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Review Article

SUPERPOROUS HYDROGELS: CHARACTERISTICS AND APPLICATIONS IN THE DEVELOPMENT OF PHARMACEUTICAL FORMULATION

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ABSTRACT

Drug delivery advancements are playing a major role in the pharmaceutical industry for delivering new chemical entities that are not able to reach the commercial market owing to challenges in their absorption, metabolism or any other issue. Gastroretentive drug delivery systems are one such approach that is being developed for drugs with narrow therapeutic index and have absorption window in stomach. Hydrogels were developed basically as a means to regulate drug release when compared to conventional dosage forms [1].

Keywords: Superporous Hydrogels, Characteristics, Applications, Development of Pharmaceutical.

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INTRODUCTION

The term Hydrogel was first coined in 1894 as a means of explanation of a colloidal gel that tended to absorb large water quantities making them rubbery and soft. Wichterle and Lim in 1960 first reported biomedical applications of hydrogels [2-4].

Hydrogels or aquagels are hydrophilic polymers that are cross linked and have structured network that consists of acidic, basic, or neutral monomers capable of absorbing high quantities of water. Cross linked polymeric chain form the solid portion of the hydrogel resembling a mesh; with spaces in between filled with fluid normally water. An elastic force is imparted when the water is upheld in the mesh. Ionizable groups are bound to polymer chain surface along with mobile ions like counter/co-ions owing to the presence of electrolyte solvent form the ionic phase of the hydrogel (fig. 1). Hydrogels are classified into non-porous, micro porous, macro porous and super porous [5-8].

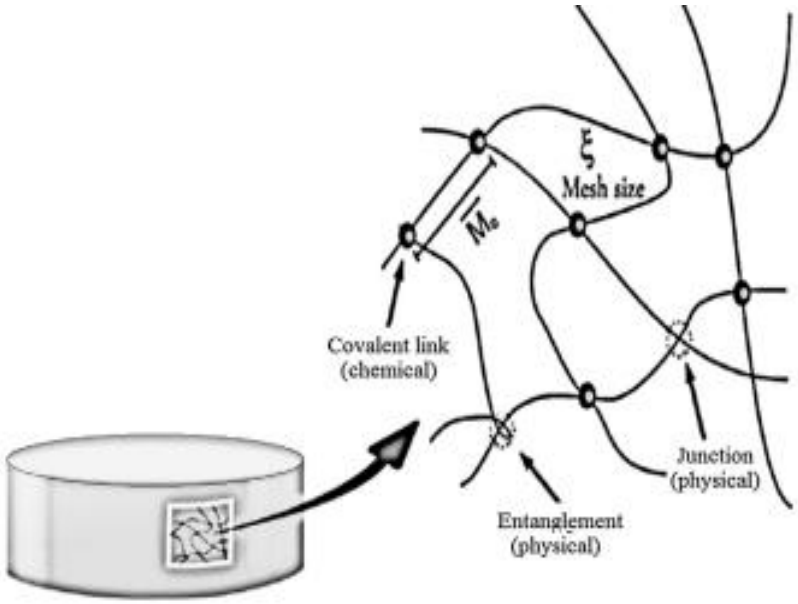

Fig. 1: Structure of a hydrogel

Super porous hydrogels

Superporous hydrogels (SPH) are one of the advancements in hydrogels that were introduced to the pharmaceutical field in 1998 and were characterized by high mechanical strength and elasticity [2]. SPH is 3-dimensional network of hydrophilic polymers capable of absorbing high amounts of water in relatively short time period. They are different from other hydrogels in terms of size of pore that ranges in 50–100 micron and manufacturing methods of the same. The pores are interconnected to form a capillary resulting in capillary wetting rather than diffusion. This results in quick swelling of SPH in minutes irrespective of their pore size owing to rapid water absorption from capillary force in preference to diffusion. Thus, this approach is for improvement of gastric retention time of the drugs concerned by swelling to large size with required mechanical strength to overcome gastric contraction pressure [9-12].

