# 1.131. Superporous Hydrogels for Drug Delivery Systems

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## Abbreviations

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| **aq** | Aqueous |
| **CD** | Circular dichroism |
| **CMC** | Carboxymethylcellulose |
| **CSPHs** | Conventional superporous hydrogels |
| **DDS** | Drug delivery system |
| **DSC** | Differential scanning calorimetry |
| **EDX** | Energy-dispersive X-ray spectroscopy |
| **FDA** | Food and Drug Administration |
| **FTIR** | Fourier transform infrared |
| **HEMA** | Hydroxyethyl methacrylate |
| **HPMC** | Hydroxypropyl methylcellulose |
| **NIPAM** | N-isopropyl acrylamide |
| **NMR** | Nuclear magnetic resonance |
| **PEG** | Polyethylene glycol |
| **PVP** | Poly(vinyl pyrrolidone) |
| **s** | Solid |
| **SEM** | Scanning electron microscope |
| **SPH** | Superporous hydrogel |
| **SPHCs** | Superporous hydrogel composites |
| **SPHHs** | Superporous hydrogel hybrids |
| **TGA** | Thermogravimetric analysis |
| **UV/VIS** | Ultraviolet/visible |

## 1.131.1. Introduction

Regardless of the payload (drug, solvent, fertilizer, pesticide, etc.), a delivery system should possess two major tools to function. It should accommodate the payload and release it later on at a controlled rate. Novel delivery systems possess an extra tool to deliver the load to a desirable site, and are intended for targeting delivery. Hydrogels have long been known for their ability to house drugs and to prevent drug release by a simple diffusion process. Due to their long polymeric chains, they provide a physical barrier to drug transport, as a result of which a drug needs to take a longer path to

diffuse out of the delivery system. The barrier properties of the polymer chains become more significant when the chains are hydrated in an aqueous medium. Although these features are attractive in controlled drug delivery, some applications require a faster transport kinetic. The presence of pores within a hydrogel structure, through which the drug can be released at a faster rate, adds another dimension to the transport process.

Pores inside a hydrogel structure are generally closed, although populated. Porous hydrogels in general have a closed pore structure, with no well-tailored size or distribution. Superporous hydrogels (SPHs), on the other hand, are hydrogels with an interconnected structure with a relatively narrow pore size and distribution. The predecessor of SPHs, that is, superabsorbent polymers, are for instance found in ultrathin or ultra-absorbent baby diapers and feminine incontinence products due to their outstanding urine or blood absorption capability. These are made of a very hydrophilic but cross-linked structure (mostly based on acrylic acid and its sodium salt) with the ability to absorb 500–1000 $g\,g^{-1}$ of distilled water and 40–70 $g\,g^{-1}$ of saline (an aqueous solution containing 0.9 wt% sodium chloride). These structures are very sensitive to pH, nonsolvents, and ionic strength of the swelling medium. Since this product is supplied in granule and particle form, its swelling rate can be adjusted by the particle size, which significantly affects the particle surface area and hence its absorption ability. In other words, the larger particles absorb aqueous fluids at a slower rate than their smaller counterparts. Superporous hydrogels with the same swelling capacity, on the other hand, absorb aqueous fluids at almost the same rate, irrespective of their size in a dry state. Increased surface area in superporous hydrogels is provided by pores inside their structure. With an increase in their pore content and decrease in pore size, more hydrogel surface would be exposed to the swelling environment, which makes the swelling kinetic faster.

## 1.131.2. Hydrogels in Drug Delivery

There are more than 100 prescription drugs in the US market, in which one excipient is commonly used, that is, hydroxypropyl methylcellulose (HPMC). Although this polymer is water soluble, it provides gelling properties when exposed to an aqueous environment. HPMC with different degrees of substitutions is used in tablet form to control the release of the drug over a longer period of time. Apparently, there are two features that enable the HPMC to function as a controlled delivery system. First, it is very hydrophilic due to its hydroxypropyl contents. Second, the HPMC chains are in a very compressed form in a tablet, which prevents them from a fast dissolution in the aqueous environment. These two features provide gelling properties such as those found in a chemically cross-linked hydrogel. Although there is no chemical cross-linker in the HPMC structure, the applied pressure during tablet preparation supplies enough entanglement and barrier for the retarded dissolution of the polymer.

## 1.131.3. Superporous Hydrogels

A superporous hydrogel is a composite polymer made of a solid hydrogel and air. The SPH is a unique class of porous

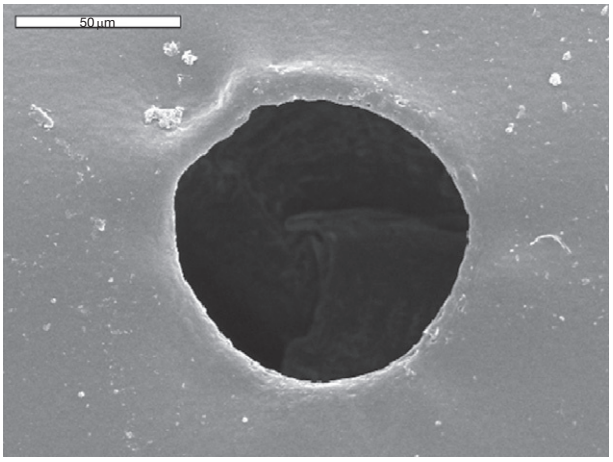


**Figure 1** A typical superporous hydrogel with an average pore size of 50 µm.

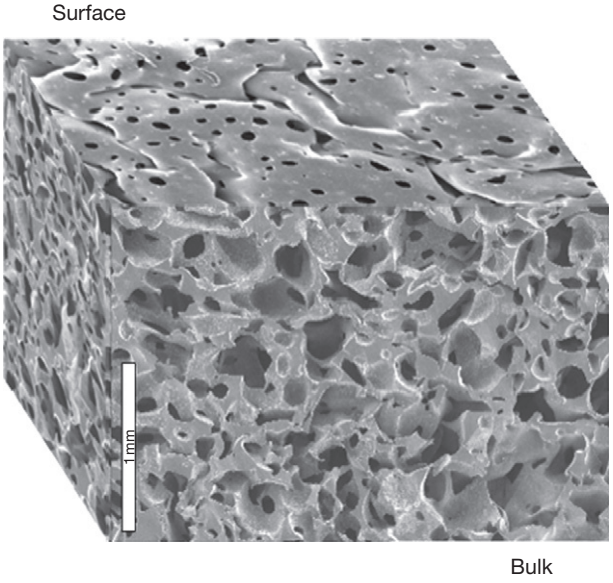


**Figure 2** A three-dimensional porous structure of a typical superporous hydrogel.

hydrogels with an average pore size of 50–100 µm (Figure 1) and an interconnected pore structure (Figure 2).[1] As its pores are open, the fluid can travel in a three-dimensional path, as a result of which the swelling rate of a typical SPH becomes independent of the SPH size in its dry state.[2] While in nonporous hydrogels the solid part is responsible for the swelling and mechanical property, the air portion of the SPH structure plays a vital role in determining the final SPH properties. Generally speaking, properties such as density, swelling capacity, and mechanical strength are improved by solid content, while the swelling rate increases as the SPH air content increases. The pore content, size, morphology, and isotropicity are all pore features of the SPH, which could potentially affect SPH stability and function to a lesser or greater extent.

