quignard, et al., 2008](#); [Robitzer, et al., 2008a](#); [Valentin, et al., 2006a](#); [Valentin, et al., 2005](#)). It is possible to differentiate two different forms of alginate

aerogels produced so far: 1) monolithic alginate aerogel following the internal setting method ([Mehling, et al., 2009](#)); 2) spherical alginate aerogel beads following the diffusion method ([Quignard, et al., 2008](#); [Robitzer, et al., 2008a](#); [Valentin, et al., 2005](#)). The general procedure of the internal setting method is to mix the alginate solution with the divalent cation (usually Ca^{2+} ions) source and a gelation inducer agent. After that the alginate solution can be poured in to a mould of the desired shape and size. Finally a gel is formed after certain time depending on the gelation mechanism. In the diffusion method, the alginate solution is dropped into a divalent cation, generally Ca^{2+} , bath. The art of generating these droplets can varied from using simple syringe to pressing the alginate solution through a micro opening mesh ([Chuah et al., 2009](#); [Escudero et al., 2009](#)). As soon as the droplets come into contact with the divalent cation bath an instantaneous gelation is induced. The size of the gel beads depend mainly on the size of the opening of the feeding device.

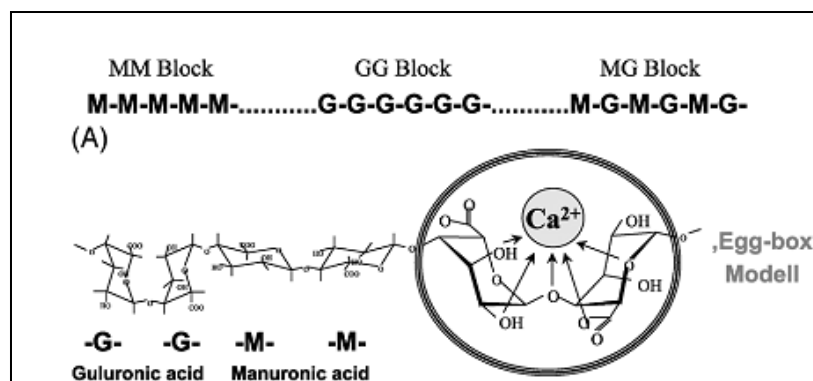


Fig. 47: General alginate, (A) block structure; (B) the formation of the “egg-box” model ([Dumitriu, 2005](#)).

The aim of this part of the work is to adapt the developed process described in section (1.1) for production of microspherical alginate aerogel particles. The adopted process was modified to meet the needs of alginate aerogel production. The modified process consist of 5 main steps (Fig. 48): (1) preparation of the dispersed aqueous phase; (2) emulsification of the aqueous phase in a continuous phase (immiscible with the first one); (3) cross-linking of the dispersed phase (liquid micro-droplets) to form stable gel microspheres; (4) multistep solvent exchange of the hydrogel with ethanol to

obtain an alcogel; (5) CO₂ supercritical extraction of the microspherical alcogel particles to obtain the final microspherical aerogel particles.

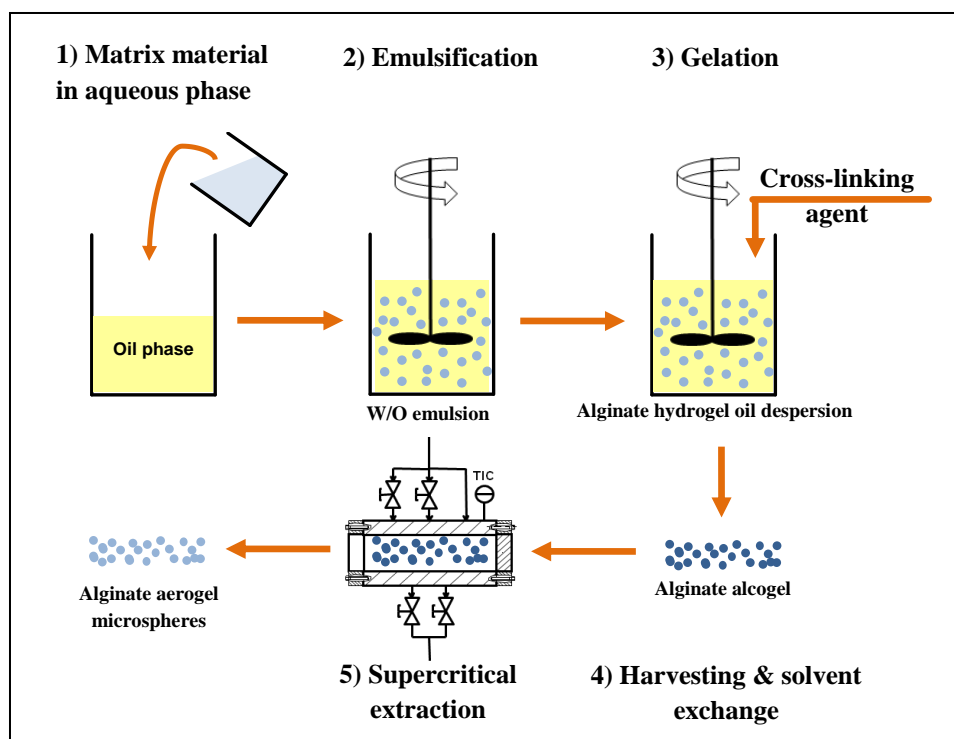


Fig. 48: Schematic overview over the five main steps in alginate aerogel microsphere preparation by emulsion method combined with supercritical extraction.

5.1 Experimental methods

5.1.1 Preparation of alginate gel microspheres

Different procedures were studied to produce alginate gel microparticles. These procedures follow the main two principles of cross-linking the alginate solution, namely, the internal setting method and the diffusion method. In the following sub-section a detailed description is provided.

5.1.1.1 Preparation of alginate stock solutions

In order to compare the results from different batches, the same stock solution of alginate was used for all experiments. Stock solutions with different alginate concentrations were prepared (1.5 wt.%, 2wt.% and 3wt.%). A certain amount of sodium alginate salt was mixed with distilled water using a magnetic stirrer to obtain the desired concentration. Mixing was left overnight to ensure

complete dehydration. The stock solutions were then stored at 5°C. The stock solution was allowed to reach room temperature before starting any preparation.

