8

Fast-Responsive Macroporous Hydrogels

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CONTENTS

8.1 Introduction

In 1960, the history of synthetic hydrogels witnessed the first generation of its application in the biomedical field. Wichterle and Lim developed the first biomaterial hydrogel based on 2-hydroxyethyl methacrylate [1]. Since then, more and more hydrogels have been introduced with biomedical and pharmaceutical applications. Interestingly, all these developments have been somehow associated with the microstructure of these hydrogels rather than with their chemical structure. Hydrogel is generally a two-phase composite network of water and solid hydrogel. The hydrogel itself is a synthetic or natural-based hydrophilic polymer with the strong ability to interact

intra- and intermolecularly with itself and with water. These two interactions are generally controlled by the composite makeup, in other words, the hydrogel structure and the amount of water inside the hydrogel. As a result, the composite is provided with properties that are known as swelling thermodynamics (capacity), swelling kinetics (rate), as well as mechanical properties.

Swelling is determined by the nature and the hydrophilic lipophilic balance (HLB) of the hydrogel that is the function of the amounts and nature of functional and side groups as well as ions. The higher the HLB value of the hydrogel, the more hydrophilic the structure is, and hence the superior will be the swelling properties. This property dictates how a hydrogel chain should approach and interact with water as the second component. As the HLB value of the hydrogel increases, affinity to the water molecules increases; this in turn increases the amount of bound water inside the hydrogel structure. Although the solid phase of the composite (the hydrogel) supplies the swelling forces and mechanical properties, the liquid phase of the composite (water) dictates the quality of these properties.

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Water normally acts as a plasticizer for the solid hydrogel that increases the diffusion of a given component (e.g., drug, oxygen, etc.) into the solid matrix. Water controls the distance between the polymer chains by which the rate of diffusion into the hydrogel structure will be controlled. Water generally acts as a mass transfer medium to control the amount of transferring material and the rate of transfer process. On the other hand, although more water facilitates the transfer process, it adversely affects the hydrogel mechanical properties. Water resides between the hydrated polymer chains and provides weak regions with less resistance to the external forces.

Thermodynamically, a hydrogel as a system is required to respond to the surroundings, which is water or an aqueous medium. Although hydrogels are entitled to respond to water because of their structure, their response rate has been challenging for many applications. By far, the most interesting but hidden property of a hydrogel is its ability to change a one-dimensional transport process to a two-dimensional process. Transport process in a solid hydrogel may be exampled to driving a car on the road, which is one-dimensional and its degree of freedom is small. Adding water into the system increases the degree of freedom and hence facilitates the transport process. An analogy to this is if a car and road are replaced by a ship and sea respectively. For the applications in which a fast diffusion is very desirable, even these hydrogels fail to perform desirably. This requires an addition of another dimension to the transport process, which then requires an addition of another phase to the composite.

A three-dimensional transport process can be achieved by adding or incorporating air into the composite. Air provides a path for an airplane in which it can move at a much faster rate and with infinite degrees of freedom. Air does the same thing in a hydrogel composite comprising solid polymer, water and air. Air provides an additional transport path or diffusion path into the hydrogel structure, by which diffusion or the transport process will

be expedited to a significant level. On the other hand, air replaces some portion of the hydrogel body, which is responsible for the hydrogel mechanical and swelling properties. It will be no surprise that the addition of air will be accompanied by an inferior swelling capacity and mechanical properties. What contributes the most in determining the swelling and mechanical properties is now partially replaced by air, which eventually weakens the intermolecular interactions.

For many pharmaceutical applications, fast swelling kinetics or a fast diffusion process is more desirable than improved mechanical properties. All smart hydrogels with the ability to respond to the changes in pH, temperature, solvent composition, or any other stimulants can benefit from this modification. In other words, air addition to a two-phase solid hydrogel/water composite is the simplest and the most practical approach to change a slow responsive system to a fast responsive system regardless of the type of the stimulation. For instance, in the pharmaceutical area, hydrogels are used to control the release of the drug. For this purpose, drugs are dispersed or dissolved in a hydrogel and their release is controlled by the molecular diffusion of the drug and relaxation of the polymer chains. However, the technological success of these applications has so far been limited by the low efficiency and slow rate of response to stimulants in the surrounding environment.

8.2 Super Water-Absorbent Polymers (SAPs)

About three decades ago, super-absorbent polymers (SAPs) were introduced into agriculture and later in diaper industries as a product with the ability of water retention. The SAPs are structurally cross-linked hydrophilic polymers, which have the ability to absorb substantial amounts of water or aqueous fluids (200–700 times their original weight or volume) in a relatively short period of time [2,3]. Depending on the manufacturing process and the materials used during their preparation, the swelling rate of SAPs ranges from a fraction of a minute to hours. The swelling kinetics, however, is mainly determined by the particle sizes of the SAP products. Although porosity can be incorporated into the SAP structure, this will weaken their position for the applications where good mechanical property in the swollen state is very much desirable. Different generations of SAPs were evolved with the intention of enhancing mechanical properties of the swollen SAP particles. The SAP industry is not worried about the swelling as the SAP formulators can control the swelling kinetics by manipulating the particle size. Although SAPs prepared by inverse suspension are intrinsically porous, there is no special and immediate need to make the SAP structure porous. The SAPs are responsive hydrogels due to the fact that their structure is generally ionic, which enables them to respond to the pH. For the same reason,

they are also responsive to the solvent composition. In summary, the SAPs are typical fast-responsive hydrogels, which are stimuli sensitive and react fast to the stimulant because of their size. This superior swelling or water-retention property of SAP materials received attention in pharmaceutical areas for gastric retention application. In 1998, superporous hydrogels (SPHs) were introduced as a different category of super water-absorbent polymers with macroporous structure.

8.3 Responsive Hydrogels

Depending on the situation in which they are used, hydrogels are referenced by a variety of terms. Hydrogels may be classified as ionic, nonionic and hydrophobically modified depending on their starting materials and structure. In terms of solubility in water, they are further classified as soluble and swellable. Swellable hydrogels are in general chemically cross-linked hydrogels. Gelling property is a term that is practically used for the hydrophobically modified hydrogels, which display sol gel transition. Table 8.1 shows how solubility, swellability, and gelling properties of hydrogels change with stimulants such as pH, temperature, and solvent composition. If the change in solubility or swellability is proportional to the change in stimulant, the response is called direct, otherwise it is the reverse.

