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Review

Polysaccharide-based aerogels—Promising biodegradable carriers for drug delivery systems

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ABSTRACT

Polysaccharides are regarded as key ingredients for the production of bio-based materials in life sciences (e.g., food, cosmetics, medical devices, pharmaceutics). The biodegradability and biocompatibility of these biopolymers, coupled to the large variety of chemical functionalities they encompass, make them promising carriers for drug delivery systems. Aerogels are a special class of nanoporous materials with growing interest in biomedical and pharmaceutical applications due to their open pore structure and high surface area. Polysaccharide-based aerogels result in highly porous (ε = 90–99%), lightweight (ρ = 0.07–0.46 g/cm^3) drug carriers with high surface area (S_a = 70–680 m^2/g), able to provide enhanced drug bioavailability and drug loading capacity. This review focuses on the state-of-the-art of the production of polysaccharide-based aerogels with emphasis on the influence of processing parameters on the resulting end material properties. Case studies on polysaccharide-based aerogels from several sources and own results as well as their behavior regarding drug loading capacity and release are described.

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Nomenclature

S_a	specific BET-surface area (m^2/g)
V_p	mesopore volume (cm^3/g)
P_r	pore radius (nm)
ρ	bulk density (g/cm^3)
ε	porosity (%)
D_p	mean particle diameter (μm)

1. Introduction

The pharmaceutical industry is constantly facing novel technological challenges and product opportunities owing to its particularly fast changing market scenario. Indeed, the use of excipients in pharmaceutical industry is evolving from their traditional auxiliary function in formulations (i.e., providing weight, volume, flowability and consistency to the product) towards their active role as drug performance enhancers in terms of stability, release and bioavailability (Beneke, Viljoen, & Hamman, 2009; Guenther, Smirnova, & Neubert, 2008). Currently, bio-based materials are regarded as key formulation ingredients for the engineering of modified drug delivery systems (García-González et al., 2010; Jagur-Grodzinski, 2010; Joshi & Müller, 2009; Pose-Vilarnovo et al., 2004). Among them, the use of natural polysaccharides and/or their derivatives are especially attractive because of their stability, availability, renewability and low toxicity, (Huang, Chen, & Yuan, 2006; Malafaya, Silva, & Reis, 2007). Moreover, the usual biodegradability and biocompatibility of these natural polymers, coupled with their capacity for chemical modification confers them ideal properties for their use in drug release systems (Domb & Kost, 1997).

The broad portfolio of bio-based polysaccharides (Domb & Kost, 1997; Dumitriu, 2005; Phillips & Williams, 2000) allows their use in pharmaceutical products with different routes of delivery, target organs and/or drug release profiles (Table 1). 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 capacity is largely influenced by the chemical structure of the matrix, the porosity and the surface area of the polysaccharide-based matrix (Leventis, Aegerter, & Koebel, 2010; Mehling, Smirnova, Guenther, & Neubert, 2009). Surface modification of the matrix can also dramatically influence the release profile and the bioavailability of the entrapped drug (Gorle, Smirnova, & Arlt, 2009).

Aerogel technology provides high added-value lightweight materials with outstanding surface area and open porosity, suitable for loading with active compounds (Rolison, 2003; Smirnova, Mamic, & Arlt, 2003; Smirnova, Suttiruengwong, & Arlt, 2004; Smirnova, Suttiruengwong, Seiler, & Arlt, 2004; Smirnova, Turk, Wischumerski, & Wahl, 2005). Aerogels are obtained from wet gels by using a suitable drying technology, usually a supercritical drying process, able to avoid the pore collapse phenomenon and keep intact the porous texture of the wet material. Efforts have been traditionally focused on silica aerogel and carbon aerogel development with a wide range of applications in different fields, e.g., aeronautics, biomedicine, construction, environmental remediation or agriculture (Akimov, 2003; Hüsing & Schubert, 1998). Nevertheless, all materials that can be obtained as wet gels by the sol–gel process are potential candidates to be turned into aerogels after supercritical drying (Pierre & Pajonk, 2002).

Kistler firstly described in 1931 the preparation of aerogels from polysaccharides (agar, nitrocellulose and cellulose) and opened up the challenge to extend this research with the statement "we see no reason why this list may not be extended indefinitely" (Kistler, 1931, 1932). Since then, many efforts have been focused on aerogel production from polysaccharide-based precursors. However, research on these aerogels addresses to biotechnological and pharmaceutical applications has only been recently started. Namely, organic aerogels from FDA- and EMEA-approved bio-based polysaccharides can afford the challenge of acting as a biocompatible plus biodegradable delivery system for the dosing of drugs. Alternatively, the resulting aerogel materials can also meet the performance criteria for other emerging niche markets, e.g., cosmetic, food and biotechnological industry (Renard, Van De Velde, & Visschers, 2006).

Table 1
Classification of polysaccharides used for drug delivery systems.

Polysaccharide class	Some examples of drug carriers
Natural	Agar, alginate, carrageenan, cellulose, hyaluronic acid, pectin, starch, and xanthan gum (Beneke et al., 2009; Domb & Kost, 1997; Rehm, 2009)
Semi-synthetic	Modified cellulose and chitosan (Beneke et al., 2009; Domb & Kost, 1997)
Synthetic	Methyl-O-(6,O-benzoyl-2,3-di-O-methyl-α-D-glucopyranosyl)-(1 → 4)-O-(2,3,6,tri-O-methyl-β-D-glucopyranosyl)-(1 → 4)-[O-(2,3,6-tri-O-methyl-α-D-glucopyranosyl)-(1 → 4)-O-(2,3,6-tri-O-methyl-β-D-glucopyranosyl)-(1 → 4)-]$_3$-O-(6-O-acetyl-2,3-di-O-methyl-α-D-glucopyranosyl)-(1 → 4)-O-(benzyl 2,3-di-O-methyl-β-D-glucopyranosyl-uronate)-(1 → 4)-O-(3,6-di-O-acetyl-2-O-benzyl-α-D-glucopyranosyl)-(1 → 4)-O-(benzyl-2,3,-di-O-methyl-α-L-idopyranosyluronate-(1 → 4)-2,6-di-O-benzyl-3-O-methyl-α-D-glucopyranoside), etc. (Rauter, Vogel, & Queneau, 2010a, 2010b)

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

2. Processing pathway

The processing steps needed for the production of polysaccharide-based aerogels are summarized in Fig. 1. This processing pathway is commonly followed in the production of aerogel from both inorganic (e.g., silica, titania, zirconia, alumina) and organic (e.g., resorcinol-formaldehyde, carbon, polysaccharides, polylactic acid) precursors, although they differ on the implementation approach (i.e., formulation specifications and operating requirements) (Hüsing & Schubert, 1998). Briefly, aerogel processing starts with the formation of a gel from an aqueous solution, i.e., a hydrogel (Section 2.1). Gel formation from a solution (*sol*) is induced by a cross-linking promoter that can be of chemical (e.g., crosslinker compound) or physical (e.g., 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 (Section 2.2). Finally, the alcohol (usually ethanol) is extracted from the gel

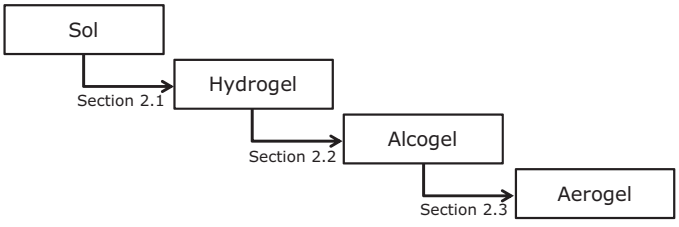

Fig. 1. Diagram of the common processing steps used for the production of polysaccharide-based aerogels.

by supercritical carbon dioxide ($scCO_2$)-assisted drying and the aerogel end material is obtained.

