Development of a System for Simultaneous Dissolution Studies and Magnetic Resonance Imaging of Water Transport in Hydrodynamically Balanced Systems: A Technical Note

Submitted: May 11, 2006; Accepted: August 28, 2006; Published: February 23, 2007

Przemysław Dorożyński,[1] Piotr Kulinowski,[2] Renata Jachowicz,[1] and Andrzej Jasiński[2]

[1]Department of Pharmaceutical Technology and Biopharmaceutics, Pharmaceutical Faculty, Jagiellonian University, Medyczna 9 Street, 30-688 Kraków, Poland
[2]Department of Magnetic Resonance, Institute of Nuclear Physics PAS, ul Radzikowskiego 152, 31-342 Kraków, Poland

KEYWORDS: Hydrodynamically balanced systems, HBS, floating dosage forms, magnetic resonance imaging, MRI.

INTRODUCTION

Hydrodynamically balanced systems (HBS) are the simplest gastroretentive dosage forms. Although floating drug delivery systems have been criticized in recent years,[1] they still remain the only way of providing controlled delivery of drugs absorbable in the proximal part of the gastrointestinal tract. HBS are usually composed of hard gelatin capsules filled with a mixture of gel-forming polymeric substances and an active pharmaceutical ingredient.[2,3] After immersion in solution (in vitro) or swallowing (in vivo), the shell of the swollen hydrogel is formed. It controls the release rate of the drug, and it maintains appropriate integrity of the HBS and low apparent density of the systems, ensuring flotation.

Among the methods for evaluating floating dosage forms, the combined method of simultaneous analysis of dissolution and magnetic resonance imaging (MRI) of the dosage form seems interesting. MRI is a noninvasive technique that can provide cross-sectional images of various solid materials and living organisms. The application of MRI in the field of pharmaceutical technology has been reported in several papers.[4-8] Fyfe et al[9] described the system for performing MRI experiments within US Pharmacopeia apparatus 4. The system was applied to record the physical changes of the tablets simultaneously with the dissolution study.

The aim of this work was to develop a system for simultaneous MR imaging and dissolution studies using a specially designed flow-through cell and to evaluate the usefulness of this method for assessment of the formation of hydrogel as a barrier that controls drug dissolution from HBS and the dry core retention that controls the floating properties of HBS.

Corresponding Author: Przemysław Dorożyński.
Tel: (+4812) 6570565; Fax: (+4812) 6570565;
E-mail: mfdorozy@cyf-kr.edu.pl

MATERIALS AND METHODS

Materials

The following materials were used in the experiment: hydroxypropylmethylcellulose (HPMC) characterized by substitution type 2208 (Metolose 90-SH) and 2 viscosities, 400 mPa·s and 100,000 mPa·s (Shin-Etsu Chemical Co, Ltd Tokyo, Japan); L-dopa (LD) (Sigma-Aldrich Inc, St Louis, MO); and hard gelatin capsules, Coni-Snap size 1 and 0 (Capsugel, Bornem, Belgium). Other reagents were of analytical grade.

The mixtures of LD and HPMC in 1:1 and 1:3 ratios were prepared in the mortar. Capsules were filled manually with noncompressed powder mixtures corresponding to 100 mg of LD.

The experiments were performed in 2 dissolution media—0.1 M hydrochloric acid-fasted state simulated gastric fluid (FaSSGF) and 0.01 M hydrochloric acid containg sodium lauryl sulfate (2.5 g/L) and sodium chrloride (2.0 g/L)-fed state simulated gastric fluid (FeSSGF)—which were prepared by dissolving sodium lauryl sulfate (2.5 g/L) and sodium chloride (2.0 g/L) in 0.01M HCl.

The experiments were performed in triplicate.

MRI

A research system with a digital MARAN DRX console (Resonance Instruments, Witney Oxon, UK), 4.7-T/310-mm horizontal bore magnet Biospec (Bruker, Ettlingen, Germany), equipped with an actively shielded gradient set of 200 mm (Magnex Scientific, Yarnton Oxfordshire, UK) was used for the MRI studies.

A special MR-compatible flow-through cell for HBS investigation was designed. The cell was made of Plexiglas. The dissolution medium was circulated through the cell from the bottom. The cone-like lower part of the cell was filled with glass beads to maintain the laminar flow of the solvent. A flow-through cell was combined with the MR probehead (Figure 1).

