Gastric retention properties of superporous hydrogel composites

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Abstract

In many applications, usefulness of conventional hydrogels is limited by their slow swelling. To improve the swelling property of the conventional hydrogels, we have synthesized superporous hydrogels (SPHs) which swell fast to equilibrium size in minutes due to water uptake by capillary wetting through numerous interconnected open pores. The swelling ratio was also large in the range of hundreds. The mechanical strength of the highly swollen SPHs was increased by adding a composite material during the synthesis. The composite material used in the synthesis of SPH composites was Ac-Di-Sol® (croscarmellose sodium). The gastric retention property of the prepared SPH composites was tested in dogs both in fasted and fed conditions. The SPH composites were placed in a hard gelatin capsule (size 000) for oral administration. All dogs tested were fasted for 36 h before experiments. Under the fasted condition, the SPH composite remained in the stomach for 2–3 h after before breaking into two pieces and being emptied. When food was given before the experiment just once following 36 h of fasting, the SPH composite remained in the stomach for more than 24 h, even though the fed condition was maintained only for the first few hours. Our study indicated that SPH composites possessed three properties necessary for gastric retention: fast swelling; superswelling; and high mechanical strength. While more improvements need to be made, the SPH composites provide the basis for the development of effective long-term gastric retention devices. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Superporous hydrogels; Hydrogel composites; Ac-Di-Sol®; Gastric retention; Fast swelling hydrogels; Superabsorbent

1. Introduction

Recent advances in controlled release technology have made it possible to release drugs at a constant rate for long periods of time ranging from days to years. The benefits of long-term delivery technology have not been fully realized for the dosage forms designed for oral administration. This is mainly due to the relatively very short gastrointestinal (GI) transit time of oral dosage forms, which is 6–8 h in human [1,2]. The average transit time from mouth to colon determined the maximum acceptable time for drug absorption regardless of the duration of the drug release from the device.

We have been developing gastric retention devices based on hydrogels. In our previous work, polyvinylpyrrolidone (PVP) hydrogels were used to show that fully swollen PVP hydrogels could remain in the canine stomach for more than a day [3–5]. We found from the work that hydrogels had to possess a few

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important properties to be used as an effective gastric retention device. They are fast swelling (i.e. swelling to equilibrium size in 20 min or less), swelling to a large size (with swelling ratio of a few hundreds), and high mechanical strength (enough to overcome pressures by gastric contractions). Recently, we have developed superporous hydrogel (SPH) composites which meet all three requirements [6]. Superporous hydrogels are hydrogels with numerous pores connected together to form open channel structures. Water is absorbed into the dried SPHs by capillary wetting rather than by diffusion. This makes swelling of dried hydrogels extremely fast (swelling in minutes) with the swelling ratio easily reaching 100 or more. To increase the mechanical strength of the fully swollen SPHs, SPH composites were synthesized by adding Ac-Di-Sol® (croscarmellose sodium) during the synthesis of SPHs. SPH composites swell to their equilibrium size in less than a few minutes regardless of the size of the dried form. We examined gastric retention property of the SPH composites in dogs.

Since the hydrogel-based gastric retention device remains in the stomach by overcoming gastric motility, it would be beneficial to briefly review the gastric emptying and various approaches used to develop gastric retentive devices.

2. Gastric emptying

One of the main functions of the stomach is to digest food and deliver chyme to the intestine for absorption. Gastric emptying occurs as a result of cyclic gastric motor activities or contractions. Gastric emptying of oral dosage forms also occurs as a result of such gastric motor activities. Thus, gastric retention devices have to be designed to overcome the gastric motility.

2.1. Gastric motility

Since the nature of the gastric contraction depends on the nature of the contents in the stomach, gastric emptying of meals is conveniently classified into gastric emptying of liquid, digestible solids, and indigestible solids [7]. The volume of liquid emptied

per unit time is directly proportional to the volume remaining in the stomach, i.e. first-order. It is generally thought that solid particles larger than 1–2 mm are retained in the stomach until they are further reduced in size [8,9], although other reports suggest otherwise [10,11]. Although there is no consensus in the minimum size of particles for gastric retention, it is generally agreed that the indigestible particles tend to stay in the stomach. The peristaltic wave resulting from contractions in the lower body of the stomach (i.e. the distal stomach) is responsible for mixing and grinding of solid food to the form required for emptying [7]. As the peristaltic wave approaches the distal antrum, the pyloric sphincter is closed and thus, large solid particles are retained in the stomach. The valve-like pyloric sphincter opens to allow only small quantities of food to pass into the duodenum.

Gastric emptying of indigestible solids (including oral dosage forms) occurs in the fasted state by a distinct cycle of electromechanical activity known as the interdigestive migrating myoelectric complex (IMMC). The size of indigestible solids emptied in the fasted state is known to vary from 1–2 [12] to 10 mm [13] with considerable intersubject differences. The IMMC is composed of four different motor activities (Phases 1–4) as shown in Fig. 1. Phase 1 (basal state) is a period without any motor activity, except for occasional contractions. In Phase 2 (pre-burst state), the intermittent peristaltic contractions occur with increased frequency and amplitude. This is followed by a burst of giant peristaltic contractions which occur three times per minute (Phase 3 or burst state). It is this Phase 3 contraction that empties indigestible solids from the stomach. Phase 3 contractions are also called 'housekeeper' waves due to its sweeping property. As a Phase 3 interdigestive contraction approaches, the pylorus remains open unlike in the fed state. The transition period from Phase 3 to Phase 1 is known as Phase 4. The IMMC begins in the proximal stomach and migrates aborally through the small bowel [7], and when a Phase 3 arrives at the colon, another Phase 3 begins in the stomach [8]. Since Phase 3 is repeated every 80 min to 2 h, gastric retention devices based on swelling properties, such as hydrogel systems, need to achieve fully swollen state before the next housekeeper wave. Practically, this means that the system has to achieve full swelling in 20 min or less.
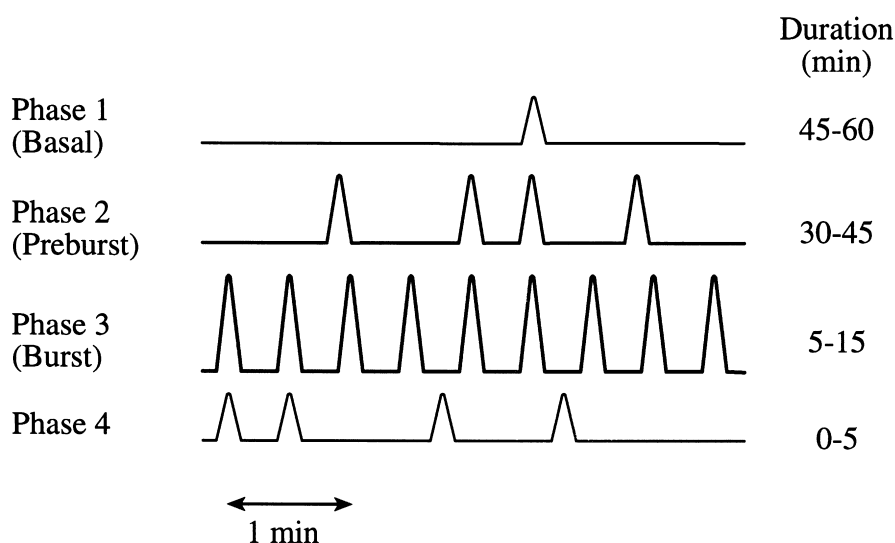
Fig. 1. The four phases and their durations of interdigestive migrating myoelectric complex (IMMC) (from Ref. [7]).

