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Communication

Quantitative magnetic resonance micro-imaging methods for pharmaceutical research

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Abstract:

The use of magnetic resonance imaging (MRI) as a tool in pharmaceutical research dates back to the early 1990s where magnetic resonance imaging was to investigate the swelling of hydrating hydroxypropylmethylcellulose (HPMC) tablets. Since then there has been a vast amount of work published in the literature concerning the use of magnetic resonance imaging and its application to pharmaceutical systems. However, a number of previous studies were not fully quantitative and generally only gave qualitative information. The aim of this paper is to focus on the use fast *quantitative* magnetic resonance techniques and how they are used to extract quantitative information that is of direct relevance to pharmaceutical research. The application of fast multi-nuclear quantitative MRI techniques to study the dynamics of tablet dissolution, drug mobilisation and tablet erosion in both static environments and in a standard USP-4 dissolution cell operated under bio-relevant conditions is described. We demonstrate it is possible to obtain local information, within the tablet, regarding dissolution media concentration, dissolution media interaction with polymer and dissolution media self-diffusion transport coefficients. In addition, we show it is also possible, through multi-nuclear MRI, to gain new insights into drug mobilisation within a tablet during the dissolution process.

Keywords: Magnetic resonance imaging; quantitative; pharmaceutical; diffusion.

1. Introduction

The use of magnetic resonance imaging (MRI) as a tool in pharmaceutical research dates back to the work of Rajabi-Siahboomi et al.[1] who used traditional spin-echo magnetic resonance imaging to investigate the swelling of hydrating hydroxypropylmethylcellulose (HPMC) tablets. Since then there has been a vast amount of work published in the literature concerning the use of magnetic resonance imaging and its application to pharmaceutical systems. Recently, there have been several excellent reviews[2-5] on the aforementioned subject which, collectively, cover a wide variety of pharmaceutically relevant research. However a number of studies contained within these reviews were not necessarily quantitative in terms of "how much?" of a particular substance one has in the system under study. Fyfe and Blazek[6] and Hyde and Gladden[7] were amongst the first to note that previous MRI investigations of liquid ingress into polymers were not quantitative as they lacked information from both the liquid and the polymer. Fyfe and Blazek[6] presented the first fully quantitative study of a pharmaceutically relevant system, namely HPMC swelling by water, using a combination of conventional T_1/T_2 relaxation NMR spectroscopy (for calibration) and T_2 weighted one dimensional non-slice selective imaging/profiling. Previous investigations of the HPMC/water system using MRI have generally used standard 1- and 2-D spin-echo imaging methods. Traditional quantitative techniques have several disadvantages for the quantitative interpretation of swelling systems, which are summarised below:

(1) Whilst, quantitative 1-D profiling of water concentration and/or determination of self-diffusion coefficients can be achieved in 2–3 min, the individual profiles are not necessarily representative of the dissolution behaviour of a 3-D dosage form.

(2) Quantitative single spin-echo slice selective 2-D imaging whilst generally alleviating the problems associated with sample anisotropy, requires a minimum acquisition time of 1–2 hours and is thus inappropriate for dynamic systems that change on the order of several minutes.

(3) Non-quantitative T_1-weighted single spin-echo 2-D slice selective imaging has been made quantitative by using external reference samples of known water concentration; post acquisition correction of 1-D profiles extracted from the images was then performed. To avoid motional blurring a reduced recycle time is used. However, this leads to a low signal-to-noise ratio in the resulting data.

Fast imaging techniques such as Rapid Acquisition with Relaxation Enhancement[8] (RARE) are not commonly used in pharmaceutical research due to the fact that, in general, they are non-quantitative. This communication describes the use of quantitative 2-D ultra-

fast RARE imaging techniques to follow: (i) a generic water/HPMC dissolution system. Whilst HPMC is not the most challenging system in terms of its dissolution time it provides a useful model for describing the level of quantitative information that can be extracted and illustrates the robustness of ultra-fast RARE sequences; (ii) The dissolution and drug release behaviour of the commercially available pharmaceutical Lescol® , under flowing conditions in bio-relevant media in a USP-4 dissolution cell. The methods presented in this paper allow the rapid, in situ, quantification of both the concentration, T_2-relaxation time and self-diffusion coefficient of dissolution media in less than 3 min, without the need for external reference correction. Finally we describe the use of ^{19}F NMR to examine the API mobilisation within the Lescol tablet.

