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SUPERPOROUS HYDROGEL: A PROMISING TOOL FOR GASTORETENTIVE DRUG DELIVERY SYSTEM

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Abstract

One of the most feasible approaches for oral drug delivery in achieving a prolonged release and predictable drug delivery profile in the gastrointestinal tract (GIT) is to control the gastric residence time (GRT). The dosage forms with prolonged GRT are also known as Gastroretentive Dosage Forms (GRDFs) include intragastric floating systems (low density systems), mucoadhesive systems, high density systems, magnetic systems, unfoldable, extendable or swellable systems and superporous hydrogels (SPHs). Superporous hydrogels (SPHs) were originally developed as a novel drug delivery system for those drugs having absorption window in stomach and upper part of the gastrointestinal tract. These systems should instantly swell in the stomach and maintain their integrity in the harsh stomach environment, while releasing the pharmaceutical active ingredient. The fast swelling property is based on water absorption through open porous structure by capillary force. The poor mechanical strength of SPHs has been overcome by developing the second-generation SPH composites (SPHCs) and the third-generation SPH hybrids (SPHHs).For years, the synthetic features and properties of these SPH materials have been modified and improved to meet the requirements for gastric retention applications. This review discusses the formulation, techniques for synthesizing superporous hydrogel, different generations and drug loading techniques, characterization and literature update of this promising tool.

Keywords: Gas blowing technique, Gastroretentive dosage form, Hydrogels, Interpenetrating networks, Superporous hydrogel composite

Introduction

The oral drug delivery system is the most convenient method for administration of drug. This delivery system shows very better compliance as well as industrial applicability. About 80% of the orally administered drugs are excreted without absorbed.[1] The scientific and technological advances in recent years enables in development of controlled oral drug delivery system by overcoming physiological adversities, such as short residence time (SRT) and unpredictable gastric emptying time (GET). Controlled release (CR) dosage forms have been extensively used to improve therapy with several important drugs. The incorporation of drug in a controlled release gastro retentive dosage forms (CR-GRDF) which can remain in the gastric region for several hours and would significantly prolong the gastric residence time of drug and improve bioavailability, reduce drug waste and enhance the solubility of the drug that are less soluble in high pH environment i.e. intestinal and colonic pH. The gastro retention could help to provide greater availability of new products and improve therapeutic activity and substantial benefits to patients[2]. The most recent advancement in the gastro retentive drug delivery is the development of various types of superporous hydrogel.

A superporous hydrogel (SPH) is a 3-dimensional network of hydrophilic polymers that are not soluble and accommodate a large amount of water in a very short period of time due to the presence of interconnected microscopic pores. The hydrogel which having pore size of hundreds of micrometers is called as superporous hydrogel and it differs from other types of porous hydrogel such as macroporous and mesoporous.[3-5] Because of the porous structure, SPHs also possess hundreds of times more surface area and shorter diffusion distance than conventional hydrogel. These features allow dried SPHs to swell very fast to a very large size on contact with water. When drug loaded superporous hydrogel administer, the swollen hydrogel may remain in stomach for a longer duration and releasing the loaded drugs as their volumes are too big to transport through pylorus sphincter of the stomach. To be used as gasroretentive device, superporous hydrogel does not have only fast swelling but also have properties like biocompatibility, biodegradability, slipperiness, higher mechanical strength, high swelling capacity and stability in acidic condition of stomach pH 1.2.[1] Swollen hydrogel should be strong enough to withstand with pressure, abrasion and shear forces generated in stomach by gastric fluid. The swollen hydrogel capable of bearing pressure more than 50-70 cm water pressure.[6] Because of unique properties, SPHs were

initially proposed to develop gastric retention devices for extending the gastric residence time of drugs for achieving long-term, oral-controlled drug delivery.

