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Review Article

SUPER POROUS HYDROGELS: A RECENT ADVANCEMENT IN GASTRORETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT

Super porous hydrogels (SPHs) were originally developed as a controlled drug delivery system to retain drugs in gastic medium. 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. Super porous hydrogels should instantly swell in the stomach and maintain their integrity in the harsh environment and release the pharmaceutical active ingredient. SPH swell fast, within minutes, the fast swelling property is based on water absorption through open porous structure by capillary force. This review discusses about the GRDDS, difference between gels and hydrogels and comparison between SAP vs. SPH. It also includes types of SPH, different generations, general synthesis, methods of preparations, gastric emptying, advantages, characterization, applications and salient features of SPH.

Key words: Superabsorbent polymers (SAP), Super porous hydrogel (SPH), Gastro retentive drug delivery system

INTRODUCTION

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) (Streubel *et al.,* 2006). 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 (Iannucelli *et al.,* 1998). 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 (Garg and Gupta, 2008). 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 (Rouge, 1998), low density (floating) systems that causes buoyancy in gastric fluid (Streubel *et al.,* 2003; Goole *et al.,* 2007; Shrma and Pawar, 2006), mucoadhesive systems that causes bioadhesion to stomach mucosa (Santus *et al.,* 1997), unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach (Klausner *et al.,* 2003; Deshpande *et al.,* 1997), superporous hydrogel systems (Park, 1988), magnetic systems etc (Fujimori *et al.,* 1994).

Floating drug delivery systems

The concept of FDDS was described in the literature as early as 1962. FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. The device must have sufficient structure to form a cohesive gel barrier, it must maintain an overall specific gravity lower than that of gastric contents (1.004-1.010) and it should dissolve slowly enough to serve as a drug reservoir.

Low density systems

Gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density systems (<1g/cm3) with immediate buoyancy have therefore been developed. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called "microballoons" because of the low-density core. Generally, techniques used to prepare hollow microspheres involve simple solvent evaporation or solvent diffusion methods. Polycarbonate, Eudragit S, cellulose acetate, calcium alginate, agar and low methoxy lated pectin are commonly used as polymers. Buoyancy and drug release are dependent on quantity of polymer, the plasticizer–polymer ratio and the solvent used.

Swellable system

Swellable systems are also retained because of their mechanical properties. The swelling usually results from osmotic absorption of water. The dosage form is small enough to be swallowed, and swells in gastric liquids, the bulk enable gastric retention and maintains the stomach in a 'fed' state, suppressing housekeeper waves.

Superporous hydrogels

Although these are swellable systems, they differ sufficiently from the conventional types to warrant separate classification with pore size ranging between 10 nm and 10 μm. Absorption of water by conventional hydrogel is very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of the dosage form may occur. Superporous hydrogel, average pore size >100μm, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores. Moreover they swell to a large size (swelling ratio 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contractions. This is achieved by a co-formulation of a hydrophilic particulate material, Ac-Di- Sol (crosscar-mellose sodium).

Hydrogels having ability to create effective pore size larger than 10μm are known as Superporous hydrogels (Amin *et al.,* 2008). SPHs possess an average pore size of greater than 100microns and swell to equivalent size within a minute because of rapid intake of water by capillary wetting through number of interconnected open pores (Chen *et al.,* 2000). SPHs have tendency to swell to a large size with a swelling ratio about 100 or more and must have mechanical strength high enough to withstand pressure by gastric contraction. This can be achieved by incorporating hydrophilic particulate material Ac- Di- Sol (Cross carmellose Sodium) (Chen and Park, 2000). A superporous hydrogel is a 3-dimensional net-work of a hydrophilic polymer which absorbs a

large amount of water in a very short period of time because of the presence of interconnected microscopic pores (Chen *et al.,* 1998). Due to porous structure, SPHs has hundreds of times greater surface area and shorter diffusion distance than conventional hydrogels do. These structures allow dried SPHs to swell very fast to a very large size on contact with water. Because of these unique properties, SPHs were initially used to develop gastric retention device that increases the gastric residence time of drugs to get long-term, oral controlled drug delivery. 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 to be absorbed primarily in the stomach (Agyilirah *et al.,* 1991). Many drugs having narrow absorption window, i.e. mainly absorbed from the proximal small intestine (Ichikawa *et al.,* 1991), bioavailability of those drugs would be increased by gastric retention. For drugs which are absorbed rapidly from the gastro-intestinal tract (GIT) (Hilton and Deasy, 1992), should have slow release from the stomach to improve the bioavailability. Gastric retention devices can also be used for those drugs that are poorly soluble at an alkaline pH or drugs that are degraded in the colon (eg, metoprolol). Several important properties of SPHs, like fast swelling capacity, large swelling ratio, and surface slipperiness, make them an excellent candidate to develop gastric retention devices. The weak mechanical property of fully swollen SPHs limits their practical application which can be overcome by making SPHs composites.

