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Review Article

Superporous Hydrogel: A Novel Approach for Safe Gastroretentive Drug Delivery System

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Abstract

Superporous hydrogel are developed initially as novel drug delivery system to retain dosage form in upper gastrointestinal tract, and absorbs drug in gastric medium. The generation-based classification of superporous hydrogel is covered in this review. The hydrophilic polymer networks formed by the molecular entanglements which absorb water up to thousands of times to their dry weight. These systems swells quickly and resist in an extremely acidic condition in stomach. This hydrogel is instantly swell through capillary force which is driven by absorption of water through an open porous structure. This system provides better solubility and bioavailability by targeting the specific site of absorption. The conventional superporous hydrogels have the poor mechanical strength which is overcome by developing the second superporous hydrogel generation composites and the third-generation superporous hydrogel hybrids. This article has mainly focused on the classification, techniques, drug loading, research papers, characterizations and applications of superporous hydrogel.

Keywords: Gastric retention, Cross-linking, Superporous hydrogel, Swelling rate, Elastic property, Hydrophilic polymer networks.

Introduction

Oral administration is most convenient and simple route for drug delivery to the systematic circulation and has also preferred due to numerous advantages such as easy administration, formulation flexibility, cost-effectiveness, ease of storage and transportation, high patient compliance. The oral drug delivery is based on various elements such as stomach emptying, gastrointestinal (GI) transit duration of dosage forms, drug release from the dosage form and drug absorption site.^{1,2} The advantageous property of gastro-retentive drug delivery system (GRDDS) is to retain in the upper part of gastrointestinal tract (GIT) for prolong period of time and thereby it is significantly longer the gastric retention time (GRT) of the drugs.³ The drug is taken by keeping the dosage form in the acidic medium of stomach, and then it is released in controlled manner into the stomach, duodenum, or intestine at a designated location.⁴

The hydrophilic polymer networks are known as hydrogels which absorb water up to thousands of times to their dry weight. Hydrogels are chemically stable or they can degrade, disintegrate, and dissolve. When the hydrogel networks are bonded by molecular entanglements and other forces such as hydrogen bonding, ionic bonding, or hydrophobic forces, they are referred to as reversible or physical gels.⁵

Superporous hydrogel

Superporous hydrogel (SPH) is a three-dimensional network of hydrophilic polymer which absorbs an enormous volume of water in a less period of time due to the presence of highly bounded interconnected microscopic pores.⁶ The superporous hydrogels have pore size ranges from 50 to 100 μm and swell to greater size in less than a minute due to quick intake of water via capillary action through a network of closely interconnected microscopic open pores. SPHs have ability to swell to a larger size and have a mechanical strength sufficient to sustain pressure from gastric contraction, this is accomplished by including the hydrophilic material such as Ac-Di-Sol (Cross Carmellose Sodium).^{7,8}

This is a new kind of hydrogel which has multiple supersize pores throughout them and swelling occurs by the capillary wetting process rather than the diffusion process. The preparation of SPH needs certain ingredients are used to mix such as initiators, cross linkers, foam stabilizers, foaming agents, foaming aids, and monomer in diluted water.⁹

The SPH have extremely quick swelling kinetics and high swelling rate but the mechanical force was too low. Due to their poor mechanical properties, the numerous swollen SPH were difficult to handle and broken easily. Generally, the mechanically strong super porous hydrogel can be created by increasing the cross-linking density, but doing so would cause very little swelling and lose the superabsorbent quality.