2. Results and Discussion.

2.1. Quantitative RARE imaging of HPMC and water.

The swelling and dissolution of HPMC tablets in water was monitored by both the T_2- and diffusion preconditioned RARE MRI techniques[9]. Consecutive T_2 and diffusion preconditioned RARE images were acquired every 30 min for 50 h. 2-D images were acquired through the centre of the tablet as shown in Figure 1. In these measurements dissolution media, i.e. "water" concentration, T_2-relaxation time, and molecular diffusion coefficients were measured from the ^1H signal associated with the spectral resonance of water.

Figure 1. (a) Schematic showing the orientation of the HPMC tablet and imaging slice location (b) the definition of radial and axial directions.

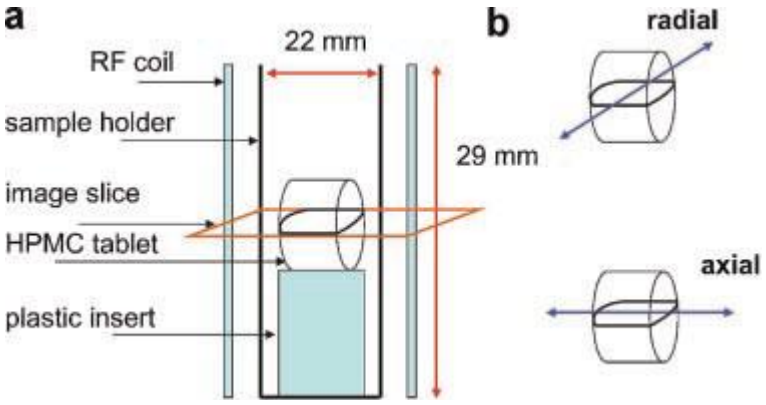


Figure 2 shows the non-quantitative water concentration maps. The interpretation of these images is straightforward. The highest signal intensity (white) is associated with the free bulk water. The dry core of the tablet appears as black since it contains no water. The pixels associated with yellow/red/blue are assigned to the presence of a polymer gel layer, formed as the HPMC dissolves in the water absorbed. Figure 3 shows the corrected water concentration maps. The interpretation of these images remains the same. However, the

formation and evolution of the gel layer appears significantly different between the data shown in Figures 2 and 3. In particular, the gel layer in Figure 2 is characterised by a range of water contents. In contrast, the gel layer in the corrected images in Figure 3 show a much more uniform water concentration across the gel layer. Analysis of the data shows that maximum signal loss in the uncorrected RARE can be as high as 74% compared with the absolute water concentration.

Figure 2. Standard RARE image intensity maps of the swollen HPMC polymer at different times (h): (a) 0.5; (b) 2; (c) 8; (d) 10.25; (e) 29.75; (f) 40.25.

