INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

BIODEGRADABLE STARCH FOAMS AS A DRUG CARRIER

Vishal D.Gholap*, Anand D. Savkare, Pooja M. Kukkar, Malavi R. Bhavsar
MVP Samaj's College of Pharmacy, Nashik-422002, Maharashtra, India.

ARTICLE INFO

Article history
Received 06/03/2017
Available online
03/04/2017

Keywords
Biodegradable Porous Starch,
Aerogel,
Nanoporous Bio-Based Material,
Poorly Water Soluble Drug,
Starch,
Starch Foam.

ABSTRACT

The application of aerogels as drug delivery system was successfully demonstrated for the starch. Biodegradable materials are beneficial as drug carrier as they possess the property of biodegradability. The biodegradability and biocompatibility of these biopolymers make them promising carriers for drug delivery systems. Structural properties of the polysaccharide aerogels depend on the preparation method and chemical nature of the gel phase. In this work starch was used to produce aerogels. 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, lightweight drug carriers with high surface area, able to provide enhanced drug bioavailability and drug loading capacity. This review focuses on the of the production of starch based aerogels with emphasis on the influence of processing parameters on the resulting end material properties.

Corresponding author
Vishal D.Gholap
MVP Samaj's College of Pharmacy,
KTHM Campus, Gangapur Road,
Nashik – 422002.
vishalgholap2838@gmail.com

*Please cite this article in press as **Vishal D.Gholap** et al. Biodegradable Starch Foams as A Drug Carrier. Indo American Journal of Pharmaceutical Research.2017:7(03).*

INTRODUCTION

Presently, there is considerable interest in improving the oral delivery of poorly water-soluble drugs. Improving the solubility of the low soluble drug is key to increasing the bioavailability. In the Biopharmaceutics Classification System [BCS], low solubility and high permeability are the characteristics of BCS Class II poorly water soluble drugs. The low solubility markedly affects the oral bioavailability of such drugs, resulting in a non-ideal therapeutic effect. Therefore, for BCS class II drugs, improving the solubility is the key to increasing the bioavailability.[1].General methods for improving aqueous solubility of poorly water soluble drugs include the formation of inclusion complexes[2] , solid dispersions[3; 13], nanoparticles[4; 14] or by controlling their polymorphic form [5]. At present, several inorganic materials, such as mesoporous silica[6; 7; 8; 9; 10], clay particles[6] and lipid–inorganic hybrids [11] , have also been employed.

In this context, BPSF, as a biodegradable starch-based porous biomaterial, has great potential as a solid dispersion carrier for oral poorly water soluble drugs, which is to date unexplored. Starch is the most common carbohydrate polymer in

Foods BPSF presents excellent characteristics compared with inorganic carriers, and has a Nanoporous structure, low density, high specific surface area and pore volume; its distinctive advantages are as follows:

1. Nontoxicity, biocompatibility, biodegradability [15, 16];
2. New functional groups can be readily introduced to the main backbone of the starch foam because of the high number of hydroxyl groups on the surface of the starch;
3. Soluble amylum as the raw material of BPSF is partially soluble in water, which facilitates the release of drug dispersed in the BPSF channels. These are particularly desirable properties for the design of carriers for the oral delivery systems of poorly water soluble drugs.

One major challenge in the preparation of aerogels is to eliminate the liquid solvent from the gel without collapsing the already existing nanoporous structure and thereby avoiding the subsequent shrinkage and cracking of the dried gel.

Generally, it is possible to differentiate three drying techniques.

