Recent developments in superporous hydrogels

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Abstract

Superporous hydrogels (SPHs) were originally developed as a novel drug delivery system to retain drugs in the gastric medium. These systems should instantly swell in the stomach and maintain their integrity in the harsh stomach environment, while releasing the pharmaceutical active ingredient. For years, the synthetic features and properties of these SPH materials have been modified and improved to meet the requirements for gastric retention applications. Furthermore, an instant swelling hydrogel has also shown potential application for peroral intestinal peptide and protein absorption. This review discusses the formulation, characterization, properties and applications of these polymers.

Introduction

Drug delivery technologies are as important as new chemical entities entering into the pharmaceutical industries, allowing more effective use of existing drugs and successful development of the new drug candidates (Park 2002). Hydrogels have long been established in this field to control the release of a drug from a conventional solid dose formulation. Hydroxypropyl methylcellulose (HPMC) is the most widely used hydrogel for this application. It gradually swells in the aqueous medium and controls drug release by both diffusion and erosion. These types of hydrogels are non-crosslinked and ultimately dissolve over time in the presence of sufficient water or the swelling medium. In contrast, crosslinked hydrogels (superabsorbent) have the ability to expand in aqueous environments up to 200–700 times their own weight in the dry state. The size, porosity, hydrophilicity and crosslink density are the major factors that control the swelling rate and swelling capacity of the hydrogel. Depending on the application, the size and structural porosity of the hydrogel will be different. The use of high swelling hydrogel particles ranging from $\mu$m to mm in size is very common in the hygiene and agricultural industries. For example, the diaper industry requires an absorbent with a high degree of swelling, rapid swelling and reasonable mechanical strength. These requirements are met, for instance, by surface-crosslinked hydrogel particles in the range of few hundred microns. There are applications, however, that require larger size hydrogel mass (not necessarily particles) with rapid and extensive swelling properties. The size of a hydrogel particle inversely affects the rate of water absorption unless water absorption is dominated by a capillary or wicking mechanism. This could be achieved by utilizing superporous structures called superporous hydrogels (SPHs) (Chen et al 1999; Omidian et al 2005a).

SPHs and SPH generations

Superporous hydrogels (Figure 1) are porous hydrophilic crosslinked structures with the ability of absorbing aqueous fluids up to a few hundred times their own weight. Maximum swelling is generally reached in a fraction of a minute with SPHs having average pores of 200 $\mu$m in size.

In the preparation of SPHs certain ingredients, including initiators, crosslinkers, foam stabilizers, foaming aids and foaming agents, are added into a water-diluted monomer. The foaming of SPHs is then driven by the interaction of acids and carbonates. For instance, acetic, acrylic and hydrochloric acids are commonly used with sodium, potassium and ammonium carbonates. Since the acid–carbonate interaction is only effective in aqueous media, the solution technique is the preferred method of polymerization in the preparation of SPHs.
First generation SPH (conventional SPHs, CSPHs)

In 1999, Chen et al prepared SPHs with fast swelling kinetics and superabsorbent properties for the first time (Chen et al 1999). They polymerized and crosslinked different vinyl monomers in the presence of a foaming agent, a foam stabilizer and a foaming aid. The authors also used alcohol to dehydrate and to preserve the porous structure of the SPHs. The rate of water absorption could be increased by creating and connecting the pores inside the hydrogel structure. Different wetting agents were also investigated to further increase the rate of water absorption to less than a minute.

The building blocks of the first generation SPH were selected among highly hydrophilic (acrylamide) or ionic (salts of acrylic acid or sulfopropyl acrylate) monomers. Sucrose-based SPHs with fast swelling properties (Chen & Park 2000a) and acrylic acid and acrylamide grafted onto a PEG acrylate substrate (Huh et al 2005) have also been prepared. Regardless of their size in the dry state, the SPHs of poly (acrylamide-co-acrylic acid) could respond to the surrounding environment equivalently (Gemeinhart et al 2000a). These SPHs swell and shrink repeatedly by switching the pH of the swelling medium between 1.2 and 7.5. In the dry state, these SPHs are rigid and brittle, which makes their handling very difficult. In the swollen state, they resemble a mass of swollen gel particles, which fall apart under light loading.

