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SUPERPOROUS HYDROGEL (SPH): A NOVEL AND ADVANCED TECHNIQUE OF ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEM

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ABSTRACT

Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site specific drug release in the upper part of GIT for local or systemic effect. Gastroretentive drug delivery system involves various approaches like: High–density system, bioadhesive system, swelling and expanding system, magnetic system, superporous hydrogel, incorporation of passage delaying food agents, ion exchange resins, bioadhesive liposomal system and floating systems. Superporous hydrogels (SPHs) were developed as novel oral controlled release drug delivery system for those drugs having absorption window in stomach and upper part of gastrointestinal tract (GIT) and to retain drug in the gastric medium. Superporous hydrogels (SPHs) are different from superabsorbent polymers (SAPs) in their very fast swelling property, within minutes, to the equilibrium swollen state regardless of their size. The fast swelling property is based on water absorption through open porous structure by capillary action. The poor mechanical strength of conventional SPHs (CSPHs) was overcome by developing the second-generation SPH composites (SPHCs) and the third-generation SPH hybrids (SPHHs) and superporous hydrogel interpenetrating network (SPHs-IPN). This review includes the differences between SAPs and SPHs, advantages, disadvantages, various generations, methods of preparation, techniques of drug loading, ingredients required for synthesis with their role, methods for synthesis, characterization and applications of SPHs.

KEYWORDS: Superabsorbent polymers, Superporous hydrogels, Mechanical strength, Pore structure, Elasticity.

INTRODUCTION

Drug delivery technologies are as important as new chemical entities entering into the pharmaceutical industries, allowing more effective use of existing drugs and successful development of new drug candidate.[1] The scientific and technological advances in controlled oral drug delivery system enable long residence time (LRT) and predictable gastric emptying time (GET).[2] About three decades ago, superabsorbent polymers (SAPs) were introduced into the agriculture industries due to their excellent water holding property. The most recent advancement in the gastro-retentive drug delivery is the development of various types of superporous hydrogel. In 1998, superporous hydrogels (SPHs) were introduced as a different category of water-absorbent polymer systems.

SAPs vs. SPHs

Superabsorbent polymers (SAPs) are structurally cross-linked hydrophilic polymers, which have capacity to absorb considerable amounts of water or aqueous fluids (10–1000 times of their original weight or volume) in relatively short periods of time.[3-4] Depending on the manufacturing process and the materials used, the swelling rate of SAPs ranges from fraction of a minute to hours. The initial wetting of SAP particles is slower than that of SPHs, and the fast swelling is mainly based on the small size of the SAP particles. Hydrogels with effective pore sizes in the range of 10 - 100 nm are termed as microporous hydrogels and pore sizes in the range 100 nm - 10 μm are termed as macroporous hydrogel.[5] SPHs are a new type of hydrogel that have numerous supersize pores inside them. Superporous hydrogels developed as novel drug delivery system for those drugs having absorption window in stomach and upper part of GIT. [6] Hydrogels having ability to create effective pore size larger than 10 micrometer are known as superporous hydrogels. SPH is a three dimensional network of hydrophilic polymer that are not soluble and absorb large amount of water in short period due to it contain numerous inter connected microscopic pores. It differs from other types of porous hydrogel like macroporous hydrogel. The superporous hydrogels (SPHs) swell immediately upon contact with water regardless of their size in the dried state. [7-9] Modern SAPs and SPHs are normally prepared by employing a gas blowing technique, in which acid induced decomposition of a bicarbonate compound is exploited. Although both SAPs and SPHs are porous in structure, they are different from each other as compared in Table 1.

Table 1: General Features of SAPs and SPHs

	SAPs	SPHs
Commonly used monomers	Acrylamide, acrylic acid, salts of acrylic acid including sodium and potassium acrylates	Acrylamide, acrylic acid, salts and esters of acrylic acid including sodium and sulfopropyl acrylates
Methods of synthesis	Bulk, solution, inverse suspension	Mostly aqueous solution
Initiating system	Thermal, redox	Mostly redox
Porous structure	Random closed to semi-open cells	Inter-connected open cells
Final product	Particle	Particle, sheet, film, rod
Water absorption mechanism	Diffusion (high), Capillary (low)	Diffusion (low), Capillary (high)
Swelling dependence on size	Size-dependent	Size-independent
Type of absorbed water	Mostly bound	Mostly free
Free swelling capacity	Very high	Very high
Retained water under pressure	High	Low
Applications	High swelling, fast-medium rate of swelling is required	Size-independent high and very fast swelling are required
Service environment	Water, saline, blood, urine	Simulated gastric fluid, simulated intestinal fluid

The unique property of size independent fast swelling kinetics of SPHs is characterized by their interconnected open cellular structure, as shown in Fig. 1.

