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A REVIEW ON CONCEPTUAL OVERVIEW ON DEVELOPMENT AND CHARACTERIZATION OF SUPERPOROUS HYDROGELS A PROMISING TOOL FOR GRDDS

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ABSTRACT

In the pharmaceutical field one of the convenient approach in oral drug delivery system to attain desired therapeutic action is done by prolonged release and desired drug delivery in GIT as most of the drugs posses short gastric retention time which eliminates the drug quickly from the stomach this will not produce desired therapeutic action, in order to overcome this, Gastroretentive dosage forms are developed which prevents the gastric emptying of the drug immediately after its administration. So as to overcome this Superporous hydrogels are developed. Superporous hydrogels are generally developed as novel drug delivery systems for those drugs whose absorption window is in stomach and upper part of GIT These systems should immediately swell in stomach and maintain their integrity in the harsh stomach environment. The water absorption by SPHs was done by capillary action not diffusion. Second generation SPH composites and third generation SPH hybrids were developed to achieve good mechanical strength as SPHs are having poor mechanical strength. The synthetic features and properties were being developed from years in order to maintain its integrity in Gastrointestinal tract(GIT). This review discusses the formulation, advantages, disadvantages, methods of synthesis, various generations, drug loading techniques, drying of SPHs and characterization of SPHs.

KEYWORDS: Superporous hydrogel, Gastric retention, Absorption window.

INTRODUCTION

Oral drug delivery system is the most convenient and preferred route for administration of drugs which involves new approaches, formulations, technologies and systems for transporting a drug into the body as required to achieve desired therapeutic active response. Recent technological advancements are made in controlled oral drug delivery systems by overcoming physiological difficulties, like shot Gastric retention time and unpredictable Gastric emptying time. Gastro retentive dosage forms are designed over the past three decades to beat these difficulties.

Several technical approaches are currently utilized for the prolongation of gastric duration, and site specific action. The Gastric emptying time mainly depends upon the design of the dosage form and physiological state of the subject, which last from some minutes to 12hrs. Gastric emptying time in human is 2-3hrs through major absorption zone i.e., stomach and upper intestine, which ends up in incomplete drug release from Drug delivery system which results in diminished efficacy of the administered dose, so for drugs which have stability problem, GRDF plays a vital role. These considerations have led to the event of oral controlled release dosage forms and sustained drug release forms possessing Gastric retention capabilities. One amongst Gastro retentive drug delivery system includes super porous hydrogels.[1-3]

Superporous hydrogels (SPHs) are originally developed as a novel drug delivery system to retain drugs with in the gastric medium. These systems swell in stomach instantly and maintain their integrity in the harsh environment. A Superporous hydrogel is a three dimensional network of a hydrophilic polymer which Absorbs a large amount of water i.e. 100 times more than its weight in a short period of time and this is due to the presence of interconnected microscopic pores which ranges 100micrometer in size. Superporous hydrogels can be distinguished from other hydrogels in terms of their pore size and methods to generate pores. Swelling of SPHs is due to the capillary action not by diffusion. When these Superporous hydrogels are used as drug carriers these swollen hydrogels increases the Gastric retention time by staying for long period of time in stomach, which releases loaded drug at the site where its action required. As the SPH 's absorb large amount of water and cannot pass through the pyloric sphincter as their size increases.[4-6]

SPHs are more widely used as Gastric retention carriers due to their unique swelling property which provides a controlled release action along with increased retention time in the stomach. In order to use Superporous hydrogel as effective gastric retention device they should posses some other properties along with fast Swelling Property and mechanical strength and the properties include following Biocompatibility, biodegradability increase swelling capacity, increased stability in acidic condition, increased absorbing nature and increased mechanical strength.[11,12]

Superporous hydrogels are suitable for drugs having narrow absorption window, i.e which are mainly absorbed in proximal part of intestines that bioavailability of those drugs can be enhanced.

