Available online at www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2016; 8(10): 1418-1422

ISSN- 0975 1556

Research Article

# Hydrogel Advancement: A New Approach for Gastroretentive Drug Delivery

Sharma P K, Asthana G S*, Asthana A

*MM College of Pharmacy, MM University, Mullana*

*Available Online: 15th October, 2016*

**ABSTRACT**

Oral administration of dosage form is the priority for the patients as per its easy administration, economical formulation and various other reasons. Drugs having good absorption in proximal gastrointestinal tract (GIT) part possess bioavailability problem due to less gastric residence time of drug in the stomach. Thus superporous hydrogel (SPH) is a supreme approach to deliver the drug in upper part of GIT. SPH are prepared by using polymers which are hydrophilic in nature and can absorb considerable amount of water and swell. These SPH increase their dimension due to high swelling and resist entry from pylorus to small intestine. Thus increase gastric residence time. There are three generations of SPH based on their swelling index and mechanical strength. First generation called Conventional SPH (CSPH); second generation called SPH composite (SPHC) and third generation called SPH hybrid (SPHH). Third generation SPH possess good mechanical properties and are elastic in nature. Thus these are more suitable for prolonged gastric residence time. Beside their utility in gastroretentive drug delivery, SPH possess various pharmaceutical applications such as peptide drug delivery, fast dissolving tablet, tissue engineering, appetite suppressant, aneurysum and chemoembolisation. This article describes a brief discussion of SPH and its various aspects related with its method of preparation; characterization; various generations of SPH and its applications.

**Keywords:** Hydrogel, gastroretentive, narrow absorption window

## INTRODUCTION

Since few decades' site specific drug delivery has become an important area of research. Delivery of drugs having narrow absorption window; good stability in acidic pH and degradation in alkaline pH; having good absorption in upper gastrointestinal tract (GIT) part are good rational for delivery of drugs at stomach site. There are various techniques for Gastro retentive drug delivery such as low density system (floating drug delivery); raft system; mucoadhesive drug delivery and swelling and expandable system. Superporous hydrogel (SPH) are swelling and expandable type of system. They consist of hydrophilic polymers that have capability to absorb large amount of water and swell quickly. Due to excellent swelling of SPH when kept in swelling medium, they have been used for gastro retentive drug delivery. Various hydrophilic monomers used for preparation of SPH include acrylamide, acrylic acid, 2-hydroxyethyl methacrylate, N-isopropyl acrylamide, N- vinyl pyrrolidone etc. After swelling size of SPH become increase that prevents the entry of SPH to pass through pylorus. But gastric retention of dosage form not only limited to swelling properties of SPH. It is also desirable to keep the dosage form in harsh gastric environment for prolong period of time. Thus with optimum swelling properties, SPH should also have good mechanical strength to withstand with stomach contractile environment. There are various methods of preparing Superporous hydrogel.

*Method of preparation of Superporous hydrogel (SPH)*

Superporous hydrogel can be prepared by following methods:

Porosigens Technique
Phase separation Technique
Cross linking Technique
Gas blowing Technique

*Drug Loading into Superporous Hydrogel*

Drug is loaded into this superporous hydrogel delivery system by using any of two techniques.

Drug loading into superporous hydrogel reservoir devices
Drug loading into superporous hydrogel polymers

*Drug loading into superporous hydrogel reservoir devices*

Whole superporous hydrogel can act as reservoir devices for the different drug delivery systems like controlled release mini tablets or microparticles. Two types of drug delivery systems have been designed:

Core inside shuttle system
Core attached to surface of shuttle system

Both systems are consisting of two components named as a core and a conveyor system. Drug blend with appropriate excipients is termed as core and conveyor is made up of SPH and SPHC[5].