5.1.1.2 Preparation of alginate gel microspheres

Procedure 1: diffusion method

The main criterion of this procedure is to obtain the gel microspheres out of alginate droplets using the principle of diffusion gelation method ([Phillips & Williams, 2000](#)). Fig. 49 shows schematically the main steps used in preparing alginate aerogel microparticles following this procedure, a detailed description can be found elsewhere ([Sheu et al., 1993](#)). For a typical experiment, sodium alginate solution was added to an oil phase, vegetable oil, which contains 0.2 wt. % Tween[®] 80, to obtain 1:5 W/O phase ratio. The mixture was emulsified in a beaker (diameter: 11 cm) using a marine propeller (diameter: 5 cm) with a certain stirring speed for 15 minute. After that 500 ml of 0.05M CaCl₂ was introduced into the previous W/O emulsion very fast but gently with constant rate at about 20 ml/sec. Finally the gel-oil dispersion was centrifuged (25 °C, 350 g, 10 min.). The collected gels were washed with distilled water, and multistep solvent exchange was carried out to prepare the microparticles for CO₂ supercritical extraction.

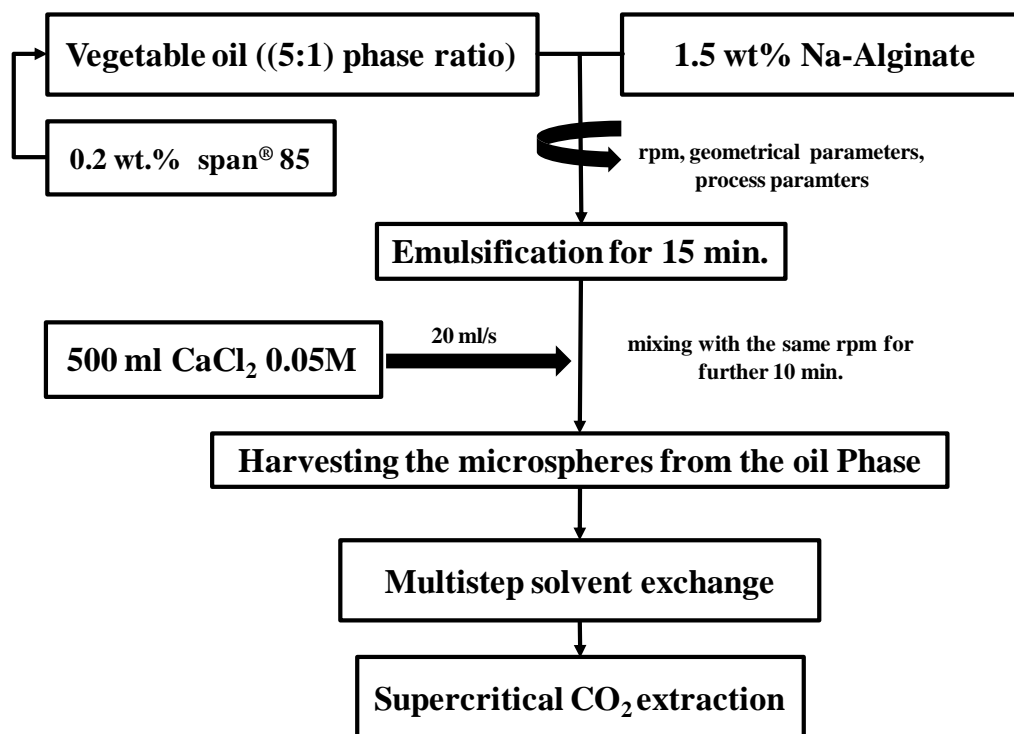


Fig. 49: Preparation of alginate aerogel microparticles following the diffusion method combined with the emulsion (procedure 1).

Procedure 2a: internal setting method

This procedure differed from the former mainly in the cross-linking method mechanism, which follow the internal setting method ([Silva, Ribeiro, Figueiredo, et al., 2006](#)). The main steps used in this procedure are schematically shown in Fig. 50. 50 g of alginate solution with the desired concentration was mixed vigorously with 5 wt% CaCO₃ solution to attain a certain molar ration (Ca²⁺/Na-alginate = 7.3 wt. %) using an ultra-turrax mixer for five minutes. Paraffin oil (continuous phase) was placed in a 500 ml vessel (diameter: 11 cm) and mixed using a marine propeller with a certain stirring rate. 1 vol.% (V surfactant / V oil) of the surfactant (Span® 80) was added to the oil phase. The dispersion (alginate solution + CaCO₃) was then poured at once into the oil phase to obtain 1:2 phase ratio (dispersion / oil). Subsequently, microsphere droplets were formed. After 15 min, 20 ml of paraffin oil + glacial acetic acid (acid/Ca²⁺ molar ratio = 3.5) was added to the system to induce the cross-linking of the alginate solution. After 15 min. the propeller was stopped and the

oil-gel dispersion was filtered to harvest the gel particles. Finally, multistep solvent exchanges were carried out to prepare the microparticles for CO₂ supercritical extraction.

