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The Macromolecular Polymers for the Preparation of Hydrodynamically Balanced Systems—Methods of Evaluation

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ABSTRACT

Evaluation of macromolecular polymers used as excipients for the preparation of hydrodynamically balanced systems (HBS) was carried out. Hard gelatine capsules were filled with polymeric substances belonging to various chemical groups (chitosan, sodium alginate, hydroxypropylmethycellulose—HPMC). The following properties of the HBS were investigated: density, hydration, erosion and floating force. The solvent penetration process into the HBS was visualized using magnetic resonance imaging (MRI) technique. Densities of the HBS in hydrochloric acid (0.1 M) ranged from 0.37 g/cm^3 to 0.71 g/cm^3. Each polymer demonstrated different hydration/erosion abilities and floating properties. The maximum floating force ($F_{float\ max}$) for capsules size 0, ranged from 26.7 mN (sodium alginate) to 64.7 mN (chitosan). HBS formulations also varied in time to reach maximum floating force ($T_{float\ max}$). HPMC and sodium alginate formulation reached $F_{float\ max}$ within half an hour after immersion, while in the case of chitosan formulations (deacetylation degree (d.d.) 66% and d.d. 93%), the time was 184 minutes and 218 minutes respectively. The floating properties of the dosage forms were reliant on type of the polymer and the medium—fasted state simulated gastric fluid (FaSSGF) or fed state simulated gastric fluid (FeSSGF). The size of the HBS influenced the floating force value. The mechanisms of erosion and swelling of the polymeric matrices play a dominant role in flotation of the dosage forms.

Key Words: Hydrodynamically balanaced systems; HBS; Floating dosage forms; Magnetic resonance imaging; MRI.

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INTRODUCTION

Properties of hydrophilic polymers were widely studied in the last few years.[1–3] In the number of studies the dynamic processes of diffusion, hydration and erosion of the polymeric systems have been related with the abilities to control the release of the drug.[4–6] Swelling of the hydrocolloid matrix systems plays essential role in the drug release, therefore various approaches have been made and numerous methods were developed to investigate the processes taking place after immersion of the dosage form in the solvent. The simplest way to study the swelling of the tablets is to record the dimensional changes outside hydrogel layer.[7] Applying photo or video camera in association with computer image analysis is another option.[8] The incorporation of colored additives in the matrix tablets connected with photo microscopic methods also gives opportunity to facilitate the recognition of movements in swelling matrix, its hydration, erosion and diffusion of the solvent into the dosage forms.[9]

The most often studied dosage forms were hydrocolloid matrix tablets, because for their geometrical shape, which makes analysis and measurements of the swelling processes easier. For better observation tablets were frequently positioned between transparent plastic discs, which enable water penetration only from the lateral surface.[10] Although, there is a lot of information in the cited research, there are some issues requiring consideration:

- Assessment of swelling of hydrogel matrices was carried out in non-standard conditions.
- Swelling is a dynamic process susceptible to alterations during the assessment procedure.
- Colouring methods have restricted range of versatility.

The data concerning the hydrogel formation, swelling and erosion are of importance in preparation of floating dosage forms. This data gives the opportunity to answer questions associated with releasing of the drug and floating properties of the dosage form simultaneously.

Floating systems could be useful for controlled delivery of the drugs acting locally in the stomach or characterized by narrow absorption window in the proximal part of the gastrointestinal tract.[11,12] Various attempts have been made to develop floating systems: floating moulded tablets containing dispersion of agar and mineral oil,[13] multiple unit systems with an air compartment,[14] floating system based on ion exchange resins,[15] floating microparticles, and tablets containing low density polypropylene foam powder[16,17] were described.

Among the other developed floating formulations, hydrodynamically balanced systems are the simplest ones. According to definition given by Ingani[18] HBS are formulations essentially composed of a drug intimately mixed with gel forming hydrocolloids, swelling in contact with gastric fluid. The hydrogel shell maintains a relative integrity of shape and a bulk density less than 1 g/cm^3. The drug is slowly released in the stomach by diffusion through the hydrogel barrier and erosion of the surface of the dosage form.

Cellulose derivatives are frequently used in such formulations. For these purposes different types of HPMC, microcrystalline cellulose, hydroxypropylcellulose in various combinations were often used.[19–22] Moreover, different types of chitosan, alginates and another polymeric substances were employed.[23–25] Although various HBS have been investigated there is a little data concerning the analysis of properties of floating systems containing hydrophilic polymers alone.

