Super porous hydrogels (SPHs) are recent advancement in gastro retentive drug delivery system (GRDDS) which also includes intragastric floating system (low density system), mucoadhesive system, high density system and swellable system. These systems should instantly swell in the stomach and maintain their integrity in the harsh stomach environment, while releasing the pharmaceutical active ingredient. SPHs could accommodate a large amount of water within short period through interconnected capillary channels. The poor mechanical strength of SPHs has been overcome by developing the second-generation SPH composites (SPHCs) and the third-generation SPH hybrids (SPHHs), super porous hydrogel interpenetrating network (SPHs-IPN). This review discusses the formulation, various generations, methods of preparation, techniques of drug loading, method for synthesis of superporous hydrogels, list of various reagent used techniques for synthesizing SPHs-IPN and characterization.

Abbreviations

SPH  Superporous hydrogel
SPHCs  Superporous hydrogel composites
SPHHs  Superporous hydrogel hybrids
IPN  Interpenetrating network
GIT gastrointestinal tract
SEM  Scanning electron microscope
DDS  Drug delivery system
PEG  Polyethyleneglycol
INTRODUCTION
Drug delivery technologies are as important as new chemical entities entering into the pharmaceutical industries, allowing more effective use of existing drugs and successful development of a new drug candidate.[1] This delivery system shows very better compliance as well as industrial applications. A more recent trend has been to develop novel drug delivery systems that improve the bioavailability and therapeutic response of currently approved drugs. [2] Hydrogels have long been established in this field to control the release of a drug from a conventional solid dose formulation. Hydrogels are made of hydrophilic polymers that have been cross-linked to form a continuous network, capable of absorbing water and other aqueous fluids. Hydrogel may be further classified into four; nonporous, microporous, macroporous and superporous.

Gastro retentive drug delivery system
Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT). These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment. [3] Also prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic
ulcer etc. Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastro retentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach, low density (floating) systems that causes buoyancy in gastric fluid, mucoadhesive systems that causes bioadhesion to stomach mucosa, unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach, superporous hydrogel systems, magnetic systems etc.

**DRUGS THOSE ARE SUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM**

Following are the suitable attributes of drug candidates useful as GRDDS.

1. Locally acting drugs in stomach e.g. Antacids, drugs against Helicobacter pylori.
2. Rapidly absorbing drugs from GIT e.g. Tetracycline & Metronidazole.
3. Drugs with narrow absorption window e.g. Atenolol & Theophylline.
4. Poorly soluble candidates in intestine e.g. Quinidine & Riboflavin.
5. Normal flora disturbing drugs e.g. Antibiotics against Helicobacter pylori. Amoxicillin.
6. Drugs that destroyed in colon e.g. Metformin HCl& Captopril.
7. Drugs having variable BA (bioavailability) e.g. Sotalol HCl.
8. Drugs primarily absorbed through upper GIT e.g. Cinnarazine & Calcium supplements.

**Unsuitable drug candidates**

Drugs that are unsuitable to be formulated as GRDDS have following characteristics.

1. Drugs that cause gastric irritation e.g. NSAIDS.
2. Drugs with limited solubility in acids e.g. Phenytoin.
3. Drugs unsuitable in stomach.
4. Selective release of drug in colon e.g. 5ASA (5-Aminosalicylic Acid).

**Advantages**

1. Enhanced patient compliance.
2. Reduced dosage frequency.
3. Buoyancy leads to enhanced GRT (Gastric residence time).
4. Targeted drug delivery to stomach can be achieved.
5. Increased BA and fluctuation in blood drug concentration is avoided.
6. Uniform drug release from dosage form and no chance of dose dumping.
7. Sustained effect leads to prevention of mucosal irritation.

Disadvantages
1. Drugs unstable & insoluble in mucosal fluids cannot be administered as GRDDS.
2. Drugs causing gastric irritation cannot be administered via this route.
3. This system requires fed state to prolong gastric emptying.
4. Not suitable for drugs undergo FPM (first-pass-metabolism)
5. Gastric retention can be influenced by various factors which can never be constant all the time; these factors are variable & unavoidable.

