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New release cell for NMR microimaging of tablets Swelling and erosion of poly(ethylene oxide)

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Abstract

A small release cell, in the form of a rotating disc, has been constructed to fit into the MRI equipment. The present work show that both qualitative and quantitative information of the swelling and erosion behavior of hydrophilic extended release (ER) matrix tablets may be obtained using this release cell and non-invasive magnetic resonance imaging (MRI) studies at different time-points during matrix dissolution. The tablet size, core size and the gel layer thickness of ER matrix formulations based on poly(ethylene oxide) have been determined. The dimensional changes as a function of time were found to correspond well to observations made with texture analysis (TA) methodology. Most importantly, the results of the present study show that both the erosion (displacement of the gel–dissolution media interface) and the swelling (decrease of dry tablet core size) proceed with a faster rate in radial than in axial direction using the rotating disk set-up. This behavior was attributed to the higher shear forces experienced in the radial direction. The results also indicate that front synchronization (constant gel layer thickness) is associated with the formation of an almost constant polymer concentration profile through the gel layer at different time-points.

Keywords: Magnetic resonance imaging; Extended release; Hydrophilic polymers; Erosion; Swelling; Dissolution

1. Introduction

Magnetic resonance imaging, MRI, is a branch of NMR spectroscopy and was first proposed by Lauterbur (1973). MRI is still a relatively new technique that has been established during the last 20 years as diagnostic tool at most major hospitals. Over the last years, the technique has grown in importance in materials science; since, it is possible to produce maps showing the spatial distribution of NMR properties, such as spin density, relaxation times or diffusion constants in the sample, which in turn relate to specific properties of the material (Price, 1998). The interest of the MRI technique from the pharmaceutical companies is high both regarding in vivo studies on animals and as a tool for pharmaceutical formulation development. A few relevant NMR microimaging reviews in the field of pharmaceutical formulations exists that covers most of the work carried out by academia and industry during the last years (Melia et al., 1998; Richardson et al., 2005). For solid oral tablet formulations, the method has generally been used to characterize the dimensions of tablets during swelling in various media under unstirred conditions (Rajabi-Siahboomi et al., 1996, 1994; Fahie et al., 1998; Fyfe and Blazek, 1997; Hyde and Gladden, 1998; Madhu et al., 1998; Kojima and Nakagami, 2002). Only a few investigations are performed under non-static conditions. By the use of a so-called flow-through cell the tablet swelling and dissolution has been studied under sink conditions simultaneously with parallel release measurements (Fyfe et al., 2000). The actual concentration of polymer or water in the swollen matrix during swelling of poly(ethylene oxide) tablets has been determined quantitatively by a combination of MRI measurements and parallel measurements of proton relaxation times (T_1 or T_2) or self-diffusion coefficients (SDC) by NMR spectroscopy for equilibrated polymer samples (Fyfe and Blazek, 1997; Hyde and Gladden, 1998; Baumgartner et al., 2005).

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The aim of the present work has been to develop a NMR microimaging (MRI) method for non-invasive studies of both the swelling and the erosion during dissolution of pharmaceutical single dose tablet formulations. Visualisation of these kinetic processes combined with simultaneous polymer release studies has not been performed extensively previously. In the present work, the extent of swelling is defined by the position of the interface between the dry (or almost dry) polymer core and erosion is defined as the process occurring at the interface between the gel layer and the dissolution media. The term dissolution is used for the amount of polymer released and its concentration determined in the dissolution media. The first goal has been to develop a MRI release cell so that MR images can be recorded directly at different time-points during the dissolution process under controlled stirring conditions with possibility for sample collection for determination of release of various components from the formulation. Secondly, the aim was to establish a microimaging method suitable for formulations composed of hydrophilic polymers, such as polyethylene oxide (PEO), and to obtain not only qualitative results but also quantitative information. A final aim was to evaluate the results obtained in this work with corresponding information obtained with other methods, such as texture analysis (TA) (Körner, 2006) and simulation tools (Borgquist, 2005).

2. Materials and methods

2.1. Materials and sample preparation

Formulations of the present investigation were based on polyethylene oxide, PEO (WSR N60K and WSR N-10), obtained from Dow Chemical. The M_w's for the PEO samples are 2.19×10^6 and 122×10^3 g/mol, respectively, and were in this work denoted as PEO 2 and PEO 0.1. The tablets of pure PEO 2 and PEO 0.1 as well as mixtures between those, PEO 8812 with a weight ratio PEO 0.1:PEO 2 of 88:12, were prepared by direct compression using 12 mm punches (Körner et al., 2005). The tablets were glued to the center of a rotating disc (Fig. 1b as described further below) using a water impermeable glue (Eudragit™ based). Prior to the MRI investigations the tablets, attached to the disc, were vacuum treated (Fyfe and Blazek, 1998). The rotating disc with the attached tablet was inserted into a separate glass container that was sealed and connected with vacuum. The duration of the vacuum treatment of the tablet was at least 5 min. Thereafter, still under vacuum, dissolution media was injected through a septum into the glass container. The dissolution media was allowed to cover the whole tablet before the vacuum treatment was stopped. The rotating disc with the glued tablet was then quickly (max 1 min) transported from the glass container to the MRI release cell (Fig. 1) which was inserted into the MRI probe in order to be able to record images directly at the beginning of the dissolution process.

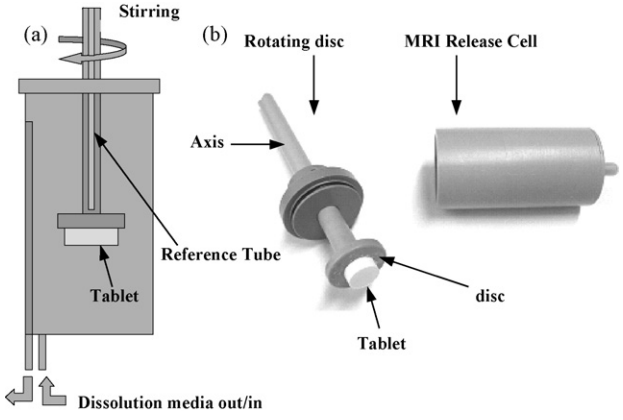

Fig. 1. Schematical drawing of the MRI release cell: closed (a) and open (b). Arrows mark the stirring, inlet and outlet of dissolution medium.

Reference polymer samples were prepared by dissolving appropriate amount of polymer in distilled water in 10 mm glass tubes. The samples were vigorously stirred for some seconds and then centrifuged once before the glass tubes were sealed by melting. In order to obtain homogeneous samples, the sealed tubes were centrifuged back and forth several times (>10 times), for at least 5 min each time, using a table centrifuge (WIFUG, Bradford, UK) at 3700 rpm (about 2400 g).

2.2. Design and construction of release cell

A small release cell, Fig. 1, made from PEEK (poly oxy-1,4-phenylenoe-oxy-1,4-phenylene-carbonyl-1,4-phenylene) that has been designed to fit into the MRI probe has been constructed (20–25 ml, $r_{outer} = 15$ mm, $r_{inner} = 12.6$ mm, $h_{outer} = 58$ mm, $h_{inner} = 53.5$ mm). The cell is equipped with a rotating disc to which the tablet may be glued. The present set-up allows the rotation speed of the rotating disc to be varied. The release cell is presented schematically in Fig. 1. A rotating axis has been constructed and arranged so that the rotating disc is situated 1 mm above the center of the MRI probe during measurements, i.e. allowing optimal placement of the attached tablet. This rotating axis has also a hole drilled in the center where a reference sample may be placed, Fig. 1a. At the top of the rotating axis a V-shaped cut into the axis is made in order to make connection to an external stirrer possible.