*Core inside the shuttle system*

In this system, core is prepared in two different forms viz. micro particles and gross mass. For micro particles preparation, the drug is dispersed in melted polymers like

**Author for Correspondence: gyatimmu@gmail.com*

Table 1: Composition used for preparation of SPH

| Ingredients | Properties |
|---|---|
| Acrylamide, acrylic acid | Monomers |
| Bis-acrylamide | Cross linker |
| Pluronic F-127 | Foam stabilizer |
| Ammonium per sulphate (APS) | Redox initiator |
| Tetramethylethylenediamine | Reaction catalyst |
| Sodium bicarbonate | Foaming agent |

PEG 6000 and then whole mixture is cooled to get gross mass. This gross mass is crushed and sieved and used as core material. SPHC is work as the body of the conveyor system because of having good 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 which were mixed with lubricant and compressed into tablets using single punch machine. The 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 (mini tablet) was put inside the holes by using bio-adhesive glue i.e. (cyanoacrylate). 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 whole assembly is kept into gelatin capsule shells of size 000.

*Drug loading into Superporous hydrogel polymers*

The amount of water used for full swelling of hydrogel is determined. Then, drug solution in determined amount of water is prepared and weighed amount of hydrogel 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[6].

*Drying of Superporous Hydrogel*

Superporous hydrogel are dried under two different conditions. Under Condition I, drying of swollen superporous hydrogel are carried out by keeping under blowing warm air (60 °C) in an oven for a day. Under Condition II, firstly absolute ethanol (5–10 ml) is used to dehydrate the swollen superporous hydrogel. After this initial dehydration step, superporous hydrogel are dehydrated further by placing them in 50 mL of absolute ethanol several times to ensure complete replacement of the water by ethanol. During the dehydration process, the soft and flexible superporous hydrogel convert into hard and brittle form. After the dehydration is completed, the excess ethanol in dehydrated superporous hydrogel is removed by draining using paper towel. Then the superporous hydrogel are dried in an oven at 55°C for a day[7]. Further various generations of SPHs were developed with improvement in these parameters like better mechanical strength, elastic properties and high swelling properties.

*Various generations of Superporous hydrogel*

There are three different generations of superporous hydrogel.

*First generation Superporous hydrogel*

These are also described as Conventional SPH (CSPH) with having fast swelling kinetics and super absorbent properties[8]. Monomers used for the preparation of CSPH Monomers include vinyl monomers like acrylamide, ionic monomer like salt of sulfopropylacrylate potassium, acrylic acid etc. Alcohol preserves the porous structure of SPH. The dried CSPHs so formed have poor mechanical strength. Conventional superporous hydrogel cannot withstand for long time in hostile gastric environment like gastric contraction, enzymatic degradation and gastric fluid content.

*Second generation Superporous hydrogel*

These are also referred as superporous hydrogel composites (SPHC) due to use of composite agents in their preparation. SPHC were prepared with some modification in CSPH[9]. These second generation superporous hydrogel possesses good mechanical strength as compared too conventional one but the SPH composites are still brittle in nature and cannot tolerate the stress for prolonged period of time and fractured. Composite agents used include Cross-linked sodium carboxy methylcellulose (Ac-Di-Sol), Carbopol, Polyvinyl alcohol (PVA). Cross-linked sodium starch glycolate (Primojel) and Cross-linked polyvinylpyrrolidone (crospovidone).

*Third generation SPH (SPHH)*

Superporous hydrogel of third generation possess excellent mechanical strength. Their excellent mechanical properties are due to use of hybrid agents that provide elastic characteristics to these superporous hydrogel[10]. Due to these elastic and rubbery characteristics SPH hybrid can tolerate stress condition for more period of time. Hybrid agents used in third generation superporous hydrogel includes Sodium alginate, sodium carboxymethyl cellulose and chitosan which possess good ionogelation properties.

*Evaluation parameters of Superporous hydrogel*

*Swelling Studies*

*Swelling time*

This is an important characteristic of superporous hydrogel. Time of swelling of hydrogel was determined by putting hydrogel in swelling media and time was noted upto equilibrium swelling.