Superporous Hydrogels (SPH)
In 1999, A superporous hydrogel (SPH) is a 3-dimensional network of a hydrophilic polymer that absorbs a large amount of water in a very short period of time due to the presence of Interconnected microscopic pores.\(^6\) SPHs are a new type of hydrogel that have numerous super size pores inside them. Swelling of superporous hydrogels is done by capillary wetting rather than by diffusion. In the preparation of SPHs certain ingredients, including initiators, crosslinkers, foam stabilizers, foaming aids and foaming agents, are added into a water-diluted monomer. Superporous hydrogel does not have only fast swelling, but also have properties like slipperiness, biodegradability biocompatibility, high mechanical strength, high swelling capacity and stability in acidic condition of the stomach. Thereby, Superporous hydrogels swell completely with in minutes regardless of their size due to absorption of water by capillary force rather than by simple absorption. Second generation Superporous hydrogels composites are developed which shows fast swelling, medium swelling ratio and improved mechanical properties, while third generation superporous hydrogel hybrid possess high elastic properties.\(^7\) Gastric retention devices would be most beneficial for local action of drugs in the stomach, e.g. antacids and antibiotics for bacteria based ulcers or drugs that are required be absorbed primarily in the stomach.

Principle of the gastric retention of superporous hydrogels\(^8\)
The gastric retention of superporous hydrogels is based on their fast swelling property. Superporous hydrogel is filled in a capsule so that the initial volume is small which is easy to swallow. After oral administration, it swells rapidly in the gastric fluid to a large size. So that its emptying into the intestine is prevented.\(^9\) When the gastric contraction reaches the
hydrogel, the gastric tissues slide over the hydrogel. As it is elastic, slippery and high mechanical strength it able to withstand gastric contraction and also due to the low density of superporous hydrogel than the gastric content it floats and releases drug in upper part of GIT.[10] When a drug is released from this dosage form, it slowly undergoes degradation in the stomach by either mechanical force or chemical/enzymatic hydrolysis of the polymer chains constituting the hydrogel.

Advantages of SPH
a. The Superporous hydrogel swell completely with in a minute regardless of the size of the dried superporous hydrogel. The swelling rate is very fast.
b. Swells to such an extent that the weight of swollen state is higher than weights of dried state.
c. Though the superporous hydrogels contain small percentage of solid content of the total weight, it can exert significant expansion force during swelling.
d. It can be made elastic to minimize their rupture.
e. The unique properties of superporous hydrogels can also be used for non pharmaceutical and non-biomedical applications.

Methods For Preparation Of Superporous Hydrogels[11]
There are four methods for preparing the gastroretentive superporous hydrogel,

• Porosigen technique
• Cross linking technique
• Phase separation technique
• Gas blowing or foaming technique.

Porosigen Technique
Porous hydrogels are prepared in presence of dispersed water soluble porosigen. Various porosigen are used to prepare the superporous hydrogel. These porosigen are hydrophilic in nature.[12] The pore size generates in the hydrogel depends on the size of porosigens.[13]

Cross linking technique
Crosslinking 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 Individual hydrogel particles can be crosslinked to form crosslinked
aggregates. This technique is limited to absorbent particles with chemically active functional groups on surface.\textsuperscript{[14]}

**Phase separation technique**

Phase separation is very critical process in generating superporous hydrogel because there is no much control over the porosity. In solution polymerization, monomers are usually mixed in diluent that is good for both monomers and polymers. The major limitation of the phase separation method is that only very limited types of porous hydrogels can be prepared. In addition, there is not much control over the porosity of the gels when prepared by phase separation.\textsuperscript{[15,16]}

**Gas blowing or foaming technique**

This is most widely used. Initially monomers, cross linking agent, foam stabilizer and distilled water are added in a test tube of specific dimensions pH adjust 5 to 6 with 5M NaOH.\textsuperscript{[17]} The gas blowing technology has been widely used in the preparation of plastic foams from materials such as polyurethanes, rubber, and poly (vinyl chloride). The key ingredient in the foaming process is a blowing agent (or foaming agent), which is defined as any substance or combination of substances capable of producing cellular structure within a polymer matrix.\textsuperscript{[18]} After synthesis, Superporous hydrogels are subjected to washing, drying using different methods.

**Ingredients Required For Preparing Superporous Hydrogel**

The ingredients required for preparing superporous hydrogel are as shown in.