1. For drugs which are rapidly absorbed in GIT should have slow release from stomach to improve bioavailability.
2. For poorly soluble drugs at an alkaline pH or drugs that are degraded in the colon.
3. Superporous hydro gels will be used as carriers for drugs with so called low absorption windows these substances are taken up only from very few specific sites of the gastrointestinal mucosa, in order

- To improve bioavailability of drugs which are mainly absorbed from upper part of GIT or degraded in alkaline pH.
- For local Action incase of pathologies of stomach.
- To increase Gastric retention time.
- To enhance Gastric emptying time.

Principle of the gastric retention of superporous hydrogels

The basic principle involved in the superporous hydrogels is gastric retention and this was mainly based on the fast swelling nature of SPH and in this the prepared superporous hydrogel is in dry form was filled into the capsule so that it is small in size and easy to swallow . After administration through oral route, it swells rapidly in the stomach by absorbing its biological fluids and increase in size with in seconds of administration and this cannot Enter through the pyloric sphincter so It cannot be passed into other part of intestine due to this gastric emptying time was prevented and gastric retention time was increased. When gastric contraction reaches the hydrogel, the gastric tissues slide over the hydrogel as its elastic and slippery. Then the drug is released from its dosage form into the stomach and slowly undergoes degradation either mechanical force or enzymatic hydrolysis of the polymeric chains constituting the hydrogel. Eventually the degraded superporous hydrogel dosage form is eliminated from the stomach.[4,7]

Advantages of Superporous Hydrogel[28,30]

Superporous hydrogels has three unique properties that conventional hydrogels don't have.

- The Superporous hydrogels swell completely in short span of time no matter with the size of the dried superporous hydrogel.
- Superporous hydrogels swell to such an extent that the load of the fully swollen superporous hydrogels is more when put next with the dried superporous hydrogelhav
- Though the superporous hydrogels contain only small percentage of solid content of its total weight, but it can exert significant expansion force during swelling.
- Superporous hydrogels also can be elastic made, which diminishes their rupture.
- The unique properties of superporous hydrogels can even be used for non pharmaceutical and non-biomedical applications.
- The Increase in gastric retention time of SPHs, enhances the bioavailability of drug**.**

Disadvantages of SPHs

- They cause a sensation due to the movement of maggots
- In case of contact lenses cause lens deposition, hypoxia, dehydration, and eye reactions.
- These are the high cost and the sensation felt by movement of the maggots.
- Its disadvantage includes thrombosis at anastomosis sets and then surgical risk associated with the device implantation and retrieval.
- Disadvantages of hydrogel in contact lenses are lens deposition, hypoxia, dehydration and red eye reactions. he main disadvantage of hydrogel is that they are nonadherent and may need to be secured by a secondary dressing and also causes sensation felt by movement of the maggots. Hydrogels have low mechanical strength and difficult to handle. They cause a sensation due to the movement of and are costly.

Various generations of SPHs

There are three different generations of SPHs as mentioned below.

- First generation SPHs (Conventional SPHs, CPLSPHs)
- Second generation SPHs
- Third generation SPHs