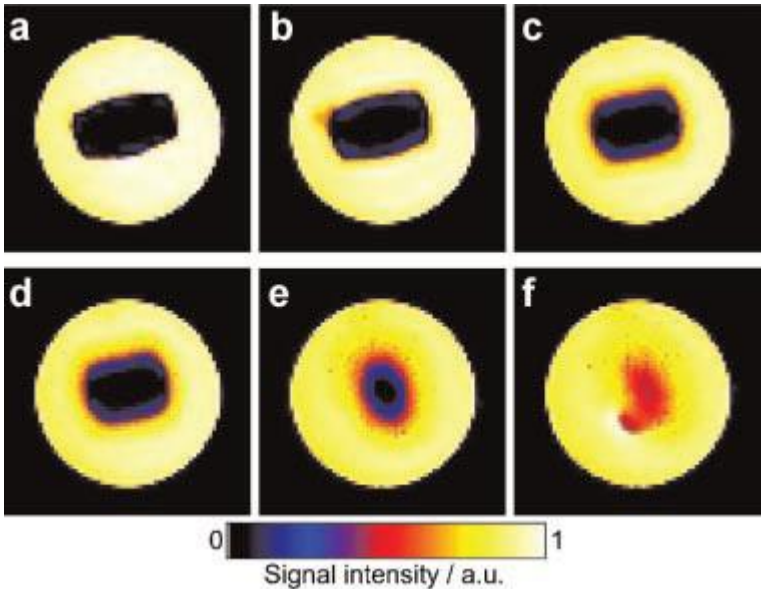


Figure 3. Quantitative water concentration (C) maps of the images shown in Figure 2 at different hydration times (h): (a) 0.5; (b) 2; (c) 8; (d) 10.25; (e) 29.75; (f) 40.25.

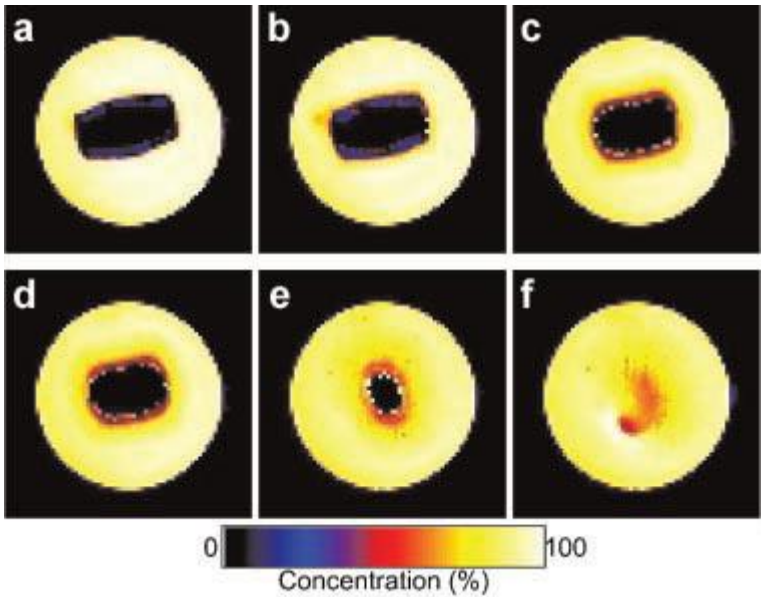
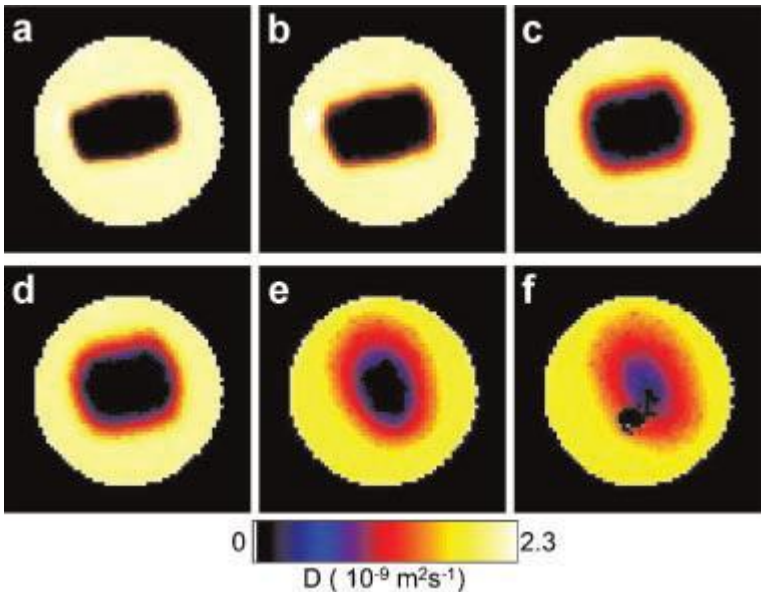


Figure 4 shows the self-diffusion coefficient (D) maps of the same sample as in figures 2 and 3 acquired at different times. The D of the free water varies from 2.15 ±0.02 x 10^{-9} m^2s^{-1} to 1.73 ±0.02 x 10^{-9} m^2s^{-1} throughout the dissolution experiment. The presence of the dissolved HPMC does not alter the water D significantly.