Principle of action

The major principle as discussed above is swelling action of SPH that results in gastric retention. A small capsule is filled with the required amount of SPH aiding in swallow for oral administration. Rapid swelling to a large size in the stomach is observed that prevents its emptying in stomach. Gastric contraction results in gastric tissue rolling over the hydrogel; but since the hydrogel is slippery, elastic with high mechanical strength, it withstands the pressure and floats in the gastric fluid owing to its low density releasing the drug. Once the drug is released, degradation of hydrogel either due to mechanical force or by enzymatic/chemical polymeric chain degradation occurs [13-16].

Classification of SPH

Strive to modify certain characteristics of SPH for a particular application gave rise to various generations. Progressing of generations indicated enhanced elasticity and mechanical properties. SPH are classified into following three generations.

First generation SPH (conventional SPHs, CSPHs)

Their discovery dates to 1999 by Chen *et al.* who reported their rapid kinetics of swelling and super absorbent nature resulting from polymerization and cross-linking various vinyl monomers with aid of foaming agent, a foam stabilizer and a foaming aid. The porous structure of SPH was preserved using alcohol assisted dehydration. The monomers used were highly hydrophilic (acrylamide) or ionic (salts of acrylic acid or sulfopropyl acrylate) monomers [17, 18].

Second generation SPH (SPH composite, SPHCs)

A critical addition that made second generation SPH different from the first ones was introduction of a swellable filler keeping the initial monomer, crosslinker and initiating system same. The preparatory process involves dispersing the filler into reacting mixture that would absorb a mixed solution of monomer, crosslinker and initiator and the water-soluble foaming additives. The filler particles that are now swollen assumed the role of a reactor, wherein polymerization and crosslinking occurred at the same time. Reaction at the interface of the swollen particles resulted in connection to each other through the extended polymeric chains that on drying resulted in formation of an interpenetrated network structure (IPN). This alteration resulted in enhanced mechanical properties [19-22].

Third generation SPH (SPH hybrid, SPHHs)

Thirst for development of hydrogels with much enhanced mechanical properties resulted in third generation ones which were elastic and superporous; the difference being these having integrated IPN structure and use of a water-soluble counterpart (hybrid agent) that undergoes even diffusion and dissolution into reacting solution resulting in formation of an integrated semi-interpenetrating network. Sodium alginate, sodium carboxymethyl cellulose and chitosan are some of the hybrid agents used [23-26].

Manufacturing techniques

Basically 4 major types of processes are employed in preparation of gastro-retentive SPH.

Porosigen technique

A dispersed hydrophilic porosigen like sodium chloride, micronized sucrose and PEG is used. Hydrogel pore size depends on the porosigen size. The porosigen can be removed by water assisted washing to leave a meshwork [27].

Cross linking technique

Particle aggregation is achieved by cross linking of every hydrogel particle. The pores are smaller than hydrogel particle size. The method is limited to absorbent particles with presence of surface chemical active groups [28].

Phase separation technique

Mixing monomers takes place in diluents that is suitable for both monomer and polymer. This technique is based on a decrease in solvent quality for polymers. The major challenge is only very restricted types of porous hydrogels (such as HEMA and NIPAM) can be processed with not much regulation on pore size of the macroporous hydrogel [29].

Gas blowing or foaming technique

In the preparation of SPHs, a bicarbonate foaming agent is used, which is water soluble and becomes active in an acidic aqueous medium. So, a solution polymerization is a preferred method of SPH synthesis. Aqueous solutions of monomer, cross-linker, foam stabilizer, and foaming aid are added in turn to the reacting mixture under very mild mixing. Following complete homogenization, the reductant and oxidant are added consecutively and are mixed quickly with the reacting mixture. In a very short period, the solid foaming agent (e. g., bicarbonate) is effectively dispersed and mixed throughout the reacting solution. The bicarbonate reacts with the foaming aid (e. g., an organic acid) to generate carbon dioxide gases; this reaction in turn increases the pH of the reacting solution, which favors the decomposition of the initiator. Due to the retarding effect of the oxygen, there is an induction, or lag period, which is followed by a fast exothermic polymerization reaction. The foaming and gelling reactions occur almost simultaneously and proceed to their maximum extent at the polymerization temperature, which is determined by the type of monomer, its concentration in the solution, and initiator concentration. A successful SPH is synthesized if the chemical gelation and physical foaming happen in a synchronized way. The formation of the SPH foam requires the CO gases to be entrapped within the hydrogel matrix, and this would be possible if the reacting hydrogel mass reaches certain viscosity [1, 14, 22, 26, 30].

