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Drug delivery applications for superporous hydrogels

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Introduction: Considerable advances have been made to hydrogels with the development of faster swelling superporous hydrogels (SPHs). These new-generation hydrogels have large numbers of interconnected pores, giving them the capacity to absorb large amounts of water at an accelerated rate. This gives SPHs the ability to be used in a variety of novel drug delivery applications, such as gastric retention and peroral intestinal delivery of proteins and peptides.

Areas covered: This review focuses on the applications of SPHs for drug transport and targeted drug therapies, as well as the characteristics and historical advancements made to SPH synthesis as it pertains to drug delivery. Manufacturing considerations and challenges that must be overcome are also discussed, such as scale-up, biocompatibility and safety.

Expert opinion: Modern SPHs have high swelling and high mechanical strength making them suitable for many diverse pharmaceutical and biomedical applications. However, demonstrative preclinical animal studies still need to be confirmed in human trials, to further address safety issues and confirm therapeutic success when using SPHs as platforms for drug delivery. The focus of forthcoming applications of SPHs is likely to be in the area of oral site-specific delivery and regenerative medicine.

Keywords: diet aid, drug delivery, gastric retention drug delivery, gastroretentive dosage form, hybrid hydrogels, intestinal drug delivery, peroral protein delivery, superdisintegrant, superporous hybrid hydrogels, superporous hydrogels

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1. Introduction

Development of pharmaceutical dosage forms typically begins when a new chemical entity is identified and ends when drug release from the formulation has been properly controlled. A more recent trend has been to develop novel drug delivery systems that improve the bioavailability and therapeutic response of currently approved drugs. In both cases, hydrogel polymers are often used in the formulation to regulate and control drug release. Hydrogels are made of hydrophilic polymers that have been cross-linked to form a continuous network, capable of absorbing water and other aqueous fluids.

The ability of hydrogels, in particular superporous hydrogels (SPHs), to control water mobility has led to increased research focused on using them as possible solutions to modern drug delivery challenges. This is because water plays an important role in just about every oral dosage form. Water not only helps to operate the controlled-release mechanisms of various delivery devices, but is also needed for dissolution of the active drug.

SPHs, as first presented by Chen *et al.* in 1999 [1], can be explained as a special type of porous hydrogel having a three-dimensional cross-linked network containing large numbers of interconnected and open pores. The mobility of the SPH polymer chains is restricted by physical and/or chemical cross-linking. The

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Article highlights.

- Characteristics of superporous hydrogels (SPHs), such as pH and temperature sensitivity, which may be modified to change the swelling capabilities and provide specific drug delivery.
- The different generations that SPHs have progressed through in the development of mechanically stronger hydrogels with improved swelling kinetics. Research highlighting the synthesis and characterization of various SPH generations.
- Delivery systems made from SPH and the loading of drug into such systems for gastric retention, peroral intestinal delivery and other applications.
- Manufacturing and scale-up for producing SPHs beyond pilot batches. Also challenges that must be overcome for successful synthesis are mentioned.
- Characterization of an SPH product. Preclinical and clinical data suggesting the feasibility of their use.

This box summarizes key points contained in the article.

equilibrium swelling capacity in SPHs ranging from 50 to 500 g/g can be reached in several minutes or as fast as a few seconds. Since the pores are open and interconnected, swelling rate is independent of the SPH size in the dry state [2]. The pore sizes of SPHs average a few hundred micrometers [3] and, along with pore content, morphology, and isotropicity, can affect the final SPH properties (**Figure 1**). Ordinarily, SPHs display isotropic swelling and, therefore, maintain their overall original shape as they imbibe fluids. However, the shape of the pores can cause a certain degree of anisotropic swelling [4]. As pore shape becomes more circular, the greater is the tendency for isotropic swelling.

The fast-swelling and high swelling capacity of SPHs is attractive for pharmaceutical applications, notably in gastric retentive drug delivery systems [5]. In this application, an SPH is used to prevent quick passage of a drug-loaded hydrogel into the small intestine after oral administration, enhancing bioavailability of drugs with narrow absorption windows [6].

This paper is intended to review the applications and challenges with using SPHs in the pharmaceutical area of drug delivery and formulation.

2. Important characteristics of SPHs

SPHs are attractive in drug delivery because they can be made to react to different external stimuli such as changes to their environment. Through proper selection of monomers, stimuli-sensitive hydrogel can be made. These smart polymers are adept in reacting to changes in their swelling medium and microenvironment. They react by increasing or decreasing their swelling capacity, which in turn corresponds to a change in their three-dimensional size. When an SPH is loaded with a drug, these changes can alter the release characteristics of the drug into the aqueous surroundings. For drug delivery applications, SPHs that react to temperature and pH are commonly designed and is a characteristic frequently studied. Moreover, the kinetics and thermodynamics of the swelling, mechanical properties and pore features of an SPH structure may be adjusted to meet the requirements in specific drug delivery application as proposed in **Table 1**.

For example, Gemeinhart *et al.* showed that an SPH synthesized from acrylamide and acrylic acid monomers could display repeated swelling and shrinking at different pHs, swelling at pH 7.5 and shrinking at pH 1.2 [7]. Equilibrium swelling ratios were, therefore, higher as the pH of the swelling medium increased. This can partially be explained by acrylic acid being protonated at the low pH and lacking a charge, compared with being ionized and more hydrophilic at higher pH. SPH based on methacrylic acid and acrylamide also showed enhanced swelling at basic pH levels [8]. A novel hydrogel produced by ionic cross-linking of chitosan with itaconic acid followed by polymerization and cross-linking with methacrylic acid produced a pH-sensitive hydrogel [9]. The equilibrium swelling was lowest at a low pH and greatest at pH 6 – 8. A dramatic change in swelling is seen depending on the ionization state of the COOH group. At a higher pH, the carboxylic groups of the acids are ionized leading to higher swelling due to enhanced osmotic and electrostatic forces. By understanding factors responsible for the swelling process, modifications to an SPH can be made to achieve a desired result.

Polymer–water interactions are important and serve as the basis for the swelling process in all types of hydrogels. The swelling process itself begins when an SPH is placed in water or other aqueous solutions. This process is first dominated by the attractive forces of the hydrophilic and ionic functional groups in the hydrogel structure. The swelling process continues until each of the functional groups is surrounded by the same amount of water. Next, as water tries to further dilute the polymer chains, an osmotic effect is created that continues to fill open pores with water until opposed by the contractive forces of the cross-linked hydrogel structure [10]. Water that is closer and surrounding functional groups is held ‘tighter’ than water at farther distances. This causes different water layers to form around each hydrophilic or ionized group. The water in each layer is generally defined as being either free or bound, reflecting the strength of the polymer–water interaction. The weakest held water in the outermost layer is easily removable, whereas water in the bound layers is more difficult to remove during drying.

3. SPH generations

The formation of pores into a hydrogel structure creates the necessary surface area needed for absorption of large amounts of fluid. In general, porous hydrogels are named according to their average pore diameters. When pore sizes become sufficiently large and in the range of 1 – 100 µm, they are termed macroporous hydrogels, while the pores in SPHs range in size between 10 and 1000 µm [11]. Various methods such as phase