1. Traditional drying procedures, e.g. ambient air drying, which is not able to preserve the gel structure leading to xerogels [17, 18]. 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 Nano pores will infer a capillary pressure gradient in the pore walls reaching pressures of up to 100–200 Mpa, able to collapse the pores [19].
2. Freeze drying technique consists in lowering the temperature of the gel below the crystallization temperature of the solvent. The solvent is then removed as a vapor by reducing the pressure [i.e., sublimation]. The end product of this process is usually called a cryogel [20-25]. However, many obstacles are associated with freeze-drying [26]: the slow rate of sublimation needed, solvent exchange may be required and, especially, the increase of the solvent volume upon crystallization. This volume expansion of the solvent induces stresses in the gel directed from the crust toward the inside, resulting in shrinkages and breakage of the crust layers as small particles. This phenomenon explains the fact that most of the freeze drying products are powders and production of monoliths is extremely difficult.
3. The supercritical drying process is an alternative drying technique assisted by the use of supercritical fluids, usually scCO2 that overcomes the problems encountered with conventional drying methods to preserve the high open porosity and superior textural properties of the wet gel in a dry form. Supercritical drying process leads to the presence of supercritical fluid mixtures in the gel pores without remnants of any liquid phase. This drying procedure thus avoids the presence of any intermediate vapor–liquid transition and surface tensions in the gel pores, preventing the gel structure from the pore collapse phenomenon [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 scCO2 throughout the process [dynamic or continuous supercritical drying] [27, 28] and in batches [static or batch supercritical drying] [29, 30].

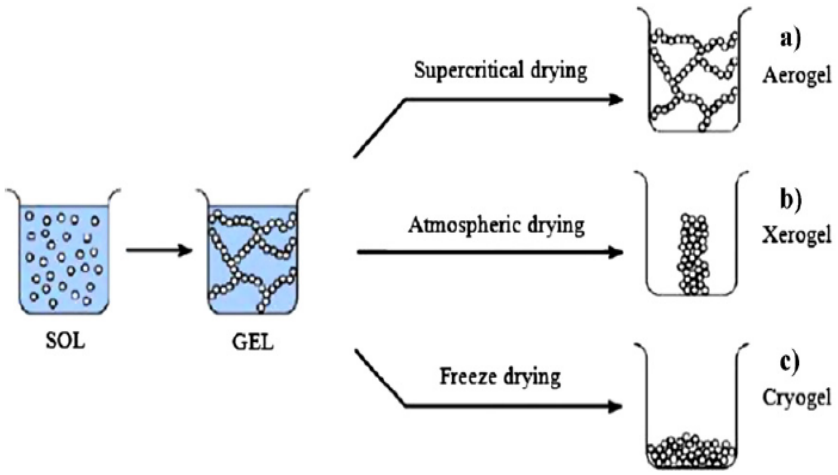

Fig.1.Effect of drying techniques on the alcogels[4].

Processing pathway-

Briefly, aerogel processing starts with the formation of a gel from an aqueous solution, i.e., a hydrogel .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 alcogels. Finally, the alcohol [usually ethanol] is extracted from the gel.[31]

Preparation of Aqua gels-

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 methyl morpholine -N-oxide – NMMO – solvent]. 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. The resulting gel can be denoted as a chemical or physical hydrogel depending on the nature of the chain cross-linking. 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]2·4H2O, CaCl2, CaCO3, CaSO4, NaCl, and KCl] can also be added to promote ionic bondings. 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. 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 for hydrogels. 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 behaviour 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.

Cylindrical samples-

Starch dispersions are made with uniform stirring and the temperature is maintained throughout the mixing. The temperature is elevated to desired range so as to initiate the gelatinization process while keeping the stirring constant until the peak viscosity is reached. The gelatinized starches are then poured into the cylindrical molds.Then they are covered with aluminium foil and refrigerated overnight. The gelatinized starches set into semi rigid aqua gels that syneresed sufficiently to facilitate removal of the aqua gels within 24 hours. The solvent water in the aqua gels is gradually displaced with ethanol by batch equilibration with a succession of ethanol baths. The number of baths and the ethanol concentration of each bath differs for samples of different thicknesses. The equilibration time for each bath is 24 hr. The sequence of bath is one time in 70 %[w/w] ethanol and three times in 100% ethanol.

Slab samples-

Starch dispersions are made with uniform stirring and the temperature is maintained throughout the mixing. The temperature is elevated to desired range so as to initiate the gelatinization process while keeping the stirring constant until the peak viscosity is reached. Viscosity measurements are taken during the process to check whether the gelatinization is complete. Starch solutions are mixed and heated until viscosity had peaked and begun to decrease The gelatinized starches are then poured into the slab molds.Then they are covered with aluminium foil and refrigerated[5°]overnight. The aqua gels then are removed from the molds and soaked for 48 hours in successive baths of ethanol.