2.1. Gel preparation

Hydrogel formation, i.e., gel swollen by water or by an aqueous solution, from polysaccharide precursors is the most common starting point. Alternatively, polysaccharide-based gels in organic solvents (lyogels) have also been reported in literature as starting gels for the production of aerogels (e.g., cellulose gel in N-methylmorpholine-N-oxide – NMMO – solvent) (Innerlohinger, Weber, & Kraft, 2006; Kraft, Muss, Adelwöhrer, Rosenau, & Röder, 2004; Liebner et al., 2009). Polysaccharide gels can be regarded as a metastable product of a hindered crystallization process, leading to a structure of alternating ordered crystalline parts linked by less organized (amorphous) chains (Blanchard & Muhr, 1982). The proper selection of the hydrogel formulation, e.g., precursor content, functional groups of the precursor, pH and cross-linker content, is crucial to obtain high-performance bio-based aerogels. The three-dimensional structure of the gel is mainly governed by the degree of crosslinking between the polysaccharide chains (Farahnaky, Guerrero, Hill, & Mitchell, 2008; Favaro et al., 2008; Rodriguez-Tenreiro, Alvarez-Lorenzo, Rodriguez-Perez, Concheiro, & Torres-Labandeira, 2006; Wang & Zhang, 2007). The resulting gel can be denoted as a chemical or physical hydrogel depending on the nature of the chain cross-linking (Omidian & Park, 2008). A *physical hydrogel* refers to a reversible crosslink formed between polymeric chains under appropriate conditions through weak forces, e.g., hydrogen bonding or ionic interactions. Inorganic salts (e.g., $Ca(SCN)_2{\cdot}4H_2O$, $CaCl_2$, $CaCO_3$, $CaSO_4$, NaCl, and KCl) can also be added to promote ionic bondings (Jin, Nishiyama, Wada, & Kuga, 2004). For some polysaccharides, the choice of either monovalent or divalent/multivalent cations will control the formation of either soluble salts or gels, respectively (Quignard, Valentin, & Di Renzo, 2008). In *chemical hydrogels*, the crosslinking of polysaccharides chains is strengthened by covalent bond 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 (Brown, Fryer, Norton, & Bridson, 2010; Mehling et al., 2009; 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 threshold value where this trend can be reversed. On the other hand, fast cross-linking kinetics could lead to non-homogeneous gel structures (Fig. 2) (Alnaief, Alzaitoun, García-González, & Smirnova, 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. In general, chemical gels allow a processing with better control of the porous structure and swelling behavior than with physical gels, but at expense of higher raw materials (chemical crosslinker *vs.* precursor cost) and processing (complex steps for the removal of traces of unreacted crosslinker may be required) costs (Omidian & Park, 2008) and more complex chemical characterization. Moreover, for certain biomedical applications, the bondings in chemical gels are often irreversible at human body temperatures and may also prevent the degradation of the entire hydrogel.

2.2. Solvent exchange

Prior to the supercritical drying, the replacement of the water contained in the pores of the hydrogel with a suitable liquid solvent (solvent exchange) is needed due to the low affinity of water to supercritical carbon dioxide ($scCO_2$) (Diamond & Akinfiev, 2003). The presence of even small amounts of water in the pores of the wet gel can cause a dramatic change in the initially highly porous polysaccharide network upon supercritical drying (Liebner et al., 2009, 2010). The usual approach is the displacement of water using a solvent with high solubility in CO_2, commonly alcohol or acetone (Chang, Day, Ko, & Chiu, 1997; Stievano & Elvassore, 2005). Solvent exchange is carried out either by soaking the gel directly in the new solvent (one-step) or by following a sequential soaking (multi-step) in different water-to-new solvent mixtures with increasing content in the new solvent after a certain time (exchange frequency) in the previous soaking step (Robitzer, David, Rochas, Di Renzo, & Quignard, 2008). The solvent chosen for water replacement must satisfy 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. 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 during this step (Mehling et al., 2009; Quignard et al., 2008; Valentin et al., 2005). 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, Pisanti, & Reverchon, 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

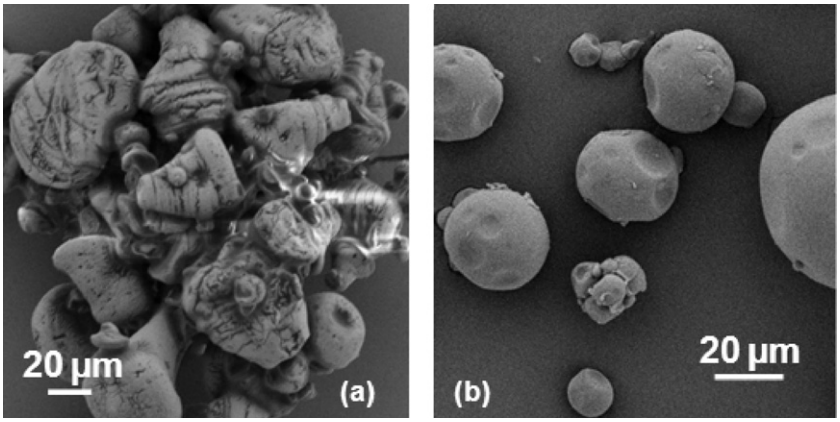

Fig. 2. Alginate aerogel particles obtained by emulsion methods using (a) fast (diffusion method; cation source: $CaCl_2$), and (b) slow (internal setting method; cation source: $CaCO_3$ released by pH control) cross-linking kinetics. In the first process, irregular particles are obtained because the alginate droplet dispersion is distorted after the $CaCl_2$ solution addition and the gelation takes place instantaneously. On the contrary, the control of the Ca^{2+} release rate by using the second method leads to microspherical aerogel particles (Alnaief, Alzaitoun, et al., 2011).

accelerating the drying process, but the resulting gels exhibited extensive shrinkage (Brown et al., 2010).

2.3. Gel drying

One major challenge for the preparation of aerogels is to eliminate the liquid solvent from the gel, whilst 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 leading to xerogels (Kistler, 1931; Valentin et al., 2005). These types of drying methods form liquid–vapor menisci in the pores of the gel which recedes during emptying of the pores of the wet gels. Upon solvent removal, the surface tension of the liquid contained in the gel nanopores will create a capillary pressure gradient in the pore walls achieving pressures of up to 100–200 MPa, able to collapse the pores (Scherer & Smith, 1995). Other drying techniques (e.g., freeze drying) lead to cryogels showing significant damages with respect to the original pore structure of the gels and the formation of cracks cannot be avoided (Jin et al., 2004).

Supercritical drying process is an alternative drying technique that overcomes the problems encountered with traditional drying methods and preserves the high open porosity and superior textural properties of the wet gel in a dry form. $scCO_2$ is the most appropriate fluid for supercritical drying of polysaccharide-based aerogels due to its mild critical point conditions (304 K, 7.4 MPa) along with its GRAS (Generally Recognized As Safe) status (MacHugh & Krukonis, 1994; Pasquali & Bettini, 2008; Sun, 2002). Since the metastable nature of polysaccharide gels is temperature-dependent, the low temperature used for the gel processing with $scCO_2$ (typically 310–330 K) minimizes the changes in the molecular level: conformation and interactions of the molecular chains of the network (e.g., H-bonding) of the wet gel upon drying (Blanchard & Muhr, 1982; Quignard, Di Renzo, & Guibal, 2010). Supercritical drying involves a two-way mass transfer of $scCO_2$ and gel solvent to and from the pores of the wet gel (Mukhopadhyay & Rao, 2008; Wawrzyniak, Rogacki, Pruba, & Bartczak, 1998). Firstly, the drying is predominantly influenced by a high dissolution of $scCO_2$ in the liquid gel solvent leading to an expanded liquid and to the spillage of the excess liquid volume out of the gel network. Secondly, the CO_2 content in the pore gel liquid increases with time until supercritical conditions are attained for the fluid mixture in the pores, without any previous intermediate vapor–liquid transition. Finally, the presence of supercritical fluid mixtures in the pores with no liquid phases leads to the absence of surface tension, thus avoiding the pore collapse phenomenon in the gel structure (i.e., changes in the macroscopic level) during solvent elimination.