2.2. Proposed gastric retentive devices

Despite numerous attempts of developing gastric retentive devices, few have been successful as a platform for oral controlled release dosage forms. Table 1 lists various approaches used to develop gastric retention devices. The concepts and improvements to be made for each method described in Table 1 were described in detail elsewhere [14]. While each approach in Table 1 has its unique mechanism for achieving gastric retention, a number of hurdles have to be overcome for any approach to be clinically useful. For example, intragastric floating systems require the presence of gastric juice to be effective, and this may not be the case in the fasted state. Most of the high density systems tested to date do not have really high density to be useful. Mucoadhesive systems can easily lose their mucoadhesive properties by interaction with any materials soluble in gastric juice. Magnetic systems require a powerful magnet and exact positioning of the extracorporeal magnet to the right place. Unfoldable, extendible, or swellable systems do not increase their size large enough to remain in the stomach. The SPH composite systems for achieving long-term gastric retention are the focus of this paper.

2.3. Concept of SPH systems

As pointed out above in Section 2.1, any gastric retention system based on swelling has to achieve its full swelling in 20 min or less. Fast swelling is critically important to avoid premature emptying by the housekeeper waves. Superporous hydrogel composites are a new type of hydrogels which have numerous supersize pores inside and contain a composite material, Ac-Di-Sol® in this particular case [6]. The most unique aspect of the SPH is that the average pore size is larger than 100 µm, usually in the range of a few hundred micrometers. Even after drying, the pores of the SPHs remain all connected to each other to form capillary channels. Because of this, dried SPHs can swell extremely fast upon contact with water. It is this fast swelling property that is important in the application as a gastric retention device.

Fig. 2 shows the concept of the gastric retention of a SPH composite system. The SPH composite can

Table 1
Devices used as platforms for gastric retention

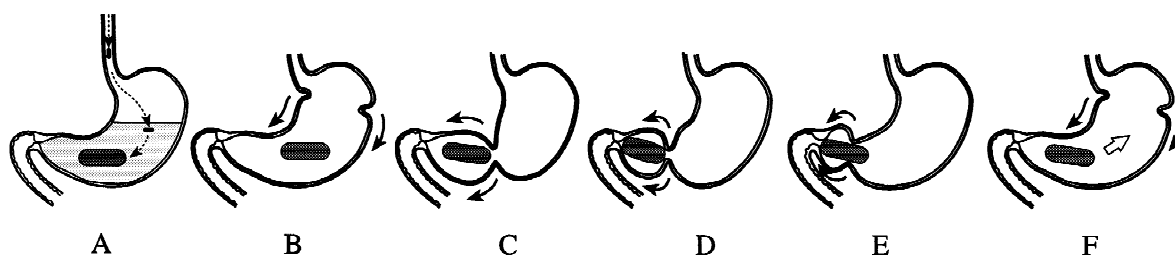| |
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| 1. Intragastric floating systems (low density systems) [15–20] |
| 2. High density systems [21–25] |
| 3. Mucoadhesive systems [26–30] |
| 4. Magnetic systems [31–34] |
| 5. Unfoldable, extendible, or swellable systems [35–39] |
| 6. Superporous hydrogel composite systems [6,40,41] |

Fig. 2. The proposed sequence showing the swelling of a dried superporous hydrogel and subsequent gastric retention overcoming pressures by gastric contractions.

swell to a few hundred times the original volume in a matter of minutes (Fig. 2A). Our previous studies using ultrasound and fluoroscopic imaging [4,5] have shown that the gastric contraction which initially pushs the hydrogel to the pylorus (Fig. 2B–D) slips over the surface of a hydrogel (Fig. 2E) to push the hydrogel back into the body of the stomach (Fig. 2F). This process repeats until the SPHs reduce in size by, for example, breaking into smaller pieces. The maximum gastric pressure in the fasted and fed states is known to range from 100 to 130 cmH_2O in humans [42,43]. Thus, any SPH dosage form should have the mechanical strength to withstand such a pressure. To maintain high mechanical strength even after fast swelling to a large size, we have developed SPH composites [6,44].

3. Materials and methods

3.1. Materials

Acrylic acid (AA), acrylamide (AM), potassium salt of 3-sulfopropyl acrylate (SPAK), N,N'-methyl-enebisacrylamide (Bis), ammonium persulfate (APS) were purchased from Aldrich (Milwaukee, WI). N,N,N',N'-tetramethylethylenediamine (TEMED) was obtained from Bio-Rad Laboratories (Hercules, CA). $NaHCO_3$ was from Mallinckrodt Specialty Chemical (St. Louis, MO). Pluronic® F127 (PF127) was a gift from BASF (Parsippany, NJ). $BaSO_4$ suspension (E-Z-PAQUE $BaSO_4$ suspension) was from E-Z-EM, (Westbury, NY). Ac-Di-Sol® (cros-carmellose sodium) was obtained from FMC (Phila-delphia, PA).