Gels vs. Hydrogels

A common misinterpretation in polymer science is the use of the terms 'gel' and 'hydrogel' synonymously. As polymeric networks, both gels and hydrogels might be similar chemically, but they are physically distinct. Dorothy Jordan Lloyd aptly described gels as, 'The colloidal condition, the gel, is one which is easier to recognize than to define (Gehrke, 2000). Technically, gels are semi-solid systems comprising small amounts of solid, dispersed in relatively large amounts of liquid, yet possessing more solid-like than liquid-like character (Klech, 1990). Sometimes, hydrogels are also described as aqueous gels because of the prefix 'hydro'. Although the term 'hydrogel' implies a material already swollen in water, in atrue sense hydrogels are a cross-linked network of hydrophilic polymers. They possess the ability to absorb large amounts of water and swell, while maintaining their three-dimensional (3D) structure (Gehrke and Lee, 1990). This definition differentiates hydrogels from gels, which are polymeric networks already swollen to equilibrium, and the further addition of fluids results only in dilution of the polymeric network (Figure 1). Although some of the gels are rigid enough to maintain their structure under a small stress, after exceeding the yield-value, gel fluidity is observed with loss of polymer structure. A hydrogel exhibits swelling in aqueous media for the same reasons that an analogous linear polymer dissolves in water to form an ordinary polymer solution. Thus, the feature central to the functioning of a hydrogel is its inherent cross-linking. Conventional gels can also develop small levels of cross-links as a result of a gain in energy under the influence of shear forces, but this is reversible because of the involvement of weak physical forces. Because the basic framework of both gels and hydrogels is the polymer network, these polymers produce systems that span a range of rigidities, beginning with a sol and increasing to mucilage, jelly, gel and hydrogel (Gehrke, 2000). Thus, hydrogel, sometimes referred to as xerogel, is a more rigid form of gel. Hydrogels are usually prepared to a measurable dimensional configuration. Sometimes, polymerrs such as Carbopol® are also referred to as hydrogels because of their cross linked configuration. Although, these polymers exhibit swelling in an aqueous environment, at equilibrium their swelling contributes to a gain in solution viscosity, leading to aqueous gel formation. Because polymeric systems are analogous to each other, several misrepresent-tations exist in their nomenclature, which can be prevented by a thorough understanding of their physical, chemical, mechanical and behavioral characteristics.

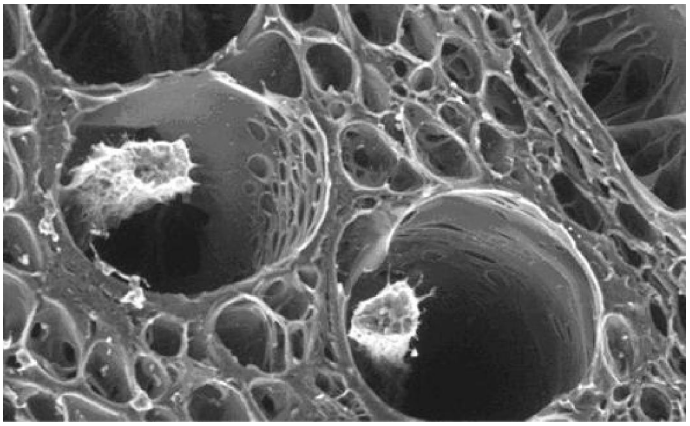

Figure 1. Pore formation in superporous hydrogel (Hilton and Deasy, 1992)

Table I. General features of superabsorbent polymers (SAPs) and superporous hydrogels (SPHs)