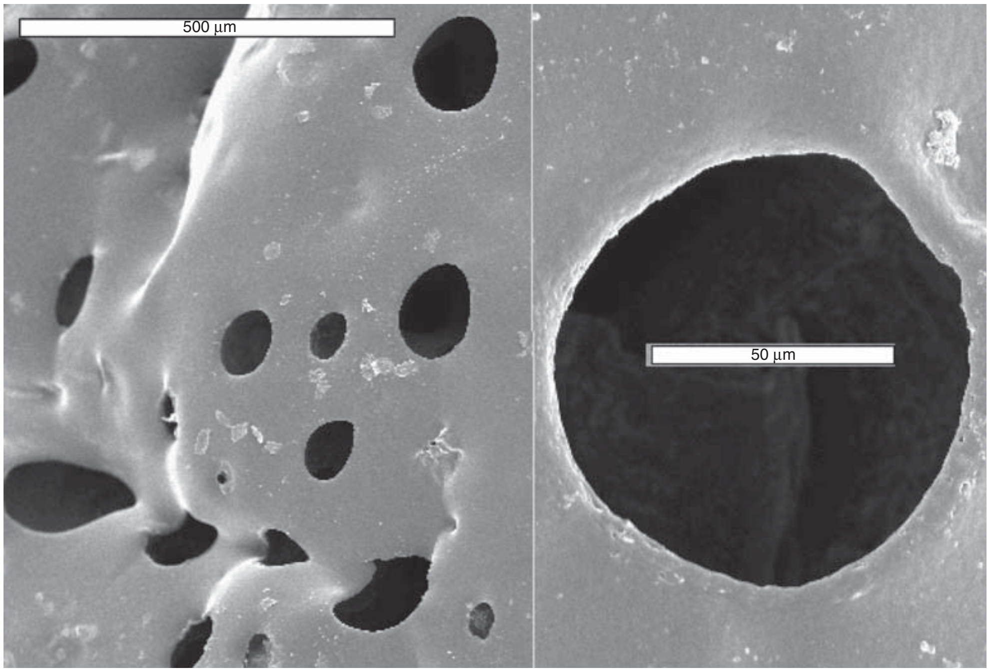

Figure 1. SEM micrograph of a superporous hydrogel hybrid.

Table 1. Modifiable superporous hydrogel (SPH) properties.

Characteristic	Comments
Temperature sensitivity	Reverse thermoresponsive hydrogels using *N*-isopropylacrylamide and methacrylamide monomers [66]; appropriate when temperature is a feasible tool to stimulate the hydrogel swelling, providing a swelling–shrinking cycle
pH sensitivity	pH-sensitive SPHs utilizing monomers such as acrylic acid [7,67], methacrylic acid [9], diethyl dimethyl ammonium chloride; appropriate when pH is a feasible tool to stimulate the hydrogel swelling, providing a swelling–shrinking cycle
Structural neutrality	Neutral SPH polymers using acrylamide, hydroxyethyl acrylate, hydroxyethyl methacrylate [68] as major monomers
Structural flexibility	Flexible and rigid SPH structures by selecting hydrophilic monomers based on glass transition temperature of their final polymers; alkyl acrylates in general provide structural flexibility and ionizing monomers provide rigidity
Swelling capacity	Improved by selecting more hydrophilic, and ionizing monomers [69]; sensitive to the ionic strength of the swelling medium [70]; improved by less pore volume; measured by weight, dimension or volume difference in hydrogel before and after swelling
Swelling rate	Improved by enhanced water-loving functionality such as carboxyl, hydroxyl, amine; improved by pore volume and smaller pore size; measured by weight, dimension or volume increase over time; kinetics order dependent on the hydrogel cross-link density [71], zero order is favored at high cross-link density
Mechanical property in swollen state	Enhanced strength is required when swelling occurs in pressurized environments and in the presence of external mechanical forces; improved by preparing semi- and fully interpenetrated structures, with less porosity and more solid content; enhanced by smaller pores and even pore size distribution; measured under static and dynamic testing in dry and swollen states in different swelling media [72-75]
Pores	Increases air content of the SPH, facilitates swelling, decreases mechanical properties, decreases stability; generally smaller pore size and polydispersity close to one is preferred; definite effect of pore morphology on swelling [76]; measured by techniques such as porosimetry, scanning electron microscopy, liquid replacement method

separation [12], emulsions [13], porogens [14,15], and freeze drying [16,17] can produce porous hydrogels. However, SPHs are largely synthesized using a gas blowing technique where foaming and gelation processes are perfectly timed [11].

Solution polymerization using the gas blowing technique is essentially a desirable approach to prepare SPHs. For such synthesis, an aqueous mixture consisting of monomer, crosslinker, foam stabilizer and foaming aid is made in a reaction vessel. The components are added sequentially and mixed to form a homogeneous mixture. A reductant and oxidant are then added consecutively and quickly mixed; this redox pair will serve as the polymerization initiator. Next, a foaming agent is added that reacts with the foaming aid (e.g., organic acid) to generate carbon dioxide gas. As the CO_2 gas rises and tries to escape, it foams and creates interconnected pores stabilized by the added foam stabilizer. During the time when the foaming agent is undergoing acid-induced decomposition, it is also neutralizing the mixture. The increase in pH favors decomposition of the initiator and accelerates polymerization. However, there is a lag time before a fast polymerization reaction is seen, due to a retarding effect from oxygen present in the environment [18]. The timing of when the foaming agent is added in relation to the start of polymerization is very critical in producing homogeneous SPHs. The whole process is optimized when gelation occurs simultaneously with foam formation [19]. If the gelling reaction occurs before the foaming reaction has started, the viscosity of the reaction mixture becomes too viscous for proper foam formation. Conversely, when the foam is produced too early, it will begin to collapse and fall before polymerization has occurred. At the completion of a successful synthesis, the SPH is washed and purified to remove residual monomer and other remaining reaction components. It is then subjected to various drying techniques to form a useable product. The first SPHs contained only one monomer in the reaction solution. The resultant hydrogels had large swelling capabilities but were brittle and extremely fragile in their swollen state (**Figure 2**).

Attempts to change certain properties of SPH for specific applications gave rise to different generations being formed. As the generations progressed, changes in mechanical strength and elastic properties were most often being optimized. To a certain extent, the first generation has many commonalities with superabsorbent polymers (SAP) currently being used in the hygiene and agriculture industries. Extensive differences between SAP and SPH, along with explicit details regarding the advancements of SPH generations, can be found in a review by Omidian *et al.* [20]. Important characteristics indicative of the different SPH generations are summarized in **Table 2**.

Many researchers have developed SPHs with various characteristics useful for drug delivery. Reports of such work typically focus on the swelling behavior, mechanical strength, biocompatibility and drug release from these hydrogels. The first SPHs were commonly prepared using acrylic acid and acrylamide. These monomers were used because of their high water affinity and availability for commercial applications. Further development produced SPHs with enhanced properties such as improved mechanical strength and swelling capabilities. Progression in research on the fabrication and characterization of various SPHs are listed in **Table 3**.

4. SPH drug delivery applications

For applications involving drug delivery, an SPH will typically serve as a vehicle into which the drug or therapeutically active component is incorporated. Different methods exist for how the drug and the SPH are assembled together to deliver the drug. The SPH can be used as a shuttle or reservoir device into which is placed a drug delivery system such as a tablet [21,22] or microparticles [23]. Alternatively, the SPH can be soaked in a solution containing the dissolved drug, allowing absorption of the aqueous drug mixture until the SPH is fully swollen [24]. The saturated SPH is then dried, leaving behind the drug throughout the hydrogel open-pore structures. The last method is the least attractive option, being challenged with impurity, purification and drug-loading issues. In this process, the drug is incorporated into the reaction mixture during hydrogel synthesis, creating a network of drug and polymer through the matrix [17,25].

For many gastric retention and peroral delivery platforms, the SPH is used to carry a solid delivery system containing the drug. The solid delivery system, such as a minitablet, is placed into a specially designed SPH delivery platform. When formulating the solid delivery system, interactions between any added excipients and the SPH need to be considered in addition to drug–SPH interactions. The placement of the drug delivery system in the SPH can either be in the center, completely surrounded by the hydrogel, or be attached to the sides. Depending on this placement, they may be termed internal or external respectively (**Figure 3**).

When making an internal delivery platform, the solid drug delivery system is placed in the center of the SPH through a man-made borehole. This hole is then closed by placing in a suitable SPH plug, essentially sealing in the drug delivery system on all sides. Before oral administration, this whole platform must be encapsulated inside an appropriately sized capsule shell. If the system is being used as a gastric retention internal platform, on being swallowed, the capsule will dissolve in the stomach and release the SPH platform into the gastric environment. In the stomach juices, the SPH will immediately swell around the solid drug core, leading to a slow drug release mainly by diffusion [26,27]. Depending on the wet strength of the SPH in stomach juices, erosion of swollen SPH layers may occur, shortening the drug diffusional path and expediting its release.