3.2. Synthesis

Poly(acrylamide-co-3-sulfopropyl acrylate) (P(AM-co-SPAK)) SPH composites were prepared in glass test tubes (1.9 cm diameter×17.5 cm height). The following components were added sequentially to a test tube: 1.2 ml of 50% AM; 0.9 ml of 50% SPAK; 0.45 ml of 2.5% Bis; 90 μl of 10% PF127; 30 μl of 50% (v/v) AA; and 45 μl of 20% APS. The test tube was shaken to mix the solution after each ingredient was added. Then 270 mg of Ac-Di-Sol® powder were added to the mixture and stirred using a spatula to mix evenly. Then 45 μl of 20% TEMED was added to the mixture and the test tube was shaken again for mixing. Finally, 100 mg of $NaHCO_3$ powder were added and the mixture was immediately stirred vigorously using a spatula for 10 s. Foaming started immediately after the addition of $NaHCO_3$ powder, and the gelling occurred within 30 s to 1 min after the addition of $NaHCO_3$ powder. Polymerization was allowed to continue for 10 min. The formed SPH composite was retrieved from the test tube and washed in 400 ml of simulated gastric fluid (SGF, pH 1.2) for 24 h. This step was called acidification of the SPH composite. The composite was then dried at room temperature for 5 days. Unless specified, all SPH composites used in this study were prepared using this procedure.

3.3. Encapsulation

Completely dried SPH composites became hard and were 1.5 cm in diameter and 2.3 cm in length on the average. This size was too big to be placed in a 000 size capsule (0.9 cm in diameter and 2.4 cm in
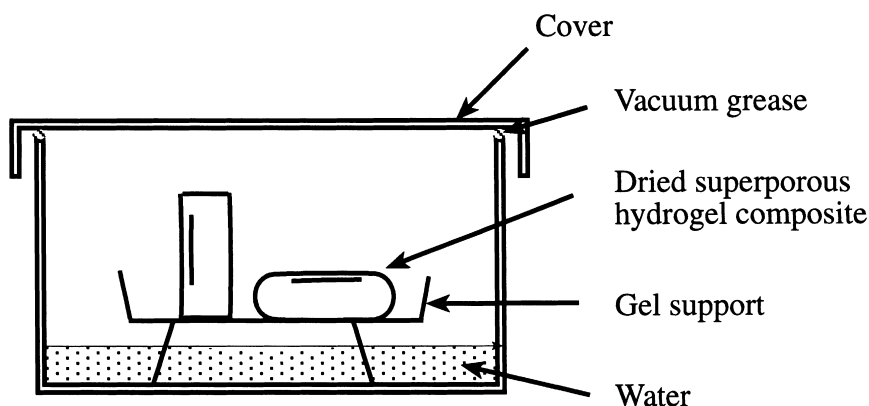
Fig. 3. Moisture chamber used for making soft superporous hydrogel composites after drying.

length). The dried SPH composites were placed in a moisture chamber shown in Fig. 3. The composites were placed on a support in a container and a small amount of water was present at the bottom of the container. The moisture chamber was then placed in a 70°C oven for 30 min. The moistened SPH composites became soft and were squeezed to smaller sizes and easily inserted into the size 000 hard gelatin capsules.

3.4. Mechanical testing of the SPH composites

The mechanical properties of the SPH composites were tested using a bench comparator. After being fully swollen in SGF, a SPH composite was placed under the lower touch of the bench comparator that was connected to a micrometer gauge. Weights were applied to the upper touch of the bench comparator. The height of the swollen SPH composite under a pressure equivalent to 100 cmH$_2$O pressure was recorded from the gauge as an indication of the swelling size under gastric contraction. The pressure applied to the SPH composite was calculated from the amount of weights and the contact area of the lower touch. The ultimate compression pressure (UCP) of a SPH composite was also determined by applying increasing amounts of weights until a point when the SPH composite started cracking [45]. The pressure at that point was defined as UCP, which was used to represent the mechanical strength of a SPH composite.

3.5. Morphological examination

The morphology of porous structures was examined with a scanning electron microscope (SEM). Superporous hydrogel composites were cut to expose their inner structure, coated with a thin layer of palladium gold alloy in Hummer I Sputter Coater Technics, Alexandria, VA), and imaged in an SEM (JSM-840, JEOL USA, Peabody, MA).

3.6. Radiopaque marker and image analysis

To monitor the gastric retention and emptying of a SPH composite, small hydrogel pellets containing BaSO$_4$ were used as the X-ray markers. The BaSO$_4$-containing hydrogel pellets were prepared in a small plastic tube (inner diameter, 3.35 mm). The following components were sequentially mixed in a glass vial: 1.3 ml of 50% AM; 0.8 ml of 2.5% Bis; 0.15 ml of 20% APS; 1.3 ml of 40% BaSO$_4$ suspension; and 80 μl of 20% TEMED. The vial was shaken to mix the ingredients after each component was added. The mixture was then injected into the plastic tube. The gelling of the mixture started within 5 min after the addition of TEMED. After curing at room temperature for 1 h, the cylindrical gel was retrieved from the plastic tube, cut into small segments, and dried in a 60°C oven for 5 h. The dried gel pellets had a diameter of 2 mm and a height of 2 mm. These pellets were used as markers in X-ray imaging.

To incorporate the X-ray image markers into a

SPH composite, small hydrogel pellets were placed in the monomer solution at the step just before the addition of APS during the synthesis of SPH composites. After addition of NaHCO$_3$, the mixture was mechanically stirred for 5–10 s to evenly distribute the pellets.

3.7. In vivo study in canine model

Dogs used in our study were about 50 lb. The fasted condition was achieved by withholding food from a dog for 36 h before experiments. The dog, however, had free access to water. The fed condition was achieved by giving a dog 450 g of canned food right before the oral administration of the dosage form. In each experiment (fasted or fed state), the dog was given 300 ml water via a stomach tube before the administration of the gelatin capsule containing a SPH composite. The capsule was swallowed by the dog with no water. X-ray pictures were taken at different time intervals after the administration of the capsule.

4. Results

4.1. Synthesis and encapsulation

We chose to synthesize SPH composites using P(AM-co-SPAK) and Ac-Di-Sol®. The presence of AM increased the overall strength of the SPH composite. SPAK, which is a strong electrolyte, made the SPH composite to swell larger than those made of other monomers. In the synthesis of P(AM-co-SPAK) SPH composites, gas bubbles were generated by AA and NaHCO$_3$ and the formed gas

bubbles were stabilized with PF127 (a foam stabilizer). Addition of NaHCO$_3$ to the monomer solution (containing AA, an acid) triggered gas bubbling and increased the polymerization kinetics due to the rise in pH. The use of PF127 allowed maintenance of stable gas bubbles during crosslinking polymerization. This resulted in pores which were interconnected throughout the polymer matrix. Ac-Di-Sol® in SPHs improved two properties: faster swelling of the dried SPH composites and increased mechanical strength of the fully swollen SPH composites. The dried SPH composites could be moistened in a controlled way so that they could be squeezed into smaller sizes. Moisture absorbed into the dried SPH composites acted as a plasticizer and the moisture could be removed by drying again after SPH composites were placed inside the gelatin capsules.