Ionic hydrogels are generally made of ionic monomers such as acrylic acid, methacrylic acid, and their sodium, potassium, or ammonium salts. These polymers in their noncross-linked form dissolve in water at a higher pH. On the other hand, cationic polymers based on cationic monomers such as diallyldimethylammonium chloride dissolve better at low pH medium. Exact solubility behavior of these polymers is determined by the pH of the solution and the hydrogel PKa. Solubility of these hydrogels is also dependent on the ionic strength of the solution and the solvent composition. As ionic strength of the solution increases or as the portion of nonsolvent increases, so does the insolubility of the hydrogel.

Nonionic hydrogel polymers are on the other hand almost insensitive to the pH and temperature changes. Instead, they are very sensitive to the solvent composition. Since they are generally soluble in water, the addition of a nonsolvent such as methanol, ethanol, or acetone will eventually lead to the precipitation of the polymer. Hydrophobically modified hydrogels are hydrogels with hydrophobic side groups. These groups have the ability to aggregate or associate at a certain temperature. At this particular temperature, polymer-polymer interactions are favored at the expense of polymer-water interactions. This change in intermolecular interactions results in gelation or sometimes precipitation.

TABLE 8.1

Solubility and Swellability of Hydrogels in Response to Environmental Stimulants

Solubility and swellability	Ionic polymers	Increases with increase in stimulant (pH)	Direct response, anionic polymers; poly(acrylic acid) and its salts, alginate, pectin
		Decreases with increase in stimulant (pH)	Reverse response, cationic polymers; polyethyleneimine, poly(diallyldimethylammonium chloride), chitosan
	Hydrophobically-associated structures (sol-gel transition)	Sol is favored with increase in temperature	Direct response, agar
		Gel is favored with increase in temperature	Reverse response, PEO-PPO-PEO triblock polymers, polyNIPAM, cellulose polymers (methyl cellulose, hydroxypropyl methylcellulose)
	Nonionic polymers	Increases with solvent increase; addition of more nonsolvent (ethanol, methanol, acetone) leads to shrinkage, precipitation	Direct response, polyacrylamide, poly(hydroxyethyl acrylate), poly(hydroxyethyl methacrylate), poly(ethylene oxide)

It should be pointed out that factors responsible for solubility are directly responsible for the swellability. Polymer solvent interactions, electrostatic forces, and osmotic pressure are determining factors in the solubility of a polymer in water or in an aqueous medium. A polymer with good solubility behavior will potentially swell more in that solvent. The only factor that differentiates the solubility and the swellability is the elastic force that is provided by the presence of cross-links. The hydrogel swellability varies with its cross-link density. Table 8.1 shows how different responsive polymers react to their corresponding stimulants.

Regardless of their structure, hydrogels respond to a given stimulant by absorbing or desorbing the surrounding fluid. Therefore, the hydrogel response is a mass transport process that is determined by the diffusion of the solvent and relaxation of the polymer chains. In either case, as the diffusion path becomes shorter, the overall mass transport process becomes faster. As mentioned earlier, the most practical way to shorten the diffusion path is to introduce porosity into the hydrogel structure. A responsive hydrogel with the porous structure is called responsive porous hydrogel. Depending

on the average size of the pores, the porous hydrogel is called macroporous (50 μm to a few millimeters) or microporous (1–50 μm).

8.4 Responsive Macroporous Hydrogels

Although pores are basically air pockets and should theoretically have no influence on the swelling properties, both swelling and mechanical properties of hydrogels are affected by the air component of the composite. On the weight basis, the porous and nonporous forms of a hydrogel should theoretically have the same swelling capacity. Pores within the hydrogel structure act like external reservoirs with the ability to hold more water. The water located within the pores is not bound to the structure and can easily be removed under pressure. This extra nonbound water also weakens the hydrogel structure as it reduces the solid content of the hydrogel. On the volume basis, both swelling capacity and swelling rate are influenced by the amount of air within the hydrogel. Another important factor is the pore size and pore size distribution. To achieve homogenous response by the whole hydrogel matrix, the pores need to be monodispersed or similar in size. Monodispersed pores provide very narrow pore size distribution that positively affects the hydrogel strength. However, if the gas blowing technique is used to make porous hydrogels, the monodispersed feature will be very difficult to achieve. Since foaming reaction will occur as gelling reaction proceeds, a poly-dispersed porosity and an open-closed cell structure will be practical and more common to achieve. This feature will depend on particle size of the foaming agent, its solubility in the reaction medium, water content, hydrophilicity-hydrophobicity of the reacting mixture, temperature, dispersibility, pH, existence of a dispersing agent, and viscosity of the medium in which the foaming agent is dispersed. By far, the most important factor in achieving a close-to-monodisperse status is a synchronized foaming and gelling reaction.

Although techniques such as freeze-drying [4], porogenation [5–7], microemulsion formation [8], and phase separation [9] are used to prepare porous hydrogels, the most practical approach has so far been the gas blowing technique utilizing acid-induced decomposition of a bicarbonate compound [10]. In the synthesis of macroporous hydrogels, the monomers are simultaneously polymerized and cross-linked using a redox initiating system in solution. The polymerization reaction may happen in the presence of air or under a blanket atmosphere. At a desirable time when the gelling mass is sufficiently thin, an acidic foaming aid reacts with a bicarbonate compound and carbon dioxide gases are generated. As gelling reaction or polymerization and cross-linking reaction proceeds, the reacting mass becomes viscous and generated gases will be entrapped within the hydrogel matrix. The foam structure will

simultaneously be stabilized using a foam stabilizer. The key to obtaining homogenous porosity or monodisperse porosity is to have the foaming reaction almost completed before the reacting mass becomes viscous. Moreover, a complete foaming reaction should immediately be followed by a very fast gelling reaction, which enables the matrix to quickly and adequately entrap the gases within the hydrogel matrix. At this point, when foaming is completed and the temperature of the reaction rises, the foaming gelling system tends to collapse because of high temperature and the surface tension of the water inside the hydrogel matrix. As soon as the foaming and gelling reactions reach a plateau as indicated by no change in foam height and temperature, the foam hydrogel is further stabilized by immersing into a nonsolvent, usually ethanol. Complete dehydration results in a porous product, which is white in color because of air dispersion in the hydrogel. Dehydration in alcohol will freeze the growing chains and any other ongoing reactions; this will conclude the hydrogel properties based on the events during the gelling reaction. In other words, the length of the polymer chains (polymer molecular weight) and the level of cross-linking reaction (crosslink density) just prior to dehydration process will determine the final hydrogel properties. This is why factors affecting the gelling reaction need to be carefully identified and evaluated. Typical materials needed to prepare a macroporous responsive hydrogel (superporous hydrogel) are shown in Table 8.2 with their corresponding effects on general synthesis and hydrogel properties.