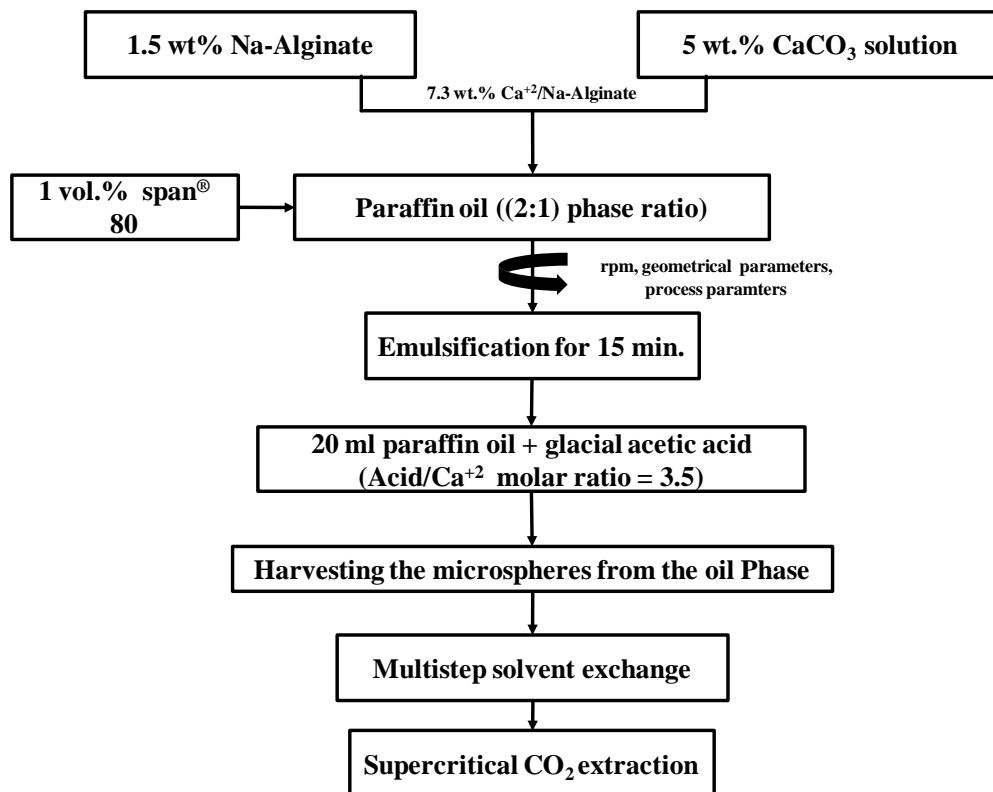


Fig. 50: Preparation of alginate aerogel microspheres following the internal setting method combined with the emulsion (procedure 2a).

Procedure 2b: internal setting method

The last used procedure follows the same principle as that of the previous one (2a). However, different mechanism was used to reduce the pH of the solution: addition of GDL was used ([Mehling, et al., 2009](#)). 50 g of alginate solution was mixed vigorously with 1 wt.% CaCO₃ (CaCO₃/Alginate solution) using ultra-turrax mixer for 5 min. After that, 0.4 wt.% GDL (GDL/Alginate solution) was added to the dispersion and mixed for further 2 minutes. The next step is the addition of the dispersion (alginate solution + GDL + CaCO₃) to the oil phase (paraffin oil), which contain 1 vol.% Span[®] 80, to reach 1:2 w/o phase ratio. The emulsion was then stirred

using a marine propeller for 30 minutes with constant stirring rate. Alginate droplet were converted to alginate gel microspheres due to the gradually reduction of the dispersion pH (upon hydrolyses of GDL). Then, the microspherical particles were harvested using filter paper. Finally, multistep solvent exchanges were carried out to prepare the microparticles for CO₂ supercritical extraction (Fig. 51).

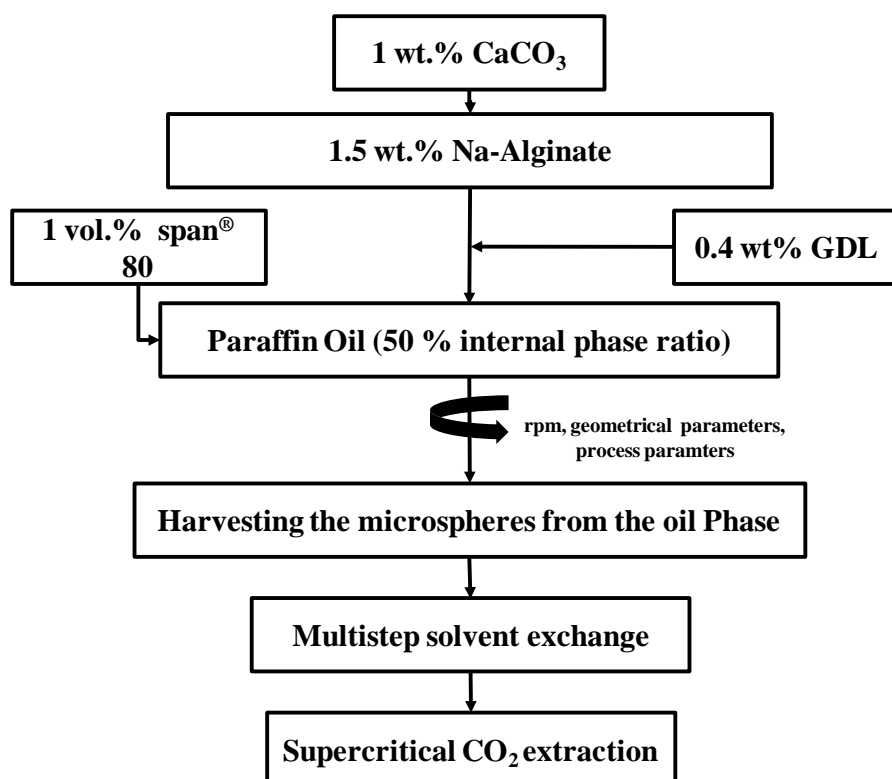


Fig. 51: Preparation of alginate aerogel microspheres following the internal setting method combined with the emulsion (procedure 2b).

5.1.2 Solvent exchange

In order to convert the gel to an aerogel using supercritical CO₂ extraction, it is obligatory to exchange the solvent of the gel (water) with one that can be extracted with sc CO₂. In this work hydrogel was converted to an alcogel using multistep solvent exchange with ethanol. In typical solvent exchange process steps of 30:70, 50:50, 70:30, 100:0 and 100:0 (ethanol/water) were used. Exchange time of 3 hours was used, except for the last step which lasts for overnight.

It should be mention that the solvent exchange plays an important role in production of organic aerogels. Till now, no sufficient studies of this process are present in the literature. The solvent exchange process and its effect on the final properties of different organic aerogels with different forms are under investigation.

5.1.3 Supercritical extraction of the alginate gel particles

In a typical experiment, the produced gel were wrapped separately in a filter paper and placed into the 4 l cylindrical stainless steel vessel. Supercritical CO₂ was delivered using a high pressure diaphragm pump and was introduced from the top of the vessel at constant flow rate (100 – 200 g/min). Temperature was maintained constant (40 °C) using an oil heating jacket. At the outlet of the vessel supercritical CO₂ loaded with solvent was directed to another 2 l cylindrical stainless steel vessel (separator), where the solvent was separated. The pressure and temperature of the separator were maintained constant at 40 °C and 60 bar respectively. Solvent-lean CO₂ was then recycled for the process. After 8 hours the extraction was completed and the aerogel microspheres was removed from the 4 l autoclave and the solvent from the bottom of the separator. Typically the recycled CO₂ was exchanged with a fresh CO₂ at least four times during the extraction process to ensure complete extraction of the aerogel.