Characterization

Swelling studies

Initial weight of completely dried SPH is noted and SPH is immersed in excess of swelling medium. At defined intervals, weight if the SPH is notes after blotting excess surface water. Swelling ratio is calculated by

$$Q = (M_s - M_d)/M_d$$

Q is the swelling ratio, M_s the mass in the swollen state and M_d the mass in the dried state.

Porosity measurement

Dried hydrogels are subjected to overnight immersion in absolute alcohol followed by weighing after excess of ethanol is blotted. Following equation is used in calculation of porosity:

$$\text{Porosity} = (M_2 - M_1)/\rho V$$

Where M_1 and M_2 are the mass of the hydrogel before and after immersion in absolute ethanol, respectively; ρ is the density of absolute ethanol and V is the volume of the hydrogel

Void fraction determination

SPH are subjected to immersion in HCl solution (pH1.2) till equilibrium is attained. This is followed by determination of dimensions of the swollen hydrogel. Difference between the weight of the swollen hydrogel and the weight of dried hydrogel gives the amount of buffer absorbed into the hydrogel's indicative of total pores volume.

The void fraction was calculated by the following equation:

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

Mechanical properties

A bench comparator is used in determination of compressive strengths of various SPH

The pressure at this point called penetration pressure (PP) was calculated by the following equation:

$$PP = F_u/S$$

Where F_u is the ultimate compressive force at complete breakage of polymer and S is the contact area of the lower touch.

Determination of drug content

The weight of SPH containing about 4 mg of drug is mixed with 10 ml HCl solution (pH 1.2) in a volumetric flask and volume made up to 100 ml. The solution is subjected to filtration and analysed for drug content in a UV-Vis spectrometer.

Measurement of density

The solvent displacement method is used for determination of apparent density of SPH. SPH mass is measured followed by placement in a graduated cylinder filled with known volume of hexane.

Density = MSPH/VSPH where

MSPH: Mass of SPH VSPH: Volume of SPH

Structural analysis

FTIR and SEM analysis are carried out to study the SPH morphology. FTIR indicates drug excipient compatibility in addition to revealing polymer chemical structure. SEM gives information on morphology of dried sample.

Stability studies

The formulated batches are placed in airtight containers and stored in stability chamber at 40±2 C and 75±5 C % RH for 3 mo followed by in vitro dissolution studies that are compared with the initial ones.

SPH characteristics

SPH can be made as an appealing drug delivery dosage form owing to their reaction to various external stimuli like changes in pH, temperature. Such polymers are called smart polymers that indicate an advanced SPH. These undergo reaction by increasing or reducing their swelling nature resulting in a change of their 3-D structure. A drug loaded with such SPH can have a altered release rate into the biological surroundings.

Applications

SPH were originally applied to medical field for sustaining retention of drugs with narrow absorption window. Delivery of drug in a SPH need to consider drug interactions with the polymer forming hydrogel caused by functional groups. As an example, high moisture content of SPH attenuate hydrolysis of drugs containing amide groups on storage [31, 32].

Gastric retention

Floating and muco-adhesion were initially designed approaches for gastro retention. Swelling has also been made use of increasing the drugs residence time with small absorption window. For a swellable hydrogel to be administered to achieve gastro retention, the hydrogel should undergo expansion by 2-3 times the original size in gastric fluid. For such systems, a sound knowledge of physiological and biopharmaceutical aspects of gastric fluid is required. As an example, rate of swelling is dependent on gastric emptying. In cases where the stomach is filled with water only, it takes about 25 min for half the water consumed to be depleted from stomach. This means that the hydrogel if not increases in size in less than 25 min, then prior depletion of hydrogel from gastric region would start [33-38].

Overall, SPH which are designed for gastric retention need to be safe chemically; maintain their features in acidic gastric pH and resist the contraction forces of the GIT. Of all, the major critical factor that needs to be taken into account is interaction of SPH-DDS platform. In a study, a drug delivery system was designed employing combination of different ratios of two polymers – HPMC and PVP. Pure drug release from SPH platform was observed in<30 min. In DDS containing higher HPMC ratio, prolonged drug release for a longer period of time was noted mimicking a zero order release. This can be explained by solubility behavior of both polymers. PVP is ready water soluble even in presence of little quantity of water whereas HPMC requires more quantity of water to undergo complete dissolution. Thus when HPMC containing DDS is enclosed in SPH, lack of water accessibility results in formation of thick gelatinous mass inside of SPH that is responsible for slow release of drug over a longer duration of time [39-43].