Figure 4 Self-diffusion coefficient maps, D, at different hydration times (h): (a) 0.5; (b) 2; (c) 8; (d) 10.25; (e) 29.75; (f) 40.25.



2.1. Quantitative RARE imaging Lescol® dissolution in a USP-4 dissolution cell

Figure 5 shows water concentration images obtained using the quantitative RARE image sequence at different time points for the dissolution process of Lescol in a USP-4 dissolution cell. For the first hour, the tablet was exposed to the SGF solution at 37 ^oC and appears not to dissolve in the SGF solution. Therefore the tablet retains much of its original shape and there is no obvious gel layer and hence any swelling behaviour is limited in this first hour. After the first hour, the SGF solution was switched (inline) to the FaSSIF solution without disturbing the dissolution process inside the USP-4 cell. Figure 5 shows that at 4 hours, a gel layer with a radial thickness of approximately 2 mm (±375 μm) is formed. The water concentration decreases from the gel/water interface towards the dry core. Figure 5 shows that the gel layer increases in size as the FaSSIF solution continuously penetrates into the tablet dry core. It also shows that between 10 and 12 hours the FaSSIF penetration fronts have met and that the water concentration gradient at this point in time lies between 90% on the outside and 50% on the inside. At t = 20 hours, some air bubbles, which are present as black dots in the images, appear to be trapped inside the polymer matrix. Figure 5 also shows that the tablet *appears* to have disintegrated at t = 30 hours. However, it is essential that the T_2-relaxation images are also examined before such a conclusion is drawn. The T_2-relxation maps shown in figure 6 indicate a quite different behaviour to their counterparts in figure 5 in that the structural integrity of the tablet remains intact, even after 30 hours. This indicates

that the gel erosion process is slow and evenly distributed. Collectively, figure 5 and figure 6 show that after 52 hours the gel matrix was highly hydrated and distributed, primarily because the polymer matrix is not soluble in the FaSSIF solution.

Figure 5. Typical water concentration maps of the dissolving tablet. FOV: 24 mm × 24 mm; resolution: 375 μm; slice thickness: 1.0 mm. Dissolution media: 0-1 h, SGF; 1-52 h, FaSSIF.

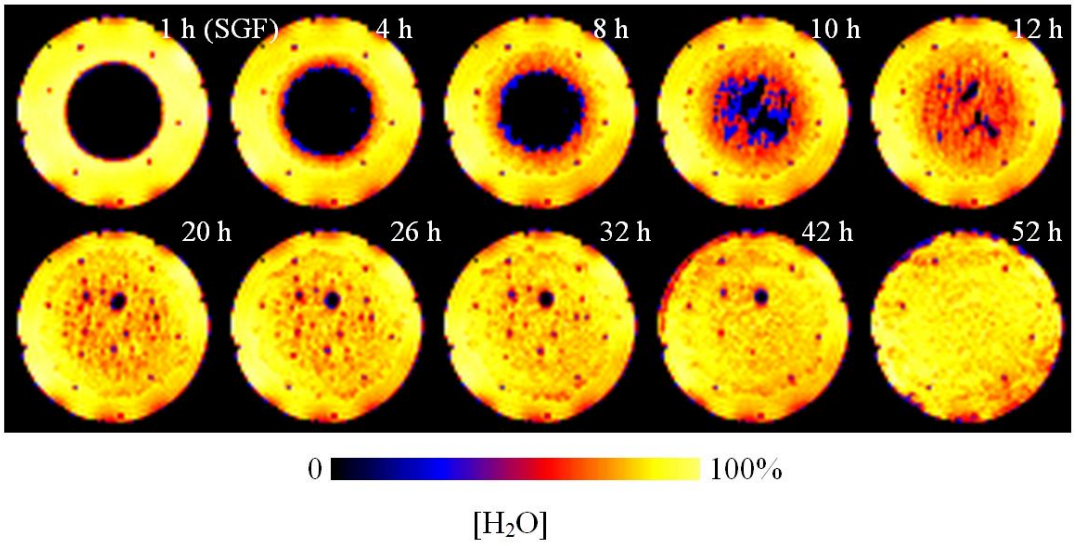
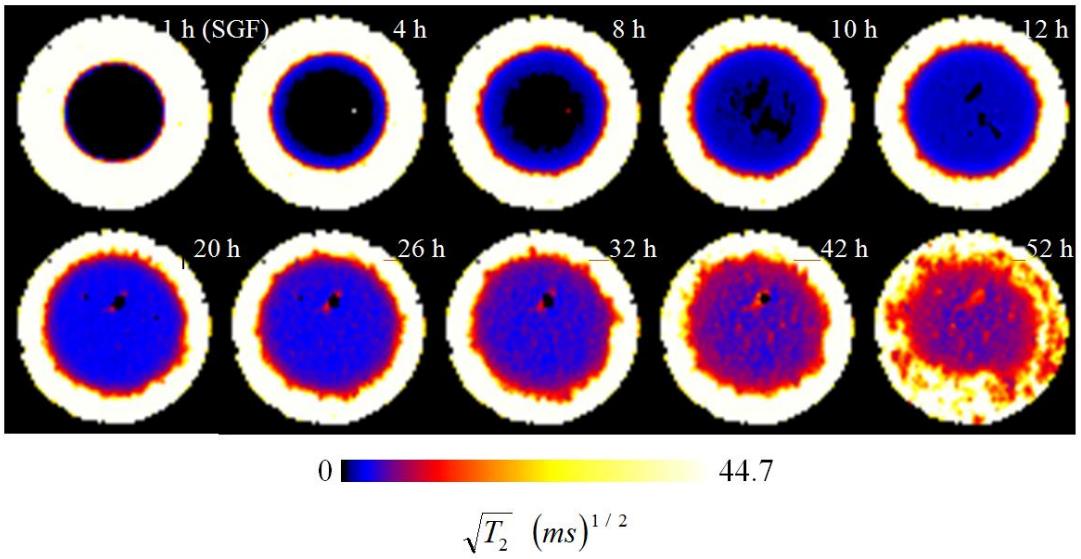


