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Original Research Article

A Novel Approach for Polysaccharide Based Aerogels Preparation as a Drug Carrier

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Abstract

This work focuses on the state-of-art of the production of polysaccharide-based aerogels with emphasis on the influence of processing parameters on the resulting end material properties. Different gel concentrations were prepared from the two precursors: alginate and starch. The alginate gels were prepared in the form of beads and $CaCl_2$ was used as a cross linker, while the starch gels were prepared in cylindrical shapes without using any cross linker. Different samples of each concentration were placed in different ethanol/water solutions. The resulting gels were dried using a supercritical drying unit forming hard solid aerogels and the surface area of each sample was measured using the Brunauer–Emmett–Teller (BET). The results showed that the surface area of the alginate is much greater than that of the starch, thus being a better drug carrier. The presented technique allows also the reduction of the gelation time.

Keywords: Nanotechnology, Polysaccharide, Starch Aerogel, Alginate Aerogel

INTRODUCTION

In last few decades, different terms have been introduced to science dictionary such as nanoscience, nanotechnology, nanoparticles, nanoscale, nanosystems, nanobio-system, nanobiomedicine, and so on. According to Campaniello (2009), Taniguchi introduced the term nanotechnology in 1974 to describe ultra-fine machining, including manufacturing of mechanical parts with finishes and tolerances in the nanometer range. Campaniello stated Nano is of Greek origin and means dwarf, a nanometer is one billionth of a meter. Roco (2005) described nanotechnology as the ability to measure, design, and manipulate at the atomic, molecular and supra-molecular levels on a scale of about 1 to 100 nm in an effort to understand, create, and use material structures, devices, and systems with fundamentally new properties and functions attributable to their small structures.

The use of nanotechnology in drug delivery shows tremendous promise for targeting specific individuals, organs, and even specific cells. These techniques can increase drug bioavailability and decrease drug degradation and harmful side effects (Kosal, 2009). The properties of nanomaterials are being leveraged to develop targeted drug delivery systems, cancer curing drugs, antibacterial drugs, etc. (Ibeh, 2010). (Chung et al, 2012). Nanoparticles occupy an outstanding position in scientific field due to their enormous applications in catalysis, electronics and thin film substrates, separation technology, sensor technology, pharmacy and agriculture (Nair et al., 2012).

The best-known application of aerogel insulation was in NASA. Being chemically inert and non-harmful to the human body, aerogels may easily find an application in the pharmaceutical industry and agriculture (Faez et al, 2005). Aerogels are highly porous, optically transparent solid materials can be prepared from different organic and inorganic substances, for example silicon, carbon, polysaccharides, etc. (Patel et al., 2009). The high porosity of aerogels makes this material the lightest solid material known at the moment (Baetens et al., 2010).

Aerogels can be synthesized from different organic and inorganic precursors (Smirnova et al, 2005), which produce nanoparticles dissolve in hydrophobic solvents but not in water (Yamamoto, 2005). In addition, the release of some active ingredients from the aerogel-drug formulation is faster than that of the crystalline drugs and commonly used formulations (Patel et al, 2009). Adsorption on to the hydrophilic aerogels found to enhance the dissolution of drug by increasing the surface area of the drug. This is the novel technique of oral drug delivery (lakshmi et al., 2012).

