

Superporous hydrogels as gastroretentive devices

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Abstract

One of the most feasible approaches for oral drug delivery in achieving a prolonged release and predictable drug delivery profile in the gastrointestinal tract (GIT) is to control the gastric residence time (GRT). The dosage forms with prolonged GRT also known as Gastroretentive Dosage Forms (GRDFs) include intragastric floating systems (low density systems), mucoadhesive systems, high density systems, magnetic systems, unfoldable, extendible or swellable systems and superporous hydrogels (SPHs). Superporous hydrogels (SPHs) are recent advancements of gastroretentive drug delivery systems. This article provides a concise review of superporous hydrogels along with their different generations, being fabricated for controlled release.

Keywords: superporous hydrogels, interpenetrating networks, gas blowing technique, hybrid hydrogels, gastroretentive dosage form, superporous hydrogel composite

Introduction

In the past few decades, pharmaceutical industry has experienced an impressive growth year after year and continuous introduction of life saving drugs has propelled this growth. The current trend in pharmaceutical industry is towards the advancements in drug delivery systems and more emphasis is given on developing new drug delivery technologies, which allows an effective use of existing drugs for successful development of new drug products. The basic reason of this shift in research area is the cost of new drug development, which is escalating every year (Park 2002). The importance of controlled drug delivery technology used for extended release has long been recognized in pharmaceutical fields. Since oral route is most convenient and commonly employed route of drug administration, the recent advancements include application of controlled release technology to oral drug delivery. However, the major limitation is the actual time for effective drug delivery being restricted by gastrointestinal transit time, which range from several h to 12 h (Wise 2000). To overcome this limitation, gastric retention devices have been developed in the last few years and lot of research has been done in development of various gastroretentive dosage forms like floating devices, high density systems, mucoadhesive dosage forms, magnetic dosage forms etc. The most recent advancement in the gastroretentive drug

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delivery is the development of various types of superporous hydrogels (SPHs) (Chen et al. 1999, Wise 2000).

Hydrogels has been used for long years back in various biomedical, agricultural applications, for their absorbent properties, biodegradability and biocompatibility. The beginning of hydrogel dates back to 1960 when Wichterle and Lim first proposed the use of hydrophilic networks of Poly (2-hydroxyethylmethacrylate) in contact lenses (Hoffman 2002). Since then, considerable progress has been made in the synthesis and application of hydrogels. These are cross linked network of hydrophilic polymers that are insoluble in water. But they tend to imbibe large amount of water and swells too much larger size than the original one and still maintain a distinct 3D structure in swollen state. The characteristic water insoluble behavior is due to chemical or physical crosslinking which provide a network structure and physical integrity to the system (Gupta et al. 2002). Due to rigid crystalline structure and low elasticity in polymer chains, hydrogels swell very slowly and it may take a few hrs to even days to achieve complete swelling. The slow swelling of hydrogels results from diffusion of water through glassy matrix of dried hydrogel. Though, the slow swelling of these hydrogels is useful in various applications but these are not applicable when faster swelling is required (Doorkhoosh et al. 2000). Therefore, a new generation of hydrogels i.e. Superporous hydrogels have been developed for this purpose. These are the hydrogels having interconnected pores of few hundred μm which swell to equilibrium size in a short period of time i.e. less than 20 minutes, to make them useful as gastroretentive device. The interconnected pores lead to the formation of open capillary channels and fast swelling is achieved via capillary wetting of interconnected pores i.e. water is rapidly absorbed by capillary attractive forces within the pores (Chen et al. 1999).

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 Interdigestive Migrating Myoelectric Complex (IMMC). IMMC is composed of four different motor activities: *Phase 1*- No motor activity except occasional contractions, lasting for 45-60 min. *Phase 2*- Intermittent peristaltic contractions with increased amplitude and frequency, lasting for 30-45 min. *Phase 3*- Burst of peristaltic contractions, empties all indigestible solids from stomach, continues for 5-10 min. 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 120 min 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 (Chen et al. 2000a).

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 (Wise 2000):

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

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 (Badigar et al. 1993).

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 (Yan et al. 1995).

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 (Lind et al. 1992).

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 (Chen et al. 1999). After synthesis, SPHs are subjected to washing, drying using different methods which influence the swelling and mechanical behavior of resulting hydrogels.

Ingredients of SPHs: 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. Glutaraldehyde (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,N-tetramethylethylenediamine, KPS/Sodium metabisulfite, 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.

Salient features of superporous hydrogels

Swelling: Superporous hydrogels achieve full swelling in 20 min or less to avoid premature emptying via housekeeper waves as to act as gastroretentive device. The sieve weighing boat is used for swelling studies to avoid direct handling of fragile SPHs in swollen state. Swelling is measured in terms of change in weight, volume and dimensions at different time intervals. Two swelling parameters mainly equilibrium swelling time and equilibrium swelling ratio are determined (Chen et al. 1999). The third swelling parameter is T_{core} which denotes transition from opaqueness in dried form to transparency in swollen form (Omidian et al. 2007). The swelling properties are influenced by the type and nature of swelling media (pH, ionic strength). The swelling of hydrogels is also affected by post synthesis treatments like method of drying and the use of wetting agent. Two different drying conditions are used. Condition I includes drying of SPHs under warm air (60°C) for 24 h and Condition II includes dehydration by absolute ethanol until complete replacement of water followed by removal of excess ethanol by draining with paper towel. Finally, the SPHs are dried in 55°C oven for 24 h, although equilibrium swelling ratio is unaffected by different drying conditions. However a significant effect is observed on equilibrium swelling time. Under Condition I of drying, the swelling time is 1 h and under condition II, it is reduced to about 4 min. The increased swelling time in condition I, indicates the disruption of capillary channels via collapse of polymer chains and pores during drying. Due to high ST of water, there is shrinkage of hydrogels indicated by high density (0.80g/cm³). In condition II, the intact pore structure is maintained *via* rigidity acquired by gel in ethanol (being poor solvent). There is less shrinkage of hydrogel indicated by low density of 0.3g/cm³. The use of wetting agent like Voranol[®] in ethanol for dehydration during drying condition II, the equilibrium swelling time is further reduced to less than 3 min. Also, an increase in moisture content of dried hydrogel from 20% to 25% of total weight leads to significant decrease in equilibrium swelling time to less than 2 min. provided the amount of sodium bicarbonate is kept to be low which is otherwise added in excess (Tanaka et al. 1979, Dusek 1993, Chen et al. 1999).