**Table 1: Role of ingredients with their examples.**\textsuperscript{[19,20]}

<table>
<thead>
<tr>
<th>Role of ingredients</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monomers</strong></td>
<td>Acrylic Acid (AA), Acrylamide (AM), 3-Sulphopropyl acrylate potassium (SPAK), Hydroxy ethyl methyl acrylate (HEMA), N-isopropyl acrylamide (NIPAM), Acrylonitrile (AN), Polyvinyl alcohol (PVA)</td>
</tr>
<tr>
<td><strong>Cross linking agents</strong></td>
<td><strong>Chemical cross linker:</strong> Glutaraldehyde, N,N’-methylenbisacrylamide (Bis), <strong>Iontropic cross linker:</strong> metal ions like calcium, iron and phosphorus</td>
</tr>
<tr>
<td><strong>Foam stabilizers</strong></td>
<td>Pluronic F127, Pluronic P105, Silwet L7605, Span, Tween</td>
</tr>
<tr>
<td><strong>Polymerization initiator</strong></td>
<td>APS/TEMED (Ammonium persulfate/N,N,N,N-tetramethylene diamine), KPS/Sodium</td>
</tr>
<tr>
<td>pairs</td>
<td>metabisulfite, APS/Sodium metabisulfite, Azoinitiator (V545)</td>
</tr>
<tr>
<td>-------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Foaming agent</td>
<td>Sodium bicarbonate, Sodium carbonate, Potassium bicarbonate</td>
</tr>
<tr>
<td>Composite agents</td>
<td>Crosslinked sodium carboxy methylcellulose (Ac-Di-Sol), Crosslinked sodium starch glycolate (Primojel) and Crosslinked polyvinylpyrrolidone (cospovidone), Carbopol, Polyvinyl alcohol (PVA)</td>
</tr>
<tr>
<td>Hybrid agents</td>
<td>Natural polymers: Sodium alginate, Sodium carboxymethylcellulose (Na CMC), Chitosan based on ionotropic gelation, Pectin Synthetic polymers: Poly vinyl alcohol (PVA) based on cryogelation</td>
</tr>
</tbody>
</table>

### 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\(^{[21]}\)
2. Drug loading into superporous hydrogel polymers.

### Drug loading into superporous hydrogel reservoir devices

Two types of drug delivery systems has been designed

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

#### 1. Core inside shuttle

In this system, core is prepared in two different forms viz. micro particles and gross mass.\(^{[22]}\)

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. 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.
2. Core attached to surface of shuttle system
Core is in the form of small tablet prepared by dispersing drug in melted polymer like PEG 6000 and sieving mass through # 400 µm, add magnesium stearate and compressed into tablet to 40N hardness. Conveyor is made up with superporous hydrogel composite in which two holes are made on counter side. Core tablet is placed inside the hole using bio-adhesive (cyanoacrylate) glue. Polymer swells when comes in contact with gastric fluids and size of holes is enlarged. Glue helps to keep the dosage forms at the site of drug absorption. Same assembly is placed into gelatin capsule shells of size 000.[23]

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.[24]

Drying of Superporous Hydrogel
Drying of superporous hydrogel are can be carried out under two different conditions.[25] 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.

Classification of superporous hydrogel
1. First generation SPH.
2. Second generation SPH.
3. Third generation SPH.
First generation SPH (conventional SPHs, CSPHs)

Conventional SPH (CSPH) was first discovered by with fast swelling kinetics and super absorbent properties in 1999.[26] It involves vinyl monomers like acrylamide, ionic monomer like salt of sulfopropylacrylate potassium, acrylic acid etc. In order to preserve porous structure of SPH, alcohol is used. Dried SPH 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 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. Their structures are easily broken apart even under very low pressures due to lack of desirable...
mechanical properties of the conventional SPHs. By incorporating wetting agent the rate of water uptake is also enhanced.\textsuperscript{[27,28]}

Figure 2: Typical swelling and mechanical properties of the first (A, B), second (C, D) and third (E, F) SPH generations.\textsuperscript{[74]}

#Second generation SPH (SPH composite, SPHCs)
In this type super porous hydrogel an extra material called super disintegrant is added (swellable filler). These have good mechanical property withstands pressure up to 2N cm\textsuperscript{2}. Baek in 2001 were made modifications to conventional super porous hydrogel to form second generation super porous hydrogel by adding super disintegrant.\textsuperscript{[29]} Composite material, which does not show any pharmacological effects but they enhance mechanical strength of hydrogels. Superporous hydrogel composite is a matrix of continuous phase having a dispersed phase incorporated within. A composite agent used in hydrogel composites is cross-linked water-absorbent hydrophilic polymer that can absorb solution of monomer, crosslinker, initiator and remaining components. Composite agent in hydrogel composites improves mechanical properties. But superporous hydrogel composites are still brittle and breakable.