For an external delivery platform, the solid drug delivery system is attached externally to the side of the SPH. This is accomplished by making a hole(s) on the outside portion of the SPH platform. Then biocompatible glue (e.g., cyanoacrylate) is used to affix the solid drug system in the hole, partially inside the

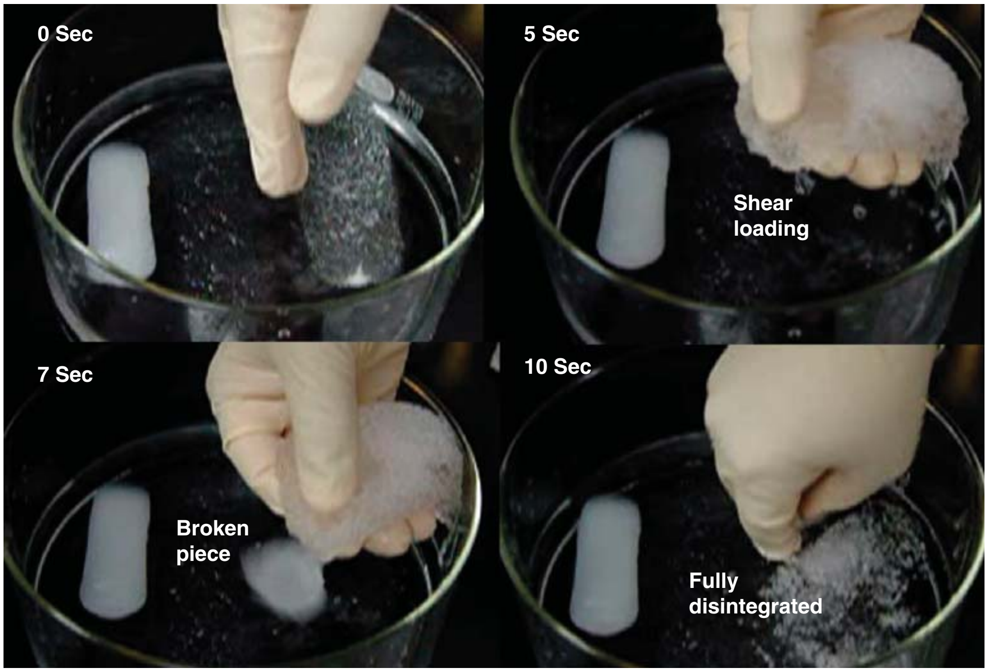

Figure 2. A first-generation superporous hydrogel with high swelling and no mechanical strength in its swollen state.

Table 2. Superporous hydrogel (SPH) generations.

First SPH generation	Also called conventional SPHs; interconnected porous hydrogel; high swelling but poor wet strength; infeasible for practical use; composed of very hydrophilic monomers (e.g., acrylamide and acrylic acid) or ionic monomers (e.g., sodium acrylate, potassium acrylate); excessive multiple layers of hydration; hydrated layers with various mechanical property [1,77]
Second SPH generation	Also called SPH composites (SPHC); a two-polymer system; contain a swellable filler such as pharmaceutical superdisintegrants; physical chain entanglement between the two systems; offer improved mechanical properties over first generation [78,79,41]
Third SPH generation	Also called SPH hybrids (SPHH); offer high mechanical elastic properties; a two-polymer system; fully interpenetrated hydrogel structure; combined chemical and physical cross-linking [80,81,20]

structure. The entire platform is then encapsulated as before. If the system is being used for peroral intestinal delivery, the capsule would be enterically coated to prevent dissolution in the stomach after dosing. When exposed to the higher pH of the intestines, the enteric coating and capsule dissolve, eventually freeing the SPH platform. This allows the platform to immediately swell, causing enlargement in size sufficient enough to forcibly push against the walls of the intestine. The externally exposed solid drug delivery system is now held against the intestinal wall and can directly release the drug through the intestinal epithelial cells [23,28].

4.1 Gastric retention

The ability to prolong the retention time of a drug in the stomach was the original purpose envisioned for SPHs in drug delivery. Drugs that are mainly absorbed in the stomach, drugs with narrow absorption windows and drugs used to treat conditions locally in the stomach were initially thought to benefit from this novel innovation. Drugs that have only a small area over which they are able to be absorbed in the intestines are often referred to as having narrow absorption windows. These drugs are typically absorbed only in the upper part of the intestine, and efforts to produce a controlled-release product have, therefore, been challenging. A gastric retentive product containing a narrow absorption window drug would work by having the drug remain in the gut, ‘upstream’ of the absorption site. Drug would then slowly be released from the product and travel ‘downstream,’ allowing a continuous supply of drug to pass over the site of absorption. Therefore, any drug that is released in the vicinity ahead of or in close proximity to the absorption site will be readily bioavailable. However, once the drug has passed the absorption segment, little if any will be absorbed. The limited time for absorption of these drugs as they travel along the

Table 3. Research on Superporous hydrogels (SPHs).

Polymer composition	Highlights and remarks
Poly(AA-co-AM)	Rapid swelling and superabsorbent properties [1]; less swelling and better mechanical strength at low pH [67]; Swelling and *in vitro* release studies of the SPH loaded with carvedilol self-nanoemulsifying drug delivery system [82]
Poly(AA-co-AM) coated with poly(ethylene glycol-*b*-tetramethylene oxide)	Slowed down kinetics through reducing pore numbers and increasing hydrophobicity with no significant effect on mechanical strength and equilibrium swelling [83]
Poly(AA-co-AM) grafted with poly(ethylene glycol)	Improved swelling kinetics, up to six times faster compared with ungrafted [84]
Poly(AA-co-AM) semi-interpenetrated with polyethyleneimine	Increased swollen mechanical strength but slower swelling kinetics [11]
Poly(AA-co-AM) semi-interpenetrated with chitosan or glycol chitosan	Both had greater swelling at low pH; the more hydrophilic glycol chitosan to a greater degree [85]
Poly(AA-co-AM) fully interpenetrated with sodium alginate	Mechanical strength was increased and swelling ratios were shown to be dependent on pH and ionic strength [86]
Poly(AM)	Taguchi experimental design to determine effect of different ingredient formulations on final properties of hydrogel; examined inhibition period, exothermic period, gelation maximum temperature, solubility, physical appearance at gelation point [87]; higher amounts of calcium carbonate microparticles as blowing agent increased swelling; higher cross-linking concentration decrease swelling [88]
Poly(AA)	Studied effect of different initiator concentrations; looked at reaction kinetics and final swelling properties using a Voigt-based viscoelastic model [89]; higher cross-linking concentrations decreased gelation time, produced higher porosity, higher concentrations demonstrated less sensitive swelling in saline solution [71]; two foaming agents have synergistic effect on swelling properties [90]
Kaolin-loaded poly(AA)	Improved strength and thermal stability; reduced swelling capacity and rate [91]
Poly(AM) fully interpenetrated with alginate	Improved mechanical and elastic properties in swollen state [80]
pHEMA	Three different porogens studied, cyclohexanol, dodecan-1-ol, saccharose; produced macro-sized pores having closed pore structure [92]. Taguchi matrix to determine the effect of starting materials and starting temperatures [93,94]
pHEMA fully interpenetrated with acrylic acid	Improved swelling and strength [94,95]
Poly(3-sulfopropyl acrylate, potassium salt) semi-interpenetrated with poly(vinyl alcohol)	Improved mechanical strength in the swollen state; suitable for use as a gastric retention device [96]
AM, AA, acrylonitrile, 3-sulfopropyl acrylate	Interpenetrated with polyacrylonitrile; significant improvements in compression and elasticity [97]
Glycol chitosan/poly(vinyl alcohol)	Exposed to various freezing/thawing cycles to form fully interpenetrating network; mechanical strength was affected more by the number of cycles than on freezing times; minimizes the use of toxic chemicals [98]
Glycol chitosan	No interpenetrated network; parameters such as polymer solution concentration and effect of sample dimensions on swelling were determined; pH sensitive [99]
Poly(NIPAM)	Made porous with the use of network silica nanoparticles, silica extracted to produce a nanoporous structure; temperature-dependent deswelling was substantially increased in the nanoporous hydrogel than from nonporous hydrogel [100]

Table 3. Research on Superporous hydrogels (SPHs) (continued).

