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An integrated system for dissolution studies and magnetic resonance imaging of controlled release, polymer-based dosage forms—A tool for quantitative assessment of hydrogel formation processes

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ABSTRACT

Controlled release (CR) dosage forms are often based on polymeric matrices, e.g., sustained-release tablets and capsules. It is crucial to visualise and quantify processes of the hydrogel formation during the standard dissolution study. A method for imaging of CR, polymer-based dosage forms during dissolution study *in vitro* is presented. Imaging was performed in a non-invasive way by means of the magnetic resonance imaging (MRI). This study was designed to simulate *in vivo* conditions regarding temperature, volume, state and composition of dissolution media. Two formulations of hydrodynamically balanced systems (HBS) were chosen as model CR dosage forms. HBS release active substance in stomach while floating on the surface of the gastric content. Time evolutions of the diffusion region, hydrogel formation region and "dry core" region were obtained during a dissolution study of L-dopa as a model drug in two simulated gastric fluids (i.e. in fed and fasted state). This method seems to be a very promising tool for examining properties of new formulations of CR, polymer-based dosage forms or for comparison of generic and originator dosage forms before carrying out bioequivalence studies.

1. Introduction

Dissolution testing is a well-established method for evaluation of properties of dosage forms. Dissolution studies are usually carried out to ensure quality control and appropriate *in vitro* performance of the manufactured product. One important application of dissolution testing is in the development of new controlled release (CR) dosage forms. The results obtained from the dissolution studies may be enriched by additional analysis of the processes occurring during wetting of the dosage form. Such an analysis could be done using different imaging methods. Most of them are destructive [1–7] and cannot be applied simultaneously with a dissolution study.

Magnetic resonance imaging (MRI) is a well-known imaging technique widely applied in medicine and biology. MRI allows one to obtain cross-sectional or 3D images of the solid materials and living organisms in a non-destructive way. In comparison with medical applications of MRI, the development of the imaging systems for pharmaceutical applications is still limited [8]

The application of MRI in pharmaceutical studies was reported in several papers [9–18]. It was used to explain the phenomena observed during the drug dissolution from CR tablets [14]. Fyfe and Blazek-Welsh [15] carried out research to assess water penetration into hydroxypropylmethylcellulose (HPMC) tablets simultaneously with determination of the diffusion rate of the model drugs (triflupromazine and 5-fluorouracil). Water penetration into the tablet's cores was imaged by 1D ^{1}H MRI and the diffusion of drugs was visualised by 1D ^{19}F MR (magnetic resonance) imaging. Harding et al. [16] employed pulse gradient spin echo (PGSE) and 2D and 3D MRI to measure the mobility and the distribution of dissolution media in submillimeter drug delivery systems. Sutch et al. [17] employed MR microscopy for investigation of release mechanisms in ethylcellulose-coated chronopharmaceutical capsules.

MRI studies of polymeric matrices and polymer-based dosage forms have been performed by various authors [19–23]. The most serious drawback of these studies was their inability to examine *in vivo* conditions with regard to pH, temperature and agitation.

The information obtained from MR images brings better understanding of the phenomena occurring during drug dissolution from dosage form. However, almost all previous MRI studies were

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carried out in static conditions, which did not reflect the agitated conditions of the pharmacopoeial dissolution studies. Fyfe et al. [18] described the system for performing MRI experiments within USP apparatus 4. Their system was applied to record the physical changes of the small tablets simultaneously with a dissolution study. The authors concluded that the information obtained from the MRI combined with dissolution profiles provides invaluable information for the development of novel drug delivery systems.

MR methods are expected to be especially useful for CR formulations. The analysis of internal hydration of dosage form appears to be an effective tool for optimisation of final properties. A special example of CR dosage forms are hydrodynamically balanced systems (HBS) where flotation on stomach content is purported to allow increased gastric residence time and result in drug release localised in the stomach [24–26]. HBS composed of the hydrophilic gel-forming polymer and drug substance in the form of a powder mixed together and placed in a hard gelatine capsule were chosen for the present study as a model CR system to examine the effectiveness of biorelevant imaging system. The simplicity of the formulation provides the opportunity for observation of direct interactions between drug and polymer, without the influence of additional factors (e.g. lubricants, fillers and binders). The capsular form was chosen to avoid compression of the mixtures of powders, which could also change properties of the systems. HBS provides the additional advantage for study as a model system since there has only been one previous report of using imaging to study these dosage forms. An MRI study of an HBS was carried out by Dorożyński et al. [13]. It showed the usefulness of MRI for analysis of properties of an HBS, but in that study MRI was used only as a supplementary method for qualitative observation of matrix polymer properties. As with other MRI studies of CR dosage forms [19–23], the method did not simulate conditions in the stomach: a small volume of solution was used, there was no flow, and no quantitative measurements were performed. The present investigation was initiated to overcome these limitations.

Under experimental conditions *in vitro,* gelatine capsules dissolve completely during the first 5–10 min and dissolved gelatine is conveyed away from the dissolution flow-through cell by the flowing solution. Experimental conditions – flowing solution and highly acidic environment (0.01 or 0.1 M HCl) at temperature 37 °C – mimic gastric conditions *in vivo* according to pharmaceutical standards (USP, Eur. Ph.). A hydrogel layer is formed simultaneously with gelatine capsule dissolution. This layer ensures shape integrity of the system after gelatine capsule dissolution. Moreover, it controls dissolution of the drug and keeps air entrapped among the particles of polymer and drug in the core of the HBS. The air entrapped in the core ensures the flotation of the dosage form.