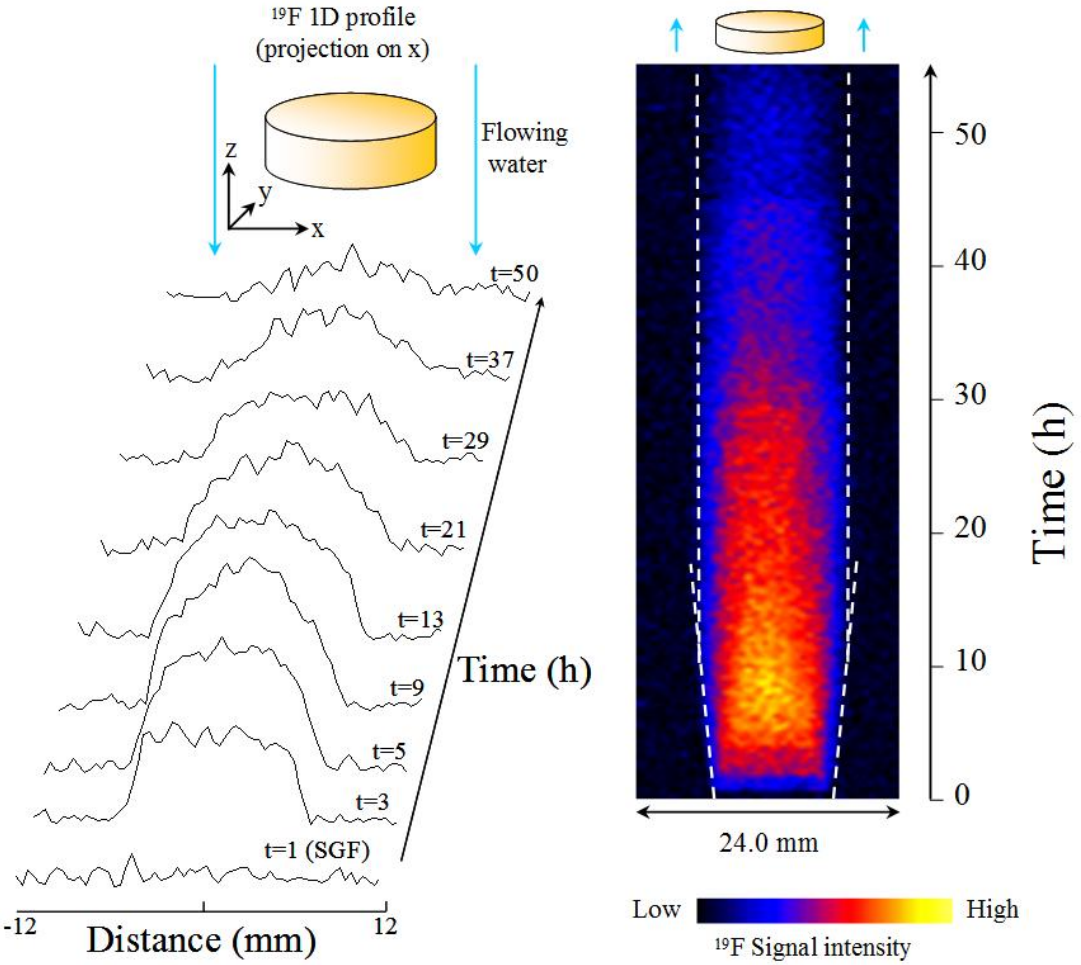
Figure 6 The corresponding T_2 relaxation maps of the dissolving Lescol tablet in figure 5. FOV: 24 mm × 24 mm; resolution: 375 μm; slice thickness: 1.0 mm. Dissolution media: 0-1 h, SGF; 1-52 h, FaSSIF.