5.2 Results and discussion:

The properties of the alginate aerogel (PSD, particle shape, structural properties, etc) produced by the suggested processes can be influenced by many factors. These parameters can be classified into two groups: 1) sol-gel parameters; 2) emulsion process parameters. The sol-gel parameters (precursors concentration, gelling criteria, cross-linking mechanism, solvent exchange, etc) influence mainly the textural properties of the produced gel. On the other hand, emulsion parameters (w/o ratio, stirring rate, surfactant, viscosity, etc) affect mainly the form and PSD of the produced gel

particles ([Alnaief & Smirnova, 2010b](#)). However, interference between different parameters should be expected.

Because of the complexity of combining all effects together, it is beneficial to study each class of properties separately. After that it would be easier to draw some conclusions by combining the parameters from both groups.

In the first part of the following discussion the influence of gelling techniques on the final properties of the produced aerogel was studied. Based on these results procedure 2a and 2b were used to investigate the effect of some emulsion parameters on the final properties of the produced microspherical gel/aerogel particles.

5.2.1 Effect of sol-gel process (gelling mechanism)

Two main gelling mechanisms were investigated in this work. Namely: 1) the diffusion method (procedure1); which is usually used to produce alginate beads ([Escudero, et al., 2009](#)); 2) the internal setting method (procedure 2); which is usually suggested to produce homogeneous gel structure ([Sheu, et al., 1993](#); [Silva, Ribeiro, Ferreira, et al., 2006](#)).

5.2.1.1 Particle shape

Fig. 52 shows four SEM images of different alginate aerogel particles produced following the three used procedures. The images are chosen to be representative for the particles results from each procedure. Fig. 52 A represents the particles results from the first procedure. Irregular particle shapes were obtained. The diffusion gelation process is known to induce fast gelation (seconds); upon breaking the emulsion by addition of the CaCl_2 solution a distortion of alginate droplet dispersion is occurred. Because of the instantaneous gelation mechanism, the deformed alginate droplets gelled and the irregularity of the droplet is preserved. On the other hand, procedure 2, the setting method, results in microspherical aerogel particles Fig. 52 B and C. Thus slow gelation

mechanism is more suitable for the combination with the proposed emulsion process. Based on these results, further investigation were restricted to the setting gelation method (procedures 2a and 2b).

5.2.1.2 Textural properties

As mentioned previously it is expected that the textural properties of the alginate aerogel microparticles depend mainly on the sol-gel process parameters. Table 18 shows the textural properties of different alginate aerogel particles produced following the three used procedures; the emulsion process parameters were kept constant (rpm=400, constant geometrical parameters, etc). It can be seen that all procedures result in relatively large surface area, large pore volume and mesopore structure. However it is clear that the alginate aerogel particles produced following the setting method shows larger internal specific surface area in comparison with those produced by the diffusion method. Slow gelation process offered by setting method (procedure 2) is the main reason behind this finding. Following this method, the production of homogeneous gel internal structure of the alginate microspheres is allowed, as a result better textural properties are obtained ([Silva, Ribeiro, Ferreira, et al., 2006](#)). However, the homogeneity of the cross-linking is one of the main challenges in the diffusion method (procedure 1) ([Kurt Ingar Draget et al., 1990](#); [Phillips & Williams, 2000](#); [Qiu, 2009](#); [Rehm, 2009](#); [Silva, Ribeiro, Figueiredo, et al., 2006](#)).

Table 18: Textural properties of alginate aerogel particles produced using different procedures.

Structural properties	Procedure 1	Procedure 2a	Procedure 2b
Surface area (BET) m ² /g	394 ± 71	590 ± 80	469 ± 54
Pore radius (BJH) nm	10 ± 2	15 ± 2	13 ± 3
Pore volume (BJH) cm ³ /g	2.70 ± 0.95	4.10 ± 0.78	2.89 ± 1.6

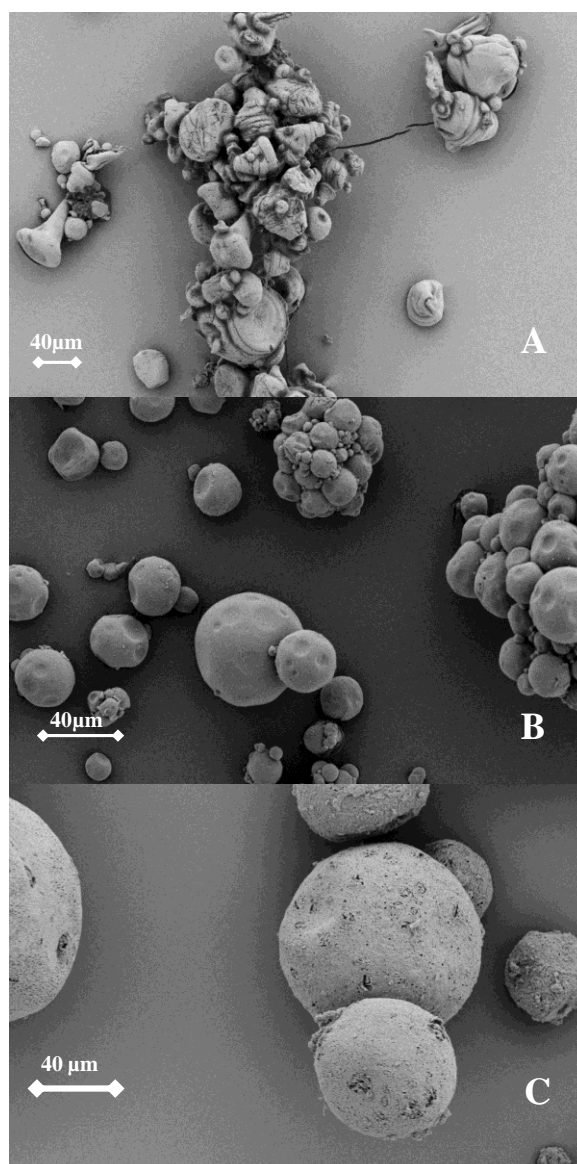


Fig. 52: Influence of gelling process on the final shape of alginate aerogel particles: A) procedure 1; diffusion gelation method, B and C) procedure 2a and 2b respectively; setting gelation method.