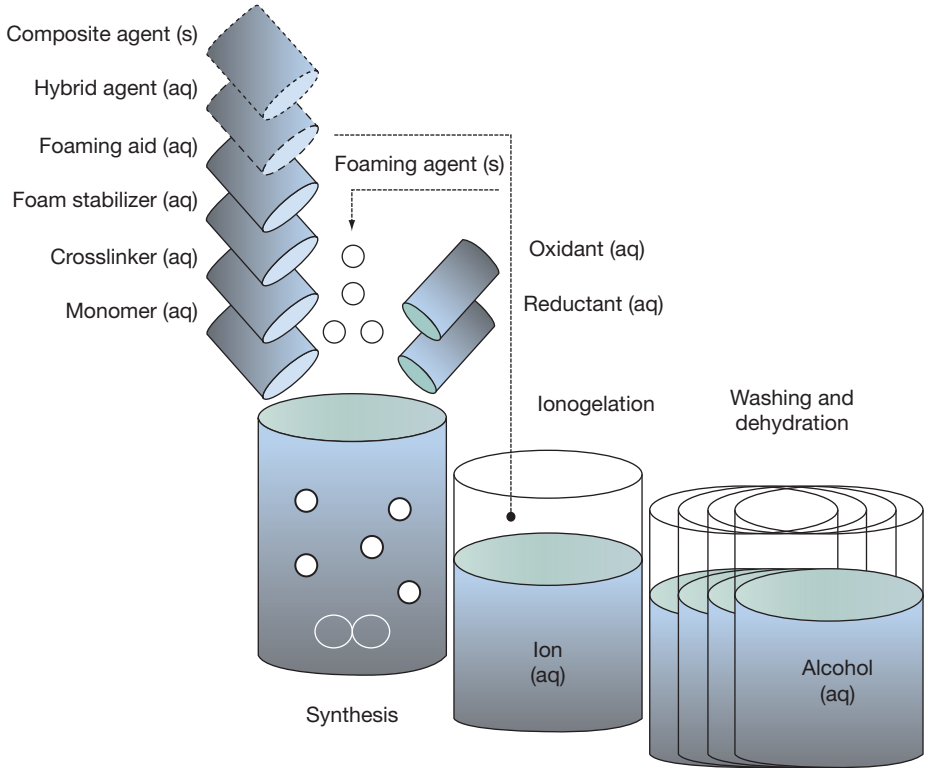


**Figure 3** Synthesis, treatment, and purification of a typical superporous hydrogel.

### 1.131.4. SPH Synthesis

In the preparation of SPHs, a bicarbonate foaming agent is used, which is water soluble and becomes active in an acidic aqueous medium. So a solution polymerization is a preferred method of SPH synthesis. Aqueous solutions of monomer, cross-linker, foam stabilizer, and foaming aid are added in turn to the reacting mixture under very mild mixing. Following a complete homogenization, the reductant and oxidant are added consecutively and are mixed quickly with the reacting mixture. In a very short period of time, the solid foaming agent (e.g., bicarbonate) is effectively dispersed and mixed throughout the reacting solution. The bicarbonate reacts with the foaming aid (e.g., an organic acid) to generate carbon dioxide gases; this reaction in turn increases the pH of the reacting solution, which favors the decomposition of the initiator. Due to the retarding effect of the oxygen, there is an induction, or lag period, which is followed by a fast exothermic polymerization reaction.[3] The foaming and gelling reactions occur almost simultaneously and proceed to their maximum extent at the polymerization temperature, which is determined by the type of monomer, its concentration in the solution, and initiator concentration. A successful SPH is synthesized if the chemical gelation and physical foaming happen in a synchronized way.[4,5] The formation of the SPH foam requires the $CO_2$ gases to be entrapped within the hydrogel matrix, and this would be possible if the reacting hydrogel mass reaches a certain viscosity, $\mu_f$. The foaming viscosity is determined by the rate at which the gelling reaction happens. At viscosities well below and beyond the $\mu_f$, the efficiency of the foaming process would be decreased significantly and no SPH would actually be formed.


**Figure 4** Steps in producing a superporous hydrogel foam.

With no increase in the foam height and no increase in the reaction temperature, both gelling and foaming reactions are slowed down and the SPH foam is then relaxed for further treatment, purification, and drying. The overall procedure of SPH synthesis is shown in Figures 3 and 4 (see Chapter 1.121, Polymer Fundamentals: Polymer Synthesis).

### 1.131.5. SPH Properties

#### 1.131.5.1. Swelling Capacity

Swelling capacity in hydrogels and SPH polymers in particular is defined by the structural hunger for an aqueous fluid. Apparently, the more hydrophilic the structure of the hydrogel, the stronger the intermolecular interactions that can be built by the hydrogel with its surrounding aqueous medium. A stronger polymer–water interaction would be established if the hydrogel structure contains ionizable groups such as carboxyl or its salt derivatives such as potassium or sodium carboxylate. These hydrophilic and ionic functional groups are responsible for the polymer–water interaction, electrostatic forces, and osmotic forces, which are the driving forces for the swelling process to occur. By far the most important consideration in hydrogel

swelling is the status of water with respect to the hydrogel core. Like the electronic layers surrounding the nucleus of an atom, several layers of water are built up around the hydrophilic and ionic groups. An electron is separated with more ease in the presence of electron-loving atoms if it is located in the outermost electronic layers. Likewise, water molecules within the hydrogel located at the outermost layers, far from the hydrophilic or ionic groups, can be separated with ease. As a result, the status of water in hydrogels is generally defined as free and bound water, which reflects the extent of polymer and water interaction within a hydrogel.

Swelling capacity in hydrogels is generally measured under free and loaded conditions. A hydrogel is simply placed in water or an aqueous solution with a little or no pressure applied on the hydrogel. The hydrogel begins the process of water absorption via its functional groups and continues to absorb water until all the functional groups receive the same amount of water. The amount of water absorbed can simply be calculated by measuring the hydrogel weight before and after the swelling.

### 1.131.5.2. Swelling Rate

The rate at which water or an aqueous medium is absorbed into the hydrogel structure depends on the hydrogel's chemical and physical structure. As far as the chemistry is concerned, the hydrogels containing more hydrophilic and ionic groups offer a faster swelling process. At the same chemical composition, hydrogels small in size or thin (film), and having a porous structure, can swell faster in an aqueous medium than nonporous, large in size, and thick (sheet) hydrogels. A nonporous hydrogel structure absorbs water at its surface layer by layer. In other words, the water is absorbed into the structure of such hydrogels following a two-dimensional path. Then, the first partially swollen layer acts as a water reservoir for the lower layers. With a porous structure, on the other hand, the whole hydrogel mass could have the same access to the water, and hence water can penetrate into the hydrogel structure following a three-dimensional path. To measure the swelling rate or the swelling kinetic, the amount of water absorbed into the hydrogel structure is measured versus time. While the amount of water absorbed at times zero and infinite reflect the weight of the hydrogel in its dry and fully swollen states, respectively, the hydrogel behavior within this time period reflects the mechanism of the swelling kinetic. For instance, the swelling kinetic would be zero order if the absorption is linear. On the other hand, the absorption occurs as a first-order kinetic if the behavior is exponential. Generally, the absorption mechanism changes with the cross-link content of the hydrogel. A zero-order kinetic is favored at higher cross-link content.

### 1.131.5.3. Mechanical Strength

A hydrogel in its swollen state is a composite material composed of solid, liquid, and air. Apparently, the extent of intermolecular forces within a solid is more extensive than in the other two. Therefore, a hydrogel with more solid properties (less water and air content) is considered stronger in its swollen state. To measure the mechanical properties, a hydrogel is stressed under static or dynamic loads until it fails.[6,7] The testing force should be selected on the basis of actual service conditions. For example, if the SPH is required to resist the compressive forces, a compression test should be designed accordingly. Similarly, if the SPH is expected to resist a dynamic compression (compression–decompression cycles) force, an appropriate dynamic test should be designed to evaluate the SPH for such an application.[7] For gastric retention studies, the SPH for instance is required to not only resist the combined forces of compression, tension, and bending altogether, but also serve in a very harsh acidic condition. A gastric simulator, which examines the mechanical strength of the SPH by mimicking the real gastric conditions, has been reported.[8–10] The SPHs for such application should quickly swell up in the acidic medium of the stomach juice to a size larger than the pyloric sphincter. The SPH is assumed to resist the mechanical pressures inside the stomach while it is saturated with the stomach fluid. Evaluating and screening hydrogels that resist the real stomach pressures have always been challenging. A texture analyzer and compressive or tensile mechanical tester are normally used to evaluate the mechanical properties of hydrogels. Although such equipment can predict the comparative properties of hydrogels, they fail to predict real mechanical properties. The simulator generates mixed forces of compression, tension, bending, and twisting, based on a water-hammer effect. The sample under test will receive almost the same amount of forces throughout its body. Finally, the stress concentrated on the weakest part of the SPH body would result in the formation of craze, crack, and finally disintegration of the whole platform. The simulator can practically measure the amount of work needed to break the hydrogel apart under real service conditions.