2.3. Set-up for MRI studies during tablet dissolution

The release cell is, via plastic tubes, connected to a larger container so that sufficient amount of dissolution media may be obtained to achieve sink-condition. Pumping (about 3 ml/min) between the two containers is gained by a peristaltic pump (HAAKEF3, Germany). The stirring was made with an Eurostar digital stirrer (IKA Werke GmbH & Co. KG, Germany). In order to connect the stirrer to the axis of the MRI release cell a long shaft made of aluminum is first used as schematically shown in Fig. 2a. With the aid of a plastic connection (made from a NMR spinner), the shaft is further connected to a long plexi glass rod (stabilized in the magnet by two additional spinners) that is thereafter connected with a small plastic part that is connected to the MRI release cell.

The dissolution media in the larger container is put into a water bath in order to keep the temperature constant. Additionally, this water bath is connected to a plastic tube surrounding

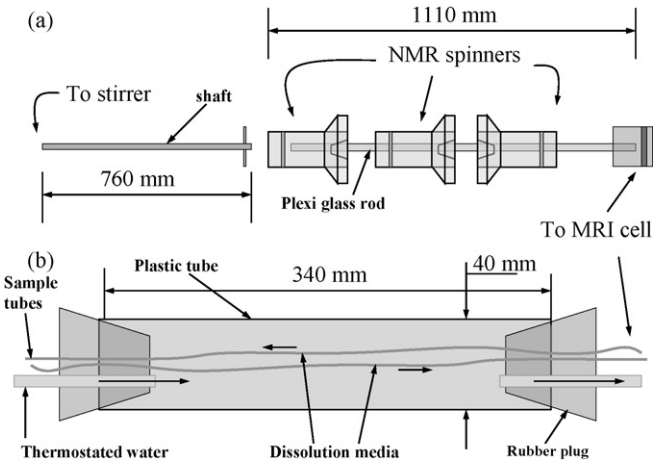

Fig. 2. (a) The shaft connecting the stirrer with the MRI release cell and (b) the tube containing water for thermosetting the moving dissolution media.

the all tubes transporting dissolution media between the larger container and the release cell, Fig. 2b. The MRI probe is also termostated to a fixed temperature. The exact temperature in the probe was determined in a separate measurement by determining the chemical shift difference between the peaks in a ^{1}H spectra of a methanol sample. Samples (1.2 ml) are taken out from the dissolution media at different time-point during the dissolution process using a Waters fraction collector II (Waters Corporation, Milford Massachusetts, USA).

The stirring, pumping and sample outtakes are programmed using a programmable logic controller (PLC, Omron SYSMAC CPM1) and trigger pulses from the NMR spectrometer. The PLC is programmed in a way so that the stirring is stopped directly by the trigger signal and the pumping is stopped 1 min later. The time during which stirring and pumping is performed is changed within the pulse program. In order to do repetitive successive measurements, the automation programs, provided as standard by the Bruker ParaVision Program, were used.

The set-up has been used to probe the ingress of distilled water into PEO tablets during the dissolution into 500 ml release media using a stirring rate of 100 and 200 rpm. Stirring of the rotating disc and pumping of dissolution media were, except for the first images, performed during at least 50 min before each MRI scan (taking about 8 min). All measurements were performed at 25 ± 1 °C.

2.4. MRI method

Magnetic resonance microimaging studies were performed using the Bruker Para Vision 3.0 software and a wb400 Bruker spectrometer with a 2.5 ^{1}H resonator. The pulse-sequences described below are provided by Bruker as a part of their standard spectrometer set-up. The ingress of dissolution media (water) into the PEO tablet formulation was studied using diffusion maps (images) obtained using pulsed field gradient (PFG) spin-echo (SE) imaging with the program m_diffse MicroImaging PV AVANCE Manual, 2004. Since the T_2 of PEO protons is relatively long and of the same order as that of water the more commonly used methods, such as m_msme, that create images weighted according to their proton T_2 may not be used. Instead the m_diffse method is used where the signal intensity obtained in the created images is weighted according to the self-diffusion coefficient (SDC) of the protons in the sample. This method is suitable for samples containing signals from protons having very different SDC's, like in the present case, and that are to close to each other on the ppm-scale to be able to use saturation techniques. The distance between proton signals from PEO and water are only 1.2 units close on the ppm-scale (Trotzig et al., 2007). Using the m_diffse pulse-sequence the intensity of the image signal is given by:

$$I(G) = I(0)[p\exp(-kD_A) + (1-p)\exp(-kD_B)] \quad (1)$$

Here, $I(G)$ and $I(0)$ are the intensities at the gradient strength G and zero, respectively. k equals $(\gamma G\delta)^2(\Delta - \delta/3)$, where γ represents the magnetogyric ratio of the nucleus under observation (in this case ^{1}H), Δ the gradient pulse interval and δ represent the width of the gradient pulse. D_A and D_B are the self-diffusion coefficients of PEO and water and p is the fraction of PEO. In order to probe the intensity of one signal only, here the ethylene oxide protons, a short diffusion time ($\Delta = 10$ ms) a high gradient ($G = 1$ *T/m*) and a relatively long gradient pulse duration ($\delta = 4$ ms) was used. Under this condition, no signal from water protons is probed and the second terms of Eq. (1) will therefore equal zero, i.e. $p = 0$. The intensity in the images will then be a function of the polymer properties only. The repetition delay T_R in this experiment was set to 2 s and two repetitions were used in order to obtain a better signal to noise ratio. The total measurement time was 8 min during which both stirring and pumping of dissolution media was stopped. Images were also probed for samples containing a known amount of polymers (see below). Using this information, an approximate estimation of the polymer concentration in the tablet gel layer was obtained. The acquisition parameters were; a field of view (FOV) of 2.5 cm × 2.5 cm digitized into 256 × 256 pixels, giving a resolution down to 0.1 mm, a slice thickness of 2 mm and Sinc^{3}250 pulses were used for excitation and refocusing (MicroImaging PV AVANCE Manual, 2004).