When studying sustained-release, polymer-based dosage forms there is a one critical feature, which could be analysed by means of MRI: formation and time evolution of the hydrogel layer, which controls the release rate of the drug. Additionally, in the case of HBS, retention of the "dry core", which enables the dosage form flotation, could be studied.

The aims of the presented work were

- to develop a system for dissolution studies and MRI of sustained-release, polymer-based dosage forms simultaneously;
- to simulate *in vivo* conditions as closely as possible;
- to analyse MR images to obtain quantitative information about processes occurring inside the dosage form during hydration;
- to evaluate the system and to assess the usefulness of this method as applied to investigations of CR, polymer-based dosage forms;
- to perform study using model dosage forms (two HBS formulations) in two different dissolution media.

2. Materials and methods

2.1. Materials

L-dopa (LD) was obtained from Sigma, HPMC Metolose grade 90 SH, viscosity 100,000 cP manufactured by Shin-Etsu was obtained from Syntapharm and hard gelatine capsules Coni-Snap size 0 were obtained from Capsugel. All other materials were of analytical grade.

The mixtures of L-dopa and HPMC in 1:1 and 1:3 ratios were prepared using mortar and pestle. Capsules were filled manually with non-compressed powders corresponded to 100 mg of L-dopa.

2.2. MRI system

2.2.1. Magnet and console

A research system with digital MARAN DRX console (Resonance Instruments), 4.7 T/310 mm horizontal bore magnet (Bruker) equipped with actively shielded gradient set of 200 mm (Magnex Scientific) was used for MRI studies.

2.2.2. Flow-through cell and RF probehead

Dissolution study could not be performed in the typical, commercially available devices for dissolution testing. Such devices contain parts made of magnetic materials, which cannot be placed in a strong magnetic field, and they do not allow the dosage form to float inside the dissolution cell. To overcome the restrictions a special, MR compatible (Plexiglass), flow-through cell for CR, polymer-based dosage forms investigation was designed (Fig. 1). The inner diameter of the cell was 35 mm, and it was sufficient to fit swelling capsules of initial length of 15–25 mm in horizontal position. Solution was flowed through the cell from the bottom. A cone-like, lower part of the cell was filled with glass beads to establish the laminar flow of the solvent. A flow-through cell was combined with the MR probehead and the holder.

The MR probehead was based on capacitively coupled saddle radio frequency (RF) coil at 40 mm ID. Probehead with the flow-through cell was mounted in the holder, which enables positioning of the cell in the magnet bore. The cell was designed to ensure the proper positioning of the dosage forms. The tablets in the flow-through cell were placed on the supporting strainer, while HBS floated under the specially profiled strainer. In both cases, the dosage form was kept in a horizontal position in the centre of RF coil and was oriented along the direction of B_0 field.

The schematic diagram of the complete system for dissolution studies and MRI of sustained-release, polymer-based dosage forms is presented in Fig. 2. The system enables MR imaging of CR, polymer-based dosage forms during dissolution test in a flow-through cell. The cell was placed in the magnet. The solvent circulation was forced in a closed loop using a peristaltic pump. Solvent temperature was maintained by a thermostatic water bath coupled with a solution temperature sensor at the outlet of the flow-through cell.

2.2.3. MR imaging pulse sequence with flow compensation

MR images were obtained using a spin echo (SE) pulse sequence, which was modified to compensate for the effects of the flowing solvent (Fig. 3).

Back-to-back bipolar gradient pulse sequences was used to design flow insensitive sequences—the method called gradient first moment nulling [27]. When two bipolar gradient pulse sequences that are equal in magnitude but reversed in polarity are applied to the spin system, the resulting phase is independent on the velocity and position (see the fragment of gradient G_z pulse sequence marked by dashed line). Both the zero-order (m_0) and the first-

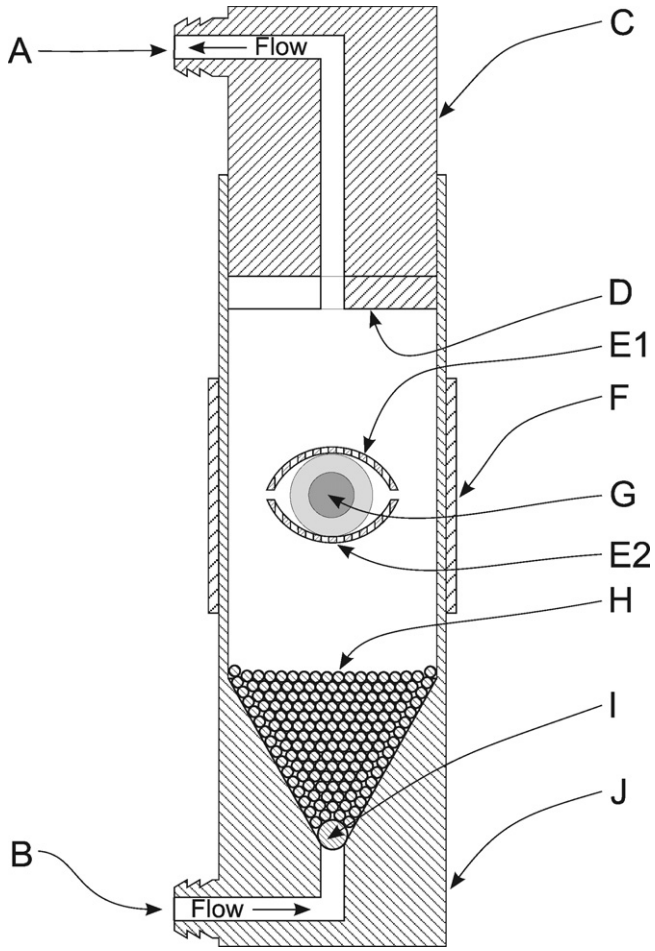

Fig. 1. Cross-section of the flow-through cell for dissolution studies of the sustained-release dosage forms: A, outlet; B, inlet; C, cell body (upper part); D, gasket; E1, strainer (for positioning HBS only); E2, strainer-support (for tablets only); F, RF coil; G, HBS in axial cross-section (hydrogel layer, light grey; "dry core", dark grey); H, glass beads; I, ceramic ball; J, cell body (lower part).