*Swelling ratio*

Firstly, hydrogel was fully dried and then keep in excess of swelling medium. At predetermined time hydrogel was taken out from the media and weighed. The swelling ratio was determined as: $Q_s=W_s-W_d/W_d{}^x100$

Where $Q_s$ - Swelling ratio, $W_s$ - Weight of hydrogel in swollen state and $W_d$ - Weight of dried hydrogel.

*Density measurement*

After drying, superporous hydrogel lose their cylindrical shape and hence it is difficult to measure their volume directly. Thus solvent displacement method is used to

Table 2: Various methods for preparation of Superporous hydrogel

| Techniques | Ingredients | Advantages | Drawbacks | References |
|---|---|---|---|---|
| Porosigen | Micronized form of sucrose, lactose, dextrin and cellulose, sodium chloride, PEG, and PEO. | Good swelling due to porosigens that generates porous structure when comes in contact with water. | Very poor mechanical strength | (1) |
| Phase separation | Monomers + Diluents (Insoluble for formed polymers) | Good swelling and improvement in mechanical strength. | Not suitable for hydrogel synthesized by HEMA and NIPAM | (2) |
| Cross linking Technique | Monomers + Cross linkers such as Glutraldehyde | Good swelling as well as mechanical strength | limited to absorbent particles with chemically active functional groups on the surface | (3) |
| Gas blowing Technique | Monomers + Cross linkers + Redox initiator (APS), Catalyst (TEMED), Foaming agent ($NaHCO_3$) | Good swelling and improvement mechanical strength | Further improvement in mechanical strength needed | (4) |

*PEG-Polyethylene Glycol; PEO- Polyethylene Oxide; HEMA- Hydroxy ethyl methyl acrylate; NIPAM- N-Iisopropyl Acrylamide; APS-Ammonium per Sulphate; TEMED- Tetramethylethylenediamine.

determine the density of SPH which represents the apparent density of SPHs. A hydrophobic solvent hexane can be used for this purpose because it is not absorbed by the SPH. By using forceps, the pre-weighed SPH immersed in hexane in graduated cylindrical. Initial volume of hexane was noted and the increase in volume was also noted. Density was calculated as: Density = Mass of superporous hydrogel / Volume of solvent displaced

*Porosity measurement*

Porosity is an important parameter that affects swelling ratio, mechanical strength and drug release profile. For determination of porosity, dried SPH was kept in hexane overnight and weight was taken after excess hexane on the surface was blotted. The porosity was calculated as

Porosity = $V_P/V_T$

Where $V_P$ ($V_T$-$V_{SPH}$) is the pore volume of SPH and VT is the total volume of SPH. Total volume of SPHC can be measured from its dimensions, as it is cylindrical in shape.

*Mechanical properties*

Mechanical properties or compressibility of SPH is determined to measure the strength of SPH to withstand at gastric fluid pressure. Chen et al described the method to measure the penetration pressure of SPH. The fully swollen hydrogel put longitudinally under the lower punch and weight was successfully applied to the upper touch until the SPH completely fractured. The pressure where SPH fractured is termed as penetration pressure (PP) which is calculated by the following equation:

$PP = F_u/S$

Where $F_u$ - Ultimate compressive force at complete breakage of polymer and

S - Contact area of the lower touch (20).

*Estimation of drug loading capacity*

The amount of drug loaded in SPH is estimated by soaking method. In this method the quantity of buffer necessary for complete swelling of SPH was determined. After that required amount of buffer is prepared and SPH is kept in drug solution and left SPH sucked up drug containing swelling media. Then the fully swollen SPH loaded with the drug is placed in an oven at 30˚C for drying overnight[14].

*Estimation of drug content*

Drug loaded SPH is weight and placed in 100 ml volumetric flask. About small quantity of buffer is added, mixed well and make up to the volume. The mixture is filtered and drug content is analyses using UV-Vis spectrophotometer at appropriate wavelength.