Supercritical drying can be classified in two types depending on the contact regime between the gel and the supercritical fluid: drying of the gel with a continuous flow of $scCO_2$ throughout the process (*dynamic supercritical drying*) or with $scCO_2$ in batches (*static supercritical drying*). A typical procedure for supercritical drying with $scCO_2$ is the dynamic operation mode sketched in the flow diagram of Fig. 3. Briefly, the wet gel is loaded into an autoclave/extractor (E1 in Fig. 3) and put in contact with a continuous flow of CO_2 at a pressure and temperature above its critical point, i.e., at supercritical conditions. The CO_2 outlet flow from the extractor, already enriched in ethanol/acetone, is partially expanded through a restrictor (V3). Because of the fluid expansion, the pressure of the fluid is decreased and $scCO_2$ turns gaseous CO_2. The lower solvation power of gaseous CO_2 induces the split in two phases in the separator (S1): a gaseous CO_2-rich stream and a liquid ethanol/acetone-rich phase. After a certain processing time under $scCO_2$ flow, the system is depressurized and the aerogel is collected from E1.

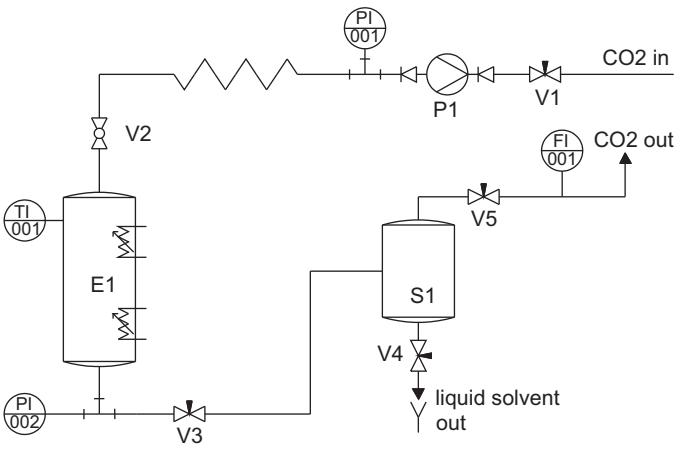

Fig. 3. Schematic diagram of aerogels supercritical drying equipment. Labels: P1: CO_2 compressor; V1–V5: valves; E1: extractor; S1: separator; PI-00*x*: pressure indicator; TI-00*x*: temperature indicator; FI-00*x*: flow indicator.

In the static supercritical drying method, $scCO_2$ is put in contact with the gel to be dried for a certain prolonged period of time in the batch mode (typically 6–12 h) (Placin, Desvergne, & Cansell, 2000; Tan, Fung, Newman, & Vu, 2001). Then, a $scCO_2$ flow is applied through the extractor to replace the CO_2 in the vessel, already enriched in ethanol, with fresh CO_2. This process can be optionally run for several cycles and, then, the pressure is released to atmospheric pressure and the temperature is decreased until room temperature.

Alternatively, some authors (Kistler, 1931, 1932) achieved the supercritical drying of the gels by going beyond the critical point of the solvent of the gel (*direct supercritical drying*), e.g., 517 K, 6.38 MPa for ethanol, 647 K, 22.1 MPa for water and 508 K, 4.7 MPa for acetone. However, the temperature conditions needed for these alternative supercritical fluids result in thermochemical degradation for many polysaccharides. In terms of process economics, costs are increased with flammable supercritical fluids (ethanol, acetone), since they should pass explosion proofs of the equipment setup, and with other fluids (water) needing special anticorrosive alloys.

3. Aerogel production strategies

3.1. Monolith aerogel processing

The size and morphology of aerogels can be customized by means of shaping of the gel by molding, extrusion or any other suitable physical technique. In the case of molding, the polysaccharide solution is poured into a mold of a defined form and then gelation occurs. In general, gels take the shape of the mold where gelation takes place and this shape is preserved in the monolithic aerogel after supercritical drying (Fig. 4). Polysaccharide-based aerogels are commonly obtained in the form of cylindrical monoliths (Fig. 5a), although many other shapes can be found in literature (spheres, tubes, membranes, etc.) (Quignard et al., 2010).

3.2. Particle aerogel processing

A large contact surface of the drug with the body fluids favors a fast dissolution rate and its absorption in the body. This contact surface may be increased by particle micronization and/or by increasing the surface area available for adsorption of the drug using a porous substrate. Therefore, drug carriers are preferred in a microparticulate aerogel form for certain pharmaceutical applications so that both approaches can be accomplished together to

Fig. 4. Aerogel monoliths take the shape of the mold where the gel is prepared: starch aerogel obtained by supercritical drying from a hydrogel prepared in a mold for Christmas cookies.

get a fast drug release (Smirnova, Suttiruengwong, Seiler, et al., 2004; Smirnova et al., 2005). The speed of drug dissolution for drug-loaded aerogel microparticles could be of three orders of magnitude faster than drug-loaded solid particles (Lee & Gould, 2006). Silica and carbon aerogels in the form of microparticles are traditionally obtained from monoliths by milling (Lee & Gould, 2006). However, a lack of particle sphericity and the absence of particle size uniformity, required for many drug delivery applications, are expected to be obtained when using conventional milling techniques.

Another manufacturing option is to process the aerogels in the form of beads (millimeter–centimeter range). The usual processing approach is to drop a solution containing the polysaccharide aerogel precursor by means of a syringe/nozzle into a solution containing the gelling promoter agent. Gelation takes place just after the droplets of the solution come into contact with the gelling promoter (e.g., pH- and/or temperature-controlled solution, presence of cations). The subsequent supercritical drying of the gel leads to the aerogel formation (Figs. 5b and 6) (Quignard et al., 2008, 2010). 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. Finally, a modification of the process using pulsed electric fields for the atomization of the aqueous precursor solution through the nozzle was reported for the preparation of microsized alginate gel particles (Zhao, Carvajal, Won, & Harris, 2007).

Aerogel microspheres (Fig. 5c) can be obtained by coupling the so-called *inverse emulsion polymerization technique* (Mayer, San Leandro, Kong, Pekala, & Kaschmitter, 1996), to the conventional aerogel technology. Using this emulsion technique, gel spherical particles (diameter of 1–3000 μm) are obtained through vigorous stirring of an aqueous phase-in-oil (or organic-in-oil) emulsion until the gelation of the dispersed phase (Alnaief, Alzaitoun, et al., 2011). Properties of the microspheres (particle size, density, surface area) can be tailored by controlling of the processing conditions and chemical formulation. The size distribution of the gel particles are mainly influenced by agitation, surfactant concentration, matrix precursor concentration and aqueous solution-to-oil volume ratios (Alnaief & Smirnova, 2011). The textural properties (surface area, pore size) of the resulting aerogel microspheres are not significantly influenced by the processing conditions (stirring rate, aqueous solution-to-oil ratio, surfactant concentration), but mainly by the composition of the sol itself (precursor concentration, crosslinker) (Alnaief, Alzaitoun, et al., 2011) (Fig. 7). Moreover, the surface area and the pore size distribution of the aerogel microparticles show similar values to those obtained with the corresponding monolithic aerogels. After gelation, the microspheres are separated from the mixture (e.g., by filtration or centrifugation) and, prior to the supercritical drying, the water contained in the microspheres is removed by solvent exchange. This method has been reported for the production of inorganic (carbon and silica) and polysaccharide-based aerogels (Fig. 5c) (Alnaief, Alzaitoun, et al., 2011; Alnaief & Smirnova, 2011; Liu, Zhang, Fu, Dresselhaus, & Dresselhaus, 2006; Mayer et al., 1996; Wang et al., 2011).