Aerogel production strategies

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. Polysaccharide-based aerogels are commonly obtained in the form of cylindrical monoliths, although many other shapes can be found in literature [spheres, tubes, membranes, etc.]

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 micro particulate aerogel form for certain pharmaceutical applications so that both approaches can be accomplished together to get a fast drug release. The speed of drug dissolution for drugloaded aerogel micro particles could be of three orders of magnitude faster than drug-loaded solid particles. Silica and carbon aerogels in the form of microparticles are traditionally obtained from monoliths by milling.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. [31]

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 supercriticaling of the gel leads to the aerogel formation. 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[31]

Methods for alcogels preparation-

1] Air-Drying of alcogels-

Air dried slabs and cylinders are made by placing samples equilibrated in 100% ethanol on perforated trays covered with sheets of whatman filter paper. The trays are then enclosed in a polyethylene chamber that is continuously flushed with stream of air that has been dried by filtering through anhydrous $CaSO_4$.The samples are kept in the chamber for one day beyond the time that ethanol odour could be detected in either the effluent or the sample.

The air drying process is less costly because it does not require expensive high pressure equipment. The processing times are limited by diffusion rate during the ethanol equilibration step and during drying.

2] Critical point drying of alcogels-

In the critical point drying of alcogels, the slabs and cylinder equilibrated in 100% ethanol are placed in autoclave designed to withstand pressures in excess of 12 Mpa.The autoclave is first filled with 100% ethanol and then loaded with the slabs and cylinders. The autoclave is then quickly drained of ethanol and filled with liquid co2.several changes of co2 are made each day to displace ethanol that is diffused out of the sample. The process is completed over a period of five day after which the autoclave is drained to approximately half full so that the liquid co2 level just covers the samples. The autoclave is then heated and further pressurised above the critical temperature[30.92°] and pressure[7.375 MPa] of co2.After reaching the critical point of co2,the chamber was slowly depressurized and the dried foam samples is recovered.

3] Freeze-Drying of aqua gels-

The aqua gels samples are placed on the trays in a freeze drier equipped with heating trays. Typically the sample freeze-dried within three days. The mechanical tests are performed on freeze dried slabs cut in 1-in.squares.

4] Liquid CO_2 extraction of alcogels-

Alcogels are placed in an autoclave and equilibrated with liquid CO_2 as described for the CPD process. After 5th day of co2 equilibration, the autoclave was slowly depressurized without reaching the critical temperature and pressure of CO_2.the samples are then tested.

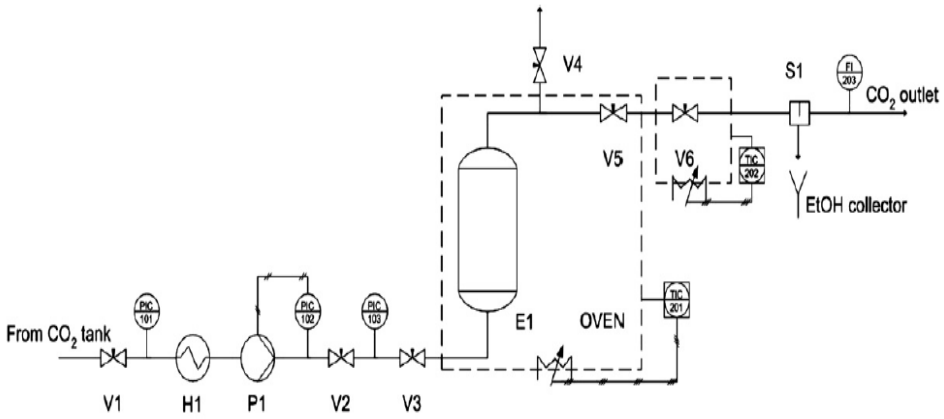

Fig.2. Process flow diagram for the equipment used for the supercritical drying of starch aerogel with carbon dioxide. Tags:v1-v7, valves; P1,pump;E1, autoclave;p1-10x, pressure gauge; T120x, thermocouples; F1-203, flow meters.[6]

Drug loading into the alcogels-

The choice of the proper medium for the drug loading step is a key processing parameter to be taken into account

1] Loading during the sol-gel process [before gelation or during solvent exchange]-

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 method 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 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.