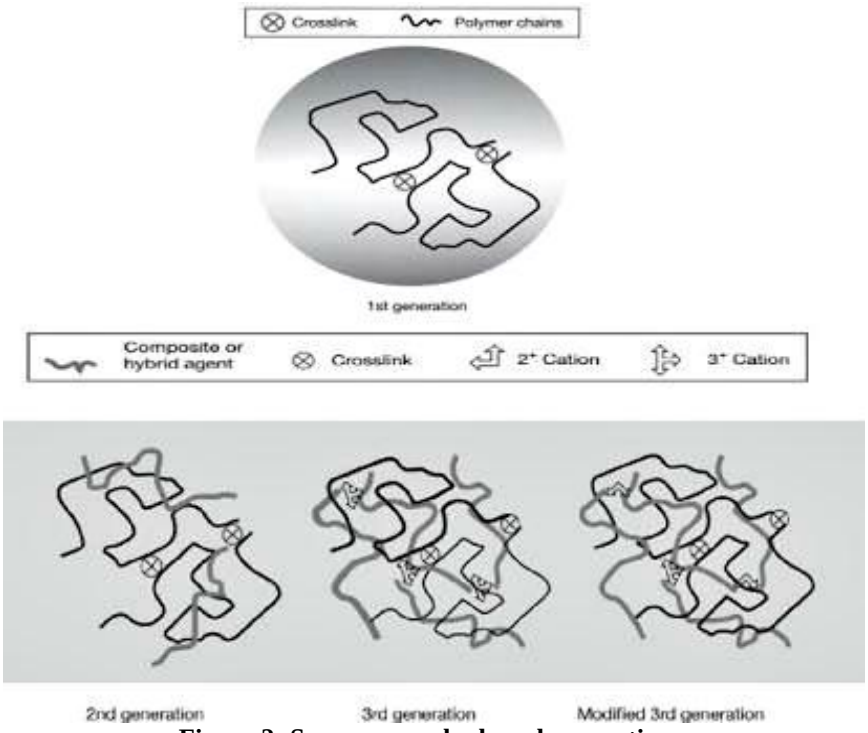

Figure 2: Superporous hydrogel generations.

First generation SPH (conventional SPHs, CSPHs)

Conventional SPH (CSPH) was first discovered by with fast swelling kinetics and super absorbent properties in 1999. 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 employed. Dried SPH hard and brittle, but the hydrophilic nature of the polymer results in moisture -induced plasticization of the rigid structures into soft and versatile structures. The swollen SPHs are sometimes difficult to handle without breaking. When the SPHs are dried, the porous structure become collapsed or shrunken because of the physical phenomenon 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 physical phenomenon of alcohol prevents the porous structure from collapsing during drying. Their structures are easily broken apart even under very low pressures thanks to lack of desirable mechanical properties of the traditional SPHs. By incorporating wetter the speed of water uptake is additionally enhanced.[29]

Second generation SPHs

The first SPH composites were introduced n 2001 by Park et a. In second generation SPS are developed to overcome the lack of desirable mechanical properties in CSPHs, by modifying the conventional SPHs with the addition of super disintegrants into the formulation. In SPH composites, composite is a matrix, which contains both dispersed phase and continuous phase. The preparation of SPH composites also includes the same monomer, i cross linker, and initiating system in CSPHs, but along with these we also use swellabe filler, i.e. composite agent (which is cross-linked water-absorbent hydrophilic polymer). While this filler dispersed into the reacting mixture, it would swells and absorbs a mixed solution of monomer, cross linker, initiator and the water-soluble foaming additives. Upon polymerization, the polymer chains are formed, since the filler serves as the local point of physical cross-linking. Each composite agent or swollen filler serves as an isolated individual reactor, throughout the polymerization process, in which cross-linking polymerization occurs. i As the cross-linking polymerization precedes entire the solution, individual composite agent particles are connected together by connecting the polymer chains.[12]

Third generation SPHs

The third generation of SPHs was developed basis of SPH hybrids. The third generation SPHs are modified advanced versions of the second generation and consists of an integrated IPN structure. A water soluble hybrid agent is intended in SPH formulations just in case of SPHHs. Although the SPHs of the second generation could provide a hydrogel with a more strength, but much higher strength was felt to be needed, for the gastric retention application particularly. This enhanced the event of the third SPH generation, also called superporous hydrogel hybrids (SPHHs), with superior mechanical properties. the primary, secondary, and tertiary approaches have up to now been disclosed. The SPH is ready in an exceedingly conventional way, but a lively material is added during SPH synthesis, which is then treated within the ion solutions. While the first approach is especially useful in making SPHs with rubbery properties, SPHs with good mechanical strength may be obtained by adopting the secondary approach. Although the mechanical properties of SPHs will be

significantly improved after an ion treatment, the ion composition was found to be a beneficial tool for better controlling the swelling and mechanical properties. reckoning on the activity of the ion (sodium, calcium, aluminum and iron in particular), any ion composition are often wont to modify and modulate SPH properties and shows the elemental structural differences between the second, the third, and also the modified SPH generations. SPH hybrids are prepared in keeping with conventional SPH I formulations but water soluble and ion gelling polymer (synthetic or natural) is introduced during hydrogel preparation. After preparation, the SPH is treated in an ion solution to become strong and elastic.[14]