Baek et al (2001), on the other hand, tried to control the swelling rate of conventional SPHs using a coating system. They coated a poly (acrylamide-co-acrylic acid) SPH with an ethanolic solution of an amphiphilic block copolymer of ethylene glycol and tetramethylethylene oxide (PEGTMO). The swelling rate of the coated SPH was delayed depending on the PEGTMO concentration. The change in hydrophilicity (as measured by contact angle) and decreased number of surface pores (as shown by scanning electron microscopy (SEM)) accounted for the slower swelling kinetics. Kim et al (2004) studied the synthesis, acidification, swelling and mechanical properties of a similar SPH. They used gelation exotherm to determine the proper time for addition of the blowing agent. Acrylic acid was found to slow the gelation rate and to decrease the SPH compressive strength. To no surprise, these gels displayed strong swelling dependency on pH because of their anionic nature.

Although a broad range of chemical crosslinkers could be used, N, N'-methylenebisacrylamide has been the crosslinker of choice for all these preparations. Pluronic F127, water, ammonium persulfate, tetramethyl ethylenediamine, sodium bicarbonate and acrylic acid have been extensively used as foam stabilizer, diluent, oxidant, reductant, foaming agent and foaming aid, respectively. Although room temperature is preferred for polymerization initiated by redox couples, there are cases for which higher temperatures have been utilized, including 60°C for 2-hydroxyethyl methacrylate, 60–85°C for N-vinyl pyrrolidone, 85°C for acrylic acid and 80°C for 2-hydroxypropyl methacrylate. Dimethyl sulfoxide (DMSO) has also been used as a diluent in the preparation of a 2-hydroxypropyl methacrylate-based CSPH.

Second generation SPH (SPH composite, SPHCs)

A major step in the evolution from the first to the second generation was to start with the same monomer, crosslinker and initiating system, but to utilize a swellable filler. Once dispersed into the reacting mixture, it would swell and absorb a mixed solution of monomer, crosslinker and initiator and the water-soluble foaming additives. The swollen filler particles would then act as an isolated individual reactor, in which polymerization and crosslinking could occur simultaneously. Since similar reactions will happen at the interface, the swollen particles would then be connected to each other through the extended polymeric chains. Upon drying, an interpenetrated network structure (IPN) would be formed. Since the whole structure is microscopically heterogeneous, this IPN-type of structure is called a non-integrated IPN. Although general features of this SPH generation remain similar to its first counterpart, this modification results in better mechanical properties.

Park et al (2001) for the first time introduced SPH composites by modifying conventional SPHs through the addition of superdisintegrants into the formulation. Crosslinked sodium carboxymethylcellulose (Ac-Di-Sol), crosslinked sodium starch glycolate (Primogel) and crosslinked polyvinyl pyrrolidone (Crosphodone) have been tried for these preparations. Chen & Park (2000b) have prepared and evaluated these SPHs for use in gastric retention applications. Kim & Park (2004) used polyethyleneimine in the preparation of poly (acrylamide-co-acrylic acid)-based SPHs. In another study, Yang et al (2004a) used poly (vinyl alcohol) to improve the mechanical properties of sulfopropyl acrylate-co-acrylic acid SPHs. In this study, they used an L9 orthogonal array to evaluate the effects of the synthetic parameters on SPH swelling and mechanical properties. Monomer composition, initiator level and polymer acidification have been evaluated.

To better understand the influential parameters affecting the mechanical properties of hydrogels and SPHs, an L18 orthogonal array was used by Omidian & Park (2002). The gel formation characteristics during the synthesis of polyacrylamide hydrogels were found to be more or less dependent on the type and concentration of the starting materials. With this study, the parameter/effect correlations were quantified and stronger SPH formulations were designed. Various approaches were further proposed by Omidian et al (2005b) to increase the mechanical properties of SPHs. A rubbery,
high modulus and rigid SPH can, respectively, be prepared by utilizing primary, secondary and tertiary approaches.