2.5. Quantitative concentrations obtained by MRI

The signal intensity in the SDC weighted images is displayed using a grey scale where the brightness correlates to the amount protons with slow SDC (i.e. polymer amount). Fig. 3 show an example of axial images of tubes containing PEO solutions (dilute to concentrated) of different concentrations and a reference sample containing glycerol. The intensity in the images is partly influenced by the T_2 of the protons and this effect is included in the $I(0)$ term of Eq. (1). At PEO concentrations above approximately 25% the T_2 effects significantly influence the results and to an increasing amount with increasing concentration. A decrease of the signal intensity is obtained since the T_2 relaxation time becomes so short that most of the signal has already relaxed at the end of the m_diffse pulse-sequence. In spite of this, it is, with information from different images of tubes with different polymer concentrations, possible to con-

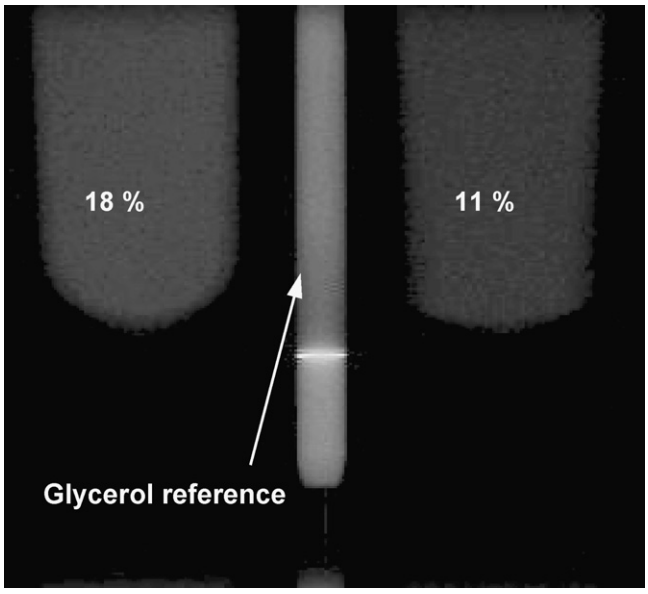

Fig. 3. SDC weighted axial images (at 0 mm offset) of two tubes containing different concentrations (% w/w) of PEO 2 in distilled water and a reference sample containing glycerol at 25 °C.

struct a calibration curve, Fig. 4. The intensity of each tube was normalized with the intensity of the reference tube containing pure glycerol having a low SDC in order to take experimental differences into account. Linear regression curves were fitted to the data in the low and the high concentration range, with a breakpoint at around 25%. The data at polymer concentrations below 5% were excluded from the fit as the signal to noise ratio was quite low for these samples. Hence, the concentration estimated at concentration below approximately 5% (w/w) is considered less accurate. The parameters for the straight lines in Fig. 4 are summarized in Table 1. These calibration curves (for high and low concentrations) were used to calculate concentration profiles within PEO based tablets, see below. Using this

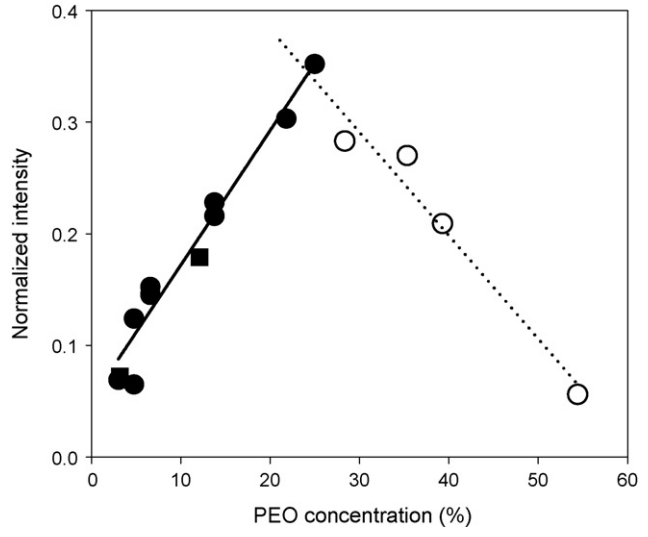

Fig. 4. The normalized intensity of PEO 2 samples of different concentration at low (●) and high (◯) concentrations. The lines are linear regression fits to the data in the two different regions.

Table 1
Fitted parameters obtained at low/high concentrations regime using the linear function

Conc. range	a	b
Low	51.4×10^{-3}	12.1×10^{-3}
High	568×10^{-3}	-9.25×10^{-3}

$I = a + bc$, where I equals the normalized intensity of the MR images and c is the concentration in % (w/w).

method, it is possible to probe a polymer concentration range of approximately 0–40% (w/w).

2.6. Polymer release

The dissolution samples taken directly from the MRI spectrometer were analysed using size exclusion chromatography (SEC) on a TSK-GEL $GMPW_{XL}$ 7.8 mm × 300 mm, particle size 13 μm, linear mixed bed size exclusion column (TosoHaas, Montgomeryville, PA, USA) connected online to a differential refractometer (Waters 410, Waters Milford, MA, USA) (Körner, 2006). A solution of 10 mM NaCl with 0.02% NaN_3 was used as mobile phase, the flow rate was set to 0.3 ml/min and the sample volume injected was 200 μl. The Millennium 32 software (Waters, Milford, MA) was used for analysis of the obtained RI chromatograms, and the polymer content in the dissolution medium was calculated using a calibration curve obtained from polymer samples of known concentration. The percentage polymer released into the solution at each sample time was calculated from the known tablet weight using the following relation.

$$\%\text{released} = \left(\frac{c_n \times (V_0 - V_s(n-1)) + V_s \sum_{n=0}^{n=1} c_n}{w_{tbl}} \right) \times 100 \quad (2)$$

Here, c_n is the polymer concentration in dissolution sample n, V_0 the total volume of the dissolution medium at time $t = 0$, i.e. 500 ml, V_s the volume of the dissolution sample, i.e. 2 ml, n the sample number in the dissolution series and w_{tbl} is the tablet weight. All release profiles were normalized to reach 100% released at the end of the experiment ($t = \infty$).

3. Results and discussion

3.1. MR Images of PEO based tablets

Images of PEO based tablet formulations were obtained using diffusion weighted imaging, as described above. The contrast in diffusion-weighted images is mainly determined by the concentration of PEO, Fig. 5a–d, where a bright signal indicates a higher polymer concentration. As the polymer concentration in the gel increases, the intensity first increases but at PEO concentrations above about 25% a decrease of the signal intensity is obtained due to decrease of relaxation time, see above and Fig. 4. The dissolution media, the dry core and the rest of the background appear dark in the image since the amount of PEO or PEO with sufficient mobility is to low in these parts. Axial