order (m_1) moments of the back-to-back bipolar gradient pulse sequence are zero, where m_1 and m_0 were expressed using the following equations:

$$m_0 = \int G(t)\,\mathrm{d}t \tag{1}$$

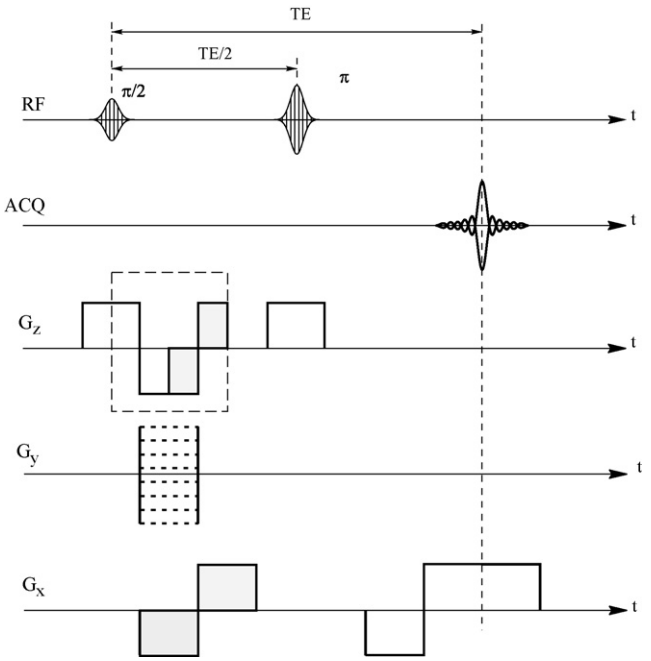

Fig. 3. Spin echo sequence with flow compensation for MR imaging.

$$m_1 = \int G(t)\,t\,\mathrm{d}t \tag{2}$$

Concerning the spin echo pulse sequence depicted in Fig. 3, the acquired signal was flow compensated in read and slice direction by adding extra bipolar gradient lobes to the standard pulse sequence (grey shaded fragments in the pulse sequence diagram). There was no flow compensation in imaging phase direction; therefore the imaging read direction was set parallel to the flow direction.

The amplitude of the signal s in a steady state is given in Eq. (3) [28]. It depends on selected TE and TR, where TR is the time between consecutive repetitions of the pulse sequence depicted in Fig. 3; TE is the echo time.

$$s(\mathrm{TR,TE}) \sim \rho(1 - \mathrm{e}^{-\mathrm{TR}/T_1})\mathrm{e}^{\mathrm{TE}/T_1} \tag{3}$$

The signal intensity obtained with SE pulse sequence is proportional to spin-density in the sample volume ρ (proton concentration) weighted by relaxation times T_1 and T_2.

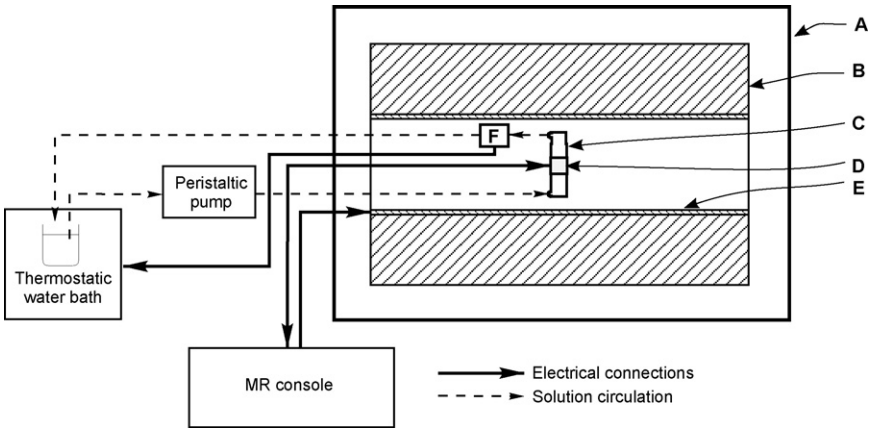

Fig. 2. Schematic diagram of the system for dissolution studies and MRI of sustained-release dosage forms: A, Faraday cage; B, superconducting magnet; C, flow-through cell; D, RF coil; E, gradient coils; F, temperature probe.

During the experiment, echo time (TE) of 19 ms and repetition time (TR) of 0.625 s were selected to obtain appropriate contrast. It gave the possibility to visualise and to distinguish fully and partially hydrated polymer. The inner part of the dosage form could be treated as a "dry core". However, "dry core" was not completely dry during the experiment—less mobile water molecules (bound water) gave a very small but increasing contribution to the MR signal. Other imaging parameters were as follows: field of view, 3.5 cm; number of slices, 7 (for saggital slices) and 23 (for axial slices); slice thickness, 1 mm; number of signal accumulations, 2 or 4.

Obtained MR images were 256×256 pixel matrices, and image intensity was encoded using 8-bit grey scale (GS). The black and dark grey colours (values near zero level) characterised "dry" regions of the dosage form. The higher values corresponded to increasing water concentration in partially and fully hydrated parts of the dosage forms and in the solvent.

