

Superporous Hydrogel: An Innovative Method for Secure Gastroretentive Drug Delivery Systems

Syeda Sadia¹, Dr. Rakesh K. Jat², Dr. Padmalatha Malthar³

Department of Pharmacy^{1,2,3}

Shri Jagdishprasad Jhabarmal Tibrewala University, Jhunjhunu Rajasthan, India

Abstract: Superporous hydrogels were initially developed as innovative drug delivery systems to retain dosage forms in the upper gastrointestinal tract and to absorb drugs in the gastric media. This review addresses the generation-based classification of superporous hydrogels. The hydrophilic polymer networks, created by molecular entanglements, can absorb water up to thousands of times their dry weight. These systems expand rapidly and endure very acidic conditions in the stomach. This hydrogel rapidly swells due to capillary forces, driven by water absorption through its open porosity structure. This technique enhances solubility and bioavailability by precisely targeting the absorption site. Traditional superporous hydrogels have inadequate mechanical strength, which is addressed by the development of second-generation superporous hydrogel composites and third-generation superporous hydrogel hybrids. This article primarily addresses the classification, methodologies, drug loading, scholarly articles, characterizations, and uses of superporous hydrogels

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

I. INTRODUCTION

Oral administration is the most convenient and straightforward method for delivering drugs to the systemic circulation, favoured for its multiple advantages, including convenience of administration, formulation versatility, cost-effectiveness, simplicity of storage and transportation, and high patient compliance. Oral drug administration relies on several factors, including gastric emptying, gastrointestinal transit time of dosage forms, drug release from the dosage form, and the site of drug absorption. The beneficial characteristic of a gastro-retentive drug delivery system (GRDDS) is its ability to remain in the upper gastrointestinal tract (GIT) for an extended duration, hence greatly prolonging the gastric retention time (GRT) of the medications. The medication is administered by placing the dosage form in the acidic environment of the stomach, where it is then delivered in a controlled manner into the stomach, duodenum, or intestine at a specified site.

Hydrophilic polymer networks, known as hydrogels, can absorb water up to hundreds of times their dry weight. Hydrogels exhibit chemical stability or may undergo degradation, disintegration, and dissolution. Hydrogel networks that are interconnected through molecular entanglements and additional forces, such as hydrogen bonding, ionic bonding, or hydrophobic interactions, are classified as reversible or physical gels.

Superporous hydrogel

Superporous hydrogel (SPH) is a three-dimensional network of hydrophilic polymers that rapidly absorbs substantial volumes of water due to the presence of extensively linked tiny pores. Superporous hydrogels possess pore sizes ranging from 50 to 100 μm and expand rapidly, within a minute, due to the swift absorption of water through capillary action via a network of densely interconnected microscopic open pores. SPHs possess the capacity to expand significantly and exhibit mechanical strength adequate to withstand pressure from gastric contractions, achieved through the use of hydrophilic materials such as Ac-Di-Sol (Cross Carmellose Sodium).

This is a novel hydrogel characterised by numerous supersized holes, with swelling occurring via the capillary wetting mechanism instead of 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.

The SPH exhibit rapid swelling kinetics and a high swelling rate; however, the mechanical force is insufficient. The multiple swelling SPH were challenging to manipulate and prone to breakage due to their inadequate mechanical characteristics. Typically, a mechanically robust super porosity hydrogel can be synthesised by augmenting the crosslinking density; however, this approach results in minimal swelling and a diminished superabsorbent capacity. Consequently, the fabrication of hyper porous hydrogels exhibiting rapid swelling, elevated absorbency, uniqueness, and substantial mechanical strength is essential. Superporous hydrogels has attributes including smoothness, biocompatibility, biodegradability, great swelling capacity, significant mechanical strength, and stability in acidic environments.