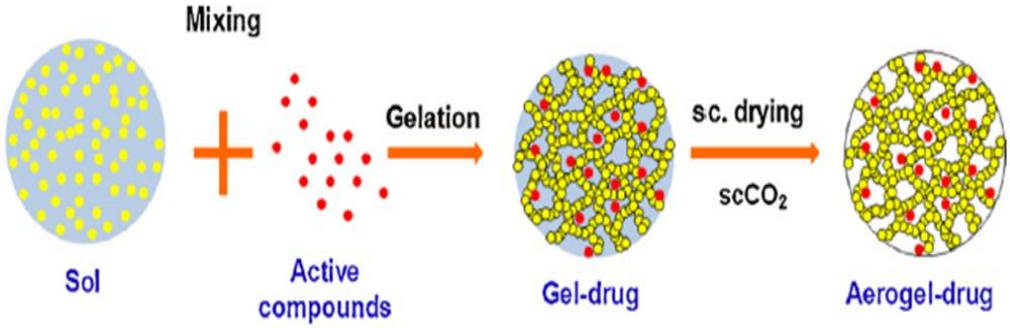

Fig 3-Loading of drug into the aerogel[1],

2] Loading in the dried aerogel matrix-

This approach implies an additional post processing step to load the target compound within the aerogel host matrix. On one hand the drug loading of the aerogel from a liquid phase is hindered by diffusional limitations of the drug passing through the pores and can also lead 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.

3] Adsorption from supercritical solutions:

Supercritical fluid assisted drug loading of aerogels overcomes the limitations of the liquid and gas phase methods. The drug loading of an aerogel from a supercritical phase encompasses both the good mass transfer [infusibility] properties of the gaseous phases and the good solvation power [drug solubility] of the liquid phases. The aerogel sample is packed in filter paper to avoid direct contact with the drug. The weighed amount of drug is placed in an open aluminium vessel and added to the preheated autoclave, being separated from the aerogels additionally by a metal grid. After closing the autoclave preheated CO2 is added until the designated pressure is reached. Under mild agitating the drug is dissolved in CO2 and adsorbed on the aerogel matrix. After approx. 70 h the pressure is reduced continuously, the autoclave is opened and the samples are removed. The resulting drug loading is calculated from the increase in weight of the aerogels samples.

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. 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. 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. 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 [31].

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. The specific loading of the drug within the polysaccharide based matrices [1–4 × 10−3 g/m2 for ibuprofen[31] 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 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 [31]. 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 behaviour 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 [31].

The performance of the polysaccharide based aerogel as a carrier can be improved by using the hybrid aerogel composed of the inorganic and organic [polysaccharide] components. The use of this dissimilar components in a single aerogel matrix will result in a novel and outstanding physicochemical properties of the aerogel[31].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.

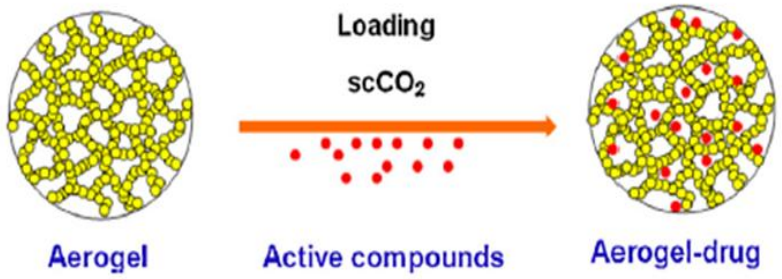

Fig 4-Loading of drug into the aerogel by sc-CO_2[6].

Future prospects and outlook-

The main cost of silica aerogel production comes from the purchase of the silica precursor. 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.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.

The subsequent quick therapeutic effect in the human body. The marketplace has currently focused its interest on this administration route .However, the search for innovative inhalation formulation strategies must be intensified in order to improve the efficiency in the delivery of drugs to the. Polysaccharide-based aerogel powder can be regarded as a promising drug matrix for the inhalation route. The low density [0.05–0.3 g/cm3] and high porosity [>90%] of the aerogel dried particles may result in a superior air flow ability to efficiently reach the lungs, reverting in fewer drug doses as well as lower dosing frequency. 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 behaviour. 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. 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.