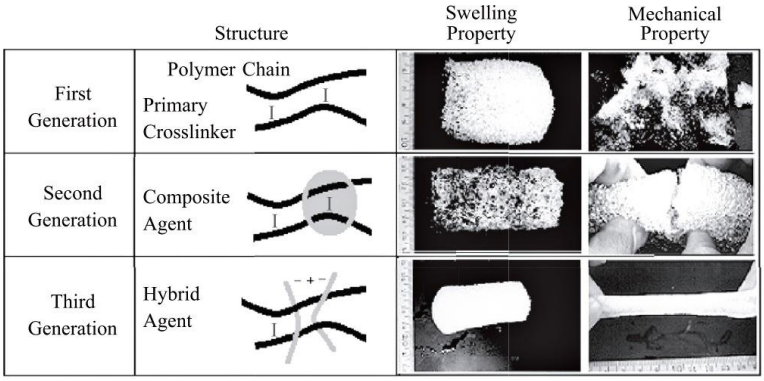

Figure 3: Structural, swelling and mechanical properties of Superporous hydrogels.

Mehod of Preparation of Sphs

SPHs can be prepared by following methods

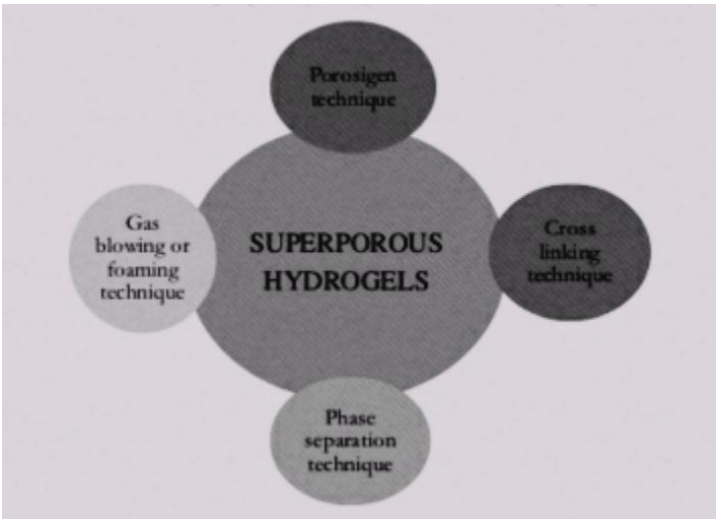

Figure 4: Methods involved in preparation of superporous hydrogels.

1. Porosigen Technique

In this technique, porosigen are used for the preparation of SPH. Highly hydrophilic nature of these porosigen solubilizes them when come in contact with water and develop the porous structure in the hydrogel. Various porosigens such as micronized lactose, micronized dextrin, micronized sucrose, micronized cellulose, sodium chloride, poly ethylene glycol (PEG), poly ethylene oxides etc. form meshwork that can be evacuated by washing with water. The pores so generated have different size that depends on the size of porosigens used. SPH made from this technique are mechanically weak.[7]

2. Phase separation Technique

In this technique, diluents are used which possess better solubility for monomers and suitable for effective mixing. If, however, non solvent diluents use for the polymer formed, then there occurred decreasing polymers solubility significantly as the polymerization proceeds. This results in polymers rnch monomers phase droplets phase separation. These small droplets join with each other and form a network heterogeneous, porous hydrogel. This process is called heterogeneous solution polymerization. Hydroxy ethyl methyl acrylate (HEMA) and N-I isopropyl acrylamide (NIPAM) based hydrogel can be prepared.[14]

3. Cross linking Technique

In these technique hydrophilic polymers having chemically active functional group in their structure undergoes cross linking result in hydrogel preparation. This technique restricted to absorbent particles with chemically active functional groups on the surface.[16]