4. Case studies on polysaccharide aerogels

4.1. Starch

Amylose and amylopectine are the two main components of starch. The relative proportion of these components varies as a function of the starch source (e.g., potato, corn, wheat, tapioca) and influences the crystallinity and molecular order of the polysaccharide (Ellis et al., 1998; Jenkins & Donald, 1995). 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 (Wootton & Bamunuarachchi, 1979). (ii) Then, *gelatinization* is observed after starch is dissolved by heating, leading to leaching of amylose molecules, irreversible physical changes and the destruction of the granule structure. (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 (Fig. 8) (Barker, 2010; White, Budarin, & Clark, 2008). Amylose molecules are detached from the starch

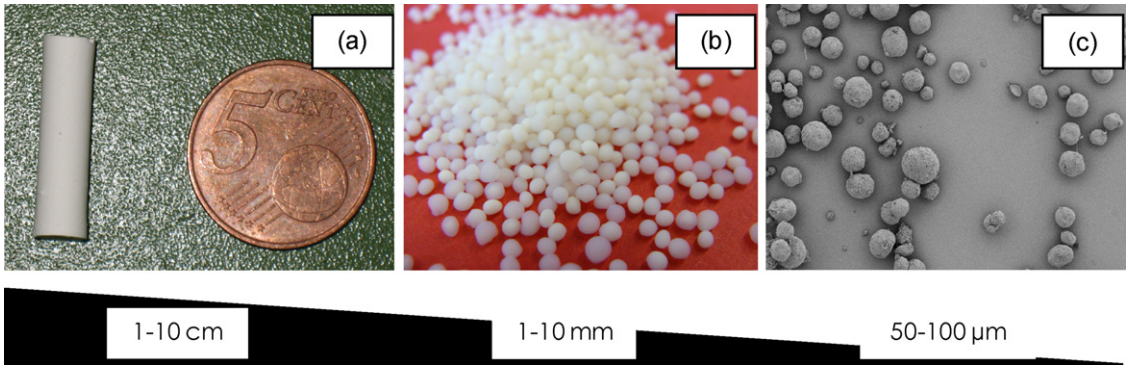

Fig. 5. Calcium-alginate aerogel obtained in different shapes: (a) monoliths (Mehling et al., 2009), (b) beads and (c) microparticles (Alnaief, Alzaitoun, et al., 2011).

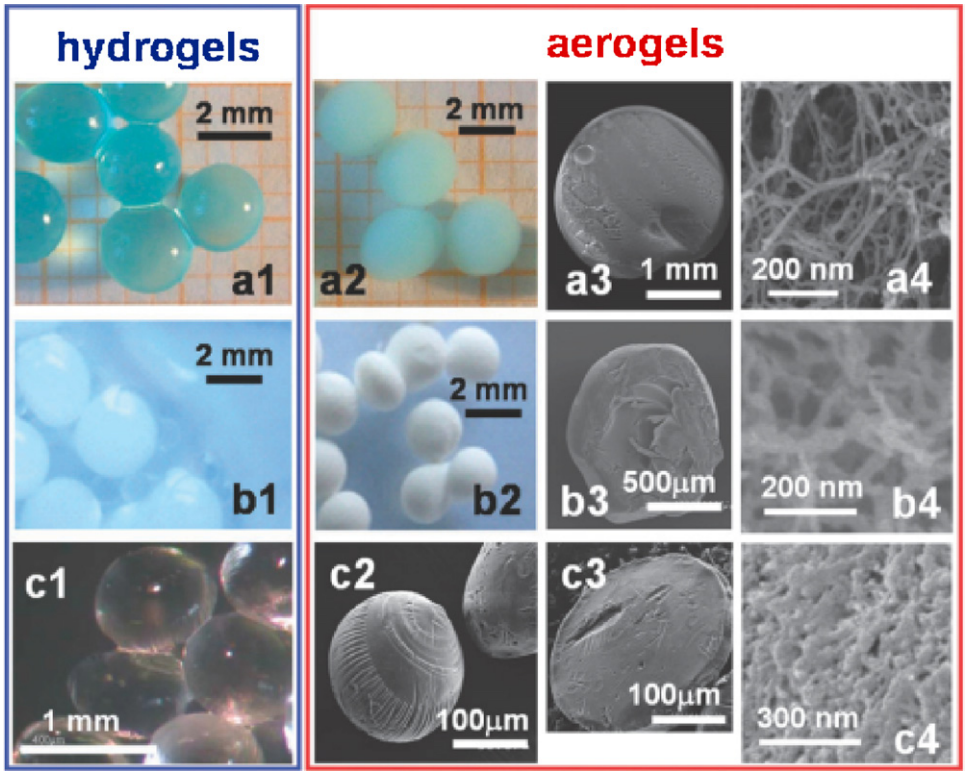

Fig. 6. Preparation of spherical polysaccharide-based aerogels (right) from hydrogel beads (first column on the left). The nature of the gel precursor (Cu-alginate: top, chitosan: middle and κ-carrageenan: bottom) ((a) Cu-alginate, (b) chitosan and (c) κ-carrageenan) influences the volume reduction (second column) as well as the textural properties (bead cross-sections of the third and fourth columns) of the resulting aerogel (Quignard et al., 2008).
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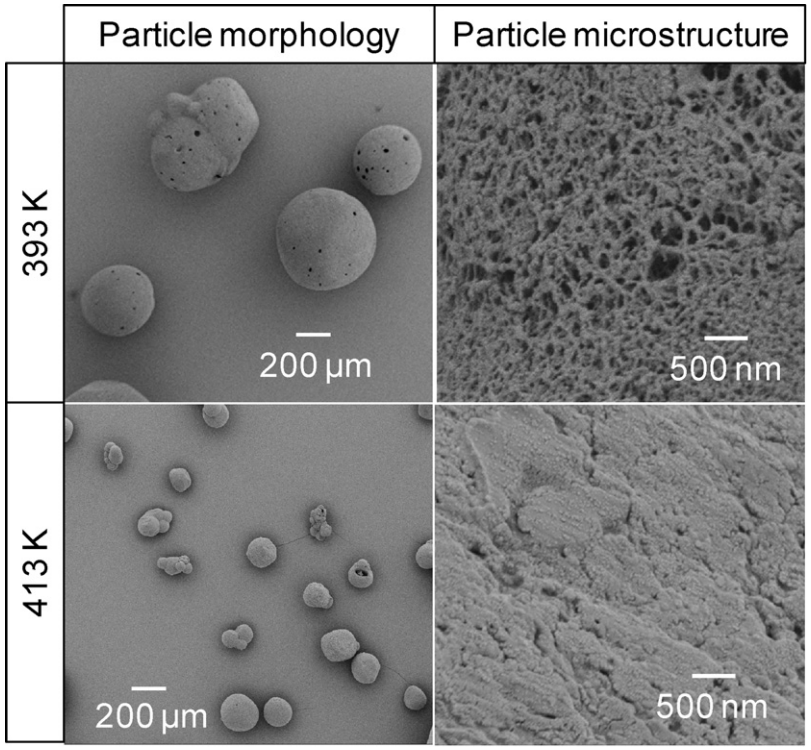

Fig. 7. Effect of gelatinization temperature (physical crosslinker) on the textural properties of the resulting starch aerogels. Starch gel microspheres were obtained by using inverse emulsion gelation process at 393 K (top) and (b) 413 K (bottom), coupled to supercritical drying. The increase in temperature during gelation led to the densification of the aerogel nanoporous structure (Mehling et al., 2009).

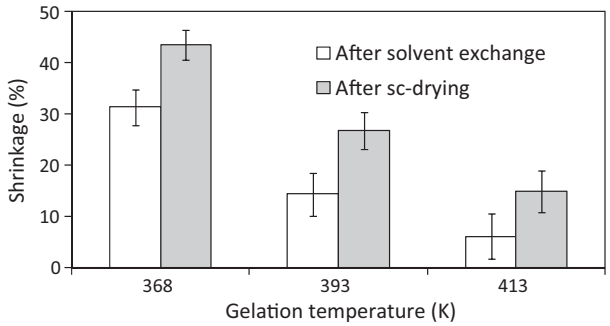

Fig. 8. Effect of gelation temperature on volume shrinkage of 15% (w/v) corn starch gels (expressed in percentage with respect to the original volume of the starch hydrogel) after solvent exchange to 100% ethanol (measured after 1 day of storage) and after supercritical drying (8 h, $scCO_2$ – 318 K, 11.0 MPa – flow at 4 NL/min). Higher cooking temperatures lead to an increase in the gel mechanical properties and a reduction in the shrinkage of the gel structure after both solvent exchange and supercritical drying steps.

granules during gelatinization and, upon retrogradation, they reassociate and deposit on the amylopectin scaffold. Amylose is the component providing a non-ordered (amorphous) character to the resulting starch gel contributing to the generation of mesoporosity in the material, whilst the ordered amylopectin exerts a certain control on the local structural ordering of the material. 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) (Fig. 7). During retrogradation, low cooling temperatures are prone to reach higher surface areas in the gel since the nucleation rate is favored (number of crystals) with respect to crystallization rate (crystal growth) (Hoover, Vasanthan, Senanayake, & Martin, 1994). Water-to-ethanol solvent exchange in starch gels is needed to avoid the collapse of the pore structure upon drying 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 amylose (Mehling et al., 2009). Upon supercritical drying, starch aerogels from different precursors (e.g., potato and corn (Eurylon 7)) can be obtained (Table 2) (Mehling et al., 2009).

