The application of magnetic resonance imaging in pharmaceutical technology for the evaluation of controlled release dosage forms has evolved over the past two decades from simple 'test tube' studies to quantitative parametric mapping carried out in flow through cells during drug dissolution.

Foundation review: MRI as a tool for evaluation of oral controlled release dosage forms

Przemysław P. Dorożyński[1], Piotr Kulinowski[2], Anna Młynarczyk[2] and Greg J. Stanisz[3]

[1] Department of Pharmaceutical Technology and Biopharmaceutics, Pharmaceutical Faculty, Jagiellonian University, Medical College, ul. Medyczna 9, 30-688 Kraków, Poland
[2] Department of Magnetic Resonance Imaging, Institute of Nuclear Physics PAN, ul. Radzikowskiego 152, 31-342 Kraków, Poland
[3] Sunnybrook Health Sciences Centre 2075 Bayview Avenue, Toronto, Canada

The magnetic resonance imaging (MRI) studies of controlled-release (CR) dosage forms can be roughly divided into two groups. The first comprises studies performed in static conditions (small solvent volumes and ambient temperature). Such studies have provided insight into molecular phenomena in hydrating polymeric matrices. The second group covers research performed in dynamic conditions (medium flow or stirring) related to drug dissolution. An important issue is supplementation of the MRI results with data obtained by complementary techniques, such as X-ray microtomography (μCT). As we discuss here, an understanding of the mechanism underlying the release of the drug from the dosage form will lead to the development of detailed, molecularly defined, CR dosage forms.

During the past decade, there has been a significant increase in the application of imaging techniques in the pharmaceutical sciences. The major reason for such expanded interest is the development of various spectroscopic techniques, which enable researchers to obtain one-, two- or three-dimensional distribution maps of physical or chemical quantities within the measured sample. Imaging extends knowledge about the structural or physico-chemical properties of a sample, and the temporal changes that occur in such samples during hydration and dissolution of the dosage forms; these are the predominant processes that influence the *in vitro* and *in vivo* performance of controlled-release (CR) dosage forms [1,2].

One of the most promising techniques is magnetic resonance imaging (MRI), which provides opportunity for nondestructive and noninvasive recording of the spatial distribution and mobility of certain particles, such as protons, in the sample. MRI is widely used in medical, material and food sciences. It is also attracting increasing interest in the field of pharmaceutical technology. Although MRI is used mainly for *in vivo* studies, there has been a noticeable increase in the number of studies looking at the *in vitro* preformulation of solid oral dosage forms.

Corresponding author:. Dorożyński, P.P. (mfdorozy@cyf-kr.edu.pl)

Przemysław P. Dorożyński Przemysław P. Dorożyński obtained his PhD from the Jagiellonian University Medical College in the Faculty of Pharmacy in 2001. Since then, he has been an assistant professor in the Department of Pharmaceutical Technology and Biopharmaceutics Jagiellonian University Kraków. His research interests include the application of magnetic resonance imaging and micro-computed tomography for the evaluation of controlled release formulations in connection with drug dissolution and the application of new materials in pharmaceutical technology.

Piotr Kulinowski obtained his PhD in experimental physics in 2002 from the Institute of Nuclear Physics Polish Academy of Sciences (PAN), Krakow, Poland. Currently, he works as an assistant professor at the Institute of Nuclear Physics, PAN and Pedagogical University, Krakow, Poland. His research activities focus on the application of magnetic resonance imaging in pharmaceutical technology and on the use of magnetic resonance spectroscopy in the investigation of skeletal muscle energetics *in vivo* during exercise.

Anna Młynarczyk PhD student in Department of Magnetic Resonance Imaging, Institute of Nuclear Physics, Polish Academy of Sciences Kraków. Prematurely passed away in September 2011.

Greg J. Stanisz received his PhD in solid state physics from the Jagiellonian University, Cracow, Poland in 1990. Since then, he has worked at Sunnybrook Health Science Centre, Toronto, Canada, and is currently a full professor in medical biophysics at the University of Toronto. His research interests consist of the use of quantitative magnetic resonance imaging techniques in neurology and cancer.

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2011.10.026

Several excellent reviews have summarized the results achieved by the application of MRI for pharmaceutical purposes [3–5]. In this article, rather than discussing particular studies, we review milestones, research directions and the evolution of approaches to the application of MRI to the analysis of CR systems. In addition, we also explore the interconnection of MRI with other imaging methods.

The studies that use MRI to investigate hydrophilic matrices are dispersed among journals belonging to several branches of science (e.g. pharmacy (especially pharmaceutical technology), physics, chemistry and polymer science). Therefore, it is sometimes tedious and difficult to gain the relevant information about the actual state-of-the-art application of MRI for the evaluation of CR dosage forms. In the studies of water–polymer systems, researchers (mainly physicists, chemists, and polymer and food scientists) have focused on changes in system properties across a wide temperature range. Although the results of such studies are important, they often cannot be directly applied to describe the behavior of CR formulations in dissolution conditions. The studies of pharmaceutical formulations should reflect physiological conditions in terms of fixed temperature, solvent type and its volume. There is no doubt that the ability to analyze the molecular interactions in the CR dosage forms will lead to better understanding of the product performance and to scientifically based development of new formulations.

Using MRI techniques to evaluate CR formulations might be beneficial for the following reasons: (i) in coming decade, an increasing number of CR formulations will out of patent. Therefore, there is a need to develop methods for complex evaluation of such formulations, especially their behavior during dissolution studies. Recently, the US Food and Drug Administration (FDA) as well as leading pharmaceutical companies have pointed out that, in the case of CR formulations, classical dissolution studies are not sufficient for a proper comparison of the originator and generic products [6]; and (ii) there is an increased demand for the implementation of new analytical techniques in the pharmaceutical industry owing to the idea of process analytical technology (PAT), which was initiated by the FDA, and then introduced into the guidelines Q8, Q9, Q10 developed by International Conference of Harmonization (ICH). One of the expected advantages of the application of PAT is enhancement of formulation and process understanding. This might be possible through observation and analysis of the processes occurring within the dosage forms during dissolution or hydration studies, which might partially reflect phenomena occurring *in vivo* [7,8].

BOX 1

Boundaries and fronts in the hydrating polymeric matrix

The structure of a hydrating polymeric matrix (pure or loaded with drug) can be divided into several layers. The characteristics of these layers depend on structural aspects, which are taken into consideration during identification. The most general classification is based on the behavior of the polymer during dissolution; based on Miller-Chou and Ueberreiter [81,82] in a wetting polymeric matrix, the following layers can be identified:

- pure polymer characterized by free volume in the form of several channels and holes of molecular dimensions;
- infiltration layer where penetrating solvent molecules fill empty spaces;
- solid swollen layer where the polymer–solvent system is still in the glassy state;
- a gel layer where the polymer occurs in a rubbery state;
- a liquid layer where the polymeric chains are loosely distributed; and
- pure solvent.

If the matrix contains active substance, the layers contained the dissolved and undissolved drug can be identified. However, the formation of particular layers will depend on the solubility of active substance.
When describing a structure defined as boundaries between layers, the term 'fronts' is frequently used. Consequently, structure evolution can be described in terms of fronts or layers. The variability of characteristics of fronts, boundaries and their spatial distribution within the swelling matrix systems occurring in literature data depends on several factors, including: (i) actual matrix composition (polymer, active substance or other excipients); (ii) theoretical assumptions, simulations, data analysis and interpretations; and (iii) experimental conditions and equipment applied in the studies. The schematic composition of the layers occurring in a hydrated matrix is presented in Fig. I.

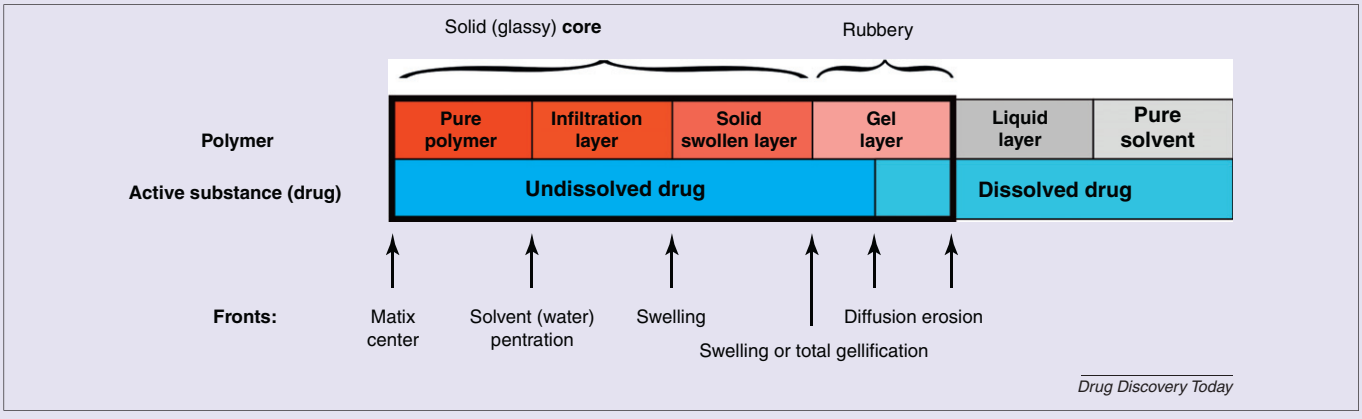

FIGURE I

Schematic of the composition of the layers occurring in a hydrated matrix.

We believe that MRI methods are mature enough to enter the pharmaceutical industry gradually. An increasing number of papers resulting from collaboration between university research centers and industrial research units confirms this belief [9–17]. In this article, we focus on the application of MRI with regard to: (i) structural analysis of CR formulations; (ii) possibilities of application of various imaging pulse sequences, their advantages and limitations; (iii) integration of MRI with dissolution techniques; and (iv) quantification of MR images and quantitative (q)MRI.