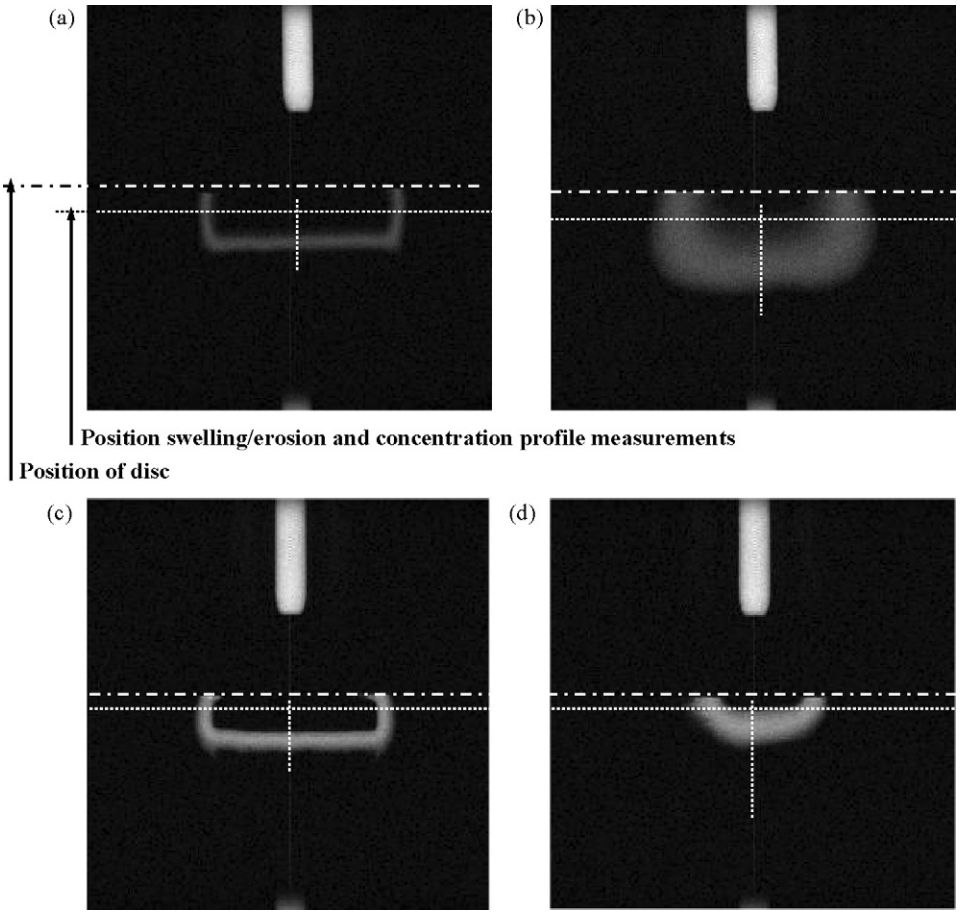

Fig. 5. A axial image of a 2 mm slice at the centre of a tablet composed of PEO 2 after dissolution in distilled water at 25 °C and 100 rpm at (a) 14 min, (b) 5.6 h for tablets of PEO 2, (c) 15 min and (d) 3.5 h for PEO 8812 tablets. The white dotted line in the figure indicates where concentration profiles are determined.

images are recorded at different time-points during dissolution and constitute the basis for the swelling and erosion curves, below.

Fig. 5a and b present images of tablets based on PEO 2 at two different time-points, immediately after immersion into the dissolution media (14 min) and at a point later during the dissolution process (5.6 h). At short times the interfaces, dry core/swelled tablet and swelled tablet/dissolution media are easily distinguished as a result of the relatively steep polymer concentration profile within the gel layer, as further discussed below. At later stages during dissolution, Fig. 5b, the interfaces becomes less distinct as a result of a less steep polymer concentration profile. For the tablet containing a large amount of low molecular weight polymer, PEO 8812, the interfaces between different regions appears more distinct both at short times (15 min) and longer times (3.5 h), indicating steeper polymer concentration profiles through the swelled polymer gel layer (Fig. 5c and d). This behavior correlate to the formation of a thinner gel layer for PEO 8812 tablets compared to PEO 2 tablets, and the fact that the water sorption of low molecular weight PEO is faster and that the strength of the formed gel is weaker as further discussed below (Apicella et al., 1993; Maggi et al., 2002; Wu et al., 2005; Körner, 2006). However, the higher intensity in these images may also partially be related to a difference in T_2-relaxation of the polymers in aqueous media resulting in lower signal intensity suppression for the polymer chains with low M_w in the sample. It should also be noted that the shape of the tablets change slightly at later times during dissolution. The PEO 2 tablet attains a teardrop shape probably as an effect of gravity combined with the viscous flow of the hydrated gel layer (Fig. 5b). For the tablet containing low M_w polymer (PEO 8812), the shape of the tablet becomes rounded at later stages of dissolution (Fig. 5d). This is a result of the sensibility of the tablet to hydrodynamic forces and that the corners of the tablets are hydrated and erode from two directions.

3.2. Swelling and erosion of PEO based tablets

Fig. 6a and b show the axial swelling and erosion of a PEO 2 based tablet in the MRI release cell as a function of time at a stirring rate of 100 and 200 rpm, respectively. It may be concluded the core of this tablet disappear quite rapidly (after about 10 h) and a constant gel layer thickness is not obtained during the time-scale of the dissolution process. At longer times, when the core has disappeared, and further movement of the swelling front is not possible, the size of the tablet start to decrease since erosion at this point dominates the dissolution process. Hence, front synchronization is not obtained. The swelling and erosion of identical tablets have been studied previously using a texture analysis method (TA) (Körner, 2006). It was found that both the

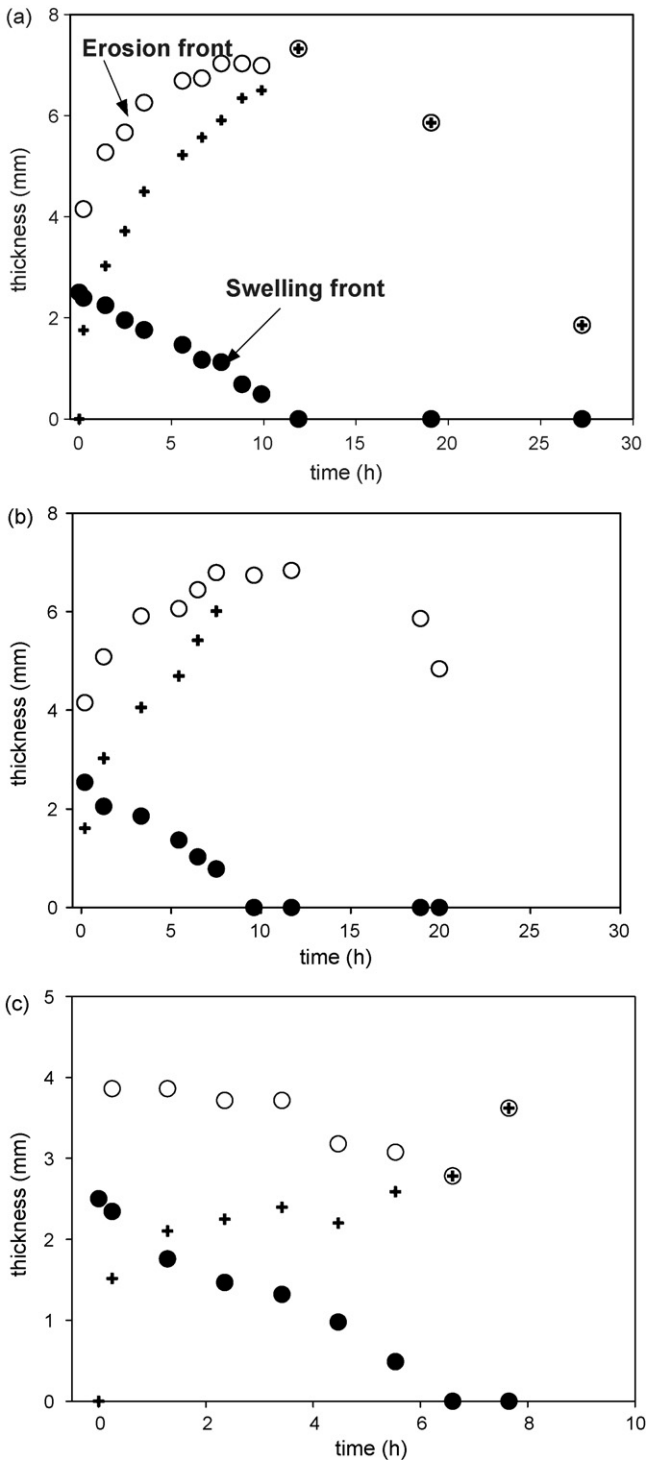

Fig. 6. Swelling and erosion of tablets composed of PEO in the rotating disc of the MRI cell in distilled water at $T = 25\,^{\circ}C$: (a) PEO 2 at 100 rpm, (b) PEO 2 at 200 rpm and (c) PEO 8812 at 100 rpm, tablet thickness (◯), core thickness (●) and gel layer thickness (+). Based on axial images. Positions of swelling and erosion fronts are indicated in a).