4. Gas blowing Technique

This technique is widely used for the preparation of SPH. In this technique, the polymerization of monomers occurs in the presence of gas bubbles and The main component used in this process for forming gas bubbles is foaming agent. Foaming agents are classified as; a) Physical foaming agent are the agents which enlarge when pressure is applied (e.g. Nitrogen and carbon dioxide) and b) Chemical foaming agents are the agents that react to form a gas (e.g., sodium bicarbonate in the presence of acid). SPH are synthesized in a test tube of particular proportion with incorporation of various ingredients like monomer, cross linker, foam stabilizer, polymerization initiator, initiation catalyst (if any) and foaming agent are added sequentially. Initially and before the addition of foaming agent, the pH of monomer solution should be maintained at 5 to 6, because low pH aids foam formation. Incorporation of foaming agent leads to bubble formation that result in increase in pH of solution. The increased pH accelerates the polymerization process. Thus, simultaneous foaming and gelation process lead to the formation of homogenous hydrogel with highly porous nature i.e. SPH. After SPHs are synthesized they undergoes washing, drying using various procedures which affect the swelling and mechanical behavior of prepared hydrogel.[18]

Drug Loading Into Superporous Hydrogel

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

A. Drug loading into superporous hydrogel reservoir devices
B. Drug loading into superporous hydrogel polymers.

A. 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 they are, micro particles and gross mass. where Micro particles are prepared by melting polymers like PEG 6000 in which the drug is dispersed and the mixture is cooled to obtain gross mass. The obtained gross mass is crushed finely in to powder by using mortar and sieved through #400 µm, which are used as core material. SPHC is used as the body of the conveyor system due its greater mechanical strength and SPH is used as the cap of the conveyor system due 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 obtained is then dried by two ways either by drying at ambient temperature or by drying at reduced pressure at 60°C. This is called as the body of conveyor which is capped by piece of SPH.[9,11]

2. Core attached to surface of shuttle

In this system, core is in the form of small tablets which are prepared by melting polymer like PEG 6000 in which the drug is dispersed and then sieving of the mass was done through # 400 um, which were combined with magnesium stearate and compressed into tablets using single punch machine 40N hardness). The second component is conveyor made up of only SPHC in which two holes were done on counter side instead of one as in previous approach. The core material in the form of small tablets was kept inside the holes with the help of bio-adhesive (cyanoacrylate) glue. The size of holes is enlarged due to swelling of polymer, when it comes in contact with gastric fluids. The dosage form was kept at the site of drug absorption with help of glue. This was placed into gelatin capsule shells of size 000.[10]

B. Drug loading into superporous hydrogel polymers

The amount of water required by SPH and SPHC for complete swelling is determined. Then, aqueous solutions of the given drug is ready in previously determined amount of water and also the weighed amount of polymer is placed in a drug solution to suck up the drug solution. Then After 20 min, the thoroughly swollen polymers were loaded with drug and placed in oven at 30 C for drying overnight.[37]

Drying Of Superporous Hydrogel

The drying of superporous hydrogel can be done under two different conditions. And they are Condition I, the swollen superporous hydrogel are dried in a food dehydrator for a day under blowing warm air (60°C)and Condition Il, swollen superporous hydrogels are first dehydrated by applying about 5-10 ml of absolute ethanol per each gel. After this first dehydration step, the superporous hydrogels are further dehydrated with help of absolute ethanol by placing them in 50ml of ethanol several times to make sure all the water was replaced by ethanol. The dehydration process was done to make sure the soft and flexible superporous hydrogels turn in to hard and brittle. After dehydration process was done, by using paper towel, the excess ethanol in dehydrated superporous hydrogel is removed by draining. Then the superporous hydrogel is dried in an oven at 55°C for 24hrs.[9,10]

Characterization of superporous hydrogel

The following parameters are to be evaluated for Superporous hydrogels

- **Physical Appearance:** In this evaluation parameter Colour shape and presence of any particles in the prepared Superporous hydrogel were examined.[15]
- **Percentage yield of SPH:** The percentage yield describes the maximum amount of product produced after drying is compared with the actual amount of

product before drying. This can be calculated by using formula,[15]

$$\text{Percentage yield} = \frac{\textit{weight of product after drying} \times 100}{\textit{weight of the product before drying}}$$

- **Scanning Electron Microscopy:** SEM studies describes the morphology of the dried Superporous hydrogel. In this the sample was coated gold using Hummer sputter coater. Then it produces the images of the sample by scanning the surface with focused beam of electrons.[33]
- **Swelling studies:** In this swelling time and swelling ratio were included.