Principle of gastric retention of superporous hydrogel

The gastric retention of SPHs is mostly attributable to their fast expansion. SPH is initially contained in a small capsule or compressed tablet that is easy to swallow; but, upon oral ingestion, it rapidly expands in the gastric acidic fluid to a larger size, obstructing its passage through the pyloric opening and into the small intestine. During gastric contractions, the stomach's contents float atop the hydrogel. Due to its elasticity, smoothness, and superior mechanical properties, it can endure gastrointestinal contractions. It administers the medicine by buoyancy in the superior segment of the gastrointestinal tract owing to its low density, as illustrated in Figure 1. Upon the initiation of drug release, the hydrogel gradually dissolves in the stomach by mechanical forces or enzymatic hydrolysis of the polymer chains.

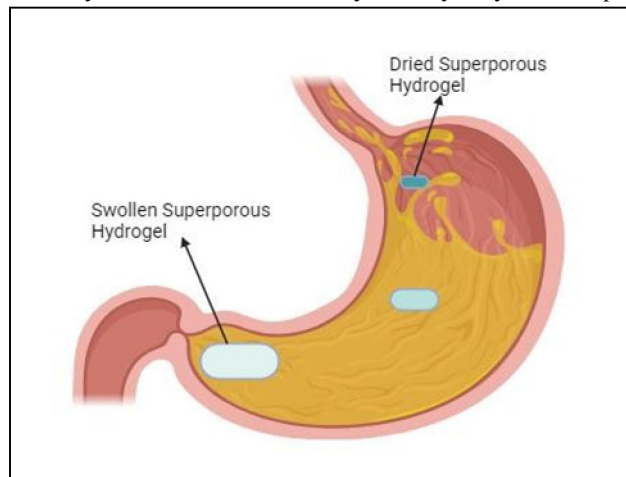


Figure 1: Principle of gastric retention of superporous hydrogel

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.

Classification of superporous hydrogel

- First generation as conventional superporous hydrogels (CSPHs)
- Second generation as superporous hydrogel composites (SPHCs)
- 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 inaugural occasion. Vinyl monomer was utilised in the manufacture of typical super porous hydrogel. The most commonly utilised monomers are those that exhibit high hydrophilicity, such as acrylamide and sulfopropyl acrylate. Hydrophilic monomers, such as carboxyl or amide in acrylic acid and acrylamide, respectively, or ionic monomers like carboxylate in sodium or potassium acrylate, may exhibit superior swelling capabilities. Due to their diminished mechanical strength, swelling SPHs are challenging to manipulate. These are fragile, and the structure may readily collapse under low pressure, while the formulation cannot remain in the stomach for an extended duration. Consequently, researchers developed the second generation, as illustrated in Figure 2.

Second generation as superporous hydrogel composite (SPHCs)

A super disintegrant is included as a swellable filler into this specific sort of super porous hydrogel. Baek (2001) converted traditional super porous hydrogel into a second generation super porous hydrogel. The dispersed phase is combined with a continuous phase. AC-Di-Sol, Primojel, and crospovidone are composite substances utilised in the formulation of SPHs. AC-Di-Sol has a significant swelling capacity and robust mechanical properties. The mechanical characteristics of SPHs can be enhanced by acidifying polymer ionizable groups, enabling the SPHs to withstand the stress of gastric contractions during the gastric motility phase. The composite agent enhances the mechanical characteristics of hydrogel composites. Nonetheless, extremely porous hydrogel composites remain delicate and brittle. Third generation as superporous hydrogel hybrids (SPHHs)

In 2003, Omidian synthesised a superporous hydrogel hybrid utilising acrylamide, methylene bisacrylamide, and a crosslinker. The mechanical or elastic properties of superporous hydrogel hybrids are exceptionally high. In contrast to super porous hydrogel composites, SPHHs incorporate a pre-cross-linked matrix swelling ingredient. A water-soluble polymer is a composite compound, such as chitosan and pectin. The synthesis of an acrylamide-based superporous hydrogel incorporating sodium alginate exemplifies an SPHH, subsequently undergoing calcium ion crosslinking with alginate chains. Elastic, water-saturated, highly porous hydrogel hybrids can withstand several forms of pressure, including compression, stiffness, twisting, and bending. The comparison of generations of superporous hydrogel is presented in Table 1.