	SAPs	**SPHs**
Commonly used monomers	Acrylamide, acrylic acid, salts of acrylic acid including sodium and potassium acrylates	Acrylamide, acrylic acid, salts and esters of acrylic acid including sodium and sulfopropyl acrylates, 2-hydroxyethyl methacrylate
Method of synthesis	Bulk, solution, inverse suspension	Mostly aqueous solution
Initiating system	Thermal, redox	Mostly redox
Porous structure	Random closed to semiopen cells	Interconnected open cells
Final product	Particle	Any shape including particle, sheet, film, rod
Water absorption mechanisms	Diffusion (high), Capillary (low)	Diffusion (low), Capillary (high)
Free swelling capacity	Very high	Very high
Retained water under pressure	High	Low
Applications	Where high swelling, fast-medium rate of swelling is required	Where size-independent high and very fast swelling are required

SAPs vs. SPHs

SAPs, just like SPHs, are structurally cross-linked hydrophilic polymers, which have the ability to absorb considerable amounts of water or aqueous fluids (10–1000 times of their original weight or volume) in relatively short periods of time. Depending on the manufacturing process and the materials used during preparation, the swelling rate of SAPs ranges from fraction of a minute to hours. The fast swelling, however, is mainly based on the small size of the SAP samples. On the other hand, the swelling kinetics of SPHs is always fast regardless of the size of the final product. The porous hydrogels are prepared using several techniques, such as freeze drying, porogenation, microemulsion formation and phase separation. On the other hand, modern SAPs and SPHs are normally prepared utilizing a gas blowing technique in which acidinduced decomposition of a bicarbonate compound is

exploited . Although both SAPs and SPHs are porous in structure, they are different from each other as compared in table I. These differences in swelling properties are also clearly demonstrated in figure 1. The SPHs swell immediately upon contact with water regardless of their size in the dried state. The initial wetting of SAP particles is slower than that of SPHs, and the fast swelling is based on the small size of SAP particles. If SAPs are made into bigger size samples, swelling would not be as fast as their smaller counterparts. The unique property of size independent fast swelling kinetics of SPHs is accounted for by their interconnected open cellular structure (Figure 2.) The open porous structure allows extremely fast absorption of water into the center of the dried matrix by capillary force. The same monomer solution can produce different types of water-absorbing polymer networks, such as nonporous, porous and superporous structures depending on the presence of foaming agent, foaming aid and foam stabilizer. The monomers are simultaneously polymerized (using a redox initiating system) and cross-linked in the solution containing bisacrylamide as a cross-linker. A combination of acetic acid (or acrylic acid) and sodium bicarbonate is used to make a foam structure, which can in turn be stabilized using poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) (PEO–PPO–PEO) triblock copolymers as surfactants. Addition of foaming aid ingredients resulted in different reaction profiles. The reaction profile can significantly affect the swelling and physical properties of the final product. The various reaction profiles are partly due to different oxygen interferences.

Gastric emptying

Gastric emptying of oral dosage forms occur as a result of gastric motor activities or contractions. Gastric retention devices should be designed to overcome the gastric motility. Gastric emptying of indigestible solids (including oral dosage forms) occurring in fasted state by a distinct cycle of electromechanical activity known as Inter-digestive Migrating Myoelectric Complex (IMMC). IMMC is composed of four different motor activities:

Phase 1- No motor activity except occasional contractions, lasting for 45-60min. Phase 2- Intermittent peristaltic contractions with increased amplitude and frequency, lasting for 30-45min. Phase 3- Burst of peristaltic contractions, empties all indigestible solids from stomach, continues for 5-10min. It is also known as "housekeeper wave" due to its sweeping property. Phase 4- Transition phase from phase 3 to phase 1. The complete cyclical pattern occurs every 120min and gastric emptying of oral nondisintegrating dosage forms which is mainly determined by onset of phase 3 activity of IMMC. Phase 3 is repeated every 80 min to 2hrs and hence, the gastric retention devices based on swelling properties need to achieve fully swollen state before next housekeeper wave or gastric retention devices must be constructed to overcome the contractions associated with phase 3 of IMMC.

Basic requirements for gastric retention of superporous hydrogels

Based upon GI Physiology, Superporous hydrogels must possess following properties in order to act as gastric retention device:

Initial size should be small enough for easy swallowing; Swelling should be fast enough to overcome gastric emptying by IMMC; Size of swollen hydrogel should be large enough to be retained in the stomach; Swollen hydrogel should be strong enough to withstand contraction pressure, abrasion and shear forces in stomach (i.e. more than 50-70cm water pressure).