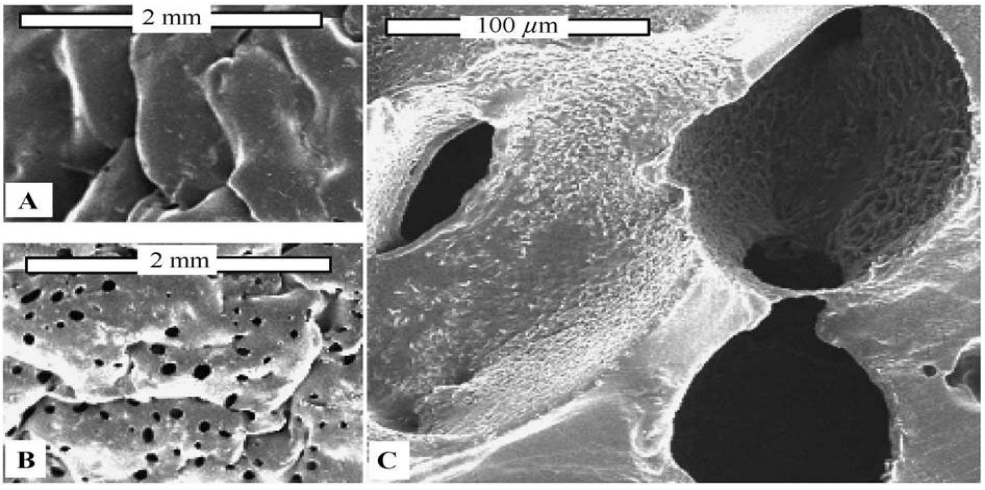


Fig.1. Scanning Electron Micrographs of a Nonporous SAP (A) and a Corresponding SPH (B and C).

The open porous structure allows extremely fast absorption of water into the center of the dried matrix by capillary action. The same monomer solution can produce different types of water-absorbing polymer networks, such as non-porous, porous and superporous structures depending on the presence of foaming agent, foaming aid and foam stabilizer, as shown in Table 2. The comparisons made in Table 2 are based on SAP and SPH prepared by using acrylamide and acrylic acid. [10-13]

Table 2: Typical Formulations for Aqueous Solution Polymerization of SAPs and SPHs.

Starting Material	Role	Nonporous SAP	Porous SAP	SPH
Acrylamide, acrylic acid	Monomer	√	√	√
Bisacrylamide	Cross-linker	√	√	√
Deionized water	Solvent	√	√	√
Ammonium persulfate	Oxidant	√	√	√
Tetramethyl ethylenediamine	Reductant	√	√	√
Glacial acetic acid	Foaming aid		√	√
Sodium bicarbonate	Foaming agent		√	√
PEO-PPO-PEO block copolymers	Foam stabilizer			√
Starting temperature (ºC)		25	25	25
Comparative swelling capacity (g/g)		9	20	33

The swelling of the compressed superporous hydrogels is slightly slower than the uncompressed superporous hydrogels but still much faster than a similar non-porous hydrogel. The density of the superporous hydrogel causes it to float in simulated gastric fluid, which will aid in the retention in the stomach prior to swelling. Swelling of superporous hydrogels in blood is very slow due to the poor wetting of the dry hydrogel and the viscous property of blood.

Advantages of SPHs [14]

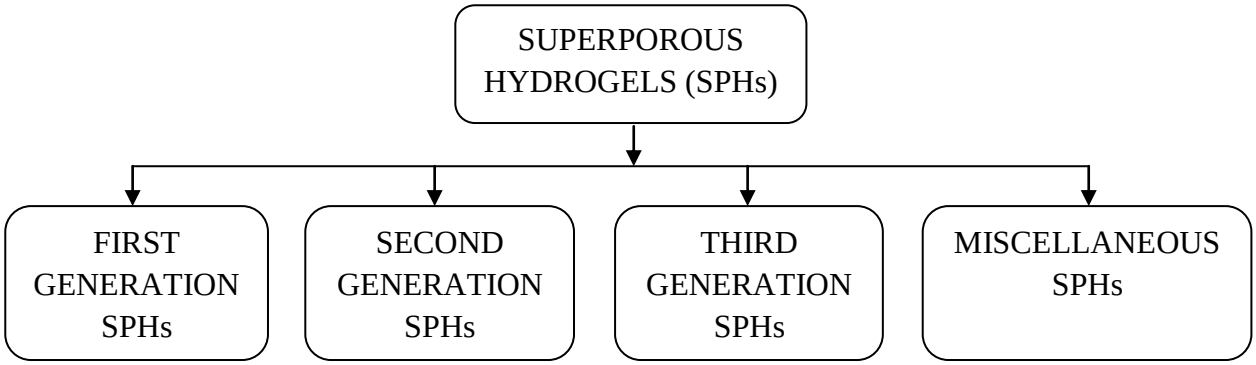
1) The swelling rate is very fast. The Superporous hydrogel swell completely within a minute regardless of the size of the dried superporous hydrogel.
2) Superporous hydrogels swell to such an extent that the weight of fully swollen superporous hydrogel is higher than the weights of dried superporous hydrogels.
3) Though the superporous hydrogels contain small percentage of solid content of the total weight, it can exert significant expansion force during swelling.
4) Superporous hydrogels can also be made elastic, which minimizes their rupture.

5) The unique properties of superporous hydrogels can also be used for non-pharmaceutical and non-biomedical applications.

Disadvantages of SPHs

1) Weak mechanical properties of fully swollen SPHs as compared to SPHCs and SPHHs.

Classification of Superporous Hydogels (SPHs)



First Generation SPHs: Conventional SPHs (CSPHs)

The first generation conventional SPHs (CSPH) are characterized by fast swelling, high swelling ratio and weak mechanical properties. The most commonly used monomers for the synthesis of the first generation SPHs are highly hydrophilic acrylamide, salts of acrylic acid and sulfopropyl acrylate.[15] When the SPHs are dried, the porous structure become collapsed or shrunken due to the surface tension of water pulling the polymer chains together during the drying process. To avoid this problem, water inside the SPH is replaced with alcohol (e.g. ethanol). The low surface tension of alcohol prevents the porous structure from collapsing during drying. The dried SPHs are hard and brittle, but the hydrophilic nature of the polymer results in moisture induced plasticization of the rigid structures into soft and flexible structures. The dried SPHs swell fast to a larger size, larger than a few hundred times of their own volume in the dried state. The rate of water absorption could be increased by creating the pores inside the hydrogel structure. Different wetting agents also increase the rate of water absorption to less than a minute. The swollen SPHs are difficult to handle without breaking due to their poor mechanical strength. An example of conventional SPH is acrylic acid and acrylamide cross-linked and polymerized on PEG acrylate substrate. [16-19]