The swelling capacity, swelling rate, and hydrogel strength are all ultimately dependent on the bound water and free water within the hydrogel. Due to the lack of accuracy in measuring the amount of water in each status, all measurements would face a larger standard deviation. Therefore, any measuring procedure or instrument needs to be validated to obtain more accurate and reliable data.

## 1.131.6. SPH Generations

Hydrogels with fast swelling and superabsorbent properties, different from conventional superabsorbent polymers, were first reported by Chen *et al.*[11] Fundamental structural and property differences between the superabsorbent hydrogels and superporous hydrogels have been reviewed, with an emphasis on the evolution of SPHs and different generations of SPHs.[12] Superporous hydrogels were evolved about a decade ago, and their introduction was triggered by a need strongly felt in the pharmaceutical area.[13] There are dozens of drugs with a limited absorption across the gastrointestinal tract, which are extensively absorbed at certain areas of the GI tract such as the upper intestine. These are called drugs with a narrow absorption window. To increase their absorption and hence their bioavailability, these drugs need to be retained in the stomach (gastric) area for an extended period of time. There are currently a few technologies available to increase the retention of such drugs in the gastric medium; among them the floatable, mucoadhesive, and swellable delivery systems have been studied extensively. With the swellable delivery system, the drug would be

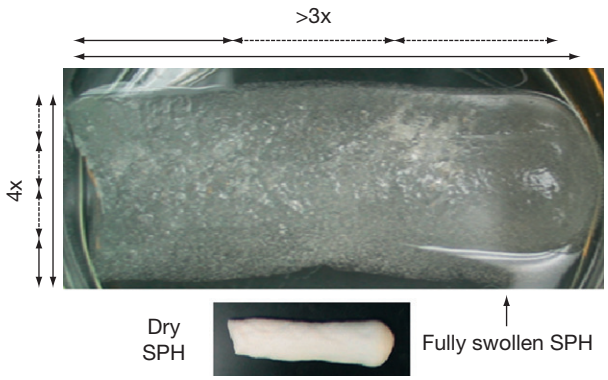


**Figure 5** Unique swelling feature of a superporous hydrogel polymer.

accommodated in the swellable hydrogel structure and take a very rough path to release itself from the platform by diffusion. In this way, the drug can stay longer in the area of interest and release itself in a more controlled manner. The early superporous hydrogels, like their superabsorbent predecessor, possessed a very high absorption capacity and a very fast swelling rate. These features were attractive enough for their development in this area of application. Figure 5 shows a typical SPH, in which its dimensions are increased to about four times the original length in about a minute after complete swelling in water.

### 1.131.6.1. The First SPH Generation

A variety of monomers and polymers, as well as approaches, have been exploited to make SPHs with different structures and properties.[11,14] Among monomers, those with very hydrophilic (e.g., carboxyl or amide in acrylic acid and acrylamide respectively) or ionic (e.g., carboxylate in sodium or potassium acrylate) functions could offer superior swelling properties. These hydrogels are generally prepared in solution by incorporating monomers, initiators, and cross-linkers, as well as foaming agents, into the reaction. The final product is a superporous hydrogel with an interconnected pore structure, which could absorb great amounts of water in a few minutes. However, these hydrogels do not possess any mechanical strength due to the vast number of water layers around their hydrophilic cores. In other words, such hydrogels contain a high proportion of free or semibound water in their swollen state, which make them weak under mechanical pressures. As there is no provision to increase their mechanical strength, these hydrogels are called conventional superporous hydrogels. Figure 6 shows a typical synthetic procedure and structure of the first SPH generation.

### 1.131.6.2. The Second SPH Generation

The need for better mechanical property triggered the development of the second generation of SPHs or the SPH composites.[15–17] These SPHs are prepared by adding a swellable filler to the original formulation of the conventional SPHs. The swellable filler is selected among pharmaceutically acceptable cross-linked and hydrophilic polymers, including cross-linked sodium carboxymethylcellulose (CMC), cross-linked poly(vinyl pyrrolidone), and cross-linked sodium starch glycolate. These are

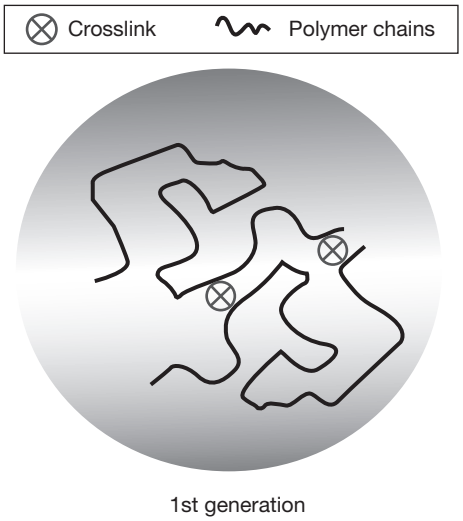


**Figure 6** A conventional superporous hydrogel.

commonly used as a superdisintegrant in the preparation of tablets and other solid doses. The use of these in hydrogel formulation could positively affect the SPH strength, presumably due to the strength nods or the physical cross-links built into the hydrogel structure (see **Chapter 4.423, Polymeric Drug Conjugates by Controlled Radical Polymerization**).

### 1.131.6.3. The Third SPH Generation

Although the SPHs of the second generation could provide a hydrogel with a better strength, much higher strength was felt to be needed, for the gastric retention application in particular. This triggered the development of the third SPH generation, also called superporous hydrogel hybrids (SPHHs), with superior mechanical properties. The primary, secondary, and tertiary approaches have so far been disclosed. The SPH is prepared in a conventional way, but an active material is added during SPH synthesis, which is then treated in the ion solutions. While the primary approach is particularly useful in making SPHs with rubbery properties, SPHs with good mechanical strength can be obtained by adopting the secondary approach.[3] Although the mechanical properties of SPHs can be significantly enhanced after an ion treatment, the ion composition was found to be a useful tool for better controlling the swelling and mechanical properties. Depending on the activity of the ion (sodium, calcium, aluminum, and iron in particular), any ion composition can be used to modify and modulate SPH properties.[4] Figure 7 displays the fundamental structural differences between the second, the third, and the modified SPH generations.

SPH hybrids are prepared according to conventional SPH formulations but a water soluble and ionogelling polymer (synthetic or natural) is added during hydrogel preparation. After preparation, the SPH is treated in an ion solution to become strong and elastic.[3,18] A dried SPH hybrid possesses a folded surface morphology as shown in Figure 8. Utilizing an ionogelling monomer in the basic monomer solution has also been practiced to obtain improved SPH structures. For example, a hydroxyethyl methacrylate (HEMA)-based SPH with modulated swelling and mechanical property has been prepared by