#Third generation SPH (SPH hybrid, SPHHs)
The third generation of SPHs was developed based on SPH hybrids. The third generation SPHs are modified versions of the second generation and assume an integrated IPN structure. A water soluble hybrid agent is introduced in SPH formulations in case of SPHHs. Although the SPHs of the second generation could provide a hydrogel with a better strength, much
higher strength was felt to be needed, for the gastric retention application in particular. This triggered the development of the third SPH generation, also called superporous hydrogel hybrids (SPHHs), with superior mechanical properties. The primary, secondary, and tertiary approaches have so far been disclosed. The SPH is prepared in a conventional way, but an active material is added during SPH synthesis, which is then treated in the ion solutions. While the primary approach is particularly useful in making SPHs with rubbery properties, SPHs with good mechanical strength can be obtained by adopting the secondary approach.\textsuperscript{[30]}

Although the mechanical properties of SPHs can be significantly enhanced after an ion treatment, the ion composition was found to be a useful tool for better controlling the swelling and mechanical properties.\textsuperscript{[31]} Depending on the activity of the ion (sodium, calcium, aluminum, and iron in particular), any ion composition can be used to modify and modulate SPH properties. displays the fundamental structural differences between the second, the third, and the modified SPH generations. SPH hybrids are prepared according to conventional SPH formulations but a water soluble and ionogelling polymer (synthetic or natural) is added during hydrogel preparation.\textsuperscript{[32]} After preparation, the SPH is treated in an ion solution to become strong and elastic.\textsuperscript{[33]} A dried SPH hybrid possesses a folded surface morphology as shown in Figure 3,4.

![Image of surface morphology](image_url)

**Figure 3**: The surface morphology of a typical Superporous hydrogel hybrid.\textsuperscript{[75]}
Figure 4: Mechanical property of a typical superporous hydrogel hybrid under various forces\textsuperscript{[76]}

Table 2: Hybrid/IPN type (Third generation superporous hydrogels)\textsuperscript{[34]}

<table>
<thead>
<tr>
<th>Type of monomer</th>
<th>Method</th>
<th>Type of superporous hydrogel</th>
<th>Drug incorporated</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA,AM,SPAK &amp; AN</td>
<td>Gas blowing technique</td>
<td>SPHC and SPH-IPNs</td>
<td>------------------</td>
</tr>
<tr>
<td>AA,AM &amp; PEI</td>
<td>Gas blowing technique</td>
<td>SPH-IPNs</td>
<td>------------------</td>
</tr>
<tr>
<td>PEG,PCL and HPGG</td>
<td>UV irradiation</td>
<td>Semi-IPN SPHs</td>
<td>Bovine serum albumin</td>
</tr>
<tr>
<td>AA,AM,SPAK &amp; AN</td>
<td>Gas blowing and crosslinking by Ca2+ ions</td>
<td>SPHH ie Full-IPN SPHs</td>
<td>------------------</td>
</tr>
<tr>
<td>Poly acrylamide/sodium alginate</td>
<td>Crosslinking via glutaraldehyde</td>
<td>SPE’s or hybrid polymeric networks</td>
<td>------------------</td>
</tr>
<tr>
<td>PVA/Chitosan</td>
<td>Redox polymerization</td>
<td>Semi-IPN SPHs</td>
<td>------------------</td>
</tr>
<tr>
<td>AA,AM and O-Carboxymethyl chitosan</td>
<td>Gas blowing technique and crosslinking by glutaraldehyde</td>
<td>SPH-IPNs(Semi and Full IPN) mucoadhesion and invitro release studies</td>
<td>Insulin</td>
</tr>
<tr>
<td>AM-Polyrethane</td>
<td>Polymerization via biscrosslinker</td>
<td>Semi-IPN SPHs</td>
<td>------------------</td>
</tr>
<tr>
<td>AA, Cationic starch</td>
<td>Blending polymerization</td>
<td>Semi-IPN SPHs</td>
<td>------------------</td>
</tr>
<tr>
<td>AA,AM and O-carboxymethyl chitosan</td>
<td>Gas blowing technique and crosslinking by glutaraldehyde</td>
<td>SPH-IPN effect of polymer integrity on insulin absorption</td>
<td>Insulin</td>
</tr>
</tbody>
</table>
Interpenetrating network hydrogels