2.2.4. Protocol for dissolution study and MR imaging

The experiments were carried out using two different solutions. The first one, fasted state simulating gastric fluid (FaSSGF) was 0.1 M HCl solution. The second, fed state simulating gastric fluid (FeSSGF) was 0.01 M HCl solution with addition of sodium laurylsulfate (2.5 g/l) and sodium chloride (2 g/l) [29]. In both cases, the addition of 5 mM of $CuSO_4$ as a relaxation agent was necessary to shorten T_1 relaxation time of the solution.

The capsule was inserted into the cell and the solution circulation was started. The total volume of dissolution medium was 1000 ml and the temperature was maintained at 37 °C. Before the image acquisition was started, a B_0 homogeneity correction was performed. The experiment was carried out for 5 h to cover the changes in process.

The images were taken every half an hour and the total acquisition time of the single image set was assumed 5 min (number of accumulations, 2) for FeSSGF and 10 min (number of accumulations, 4) for FaSSGF, which ensured good signal-to-noise ratio.

For dissolution study, solution aliquots (5 ml) were withdrawn every half an hour during the experiment. Equal amounts of dissolution media were replaced after withdrawal of each aliquot. The concentration of L-dopa was determined spectrophotometrically at a wavelength $\lambda = 280$ nm (Helios Beta UV–Visible spectrophotometer, Unicam, Cambridge, UK). Each measurement was carried out in triplicate.

3. Results and discussion

3.1. Setup of the MRI experiment

A preliminary study was performed using HBS formulation containing L-dopa and HMPC in 1:3 ratio. MR images were recorded for 5 h to visualise the process of hydrogel formation according to the protocol described above.

When performing a study using FaSSGF, the acquisition time was doubled compared with FeSSGF but the signal-to-noise ratio was lower due to heavy loading of the probe by FaSSGF (a strong electrolyte, 0.1 M HCl) [30]. Solvent penetration inside the HBS capsules was detected through observation of changes in proton signal intensity. The typical saggital images of examined HBS captured in the FaSSGF and FeSSGF during 5 h are presented in Fig. 4. The dry polymer in the inner space of the system remained dark due to the low intensity of the proton signal.

In several published works, a "moving front" term was introduced [3,4]. The moving front denotes the position in CR matrix where the physical conditions sharply change. "Swelling front" denotes a position, which separates dry polymer in its glassy state and moistened polymer in its rubbery state. A "diffusion front" is the boundary that separates wet polymer and clear hydrogel. An "erosion front" separates polymeric matrix (i.e. hydrogel) from the solvent. This terminology was adapted as a starting point to the MR image analysis of the model dosage form (HBS).

The image pre-processing and segmentation were carried out in the following steps:

1. A fragment of the image containing all fractions of the model dosage form and solution in approximately equal areas was chosen.
2. A histogram of the selected fragment was made and fitted using a set of Gauss functions.
3. Fitted peaks were grouped, and the groups were attributed to the areas on the image, which have certain properties, i.e. to areas between the fronts.
4. The thresholds, which enable separation of the areas, were chosen.
5. The images were segmented using selected thresholds.

An example of the image segmentation is presented in Fig. 5. A histogram and its fit are presented in Fig. 5E. The intensities of the "dry core" in the original image were in the range of 0–30. The partially hydrated polymer was characterised by the intensities in the range of 31–70 while intensities of fully hydrated polymer were in the range of 71–147. Fig. 5A shows the original image, while the results of image segmentation are presented in Fig. 5B–D ("dry core" region, hydrogel formation region and diffusion region, respectively).

In previous scientific articles concerning water penetration into polymeric matrices [4], the front positions were measured as a distance from the centre of the matrix. Because the shape of examined HBS has no circular symmetry, the front positions could not be determined in this way. The areas between the fronts were utilised rather than positions of fronts themselves.

The areas encircled by the fronts were measured on a central longitudinal cross-section of HBS. The region between the erosion and diffusion front containing hydrogel was identified as the diffusion area. In this part of the dosage form, drug dissolution and diffusion as well as water diffusion occur. The swelling front encircles the "dry core" area, which contains non-compressed powder and the air trapped among the powder grains. It is responsible for floating properties of this HBS. The space between these two areas, where the hydrogel was formed, is identified as area of hydrogel formation.

Based on these arrangements, analysis of the time evolution of areas of HBS regions was undertaken. Moreover, because the length and radial dimension of the capsule were changing, not only areas but also global dimensions of HBS were taken into consideration.

3.2. Comparative study using HBS as a model dosage form

To show the versatility of the method, a study using two formulations of HBS and two dissolution media was performed. Formulations containing L-dopa and HPMC in 1:1 and 1:3 ratios were examined in FeSSGF and FaSSGF by means of the methodology described above.

3.2.1. MRI study

Based on image sets presented partially in Fig. 4, the dimensional changes of the systems were measured. The length of the HBS 1:3 in FaSSGF increased about 42% from 2.4 ± 0.1 cm at the beginning of the experiment to 3.4 ± 0.2 cm after 5 h. At the same time the radial dimension of the dosage form decreased 15.4% from 0.65 ± 0.03

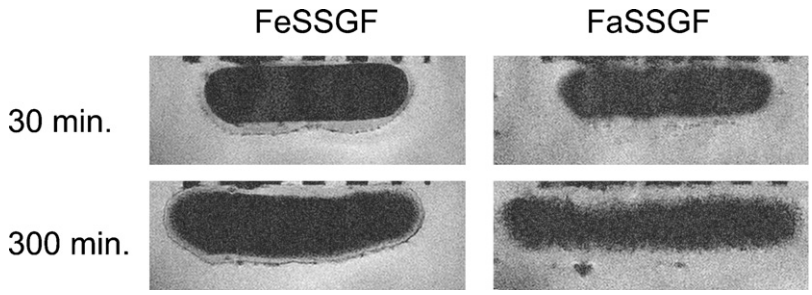

Fig. 4. Saggital MR images of HBS containing mixture L-dopa and HPMC in 1:3 ratio in FeSSGF and FaSSGF at 60 and 300 min.

to 0.55 ± 0.02 cm. Mitchell et al. [7] observed similar phenomena for small tablets containing various kinds of HPMC. In FeSSGF, the expansion of swelling hydrogel was more restricted. The length of the HBS increased only 25% from 2.4 ± 0.1 to 3.0 ± 0.1 cm. Radial dimension was 0.65 ± 0.02 and was constant during the experiment.