Third generation SPH (SPH hybrid, SPHHs)

Desire for enhanced mechanical properties motivated research activity towards the formulation of elastic superporous hydrogels (Omidian et al 2005b, 2006). The third generation SPHs are modified versions of the second generation and assume an integrated IPN structure. In contrast to the second generation, which uses a crosslinked hydrophilic polymer as swellable filler, a water-soluble counterpart (hybrid agent) is employed with the third generation SPH formulations. Since the additive can evenly diffuse and dissolve into the reacting solution, an integrated semi-interpenetrating network will be formed first. An integrated IPN structure will then be formed upon treating the hybrid agent. Each hybrid agent may require specific treatment. Depending on the agent type and its associated treatment, various third generation SPHs can be created, ranging from high modulus to highly elastic and rubbery (in their water-swollen states) (Omidian et al 2005b; Rocca et al 2004). Sodium alginate, sodium carboxymethyl cellulose and chitosan were found to be the most appropriate hydrocolloids with outstanding ionogelation properties. The underlying mechanism accounting for the elastic behaviour has further been discussed.

Omidian et al (2005b) used acrylamide and methylenebisacrylamide as their preferred monomer and chemical crosslinker to formulate their SPHHs. Water-soluble hydrocolloids, including sodium alginate, sodium carboxymethyl cellulose and chitosan, have been used alone or in combination as the preferred hybrid agents. To induce ionotropic gelation of these hydrocolloids, calcium, iron and phosphates have been used respectively.

Ethylenebisacrylamide has been utilized as a thermally resistant chemical crosslinker. Cerium ammonium nitrate was used to prepare grafted SPHHs. Stronger SPHHs were prepared by replacing the diacrylate crosslinker with a trifunctional acrylate. The SPHHs with lower salt sensitivity could be prepared using a quaternary ammonium salt (diallyldimethyl ammonium chloride) as a secondary monomer. Mixed ionotropic (using calcium) and chemical (using glutaraldehyde) gelation of the hydrocolloids have also been attempted with sodium alginate in the acrylamide/alginate-based SPHH preparation. Another class of SPHH polymers has been prepared based on cryogelation utilizing poly (vinyl alcohol) as a hybrid agent. To optimize the swelling and mechanical properties, the SPHHs have been treated with mixed calcium, aluminium and iron cations as described by Omidian & Rocca (2006).

The general synthetic features of the different SPH generations are summarized in Table 1. Typical swelling and mechanical properties of the first (A & B), second (C & D) and third (E & F) SPH generations are shown in Figure 2.

Miscellaneous SPHs

Development of SPHs with mechanical properties similar to that of SPHCs has been attempted utilizing different approaches, including acidification (using HCl), impregnation (using diallyldimethyl ammonium chloride or cationic polyethyleneimine or cationic resin of polyamidoamine-epichlorohydrin), rubberization (incorporating rubber emulsions), surface crosslinking (using glycerin), bulk crosslinking (using higher concentration of a chemical crosslinker), ionotropic gelation (using synthetic polymers other than hydrocolloids; e.g. polyvinyl acetate), ionotropic gelation (using ion-complexable co-monomers; e.g. acrylic acid) and thermogelation (using ovalbumine protein, egg white) (Omidian et al 2005b).

SPH characterization

Gemeinhart et al (2000b) used SEM to assess the surface morphology of conventional SPHs. They also measured the porosity of the hydrogel structure using a mercury porosimeter. They found that the swelling kinetics of the SPHs was predominantly influenced by the internal pore structure and not by surface porosity. Thangamatesvaran et al (2004) studied the structure and thermal properties of the SPH hybrids using $^{13}$C nuclear magnetic resonance (NMR) and differential scanning calorimetry (DSC). They found the glass transition temperatures of the hybrids were lower than that of the control. The authors suggested using X-ray scattering and molecular probes for further SPH characterization. Dorkoosh et al (2000) also used NMR for the structural characterization of SPH and SPH composites.

Gemeinhart et al (2001) evaluated the compression effect on SPH swelling property. They found swelling was dependent on both the force of compression and the direction of the applied force. Although compression generally slows the swelling kinetics, force applied parallel to the direction of pore formation imposed minimal effect on pore structure.