Structural analysis of CR matrix systems: state of the art

Hydrophilic polymer matrix systems are the most popular CR formulations. The distribution and mobility of solvent within the dosage form and their effects on the physico-chemical characteristics of particular regions of the matrix during hydration are essential for the identification of drug dissolution and transport mechanisms.

Analysis of the behavior of CR systems during hydration and release of the drug substance emerged during the early 1980s, resulting in the proposed definition of 'moving fronts' [18]. This was based on implementation of the theory of glassy–rubbery transitions in polymeric matrices. Currently, data exist in the literature that confound the variability of definitions and characteristics of layers and fronts identified in hydrated polymeric matrices. These are discussed further in Box 1.

A simple way to study the behavior of swelling matrices is to register the dimensional changes of the gel layer, by photo, video or light-scattering measurements [19–24]. Other optical methods are based on the incorporation of active substances or additives (e.g. buflomedil pyridoxal phosphate) [23,25–28] into the tablets or on the coloring of the medium that is used in the study [28,29]. These methods require the clamping of the tablets between transparent plates, which allows water penetration only from the lateral surface and disrupts the formation and expansion of a gel layer in the axial direction [25,30]. A more advanced spectroscopic imaging technique was proposed by Van der Weerd and Kazarian [31,32]. These authors used chemical imaging based on attenuated total reflection Fourier transform infrared (ATR-FTIR) microscopy in combination with standard macrophotography to study the swelling of hydroxypropylmethyl cellulose (HPMC)-based systems as well as the evolution of water and drug concentrations within the matrix. Furthermore, various ultrasound techniques or penetrometric textural analyses have been proposed to investigate the thickness and strength of the gel layer formed on the surface of swollen tablets [33–36].

MRI techniques have been applied relatively recently for the structural assessment and analysis of the properties of CR dosage forms. The earliest publications in this field were published during the mid 1990s by a group from the University of Nottingham [37,38]. The group monitored gel layer formation in hydrating drug-loaded HPMC tablets immersed in distilled water, using a diffusion-weighted and T_2-weighted spin echo sequence.

MRI: principles, useful sequences, applications and limitations

MRI has been in use for more than two decades and is a term invented by radiologists to describe nuclear magnetic resonance (NMR) imaging. There have been many books describing both NMR fundamentals and MRI methods and protocols (e.g. [39–41]). Here, we provide a brief description of the origins of the MR signal and its interesting properties in the context of CR formulation imaging.

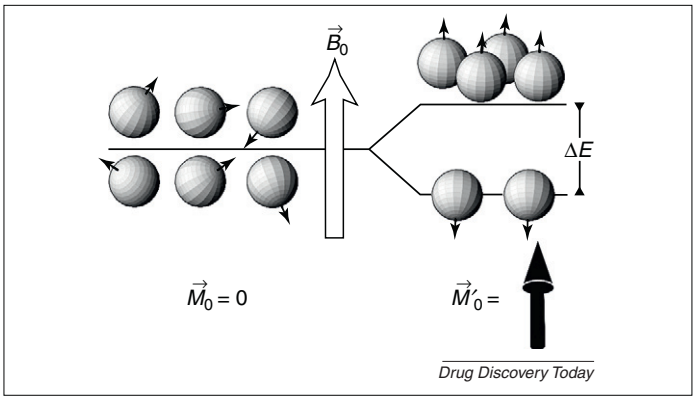

FIGURE 1

The concept of magnetization. For further details, see main text.

The source of the NMR phenomenon is that every proton and neutron has spin, which is an intrinsic quantum mechanical property. Neutrons and protons combine to form the nucleus, which has a net spin provided that there is an odd number of protons or neutrons (e.g. ^{1}H or ^{13}C). This is the magnetic property of nuclei and spin interactions with external magnetic fields that are used in MRI to produce images with such detail and contrast. The most common type of nuclei used in MRI is that of hydrogen associated with water molecules. In a typical MRI experiment, an object (e.g. sample or patient) is placed in the strong magnetic field (of the order of a few Tesla). In the presence of this strong magnetic field, hydrogen spins act as magnetic dipoles that align with the magnetic field in two possible orientations (parallel and antiparallel directions) with respect to the magnetic field (Fig. 1). The number of spins in those two directions is not equal. The reason for this imbalance is the fact that the energy state of a spin in the direction parallel to the magnetic field is lower than in the antiparallel direction. This energy difference is proportional to the external magnetic field and also depends on the type of nuclei. Therefore, there are slightly more spins in the parallel direction and this imbalance produces a net magnetization vector (sum of the spins) in the direction parallel to main magnetic field. This magnetization and its characteristic behavior are a key element of MRI contrast in a variety of systems (tissues, sample, water solutions, among others).

As presented in Fig. 1, in the absence of magnetic field magnetic moments (spins) associated with water, molecules are randomly oriented (left). The magnetization vector M_0, which is a vector sum of the magnetic moments, is equal to zero. Upon application of the external, strong magnetic field magnetic, B_0 moments associated with individual molecules align in the direction parallel or antiparallel to the magnetic field (right). The energy states associated with those two orientations are different and a low energy state (parallel spins) is preferable, resulting in a nonzero magnetization vector, M_0 aligned with magnetic field, B_0.

Every spin (and hence magnetization) precesses around the main magnetic field, B_0 with a specific frequency (the Larmor frequency), which is characteristic for a given type of nuclei and is

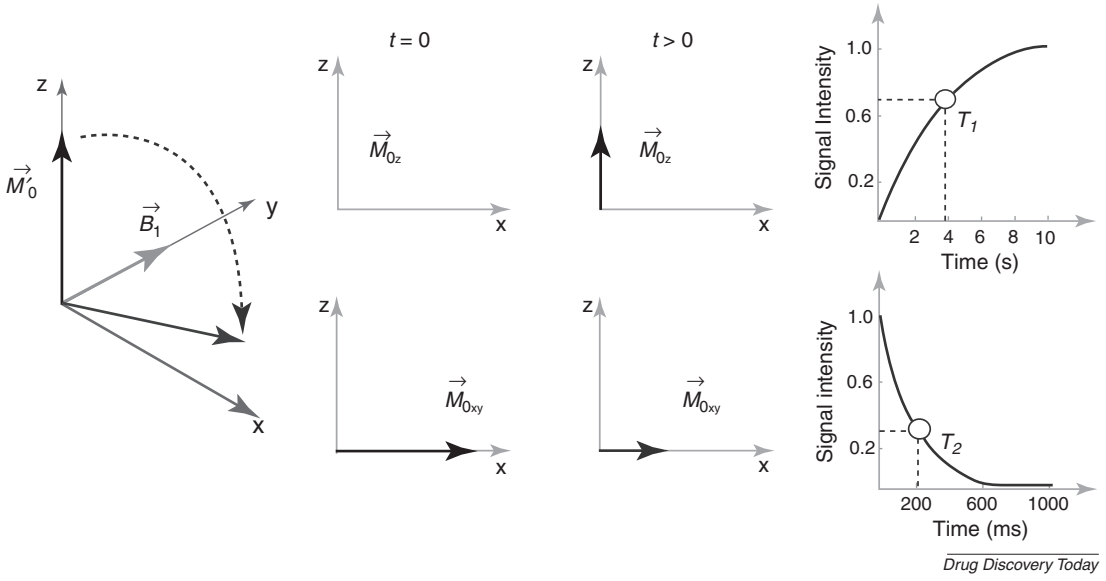

FIGURE 2

Magnetic resonance signal detection and behavior. For further details, see main text.

proportional to the strength of the magnetic field. For example, for hydrogen nuclei at 1.5 T, frequency of this precession is approximately 64 MHz (radio frequencies – FM band). This phenomenon is used in MR signal detection. In a typical MR experiment, additional oscillating field B_1 at or close to the Larmor frequency is applied (Fig. 2), which 'tips' the magnetization vector in the direction perpendicular to the main magnetic field, B_0. The B_1 field is generated in an RF-coil, usually used for signal detection. The magnetization vector precesses around the main magnetic field with the Larmor frequency and produces a changing magnetic field (a source of radio-frequency signal) that can be readily detected.

Initially, magnetization M_0 is aligned with the direction of the external magnetic field, B_0. Upon application of a small magnetic field, B_1 perpendicular to B_0, magnetization rotates around B_1. At time $t = 0$, the magnetic field B_1 is switched off and the entire magnetization, M_0 is in the transverse (x–y) plane. The transverse component of this magnetization can be measured and therefore produces an MR signal. Furthermore, temporal evolution of this magnetization is a key contributor to the MR signal. Once in the transverse plane, magnetization recovers to the equilibrium position (along the main magnetic field, z-direction). This process is relatively long (on the order of seconds) and is described by the so-called 'longitudinal relaxation time constant', T_1. In addition, magnetization in the transverse plane decays with a specific time constant T_2. Magnetization decay in the transverse plane is caused by a loss of spin coherence owing to a locally fluctuating magnetic field that results from the rotation and diffusion motion of other spins in the sample. In pure liquids, $T_2 = T_1$, whereas in more solid environments, such as gels or tissues, $T_2 < T_1$ and is on the order of tens of milliseconds. However, the presence of para- or ferromagnetic particles can significantly reduce both relaxation times.

MR contrast mechanisms

Sample magnetization depends on many external and internal characteristics of the measured system. There are several characteristics of magnetization vector that are used to produce the MR signal and contrast. What distinguishes MRI from other imaging modalities, such as computed tomography (CT) or ultrasound, is not only the plethora of different contrast mechanisms, but also the flexibility of the user to influence the measured signal. This intrinsic characteristic of MRI stems from the fact that measured magnetization is significantly influenced by the physicochemical properties of water in the sample. Magnetization magnitude, for example, is not only directly proportional to water (or spin density) in the sample, but also increases with the B_0 magnetic field and depends on the amplitude and duration of the 'tipping' external magnetic field B_1. More interesting is the time evolution of the magnetization (Figs 1 and 2), which is used by MRI. The MRI parameters, T_1 and T_2 are intrinsic properties of water molecules in the sample and, in general, depend on the water molecular environment, such as the presence of other large molecules that significantly decrease their rotational and diffusional motion. For pure water, T_1 and T_2 relaxation times are roughly equal and at 1.5 T they are approximately 3 s. Even a small amount of macromolecules, such as agar, can significantly reduce both relaxation times. For example, for 2% agar solution (by weight) $T_1 = 1880 \pm 10$ ms and $T_2 = 75 \pm 11$ ms [42] and these values linearly decrease with agar concentration (for 8% concentration $T_1 = 740 \pm 13$ ms and $T_2 = 18 \pm 3$ ms).