4.2. Pectin

Pectin is a linear polysaccharide of α-linked anhydrogalacturonic acid with a certain degree of methyl esterification of carboxyl groups (degree of esterification) depending on the polysaccharide quality and source (Imeson, 2009). Pectin can undergo gelation by thermal, acidic or cationic treatment. The choice of the pectin source as well as the gelation mechanism significantly influences the resulting gel nanostructure (Sriamornsak, 2003). Indeed, the degree of esterification and the distribution of methoxyl-esters of each pectin type determine the main interactions between the polymer chains taking place (hydrogen bonding, hydrophobic and ionic interactions) and the extent of chain alignment (*junction zones*) (Imeson, 2009; Sila et al., 2009). Thermal treatment (heating) promotes the dissolution of pectin in water and, upon cooling below the so-called setting temperature, gelation takes place by hydrogen bonding between free carboxyl groups on the pectin molecules and also between the hydroxyl groups of neighboring molecules. Acidic gelation promotes the hydrolysis of the methyl esters inducing a pectin structure predominantly composed of galacturonic acid (White, Budarin, Luque, Clark, & MacQuarrie, 2009). Finally, low methyl-esterified pectins require the presence of divalent cations (usually Ca^{2+}) for proper gel formation through 'egg-box' gelation model mechanism by interaction of the cations with the galacturonic acid (El-Nawawi & Heikal, 1995; Grant, Morris, & Rees, 1973; Sila et al., 2009). The presence of sugar (10–20 wt.%) may also contribute to the decrease of shrinkage 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 (White, Budarin, & Clark, 2010) (Table 2), thus avoiding the massive shrinkage observed using other drying techniques (Fig. 9).

4.3. Alginate

The chemical structure of alginate consists on a copolymer of 1,4-linked-β-D-mannuronic acid (M) and α-L-guluronic acid (G) of varying composition and sequence (Domb & Kost, 1997; Dumitriu, 2005; Phillips & Williams, 2005; Rehm, 2009; Walter, 1998). The presence of carboxylate groups within G units confers a global negative charge at pH = 7 usually compensated by the use of Na^+ cations as counterions. Gelation of alginate takes place by inducing the cross-linking of the alginate polymers with divalent cations (Ca^{2+} usually) following the 'egg-box' gelation model mechanism (Grant et al., 1973; Phillips & Williams, 2005; Rehm, 2009). The properties of the alginate gel are mainly influenced by the divalent cation content and the G-to-M ratio and sequence (Draget, Østgaard, & Smidsrød, 1990; Dumitriu, 2005; Rehm, 2009). Addition of the cross-linking ion can be carried out by dropping the alginate solution into the cation source solution (*diffusion method*) (Escudero, Robitzer, Di Renzo, & Quignard, 2009; Quignard et al., 2008; Robitzer et al., 2008; Valentin, Horga, Bonelli, Garrone, Di Renzo, & Quignard, 2005, 2006) or by the controlled release of the cross-linking ion, already dispersed as an inert source, within the alginate solution (*internal setting method*) (Alnaief, Alzaitoun, et al., 2011; Mehling et al., 2009; Silva, Ribeiro, Ferreira, & Veiga, 2006; Silva, Ribeiro, Figueiredo, Gonçalves, & Veiga, 2006). Alternatively, alginic acid gels can be formed by decreasing the pH of a Na-alginate solution (Quignard et al., 2010) or from native alginic acid (White, Antonio, et al., 2010). The shrinkage of the alginate gels mainly takes place during the water-to-ethanol solvent exchange and can be controlled by establishing a proper protocol (e.g., exchange steps and frequency) (Fig. 10) (Mehling et al., 2009). The increase in ethanol concentration in the gel infers the concomitant release of water from the gel structure, leading to a reduction in the surface tension in the gel pores (Mehling et al., 2009). This decrease in the capillary pressure of the gel structure is responsible for the reduction in volume of the gel following a second-order kinetics of shrinkage for alginate gels (Rehm, 2009). Multi-step and low frequency solvent exchange decreases the diffusion rate of water out from the gel mitigating the shrinkage of the gel. An increase in alginate concentration leads to a slight reduction in volume shrinkage, likely due to the increase in the gel strength (Martinsen, Skjak-Braek, & Smidsrod, 1989). The subsequent supercritical drying of the alcogels leads to the formation of alginate aerogels (Fig. 6a) (Table 2) (Alnaief, Alzaitoun, et al., 2011; Mehling et al., 2009; Quignard et al., 2008, 2010; Robitzer et al., 2008; Robitzer, Renzo, & Quignard, 2011; Valentin et al., 2005, 2006). Different morphologies are reported in literature for alginate aerogels: monoliths, beads and microspheres.

4.4. Chitin and chitosan

Chitin is an abundant in nature linear aminopolysaccharide formed by N-acetylglucosamine units connected through β-(1,4) linkages (Kumar, 2000). Chitin is sparsely soluble in conventional solvents due to its high crystallinity based on strong hydrogen

Table 2
Textural properties of polysaccharide-based aerogels reported in literature.