Mechanical strength: Superporous hydrogels are required to possess sufficient mechanical strength to withstand gastric pressure associated with different contractions. Various mechanical testers like bench comparator have been used to measure the mechanical strength in terms of swelling height under 100 cm water pressure and ultimate compression pressure (UCP) (Chen and Park 2000b). Another device reported is the use of gastric simulator to evaluate SPHs devised for gastroretentive purpose. This applies controlled amount of different type of stresses on the hydrogel (to be tested) immersed in testing fluid to simulate stress conditions in GI fluids. It measures the energy absorbed by the sample until it fails under the stresses applied (Omidian et al. 2007). Different post synthetic treatments like acidification, drying and slipperiness affect

the mechanical strength. Superporous hydrogels without washing step or any treatment are found to be weaker as compared to those with washing step. This is indicated by mechanical strength testing which shows less Ultimate Compression Strength (UCP) of 189 cm water pressure. The washing step partially acidifies the anionic SO_3^- groups into SO_3H which changes the properties of hydrogels. Effect of drying method on mechanical strength revealed that air dried hydrogels are stronger (UCP: 368 CM water pressure) than those dried in oven (UCP: 284 cm water pressure) (Wise 2000).

The slippery property of hydrogel surface helps in smooth migration of peristaltic waves over the surface of hydrogel. Mucin from porcine stomach provides the slippery nature to the hydrogel surface. Mucin (10% solution) is applied by cotton swab on the surface and then hydrogels are heated in 130°C oven for 40 min. The slipperiness was maintained even after washing in SGF for 2days but if hydrogels are air dried after mucin coating then slipperiness kept only for 1 h. The reason behind this is the crosslinking of mucin networks at high temperature whereas it is only the adsorption of mucin layer during air drying which is washed away in SGF. However, mucin coating and heating at 130°C leads to increased swelling time (5-6 min) as well as reduction in UCP i.e. mechanical strength is decreased. This may be due to destruction of hydrogel networks at high temperature (Arshady 1990, Shalaby 1992).

Harmonized foaming and polymerization (Gelation): During the synthesis of SPHs via gas blowing technique, gelation and foaming processes lead to formation of porous SPHs. The following points should be considered for better synchronization between these two processes to get homogenous porous product (Chen et al. 1999, Omidian et al. 2005)

Since hydrophilic monomers are used in this technique which have a very high heat of polymerization. That is why their bulk polymerization is an exothermic reaction which results in heterogeneity in the structure. For this, monomers are diluted with water at room temperature by gentle mixing.

Since acid dependant foaming agent (sodium bicarbonate) is used as foaming agent, the glacial acetic acid or acrylic acid should be added to interact with bicarbonate ions for generation of gas bubbles. The addition of acid also maintains the pH of the monomer solution between 5 to 6, which favors foaming but polymerization is slow at this pH. The reason is that in monomer solution at this pH (5-6), TEMED catalyzed free radical generation of APS was inhibited due to protonation of TEMED, resulting in very slow polymerization.

Addition of bicarbonate also increases the pH of the monomer solution to 7-8 which favors polymerization. At this pH, TEMED in its free base form, catalyze free radial generation from APS and accelerate polymerization. Excess of sodium bicarbonate (100-120 mg) is used to increase the final pH of monomer solution above neutral and act as a trigger for accelerated polymerization.

Thus, foaming and gelation are two processes which are required to occur simultaneously to get homogenous porous hydrogels. For this, the timing of addition of foaming agent and the onset of gelling are controlled carefully. If foaming starts too early or polymerization occurs too slowly then the foam get raised and subsided before onset of gelling, resulting in formation of poorly or nonporous hydrogels. If foaming starts too late, the solution becomes too viscous for even

distribution of gas bubbles, resulting in formation of porous heterogeneous hydrogels. The whole process can be divided into three stages i.e. Stage I: showing 80% foaming with no gelation (as there is no rise in temperature of reaction medium). Stage II: shows further rise in foaming with 5-10°C rise in temperature indicating the onset of gelling. Stage III: shows no foaming and accelerated gelation where, liquid soft hydrogel of stage I and II converts to solid flexible rubber like hydrogel.

Gelling or crosslinking polymerization Process is also governed by careful selection of monomer, initiator pair, temperature, solvent system etc (Chen et al. 1999). For Example, AA, AM, SPAK, NIPAM monomers at more than 10% concentration, show fast gelling (1-2 min) in aqueous solution with APS/TEMED initiator pair (1-2%), whereas HEMA, HPMA, VP show fast gelling at high temperature (60°C - 80°C) with APS/TEMED pair. Vinylpyrrolidone (VP) and acrylic acid monomers show effective gelling with azo-initiator (V545).

Foaming process is governed by control on timing for addition of foaming agent and start of gelling process. Gelling should start in stabilized foam to get homogenous porous hydrogel. The foam stabilizer like Pluronic F127 (0.5-1.0%) produce adequate and prolonged foam stability with acrylate monomers and a combination of Pluronic F127, Pluronic P105 and Silwet L7605 has been used with hydrophobic monomers like NIPAM and HEMA. Also the foam size is controlled by amount of acid present in the monomer solution (Chen et al. 1999).

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.