Therefore making super porous hydrogels with quick swelling, high absorbency, distinctiveness and high mechanical strength is required.⁷ Superporous hydrogel have properties such as smoothness, biocompatibility, biodegradability, a high swelling capacity, a high mechanical strength, and stable in acidic conditions.¹⁰

Principle of gastric retention of superporous hydrogel

SPHs gastric retention is primarily due to their rapid swelling. SPH is initially filled in a small capsule or compressed tablet that is convenient to swallow, but after oral intake, it expands quickly in the gastric acidic fluid to a greater size, preventing it from passing the pyloric aperture and emptying into the small intestine. When the gastric contraction occurs in the stomach, the gastric content floats over the hydrogel. Because it is elastic, slippery, and a high mechanical property for capable of withstanding gastric contraction. It releases drug by floating in the upper region of the gastrointestinal tract due to its low density as shown in **figure 1**. When the drug release start, it slowly degrades in the stomach by either mechanical force or by enzymatic hydrolysis of the polymer chains constituting the hydrogel.¹¹

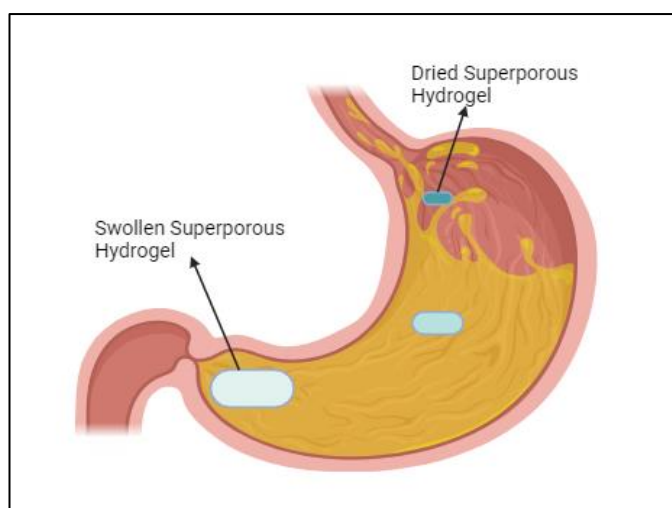


Figure 1: Principle of gastric retention of superporous hydrogel

Advantages of superporous hydrogels

- The superporous hydrogels have fast swelling rate, within a minute by its original size.
- It contains small amount of solid mass in total weight, it employs significant expansion force during swelling.
- Elasticity prevents minimization of their rupture.
- Superporous hydrogels can also be used outside of the pharmaceutical and biomedical fields.
- Uniform drug release from dosage form and no possibility of dose dumping.^{12,13}

Classification of superporous hydrogel

- 1) First generation as conventional superporous hydrogels (CSPHs)
- 2) Second generation as superporous hydrogel composites (SPHCs)
- 3) Third generation as superporous hydrogel hybrids (SPHHs)

First generation as conventional superporous hydrogels (CSPHs)

In 2000, Chen created super porous hydrogel with quick swelling and outstanding absorption capabilities for the first time.¹⁴ For the preparation of conventional super porous hydrogel, vinyl monomer was employed. The most widely used monomer are those that are highly hydrophilic for example acrylamide and sulfopropyl acrylate. Particularly hydrophilic monomers such as carboxyl or amide in acrylic acid and acrylamide respectively or ionic monomer such as carboxylate in sodium or potassium acrylate may have better swelling properties.¹⁵ Because of their low mechanical strength, swollen SPHs are difficult to handle. These are delicate, and the structure may collapse easily under low pressure and the formulation cannot retain in stomach for longer period of time.¹⁶ As a result, researchers created the second generation as shown in **figure 2**.

Second generation as superporous hydrogel composite (SPHCs)

As a swellable filler, a super disintegrant is incorporated into this type of super porous hydrogel. Baek (2001) transformed conventional super porous hydrogel into second generation super porous hydrogel. In this, dispersed phase is mixed with a continuous phase. AC-Di-Sol, Primojel, and crosppidone are composite materials used in the preparation of SPHCs. AC-Di-Sol has a high swelling rate as well as mechanical properties.^{17,18} The mechanical properties of SPHCs can be improved by acidifying polymer ionisable groups, allowing the SPHCs to resist the stress of a gastric contraction during the gastric motility phase. The composite agent improves the mechanical properties of hydrogel composites. However, super porous hydrogel composites are still fragile and brittle.¹⁹

Third generation as superporous hydrogel hybrids (SPHHs)