8.5 Development of SPHs

The macroporous hydrogel prepared via simultaneous polymerization and cross-linking and synchronized foaming-gelling reactions is a high swelling polymer with almost no mechanical strength. This hydrogel can swell up to 100–1,000 times its own weight in distilled water depending on the monomer and the cross-linking process. The concentration of hydrogel in the swollen mass of hydrogel and water will be about 0.1–1.0%, which justifies why mechanical properties are so poor. The hydrogel will be very desirable for applications where a high and fast swelling property is needed. These features make the hydrogel a good candidate for conventional super water-absorbing applications. However, other properties such as good compressive or fatigue properties may be required for biomedical and pharmaceutical applications. Macroporous hydrogels intended for cell culture or gastric retention are required to be strong and tough in their swollen state. As a result, the desire for tailor-made swelling and mechanical properties in particular applications has evolved into three different generations of SPHs. Conventional or first generation SPHs are identified by fast swelling, high swelling capacity, and weak or no mechanical properties. The SPH composites or the second

TABLE 8.2

Ingredients Necessary to Make Macroporous (or Superporous) Hydrogels

Ingredient	Role
Monomer	Building block of the polymer, accelerates the gelling reaction
Diluent	Helps produce a smooth and controllable reaction; retards and suppresses the exothermic reaction
Cross-linker	Links the linear polymer chains; accelerates the gelling reaction
Foaming aid	Generally acidic; reacts with foaming agent to produce gases; retards the gelling reaction; increases the foam height
Foam stabilizer	No sensible effect on gelling reaction, contributes to a well-formed cellular structure
Comonomer (ionic)	Retards the gelling reaction; helps better bicarbonate dispersion; modifies swelling and mechanical properties
Hybrid agent	Generally retards the gelling reaction; leads to poorer SBC dispersion; significantly contributes in mechanical properties
Reductant and oxidant	Redox system; accelerates reaction; leads to less control on the reaction, which leads to more heterogeneity in hydrogel
Cation (III), very reactive	Ionotropic gelation; contributes in SPH rigidity and toughness; decreases swelling; provides brittle fracture mechanism
Cation (III), not very reactive	Contributes to a flexible to tough SPH; decreases swelling but not significantly; provides ductile fracture mechanism
Cation (II)	Contributes to flexible SPH; has almost no effect on swelling; provides weak mechanical property
Nonsolvent	Replaces water in the SPH; stabilizes the foam structure

generation SPHs are characterized by fast swelling, medium swelling capacity, and improved mechanical properties. The third generation SPH or SPH hybrids possess elastic properties that can be highly useful in the development of gastrointestinal devices, as well as in other pharmaceutical and biomedical applications. A micrograph of a typical SPH structure is shown in Figure 8.1a–c. Unique SPH swelling and mechanical properties are partially accounted for in terms of surface microwrinkles, surface micropores, and internal interconnected micropores.

8.6 The First Generation SPHs: Conventional SPHs

The first generation SPHs are similar to the currently marketed superabsorbent polymers except that their swelling capacity is independent of their

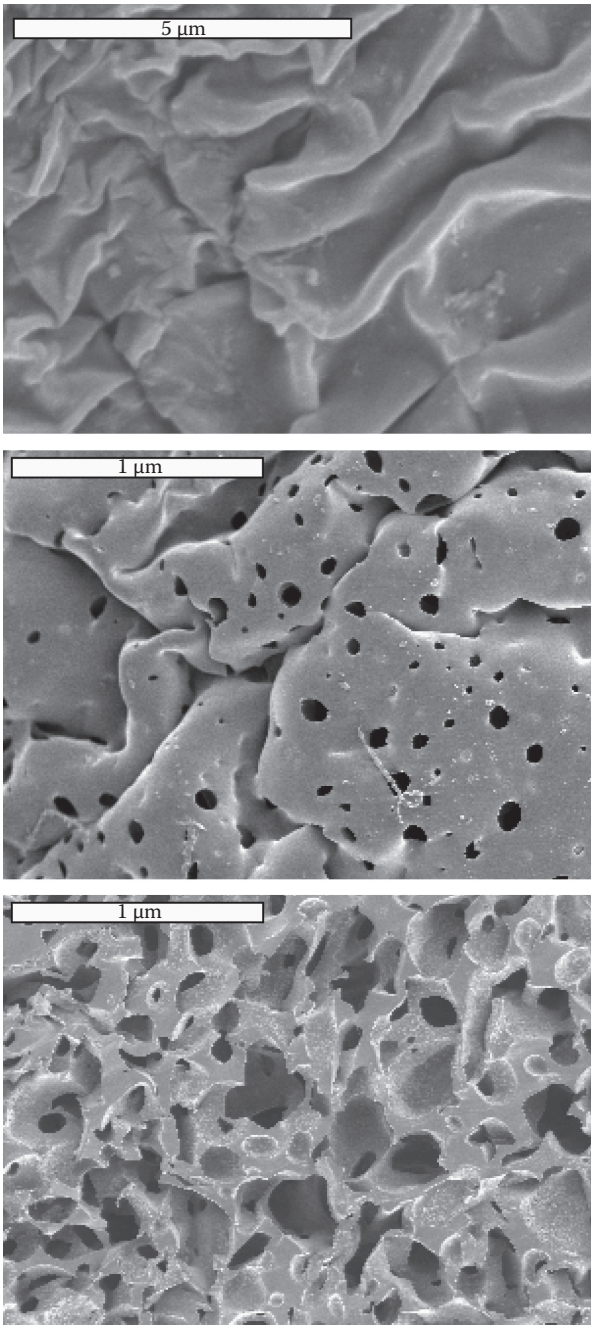


FIGURE 8.1
Fast responsive macroporous hydrogels with surface microwrinkles (top), surface micropores (middle), and internal interconnected micropores (bottom).

size in the dry state. Because of their structural superporosity, the small or large SPH products can reach to their ultimate or equilibrium swelling capacity almost at the same time. Since the objective has been to achieve ultimate swelling properties, the formulation design requires using ionic (acrylic acid, methacrylic acid and their sodium, potassium, or ammonium salts) or nonionic but very hydrophilic monomers (acrylamide). Moreover, the amount of cross-linker in the formulation should be kept very low. One very important formulation aspect in preparation of macroporous hydrogels is the minimum cross-linker concentration (MCC). Below this value, although favoring the swelling capacity, the hydrogel cannot maintain its porosity during the foaming-gelling reaction, which severely affects its swelling kinetics. The MCC needs to be determined based on the hydrogel formulation and the reaction conditions.