Table 1: Comparison of all three generations of superporous hydrogel 2

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

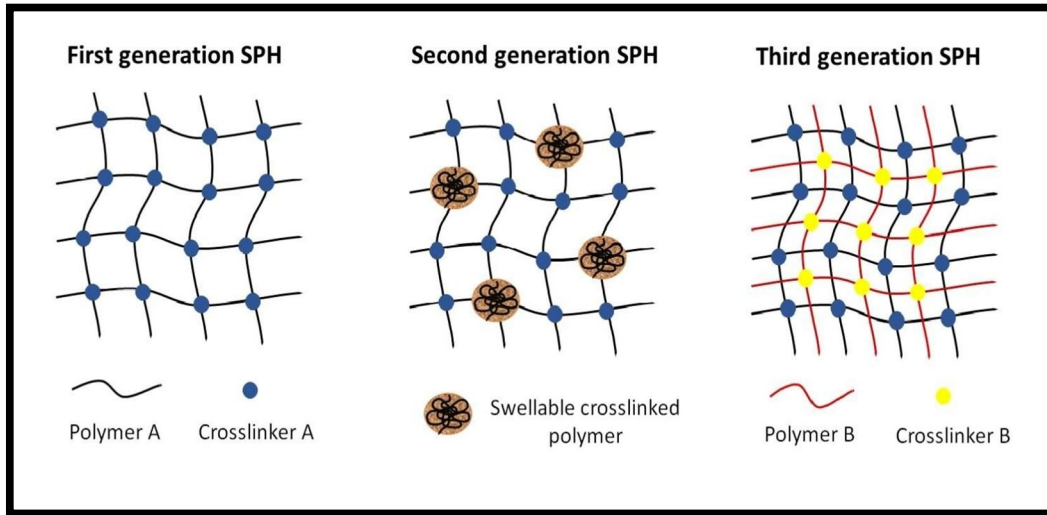


Figure 2: Generations of superporous hydrogel

Techniques for the preparation of superporous hydrogel

Gas blowing technique

This is the most conventionally employed approach. Initially, a test tube contains a mixture of monomer, crosslinking agent, foam stabiliser, and distilled water, with precise dimensions and a pH set to 5-6 using 5 M NaOH. Low pH promotes the polymerisation reaction; subsequently, a foaming agent is incorporated into the reaction mixture, resulting in the creation of gas bubbles and a progressive increase in the solution's pH. The polymerisation process is accelerated by an increase in pH levels. Gas bubbles are simultaneously entrapped by both gellification and foaming reactions in the reaction mixture, as illustrated in Figure 3. Subsequent to synthesis, the highly porous hydrogel undergoes washing and drying through various processes.

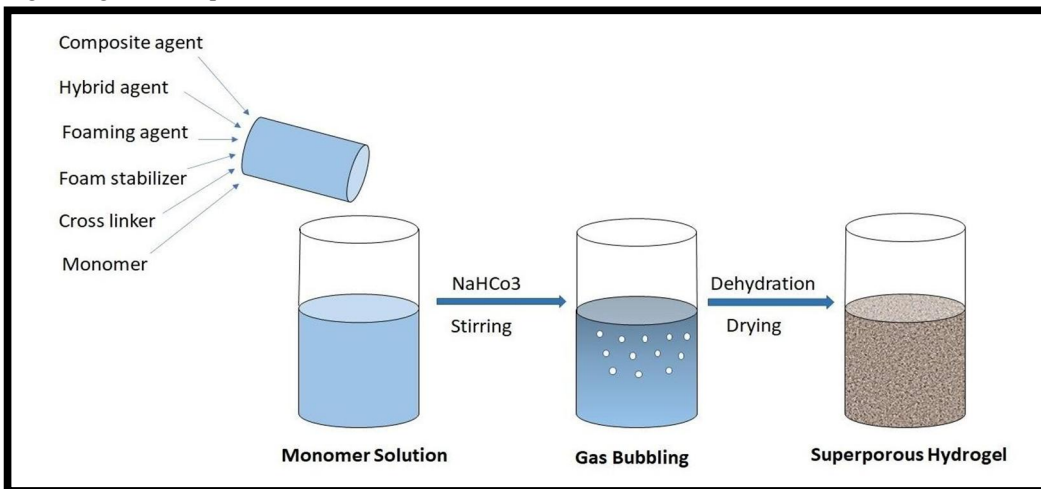


Figure 3: Gas blowing technique

Porosigen technique

Porosigens exhibit solubility in water and possess hydrophilic characteristics. Upon contact with water, these porosigens create a porous structure. The pore size creation in SPH is contingent upon the dimensions of porosigens.