Polymer composition	Highlights and remarks
Poly(NIPAM-co-AM)	Thermoresponsive, 30 cm^3 change in volume when increased from 10°C up to 65°C; hydrophobic interactions are favored at higher temperatures, causing a decrease in hydrophilic interactions and lower water affinity [77]
CMC-NIPAM copolymer	Irradiation cross-linking; swelling properties depended on composition and applied irradiation dose; foaming agent enhanced pore structure; biodegradable [101]
Sucrogels (Sucrose-based SPH)	Made by reacting sucrose with glycidyl acrylate, this is followed by polymerization with the gas blowing agent, faster swelling and degradation over a large pH range compared with non-superporous sucrogels [102]
Starch based with and without AA as comonomer	Biodegradable; all hydrogels were enzymatically degraded in the presence of 280 units of α-amylase per gram. After 10 h of enzymatic treatment, only about 20% of the original hydrogel mass remained and only hydrogel fractures were observed [103]
Poly(HEMA-co-AA) grafted onto xanthan gum	Improved thermal stability; pH-dependent swelling; swelling was decreased in salt solution and depended on concentration and salt used; biodegradable [104]

gastrointestinal (GI) tract led researchers toward gastric retention devices as a possible solution. By retaining a drug in the stomach and regulating its release over time, continuous drug absorption over a controlled time period may occur. This can lead to an increase in the extent to which the drug is absorbed. In addition, those drugs that are best absorbed in the high pH of the stomach, or that may be unstable in other parts of the GI tract, may benefit from gastric retention to improve bioavailability. Furthermore, drug treatments for conditions such as stomach cancers and ulcers may become more effective when used with a gastric retention device that can prolong local action of the drug in the stomach. For example, to treat the gastric bacterial pathogen *Helicobacter pylori*, which resides deep within stomach mucous layers, gastric retention devices have been formulated to provide the prolonged local action needed for effective treatment [29]. Methods for retaining drugs in the stomach other than swellable SPHs include devices such as floating systems [30,31], magnetic systems [32], floating ion exchange resins [33] and mucoadhesion [34].

The use of an SPH for gastric retention applications requires that the platform quickly swell to a size large enough to be retained in the stomach after being swallowed. Failure to swell to a sufficient size will cause passage of the platform through the pyloric sphincter (average diameter 1.5 – 2 cm) and into the small intestines. To provide ease of oral administration and prevent premature swelling, an SPH platform must be compressed and placed into a suitable size capsule. A 00 size capsule generally fulfills this requirement. An SPH platform that is encapsulated into a 00 capsule must quickly swell to about 12 times its initial volume to be retained in the stomach (**Figure 4**).

Many factors can influence gastric emptying rates and affect the speed at which an SPH must swell after entering the stomach. For instance, a quicker gastric emptying rate will require an SPH with faster kinetic swelling properties. Inter- and intra-gastric emptying rates are variable and factors such as food, drink and calorie content of a meal also add to the variations. To minimize such deviances when using a gastroretentive SPH platform, a fasting state is suggested and only water should be taken during administration. Drinking just water on a fasted stomach will require about 25 min for 50% of the volume to empty into the intestines. Hence, maximum swelling for an SPH should occur within 10 – 15 min for successful retention. However, a true fasting-state gastric retention study may still result in inconsistent retention data due to intra- and inter-subject variability.

The mechanical strength of the platform must also be sufficient to withstand the gastric contraction and expansion forces of digestion that mix food and force stomach contents into the small intestine. Conversely, it must be weak enough to eventually disintegrate and allow passage throughout the entire GI tract. The most powerful gastric contractions occur during what are called ‘housekeeper waves,’ where peristaltic contractions empty the stomach of all contents in sweeping waves. The design of the SPH platform must be sufficiently

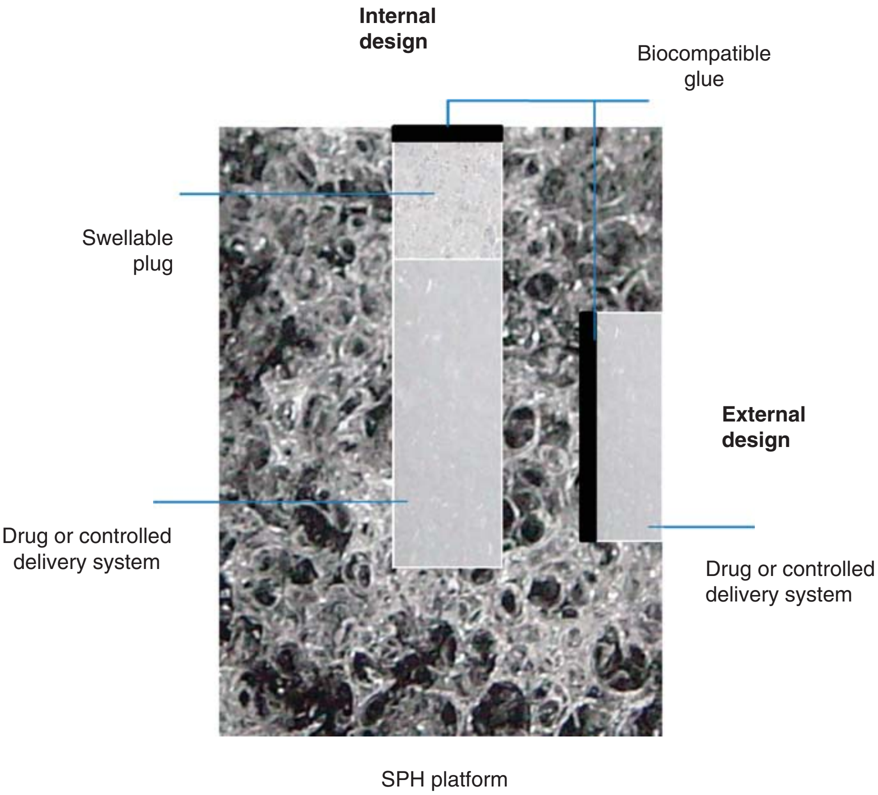

Figure 3. Superporous hydrogel platform with external and internal drug delivery systems.

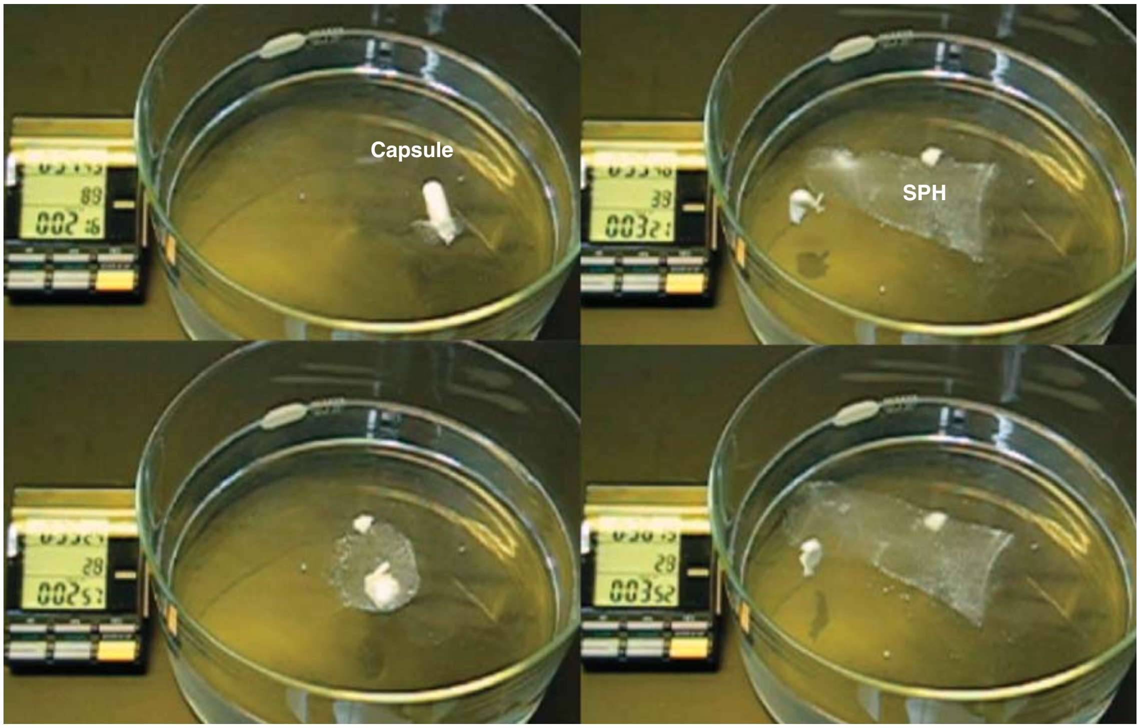

Figure 4. Swelling kinetics of a high swelling superporous hydrogel loaded into a 00 capsule.