Second Generation SPHs: SPH composites

The second generation SPH composites (SPHC) are characterized by fast swelling, medium swelling ratio and improved mechanical properties. For making SPH composites, a matrix-

swelling additive or swellable filler or a composite agent is used. A composite is a matrix of a continuous phase having a dispersed phase incorporated in it. [20] A composite agent used in SPH composites is a cross-linked water-absorbent hydrophilic polymer that can absorb the solution of monomer, cross-linker, initiator and remaining components of the SPH synthesis. During the polymerization process, each swellable filler particles act as an isolated individual reactor in which polymerization and cross-linking could occur simultaneously. Since, cross-linking polymerization proceeds throughout the solution, the individual swollen particles are connected together through the extended polymeric chains. The presence of composite agent in SPH composites results in improved mechanical properties over conventional SPH, but the SPH composites are still brittle and thus break into pieces upon application of stresses. This modification over conventional SPHs resembles modification of superabsorbent polymers through surface cross-linking. Overall, this type of modification results in a higher modulus polymer network in the swollen state, which is susceptible to failure under the brittle fracture mechanism. The most widely used composite agents are crosslinked sodium carboxymethylcellulose (Ac-Di-Sol), crosslinked sodium starch glycolate (Primojel) and crosslinked polyvinylpyrrolidone (Crosspovidone). Polyvinyl alcohol and carbopol are also used to improve the mechanical strength of SPHs. The second generation SPHs is an attractive approach for peroral and intestinal drug delivery system. Though, this modification leads to polymeric networks with improved mechanical strength in swollen state but still these are prone to breakdown under high tensile stress. SPH composite can withstand compression forces of up to 2 N. [21-23]

Third Generation SPHs: SPH hybrids

The third generation SPH hybrids (SPHH) are characterized by very high mechanical or elastic properties. Due to addition of hybrid agent a cross linked structure of SPH was formed. The hybrid agent is a water-soluble or water-dispersible polymer that can form cross-linked structure (in a manner similar to forming interpenetrating network (IPN) through chemical or physical cross-linking. [24-26] Due to interpenetrating network, SPH hybrids are also known as SPH-IPNs. Each hybrid agent may require specific treatment. Depending on the type of agent and its associated treatment, various third generation SPHs can be created ranging from high modulus to high elastic and rubber (in their water swollen states). Examples of hybrid agents are polysaccharides, sodium alginate, pectin, chitosan or synthetic water-soluble hydrophilic polymers such as poly(vinyl alcohol). Natural hydrocolloids show ionotropic gelation via treatment with metal ion like calcium, iron etc. (e.g. sodium alginate

with Ca^{+2} ions, chitosan with phosphates). One of the unique properties of SPH hybrids is that the gels are highly elastic in the swollen state. As compares with conventional SPHs and SPH composites, SPH hybrids are not easily breakable when stretched. The elastic and rubber properties make SPH hybrids a choice for various applications where resilient gels are preferred. SPH hybrids can resist various types of stresses, including tension, compression, bending and twisting. An example of SPH hybrids is the synthesis of acrylamide based SPH in the presence of sodium alginate. SPH hybrid of alginate polyacrylamide could withstand compression forces of up to 25 N. [27, 28] General features of various SPHs generations are listed in Table 3.

Miscellaneous SPHs

Development of SPHs with mechanical properties identical to that of SPHCs has been attempted applying different approaches, including acidification (using HCl), impregnation (using diallyl dimethyl ammonium chloride or cationic polyethyleneimine or cationic resin of polyamido amineepichlorohydrin), rubberization (adding rubber emulsions), surface crosslinking (using glycerin), ionotropic gelation (using synthetic polymers other than hydrocolloids; like polyvinyl acetate), bulk crosslinking (using higher concentration of a chemical crosslinker), thermogelation (using ovalbumine protein, egg white) and ionotropic gelation (using ion-complexable co-monomers; e.g. acrylic acid).[29, 30] General structural, swelling and mechanical properties of different generations of SPHs are shown in Fig. 2.