The measurements of the HBS containing mixtures of HPMC and L-dopa in a 1:1 ratio have shown that the axial swelling of the system was larger then for the 1:3 ratio. In FaSSG the length of the system increased about 54%, whilst in FeSSGF it increased about 35%. Similarly, as in the case of HBS 1:3 in FaSSGF, the longitudinal stretching of the system was connected with the decrease of the radial dimension of HBS.

The areas of the diffusion, hydrogel formation and "dry core" regions of the systems as defined in the previous section were measured on consecutive MR images. The results of these measurements are presented in Figs. 6–8. The changes of areas have been expressed as a percentage of total initial area of the dosage form cross-section.

For the mixture of HPMC and L-dopa in a 1:3 ratio diffusion area (Fig. 6) remained constant after an initial increase. In FeSSGF, the diffusion area initially increased to 31.2% at 30 min, then remained at 27.4% between 90 and 270 min. In FaSSGF diffusion area initially increased to 30.1% at 120 min, then it remained at 31.6%, between 120 and 210 min.

For HPMC and L-dopa in a 1:1 ratio, the time evolution of the diffusion area was more complicated. In FeSSGF, the diffusion area initially increased reaching a maximum (52.9%) at 120 min, then decreased to 33.9% at 210 min. In FaSSGF it initially increased to 30.5% at 60 min, then slowly increased (0.0379%/min) with average area 33.9% between 60 and 210 min. Finally, a rapid increase up to 64.7% at 300 min was observed.

For a 1:3 formulation, linear increases of the hydrogel formation area with a rate of 0.049%/min ($R^2 = 0.983$) in FeSGGF and

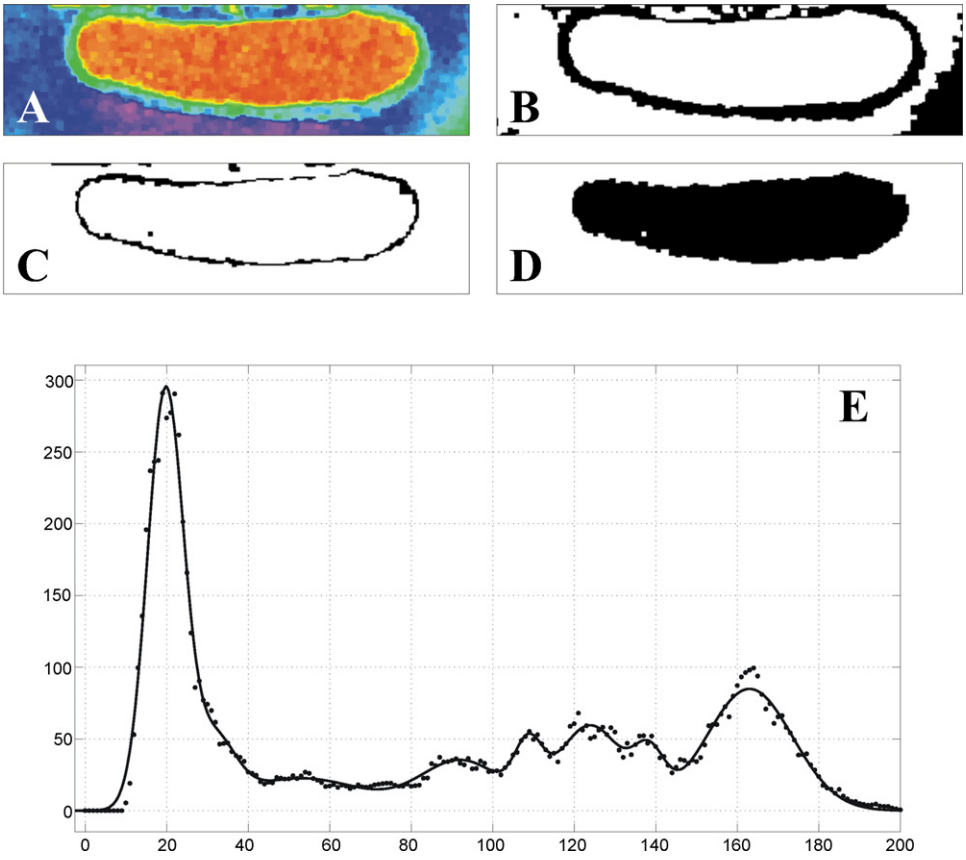

Fig. 5. Image segmentation: A, original image; B, segmented "dry core" area; C, segmented hydrogel formation area; D, segmented diffusion area; E, histogram of the original image (points) and its Gaussian fit (continuous line). Threshold values for segmentation were set as follows: 31, 71 and 147.