durable, but flexible enough to retain its shape when exposed to gastric motility forces in its fully swollen state as represented in **Figure 5**. In addition, the required swelling and mechanical forces must be maintained in the acidic environment of the stomach. Starting in the dry state, both the drug (solid drug delivery system) and the SPH must fit into the volume space of a 00 capsule. This then limits the solid content the SPH may be composed of when trying to provide for stronger mechanical forces.

The solid drug delivery system that is incorporated into an SPH gastric platform can be formulated to release drug at various rates from within the hydrogel network. For example, different drug delivery devices were made using various ratios of a slow-dissolving hydroxypropyl methylcellulose (HPMC) and fast-dissolving poly(vinylpyrrolidone) polymers and placed into an acrylate ester-based SPH platform [35]. The higher the content of HPMC the more prolonged the drug release was and the closer it followed a zero-order release profile. The fast-dissolving polymer showed little effect on drug release, possibly due to its quick dissolution in the testing medium.

Park *et al.* looked at the swelling characteristics of chitosan- and glycol chitosan-based SPHs in simulated gastric fluid to evaluate their potential as gastric retention platforms [36]. Glycol chitosan showed better swelling properties due to its more hydrophilic structure; this swelling was dependent on the pH and was reduced at higher cross-linking ratios. In other experiments, the glycol chitosan SPHs were loaded with the antibiotic amoxicillin through either physical dispersion or chemical conjugation [37]. Sustained release of the drug was achieved only when amoxicillin was formed as a prodrug through conjugation. Slower release kinetics may be more favorable in applications where a prolonged or sustained release of drug is needed in the gastric environment. Chitosan SPHs were loaded with the drug rosiglitazone and displayed pH-responsive swelling [38]. The chitosan SPH was later interpenetrated with poly(vinyl alcohol) and again loaded with the drug rosiglitazone [39]. This stronger hydrogel showed the same high swelling ratios at low pH and may serve as an ideal platform for drugs such as rosiglitazone, which are unstable at basic pH and extensively absorbed in the stomach.

4.2 Peroral intestinal delivery

SPHs can be designed to delay rapid swelling in the stomach and instead swell once they have entered into the intestinal tract. By use of different coatings at different thicknesses, an SPH platform can be targeted to various regions in the GI tract. A large amount of research for peroral intestinal delivery using SPHs has focused on protein and peptide drugs.

4.2.1 *Protein/peptide drug delivery*

The desire for an oral delivery system that can safely deliver peptides and proteins to the GI tract for proper absorption is currently of great interest, especially with the rise in biotechnology products. Such delivery devices are advantageous since oral delivery still remains the most convenient and patient-friendly way for drug administration. However, protein and peptide drugs must primarily be given by the parenteral routes since oral bioavailability of these macromolecules is extremely low. The oral route poses an immediate threat to protein stability and activity. The digestive enzymes present in the stomach can cause degradation and quickly lead to inactivation of the protein or peptide. Bioavailability is also threatened due to the poor permeability of the intestinal epithelium to these macromolecules. A novel dosage form capable of delivering these drugs must have the ability to stabilize, protect and promote intestinal absorption.

The special properties of SPHs may be exploited to produce delivery systems capable of transporting proteins and peptides for both local action to the GI tract and for systemic absorption following oral administration. An SPH platform used in peroral intestinal delivery must first protect the drug from the acid environment of the stomach. Next, it has to achieve maximum swelling at an ideal spot along the intestines. Enlargement of the delivery platform during rapid swelling causes it to adhere onto the intestinal wall by mechanical pressure. During this swelling and subsequent attachment, the applied mechanical pressure disrupts and opens the intestinal epithelial tight junctions [40]. Large molecules are then able to pass between the epithelial cells by paracellular absorption. Together, the prolonged residence time and physical attachment of the SPH platform to intestinal wall help improve bioavailability. Potential interactions between the drug (protein) and the polymer chains of the SPH must also not be overlooked as a potential threat to decreased absorption or activity. The main characteristic needed of an SPH platform for peroral intestinal delivery is that it can physically hold the dosage form at the site of absorption. Additionally, the mechanical strength must be strong enough to resist peristaltic movements of the intestines while being weak enough to break up over time.

SPHs are also thought to inactivate intestinal proteolytic enzymes such as trypsin. The ability of SPHs to inhibit proteolytic enzymes is thought to be due to the entrapment of calcium by carboxylate ions. Therefore, studies looking at trypsin inhibition and Ca^{2+} binding are often done when exploring an SPH for possible peroral delivery of proteins. Before an SPH releases its protein or peptide drug load, a lag time should exist to allow for inactivation of luminal enzymes and opening of tight junctions by the swollen hydrogel [21].

Dorkoosh *et al.* synthesized a conventional first-generation SPH using poly(acrylic acid-co-acrylamide) (poly(AA-co-AM)) and a second-generation SPH composite by addition of Ac-Di-Sol® as a composite agent [41]. Both first- and second-generation SPHs were characterized for their potential as oral delivery systems for site-specific delivery of proteins and peptides to the intestine [21]. Results demonstrated *in vitro* that both could partially inhibit trypsin, possibly by the uptake of Ca^{2+} ions. The safety and mechanical fixation

Figure 5. A third-generation superporous hydrogel hybrid with elastic property in its swollen state.

of these hydrogel platforms were later proven by the lack of morphological damage and strong attachment to porcine intestinal epithelium *ex vivo* [28]. Dorkoosh *et al.* also evaluated paracellular peptide drug permeability enhancement through Caco-2 cell monolayers by these SPHs and superporous hydrogel composites (SPHCs), and further examined their cytotoxicity effects [42]. Stability and *in vitro* drug release characteristics were determined using the different molecular weight peptide drugs of buserelin, octreotide and insulin from the SPH and SPHC platforms [43]. Using an external delivery platform, solid tablets containing desmopressin were attached to the side of the second-generation SPH, and *in vitro* absorption across porcine intestinal membranes was shown to be enhanced [22]. A study in nondiabetic pigs showed that these SPH and SPHC in both internal and external platforms enhanced insulin plasma levels compared with an oral insulin solution; however, the glucose-lowering effect was not substantial [44].