Peroral intestinal delivery

Peptide and protein administration by peroral route have been studied broadly by formulating in various generations of SPH. F. A Dorkoosh *et al.* studied SPH and SPH composites polymers for improvement of insulin absorption through in healthy pigs. Relative bioavailability with respect to intraduodenal insulin administration were about 1.3-1.9%. In other studies, release pattern of peptides like Buserelin, Octreotide, and insulin, desmopressin in vitro intestinal absorption, and paracellular tight junction opening mechanism in the Caco-2 cells have been examined [44-47].

SPHs as diet aid

A SPH with high selling potential can be designed to occupy a large volume of gastric part to give the feeling of fullness. To achieve this, about 400 ml of stomach should be occupied by SPH. Moreover, water should also be studied as control to check if it can induce fullness. SPH can also be formulated with other excipients that adjust pH of stomach or its mobility to achieve this feat.

SPHs as superdisintegrant

In general, super disintegrants are polymers that are based on cellulose, PVP and derivatives of starch characterized by tailor made swelling property. These are mixed in various solid dosage forms to attain a specific disintegration rate. SPH also are crosslinked hydrophilic polymeric network with same swelling property and thus can be modified to achieve super disintegration. A major concern that needs to be taken care of is SPH is employed as a single platform, conferred to a cylindrical shape for purpose of gastric or intestinal retention. However to achieve super disintegration, particulates of SPH need to be produced in powder form that can be achieved by SPH slab grinding or can be directly formulated in powdered form by inverse dispersion method (fig. 11). Super disintegrant made out of SPH and conventional polymers differ in way that the former provides larger surface area owing to its small size and pore content [48, 49].

Biomedical applications

SPH are being frequently researched in biomedical field for their porous nature and considerable surface area that is biocompatible allowing a number of sites for attachment and growth of cell thus serving the ideal purpose of cell scaffolding. SPHs based on poly(2-hydroxyethyl methacrylate) (pHEMA) are quite popular for tissue engineering applications. As an example pHEMA based SPH has been studied for bone tissue engineering. Other scaffolds that have been researched are pHEMA--gelatin SPHs, glycerol phosphate-cross-linked pHEMA--gelatin SPHs. These swellable hydrogels have also been studied in chemotherapy and chemoembolization [50-52].

Manufacturing considerations

Following are the major factors that need to be kept in mind while working on SPH:

Ability to take laboratory pilot synthesis to a larger scale, including full production.

Producing a consistent and well-characterized product will be necessary for approval by regulatory agencies

Range and variances for specific characterizations such as pore size and its distribution, mechanical strength and swelling must be maintained and reproducible in production allowing proper identification and characterization of the SPH dosage form Safety and efficacy must also be established

The safety of SPHs may be addressed by demonstrating biocompatibility and purity of the final product

Since SPHs are subject to degradation over time, unwanted byproducts may be produced from interactions with their surrounding environment on long-term storage. Understanding the changes that can alter the identity of an SPH will allow for techniques that minimize or eliminate them, producing a more stable product

Formulation of superporous hydrgel

For the synthesis of SPHs, the following substances were subsequently added into a beaker: Varying concentrations of Chitosan aqueous

solution 6 %w/v, 3 ml AM 50 %w/v; 2 ml AA 50 %v/v; 0.7 ml BIS 2.5 %w/v; 0.3 ml span 80 10 %v/v; 0.25 ml APS 20 %w/v; 0.25 ml TEMED 20 %v/v; and 20g of sodium bicarbonate. In this procedure, polymerization was allowed to continue for approximately 10 min. After adding each substance to beaker, the reaction mixture was vigorously with mechanical stirrer. Finally, sodium bicarbonate was added very quickly to the solution and stirred for required time based upon formulation requirement. Synthesized SPHs were removed with a spatula, allowed to dry in oven at 55 °C for 48 h. The SPHs were washed with hexane. This treatment dehydrated the SPHCs rapidly as well as provided drying. These SPHCs were stored in an airtight container until further characterization; shown in fig. 1. After characterization, optimized SPH were crushed into powder and used as superdisintegrant to formulate mirtazapine oral disintegrating tablets.