2.1. ^{19}F imaging of API mobilisation.

Figure 7 shows the progression of the one-dimensional ^{19}F signal profile as a function of time on stream during dissolution for the same lescol tablet as shown in figures 5 and 6. The signal is acquired from the whole USP-4 cell and is a projection of the ^{19}F signal along the x-

Figure 7. 1D-MRI profiles of ^{19}F MRI signal as a function of time. Left: Typical 1D profiles of ^{19}F MRI signal acquired during the experiment. Right: Full experiment results using colours to represent the signal intensity



direction. These one-dimensional profiles are not truly quantitative as they have not been corrected for T_2 relaxation effects (because a minimum echo time imaging sequence was used) but it is likely that brighter areas correspond to a greater amount of fluvastatin drug and are indicative of the dissolution/mobilisation profiles of the drug inside the gel matrix. It can be noted that there is no evidence for signal outside the boundaries of the tablet's geometry. For the first hour, figure 5 showed that there was no obvious gel layer formed in the SGF solution, and thus the corresponding ^{19}F signal is also unnoticeable. After 1 hour, with the build up of the gel layer in the FaSSIF solution, more drug is dissolved/mobilised and thus accumulates inside the polymer matrix. The ^{19}F signal reaches its maximum at around 10 hours in figure 7, which corresponds to the point where the tablet is totally

penetrated by water (Figure 5). Moreover, the gel layer boundary in figure 7 shows (white dashed line) that the gel layer continues to expand for the first 10 hours; the diameter of the tablet then shows a constant behaviour for the following hours (Figure 6). After 42 hours, although the T_2 relaxation map (Figure 6) still shows a large gel area, the drug is only distributed in the middle of the gel matrix (Figure 7) and thus is direct evidence of drug mass transfer resistance.

3. Experimental Section

The oval shaped HPMC tablets (Dow Methocel K100LV, Mw=1333300, methoxyl groups=23%, hydroxypropoxyl groups=8.5%) were prepared by direct compression with a Carver press at 1400 lbs for 10 s. The final tablets have a diameter of 12 mm, thickness of 4 mm and weight of 600 mg. For HPMC/water studies each tablet was fixed on a chemically resistant, 19 mm cylindrical plastic insert and placed in a chemically resistant plastic tube. Ten millilitres of deionised water was added at the beginning of the imaging. Experiments involving Lescol tablet dissolution were performed by placing the tablet in the centre of a nylon cage that was subsequently placed in a standard 25.0 mm diameter USP-4 dissolution cell. A flow loop containing separate vessels of SGF and FaSSIF dissolution media at a temperature of 37.5 degrees Celsius was then connected the USP-4 cell prior to imaging experiments. Each tablet contains 80 mg of Sodium Fluvastatin. HPMC (K100LV) is used as the polymer matrix to control the drug release rate