Insulin is a prevalently used peptide drug that has to be injected for use; therefore, a great desire exists to produce an oral dosage form capable of delivering this drug by the oral route. Improving on the mechanical strength of the third-generation SPHs, Yin *et al.* studied an interpenetrating hydrogel network based on poly(AA-co-AM) and *O*-carboxymethyl chitosan with enhanced mechanical properties [24]. This SPH was sensitive to changes in pH, having a lower swelling in acid conditions and greater swelling near physiological pH [45]. This study also determined biocompatibility of the SPH, making it an excellent vehicle for site-specific delivery to the more basic environment of the intestines. When loaded with insulin, this hydrogel was able to prevent protein degradation from the proteolytic enzymes trypsin and α-chymotrypsin while preserving bioactivity following release *in vitro* [46]. Additionally, *in vivo* absorption studies in rat (using an enteric-coated capsule containing insulin-loaded polymer) showed the capability of this platform to lower glucose. A relative pharmacological bioavailability of 4.1% was calculated from this hypoglycemic effect compared with subcutaneous (SQ) insulin injection. Very low concentrations of residual monomer and cross-linker were found in this type of SPH, and cytotoxicity and genotoxicity studies further demonstrated a safe and biocompatible drug vehicle [47]. Yin *et al.* also compared the absorption mechanisms and enzyme inhibition differences between two insulin-loaded SPHs, where one was made as a single intact unit and the other was broken up into smaller particles creating a powder [48]. The intact form showed enhanced paracellular permeation, and when given orally to rats, a hypoglycemic effect was shown; the particle form of the SPH was ineffective. It was concluded that an SPH should remain intact and quickly swell to mechanically fixate itself to the intestinal wall, otherwise a reduction in particle size may lower high swelling ratios, lessen fixation and lead to reduced permeation enhancement. Tang *et al.* incorporated aqueous solutions of Carbopol® into a poly (AA-co-AM) SPH to improve mucoadhesion and swelling behavior [49]. Further research was done to prepare these hydrogels as a carrier for insulin and other hydrophilic macromolecules for peroral delivery.

The SPHs were soaked in an insulin solution and later dried. The hydrogels demonstrated pH-dependent swelling with minimal swelling rations at pH 1 and higher ratios at pH 7.4. *In vitro* release studies in pH 7.4 phosphate-buffered saline showed rapid release of insulin (90%) within 30 min and almost complete release after 1 h, ideal for peroral insulin delivery [24].

Graft polymerization of acrylic acid was done on the backbone of superporous polyacrylamide gels using potassium diperiodatocuprate. The grafted hydrogels demonstrated higher swelling as pH increased and an improved binding capacity for high-molecular weight lysozyme protein as the degree of grafting increased [50]. Temperature-sensitive macroporous poly(*N*-isopropylacrylamide) (poly(NIPAM)) hydrogels were prepared in aqueous sodium chloride solutions [51]. Performing the polymerization in the salt solution gave rise to hydrogels of improved swelling and swelling response. Release of bovine serum albumin from these SPHs was shown to be controlled by a change in temperature; greater release was seen at lower temperatures whereas higher temperatures closed the pores slowing the release. Biocompatibility studies further demonstrated the SPHs' practicality as a delivery system for peroral protein/peptide delivery.

4.2.2 *Other delivery systems*

Macromolecules are not the only type of drug that may benefit from peroral intestinal delivery. For example, drugs that cause side effects such as stomach irritation, peptic ulcers, nausea or vomiting could benefit from delaying their release till passage into the intestine. Hence, intestinal drug delivery using SPHs could be a useful therapeutic option. This approach was used to make a stimuli-sensitive pectin-based SPH loaded with the nonsteroidal anti-inflammatory drug (NSAID) ibuprofen [52]. When taken orally, NSAIDs commonly cause nausea, heartburn, stomach pains and ulceration. Release of ibuprofen from the pectin-based SPHs was dependent on many factors including pH, temperature and hydrogel porosity. This biodegradable hydrogel reacted to changes in its environment, releasing minimal ibuprofen at pH 1.2 (14%) and greater ibuprofen at a higher pH 7.4 (79%), making it an ideal SPH platform for targeted drug delivery to the intestines. Proton pump inhibitors (PPIs) are another class of drugs that may benefit from peroral intestinal delivery from SPHs. These drugs are generally acid labile and are commonly coated with an enteric coating to delay release until the proximal small intestine where absorption is greatest [53]. Poly(methacrylic acid-co-acrylamide) interpenetrated with Ac-Di-Sol was used as a carrier for the PPI drug pantoprazole [8]. FT-IR analysis demonstrated polymer–drug compatibility in dried SPHs that were soaked in a solution of the drug. Additionally, the hydrogels showed pH-dependent swelling, increasing with an increase in pH. Drug release was shown to be minimal (3%) at low pH but increased over time at a pH of 7.4, indicating possible use of this SPH for site-specific delivery to the intestines.

4.3 Diet aid SPHs

One strategy for weight loss is to restrict or decrease food consumption, and subsequent caloric intake per day. This is a challenging feat and some have even resorted to surgical methods such as gastric bypass and laparoscopic gastric banding. The idea behind these surgical approaches is to decrease the space in the stomach for food and cause satiety after only small amounts of a meal are taken. An SPH that can swell and be retained in the gastric environment may be a nonsurgical alternative to achieve satiety. A high-swelling SPH with gastric retention properties can occupy a significant space in the stomach and leave less room for food and beverage. For a sense of satiety to be felt, it is approximated that at least 400 ml of stomach space be occupied by an SPH. With the swelling capacity of current SPHs in acid mediums, multiple doses (assuming 00 capsule size) would be needed to achieve this volume. The administration of multiple doses may subject a patient to an increased risk of esophageal obstruction. Simultaneous multiple doses may also cause abrupt exposure to high levels of residual monomers and other impurities leading to a safety concern [54].

Large amounts of water must additionally be consumed with each dose for proper swelling of the SPHs. This makes it more difficult to determine whether the true feeling of fullness is due to the SPHs, the high concentration of water in the stomach or both. Published research in this area is lacking; however, future research may explore the use of excipients that enhance swelling or include therapeutically active components that decrease motility and prolong gastric retention.

4.4 SPH as superdisintegrants

The fast-swelling SPHs have found use as superdisintegrants in solid dosage forms. The disintegration process starts when a solid dosage form breaks apart in an aqueous environment, allowing release of the active ingredient for dissolution. When a superdisintegrant is added as an excipient in the tableting formulation, it can increase the speed and efficiency of disintegration at lower levels compared with standard disintegrants. Polymers such as poly(vinylpyrrolidone), cellulose and starch-based derivatives have been cross-linked and manufactured for this purpose. The use of SPHs for this application is possible since they are hydrophilic, cross-linked, quickly expand on swelling and can be tailored to optimize a product's disintegration.

For use as a superdisintegrant, an SPH must be made into a particle form. A single SPH unit may be synthesized and then mechanically ground to an appropriate particle size to be used as a tableting excipient [55]. Another proposed approach may be to synthesis the SPH using an inverse dispersion technique that will result in small-particle formations during the polymerization step. The first approach by grinding may be more attractive commercially due to a lower production cost and ease of processing [56]. However, the hygroscopic nature of SPH requires manufacturing to be conducted in a very dry environment.

Porous microparticles based on poly(acrylic acid) have been prepared and used as a superdisintegrant to make fast-disintegrating tablets [57]. The superdisintegrant particles can swell up to 80 times in distilled water and 50 times in pH 6.8 phosphate buffer and were used to make ketoprofen tablets [55]. The tablets were formulated to disintegrate/dissolve quickly in the mouth with little or no water, and demonstrated disintegration times as fast as 15 sec.

4.5 Biomedical applications of SPH

SPHs are also gaining popularity in the biomedical field. The porous nature and extensive biocompatible surface area allow for numerous sites of cell attachment and growth, ideal for serving as cell scaffolding. SPHs based on poly(2-hydroxyethyl methacrylate) (pHEMA) are popular in this area of tissue engineering [58]. For example, a pHEMA-based SPH can be used as a scaffold for bone tissue-engineering applications [59]. Also pHEMA–gelatin SPHs and glycerol phosphate-cross-linked pHEMA–gelatin SPHs are potential scaffolds for similar applications [59]. When poly(ethylene glycol) diacrylate SPH scaffolds were implanted into the dorsal skin of mice, vascularization was seen within the hydrogel network, demonstrating possible use for future implantable tissue-engineering applications [60].

Other biomedical applications of swellable hydrophilic hydrogels such as a combined chemotherapy and embolizing (chemoembolization) therapy for cancer [61] and treatment for aneurysms [62] are being studied. In terms of porous structure, Cavilink™ polymers having micrometer-sized and interconnected pores are very similar to SPHs. However, the Cavilink™ polymers are generally based on hydrophobic polymers, mainly polystyrene and polymethyl methacrylate [63]. Therefore, they do not swell in water and are lyophobic, whereas SPHs are mainly hydrophilic and lyophilic. Further biomedical and drug delivery applications are likely to come about in the future as technology and innovation continue to progress at a rapid rate.