swelling (core/gel) and erosion (gel/water) fronts determined with these two completely different methods correspond very well to each other. Both these methods show that the dry core of the tablets disappears only slightly faster at the high stirring rate conditions. The largest difference in tablet dissolution behavior

Table 2
The rate of dry core size decrease (v_{core}), in axial and radial direction, as defined by the slope of the linear part of the erosion front position change, Figs. 6 and 7

Tablet type and stirring	v_{core} (axial) (mm/h)	v_{core} (radial) (mm/h)
PEO 2 (100 rpm)	0.19	0.54
PEO 2 (200 rpm)	0.26	0.44
PEO 8812 (100 rpm)	0.30	0.66

is observed after the point when the dry core of the tablets has disappeared, here the gel thickness decreases more rapidly with the highest rotation speed. The dissolution of tablets composed of a mixture of low and high molecular weight PEO, PEO 8812, has also been studied, Fig. 6c. In line with previous observations, the dry core of the tablet disappears at a faster rate in the system containing lower M_w PEO (Apicella et al., 1993; Wu et al., 2005; Körner, 2006). In contrast to the pure PEO 2 tablets, synchronization of the moving fronts, the dry core/gel and the gel/water, may be observed (Kim, 1995). It is interesting to note that for this PEO 8812 system the dimensional changes observed by MRI and TA correlate only regarding the position of the dry core/gel interface (Körner, 2006). For the total thickness of the tablet (the interface between the dissolution media and the gel layer), MRI gives slightly larger values though. This difference may have several causes: (i) the mechanical strength of the gel layer formed around the low M_w tablet is weaker and may have been disturbed during TA measurements, (ii) the position of the tablet is changed up-side down during TA which may give effects caused by gravitational forces and (iii) the MRI measurements continues during 8 min after the determined time-point during which swelling may continue.

The swelling/erosion behavior of the system was also determined using radial images, Fig. 7a–c. As may be noted, the tablet size does not increase as rapidly in the radial direction compared to the axial direction. This might be due to larger shear forces on the tablet in the radial direction. Due to the lower shear forces in the axial direction the tablet size is allowed to increase faster. Alternatively, the larger increase of the tablet size in the axial direction may arise as a result of the compaction of the tablets. Stresses induced in the polymer system during tabletting may differ in various directions and this may be manifested in varying swelling/erosion behavior. The reduction of the dry core size, on the other hand, seem not be largely affected by the different shear forces induced by changing the stirring conditions (compare 100 and 200 rpm). Note also that in both directions (axial/radial) the core appears to disappear at close to the same time-point. However, the rate of disappearance of the dry core of the tablet differs quite significantly in different directions. In all cases, excluding the initial rapid decrease of the position of the swelling front, the rate of dry core size diminishes constantly over a large part of the dissolution process and approximate slopes of the curves in Figs. 6 and 7 may be calculated, Table 2. Interestingly, the dry core size decrease is two to three times faster in the radial than in the axial direction. These differences are important since the factors determining the release of polymer, and under normal conditions also drug substance, may under certain conditions be directly correlated to the core diminishing. To our knowledge,

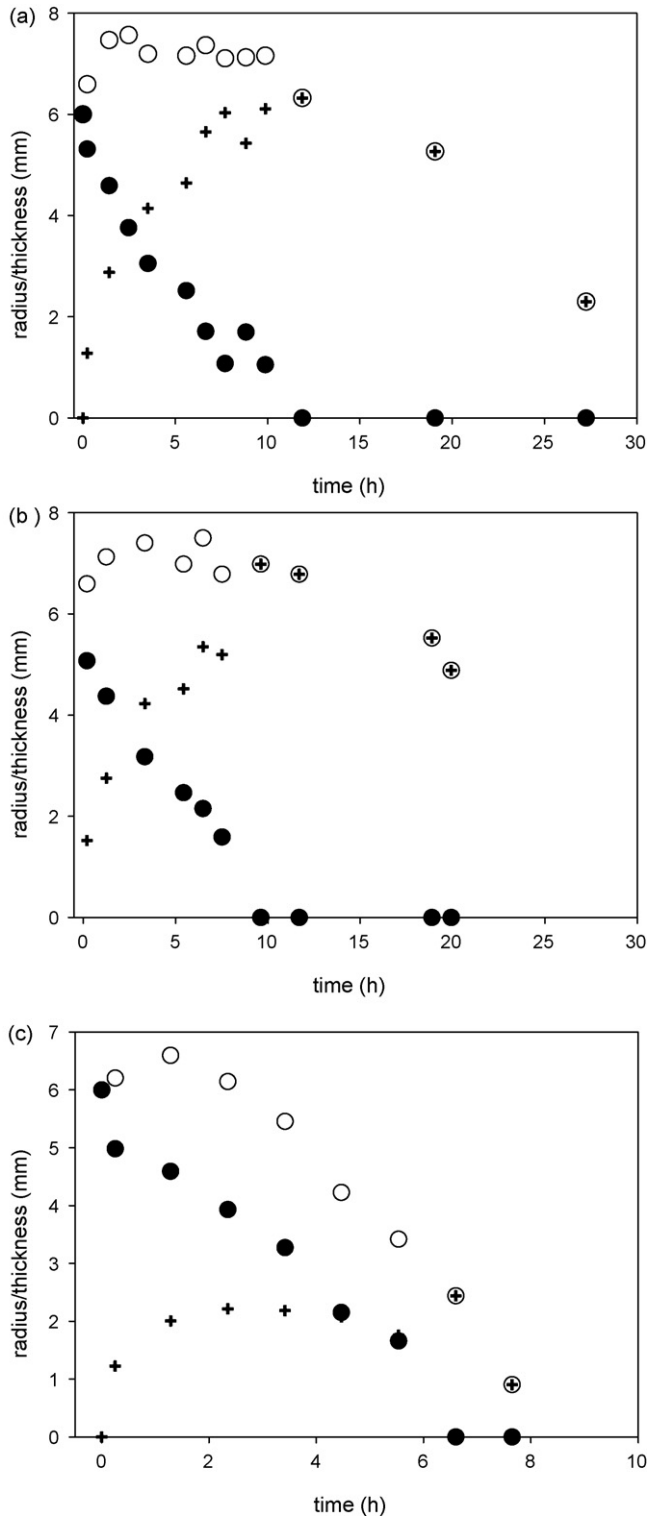

Fig. 7. Swelling and erosion of tablets composed of PEO in the rotating disc of the MRI cell in distilled water at $T = 25\,^{\circ}C$: (a) PEO 2 at 100 rpm (measured 1 mm from the disc see Fig. 5), (b) PEO 2 at 200 rpm (1 mm from disc) and (c) PEO 8812 at 100 rpm (0.5 mm from disc), tablet thickness (◯), core thickness (●) and gel layer thickness (+). Based on radial images.