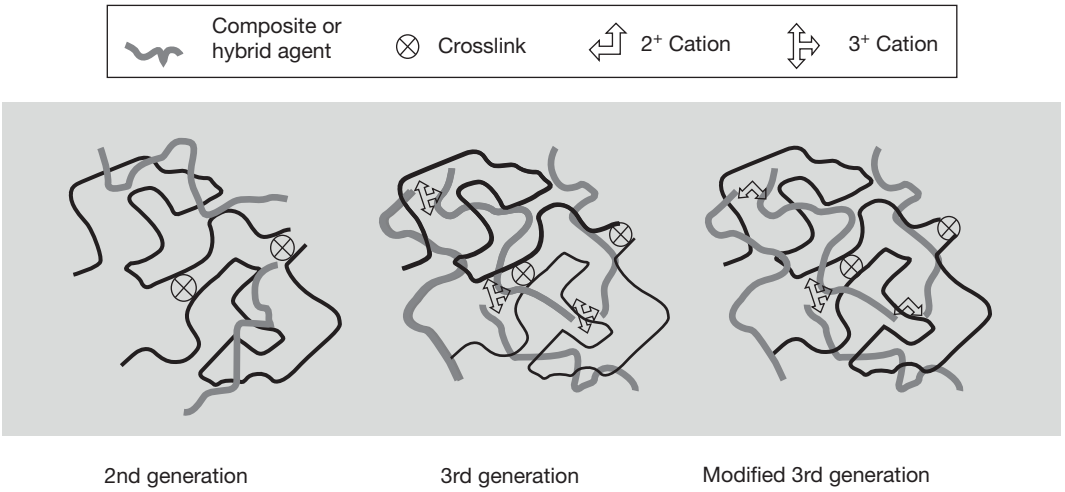


**Figure 7** Different superporous hydrogel generations.

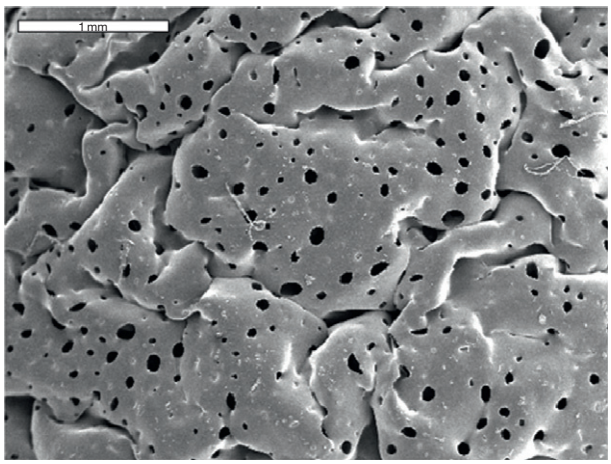


**Figure 8** The surface morphology of a typical superporous hydrogel hybrid.

adding acrylic acid into the HEMA formulation containing a cross-linker. After formation, the SPH foam is treated in calcium or aluminum ions to improve the SPH strength and swelling. It then displays stable swelling and mechanical properties in a very harsh service environment such as gastric medium.[5]

### 1.131.6.4. Research on SPHs

By far the most common monomers used in the preparation of SPHs are acrylic acid and acrylamide. The swelling response of SPHs based on acrylamide and acrylic acid has been studied with the change in the pH of the swelling medium and pressure.[19,20] Solid-state NMR, swelling, density, and scanning electron microscopy were utilized to characterize the SPH composites of acrylamide and acrylic acid polymers cross-linked with *N*,*N*′-methylenebisacrylamide. Apparent density and SEM measurements showed that the SPH composites are more porous than conventional SPHs, which results in hydrogels with superior swelling but weaker mechanical properties.[21] Due to their ionic structures, the swelling property of the poly(acrylamide-*co*-acrylic acid) copolymeric SPHs are dependent on the pH and ionic strength of the solution. These SPH structures display a fast 'on–off' shrinking–swelling cycle in the pH range of 1.2 and 7.5, respectively.[19] Floatable SPHs loaded with vitamin B12 were prepared via copolymerization of acrylamide and acrylic acid in the presence of a porogen and a catalyst.[22] The increased surface area of SPHs has been utilized for grafting purposes. Acrylic acid could be grafted at a high grafting efficiency on polyacrylamide gels using potassium diperiodatocuprate. This feature also helps with the purification process by facilitating the mass transfer process as well as the adsorption of ligands.[23] The PEG-grafted superporous hydrogels based on acrylic acid and acrylamide are prepared in the presence of PEG acrylate and a foaming agent. This modification has caused about sixfold increase in the swelling rate.[24] An amphiphilic coating based on poly(ethylene glycol–tetramethyleneoxide) has been used to improve the swelling kinetics of SPHs.[25] The effect of acidification has been examined on the swelling and mechanical properties of poly(acrylamide-*co*-acrylic acid) SPHs. SPH swells much less in acidic water than in distilled water. Acidification reduces the swelling ratio but improves the mechanical properties.[26] The interpenetrating network of cross-linked poly(acrylamide-*co*-acrylic acid) with polyethyleneimine has also been examined.[27] The effect of synthetic factors on the swelling of superabsorbent hydrogels based on neutralized acrylic acid and methylenebisacrylamide has been studied. The swelling was interpreted by a Voigt-based viscoelastic model, and the hydrogel kinetic and thermodynamic parameters were found accordingly.[28] A partially neutralized acrylic based superabsorbent hydrogel has been studied using different water-soluble and oil-soluble cross-linkers and a combined porogen system of bicarbonate/acetone system. Highly porous gels were obtained under conditions where the gelation period was short. Highly cross-linked hydrogels showed almost no swelling dependence on salt.[29] SEM morphological studies and swelling studies show the synergistic effect of the combined porogen system compared to the use of individual gas blowing systems.[30] Porous polyacrylamide has been synthesized using calcium carbonate microparticles, followed by an acid treatment. The hydrogel

swelling is adversely affected by the calcium microparticles and the chemical cross-linker.[31] In another study, a Taguchi experimental design was used to evaluate the effect of the synthetic variables on the gel strength of the acrylamide-based hydrogels and superporous hydrogels.[32] Poly(vinyl alcohol) has been used to improve the strength of the SPHs based on potassium salt of sulfopropyl acrylate, acrylic acid, and PEG diacrylate. The SPH is intended for gastric retention application.[33] An SPH hybrid of acrylamide and sodium alginate has been prepared via a two-step polymerization and treatment. The process involves polymerization and cross-linking of acrylamide in the presence of alginate, followed by treating the prepared SPH in an ion solution. The SPH prepared via this approach possesses superior mechanical and elastic properties.[18] The mechanical property of the conventional SPH polymers has been improved via network-in-network formation by including polyacrylonitrile in the reaction.[34] In another study, the gel strength of the superabsorbent hydrogel was increased via addition of kaolin during the hydrogel synthesis. FT-IR study confirmed the existence of acrylic grafts on the kaolin surface. Despite an increase in gel strength, the swelling property of the hydrogel was reduced to a great extent. The thermal property of the prepared hydrogels has been characterized using thermal analysis including DSC and TGA.[35] Interpenetrated SPH network of poly(acrylamide-*co*-acrylic acid) with chitosan and glycol chitosan was prepared. In distilled water, both systems behave similarly but swelling increases in acidic medium with increase in chitosan concentration. Since glycol chitosan is more hydrophilic than chitosan, a significant increase in swelling rate was observed[36] (see **Chapter 2.213, Chitosan**).

*N*-isopropyl acrylamide (NIPAM) and acrylamide have been used to prepare thermosensitive SPHs with pore size of about 100 μm. An on–off swelling–shrinking cycle is obtained if a certain composition of the thermosensitive superabsorbent SPH is heated up from a low (e.g., 10 °C) to a high (e.g., 65 °C) temperature.[14] A higher temperature favors the hydrophobic interactions and the polymer loses its water affinity due to a weaker hydrophilic interaction. A temperature-sensitive poly (NIPAM) hydrogel was prepared in an aqueous sodium chloride solution. This technique resulted in a hydrogel with significantly higher swelling and swelling response due to the effect of salt, which was claimed to be responsible for phase separation and heterogeneity of the structure. These porous hydrogels are characterized by a larger pore and smaller pore at low and high temperature respectively, which result in complete and no release of the bovine serum albumin, respectively.[37] Superporous hydrogel of CMC–NIPAM hydrogel was attained via simultaneous irradiation cross-linking and addition of a foaming agent.[38] Sucrose-based hydrogels and their SPH counterparts were prepared by reacting sucrose with glycidyl acrylate, followed by its polymerization. The superporous sucrogels showed faster swelling and degradation in both acidic and basic media.[39]

A combined gas-foaming and freeze-drying technique has been used to prepare interpenetrated SPHs based on glycol chitosan and poly(vinyl alcohol). It was shown that the number of freezing–thawing cycles has a more significant effect on the hydrogel strength than the freezing time. A differential scanning calorimetry was used to evaluate the thermal behavior associated with the hydrogen bond-induced crystalline structure of the hydrogel.[40] Highly porous poly(2-hydroxyethyl methacrylate) slabs were prepared by a simultaneous polymerization and cross-linking of the HEMA monomer and ethylene dimethacrylate. Porosity was achieved using porogens such as cyclohexanol, dodecan-1-ol, and saccharose. Low density values for these hydrogels indicate a closed cell rather than an interconnected structure. Mercury porosimetry was used to evaluate the superporosity and microporosity status of the gels.[41] Hydrofluoric acid (HF) treatment was also used to extract nanosized silica particles from a hydrogel matrix to make a porous hydrogel.[42]