*Surface morphology*

Scanning electron microscope (SEM) was used for determination of morphology of superporous hydrogel. SEM study is useful in determination of Porous structure and pore size of superporous hydrogel.

*Determination of gelation kinetics*

The gelation time is defined as the time required for gel formation after addition of initiators. The time taken by the hydrogel to keep in descending tilting position was determined.

*In vitro release studies*

The *in vitro* studies of drug loaded SPH is determine with the help of USP type II dissolution testing apparatus. The drug release study is performed in 900 ml swelling media at 37 ± 0.5°C and 50 rpm. Sample is taken at predetermine interval times and replenishment is done with same quantity of fresh medium. The withdrawal sample is filter by passing through 0.45 µm membrane filter and diluted the sample if needed. The absorbance of these solutions is measured at appropriate wavelength UV/Vis double beam spectrophotometer. The cumulative percentage of drug release is calculated using an equation obtained from a standard curve.

*Release kinetic studies*

The *in vitro* drug release data can be analyzed by putting them to different kinetic models as Zero order release, First order release, Higuchi, Hixson- Crowell's, Korsmeyer Peppas, Weibull, Hopfenberg in order to evaluate release mechanism of drug from SPHs.

Table 3: SPH and SPHC formulation of various drugs

| Drug | Formulations | Purpose | References |
|---|---|---|---|
| Metformin | Fast swelling SPH | Effect of cross linker and Acdisol concentration on swelling ratio and mechanical strength. | 11 |
| Pentoprazole | SPH and SPHC | Conventional and composite superporous hydrogel preparation as pH-sensitive drug delivery systems for Pantoprazole sodium. | 12 |
| Ranitidine | SPH composite (SPHCs) | Good absorption in upper part of GIT, Colonic degradation | 13 |
| Rosiglitazone | SPH | Overcome slow absorption due to short residence time in stomach and thus improve bioavailibility | 14 |
| Zidovudine | SPHCs | To prolonge the therapeutic activity of drug | 15 |
| Verapamil HCl | SPH hybrid | 1) To provide good mechanical strength, better control release as compared too conventional SPH. 2)To overcome bioavailability issues, | 16 |
| Fluconazole | SPH beads | Effect of calcium salt concentration beneficial for improvement in mechanical strength. | 17 |
| Cefditoren pivoxil | SPH tablet | To improve absorption and bioavailibility | 18 |
| Furosemide | (SPHCs) | For development of control release and gastro retentive device | 19 |

*Stability studies*

The stability studies of SPH formulation is carried out by keeping them in in airtight containers and stored in stability chamber at 40°C/75%RH for three months. Results for *in vitro* dissolution studies obtained after three months will be compared with the data obtained at the time of preparation.

*Pharmaceutical application of Superporous hydrogel*

*Gastro retentive drug delivery*

SPH can be a better device for gastro retentive delivery of drug. This device is helpful to reside the dosage form in stomach for prolonged period of time and resist the passing of dosage form through pylorus. Prolonged gastric residence time is suitable for the drug possesses narrow absorption window, Drugs acting locally and primarily absorbed in the stomach, drug that degrade in the colon and unstable at alkaline pH. Various SPH formulation have been prepared for drugs like zidovudin[15], verapamil hydrochloride[16], metformin[11] and rosiglitazone[14] etc.

*Peptide drug delivery*

Till recent, delivery of proteins and peptides through injections have been the common mean of their administration because of their poor oral bioavailability. However oral route is the most preferred route because of ease of administration and patient acceptance. Designing and formulating a polypeptide drug delivery through the gastro intestinal tract has been a persistent challenge because of their unfavorable physicochemical properties, which includes enzymatic degradation, poor membrane permeability and large molecular size. Superporous hydrogels have been used in the development of peptide delivery systems via oral administration. SPH have the tendency to increase their volume by 200 fold. Such volume increase allowed the gels to mechanically stick to the intestinal gut wall and deliver the incorporated drug directly to the gut wall[5].