the dimensional changes of hydrophilic matrix tablets in several directions in situ during the dissolution process (probing both swelling and erosion fronts) has not been studied extensively previously (Fyfe et al., 2000; Rajabi-Siahboomi et al., 1996) and further studies are needed to investigate the relation between the release and the core size reduction. It is therefore interesting to compare the results from MRI with the results from models simulating both polymer dissolution and dimensional changes of identical tablets (Borgquist, 2005; Borgquist et al., 2006). It appears that the dimensional changes of PEO 2 tablets observed both in the radial and the axial direction may be simulated within the frame of the model of Borgquist et al. (Borgquist, 2005). It is interesting to note that both the model and the MRI results indicate that the dimensional changes of the tablet in the radial direction, at the end of the dissolution process, appears to increase in rate and to some extent seem to be determined by the changes in the axial direction, which is smaller (for the PEO 2 tablet the initial thickness is 2.5 mm compared to a radius of 6 mm). This behavior seem to be more significant at high stirring conditions and for lower M_w polymers, where a larger extent of front synchronization is observed (Apicella et al., 1993). However, the model of Borgquist et al. (Borgquist, 2005) predict a larger increase of the rate of radial disappearance of the dry core at the end of the dissolution process, than shown by MRI, since the core vanishes first in axial direction due to the assumption of identical dissolution rate in both directions.

3.3. Polymer concentration profiles from MR images

Semi-quantitative information of polymer concentration profiles for PEO 2 tablets were determined using the low concentration fit of Fig. 4, Section 2, up to approximately 20–25% (w/w) polymer and thereafter the high polymer concentration fit was used. By combining these two calibration curves, it was possible to obtain a good estimate of the polymer concentration in the range 3–5 to 45% (w/w). Due to the curvature of the experimental data in Fig. 4 and the overlap between the two calibration curves the deduced values are less accurate around 20–25% (w/w) polymer. The calibration curve for the low concentration range may also give a reasonable estimate of the concentration profile for the PEO 8812 tablet all the way up to about 30–35% (w/w). This is due to the fact that the decay of the intensity at higher concentrations, due to relaxation effects, probably appear at later stages (Fig. 4) for PEO 8812 tablets and that the diffusion of PEO is very low for both M_w's in the investigated concentration range. With the experimental parameters and the pulse sequence used in the present work, it is estimated that less than 0.5% for the PEO signal intensity will disappear as a consequence of diffusion (Trotzig et al., 2007; Håkansson et al., 2000; Brown, 1984). However, due to slower relaxation of the low molecular weight polymer the values of the polymer concentration obtained in PEO 8812 tablets will possibly be slightly overestimated.

Line plots of the polymer concentration determined through a tablet at specific points during the dissolution process, Fig. 8 (axial direction) and Fig. 9 (radial direction), show that the concentration profiles initially are slightly steeper in the radial compared to the axial direction (based on data up to 25% poly-

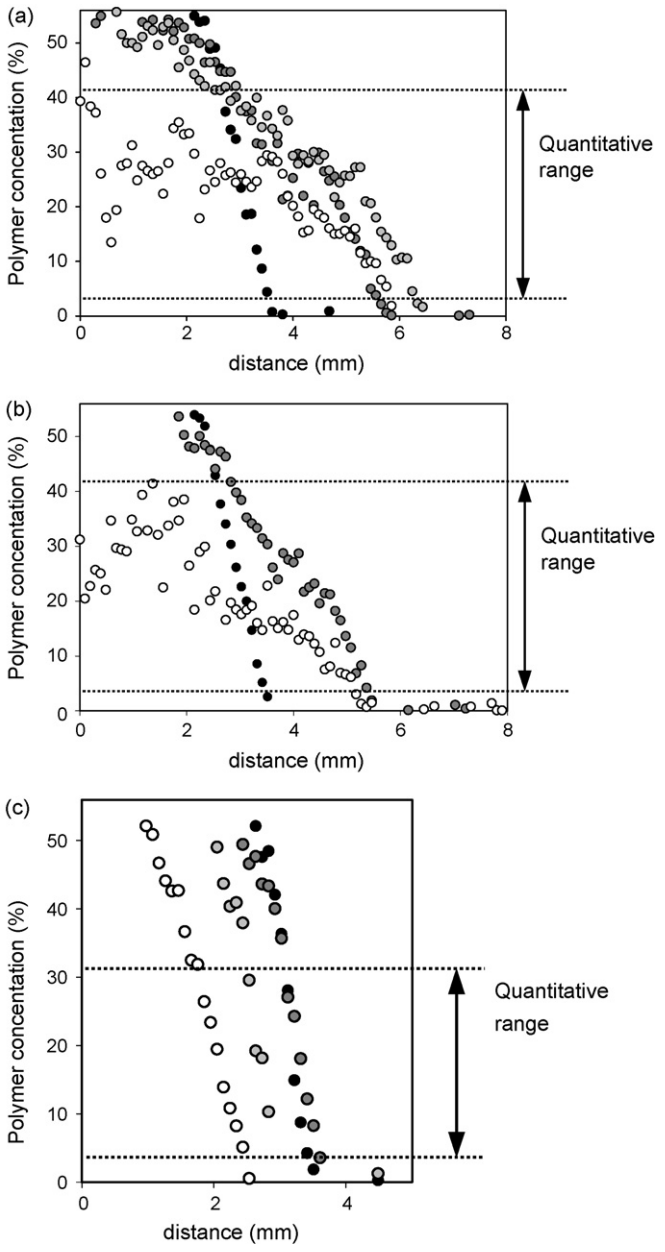

Fig. 8. Axial concentration profiles for a tablet formulation based on PEO 2: (a) at a stirring of 100 rpm; (b) 200 rpm, after dissolution in distilled water at 25 °C for 12–14 min (●), 3.3–3.5 h (dark grey), 7.7 h (grey) and 19 h (◯); (c) PEO 8812 after 15 min (●), 1.3 h (dark grey), 4.5 h (grey) and 6.6 h (◯). The dotted line indicates the approximate quantitative concentration range.