4.2. Swelling kinetics

The presence of Ac-Di-Sol® as a composite material was essential for fast swelling of the squeezed SPH composites. Table 2 compares the physical characteristics of SPH composites at different stages of preparation. A SPH composite fully swollen in SGF was 2.4 cm in diameter×3.4 cm in length with a weight of 13.6 g. After air drying, the size became smaller to 1.5 cm in diameter×2.3 cm in length with a weight of only 1.35 g. After being moistened and squeezed into a 000 gelatin capsule, this size of the SPH composite was further reduced to 0.9 cm in diameter and 2.4 cm in length. The density was increased from 0.33 to 0.88 g/cm^3. The dried SPH composite swelled to its equilibrium size in a minute. The swelling of a conventional hydrogel with the same size would take at least several hours.

Table 2
Physical characteristics of SPH composites under swollen, dried and squeezed states

Physical state	Diameter (cm)	Length (cm)	Weight (g)	Density (g/cm^3)	Swelling time in SGF at 37°C
Fully swollen in SGF[a]	2.4	3.4	13.6		
Completely dried	1.5	2.3	1.35	0.33	1 min
Squeezed into a 000 size hard gelatin capsule	0.9	2.4	1.35	0.88	6 min

[a] SGF, simulated gastric fluid.

To measure the swelling time of a SPH composite in a gelatin capsule, the SPH composite was removed from the capsule and placed in SGF. It took 6 min to swell to an equilibrium size. It was 5 min longer than the swelling time by the dried hydrogel composites without squeezing. To find out why the swelling time was increased by the squeezing process, the morphology of SPH composites was examined by SEM. As shown in Fig. 4, the porous structures were changed by the squeezing process. Fig. 4A shows a highly porous structure of the dried SPH composite. The pore size was in the range of several hundred micrometers. The presence of these pores made the swelling so fast. Fig. 4B shows the structure of a squeezed SPH composite. Many of the capillary channels were partially closed by the squeezing process, and this may be the reason for the slower swelling than the control dried SPH composite.

4.3. Mechanical strength

One of the most important requirements for gastric retention of a SPH composite is its structural integrity or mechanical strength. In our study, the mechanical strength was tested by measuring the swelling height under 100 cmH_2O pressure. We chose the 100 cmH_2O pressure, since the pressure during the gastric contraction was reported to range from 50 to 130 cmH_2O pressure [7,42,43,46]. We also measured UCP to find out when the SPH composites started to form a crack, since it was possible to have much higher pressure in the stomach than the reported values in the stomach. The mechanical strength of SPH composites was larger than that of SPHs. Making composites by adding Ac-Di-Sol® increased the mechanical strength. To examine the effect of Ac-Di-Sol® on increase in mechanical strength of the SPH composites, the amount of Ac-Di-Sol® was varied up to 300 mg. As shown in Fig. 5, incorporation of Ac-Di-Sol® slightly decreased the swelling height of the SPH composites under 100 cmH_2O pressure from 1.79 to 1.24 cm. However, the UCP value was increased considerably by the addition of Ac-Di-Sol® from 142 to 212 cmH_2O. The presence of Ac-Di-Sol® increased the overall cross-linking density of the SPH composite by physical entanglement of the polymer chains with Ac-Di-Sol® fibers. When Ac-Di-Sol® fibers were added to the monomer

solution, they swelled and absorbed the monomer solution. This resulted in physical entanglements of polymer chains through the Ac-Di-Sol® fibers. This structure is expected to share the mechanical load between Ac-Di-Sol® fiber and the polymer structure. The mechanical strength could be further improved by the acidification of the SPAK residues. The acidification process partially protonized the anionic SO_3^- group to SO_3H group. The decrease in overall negative charges is expected to increase interactions between polymer chains and thus increase in mechanical strength. The UCP value of the acidified SPH composite increased by 60% (e.g. from 189 to more than 300 cmH_2O pressure. While the acidification resulted in increase in mechanical strength, it also reduced the size of the swollen SPH composites. The fully swollen size was reduced from 3.0 cm in diameter×4.7 cm in length to 2.4 cm in diameter× 3.7 cm in length.