Omidian created a superporous hydrogel hybrid in 2003 by using acrylamide, methylene bisacryl amide, and a cross linker. The mechanical or elastic properties of superporous hydrogel hybrids are extremely high. Unlike super porous hydrogel composites, SPHHs contains a pre-cross-linked-matrix swelling additive. A water-soluble polymer is a hybrid agent such as chitosan and pectin. The preparation of an acrylamide based superporous hydrogel in the presence of sodium alginate is an example of a SPHHs which is followed by calcium ion cross-linking with alginate chains.¹⁵ Elastic water-swollen super porous hydrogel hybrids can sustain several types of pressure like compression, stiffness, twisting and bending.²⁰ The comparison of generations of superporous hydrogel as shown in **table 1**.

Table 1: Comparison of all three generations of superporous hydrogel ²¹

Parameters	CSPH	SPHC	SPHH
Texture during synthesis	Soft, sticky and less flexible	Soft and less flexible	Soft and flexible
During ethanol dehydration	No immediate hardening	Hard and brittle	Hard
Swelling capacity	100-300 g g ⁻¹	100-300 g g ⁻¹	Upto about 50 g g ⁻¹
Swelling rate	5-30 s	5-30 s	5 s to a few min
Mechanical strength	No mechanical strength	Resist up to 2 N cm ⁻²	Resist up to 20- 100 N cm ⁻²
After swelling	Completely transparent	Not completely transparent	Non- sticky creamish opaque

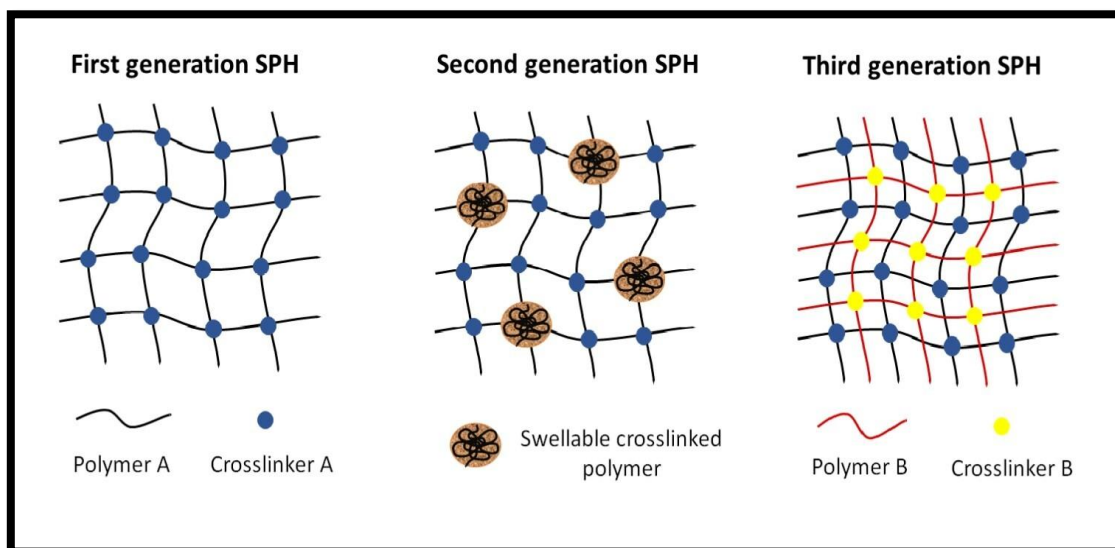


Figure 2: Generations of superporous hydrogel

Techniques for the preparation of superporous hydrogel

Gas blowing technique

This is most conventionally used method. Firstly, in a test tube monomer, crosslinking agent, foam stabilizer and distilled water are mixed of specific dimension and pH adjusted with 5-

6 with 5 M NaOH. Low pH favours polymerization reaction, then foaming agent is included to the reaction mixture which leads to formation of gas bubbles followed by gradually increase in pH of solution. Polymerization process increases by enhance the rate of pH. Gas bubbles entrapped by both of the gellification and foaming reactions occur simultaneously in reaction mixture as shown in **figure 3**. After synthesis, super porous hydrogel is washed and dried using different methods.²²