5. Manufacturing considerations for SPH

An important process for pharmaceutical consideration of SPHs in drug delivery is the ability to take laboratory pilot synthesis to a larger scale, including full production. Just because a batch is successful at a smaller scale does not ensure its success on a larger scale. Producing a consistent and well-characterized product will be necessary for approval by regulatory agencies. Range and variances for specific characterizations such as pore size and its distribution, mechanical strength and swelling must be maintained and reproducible in production. This will allow for proper identification and characterization of the SPH dosage form. In addition to producing a well-characterized product, safety and efficacy must also be established. The safety of any drug product is of top concern for patients and regulatory agencies alike. Therefore, an SPH being used for any application must demonstrate safety and the absence of toxicity. The safety of SPHs may be addressed by demonstrating biocompatibility and purity of the final product. Also the SPH platform itself must be safe to take both on administration and throughout its duration of use. Since SPHs are subject to degradation over time, unwanted byproducts may be produced from interactions with their surrounding environment on long-term storage. Understanding the changes that can alter the identity of an SPH will allow for techniques that minimize or eliminate them, producing a more stable product. All these manufacturing challenges, including scale-up, identity, purity, potency and safety of SPHs are addressed in **Table 4**.

6. Preclinical and clinical studies

To gain acceptance by regulatory agencies, clinical trials must be performed for an SPH drug product. Clinical trials are needed to further establish safety and efficacy, the beginnings of which are preclinical studies in animals. To characterize the pharmacokinetics of a new SPH drug product, drug bioavailability studies will be needed. The literature demonstrating *in vivo* feasibility and bioavailability of various drug products from SPHs is lacking. However, protein and peptide drug delivery has moved very much forward and is emphasized below.

Preclinical studies using SPH drug delivery systems for peroral intestinal delivery are useful in determining different factors. They help define the systemic availability of the drug from the SPH platform, the therapeutic blood levels obtainable after administration and absorption rate or lag time. These factors can be measured using percent relative or absolute bioavailability (F%), maximum blood concentration (C_{max}) and time for maximum drug concentration to occur (T_{max}).

Dorkoosh *et al.* performed studies in healthy pigs to assess the intestinal absorption of insulin using an SPHC as the main carrier for both internal and external drug delivery systems [44]. The internal platform was loaded with insulin microparticles and the external platform had insulin-based minitabs attached. The platforms were administered via intraduodenal fistula and insulin test solution served as a control. Relative bioavailability was determined using SQ injection as the reference standard. As seen in **Table 5**, both internal and external delivery devices increased insulin plasma levels compared with test solution. However, this increase in systemic insulin provided only minimal hypoglycemia, especially as compared with SQ injection. Bioavailability values were relatively low but did provide up to a 3.8-fold increase compared with the insulin test solution. In another study, insulin-soaked SPH hybrids were dried and either kept intact or powdered into microparticles before being placed into enteric-coated capsules [48]. The two different-type capsules were given orally to rats with plasma insulin levels and glucose levels being monitored. Insulin solution was given orally to act as a control and SQ injection was used to measure relative bioavailability. No appreciable amount of insulin was absorbed after the oral insulin solution or when the microparticle-containing capsules were given. The capsules

Table 4. Manufacturing and production challenges for superporous hydrogels (SPHs).

Scale-up	
High heat of polymerization	Exothermic reaction needs to be controlled; SPHs tend to insulate and trap heat; temperature increases lead to faster gas formation, faster polymerization and cause popcorn polymerization; maximize surface area of reaction vessel for optimal heat dissipation
Foaming-agent dispersion	Homogeneous dispersion must occur rapidly; needed for uniform pore formation; improper dispersion leads to local hot spots and heterogeneous product; alter foaming agent particle size to control reaction
SPH identity	
Water	Stability of product will depend on controlling water in and around hydrogel; residual water may cause hydrolysis of susceptible functional groups; environment must be low in moisture due to hygroscopic nature of SPH; desiccants such a silica gel can be used for storage; proper drying techniques such as freeze-drying can minimize residual moisture
Oxygen	Oxidation can be problematic for stability of susceptible functional groups; residual water increases fluidity of hydrogel (plasticizing effect) and ease of oxygen inclusion; oxidation produces color change in material from white to pale yellow; use of an appropriate antioxidant may reduce occurrence
Light	Absorption of high-energy ultraviolet light may lead to photodegradation of susceptible functional groups; should be investigated if product will be exposed to light; can be prevented with suitable packaging and storage materials including amber-colored or opaque bottles, cardboard or foil outer wrappers
SPH purity	
Byproduct formation	Can be formed during reactions such as hydrolysis or oxidation occurring on the SPH or between the SPH and drug/excipients; may occur during storage or use; oral SPH products may form byproducts from interactions with food, beverage or gastric acid; analytical techniques must be capable of identifying these byproducts
Residual impurities	Residual byproducts from unused components during manufacturing; improve purity by use of low or high glass transition monomers, different washing methods, and separation techniques including rubbing, filtration, centrifugation, compression and cutting [105]; polymerization by gamma ray irradiation eliminates use of certain contaminants [106]; sterilization of product occurs during radiation polymerization [107]; porous nature of SPHs facilitates removal of contaminants by washing; washing techniques must have final stage to rid residual water
Analytical tests	Validated analytical methods are needed to identify all byproducts for safety and to establish proper expiration date through which the strength and potency of the product can be assured
SPH potency	
Swelling power	Potency can be defined as swelling power; must be maintained during shelf life; on long-term storage entanglement or complexation with ions may occur causing cross-linking in the structure and changes swelling kinetics; encapsulated products may have interaction between components possibly reducing swelling; during encapsulation proper compression orientation is essential to keep pores open; food and beverage can affect swelling; salt intake affects osmotic pressures and fats/oil will not be attracted toward the hydrophilic polymer network; swelling behavior may change when a liquid with varying pH values are used as the swelling medium [108]
Measurement	Measured by how much fluid a standard weight of the SPH (e.g., one gram) can absorb over time
SPH safety	
Oral administration	Fast-swelling properties increase risk of esophageal obstruction; SPH must be properly encapsulated or protected to prevent premature exposure on swallowing; no adverse effects should occur after being exposure to both single and multiple doses
Biocompatibility	Biocompatibility must be established as product will be exposed to body and body fluids; SPH must allow body to function without adverse effects such as allergic reaction and cytotoxicity; leaching of residual components such as monomer may be harmful, corrosion or formation of toxic byproducts can occur along the GI tract; biocompatibility shown for first- and second-generation SPH measuring cytotoxicity in Caco-2 monolayers [42] and monitoring morphological changes in porcine intestinal epithelia [28], and in third generation by showing no significant cell or mucosal damage to rat intestine morphology [86]

containing the intact hydrogel showed a delay in insulin absorption, peaking at about 4 h with good bioavailability compared with SQ injection as shown in **Table 5**. The glucose-lowering effect from the intact capsules was significant, almost 50% of that at time zero. This hypoglycemia was still less than that observed from SQ injection but was more prolonged. A different study used octreotide loaded into an external delivery platform (minitablet) and as an internal delivery platform (microparticles) was performed to monitor oral absorption in a pig model [23]. This time a penetration enhancer (trimethyl chitosan chloride) was added to the external delivery platform. The absolute bioavailability of all formulations was much higher than that of control solution and the penetration enhancer was shown to be beneficial (**Table 5**).

No clinical trials showing pharmacokinetic profiles of drugs from SPH platforms were found in our literature search. However, the proof of principle for the delivery platform itself has been studied. The retention time of a possible peroral intestinal delivery SPHC made of poly(AA-co-AM) interpenetrated with Ac-Di-Sol was studied in man. The SPHC was radiolabeled with Tc-99 m, encapsulated, enteric coated and then given to fasting volunteers who were being monitored by gamma camera [64]. Passage of the intact capsule into the intestines occurred between 75 and 150 min. Once emptied from the stomach, the retention time in the upper small intestine ranged from 45 to 60 min. The full residence time in the small intestine was not determined as the study protocol required the test to end 3 – 4 h after ingestion. However, no discomfort was reported by the volunteers up to 48 h post dose.