Since ionic monomers are the monomers of choice for the first generation SPH, the SPH product either in its dried or swollen state will be rigid and brittle. In its dry state, the rigidity of the SPH will be high because of high glass transition temperature of the polymer. On the other hand, the ionic structure or very hydrophilic structure of the SPH has the ability to quickly absorb moisture from the surrounding environment. If there is no provision made to prevent the SPH from absorbing moisture, the SPH will be significantly plasticized to a level that may irrecoverably lead to losing the porous structure. One important step in stabilizing the porous structure of the SPHs is to minimize its water content by dehydrating it in alcohol. The lower surface tension of alcohol prevents the porous structure of the SPH from collapsing during drying. In the swollen state, the solid content of the swollen hydrogel mass will be very low, which leads to very poor mechanical properties. If the application requires the swollen hydrogel to possess certain mechanical properties, such as cell culture, gastric retention, or diet aid, a stronger swollen hydrogel would be needed. The desire for better mechanical properties triggered the further development of the later SPH generations.

8.7 The Second Generation SPHs: SPH Composites

The first attempt to make stronger SPH was to use active water swellable fillers in the conventional SPH formulations. The filler is selected among conventional pharmaceutical superdisintegrants including cross-linked carboxymethylcellulose or cross-linked poly (vinyl pyrrolidone). The filler in its dry state is added into the SPH formulation before foaming-gelling reactions starts. Once added, depending on the filler swelling capacity, certain amounts of the reacting mixture containing monomer, initiator, cross-linker, and foaming agent will be absorbed into the filler structure. Polymerization

will occur in the free and entrapped reacting mixtures simultaneously. After drying, the entrapped chains of the SPH hydrogel will increasingly interact with the filler chains, which reinforce the whole SPH composite. In fact, swellable filler acts as reinforcing filler in the SPH composite, which increases the modulus of the hydrogel. Under mechanical stress, a higher modulus hydrogel will fail or break under brittle fracture mechanism, which prevents the hydrogel from repeated use. In other words, upon developing a craze or crack under certain mechanical force, the failed area will grow almost instantly to the entire bulk of the product, which results in complete disintegration. If the application requires multiple uses of hydrogel or multiple loading or unloading cycles, the second generation SPH will not meet the requirements. They still swell to a large size with mechanical properties improved to a minor extent. For many years, these macroporous hydrogels have been an attractive research tool for developing peroral and intestinal drug delivery systems [11–13].

More approaches to make second generation SPHs are acidification, impregnation (interchain complexation), addition of latex into SPH formulation, addition of gelatin followed by its cross-linking, ionotropic gelation of nonpolysaccharides added into the SPH formulation (polyvinyl acetate or polyvinyl alcohol treated with sodium tetraborate decahydrate), ionotropic gelation of complexable monomers (acrylic acid, acrylamide), surface cross-linking (using a cationic resin of polyamidoamine-epichlorohydrine adduct or glycerin), and thermogelation of the protein incorporated into the SPH formulation (egg white ovalbumin protein).

Gastric retention application requires the swollen macroporous hydrogel to resist multiple loading and unloading cycles of stresses during contractions and expansions of the stomach. This requires the hydrogel to be either tough or elastic. In both cases, the swollen hydrogel will eventually fail desirably under the ductile failure mechanism. This means if a craze or crack is developed at the surface or inside the structure, it will not grow quickly and the whole platform will have a much longer service life under applied stresses. This feature and desire led to development of the third generation SPH with superior mechanical properties.

8.8 The Third Generation SPHs: SPH Hybrids

To synthesize SPHs with very high mechanical or elastic properties, the conventional SPH formulation is hybridized with a polymer having complexation ability. As opposed to SPH composites wherein a cross-linked, water-swellable filler is used, the SPH hybrids are benefiting with a water-soluble polymer, a hybrid agent that undergoes cross-linking followed by SPH formation. Depending on the monomer and its compatibility with

the hybrid agent, polysaccharides such as sodium alginate, chitosan, carboxymethyl cellulose can successfully be used to develop a third generation SPH. The advantage of hybrids over composites is that the former produces an interpenetrated homogeneous network structure while the latter produces interpenetrated heterogeneous network structure. Elastic or resilient properties of the acrylamide-alginate hydrogel hybrids have been shown by Omidian et al. [14]. A polyacrylamide hydrogel interpenetrated with calcium-treated sodium alginate at high cation concentration displays rubbery properties in its swollen state. The swollen hydrogel can resist static compressive forces of about 25 N and can withstand loading and unloading cycles. Omidian et al. [15] have shown that a successful hydrogel hybrid with superior mechanical properties can be prepared if the hybrid agent can undergo a very effective ionotropic gelation. Alginate, chitosan, and CMC in the presence of calcium, sodium tripolyphosphate, and iron respectively can potentially be used to hybridize the conventional SPHs.

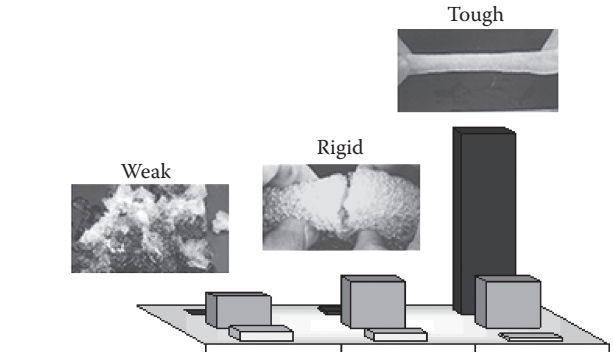
With an alginate approach, the alginate viscosity (low viscous, medium viscous, and high viscous), alginate grade (M/G ratio), and the cation type (II valence or III valence) are the critical factors that need to be considered. Iron-treated alginate generally results in a hydrogel hybrid with a very porous skin, which enables the hydrogel to absorb water very quickly. The rate of ionotropic gelation reaction can be controlled by the reactivity of the cation (iron much greater than aluminum) and its compound (calcium chloride much greater than calcium gluconate). The same discussion is valid for the carboxymethyl cellulose (CMC) as a hybrid agent. Because of its anionic nature, nonionic monomers like acrylamide can effectively and safely be hybridized with sodium alginate and CMC. In the case of ionic monomers, these two hybrid agents can be cautiously used at a lower concentration. Similar to alginate and CMC, the chitosan can also undergo a very effective gelation in the presence of phosphates. Chitosan as a cationic hydrocolloid can effectively be used with nonionic monomers but its use with ionic monomers should cautiously be limited to a very low concentration.