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 particles 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

(Crosopvidone). 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. (Table 1)

Table 1. Traditional SPHs and SPHCs (First and second generation superporous hydrogels)

Name of monomer/polymer	Method of preparation	Type of superporous hydrogel	Drug incorporated	Reference
AA, AM, Na-AMPS, ATMS, NIPAM, SPAK, HEMA, VP	Gas blowing technique	CSPH	--	Chen et al. 1999
AA, AM, SPAK Ac-Di-Sol	Gas blowing technique	SPHC	--	Chen and Park 2000b
AM, SPAK	Gas blowing technique	SPHC, in vivo study in canines	--	Chen et al. 2000a
AA, AM, SPAK	Gas blowing technique	CSPH, SPHC	--	Doorkhoosh et al. 2000
AM, AA	Gas blowing technique	CSPH& SPHC,	BAEE (N- α -bezoyl-L-arginine-ethyl ester)	Doorkhoosh et al. 2001
AM, AA	Gas blowing technique	CSPH & SPHC,	Buserelin, Octreotide and Insulin	Doorkhoosh et al. 2002a
AM, AA	Gas blowing technique	CSPH & SPHC	Insulin	Doorkhoosh et al. 2002c
AM, AA	Gas blowing technique	CSPH & SPHC	BAEE and Fluorescein isothiocyanate – dextran 4400 (FD4)	Doorkhoosh et al. 2002b
AM, AA	Gas blowing technique	CSPH & SPHC	Peptides	Doorkhoosh et al. 2004
AM and SPAK	Gas blowing technique	CSPH & SPHC	Desmopressin	Polnok et al. 2004
AA, AM and Carbopol 934p, 974p	Gas blowing technique	CSPH and SPHC	--	Tang et al. 2005
PVA, PVP	Double emulsion and crosslinking via freeze-thaw cycling	SPHs	Biomedical tissue engineering of cartilage	Spiller et al. 2008
Polyaniline, Polyacrylamide	Graft copolymerization	Conducting SPHCs	--	Tang et al. 2000b

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 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 withstand 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 SPH-IPNs (Table 2) has been reported for delivery of peptides, hormones and evaluated for controlled release.

Table 2. Hybrid/IPN type (Third generation superporous hydrogels)

Type of monomer	Method	Type of superporous hydrogel	Drug incorporated	Reference
AA, AM, SPAK & AN	Gas blowing technique	SPHC and SPH-IPNs	--	Qiu et al. 2003
AA, AM & PEI	Gas blowing technique	SPH-IPNs	--	Kim et al. 2004
PEG, PCL and HPGG	UV irradiation	Semi-IPN SPHs	Bovine serum albumin	Zhao et al. 2006
Poly acrylamide/ Sodium alginate	Gas blowing and crosslinking by Ca ²⁺ ions	SPHH ie. Full-IPN SPHs	--	Omidian et al. 2006
PVA/ Chitosan	Crosslinking via glutaraldehyde	SPE's or Hybrid polymeric networks	--	Rodrigues et al. 2007
AA, AM and O-Carboxymethyl chitosan	Gas blowing technique and cross linking by glutaraldehyde	SPH-IPN (semi and full IPN) Mucoadhesion and <i>in vitro</i> release studies.	Insulin	Yin et al. 2007
PVA, PAM	Redox polymerization	Semi-IPNs	--	Mishra et al. 2008
AM-Polyurethane	Polymerization via bis crosslinker	Semi IPN	--	Merlin et al. 2009
AA, Cationic starch	Blending polymerization	Semi-IPNs	--	Li et al. 2009
AA, AM and O-Carboxymethyl chitosan	Gas Blowing technique and cross linking by glutaraldehyde	SPH-IPN, effect of polymer integrity on insulin absorption	Insulin	Yin et al. 2010

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 (Gupta et al. 2002). 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 (Mathiowitz 1999). 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. (Mathiowitz 1999). Among natural polymers albumin (Park et al. 1998) and gelatin (Welz and Ofner 1992) have been studied. The HEMA based pH sensitive polymeric network has been reported as self regulated device for insulin delivery (Klumb and Horbett 1992). Chemically modified polyacrylamide-guar gum based anionic pH sensitive hydrogels have been developed for controlled delivery of diltiazem hydrochloride and nifedipine (Soppimath et al. 2001). Chitosan based antibiotic delivery has been reported via chitosan/ polyethylene oxide semi IPNs (Patel and Amiji 1996).

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 (n-isopropylacrylamide). At this temperature, the entropy driven release of water molecules around the hydrophobic isopropyl side chains leads to deswelling (Umamaheswari et al. 2002). A number of hydrogel systems have been reported based on poly (n-isopropylacrylamide) like pulsatile release of indomethacin (Bae et al. 1991), temperature controlled release of heparin (Brazel and Peppas 1996) etc.

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

Drug loading into superporous hydrogel reservoir devices: 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 (Doorkhoosh et al. 2001 and 2002c).

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 #400 μm , which are used as core material. SPHC is used as the body of the conveyor system (Chen et al. 1999) 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 # 400 μm , 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. (Doorkhoosh et al. 2002a)

SPHs as controlled release devices

A lot of research has been reported on fabrication and generation of different types of hydrogels and their characterization in terms of swelling and mechanical behavior, which is summarized in Table 1. SPHs based on different vinyl monomers were first time synthesized by Chen et al. (1999) using gas blowing technique and the effect of various processing parameters like drying method, monomers, wetting agent on the swelling kinetics was observed. SPHC based on vinyl monomers with Ac-Di-Sol as composite agent (Chen et al. 2000a) were synthesized to improve mechanical strength of SPHs and increased gastric retention was reported in dogs by X-ray analysis showing GRT of 2-3 h in fasted state and more than 24 h in fed state.

Another study on SPHC based on vinyl monomers with Ac-Di-Sol, showed contribution of composite agent in increasing mechanical strength as well as in foam stabilization (Chen et al. 2000b). Doorkhoosh et al. (2000) reported SPHC based on AA-co-AM and AM-co-SPAK and studied effect of drying on mechanical strength and density measurement by solvent replacement technique. In continuation, SPH and SPHC reservoir devices were synthesized and used to incorporate different compounds like BAEE as model drug (Doorkhoosh et al. 2001), different peptides like Buserelin, Octreotide and Insulin and studied drug release and drug integrity (Doorkhoosh et al. 2002a). Ex vivo studies in porcine intestine of drugs like BAEE and FD4 encapsulated into SPH and SPHC based reservoirs had been reported along with increased mucoadhesion to intestinal wall (Doorkhoosh et al. 2002b). Intestinal absorption studies of Insulin housed into SPH and SPHC based reservoirs showed enhanced absorption (Doorkhoosh et al. 2002c). Doorkhoosh et al. (2004) also carried out *in vivo* studies of SPH and SPHC in human volunteers by gamma scintigraphy showing increased gastric retention (75-150 min in fasted state) due to increased adhesion to upper intestine for 45-60 min. The incorporation and release of Desmopressin into and from SPHC (Polnok et al. 2004) was studied and also the effect of use of absorption enhancer (Trimethyl chitosan, TMC) on drug transport (4-fold increase without TMC and 6-fold with TMC) was reported. The porous yet mechanically strong SPH matrix based on PVA/PVP were prepared by different technique i.e. double emulsion and physically crosslinked via freeze-thaw cycling (Spiller et al. 2008).