DEFINITION OF IPN

An IPN is a composite of at least two polymers, exhibiting varied characteristics, which is obtained when at least one polymer network is synthesized or crosslinked independently in the immediate presence of the other or in other words an IPN is a combination of at least two polymers chains each in network form, of which at least one is synthesized and/or cross-linked in the immediate presence of the other without any covalent bonds between them or The two or more networks can be envisioned to be entangled in such a way that they are concatenated and cannot be pulled apart, but not bonded to each other by any chemical bond.

The concept of IPN goes back as far as 1914 and the first interpenetrating polymer network (IPN) was invented by Aylsworth and the term IPN was firstly given by Miller in 1960s in a scientific study about polystyrene network. An Interpenetrating polymer network may be defined as any material which contains two or more polymers in the network form. IPN is obtained when at least one of the polymers is synthesized or cross-linked in the immediate presence of the other polymer without any covalent bond between them.

In other words, IPN may also be defined as the combination of two or more polymers in the network form in which one polymer is cross-linked in the presence of other.[35] There are three conditions of polymer which are necessary in the composition of IPN.

These conditions are as follows

1) At least two polymers must be synthesized and crosslinked in the presence of the other.
2) Both polymers have similar kinetics.
3) Polymers are not dramatically phase separated.

An IPN is differentiating from other polymer combination in two ways.

1) IPN swells, but does not dissolve in the solvent.
2) Prevents the action of creep and flow.

They are also different from polymer complex and graft co-polymer because they either involve in chemical bond or in low degree of cross-linking. From this point of view only, IPN can be generally named as “polymer alloys”. IPN is obtained when at least one of the polymers is synthesized or cross-linked in the immediate presence of the other polymer without any covalent bond between them.
ADVANTAGES OF IPN

When ever an IPN hydrogel is formed from two polymers at a given temperature, the physical phase separation between the component polymers would be almost impossible because of the infinite zero viscosity of the gel.

# IPN enhance the mechanical properties and phase stability of the final product.
# As long as the reacting ingredients are blended thoroughly during the synthesis, thermodynamic incompatibility is overcome due to the permanent interlocking of the network segments.
# When the blends are subjected to stress, they can keep the separate phases together.
# Due to the infinite zero-viscosity of the gel phase separation between the component polymers is almost impossible.

Disadvantages of IPN\(^{[36]}\)

The main disadvantage of IPN is that, sometimes the polymers interpenetrate to such an extent and the drug released from the matrix becomes difficult. The problem with the non-covalent system is that it can also be a problem with the covalent system due to the lack of an effective interface.

Based on the methods of preparation, hydrogels may be classified as

(1) homo-polymers
(2) copolymers
(3) semi-interpenetrating networks
(4) interpenetrating networks.

Homo-polymer hydrogels are crosslinked networks of one type of hydrophilic monomer unit, whereas copolymer hydrogels are produced by the crosslinking of two co-monomer units, at least one of which must be hydrophilic to render them swellable. Finally, interpenetrating polymeric hydrogels are produced by preparing a first network that is then swollen in a monomer. The latter reacts to form a second interpenetrating network structure.\(^{[37]}\)

Homo-polymeric hydrogel

Homo-polymers refer to polymer networks derived from single species of monomer. It is the basic structural unit, comprising of any polymer network. Homo-polymers may have a crosslinked skeletal structure depending on the nature of the monomer and polymerization technique. Polyethyleneglycol (PEG) based hydrogels are responsive towards external stimuli.
and hence, these smart hydrogels are widely used in drug delivery systems. Chemically crosslinked PEG hydrogels are used as scaffolds for protein recombination and functional tissue production. It is a suitable biomaterial for the efficient and controlled release of drugs, proteins, biomolecules and growth factors.

Co-polymeric hydrogel

Co-polymeric hydrogels are composed of two types of monomer in which at least one is hydrophilic in nature. synthesized the biodegradable triblock poly(ethylene glycol)-poly(ε-caprolactone)-poly(ethylene glycol) (PECE) co-polymeric hydrogel for the development of drug delivery systems. The mechanism involved here is the ring-opening copolymerization of ε-caprolactone. In the triblock synthesis, mPEG was used as the initiator, stannous octoate as the catalyst and hexamethylene diisocyanate as the coupling agent. This copolymeric block is capable of forming a hydrogel when it is applied in-situ.