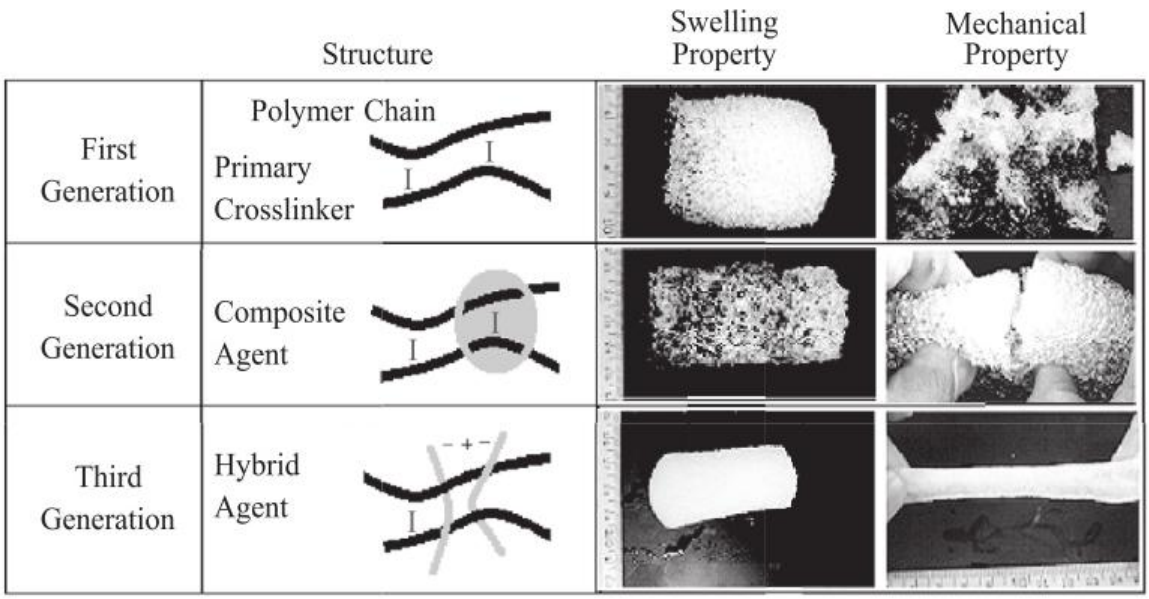


Fig. 2 Structural, Swelling and Mechanical Properties of Different Generations of SPHs.

Table 3: General Features of SPH Generations [1]

Formulation	CSPH	SPHC	SPHH
Property modifier	None	Superdisintegrants-crosslinked CMC; polyvinyl pyrilidone and starch glycolate	Water–soluble CMC, alginate,chitosan, polyvinyl alcohol
Swelling capacity	100-300 g g-1	100-300 g g-1	Up to about 50 g g-1
Swelling rate	5-30 s	5-30 s	5s to a few min
Mechanical properties	No mechanical strength	Resists up to 2 N cm-2	Resists up to 20-100Ncm-2
Treating agent	No	No	Iron, calcium, aluminium, phosphate, copper
Water washing ability	Impractical because of high swelling in water	Very difficult, because of high swelling in water	Readily possible because of high strength and low swelling
Drying	Forced and vacuum	Forced/vacuum and freeze drying	Forced/vacuum and freeze drying
Physical appearance in dried state	Rigid brittle	Rigid brittle	Rigid brittle
Characterization	Fast swelling and weak mechanical properties; moisture induced plasticization, fragile against bending, compression and tensile stresses	Fast swelling, and improved mechanical properties, moisture induced plasticization, higher modulus networks fail under brittle fracture mechanism	Fast swelling and improved mechanical properties, moisture induced plasticization, highly elastic in swollen state very resistant against different stresses, ductile fracture mechanism

Methods for preparation of superporous hydrogels

Following methods are useful in the preparation of superporous hydrogels:

1) Porosigen technique
2) Cross linking technique
3) Phase separation technique
4) Gas blowing technique

1) Porosigen technique

Porous hydrogels can be made by preparing the hydrogels in the presence of dispersed water-soluble porosigen. These porosigen are hydrophilic in nature. So, they solubilize as they come in contact with water and generate the porous structure in the hydrogel. The pore size

generated in the hydrogel depends on the size of porosigens. Examples of effective porosigens are micronized sucrose, lactose, dextrin, cellulose, sodium chloride, poly ethylene glycol (PEG) and poly ethylene oxides which form meshwork that can be removed by washing with water. [31-33]

2) Cross linking technique

Individual hydrogel particles can be cross-linked to form cross-linked aggregates. Cross linking of individual hydrogel particles lead to formation of aggregates of particles. The pores in such structures are present between hydrogel particles. The size of pores is much smaller than the size of particles. Pores are formed between the hydrogel particles. Such aggregate macrostructures were prepared by initially mixing the hydrogel particles (in the range of a few hundred micrometers) with a solution of a cross-linking agent, water and hydrophilic organic solvent such as isopropanol. This technique is limited to absorbent particles with chemically active functional groups on the surface. [34, 35]

3) Phase separation technique

In solution polymerization, monomers are usually mixed in diluent that is good for both monomers and polymers. If, however, the diluent is a nonsolvent for the polymer formed (e.g. Poly Hydroxy Ethyl Methyl Acrylate in water), the solubility of the polymers dramatically decreases as the polymerization proceeds. This results in phase separation of the polymer rich monomer phase into droplets, which then join together to form a network called with large spaces (e.g. heterogeneous, porous hydrogels) by the end of the polymerization process. This process is called heterogeneous solution polymerization. The pore sizes of macroporous hydrogels prepared by phase separation are typically only a few micrometers. In addition, the overall porosity is very low, and this implies that the pores are not well interconnected. The major limitation of the phase separation method is that only very limited types of porous hydrogels can be prepared. In addition, there is not much control over the porosity of the gels when prepared by phase separation. [36-38]

4) Gas blowing (or foaming) technique

Hydrogels can be prepared in the presence of gas bubbles. In this technique the monomers are polymerized or water-soluble polymer chains are cross-linked around gas bubbles generated by a blowing agent. The gas blowing technology has been widely used in the preparation of plastic foams from materials such as polyurethanes, rubber, and poly (vinyl chloride). The key ingredient in the foaming process is a blowing agent (or foaming agent), which is defined

as any substance or combination of substances capable of producing cellular structure within a polymer matrix. Foaming agents are classified as:

a) Physical foaming agents that expand when pressure is released (e.g., nitrogen and carbon dioxide) and
b) Chemical foaming agents that decompose or react to form a gas (e.g., sodium bicarbonate in the presence of acid).