For example, micronized lactose, micronized sucrose, micronized dextrin, micronized cellulose, sodium chloride, and polythene glycol (PEG) constitute a network.

Phase separation technique

This technique is intricate for producing extremely porous hydrogel because to the lack of control over porosity in this process. In solution polymerisation, heterogeneous superporous hydrogels possess extensive network voids. This is known as heterogeneous solution polymerisation. The superporous hydrogel produced by this approach has minimal porosity. This approach has restricted applicability for the manufacture of hydrogel using HEMA (hydroxyethyl methyl acrylate) and NIPAM (N-isopropyl acrylamide).

Cross linking technique

The crosslinking of hydrogel particles induces particle aggregation. In this structural configuration, supports are located between hydrogel particles, which are far smaller than the particles themselves. A crosslinking agent, water, and a hydrophilic organic solvent are utilised to prepare the macrostructure. This approach is applicable only to absorbent particles that possess active functional groups on their surfaces. The excipients utilised for the preparation of the superporous hydrogel are detailed 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, Hydroxyethyl 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 crospovidone, 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.

Patent and research papers related to superporous hydrogel formulations

Omidian et al., patented regarding the formation of superporous hydrogel using an ion- Equilibration methodology. Anionic polysaccharides are included into the hydrogel reaction mixture, and cations are introduced either during or subsequent to the hydrogel formation. Superporous hydrogels can be synthesised that exhibit great absorbency along with attributes such as strength, durability, and resilience.

Juthi et al. developed a novel pH-responsive super-porous hybrid hydrogel, which was infused with amoxicillin trihydrate and comprised of pectin, poly 2-hydroxyethyl methacrylate (2-HEMA), and N,N'-methylene-bis-acrylamide. This study demonstrates significant edoema and delayed drug release at pH levels of 1.2 (97.99%) and 7.4 (88%).

Chintalapati V.S. and Gopinath formulated SPH utilising changing quantities of two separate polymers, polyvinyl alcohol (PVA) and chitosan, along with a crosslinking agent, glutaraldehyde, to achieve the required controlled release profile, demonstrating extended gastro-retention for up to 18 hours, with a lag time of 11 to 16 minutes.

Jihad and J. Al-Akkam synthesised gastroretentive superporous hydrogels containing carvedilol by using chitosan, polyvinyl alcohol, acrylamide, methylene bis-acrylamide, and glutaraldehyde to produce SPH hybrids. The SPH formulated capsules containing carvedilol are specifically engineered for gastric delivery due to their enhanced residence time and superior solubility.

Ramya et al. synthesised SPH formulations incorporating lafutidine, an H2-receptor antagonist that inhibits gastric acid production, utilising several composite agents like Carbopol, sodium alginate, pectin, and chitosan. The swelling properties of SPH were assessed by systematically decreasing the swelling duration from 45 minutes to 16 minutes.

Hitesh Chavda et al. developed bioadhesive superporous hydrogel composite particles for the intestinal administration of metoprolol succinate, employing chitosan and HPMC as release retardant and bioadhesive polymers, respectively. This method maintains bioadhesion for up to 8 hours in the intestine.

Characterizations of superporous hydrogel

FT-IR spectroscopy: It is used to determine the compatibility between the drug and the Polymers. The infrared spectra of the pure medication and a physical mixture of the formulation's components are recorded. The FTIR spectrum is obtained within the region of 400 – 4000 cm-1 utilising the KBr pellet method with a Fourier-Transform Infrared (FT-IR) spectrophotometer.

Investigation of edoema. It is dictated by the following two parameters:

Duration of swelling: The dried superporous hydrogels are immersed in deionized water and 0.1N HCl, and the necessary duration to attain swelling equilibrium is determined.