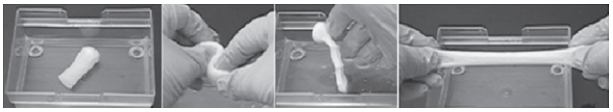


**Figure 9** Mechanical property of a typical superporous hydrogel hybrid under various forces.

Superporous hydrogels interpenetrated with sodium alginate have displayed pH- and salt-responsive swelling properties. Moreover, the alginate-modified SPH shows no significant cell or mucosal damage based on thiazolyl blue, lactate dehydrogenase assays, as well as rat's intestine morphology.[43] A fully interpenetrated superporous hydrogel with superior mechanical and elastic properties is obtained when a synthetic monomer is polymerized and cross-linked in the presence of a hydrocolloid with ionogelling ability. A fully interpenetrated network is obtained when the hydrogel is treated in an ion solution containing calcium, iron, or aluminum.[18] **Figure 9** shows a typical acrylamide–alginate-based SPH hybrid in its fully swollen state, which resists compression, bending and tensile forces for a long period of time before it breaks apart. Pectin has been used as a base for an intelligent superabsorbent polymer with pH and thermosensitive swelling properties, which can potentially be used for controlled delivery of nonsteroidal anti-flammatory drugs. Results have shown that the drug could be delivered to the intestine without being lost in the stomach.[44]

## 1.131.7. SPH Scale Up

Scale up is the process of preparing the SPH on a large scale. A larger scale means an increase in the starting materials, an increase in the container size, and dealing with a very exothermic reaction on a large scale. If the synthesis of an SPH is successful in a container with a certain geometry, it does not necessarily mean a successful synthesis on a larger scale. During the SPH polymerization, heat is released, which is entrapped in the reacting mix due to the insulation property of the pores inside the forming SPH structure. The heat buildup can increase the rate at which normal polymerization happens, the rate of gas formation, and also the chance of popcorn polymerization by which cross-link density of the SPH increases to a great extent. To release the heat from the reacting mixture, an adequate surface should be provided, which is determined by the aspect ratio of the container (diameter/height ratio).

Dispersion of the foaming agent into the SPH formulation during the synthesis is a typical active suspension process. There are generally three types of suspension processes: dispersion of a nonreactive filler into a nonreactive medium (e.g., paint formulation), dispersion of a nonreactive filler into a reacting medium (e.g., kaolin in hydrogel synthesis), and finally, dispersion of a reactive filler into a reactive medium (e.g., bicarbonate in SPH synthesis). Once dispersed, the bicarbonate particles can increase the pH by consuming the acid component of the formulation, which in turn increases the rate at which the redox couple would react. This in turn increases the magnitude of the polymerization reaction and its exothermicity. In other words, the extent of the gelling reaction would critically depend on the amount of the bicarbonate in the system. If not well-dispersed, a so-called 'local hot spot' is produced around which a polymerization to a very high extent is expected. This causes an undesirable heterogeneity in the SPH structure. By far the most challenging aspect of the manufacture of SPHs on a large scale is the dispersion of bicarbonate into an ongoing reaction. An SPH with a uniform pore size and distribution is achieved if the bicarbonate is evenly dispersed into the gelling mass. In general, the bicarbonate dispersion within the reacting mass should be completed in a few seconds. If not, the gelling and foaming reactions would become closely dependent on each other and would affect progress to a great extent. The bicarbonate can effectively be dispersed if a high-pressure gun powder is used.[45] Moreover, the mixing agitator should have a very specific function, to be able to sweep the bottom part of the reaction very effectively to avoid the formation of a nonporous hydrogel at the bottom of the container. Heat buildup, and hence a faster hydrogel formation, may be observed in areas where mixing is not effective. Another important operational factor is the size of the bicarbonate particles. As these particles are reactive, their reactivity would be dependent on their size. As bicarbonate size decreases, its surface area increases. This in turn increases the rate at which pH increases, the rate at which $CO_2$ gases are formed, and the rate of both chemical gelling and physical foaming reactions. The corresponding rates of these two critical reactions can be controlled by selecting appropriate bicarbonate or mixing bicarbonates of different sizes.

## 1.131.8. SPH Stability

In determining the stability of a given drug, adequate documentation is provided to the FDA or similar organizations to prove the identity, purity, and potency of the drug. For a superporous hydrogel product, the same procedure should be followed.

### 1.131.8.1. SPH Identity

There are certain instances in which the identity of an SPH product may change. Moisture, oxygen, ultraviolet light, and heat are potentially the most important factors. The moisture originates from two sources, the moisture retained in the product, and environmental moisture. The product moisture can be minimized by freeze drying, while the environmental moisture is minimized by storing the SPH product under a dry condition using silica gel. Although the SPH itself is also hygroscopic, a silica gel is more effective and faster in moisture absorption. As far as the chemical structure is concerned, an SPH containing, for example, ester (–COO), amide (–NHCO), and anhydride (–COOC) groups would be more susceptible to hydrolysis.

If the SPH contains groups such as ethers (ROR′), and aldehyde (–RCHO), it needs to be protected from oxidative reactions. The most common way to protect the SPH from oxygen invasion is to use different primary, secondary, and tertiary antioxidants. Primary antioxidants such as butylated hydroxyl anisol (BHA), butylated hydroxyl toluene (BHT), tocopherol (vitamin E), and propyl gallate can provide electrons to free radicals and act as free radical scavengers. Compounds such as ascorbic acid and sodium bisulfite are secondary antioxidants and can consume oxygen through autooxidation. The last group of antioxidants, that is, tertiary antioxidants, can react with the ions responsible for initiating the oxidation reactions. The ion scavengers include citric acid, tartaric acid, and ethylenediamine tetraacetic acid.

Functional groups including carbonyl (–CO–) and the C=C bond make a superporous hydrogel sensitive to ultraviolet light. Theoretically, these groups may absorb light at or greater than 280 nm. Photolysis can be prevented by storing the SPHs in an opaque or a dark-colored container. Heat can also change the SPH identity by expediting the hydrolytic, oxidative, and photolytic reactions.

### 1.131.8.2. SPH Purity

The SPH impurities can be classified as primary, secondary, and tertiary. Primary impurities are residual monomer, initiator, and cross-linker left from the polymerization and cross-linking reaction. Due to incomplete conversion of the monomer to polymer, and incomplete inclusion of the cross-linker into the polymer structure, unreacted monomers and cross-linkers need to be removed after SPH synthesis. Many researchers attempt to find ways to reduce residual monomers, but reducing the residual initiators is also a very important consideration. Following monomer removal, the SPH is generally washed with water and alcohol solutions for complete purification. These two are considered secondary impurities. More water will be removed by adding more alcohol and alcohol itself is removed by low pressure drying. One of the very major challenges regarding SPHs for pharmaceutical applications is that they must be reasonably pure. Different methods have been proposed to make a pure SPH. These include the use of low and high glass transition monomers during the SPH synthesis and the use of physically induced expansion and contraction in a solvent–nonsolvent system, as well as the use of mechanical processes such as filtration, rubbing, and centrifugation.[45] The last type of impurities originate from two sources, that is, during SPH storage and SPH service. Since water exists in the SPH even at a very low concentration, this may result in a long-term hydrolysis. Oxidative reactions may also proceed in a given SPH as moisture can act as a plasticizer and facilitate the inclusion of oxygen into the SPH structure. Generally speaking, these reactions are associated with a change in the SPH appearance and color, from snow-white to off-white or pale yellow. During service, the SPH may face a harsh environment such as

very low acidic conditions, and so on, so its structure may be changed or degraded, which is associated with the generation of impurities. Appropriate analytical tests and methods should be developed for a complete characterization of all types of impurities within the SPH product.