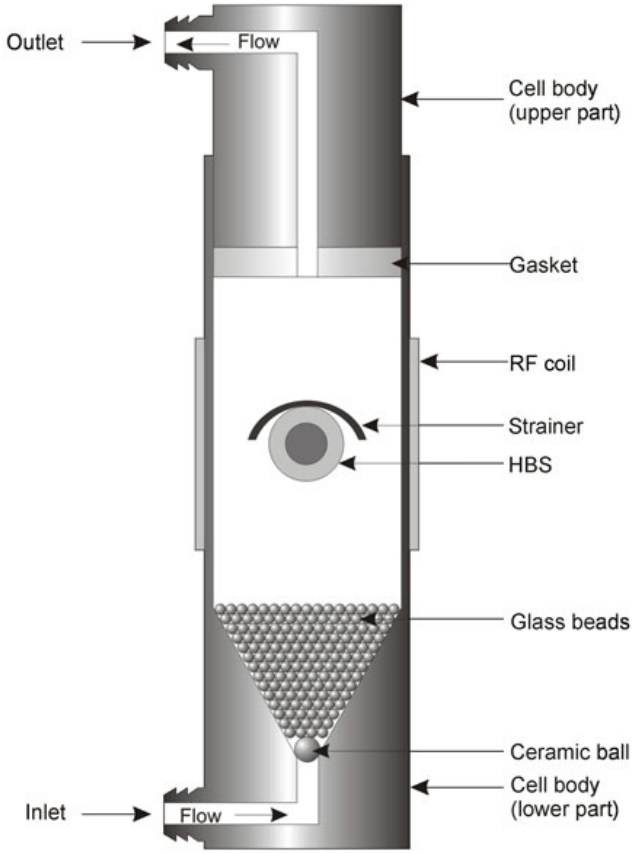

Figure 1. Cross-section of the flow-through cell for dissolution studies of HBS. HBS indicates hydrodynamically balanced systems.

The MR probehead was designed on the base of capacitively coupled radio frequency (RF) saddle coil.

Images were acquired using a modified spin-echo sequence. The flow interferences with echo signal were compensated in the read-and-slice direction by adding extra bipolar gradient lobes to the gradient waveform sequence. There was no compensation in the imaging phase direction; therefore, the imaging read direction was fixed in the flow direction. Imaging parameters were as follows: field of view 3.5 cm, 256 × 256-pixel matrices, slice thickness 1 mm, echo time 19 ms, repetition time 0.625 s, number of accumulations 4, and number of echoes 1. The images were weighted by relaxation times T_1 and T_2.

The image analysis was conducted using ImageJ software (National Institutes of Health, Bethesda, MD).

Dissolution Study

The dissolution of LD was examined using the above-described flow-through cell. The dissolution medium was 1000 mL of FaSSGF or FeSSGF, and the temperature was maintained at 37°C. The samples were taken every half-hour. The withdrawn amounts of solution were replaced by fresh medium. The concentration of LD was determined spectrophotometrically at the wavelength λ 280 nm (Helios β, Unicam, Cambridge, UK).