Swelling ratio: The desiccated SPH is allowed to hydrate in an adequate volume of deionized water at ambient temperature. Following the removal of excess water through gentle blotting, the weight of the hydrated sample is documented at multiple time intervals. The swelling ratio of SPH is determined as follows:

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

Ws - Weight of completely swollen hydrogel,

Wp - Weight of superporous hydrogel at different exposure times.

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,

M1 and M2 - Masses of hydrogel before & after submerged in absolute ethanol respectively.

Determination of void fraction

The desiccated superporous hydrogel is submerged in 0.1N HCl until equilibrium is attained. The volumetric dimensions of the expanded hydrogel are computed subsequent to measuring its dimensions. The quantity of buffer absorbed by the hydrogels is determined by subtracting the weight of dry SPHs from the weight of swollen hydrogels,

with the resultant value being ascertained based on the total volume of pores within the SPHs. The void fraction is calculated using the subsequent 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.

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,

$$WRT = (WP - Wd) / (Ws - Wd)$$

Wd - Weight of dry SPH,

Ws - Weight of completely swollen hydrogel,

Wp - Weight of superporous hydrogel at different exposure times.

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,

$$PP = F_u / S$$

Fu - Compressive strength at which the polymer breaks completely,

S - Lower touch area.

Scanning electron microscopy (SEM): The dimensions and shape of superporous hydrogel are ascertained using SEM analysis. The samples are affixed on a double-sided tape on an aluminium stub. The samples are gold-coated using a cool spotter to ascertain the thickness of the photomicrograph, captured at an accelerated voltage of 20 kV and a chamber pressure of 0.6 mm Hg. Following the application of a coating to the sample with a Hammer Sputter Coater, a scanning electron microscope is employed at an accelerating voltage of 5 kV.

In-vitro drug release study: The medication is released in vitro from the formulated preparations utilising the USB type II dissolution apparatus, with a rotational speed of 100 RPM in 900 ml of 0.1 N HCl at a pH of 37°C ± 0.5°C. To sustain a consistent volume, aliquots of 5 ml samples are extracted at specified intervals and replaced with fresh dissolving media. The UV Spectrophotometer is employed for sample analysis.

Applications of superporous hydrogel

Gastroretentive platforms

The gastroretentive platforms may enhance the administration of many pharmaceuticals. This is particularly beneficial for pharmaceuticals that predominantly absorb in the upper gastrointestinal system, such as antacids and antibiotics, or for treatments that exert local effects in the stomach. Controlled release can enhance bioavailability for medications with a limited absorption window or those absorbed from the small intestine, including levodopa, riboflavin, and p-aminobenzoic acid. Pharmaceuticals that degrade in the colon, such as metoprolol, or those that are unstable in an alkaline pH environment, can also be addressed with gastroretentive systems.

Gastroretentive tablet

The gastroretentive pill is engineered to remain in the stomach and is made through blending and direct compression. Acrylic acid or sulfopropyl acrylate copolymer SPH particles were integrated with gelatine and tannic acid using hydrogen bonding prior to tablet formation via direct compression. Furthermore, the expanded tablet can endure a compressive stress of up to 16 KPa before shattering.

As a superdisintegrant

Superdisintegrants are pharmaceutically suitable polymers, including starch derivatives, cellulose, and poly(vinyl pyrrolidone), specifically engineered for their swelling properties. SPH functions as a disintegrating agent, incorporated in fine particle form within a solid dose formulation. The SPH superdisintegrant, due to its size and pore structure, markedly varies from conventional superdisintegrants by providing a significantly higher surface area.

Protein or peptide delivery systems

The utilisation of CSPH and SPHC for oral peptide delivery has been examined. This technology is designed to physically attach to the intestinal wall and be given directly to the specific spot. The carboxyl-functionalized SPH facilitates calcium extraction, hence opening closed junctions and neutralising harmful gastrointestinal enzymes. The appropriate selection of enteric coating aims to direct this dose form to a specific area in the small intestine or the colon.

Chemoembolization and occlusion devices

Chemotherapy and embolisation are integrated in the method known as chemoembolization. Embolisation has been employed to treat cancer by obstructing the oxygen supply to proliferating cancers. Local delivery can be accomplished by minimising systemic toxicity. In chemoembolization therapy, SPHs may be infused with chemotherapeutic and anti-angiogenic drugs. The robust SPH facilitates superior adaptation within the blood artery and enhances occlusion.