The aim of this research is to prepare aerogels from polysaccharides (starch and sodium alginate) that provides the pharmaceutical industry with safe and cost efficient materials, characterized by high biodegradability and bioavailability, which can be used as a drug carrier for fast and suitable drug delivery. Lakshmi et al, (2012) concluded that aerogel is the most suitable approach for lipophillic drugs, water insoluble drugs or poorly soluble drugs, and this technique is most ideally suitable for low dose chemical entities. Caputo (2013) stated that the poor water solubility of some drugs limited their bioavailability. Different researchers used different methods and materials for preparing aerogels. David (2004) had prepared silica gels from reacting sodium silicate with hydrochloric acid. Popwscuet, et al (2007) prepared TiO_2-SiO_2 aerogels by sol-gel method followed by supercritical drying with liquid CO_2 and heat treatment, and found that the efficiency of the TiO_2-SiO_2 catalyst strongly depends upon the heat treatment temperature and the silica content. Shalev and Miriam (2011) stated that silica-based sol-gel matrixes can be designed with a wide range of physical properties and can be processed under a wide variety of conditions including ambient temperatures, moderate pH values and short gelation times, making silica alkoxides the most preferred precursors. Gowtham et al. (2011) prepared aerogels of resorcinol formaldehyde hydrogels by using water as solvent and sodium carbonate as pH regulator. The final texture of hydrogel is governed by molar ratio of resorcinol to sodium carbonate. This method of preparation leads to porous hydrogels with no shrinkage during drying process. Li et al,(2012) explored one-step synthesis of hydrophobic silica aerogel by in situ surface modification at ambient pressure with tetraethoxysilane and trimethylchlorosilane co-precursors method. In contrast to the multiple chemical modification approach, the procedure for one-step synthesis was simplified and the processing time was shortened from 2 weeks to 2 days. Nair et al, (2012) prepared silica nano-particles from tetraethylorthosilicate dissolved in ethanol followed by base-catalyzed condensation. They reduced the four parameters, namely concentration of tetraethylortho-silicate, ethanol, water and ammonia solution to optimize the size tuning of silica they achieved size tuning of 5-250 nm by varying a single synthesis parameter, the concentration of ammonia solution. Han (2013) study aimed to further improve ambient pressure drying to achieve a lower cost and environmental requirement. It attempted to synthesize the silica wet-gels followed a hydrolysis process with a tetraethylsilicate-based precursor.

Faez et al., (2005) loaded both hydrophobic and hydrophilic aerogels with pharmaceuticals by means of adsorption from corresponding liquid solutions. The resulting powder was dried and could be used as a drug delivery system. Chaturvedi (2012) studied a topical delivery into the psoriatic skin by the colloidal carrier systems, such as silica aerogel and lipid micro-emulsion. The application of lipids in these formulations resolves the problem of lipid imbalance and lack of moisture content. Thus, these carriers can result in an effective delivery of drugs across psoriatic skin. García-González et al, (2011) concluded that the polysaccharides are regarded as key ingredients for the production of bio-based materials in life sciences. Comin (2011) said that many polysaccharide polymers are renewable and have the ability to form a gel, so an aerogel can be produced by using a gelling polysaccharide, and because of their high porosity and low density cross-linked network structure, polymer aerogels can be impregnated with high value compounds for enhanced delivery. Alnaief (2011)stated 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.

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., 2011).

The Starchis acarbohydrate consisting of a large number of glucoseunits joined by glycosidic bonds. Polysaccharides present in the leaves, seeds and tubers of many vegetables in the form of granules as an energy store (figure 1). It consists of two types of molecules: the linear andhelicalamylose and the branche damylopectin. The relative proportion of these components varies as a function of the starch source and influences the crystallinity and molecular order of the polysaccharide (García-González et al., 2011). Depending on the plant,