#### 1.131.8.3. SPH Potency

The SPH potency can be defined as its swelling power, which depends on the exact amounts of the SPH and its chemical structure. For instance, the SPH potency for a typical gastric retention application may be defined as the amount of HCl solution that one gram of the SPH can absorb over a certain period of time, that is, $g\,g^{-1}\,s^{-1}$ or $ml\,g^{-1}\,s^{-1}$. The cross-link density and the pore structure of the SPH can affect this factor significantly. Although complete care needs to be taken to purify the SPH product, increased cross-link density (physical or chemical) may arise from other sources including polymer crystallization, polymorph formation, entanglement, and complexation. Polymer chains can adopt different conformations during long-term storage, which might affect their swelling ability. Since the SPH is required to be compressed for proper encapsulation, this partial pressure would increase the intermolecular forces between the chains, by which the swelling rate would be affected. The most common sources of increased cross-link density are the SPH interaction with the oppositely charged species such as calcium, aluminum, iron, sulfate, and phosphate ions. The SPH as a final product when it is encapsulated in an orally administrable capsule may face another instability due to the SPH–capsule interaction either directly or indirectly. For instance, this may happen due to a charge difference between the SPH structure and the structure of the capsule or due to the interaction between the ions within the SPH structure and the capsule material, which results in polymer–polymer interchain complexation and ion–polymer complexation, respectively.

Although the SPH potency should not theoretically be correlated to the amount of pore, the pore can affect both the SPH swelling capacity and its rate. Since the SPH product is soft in general, and the pores are embedded into a soft SPH matrix, their shape and size can be changed upon application of minor pressures. Pores not only provide capillary action to the water diffusion process, but they also increase the contact surface area with the aqueous medium. Any change in the shape and size of the pores would imbalance the swelling–pore correlation. As SPHs for oral delivery are required to be encapsulated, the original size of the SPH needs to be reduced in order to fit the capsule size. This compression effect apparently affects the SPH pore structure, which might affect the ultimate swelling property of the SPH. A swelling–compression correlation has been found, whose magnitude depends on the orientation of the SPH during compression. In other words, the original noncompressed SPH swelling is preserved if the SPH is compressed along the gas movement line which is from the bottom to the top. Compression force applied in the opposite direction severely affects the swelling kinetic of an SPH.[20] The SEM and swelling studies displayed that the swelling kinetics of the SPH is not affected by the surface morphology and surface porosity measured via mercury porositometry. Studies show that SPH swelling is predominantly determined by the internal SPH structure.[1]

From the biopharmaceutics perspective, the SPH may lose its potency due to interaction with foods or beverages. Fatty foods, oils, and materials of such nature may reduce the SPH potency by making the swelling environment more lypophilic. On the other hand, more basic or more acidic juices as well as salts may also affect the SPH potency to a lesser or greater extent. If the SPH is ionic in nature, its potency would dramatically be reduced by increasing the ionic strength of the swelling medium. The effect of different beverages on the swelling behavior of multiple SPH formulations has been studied for gastric retention applications.[46]

### 1.131.9. SPH Safety

The SPH may be considered safe if it does not affect the human body either chemically or physically. To be considered chemically safe, the SPH should contain less than tolerated amounts of residual materials. This requires developing a very effective purification process and very accurate analytical methods. The SPH is considered physically safe if its administration does not pose any threat to the human body. One of the most serious concerns in administrating a swellable material is esophagus obstruction. Due to its rapid water absorption, a naked SPH may absorb water in the esophagus area, become expanded and hence obstruct the area. This can be avoided by using proper encapsulation materials and methods. Multiple SPH doses may be administered to ensure that esophagus obstruction does not occur under severe and aggressive conditions.

Another aspect of an SPH dosage form is its chemical interaction with the stomach acids. For instance, an ester-based superporous hydrogel is susceptible to ester hydrolysis under severe acidic conditions in the stomach, in particular under long-fasting gastric conditions. An adequate number of studies should be conducted to ensure that there are no, or only safe, by products of such a reaction. In the preparation of SPHs and their dosage form for human clinical studies, care must be taken to use materials with nonanimal origin, which require a TSE (transmissible spongiform encephalopathy) certificate for every starting material.

### 1.131.10. SPH Platform Design for Drug Delivery

To deliver a drug via a swellable platform, the drug needs to be incorporated into the SPH platform. The drug is first formulated into a drug delivery system (DDS) and the DDS is then incorporated into the SPH platform. Although many designs are possible, two designs have been practiced for gastric retention and peroral intestinal delivery of different drugs. Depending on the position of the DDS with respect to the SPH platform, these may be called internal DDS and external DDS designs as shown in Figure 10. In the former, the DDS is placed in the center of the SPH platform and is held in place using an SPH plug. The SPH plug is also held in place by gluing it onto the SPH body from the top. The whole platform is then encapsulated inside an orally administrable capsule.

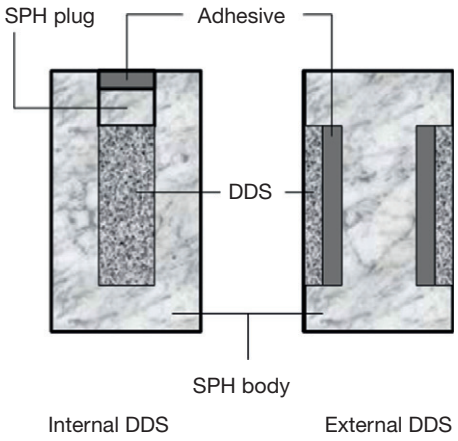


**Figure 10** Different platform designs for the superporous-hydrogel-based drug delivery.

Upon administration and the exposure of the capsule to the stomach acid (for gastric retention), the capsule is dissolved and the SPH platform would be exposed to the gastric contents. This results in an immediate expansion of the SPH to its full extent, which is followed by drug release by diffusion.[47–50] In the external DDS approach, the SPH is attached externally to the SPH body using biocompatible glue, and the platform is then encapsulated in an oral capsule. For peroral intestinal delivery, the capsule itself is enterically coated to prevent the capsule and the SPH from premature dissolution or swelling in the gastric medium. Upon entering the intestine area, the higher pH favors capsule dissolution, which is followed by SPH expansion. The SPH would expand to a size large enough to dock itself into the intestinal wall. The drug is then released directly through the intestinal cells.[51–53]

## 1.131.11. SPH in Drug Delivery and Other Areas

SPHs were originally intended for prolonging retention of drugs with a narrow window of absorption. In designing a superporous hydrogel for such applications, one needs to consider the drug–SPH interaction, which is caused by interaction of their functional groups. Drugs such as acetohydroxamic acid (AHA),[54] repaglinide,[56] metoclopramide,[57,58] and amoxicillin[59,60] contain amide groups. Amine groups can be found in drugs such as acyclovir,[61] amoxicillin, cefuroxime axetil,[62] furosemide,[63] gabapentin,[64] levodopa,[65–67] metformin HCl,[68] metoclopramide, ranitidine HCl,[69] and famotidine.[70] The carboxyl groups are part of amoxicillin, ciprofloxacin,[71] furosemide, gabapentin, ibuprofen,[57] levodopa, and repaglinide-can structures. All these drugs have been examined for gastric retention applications via different methods. From a compatibility perspective, SPHs containing ion may not be a good choice to prolong the gastric retention of levodopa or gabapentine, which contain carboxyl groups. SPHs containing carboxyl groups may interact via hydrogen bonding with the drugs containing carboxyl and amine groups. SPHs, due to their moisture content, may expedite the hydrolysis of amide-containing drugs during storage. SPH compatibility with other excipients used to make the DDS also requires careful evaluation.