Aerogel type	Morphology	Textural properties	Reference
Starch (potato)	Monolith (by thermal gelation)	$\rho \approx 0.46\ g/cm^3$; $S_a = 72\ m^2/g$; $V_p = 0.47\ cm^3/g$	Mehling et al. (2009)
Starch (corn: Eurylon7)	Monolith (by thermal gelation)	$\rho \approx 0.34\ g/cm^3$; $S_a = 90\ m^2/g$; $V_p = 0.37\ cm^3/g$	Mehling et al. (2009)
Starch (from native corn granules)	Microspheres (by thermal gelation method coupled to emulsion techniques), $D_p = 300–1200\ \mu m$	$S_a = 34–111\ m^2/g$; $V_p = 0.12–0.37\ cm^3/g$; $P_r = 2–9\ nm$	This work
Pectin (from citrus peel)	Powder (by thermal gelation)	$\rho \approx 0.20\ g/cm^3$; $S_a = 485\ m^2/g$; $V_p = 3.62\ cm^3/g$	White, Budarin, et al. (2010)
Pectin (from citrus peel)	Monolith (by acidic gelation)	$\rho \approx 0.07\ g/cm^3$; $S_a = 200\ m^2/g$; $V_p = 0.38\ cm^3/g$	White, Antonio, et al. (2010)
Alginate (from Ca-alginate)	Monolith (by internal setting method)	$\varepsilon = 94\%$, $\rho \approx 0.13\ g/cm^3$; $S_a = 150–300\ m^2/g$; $V_p = 1.9\ cm^3/g$; $P_r = 12\ nm$	Mehling et al. (2009)
Alginate (from Ca-alginate)	Beads (by diffusion method)	$\varepsilon = 99\%$; $S_a = 300–580\ m^2/g$; $V_p = 1.1–1.2\ cm^3/g$; $P_r = 13–19\ nm$	Alnaief, Alzaitoun, et al. (2011), Mehling et al. (2009), Quignard et al. (2008, 2010), Robitzer et al. (2008), Robitzer, Renzo, & Quignard (2011) and Valentin et al. (2005, 2006)
Alginate (from Ca-alginate)	Microspheres (by internal setting method coupled to emulsion techniques), $D_p = 75–547\ \mu m$	$S_a = 318–680\ m^2/g$; $V_p = 2.15–4.05\ cm^3/g$; $P_r = 9–15\ nm$	Alnaief, Alzaitoun, et al. (2011)
κ-Carrageenan	Beads (thermal treatment with cationic salts addition)	$\varepsilon = 52\%$; $\rho \approx 1.48\ g/cm^3$; $S_a = 200–230\ m^2/g$; $V_p = 0.8–1.2\ cm^3/g$; $P_r = 9–11\ nm$	Quignard et al. (2008)
Agar gel	Beads (by thermal gelation)	$\varepsilon = 89\%$; $S_a = 320\ m^2/g$; $V_p = 0.3\ cm^3/g$; $P_r = 18\ nm$	Robitzer, Renzo, & Quignard (2011)
Cellulose (from eucalyptus pulp, Solucell)	Monoliths (by solvent dissolution)	$\rho \approx 0.02–0.5\ g/cm^3$; $S_a = 50–420\ m^2/g$	Innerlohinger et al. (2006)
Cellulose (from native cellulose)	Monoliths (by solvent dissolution)	$\varepsilon = 95\%$; $\rho \approx 0.06–0.3\ g/cm^3$; $S_a = 200–300\ m^2/g$	Gavillon and Budtova (2008)
Cellulose (from bacterial cellulose)	Monoliths (by bacteria, treated thermally and with 0.1 aqueous NaOH)	$\rho \approx 0.008\ g/cm^3$; $S_a = 200\ m^2/g$; $V_p = 0.5\ cm^3/g$; $P_r = 5\ nm$	Liebner et al. (2010)
Chitosan	Beads (by dropping acidic chitosan solution in alkaline solution)	$S_a = 330\ m^2/g$; $V_p = 0.4\ cm^3/g$; $P_r = 6\ nm$	Kadib et al. (2011) and Quignard et al. (2008)
Chitosan	Monoliths (by crosslinking with aldehydes in acidic aqueous solution)	$\rho \approx 0.38–0.92\ g/cm^3$; $S_a = 66–845\ m^2/g$; $V_p = 0.1–3.5\ cm^3/g$; $P_r = 2–5\ nm$	Chang et al. (2008)
Chitin	Monoliths (by solvent dissolution)	$\varepsilon = 84–92\%$; $\rho \approx 0.12–0.22\ g/cm^3$; $S_a = 220–363\ m^2/g$; $P_r = 1–3\ nm$	Tsioptsias et al. (2009)
Chitin	Monoliths (by solvent dissolution of reacetylated chitosan)	$S_a = 560\ m^2/g$; $V_p = 1.2\ cm^3/g$; $P_r = 10\ nm$	Robitzer, Tourrette, et al. (2011)

bonds between chains (Gardner & Blackwell, 1975), but can be solubilized by using some special organic solvents (e.g., concentrated formic acid, calcium chloride dehydrate-saturated methanol, lithium chloride + N,N-dimethylacetamide mixture) (Furda, 1984; Tsioptsias, Michailof, Stauropoulos, & Panayiotou, 2009; Zakaria, Muda, & Abdullah, 1995). Thus, chitin gels can be formed either by simple aging or by diluting the resulting chitin solutions in large excess of water (hydrogel) or alcohol (alcogel) (Tamura, Nagahama, & Tokura, 2006). Optionally, chitin hydrogels can be also obtained from reacetylated chitosan in an aqueous alcoholic solution (Robitzer, Tourrette, et al., 2011). After solvent exchange to an alcohol, chitin alcogels can then be supercritically dried to obtain chitin aerogels of high porosity, high surface area and low density with changes in value depending on the chitin concentration and the alcohol solvent used in the original wet gel (Table 2) (Tsioptsias et al., 2009).

Fig. 9. Effect of gel drying method: gel monolyths of pectin of the same dimensions prepared by thermal gelation (White, Budarin, et al., 2010) dried under supercritical drying (aerogel) and under air drying (xerogel).

Chitosan is obtained by deacetylation of chitin in a degree beyond 50% and it is easily soluble in dilute acids (pH < 6). Gelling properties of chitosan are mainly influenced by the degree of deacetylation and the source of the chitin precursor (Quignard et al., 2010). Physical hydrogels of chitosan can be obtained by precipitation of an acidic chitosan solution in an alkaline solution (Fig. 6b) (Quignard et al., 2008). After aging for a certain time, the chitosan gels are washed several times with distilled water until neutral pH is reached (Kadib, Molvinger, Cacciaguerra, Bousmina, & Brunel, 2011). After a sequential water-to-ethanol solvent exchange, alcogels are dried upon supercritical drying leading to volume shrinkages of 60% during the overall process (Fig. 6b) (Quignard et al., 2008). Preparation of chemical hydrogels of chitosan in acidic solutions using mono- and dialdehydes as crosslinkers were also reported (Chang, Chen, & Jiao, 2008). After aging and solvent exchange to ethanol at room temperature,

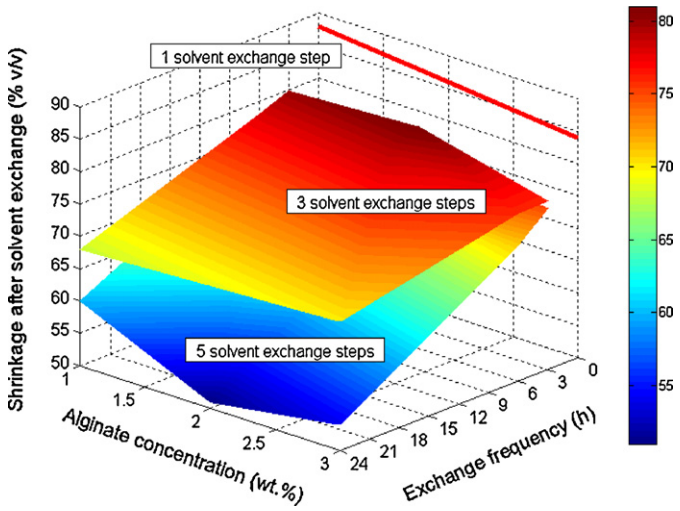

Fig. 10. Influence of gel formulation (gel precursor concentration) and processing parameters (number of exchange steps – 1, 3, 5 – and frequency – 3 h, 24 h) on the volume shrinkage from hydrogel to alcogel (ethanol) of alginate gel monoliths after one day of storage following a complete water-to-ethanol solvent exchange (1 step = 0:100; 3 steps = 50:50; 0:100 (2×); 5 steps = 70:30, 50:50, 30:70, 0:100 (2×) water:ethanol (v/v)). Alginate hydrogels were prepared by the internal setting method reported in literature (Alnaief, Alzaitoun, et al., 2011).

the chitosan aerogels prepared by supercritical drying showed a mesoporous structure with increasing surface area as the chitosan concentration increases and the cross-linker content decreases from 1:7 to 1:70 (cross-linker to water content in the gel (v/v)). In general, chitosan aerogels obtained from chemical gels present better textural properties than those obtained from physical gels (Table 2).

4.5. Carrageenan

Carrageenan is being widely investigated in pharmaceutical technology (Garcia & Ghaly, 2001; Hoffman, 2002; Park, Lee, Jung, & Park, 2001; Picker, 1999; Yamada et al., 2005; Yoo, 2009) since its inclusion in the US Pharmacopoeia (USP 31 NF26, 2008). The chemical structure is formed by units of D-galactose and anhydro galactose joined by glycosidic linkages and containing ester sulfate groups (Bubis, 2000). The number and position of the ester sulfate groups as well as the anhydro galactose content influences the type of carrageenan (kappa – κ, iota – ι and lambda – λ carrageenans), the solubility temperature and the gelation behavior. Hot aqueous solution of κ- and ι-carrageenans forms thermoreversible gels upon cooling. Cationic salts (monovalent cations – K, Rb, and Cs – for κ-carrageenan and divalent cations – Ca – for ι-carrageenan) are needed to obtain the hydrogel and their content strongly influences the mechanical properties of the gel. λ-Carrageenan is a non-gelling polysaccharide (Bubis, 2000; Shchipunov, 2003). Shrinkage of carrageenan gels with storage and/or solvent exchange also depends on the polysaccharide type (κ-carrageenan presents syneresis, whereas ι-type not) (Quignard et al., 2008; Thrimawithana, Young, Dunstan, & Alany, 2010). The extensive shrinkage of the gel structure also takes place during the supercritical drying of carrageenan alcogels leading to an important volume reduction (*ca.* 95% for κ-carrageenan) (Fig. 6c) (Rauter, Vogel, & Queneau, 2010a). This massive reduction in volume of the resulting aerogel largely influences the textural properties of the dried material (Fig. 6c) (Table 2).