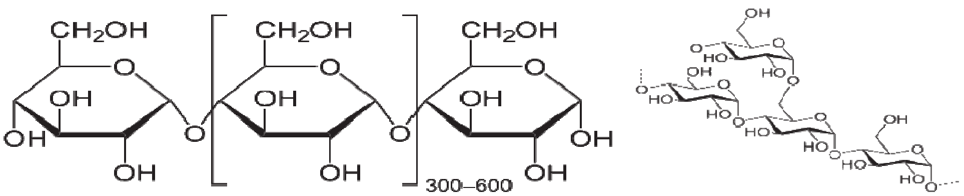

Figure 1. Amylose molecule structure on the right and amylopectin on the left

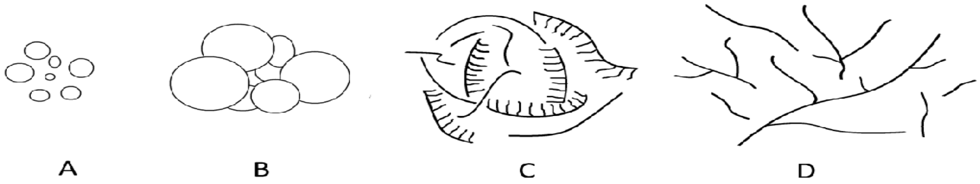

Figure 2. Schematic representation of the gelatinization process: A: Starch grains before the addition of water, B: swelling of the starch granules, C: Decay of the granular structure, D: colloidal solution (Rathjens, 2010).

starch generally contains 20 to 25% amylose and 75 to 80% amylopectin by weight.

The hydrogel formation of starch takes place in three basic steps, which are: the swelling, gelatinization, and subsequent retrogradation.

In the first step, water molecules are adsorbed in the hydrophilic starch granules. Minimum water content, above the water binding capacity of starch, is needed for gelatinization to occur (Wootton and Bamunuarachchi, 1979).Afterwards, the starch solution is heated causing the release of amylose molecules, irreversible physical changes and the destruction of the granule structure (García-González et al, 2011). If the granular structure is not destructed completely, and some residues are still present, this leads to lower surface areas in the resulting aerogel (Mehling et al, 2009). Finally, cooling and aging of the starch solution takes place, followed by the reorganization and the partial recrystallization of the polysaccharide structure. This is called the retrogradation step. Amylose content and gelatinization temperature are the most important factors in the gel formation (Barker, 2010; White et al, 2008). During gelatinization, amylose molecules are separated from the starch granules, and as soon as retrogradation occurs, they join together again and are responsible for the mesoporosity of the gel. Retrogradation rate occurs faster, when the amylose content is higher. Figure 2 shows the high gelatinization temperatures promote amylose release from the granules, however, an increase in the crystallinity, rigidity and density of the resulting aerogel will take place, if the gelatinization temperatures were too high (Mehling et al, 2009; White et al, 2008). If gelatinization of starch takes place at low temperatures, this would lead to a more extensive shrinkage as well as a decreasing content in amylose during solvent exchange to ethanol. Upon supercritical drying, starch aerogels from different types of starch can be obtained (Mehling et al., 2009)

Na-Alginate

Alginate, also called alginic acid is an anionic polysaccharide distributed widely in the cell walls of brown algae (brown seaweeds). Its color ranges from white to yellowish-brown. Alginate absorbs water quickly, which makes it useful as an additive in dehydrated products. It is composed of a linear copolymer composed of 1,4-linked-â-D-mannuronic acid (M) and á-L-guluronic acid (G) covalently linked together with varying composition and sequence. The M-blocks have a more ribbon-like structure that gives them more flexibility. The G-blocks on the other hand have a sheet structure. This property ensures a much higher mechanical strength (Draget, 2000). The presence of the carboxylate group within G blocks rings bears a global negative charge at pH 7 usually compensated by sodium cations (García-González et al., 2011). Adding divalent ions like Ca^{2+} induces the cross-linking of the polymer and thus the formation of a gel (Rehm, 2009). As a result, as M/G ratio decreases, gel strength increases, and as M/G ratio increases, gel strength decreases. M/G ratio differs depending on the source. This property was explained by the so-called “egg-box” model, suggesting a possible binding site for Ca^{2+} in a single alginate chain (Phillips and Williams, 2000; Rehm, 2009). Gelling of alginate depends mainly on the strength, number and length of cross-linking; as a result, 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 as present in figure 3 (Draget et al,