SPH properties

Swelling

The SPHs in general are mostly characterized by their swelling and mechanical properties in different media. The swelling properties are measured by weight, volume and dimension at different time intervals (to obtain swelling rate) or at equilibrium (to obtain swelling capacity). Since SPHs are mostly based on hydrophilic and ionic monomers, their swelling and mechanical properties are generally sensitive to the type and nature of the swelling medium. Ionic strength, pH, salts, organic solvents and pressure are the most important factors. The SPH swelling properties (measured by volume (VSR) or weight (WSR)) generally increase with an increase in pH, and a decrease in ionic strength, salt concentration, cation valence and pressure. Although swelling is mostly measured gravimetrically and volumetrically, a texture analyser was used to obtain the SPH swelling properties under load (Figure 3). In addition, the swelling medium can be tap water, distilled water, aqueous media of different ionic strengths and pHs, combined aqueous/organic media, simulated intestinal fluid (gastric retention application), simulated intestinal fluid (intestinal application) and so on. Moreover, swelling parameters can be evaluated at low (room temperature) or medium/high temperatures (body fluid temperature of 37°C). Another swelling parameter exclusive to the SPHs is the so-called $T_{core}$. The SPHs are opaque in their dry state and become transparent in their hydrated, swollen state. The $T_{core}$ identifies the opaque/transparent transition in SPHs.
<table>
<thead>
<tr>
<th>Formulation</th>
<th>CSPH</th>
<th>SPHC</th>
<th>SPHH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monomer: acrylic acid (AAc), salts and esters; acrylamide (AAm)</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Crosslinker</td>
<td>Diacrylate, bisAAm</td>
<td>Diacrylate, bisAAm</td>
<td>Higher MW acrylates</td>
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<tr>
<td>Solvent: water</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>Foaming agent: bicarbonates</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Foaming aid: organic and inorganic acids</td>
<td>AAc; acetic acid; hydrochloric acid</td>
<td>AAc; acetic acid</td>
<td>AAc; acetic acid; citric acid</td>
</tr>
<tr>
<td>Foam stabilizer: PEO-PPO block copolymers</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Property modifier: a material used to enhance mechanical properties; these include crosslinked and non-crosslinked hydrophilic natural and synthetic polymers</td>
<td>None</td>
<td>Superdisintegrants including crosslinked CMC; polyvinyl pyrrolidone and starch glycolate</td>
<td>Water-soluble CMC, alginate, chitosan, polyvinyl alcohol</td>
</tr>
<tr>
<td>Initiator</td>
<td>Persulfate/diamine; water-soluble azo</td>
<td>Persulfate/diamine</td>
<td>Persulfate/diamine</td>
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<tr>
<td>Post-synthesis other than purification/drying</td>
<td>No</td>
<td>No</td>
<td>Physical or chemical crosslinking</td>
</tr>
<tr>
<td>Swelling capacity</td>
<td>100–300 g g⁻¹</td>
<td>100–300 g g⁻¹</td>
<td>Up to about 50 g g⁻¹</td>
</tr>
<tr>
<td>Swelling rate</td>
<td>5–30 s</td>
<td>5–30 s</td>
<td>5 s to a few min</td>
</tr>
<tr>
<td>Mechanical properties</td>
<td>No mechanical strength</td>
<td>Resists up to 2 N cm⁻²</td>
<td>Resists up to 20–100 N cm⁻²</td>
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<tr>
<td>Treating agent</td>
<td>No</td>
<td>No</td>
<td>Ion; calcium, aluminum, iron, phosphates, copper</td>
</tr>
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<td>Water washing ability</td>
<td>Impractical because of high swelling in water</td>
<td>Very difficult, because of high swelling in water</td>
<td>Readily possible because of high strength and low swelling</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Alcohol</td>
<td>Alcohol</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Drying</td>
<td>Forced and vacuum</td>
<td>Forced/vacuum and freeze drying</td>
<td>Forced/vacuum and freeze drying</td>
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<td>Physical appearance in dried state</td>
<td>Rigid brittle</td>
<td>Rigid brittle</td>
<td>Rigid brittle</td>
</tr>
<tr>
<td>Application</td>
<td>General when high and fast swelling but no mechanical properties are required</td>
<td>Peroral intestinal absorption of peptides; superdisintegrant</td>
<td>Orally administrable swellable drug delivery system; gastric retention; biomedical</td>
</tr>
<tr>
<td>Characterization</td>
<td>Fast swelling, high swelling and weak mechanical properties; moisture-induced plasticization; fragile against bending, compression and tensile stresses</td>
<td>Fast swelling, medium swelling ratio and improved mechanical properties; moisture-induced plasticization; higher modulus networks fail under brittle fracture mechanism</td>
<td>Fast swelling, medium swelling and very high mechanical properties; moisture-induced plasticization; highly elastic in swollen state; very resistant against different stresses; ductile fracture mode</td>
</tr>
</tbody>
</table>