Various types of IPN type SPHs i.e. third generation has been synthesized and characterized by various researchers and reported for enhanced delivery of various peptides (Table 2). For example, Qui et al. (2003) synthesized SPH-IPN using Polyacrylonitrile i.e. PAN (second polymer network) with acrylamide and SPAK polymer combination. The resulting IPN showed 50 times increased mechanical strength and increased elasticity (170 % elongation of its original length). Highly oriented polyacrylonitrile (PAN) network lead to scaffold like open pore structures which are interconnected with the pore walls. Kim and Park (2004) reported another type of IPNs based on P(AM-co-AA) and Polyethyleneamine (PEI), prepared by addition of aqueous solution of PEI to monomer solution in different weight ratios and gelation kinetics, swelling behavior, mechanical strength was studied of resultant hydrogels. Gelation time increased with increasing acrylic acid or decreasing PEI concentration, whereas swelling

kinetics indicated slow water absorption at high concentration of PEI or PAA. Mechanical strength increased with increase in PEI concentration. Zhao et al. (2006) reported Semi IPN based on PEG-co-poly (ϵ -caprolactone) and hydroxypropyl guar gum (HPGG) prepared by UV light irradiation. Bovine serum albumin was incorporated into resulting hydrogels. These were characterized by FTIR, WAXD, Thermal analysis etc. Improved swelling and mechanical strength along with increased elastic modulus was reported. Increase in HPGG, increased the crystallinity of PEG and the release of drug was found to be decreased. Omidian (2006) synthesized hybrid hydrogels using polyacrylamide and sodium alginate *via* treatment with metal ions to induce metal complexation of alginate portion of SPH structure (ionotropic gelation). With the increase in metal ions, mechanical strength was improved but swelling was decreased. Resulting SPHH were very elastic in swollen state and can be stretched to 2-3 times of its original length and can withstand 10 N mechanical pressure. Rodrigues et al (2007) reported conducting hybrid polymeric networks (HPNs) of poly vinyl alcohol (PVA) and chitosan (also named as SPEs i.e. solid polymeric electrolytes) by using glutaraldehyde as crosslinking agent. Polymer blends and HPNs were compared by impedance studies. Blends showed increased ionic conductivity with increasing PVA and vice-versa in case of HPNs. Yin et al. (2007) reported improved compression and tensile modulus acrylamide based insulin loaded IPNs, by using O-CMC as other polymeric network and glutaraldehyde as crosslinking agent. Decreased swelling ratio with increased GA, O-CMC and crosslinking time was achieved. However, mechanical strength and mucoadhesion was improved. Mishra et al (2008) synthesized semi IPNs based on PVA and crosslinked polyacrylamide (PAM) using methylenebisacrylamide as crosslinker and characterized in terms of mechanical properties like tensile strength, percent elongation and deformation under stress. Merlin and Sivasankar in 2009 reported semi IPNs based on acrylamide – polyurethane (NCO-terminated prepolymer) networks with enhanced mechanical strength due to higher crosslinked density of IPNs. The hydrolytic stability studies in phosphate buffer showed more stability of IPNs as compared to polyacrylamide networks. Li et al (2009) synthesized semi IPNs by blending polymerization of acrylic acid (AA) with cationic starch (CS) using poly-(methacryloyloxyethyl trimethylammonium chloride) (PDMC) solution as crosslinker with increased mechanical strength and good swelling property of resulting networks. Yin et al (2010) studied the effect of polymer integrity on insulin absorption mechanisms using AM/AA and O-CMC based SPH interpenetrating networks and enhanced insulin permeability was reported with integrated SPH-IPNs through Caco-2 monolayers and excised rat intestine.

A number of smart hydrogels i.e. stimuli responsive hydrogels had been synthesized and reported, for controlled delivery of various drugs (Table 3). Gemeinhart (2000) reported pH sensitive swelling behavior of P (AM-co-AA) based smart hydrogels showing repeated swelling and shrinkage between pH-1.2 to 7.5. Chitosan/PVP based semi IPNs (Risbud et al. 2000) have been designed using glyoxal as crosslinker. Park et al. (2005) developed pH sensitive superporous hydrogels based on glycol chitosan/chitosan. Chitosan has abundant amine groups in within polymer chain and it dissolves in acidic solution and forms a gel with aldehydes like glyoxal, glutaraldehyde. Glyoxal chitosan is a 6-(2-hydroxyethyl) ether derivative of chitosan shows greater swelling in acidic solution.

Table 3. Stimuli sensitive hydrogel networks / superporous hydrogels

Type of monomer	Method	Type of superporous hydrogel	Drug incorporated	Reference
Poly (AM-co-AA)	Gas blowing technique	Thermo and pH sensitive SPHs	--	Gemeinhart et al. 2000
Chitosan/ PVP	Crosslinking via glutaraldehyde	pH sensitive semi-IPN, SPHs	Amoxycillin	Risbud et al. 2000
Chitosan/ Glycol Chitosan	Gas blowing with air and freeze drying	pH sensitive SPHs	--	Park et al. 2005
PNIPAM/Polyurethane	Free radical polymerization	Thermosensitive SPHCs	--	Liu et al. 2008
Chitosan / PNIPAM	Chemical combination of crosslinked networks	Thermosensitive full-IPN SPHs	--	Wang et al. 2001
Chitosan/ PEO	Crosslinking using Glyoxal	pH sensitive semi-IPN SPHs	--	Khalid et al. 2002
PVA/ Chitosan	UV Irradiation	pH and Temp. sensitive IPN-SPHs	--	Kim et al. 2003
Sodium Alginate/ PNIPAM	Crosslinking via Ca ²⁺ ions	Thermosensitive SPH-IPNs	--	Moura et al. 2005
Glycol Chitosan / PVA	Gas blowing and cross linking with glyoxal	pH sensitive SPH-IPNs	--	Park and Kim 2006
Polyacrylate/ Polyaniline	Aqueous polymerization	Thermo and pH sensitive SPHH	Methylrosaniline chloride	Tang et al. 2008a
Poly(AA-co-AM), O-CMC	Gas blowing technique	Ionic strength and pH sensitive full IPNs	Insulin	Yin et al. 2008
Poly(AA-HEMA), PVA	Radical precipitation copolymerization using glutaraldehyde	pH sensitive IPN films	Crystal violet as model drug	Yue et al. 2009
Poly(n-vinyl-2-pyrrolidone PEG diacrylate) chitosan	Free radical polymerization	pH sensitive hydrogel	Theophylline and 5-FU	Shantha and Harding 2000
P(NIPAM-co-SA)	Aqueous free radical polymerization	Thermo and pH sensitive hydrogels	--	Mohan et al. 2007
P(NIPAM-co-AA)	Gas blowing	Thermosensitive hydrogel	--	Silva and Oliveira 2007
PNIPAM / PVP	Free radical polymerization using PEG-dimethacrylate crosslinker	Thermoresponsive hydrogels	Diclofenac Sodium and Procaine HCl as model drugs	Geever et al. 2008
PNIPAM/ PVP	Graft copolymerization	Thermoresponsive hydrogels	--	Jin et al. 2008
MAA/ AN	Polymerization via bis crosslinker	Ionic strength and pH sensitive	Theophylline as model drug	Luo et al. 2009
NIPAM/ IA	Crosslinking polymerization	pH and temp. sensitive IPN-SPHs	Hydrophilic model protein drug Lipase	Milasinovic et al. 2010