*Fast dissolving tablet*

Fast dissolving tablets (FDTs) are meant for dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. FDTs are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water. This is useful particularly for children and elderly patients. There are three different methods to formulate the fast dissolving tablet including freeze drying, sublimation and direct compression. In first two methods, tablets are prepared that are intend to dissolve within 5-15 seconds but these methods are very expensive and tablets prepared from these method possess poor mechanical strength. But the direct compression method involves addition of fine particles of SPH to the granulation or powder formulation. The SPH microparticles within the tablet core expedite water absorption by an increased wicking mechanism. Tablets prepared by direct compression in the presence of SPH microparticles disintegrate in less than 10 seconds[21-22].

*Application in Biomedical field*

SPHs have been widely used in the biomedical field for various purposes such as tissue engineering, Chemoembolization and aneurysm. Tissue Engineering: Poly (2-hydroxyethyl methacrylate) (PHEMA) is most popular polymer used in SPH formulation for tissue engineering[23-24].

## CONCLUSION

Hydrogel are cross linking polymeric system that swell in water with some mechanical strength. But their swelling index and mechanical strength are not so enough so continuous work was carried out to enhance their swelling and mechanical strength as well. With improvement in properties of hydrogel, their use in various biomedical applications also improved. SPH is new advance technology of hydrogel with improve characteristics such as fast swelling and good mechanical properties. SPH have been used in various applications such as peroral peptide delivery, intestinal delivery and gastro retentive delivery due to their large size to remain in the stomach for prolonged period of time.