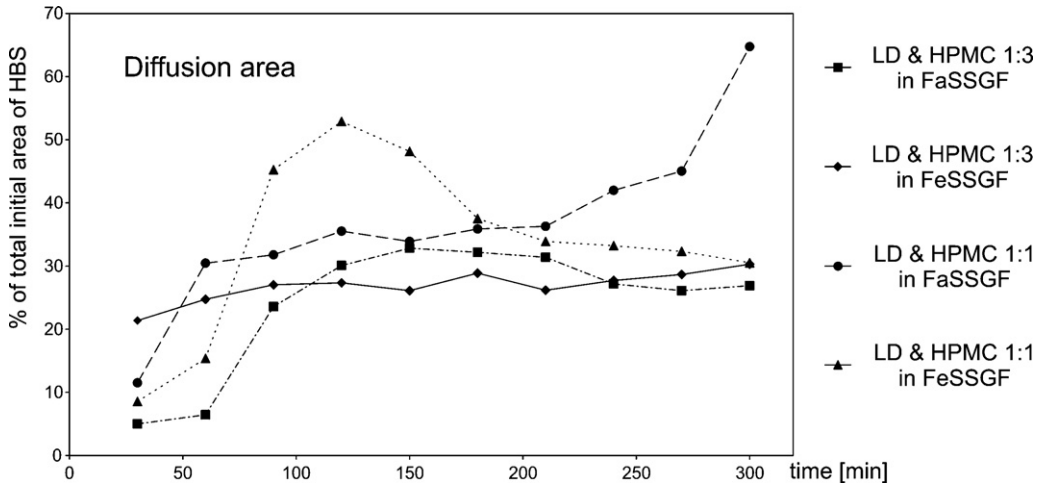

Fig. 6. Time evolution of diffusion area of central, longitudinal cross-section of two HBS formulations in FeSSGF and FaSSGF.

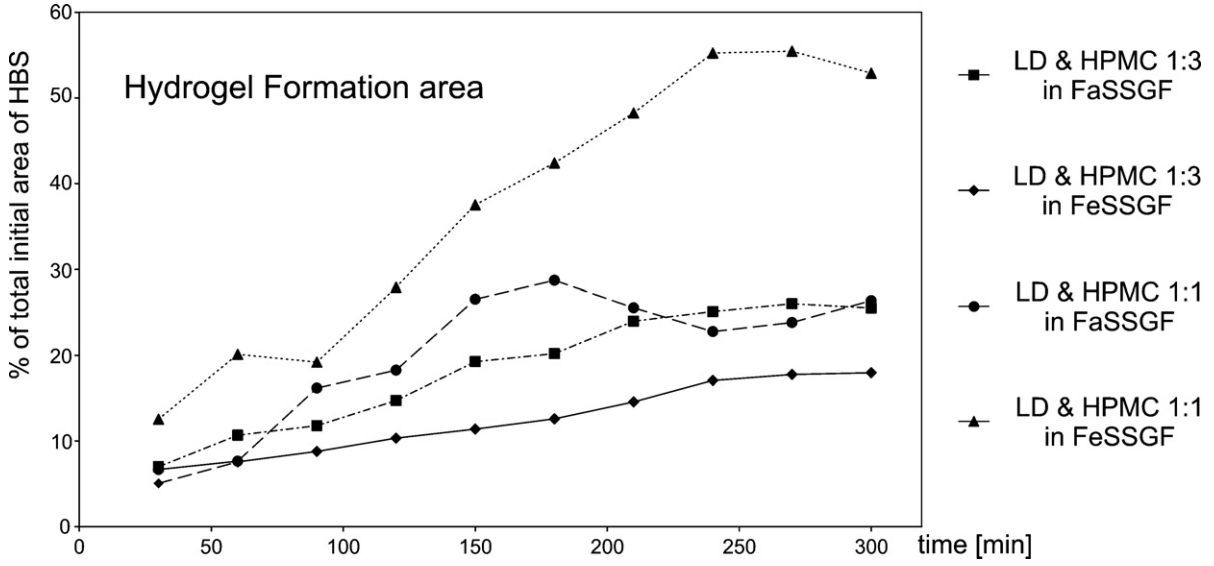

Fig. 7. Time evolution of hydrogel formation area of central, longitudinal cross-section of two HBS formulations in FeSSGF and FaSSGF.

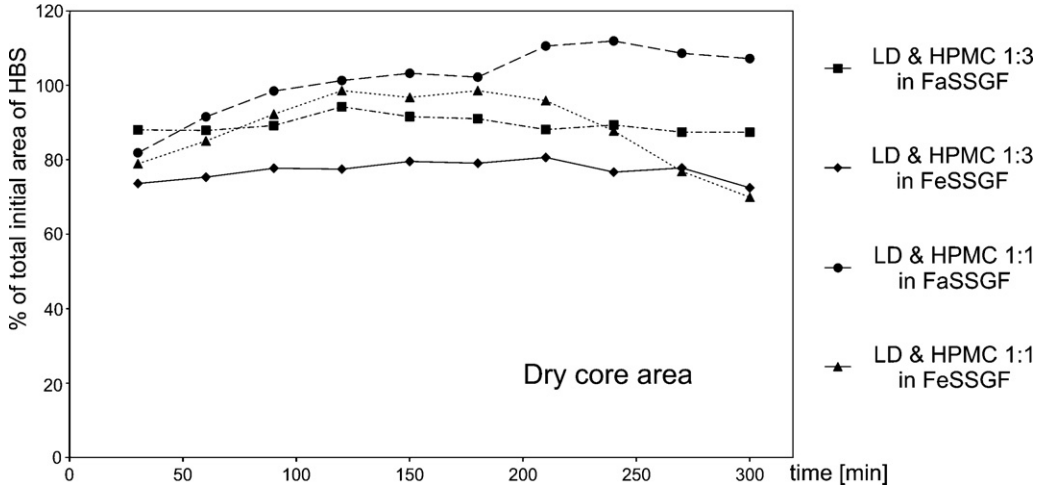

Fig. 8. Time evolution of "dry core" area of central, longitudinal cross-section of two HBS formulations in FeSSGF and FaSSGF.