Recently, the gas blowing technique was used in laboratory to prepare SPHs. Because this technique used is for the preparation of SPHs, they were also called "hydrogel foams." In the synthesis of SPHs by the gas blowing technique, foaming and polymerization have to occur simultaneously. They are safe, cheap and easy to use. [39] For this reason, it is important to control the timing for foaming and polymerization. In the study mentioned above, inorganic carbonates, such as sodium carbonate and sodium bicarbonate were used as the foaming agent. These inorganic carbonates have long been used safely as a gas-forming ingredient in effervescent tablets for antacids.

Drug Loading Into Superporous Hydrogel [40-43]

There are two methods for drug incorporation into superporous hydrogel:

1) Drug loading into superporous hydrogel reservoir devices
2) Drug loading into superporous hydrogel polymers

1) Drug loading into superporous hydrogel reservoir device

Two types of drug delivery systems have been designed:

1) Core inside shuttle system
2) Core attached to surface of shuttle system

These systems involve two components: a core and a conveyor system. Core is the part which contains drug blend with appropriate excipients and conveyor is made up of SPH and SPHC.

Core inside the shuttle system: In this system, core is prepared in two different forms viz. micro particles and gross mass.

Micro particles: These are prepared by dispersing the drug in melted polymers like PEG 6000 and cooling of the mixture to get gross mass. This gross mass is crushed in mortar and sieved through mesh size 400 µm, which is used as core material. SPHC is used as the body of the conveyor system because of its greater mechanical strength and SPH is used as the cap

of the conveyor system because of its high swelling ratio. A hole is made inside SPHC in its swollen state by use of borer, as the core has to be incorporated inside SPHC. The SPHC is then dried by either at ambient temperature or by reduced pressure at 60°C. This is called as the body of conveyor which is capped by piece of SPH.

Core attached to surface of shuttle system: In this system, core is in the form of small tablets which are prepared by dispersing the drug in melted polymer like PEG 6000 and sieving the mass through mesh size 400 μm, which were mixed with magnesium stearate and compressed into tablets using single punch machine (40 N hardness). The second component is conveyor made up of only SPHC in which two holes were made on counter side instead of one as in previous approach. The core material in the form of small tablets was placed inside the holes by using bio-adhesive (cyanoacrylate) glue. The polymer swells when it comes in contact with gastric fluids and the size of holes is enlarged. The glue helps to keep the dosage forms at the site of drug absorption. The same assembly is placed into gelatin capsule shells of size 000.

2) Drug loading into superporous hydrogel polymers:

The amount of water required for complete swelling of specific weights of SPH and SPHC is determined. Then, aqueous solutions of given drug is prepared in previously determined amount of water and weighed amount of polymer is placed in drug solution to suck up the drug solution. After 20 min, completely swollen polymers loaded with drug are placed in oven at 30°C for drying overnight.

Drug loading by using wide opening syringe: Wide opening syringe is used to load drug into superporous hydrogel. Drug is loaded at centre of SPH carrier in certain depth this avoids the use of biodegradable glue. Drug is directly dispersed or dissolves into mixture of monomers or initiators this avoids drug loss during loading.

Ingredients Required for Preparation of Superporous Hydrogel

The ingredients required for preparation of superporous hydrogel are shown in Table 4.

Table 4: List of Ingredients Required With Their Role for Preparation of SPHs [2]

Sr. No.	Role of Ingredients	Examples
1	Monomers	Acrylic Acid(AA),Acrylamide(AM), 3-Sulphopropyl acrylate potassium(SPAK),Hydroxy ethylmetyl acrylate (HEMA),N-isopropyl acrylamide (NIPAM), Acrlonitrile (AN), Polyvinyl alcohol(PVA)
2	Cross linking agents	**Chemical cross linker:** Glutaraldehyde,N,N-methylenebisacrylamide(BIS) **Ionotrpic cross linker:** Metal ions like calcium iron and phosphorus
3	Foam Stabilizers	Pluronic F127,Pluronic P105,Silwet L7605,Span,Tween
4	Polymerization initiator pairs	APS/TEMED(Ammonium persulfate /N,N,N,N-tetramethylenediamine, KPS/Sodium metabisulfite, APS/ Sodium metabisulfite, Azo-initiator(V545)
5	Foaming agents	Sodium bicarbonate, Sodium carbonate, Potassium bicarbonate
6	Composite agents	Crosslinked sodium carboxy methylcellulose(Ac-Di-Sol), Crosslinked sodium starch glycolate(Primojel), and Crosslinked polvinylpyrrolidone (crospovidone), Carbopol, Polyvinyl alcohol(PVA)
7	Hybrid agents	**Natural polymers:** Sodium alginate, Sodium carboxy methylcellulose (Na CMC), Chitosan based on ionotropic gelation,Pectin **Synthetic polymers:** Poly vinyl alcohol(PVA) based on cryogelation

SAP and SPHs Synthesis

Synthesis treatment

Since no foam stabilizer is normally used in the synthesis of SAPs, the foam spontaneously collapses under its weight and shrinks into a smaller volume. Synthesis of superporous hydrogels is same to the synthesis of ordinary hydrogels but the only difference is that a foaming agent is added to prepare superporous hydrogels. The timing of the polymerization has to be matched with the timing of foam formation. If the kinetics of the two processes is not matched, then superporous hydrogels with interconnected pores will not be formed. Fig. 3 explains the foaming process for the preparation of superporous hydrogels. The important step of this process is to use acid to control the polymerization kinetics. Addition of NaHCO3 leads to foam formation as well as rise in pH, which accelerates the polymerization process. After the addition of NaHCO3, polymerization becomes complete within a few minutes. The pH of the monomer mixture is low because of the addition of acid (A), and this makes polymerization very slow. The addition of NaHCO3 results in foaming and at the same time the pH of the solution rises (B). As pH increases it accelerates the polymerization process, which is completed before the foam subsides. This results in formation of superporous hydrogel (C). [44, 45]