Fig. 2: Superporous hydrogels

Table 1: SPH formulations

S. No.	Ingredient	MSPH1	MSPH2	MSPH3	MSPH4	MSPH5
1	Acrylic acid 50%v/v (ml)	2	2	2	2	2
2	Acrylamide 50%w/v (ml)	1	2	3	4	5
3	Chitosan 6%w/v (ml)	4	4	4	4	4
4	BIS 2.5%w/v (ml)	0.7	0.7	0.7	0.7	0.7
5	Span 80 10%v/v (ml)	0.3	0.3	0.3	0.3	0.3
6	Ammonium persulphate 20%w/v (ml)	0.25	0.25	0.25	0.25	0.25
7	TEMED 16.7%w/v (ml)	0.25	0.25	0.25	0.25	0.25
8	Sodium bicarbonate (g)	2.9	2.9	2.9	2.9	2.9

Table 2: Role of excipients in formulation of superporous hydrogels

Excipients	Role
Acrylamide, Acrylic Acid	Monomers
Cross-Linker	Bisacrylamide (BIS)
Solvent	Deionized Water
Oxidant/Initiator	Ammonium Persulfate
Reductant	TetramethylEthylenediamine (TEMED)
Foaming Agent	Sodium Bicarbonate
Foaming Aid	Glacial Acetic Acid
Property Modifier/Composite Agent	Chitosan
Surfactant	Span 80

Evaluation of SPH

Porosity

The porosity of the hydrogel films was measured in a 20 ml beaker, and then the empty beaker weight (W_1) was measured. Up to 1 g of hydrogel film was placed into the beaker, and an inert solvent, cyclohexane, was slowly poured in. The weight (W_2) of the beaker was then measured. After that, the hydrogel films were removed and weighed (W_3). The hydrogel film pores were full of cyclohexane, and the volume of cyclohexane in a hydrogel film pore was taken as the pore volume of the hydrogel films. The porosity of the porous gel (P) was calculated using the following equations [53].

- $Vg = 20 – (W_2\text{-}W_1\text{-}1)/\rho h$
- $\rho g = 1/Vg$
- $Vp = (W_2\text{-}W_3\text{-}1)/\rho h$
- $P = Vp/Vp+Vg$

Where ρg is the density of the hydrogel (g/cm^3), ρh is the density of the cyclohexane (g/cm^3), Vg is the volume of the hydrogel (cm^3), and Vp is the volume of cyclohexane in the pore (cm^3).

Mechanical strength

The Laboratory comparators are used to test the mechanical properties of Superporous hydrogels and their compounds. The sample swelled in simulated gastric juice was placed longitudinally under the bottom of a bench-top comparator connected to a micro-weather pressure gauge. The weight is placed on the top contact of the bench-top comparator at increasing intervals. A pressure gauge was used to measure the swelling height of the superporous hydrogel under pressure. Calculate the pressure exerted on the Superporous hydrogel based on the weight and the contact area. In order to characterize the mechanical properties of the Superporous hydrogel, two parameters were determined: the swelling height under a water pressure of 100 cm and the final compression pressure [54].

CONCLUSION

Superporous hydrogels represent a significant advancement in hydrogel technology due to their unique ability to absorb large amounts of water rapidly and retain their structure. Their interconnected porous network provides rapid swelling and excellent mechanical properties, making them highly suitable for applications in drug delivery, tissue engineering, and wound care. Continued research and development could further optimize their performance and open doors to even broader biomedical and industrial applications.

The development of superporous hydrogels has provided researchers with a versatile platform for addressing challenges in controlled drug release and tissue engineering. Future work should focus on enhancing their biodegradability, biocompatibility, and functionalization to match specific therapeutic needs.

Given their remarkable swelling capabilities and structural stability, superporous hydrogels are poised to revolutionize fields such as targeted drug delivery and regenerative medicine. Their adaptability allows for tailored modifications, potentially improving patient outcomes in a range of clinical scenarios.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

Declared none

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