The analysis of the swelling properties of HBS by photomicroscopy, or by addition of colorants seems to be rather problematic regarding the delicate structure of hydrogel and the shape of the capsules. From this point of view the Magnetic Resonance Imaging (MRI) seems to be a valuable method for the analysis of processes occurring in the HBS after immersion in artificial gastric juice. The MRI is a non destructive, non invasive method, it allows to visualise the internal structure of the HBS systems. For this facts MRI is a perfect tool which enables to observe processes occurring inside the gel-like structure of swelling HBS. Performing the analysis of MR images (which reflect proton density in investigated object) the evaluation of swelling, hydration and erosion is possible.

The application of the MRI in a field of pharmaceutical technology was previously reported in several papers.[26–28] It was used in order to explain the phenomena occurring during the drug release from tablets of regulated release, to analyse the mechanisms of triflupromazine and 5-fluorouracil release from HPMC matrix tablets and to visualise the distribution and mobility of dissolution media in submilimetre drug delivery systems.

The aim of study was: comparative evaluation of the properties of polymers which might be useful for the preparation of HBS. Several methods were selected to investigate floatation, swelling and erosion of hydrodynamically balanced systems containing various polymers. The evaluation of properties of HBS in

different conditions (FaSSGF, FeSSGF) using methods including gravimetric methods, floating force measurements and MRI imaging of the hydrogel polymeric systems is important to understand the phenomenon of the floatation of the HBS.

MATERIALS AND METHODS

Materials

Sodium alginate was obtained from BDH Chemicals Ltd., low viscosity Hydroxypropylmethylcellulose from Fluka, Methylcellulose—Methocel MC in various viscosity grades from Fluka. Chitosan-66 and Chitosan-93 were a gift from Sea Fishery Institute—Gdynia. All other materials were of at p.p.a. grade. The properties of the polymers were presented in Table 1.

Preparation of Hydrodynamically Balanced Systems

The polymers were used as received. The hard gelatine capsules Coni-Snap® size 5, 0, 000 from Capsugel were filled volumetrically with non compressed powders by means of manual filling method. The mean weight of the filled capsules ranged from 247 mg for chitosan 66 to 467 mg for sodium alginate. The differences in weight of HBS filled with particular polymers did not exceed 3%. The density of each of the batches was assessed using electronic densimeter type EW200SG (A and D).

Assessment of Hydration and Erosion of the Polymers

The capsules were placed in baskets made of Plexiglas and stainless steel mesh. The dimensions of the basket were: diameter 4 cm height 2,5 cm. It was enough space guaranteed possibility of free floatation of the HBS without contact of the walls of the basket. The dosage form has only contact with the stainless steel mesh. The baskets were accurately weighted and placed on the bottom of the beaker which was filled with 1000 mL of medium. The beakers were placed in a thermostatic water bath (VanKel VK700). The measurements were carried out at 37°C using 0.1 M HCl solution—simulating gastric fluid in a fasted state—(FaSSGF) and 0.01 M HCl with addition of sodium laurylsulphate (2.5 g/L) and sodium chloride (2.0 g/L)—simulating gastric fluid in a fed state (FeSSGF).

After dissolution of the hard gelatine capsule, the hydrogel layer was formed. It sorrounded the dry core of the HBS . After appropriate time interval (10, 20, 30, 40, 50, 60, 120, 180, 240, 300 minutes) the baskets were removed from the medium blotted with absorbent tissue and accurately weighted. The swollen polymeric mass was rather soft but enough cohesive to transfer onto the Petri dish and dried in an oven for two hours at 60°C and at room temperature overnight. The dried mass was weighted. The method of calculation of hydration and erosion of the systems was similar to reported by Roy et al.[29]

The hydration (H) of the hydrodynamically balanced systems was defined as:

$$H = \frac{W_t}{W_0} \cdot 100 \quad (1)$$

where W_t=weight of hydrogel at time t and W_0=initial weight of dry HBS.

The erosion (E) of HBS was defined as:

$$E = \frac{Wd_t}{W_0} \cdot 100 \quad (2)$$

where Wd_t=weight of dried hydrogel at time t and W_0=initial weight of dry HBS.

All studies were carried out in triplicate (Figs. 2–4).

Table 1. Properties of the polymers.

Polymer	Properties	Manufacturer
Hydroxypropylmethylcellulose	Viscosity 50 mPa·s	Fluka
Methylcellulose—Methocel MC 25 mPa·s	Viscosity 25 mPa·s	Fluka
Methylcellulose—Methocel MC 4000 mPa·s	Viscosity 4000 mPa·s	Fluka
Chitosan 66	Deacetylation degree (d.d.) 66%, viscosity (v.) 196.6 mPa·s	Sea Fishery Institute—Gdynia
Chitosan-93	Deacetylation degree 93%, viscosity 771 mPa·s	Sea Fishery Institute—Gdynia
Sodium Alginate	Low viscosity	BDH Chemicals

Floating Force Determination

Floating force measurement was carried out using an apparatus shown in (Fig. 1) consisting of an electronic balance 1), a lever 2), basket for maintaining the sample in appropriate position 3) and beaker 4) placed in thermostatic water bath (37°C) 5). The HBS was placed in the basket and immersed in one of the simulated gastric fluids. The measurements were carried out in triplicate after 10, 20, 30, 40, 50, 60, 120, 180, 240, 300 min.