Different generations of superporous hydrogels

First generation

These are first introduced by Chen *et al.* (1999) for gastroretentive drug delivery, also known as conventional superporous hydrogels (CSPH) with fast swelling kinetics and highly porous structure. Commonly used monomers are highly hydrophilic vinyl monomers like acrylamide, ionic monomers like salts of acrylic acid, sulfopropylacrylate potassium etc. Dried SPHs are hard and brittle while swollen forms were soft and flexible due to moisture induced plasticization. Regardless of their size in dry state, these swell to large sizes which is few

hundred times of its own volume in dried state. These show repeated and rapid swelling and shrinking characteristics at different pH values (1.2-7.5). Swollen forms are fragile against bending or stress and get easily broken under light loading due to lack of sufficient mechanical strength.

Acrylamides and salts of acrylic acid are used as monomers, Ammonium persulphate and diamines are used as initiators. Bicarbonates are utilized as foaming agent,while acrylic acid and other acids are used as foaming aids and water is used as solvent. Alcohol is also used to dehydrate and to preserve the porous structure of the SPHs. The rate of water absorption can be increased by creating and interconnecting the pores within the hydrogel structure. Highly hydrophilic (acrylamide) or ionic (salts of acrylic acid or sulfopropyl acrylate) monomers are selected as building blocks for the preparation of first generation SPHs. Sucrose-based SPHs with fast swelling properties (Chen and Park, 2000) and acrylic acid and acrylamide deposited onto a PEG acrylate substrate (Huh *et al.,* 2005) have also been prepared The swelling rate of conventional SPHs can be controlled using a coating system (Baek *et al.,* 2001).

Second generation

These are also known as superporous hydrogels composites (SPHC). These higher modulus hydrogels were introduced by Chen *et al.* in 2000 as an improvement over CSPH in terms of higher mechanical strength. A composite agent or matrix swelling additive was incorporated into the same monomer system (as with CSPH). The composite agent or swellable filler is a cross linked water absorbent hydrophilic polymer that can absorb the solution of monomer including other ingredients. These swollen filler particles act as individual reactor in crosslinking polymerization and as polymerization proceeds, these individual swollen partices are connected together through extended polymeric chains. Upon polymerization, the composite agent acts as local point for physical crosslinking of formed polymeric chains resulting in the formation of heterogenous non-integrated interpenetrating networks. The most widely used composite agents are crosslinked sodium carboxymethylcellulose (Ac-Di-Sol), crosslinked sodium starch glycolate (Primojel) and crosslinked polyvinylpyrrolidone (Crospovidone). PVA, PEI, Carbopols are also used to improve the mechanical strength of SPHs. Though, this modification leads to polymeric networks with improved mechanical strength in swollen state but still these are prone to breakdown under high tensile stress. A number of SPHs and SPHC have been designed and characterized which are used as attractive devices for peroral and intestinal delivery of peptides, hormones etc.

A major step in the evolution from the first to the second generation was to start with use of swellable filler with the same monomer, crosslinker and initiating system. It is able to absorb the solution of monomer, crosslinker, initiator and other components. During formation of SPHs, all absorbed and not absorbed components participate in the process of polymerization, which results in formation of interpenetrating polymer network. The composite materials used in preparation of SPHs are most of the superdisintegrants like Ac-Di-Sol, Primojel, and crospovidone. Out of these, Ac- Di-Sol imparts great swelling rate as well as mechanical property. The mechanical property of SPHs can be increased by acidification of ionisable groups of polymer which makes the SPHs to withstand the stress of gastric contraction.

After dispersion into the reacting mixture, the swellable filler would swell and absorb a mixed solution of monomer, crosslinker and initiator and the water-soluble foaming additives. The swollen filler particles then act as an isolated individual reactor, in which polymerization and crosslinking could occur simultaneously (Chen and Park, 2000; Huh *et al.,* 2005; Baek *et al.,* 2001).

Third generation

Further advancement in mechanical strength lead to third generation SPHs which includes Superporous Hydrogels Interpenetrating Networks (SPH IPNs) and Superporous Hybrid Hydrogels (SPHHs). A second polymeric network is incorporated into SPH frame to form interpenetrating network structure in case of SPH IPNs. A water soluble hybrid agent is introduced in SPH formulations