Figure 3 provides a schematic presentation of the most commonly used contrast mechanisms. Although T_1 and T_2 relaxation mechanism are the most commonly used MR contrast mechanisms, there are other physical phenomena that are often frequently utilized. In the context of this review, two other contrast mechanisms are worth mentioning: diffusion and magnetization transfer (MT). Diffusion is a process of stochastic random motion of water molecules that is not only highly dependent on temperature and viscosity, but also, more importantly, on any barriers to this motion, such as obstructive porous media or cell membranes. Given that MRI is very sensitive to motion, it was used early on to measure diffusion noninvasively [43]. In most biological

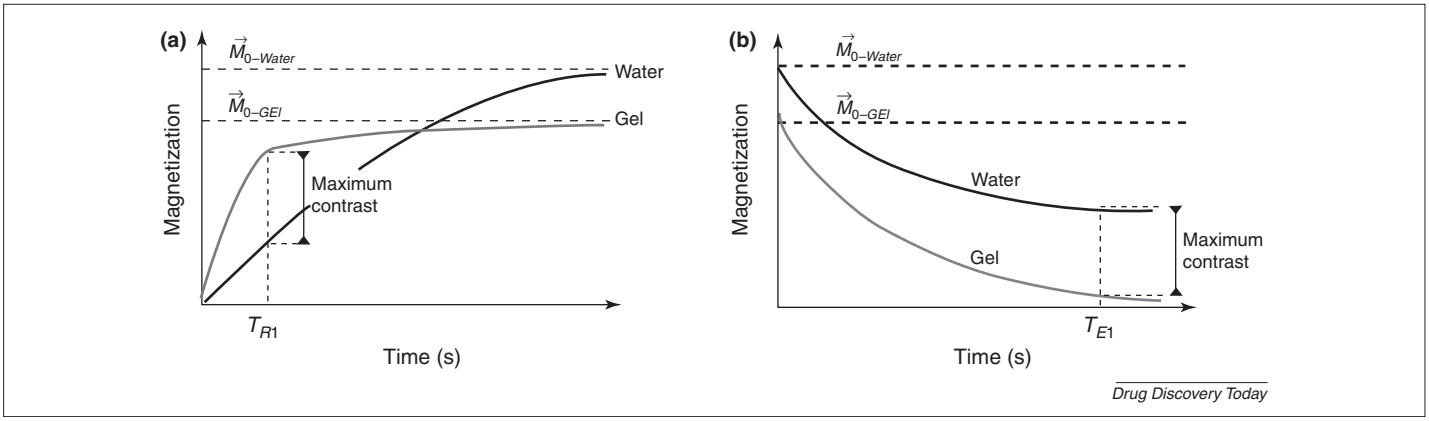

FIGURE 3

The most commonly used magnetic resonance (MR) contrast mechanisms: longitudinal magnetization recovery, T_1 **(a)** and transverse magnetization decay, T_2 **(b)**. At time = 0, the majority of contrast is related to differences in initial magnetization (proton density). Water in gel, owing to reduced molecular motion and interactions with gel macromolecules, exhibits shorter T_1 and T_2 relaxation times. These phenomena can be used to manipulate (or optimize) the amount of contrast (i.e. difference in the MR signal) between the gel and media.

systems, diffusion motion is highly restricted and significantly reduced [44], and an accurate measure of diffusion phenomena allows for evaluation of the cellular microstructure [45]. In the case of hydrated hydrophilic polymer matrices, the reduction of the apparent diffusion coefficient (ADC) can be associated with changes in viscosity and/or the appearance of micropores that can entrap water. In principle, it is possible to estimate pore size using porous media theory [46].

MT in an MRI context was discovered accidentally by Bob Balaban *et al.* (Bob Balaban, personal communication). These investigators were attempting to perform a spin transfer experiment by selective saturation of urea to look for small signal suppression in water. Instead, they found a significant loss of image intensity from the proton signal in tissue, which did not depend on the specific offset frequency of the irradiation. This generalized signal suppression, now known as MT, has become accepted as an additional way to generate unique contrast in MRI that can be used to advantage in a variety of clinical applications. The detailed underlying biophysics of MT is quantitatively understood, enabling it to be optimally exploited in MRI [42]. Briefly, MT is a process of magnetization exchange between protons associated with water molecules and 'invisible' (owing to short T_2 relaxation times) protons on the –OH groups of large macromolecules. MT enables the assessment of these macromolecular protons indirectly and the estimation of the macromolecular content of the sample [42]. Additional parameters, such as MT exchange ratio and T_2 relaxation of macromolecular protons, are specific to the type of molecules taking part in the MT exchange [47]. For example, MT experiments have been demonstrated to be sensitive to changes in macromolecular macrostructure, such as lipid aggregation and decomposition [48].

Imaging considerations

So far, we have discussed the general principles of NMR. The contrast mechanisms presented above can be readily applied in the context of MR imaging. To produce two- or three-dimensional 'maps' of the sample, NMR has to be extended to include spatial encoding of the measured signal. This is achieved by applying the magnetic field gradient that modifies either the Larmor frequency or phase (spatial orientation) of the measured magnetization vector in a given sample position. The total signal can then be easily decoded (from its frequency and/or phase) domain to the actual physical space by Fourier transformation, resulting in a two- or three-dimensional image representing magnetization (or signal amplitude) in x,y coordinates (Fig. 4).

MRI therefore requires additional hardware that is able to produce B_0 gradients and specially designed sequences that are tailored to provide desired contrast mechanism (T_1, T_2, diffusion or MT) followed by a spatial readout of the signal. MRI sequences allow for sophisticated magnetization manipulation and, therefore, MR signal detection. An MRI sequence consists of RF pulses, pulses inducing B_0 gradients and signal acquisition periods in a specific order and timing. MRI sequences can be roughly divided to be specific for liquids or liquid-like samples [e.g. (hydro) gels or soft tissues] and sequences specific for solid or solid-like samples (e.g. nonhydrated polymeric matrix or cartilage). They can be prepared to be sensitive or insensitive for particular macro- or molecular phenomena (e.g. flow, diffusion, perfusion, relaxation or chemical exchange). For further sequence descriptions, see [39–41] or a review in Ref. [5].

However, the introduction of spatial encoding poses significant problems that need to be considered. The resolution of the image (the so-called 'voxel size'), and the field of view (FOV) covered are generally defined by a user, but they are limited by the system hardware (gradient strength) and RF coils (to receive the MR signal). Typical human scanners allow for sub-mm resolution for the FOV of up to 50 cm, whereas in high-field MRI systems used for animal or sample imaging, it is possible to obtain an isotropic resolution on the order of tens of micrometers for 3–5 cm-sized object. High resolution, however, comes with a significant price. This is because the signal in the voxel is directly proportional to the amount of water the voxel contains and, therefore, is proportional to the voxel volume. To achieve high-quality images at high resolutions, it is often necessary to perform signal averaging to increase the signal to noise ratio (SNR). There is therefore a trade-off between imaging time and image quality that, in the case of microimaging, can be substantial.

There are generally two approaches to MRI: (i) a qualitative approach that maximizes the contrast between various regions of

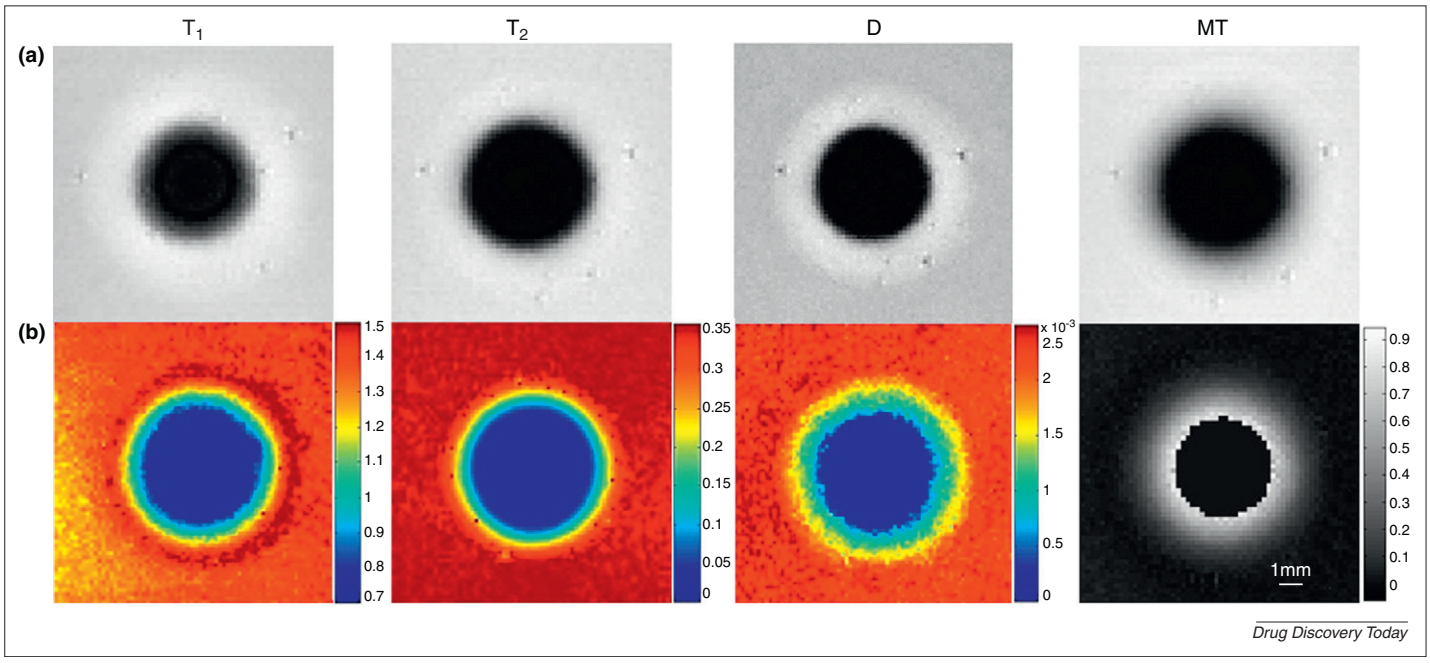

FIGURE 4

Diversity of magnetic resonance contrast mechanisms. T_1, T_2, diffusion (D) and magnetization (MT)-weighted images **(a)** of HPMC polymer matrix tablets (5–6 hours of hydration) and the corresponding parametric images of physical properties of the measured sample **(b)**. The color scales for the images in (b) are scaled in seconds for the T_1 and T_2 maps; in mm^2/s for the D map and in arbitrary units for the MT map (Młynarczyk *et al.*, unpublished data).

the sample and (ii) a quantitative approach that attempts to obtain the physical properties of the measured object that can be further linked to sample microstructure and water environment (i.e. quantitative parametric mapping or qMRI).