**Figure 2** Typical swelling and mechanical properties of the first (A, B), second (C, D) and third (E, F) SPH generations.
Superporous hydrogels Although the measurement of SPH swelling properties is straightforward, quantifying the SPH mechanical properties has been challenging. The SPHs in their swollen state are generally weak, contain pores of different sizes and their overall microstructure is very complex. Regular mechanical testers and texture analysers are commonly used to evaluate SPH mechanical properties. As shown in Figure 4, the mechanical probe of a tester touches the SPH surface at point I, and the sample will resist the applied force as the probe continues to compress at a given loading speed. At point II, the SPH starts to fail as a result of microstructure failure. From points II to III, the micro failures are magnified and result in mass breakdown. The mechanogram of this type offers three critical mechanical data. The load changes from point I to II is an indication of the sample's modulus. As seen in the graph, the soft SPH sample possesses a lower modulus, while the more rigid SPH exhibits a higher modulus, as shown by the steepness of the load/deformation change. Point II corresponds to the maximum load that the subject could resist. A rigid sample displays a higher maximum load as a result of its structural ruggedness. The mechanism by which the structure fails can clearly be seen when the load travels from point II to III. The soft sample will presumably fail under ductile mode (mild slope) while the rigid sample fails by a brittle fracture mechanism (sharp slope). Although these parameters are vital to characterize the SPH mechanical properties, there are additional concerns that need to be addressed for a special application like gastric retention.

Gastric simulator Pores inside the SPH generally vary from 100 to 1000 μm in size. Under homogeneous loading, pores of different sizes resist deformation differently. The SPH mass will break apart from its weakest point, which cannot be monitored by using regular mechanical testers. A gastric simulator (Figure 5), based on the water-hammer theory, applies a controlled amount of different types of stresses on objects immersed in the testing fluid to simulate the forces a sample might receive upon ingestion in the body. The stress concentrated on the weakest part of the SPH body will result in the formation of craze, crack and, finally, disintegration of the whole platform. The simulator measures the amount of energy absorbed by the sample until it fails under certain stresses (Figures 6 and 7). The gastric simulator has been shown to be valuable in screening formulations and in designing SPH-based gastroretentive platforms.

Safety/toxicity The safety and non-toxicity of synthetic superporous hydrogels must be demonstrated before these delivery systems can be pharmaceutically acceptable. One study investigated the safety of novel gastroretentive SPH platforms in a swine emesis model (Townsend et al 2005). The pigs (female Yorkshire) were approximately 3–4 months old and weighed 31.0–39.0 kg before dosing. Clinical observations, clinical pathology, chemistry and haematology, ethylene glycol and glycolic acid were monitored during this study. The study was also designed to evaluate SPH acute toxicity. Oral administration of up to four SPH gastroretentive platform capsules in pigs under the conditions of this study resulted in no apparent local or systemic toxic effects. Induction of emesis within approximately 45 min to 2 h post-dose did not cause any safety concerns such as oesophageal obstruction. Ethylene glycol/glycolic acid levels were below clinically acceptable values even when residence time in the stomach was 24 h. Most samples were found intact 24 h after administration (Figure 8).
Dorkoosh et al (2004a) studied the retention time of SPH composites in man using scintigraphy. The SPHC polymers were radiolabelled with Tc-99 and administered orally using an enteric-coated gelatin capsule. In the fasted state, the capsules remained in the stomach for 75–150 min post-dose and the SPHC polymers were found attached to the upper part of the small intestine for at least 45–60 min. The oral administration of SPH composites was considered safe, as human subjects reported no discomfort.

Chen et al (2000) studied the gastric retention properties of SPH composites in a beagle dog under fasted and fed conditions. They encapsulated the SPHs in 000 gelatin capsules and found gastric retention times of 2–3 and 24 h in fasted and fed conditions, respectively.