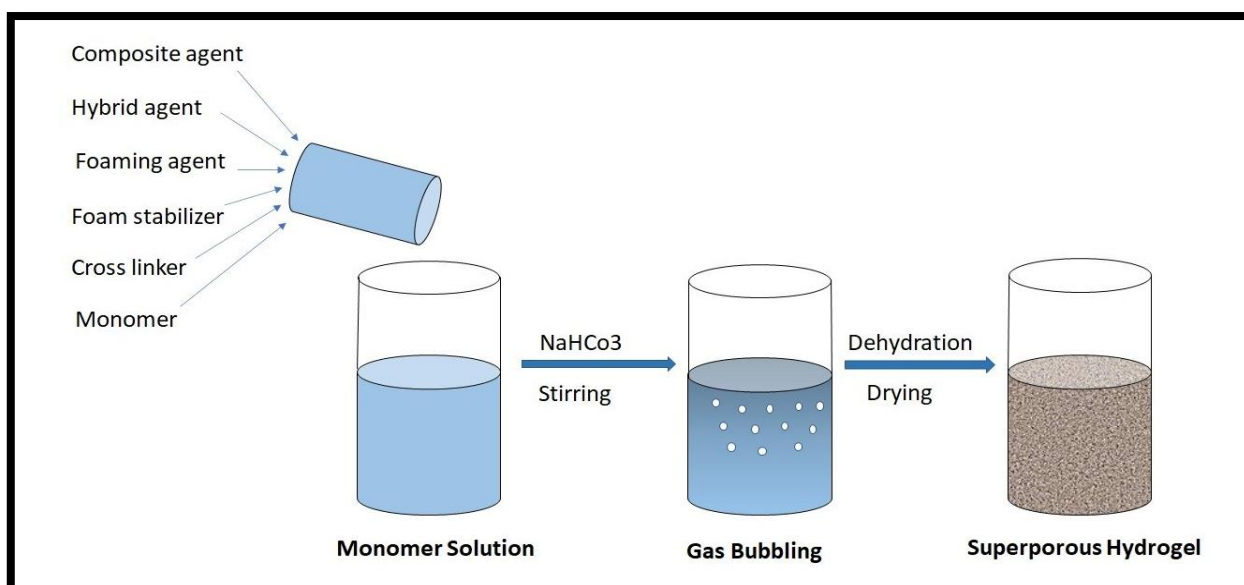


Figure 3: Gas blowing technique

Porosigen technique

Porosigens are soluble in water and hydrophilic in nature. When these porosigen come in contact with water, the porous structure is formed. The formation of pore size in SPH depends on the size of porosigens. e.g., micronized lactose, micronized sucrose, micronized dextrin, micronized cellulose, sodium chloride, polyethylene glycol (PEG) etc. form network.¹¹

Phase separation technique

This technique is complicated for creating super porous hydrogel because porosity is not controlled by this process. In solution polymerization, heterogenous superporous hydrogels have large network spaces. This is referred to as heterogenous solution polymerization. The superporous hydrogel formed by

this method has very low porosity. Therefore, this method has limited use for preparation of hydrogel by HEMA(hydroxyethyl methyl acrylate) and NIPAM (N-isopropyl acrylamide).²²

Cross linking technique

The crosslinking of hydrogel particles causes aggregation of particle. In this type of structure, supports are present between hydrogel particles size is much smaller than size of particles. The cross-linking agent, water and hydrophilic organic solvent is used to prepare macrostructure. This technique has limited use to absorb particles which have active functional group present on the surface.²³ The excipients for preparing the superporous hydrogel as shown in **table 2**.