*AM: Acrylamide, AA: Acrylic acid, NIPAM: N-isopropylacrylamide, HEMA: Hydroxyethylmethacrylate, HPMA: Hydroxypropylmethacrylate, SPAK: Sulfopropylacrylate potassium, VP: Vinylpyrrolidone, AMPS: 2-acrylamido-2-methyl-1-propanesulfonic acid, ATMS: (2-(acryloyloxy)ethyl) trimethylammonium methyl sulfate, PCL: Polycaprolactone, HPGG: Hydroxypropyl guar gum, PEI: Polyoxyethyleneimine, AN: Acrylonitrile, PANI: Polyaniline, MAA: Methacrylic acid, PVP: Polyvinylpyrrolidone, PVA: Polyvinylalcohol, CMC: Carboxymethylcellulose, PEO: Polyethyleneoxide, IA: Itaconic Acid

Liu et al. (2008) synthesized P (NIPAM) hydrogels composite by reinforcing polyurethane foam as composite material. The elastic modulus and swelling ratio of composite were found to be temperature dependent. Another study includes chemical combination of chitosan crosslinked with formaldehyde (HCHO) and poly (n-isopropylacrylamide) crosslinked with methylene bis-acrylamide (MBAM) to develop both semi IPN and full IPN and their swelling/deswelling behavior with respect to temperature and mechanical properties (Wang et al. 2001).

Khalid et al. (2002) synthesized pH sensitive semi IPNs based on CS-PEO and compared with CS hydrogels and reported improved swelling and mechanical strength of semi IPNs attributed

to the presence of hydrophilic PEO chains. Kim et al. (2003) synthesized PVA/CS pH and temperature sensitive IPNs by UV irradiation. Resulting hydrogel networks exhibited higher swelling ratio and stimuli sensitivity due to association and dissociation of H-bonding between –OH group in PVA and NH₂ group in CS. Temperature sensitive superporous hydrogels IPNs based on poly (n-isopropylacrylamide)/Sodium alginate have been developed (Moura et al. 2005). In these, second polymer network i.e. sodium alginate get further crosslinked with Ca²⁺ ions thereby enhancing the mechanical strength of hydrogel device. Superporous hydrogels IPNs based on glycol chitosan/PVA has been reported (Park and Kim 2006) where PVA is incorporated in glycol chitosan to improve mechanical strength. Tang et al. (2008a) reported pH responsive and temperature responsive conducting polyacrylate/polyaniline hybrid network synthesized by aqueous polymerization where aniline monomers were first absorbed in the network of polyacrylate followed by polymerization reaction between aniline monomers. Yin et al. (2008) synthesized stimuli sensitive P(AA-co-AM)/O-CMC full IPNs and studied the release characteristics and diffusion behavior of insulin in mice. Enhanced mucoadhesion of hydrogel lead to increased retention time in GIT and therefore, transport of insulin across rat intestine and colon ex vivo was observed to improve. Yue et al. (2009) synthesized pH responsive P(AA-co-HEMA)/PVA micro structured interpenetrating hydrogel films by radical precipitation copolymerization using glutaraldehyde as crosslinker. The films showing good mechanical strength were studied as controlled release device in different pH (pH 4.0 and 7.0).

Shantha and Harding (2000) prepared biodegradable pH responsive interpolymeric hydrogels based on N-vinylpyrrolidone (NVP), polyethylene glycol diacrylate (PAC) and chitosan by free radical polymerization using azo-bis-iso-butyronitrile (AIBN) as initiator and MBS as crosslinker. Theophylline and 5-FU were used as model drug for release studies which showed more than 50% release in first 2 h at gastric pH and rest was released slowly. Mohan et al. (2007) reported stimuli sensitive P-(NIPAM-co-SA) hydrogel networks by aqueous free radical copolymerization using APS/TEMED as initiator pair and MBS as crosslinker. The hydrogel showed higher swelling capacities due to SA (sodium acrylate) units with non-fickian diffusion behaviour. Geever *et al* in 2009 synthesized temperature responsive PNIPAM/PVP random copolymers by free radical polymerization using UV light sensitive initiator and PEG-dimethacrylate as crosslinking agent. The release studies of model drug (Diclofenac Sodium and Procaine HCl) showed slower release rates above phase transition temperatures. Jin *et al* in 2008 fabricated temperature sensitive (PVP-g-PNIPAM) networks by grafting of PNIPAM from PVP synthesized with free radical polymerization using ATRP as initiator. Temperature sensitive behavior was investigated by fluorescence anisotropy and UV-Vis transmittance measurements. Rapid response to change in temperature due to free, graft chains with (PVP-g-PNIPAM) compared with P(VP-co- NIPAM) networks. Luo et al. (2009) synthesized pH and ionic strength sensitive copolymer hydrogels based on MAA and AN monomers. The swelling ratio of gels in SIF was found to be higher than those in SGF. Addition of hydrophobic AN units lead to improved mechanical strength as well as decreased release rates of theophylline in SIF and SGF. Milasinovic et al. (2010) reported pH and temperature sensitive hydrogels based on NIPAM/itoconic Acid (IA) by crosslinking polymerization for the delivery of model protein lipase. Crosslinking degree and ration of NIPAM/IA was found to affect the mechanical

strength, swelling kinetics, hydrogel structure and morphology under different temperature and pH conditions.