Site-specific drug delivery

This is particularly beneficial for medications absorbed in the stomach or the proximal small intestine, such as furosemide and riboflavin. A bilayer-floating capsule engineered for the topical delivery of misoprostol, a synthetic counterpart of prostaglandin E1 utilised in the treatment of NSAID-induced gastric ulcers. Misoprostol is gradually sent to the stomach, facilitating the attainment of optimal therapeutic levels and minimising drug wastage.

Development of diet aid

Diet soft beverages, meal replacement shakes, diet medications, and surgical procedures have been utilised for weight loss. The SPH's rapid and wide swelling capacity may theoretically occupy a substantial amount of the stomach, hence reducing meal capacity and diminishing appetite. This device has the potential to assist obese individuals in weight loss.

Future prospective of superporous hydrogel

Superporous hydrogels are emerging as a significant area of research and improvement in the pharmaceutical profession. Advancements may result in increased biocompatibility, bioavailability, solubility, swelling and mechanical qualities, as well as controlled porosity, allowing for customisation for specific biomedical applications. This method is designed for gastroretentive dosage forms, oral peptide delivery, targeted drug delivery, chemoembolization and occlusion devices, site-specific drug delivery, superdisintegrants, dietary assistance, personalised medicine, artificial organs, and prosthetics.

II. CONCLUSION

Superporous hydrogels are an innovative class of hydrogel materials that expand swiftly to a size far bigger than their original dimensions, owing to their swelling characteristics and mechanical strength, rendering them a promising option for gastro-retentive delivery systems. Multiple generations of SPHs have been effectively examined for gastric retention. Furthermore, the application of SPH in oral solid and semi-solid dose forms has been examined. The study examines the application of superporous hydrogel in many medicinal domains necessitating fast swelling. Superporous hydrogel is utilised as a medication carrier in the biomedical industry.

ACKNOWLEDGMENT

I would like to thank my teachers and guide for all the support and guidance.