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. 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.[31]

Table: Properties of Aerogel[6].

Aerogel properties					
Electrical properties Lowest dielectric constant	**Mechanical properties** Elastic Light weight	**Acoustics properties** Low speed of sound	**Optical properties** Low refractive index Multiple composition Transparent	**Microstructural properties** Open pore structure High surface area Low density Composite material	**Thermal properties** Best insulating material Low density Thermal stability Transparency
Aerogel applications					
• Spacer for vacuum electrodes • Dielectrics for integrated circuits • Capacitors	• Explosion proof wall • Hypervelocity particles trap • Energy absorber	• Ultrasonic sensors • Sound proof rooms • Acoustic impedance	• Cherenkov detectors • Light guides • Light weight optics	• Filters • Sensors • Templates • Fuel storage • Pigments carriers • Targets for ICF (inertial confinement fusion) • Ion exchange • Catalysts & catalyst carriers • Carrier materials • Supercritical fluid chromatography	• Metal melts moulds • Cryogenic insulation • Building construction and insulation • Hydrogen storage media • Solar devices • Space vehicles

REFERENCES

1. Chao Wu, Zhongyan Wang, Zhuangzhi Zhi, Tongying Jiang, Jinghai Zhang, Siling Wang : Development of biodegradable porous starch foam for improving oral delivery of poorly water soluble drugs.International Journal of Pharmaceutics. January 2011; 403,1–2, 17:162–169
2. Badr-Eldin, S.M., Elkheshen, S.A., Ghorab, M.M. Inclusion complexes of tadalafil with natural and chemically modified b-cyclodextrins I: preparation and in vitro evaluation. Eur. J. Pharm. Biopharm. 2008; 70: 819–827.
3. Karavas, E., Georgarakis, E., Sigalas, M.P., Avgoustakis, K., Bikiaris, D Investigation of the release mechanism of a sparingly water-soluble drug from solid dispersions in hydrophilic carriers based on physical state of drug, particle size distribution and drug–polymer interactions. Eur. J. Pharm. Biopharm 2007; 66: 334–347.
4. Matteucci, M.E., Brettmann, B.K., Rogers, T.L., Elder, E.J., Williams, R.O., Johnston, K.P . Design of potent amorphous drug nanoparticles for rapid generation of highly supersaturated media .Mol. Pharmcol 2007; 4: 782–793.
5. Masuda, K., Tabata, S., Kono, H., Sakata, Y., Hayase, T., Yonemochi, E., Terada, K.. Solid-state13C NMR study of indomethacin polymorphism. Int. J. Pharm 2006; 318: 146–153.
6. Zhang, Y.M., Hu, L.Y., Han, J.C., Jiang, Z.H., Zhou, Y.F:Soluble starch scaffolds with uniaxial aligned channel structure for in situ synthesis of hierarchically porous silica ceramics. Micropor. Mesopor. Mater 2010; 130:327–332.
7. Huang, X.L., Teng, X., Chen, D., Tang, F.Q., He, J.Q: The effect of the shape of mesoporous silica nanoparticles on cellular uptake and cell function. Biomaterials 2010; 31: 438–448.
8. Shi, X.T., Wang, Y.J., Ren, L., Zhao, N.R., Gong, Y.H., Wang, D.A.:Novel mesoporous silica-based antibiotic releasing scaffold for bone repair. Acta Biomater 2009; 5:1697–1707.
9. Kilpeläinen, M., Riikonen, J., Vlasova, M.A., Huotari, A., Lehto, V.P., Salonen, J., et al: In vivo delivery of a peptide, ghrelin antagonist, with mesoporous silicon microparticles. J. Control. Release 2009;137:166–170.
10. Nunes, C.D., Vaz, P.D., Fernandes, A.C., Ferreira, P., Romao, C.C., Calhorda, M.J: Loading and delivery of sertraline using inorganic micro and mesoporous materials. Eur. J. Pharm. Biopharm 2007; 66: 357–365.
11. Tan, A., Simovic, S., Davey, A.K., Rades, T., Prestidge, C.A: Silica–lipid hybrid [SLH] microcapsules: a novel oral delivery system for poorly soluble drugs. J. Control. Release 2009; 134: 62 70.
12. Marques, A.P., Reis, R.L., Hunt, J.A: The biocompatibility of novel starch-based polymers and composites: in vitro studies. Biomaterials 2002;23: 1471–1478.
13. Tran, P.H.L., Tran, H.T.T., Lee, B.J: Modulation of microenvironmental pH and crystallinity of ionizable telmisartan using alkalizers in solid dispersions for controlled release. J. Control. Release 2008; 129: 59–65.
14. Oh, W.K., Yoon, H., Jang, J: Size control of magnetic carbon nanoparticles for drug delivery. Biomaterials 2010; 31:1342–1348.
15. Marques, A.P., Reis, R.L., Hunt, J.A: The biocompatibility of novel starch-based polymers and composites: in vitro studies. Biomaterials 2002; 23: 1471–1478.
16. Araujo, M.A., Cunha, A.M., Mota, M: Enzymatic degradation of starch-based thermoplastic compounds used in protheses: identification of the degradation products in solution. Biomaterials 2004;25:2687–2693.