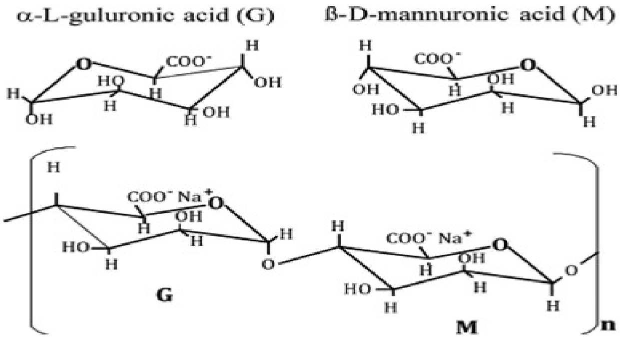

Figure 3. Na-Alginate Structure

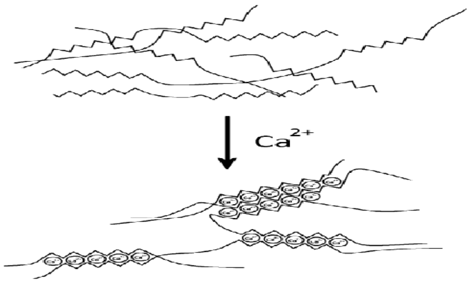

Figure 4. Egg-box Model (Rathjens, 2010).

1989; Dumitriu, 2005;Rehm, 2009).

Methods for the gelation of the alginate

Diffusion method: The cross-linking ion diffuses from a large reservoir into an alginate solution (Trens et al, 2007; Valentin et al, 2006; Valentin et al., 2005). Alginate solution is dropped using a syringe/micro mesh into a divalent cation(usually Ca^{2+}) bath. As soon as the droplets of the alginate solution come into contact with the divalent cation bath an instantaneous gelation is induced forming the spherical alginate aerogel beads. The size of the gel beads depend mainly on the size of the opening of the feeding device (Alnaief, 2011). Internal setting method: In this method the cross-linking ion(usually Ca^{2+}) is dipersed as an inert source within the alginate solution as present in figure 4. Usually the release of the cross-linking ions is altered by pH control or by limiting solubility of the ion salt. Phosphate, citrate and acids are responsible for this process. It is also possible with complexing agents such as EDTA or GDL. After that, the alginate solution can be poured in to a mould of the desired shape and size. The time of gel formation depends mainly on the gelation mechanism (Alnaief, 2011).

Alginate gels and the previously mentioned starch gels are biodegradable, which makes them particularly interesting for technical applications. Alginate may be used for the immobilization of active substances, for example, for wrapping of insulin (Silva et al., 2006). However, it is also possible to use them in the loading of paracetamol or ibuprofen (Mehling, 2009).

Finally, we can conclude that Aerogels are low density nonporous materials composed of a few nanometers in size. The gel can be prepared from organic or inorganic materials, where each type is developed for certain application. Structural properties of the aerogels depend mainly on the preparation method and chemical nature of the gel phase. Aerogel processing starts with the formation of a gel from an aqueous solution (hydrogel). Gel formation from a solution (solgel) is induced by a cross-linking promoter that can be of chemical (eg, crosslinker compound) or physical (eg, pH, temperature) nature. The next step is the replacement of the water present in the gel structure by a solvent (alcohol) to lead to an alcogel. One major challenge for the preparation of aerogels is to eliminate the liquid solvent from the gel, while avoiding collapse, shrinkage or cracking of the dried gel. Traditional drying procedures such as ordinary air-drying are not able to preserve the gel structure leading to shrinkage upon solvent removal such aerogels are called xerogels. Other drying techniques such as freeze drying lead to significant damage in the original pore structure of the gels, such aerogels are called cryogels. Supercritical drying process is an alternative drying technique in which the gel is heated under high pressure, which causes the liquid to become supercritical

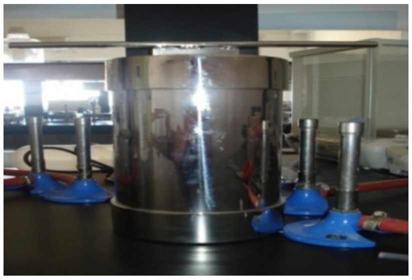

Figure 5. Pressure vessel used for heating the starch samples at 120˚C.

Figure 6. Cylindrical starch samples after retrogradation and aging steps.

and loses its surface tension, the liquid is then removed from the gel by applying additional supercritical CO_2, leaving behind a solid with extremely high porosity and superior textural properties.