A number of polyionic complexes have been developed for controlled antibiotic delivery in the treatment of peptic ulcer caused by *Helicobacter pylori* (Table 4).

Table 4. Miscellaneous type hydrogel networks

Type of monomer	Method	Type of superporous hydrogel	Drug incorporated	Reference
Poly(acrylic acid)/chitosan	Solution casting	Polyionic complexes, influence of ionic strength on hydrogel medium	--	Torre et al. 2003
Poly(acrylic acid)/chitosan	Solution casting	Polyionic complexes	Amoxicillin	Torrado et al. 2004
Chitosan/CMC-Na	Simple mixing, sieving and compression	Interpolymer complexes	Clarithromycin	Gomez- Burgez et al. 2008

Torrado et al. (2004) studied gastric residence time of PAA-CS interpolymeric complexes. Gastric emptying rate was determined by ^{13}C octanoic acid breath test and gastric half emptying time of the interpolymeric complexes was significantly delayed (164 ± 26.72 min) as compared to reference formulation (65.0 ± 11.50 min). Gomez-Burgaz et al. (2008) reported CS-Sodium CMC interpolymeric complexes and evaluated for clarithromycin (CAM) release. Swelling kinetics and erosion characteristics were dependent on chitosan molecular weight and CAM release showed dependence on media pH and polymer composition. Fastest release was observed with high molecular weight CS in pH 1.2 and drug diffusion was fickian i.e. the process was governed by swelling or erosion whereas at pH 4.2, CAM release followed zero order kinetics i.e. release was controlled by CAM low solubility with no influence of molecular weight of CS.

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. 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.

References

Abdelaal, M.Y., Abdel- Razik, E.A., Abdel- Bary, E.M. and El-Sherbiny, I.M. (2007). Chitosan based interpolymeric pH-responsive hydrogels for in vitro drug release. *J. Appl. Polym. Sci.* 103: 2864-2874.

- Arshady, R. (1990). Albumin microspheres and microcapsules: methodology of manufacturing. *J. Controlled Release* 14: 111-131.
- Badiger, M.V., McNeill, M.E. and Graham, N.B. (1993). Porogens in the preparation of microporous hydrogels based on poly (ethylene oxides). *Biomaterials* 14: 1059-1063.
- Bae, Y.H., Okano, T. and Kir, S.W. (1991). On-off thermocontrol of solute transport II: Solute release from thermo sensitive hydrogels. *Pharm. Res.* 8: 624-628.
- Brazel, C.S. and Peppas, N.A. (1996). Pulsatile local delivery of thrombolytic and antithrombotic agents using poly (n-isopropylacrylamide-co—methacrylic acid) hydrogels. *J. Controlled Release* 39: 57-64.
- Chen, J., Park, H. and Park, K. (1999). Synthesis of superporous hydrogels: hydrogels with fast swelling and superabsorbent properties. *J. Biomed. Mater. Res.* 44: 53-62.
- Chen, J., Blevins, W.E., Park, H. and Park, K. (2000a). Gastric retention properties of superporous hydrogel composites. *J. Controlled Release* 64: 39-51.
- Chen, J. and Park, K. (2000b). Synthesis and characterization of superporous hydrogel composites. *J. Controlled Release* 65: 73-82.
- Doorkoosh, F.A., Brussee, J., Verhoef, J.C., Borchard, G., Rafiee-Tehrani, M. and Junginger, H.E. (2000). Preparation and NMR characterization of superporous hydrogels (SPH) and SPH composites. *Polymer* 41: 8213-8220.
- Doorkoosh, F.A., Brussee, J., Verhoef, J.C., Borchard, G., Rafiee-Tehrani, M. and Junginger, H.E. (2001). Development and characterization of a novel peroral peptide drug delivery system. *J. Controlled Release* 71: 307-318.
- Doorkoosh, F.A., Verhoef, J.C., Ambagus, M.H.C., Rafiee-Tehrani, M., Borchard, G. and Junginger, H.E. (2002a). Peroral delivery systems based on superporous hydrogel polymers: release characteristics for peptide drugs busserelin, octreotide and insulin. *Eur. J. Pharm. Sci.* 15: 433-439.
- Doorkoosh, F.A., Borchard, G., Rafiee-Tehrani, M., Verhoef, J.C. and Junginger, H.E. (2002b). Evaluation of superporous hydrogel and SPH composite in porcine intestine ex-vivo: assessment of drug transport, morphology effect and mechanical fixation to intestinal wall. *Eur. J. Pharm. Biopharm.* 53: 161-166.
- Doorkoosh, F.A., Verhoef, J.C., Borchard, G., Rafiee-Tehrani, M., Verheijden, J.H.M. and Junginger, H.E. (2002c). Intestinal absorption of human insulin in pigs using delivery systems based on superporous hydrogel polymers. *Int. J. Pharm.* 247: 47-55.
- Doorkoosh, F.A., Stokkel, M.P.M., Blok, D., Borchard, G., Rafiee-Tehrani, M., Verhoef, J.C. and Junginger, H.E. (2004). Feasibility study on the retention of superporous hydrogel composite polymer in the intestinal tract of man using scintigraphy. *J. Controlled Release* 99: 199-206.
- Dusek, K. (1993). *Responsive Gels: Volume Transitions II*, Springer. New York, p. 81-144.
- Garg, S. and Sharma, S. (2003). *Gastroretentive Drug Delivery Systems*. Business Briefing. Pharmatech. 160-166.
- Geever, L.M., Cooney, C.C., Lyons, J.G., Kennedy, J.E., Nugent, J.D.M., Devery, S. and Higginbotham, C.L. (2008). Characterization and controlled drug release from novel drug loaded hydrogels. *Eur. J. Pharm. Biopharm.* 69: 1147-1159.
- Gemeinhart, R.A., Chen, J., Park, H. and Park, K. (2000). pH sensitivity of fast responsive superporous hydrogels. *J. Biomater. Sci. Polym. Ed.* 11: 1371-1380.
- Gohel, M.C., Mehta, P.R., Dave, R.K. and Bariya, N.H. (2004). A more relevant dissolution method for evaluation of floating drug delivery system. *Dissolut. Technol.* 11: 22-25.
- Gomez-Burgaz, M., Garcia-Ochoa, B. and Torrado-Santiago, S. (2008). Chitosan-carboxymethylcellulose interpolymer complexes for gastric-specific delivery of clarithromycin. *Int. J. Pharm.* 359: 135-143.
- Gupta, P., Vermani, K., and Garg, S. (2002) Hydrogels: from controlled release to pH-responsive drug delivery. *Drug Deliv. Technol.* 7(10): 569-579.