SPH hybrids with different swelling and mechanical properties were evaluated using swine as an animal model in two studies conducted by Han et al (Han et al 2003, 2004). The studies were aimed at determining the control over gastric retention based on SPH disintegration. The swine were fed a mixture of 74% ground corn, 25% extracted cooked soybean and 1% nutrition supplements. The SPHs were administered in the fed and fasted states. No noteworthy incidences (like oesophagus obstruction) were observed during or after dosing. Gels were recovered intact after 6 h in the fasted and fed states. Although some formulations remained intact up to 24 h after administration, SPH disintegration was generally found to begin after 6 h (Figure 9).

Since the friction between gel and coarse powder may affect SPH retention time, a second study was performed using a diet similar to the human diet. The animals were fed cooked rice and milk products for four days before dosing. Diets were
Superporous hydrogels balanced with vitamin and mineral premixes to supply more than adequate nutrients for animals of this class and size. Regardless of the animal diet (fed or fasted) and the presence of fine food, SPH hybrids in this study were able to offer at least 6 h gastric retention. Although presented in-vivo results indicate that these platforms may find applications as gastroretentive drug delivery systems, better-designed animal studies using more appropriate models are required to demonstrate the principle in man. A summary of both studies is shown in Table 2.

Applications

Superporous hydrogels were initially proposed as gastric retention devices. However, SPHs may be tailor-made for applications other than gastric retention in the pharmaceutical and biomedical industries and these potential uses are also discussed below.

Gastric retention devices

Over the last 2 decades there has been a multitude of approaches using well-established principles to prevent the dosage form from exiting the pylorus during gastric emptying. Rocca et al (2003, 2005) reviewed different gastroretentive drug delivery systems and highlighted the use of SPHs as novel orally administerable gastroretentive platforms. Gastric retention devices may be extremely useful for the delivery of many drugs. Such devices would be most beneficial for drugs that act locally in the stomach (e.g., antacids and antibiotics for bacteria-based ulcers), or for those drugs that are primarily absorbed in the stomach (Agyilirah et al 1991). For drugs that have a narrow absorption window (i.e., mainly absorbed from the proximal small intestine), such as riboflavin, levodopa, p-aminobenzoic acid (Ichikawa et al 1991a, b), a controlled release in the stomach would improve bioavailability. For drugs that are absorbed rapidly from the gastrointestinal tract, bioavailability could be improved by a slow release from the stomach (Hilton & Deasy 1992). Gastric retention devices can further be used for drugs that are poorly soluble in an alkaline pH medium or for drugs that degrade in the colon (e.g., metoprolol). Prolonged gastric retention, however, is not desirable for all drugs. Gastric retention is not desirable for aspirin and non-steroidal anti-inflammatory drugs, or for drugs that are unstable in acidic pH. In addition, for those drugs that are primarily absorbed in the colon, a longer gastric retention may not be necessary because the time spent in the colon can sustain blood levels for up to 24 h (Swanson et al 1987).

SPH-based gastroretentive platforms

Park et al (2005) evaluated the feasibility of chitosan and glycol chitosan hydrogels for the gastric retention application. They prepared the hydrogels after optimizing the gelation and foaming kinetics in different acidic conditions. They concluded that glycol chitosan hydrogels offer better swelling properties over the chitosan alone. Moreover, the hydrogel swelling property was found significantly dependent on the foaming/drying method, pH and crosslink density. The kinetics of the
SPH degradation has also been studied in the simulated gastric fluid (SGF).

Omidian et al (2006) prepared and evaluated a variety of SPH hybrids for this application. The major requirements for a swellable gastroretentive platform were found to be swelling rate (within minutes), swelling capacity (preferably 8–15% v/v), shape, mechanical strength (resist pressures in the range 0.5–2.0 N cm\(^{-2}\), preferably in the fed state), flexibility, a controlled disintegration, ease of drug loading, stability and pharmaceutical acceptability. Having all these concerns addressed by a single SPH platform requires careful selection of monomers and other actives, reaction conditions, type of additives, treatment method, purification and necessary steps during the entire preparation process. The SPH is prepared as a reservoir system (Figure 10) with the ability to house a drug delivery system (DDS). The DDS itself can be a controlled-release tablet or semi-solid carrier for example. The whole platform is encapsulated in a regular capsule (e.g. 00 HPMC or gelatin) for oral administration.