Qualitative images can be optimized for contrast and, because they are relatively fast to implement, they are useful for studies of temporal changes in CR dosage forms during hydration. However, comparison between different imaging sessions might pose a problem, because image intensities also depend on the position of the sample in the magnet and, owing to hardware and field heterogeneities, the position might vary from sample to sample. Quantitative imaging offers a unique opportunity to measure the physical properties of hydrated dosage forms that are independent on performed experiments and are intrinsic to the measured sample. However, they do require a series of MR images to produce parametric images, which therefore results in an increased imaging time.

Finally, MR vendors offer a variety of MR sequences tailored for specific applications and contrast mechanisms. However, owing to patent considerations, almost identical sequences can have slightly different vendor names. Moreover, MR protocols are often designed to obtain specific contrast in the measured sample and can be further optimized for specific magnetization properties. They are in general designed to provide maximum contrast and speed (which is helpful for qualitative imaging) at the expense of quantitative abilities.

In Fig. 4, the application of various contrast mechanisms for the imaging of tablet hydration is presented: T_1, T_2, diffusion and MT-weighted images (Fig. 4a) of polymer HPMC (5–6 hours of hydration) and the corresponding parametric images of physical properties of the measured sample (Fig. 4b). MR-weighted images (Fig. 4a) are optimized for contrast and take, on average, a few minutes to collect. Parametric images are calculated from the series of T_1, T_2, diffusion and MT-weighted sequences. The range of longitudinal, T_1, transverse, T_2 relaxation time, ADC and MT are also presented in the figure. It can be seen that the parametric images reveal slightly different aspects of the hydrated HPMC matrix. The images represent 1-mm thick sections with an in-plane resolution of 200 μm.

MRI in static conditions

The MRI studies of CR dosage forms can be generally divided into two groups. The first consists of extensive studies performed in a static state in a limited volume of solvent. These studies provide insight into the molecular processes occurring during the hydration of dosage forms. To the second group, which are still few in number, belong the studies performed under dynamic conditions (i.e. at dissolution medium flow or stirring) using simulated gastric fluids. Studies under dynamic conditions are discussed in the next section.

Experimental studies that use MRI for testing the CR dosage forms in static conditions cover the following topics: (i) pure polymeric matrix systems [49–51]; (ii) bulk relaxometry as a complementary measurement for calibration studies and quantitative analyses with the application of hydrogels with a known polymer concentration [52,53]; (iii) polymeric tablet matrix systems with model drugs [54–57]; and (iv) other dosage forms, such as chronopharmaceutical capsules [58,59]. The details of MRI experimental studies carried out in static conditions are summarized in Table 1.

Of the studies of polymeric matrices presented in Table 1, more than half concern HPMC-based matrix systems, mostly tablets. These studies have been carried out in water or aqueous solutions, such as alkaline buffers or acidic media. In certain cases, applied

TABLE 1

An overview of MRI studies carried out under static conditions.

Year of publication/Refs.	Sample characteristics			Study conditions		
	Sample	Active substance	Excipient	Medium	Temperature	Imaging sequence[a]
1994 [33]	Tablets	None	HPMC	Water	37°C	SWI
1997 [66]	Gels, tablets	None	HPMC	Water	22°C	SE
1998 [83]	Tablets	None	HPMC	Water, solution containing $CuSO_4$ 10 mM	Not specified	SE
1998 [49]	Slabs	None	PEO	Water, D_2O	Room	SE
2000 [67]	Tablets	5-Fluorouracil, triflupromazine hydrochloride	HPMC	Water	Not specified	PGSE
2000 [54]	Tablets	Naproxen sodium, naproxen	HPMC	Water	25°C	CPMG
2002 [62]	Tablets	None	HPMC	Water (pH 6), hydrochloric acid solution (pH 2)	25°C, 37°C	SE
2003 [58]	Capsules	Propranolol	Not specified	Water	Room	2D FT, RARE
2004 [55]	Tablets	Tetracycline hydrochloride	HPMC	Hydrochloric acid solution (pH 2)	37°C	SE
2004 [50]	Capsules	None	HPMC, chitosan, sodium alginate	Hydrochloric acid solution 0.1 M	Room	SE
2005 [51]	Tablets	None	HPMC	Alkaline solution (pH 12)	37°C	CPMG, PGSE
2005 [61]	Tablets	None	HPMC	Acidic solution (pH 2); neutral solution (pH 7); alkaline solution (pH 12)	37°C	CPMG
2005 [52]	Tablets, hydrogels	None	Cellulose ethers	Not specified	Room	CPMG
2006 [73]	Tablets	Diltiazem hydrochloride	Eudragit	Water with $3.7\ 10^{-4}$ M $CuSO_4$ phosphate buffer	Not specified	SE
2007 [56]	Tablets	Diltiazem hydrochloride	Eudragit	Water with $3.7\ 10^{-4}$ M $CuSO_4$	Not specified	SE
2007 [13]	Tablets	Solid dispersion of antipyrine	HPMC	D_2O	Not specified	FLASH, SE, SPI
2008 [83]	Hydrogels	Sodium salicylate	HPMC	Water, D_2O	37°C	SE
2009 [57]	Tablets	Ciprofloxacin, acetaminophen	Cross-linked high-amylose starch	Water and D_2O 1:1	Not specified	SE, PGSE
2010 [59]	Bilayer osmotic tablets	Doxazosin mesylate	Not specified	Water	20°C	SE
2010 [11]	Tablets, hydrogels	None	HPMC	Water	Room	CPMG, RARE
2010 [53]	Tablets	None	HPMC, microcrystalline cellulose lactose	Phosphate buffer (pH 7.4) with addition of sodium chloride	Room	CPMG
2010 [66]	Tablets, gels	None	Xanthan gum	HCl pH 1.2 + NaCl replaced after 2 h by water at pH 5.7	Room	SE, SPI
2010 [12]	Tablets	Antypirine	HPMC	Water, D_2O	Not specified	FLASH, SE, SPI

[a] *Abbreviations*: CPMG, Carr–Purcell–Meiboom–Gill; FLASH, fast low angle shot; PGSE, pulsed gradient spin echo; SPI, single point imaging; SE, spin echo; RARE, rapid acquisition with relaxation enhancement; 2D FT, two dimensional Fourier transform; SWI, spin warp imaging.

media are lightly doped with copper sulfate to shorten the measurement time or to improve the SNR by reducing the longitudinal relaxation time (T_1). In a few cases, where it is desirable to observe the behavior of protons associated with a solid polymer, heavy water (D_2O) is used instead of water. An overwhelming number of studies using static conditions have been carried out in test tubes in small volumes of liquid. In such cases, the saturated solution is easily reached and affects the further dissolution of the matrix

constituents. This, in general, can influence the mechanism of solvent penetration into the matrix and gel layer formation.

Experimental conditions among studies often differ. For example, the temperature maintained during measurements varies from 20°C (room temperature) to the physiologically relevant 37°C. Taking into account that one of the main phenomena responsible for the formation of the gel layer is the temperature-dependent glassy–rubbery transition, it is difficult to compare the results obtained at different temperatures. Therefore, it is usually not possible to correlate reported MRI results to the drug-release studies and to extrapolate the results to *in vivo* behavior of the dosage form.

A plethora of pulse sequences used during imaging demonstrates the potential of MRI techniques to match the needs of specific research.

There are four major themes that are the main foci of MRI studies of CR dosage forms: (i) identification of regions separated by fronts or transition zones; (ii) spatial and temporal evolution of particular regions in the matrices; (iii) physical properties of the CR dosage forms. For this purpose, mapping of the distribution of physical parameters, such as proton density (PD), ADC or transverse relaxation time, T_2, is carried out; and (iv) interactions between water and polymeric chains in particular regions of the matrix (e.g. how water is bounded with polymer and how the mass transfer occurs within the matrix).

One of the earliest publications reporting the analysis of gel layer properties forming on the surface of polymeric tablets during hydration was presented by Rajabi-Siahboomi *et al.* [38]. MRI was applied for monitoring of the swelling and hydrogel layer formation in HPMC-based tablets. On the basis of diffusion and relaxation measurements, the presence of a water mobility gradient across the gel layer was reported. The outer part of the layer was characterized by ADC values similar to those of free water; the ADC decreased toward the center of the matrix, indicating either changes in material viscosity or the emergence of restricted diffusion. The molecular mobility of water within the gel layer was found to be dependent on the substitution type of the polymer. Water diffusivity is one of the issues of interest in the evaluation of polymeric matrix CR systems. The water diffusion within the matrix determines the kinetics of the gel layer formation and influences the drug dissolution. The ADC has been used as a key parameter to demonstrate hydration differences of matrix systems by several investigators [51,54,57,60,61]. The comparison of ADC distribution in HMPC and PVA matrix tablets showed the influence of polymer type on the properties of the systems. The gel formed owing to PVA hydration restricted water mobility more effectively than did HPMC [60].