• **Swelling time:** Swelling time is the time taken by the superporous hydrogel to reach its equilibrium swelling point where further swelling cannot be attained. And this is usually measured gravimetrically and volumetrically a texture analyzer is used to calculate swelling time. Here, Dried SPH was immersed in deionized water as well as 0.1HCl at room temperature. At different time period s, the SPH was separated from the solution and measured after excess solution on the surface was drained.[30]

• **Swelling ratio**: Swelling ratio was used to determine the fractional increase in the weight of the superporous hydrogel due to the absorption of water. This was carried out by ' T ' bag weight method, in this 0.1g of sample was added to a small bag made of nylon (50×90mm) 200mesh. The bag was completely immersed in the swelling media 200ml simulated gastric fluid of pH 1.2 at room temperature for one day to reach its equilibrium. Any excess liquid droplets attached to the surface of sample were removed by blotting tissue paper. After this the swollen SPH are then dried in oven at 60°C for 6hrs .the equilibrium swelling was defined by using a formula,[30]

$$\text{Qs} = \frac{(Ws - Wd)}{Wd}$$

Where Was means the weight of swollen SPH, Wd means the weight of dried SPH and Qs is the equilibrium swelling ratio.

- **Density Measurement**: This was determined by using Solvent displacement method in which sample was placed in a graduated cylinder which contains predetermined volume of hexane and the rise in hexane volume was measured as the volume of polymer. Density was calculated by.[15]

$$\text{Density} = \frac{MSPHC}{VSPHC}$$

Where, MSPHC is the mass of the SPHC, VSPHC is the volume of the solvent displaced by SPHC.

- **Porosity Measurement**: Porosity measurement is a method through which we can measure the pore spaces between the Superporous hydrogel and this the type of the porosity was indicated. This was done by using Solvent replacement method The dried hydrogels were placed in absolute ethanol and left over night to get absorbed and weighed after unwanted ethanol on the surface was blotted. This was calculated by the following formulae.[15]

$$\text{Porosity} = \frac{M2 - M1}{\rho v}$$

Where, M1 and M2 are the mass of the hydrogel before and after absorbed in absolute ethanol, p is the density of absolute ethanol and V is the volume of the hydrogel.

- **Water retention:** Water retention is method used to determine the amount of water that can be with hold by the sample (Superporous hydrogel). It is the function of the time of exposure at 37°C, the water loss of fully swollen polymer at time intervals was determined by gravimetry. This was calculated by following formulae,[36]

$$\text{WRt} = \frac{(WP - Wd)}{(Ws - Wd)}$$

Where Wd is the weight of the dried hydrogel Ws is the weight of the fully swollen hydrogel and Wp is the weight of the hydrogel at various exposure time intervals.

- **Stability studies:** The stability studies were carried out to check the extent to which a product retains with in its specified limits through out its period Of storage. For this purpose the prepared Samples are placed in airtight containers and stored the container in stability chamber at 40 "C/ 75% RH for three months. In vitro dissolution study data was determined after three months will be compared with the data obtained at the time of preparation.[37]

- **Gelation Kinetics**: As polymerization reaction proceeds, viscosity continuously increases until full network gel structure is formed. Gelation time is measured by simple tilting method after adjustment of pH to 5.0 with acetic acid. It is determined by the duration of time taken by reactant mixture to become viscous and henceforth viscous solution no longer falls down in tilted tube position.[38]

- **In-vitro drug release studies:** Release rate of drug from Superporous hydrogels is carried out at 37± 0.5C in 900ml stimulated gastric fluid SGF of O.1N HCl using USP paddle type. Medium is stirred at 50rpm and 5ml aliquots are withdrawn at specified time intervals, maintain sink conditions, then assayed spectrophotometrically to get cumulative percentage of drug release.[40]

Applications Of Superporous Hydrogel[11,12,28,29]

1. **Sustained Drug Delivery:** Gastro retentive system plays an important role for drugs that act locally in stomach (antacids, antibiotics). Controlled release enhances the bioavailability of drugs with narrow absorption window (riboflavin, levodopa). These systems have a bulk density of less than one so they are floating on gastric contents or relatively large in size so that cannot pass through pyloric opening. These can also be

used as pH-sensitive drug delivery systems due to the swelling properties of both Superporous hydrogel and composite are pH dependent.