4.4. In vivo study

The gastric retention property of the encapsulated SPH composites was examined in dogs. In the first set of animal experiments, SPH composites were prepared without the acidification step. A total of six $BaSO_4$ hydrogel pellet markers were incorporated in each SPH composite. In SGF, the SPH composites swelled to equilibrium size of 3.3 cm in diameter×4 cm in length. The UCP of these SPH composites was 170 cmH_2O pressure. After this SPH composite was administered to a fasted dog, X-ray pictures were taken at every 30 min. All six X-ray markers were shown in the stomach at 2.0 h. The SPH composite was remained intact since all six markers in the X-ray picture maintained their relative positions. At 2.5 h, all six markers were still in the stomach, but one was apart from the others, indicating the beginning of fragmentation of the SPH composite. At 3 h, the SPH composite broke into two pieces and partial emptying was observed. Two markers were in the small bowel, while the other four still remained in the stomach. At 4 h, all six pellets were found in the small bowel indicating total emptying of the SPH composite. This particular set of experiments suggested that the size of the SPH composite was large enough to be retained in the stomach during the first 2 h. The SPH composite, however, did not appear to
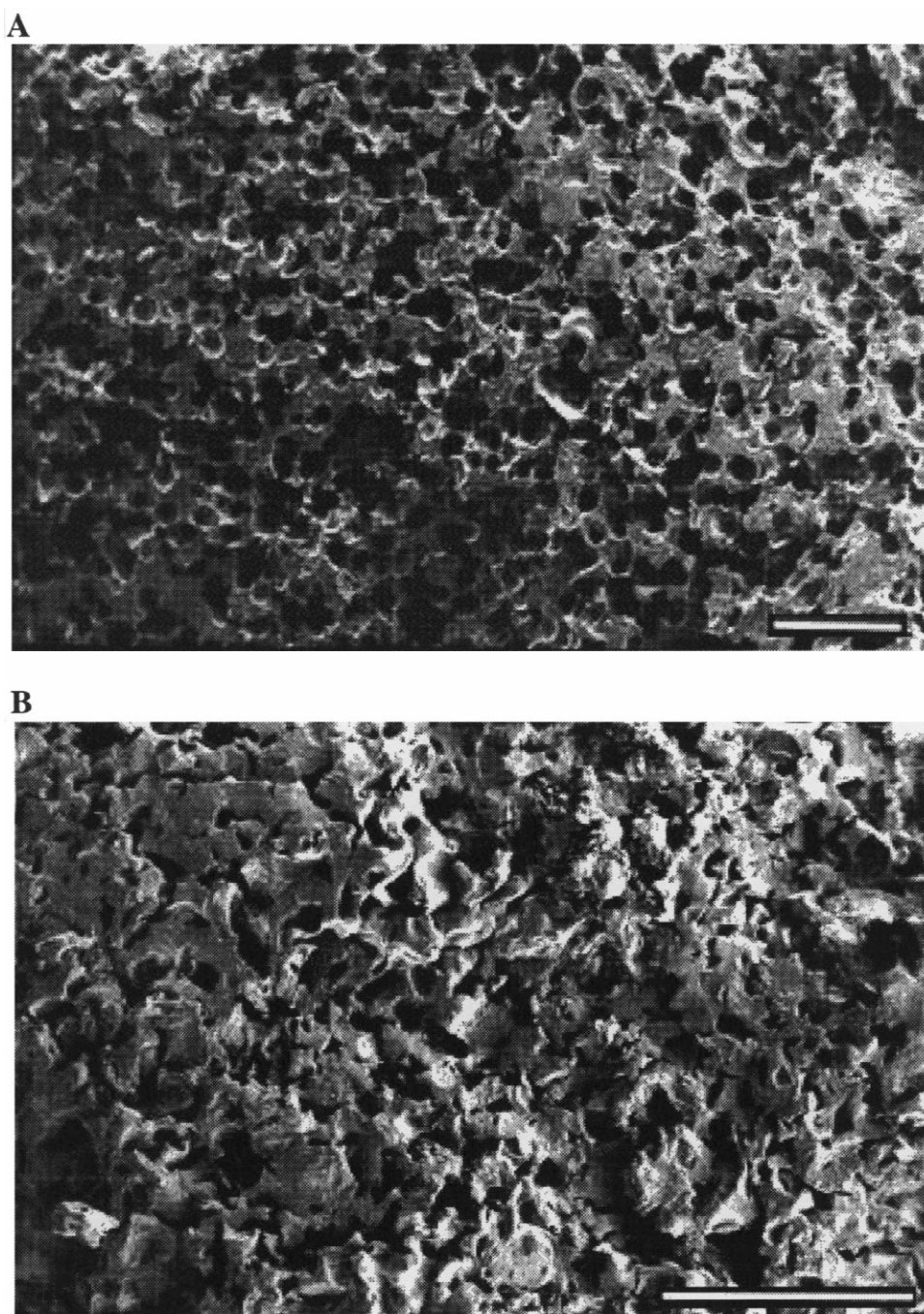
Fig. 4. SEM pictures of superporous hydrogel composites after air-drying of the fully swollen hydrogels (A) and after placed into a size 000 hard gelatin capsule by squeezing (B). The scale bare indicates 1 mm length (magnifications were 15 and 30 for A and B, respectively).
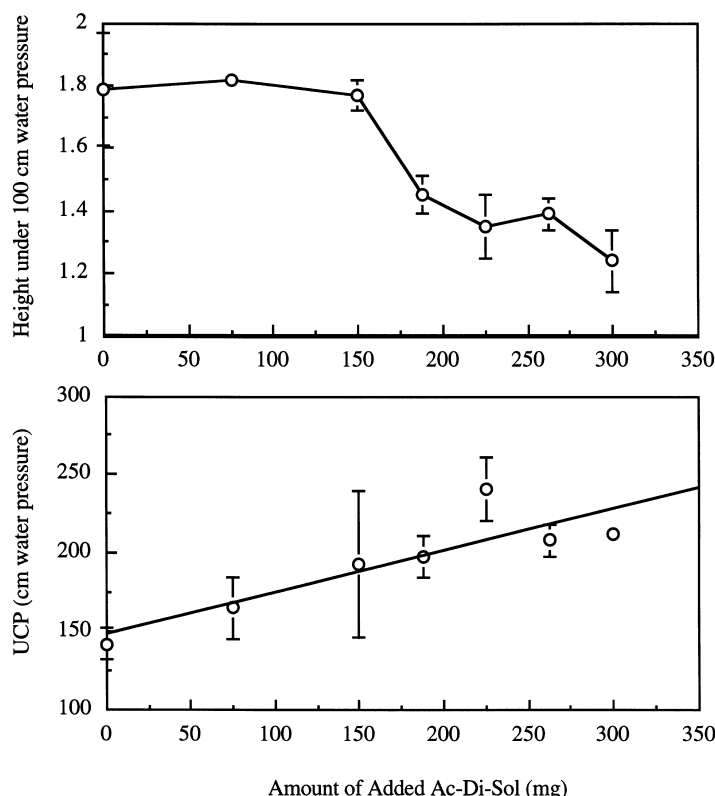
Fig. 5. The effect of Ac-Di-Sol® on the swollen height (in cm) under 100 cm water pressure (A) and UCP (B) of the poly(AM-co-SPAK) superporous hydrogel composites.

be strong enough to withstand the repetitive gastric contraction and fragmentation resulted in emptying. Even though the UCP of the tested SPH composite was 170 cmH_2O pressure, significantly higher than the maximum gastric pressure reported in the literature (50–130 cmH_2O pressure) [7,42,43,46], the SPH composite still broke apart. It was possible that the local pressure and the abrasion and shear forces exerted to the SPH composite were much stronger than the value reported in the literature. Gel composites with even stronger mechanical strength may be necessary to remain intact by overcoming the repetitive gastric contraction.