METHODOLOGY

Preparation of Starch Gels with Various Concentrations

The aim of this research is to prepare homogenous starch gels and to investigate the effect of gelatinization temperatures, starch concentration and retrogradation step on the final gel formation. The effect of increasing the gelatinization temperature (120°C) on the final gel structure was made using a small pressure vessel (figure 5). Gelatinization temperatures and amylose content are the main process parameters influencing the gel formation and structure. 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 crystalline and molecular order of the polysaccharide.

Materials used

Cornstarch powder with amylase content 52.6% and deionized water.

Procedure

1) Different starch solutions with various concentrations were prepared:9%,11%, 15% and 20% starch solution
2) The prepared solutions were all heated on a heating plate with constant stirring to ensure having a homogeneous mixture and to prevent coagulation of starch molecules until they reached the boiling point, which was between 95°C and 100°C. At this point, the solutions were left to boil for 10 minutes. This is called the gelatinization and crosslinking step. Half of each solution was poured in the pressure vessel and was placed in the oven at 120°C for almost an hour (High gelatinization temperatures to promote amylose release from the starch granules).
3) After the gelatinization step, the solutions were put in 5ml syringes and then covered with Parafilm (figure 6). The syringes were then left for 2 days at a temperature of -18°C. This is called the retrogradation and aging step (Upon retrogradation, the amylose molecules re-associate 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).
4) After being removed from the Freezer each concentration samples were put in a separate container. For each concentration, 3 solvent exchange procedures were performed: first sample was placed in 100% ethanol

Figure 7. Different Concentrations of Na-Alginate Stock Solutions.

Figure 8. Na-Alginate Beads Soaked in Ethanol.

and left overnight. Second sample was placed in 50:50 ethanol/water for 2 hours, then moved to 100% ethanol and left overnight. Third sample was placed in 30:70 ethanol/water and left for 1 hour, then moved to a 50:50 ethanol/water and left for 1 hour, then to a 70:30 ethanol/water and left for 1 hour and then to 100% ethanol and left overnight.

After the solvent-exchange steps were over, all the samples were moved to 100% ethanol one more time to remove the last traces of water before performing the supercritical drying step.

Preparation of Na-Alginate Gels by using the Diffusion Method

This section aims to prepare Na-alginate gels using $CaCl_2$ as a chemical crosslinker with Different Concentrations of Na-Alginate Stock Solutions (figure 7).

Materials used

Sodium alginate powder, Deionized water, and $CaCl_2$ Powder.

Procedure

1) Different Na-Alginate stock solutions were prepared:1.0wt.% , 2.0 wt.%, 3.0 wt.% Na-Alginate.
Each solution was left under constant stirring overnight.
2) The stock solutions were stored the next day at 5°C.
3) 0.05M $CaCl_2$ solution was then prepared and pored to 3 beakers.
4) Na-Alginate solutions were allowed to reach room temperature before being used in any preparation.
5) Approximately 100ml of each Na-Alginate stock solution was dropped into the $CaCl_2$ solution using a simple syringe. As soon as the droplet came into contact with the divalent cation bath (Ca^{2+}) an instantaneous gelation was induced, this is called the "egg-box" model.
6) The formed beads were left in the $CaCl_2$ overnight.
7) The Na-Alginate beads were removed the next day from the $CaCl_2$ solution and washed with distilled water. After that the solvent exchange steps were done as follows:
a) For the 1wt% solution: The sample was first placed in 50:50 ethanol/water for 2 hours, and then moved to 100% ethanol and left overnight as showing in figure 8.
b) For the 2wt% solution: 1.half of the prepared sample was first placed in 50:50 ethanol/water for 2 hours, and then moved to 100% ethanol and left overnight. 2. the rest of the sample was first placed in 10:90 ethanol/water for 1 hour, then moved to 30:70 ethanol/water and left for 1 hour, then to 50:50 ethanol/water and left for 1 hour, then to 70:30 ethanol/water and left for 1 hour and then to 100% ethanol and left overnight. For the 3wt% solution: The same steps performed for the 2wt% solution were repeated.