All MRI experiments were performed on a Bruker AV 400 NMR spectrometer equipped with micro imaging facilities, at a ^{1}H frequency of 400.23 MHz. A 25 mm diameter ^{1}H birdcage proton coil was used. Ninety degree excitation and 180 degree refocusing hard pulses of 45 and 90 μs, respectively, were used for all experiments involving hard (non-selective) pulses. For imaging sequences a Gaussian shaped 180^{o} refocusing pulse of 512 μs was used. For imaging experiments two sets of MRI data were recorded using the following pulse sequences: (i) a T_2-preconditioned RARE pulse sequence; and (ii) a diffusion-preconditioned RARE pulse sequence. Both types of image experiment were acquired with a field-of- view of 30 mm x 30mm, a slice thickness of 1.5 mm and a imaging acquisition bandwidth of 100,000 Hz. The images were acquired with a matrix size of 64 x 64 data points with a RARE factor of 64, giving an in-plane resolution of 469 μm x 469 μm. ^{19}F NMR profiles were acquired at 376.58 MHz with a standard one-dimensional spin-echo profiling sequence with the presence of a magnetic gradient along the x-direction. The number of scans was 32 and a recycle time of 6 s was chosen to be at least five times the longest measured liquid T_1 value (the measured T_1 value of a saturated drug solution is 1.2 s). The echo time of the 1D spin-echo sequence was 1.2 ms. 64 pixels were acquired in a field-of-view of 24.0 mm thereby giving an inherent pixel resolution along the axial length of 375 μm.

4. Conclusions

This paper has shown that quantitative RARE imaging can be used to characterize water concentration, water self-diffusion and water interaction within bio-relevant polymers and a commercial pharmaceutical tablet that change on the timescales of several 10s of minutes. In addition we have shown that ^{19}F imaging can provide new insights into the unique behavior of an active pharmaceutical ingredient within a dynamically swelling gel layer during dissolution under bio-relevant conditions

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References and Notes

[1] A.R. Rajabisiahboomi, R.W. Bowtell, P. Mansfield, A. Henderson, M.C. Davies, C.D. Melia, 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, Journal of Controlled Release, 31 (1994) 121-128.
[2] C.D. Melia, A.R. Rajabi-Siahboomi, R.W. Bowtell, Magnetic resonance imaging of controlled release pharmaceutical dosage forms, Pharmaceutical Science & Technology Today, 1 (1998) 32-39.
[3] J.C. Richardson, R.W. Bowtell, K. Mäder, C.D. Melia, Pharmaceutical applications of magnetic resonance imaging (MRI), Advanced Drug Delivery Reviews, 57 (2005) 1191-1209.
[4] J.A. Zeitler, L.F. Gladden, In-vitro tomography and non-destructive imaging at depth of pharmaceutical solid dosage forms, European Journal of Pharmaceutics and Biopharmaceutics, 71 (2009) 2-22.
[5] K.P. Nott, Magnetic resonance imaging of tablet dissolution, European Journal of Pharmaceutics and Biopharmaceutics, 74 (2010) 78-83.
[6] C.A. Fyfe, A.I. Blazek, Investigation of hydrogel formation from hydroxypropylmethylcellulose (HPMC) by NMR spectroscopy and NMR imaging techniques, Macromolecules, 30 (1997) 6230-6237.
[7] T.M. Hyde, L.F. Gladden, Simultaneous measurement of water and polymer concentration profiles during swelling of poly(ethylene oxide) using magnetic resonance imaging, Polymer, 39 (1998) 811-819.
[8] J. Hennig, A. Nauerth, H. Feiedburg, RARE Imaging: A Fast Method for Clinical MR, Magnetic Resonance in Medicine 3(1986) 823-833.
[9] Y.Y. Chen, L.P. Hughes, L.F. Gladden, M.D. Mantle, Quantitative Ultra-Fast MRI of HPMC Swelling and Dissolution, Journal of Pharmaceutical Sciences, 99 (2010) 3462-3472.