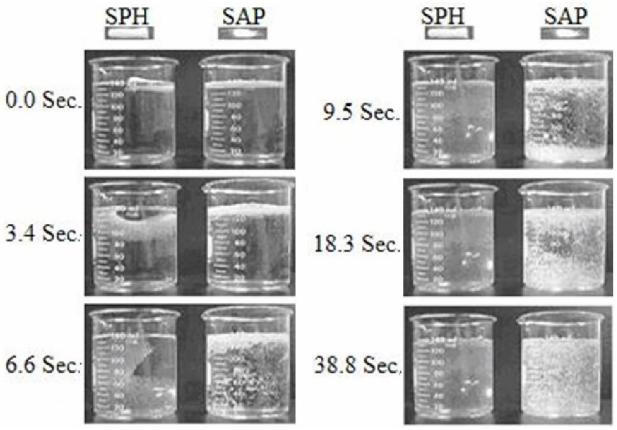

Figure 2. swelling kinetics of SPH

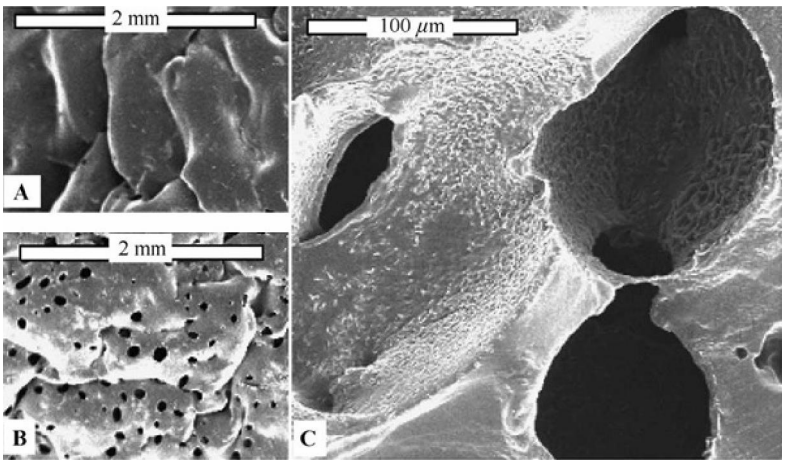

Figure 3. Scanning electron micrographs of a nonporous SAP (A) and a corresponding SPH (B and C)

in case of SPHHs. The hybrid agent evenly diffuses and dissolves into polymer solution leading to formation of integrated semi interpenetrating network which upon treatment of hybrid agent yields integrated IPN structure. They can with stand various types of stresses like compression, bending and twisting *etc.* Various hybrid agents have been used and specific treatment has been applied to get integrated IPN Hydrogels e.g. natural hydrocolloids like sodium alginate, chitosan, sodium CMC, Pectin and synthetic water soluble PVA. Natural hydrocolloids show ionotropic gelation via treatment with metal ion like Calcium, iron etc. (e.g. Sodium alginate with Ca2+ ions, chitosan with phosphates). A number of SPHIPNs has been reported for delivery of peptides, hormones and evaluated for controlled release.

SPHH (super porous hydro gel hybrid) is developed to improve the mechanical and elastic properties (Omidian *et al.,* 2005; Omidian *et al.,* 2006). It consists of a water soluble counterpart i.e. hybrid agent instead of the swellable filter which can form a cross linked structure, like interpenetrating polymer network by physical or chemical crosslinking.

The unique properties of SPHHs are their elasticity and spongy nature. SPHHs are strong enough to withstand the stresses like compression, bending, twisting. They are not easily breakable upon stretching. Each hybrid

agent may require specific treatment. Various third generation SPHs can be prepared ranging from high modulus to highly elastic and rubbery (in their water-swollen states) depending on the type of hybrid agent and its associated treatment (Rocca *et al.,* 2004). Sodium alginate, sodium carboxymethyl cellulose and chitosan are the most appropriate hydrocolloids having outstanding ionogelation properties. Acrylamide and methylenebisacrylamide are used as the preferred monomer and chemical crosslinker to formulate the SPHHs. Water-soluble hydrocolloids, including sodium alginate, sodium carboxymethyl cellulose and chitosan, are used alone or in combination as the preferred hybrid agents. To induce ionotropic gelation of these hydrocolloids, calcium, iron and phosphates are used respectively. Ethylenebisacrylamide is used as a thermally resistant chemical crosslinker. Cerium ammonium nitrate is used to prepare grafted SPHHs. Stronger SPHHs can be prepared by replacing the diacrylate crosslinker with a trifunctional acrylate. The SPHHs having lower salt sensitivity can be prepared using a quaternary ammonium salt (diallyldimethyl ammonium chloride) as a secondary monomer.