### 1.131.11.1. Gastric Retention

A holy grail in oral drug delivery is to develop a dosage form with the ability to control drug release for a relatively long period of time. Besides floating and mucoadhesion concepts, a swelling concept has also been exploited to extend the residence time of the drugs with a narrow absorption window.[47,49,72–75] Following the discovery of *Helicobacter pylori*, a need for an efficient dosage form with the ability to remain in the gastric medium was also felt. A gastroretentive platform needs to be designed based on a good knowledge of physiological factors and biopharmaceutical aspects of the gastric medium.[76] The SPH design for gastric retention applications has been the subject of several articles.[15,77,78]

Gastric retention requires the swellable platform to stay in the gastric medium for a reasonable period of time, that is, a few hours after dose administration. The mechanism by which a platform would stay in the gastric medium is by swelling, and this requires the SPH to swell to a size larger than the pylorus diameter. Assuming an average pylorus diameter of 1.5–2 cm, at least two out of three dimensions of the hydrogel should be larger than 2 cm. On the other hand, the platform needs to be administered orally using a conventional capsule for human administration. Generally, a 00 gelatin or HPMC capsule with an outer diameter of 8.53 mm, height of 23.30 mm, and volume of 0.95 ml is used. A simple calculation shows that a swellable hydrogel for such an application should expand in the gastric medium to at least 2.3 times its original dimension, or to at least 12 times its original volume. The required rate at which a swellable hydrogel should expand is dependent on many factors, which affect gastric emptying. For example, if the stomach contains only water, it takes about 25 min to have half of the consumed water depleted from the stomach. This is a good assumption to design a platform with a desirable swellability. The hydrogel would face a premature depletion from the stomach if it cannot swell to its maximum size in less than 25 min. In order to stay integrated in the gastric medium for a desirable period of time, the SPH should resist gastric contraction and expansion forces, which are maximized during the housekeeping period of the phase III stomach motility. By far, this is the most challenging part in designing SPHs for such applications. The maximum volume that the SPH can acquire in its dry state is about 0.95 ml for encapsulation into, for example, a 00 gelatin capsule. Depending on the drug loading capacity, a certain volume of the SPH is occupied by the drug or the DDS. In other words, the effective capsule volume occupied by the SPH would be around 0.6 ml. With the SPH having a density of 1 g $ml^{-1}$, the maximum feasible weight of the SPH inside the capsule would be around 0.6 g. The calculation shows that the SPH in its fully swollen state would contain about 95 wt% of water. Ironically, a hydrogel which contains 5% of solid and 95% of water should resist the very aggressive stomach forces, which requires significant intermolecular forces within the swollen SPH structure to preserve the SPH integrity in such conditions. Moreover, the SPH needs to possess all these required properties under a very low pH condition of the stomach. The SPH screened for such application also requires to be very safe chemically and physically, and this needs to be proved first in animals. As far as its efficacy is concerned, the proof of gastric retention can be first conducted

in animal models, but for many reasons the results would not necessarily prove the concept in humans. Since no animal has proved to be a reliable model for such studies, the proof of gastric retention would at best be confirmed by conducting a small-scale study in humans.

One of the most important considerations in using swellable platforms for gastric retention is the SPH–DDS interaction. Two studies have been conducted in which the drug model was formulated into a wax and a solid based delivery system. In both studies, the dissolution was performed in a USPII paddle type apparatus using 900 ml of 0.01 N HCl (pH 2.0) at $37 \pm 0.2\,^{\circ}C$ and 100 rpm. An HP8453 UV/VIS was used to measure the absorbance of the drug model at 280 nm. Different formulations were prepared by including a model drug into a low (Gelucire) and high (Compritol) molecular weight wax.[50,79] The amount of drug loaded into the wax system was about 20 wt%. An HPMC capsule was used to encapsulate both the wax and the wax-loaded SPH. The study showed that the same amount of drug is released from the wax system and the SPH–wax system when a low melting wax was used as the delivery system. On the other hand, a prolonged release was observed over a much longer period of time for the higher melting wax system. Apparently, as shown in Figure 11, the low melting wax is removed from the SPH system at the dissolution temperature of 37 °C, while the majority of the high melting wax still remains over the same retention time (i.e., 48 h) in the dissolution medium. With the latter, the SPH pores are presumably blocked by the wax, which results in a much slower drug release.

In another study, a delivery system with a drug loading of 75 wt% was designed using the combination of a fast dissolving polymer (polyvinyl pyrrolidone) and a slow dissolving polymer (hydroxypropyl methylcellulose) at different ratios.[80] While the pure drug model was released from the SPH in less than 30 min, the delivery system containing higher HPMC contents showed an extended release over a much longer period of time resembling a zero-order kinetic at the highest HPMC/PVP ratio as shown in Figure 12. These observations may be accounted for in terms of the solubility behavior of the two polymers. As the PVP is very water soluble, it can be dissolved in water even when only a small amount of water is available. On the other hand, a complete dissolution of HPMC requires much more water to be freely available to the polymer. When a tablet containing HPMC is enclosed within the SPH platform, the HPMC, due to the lack of water availability, produces a very thick gelatinous mass inside the SPH. This causes the drug to experience a much longer path for its complete release from the platform.

The proof of the gastric retention principle for various SPH hybrids has been studied in swine. The study showed that an acrylate–chitosan hybrid could provide a minimum of 24 h retention in the swine stomach under different fed and fasted conditions.[81,82] The safety and toxicity of different hydrogel formulations have been studied for gastric retention applications.[83] SPH retention in man has been studied using scintigraphy. SPHs radiolabeled with $^{99}Tc$ were encapsulated in an enteric-coated gelatin capsule and administered orally.[84] In a study on SPHs based on chitosan and glycol chitosan for gastric retention application, it was found that the swelling property of the glycol chitosan is superior to that of chitosan alone.[85] Superporous hydrogel of (acrylic acid-*co*-acrylamide)/*O*-carboxymethyl chitosan has been evaluated for oral insulin delivery. Followed by insulin loading and release, the circular dichroism (CD) spectra indicated a stable insulin conformation as well as its bioactivity according to hypoglycemic effect in mice. The hydrogel could bind to $Ca^{2+}$ and entrap enzymes, which resulted in inactivation of trypsin and α-chymotrypsin. Results of this study showed a significant hypoglycemic effect for insulin loaded into the SPH and better bioavailability compared to subcutaneous insulin injection.[86] Another study with the same polymer indicated a physical interaction between the polymer and insulin.[87] The polymer was also examined for its cytotoxicity and genotoxicity. The study showed that the SPH caused minimal damage to cell viability, lysosomal activity, and metabolic activity. A study on mice showed that the SPH which contains minute amounts of monomer and cross-linker, is truly biocompatible and can be considered a safe carrier for protein delivery.[88] Glycol chitosan SPHs were prepared and loaded with dispersed and conjugated amoxicillin to treat the

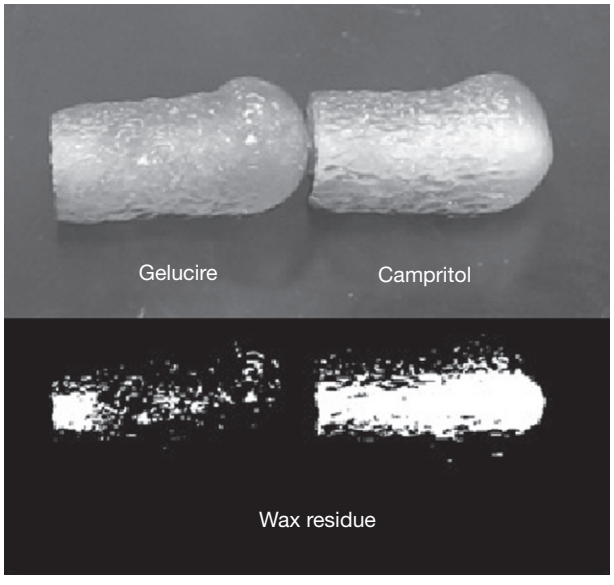


**Figure 11** Superporous hydrogel with wax-based delivery systems.

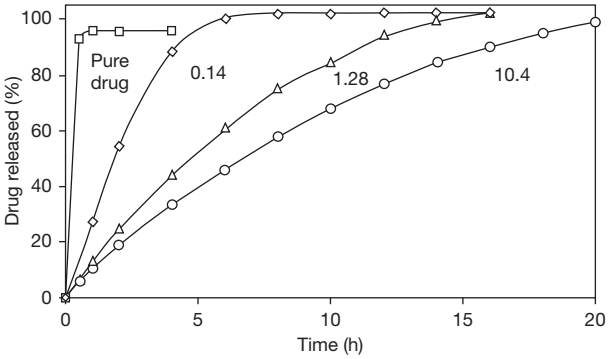


**Figure 12** Drug release from superporous hydrogel with solid-based delivery systems.

*H. pylori*. A prolonged drug delivery effect was observed for the conjugated system whose release mechanism was due to hydrolysis as opposed to diffusion for the dispersed drug.[89]