The advantage of utilizing this approach is the SPH hybrids with a vast variety of mechanical properties can be prepared by manipulating the functional parameters. Among those, the type and concentration of the hybrid agent, and the type and concentration of the ion are the most effective ones. For instance, CMC can be cross-linked with calcium and aluminum. A soft pliable and rigid brittle hydrogel hybrid can be obtained if the hydrogel is treated with calcium and aluminum respectively. Omidian et al. [16] used a cation combination to manipulate the hydrogel mechanical properties. Different macroporous hydrogel preparations are shown in Table 8.3. Figure 8.2 clearly shows how different SPH generations differ in their swelling and mechanical properties.

TABLE 8.3

Example of Formulations to Prepare Different Generations of SPHs

	SAP	SPH 1st	SPH 2nd	SPH 3rd	SPH 3rd-Modified
Acrylamide (50 wt %), aq. μg	600	600	600	600	600
Bisacrylamide (1 wt %), aq. μg	100	100	100	100	100
Pluronic F127 (10 wt %), aq. μg	—	200	200	200	200
Distilled water, μg	500–1,500	500–1,500	500–1,500	500–1,500	500–1,500
Composite agent, cross-linked CMC powder, mg	—	—	10–50	—	—
Hybrid agent, Linear CMC, aq. 2 wt % Solution, μg	—	—		500	500
Acetic acid, μg	40	40	40	40	40
Tetramethylethylene-diamine (40 v/v %), aq. μg	50	50	50	50	50
Ammonium persulfate (20 wt %), aq. μg	50	50	50	50	50
Sodium bicarbonate, mg	30	30	30	30	30
Cation (II), 10 wt % aq.	—	—	—	+	+
Cation (III), 10 wt % aq.	—	—	—		+



	1st	2nd	3rd
Swell ratio, v/v	36	27	12
Swell time, sec	120	180	180
Modulus, kPa	3	12	700

FIGURE 8.2
Comparison of the three typical SPH generations.

8.9 SPH Properties

8.9.1 Swelling Property

The SPHs in general are characterized by their swelling and mechanical properties in different media. Swelling is generally measured by weight, volume, or dimension. With nonporous hydrogels or less porous hydrogels, swelling measurement by weight is almost accurate and is good for comparative studies. As porosity within the structure increases and pore morphology changes from closed to interconnected, weight measurement will be more challenging. These features result in less swelling values because even the SPH weight can cause unbound water inside the gel to be removed via capillary desorption mechanism. In these circumstances, volume or dimensional swelling ratios are preferred. Depending on the application, the swelling properties should be measured in its corresponding liquid. For instance, gastric retention application requires swelling in a low pH of gastric medium. Intestinal absorption requires higher pH medium. Urine or blood absorptions require swelling medium containing salts and so forth. During swelling measurement, the homogeneity of the pores can also be evaluated. The gels are opaque in the dry state and become transparent in the swollen state. Transition from opaque to transparent is an indication of pore homogeneity and morphology. With monodisperse interconnected pores, this transition occurs in a very short period of time. As pores become polydispersed and closed, transition requires a longer time [17].

For some applications, the swelling property of the gel needs to be simultaneously measured under stress. The stress can be compression, tension, twisting, bending, or even fatigue depending on the application. Gastric retention for instance requires the gel to retain its integrity in the swollen state under constant static and dynamic forces. Swelling property of a typical fast-responsive macroporous hydrogel is shown in Figure 8.3.

8.9.2 Mechanical Property

The SPHs in their swollen state are generally weak and contain pores of different sizes ranging from 100 to 1,000 μm. The hydrogel regions surrounded by pores of different sizes behave differently in response to an applied mechanical stress. Regular mechanical testers and texture analyzers are generally used to evaluate the SPH mechanical properties. From a typical mechanogram, three important mechanical properties can be extracted, for example, gel modulus, gel failure or breaking point, and finally the mode of gel failure (brittle or ductile). These types of measurements provide selective or local assessment because a certain area of a swollen gel is exposed to the probe of the mechanical tester. If other unexamined parts of

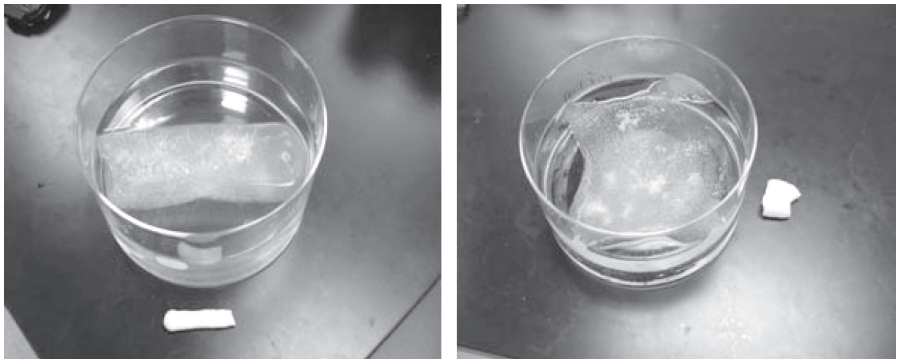


FIGURE 8.3
Examples of swelling with fast responsive superporous hydrogel in distilled water.

the sample contain a defective structure, it will be overlooked during the measurement. Real mechanical response of the hydrogel will be obtained if the whole platform is exposed to the real stresses existing in the application environment [18,19].

8.10 SPH Stability

The final properties of the SPH product will be dependent on the materials, method of polymerization, reaction conditions, and more importantly its porous structure. Since the advantage of SPHs over SAPs is the kinetic of swelling, this property needs to be maintained during storage and on the shelf. The SPH as a final product can be used by itself or in encapsulated form. If used alone, the SPH can be stored in a very dry condition in the presence of moisture absorbing materials like silica gel. Although SPH itself can also absorb moisture from the environment, silica gel materials can absorb less moisture but at a much faster rate, which is very desirable for the SPH during storage. By keeping the surrounding environment dry, the pore morphology of the prepared SPH can most likely be maintained. This assures stability of the SPH product in terms of its swelling properties. Another stability aspect will be appearance and extractables. By appearance, the SPH material is required to maintain its color (original color, off-white to white) over the stability period. Any stain or discoloration requires careful observation.

Another very important stability issue is the amount of extractables in the final SPH product. Based on an in-house specification that needs to be set up according to the toxicity values of the ingredients, the final purified SPH should contain impurities less than or equivalent to the acceptable values.