Suitable Drug Candidates for Gastroretention

Generally, suitable candidates for CR-GRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

1. Narrow therapeutic window in GIT, e.g., riboflavin and levodopa
2. Primarily absorbed from stomach and upper part of GIT, e.g., calcium supplements, chlordiazepoxide and cinnarizine
3. Drugs that act locally in the stomach, e.g., antacids and misoprostol
4. Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole
5. Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate

Methods For Preparation of Superporous Hydrogels (SPHS)

There are four methods for preparing the gastroretentive superporous hydrogel

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

Porosigen Technique

Various porosigen are used to prepare the superporous hydrogel. These porosigen are hydrophilic in nature. So, they solubilize as they come in contact with water and generate the porous structure in the hydrogel e.g. micronized sucrose, micronized lactose ,micronized dextrin, micronized cellulose, sodium chloride, poly ethylene glycol (PEG), poly ethylene oxides etc. which form meshwork that can be removed by washing with water. The pore size generates in the hydrogel depends on the size of porosigens.[7]

Phase separation technique

Phase separation is very critical process in generating the superporous hydrogel because there is no much control over the porosity of hydrogel. As well this method can be applied to limited type of hydrogel prepared by HEMA (Hydroxy ethyl methyl acrylate) and NIPAM (N- isopropyl acrylamide).[8]

Cross linking technique

Cross linking of individual hydrogel particles lead to 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. This technique is limited to absorbent particles with chemically active functional groups on the surface.[9]

Gas blowing technique

Gas blowing technique is widely used technique in the preparation of gastroretentive superporous hydrogel in which cross linking and polymerization occurs in the presence of the gas bubbles. In a test tube of specific dimensions, different ingredients like monomer, cross linker, foam stabilizer, polymerization initiator, initiation catalyst (if any) and foaming agent are added sequentially. Initially and before addition of foaming agent, the pH of monomer solution is maintained at 5 to 6, because low pH favors foaming process. The addition of foaming agent leads to formation of bubbles followed by increase in pH of solution. The increased pH accelerates the polymerization process. Thus, simultaneous foaming and gelation lead to the formation of homogenous porous hydrogel i.e. superporous hydrogel. After synthesis, SPHs are subjected to washing, drying using different methods which influence the swelling and mechanical behavior of resulting hydrogel.[3]

Ingradients Required For Preparing Superporous Hydrogel

The ingredients required for preparing superporous hydrogel are as shown in **Table-1**

Table-1: Role of ingredients with their examples.

Role of ingredients	**Examples**
Monomers	Acrylic Acid (AA), Acrylamide (AM), 3- Sulphopropyl acrylate potassium (SPAK), Hydroxy ethyl methyl acrylate (HEMA), N-isopropyl acrylamide (NIPAM), Acrylonitrile (AN), Polyvinyl alcohol (PVA)

Cross linking agents	***Chemical cross linker:*** Glutaraldehyde, N,N'-methylenebisacrylamide (Bis), ***Ionotrpic cross linker:*** metal ions like calcium, iron and phosphorus
Foam stabilizers	Pluronic F127, Pluronic P105, Silwet L7605, Span, Tween
Polymerization initiator pairs	APS/TEMED (Ammonium persulfate/N,N,N,N-tetramethylethylenediamine, KPS/Sodium metabisulfite, APS/Sodium metabisulfite, Azo-initiator (V545)
Foaming agent	Sodium bicarbonate, Sodium carbonate, Potassium bicarbonate
Composite agents	Crosslinked sodium carboxy methylcellulose (Ac-Di-Sol), Crosslinked sodium starch glycolate (Primojel) and Crosslinked polyvinylpyrrolidone (crospovidone), Carbopol, Polyvinyl alcohol (PVA)
Hybrid agents	***Natural polymers***: Sodium alginate, Sodium carboxymethylcellulose (Na CMC), Chitosan based on ionotropic gelation ,Pectin ***Synthetic polymers***: Poly vinyl alcohol (PVA) based on cryogelation.

Drug Loading into Superporous Hydrogel

Two techniques are reported for loading the drug into this superporous hydrogel delivery system.

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

Drug loading into superporous hydrogel reservoir devices

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

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

Each of these shuttle systems are composed of 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.[10, 11]

Core inside the shuttle system

In this system, core is prepared in two different forms viz. micro particles and gross mass. Micro particles 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 #400 μm, which are 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.[4] 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 # 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.