The floating force of the HBS is a vectorial sum of gravity and buoyancy forces, which have an effect on the immersed object. For determining the value of the floating force the apparatus was calibrated using the 5 g weight. The weight was put on the lever. The gravity force of the weight was partially balanced by floating force of the HBS. The resultant force was shown by means of resultant weight on the balance display (Figs. 8–10). The parameters: $F_{float\ max}$, $T_{float\ max}$, area under the curve: resultant floating force versus time (AUC_{float}) is expressed as $AUC_{0\rightarrow300}$ computed by means of trapezoidal method.

Magnetic Resonance Imaging of the HBS

The process of solvent penetration inside the dosage form was visualized using MRI. MRI studies were done using a research MRI system consisting of a digital console MARAN DRX (Resonance Instruments Ltd.) and 4.7T/310 mm horizontal bore superconductive magnet (Bruker) equipped with an actively shielded gradient set of 200 mm ID (Magnex Scientific) and a dedicated RF probehead. The probehead was built as an inductively coupled, modified saddle RF coil of 30 mm ID and 40 mm long. Multislice Spin Echo (MSE) sequence was used to record images of capsules immersed in solution. The following MR imaging parameters were used: Field of View = 3.5 cm, slice thickness = 1 mm, image matrix: 256×256, echo time TE = 35 ms, repetition time TR = 1 s, number of scans NS = 1.

The floating systems were immersed in horizontally positioned cylinder of 27.5 mm inner ID filled with 40 mL of FaSSGF. Any remaining air was removed from the cylinder immediately after capsule immersion. Capsule floated freely in solution and quickly stabilized its position under the cylinder surface. The cylinder with capsule was inserted into the probehead and MR images were recorded for 6 hours (Figs. 5–7). Images were 256×256 pixel matrices. Image intensity was encoded in 8 bit grey scale. The pixel is proportional to proton concentration weighted by relaxation times T_1 and T_2. So the grey level intensity near zero level characterised dry regions of the HBS and the highest values corresponded with increasing water concentration in hydrated parts of the dosage forms. The image analysis was carried out using ImageJ ver 1.26 program (NIH—USA).

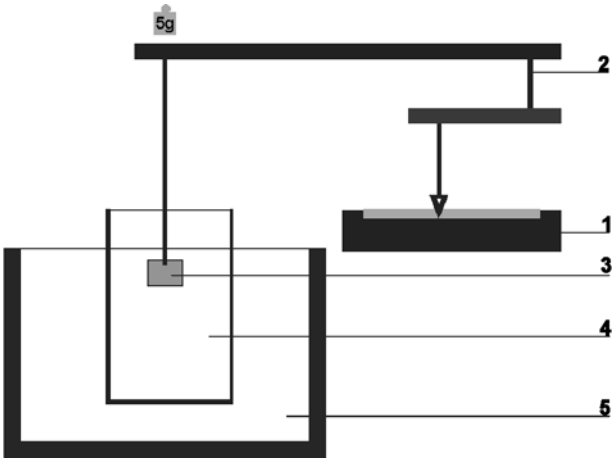

Figure 1. Apparatus for floating force determination; 1—electronic balance, 2—lever, 3—basket for maintaining sample in appropriate position, 4—beaker, 5—water bath.

RESULTS AND DISCUSSION

All capsules filled with various polymers floated immediately after immersion in FaSSGF. The density of HBS ranged from 0.37 g/cm^3 to 0.71 g/cm^3. The capsules filled with chitosans had the lowest densities, the highest density occurred in the capsules containing sodium alginate.

The solvent uptake by the polymers in FaSSGF was diversified. The weight of the HBS has gradually grown (Fig. 2). The most effective hydration was observed in case of chitosans. The mass of the HBS increased almost 10 times after 1 hour, in both types of polymers. After five hours the weight of capsules filled with chitosan-93 increased 35 times whilst the weight of the system containing chitosan-66 increased only 20 times. The hydration of the HBS filled with HPMC and sodium alginate was lower.