17. F. Di Renzo, R. Valentin, M. Boissiere, A. Tourrette, G. Sparapano, K. Molvinger, J.-M. Devoisselle, C. Gerardin, F. Quignard: Hierarchical macroporosity induced by constrained syneresis in core–shell polysaccharide composites, Chemistry of Materials 2007;17:4693–4699.
18. .S.S. Kistler: Coherent expanded aerogels and jellies, Nature:1931;127:741.
19. .G.W. Scherer, D.M. Smith, Cavitation during drying of a gel, Journal of Non- Crystalline Solids: 1995; 189:197–211.
20. .F.M. Plieva, P. Ekstrom, I.Y. Galaev, B. Mattiasson:Monolithic cryogels with open porous structure and unique double-continuous macroporous networks, Soft Matter 2008;4: 2418–2428.
21. Jungbauer, R. Hahn, Monoliths for fast bioseparation and bioconversion and their applications in biotechnology, Journal of Separation Science 2007;27:767–778.
22. S.R. Mukai, H. Nishihara, S. Shichi, H. Tamon, Preparation of porous TiO2 cryogel fibers through unidirectional freezing of hydrogel followed by freeze-drying, Chemistry of Materials 2004; 16: 4987 4991.
23. F.M. Plieva, I.N. Savina, S. Deraz, J. Andersson, I.Y. Galaev, B. Mattiasson:Characterization of supermacroporous monolithic polyacrylamide based matrices designed for chromatography of bioparticles, Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences 2004;807: 129–137.
24. L.R. Rey, J.C. May:Freeze-drying/lyophilization of pharmaceutical and biological Products, 2. Rev. and exp. ed., Dekker, New York, 2004.
25. F. Franks, Freeze-drying of bioproducts: putting principles into practice, European Journal of Pharmaceutics and Biopharmaceutics 1998;45:221–229.
26. M. Alnaief, M.A. Alzaitoun, C.A. Garcia-Gonzalez, I. Smirnova:Preparation of biodegradable nanoporous microspherical aerogel based on alginate, Carbohydrate Polymers 2011;84:1011–1018.
27. Smirnova, W. Arlt, Synthesis of silica aerogels: influence of the supercritical CO2 on the sol–gel process, Journal of Sol–Gel Science and Technology 2003 ;28:175–184
28. Tan, B.M. Fung, J.K. Newman, C. Vu: Organic aerogels with very high impact strength, Advanced Materials 2001;13: 644–646.
29. F. Placin, J.P. Desvergne, F. Cansell, Organic low molecular weight aerogel formed in supercritical fluids, Journal of Materials Chemistry 2000; 10: 2147–2149.
30. C.A.Garcia-Gonzalezz,M.Alnaief,I.smirnova.Polysaccharide-based aerogels-promising biodegradable carriers for drug delivery system.Carbohydrate polymers 2011; 86:1425-143
31. C.A. Garcia-Gonzaleza,∗, M.C. Camino-Rey, M. Alnaief, C. Zetzl, I. Smirnova,∗ Supercritical drying of aerogels using CO2: Effect of extraction time on the end material textural properties.J. of Supercritical Fluids 2012; 66:297– 306.

5487847845**1170306**