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.[12]

Drying of Superporous Hydrogel

Drying of superporous hydrogel are can be carried out under two different conditions. Under Condition I, swollen superporous hydrogel are dried for a day under blowing warm air (60 °C) in a food dehydrator. Under Condition II, swollen superporous hydrogel are dehydrated first by applying about 5–10 ml of absolute ethanol per each gel. After this initial dehydration step, superporous hydrogel are dehydrated further by placing them in 50 mL of absolute ethanol several times to ensure replacement of all the water by ethanol. During the dehydration process, the soft and flexible superporous hydrogel become hard and brittle. 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 a oven at 55°C for a day.[3]

Various Generation of Superporous Hydrogel

First generation

Chen et al. in 1999 discovered first gastroretentive drug delivery, also known as conventional superporous hydrogel (CSPH) with fast swelling kinetics by altering the pH of the swelling medium between 1.2 to 7.5 and highly porous structure.[3] The most commonly used monomers are highly hydrophilic vinyl monomers like acrylamide, ionic monomers like salts of acrylic acid, sulfopropylacrylate potassium etc. They polymerized and crosslinked different vinyl monomers in the presence of a foaming agent, a foam stabilizer and a foaming aid. To dehydrate and to preserve the porous structure of the SPHs, the authors also used alcohol. 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 large size, larger than a few hundred times of their own volume in the dried state. Due to extremely small fraction of the polymer in the swollen state, the swollen SPHs are sometimes difficult to handle without breaking. 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 SPHs is replaced with alcohol (e.g., ethanol). The low surface tension of alcohol prevents the porous structure from collapsing during drying. The rate of water absorption could be increased by creating and interconnecting the pores inside the hydrogel structure. The rate of water absorption could also enhanced by using different wetting agents.

Second generation

Second generation superporous hydrogel called as superporous hydrogel composites (SPHC). These higher modulus hydrogel were introduced by Chen et al. in 2000 as an improvement over CSPH in terms of higher mechanical strength.[1] In first generation monomer system as with Conventional Superporous hydrogel CSPH), additional composite agent or matrix swelling ingredient was incorporated. Once dispersed into the reacting mixture, it would swell and absorb a mixed solution of monomer, cross linker and initiator and the water-soluble foaming additives. The swollen filler particles would then act as an isolated individual reactor, in which polymerization and cross linking could occur simultaneously. Since similar reactions will happen at the interface, the swollen particles would then be connected to each other through the extended polymeric chains. Upon drying, an interpenetrated network structure (IPN) would be formed. Since the whole structure is microscopically heterogeneous, this IPN type of structure is called a non-integrated IPN. Although general features of this SPH generation remain similar to its first counterpart, this modification results in better mechanical properties. The most widely used composite agents are crosslinked sodium carboxymethylcellulose (Ac-Di-Sol), crosslinked sodium starch glycolate (Primojel) and crosslinked polyvinylpyrrolidone (Crospovidone).[13] PVA, Carbopols are also used to improve the mechanical strength of SPHs. The presence of composite agent in SPH composites results in improved mechanical properties over conventional (i.e., the first generation) 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. [11, 14, 15]

Third generation

Further advancement in the hydrogel enhances the mechanical strength by constructing the interpenetrating network of polymers. The third generation of SPHs was developed based on SPH hybrids. Unlike SPH composites wherein a pre-cross-linked matrix-swelling additive is added, SPH hybrids are prepared by adding a hybrid agent that can be cross-linked after SPH is formed. The hybrid agent is a water-soluble or water-dispersible polymer that can form crosslinked structure (in a manner similar to forming interpenetrating network)

through chemical or physical cross-linking. Once the second network is formed, the whole system becomes similar to interpenetrating polymer networks. The hybrid agent evenly diffuses and dissolves into polymer solution leading to formation of integrated semi interpenetrating network which upon treatment of hybrid agent yields integrated IPN structure. They can withstand various types of stresses like compression, bending and twisting etc.[16]