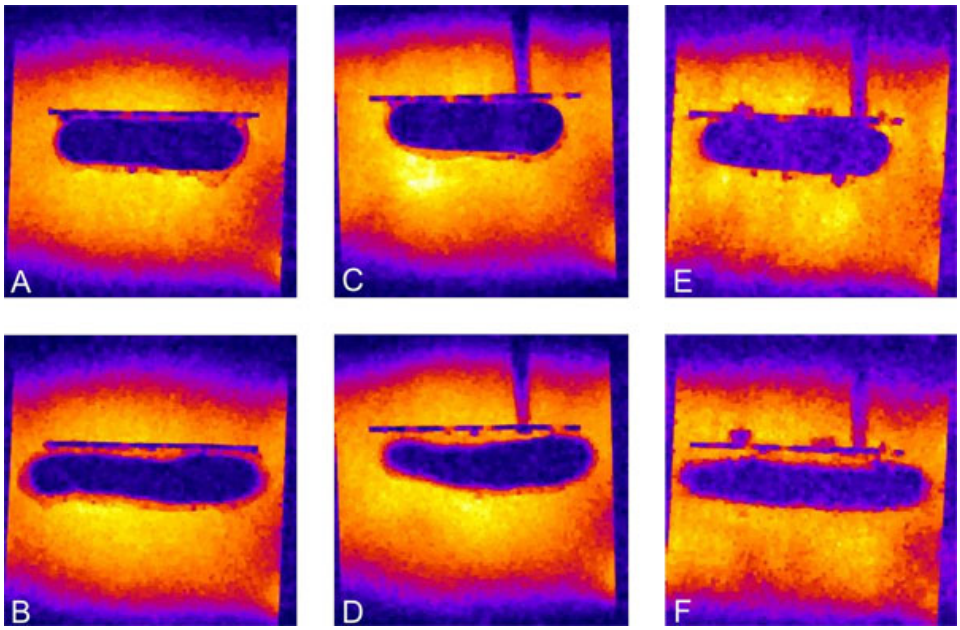

Figure 2. Sagittal MR images of HBS-containing mixtures of L-dopa and HPMC in a 1:3 ratio. (A) HPMC 400 mPa·s after 30 minutes in FeSSGF; (B) HPMC 400 mPa·s after 300 minutes in FeSSGF; (C) HPMC 100,000 mPa·s after 30 minutes in FeSSGF; (D) HPMC 100,000 mPa·s after 300 minutes in FeSSGF; (E) HPMC 100,000 mPa·s after 30 minutes in FaSSGF; (F) HPMC 100,000 mPa·s after 300 minutes in FaSSGF. MR indicates magnetic resonance; HBS, hydrodynamically balanced systems; HPMC, hydroxypropylmethylcellulose; FeSSGF, fed state–simulating gastric fluid; FaSSGF, fasted state–simulating gastric fluid.

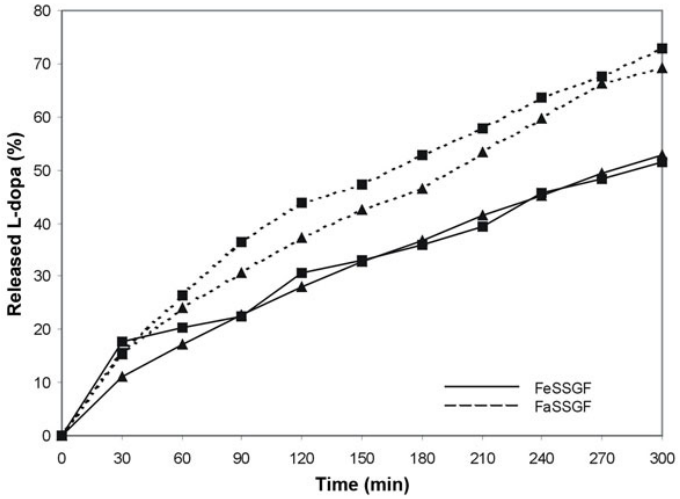

Figure 3. Dissolution profiles of L-dopa from hydrodynamically balanced systems: ■ = L-dopa and HPMC 400 mPa·s (1:3); ▲ =- L-dopa and HPMC 100,000 mPa·s (1:3). HPMC indicates hydroxypropylmethylcellulose; FeSSGF, fed state–simulating gastric fluid; FaSSGF, fasted state–simulating gastric fluid.

Results and Discussion

The hydrogel formation on the surface of the HBS was dependent on the viscosity of the HPMC, its concentration, and the solvent used in the experiment, which was visible on MR images (Figure 2).

When the HBS came into contact with FeSSGF, wetting and dissolving of the hard gelatin shell occurred. In the minutes that followed, the hydrogel was formed on the surface of the HBS. It is clearly visible on the images obtained after a half-hour. The swelling of the polymeric chains had been increasing with an increase of polymer viscosity, but the highly viscous polymers formed a consistent hydrogel that blocked the solvent's deeper penetration into the core of the HBS. It should be noted that during the 5 hours of the experiment, the dry core of the HBS was retained in all cases. The dimensional changes of the HBS were more distinct for the system that contained HPMC 400 mPa·s. In this case the liquid gradually penetrated into the dosage form. In the case of the HBS containing HPMC 100,000 mPa·s, the solvent penetration was hindered after formation of the external layer of swollen polymer.