5.2.2 Effect of emulsion process on alginate aerogel particles

Emulsion process parameters, including, surfactant concentration, stirring rate, dispersed phase viscosity (alginate concentration), were investigated using procedure 2. In all preparation a marine propeller were used to emulsify 150 ml of emulsion in a beaker (diameter = 9 cm) at room temperature.

5.2.2.1 *Effect of surfactant concentration*

A stabilizer (surfactant) is generally added to the continuous phase to prevent coalescence of the droplets. ([G. S. Banker & C. T. Rhodes, 2002](#)). For the first set of experiments the effect of surfactant was investigated using both procedures 2a and 2b. SEM images were used to evaluate the impact of surfactant concentration on alginate aerogel particles produced by the two procedures. It is clear that procedure 2a results in less aggregated spherical particles in comparison to procedure 2b (Fig. 53). Moreover, a higher surfactant concentration is needed for procedure 2b in order to get uniform spherical particles (Fig. 53). Although, both procedures follow the same gelation mechanism, they differ in the way of pH reduction. In procedure 2a pH reduction occurred through the addition of diluted glacial acetic acid to the emulsion during stirring. As a result a global homogeneous reduction of pH is obtained within a short time. This assists finalizing the gelation process at least on the alginate microspherical shell; no more cross-linking on the surface is possible. However, the mechanism of pH reduction following procedure 2b differs from the former one by slow release of protons by GDL hydrolysis. Consequently, the gelation starts from the very beginning of mixing, since GDL is present in the dispersion before the emulsification. Nevertheless, the degree of cross-linking increased with time, more GDL is hydrolyzed (lower pH values). At these conditions a contact between the micro-droplets during the emulsification process may result in an ionic bond (stable aggregate formation). Using higher concentration of surfactant helps to stabilize the micro-droplets until complete gelation is obtained. Based on this finding and the textural properties presents in Table 18, procedure 2a was found to be the most suitable one for coupling with emulsion process and was used to investigate further emulsion process parameters.

The spherical particles produced by procedure 2 shows a kind of deformation (Fig. 53). The deformations look like a print or a position of other particles, which has detached from the surface.

During harvesting of the particles from the oil dispersion, a vacuum filtration step was used. Accordingly, the particles were subject to a suction pressure, which can deform the particles.

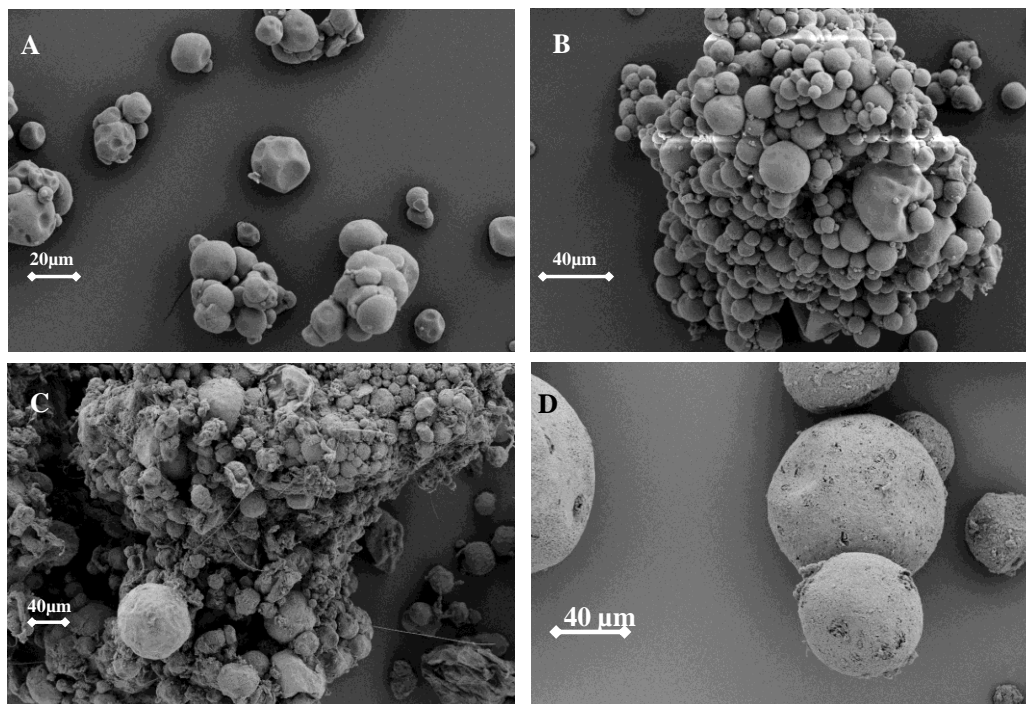


Fig. 53: Influence of surfactant concentration of the emulsion on the PSD of alginate aerogel particles: A) procedure 2a 1 vol.% Span® 80; B) procedure 2a 5 vol.% Span® 80; C) procedure 2b 1 vol.% Span® 80; D) procedure 2b 5 vol.% Span® 80.

Table 19 shows the effect of Span® 80 concentration on the final PSD of alginate gel microspheres. It can be noticed that the Sauter mean diameter was reduced from 259 μm to 115 μm by increasing the surfactant concentration from 0 to 3 vol.% at the same stirring condition (400 rpm). Increasing the surfactant concentration leads to a reduction of the interfacial surface tension between the two phases of the emulsion, this implement that less energy is needed to build the same interfacial surface area between the two phases ([Chern, 2008](#); [S. Freitas, et al., 2005](#); [Leal-Calderon et al., 2007](#)).