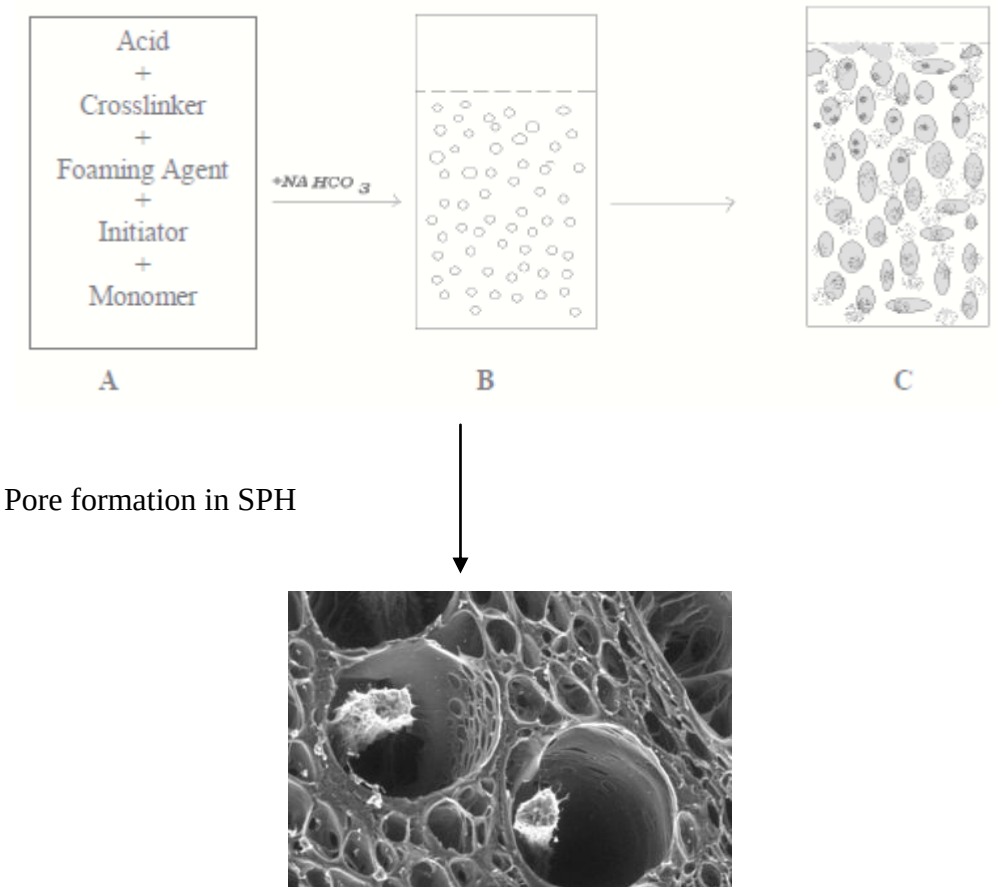


Fig. 3 Schematic representation of the superporous hydrogel preparation.

Postsynthesis treatment

In case of SAPs, the foamed product is then dried and mechanically ground. The ground mass, which is a mixture of granules and particles of different sizes, is screened in order to obtain a desired particle size distribution. It is these small granules and particles that provide superabsorbent property.

In case of SPHs, the foamed product is soaked into a nonsolvent, usually ethanol, for complete dehydration. Dehydration using ethanol helps to stabilize the foamed product and prevent it from shrinking. Complete dehydration results in a solid, brittle porous product, which is white in color because of heterogeneous combination of polymer and pores. Ethanol can be removed from the stabilized product by a short drying process. The final product can be ground into a particle shape, sliced into absorbent sheets or machined into any shape and size. Comparison of postsynthesis steps of SAPs and SPHs are shown in Fig. 4. [46]

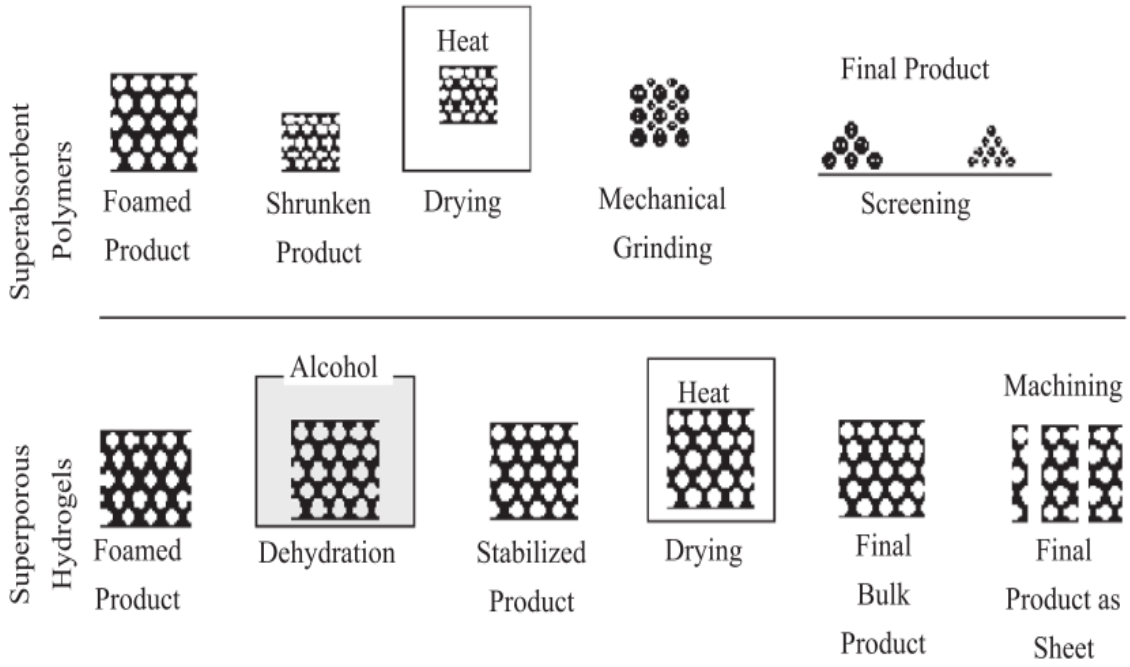


Fig. 4 Post-synthesis steps of SAPs and SPHs.