High performance liquid chromatography and gas chromatography are the common methods to determine impurities in the final product. The level of impurities can be changed if the SPH product is exposed to high temperature and a high humid environment. Moisture and temperature can plasticize the SPH structure, reduce its glass transition temperature, and increase permeation of moisture and oxygen into the structure. Besides, the UV light might also adversely affect the SPH structure depending on the monomers used. These interactions may either increase the levels of impurities to the accepted values or change the accepted properties to an unacceptable level. Apparently, storing at a low temperature and dry condition away from light will significantly enhance the SPH stability for the duration of storage. The situation will be more complicated if SPH is encapsulated in an orally administrable capsule.

For the encapsulation process, the SPH structure needs to be adequately flexible. This is automatically achieved with low glass transition polymers (acrylic esters), but it requires moisture activation if a high glass transition polymer (acrylic acid, acrylic salt) is used. Under both circumstances, polymer chains will gain more mobility that increases their intermolecular interactions. This in turn will change the SPH swelling properties and the swelling kinetics in particular. Although change in pore morphology will negatively affect the swelling rate, it will enhance the SPH mechanical properties. Any change in pore morphology is irrecoverable and changes in SPH properties will hence be permanent. Therefore, strict care needs to be taken to preserve the desirable porosity of the SPH structure. Overall, it would be anticipated that an encapsulated SPH product might have a shorter half-life and requires stringent storing regulations.

Another very important stability issue is related to the moisture content of the SPH and the capsule. The gelatin-based and HPMC-based capsules contain 13–16% and 4–6% moisture respectively. The amount of moisture within the hydrogel product needs to be adjusted based on the type of the capsule. At low moisture content, the SPH would be able to absorb moisture from the gelatin capsule, which results in capsule rigidity and brittleness. On the other hand, if the SPH contains high moisture, the moisture can migrate to the HPMC capsule through which the capsule will be softened and becomes less stable. If the moisture content of the capsule and the SPH is not equilibrated, the drug stability might be affected unless protected against moisture.

In performing a stability study as a necessary step to conduct a clinical trial, one needs the information listed in Table 8.4 to be incorporated into the stability protocol. Although more information can always be included, this will depend on the timeline and the budget assigned to the activity. Nevertheless, all data collected throughout the stability period will be used to justify the use of potentially stable and effective SPH for the clinical human trial.

TABLE 8.4

Information Necessary for Stability Study before Conducting Human Study

Supplies	SPH (item code, lot number, material, moisture content); Capsule (item code, size, material, manufacturer, moisture content); container (type, material, capacity, manufacturer); silica gel (type, manufacturer, item code)
Appearance	SPH (stain, discoloration, uneven surface, uneven diameter across the length); Encapsulated SPH (discoloration, stain, crack on capsule, SPH stickiness to the capsule, capsule rigidness)
Swelling property	SPH (pre- and postswelling dimensions at time zero and after full stability period); for the encapsulated SPH, pre- and postswelling numbers are generally lower; average of at least five samples needs to be examined
Extractable	SPH (pre- and poststability values; monomers, initiators, cross-linker, foaming aid (acetic or citric acid), dehydrant (alcohol); no need to examine capsule
Stability condition	Room temperature of 25 ± 2°C and 60 ± 5% relative humidity

8.11 SPH Scale Up

A successful SPH preparation in a glass tube, a beaker, or in a tray does not necessarily mean the SPH can easily be scaled up. For any scale up, a number of parameters need to be optimized and some of the important factors are listed in Table 8.5.

8.11.1 SPH Safety and Nontoxicity

Safety and nontoxicity of the SPH products either alone or in encapsulated forms should be verified in animal models before conducting a human clinical trial. A SPH product will be regarded safe if it offers no treatment during administration for which the esophagus obstruction will be the most concerning issue. It has to be verified that with multiple administration of SPHs, the esophagus area will not be obstructed. On the other hand, the SPH product should contain less than permitted values of unwanted ingredients either from the synthesis such as residual monomer, initiator, and cross-linker or from the dehydration step such as alcohols. It also needs to be confirmed that the SPH retention inside the GI tract will not produce any other unwanted compounds such as hydrolysis product in the harsh acidic conditions. Apparently, the hydrolysis reaction will be favored at lower pHs and also at higher temperatures.

Another safety aspect of hydrogel formulations for human clinical trial is transmissible spongiform encephalopathies (TSEs) also known as prion diseases. The disease that is originated from animals can affect the brain

TABLE 8.5

Parameters to Consider for Scale-Up Production of SPHs

Fill-up Ratio	The optimum amounts of the reacting solution in the reactor
Aspect ratio	Ratio of the diameter to the height of the reacting solution that determines the surface/volume ratio of the reacting mixture; affects the heat transfer The aspect ratio needs to be optimized based on the optimum fill-up ratio
Heat	During scale up, volume significantly increases and hence the level of reaction exothermicity
Gas dispersion	Best SBC dispersion technique needs to be practiced Nonuniform dispersion results in generating hot spots (with SBC lumps) nonuniform dispersion results in heterogeneous macroporous mass
Synchronized foaming and gelation	If foaming rate is more than the gelling rate, gases will escape faster, which results in a less porous hydrogel If foaming rate is less than the gelling rate, less gas will be generated, which results in a less porous hydrogel
Purity	Change in the scale can affect the purity of the product because of the change in pore content; more porous hydrogel will be more pure

and nervous system and can be transferred to the other species. This issue requires that every material that is used in hydrogel preparation be provided with a TSE certificate. The certificate should clearly state that no raw material used in the manufacturing of a particular ingredient or product is derived from or has been exposed to any animal sources.

8.12 Hydrogel Characterization

A macroporous hydrogel can be characterized in terms of its structure, pore morphology (size, shape, closed cell, open cell, interconnected) as well as its swelling and mechanical properties. Thermal properties will be evaluated when the hydrogel is thermosensitive or thermoresponsive. Table 8.6 shows techniques and equipment which have so far been used in the characterization of porous hydrogels.