The behavior of the HBS in FeSSGF and FaSSGF was significantly different. In FeSSGF the hydrogel layer on the surface of the system was well pronounced. It controlled the solvent penetration into the matrix (Figure 2A-2D). In FaSSGF the external surface of hydrogel was quickly removed (Figure 2E-2F). The stretching of the system caused exposition of new layers of the polymer, and for this reason the dimensional changes of the HBS were greater. It should be noted that the changes in the dimensions of the HBS were not the same in all directions. The axial swelling of the system was intensive, while the radial swelling was insignificant. In fact, the system was extended in the axial direction and became thinner in the radial orientation. The axial swelling was more prominent than the radial swelling because of the expansion of polymeric chains, which sum up in the direction parallel to the axis of HBS. This phenomenon induces force with stretching of the system and caused displacement of the dry particles in the core of the system.

The dissolution of LD from the HBS containing HPMC 400 mPa·s or 100,000 mPa·s (1:3) was incomplete. The differences were observed between releasing profiles of LD obtained in FaSSGF and FeSSGF (Figure 3). In fasted conditions almost 75% of the active substance was released after 5 hours. Only ~50% of the drug was released after 5 hours in FeSSGF.

This difference was probably partially caused by the change of the pH of the solution from ~1.2 for FaSSGF to 2.15 for FeSSGF. For a better explanation of this phenomenon, the analysis of dimensional changes of the systems seems to be important. As stated above, the HBS in FaSSGF were intensively stretched because of the swelling hydrogel. The stretching of the system might have caused displacement of the particles inside the dry core of the system. Bettini et al[10] reported that the translocation of the drug particles toward the hydrogel layer with a spring-like action of the wet polymeric matrix influenced the increase in the amount of dissolved drug. Moreover, the layer of hydrogel was relatively thin, so the diffusion distance for dissolved LD was short.

Summary and Conclusions

Without disturbing the observed processes, the MRI methods combined with the dissolution studies provide insight into the phenomena occurring when the dosage form comes into contact with aqueous fluids. The MR images allow one to observe the solvent penetration into the hydrophilic matrix and the hydrogel formation. The data obtained in the MRI studies complement information obtained from the dissolution studies. The analysis of MR images may support the explanation of differences in the drug-releasing or floating properties of HBS.

Acknowledgments

The Ministry of Science and Informatics supported this work, under grant No 2P05F 004 28.

References

1. Davis SS. Formulation strategies for absorption windows. *Drug Discov Today.* 2005;10:249–257.

2. El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral delivery system. *Int J Pharm.* 2001;220:13–21.

3. Choi BY, Park HJ, Hwang SJ, Park JB. Preparation of alginate beads for floating drug delivery system: effect of CO_2 gas-forming agents. *Int J Pharm.* 2002;239:81–91.

4. Richardson JC, Bowtell RW, Mäder K, Melia CD. Pharmaceutical applications of magnetic resonance imaging (MRI). *Adv Drug Deliv Rev.* 2005;57:1191–1209.

5. Dorożyński P, Jachowicz R, Kulinowski P, et al. The macromolecular polymers for the preparation of hydrodynamically balanced systems—methods of evaluation. *Drug Dev Ind Pharm.* 2004;30: 947–957.

6. Fyfe CA, Blazek-Welsh AI. Quantitative NMR imaging study of the mechanism of drug release from swelling hydroxypropylmethylcellulose tablets. *J Control Release.* 2000;68:313–333.

7. Harding S, Baumann H, Gren T, Seo A. NMR microscopy of the uptake distribution and mobility of dissolution media in small, sub-millimetre drug delivery systems. *J Control Release.* 2000;66: 81–96.

8. Sutch JCD, Ross AC, Köckberger W, et al. Investigating the coating-dependent release mechanism of a pulsatile capsule using NMR microscopy. *J Control Release.* 2003;92:341–347.

9. Fyfe CA, Grondey H, Blazek-Welsh AI, Chopra SK, Fahie BJ. NMR imaging investigations of drug delivery devices using a flow-through USP dissolution apparatus. *J Control Release.* 2000;68: 73–83.

10. Bettini R, Cattellani PL, Santi P, Massimo G, Peppas NA, Colombo P. Translocation of drug particles in HPMC matrix gel layer: effect of drug solubility and influence on release rate. *J Control Release.* 2001;70:383–391.