Table 2: Excipients for preparing superporous hydrogel ^{13, 24}

Role	Example
Monomers	Polyvinyl alcohol, Acrylic Acid, Acrylamide, Acrylonitrile, 3-Sulphopropyl acrylate potassium, Hydroxy ethyl methyl, acrylate, N- isopropyl acrylamide, etc.
Cross-linking agents	Chemical cross-linker: Glutaraldehyde, Glyoxal, N, N'-Methylene bisacryl amide, Formaldehyde. Iontropic cross-linker: Metal ions like calcium, iron and phosphorus
Foam stabilizers	Span 80, Tween, Pluronic F-127, Pluronic P-105, Silwet L-7605
Foaming agents	Sodium bicarbonate, Potassium bicarbonate, Sodium carbonate
Polymerization initiator pairs	Ammonium persulfate/ N,N,N,N tetramethyl ethylene diamine (APS/TEMED), Potassium per sulfate/ Sodium metabisulfite, Ammonium per sulphate/ Sodium metabisulfite, Azo-initiator
Composite agents	Crosslinked sodium carboxy methylcellulose, Crosslinked Primojel and crosopovidone, Polyvinyl alcohol, Carbopol
Hybrid agents	Natural polymers: Chitosan based on ionotropic gelation, Sodium alginate, Pectin, Sodium carboxymethylcellulose Synthetic polymer: Polyvinyl alcohol based on cryogelation.

Drug loading into superporous hydrogel delivery system

- Drug loaded superporous hydrogel by reservoir devices
- Drug loaded superporous hydrogel by polymer matrix

Drug loaded superporous hydrogel by reservoir device

- Core inside the shuttle system
- Core attached to surface of shuttle system

The shuttle system contains two main components- the core and the conveyor. Core part mainly composed of drug blend and conveyor is composed of superporous hydrogel.

Drug loaded superporous hydrogel by polymer matrix

A specific weight of superporous hydrogel is weighed, and the certain amount of water needed for completely swelling is measured. To absorb the solution of drug, a weighed quantity of polymer is added to an aqueous drug solution which prepared in certain volume of water. After 20 min, drug-loaded polymers are dried overnight at 30°C in an oven.²⁴

Patent and research papers related to superporous hydrogel formulations

Omidian et al., patented regarding the formation of superporous hydrogel using an ion- equilibration technique. Anionic polysaccharides are included in the hydrogel reaction mixture and cations are also added during or after the formation of hydrogel. Superporous hydrogel can be formed

that are highly absorbent including properties such as strength, ruggedness, and resiliency.²⁵

Juthi et al., formulated a novel pH-responsive super-porous hybrid hydrogels were loaded with amoxicillin trihydrate and composed of pectin, poly 2- hydroxyethyl methacrylate (2-HEMA), and N, N methylene-bis-acrylamide. This study shows excellent swelling and delayed drug release at different pH 1.2 (97.99%) and 7.4 (88%).²⁶

Chintalapati V.S. and Gopinath, developed SPH using varying concentrations of two distinct polymers polyvinyl alcohol (PVA), chitosan, and a crosslinking agent glutaraldehyde to get the desired controlled release profile and shown extended gastro-retention up to 18 h, with a lag time 11- 16 min.²⁷

Jihad and J. Al- Akkam, synthesized gastroretentive superporous hydrogel of carvedilol by adding Chitosan, polyvinyl alcohol and acrylamide, methylene bis- acrylamide, glutaraldehyde was used to prepare SPH hybrids. The SPH prepared capsules containing carvedilol are particularly designed to be delivered to the stomach because of their increased residence time and improved solubility.²⁸

Ramya et al., synthesized SPH formulations containing lafutidine which is a H₂- receptor antagonist that suppresses the production of stomach acid and prepared by different composite agents such as Carbopol, sodium alginate, pectin, and chitosan. Swelling characteristics of SPH was evaluated by progressively reducing the swelling time from 45 to 16 min.²⁹

Hitesh Chavda et al., formulated bioadhesive superporous hydrogel composite particles for an intestinal delivery of metoprolol succinate along with chitosan and HPMC were utilized as release retardant and bioadhesive polymers, respectively. This system remains bioadhesive up to 8 hours in intestine.³⁰

Characterizations of superporous hydrogel

FT-IR spectroscopy: It is used to determine the compatibility between the drug and the polymers. The infrared spectrums of pure drug and a physical mixture of ingredients of the formulation is recorded. The FTIR spectrum is recorded over the range of 400 – 4000 cm^{-1} using KBr pellet method by Fourier – Transform Infrared (FT-IR) spectrophotometer.

