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Research paper

Magnetic resonance imaging of tablet dissolution

Kevin P. Nott *

Oxford Instruments Magnetic Resonance, Oxon, United Kingdom

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ABSTRACT

Magnetic resonance imaging (MRI) is the technique of choice for measuring hydration, and its effects, during dissolution of tablets since it non-invasively maps ^{1}H nuclei associated with 'mobile' water. Although most studies have used MRI systems with high-field superconducting magnets, low-field laboratory-based instruments based on permanent magnet technology are being developed that provide key data for the formulation scientist. Incorporation of dissolution hardware, in particular the United States Pharmacopeia (USP) apparatus 4 flow-through cell, allows measurements under controlled conditions for comparison against other dissolution methods. Furthermore, simultaneous image acquisition and measurement of drug concentration allow direct comparison of the drug release throughout the hydration process. The combination of low-field MRI with USP-4 apparatus provides another tool to aid tablet formulation.

1. Introduction

Magnetic resonance imaging (MRI) is commonly known as an excellent tool for clinical diagnosis because of its ability to distinguish between soft tissues as well as to sensitise to a variety of other parameters including flow, diffusion and temperature. However, over the last two decades, there has also been a growing body of work in the field of non-medical applications as a result of the availability of microimaging accessories for conventional nuclear magnetic resonance (NMR) spectrometers. This work is often limited to centres with specific expertise in the use of high-field NMR instruments that incorporate superconducting magnets. The pharmaceutical sector is a good example, where formulations have been studied by observing tablet hydration and its effects during dissolution [1,2].

In contrast, the use of low-field MRI instruments has been scarce, except in the oil industry where they have been used for the measurement of porosity and fluid distributions in porous reservoir rocks [3]. Such instruments are based on permanent magnets and therefore do not require cryogens. This technology is also associated with bench-top NMR analysers that have found widespread use in analytical laboratories across the food, polymer and petrochemical sectors for measurement of oil, moisture and other quality control parameters.

The purpose of this article is to review the current state of the art for MRI measurements and instrumentation that are relevant to tablet dissolution. It starts by providing some background on the techniques and then describes the array of measurements and information that can be obtained. Finally, the development of hardware and instrumentation that can provide measurements which are relevant to the formulation scientist is discussed.

2. Background

MRI is based on the phenomenon of nuclear magnetic resonance, in that certain nuclei such as protons (^{1}H) align their nuclear spins either parallel or anti-parallel to a static magnetic field. Since there is an energy difference between the two states, the difference in spin populations (governed by the Boltzmann distribution) produces a net magnetisation in one direction. The energy-and, as a consequence, the population-difference between the two states increases with the static magnetic field (in Tesla), as does the signal-to-noise. Application of another magnetic field, in the form of a short radio-frequency pulse, momentarily alters the spin population distribution (rotating the net magnetisation), thereby inducing a signal in the radio-frequency coil. In the absence of this pulse, the signal decreases with time as the spins relax back to their equilibrium position due to two processes called spin–lattice (T_1) and spin–spin (T_2) relaxation. The resultant NMR signal is the free induction decay (FID).

If the number of spins in each state is equalised by a saturation pulse (rotating the net magnetisation by 90°), the NMR signal

* Oxford Instruments Magnetic Resonance, Tubney Woods, Abingdon, Oxon OX13 5QX, United Kingdom. Tel.: +44 (0) 1865 393200; fax: +44 (0) 1865 393333.
E-mail address: kevin.nott@oxinst.com.