In several MRI studies of CR drug delivery systems, the concept of water fronts, taken from optical studies (Box 1), is applied to describe the spatial and temporal changes occurring in the hydrated part of the matrix [52,56,60–62]. In some cases, the observation of moving fronts was performed together with calibration approaches, applied for the identification of the polymer–water concentration in particular regions of the gel [52,63,64]. For this purpose, a combination of standard imaging sequences (e.g. standard spin echo; SE) with T_1/T_2 bulk relaxometry is applied. Nonspatially resolved relaxometry studies are used for measurements of transverse relaxation time, T_2 of volume samples with predefined water–polymer concentration ratios. The calibrated T_2 values are then applied to spatially resolved data for estimation of polymer concentrations in particular regions of the hydrating matrix. Such samples are prepared to be highly homogenous and preparation methods include heating and/or cooling, intensive mixing and seasoning of the samples, whereas in the hydrated polymeric matrices, water is not distributed within the layer as homogeneously as in specially prepared reference samples. The presence of air trapped in the polymeric matrix during preparation typically causes overestimation of the polymer concentration [64]. Despite the drawbacks, this approach makes it possible to find differences in the polymer concentration profiles at particular time points. These differences arise owing to the properties of HPMC applied as a model polymeric matrix (i.e. different substitution type, molecular mass, hydrophilicity and particle size) [52].

Measurements of temporal changes in the gel layer thickness allow for comparison, in a relatively simple manner, of various CR formulations, and the evaluation of how different variables influence the performance of the dosage form (e.g. polymer type, particle size, among others). The advantage of MRI over other techniques results from the ability to obtain spatially resolved information about the physical parameters of particular regions in the gel layer (e.g. T_2 relaxation times and proton densities attributed to solvent transported within the polymeric matrix). PD and T_2 profiles (one-dimensional images) have been analyzed together in the HPMC matrix systems by Tritt-Goc *et al.* [61]. In the hydrated part of the matrix region, distribution of water concentration (PD) is uniform, with a sharp transition gradient between the hydrated area and the dry core. The corresponding profiles of the apparent T_2 demonstrate a gradual decrease of T_2 relaxation toward the core of the system [51,55,61,62]. The authors suggested several transport mechanisms in the HPMC matrix: Fickian diffusion for alkaline solvents, and case II and anomalous diffusion for acidic and neutral solvents. The PD parameter was also applied in one of the most recent studies describing hydration and swelling properties of tablets made of chitosan and carboxymethyl starch [65].

^{1}H MRI studies enable the behavior of the polymer to be analyzed indirectly by recording the distribution and mobility of water molecules in a polymeric system. The first attempt at polymeric matrix visualization was by Hyde and Gladden [49]. They conducted a quantitative study measuring the changes in water and polymer concentrations within the polyethylene oxide (PEO) matrix using a one-dimensional MRI technique. Based on the T_1 measurements, it was observed that both water penetration and swelling of the polymer matrix were controlled by the processes of diffusion. To analyze the behavior of the polymer, heavy water has been used as a solvent. It provides an opportunity to observe the distribution of protons in the polymeric chains, because hydrating deuterated water is not detectable at the ^{1}H frequency [49,53,57,65,66].

Dahlberg *et al.* [12,13] focused on the imaging of mobilization of polymeric components in HPMC tablets. Swelling of the HPMC matrix and release of the antipyrine have been suggested to be diffusion driven and drug release has been correlated with polymer chains mobility. Interestingly, the rate of water penetration is not directly related to drug-release kinetics. Moreover, it has been shown that hydration of the polymer grains within the matrix

varies strongly with changes in their size. Small HMPC particles tend to form a more homogenous gel, which effectively delays the drug release. Matrices with larger polymeric grains develop into heterogeneous gels, enabling faster drug release through water-rich regions in the matrix.

MRI provides an opportunity to record the distributions of nuclei other than protons (e.g. fluorine, sodium or carbon). It also enables fluorine-containing model drugs to be detected within the matrix. Unfortunately, the level of MRI signal is much lower than in proton imaging and, therefore, the acquisition time is much longer for an acceptable SNR. An interesting example of applications of one-dimensional ^{19}F MRI is the work published by Fyfe and Blazek-Welsh [67]. They investigated the penetration of water into tablets of HPMC and the release of drugs containing fluorine (triflupromazine and 5-fluorouracil). It has been observed that freely soluble 5-fluorouracil was released by the process of diffusion from hydrogel containing up to 30% HPMC, whereas poorly soluble triflupromazine was released by erosion of the outer hydrogel layer, which contained not more than 10% HPMC. From practical point of view, it must be pointed out that the application of such methodology is restricted to a narrow group of dosage forms containing fluorine.

In the MRI studies discussed above, several factors influencing both the drug dissolution and the polymer hydration were presented. The performance of the CR systems can be critically influenced by variables such as: (i) the type of polymer or polymers and their ratios in the matrix [16,68]; (ii) the solubility of drug; (iii) the polymer:drug ratio; (iv) the particle size of the drug and the polymer; and (v) the type and amount of fillers used in the formulation. MRI can be applied as a useful tool to examine the influence of parameters (e.g. temperature, pH, molecular mass and degree of substitution of polymer) on the polymer swelling.

Recently, a small pharmaceutical MRI system based on the NMR relaxometer with a permanent magnet has been introduced [69]. Such systems provide the opportunity to perform MR imaging at relatively low cost. It is achieved by the application of a low magnetic field (approximately 0.5 T), whereas previously discussed MR studies have been performed using superconducting magnets of fields starting at 4 T. The low magnetic field implicates a lower SNR and, therefore, a lower spatial resolution or longer acquisition time. The typical slice thickness in the studies applying low field magnets is approximately 5 mm, whereas in high field magnets it is 1 mm or less.

Strübing *et al.* [70,71] studied the hydration and swelling of floating tablets using a low field system (0.5 T). They carried out dissolution by the paddle method and transferred the samples to the MR system for imaging. The floating properties of the formulations were based on CO_2 generation from an effervescent mixture embedded in the core of coated tablets. A similar benchtop MR imaging system was used to study the influence of composition on the drug release mechanisms from osmotic push–pull release systems [72]. The authors demonstrated a correlation between the amount of released drug substance and the hydration of the osmotic dosage form.

MR imaging studies have been carried out mainly on CR tablets. An example of the study of capsules is that of Sutch *et al.* [58]. These authors used pulsatile capsules filled with propranolol and plugged with a controlling release plug. The study enabled the authors to explain the phenomena occurring during penetration of water into the capsule and to show the differences between capsules coated with different polymers.

It should be emphasized that, in the reports already discussed, the experimental conditions differ substantially from the pharmacopoeial requirements typically applied in drug dissolution testing studies.

Toward MRI in dynamic conditions

Although MRI in static conditions provides valuable information about the structure and behavior of polymer systems during hydration, a possibility of simultaneous MRI and drug dissolution in dynamic conditions with media change is especially meaningful for understanding CR dosage form performance.

Some drawbacks of MRI of CR formulations in static conditions have been already discussed. For example, static conditions do not allow proper evaluation of the influence of erosion upon the drug dissolution process. Moreover, swelling analyses carried out in small volumes of liquid, without stirring or flow, cannot be related directly to the results of dissolution studies, owing to the unfeasibility of maintaining sink conditions. The advantages and disadvantages of MRI in static and dynamic conditions are presented in Table 2.

The limitations in combing imaging with drug dissolution techniques arise primarily from the MRI hardware used. For this purpose, vertical superconducting magnets are typically utilized. Effective bore diameter of the magnet (and therefore total sample diameter) available for a sample rarely exceeds 20 mm. Samples are usually fixed in a test-tube filled with solvent and/or medium [66,73].

The small inner diameter of MR devices significantly reduces both the possibility of implementation of additional equipment and the selection of objects for MR imaging. Another compounding difficulty is the requirement for the use of nonmagnetic,

TABLE 2

Advantages and disadvantages of MRI studies carried out under static or dynamic conditions.

Features	MRI in flow-through cell (dynamic)	'Test-tube' MRI (static)
Erosion of CR matrix accounted	Fully	To a small degree
Sink conditions	Possible	Impossible
CR matrix system evolution	Highly unrestrained	Restricted or very restricted
Simultaneous dissolution and MRI	Possible	Pointless
Application of pharmacopoeial regulations	Possible	Impossible
Flexibility to use various MR pulse sequences	Low (high if medium flow halted)	High

TABLE 3

An overview of MRI studies carried out in dynamic flow conditions.[a]