Characterization of superporous hydrogel (SPH)

1) Density

The density (d) of the dried hydrogels was calculated by equation:

$$d \equiv W_d / V_d$$

where, W_d is the weight of dried hydrogel,

V_d is its volume.

The volume of the hydrogel was determined by the solvent displacement method using hexane as the displacement fluid. Hexane was used because it is very hydrophobic and superporous hydrogels do not absorb it. [47]

2) Swelling time

Swelling time is the time taken by the hydrogel to attain its equilibrium swelling point. After this point the swelling of hydrogel was stopped. Swelling time was calculated by placing SPH in distilled water until it attained equilibrium swelling. Time required for equilibration was noticed. [48]

3) Swelling ratio

The dried SPH was allowed to hydrate in excess of deionised water at room temperature. The weight of fully swollen hydrogel is measured at different time interval, remove excess of water from surface by gental blotting. [49] The swelling ratio was determined by equation:

$$Qs = \frac{W_s - W_d}{W_d} \times 100$$

where, W_s is the weight of the swollen hydrogel,

W_d is the weight of the dried hydrogel,

Q_s is the equilibrium swelling ratio.

4) Water Retention time

Water retention capacity as a function of time determined from the following equation:

$$WR_t = \frac{W_p - W_d}{W_s - W_d} \times 100$$

Where, W_d = weight of the dried hydrogel,

W_s = weight of the fully swollen hydrogel,

W_p = weight of the hydrogel at various exposure times,

WR_t = Water Retention time.

For determination of the water-retention capacity of the hydrogels as a function of time and exposure at 37ºC, the water loss of fully swollen polymer at time intervals was determined by gravimetry. [34]

5) Porosity Measurement

The porosity of superporous hydrogel measured by immersing dried SPH in absolute ethanol over night and weighed after excess of ethanol on the surface was blotted. [37] The porosity was measured by following equation:

$$Porosity = \frac{M_2 - M_1}{\rho V} \times 100$$

where, M_2 = Mass of SPH in swollen state,

M_1 = Mass of SPH in dried state,

ρ = Density of ethanol,

V = volume of the hydrogel

6) Floating time

Floating time was performed by placing piece of superporous hydrogel in a beaker containing 100 ml of 0.1N HCl and at 37±0.5°C. Time taken by piece of hydrogel to rise on surface and float was taken as a floating lag time. The time for which it remains float is called total floating time. [50]

7) Gelation Kinetics

As gelation (polymerization reaction) proceeded, the viscosity of the mixture continuously increased until the full network (gel) structure was formed. Gelation time was defined as the duration of gel formation and was measured by a simple tilting method after adjustment of pH to 5.0 with acetic acid. It is determined by the duration of time taken by the reactant mixture to become viscous and henceforth the viscous solution no longer falls down in the tilted tube position. [41]

8) Mechanical strength

In order to withstand the pressure exhibited by gastric contents and its contractions, any hydrogel must show sufficient mechanical strength. Mechanical strength was measured by using bench comparator and gastric simulator. A gastric simulator, based on the water-hammer theory, utilizes a controlled amount of different types of stresses on objects immersed in the testing fluid to simulate the forces that a sample might receive upon ingestion in the body. The stress concentrated on the weakest part of the SPH body will lead to the formation of craze, crack and finally rupturing of the whole platform. The simulator measures the amount of energy absorbed by the sample until it fails under certain stresses. Conventional superporous hydrogels showed low mechanical strength when compared with others. [13]

9) Determination of void fraction

The void fraction can be calculated by the following equation:

Void fraction = Dimensional volume of the hydrogel / Total volume of pores

The void fraction inside superporous hydrogels is determined by immersing the hydrogels in HCl solution (pH 1.2) up to equilibrium swelling. The dimensions of the swollen hydrogels are measured and by using these data, sample volumes are determined as the dimensional volume. In the meantime, the amount of absorbed buffer into the hydrogels is determined by subtracting the weight of dried hydrogel from the weight of swollen hydrogel and the resulting values are assigned as the total volume of pores in the hydrogels. [15]

10) Scanning Electron Microscopy (SEM)

In order to ensure that porous structure generated during SPH synthesis, SEM analysis was performed to identify the morphology of a dried superporous hydrogel. The samples were coated with gold using Hummer sputter coater, then carried using a Jeol JSM-840 scanning electron microscope and captured the images using a digital capture card and Digital Scan Generator. [51]

11) In-vitro drug release studies

In vitro drug release of drug from the superporous hydrogels was evaluated in triplicate at 37±0.5ºC using a United States Pharmacopoeia (USP) Dissolution Test Apparatus Type 2 (paddle method) at a rotation speed of 50 rpm in 900 ml of 0.1M HCl (pH 1.2 buffer) for 6 h. At regular time intervals, 10 ml sample of the dissolution medium were withdrawn, replaced with an equivalent volume of fresh dissolution fluid and analyzed for the drug using a UV-Vis spectrophotometer at given wavelength. The release data obtained were fitted into various release models. [26]