Miscellaneous SPHs

Development of SPHs with mechanical properties identical to that of SPHCs has been attempted applying different approaches, including acidification (using HCl), imprenation (using diallyldimethyl ammonium chloride or cationic polyethyleneimine or cationic resin of polyamidoamineepichlorohydrin), rubberization (adding rubber emulsions), surface crosslinking (using glycerin), ionotropic gelation (using synthetic polymers other than hydrocolloids; like polyvinyl acetate), bulk crosslinking (using higher concentration of a chemical crosslinker) thermogelation (using ovalbumine protein, egg white) and ionotropic gelation (using ion-complexable co-monomers; e.g. acrylic acid).

Types of hydrogels

Stimuli sensitive superporous hydrogels

An ideal drug delivery system should respond to physiological requirements, sense the changes and alter the drug release pattern. Hydrogels are said to be smart or intelligent in the sense that they can perceive the prevailing stimuli and respond by exhibiting changes in their physical or chemical behavior resulting in controlled release of drug entrapped. A number of stimuli (external/internal) exist to control structural changes in polymer network but the main concern here is toward pH sensitive and thermosensitive hydrogels.

pH sensitive hydrogels

These are composed of polymeric backbone with ionic pendant groups. In aqueous media of appropriate pH and ionic strength, the pendant groups ionize and develop fixed charges on the polymer network, generating electrostatic repulsive forces responsible for pH dependant swelling/ deswelling of hydrogel thereby controlling the drug release. Small change in pH can alter the pore size of hydrogels. Most commonly used ionic polymers for pH sensitive behavior include poly (acrylamide), poly (acrylic acid), poly (methacrylic acid), poly (diethylaminoethylmethacrylate) etc. Among natural polymers albumin and gelatin have been studied. The HEMA based pH sensitive polymeric network has been reported as self regulated device for insulin delivery. Chemically modified polyacrylamide guar gum based anionic pH sensitive hydrogels have been developed for controlled delivery of diltiazem hydrochloride and nifedipine.

Thermosensitive hydrogels

These hydrogels include various temperature sensitive polymers like N-substituted Acrylamide, methacrylamide, polyethylene oxide etc. it has been reported that the kinetics, duration and rate of drug release from hydrogels is affected by structural properties of the polymer such as degree of crystallization, size of crystallites, degree of swelling etc. The temperature sensitive polymers show a lower critical solution temperature (LCST) which induces hydration change of the polymer e.g. poly (n-isopropylacrylamide) shows LCST of 34°C and 32°C in case of isopropylamylburide hydrogels. Below critical solution temperature polymers are hydrated or soluble and swell to significantly higher degrees and above this temperature, polymers are dehydrated or

hydrophobic and do not swell significantly in water. This leads to shrinkage of network above LCST and decrease in network volume releasing the entrapped drug. An abrupt change in swelling has been observed around 32°C in case of poly (nisopropylacrylamide). At this temperature, the entropy driven release of water molecules around the hydrophobic isopropyl side chains leads to deswelling. A number of hydrogel systems have been reported based on poly (n-isopropylacrylamide) like pulsatile release of indomethacin, temperature controlled release of heparin etc.

General 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). HEMA (800 mL) was placed into a test tube; to this, 15 mL of Swelling and Mechanical Properties of Modified HEMA-based SPHs 485 PEGDA, 50v/v% aqueous acetic acid solution, 30, 60, and 90mL of an aqueous acrylic acid solution (50v/v%), and 100mL of 10w/v% aqueous Lutrol F127 solution were added under mild shaking. After some vigorous shaking of the complete mixture, 25mL of TEMED (40v/v%) was added with shaking for 30s, then 25mL of distilled water was added. This was followed by the addition of 50mL APS solution (20w/v%). The contents of the test tube were mixed for 90s. Sodium bicarbonate (170 mg) was immediately added and carefully dispersed using a spatula and the reaction mixture placed into a 658°C water bath. The hydro gels obtained were thoroughly washed in distilled water and their swelling sizes and strengths were determined. All concentrations of acrylic acid were expressed based on 800mL of the primary HEMA monomer. Ionotropic gelation of hydro gels: The hydrogel samples synthesized above were placed in separate solutions including distilled water, 10wt% calcium chloride solution, and 10wt% aluminum chloride solution for 1h. All hydrogel samples were thoroughly washed in water and were subjected to further evaluations. Digital caliper was used to measure the dimensions of the cylindrical hydro gels in their swollen state. A Chatillon TCD-200 test stand with a DFGS force gage was used for each strength measurement. The fully swollen hydro gels were loaded under the probe of the mechanical tester at a constant rate.