Inter Penetrating Network (Semi-IPN)

If one polymer is linear and penetrates another crosslinked network without any other chemical bonds between them, it is called a semi-inter penetrating network. Semi-IPNs can more effectively preserve rapid kinetic response rates to pH or temperature due to the absence of a restricting interpenetrating elastic network, while still providing benefits like modified pore size and slow drug release. One example to justify the situation is the entrapment of linear cationic polyallylammonium chloride in acrylamide/acrylic acid copolymer hydrogels, which impart both higher mechanical strength and a fully reversible pH switching of theophylline release. This pH sensitive semi-IPN was synthesized by template copolymerization in the presence of N, N'-methylene bisacrylamide as a crosslinking agent. The network contained both covalent and ionic bonds. The covalent bonds retained the three-dimensional structure of the hydrogel and the ionic bonds imparted higher mechanical strength and pH responsive reversibility to the hydrogel. Potential applications for semi-IPNs that have received much attention are as solid polymer electrolytes for fuel cells and as soft mechanical actuators. Figure 5 compares the electro mechanical strains obtained in a silicone elastomer known to have high actuator performance with a semi-IPN based on the same polymer incorporated into a.
network of a room-temperature vulcanizing (RTC) silicone. The semi-IPN morphology improves actuation strains and the break down strength.

**Inter Penetrating Network (Full-IPN)**

IPNs are conventionally defined as the intimate combination of two polymers, at least one of which is synthesized or crosslinked in the immediate presence of the other. This is typically done by immersing a pre-polymerized hydrogel into a solution of monomers and a polymerization initiator. The IPN method can overcome the thermodynamic incompatibility that occurs due to the permanent interlocking of network segments and a limited phase separation can be obtained. The interlocked structure of the crosslinked IPN components are believed to ensure the stability of the bulk and surface morphology. The main advantages of IPNs are that relatively dense hydrogel matrices can be produced which feature stiffer and tougher mechanical properties, controllable physical properties and a more efficient drug loading compared to conventional hydrogels. Drug loading is often performed in conjunction with the polymerization of the interpenetrating hydrogel phase. The IPN pore sizes and surface chemistries can also be controlled to tune the drug release kinetics, and the interaction between the hydrogel and the surrounding tissues along with its mechanical properties. Since the glass transition temperature becomes size dependent for small domains, only one transition is expected for IPNs. However, a distribution of phase sizes gives rise to very broad glass transitions (with respect to both the temperature and frequency), a property exploited in acoustic damping and vibration isolation applications.
loss tangent, which occurs at a temperature near the glass transition, for IPNs of polydimethylsiloxane and cellulose.\cite{45}

Figure 6: Ratio of loss to storage modulus for polydimethylsiloxane, acetate butyrate cellulose, and three IPNs. The transitions for the blends are broader and intermediate in temperature to the pure components (Data from)\cite{78}

SPH-based gastroretentive platforms

Hossein Omidian in 2006 prepared and evaluated a variety of SPH hybrids for this application. The major requirements for a swellable gastroretentive platform were found to be swelling rate (within minutes), swelling capacity (preferably 8–15% v/v), shape, mechanical strength (resist pressures in the range 0.5–2.0 N cm-2, preferably in the fed state), flexibility, a controlled disintegration, ease of drug loading, stability and pharmaceutical acceptability. Having all these concerns addressed by a single SPH platform requires careful selection of monomers and other actives, reaction conditions, type of additives, treatment method, purification and necessary steps during the entire preparation process. The SPH is prepared as a reservoir system (Figure 7) with the ability to house a drug delivery system (DDS). The DDS itself can be a controlled release tablet or semi-solid carrier for example. The whole platform is encapsulated in a regular capsule (e.g. 00 HPMC or gelatin) for oral administration. Feasibility of these platforms for a solid dose (tablet) or semi-solid (wax) drug delivery system has been studied. The tablet/platform study showed that SPH has a certain retardation effect on drug release, which was found to be dependent on the platform structure and the formulation of the tablet matrix. (Figure 8) displays the SPH retardation effect as a function of the ratio of the two polymers (hydroxypropyl methylcellulose and poly(vinyl pyrrolidone)) used to formulate the tablet matrix. Theoretically, the net SPH
retardation effect (for the tablet matrix of this study) is estimated if the experiment enables us to correspond an instant release of the drug to a Methocel/Povidone ratio. For.