Year of publication/Refs.	System			Sample			Medium and temperature	Pulse sequence
	Cell	Pump	Magnet	Dosage form	Excipients	Active substance		
2000 [14]	Pharmacopoeial	Peristaltic	Vertical Bruker MSL 400	Tablets, osmotic tablets	HPMC	Ranitidine, salbutamol	Simulated gastric fluid + 5 mM $CuSO_4$	SWI
2007 [76]	40 mm in diameter flow through cell dedicated for floating systems;	Piston	Horizontal 4.7 T Bruker	Capsules: HBS	HPMC	L-Dopa	Fed state, simulated gastric fluid + $CuSO_4$; fasted state, simulated gastric fluid + $CuSO_4$, 37°C	SE flow compensated
2007 [9]	Specially designed flow through equipped with rotating disc	Peristaltic	wb400 Bruker spectrometer with a 2.5 ^{1}H resonator	Tablets	PEO	None	Water, 25°C	PFG SE
2008 [74]	40 mm in diameter flow through cell dedicated for floating systems	Piston	Horizontal 4.7 T Bruker	Capsules: HBS	HPMC	L-Dopa	Fed state, simulated gastric fluid + $CuSO_4$; fasted state, simulated gastric fluid + $CuSO_4$, 37°C	SE flow compensated
2009 [10]	Specially designed flow through equipped with rotating disc	Peristaltic	wb400 Bruker spectrometer with a 2.5 ^{1}H resonator	Tablets	HPMC	Calcium phosphate, mannitol	Phosphate buffer pH 6.8, 37°C	MSME
2010 [8]	40 mm in diameter flow through cell dedicated for floating systems	Piston	horizontal 4.7 T Bruker	Capsules: HBS	HPMC	L-Dopa	Fed state, simulated gastric fluid + $CuSO_4$; fasted state simulated gastric fluid + $CuSO_4$, 37°C	SE flow compensated
2010 [75]	Pharmacopoeial	Peristaltic	MRI, low field 0.5 T	Tablets	Not specified	Chlorpheniramine maleate	Water, 37°C	Not specified
2010 [78]	Pharmacopoeial	Peristaltic	MRI, low field 0.5 T	Tablets	Spray-dried chitosan	Diclofenac sodium, theophylline,	0.1 N HCl; buffers Tris–HCl pH 6.8 and pH 5.0; 37°C	SE
2010 [75]	Pharmacopoeial	Peristaltic	MRI, low field 0.5 T	Tablets	PEG, PEO	Acetaminophen	Water; 37°C	SE
2011 [16]	Specially designed flow through equipped with rotating disc	Peristaltic	wb400 Bruker spectrometer with a 2.5 ^{1}H resonator	Tablets	HPMC	Theophylline, carbamazepine	Phosphate buffer pH 6.8; 37°C	SE
2011 [68]	Pharmacopoeial	Piston	Horizontal 4.7 T Bruker	Capsules: HBS	Carrageenans	L-Dopa	HCl solution 0.1 M; 37°C	SE flow compensated
2011 [17]	Pharmacopoeial	Peristaltic	Vertical 9.4 T Bruker AV 400	Tablets	HPMC	Fluvastatin	Simulated gastric fluid; fasted state, simulated intestinal fluid; 37°C	RARE

[a] *Abbreviations*: HBS, hydrodynamically balanced system; MSME, multislice multiecho; PFG, pulsed field gradient.

MR-compatible materials. Owing to the strong magnetic field generated by the magnet, all additional equipment, such as dissolution cells, heating elements, temperature probes and flow devices, need to be constructed from diamagnetic materials or placed outside the magnet. Otherwise, they can significantly influence the MR signal, creating a plethora of image artifacts and distortions, whereas electrical and/or electronic devices can simply malfunction. Furthermore, an acidic environment substantially changes the working conditions of the RF coils used for MR signal detection. Therefore, MR coils need to be optimized to provide a satisfactory level of MR signal under these conditions. Finally, MR measurements are sensitive to motion. Performing dissolution experiments under flow conditions requires specially designed imaging protocols to minimize flow artifacts. These sequences, however, significantly limit the ability to derive quantitative MR parameters. The overview of MRI studies carried out in dynamic flow conditions is presented in Table 3.

Seminal work by Fyfe *et al.* marked the beginning of MRI studies under pharmacopoeial dissolution conditions [14]. In this study, the authors used USP4 flow-through cells made entirely of nonmagnetic materials, which are placed in a Bruker MSL 400 NMR (9.4 T) spectrometer equipped with a microimaging apparatus. The matrix tablets of ranitidine hydrochloride and salbutamol were used as an example to demonstrate of the ability to simultaneously image the fluid distribution within the tablet matrix and dissolution studies in accordance with pharmacopoeial requirements.

Over the past few years, two approaches for imaging in medium-flow conditions have been reported: (i) application of a nonpharmacopoeial small dissolution cell that combines mixing and stirring of the medium. In this method, the sample rotation as well as medium flow is stopped before imaging and (ii) integration of the dissolution apparatus with MRI equipment and imaging during flow. This method requires MRI flow-insensitive sequences.

Simultaneous MR imaging and dissolution seems to be ideal, because it allows for direct correlation between the drug dissolution and CR dosage form behavior (e.g. structure evolution) during hydration. However, there are several technical problems that make such approaches difficult: (i) medium movement can cause artifacts and significant MR image distortions. To avoid this, specially designed, flow-insensitive MR sequences need to be used or the medium flow or agitation has to stop for the duration of the MRI measurement [9,10]; (ii) medium flow and polymer matrix swelling can cause displacement of the sample and severely inhibit reproducibility. For proper positioning of the sample during dissolution, samples are positioned on a plastic stage [67], held within a specially designed strainer [74], plastic holder [10,75] or nylon cage [17], and then placed on glass beads or glued to the rotating disc [9]; and (iii) dissolved gases can form large bubbles in the vicinity of the dosage form and can negatively influence the analytical results of dissolution. Moreover, owing to differences in the magnetic susceptibility between air, gel and water, air bubbles can cause MRI image artifacts [65].

In 2007, Abrahmsen-Alami *et al.* [9] proposed a specially designed dissolution cell for simultaneous drug dissolution and MRI. The cell was equipped with a rotating disc to position the tablet in the center of the MRI probe. Although rotation is a main source of tablet erosion, medium flow was induced mainly to maintain sink conditions within the cell during dissolution. The tablets were glued to the rotating disc and imaging was performed when both rotation and flow were halted. The authors recorded the swelling and erosion of PEO tablets and observed differences in the rate of dimensional changes: the faster rate was observed in the radial than in the axial direction of the tablet. The dissolution cell described above was then successfully applied by Tajarobi *et al.* [10] to study the behavior of HPMC matrix tablets with incorporated substances of different solubility. Front's evolution in the HPMC, HPMC–mannitol and HPMC–di-calcium phosphate matrix tablets was measured by MRI. Simultaneously, dissolution of the matrix and additives were measured by liquid chromatography with mass detector (LCMS), size exclusion chromatography with refractive index detector (SEC-RI) and focused beam reflectance measurements (FBRM). The same equipment was applied by Viriden *et al.* [15] to investigate the effects of HPMC heterogeneity on theophylline and carbamazepine release from matrix tablet systems. In both cases, the authors observed substantial differences in the rate and the mechanism of water penetration and in the active substance dissolution according to the solubility of substance embedded in the matrix. Release of the highly soluble substance has been suggested to be governed by diffusion, whereas the poorly soluble drugs were released at a rate comparable with erosion of the matrix.

A similar approach for simultaneous imaging and dissolution has been presented by the authors of the current article [74,76]. An integrated system for MRI and drug dissolution studies was implemented that utilized a 4.7 T horizontal magnet with a bore diameter of 300 mm. Two types of cells [standard pharmacopoeial (diameter 22 mm) and flow-through cell with a diameter of 40 mm for extensively swelling floating dosage forms] were used in these studies. The system was used to examine mainly floating dosage forms: hydrodynamically balanced systems containing L-dopa as a model drug and HPMC or various types of carrageenans as gel-forming and dissolution-controlling excipients. Measurements were carried out in simulated gastric juice in a fed or fasted state [69]. The same equipment was applied for the evaluation of the properties of commercial CR formulations with quetiapine fumarate [77].

The range of MRI studies performed under dynamic conditions could be extended with additional methods. For example, the multinuclear study of polymeric matrix and drug behavior during dissolution at 9.4 T (^{1}H two-dimensional imaging, ^{19}F one-dimensional imaging and ^{19}F bulk relaxometry) in USP apparatus 4 was recently presented. For the purpose of the study, a commercial HPMC-based drug product, Lescol XL, containing fluvastatin, was used [17]. The T_2 preconditioned rapid acquisition with relaxation enhancement (RARE) sequence [11] was applied to obtain the solvent concentration and T_2 relaxation time maps. Mobility of fluvastatin was registered with fluorine bulk relaxometry.

Further extension of these experimental imaging methods will include quantitative measurements (qMRI) of various MR-detectable parameters (e.g. T_2, T_1, ADC and MT) of CR dosage forms, together with drug dissolution studies. An example of the results of such studies performed using the USP4 apparatus is presented in Fig. 4b (Młynarczyk *et al.* unpublished data).

One of the advantages of MRI is the ability to determine differences in the physico-chemical features of various formulations, which are otherwise characterized by similar dissolution profiles. For example, floating formulations with HPMC with different viscosities and substitution types demonstrate significant variability in the processes of hydrogel formation and swelling, despite similar drug dissolution profiles [8]. This suggests that there might be potential bioavailability or bioequivalence challenges and justifies the need to study discriminatory conditions for drug dissolution in more depth.

In recent years, commercial devices for MRI imaging and drug-release studies have been introduced. The first application of a low-field MR system (0.5 T) equipped with a flow-through cell was presented by Nott in 2010 [75]. In the following year, two papers discussed the potential usefulness of this commercial system. In these studies, chitosan-based polymeric systems [78] and PEG/PEO mixtures were investigated [16]. These studies demonstrated the dependence of paracetamol dissolution on the polymer content ratio.

Although authors determine and parameterize the structural properties of analyzed dosage forms (e.g. gel layer thickness assessment), the methods of discrimination are often not fully discussed. It is probably that the first-time image analysis was discussed only in the context of MRI coupled with USP apparatus 4. Two approaches were described recently in detail by Nott [75] and Kulinowski [77]. In the work by Nott, the author applied operator-dependent criteria for separating the medium and gel and inflexible segmentation of the matrix interior. The latter assumes two regions regardless of the real matrix structure during hydration. A more flexible approach has been presented by Kulinowski. Gel-medium separation was performed using texture analysis (highly user independent) and no assumptions were made concerning internal structure; instead, it was determined using an image intensity histogram.