Water absorption mechanisms

Regardless of the synthetic method, various grades of SAPs are normally prepared as nonporous to porous particles. Nonporous hydro gels can find applications where high mechanical strength properties are required, as in agriculture when the hydrogel is applied in deep soil and should withstand the associated pressure. They can also be used in applications where the rate of water absorption is not primary. The outermost dry layer of granular particles is first moistened upon contact with water to result in two phases of partially swollen and dry polymer. Diffusion of water continues through the partially swollen layer towards the core. In case of porous SAPs, pores created on the surface and in the bulk of the polymer enhance water absorption by capillary forces. The industrial grade SAPs are produced in desired range of particle sizes to fulfill the requirements for specific applications. This can be achieved because of the resistance of the bulk polymer to the mechanical forces applied during grinding. Unlike SAPs, SPHs swell very fast regardless of their size, and this is due to the interconnected porous structure. The interconnected structural pores provide water absorption into the center of the SPHs by capillary force.

Drug loading into superporous hydrogels

Superporous hydrogels can act as reservoir devices or the delivery of different drug delivery systems like controlled release mini tablets or microparticles. Drug solution can be simply absorbed into SPH Polymers.

Two types of drug delivery systems has been designed, i.e. Core inside shuttle system and Core attached to surface of shuttle system. Each of these shuttle systems are composed of two components: a core and a conveyor system. Core is the part which contains drug blend with appropriate excipients and conveyor is made up of SPH and SPHC.

Core inside the shuttle system

In this system, core is prepared in two different forms viz. micro particles and gross mass. Micro particles are prepared by dispersing the drug in melted polymers like PEG 6000 and cooling of the mixture to get gross mass. This gross mass is crushed in mortar and sieved through #400μm, 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.

Core attached to surface of shuttle system

In this system, core is in the form of small tablets which are prepared by dispersing the drug in melted polymer like PEG 6000 and sieving the mass through # 400μm, which were mixed with magnesium stearate and compressed into tablets using single punch machine (40 N hardness). The second component is conveyor made of only SPHC in which two holes were made on counter side instead of one as in previous approach. The core material in the form of small tablets was placed inside the holes by using bio-adhesive (cyanoacrylate) glue. The polymer swells when it comes in contact with gastric fluids and the size of holes is enlarged. The glue helps to keep the dosage forms at the site of drug absorption. The same assembly is placed into gelatin capsule shells of size 000.

Drug loading into superporous hydrogel polymers

The amount of water required for complete swelling of specific weights of SPH and SPHC is determined. Then, aqueous solutions of given drug is prepared in previously determined amount of water and weighed amount of polymer is placed in drug solution to suck up the drug solution. After 20 min, completely swollen polymers loaded with drug are placed in oven at 30°C for drying overnight.

Superporous hydrogels for gastric retention

Any vinyl monomer can be used to prepare superporous hydro gels using the process described in figure 3. The type of monomer included in the superporous hydrogel preparation significantly affects the overall properties of the superporous hydro gels. Mechanical property is the important property of SPHs. The superporous hydro gels has neither large swelling volume nor good mechanical strength, when acrylamide (AM) is used as the only monomer. When sulfopropylacrylamide potassium salt (SPAK) is used alone, the superporous hydro gels swells to a large size in the simulated gastric fluid (SGF) but are not strong. When AM and SPAK are copolymerized, however, superporous hydro gels shows good swelling as well as good mechanical properties.

Superporous hydrogel composites

The mechanical strength of superporous hydro gels can be improved greatly by incorporating a composite material. Among the many composite materials, Ac-Di-Sol is superior to others in improving the mechanical strength of superporous hydro gels. Ac-Di-Sol can be added to the monomer solution before polymerization and foaming. Addition of Ac-Di-Sol increases structural integrity by increasing the (physical) crosslinking density of the superporous hydrogel. If Ac-Di-Sol is incorporated in very large proportion however, a good mixing of all the ingredients becomes difficult because of increase in the viscosity of the solution.

Acidification of the SPAK superporous hydro gels

Pretreatment of SPHs by acidification increase the mechanical strength of the superporous hydro gels. The ultimate compression pressure (UCP) is used to measure the mechanical strength of superporous hydro gels. UCP value is determined by applying increasing amounts of weights until a point when the superporous hydrogel started cracking.