Characterization of Superporous Hydrogel

Measurement of Density

As the dried superporous hydrogel lose their cylindrical shape after drying, direct measurement of their volumes is difficult. The solvent displacement measurement method is used for density measurement. The dried superporous hydrogel, which are treated with different solvents, are used for density measurements, which actually show apparent densities of SPHs. The pieces of SPHs are taken and weighed in order to determine mass of each piece. A hydrophobic solvent such as hexane that is not absorbed by the SPHs are used for this purpose. By the use of forceps, a piece of polymer is immersed in a predetermined volume of hexane in a graduated cylinder and the measurement in the hexane volume is measured as the volume of the polymer. The density is calculated from the following equation

$$\text{Density} = M_{SPH}/V_{SPH}, \quad (1)$$

Where, V_{SPH} is the volume of solvent displaced by SPH and M_{SPH} is the mass of the SPH.[13]

Measurement of porosity

For porosity measurement, dried SPH is immersed in hexane over night and weighed after excess hexane on the surface is blotted. The porosity is calculated from equation 2:

$$Porosity = V_P/V_T, \quad (2)$$

Where, $V_P = (V_T - V_{SPH})$ is the pore volume of SPH and V_T is the total volume of the SPH. Total volume of SPH can be measured from its dimensions, as it is cylindrical in shape.[17]

Swelling studies

Swelling time

Swelling time is calculated by immersing the hydrogel in deionized water as well as 0.1N HCl as it is gastroretentive and calculating the time required to attain equilibration in swelling.[18]

Swelling ratio

The equilibrium swelling ratio can be calculated from equation 3

$Q = (M_s - M_d)/M_d \times 100$, (3)

Where, Q is the equilibrium swelling ratio, M_s is the mass in the swollen state, and M_d is the mass in the dried state. At the beginning of each experiment, the dried gel is measured gravimetrically to obtain M_d and then it is immersed in an excess of medium for swelling. At various time intervals, the hydrogel is removed from the medium and weighed when excessive medium on the surface is blotted to determine M_s.[12 (6A)]

Estimation of drug loading studies

The method of soaking or equilibration is employed for drug loading. In this method the amount of buffer necessary for complete swelling of superporous hydrogel is determined. Thereafter the drug solution in the determined amount of buffer required for complete swelling is prepared. Subsequently, superporous hydrogel is placed in the drug solution and left until all the drug solution is sucked up. Then the completely swollen superporous hydrogel loaded with the drug is placed in an oven at 30^0C for drying overnight.[19]

Determination of drug content

A weight of superporous hydrogel containing required amount of drug is taken in 100 ml volumetric flask. About 10 ml of required buffer is added, mixed well and make up to volume. The mixture is filtered and drug content is determined using UV-Vis spectrophotometer at appropriate wavelength.[20]

In vitro buoyancy studies

The *in vitro* buoyancy is determined by floating lag time, as per the method described by Rosa *et al*.[21] The piece of hydrogel are placed in 100 ml 0.1N HCl at 37 ± 0.5 °C. The time required for piece of hydrogel to rise to the surface and float is taken as the floating lag time. Total time period for which tablet or piece of hydrogel remains buoyant is considered as a total floating time.

Morphological analysis

The surface morphology of superporous hydrogel is determined using a scanning electron microscope.

Drug excipients compatibility

FT-IR spectroscopy is employed to ascertain the compatibility between selected drugs and the polymers. The prepared superporous hydrogel are subjected to FT-IR analysis by KBr pellet method using Fourier-Transform Infrared (FT-IR) spectrophotometer and recorded over the range of 400- 4000 cm^{-1}.

Determination of gelation kinetics

The gelation time is defined as the duration time for gel formation after addition of initiator. It is measured by a simple tilting method after adjustment of pH to 5.0 with sodium hydroxide solution. It is determined by the duration time until the reactant mixture is no longer descending in the tilted tube position. [22]

Mechanical strength

Mechanical strength of dried SPH is measured by applying the weight on swelled superporous hydrogel, until the hydrogel fractured. [1, 23]

Evaluation of degradation kinetics

The degradation kinetics of the hydrogel is examined by measuring the swelling ratio as a function of water retention. The hydrogel are placed in pH 1.2 (0.1 M HCl) medium at 37^0C for 12 h, and the samples are periodically weighed at 6 h interval.[24] Water retention capacity (WRt) as a function of time is assessed as in Eq 4.

$$WRt = (W_p - W_d) / (W_s - W_d) \quad (4)$$

Where, W_d is the weight of the dried hydrogel, W_s the weight of the fully swollen hydrogel, and W_p the weight of the hydrogel at various exposure times.