Table 19: PSD of alginate gel microspheres as a function of surfactant concentration on the PSD (procedure 2a, 400 rpm, 1.5 wt% alginate solution).

span vol. %	0	1	2	3
Average [μm]	909 \pm 18	534 \pm 44	480 \pm 44	221 \pm 10
D₃₂ [μm]	259 \pm 8	177 \pm 16	135 \pm 10	115 \pm 8
D₁₀ [μm]	271 \pm 40	80 \pm 22	47 \pm 4	65 \pm 2
D₅₀ [μm]	955 \pm 34	508 \pm 46	446 \pm 36	186 \pm 10
D₉₀ [μm]	1432 \pm 16	1003 \pm 50	945 \pm 100	405 \pm 50

5.2.2.2 Effect of stirring rate

In order to investigate the effect of the stirring, the marine propeller stirrer (diameter = 5 cm) was used to emulsify 150 ml of system (alginate solution : oil phases; volume ratio= 1:2) with different stirring rates. The particle size distributions (PSD) as a function of the stirring speed are reported in Table 20. The sauter mean diameter (D_{32}) varies from 168 μm to 34 μm , when the stirrer revolution rate increased from 200 to 1400 rpm respectively (Table 20). Increasing the mixer speed results in a higher energy input to the system, this allows the building of larger interfacial surface area, thus the dispersed droplets become smaller, and consequently the gel microspheres will have a smaller mean size ([Yang, et al., 2000](#)). These results confirmed that the main factor in controlling the PSD is the stirrer revolution rate ([S. Freitas, et al., 2005](#)). It can be noticed that the PSD is relatively broad in all cases. Among many other factors, viscosity of the dispersed as well as the continuous phase plays a major role in controlling PSD in the emulsion process. In our process, the viscosity of the continuous phase remains nearly constant (1000 cP) throughout the experiment; however, the viscosity of the dispersed phase (sol phase) increases continuously with time until the formation of the gel particles. This might lead to the broadening of the resulting particle size distribution (Table 20). Another possible reason is that the used geometry may need optimization in order to distribute the energy evenly throughout the complete volume of the emulsion. Moreover, comparing the results from the laser diffractometer measurement with the SEM images may help to understand the process. Fig. 54 shows a typical aggregated alginate aerogels microspheres produced at 600 rpm, 1.5

wt.% alginate concentration and 1 vol.% Span[®] 80 concentration. It can be noticed that almost none of the particles are larger than 50 μm , whereas the aggregate body is much larger.

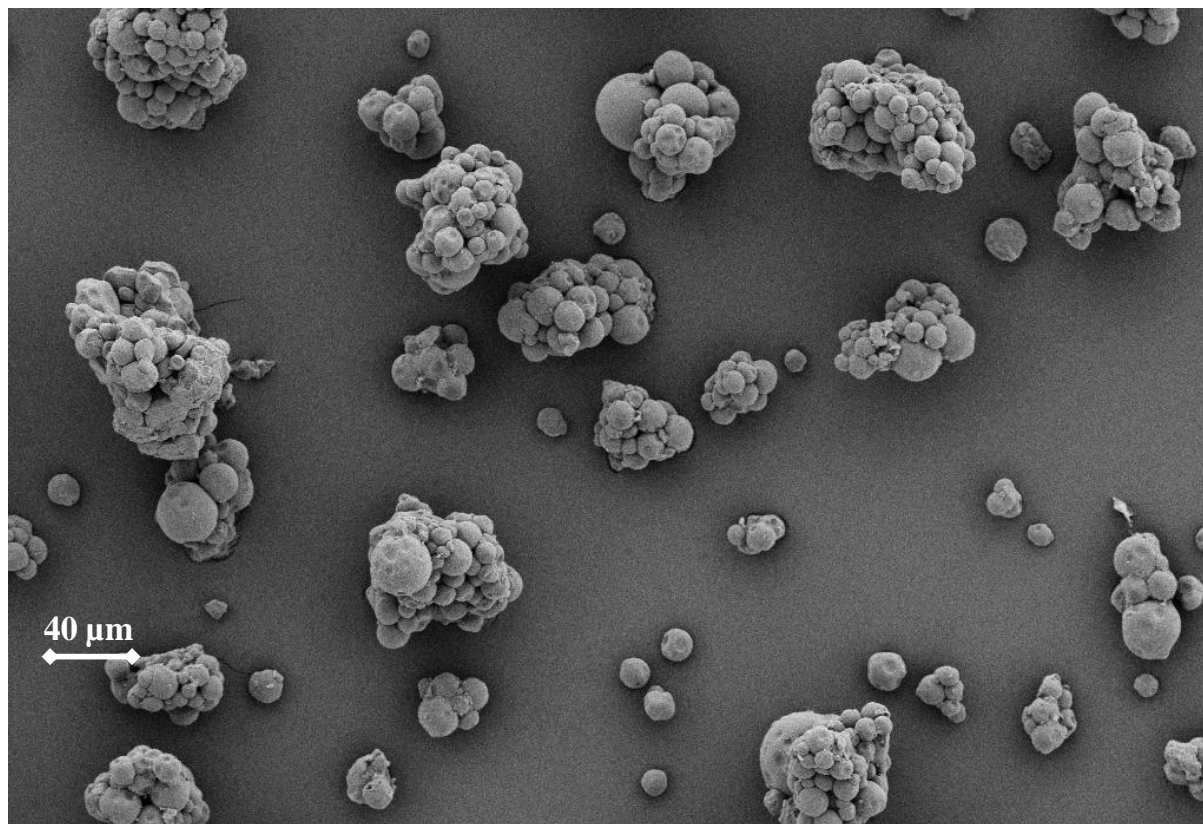


Fig. 54: Aggregated form of the resulted alginate aerogel microspheres (600 rpm, 1.5 wt.% alginate and 1 vol.% Span[®] 80).

Table 20: PSD of alginate gel microspheres as a function of the stirring rate (procedure 2a, 1.5 wt% alginate solution, 1 vol% Span[®] 80).