In the next two sets of experiments, the SPH composites were acidified to further increase the mechanical strength. The gastric retention of acidified SPH composites was examined in the fasted as well as in the fed state. When placed in SGF, a SPH composite swelled to 2.1 cm in diameter×3.9

cm in length after 6 min, and the UCP of these SPH composites was 370 cmH_2O pressure. When these SPH composites administered to fasted dogs, the gastric retention was between 2 and 3 h. Up to 2 h, all the X-ray markers were located in the stomach and maintained their relative positions, indicating that the SPH composite remained intact. At 3 h, however, the SPH composite was found intact in the colon. This particular study demonstrated that the mechanical strength of this SPH composite was high enough to withstand the gastric contraction, but its size might not have been ideal. Another set of SPH composites were administered to dogs in the fed state. The dog was in the fasted condition for 36 h before food was given at the onset of the experiment. According to X-ray analysis, the fed state was sustained for the first few hours, and the fasted condition was maintained until the end of this experiment. In SGF, the acidified SPH composites

swelled to equilibrium size of 2.4 cm in diameter× 3.5 cm in length in 6 min, and the UCP was 370 cmH_2O pressure. These SPH composites were administered to dogs in the fed state. Fig. 6 shows a series of X-ray images showing the gastric retention of a poly(AM-co-SPAK) SPH composite. Fig. 6A shows the stomach area right before the oral administration of a SPH composite in a gelatin capsule. No marker was seen in the stomach. Three hours after administration, three markers maintained their relative position, indicating that the dosage form remained intact. The picture taken 8 h after administration showed that the SPH composite still remained

intact (Fig. 6B). Three X-ray markers (labeled as 1, 2 and 3 in Fig. 6B) still maintained their relative positions. The stomach was empty by this time. Fig. 6C shows a picture taken 27 h after administration. The dosage form still remained intact in the stomach as shown by the presence of the three markers in the same place. The image taken at time 32 h, however, showed that one marker was emptied into the small bowel while the other two remained in the stomach (Fig. 6D). This means that the fragmentation occurred between 27 and 32 h. Once the fragmentation started, the superporous hydrogel composite emptied quickly. This experiment clearly shows that
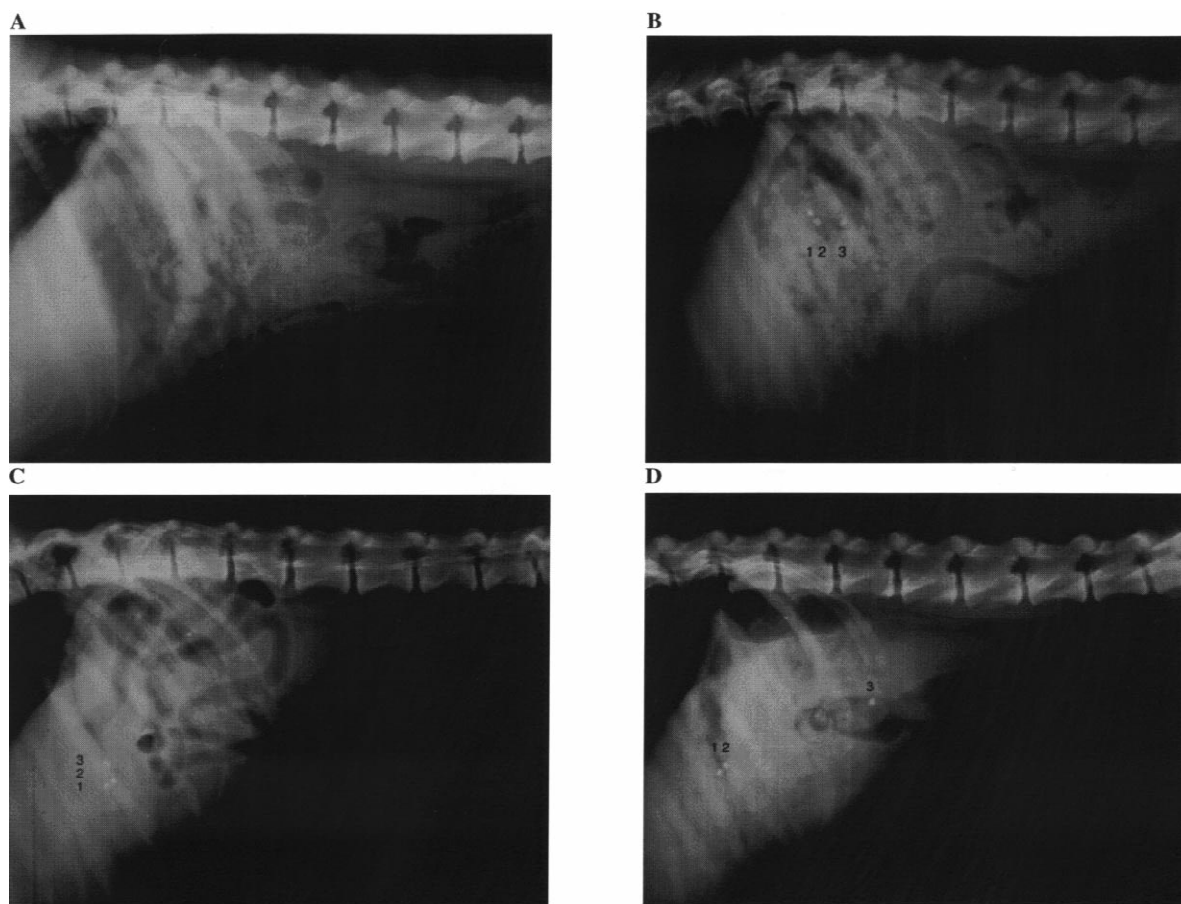

Fig. 6. X-ray images showing gastric retention of a poly(AM-co-SPAK) superporous hydrogel composite in a canine model. Three X-ray markers (labels 1, 2, and 3) in the superporous hydrogel composite are visible. (A) Image showing the control stomach with no X-ray markers. (B) Image taken 8 h after the oral administration of the gel composite. Three markers maintained their relative positions. (C) Image taken 27 h after the oral administration. The dosage form still remained intact in the stomach. (D) Image taken 32 h after the oral administration. One marker (label 3) was separated from the other two markers, indicating breaking of the gel composite.

superporous hydrogel composites with improved mechanical strength could prolong the gastric retention time to more than 27 h. Since it is highly likely to have food a few times a day, it is expected that the gel composites remain in the stomach for over 24 h.