After the solvent-exchange steps were over, all the samples were moved to 100% ethanol and drying as present in figure 9.

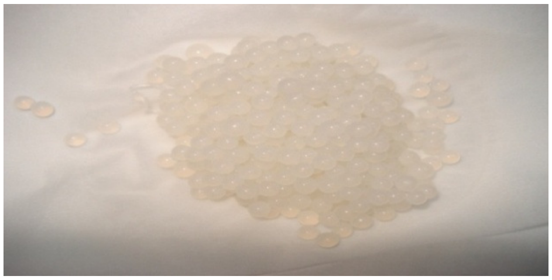

Figure 9. Na-Alginate Beads after Solvent Exchange.

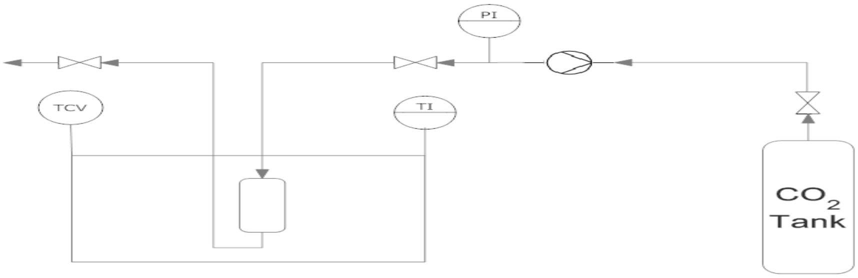

Figure 10. Schematic diagram for the supercritical extraction unit.

Figure 11. Supercritical extraction unit used.

Supercritical Drying for Different Types of Gels

This section aims to produce starch and alginate aerogels by extracting the liquid ethanol from the gel using supercritical CO_2 drying as present in schematic diagram (figure 10) for the supercritical extraction unit.

Setup

The previously produced gels were dried using a 250ml autoclave. The supercritical CO_2 was used to extract the solvent. Ethanol was added to the autoclave and then the samples were added. The pressure was kept above 90 bars and the temperature in a range of 40±1°C. A flow rate of 100-200 milliliters CO_2/min was used to dry the samples for 4 hours.

The following are the supercritical CO_2 drying unit parts:

1) CO_2 Tank.
2) Autoclave (stainless steel vessel).
3) Tubing system to connect the individual parts.
4) Different valves to control the pressure of the system.
5) Compressor (pump) with maximum output pressure of 2000 psi.
6) Pressure gauge.
7) Heating jacket (temperature controller and a thermocouple).

Procedure

1) The gel samples were wrapped with filter paper and placed in the ethanol inside the autoclave (figure 11)
2) The autoclave was then closed firmly to start the process.
3) The water bath was heated to 40°C using an electrical heater.
4) The exit valve was closed and the CO_2 cylinder was opened to start the process.
5) The pressure and flow rate of CO_2 were set to the

Figure 12. Used BET Instrument

desired conditions.

6) The exit valve was partially opened to ensure that the ethanol is coming out of the unit and is replaced by CO_2 gas, as well as to ensure having a continuous flow of CO_2 gas. However the flow rate of CO_2 was continuously monitored, as dry ice was formed and accumulated at the exit valve. Dry ice was removed by opening the valve a little bit more and the flow rate was set again.

7) The pressure was monitored to stay around 1500psi to ensure continuous drying of the gel.

Characterization and analysis of the formed aerogels using Brunauer–Emmett–Teller (BET) analytical method

The aim of this section is to measure the surface area of the aerogels using BET (Figure 12 BET Instrument**)** method and the average pore volume using BJH method. The surface area of starch should be between 80-100m^2/g. For Na-alginate; the average reported values fall in the range of 200-400m^2/g and average pore volume of 0.8-2cm^3/g (Escudero et al., 2009; Horga et al., 2007; Robitzer et al., 2008; Trens et al, 2007; Valentin et al., 2005).