![Figure 7: A reservoir-type SPH-based platform](image)

**Figure 7: A reservoir-type SPH-based platform**

![Figure 8: Drug release profile from tablet and tablet/SPH platform](image)

**Figure 8: Drug release profile from tablet and tablet/SPH platform**

the tablet matrix of this study containing Methocel K-90 and Povidone E-10 polymers, an instant release can theoretically be achieved at E-10/K-90 ratio of 0.028 (or K-90/E-10 ratio of 35.7). At this ratio, the SPH could retard the complete release of the model drug by 4 h. Depending on the tablet matrix formulation and the SPH properties, the release retardation period could presumably be shorter or longer.

**synthesis for superporous hydrogels**

To make SPHs, a monomer, crosslinker, water, foam stabilizer, acid, polymerization initiator, initiation catalyst and foaming agent were added sequentially to a glass test tube (25mm outer diameter, 150mm height). A bicarbonate foaming agent is used, which is water soluble and becomes active in an acidic aqueous medium. Following a complete homogenization, the
reductant and oxidant are added consecutively and are mixed quickly with the reacting mixture. In a very short period of time, the solid foaming agent(e.g., bicarbonate) is effectively dispersed and mixed throughout the reacting solution.

The important step of this process is to use acid to control the polymerization kinetics. Addition of NaHCO3 leads to foam formation as well as rise in pH, which accelerates the polymerization process. After the addition of NaHCO3, polymerization becomes complete within a few minutes. The foaming and gelling reactions occur almost simultaneously and proceed to their maximum extent at the polymerization temperature, which is determined by the type of monomer, its concentration in the solution, and initiator concentration. A successful SPH is synthesized if the chemical gelation and physical foaming happen in a synchronized way.\textsuperscript{[47]}

**Characterization of Superporous Hydrogel**

These are the various properties of SPHs.

**Swelling studies**

**Swelling time**

Swelling time was calculated by immersing the hydrogels in deionized water as well as 0.1N and calculating the time required to attain equilibration in swelling.\textsuperscript{[48]}

**Swelling ration**

The dried SPH was allowed to hydrate in excess of deionized distilled water at room temperature. The weight of hydrating sample was measured at time intervals, after excess water was removed by gentle blotting. The swelling ratio was defined as\textsuperscript{[49,50]}

\[
QS = \frac{(WS - Wd)}{(Wd \times 100)}
\]

Ws is weight of welled hydrogel, Wd is weight of dried hydrogel and Qs is equilibrium swelling ratio.
For example.\textsuperscript{[51]}

![Swelling ratio curves for SPH polymers dried with various methods](image)

\textbf{Figure 9:} Swelling ratio curves for SPH polymers dried with various methods: (V) drying with absolute ethanol; (B) drying with acetone; (O) drying with diethyl ether; (E) freeze-drying for 2 days; (W) freeze-drying for 1 day. Data are depicted as the mean ± SD of three experiments.\textsuperscript{[80]}

The SPH polymers dried by different procedures were used for the swelling ratio studies. As shown in Fig. 9, the polymers dried by freeze-drying for 1 day, have the lowest swelling ratio, indicating that these polymers were not dried completely. When the polymers were dried with organic solvents and subsequently dried at 608C, the swelling ratios were found to be between those after 1 and 2 days freeze-drying. There was no difference between drying with acetone and absolute ethanol. With diethyl ether, however, the swelling ratio was less, probably due to its fast evaporation and reduced water miscibility that resulted in closing of some of the pores in the polymer.