5. Discussion

We have been developing a hydrogel system which swells fast to a large size and maintains high mechanical strength. Our SPH composites meet all three requirements. They swell to equilibrium size in a matter of minutes and the swelling ratio is more than 100 and can easily reach a few hundred. The main mechanical strength of SPH composites comes from the composite material, Ac-Di-Sol® in our study. Ac-Di-Sol® is a common pharmaceutical superdisintegrant which exists as long fibers with hollow lumens [47]. The action of Ac-Di-Sol® in promoting the swelling of squeezed SPH composite is believed to be similar to its action in tablet disintegration [47]. In contact with aqueous media, Ac-Di-Sol® absorbed water and expanded. This expansion opened up the closed capillary channels in the squeezed SPH composites and allowed them to swell rapidly through capillary action. Other superdisintegrants, such as sodium starch glycolate (Explotab®, Primojel®) and crosslinked polyvinyl-pyrrolidone (Crospovidone®), were also tested and showed improvement in the swelling kinetics. Among these superdisintegrants, Ac-Di-Sol® showed the best improvement. The mechanical strength of the SPH composites could be increased further by acidification of ionizable groups of the polymer. The combination of the use of a composite material and acidification resulted in mechanical strength high enough to overcome the gastric contractions, although room for further improvements exists. Superporous hydrogel composites can be made biodegradable. Adding the biodegradable property to the SPH composites can be done quite easily simply by using biodegradable crosslinkers, e.g. poly(lactic-co-glycolic acid) or functionalized albumin [5], during the synthesis of the SPH composites.

Gastric retention experiments in dogs showed promising results. When the dog was maintained in fasted condition for 36 h before the experiment, the SPH composites remained in the stomach for 2–3 h, after which the SPH composites broke into two pieces and emptied into the intestine. On the other hand, when the initial fed state was maintained for the first few hours, the SPH composites stayed in the stomach for more than 24 h. This observation was reproduced in at least three different experiments. The gastric emptying after a few hours in the completely fasted condition is understandable. The mechanical strength of SPH composites may have to be improved further. But, the same SPH composites were able to remain in the stomach if the fed state was maintained in the beginning of the experiment. After a few hours of the experiment, the dogs entered into the fasted condition, but the SPH composites were able to remain in the stomach. While we need to have more experiments to understand exactly how the SPH composites are retained in both fasted and fed (followed by fasted) conditions, it is reasonable to assume that normally nobody is fasted for more than 36 h. For this reason, it may be safe to assume that there would be some food in the stomach when the SPH composites are administered. And this may result in long-term gastric retention. This, of course, can be answered only by further experiments.

The observations that the SPH composites can remain in the stomach for a few hours even in the completely fasted condition are actually very encouraging. As mentioned above, there would be some food in normal situations and the gastric retention is expected to be much longer than a few hours. This led us to question how to use the SPH composites for actual drug delivery. Since SPH composites are a platform for oral controlled drug delivery systems, they can be used in conjunction with other controlled release devices. For example, the SPH composites can be used to wrap around the existing oral dosage forms, such as oral osmotic tablets or microparticular systems. In addition, the SPH composites can be made into a capsule shape to incorporate drug reservoir in the center. This type of gastric retention device may be ideal for the delivery of drugs of which primary target is in the stomach or in the upper small intestine.

In addition to oral drug delivery, SPH composites can be used in other non-pharmaceutical applica-

tions. The presence of a bulky gel composite or a few SPH composites in the stomach is expected to reduce the amount of food intake, and this particular potential can be used as a diet control aid. This approach, if working properly, would be a better way of achieving weight reduction than methods utilizing drugs. SPH composites can be best used in situations where a fast absorbing property is most useful. During surgery, blood can be easily removed by the SPH composites. Furthermore, they can be used to fill up any space inside the body. Since the SPH composites can be used as a drug delivery system, they can be used to treat the wounded areas. Since the SPH composites can be made to be sensitive to changes in environmental condition, such as temperature or pH, they can also be used for bio-separation of a number of compounds including protein drugs. When the toxic materials are spilled, they can be easily absorbed by SPH composites.

Acknowledgements

References

[1] R.W. Fische, A. Boertz, S.S. Davis, R. Khosla, W. Cawello, K. Sandrock, G. Cordes, Investigation of the gastrointestinal transit and in vivo drug release of isosorbide-5-nitrate pellets, Pharm. Res. 4 (1987) 480–485.

[2] A. Parr, An overview of GI physiology and transit times and their impact on drug absorption, 39th Annual International Industrial Pharmaceutical Research and Development Conference, 39 (1997) Ch. 3.

[3] K. Park, Enzyme-digestible swelling hydrogels as platforms for long-term oral drug delivery: synthesis and characterization, Biomaterials 9 (1988) 435–441.

[4] W.S.W. Shalaby, W.E. Blevins, K. Park, Use of ultrasound imaging and fluoroscopic imaging to study gastric retention of enzyme-digestible hydrogels, Biomaterials 13 (1992) 289–296.

[5] W.S.W. Shalaby, W.E. Blevins, K. Park, In vitro and in vivo studies of enzyme-digestible hydrogels for oral drug delivery, J. Control. Release 19 (1992) 131–144.

[6] J. Chen, in: Superporous Hydrogels: Synthesis and Applications, Purdue University, West Lafayette, 1997, p. 188.

[7] H. Minami, R.W. McCallum, The physiology and patho-physiology of gastric emptying in humans, Gastoenterology 86 (1984) 1592–1610.

[8] K.A. Kelly, Motility of the stomach and gastroduodenal junction, in: L.R. Johnson (Ed.), Physiology of the Gastrointestinal Tract, Raven Press, New York, 1981, pp. 393–410.

[9] J.H. Meyer, J.B. Thompson, M.B. Cohen, Sieving of solid food by the canine stomach and sieving after gastric surgery, Gastroenterology 76 (1979) 804–813.

[10] J.H. Meyer, J. Dressman, A. Fink, G. Amidon, Effect of size and density on canine gastric emptying on non-digestible solids, Gastroenterology 89 (1985) 805–813.

[11] R. Khosla, L.C. Feely, S.S. Davis, Gastrointestinal transit of non-disintegrating tablets in fed subjects, Int. J. Pharm. 53 (1989) 107–117.

[12] J.H. Szurszewski, A migrating complex of the canine small intestine, Am. J. Physiol. 217 (1969) 1757–1763.

[13] J. Timmermans, A.J. Moës, Cutoff size for gastric emptying of dosage forms, J. Pharm. Sci. 82 (1993) 854–859.

[14] S.-J. Hwang, H. Park, K. Park, Gastric retentive drug delivery systems, Crit. Rev. Therapeutic Drug Carrier Sys. 15 (1998) 243–284.

[15] P.R. Sheth, J.L. Tossounian, Sustained release pharmaceutical capsules, US Patent 4,126,672, 1978.