After drying of the systems its weight decreased gradually with exception of methylcellulose that have disintegrated within half an hour (Fig. 3). The erosion of chitosan hydrogel was slow—after two hours the weight of capsules containing chitosan-93 decreased less than 10%. At the same time the decline of weight

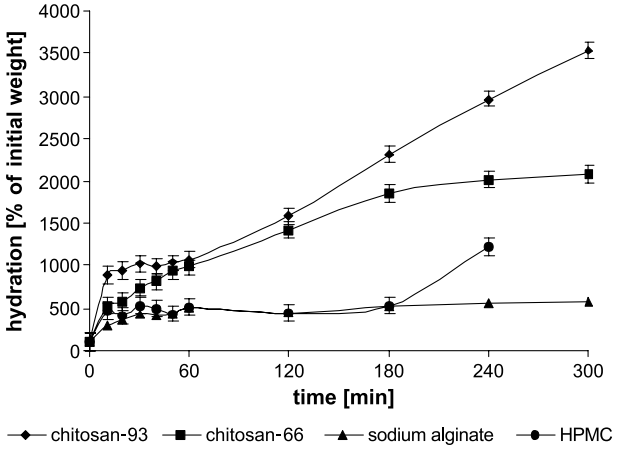

Figure 2. Hydration of hydrodynamically balanced systems containing various polymers in fasted state simulating gastric fluid.

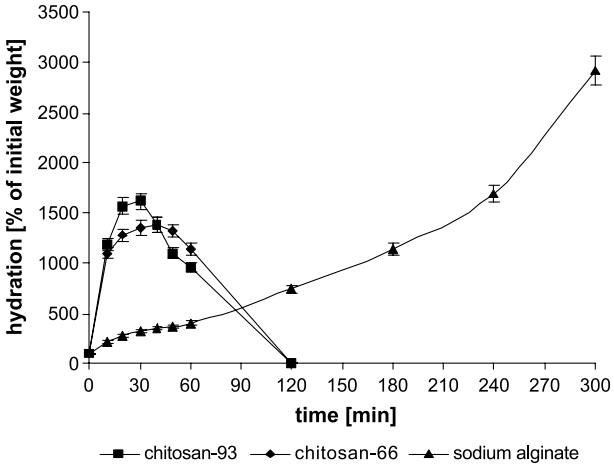

Figure 4. Hydration of hydrodynamically balanced systems containing various polymers in fed state simulating gastric fluid.

of the other systems ranged from 28% for chitosan-66 to 40% for HPMC.

The water penetration into the systems immersed in FeSSGF was very fast in formulations containing chitosan—after two hours they eroded completely (Fig. 4). Hydration process of HBS based on sodium alginate was observed for five hours.

The processes of hydrogel formation, consecutive swelling and erosion of the outside surface barrier were depicted in this study using MRI. Comparative analysis of obtained the images have shown that the mechanism of water penetration into the polymeric network was related to the type of polymer. MR images of HBS showed not only the general shape of the capsule but also its structural characteristics (Figs. 5–7).

In the early stages of hydration of the system containing sodium alginate the dimensional changes of HBS were evident in both axial and radial directions. The overall length of the capsule increased during 90 minutes by 30% from 24.6 mm to 32.6 mm. The transversal MR images illustrated the hydrogel formation on the surface of the system (Fig. 7). The swollen polymeric barrier was established within 1.5 hours. In the low pH level (FaSSGF) the layer of swollen polymer surrounding the HBS reminded in rubbery state.

For this reason the outside barrier was not so cohesive as in case of hydrogel. The process of solvent penetration into the dry core of HBS was recorded in transversal sections of the capsule (Fig. 7). After about 150 minutes the hydrogel layer was broken and the system lost its floating capabilities. This observation is in agreement with the results of floating force measurements in FaSSGF (Fig. 8).

In the case of HPMC rapid size increase in axial direction was observed upon placement in FaSSGF. The erosion of the system was the main process controlling changes in radial dimensions of the dosage forms and its floating properties. The length of the swollen system increased from 26.4 mm to 34.2 mm after 90 minutes, while the radial dimension of the system decreased about 3 mm. The HPMC hydrogel barrier was relatively thin during the experiment. The formulation was fragmented in the subsequent hour, as a result of two opposite phenomena: fast expansion of the hydrogel in axial direction and erosion of the

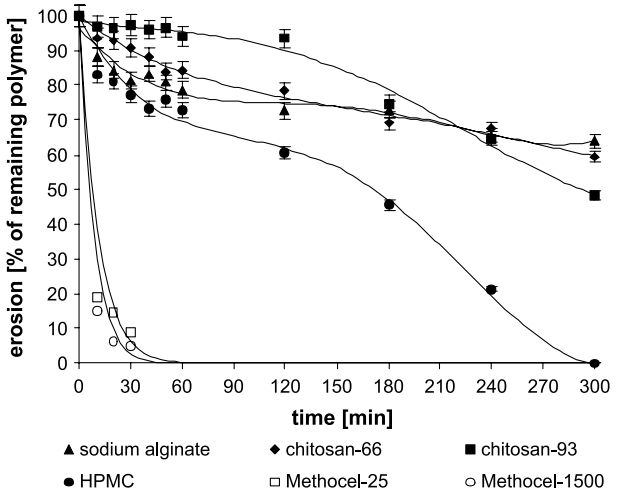

Figure 3. Erosion of hydrodynamically balanced systems containing various polymers in fasted state simulating gastric fluid.