The pressure at this point is defined as penetration pressure (PP) and calculated by the following equation:

$PP = Fu/S$

Where Fu is the ultimate compressive force at complete breakage of polymer and S is the contact area of the lower touch (Dergunov *et al.,* 2004).

Methods for preparation of superporous hydrogels (SPHS)

Porosigen technique

Porous hydrogels are prepared in the presence of dispersed water soluble porosigens e.g. micronized cellulose, sodium chloride, PEG etc. which forms meshworks that can be removed by washing with water. The pore size of hydrogels depends on the size of porosigens.

Phase separation technique

This method is applicable for limited type of porous hydrogels e.g. HEMA, NIPAM. However, there is not much control over porosity of prepared hydrogels.

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. This technique is limited to absorbent particles with chemically active functional groups on the surface.

Gas blowing technique

This is the most widely used method for the preparation of superporous hydrogels, where, superporous hydrogels are prepared by crosslinking polymerization of monomers in the presence of gas bubbles. Different ingredients like monomer, crosslinker, foam stabilizer, polymerization initiator, initiation catalyst (if any) and foaming agent are added sequentially in a test tube of specific dimensions. Initially and before addition of foaming agent, the pH of monomer solution is maintained at 5 to 6, because low pH favors foaming process. The addition of foaming agent leads to formation of bubbles followed by increase in pH of solution. The increased pH accelerates the polymerization process. Thus, simultaneous foaming and gelation lead to the formation of homogenous porous hydrogels i.e. Superporous hydrogels. After synthesis, SPHs are subjected to washing, drying using different methods which influence the swelling and mechanical behavior of resulting hydrogels.

Ingredients of SPH_S

Following is the list of basic ingredients which are used in synthesis of SPHs and its different generations.

Monomer: Acrylic Acid, Acrylamide, SPAK, HEMA, NIPAM etc; Crosslinking agent; N,N'-methylenebisacrylamide (Bis) is used most widely in blowing technique. Glutarldehyde (chemical crosslinker), metal ions like calcium, iron and phosphorus are used in ionotropic crosslinking of hydrocolloids; Foam stabilizer: Pluronic F127, Pluronic P105, Silwet L7605, Span, Tween etc; Polymerization initiator pair: APS/TEMED (Ammonium persulfate/N,N,N,Ntetramethylethylenediamine, KPS/Sodium metabisufite, APS/Sodium metabisulfite, Azo-initiator (V545) etc; Foaming agent: Sodium bicarbonate; Composite agent: Various superdisintegrants like crosslinked sodium carboxy methylcellulose (Ac-Di-Sol), crosslinked sodium starch glycolate (Primojel) and crosslinked polyvinylpyrrolidone (crospovidone) are mostly used; Hybrid agent: Natural polymers like sodium alginate, sodium carboxymethylcellulose, chitosan based on ionotropic gelation and synthetic polymers like Poly vinyl alcohol (PVA) based on cryogelation.

Advantages of SPHs

Superporous hydrogels have three unique properties that conventional hydro gels do not have. The swelling rate is very fast. The Superporous hydro gels swell completely within a minute regardless of the size of the dried superporous hydrogel. Superporous hydro gels swell to such an extent that the weight of fully swollen superporous hydrogel is higher than the weights of dried superporous hydro gels.

Though the superporous hydro gels contain small percentage of solid content of the total weight, it can exert significant expansion force during swelling. Superporous hydro gels can also be made elastic, which minimizes their rupture. The unique properties of superporous

hydro gels can also be used for non-pharmaceutical and non-biomedical applications.

Applications of SPHs

Sustained drug delivery; Site-specific drug delivery; Gastroretentive tablets; Peroral peptide delivery systems; Fast-dissolving tablets; Development of diet aid; Chemoembolization and occlusion devices; Development of occlusion devices

CONCLUSION

A modified release drug delivery system with prolonged residence time in stomach is desired with many drugs and superporous hydrogels (SPHs) are promising tools to achieve this target. Different generations of SPHs have been developed to accomplish the needs for certain pharmaceutical applications, including gastric retention. The SPH, SPH composite and 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. Superporous hydrogels swell to equilibrium size in a short period of time due to capillary wetting of interconnected open pores and water is rapidly absorbed by capillary attraction forces within the pores and these polymers swell to their maximum very quickly. SPHs, SPHC and SPH-IPNs holds a lot of potential with Pharmaceutical and Biomedical applications and the responsibility lies on future workers to effectively harness its superb swelling and mechanical properties for the comfort and betterment of mankind.

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