[16] D. Khattar, A. Ahuja, R.K. Khar, Hydrodynamically balanced systems as sustained release dosage forms for propranolol hydrochloride, Pharmazie 45 (1990) 356–358.

[17] V.B. Babu, R.K. Khar, In vitro and in vivo studies of sustained-release floating dosage forms containing salbutamol sulfate, Pharmazie 45 (1990) 268–270.

[18] A. Menon, W.A. Ritschel, A. Sakr, Development and evaluation of a monolithic floating dosage form for furosemide, J. Pharm. Sci. 83 (1994) 239–245.

[19] R. Gröning, G. Heun, Oral dosage forms with controlled gastrointestinal transit, Drug Dev. Ind. Pharm. 10 (1984) 527–539.

[20] S. Watanabe, M. Kayano, Y. Ishino, K. Miyao, Solid therapeutic preparation remaining in stomach, US Patent 3,976,764, 1976.

[21] J.R. Cardinal, Controlled drug delivery: Veterinary applications, J. Control. Release 2 (1985) 393–403.

[22] H. Bechgaard, K. Ladefoged, Distribution of pellets in the gastrointestinal tract. The influence on transit time exerted by the density or diameter of pellets, J. Pharm. Pharmacol. 30 (1978) 690–692.

[23] P.K. Gupta, J.R. Robinson, Effect of volume and viscosity of coadministered fluid on gastrointestinal distribution of small particles, Int. J. Pharm. 125 (1995) 185–193.

[24] S.A. Müller-Lissner, A.L. Blum, The effect of specific gravity and eating on gastric emptying of slow-release capsules, New Engl. J. Med. 304 (1981) 1365–1366.

[25] L.C. Kaus, The effect of density on the gastric emptying and intestinal transit of solid dosage forms: Comments on the article by Davis et al., Pharm. Res. 4 (1987) 78.

[26] K. Park, J.R. Robinson, Bioadhesive polymers as platforms for oral controlled drug delivery: method to study bioadhesion, Int. J. Pharm. 19 (1984) 107–127.

[27] N.A. Peppas, P.A. Buri, Surface interfacial and molecular

aspects of polymer bioadhesion on soft tissue, J. Control. Release 2 (1985) 257–275.

[28] L. Achar, N.A. Peppas, Preparation, characterization and mucoadhesive interactions of poly(methacrylic acid) copolymers with rat mucosa, J. Control. Release 31 (1994) 271–276.

[29] Y. Akiyama, N. Nagahara, T. Kashihara, S. Harai, H. Toguchi, In vitro and in vivo evaluation of mucoadhesive microspheres prepared for the gastrointestinal tract using polyglycerol esters of fatty acids and a poly(acrylic acid) derivative, Pharm. Res. 12 (1995) 397–405.

[30] G. Borchard, H.L. Leussen, A.G. De Boer, J.C. Verhoef, C.-M. Lehr, H.E. Junginger, Potential of mucoadhesive polymers in enhancing intestinal peptide absorption. Part 3. Effects of chitosan glutamate and carbomer on epithelial tight junctions in vitro, J. Control. Release 39 (1996) 131–138.

[31] R. Gröning, M. Berntgen, M. Werner, M. Georgarakis, Magnetic dosage forms with controlled gastric residence time, Eur. J. Pharm. Sci. 2 (1994) 181–183.

[32] R. Gröning, M. Werner, M. Berntgen, M. Georgarakis, Peroral controlled release dosage forms with internal magnets and extracorporeal magnetic guidance: investigations into the renal elimination of riboflavin, Eur. J. Pharm. Biopharm. 42 (1996) 25–28.

[33] J. Fujimori, Y. Machida, T. Nagai, Preparation of magnetically-responsive tablet and confirmation of its gastric residence in beagle dogs, STP Pharma Sci. 4 (1994) 425–430.

[34] R. Ito, Y. Machida, T. Sannan, T. Nagai, Magnetic granules: novel system for specific drug delivery to esophageal mucosa in oral administration, Int. J. Pharm. 61 (1990) 109–117.

[35] W.J. Curatolo, J. Lo, Gastric retention system for controlled drug release, US Patent 5,002,772, 1991.

[36] L.J. Caldwell, C.R. Gardner, R.C. Cargill, Drug delivery device which can be retained in the stomach for a controlled period of time, US Patent 4,735,804, 1988.

[37] J.A. Fix, R. Cargill, K. Engle, Controlled gastric emptying. Part 3. Gastric residence time of a nondisintegrating geometric shape in human volunteers, Pharm. Res. 10 (1993) 1087–1089.

[38] A.S. Michaels, Drug delivery device with self actuated mechanism for retaining device in selected area, US Patent, USA 3,786,813, 1974.

[39] R.H. Johnson, E.L. Rowe, Medicinal dosage forms of unpolymerized thiolactated gelatin with a cross-linking accelerating agent providing slowly released medication from a swollen matrix, US Patent 3,574,820, 1971.

[40] H. Park, K. Park, Honey, I blew up the hydrogels!, Proc. Int. Symp. Control. Release Bioact. Mater. 21 (1994) 21–22.

[41] H. Park, K. Park, Hydrogel foams: a new type of fast swelling hydrogels, Trans. Soc. Biomater. 17 (1994) 158.

[42] L.A. Hougton, N.W. Read, R. Heddle, G.J. Maddern, J. Downtown, J. Toouli, J. Dent, Motor activity of the gastric antrum, pylorus, and duodenum under fasted conditions and after liquid meal, Gastroenterology 94 (1988) 1276–1284.

[43] L.A. Hougton, N.W. Read, R. Heddle, M. Horowitz, P.J. Collins, B. Chatterton, J. Dent, Relationship of the motor activity of the antrum, pylorus, and duodenum to gastric emptying of a solid–liquid mixed meal, Gastroenterology 94 (1988) 1285–1291.

[44] K. Park, J. Chen, H. Park, Superporous hydrogel composites having fast swelling, high mechanical strength, and superabsorbent properties, USA, US Patent application Serial No. 08/855,499, 1977.

[45] W.S.W. Shalaby, K. Park, Biochemical and mechanical characterization of enzyme-digestible hydrogels, Pharm. Res. 7 (1990) 816–823.

[46] A.C. Guyton, in: Basic Human Physiology: Normal Function and Mechanisms of Disease, 2, W.B. Saunders, Philadelphia, 1977, pp. 662–664.

[47] R. Shangraw, A. Mitrevej, M. Shah, A new era of tablet disintegrants, Pharmaceutical Technol. October (1980) 49–57.