### 1.131.11.2. Peroral Intestinal Delivery

Conventional and composite generations of SPHs have been widely studied for peroral peptide and protein administration.[90] The CSPHs and SPHCs were evaluated for enhancing the drug transport (different molecular weights) across the porcine intestine (*in vitro* study).[51] Among the factors studied were the possible damage to intestinal cells, the ability of SPH for mechanical fixation, the SPH effect on paracellular drug permeability, and cytotoxicity in Caco-2 monolayers.[91] The release behavior of peptides such as buserelin, octreotide, and insulin,[92] the intestinal *in vitro* absorption of desmopressin,[93] and the mechanism of paracellular tight junction opening in the Caco-2 cells[94] have also been studied. Due to improved mechanical properties, *in vitro* mucoadhesion forces and loading capability, hydrogels based on acrylic acid-*co*-acrylamide and *O*-carboxymethyl chitosan have been proposed as a potential mucoadhesive system for peroral delivery of proteins and peptides.[95]

### 1.131.11.3. SPHs as Diet Aid

A highly swelling SPH with gastric retention ability can be designed to occupy a large portion of the stomach volume to induce fullness in humans. To achieve a sense of fullness, a minimum of 400 ml of the stomach volume should presumably be occupied by the SPH. If a pure SPH with no drug or DDS is used for this application, around 0.6 g of the SPH can be housed in a 00 capsule as mentioned before. To be effective in such application, a single 0.6 g dose of SPH should have a potency of at least 650 ml $g^{-1}$. Using conventional materials and techniques, this potency can hardly be achieved under very low acidic conditions of the stomach. Therefore, the application requires the use of multiple doses of SPH to achieve adequate volume, which brings more safety risks as related to the impurities and physical esophagus obstruction. Moreover, water itself due to the high concentration (minimum of 650 ml) should also be studied as a control to see if it can induce any fullness effect at such concentration. Potentially, an SPH platform as a diet aid may be formulated with other excipients to achieve its maximum potency. These may include excipients to adjust stomach pH or relax stomach motility.

### 1.131.11.4. SPHs as Superdisintegrant

Superdisintegrants are pharmaceutically acceptable polymers based on cellulose, poly(vinyl pyrrolidone), and starch derivatives, which have a tailor-made swelling property. These are supplied in particle form and mixed into a solid dosage formulation to offer a desirable disintegration. The SPHs are also cross-linked hydrophilic polymers, whose swelling capacity and rate can be tailored for such applications. Nonetheless, there are issues that need to be addressed before the use of SPH particles can be justified. For gastric retention, intestinal retention, and diet application, the SPH is produced and used as a single platform, generally in a cylindrical shape as shown in

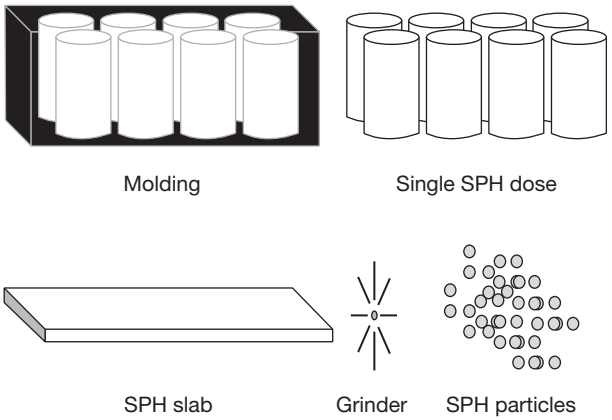


**Figure 13** Manufacturing superporous hydrogels for various applications.

Figure 13. The SPH particulates on the other hand can be produced in powder form by grinding the SPH slabs using appropriate equipment or can be produced directly in particle form by an inverse dispersion technique. With the grinding technique, which is cost effective and commercially more attractive, the most challenging issue would be to keep the production environment as dry as possible. The SPH dust can sit and make a gel coat on almost any piece of equipment during processing. A major difference between the SPH superdisintegrant and conventional superdisintegrants is that the former can provide a much larger surface due to its size and its pore content. In one study, the SPH particles, in particular those based on poly(acrylic acid) were used as a wicking agent in the formulation of fast-disintegrating tablets.[96]

### 1.131.11.5. Other Applications

Sodium CMC and hydroxyethyl cellulose cross-linked with divinyl sulphone have been used to remove body fluids during surgery and to collect body fluids in the treatment of edema. The polymer biocompatibility is also promising in diuretic therapy.[97,98] Sodium CMC and hydroxyethyl cellulose as well as poly(ethylene glycols) of different molecular weights have been used in developing orally administrable hydrogels for water absorption.[98] High capacity super water absorbents were injected intracerebrally for studying hypothalamic areas in controlling the female production cycle.[99] The SPH microspheres were used in the clinical evaluation of transcatheter arterial embolization for hypervascular metastatic bone tumor.[100] In another biomedical application, freeze-dried water absorbents were used to design plugs and haemostatic and other medical devices.[101] These were also used in compact and light-weight bags[102] and in surgical drapes[103] to manage body fluids. As the core for wound dressing, the polyacrylate water absorbents could retain microorganisms and reduce the number of viable germs.[104] Hydrogels based on sodium acrylate, *N*-vinyl pyrrolidone, and silver were also studied for their antibacterial activity[105] (see **Chapter 1.122, Structural Biomedical Polymers (Nondegradable)**).

In cell scaffolding, PEG diacrylate has been studied for cell infiltration and vascularization.[106] To be used as a support for

cell cultivation, an SPH based on HEMA and ethylene dimethacrylate has been prepared. The porosity of the structure was achieved via a salt-leaching technique using sodium chloride and ammonium persulfate. Different techniques including SEM, mercury porositometry, and dynamic desorption of nitrogen were used to characterize the hydrogels.[107] A hydrogel with good mechanical properties to function with a healthy cartilage, yet porous to allow tissue integration, is very much needed for articular cartilage repair. Such a potential material has been prepared using poly(vinyl alcohol) and poly(vinyl pyrrolidone) through a double emulsion process followed by a freezing–thawing process.[108] Superporous hydrogels have the potential to be used as scaffold for cell transplantation. A highly interconnected poly(ethylene glycol) diacrylate with macropores in the range of 100–600 μm has shown a rapid cell uptake and cell seeding.[109] The SPH formulation containing hydroxyapatite as filler can potentially be used as scaffold in bone tissue engineering due to improved mechanical strength.[110] Different techniques including FTIR, SEM/EDX, and cytocompatibility using L929 fibroblasts were utilized to characterize the prepared SPHs. A photo-cross-linking reaction and a foaming process have been utilized in developing a PEG-based superporous hydrogel with high pore interconnectivity. This feature is essential for applications such as tissue engineering where tissue invasion and nutrient transport are basic requirements.[111] Kroupova *et al.* have shown that SPHs have the potential to initiate the differentiation of embryonic stein (ES) cells[112] (see **Chapter 1.132, Dynamic Hydrogels**).

## 1.131.12. Conclusions

Due to their hydrophilic, cross-linked, and porous structure, SPH polymers display a swelling behavior different from that of conventional water swelling hydrogels. This feature has been utilized in developing swellable platforms for drug delivery applications. SPHs have been studied for prolonging the retention of drugs with a narrow window of absorption, and for peroral intestinal absorption of peptide and protein drugs. The feasibility of SPHs in pharmaceutical applications relies on many factors, including its scale up, safety, and stability. This chapter discusses the basic concepts in developing a synthetic swellable platform for certain pharmaceutical and biomedical applications.

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