Feasibility of these platforms for a solid dose (tablet) or semi-solid (wax) drug delivery system has been studied (Rocca et al 2004). The tablet/platform study showed that SPH has a certain retardation effect on drug release, which was found to be dependent on the platform structure and the formulation of the tablet matrix. Figure 11 displays the SPH retardation effect as a function of the ratio of the two polymers (hydroxypropyl methylcellulose and poly (vinyl pyrrolidone)) used to formulate the tablet matrix. Theoretically, the net SPH retardation effect (for the tablet matrix of this study) is estimated if the experiment enables us to correspond an instant release of the drug to a Methocel/Povidone ratio. For the tablet matrix of this study containing Methocel K-90 and Povidone E-10 polymers, an instant release can theoretically be achieved at E-10/K-90 ratio of 0.028 (or K-90/E-10 ratio of 35.7). At this ratio, the SPH could retard the complete release of the model drug by 4 h. Depending on the tablet matrix formulation and the SPH properties, the release retardation period could presumably be shorter or longer.

SPH platforms containing a wax-based drug delivery system are shown in Figure 12. While the original size of the SPH is similar to the size of the housing system (00 HPMC capsule; 8 mm by 23 mm), the SPH dimensions substantially expand in the dissolution medium to about 27 mm and 49 mm.

Figure 13 shows the release profiles of the active ingredient imbedded into two different matrices (wax and wax/SPH systems). Upon capsule disintegration, the active ingredient is quickly released and dissolved in the dissolution medium. After about 1 h, the concentration of the active ingredient in the dissolution medium was about 100% and 30%, respectively, for the wax and the wax/SPH systems. While the active compound is almost completely released from the wax system, its release from the wax/SPH system continues in a linear trend. With Compritol 888 as a high molecular weight wax, a release of about 80% was achieved after 48 h.

In another experiment with a similar wax formulation and SPH platform, the Compritol 888 was replaced by the low-molecular-weight Gelucire 43/01. As shown in Figure 14, the SPH was shown to impose no retarding effect on drug release.

**Gastroretentive tablets**

Common processes of dry blending and direct compression have been used to make gastroretentive tablets. The SPH particles of acrylic acid/sulfopropyl acrylate copolymers were mixed with gelatin and tannic acid, then tableted by direct compression. Hydrogen bonding between gelatin and tannic acid, as well as the carboxyl groups on the polymeric carrier, create an integrated matrix, which was shown to be stable after swelling. In a 40-min period, the gastroretentive tablet could swell up to 30 times its own volume while maintaining its original shape. Furthermore, the swollen tablet could withstand up to 16 KPa compression force before breaking apart. Depending on the pH of the swelling medium, the gelatin can be replaced by carboxymethylcellulose or other polysaccharides (Omidian et al 2005b).

**Peroral peptide delivery systems**

The feasibility of using CSPHs and SPHCs for peroral peptide delivery has been investigated (Dorkoosh et al 2002a, b, c). These systems are designed to swell in the intestine with the SPH physically adhering to the gut wall and delivering the incorporated peptide directly to the site. The carboxyl-carrying SPHCs can potentially induce calcium extraction, presumably causing the tight junctions of the gut wall to open and deactivating the harmful gut enzymes. After peptide delivery and absorption across the gut wall, the SPH becomes overhydrated and is broken apart by the peristaltic forces of the gut. The proper selection of the type and thickness of enteric coating will potentially help to target this dosage form to any specific site in the small intestine or to the colon.

Dorkoosh et al (2002d) used conventional SPH and SPH composites to enhance the transport of N-alpha-benzoyl-L-
arginine ethylester (BAEE) and fluorescein isothiocyanate-dextran 4400 (FD4) across porcine intestinal epithelium. They found that SPH composites could increase BAEE and FD4 transport across the intestinal mucosa by 2–3 fold. The SPH composites did not change the morphology of the intestinal lumen in this study. The authors claim the SPH could presumably open the tight junctions in Caco-2-cell monolayers, by which the drug transport would be facilitated. This study and similar studies anticipate a promising application for the SPH composites in enhancing the intestinal absorption of peptide and protein drugs, including buserelin, octreotide, insulin and desmopressin (Dorkoosh et al 2001, 2002c, e, f, g, 2004b; Polnok et al 2004).