Rpm	200	400	600	1400
Average [μm]	547 ± 32	534 ± 44	486 ± 100	75 ± 10
D_{32} [μm]	168 ± 16	177 ± 16	145 ± 16	34 ± 4
D_{10} [μm]	67 ± 10	80 ± 22	56 ± 6	15 ± 4
D_{50} [μm]	463 ± 46	508 ± 46	381 ± 70	60 ± 10
D_{90} [μm]	1139 ± 140	1003 ± 50	1066 ± 150	151 ± 6

5.2.2.3 Effect of alginate content

The effect of alginate content on the final properties of the produced alginate aerogels microspheres is intricate. On one hand, this influences the sol-gel process itself, since increasing the concentration of alginate solution means more cross linking. On the other hand, increasing the alginate concentration means increasing the viscosity of the dispersed phase during the emulsification process. Table 21 shows the PSD of the alginate gel produced using different alginate solution concentration. The mean Sauter diameter decreases from 177 μm to 102 μm by increasing the alginate concentration from 1.5 wt.% to 3 wt.%. It is expected that by increasing the viscosity of the disperse phase more energy is needed to create the same interfacial surface area, as a results larger particles is expected to be formed ([S. Freitas, et al., 2005](#)). However, here also the sol-gel process should be considered. Gelation induced following the internal setting method implies that gelation starts simultaneously in large number of locations. Accordingly, some topological strains will affect some of alginate molecules. After the primary gelation is occurred, it is expected that theses location may contains free elastic G blocks, which can form further junction points, if there is free Ca^{2+} cation and another free G block nearby ([Phillips & Williams, 2000](#)). Increasing the alginate concentration will increase the possibility of further junction points; as a result, more syneresis is expected. Table 22 shows the textural properties of alginate aerogel microspheres produced using different initial alginate concentration. As expected the textural properties were improved (in respect to: specific surface area, pore volume and pore size) by increasing the alginate concentration in the solution. As previously discussed increasing the initial concentration of alginate leads to form denser internal network with more cross-linking, which usually enhance the textural properties of the produced aerogel.

Table 21: PSD of alginate gel microspheres as a function of alginate concentration on PSD (procedure 2a, 400 rpm, 1vol% span® 80).

Concentration of alginate solution [wt.%]	1.5	2	3
Average [μm]	534 ± 44	504 ± 41	298 ± 24
D_{32} [μm]	177 ± 16	181 ± 18	102 ± 8
D_{10} [μm]	80 ± 22	163 ± 36	42 ± 5
D_{50} [μm]	508 ± 46	491 ± 41	259 ± 20
D_{90} [μm]	1003 ± 50	855 ± 50	591 ± 70

Comparing the textural properties of the aerogel produced by the proposed method with those presents in the literatures shows that the proposed method results in the highest reported surface area for alginate aerogel. Reproducible high surface area $680 \text{ m}^2/\text{g}$ (based on at least three experiments) with a large pore volume $4 \text{ cm}^3/\text{g}$ and pore average pore radius of 15 nm were obtained. The maximum values reported in the literature following the setting gelation method where $300 \text{ m}^2/\text{g}$ with an average pore volume of $1.9 \text{ cm}^3/\text{g}$ ([Mehling, et al., 2009](#)). However, most of other reported methods for alginate aerogels production follow the diffusion gelation method. The average reported values fall in the range of $(200 - 400) \text{ m}^2/\text{g}$ and average pore volume of $(0.8 - 2) \text{ cm}^3/\text{g}$ ([Escudero, et al., 2009](#); [Horga, et al., 2007](#); [Robitzer et al., 2008b](#); [Trens, et al., 2007](#); [Valentin, et al., 2005](#)). The best reported values fall in the range of $(500-570) \text{ m}^2/\text{g}$, average pore volume of $(1 - 2) \text{ cm}^3/\text{g}$ and pore radius of $(12-17) \text{ nm}$ ([Quignard, et al., 2008](#); [Trens, et al., 2007](#)). Accordingly the presented method is suitable to produce alginate aerogel microspherical particles with superior textural properties.

Table 22: Effect of alginate solution concentration on the textural properties of alginate aerogel particles (procedure 2a, 400 rpm, 1 vol% Span® 80).

Structural properties	1.5 wt.%	2 wt.%	3wt.%
Surface area (BET) m^2/g	318 ± 45	440 ± 27	608 ± 60

Pore radius (BJH) nm	9 ± 2	9 ± 2	15 ± 2
Pore volume (BJH) cm ³ /g	2.15 ± 0.60	2.32 ± 0.38	4.05 ± 0.54

Further optimization should allow the production of a tailor made particles with the needed textural and shape properties to meet the desired application.

5.3 Conclusions

The combination of the sol-gel process with supercritical extraction of the solvent from the alcogel dispersion is proposed as a versatile method for industrially relevant production of alginate aerogel microspheres in a robust and reproducible manner. The process was demonstrated for alginate aerogel microspheres. The textural properties of alginate aerogel produced following the internal setting method shows an improvement over those produced by the diffusion method. The diffusion method is not suitable to be coupled with the emulsion process for production of microspheres particles. Among many emulsion parameters, stirrer revolution rate was found to be the main factor that controls the PSDs of the produced microspheres. Depending on the production conditions, alginate aerogel microspheres with a mean diameter of 30 μm up to several hundred microns were produced. Alginate aerogel microspheres with superior internal properties (surface area of 680 m²/g, pore volume of 4 cm³/g, pore radius of 15 nm) over the reported values in literature were produced following the suggested method. Principally, the process suggested in this work allows large scale production of supercritically dried polysaccharide based aerogel microspheres.

Summary and Conclusions

Aerogel in the form of monoliths or beads are the state of the art for aerogel technology. However, for wide range of applications, microparticles with controlled architecture and morphologies are of high potential. The main goal of this work was to extend the use of aerogels in life science applications, namely pharmaceuticals. The approach was to develop new production processes that allow controlling the morphology and the functionality of the end aerogel product to meet the targeted application field. In the following are the main scientific achievements of this work:

- A new process for production of aerogels in form of microspheres was developed. Combining the sol-gel process with the emulsion process is a versatile approach that enables in situ production of microspherical gel particles. Adjusting the emulsion process parameters allows controlling the PSDs of the resulted gel-oil dispersion. Supercritical extraction of the oil-gel dispersion results in the production of aerogel microspheres. Silica aerogels microspheres with a controlled PSDs range from few microns to few millimeters and high specific surface area up to $1100 \text{ m}^2/\text{g}$ were produced following the developed process. The textural properties of the produced aerogel depend mainly on the sol-gel process and not on the emulsion process. The extraction time of the produced gel particles is far shorter than that for monolithic gels. The developed process allows the mass production of microspherical aerogel particles in a robust and reproducible manner which can be a forward step toward commercialization of aerogel technology.
- The developed emulsion process was successfully adapted for production of alginate based microspherical gel for industrially relevant production. The adapted process was

modified according to the art of sol crosslinking. Different crosslinking methods were evaluated for the properties of the end product. The diffusion method seems to be not suitable to be coupled with the emulsion process for production of microspheres particles. Further, the textural properties of alginate aerogel produced following the internal setting method shows an improvement over those produced by the diffusion method. Alginate aerogel microspheres with the best reported textural properties were produced in a robust and reproducible manner (surface area of 680 m²/g, pore volume of 4 cm³/g and pore radius of 15 nm). Principally, the process developed in this work allows large scale production of supercritically dried polysaccharide based aerogel microspheres.