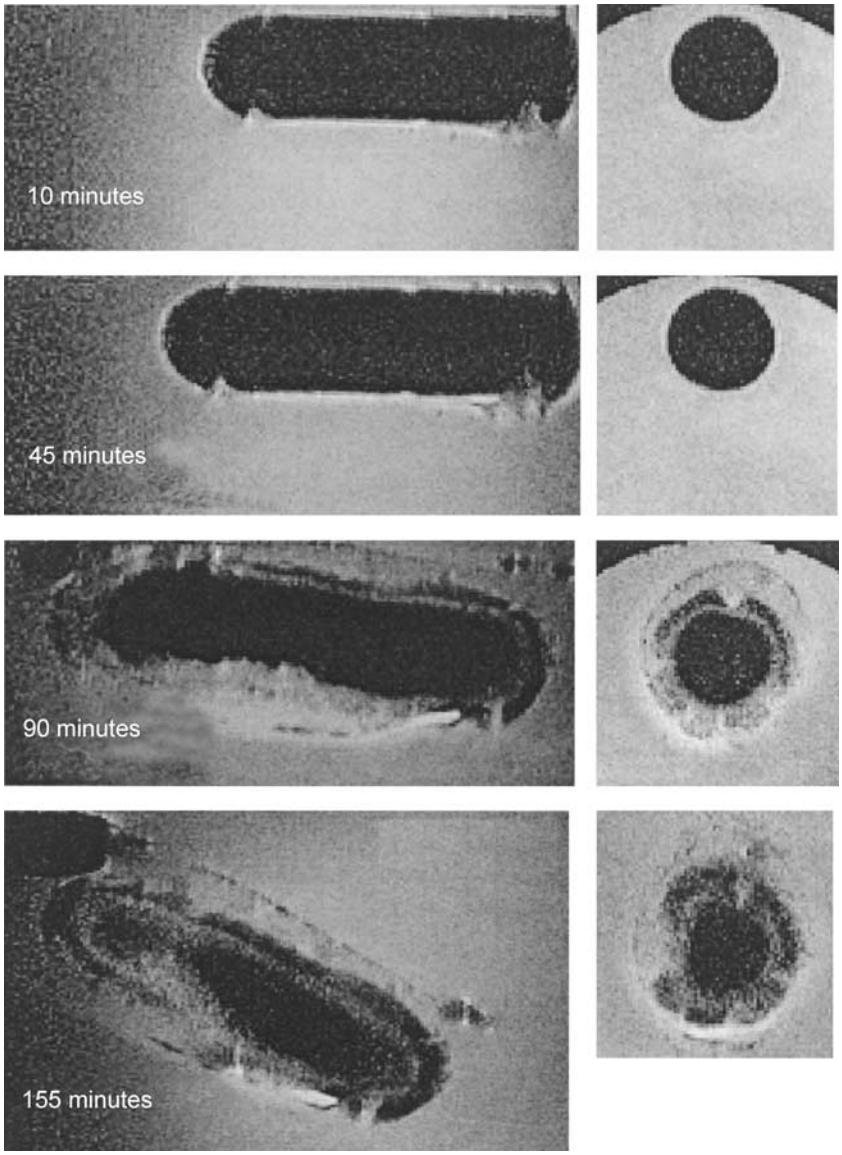

Figure 5. Longitudinal (left) and transversal (right) MR images illustrating solvent penetration into the HBS containing sodium alginate in fasted state simulating gastric fluid.

polymer observed in radial direction (Fig. 6). Moussa[4] explained axial increase of the HPMC polymeric systems by the expansion of the core of the dosage form. He suggested that the core does not remain completely dry. The small amounts of solvent or its vapours penetrated towards the centre of the system causing swelling of the polymer particles without hydrogel formation.

The best results were obtained in both chitosans, where the dry core of HBS was enclosed in the hydrogel shell within 10 minutes after immersion in FaSSGF. This barrier effectively controlled the penetration of solvent into the system and its floating capability. The Fig. 7 shows that the thickness of hydrogel layer increased progressively in subsequent five hours. The production of the homogenous hydrogel barrier on the surface of the dosage form gives excellent opportunities for the controlled drug release and floatation of the system.