12) Safety studies

The safety and non-toxicity of synthetic superporous hydrogels must be demonstrated before these delivery systems can be pharmaceutically acceptable. Swine emesis model study has been used to investigate the safety of novel gastro retentive SPH platforms. [14]

Pharmaceutical applications of superporous hydrogels (SPHS)

1) Development of Gastro Retentive Tablets

Dry blending and direct compression is used to make gastro retentive tablets. The SPH particles of acrylic acid/sulfopropyl acrylate copolymers are mixed with gelatin and tannic acid, and then tableted by direct compression. Formation of hydrogen bond between gelatin and tannic acid, as well as the carboxyl groups on the polymeric carrier, produce an integrated matrix, which is shown to be stable after swelling. The gastro retentive tablet can swell up to 22 times its own volume within a 40 min. period maintaining its original shape.[17]

2) Development of Fast-Dissolving Tablets

Fast-dissolving tablets are orally administered without the need for water and swallowing which is beneficial especially to children and the elderly. The methods used to prepare fast-melting tablets are freeze-drying, sublimation and direct compression. The first two methods make tablets that dissolve within 5–15 sec, but the technology is expensive and tablets

prepared are not strong mechanically. Another method of preparation of fast-dissolving tablets by the direct compression method is the addition of fine particles of SPH to the granulation or powder formulation. The SPH microparticles within the tablet core accelerate water absorption by an increased wicking mechanism. Tablets prepared by direct compression with the use of SPH microparticles disintegrate in less than 10 sec. [52]

3) Development of Sustained Release Drug Delivery

These systems can remain in the stomach for longer period of time and thereby can release the drug over a prolonged period. The problem of short gastric residence time encountered with an oral controlled release formulation can be overcome with these systems. These systems have a bulk density of less than one, as a result of which they can float on the gastric contents. These systems are relatively large in size so that they cannot pass through pyloric opening. [53]

4) Development of Site Specific Drug Delivery

These systems are specifically useful for drugs that are specifically absorbed from stomach or the proximal part of the small intestine e.g. riboflavin and furosemide. By targeting slow delivery of the drug to the stomach, desired therapeutic levels could be achieved and drug waste could be reduced. [54]

5) Development of Peroral Peptide Delivery Systems

Conventional SPHs and SPHCs for peroral peptide delivery have been investigated. These systems are designed to swell in the intestine with the SPH physically adhering to the gut wall and delivering the incorporated peptide directly to the site. The carboxyl-carrying SPHs can potentially induce calcium extraction, presumably causing the tight junctions of the gut wall to open and deactivating the harmful gut enzymes. After peptide delivery and absorption across the gut wall, the SPH becomes over-hydrated and is broken apart by the peristaltic forces of the gut. The proper selection of the type and thickness of enteric coating will potentially help to target this dosage form to any specific site in the small intestine or to the colon. [36]

6) Development of Diet Aid

The main aim of this approach is to control the body weight by reducing the food intake with the administration of superporous hydrogel tablets. When these tablets are taken they occupy a major portion of the stomach space, leaving less space for food and they suppress the

appetite. For diet control, the superporous hydrogels can be prepared which are taken orally are modified to delay the swelling. Superporous hydrogels can be loaded inside hard gelatin capsules for delaying the swelling. This will reduce any disquiet on the early swelling of superporous hydrogels for clinical applications. [9]

7) Development of Occlusion Devices for Treatment of Chemoembolization

Chemoembolization is a combined method of embolization and chemotherapy. Embolization has been used for cancer treatment by restricting the oxygen supply to the growing tumours. This method could be combined with chemotherapeutic agents to achieve local delivery and low systemic toxicity. A chemotherapeutic agent and an anti-angiogenic agent could be loaded into SPHs for chemoembolization therapy. The strong SPHs are better candidates for this application because they fit better in the blood vessels and provide better blocking.[12]

8) Development of Occlusion Devices for Treatment of Aneurysum

SPHs can also be used to produce biomedical devices for the treatment of aneurysms. An equivalent SPH is prepared in smaller size after determining the size and shape of an aneurysm site. When a superporous hydrogel is positioned at the aneurysm site, it swells quickly to occupy the space and make the blood clot. Deposition of superporous hydrogels can result in up to 95% aneurysm occlusion without any evidence of parent artery compromise and inflammatory response. A new occlusion device prepared by combination of superporous hydrogel and platinum coils, called as Hydrocoil. [29]

9) Biomedical applications

In the biomedical area, SPHs and SPH composites can be used to make various biomedical devices, such as artificial pancreas, artificial cornea, artificial skin, articular cartilage, soft tissue substitutes, cell growth substrates in tissue engineering, burn dressings, surgical augmentation of the female breast or hemoperfusion in blood detoxification and in the treatment of uremia. Vascular ingrowth into superporous hydrogels are useful for cell transplantation, tissue engineering and in combination with cell therapies. Hydroxyapatite containing super porous hydrogel composites 35 and novel scaffolds of poly (2-hydroxyethyl methacrylate) super porous hydrogels are useful for bone tissue engineering. [27]

10) Biotechnological applications

Biotechnologically, SPHs are used in the separation of macromolecules and cells from the medium. SPHs and SPH composites are ideal materials for chromatographic supports due to

their extremely larger pores. [3]

11) Structural applications

The low density of SPHs and SPH composites allows applications as a high-strength, light-weight structural material as well as a packaging material. They will be also good as insulators and fillers in structures with energy sensitive applications. [14]

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