Setup

Surface analyzer Nova (Quantachrom Instruments) was used to characterize the textural properties of the produced aerogels.

Procedure

Weighted samples were pretreated under vacuum at 80°C for about 20 hours to remove the adsorbed water and to avoid undesired conformation. Then, the samples were subjected to N_2.

RESULTS AND DISCUSSIONS

Different homogeneous concentrations of cornstarch gel were prepared at 100°C and 120°C. After heating up to 100°C the different starch solutions had a milky color and the ones' heated up to 120°C were clearer. The increase in temperature caused a progressive disruption of the granular structure in the starch solution, so during recrystallization more molecules are rearranged to form a highly porous network forming stronger aerogels. At higher temperatures, depolymerization can also occur. The gelation time decreased with increasing starch content. While the stiffness of the gel increased steadily with the amount of starch in the solution. The increased starch content also increases the modulus of elasticity. This is because; more chains are arranged parallel in the retrogradation step, which forms more hydrogen bonds in the same volume element. The hardness of the gel depends mainly on the preparation temperature and the concentration of the precursor. Different homogeneous concentrations of Na-Alginate where prepared and $CaCl_2$ was used as a cross linker to prepare the gel beads. The gelation time decreased while the stability increased with increasing the amount of $CaCl_2$.The amount of the cross linking material must be sufficient in order to get a hard and stable gel. The presented technique allows also the reduction of the gelation time.

Alginate aerogels were formed with almost the same original volume. However, in case of starch, shrinkage was observed (figure 13).

Supercritical drying is the most suitable way to dry the liquid content of the gel without losing its initial volume, giving the greatest surface area possible as present in figure 14. The adsorbed amount of nitrogen in a monolayer can be calculated. The pore volume can be determined, by knowing the surface that a nitrogen molecule occupies on the tested samples. Table 1 shows the BET analysis results, for alginate samples, the surface areas were high, but pore volumes were low. On the other hand, the starch samples gave very low surface areas and pore volume.

Figure 13. Starch aerogels after supercritical drying.

Figure 14. Na-Alginate aerogels after supercritical drying.

Table 1. BET results for Alginate and Starch

Sample	Surface Area A_{BET} (m^2/g)	Pore Size d_p (nm)	Pore Volume V_p (cm^3/g)
Alginate 2%, (4 steps solvent exchange)	341.0	26.21	0.1404
Alginate 3%, (2 steps solvent exchange)	421.1	22.70	0.1785
Starch 15% at 100˚C (4 steps solvent exchange)	17.57	38.20	0.005928
Starch 11% at 120˚C (4 steps solvent exchange)	7.935	34.69	0.002597

The surface areas of Na-alginate samples were in the reported range stated above. As a result, these samples are considered to be good candidates as drug carriers. However, starch samples can't be used as drug carriers, due to their very low surface area.

CONCLUSION

Different gel concentrations were prepared from the two precursors–alginate and starch. The alginate gels were prepared in the form of beads and $CaCl_2$ was used as a cross linker, while the starch gels were prepared in cylindrical shapes without using any cross linker. Different samples of each concentration were placed in different ethanol/water solutions. The resulting gels were dried using a supercritical drying unit forming hard solid aerogels and the surface area of each sample was measured using the BET. The results showed that the surface area of the alginate is much greater than that of the starch, thus being a better drug carrier. The presented technique allows also the reduction of the gelation time. Productions of polysaccharides aerogels have the advantage of developing high-performance materials from low-cost and virtually unlimited precursors. The target technology is the production of unique drug carrier materials using biocompatible and biodegradable precursors in a sustainable way. The use of polysaccharides as drug carriers is an attracting strategy as they are nontoxic, more stable and renewable. Also the minimization of the consumption of the intermediate solvent to be used to replace water with carbon dioxide, as well as the optimization of the supercritical drying time of gels are regarded as the key steps to be studied to get an economical and environmental efficient aerogel production process.

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