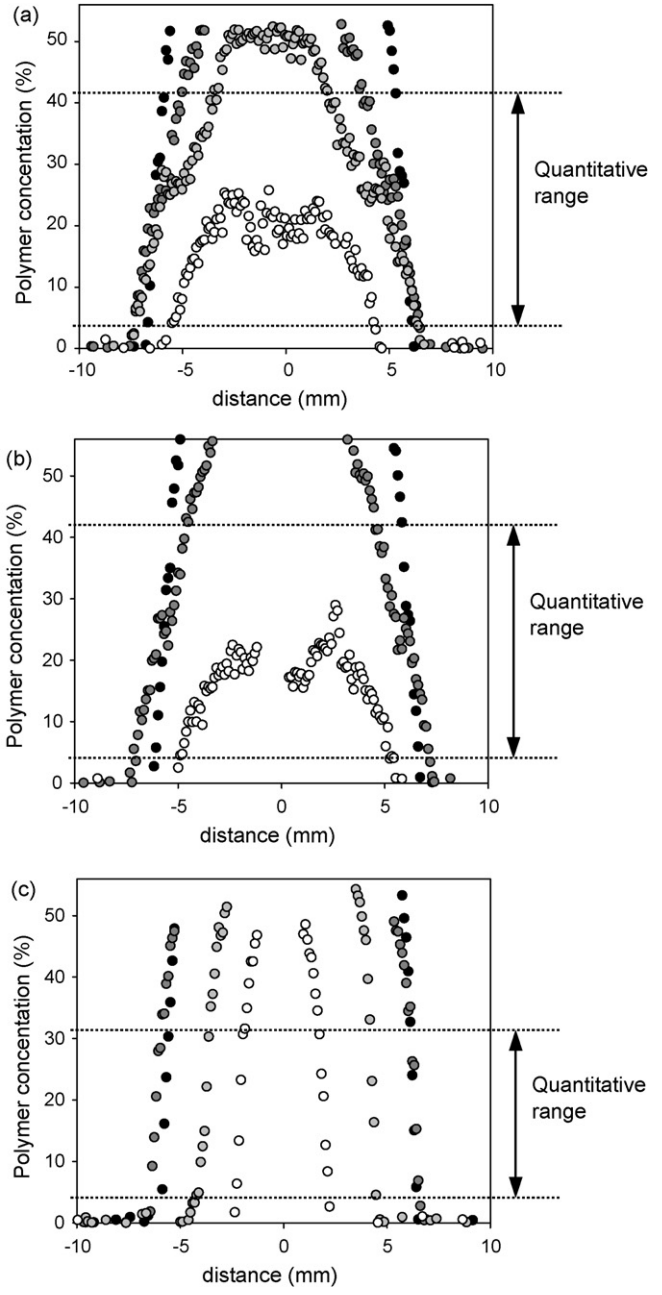

Fig. 9. Radial concentration profiles for a tablet formulation based on PEO 2: (a) at a stirring of 100 rpm; (b) 200 rpm, after dissolution in distilled water at 25 °C for 12–14 min (●), 3.3–3.5 h (dark grey), 7.7 h (grey) and 19 h (◯); (c) PEO 8812 after 15 min (●), 1.3 h (dark grey), 4.5 h (grey) and 6.6 h (◯). The dotted line indicates the approximate quantitative concentration range.

mer), Table 3. The reason for this is probably related to the difference in hydrodynamics in the two regions as discussed above. On the other hand, as the dissolution proceed this difference decreases and for PEO 2 at 100 rpm, where the process is less synchronized, the slope in the axial direction appears to be slightly steeper (at 7.7 h). It should, however, be noted that the accuracy of the estimated values decreases as the process proceed. Even so, it may be noted that the concentration profiles seem to be quite linear in the investigated concentration range. This may be reasonable even though texture analysis studies indicate that the force exerted on the probe as a function of the penetration depth through the swelled gel layer that may have a non-linear shape, upon approaching the dry core, at higher polymer concentration (Körner, 2006).

As the dissolution of the PEO 2 tablet proceed the slope of the concentration profile decreases, Figs. 8a and b and 9a and b. This corresponds well to the decrease of the slope in the force–displacement curve as probed by TA (Körner, 2006). In correspondence with the swelling/erosion data above the difference between profiles probed at different rotation speed, 100 and 200 rpm, appear to be small. For systems containing low M_w polymer, the slope of the concentration profile through the

Table 3
Estimations of absolute values of slopes of the polymer concentration profiles of various tablets at different time-points and directions ($\langle c_{slope} \rangle$), in axial and radial direction, as defined as the slope of the linear part of the change of erosion front position

Tablet type and stirring	Time	$\langle c_{slope} \rangle$ (axial) (%/mm)	$\langle c_{slope} \rangle$ (radial) (%/mm)
PEO 2 (100 rpm)	12–14 min	38	44
	3.3–3.5 h	25	19
	7.7 h	20	13
PEO 2 (200 rpm)	12–14 min	43	49
	3.3–3.5 h	17	19
PEO 8812 (100 rpm)	15 min	65	83
	1.3 h	60	66
	4.5 h	38	≈30

swollen gel layer at different time-points appears to vary less than for the pure PEO 2 system, Figs. 8c and 9c and Table 3. A corresponding observation was made by TA in the part of the dissolution process where the gel layer thickness appear to be quite constant and the dry core of the tablet has not yet disappeared (Körner, 2006). For the PEO 8812 system, front synchronization is achieved and a "quasi equilibrium" state is attained resulting in almost constant concentration profiles. Finally, remark that the difference in steepness of the concentration profiles for the various systems appears to correlate qualitatively to the difference in release rate.

3.4. Polymer dissolution profiles

Simultaneously with the probing of the swelling and erosion of PEO tablets, samples were taken from the MRI release cell to determine polymer dissolution, Fig. 10. The data for PEO 2 at 200 rpm have been determined at two different time-points with tablets of different batches indicating a good reproducibility of the method and the sample handling. The release obtained

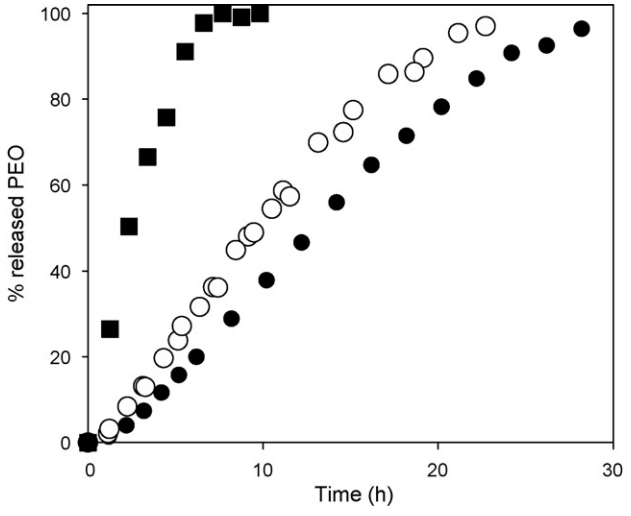

Fig. 10. Dissolution/release of PEO in distilled water at 25 °C into the MRI release cell: PEO 2 at 100 rpm (●) and 200 rpm (○) and PEO 8812 at 100 rpm (□).

using the MRI rotating disc method is in all cases only slightly faster than that of the rotating disc set-up of the TA, hence the methods appear to correlate at least semi-quantitatively (Körner, 2006). As the rotating speed increases, only a small increase in release rate is observed, Fig. 10. A very significant difference between the two tablet systems that is worth pointing out is the fact that for the PEO 2 system only about 40% (w/w) of the polymer has released at the point when the dry core of the tablet disappear, whereas more than 95% (w/w) of PEO has released at the corresponding point for the PEO 8812. This pinpoints the higher capacity of high M_w polymers to hold large amount of water in a gelled state while maintaining sufficient integrity.