\textbf{Determination of gelation kinetics}\textsuperscript{[52]}

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.\textsuperscript{[53]} It is determined by the duration time until the reactant mixture is no longer descending in the tilted tube position.\textsuperscript{[54]}

\textbf{Measurement of Density}

It was difficult to measure the density of super porous hydrogel directly. Density of superporous hydrogel determined by solvent displacement method.\textsuperscript{[55]} Actually it was an apparent density. Mass of SPH was measured then this SPH placed in graduated cylinder
containing measured volume of absolute hexane. Density calculated as follows.

\[ \text{Density} = \frac{\text{MSPH}}{\text{VSPH}} \]

Where, MSPH: Mass of SPH
VSPH: Volume of SPH

**Porosity Measurement**

Here solvent replacement method is used. Dried hydrogels are immersed overnight in absolute ethanol. It absorbed ethanol and swollen, which leaded to blotting of ethanol on the surface. Porosity is calculated from following equation.

\[ \text{Porosity} = \frac{(\text{M} - \text{M1})}{\rho\text{V}} \]

Where, M1 and M2 are mass of hydrogel before and after immersion in absolute ethanol, respectively; \( \rho \) is density of absolute ethanol and V is volume of hydrogel.

**#Mechanical strength**

Quantifying superporous hydrogel mechanical properties is challenging is measure by applying weight on swelled superporous hydrogel until it break. Mechanical strength is measure by using bench comparator and gastric simulator. A gastric simulator, based on the water hammer theory, utilizes a controlled amount of different types of stresses on objects immersed in the testing fluid to simulate forces that a sample might receive upon ingestion in body.

**# 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.

**Fourier transform infrared spectroscopy**

In FTIR spectroscopy investigation of Superporous hydrogels, FTIR spectrum was recorded over the range of 400 - 4000 cm\(^{-1}\). KBr pellet is a method of choice in which Transform Infrared FT-IR spectrophotometer are generally used.

For example.
The FTIR spectra of chitosan and superporous hydrogel are represented in Figure 10. Chitosan exhibited the main characteristic bands of carbonyl (C=O-NHR) and amine group (–NH2) at 1653 cm$^{-1}$ and 1560 cm$^{-1}$, respectively. The broad band due to the stretching vibration of –NH2 and –OH group was observed at 3400 – 3500 cm$^{-1}$. The bands at 1000 – 1200 cm$^{-1}$ are attributed to the saccharide structure of chitosan. The peak at 1381 cm$^{-1}$ represents the –C=O stretch of primary alcoholic group (CH2-OH). These peaks, with minor shifts, are clearly seen in the IR spectra of superporous hydrogel indicating the presence of chitosan in the structure of the hydrogel. There was no interaction between the drug and chitosan in the hydrogel.

# Scanning electron microscopy

SEM analysis is helpful to study morphology of a dried superporous hydrogel. Samples are coated with gold using Hummer sputter coater. Use Jeol JSM-840 scanning electron microscope to capture images using digital capture card and Digital Scan Generator. This picture clearly indicates pores in its structure.
For example

**Figure 11:** SEM structure of optimized batch[CH4f] outer surface.\(^{[82]}\)

**Figure 12:** SEM structure of optimized batch[CH4f] inner surface.\(^{[83]}\)

SEM photomicrographs of optimized formulations as shown in figure 11 and 12 were used to examine the detailed structures of the inside of SPH in the drystates. The pore size is approximately 100 µm, and the pores are all interconnected.

**# In vitrelease studies**\(^{[69]}\)

The in vitro buoyancy is determined by floating lag time, as per the method. The piece of hydrogel are placed in 100 ml 0.1N HCl at 37 ± 0.5 °C.\(^{[70]}\) 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.\(^{[71]}\)
For example.\cite{72}

![Figure 13: In vitro release profiles of Rosiglitazone maleate from the prepared formulations (n = 3, mean ± standard deviation)\cite{84}](image)

The drug release profiles of the drug from the hydrogels are shown in figure 13. The release of the drug was found to be dependent to the amount of chitosan and crosslinker and as the amount of chitosan increased, the release was faster since chitosan is a pH sensitive monomer.

**CONCLUSION**

Superporous hydrogels are a new class of hydrogel materials that, regardless of their original size, rapidly swell to a large size. The SPH, SPH composite and SPHH(interpenetrating network systems) for achieving long term gastric retention can be used successfully as novel carriers for oral controlled drug delivery. Hydrogels, the cross linked polymers with a network structure consisting of acidic, basic and neutral monomers are able to imbibe a large amount of water. The network structure and possibility of rearrangements of hydrophobic/hydrophilic domains during swelling process, including entanglements and crystalline regions make these polymers water insoluble. Now, a lot of work is running to develop different types of gastroretentive delivery systems of various drugs. Applications of SPHs will be further realized as scientists in different disciplines become aware of the unique properties of these new materials.

**REFERENCE**