- Hoffman, A.S. (2002). Hydrogels for biomedical applications. *Adv. Drug Del. Rev.* 43: 3-12.
- Horak, D., Hlidkova, H., Hradil, J., Lapcikova, M. and Slouf, M. (2008). Superporous poly(2-hydroxyethyl methacrylate) based scaffolds: Preparation and characterization. *Polymer* 49: 2046-2054
- Jin, S., Liu, M., Chen, S. and Gao, C. (2008). Synthesis, characterization and the rapid response property of the temperature responsive PVP-g-PNIPAM hydrogel. *Eur. Polym. J.* 44: 2162-2170.
- Khalid, M.N., Agnely, F., Yagoubi, N., Grossiord, J.L. and Couarraze, G. (2002). Water state characterization, swelling behaviour, thermal and mechanical properties of chitosan based networks. *Eur. J. Pharm. Sci.* 15: 425-432.
- Kim, S.J., Park, S.J. and Kim, S.I. (2003). Swelling behavior of interpenetrating polymer network hydrogels composed of poly (vinyl alcohol) and chitosan. *React. Funct. Polym.* 55: 53-59.
- Kim, D. and Park, K. (2004). Swelling and mechanical properties of superporous hydrogels of poly (acrylamide-co-acrylic acid)/ polyethylenimine interpenetrating polymer networks. *Polymer* 45: 189-196.
- Klausner, E.A., Lavy, E., Friedman, M. and Hoffman, A. (2003). Expandable gastroretentive dosage forms: A Review. *J. Controlled Release* 90: 143-162.
- Klumb, L.A. and Horbett, T.A. (1992). Design of insulin delivery devices based on glucose sensitive membranes. *J. Controlled Release* 18: 59-80.
- Li, X., Xu, S., Wang, J., Chen, X. and Feng, S. (2009). Structure and characterization of amphoteric semi-IPN hydrogel based on cationic starch. *Carbohydr. Polym.* 75: 688-693.
- Lind, E.J. (1992). Enhancing absorption rates of superabsorbents by incorporating a blowing agent. U.S. Patent No 5,118,719.
- Liu, K., Ovaert, T.C. and Mason, J.J. (2008). Preparation and mechanical characterization of a PNIPAM hydrogel composite. *J. Mater. Sci.: Mater. Med.* 19:1815-1821.
- Luo, Y., Zhang, K., Wei, O., Liu, Z. and Chen, Y. (2009). Poly (MAA-co-AN) hydrogels with improved mechanical properties for theophylline controlled delivery. *Acta Biomater.* 5: 316-32.
- Mathiowitz, E. (1999). Encyclopedia of Controlled Drug Delivery, John Wiley & Sons. New York, pp. 445-459, 397-418.
- Merlin, D.L. and Sivasankar, B. (2009). Synthesis and characterization of semi-interpenetrating polymer networks using biocompatible polyurethane and acrylamide monomer. *Eur. Polym. J.* 45: 165-170
- Milasinovic, N., Krusic, M.K., Knezevic-Jugovic, Z. and Filipovic, J. (2010). Hydrogels of N-isopropylacrylamide copolymers with controlled release of model protein. *Int. J. Pharm.* 383: 53-61.
- Mishra, S., Bajpai, R., Katare, R. and Bajpai, A.K. (2008). On the mechanical strength of biocompatible semi-IPNs of polyvinyl alcohol and polyacrylamide. *Microsyst. Technol.* 14:193-198.
- Mohan, Y.M., Premkumar, T., Joseph, D.K. and Geckeler, K.E. (2007). Stimuli-responsive poly (N-isopropylacrylamide-co-sodium acrylate) hydrogels: A swelling study in surfactant and polymer solutions. *React. Funct. Polym.* 67: 844-858.
- Moura, M.R., Guilherme, M.R., Campese, G.M., Radovanovic, E., Rubira, A.F. and Muniz, E.C. (2005). Porous alginate-Ca²⁺ hydrogels interpenetrated with PNIPAAm networks: Interrelationship between compressive stress and pore morphology. *Eur. Polym. J.* 41(12): 2845-2852.
- Omidian, H., Park, K. and Rocca, J.G. (2007). Recent Developments in superporous hydrogels. *J. Pharm. Pharmacol.* 59: 317-327.
- Omidian, H., Rocca, J.G. and Park, K. (2005). Advances in superporous hydrogels: A Review. *J. Controlled Release* 102: 3-12.
- Omidian, H., Park, K. and Rocca, J.G. (2006). Elastic superporous hydrogel hybrids of polyacrylamide and sodium alginate. *Macromol. Biosci.* 6: 703-710.