8.13 Applications

A major constraint in oral-controlled release drug delivery is that not all drug candidates are absorbed evenly throughout the gastrointestinal (GI) tract. Some are only absorbed in a particular portion or are absorbed to different extents in various segments of the GI tract. Such drugs are said to have an absorption window. These drugs generally suffer from low bioavailability

TABLE 8.6

Techniques Used for Characterization of Hydrogels

Property	Technique	Reference
Gelation	Temperature measurement	31
Porosity	SEM	10,32,33,34, 35,36
	Mercury porositometry	37
	Cryogenic transmission electron microscopy	38
Pore structure, pore size, and surface morphology	SEM	2,39,40,41, 37,42,43,44,45,46,47,48
	Size exclusion chromatography	49
	Mercury intrusion porositometry (MIP), helium pycnometry, X-ray microtomography (XMT), SEM	50
	Cryo-transmission electron, laser scanning confocal microscopies	51,52
	Coulter porositometer	53
Swelling	SEM	54,24
	Video monitoring, conductivity measurements	55
	Volume and weight measurements	14
	Atomic force microscopy (AFM)	53
Hydrogel morphology	Optical microscopy, SEM	56
	X-ray photoelectron spectroscopy, atomic force microscopy, FTIR and surface plasmon resonance (SPR)	57,53
Hydrogel micropattern and microstructure	Optical and atomic force microscopy	58
	Laser scanning confocal microscopy, ultra small angle neutron scattering	38
Thermal stability	TGA, DSC	32,59,60,61, 62,46
Chemical structure and composition	FTIR	32,54,61,46, 50,47,53
	Solid state ^{13}C-NMR	24, 63
Mechanical properties	Rheometric studies	64
	Mechanical tester	31
Drug release	UV spectroscopy	56
Hydrogel-protein interaction	FTIR	28
Hydrogel-cell interaction	SEM, phase-contrast microscope	36
Hydrogel-filler interaction	FTIR	65
Hydrogel functional property	Immunoaffinity chromatography	66
State of water	DSC	48

because they are simply provided with a short residence time at the site of absorption, normally in the small intestine area. The idea of extending the gastric residence time of drugs with low absorption window is a *holy grail* in oral drug delivery. If a drug having a low absorption window passes the absorption segment, it will be wasted away with no further absorption across the gastrointestinal tract. Harsh stomach environment, diet status (fed or fasted), intra and intersubject variability, stomach motility, dynamic change of the stomach pH, food effect, and so on are all accounted for a gastric retention program to be a very challenging one.

Even though a few concepts including swelling and unfolding have been utilized in designing gastric retention platforms, no technology has so far proved to be commercially feasible and therapeutically effective in enhancing the absorption and bioavailability of the drugs with a low absorption window. Gastric retention will help to increase the drug absorption and its bioavailability by prolonging the residence time of the drug in the stomach. It can also help drugs with local action in the upper part of the small intestine, for example in the treatment of peptic ulcer disease. On the other hand, there are certain situations where gastric retention is undesirable. Aspirin and nonsteroidal, anti-inflammatory drugs are known to cause gastric lesions, and hence slow release of such drugs in the stomach is unwanted. Drugs that may irritate the stomach lining or are unstable in acidic environments should not be formulated in gastroretentive systems. Drugs, such as isosorbide dinitrate that are absorbed equally well throughout the GI tract, will not benefit from a gastric retention system. From a patient prospective, gastric retention is not recommended for individuals with gastric hypomotility (gastroparesis).

To achieve gastric retention, the platform must withstand the forces caused by peristaltic waves in the stomach and by the constant grinding and churning processes. A gastric retention platform must resist premature gastric emptying, and once the purpose has been served, it should be removed from the stomach with ease. Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These include bioadhesive systems, high-density, low-density floatable systems, expandable, and swellable systems. Regardless of the type of technology to prepare gastric retention platforms, there are certain requirements that need to be met by the platform as shown in Table 8.7.

In summary, a successful gastric retention platform is expected to stay in the stomach, preferably in fasted state for a few hours (6–8 hrs), to release its imbedded drug in a controlled manner and finally to disintegrate for a safe removal from the body. Overall, a potential gastric retention platform should generally meet the requirements including pharmaceutical acceptability, mechanical properties, retention, ease of processing, and disintegration.

To be utilized as a gastroretentive platform, a typical macroporous hydrogel should have a specific shape such as a cylinder, should swell in the stomach fluid within minutes to a size of about 20 times its volume, and

TABLE 8.7

Requirements for Developing Gastric Retention Platforms

Mechanical properties	A gastric retention platform has to be able to resist strong stomach forces during the housekeeping wave sweeping period of stomach motility.
Physical properties	A gastric retention platform should be orally administrable.
Gastric pH	A gastric retention platform should be robust (intact and stable) to pH fluctuations. The gastric pH under fast conditions is 1 to 2, while under fed conditions is about 3 to 4 following the meal.
Food effects	A gastric retention platform should not interfere with the normal physiological gastric emptying of food.
Elimination	A gastric retention platform should be eliminated following its complete retention in the stomach. It can be biodegraded in the intestine or can be disintegrated anywhere in the GI tract.
Pharmaceutical acceptability	A gastric retention platform should contain materials that are generally recommended as safe (GRAS).
Toxicity and safety	A gastric retention platform should not threaten the life or health of a subject. The challenging issues will be the esophagus obstruction and residual toxic materials.

should resist pressures ranging from 0.5–2.0 N/cm^2 presumably in the fed state. It also has to be flexible for the encapsulation process, should be disintegrated in a controlled manner, should have the drug loading capability, and should be stable and pharmaceutically acceptable. With the hope that all meet these requirements, the strong and elastic SPH hybrids have been considered and studied for this application. The SPH is prepared as a reservoir that houses the drug or drug delivery system within. The drug itself can be formulated as a single unit (tablet or wax) or multiple units (microparticles or macroparticles). The platform is encapsulated in a regular capsule and is orally administered. Feasibility of these platforms for the solid dose (tablet) and semisolid (wax) drug delivery systems [20,21], peroral peptide delivery systems [12,13,22–29], and fast dissolving tablets [30] has so far been studied.

A very electrifying but far-reaching application for macroporous SPHs is a platform that induces satiety in humans. Because of their high and fast swelling properties, the SPHs can presumably occupy a significant portion of the stomach volume, leaving less space for food, and hence suppress the appetite [30]. This may potentially benefit obese people. To achieve satiety, a swollen SPH should occupy at least 400 ml of the stomach volume. A 00 HPMC or gelatin capsule can accommodate at most 1 gram of the hydrogel. This can be translated to a swelling capacity of at least 400 ml/g for a given hydrogel having density of one. The authors cannot recall any hydrogel with this level of swelling capacity in the very harsh acidic stomach conditions. Moreover, the hydrogel is expected to reside in the gastric area for at least a few hours. The most challenging part will be if the high swelling hydrogel can resist the phase III of the stomach motility which occurs almost every two hours in the

fasted state. This requires the hydrogel to be at least formulated with other excipients, which can potentially suppress the stomach activities.