For gastric retention purposes, an SPHC was encapsulated and given orally to dogs to investigate retention times [65]. During the SPHC synthesis, $BaSO_4$ pellets were incorporated and used as an X-ray marker. The swollen hydrogels remained in the stomach for 2 – 3 h before being broken apart. When given in the fed state with subsequent fasting, the SPHC remained in the stomach for more than 24 h.

7. Conclusion

The use of SPHs in drug delivery is primarily based on controlling the influx rate of aqueous solutions into the hydrogel. Therefore, when incorporated into a product, swelling properties is what may ultimately determine drug release. Some pharmaceutical applications require fast water transport into the hydrogel structure while others may require slower or more controlled swelling. SPHs can easily be manipulated to achieve these properties and will potentially play a part in controlled and targeted drug delivery in the upcoming years.

8. Expert opinion

A successful oral drug delivery platform that uses SPHs is expected to meet certain criteria including safety, effectiveness, desirable drug loading and release, feasible manufacturing as well as minimum interactions with gastric contents.

Safety: The safety is determined by having an SPH that is pure of residual components and stable throughout its duration of use and during its full shelf life. This will require a detailed knowledge of the source(s) of impurities, analytical methods capable of identifying them and other possible threats from synthesis to use. Another important safety aspect that is common to all swellable platforms, including SPHs, is the risk of esophagus obstruction during oral administration. Once these factors have been recognized and addressed accordingly, the SPH platform can be evaluated for purity utilizing validated and reliable *in vitro* analytical test methods and equipment. Evaluation of safety and biocompatibility of the SPHs can then move forward to test in an appropriate animal model at low and high doses before advancing to human trials.

Effectiveness: A chemically and physically safe SPH platform requires possessing a desirable swelling and mechanical property profile. For gastric retention, swelling should ideally occur within 10 min following administration and enlarge to a size greater than the pylorus to avoid passage. Moreover, the swollen SPH must be resistant to the harsh chemical and mechanical environment of the stomach, requiring stability in the low gastric pH and during dynamic contraction and expansion forces. However, such physical stability must be followed by an appropriate and effective degradation mechanism to ensure a safe removal of the SPH after its service is done. For such purpose, well-designed *in vitro* swelling and mechanical testing are needed in conjunction with a small-scale human trial as part of the proof-of-principle studies.

Manufacturing: Of special consideration is the physical structural homogeneity of the SPH platform, achieved with a cost-effective purity profile. The former is critically determined by the effective and even dispersion of the reactive foaming agent into the system. This requires that the gelling and foaming reactions occur simultaneously in a well-synchronized manner. The purity profile, on the other hand, is vitally dependent on the synthesis variables, as well as pore parameters. All these need to be well identified and addressed properly. Studying new ways of polymerization and foaming, as well as using non-polymerizing systems devoid of small reactive chemicals will help combat these issues.

Drug loading and encapsulation: Active drug should not be present in the reaction solution during the polymerization process, but rather be incorporated later on during the manufacturing process. This is because the produced SPHs still have to be treated to remove residual components left over from the polymerization reaction. The washing process will simply remove drug and defeat the purpose of loading into the platform. After the fully formed SPH platform is designed, it must ultimately be reduced in size and encapsulated. The use of larger capsule sizes such as 000 may be a deterrent for patient compliance as they are generally too big to swallow and typically reserved for vaginal and rectal use. Producing an oral product that

Table 5. Superporous hydrogel (SPH) bioavailability studies for peroral intestinal delivery.

SPH composition and platforms	F%	T_{max} (min)	C_{max}	Drug	Animal model	Ref.
Poly(AA-co-AM) + Ac-Di-Sol®				Insulin	Pig	[44]
External delivery platform	1.3*	90	27 µU/ml			
Internal delivery platform	1.9*	60	35 µU/ml			
Insulin test solution	0.5	n/a	8.7 µU/ml			
SQ injection	RS	30	55 µU/ml			
Poly(AA-co-AM)/*O*-carboxymethyl chitosan				Insulin	Rat	[48]
SPHH (encapsulated-intact)	5*	240§	55 µU/ml§			
SQ injection	RS	30§	130 µU/ml§			
Poly(AA-co-AM) + Ac-Di-Sol				Octreotide	Pig	[23]
External delivery platform	8.7‡	250	152.0 ng/ml			
External + penetration enhancer	16.1‡	285	157.9 ng/ml			
Internal delivery platform	12.7‡	252	175.9 ng/ml			
Drug only	1.0‡	245	17.8 ng/ml			
i.v. Injection	RS	n/a	n/a			

Not all test formulations are shown.
*Relative bioavailability.
‡Absolute bioavailability.
§Estimated from graph.
F: Bioavailability; RS: Reference standard for F; SPHH: Superporous hydrogel hybrid; poly(AA-co-AM): Poly(acrylic acid-co-acrylamide); SQ: Subcutaneous.

uses the smallest capsule size will, therefore, become important in development. Care must also be taken that the SPH is not retained in the stomach or intestines after repeated uses, which can lead to blockages or malabsorption of food, nutrients and other drugs. Biodegradable polymer platforms may be used to decrease these risks. Nonetheless, oral delivery is still preferred and may always be the 'gold standard.' Since injections are high in cost, painful and inconvenient to patients, this may help drive the area of research for peroral intestinal delivery and absorption of biopharmaceutical drug products. If absorption and efficacy can be demonstrated in clinical trial, SPHs may become a safe platform for drug delivery in the future.

Drug release: A well-controlled release rate of the drug is desirable with minimal SPH–drug interactions. For success, the SPH chemical and physical structures and essential formulation and processing excipients should be carefully selected based on the chemical structure of the active pharmaceutical ingredient.

SPH platform design: Either internal or external, the designed SPH drug delivery platforms are reliant on a biocompatible adhesive that is needed to attach the drug delivery system to the SPH shuttle. Since the SPH is expected to serve in its swollen state, the adhesive property of the glue line should remain stable in the presence of aqueous medium at low or high pHs when utilized in gastric retention and peroral intestinal delivery applications. Furthermore, the shape of the SPH shuttle should avoid stress concentration areas such as straight lines in the periphery of the structure. Under local stress caused by the contraction and expansion forces of the GI tract, weak areas of the structure can abruptly break apart and undesirably cause a premature disintegration of the whole shuttle structure.

Pharmaceutical development of SPH: Since traditional pharmaceutical companies are lacking the infrastructure needed to develop a successful SPH carrier for any particular drug, in all likelihood the development must be outsourced to a third manufacturing party. This adds more steps to the approval process of such novel platforms being used for pharmaceutical applications.

Characterization and analytical aspects: An SPH platform is an extremely porous structure; therefore, porosity (pore volume, pore size, pore size distribution, pore shape) will play a major role in the swelling, mechanical properties and drug release profile from the SPH. Consequently, pore morphology and structure of the SPHs should be completely characterized for further utilization. Of greatest importance, the complete structure of the polymer itself should be identified and characterized using appropriate analytical equipment and assays.

SPH mechanical properties: The SPH structure is being used as a carrier for the active ingredient. Therefore, desirable gastric retention or intestinal retention can be achieved only if the SPH possesses adequate mechanical strength to resist the different forces in the service environment. Apparently, such forces will be of different nature depending on the SPH application. Identifying these forces and lack of experimental methods that can realistically evaluate the SPH platforms under forced conditions would remain a major challenge for a formulation scientist.

SPH prospect: Due to a wide spectrum of materials that can be used for SPH synthesis, together with their broad swelling, mechanical properties, biocompatibility and proven safety, the SPHs have a great potential for use in controlled delivery. Their range is far reaching, capable of transporting current chemical entities, enhancing absorption of small and large macromolecules, serving as platforms for cell growth and being used as novel medical therapies.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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