**REFERENCES**


1. Badiger, M.V., McNeill, M.E. and Graham, N.B. (1993). Porogens in the preparation of of microporous hydrogel based on poly (ethylene oxides). *Biomaterials* 14: 1059-1063.
2. Yan Q, and Hoffman AS, "Synthesis of Macroporous Hydrogels with Rapid Swelling and Deswelling Properties for Delivery of Macromolecules", *Polymer Communication*, 1995, 36, 887-889.
3. Bagadiya A, Kapadiya M and Mehta K, "Superporous Hydrogel: A Promising Tool for Gastoretentive Drug Delivery System", *International Journal of Pharmacy and Technology*, 2011, 3(4), 1556-1571.
4. Nagpal M, Singh SK and Mishra D, "Superporous Hydrogels as Gastroretentive Devices", Acta Pharmaceutica Scienci, 2011, 53, 7 – 24.
5. Doorkoosh FA, Brussee J, Verhoef JC, Borchard G, Rafiee-Tehrani M and Junginger HE, 2001), "Development and Characterization of a Novel Peroral Peptide Drug Delivery System", *Journal of Control Release*, 2001, 71, 307-318.
6. Doorkoosh FA, Verhoef JC, Ambagus MHC, Rafiee-Tehrani M, Borchard G and Junginger, HE, "Peroral Delivery Systems Based on Superporous Hydrogel Polymers: Release Characteristics for Peptide Drugs Buserelin, Octreotide and Insulin" *European Journal of Pharmaceutical Science*, 2002, 15: 433-439.
7. Abdel Halim SA, Yehia SA and El-Nabarawi MA, "Chromium Picolinate Loaded Superporous Hydrogel and Superporous Hydrogel Composite as a Controlled Release Device: *In Vitro* and *In Vivo* Evaluation", *Journal of Drug Delivery Science and Technology*, 2014, 24 (4), 326-337.
8. Chen J, Park H and Park K, "Synthesis of Superporous Hydrogels: Hydrogels with Fast Swelling and Superabsorbent Properties", *Journal of Biomedical Material and Research*, 1999, 44(1), 53-62.
9. Park K, Chen J and Park H "Hydrogel Composites and Superporous Hydrogel Composites Having Fast Swelling, High Mechanical Strength, and Superabsorbent Properties", *US Patent No*. 6271278, 2001.
10. Omidian H, Park K and Rocca JG, "Recent Developments in Superporous Hydrogels", *Journal of Pharmacy and Pharmacology*, 2007, 59, 317–327.
11. Kumar A, Pandey M, Koshy M K and Saraf SA, "Synthesis of Fast Swelling Superporous Hydrogel: Effect of Concentration of Crosslinker and Acdisol on Swelling Ratio and Mechanical Strength", *International Journal of Drug Delivery*, 2010, 2, 135-140.
12. Gupta NV and Shivakumar HG, "Preparation and Characterization of Superporous Hydrogels as pH-Sensitive Drug Delivery System for Pantoprazole Sodium", *Current Drug Delivery*, 2009, 6(5), 505-510.
13. Chavda H and Patel C, "Chitosan Superporous Hydrogel Compositebased Floating Drug Delivery System: A Newer Formulation Approach", *Journal of Pharmacy and Bioallied Sciences*, 2010, 2 (2), 124-131.
14. Gupta NV and Shivakumar HG, "Preparation and Characterization of Superporous Hydrogels as Gastroretentive Drug Delivery System for Rosiglitazone Maleate", DARU, 2010, 18 (3), 200-210.
15. Kumar KA, Madhusudhan Reddy AM and Babu PS, "Preparation and Characterization of Swellable Polymer Based Gastro-Retentive Zidovudine Superporous Hydrogel Composite", *Research Journal of Pharmaceutical Sciences*, 2012, 1(2), 13-19.
16. Nagpal M, Singh SK and Mishra D, "Superporous Hybrid Hydrogels Based on Polyacrylamide and Chitosan: Characterization and *In Vitro* Drug Release", *International Journal of Pharmaceutical Investigation*, 2013, 3(2), 88-94.
17. Kumar JR, Muralidharan S, Parasuraman S and Arumugam Dhanaraj SA, "Development and *In Vitro* Evalution of New Generation Superporous Hydrogel Beads (SPHBS) Containing Fluconazole", Journal of Pharmaceutical Science and Research, 2013, 5(12), 259- 264.
18. Venugopalarao G, Lakshmipathy R, Gadamsetty G and Sarada NC, "Absorption and Bioavailability of Cefditoren Pivoxil in Hydrogels *in Vitro* and *In Vivo*", *Journal of Taibah University for Science*, 2015, 9, 1–6.
19. Latif R, Abdel Halim SA and Abdel Kader OM, "Furosemide Loaded Superporous Hydrogel Composite as a Controlled Release Device: Different Strategies for Drug Loading", *Journal of Pharmaceutical Research and Opinion*, 2013, 3, 6, 28-35.
20. Chavda HV, Patel CN and Karen HD, "Preparation and Characterization of Chitosan-Based Superporous Hydrogel Composite", *Journal of Young Pharmacist*, 2009, 1(3), 199-204.
21. Yang S, Fu Y, Jeong SH and Park K, "Application of Poly (Acrylic Acid) Superporous Hydrogel Microparticles as a Super-Disintegrant in Fast-Disintegrating Tablets", *Journal of Pharmacy and Pharmacology*, 2004, 56(4), 429-436.
22. Chavda HV, Patel RD, Modhia IP and Patel CN, "Role of Superporous Hydrogel Particles as A Superdisintegrant in Fast Disintegrating Tablet of Glipizide", *Chronicles of Young Scientists*, 2014, 5 (1) 11-19.
23. Cetin D, Kahraman AS and Gumusderelioglu M, "Novel Scaffolds Based on Poly (2-Hydroxyethyl Methacrylate) Superporous Hydrogels for Bone Tissue Engineering", *Journal of Biomaterials Science, Polymer Edition*, 2011, 22(9), 1157-1178.
24. Kubinova S, Horak D and Sykova E, "Cholesterol-Modified Superporous Poly (2-Hydroxyethyl Methacrylate) Scaffolds for Tissue Engineering", *Biomaterials*, 2009, 30, 4601–4609.