Integration and supplementation of MRI with other techniques

During the past few years, many attempts to supplement MRI results with data from other techniques have been undertaken. MRI has been supplemented by microscopic, X-ray CT and μCT to detect air voids occurring in hydrating insoluble Eudragit matrix tablets loaded with diltiazem hydrochloride (a freely soluble drug) [56]. In another study, the movement of glass microspheres and the position of the advancing hydration front as observed by MRI were combined in the same diagram for a swelling HPMC matrix with fillers by Laity [53]. In this case, glass microbeads were used as a μCT tracer for mechanical mass transport inside the core of the matrix, which could not be detected by MRI.

As previously pointed out, one of the major difficulties in qMRI is the determination the water–polymer concentration in particular zones of the gel layer. In contrast to previously described calibration approaches based on bulk relaxometry of samples of different water–polymer concentration [52,53,63], Tajiri *et al.* [16] proposed using FTIR spectroscopy on samples of gel peeled from hydrated PEG/PEO tablets to evaluate water content in the gel layer observed by MRI.

Special attention should be focused on theoretical *a priori* models and *a posteriori* models. Chronologically, the first subject and/or goal of modeling was drug dissolution prediction, whereas dissolution testing was a basic tool in the research and development of pharmaceutical products. With the advent of imaging techniques, modeling started to take into account structural and/or geometrical changes (i.e. front position or layer thickness). So far, only some theoretical models predicting matrix structure and its evolution have been related to MRI results and/or data. MRI was used to validate a model of PEO dissolution, calibrated by means of mechanistic parameters by Kaunisto [79], whereas a model of HPMC dissolution developed during the mid-1990s by Ju [80] was related to MRI data (qualitative comparison) by Kulinowski to justify the image segmentation [77].

By contrast, *a posteriori* modeling utilizes data sets obtained from several formulations, using various methods as well as chemical descriptors for applied constituents to provide single 'what if'-type model. The first attempt at such approach that included MRI data, was by Dorożyński [8]. A multivariate analysis was performed to create *a posteriori* model introducing the amount of drug released, the amount of hydroxypropoxy groups, the amount of methoxy groups, viscosity, dry core and gel thickness of gastro-retentive HPMC-based formulations. Another approach to modeling MRI data was presented by Broadbent *et al.* [59]. They applied a simple one-dimensional mass conservation model for the identification of the dominant transport mechanism in gastrointestinal therapeutic system (GITS) tablets.

Concluding remarks and future perspectives

MRI is a useful technique and its wide application to preformulation studies is likely to occur over the next few years. It could be expected that the results of such studies could be used for making decisions on the preferred directions of research and will set new criteria for assessing the performance of CR formulations. The introduction of commercial, small laboratory systems for integrated MRI and dissolution will make this valuable technique more available for industrial pharmaceutical research laboratories. In the near future, an increasing number of studies can be expected that apply various MRI techniques for the elucidation of phenomena occurring in CR systems, whereas further development of the integration of MRI with dissolution techniques could yield quantitative imaging under dynamic conditions.

Image analysis of MR data and modeling of CR dosage forms structure evolution could have a crucial role in a further understanding of drug matrix dissolution phenomena. Application of MRI to determine matrix structure and its evolution, together with dissolution data and *a priori* or *a posteriori* modeling, should lead to knowledge-based formulation design. The goal is to shorten formulation development, which could be achieved by higher precision when preparing preformulation studies.

The most important challenges in the coming years therefore include: (i) the development of protocols for data analysis and, in the case of routine studies, setting of acceptance criteria for the results; (ii) determination of the repeatability and reproducibility of the results; (iii) application of qMRI, resulting in one-, two- or three-dimensional maps of MR detectable parameters (T_1, T_2, ADC and MT); (iv) development of quantitative methods and criteria of reliable structure determination from MR images; and

(v) systematic studies of the structure and properties of various polymeric matrix systems loaded with drugs and other excipients characterized by different solubilities.

As a result, one can expect the appearance of detailed, molecularly defined, CR dosage forms in the near future. The techniques discussed above are likely to be used for patenting of the unique properties of dosage forms as defined by their manufacturers.

Acknowledgment

We would like to thank Firas Moosvi for his help in the preparation of this manuscript.

References

1 Gendrin, C. *et al.* (2008) Pharmaceutical applications of vibrational chemical imaging and chemometrics: a review. *J. Pharm. Biomed. Anal.* 48, 533–553
2 Gurny, R. and Mäder, K. (2010) Imaging tools for pharmaceutical development. *Eur. J. Pharm. Biopharm.* 74, 1
3 Richardson, J.C. *et al.* (2005) Pharmaceutical applications of magnetic resonance imaging (MRI). *Adv. Drug Deliv. Rev.* 57, 1191–1209
4 Zeitler, J.A. and Gladden, L.F. (2008) *In vitro* tomography and non-destructive imaging at depth of pharmaceutical solid dosage forms. *Eur. J. Pharm. Biopharm.* 71, 2–22
5 Mantle, M.D. (2011) Quantitative magnetic resonance micro-imaging methods for pharmaceutical research. *Int. J. Pharm.* 417, 173–195
6 Chen, M.L. *et al.* (2010) Challenges and opportunities in establishing scientific and regulatory standards for assuring therapeutic equivalence of modified release products: workshop summary report. *Eur. J. Pharm. Sci.* 40, 148–153
7 Roggo, Y. *et al.* (2005) Characterizing process effects on pharmaceutical solid forms using near-infrared spectroscopy and infrared imaging. *Eur. J. Pharm. Biopharm.* 61, 100–110
8 Dorożyński, P. *et al.* (2010) Novel application of MRI technique combined with flow-through cell dissolution apparatus as supportive discriminatory test for evaluation of controlled release formulations. *AAPS PharmSciTech* 11, 588–597
9 Abrahmsen-Alami, S. *et al.* (2007) New release cell for NMR microimaging of tablets. Swelling and erosion of poly(ethylene oxide). *Int. J. Pharm.* 342, 105–114
10 Tajarobi, F. *et al.* (2009) Simultaneous probing of swelling, erosion and dissolution by NMR-microimaging. Effect of solubility of additives on HPMC matrix tablets. *Eur. J. Pharm. Sci.* 37, 89–97
11 Chen, Y.Y. *et al.* (2010) Quantitative ultra-fast MRI of HPMC swelling and dissolution. *J. Pharm. Sci.* 99, 3462–3472
12 Dahlberg, C. (2010) Relationships between solid dispersion preparation process, particle size and drug release – an NMR and NMR microimaging study. *Eur. J. Pharm. Biopharm.* 76, 311–319
13 Dahlberg, C. *et al.* (2007) Polymer mobilization and drug release during tablet swelling. A ^{1}H NMR and NMR microimaging study. *J. Control. Release* 122, 199–205
14 Fyfe, C.A. *et al.* (2000) NMR imaging investigations of drug delivery devices using a flow-through USP dissolution apparatus. *J. Control. Release* 68, 73–83
15 Viriden, S. *et al.* (2011) Release of theophylline and carbamazepine from matrix tablets – consequences of HPMC chemical heterogeneity. *Eur. J. Pharm. Biopharm.* 10.1016/j.ejpb.2011.02.003
16 Tajiri, T. *et al.* (2010) Release mechanisms of acetaminophen from polyethylene oxide/polyethylene glycol matrix tablets utilizing magnetic resonance imaging. *Int. J. Pharm.* 395, 147–153
17 Zhang, Q. *et al.* (2011) *In vitro* quantitative 1H and 19F nuclear magnetic resonance spectroscopy and imaging studies of fluvastatine™ drug release from Lescol® XL in a USP-IV dissolution cell. *J. Control. Release* 10/1016/j.jconrel.2011.08.039
18 Peppas, N.A. *et al.* (1980) Modelling of drug diffusion through swellable polymeric systems. *J. Membr. Sci.* 7, 241–253
19 Lindner, W.D. and Lippold, B.C. (1995) Drug release from hydrocolloid embeddings with high or low susceptibility to hydrodynamic stress. *Pharm. Res.* 12, 1781–1785
20 Panomsuk, S.P. *et al.* (1995) A study of the hydrophilic cellulose matrix: effect of indomethacin and a water-soluble additive on swelling properties. *Int. J. Pharm.* 126, 147–153
21 Kim, H. and Fassihi, R. (1997) A new ternary polymeric matrix system for controlled drug delivery of highly soluble drugs: I. Diltiazem hydrochloride. *Pharm. Res.* 14, 1415–1421
22 Talukdar, M.M. *et al.* (1998) The release mechanism of an oral controlled-release delivery system for indomethacin. *Pharm. Dev. Technol.* 3, 1–6
23 Colombo, P. *et al.* (1995) Drug diffusion front movement is important in drug release control from swellable matrix tablets. *J. Pharm. Sci.* 84, 991–997
24 Gao, P. and Meury, R.H. (1996) Swelling of hydroxypropyl methylcellulose matrix tablets. 1. Characterization of swelling using a novel optical imaging method. *J. Pharm. Sci.* 85, 725–731
25 Bettini, R. *et al.* (1994) Swelling and drug release in hydrogel matrices: polymer viscosity and matrix porosity effects. *Eur. J. Pharm. Sci.* 2, 213–219
26 Colombo, P. *et al.* (1996) Analysis of the swelling and release mechanisms from drug delivery systems with emphasis on drug solubility and water transport. *J. Control. Release* 70, 383–391
27 Freichel, O.L. and Lippold, B.C. (2000) A new oral erosion controlled drug delivery system with a late burst in the release profile. *Eur. J. Pharm. Biopharm.* 50, 345–351
28 Sujja-areevath, J. *et al.* (1998) Relationship between swelling, erosion and drug release in hydrophilic natural gum mini-matrix formulations. *Eur. J. Pharm. Sci.* 6, 207–217
29 Ferrero, C. *et al.* (2000) Fronts movement as a useful tool for hydrophilic matrix release mechanism elucidation. *Int. J. Pharm.* 202, 21–28
30 Zuleger, S. *et al.* (2002) Polymer particle erosion controlling drug release. II. Swelling investigations to clarify the release mechanism. *Int. J. Pharm.* 247, 23–37
31 van der Weerd, J. and Kazarian, S.G. (2005) Combined approach of FTIR imaging and conventional dissolution tests to drug release. *J. Control. Release* 98, 295–305
32 Kazarian, S.G. and van der Weerd, J. (2008) Simultaneous FTIR spectroscopic imaging and visible photography to monitor tablet dissolution and drug release. *Pharm. Res.* 25, 853–860
33 Konrad, R. *et al.* (1998) The use of ultrasound and penetrometer to characterize the advancement of swelling and eroding fronts in HPMC matrices. *Int. J. Pharm.* 163, 123–131
34 Yang, L. *et al.* (1998) Determination of continuous changes in the gel layer thickness of poly(ethylene oxide) and HPMC tablets undergoing hydration: a texture analysis study. *Pharm. Res.* 15, 1902–1906
35 Jamzad, S. *et al.* (2005) Analysis of macromolecular changes and drug release from hydrophilic matrix systems. *Int. J. Pharm.* 292, 75–85
36 Leskinen, J.T.T. *et al.* (2011) Monitoring of swelling of hydrophilic polymer matrix tablets by ultrasound techniques. *Int. J. Pharm.* 404, 142–147
37 Bowtell, R. *et al.* (1994) NMR microscopy of hydrating hydrophilic matrix pharmaceutical tablets. *Magn. Reson. Imaging* 12, 361–364
38 Rajabi-Siahboomi, A.R. *et al.* (1994) Structure and behavior 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. Control. Release* 31, 121–128
39 Brown, M.A. and Semelka, R.C., eds) (1995) *MRI: Basic Principles and Applications*, Wiley-Liss
40 Haacke, E.M. *et al.* eds (1999) *Magnetic Resonance Imaging: Physical Principles and Sequence Design*, Wiley-Liss
41 Liang, Z.-P. and Lauterbur, P.C., eds) (2000) *Principles of Magnetic Resonance Imaging: A Signal Processing Perspective*, Wiley-IEEE Press
42 Henkelman, R.M. *et al.* (1993) Quantitative interpretation of magnetization transfer. *Magn. Res. Med.* 29, 759–766
43 Stejskal, E.O. and Tanner, J.E. (1965) Spin diffusion measurements: spin echoes in the presence of a time-dependent field gradient. *J. Chem. Phys.* 42, 288–292
44 Henkelman, R.M. *et al.* (1994) Anisotropy of NMR properties of tissues. NISOTROPY. *Magn. Res. Med.* 32, 592–601
45 Stanisz, G.J. *et al.* (1997) An analytical model of restricted diffusion in bovine optic nerve. *Magn. Res. Med.* 37, 103–111
46 Mitra, P.P. *et al.* (1992) Diffusion propagator as a probe of the structure of porous media. *Phys. Rev. Lett.* 68, 3555–3558
47 Stanisz, G.J. *et al.* (2005) T-1, T-2 relaxation and magnetization transfer in tissue at 3 T. *Magn. Res. Med.* 54, 507–512
48 Smith, S.A. (2009) Quantitative magnetization transfer characteristics of the human cervical spinal cord *in vivo*: application to adrenomyeloneuropathy. *Magn. Res. Med.* 61, 22–27
49 Hyde, T.M. and 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