- Park, H., Song, I., Kim, J. and Kim, W. (1998). Preparation of thermally denatured albumin gel and its pH-sensitive swelling. *Int. J. Pharm.* 175: 231-236.
- Park, K. (2002). Superporous hydrogels for pharmaceutical and other applications. *Drug Deliv. Technol.* 2: 38-44.
- Park, H., Park, K. and Kim, D. (2005). Preparation and swelling behavior of chitosan based superporous hydrogels for gastric retention application. *J. Biomed. Mater. Res.* 76: 144-150.
- Park, H. and Kim, D. (2006). Swelling and mechanical properties of glycol chitosan / poly (vinyl alcohol) IPN-type superporous hydrogels. *J. Biomed. Mater. Res.* 78: 662-667.
- Patel, V.J., Amiji, M.M. (1996). Preparation and characterization of freeze dried chitosan – poly(ethyleneoxide) hydrogels for site-specific antibiotic delivery in stomach. *Pharm. Res.* 13: 588-593.
- Polnok, A., Verhoef, J.C., Borchard, G., Sarisuta, N. and Junginger, H.E. (2004). In vitro evaluation of intestinal absorption of desmopressin using drug delivery systems based upon superporous hydrogels. *Int. J. Pharm.* 269: 303-310.
- Qiu, Y. and Park, K. (2003). Superporous IPN Hydrogels having enhanced mechanical properties. *AAPS Pharm. Sci. Tech.* 4: 406-412.
- Risbud, M.V., Hardikar, A.A., Bhat, S.V. and Bhonde, R.R. (2000). pH sensitive freeze-dried chitosan-polyvinylpyrrolidone hydrogels as controlled release system for controlled release for antibiotic delivery. *J. Controlled Release* 68: 23-30.
- Rocca, J.G., Omidian, H. and Shah, K.U. (2007). Commercial status of Gastric Retention Technologies. *Drug Deliv. Technol.* 5: 50-57.
- Rodrigues, I.R., de Camargo Forte, M.M., Azambuja, D.S. and Castagno, K.R.L. (2007). Synthesis and characterization of hybrid polymeric networks (HPN) based on polyvinyl alcohol/chitosan. *React. Funct. Polym.* 67: 708-715.
- Shalaby, W.S.W., Blevins, W.E. and Park, K. (1992). In vitro-in vivo studies of enzyme digestible hydrogels for oral drug delivery. *J. Controlled Release* 19: 131-144.
- Shantha, K.L. and Harding, D.R. (2000). Preparation and in vitro evaluation of poly (N-vinyl-2-pyrrolidone-polyethylene glycol diacrylate)-chitosan interpolymeric pH-responsive hydrogels for oral drug delivery. *Int. J. Pharm.* 207: 65-70.
- Silva, R.D. and Oliveira, M.G. (2007). Effect of the cross-linking degree on the morphology of poly (NIPAAm-co-AAc) hydrogels. *Polymer* 48: 4114-4122.
- Soppimath, K.S., Kulkarni, A.R. and Aminabhavi, T.M. (2001). Chemically modified polyacrylamide-g-guar gum based crosslinked microgels as pH sensitive drug delivery systems: preparation and characterization. *J. Controlled Release* 75: 331-345.
- Spiller, K.L., Laurencin, S.J., Charlton, D., Maher, S.A. and Lowman, A.M. (2008). Superporous hydrogels for cartilage repair: Evaluation of the morphological and mechanical properties. *Acta Biomater.* 4: 17-25.
- Tanaka, T. and Fillmore, D.J. (1979). Kinetics of swelling of gels. *J. Chem. Phys.* 70: 1214-1218.
- Tang, C., Yin, C., Pei, Y., Zhang, M. and Wu, L. (2005). New superporous hydrogels composites based on aqueous Carbopol® solution (SPHCs): synthesis, characterization and in vitro bioadhesive force studies. *Eur. Polym. J.* 41: 557-562.
- Tang, O., Wu, J. and Lin, J. (2008). A multifunctional hydrogel with high conductivity, pH-responsive, thermo-responsive and release properties from polyacrylate/polyaniline hybrid. *Carbohydr. Polym.* 73: 315-321
- Tang, O., Wu, J., Sun, H., Lin, J., Fan, S. and Hu, D. (2008). Polyaniline/polyacrylamide conducting composite hydrogel with a porous structure. *Carbohydr. Polym.* 74: 215-219.

- Torrado, S., Prada, P., Torre, P.M., Torrado S (2004). Chitosan –Polyacrylic acid polyionic complex: invivo study to demonstrate prolonged gastric retention. *Biomaterials* 25: 917-923.
- Torre, P.M. and Torrado, S. and Torrado Santiago (2003). Interpolymeric complexes of poly (acrylic acid) and chitosan: influence of the ionic hydrogel forming medium. *Biomaterials* 24: 1459-1468.
- Umamaheswari, R.B., Jain, P. and Jain, N.K. (2002). Hydrogel – A novel drug delivery system. *Indian Drugs* 39(5): 243-256.
- Wang, M., Fang, Y. and Hu, D. (2001). Preparation and properties of chitosan-poly (N-isopropylacrylamide) full-IPN hydrogels. *React. Funct. Polym.* 48: 215-221.
- Welz, M.M. and Ofner, C.M. (1992). Examination of self crosslinked gelatin as a hydrogel for controlled release. *J.Pharm.Sci.* 81: 85-90.
- Wise, D.L. (2000). Handbook of Pharmaceutical Controlled Release Technology, Marcel Dekker. New York, pp. 211-224.
- Yan, Q. and Hoffman, A.S. (1995). Synthesis of macroporous hydrogels with rapid swelling and deswelling properties for delivery of macromolecules. *Polym. Comm.* 36: 887-889.
- Yin, L., Fei, L., Cui, F., Tang, C. and Yin, C. (2007). Superporous hydrogels containing poly(acrylic acid-co-acrylamide)/O-carboxymethylchitosan interpenetrating polymer networks. *Biomaterials* 28 (6):1258-1266.
- Yin, L., Ding, J.Y., Fei, L., Heb, M., Cui, F., Tang, C. and Yin, C. (2008). Beneficial properties for insulin absorption using superporous hydrogel containing interpenetrating polymer network as oral delivery vehicles. *Int. J. Pharm.* 350: 220–229.
- Yin, L., Ding, J., Zhang, J., He, C., Tang, C. and Yin, C. (2010). Polymer integrity related absorption mechanism of superporous hydrogel containing interpenetrating polymer networks for oral delivery of insulin. *Biomaterials* 1-10. (Article in press)
- Yue, Y., Sheng, X. and Wang, P. (2009). Fabrication and characterization of microstructured and pH sensitive interpenetrating networks hydrogel films and application in drug delivery field. *Eur. Polym. J.* 45: 309–315.
- Zhang, K. and Wu, X.Y.X.Y. (2004). Temperature and pH-responsive polymeric composite membranes for controlled delivery of proteins and peptides. *Biomaterials* 25: 5281-5291.
- Zhao, S., Ma, D. and Zhang, L. (2006). New semi-interpenetrating network hydrogels: synthesis, characterization and properties. *Macromol. Biosci.* 6: 445-451.

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