- Functionalization of aerogels was proposed for tailoring the properties of aerogel to the needed functionality. Three different approaches were developed to allow amino functionalization of silica aerogels to modify the dosage concentration of ketoprofen (model drug) on aerogel. For the first time it was possible to functionalize silica aerogels with aminogroups without affecting their transparency and textural properties significantly. Controlling the functionalization process parameters allow adjusting the final aminogroups concentration on aerogel surface. Liquid phase functionalization was found to be the most efficient method for functionalization of silica aerogels. The adsorption capacity of silica aerogel toward model active agent (ketoprofen) was modified according to the concentration of active aminogroups. The release properties of the loaded drug agent were not affected with the extent of functionalization. Fast release comparable to that of unfunctionalized aerogels was obtained.

- Aerogel coating was proposed as a novel process for enabling controlled drug release. Hydrophilic silica aerogels cannot be coated directly with aqueous coating without affecting their textural properties dramatically. Applying a polymeric coating from melts serve as a final coating with the desired controlled release profile or as intermediate protection layer for aerogel prior coating from aqueous dispersions. Spouted beds are a versatile apparatuses that can meet the severe requirements of fluidizing and coating of aerogels. Adjusting coating process parameters allow controlling the thickness of the applied coating material and subsequently the final release profile of the aerogel-drug formulation. This process was successfully demonstrated for pH controlled release of Ibuprofen from aerogel microspheres. For the first time it was possible to provide a control drug release mechanism based on aerogels. Coating of aerogel is a versatile process that can extend the functionality of aerogels for new applications. Beside pharmaceutical industry, coated aerogel can be used for those applications where aerogels need to be isolated from the external environment to maintain their properties. A large market for this application would be the insulation based on aerogels. The developed process is of high potential; however, further optimization and investigation are needed.

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2. Alnaief M, Smirnova I. “In situ production of spherical aerogel microparticles” J. of Supercritical Fluids 55 (2011) 1118–1123.
3. M. Alnaief*, M. A. Alzaitoun, C.A. García-González, I. Smirnova, “Preparation of Biodegradable Nanoporous Microspherical Aerogel Based on Alginate” J. Of Carbohydrate Polymers, DOI: 10.1016/j.carbpol.2010.12.060.
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- ❖ **Submitted articles:**

1. M. Alnaief, S. Antonyuk, C. M. Hentschel, C. S. Leopold, S. Heinrich, I. Smirnova “A Novel Process for Coating of Silica Aerogel Microspheres for Controlled Drug Release Applications” J. Microporous and Mesoporous Materials

2. C.M. Hentzschel, M. Alnaief, I. Smirnova, A. Sakmann, C.S. Leopold "Tableting Properties of Silica Aerogel and other Silicates" J of Drug Development and Industrial Pharmacy
3. C.M. Hentzschel, M. Alnaief, I. Smirnova, A. Sakmann, C.S. Leopold "Enhancement of griseofulvin release from hydrophilic aerogel formulations and liquisolid compacts" European Journal of Pharmaceutics and Biopharmaceutics
4. K. Wörmeyer, M. Alnaief, I. Smirnova "Amine functionalized Silica-Aerogels for CO₂-Adsorption" Journal of Adsorption.

❖ **Conferences (presentation)**

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3. Hentzschel C.M., Sakmann A., Alnaief M., Smirnova I., Leopold C.S. „Tableting properties of silica aerogel and various silicates" DPhG Jahrestagung 2009, Jena, Deutschland (2009).
4. M. Alnaief, I. Smirnova. "Production of Spherical Aerogel Microparticles by Supercritical Extraction of Emulsion" 12th European Meeting on Supercritical Fluids, Graz (2010) (**Keynote Lecture**).
5. M. Alnaief, I. Smirnova. "Production and Coating of Silica Aerogel Microspheres for Advance Drug Delivery" CHISA 2010 & ECCE 7, Prague (2010).
6. P. Gurikov, A. Kolnoochenko, A. Didenko, M. Alnaief, I. Smirnova, N. Menshutina. "Adsorption of drug from sc. CO₂ and their release from aerogel based formulations: modeling using cellular automata" CHISA 2010 & ECCE 7, Prague (2010).
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2. Alnaief, M.; Smirnova, I. "Production of Spherical Aerogel Microparticles by Supercritical Extraction of Emulsion and Spray Drying" Jahrestreffen der FA Fluidverfahrenstechnik und Hochdruckverfahrenstechnik, Fulda (2010)
3. M. Alnaief, I. Smirnova, S. Antonyuk, S. Heinrich, C.M. Hentzschel, R. Conradi, C.S. Leopold. "Aerogel based solid dosage forms for target drug release" 7th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Malta (2010)
4. M. Alnaief, I. Smirnova, R.H.H. Neubert. "Polysaccharide aerogels: nanoporous material with high surface area and potential to stabilize amorphous drug forms" 7th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Malta (2010)
5. C.M. Hentzschel, M. Alnaief, I. Smirnova, A. Sakmann, C.S. Leopold. "Hydrophilic Silica Aerogels and Liquisolid Systems - Two drug delivery systems to enhance dissolution rates of poorly soluble drugs". The 37th Annual Meeting and Exposition of the Controlled Release Society, Portland, Oregon, U.S.A 2010
6. M. Alnaief, I. Smirnova. "Biodegradable nanoporous microspheres for advanced drug carrier systems" Innovative materials and technologies in chemical-pharmaceutical industry, Moscow (2010).
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