4.6. Agar

Agar consists on a combination of agaropectin and agarose, the component responsible of gelation (Phillips & Williams, 2005). At temperature above 358 K, 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 leading to the formation of a 3D-network capable of immobilizing water molecules. Brown et al. have reported the production of agar aerogels as monoliths. The agar solution (agar powder – 1–2% (w/v) with sucrose – 1–10% (w/v)) was heated to insure complete dissolution and then poured into molds and left to cool down. After that, the authors have performed the drying using $scCO_2$ or ethanol-modified $scCO_2$. Both drying techniques led to extensive shrinkages and voidages of 48% and 68% for pure and modified CO_2 drying, respectively (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 using microwave oven. The solution was then cooled by adding it dropwise to cold water using a syringe. To obtain aerogels (Table 2), the beads were subjected to successive ethanol-water solvent exchange steps (10, 30, 50, 70 and 100%) (Robitzer, Renzo, & Quignard, 2011).

4.7. Cellulose

Cellulose consists of two repeating anhydroglucose units (β-glucopyranose) connected through 1,4-glucosidic bonds. The properties of the cellulose polymers depend mainly on the length of the polymer chain and their degree of polymerization (Phillips & Williams, 2005). Generally, cellulose aerogels preparation followed the classical aerogel preparation route. However, it is possible to differentiate two main preparation methods of the gel: (1) formation of the gel by dissolving the cellulose in a solvent (e.g., NMMO, calcium thiocyanate, NaOH–water solution or ionic liquids) followed by removal of the solvent using water or alcohol (Duchemin, Staiger, Tucker, & Newman, 2010; Gavillon & Budtova, 2008; Hoepfner, Ratke, & Milow, 2008; Innerlohinger et al., 2006; Jin et al., 2004; Liebner, Potthast, Rosenau, Haimer, & Wendland, 2008; Sescousse, Gavillon, & Budtova, 2011); (2) using cellulose nanofibers prepared by either bacterial cellulose (Liebner et al., 2010; Maeda, Nakajtma, Hagiwara, Sawaguchi, & Yano, 2005) or microfibrillated cellulose prepared via native cellulose mechanical disintegration and enzymatic treatment (Paakko et al., 2008). Thereafter, multistep solvent exchange takes place to replace the water with ethanol or acetone. Finally, the cellulose aerogel is obtained as soon as the network solvent is removed using supercritical drying. Following the processing method (1), low density cellulose aerogels are reported (Table 2), although with significant shrinkages (36–55%) during the preparation steps (Innerlohinger et al., 2006). Gavillon et al. have used the preparation method (1) to produce aerogels with high porosity (Table 2) by using a surfactant to trap air into the sol before gelation to influence the pore structure of the produced aerogel. Finally, ultra light aerogels were reported following the preparation method (2) using fine cellulose fibers prepared by bacteria as aerogel precursor (Table 2) (Liebner et al., 2010).

5. Aerogel as carriers: drug release assessment

Since the 60s decade when silica aerogels were introduced as additives for cosmetics and toiletries, research on the use of aerogels for life sciences applications is being increasingly studied. Namely, there is an increasing interest for the use of biocompatible aerogels and composite aerogel materials as host matrices for pharmaceuticals and other bioactive compounds, e.g., enzymes, proteins. Two different approaches can be found in literature for the loading of the aerogel matrix with the active compound (Fig. 11):

(i) *Loading during the sol–gel process* (before gelation, Lee & Gould, 2006 or during solvent exchange, Mehling et al., 2009). The active compound can be loaded either in the sol before the formation of the gel (co-gelation), or during solvent exchange by adsorption in the wet gel structure of the active compound previously dissolved in the new fresh solvent. This strategy is regarded as the simplest and most versatile method of loading of active compounds. However, the drug should comply with a certain set of requirements to be loaded using this approach, among them:
- Solubility and/or dispersibility in the sol phase (in the case of co-gelation);
- Stability under the co-gelation conditions (pH, temperature, etc.);
- Stability and low affinity (solubility) to the solvent used in the solvent exchange step;
- Low solubility in $scCO_2$ to avoid active compound removal upon supercritical drying.

(ii) *Loading in the dried aerogel matrix.* This approach implies an additional post-processing step to load the target compound within the aerogel host matrix. The choice of the proper medium for the drug loading step is a key processing parameter to be taken into account. On one hand, the drug loading of the aerogel from a liquid phase (Buisson, Hernandez, Pierre, & Pierre, 2001; Schwertfeger, Zimmermann, & Krempel, 2001) is hindered by diffusional limitations of the drug passing through the pores and can also lead to the collapse of the aerogel structure itself due to capillary forces. On the other hand, the drug loading from a gaseous phase improves the drug diffusion through the pore structure but it is often limited by the low solubility of the drug in the gas phase. Supercritical fluid-assisted drug loading of aerogels overcomes the limitation of the liquid- and gas-phase methods. The drug loading of an aerogel from a supercritical phase encompasses both the good mass transfer (diffusibility) properties of the gaseous phases and the good solvation power (drug solubility) of the liquid phases. Langmuir-like adsorption isotherms in the form of amorphous drugs are usually obtained using supercritical fluids media for drug loading in aerogels (Smirnova et al., 2003; Smirnova, Suttiruengwong, & Arlt, 2004; Smirnova, Suttiruengwong, Seiler, et al., 2004; Smirnova et al., 2005).

The research of aerogels for drug delivery systems has been first focused on silica aerogels. The textural properties of aerogels (density, pore size, surface area) not only influence the drug adsorption behavior in the aerogel matrix, but also the maximum drug loading capacity of the aerogel. As a rule-of-thumb, the loading capacity of a given drug increases with a higher surface area and pore volume of the aerogel. The high surface area and network structure of aerogels also influence the drug release profile of the loaded drug resulting in faster dissolution rates than that of drugs in the crystalline form (five times higher reported in literature for ketoprofen, Smirnova, Suttiruengwong, & Arlt, 2004; Smirnova, Suttiruengwong, Seiler, et al., 2004; Smirnova et al., 2005) and in more effective *in vitro* absorption (Aulton, 2002; Gad, 2008; Schwertfeger et al., 2001). The reason for this enhanced dissolution profile for the drug loaded in aerogels relies on the fact that the drug adsorption in the amorphous form as a thin layer on the aerogel surface, as well as the quick collapse of the aerogel structure when put in contact with water. The tuning of the drug release profile was assessed by surface derivatization of aerogels with hydrophobic groups (Schwertfeger et al., 2001). Burst release (hydrophilic aerogels) or sustained release (hydrophobic aerogels) profiles can be thus "tailor-made" for the drug loaded within the aerogel matrix depending on the surface functionalization method used. On the other hand, silica aerogel powder has proven to be an effective free flow agent for pellet production (Bayerisches Zentrum für Angewandte Energieforschung eV, 1998). The combination of the drug loading capacity (e.g., up to 70% in weight of loaded ibuprofen for silica aerogel) coupled with its free-flowing capacity opens up the possibility of the use of aerogels for innovative drug delivery formulations (Leventis et al., 2010).