The MRI study showed that the processes of water penetration into the swelling polymeric systems depended on the type of polymer. The analysis of the MRI data gives possibility to explain the properties of the systems (for instance its floating abilities). The

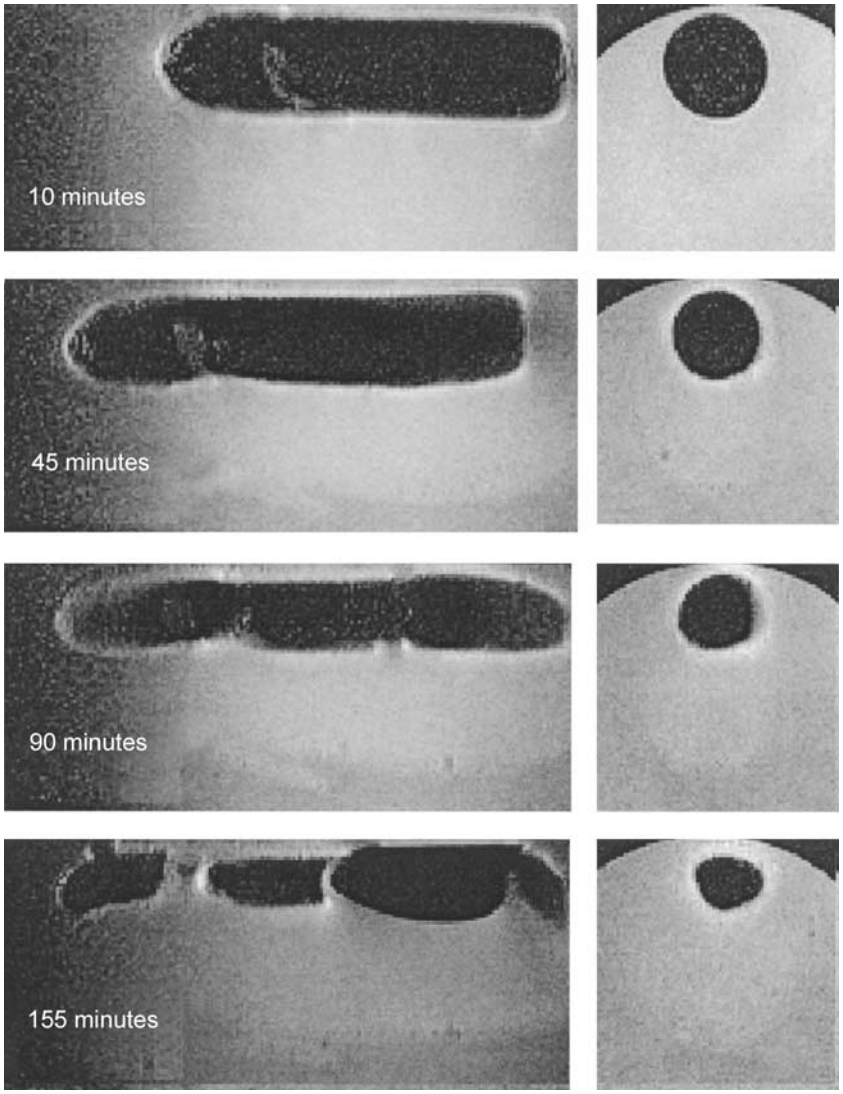

Figure 6. Longitudinal (left) and transversal (right) MR images illustrating solvent penetration into the HBS containing HPMC in fasted state simulating gastric fluid.

flotation of the systems relays on the type of polymer applied for its preparation (Fig. 10).

The HBS based on HPMC floated for 4 hours whereas the system containing sodium alginate floated only for two hours. The values of $F_{float\ max}$ ranged from 26.7 to 64.6 mN. HBS formulations were also varied in concerning $T_{float\ max}$. $F_{float\ max}$. For HPMC and sodium alginate formulations they reached $F_{float\ max}$ in 30 minutes. In the case of HPMC the outer hydrogel barrier formation and swelling was weakly manifested.

The best results occurred for capsules filled with chitosans: 184 minutes for chitosan-66 and 218 minutes for chitosan-93. Resultant floating force curves for chitosans were divided into two parts: the increasing part corresponding to swelling of HBS and the decreasing part corresponding to erosion of swollen polymer hydrogel.

In the FeSSGF systems filled with the chitosans lost its floating capability rapidly (Fig. 9). The chitosans did not form the hydrogel barrier, the flakes of the polymers were spread in the medium after dissolution of outer gelatine shell. The systems were disintegrated completely within 30 minutes. These observations corresponded with data obtained during hydration/erosion investigations (Fig. 4).