**Fast-dissolving tablets**

Fast-dissolving tablets are orally administered without the need for water and swallowing. This feature is especially beneficial to children and the elderly. Freeze-drying, sublimation and direct compression are utilized to make fast-melting tablets. The first two methods make tablets that dissolve in 5–15s, but the technology is rather expensive and tablets are not mechanically strong. One way of making fast-dissolving tablets by the direct compression method is to add fine particles of SPH to the granulation or powder formulation. The SPH microparticles within the tablet core expedite water absorption by an increased wicking mechanism. Tablets prepared by direct compression in the presence of SPH microparticles disintegrate in less than 10 s (Park 2002).

Yang et al (2004b) used poly (acrylic acid)-based SPH microparticles to make fast-melting tablets of ketoprofen. They evaluated the disintegration time and tensile strength of the tablet as a function of active concentration, SPH particle size, filler and tableting pressure. The tablets could swell to about 80 and 50 times in distilled water and 0.2 M phosphate buffer, respectively. Tablets prepared with 2.5% w/w SPH microparticles (75–106 μm) under 63 MPa pressure displayed a tensile strength of 84.4±4.1 N cm⁻² and disintegration time of 15.0±2.0s.

**Chemoembolization and occlusion devices**

Chemoembolization is a combined method of embolization and chemotherapy (Jayakrishnan et al 1994). Embolization has been used for cancer treatment by restricting the oxygen supply to the growing tumours. This method could be combined with chemotherapeutic agents to achieve local delivery and low systemic toxicity. A chemotherapeutic agent...
and an anti-angiogenic agent could be loaded into SPHs for chemoembolization therapy. The strong SPHs would likely be better candidates for this application as they fit better in the blood vessels and provide better blocking.

SPHs can also be used to develop biomedical devices for treating aneurysms. After determining the size and shape of an aneurysm site, an equivalent SPH is prepared in smaller size. Because of the rapid and extensive swelling properties, the hydrogel will swell at the aneurysm site and clot the blood (Tellez et al. 1998). Studies have shown that the SPH results in a 95% aneurysm occlusion without parent artery compromise and without inflammatory response. New occlusion devices are also under investigation (Tellez et al. 1998). One such system, known as Hydrocoil, consists of SPH and platinum coils, and is currently under development by Microvention, Inc (Park 2002).

**Development of diet aid**

Diet soft drinks, meal replacement shakes, diet drugs and even surgical methods have been used to lose weight. Because of their rapid and extensive swelling, the SPHs can theoretically occupy a significant portion of the stomach space, leaving less space for food, and hence suppressing appetite (Park 2002). This type of system has the potential to facilitate weight loss in obese people. The major challenges to using SPHs as a weight loss aid will be to maintain the integrity and volume of the swollen SPH for a substantial period of time.

**Other applications**

SPHs can be used in industries other than pharmaceutical and biomedical, where rapid and extensive swelling in an aqueous medium are major requirements. Hygiene, agriculture, horticulture, pet, toy and many other industries may benefit from the use of SPHs in their products. As shown with the superabsorbent polymers (Omidian et al. 2004), children can enjoy the immediate swelling of SPHs and learn the associated science and knowledge. The SPHs can be coloured and may find decorative applications. SPHs quickly absorb moisture from the surrounding environment and may be a suitable substitute for silica gel. The high swelling pressure of SPHs can potentially be used to trigger an alarm system upon the incursion of water. Applications of SPHs will be further realized as scientists in different disciplines become aware of the unique properties of these new materials.

**Conclusions**

Superporous hydrogels are a new class of hydrogel materials that, regardless of their original size, rapidly swell to a large size. Different generations of SPHs evolved to address the needs for certain pharmaceutical applications, including gastric retention. Studies have shown that some SPH formulations are potentially exploitable for heavy-duty applications in which superb swelling and mechanical properties are required in harsh swelling media. The feasibility of using these SPHs in oral solid and semi-solid dose formulations have also been studied. Preliminary safety and efficacy of certain SPH formulations have been evaluated in-vivo, paving the way for further development of these materials for pharmaceutical, food and biomedical applications.

**References**