50 Dorożyński, P. *et al.* (2004) The macromolecular polymers for the preparation of hydrodynamically balanced systems – methods of evaluation. *Drug Dev. Ind. Pharm.* 30, 947–957

51 Tritt-Goc, J. and Kowalczuk, J. (2005) Spatially resolved solvent interaction with glassy HPMC polymers studied by magnetic resonance microscopy. *Sol. State Magn. Res.* 28, 250–257

52 Baumgartner, S. *et al.* (2005) Quantitative evaluation of polymer concentration profile during swelling of hydrophilic matrix tablets using ^{1}H NMR and MRI methods. *Eur. J. Pharm. Biopharm.* 59, 299–306

53 Laity, P.R. *et al.* (2010) Magnetic resonance imaging and X-ray microtomography studies of a gel-forming tablet formulation. *Eur. J. Pharm. Biopharm.* 74, 109–119

54 Katzhendler, I. *et al.* (2000) Structure and hydration properties of hydroxypropyl methylcellulose matrices containing naproxen and naproxen sodium. *Int. J. Pharm.* 200, 161–179

55 Kowalczuk, J. *et al.* (2004) The swelling properties of hydroxypropyl methyl cellulose loaded with tetracycline hydrochloride: magnetic resonance imaging study. *Sol. State Magn. Res.* 25, 35–41

56 Karakosta, E. and McDonald, P.J. (2007) An MRI analysis of the dissolution of a soluble drug incorporated within an insoluble polymer tablet. *Appl. Magn. Res.* 32, 75–91

57 Thérien-Aubin, H. and Zhu, X.X. (2008) Membrane formation and drug loading effects in high amylose starch tablets studied by NMR imaging. *Biomacromolecules* 9, 1248–1254

58 Sutch, J.C.D. *et al.* (2003) Investigating the coating-dependent release mechanism of a pulsatile capsule using NMR microscopy. *J. Control. Release* 92, 341–347

59 Broadbent, A.L. *et al.* (2010) Magnetic resonance imaging and relaxometry to study water transport mechanisms in a commercially available gastrointestinal therapeutic system (GITS) tablet. *Int. J. Pharm.* 397, 27–35

60 Madhu, B. *et al.* (1998) Studies of the internal flow process in polymers by H NMR microscopy at 500 MHz. *J. Control. Release* 56, 95–104

61 Tritt-Goc, J. *et al.* (2005) MRI Study of Fickian, case II and anomalous diffusion of solvents into hydroxypropylmethylcellulose. *Appl. Magn. Res.* 29, 605–615

62 Tritt-Goc, J. and Piślewski, N. (2002) Magnetic resonance imaging study of the swelling kinetics of hydroxypropylmethylcellulose (HPMC) in water. *J. Control. Release* 80, 79–86

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

64 Fyfe, C.A. and Blazek, A.I. (1998) Complications in investigations of the swelling of hydrogel matrices due to the presence of trapped gas. *J. Control. Release* 52, 221–225

65 Wang, Y.J. *et al.* (2011) NMR imaging of chitosan and carboxymethyl starch tablets: swelling and hydration of the polyelectrolyte complex. *Int. J. Pharm.* 10.1016/j.ijpharm.2011.08.008

66 Mikac, U. *et al.* (2010) A new approach combining different MRI methods to provide detailed view on swelling dynamics of xanthan tablets influencing drug release at different pH and ionic strength. *J. Control. Release* 145, 247–256

67 Fyfe, C.A. and Blazek-Welsh, A.I. (2000) Quantitative NMR imaging study of the mechanism of drug release from swelling hydroxypropylmethylcellulose tablets. *J. Control. Release* 68, 313–333

68 Dorożyński, P. *et al.* (2011) Gastroretentive drug delivery systems with L-dopa based on carrageenans and hydroxypropylmethylcellulose. *Int. J. Pharm.* 404, 169–175

69 Metz, H. and Mäder, K. (2008) Benchtop-NMR and MRI – a new analytical tool in drug delivery research. *Int. J. Pharm.* 364, 170–175

70 Strübing, S. *et al.* (2008) New insights on poly(vinyl acetate)-based coated floating tablets: characterisation of hydration and CO_2 generation by benchtop MRI and its relation to drug release and floating strength. *Eur. J. Pharm. Biopharm.* 69, 708–717

71 Strübing, S. *et al.* (2008) Characterization of poly(vinyl acetate) based floating matrix tablets. *J. Control. Release* 126, 149–155

72 Malaterre, V. *et al.* (2009) Benchtop-magnetic resonance imaging (BT-MRI) characterization of push–pull osmotic controlled release systems. *J. Control. Release* 133, 31–36

73 Karakosta, E. *et al.* (2006) Observations of coarsening of air voids in a polymer – highly-soluble crystalline matrix during dissolution. *Phys. Rev.* 74 01504-1–01504-7

74 Kulinowski, P. *et al.* (2008) 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. *J. Pharm. Biomed. Anal.* 48, 685–693

75 Nott, K. (2010) Magnetic resonance imaging of tablet dissolution. *Eur. J. Pharm. Biopharm.* 74, 78–83

76 Dorożyński, P. *et al.* (2007) Development of a system for simultaneous dissolution studies and Magnetic Resonance Imaging of water transport in hydrodynamically balanced systems: a technical note. *AAPS PharmSciTech* 8, 15

77 Kulinowski, P. *et al.* (2011) Magnetic Resonance Imaging and image analysis for assessment of HPMC matrix tablets structural evolution in USP Apparatus 4. *Pharm. Res.* 28, 1065–1073

78 Huanbutta, K. *et al.* (2011) Swelling kinetics of spray-dried chitosan acetate assessed by magnetic resonance imaging and their relation to drug release kinetics of chitosan matrix tablets. *Eur. J. Pharm. Biopharm.* 77, 320–326

79 Kaunisto, E. *et al.* (2010) A mechanistic modelling approach to polymer dissolution using magnetic resonance microimaging. *J. Control. Release* 147, 232–241

80 Ju, R.T.C. *et al.* (1995) Drug release from hydrophilic matrices. 2. A mathematical model based on the polymer disentanglement concentration and the diffusion layer. *J. Pharm. Sci.* 84, 1464–1477

81 Miller-Chou, B.A. and Koenig, J.L. (2003) A review of polymer dissolution. *Prog. Polym. Sci.* 28, 1223–1270

82 Ueberreiter, K. (1968) The solution process. In *Diffusion in Polymers* (Crank, J. and Park, G.S., eds), pp. 219–257, Academic Press

83 Ferrero, C. *et al.* (2008) Towards elucidation of the drug release mechanism from compressed hydrophilic matrices made of cellulose ethers. I. Pulse-field-gradient spin-echo NMR study of sodium salicylate diffusivity in swollen hydrogels with respect to polymer matrix physical structure. *J. Control. Release* 128, 71–79