The cationic characteristic of the chitosans caused different behaviour of HBS according to applied

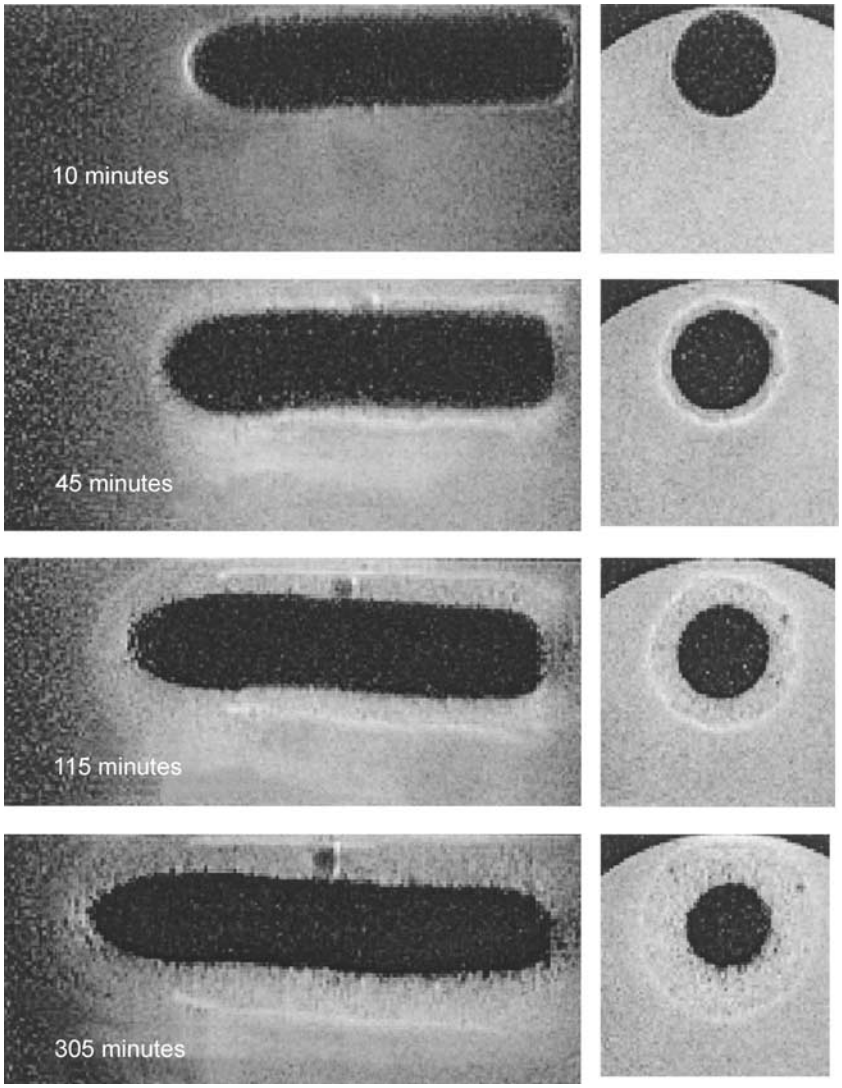

Figure 7. Longitudinal (left) and transversal (right) MR images illustrating solvent penetration into the HBS containing chitosan 66 in fasted state simulating gastric fluid.

solvent. In acidic environment of FaSSGF the HBS containing chitosan swelled and formed the hydrogel barrier controling flotation of the system. The amino groups of chitosan were ionised at low pH, which caused the hydration and hydrogel formation (Fig. 7). In the FeSSGF the formation of hydrogel layer was not observed. The HBS loosed its floating capacity quickly (Fig. 9). The properties of the gastric fluid have influenced the chitosan hydrogel formation therefore must be taken under consideration. The acidic gastric content gives the appropriate environment for initial hydrogel formation and maintain the floating properties of the HBS. In FeSSGF the best buoyancy was observed for HBS containing sodium alginate but generally the range of the floating force values were lower than in the simulated gastric fluid in the fasted state.

The investigation of influence of the size of HBS upon the floating force has shown that the floating force increased with increasing size of HBS (Fig. 10).

The initial floating force was highest in case of the capsules 000—the values ranged from 88 mN for capsules filled with HPMC to 111 mN for capsules contained chitosan-93. Floating properties of the capsules changed gradually during the experiment according to dimensional changes of the dosage forms. It was pointed earlier in case of HPMC where the main mechanism influenced on the flotation was erosion.

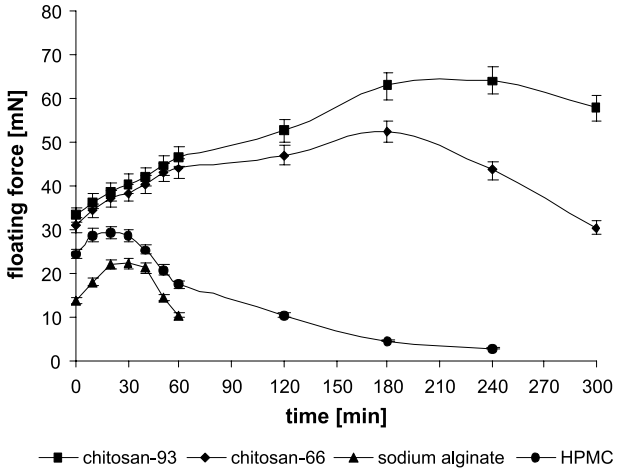

Figure 8. Flotation of hydrodynamically balanced systems containing various polymers in FaSSGF.