8.14 Researches on SPH

The past 10 years has witnessed a great number of research activities on macroporous SPHs. The research has focused on different aspects of synthesis, characterization, development, processing, applications, safety, preclinical, and clinical studies. A summary of these activities is compiled in Table 8.8.

TABLE 8.8

Some of the Recent Research Activities on Superporous Hydrogels

Hydrogel Properties	
Cross-linking and polymerization of acrylamide and acrylic acid in the presence of $NaHCO_3$; a pH-sensitive hydrogel intended for general water-absorbent applications	40
Study surface morphology by SEM, measure porosity using mercury porositometry; interconnected pores of a few hundred micrometers; swelling feature is predominantly determined by internal pores and not surface pores	37
Modify hydrogel swelling and mechanical properties; interpenetrating polymer network via interchain complexation of poly(acrylamide-co-acrylic acid)/ polyethylenimine	67
Development of Superporous Hydrogels	
Use of superdisintegrants in preparing SPH composites from conventional SPHs; high swelling and good mechanical properties, gastric retention tested in fasted and fed dogs; Gastric retention for 2–3 hrs in fasted and for 24 hrs in fed conditions	68
Structural characterization of SPH composites; solid state ^{13}C NMR to study polymer structure; SPH composites are less porous, have lower swelling ratio but better mechanical property than conventional SPHs	24
Effect of acidification on swelling and mechanical properties of poly(acrylamide-co-acrylic acid) SPHs	69
Use of Taguchi experimental design in the synthesis of mechanically strong macroporous SPH; examine the effects of the formulation parameters on the gelation status	31
Combined chemical cross-linking and physical ionotropic gelation to make very tough elastic SPHs intended for gastric retention application; SPH based on interpenetrating network of acrylamide and calcium alginate	14
Perform freeze-thawing and drying to achieve mechanically strong SPH of Glycol chitosan/PVOH; number of freezing/thawing cycles were found to be much more effective than freezing time on hydrogel property	70
Polyacrylamide SPH grafted with acrylic acid used to absorb low MW (Cu(II)) and high MW (lysozyme) ligands	71

(*Continued*)

TABLE 8.8 (Continued)

Polyacrylamide SPH grafted with different water-insoluble monomers like glycidyl methacrylate and t-butyl acrylamide; grafting of water-soluble monomers proceed better in aqueous media; grafting of water-insoluble monomers proceed better in water-DMSO solutions	72
Introduce ion equilibration as a novel approach to synthesize strong SPHs	16
Review chemistry, structure, preparation, and processing of superabsorbent polymers and SPH generations	73
Review swelling devices based on SPHs	74
Evaluate fatigue properties of SPHs	18
Introduce a novel mechanical tester that simulates real service conditions	19, 75
Evaluate swelling properties of SPHs in different swelling media	76
Safety and toxicity studies on SPHs using swine emesis model	77
Structural and calorimetric characterization of SPH hybrids	78
Morphology, hydration and mechanical properties of SPH hybrids	79
Acrylamide-based SPH composite containing hydroxyapatite; hydroxyapatite had no effect on pore structure, but increased the mechanical property to almost tenfold; it is cytocompatible toward fibroblasts; intended for bone tissue engineering	80
Poly(acrylic acid) SPH particles as tablet superdisintegrant; evaluate the effect of SPH on tablet swelling and mechanical properties	81
Drug Delivery	
To enhance transport of drugs across porcine intestinal epithelium and to study attachment to the gut walls; intended for intestinal protein and peptide delivery	22
Study mechanism of opening in tight junctions; using SPH as permeation enhancer for peptide delivery	23, 26
Scintigraphy using Tc-99 to study the SPH movement throughout the GI tract; intended for targeted intestinal protein and peptide delivery	27
Release rate and mechanism, drug stability under different environmental conditions, drug-platform interaction; intended for peroral peptide delivery of buserelin, octreotide, and insulin	28
In vivo pig study of using platforms to improve intestinal absorption of insulin; intended for intestinal protein delivery	12
To improve kinetics of swelling and shrinking of conventional hydrogels; study swelling dependency on pH and ionic strength; evaluate single versus multiple unit drug delivery systems	82
Study compression effect on swelling property and pore structure; intended for gastric retention application	83
Review concepts, developments and approaches to extend gastric residence time of orally administrable dosage form	84
Review development of different SPH generations intended for gastric retention and intestinal absorption of proteins	17
Highly pH-sensitive hydrogels based on chitosan and glycol chitosan with mechanical stability over swelling and de-swelling cycles; intended for gastric retention applications	85
Utilize SPH composites to improve intestinal transport of the peptide drug desmopressin in vitro	11
Poly(acrylamide-co-acrylic acid) interpenetrated with chitosan or glycol chitosan; better swelling properties in SGF than in water with increase in chitosan concentration; glycol chitosan provides better swelling kinetic because of its higher affinity to water	86

(*Continued*)

TABLE 8.8 (Continued)

Carbopol-containing SPH composites with different responsive properties; Internal interconnected porous and external nonporous structure with the ability to adhere faster and better to the intestinal mucosal than regular SPHs; intended as potential candidate for transmucosal delivery	35
Carbopol-containing SPHs studied in various salt and pH solutions, their biocompatibility evaluated using tissue damage and cytotoxicity studies; claimed to be an effective carrier for peroral delivery of peptide and protein drugs	87
Review gastroretentive floating and SPHs intended to fight H. pylori	88
Poly(acrylic acid-co-acrylamide)/O-carboxymethyl chitosan full interpenetrating network with mucoadhesive properties intended for peroral absorption of insulin	89, 47
Anion exchanger agarose prepared by incorporating ethylene imines and quaternary amine functionality; with the ability to allow large molecules such as plasmids to transport into their interior; plasmid binding capacity was found much higher with smaller diameter superporous agarose beads	90
Tissue Engineering	
Poly(vinyl alcohol) and poly(vinyl pyrrolidone) prepared by double emulsion process; hydrogel emulsions were physically cross-linked by freeze-thaw cycles; intended as articular cartilage repair that should have good mechanical properties to function synergistically with healthy cartilage and porous enough to allow for tissue integration	91

Summary

Because of their porous structure, the responsive macroporous hydrogels can respond to their surrounding environment very quickly. The basic properties of these hydrogels include swelling capacity, swelling rate, and mechanical strength and are critically dependent on the pore size and morphology. This feature has opened a new era in the hydrogel history that can extend their application into the pharmaceutical and biomedical area. In this article, the basic concepts, formulation, development, scale up, characterization, properties, safety, stability, and applications of the most recent type of responsive macroporous hydrogels are examined.

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