2. Site specific Drug delivery: The drugs like Riboflavin and furosemide which are absorbed from stomach or proximal part of small intestine can be absorbed at specific site by producing prolong action. For local delivery of drug misoprostol a bilayer-floating capsule was developed by which targeting slow delivery of misoprostol to stomach desired therapeutic activity could be achieved and wastage of drug can be minimized.

3. Preoral peptide drug delivery systems: The exceptional properties of SPHs may be utilized to produce delivery systems that are capable of transporting proteins and peptides for both local action to the Gl tract and for systemic absorption following through oral administration. Firstly The drug must be protected from the acid environment of the stomach for SPHs used in peroral intestinal delivery. Next, the maximum swelling must be produced at an ideal spot along the intestines. Enlargement of the delivery platform during rapid swelling causes it to adhere onto the intestinal wall with the help of mechanical pressure. Large molecules are able to pass between the epithelial cells by paracellular absorption due the swelling and subsequent attachment, that applies mechanical pressure disrupts and opens the intestinal epithelial tight junctions. Bioavailability was improved together, with the prolonged residence time and physical attachment of the SPH platform to intestinal wall.

4. Diet aid SPHs: One strategy for weight loss is to avoid or decrease food intake, and subsequent caloric consumption per day. This is a challenging fact and some have even undergoing surgical methods such as gastric bypass and laparoscopic gastric banding. The main stratagey behind this surgical approaches is to reduce the size of the stomach that reduces the space for food where less quantity of food is consumed which cause fullness. An SPH may be a non surgical alternative to achieve satiety that can swell and be retained in the gastric environment. The high swollen property and gastric retention of SPHs can occupy a large space in the stomach which leaves less space for food and beverage this reduce food intake.

5. SPHs as Superdisintegrants: The fast-swelling SPHs was found to be used as superdisintegrants in solid dosage forms. The disintegration process starts when a solid dosage form breaks apart in an aqueous environment, allowing release of the active ingredient for dissolution, the speed and efficacy of disintegration can be enhanced at lower levels When a superdisintegrant is incorporated as an excipient in the tablet formulation than using the standard disintegrants. The Polymers such as poly (vinylpyrrolidone), cellulose and starch-based derivatives have been crosslinked and manufactured for this purpose. As they are hydrophilic in nature, crosslinked, quickly expand on swelling and can be tailored to optimize a products disintegration SPHs are used for this purpose For manufacture of fast disintegrating tablets porous microparticles based on poly (acrylic acid) have been prepared and used as a super disintegrant.

CONCLUSION

The present review is about the awareness of superporous hydrogels in novel drug delivery. These are new advanced class of hydrogels which posses more advantages over hydrogels where SPHs absorb large amount of water in short period of time compared to hydrogels. Superporous hydrogels swell to large size with irrespective of its size .Various generations of SPHs are evolved as novel carriers in oral controlled drug delivery system. SPHs are more widely used by poorly soluble drugs and drugs that are rapidly soluble in GIT. And also SPHs are used mostly by the drugs which have short gastric retention time by enhancing gastric retention thus by producing prolong action which produces efficient therapeutic activity and local action can be produced at the site. These are stable and elastic in nature which diminishes the rupture. The main disadvantage involved is high cost and causes a sensation like movement of maggot Due to the presence of peculiar characteristics in superporous hydrogels opens a new field of application in controlled drug delivery. SPHs have been used in various applications such as Peroral intestinal delivery, sustained drug deliver, protein /peptide drug delivery, and gastroretentive delivery and also as diet aids and, superdisintegrants due to their large size to remain in stomach for prolonged period of time. The focus of further application of superporous hydrogels is like to be in the area in solid and semisolid dosage formulation in oral site specific drug delivery and regenerative medicine.

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