Swelling studies: It is determined by following two parameters:

Swelling time: The dried superporous hydrogels is submerged in deionized water and 0.1N HCL and required time is calculated to achieve swelling equilibration.

Swelling ratio: The dried SPH is permitted to moisten in sufficient amount of deionized water at room temperature, after removing excess water with gentle blotting the weight of the moistening sample is recorded at various time intervals. The SPH swelling ratio is calculated as follows:

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

W_s - Weight of swelled state SPH,

W_d - Weight of dry SPH.^{31,32}

Porosity Measurement: The dried superporous hydrogel is created after being submerged in absolute ethanol overnight for the measurement of porosity. Its size become larger after absorbing ethanol. The measurement of porosity is calculated by the following equation:

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

ρ - Density of absolute ethanol,

V - Volume of hydrogel,

M_1 and M_2 - Masses of hydrogel before & after submerged in absolute ethanol respectively.³³

Determination of void fraction: The dried superporous hydrogel immersed in 0.1N HCL until equilibrium is reached. The dimensional volume of the swollen hydrogel is calculated after measuring its dimensions. Meanwhile, the amount of buffer absorbed into the hydrogels is calculated by eliminating the weight of dry SPHs from the weight of swollen hydrogels and the obtained value is determined by the total volume of pores inside the SPHs.³⁴ The void fraction is determined by the following equation:

$$\text{Void Fraction} = \frac{\text{Dimensional volume of the superporous hydrogel}}{\text{Total volume of pores}}$$

Determination of drug content: Accurately weigh 5mg of super porous hydrogel and transfer to 100ml volumetric flask containing 10ml of 0.1 N HCL of pH 1.2 and makeup to the volume. After filtering the mixture, the drug content is determined using UV visible spectroscopy.³⁵

Degradation kinetics: The hydrogel degradation kinetics are evaluated by swelling ratio. The hydrogel is kept in pH 1.2 of 0.1 M HCL medium at 37°C for 12 hrs, and the samples are weighed every 6 hours interval. The time is required for obtaining the water retention capacity (WRT) are as follows,

$$WRT = \frac{(W_p - W_d)}{(W_s - W_d)}$$

W_d - Weight of dry SPH,

W_s - Weight of completely swollen hydrogel,

W_p - Weight of superporous hydrogel at different exposure times.³⁶

Mechanical properties: The penetration pressure (PP) of SPHs is determined using a bench comparator. Under the lower touch, the completely swollen hydrogel is positioned longitudinally, and weights are gradually applied to the upper touch until the polymer completely rupture. The measuring devices can be used to determine the compressive force, and the penetration pressure can be calculated as,

$$PP = \frac{Fu}{S}$$

Fu - Compressive strength at which the polymer breaks completely,

S - Lower touch area.³⁷

Scanning electron microscopy (SEM): The size and morphology of superporous hydrogel is determined by SEM. The samples are battle-dusted onto a double-sided tape on an aluminum stub. The samples are coated with gold using a cool spotter to determine the thickness of photomicrograph, which is taken at the accelerated voltage of 20 kW and chamber pressure of 0.6 mm Hg. After coating the sample using a Hammer Sputter Coater, a scanning electron microscope is used having 5kV accelerating voltage.²⁶

In-vitro drug release study: The drug is released *in-vitro* from the prepared formulations using the USB type II dissolution apparatus, at a rotational speed of 100 RPM in 900 ml 0.1 N HCL pH at 37°C \pm 0.5°C. To maintain a constant volume, aliquots of 5ml sample are withdrawn at certain times and replenish with fresh dissolution medium. The UV Spectrophotometer is used to analyze the samples.³⁸