4. Conclusions

The present work has demonstrated that magnetic resonance micro imaging (MRI) is a versatile tool to investigate tablet formulations during release under sink condition. The construction of a release cell for the MRI system, in the form of a rotating disc, has allowed possibility to simultaneously obtain both qualitative and quantitative information of swelling, erosion and polymer dissolution under non-invasive conditions. The system has been tested on tablets composed of PEO, a hydrophilic polymer that is increasingly used in extended release oral formulations. Tablets composed of high molecular weight PEO ($M_w = 2.19 \times 10^6$ g/mol) showed a significant increase in size in the axial direction but a slower increase in the radial direction during the course of the dissolution process. The size of the dry core of the tablet seemed to disappear at the same point in both directions. However, due to the dimensional differences in size in axial versus radial direction, the rate of the disappearance of the dry core was found to be significantly faster in radial direction. This behavior was attributed to the higher shear forces attained in the radial direction and supported by the fact that the polymer concentration profiles obtained in the radial direction in most cases appeared to be steeper. For the PEO 2 system, the swelling and erosion fronts were never fully synchronized during the time course of the dissolution process and a constant gel layer thickness was therefore not obtained. For the same reason, the slope of the polymer concentration profile changed during dissolution. For a tablet composed of PEO 2 mixed with a polymer of lower molecular weight ($M_w = 122 \times 10^3$ g/mol) the size of the tablet decreased faster. Due to faster erosion, the synchronization of the fronts and a constant gel layer thickness were obtained and maintained during a larger part of the dissolution process. The synchronization was associated with the formation of an almost constant polymer concentration profile through the gel layer at different time-points. Also the difference in swelling/erosion behavior in different direction was smaller for the low M_w PEO containing system. The dimensional changes observed by the MRI method and the polymer release from the MRI release cell were found to correlate well to previous TA and release measurements in most cases. Only for the tablet containing low M_w PEO a slightly larger tablet size was obtained with MRI compared to TA. This was possibly related to differences in the experimental procedures.

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References

Apicella, A., Cappello, B., Del Nobile, M.A., La Rotonda, M.I., Mensitieri, G., Nicolais, L., 1993. Poly(ethylene oxide) (PEO) and different molecular weight PEO blends monolithic devices for drug release. Biomaterials 14, 83–90.

Baumgartner, S., Lahajnar, G., Sepe, A., Kristl, J., 2005. Quantitative evaluation of polymer concentration profile during swelling of hydrophilic matrix tablets using 1H NMR and MRI methods. Eur. J. Pharm. Biopharm. 59, 299–306.

Borgquist, P., 2005. Modelling of drug release from reservoir and matrix formulations. Ph.D. thesis. Lund University, Sweden.

Borgquist, P., Körner, A., Piculell, L., Larsson, A., Axelsson, A., 2006. A model for the drug release from a polymer matrix tablet-effects of swelling and dissolution. J. Controlled Release 113, 216–225.

Brown, W., 1984. The concentration dependence of diffusion in semi-dilute polymer solutions. Polymer 25, 680–685.

Fahie, B.J., Nangia, A., Chopra, S.K., Fyfe, C.A., Grondey, H., Blazek, A.I., 1998. Use of NMR imaging in the optimization of a compression-coated regulated system. J. Controlled Release 51, 179–184.

Fyfe, C.A., Blazek, A.I., 1997. Investigation of hydrogel formation from hydroxypropylmethylcellulose (HPMC) by NMR spectroscopy and NMR imaging techniques. Macromolecules 30, 6230–6237.

Fyfe, C.A., Blazek, A.I., 1998. Complications in investigations of the swelling of hydrogel matrices due to the presence of trapped gas. J. Controlled Release 52, 221–225.

Fyfe, C.A., Grondey, H., Blazek-Welsh, A.I., Chopra, S.K., Fahie, B.J., 2000. NMR imaging investigations of drug delivery devices using a flow through USP dissolution apparatus. J. Controlled Release 68, 73–83.

Hyde, T.M., Gladden, L.F., 1998. Simultaneous measurement of water and polymer concentration profiles during swelling of poly(ethylene oxide) using magnetic resonance imaging. Polymer 39, 811–819.

Håkansson, B., Nydén, M., Söderman, O., 2000. The influence of polymer molecular weight on pulsed field gradient nuclear magnetic resonance self-diffusion experiments. Colloid Polym. Sci. 278, 399–405.

Kim, C.J., 1995. Drug release from compressed hydrophilic POLYOX-WSR. J. Pharm. Sci. 84, 303–306.

Kojima, M., Nakagami, H., 2002. Investigation of water mobility and diffusivity in hydrating micronized low-substituted hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and hydroxypropyl cellulose matrix tablets by magnetic resonance imaging (MRI). Chem. Pharm. Bull. (Tokyo) 50, 1621–1624.

Körner, A., 2006. Dissolution of polydisperse polymers in water. Ph.D thesis Lund, University.

Körner, A., Larsson, A., Piculell, L., Wittgren, B., 2005. Molecular information on the dissolution of polydisperse polymers: mixtures of long and short poly(ethylene oxide). J. Phys. Chem. 109, 11530–11537.

Lauterbur, P.C., 1973. Image formation by induced local interactions: examples employing nuclear magnetic resonance. Nature 242, 190–191.

Madhu, B., Hjärtstam, J., Soussi, B., 1998. Studies of the internal flow process in polymers by H NMR microscopy at 500 MHz. J. Controlled Release 56, 95–104.

Maggi, L., Segale, L., Torre, M.L., Ochoa Machiste, E., Conte, U., 2002. Dissolution behaviour of hydrophilic matrix tablets containing two different polyethylene oxides (PEOs) for the controlled release of a water-soluble drug. Dimensionality study. Biomaterials 23, 1113–1119.

Melia, C., Rajabi-Sihboomi, A.R., Bowtell, W., 1998. Magnetic resonance imaging of controlled release pharmaceutical dosage forms. Pham. Sci. Tech. Today 1, 32–39.

MicroImaging PV AVANCE Installation/User Manual. 4.0, 2004, Bruker Analytik GmbH, Rheinstetten, Germany.

Price, W.S., 1998. NMR imaging. Annual Reports on NMR Spectroscopy, vol. 35, pp. 139–217.

Rajabi-Siahboomi, A.R., Bowtell, R.W., Mansfield, P., Davis, M.C., Melia, C., 1996. Structure and behaviour in hydrophilic matrix sustained release dosage forms: 4. Studies of water mobility and diffusion coefficients in the gel layer of HPMC tablets using NMR imaging. Pharm. Res. 13, 376–380.

Rajabi-Siahboomi, A.R., Bowtell, R.W., Mansfield, P., Henderson, A., Davis, M.C., Melia, C., 1994. Structure and behaviour in hydrophilic matrix sustained release dosage forms: 2 NMR imaging studies of dimensional changes in the gel layer and core of HPMC tablets undergoing hydration. J. Controlled Release 31, 121–128.

Richardson, J.C., Bowtell, R.W., Mäder, K., Melia, C.D., 2005. Pharmaceutical applications of magnetic resonance imaging (MRI). Adv. Drug Deliv. Rev. 57, 1191–1209.

Trotzig, C., Abrahmsén-Alami, S., Maurer, F., 2007. Structure and mobility in water plasticized poly(ethylene oxide). Polymer 48 (11), 3294–3305.

Wu, N., Wang, L.-S., Tan, D.C.-W., Moochhala, S.M., Yang, Y.-Y., 2005. Mathematical modeling and in vitro study of controlled drug release via a highly swellable and dissoluble polymer matrix: polyethylene oxide with high molecular weights. J. Controlled Release 102, 569–581.