0.075%/min (R^2 = 0.949) in FaSSGF throughout the whole period of 5 h were observed (see Fig. 7).

When studying 1:1 formulation in FeSSGF, the hydrogel formation area increased up to 55.2% at 240 min. Between 60 and 240 min, it increased with a rate of 0.234%/min (R^2 = 0.988). In FaSSGF, maximum (28.7%) was reached at 180 min after a steady increase of 0.161%/min (R^2 = 0.962) between 30 and 180 min. After the maximum area was reached, a slight decrease was observed in both cases.

For the mixture of HPMC and L-dopa in a 1:3 ratio, the "dry core" (Fig. 8) was stable during the experiment with an average area of 77% in FeSSGF and 89.4% in FaSSGF.

For the 1:1 formulation, "dry core" area increased in FaSSGF from 81.8% at 30 min to 107.1% at 300 min. In FeSSGF, the "dry core" area evolved from 78.9% at 30 min to an average area of 97.9% between 120 and 180 min. Finally, it decreased to 69.8% at 300 min.

3.2.2. Dissolution study

Dissolution study was performed once with MR imaging, and additionally two times using the flow-through cell outside the magnet. The results presented in Fig. 9 are mean values ± S.D. The cumulative dissolution profiles of LD in both simulated gastric fluids are shown in Fig. 9. LD released gradually from the HBS. The amounts of LD released in FaSSGF from both formulations (1:1, 1:3) were greater than in FeSSGF. In fasted condition, almost 75% of active substance was released after 5 h. In the same time, in fed condition, only about 50% of drug was released. This difference was probably caused by the pH difference of the solutions (pH 1.2 for FaSSGF and pH 2.15 for FeSSGF).

The dissolution profiles in the fed state (in FeSSGF) for 1:3 and 1:1 formulations were very similar, except for the initial dissolution rate (see Fig. 9). About 18% of active substance was dissolved after the first 30 min for the 1:3 formulation and about 11% for the 1:1 formulation, consistent with the MRI results. One could observe a faster initial diffusion region development for the 1:3 formulation in FeSSGF (21.4% of initial area of HBS after the first 30 min for 1:3 formulation vs. 8.5% for 1:1 formulation) (for comparison see Fig. 6).

The results of dissolution studies indicate that the main factor influencing the drug dissolution is the type of medium. Surprisingly, the concentration of HPMC in the formulation had no significant influence on drug release. MRI studies have shown the differences in the behaviour of polymeric matrices during dissolution. This suggests that the drug dissolution mechanism may vary with the composition of the dosage form, although it was not clearly seen in the dissolution profiles. It is possible, that such formulations behave differently *in vivo* taking into consideration the properties of the hydrogel matrix.

Dissolution is widely used as an evaluation tool for CR dosage form development. For example, in generics industry, it serves as a basic tool for retracing properties of the originator drug. Combining information from dissolution experiment and MR imaging provides additional knowledge, which could be helpful in rationalising pharmacokinetics and help achieve a desired profile (e.g. bioequivalence to a competitor product).

3.2.3. Common observations

As was stated above, the HBS in FaSSGF was intensively stretched in a longitudinal direction due to hydrogel swelling. It seems that the process of hydrogel formation determine the shape of the studied HBS. The "dry core", composed of the non-compressed powder, adapts to the shape of hydrogel. "Dry core" dimensions were retained throughout the experiment, despite of substantial changes in the overall linear dimensions. The presence of the "dry core" of the HBS ensures that the floating properties of the dosage form were retained.

A high percentage of the active substance dissolved while most of the "dry core" remained intact. This may reflect the high drug solubility or could support alternative mechanisms of water transport in polymers [31], which do not require a concentration gradient. Detailed discussion of this topic is out of the scope of the article.

3.3. Comparison with previous MRI studies

According to our knowledge, most of the MRI investigations of polymeric matrices so far were performed using narrow-bore MR systems (diameter of radiofrequency coil about 10 mm) [19–23]. It limits the size of a dosage form (up to diameter of 10–12 mm) and the experimental conditions (first of all relatively small volume of the dissolution medium) that can be used.

Experimental conditions of the selected studies are collected in Table 1.

Drawbacks of previous methodologies can be summarised as follows:

- dosage form size and its expansion highly restricted,
- small volume of the medium (volume of the medium rarely given explicitly as an experimental parameter),