Applications of superporous hydrogel

Gastroretentive platforms

The gastroretentive platforms may benefit for the delivery of various drugs. It is especially helpful for medications that primarily absorb in the upper part of gastrointestinal tract, such as antacids and antibiotic, or for treatments that act locally in the stomach. Controlled release can increase bioavailability for drugs with a narrow absorption window or for that absorbed from the small intestine, such as levodopa, riboflavin, p-aminobenzoic acid. Drugs that deteriorate in the colon like metoprolol, or drugs which is unstable in an alkaline pH medium can also be treated with gastroretentive platforms.³⁹

Gastroretentive tablet

The tablet for gastroretentive system is formulated to remain in stomach and prepared by blending and direct compression. SPH particles of acrylic acid or sulfopropyl acrylate copolymers were combined with gelatin and tannic acid by involving hydrogen bonding before being tableted by direct compression. Moreover, the swollen tablet can withstand a compression force up to 16 KPa until fracturing off.²¹

As a superdisintegrant

Superdisintegrant are pharmaceutically appropriate polymers such as starch derivatives cellulose and poly (vinyl pyrrolidone), which is specially designed for the swelling property. As a disintegrating agent, SPH is involved in fine particle form and mixed into a solid dosage form. Because of its size and pore content, the SPH superdisintegrant differs

significantly from conventional superdisintegrant is that it can offer a considerably larger surface.¹⁵

Protein or peptide delivery systems

The CSPH and SPHC are employed for peroral peptide delivery has been investigated. This system is intended to physically adhere to the intestinal wall and administered directly to the targeted site. The SPH carrying carboxyl has the ability to promote calcium extraction, which open the closed junctions and neutralizes the toxic gut enzymes. The correct choice of enteric coating is to target this dosage form to any specific region in the small intestine or to the colon.³⁰

Chemoembolization and occlusion devices

Chemoembolization is a procedure that combines chemotherapy and embolization. Embolization has been used to treat cancer by preventing supply of oxygen to growing tumours. Local delivery can be achieved by reducing systemic toxicity. For chemoembolization therapy, SPHs may be loaded with chemotherapeutic and anti-angiogenic agents. The strong SPH is used for better adjustment in the blood vessel and provides better blocking.²⁴

Site-specific drug delivery

It is especially helpful for drugs that are absorbed from the stomach or the proximal part of the small intestine like furosemide and riboflavin. A bilayer-floating capsule designed for the topical administration of misoprostol, a synthetic analogue of prostaglandin E1 used to treat stomach ulcer which is induced by the use of NSAIDs. Misoprostol is slowly targeted to the stomach which helps to reach the desired therapeutic levels and the wastage of drug could be reduced.¹¹

Development of diet aid

To lose weight, diet soft drinks meal replacement shakes, diet medicines, and even surgical techniques have been employed. Due to its rapid and extensive swelling property, the SPH might theoretically occupy a significant large portion of the stomach area due to their quick and expansive swelling leaving less capacity for meals, and so decreasing appetite. This type of device has the potential to help obese people to lose weight.⁴⁰

Future prospective of superporous hydrogel

The superporous hydrogel are evolving as an emerging research and advancements in pharmaceutical field. Advancements may lead to enhanced biocompatibility, bioavailability, solubility, improved swelling and mechanical properties, and controllable porosity, enabling them to be tailored for specific biomedical applications. This system is developed as a gastroretentive dosage forms, peroral peptide delivery, targeted drug delivery system, chemoembolization and occlusion devices, site-specific drug delivery system, as a superdisintegrant, as a diet aid, personalized medicine, artificial organs and prosthetics.

Conclusion

Superporous hydrogels are a new type of hydrogel material that swells rapidly to a larger size to its original size on the basis of its swelling property and mechanical strength and making it a promising device for gastro-retentive delivery system. Various generations of SPHs have been successfully discussed for gastric retention. Additionally, the use of SPH in oral solid and semi-solid dosage forms has also been investigated. The research of investigating the utility of superporous hydrogel in various pharmaceutical fields where rapid swelling is required. Superporous hydrogel is also finds its application as a drug carrier in biomedical field.

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