REFERENCES

- [1]. Akki R, Ramya MG, Shaik R. A Review on: Super porous hydrogel in drug delivery system. *Int J Pharm Sci Health Care*. 2018;5(8). <https://doi.org/10.26808/rs.ph.i8v5.01>
- [2]. Bagadiya A, Kapadiya, M. Superporous hydrogel: A Promising tool for gastroretentive drug delivery system. *Int J Pharm Ther*. 2011;3(4):1556-1571.
- [3]. Chaudhury S, Sharma S, Rajput G, Banshraj. Superporous hydrogel: A Review. *Int J Pharma Profess Res*. 2013;4(3):905-911.
- [4]. Chavda H, Modhia I, Mehta A, Patel R, Patel C. Development of Bioadhesive Chitosan Superporous Hydrogel Composite Particles Based Intestinal Drug Delivery System. *Hindawi*. 2013;13. <https://doi.org/10.1155/2013/563651> PMID:23984380 PMCID:PMC3747347
- [5]. Chavda H, Patel C. Effect of crosslinker concentration on characteristics of superporous hydrogel. *J Pharm Innov*. 2010;1(1):17-21. <https://doi.org/10.4103/2230-973X.76724> PMID:23071915 PMCID:PMC3465110
- [6]. Chen J, Blevins WE, Park H, Park K. Gastric retention properties of superporous hydrogel composites. *J Control Release*. 1998;64:39- 51. [https://doi.org/10.1016/S0168-3659\(99\)00139-X](https://doi.org/10.1016/S0168-3659(99)00139-X) PMID:10640644
- [7]. Desu PK, Pasam V, Kotra V. Formulation and in vitro evaluation of superporous hydrogel based gastroretentive drug delivery system of vildagliptin. *J Res Pharm*. 2019;23(5):873-885. <https://doi.org/10.35333/jrp.2019.35> 39. Park H, Park K, Kim D. Preparation and swelling behavior of chitosan-based superporous hydrogels for gastric retention application. *J Biomed Mater Res*. 2005;76A(1):144-150. <https://doi.org/10.1002/jbm.a.30533> PMID:16258961
- [8]. El-said IA, Aboelwafa AA, Khalil RM, ElGazayerly ON. Baclofen novel gastroretentive extended release gellan gum superporous hydrogel hybrid system: in-vitro and in-vivo evaluation. *Informa Healthcare*. March 2014;14:1-12. <https://doi.org/10.3109/10717544.2014.905654> PMID:24786486
- [9]. Farag MM, Louis MM, Badawy AA, Nesses DI, Elmalak NSA. Drotaverine Hydrochloride Superporous Hydrogel Hybrid System: A Gastroretentive Approach for Sustained Drug Delivery and Enhanced Viscoelasticity. *AAPS Pharm Sci Tech*. 2022;23(5):124. <https://doi.org/10.1208/s12249-022-02280-2> PMID:35471680
- [10]. Gupta NV, Shivakumar HG. Preparation and characterization of superporous hydrogels as pH-sensitive drug delivery system for Pantoprazole sodium. *Curr Drug Deliv*. 2009;6(5):505-510. <https://doi.org/10.2174/156720109789941722> PMID:19863492
- [11]. Jihad HM, J. Al- Akkam E. Formulation and in-vitro Evaluation of Carvedilol Gastroretentive Capsule as (Superporous Hydrogel). *Iraqi J Pharm Sci*. 2021;30(2):196-207. <https://doi.org/10.31351/vol30iss2pp196-207>
- [12]. Juthi AZ, Li F, Wang B, Alam MM, Talukder ME, Qiu B. pH- Responsive Super-Porous Hybrid Hydrogels for Gastroretentive Controlled-Release Drug Delivery. *MDPI*. 2023;15(816):1-14. <https://doi.org/10.3390/pharmaceutics15030816> PMID:36986676 PMCID:PMC10053105
- [13]. Keshavlal Ladola M. Superporous hydrogel (SPH): A novel and advanced technique of oral controlled release drug delivery system. *World J Pharma Res*. 2014;3(5):297-319.
- [14]. Khan A, Rana T, Naeem Z, et al. Hydrogels: A Novel Drug Delivery System. *J Biomed Res Environ Sci*. 2020;1(8):439-451. <https://doi.org/10.37871/jbres1176>
- [15]. Kumar K A, Reddy MS, P M, Babu P S. A Review on gastroretentive superporous hydrogels and its generations. *J Chem and Pharm sci*. 2012;5(2):78-81.
- [16]. Kumar K, Dey A, Pal I, Mandal K, Bhowmick B, Sarkar T. Recent Advances in Gastroretentive Drug Delivery Systems: A Review. *Asian J Pharm*. 2022;16(03):250-260. <https://doi.org/10.22377/ajp.v16i3.4474>
- [17]. Kumari PVK, Sharmila M, Rao YS. Super Porous Hydrogels: A Review. *J Pharm Res Innov*. 2020;32(13):153-165. <https://doi.org/10.9734/jpri/2020/v32i1330595>