The values of the floating force decreased for five hours. The swelling of the chitosan was connected with the growth of the floating strength of the capsules. The values of the floating force have grown faster in case of chitosan characterised by higher deacetyltion degree. The maximum floating force—149 mN was observed after two hours. In the consecutive 3 hours the floating force of the capsules decreased to 87 mN at the end of experiment. The values of floating forces for smaller capsules (0, 5) were significantly lower and ranged from 34 mN to 19 mN. The differences in the floating properties between these two sizes of capsules were not thus apparent.

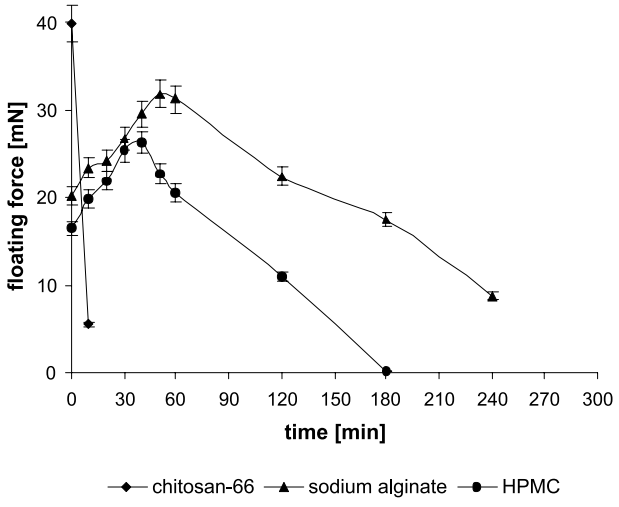

Figure 9. Flotation of hydrodynamically balanced systems containing various polymers in fed state simulating gastric fluid.

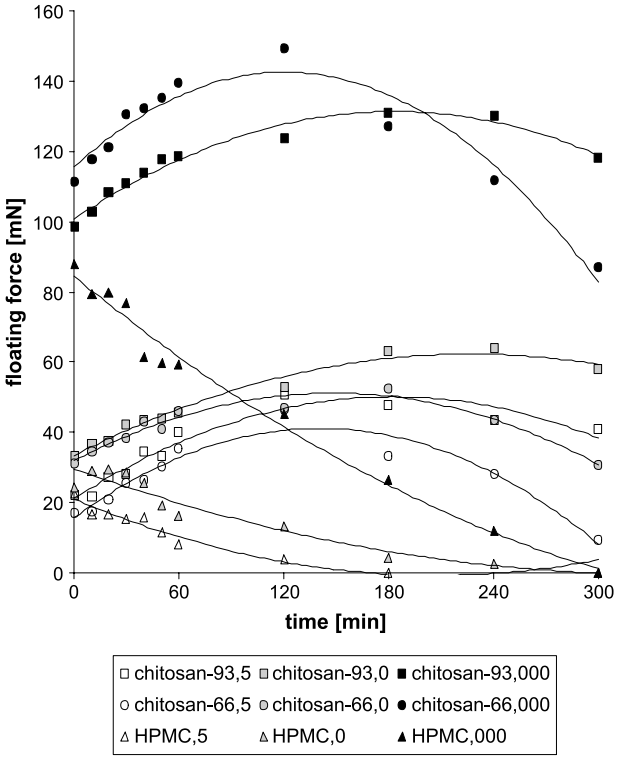

Figure 10. Flotation of different sizes (5, 0, 000) of hydrodynamically balanced systems containing various polymers in fasted state simulating gastric fluid.

CONCLUSIONS

Each polymer demonstrated different hydration/erosion abilities and floating properties. The properties of ionic polymers were depended on the type of solution applied in the experiment. For chitosans the acidic environment of FaSSGF gives the opportunity for swelling and formation hydrogel layer controlling flotation of the HBS. In opposition to chitosans sodium alginate gives the better floating properties of HBS in the FeSSGF. The viscosity of HPMC was too low for establish sufficiently cohesive polymeric layer to control floating capacity of HBS for five hours.

The MR imaging analysis confirmed these results. The mechanisms of erosion and swelling of the polymeric matrices appeared to play dominant role in the flotation of the dosage forms. MRI method is useful in case of imaging of water penetration into the HBS. It was found that hydrogel layer formation process, which enables flotation and release of drug substance, depends on polymer type. The investigations of hydrogel swelling, and floating properties of HBS containing various polymers allow to characterise and

to differentiate mechanisms of water penetration into the cores of the systems. It allows to elucidate mechanisms of flotation and possible behaviour in changing conditions of the upper part of gastrointestinal tract.

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