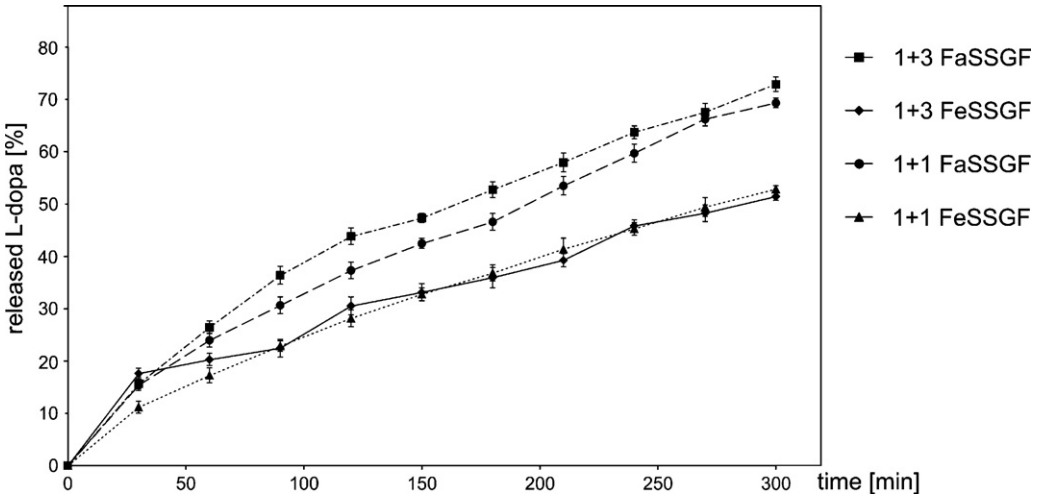

Fig. 9. Dissolution profiles of LD in FeSSGF and FaSSGF from two formulations of HBS (mean values ± S.D.).

Table 1
Comparison of selected MRI studies of hydrophilic matrices

Reference	Size of the matrix	Matrix type	Active substance	Dissolution medium	Volume of dissolution medium	State of dissolution medium	Temperature of the dissolution medium	Simultaneous MRI/dissolution study
[19]	Diameter of 9 mm, thickness of 3 mm	Tablet compressed at 0.3 GPa (Eudragit)	Diltazem hydrochlorie	Water	N.A.	Static	Room temperature	No
[20]	Diameter of 12 mm, thickness of 4.4–5 mm	Tablet compressed at 100 N (HEC, HPC, HPMC)	No	Purified water	N.A.	Static	Room temperature	No
[21]	Diameter of 10 mm	Tablet	Theophylline anhydrous procaine amide hydrochloride	Ultra-pure water	15 ml	Static	Room temperature	No
[22]	N.A. (~30 mm long, 10 mm wide)	Immediate release tablet	Paracetamol	Water + hydrohloric acid (pH 2)	N.A.	Static	Controlled: 19 and 37 °C for 2D images	No (disintegration study only)
[23]	Diameter of 10 mm	Tablet (L-HPC, P-HPC, HPMC)	No	Ultra-pure water	N.A.	Static	Room temperature	No
This study	Up to 3.5 cm long after swelling	HPMC powder	L-dopa	0.1 M HCl (pH about 1.2) and 0.01 M HCl (pH about 2.15) + sodium laurylsulphate + sodium chloride	70 ml in the cell and 1 l in circulation	Dynamic (flow)	Controlled: 37 °C	Yes

- water, even ultra-pure water, as a dissolution medium,
- medium in static condition,
- medium at room temperature,
- lack of comparison with dissolution of the drugs.

It is known that many factors such as temperature, pH and active substances could influence polymeric matrix phase transitions and thereby influence the formation and erosion of the hydrogel layer, and consequently influence drug dissolution. In addition, use of ultra-pure water as a dissolution medium at room temperature could provide non-predictive results.

In contrast, the presented system has a coil diameter of 4 cm. It was therefore possible to perform studies of dosage forms up to 3.5 cm long (e.g. CR tablets or swollen HBS). Volumes of the dissolution media inside the flow-through cell were about 70 ml, and the total volume of recirculating medium was 1 l. The present study was performed for two types of the media: 0.1 M HCl (simulated gastric fluid in fed state) and 0.01 M HCl with addition of sodium laurylsulfate and sodium chloride (simulated gastric fluid in fasted state). The present system enabled a more realistic dissolution condition (USP4) to be used. The setup allows changing pH of the solution during the study as a mimic of the *in vivo* situation.

The influence of the meal composition on the properties of the dosage forms is often reported in the scientific papers [32,33]. The proposed method enables the possibility of analysing the influence of various media compositions, including media with addition of meal components (e.g. fats, proteins, sugars) on the properties of CR dosage forms *in vitro*.

4. Conclusions

The main and the original results of the study are

- Development of a system for simultaneous MR imaging and dissolution studies of CR, polymer-based dosage forms – tablets and HBS up to 3.5 cm long – under flow condition with an acidic environment;
- Performing MR imaging simultaneously with the dissolution study of L-dopa from the model dosage form (HBS) in conditions, which are the best to date simulation of *in vivo* situation regarding temperature, volume, state and composition of dissolution media;
- Obtaining time evolution profiles of cross-sectional areas of the model dosage form regions (i.e. diffusion, hydrogel formation, "dry core" regions) from MR images for two formulations in two different solutions.
- Unique possibility to study together several phenomena, which influence properties and performance of the CR, polymer-based dosage forms, i.e. hydrogel formation and erosion, drug dissolution and flotation.
- Unique possibility to assess and contrast the properties of dosage forms having similar dissolution profiles—these properties can influence *in vivo* performance (especially useful for comparison of generic and originator dosage forms before carrying out bioequivalence studies).

As was stated in Section 1, earlier studies lacked quantitative results [13,15]. Comparing with literature data it was shown that quantitative measurements are possible, i.e. time evolution of the hydrogel region of a CR dosage form.

Observation and quantification of dynamics of hydrogel formation, erosion and "dry core" retention of CR, polymer-based dosage forms have not been possible using other imaging methods. MRI can be used to observe these processes in a non-destructive and non-

invasive way without any manipulation. The dosage form remains all the time inside the flow-through cell under the continuous flow conditions.

Insight into the processes of formation of an external polymeric layer together with data describing drug release rates, gives the opportunity to formulate CR systems with desired properties. For example, the possibility exists of finding a composition of a polymeric matrix and drug, which gives a synchronised development of moving fronts. Particularly, this could give a rationalised method for design of formulations with predefined drug release kinetics (e.g. zero-order).

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