- [18]. Mastropietro DJ, Omidian H, Park K. Drug delivery applications for superporous hydrogels. *Expert Opin Drug Deliv.* 2012;9(1):71-89. <https://doi.org/10.1517/17425247.2012.641950> PMID:22145909
- [19]. Mishra D, Nagpal M, Singh S. Superporous hybrid hydrogels based on polyacrylamide and chitosan: Characterization and in vitro drug release. *Int J Pharma Investig.* 2013;3(2):88. <https://doi.org/10.4103/2230-973X.114906> PMID:24015380 PMCID:PMC3757904
- [20]. More S, Gavali K, Doke O, Kasgawade P. Gastroretentive Drug Delivery System. *J Drug Delivery Ther.* 2018;8(4):24-35. <https://doi.org/10.22270/jddt.v8i4.1788>
- [21]. Nayak AK, Maji R, Das B. Gastroretentive drug delivery systems: a review. *Asian J Pharm Clinical Res.* 2010;3(1):2-10.
- [22]. Omidian H, Park K, Rocca JG. Recent developments in superporous hydrogels. *Journal of Pharmacy and Pharmacology.* 2010;59(3):317-327. <https://doi.org/10.1211/jpp.59.3.0001> PMID:17331335
- [23]. Omidian H, Park K. Superporous Hydrogels for Drug Delivery Systems. Elsevier. 2011:563-575. <https://doi.org/10.1016/B978-0-08-055294-1.00044-1>
- [24]. Omidian H, Rocca JG. Formation of strong superporous hydrogels. US Patent 7056957 B2, June 6, 2006. <https://doi.org/10.1002/mabi.200600062> PMID:16967483
- [25]. Patel PK, Mistry SN, Patel GJ, Bharadia PD. Recent in Controlled Drug Delivery System: Superporous Hydrogels. *J Pharm and cos.* 2011;1(5):54-65.
- [26]. Pati NB, Velivela S, Mayasa V, Gupta VRM. Gastroretentive Superporous Hydrogel Tablets of Dexlansoprazole. *Int Jour Pharm Sci Res.* 2016;7(11):4678-4685. [https://doi.org/10.13040/IJPSR.0975-8232.7\(11\).4678-85](https://doi.org/10.13040/IJPSR.0975-8232.7(11).4678-85) PMID:26913287
- [27]. Patil PR, Khairnar SK, Shadab HA, Gangurde AB, Bairagi VA. A Review: Superporous Hydrogels. *Int J Crea Res Thoughts.* 2021;9(2):2320-2882.
- [28]. Patil-Vibhute PB, Hajare AA. Preparation and Characterization of Superporous Hydrogel as Gastroretentive Drug Delivery System for Atenolol. *Int J Pharm Sci Res.* 2019; 10(1):272-285. [https://doi.org/10.13040/IJPSR.0975-8232.10\(1\).272-85](https://doi.org/10.13040/IJPSR.0975-8232.10(1).272-85)
- [29]. Qiu Y, Park K. Superporous IPN hydrogels having enhanced mechanical properties. *AAPS Pharm Sci Tech.* 2003;4(4):406-412. <https://doi.org/10.1208/pt040451> PMID:15198546 PMCID:PMC2750644
- [30]. Ragunathan M, Parthiban KG, Dilna D. Formulation and Evaluation of Superporous hydrogel tablet of Rabeprazole sodium as a gastroretentive system. *Eur J Pharm Med Res.* 2018;5(12):271- 278.
- [31]. Ramya MG, Akki R, Kathirvel S. Formulation and In-vitro Characterisation of Controlled Release Lafutidine Superporous Hydrogel Tablets. *Int J Pharm Sci Res.* 2020;11(8):3745-3762. [https://doi.org/10.13040/IJPSR.0975-8232.11\(8\).3745-62](https://doi.org/10.13040/IJPSR.0975-8232.11(8).3745-62)
- [32]. Rezanejade Bardajee G, Boraghi SA, Mahmoodian H, Rezanejad Z, Parhizkari K, Elmizadeh H. A salep biopolymer-based superporous hydrogel for ranitidine delivery: synthesis and characterization. *J Polym Res.* 2023;30(2):66. <https://doi.org/10.1007/s10965-023- 03436-9>
- [33]. Sadhu PK, Baji AA, Shah NV, et al. An Approaches and Patents on Controlled Release Gastroretentive Drug Delivery System - A Review. *Int J Pharm Res.* 2020;12(2):2047-2059. doi: <https://doi.org/10.31838/ijpr/2020.12.02.275>
- [34]. Tripathi J, Thapa P, Maharjan R, Jeong SH. Current State and Future Perspectives on Gastroretentive Drug Delivery Systems. *Pharmaceutics.* 2019;11(4):193. <https://doi.org/10.3390/pharmaceutics11040193> PMID:31010054 PMCID:PMC6523542
- [35]. Verma NK, Singh AK, Yadav V, Singh P, Yadav A, Jaiswal S. Super Porous Hydrogel Based Drug Delivery System: A Review. *South Asian Res J Pharm Sci.* 2021;3(6):103-110. doi: <https://doi.org/10.36346/sarjps.2021.v03i06.004>