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 under investigation (Berg, Michael, Jere, & Jo, 1995). The specific loading of the drug within the polysaccharide based matrices ($1–4 \times 10^{-3}$ g/m^2 for ibuprofen, Mehling et al., 2009) are in the range of the values obtained for silica aerogels. However, the release profile of the drug-loaded organic aerogels was observed to be influenced by the degree of crystallinity 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,

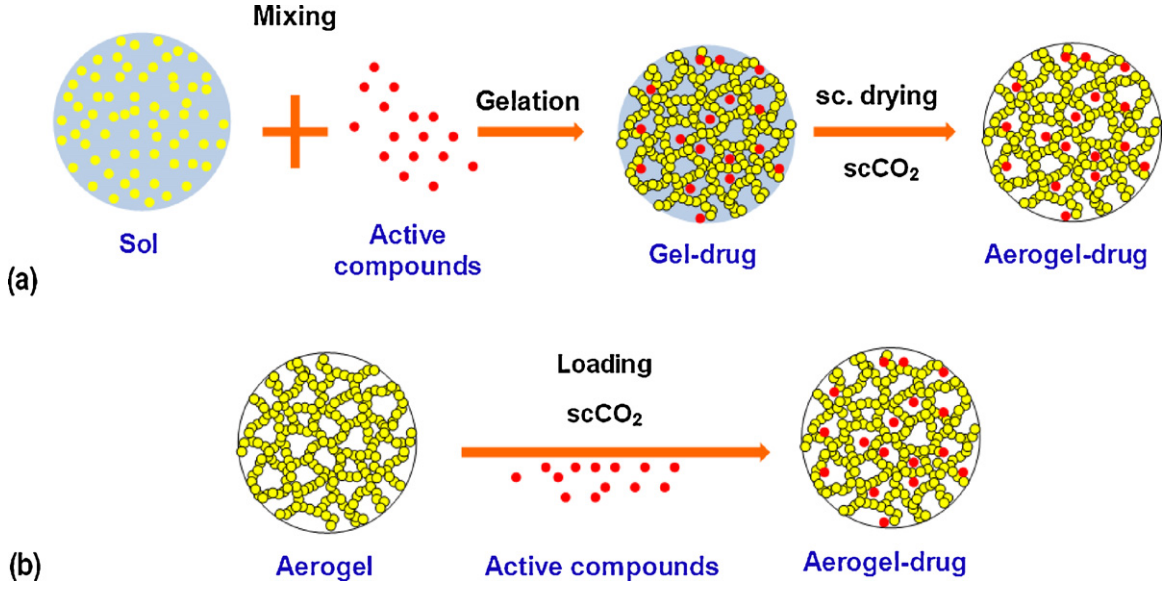

Fig. 11. Drug loading of aerogels: (a) during the sol–gel process (co-gelation); (b) in the aerogel matrix by supercritical impregnation post-treatment method.

the release profiles of hydrophilic drugs (paracetamol) from starch aerogels (starch from potato and corn origin) loaded during solvent exchange were similar to that of crystalline paracetamol (Mehling et al., 2009). On the contrary, drug (ibuprofen) on the amorphous form was obtained by means of supercritical fluid-assisted drug loading on organic aerogels. For some amorphous drug-loaded organic aerogels, faster dissolution rates than for the crystalline drug were obtained (corn starch and alginate). Finally, other important parameters to be taken into account in the release behavior of drugs adsorbed on aerogels are the nature of the matrix and the textural properties of the aerogel. The tuning of these variables dramatically changes the mechanical properties and porous structure of the aerogel matrix and, thus, 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 use of these dissimilar components in a single aerogel matrix will result in novel and outstanding physicochemical properties of the aerogel (El Kadib, Molvinger, Guimon, Quignard, & Brunel, 2008; Molvinger, Quignard, Brunel, Boissière, & Devoisselle, 2004). These materials can encompass the intrinsic properties of aerogels (high porosity and surface area) with the mechanical properties of inorganic components and the functionalities and biodegradability of biopolymers. Moreover, the accessibility of functional groups of some polysaccharides, e.g., amino groups in chitosan, to promote the adsorption of chemical species can be enhanced using these hybrid aerogels. Improved accessibility to amino groups was obtained for silica–chitosan (80:20, w/w) hybrid aerogel system (S_a = 73–149 m^2/g) 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 showed 17 wt.% gentamicin loaded within the hybrid aerogel (Miao, Jing-xiao, Fei, Ji-hong, & Shuang, 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 (S_a = 450–480 m^2/g; V_p = 1.3–1.9 cm^3/g; P_r = 35–56 nm), mechanical stability against acidic (0.1 N acetic acid) and basic solutions (0.1 N NaOH), not attained by aerogels from each individual component of the hybrid material.

6. Future prospects and outlook

The main cost of silica aerogel production comes from the purchase of the silica precursor (Carlson, Lewis, McKinley, Richardson, & Tillotson, 1995). Production of polysaccharides aerogels can meet the criteria of the development of high-performance materials from low-cost plus virtually unlimited precursors. The target technology is the production of materials with tailored properties from these biocompatible and biodegradable precursors in a sustainable way, following the waste valorization and responsible care guidelines (European Technology Platform for Sustainable Chemistry (SusChem), 2005, 2010; Sun, 2010). In this sense, the use of non-food polysaccharides is an especially attracting strategy as it would infer no virtual impact on food supply and prices. Also in accordance to these criteria, the minimization of the consumption of the intermediate solvent to be used to replace water (hydrogel) with carbon dioxide (aerogel), 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 plus environmental efficient aerogel production process.

Inhalation route is known to provide a means of rapid access of the drug to the lungs and to the general blood circulation, with the subsequent quick therapeutic effect in the human body. The marketplace has currently focused its interest on this administration route (European Medicines Agency (EMEA), 2006a, 2006b, 2007). However, the search for innovative inhalation formulation strategies must be intensified in order to improve the efficiency in the delivery of drugs to the lungs (Chow, Tong, Chattopadhyay, & Shekunov, 2007; Mastrandrea, 2010; Pandey & Khuller, 2005). Polysaccharide-based aerogel powder can be regarded as a promising drug matrix for the inhalation route. The low density (0.05–0.3 g/cm^3) and high porosity (>90%) of the aerogel dried particles may result in a superior air flowability to efficiently reach the lungs, reverting in fewer drug doses as well as lower dosing frequency.

Fabrication of biodegradable materials for regenerative biomedicine with precise control over surface microarchitecture, topography and size remains an important challenge for polysaccharide-based gels for being used in tissue engineering (Annabi et al., 2010; Lu & Chen, 2004; Malafaya et al., 2007; Reverchon, Cardea, & Rapuano, 2008). A compromise solution should be attained for the porous network to create an accurate microenvironment to promote tissue development (Gkioni, Leeuwenburgh, Douglas, Mikos, & Jansen, 2010; Langer & Vacanti, 1993; Malafaya et al., 2007; Shi, 2004; Yang, Du, & Chua, 2001). The preparation of aerogels for tissue engineering from polysaccharides (chitosan) (Cardea et al., 2010) has recently been reported. Further research on controlling the pore size distribution of aerogels to target values still remains to be studied.

On the other hand, the matrix–drug chemical interaction plays an important role in the design of products for drug delivery systems with controlled release behavior. This variable will not only influence the drug adsorption yield in the aerogel but also the drug release profile. Natural polysaccharides already bear an intrinsic broad portfolio of different functional groups (e.g., carboxylic – pectin, sulfonic – carrageenan, and hydroxyl – agar groups) and ionic forms (anionic – alginate, cationic – chitosan, non-ionic – starch) and are a promising starting point for the development of aerogel matrices with controlled properties. Alternatively, derivatization treatments can confer further functionalities to polysaccharides that will either compatibilize or enhance the matrix surface-loaded drug interaction (Belyaev, 2000; Doi, Clark, Macquarrie, & Milkowski, 2002; Lenaerts et al., 2000).

Finally, the sensitivity of aerogel texture to the presence of liquid solvents hinders the conditions for manufacturing, applicability and storage of this type of materials. The engineering of the drug release profile by coating of aerogel-based particles for targeted drug delivery systems will confer added value to the product. The individual coating of aerogel particles with biodegradable polymers using spout-fluidized bed technology was reported as a technological solution to overcome the premature release of the drug from the matrix prior to the target site (Alnaief, Antonyuk, et al., 2011). However, the development of drug delivery technology systems consisting of the coating of aerogels with a precise control over layer thickness whilst avoiding aerogel structure collapse still remains a challenge.

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