In vitro release studies

The release rate of drug from SPH-DDS is carried out using USP type II dissolution testing apparatus. The dissolution test is performed using 900 ml stimulated gastric fluid SGF, at 37 ± 0.5˚C and 50 rpm. Aliquots withdraw at predetermined interval times for 18 h from the dissolution medium and replace immediately with fresh medium. The samples are passed through 0.45 μm membrane filter and diluted (if needed) to a suitable concentration with SGF. The absorbance of these solutions is measured at appropriate wavelength V/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 of all the batches can be analyzed by fitting them to different kinetic models as zero order release, First order release, Higuchi, Hixson- Crowells, Korsmeyer Peppas, Weibull, Hopfenberg in order to evaluate release mechanism of drug from SPHs.[25]

Stability studies

The prepared batches are kept 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.

Literature update for polymerization initiation pair, foaming agent, composite agent and techniques used for synthesis of hydrogel are as shown in **Table-2.**

Literature updates for monomers, crosslinking agents, stabilizers are as shown in **Table-3.**

Table-2: Literature update for polymerization initiation pair, foaming agent, composite agent and techniques used for synthesis of hydrogel.

Drug	Polymerization Initiation Pair	Foaming Agent	Composite Agent	Technique	Ref No.
Metformin	Tetramethylenediamine, Ammonium Persulphate	Sodium bicarbonate	Crosslinked sodium carboxy methylcellulose (Ac-Di Sol)	Gas blowing Technique	18
Pantoprazole	Tetramethylenediamine, Ammonium Persulphate	Sodium bicarbonate	Crosslinked sodium carboxy methylcellulose (Ac-Di-Sol)	Gas blowing Technique	26
Ranitidine	Tetramethylenediamine, Ammonium Persulphate	Sodium bicarbonate	-	Gas blowing Technique	27

Rosiglitazone	-	Sodium bicarbonate	-	Gas blowing Technique	28
Rosiglitazone	-	Sodium bicarbonate	-	Gas blowing Technique	29
Ranitidine (Bioadhesive)	Tetramethylenediamine, Ammonium Persulphate	Sodium bicarbonate	-	Gas blowing Technique	30
Clarythromycin	Ammonium Persulphate	-	Polyvinylpyrrolidone	Chemical crosslinking	31
Amoxicillin	-	Sodium bicarbonate	-	Gas blowing Technique	32
Carvedilol	Tetramethylenediamine, Ammonium Persulphate	Sodium bicarbonate	-	Gas blowing Technique	33

Table-3: Literature update for monomers, crosslinking agents, stabilizers.

Drug	Monomers	Crosslinking Agent	Stabilizer	Ref No.
Metformin	Acrylic acid, Acrylamide, 3-Sulphopropylacrylamide (SPAK)	N, N'-methylenebisacrylamide	Pluronic F68	18
Pantoprazole	Acrylamide, Methaacrylamide	N,N'-methylenebisacrylamide	Pluronic F127	26
Ranitidine	Acrylic acid, Acrylamide	N, N'-methylenebisacrylamide	Span 80	27
Rosiglitazone	Chitosan	10% Aqueous Glyoxal Solution		28
Rosiglitazone	Chitosan, Polyvinyl alcohol	10% Aqueous Glyoxal Solution		29

Ranitidine (Bioadhesive)	Acrylic acid, Acrylamide, Hydroxypropylmethyl cellulose, Carbopol 934P, Ethyl cellulose,	N, N'-methylenebisacrylamide	Span 80	30
Clarythromycin	Acrylic acid, Chitosan	N, N'-methylenebisacrylamide, Glutaraldehyde	-	31
Amoxicillin	Glycol Chitosan	40% Aqueous Glyoxal Solution	-	32
Carvedilol	Acrylamide, Acrylic acid	N, N'-methylenebisacrylamide	Pluronic F127	33

Conclusion

Superporous hydrogel are a novel class of hydrogel and promising device for gastroretentive delivery of drug for prolonged period. Different generation of superporous hydrogel are investigated successfully for gasric retention. The polymers having acidic, basic and neutral monomers having ability to absorb large amount of water and high swelling capacity and show better drug release.

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