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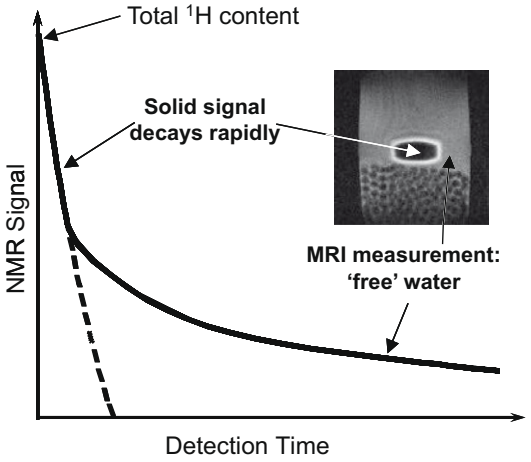

Fig. 1. Schematic of basic NMR signal, the free induction decay (FID), after a saturation radio-frequency pulse.

immediately after the pulse reflects the total number of ^{1}H nuclei; thereafter, the signal decays. ^{1}H nuclei associated with solids decay rapidly and therefore may be undetectable. Subsequently, ^{1}H nuclei associated with liquids, usually from water and lipids, decay according to their 'molecular viscosity' (Fig. 1).

In practice, a multi-spin-echo [4,5] (or Carr–Purcell–Meiboom–Gill, CPMG, as it is commonly known) experiment is employed to characterise the T_2 decay, which reflects the physical properties of only the sample. In addition to the distinction between solids and liquids, T_2 can characterise chemical exchange between free water and that bound to 'immobile' macromolecules, or diffusive exchange between compartments, which can reflect the pore-size distribution. In addition, pulsed field gradient (PFG)-NMR experiments can be employed to measure the diffusion properties [6], in particular the self-diffusion coefficient, which are also sensitive to restricted diffusion in porous media and can be used to measure droplet-size distributions in emulsions.

If orthogonal magnetic field gradients are applied across the uniform static magnetic field during NMR acquisition, it is possible to spatially encode the signal in three dimensions. In general, the signal intensity of a spin-echo image is dependent on the ^{1}H density, which is related to water concentration, as well as the T_1 and T_2 values, which are related to water mobility; this is illustrated in Fig. 2 and given by the following equation:

$$\text{Signal intensity} \propto \text{PD} \cdot \exp(-\text{TE}/T_2) \cdot (1 - \exp(-\text{TR}/T_1))$$

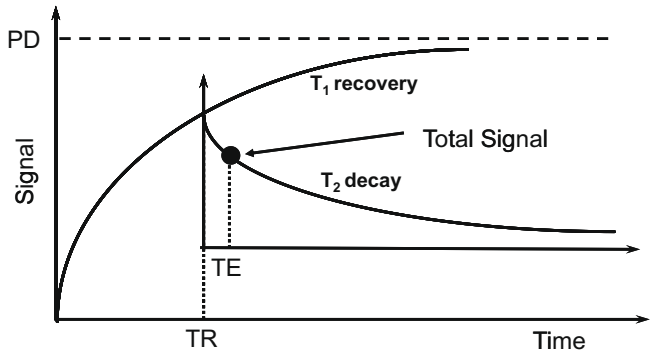

Fig. 2. Representation of the acquired MRI signal intensity (for a given voxel, or 3D volume element), which is dependent on the sample parameters M_0, T_1 and T_2 as well as the choice of experimental parameters TR and TE for the spin-echo imaging protocol.

where TE and TR are the experimental, echo and repetition time parameters, respectively. PD is the ^{1}H density.

To acquire images that are weighted by water concentration, TE has to be as short as possible, whereas TR has to be $5 \times T_1$. Since T_1 of pure water can be 3–5 s and the image acquisition time is proportional to TR, this can lead to poor temporal resolution. In addition, the shortest achievable TE is restricted by the finite time required to turn the gradients on and off, limited by the hardware, as well as the time to record the signal. Therefore, in general, MRI typically observes the mobile ^{1}H associated with free water (Fig. 1), whereas the fast decaying ^{1}H nuclei associated with macromolecules and bound water will essentially be invisible. As a consequence, the majority of MRI studies have used T_1/T_2 'weighted' or contrast images to highlight various features related to their water-concentration and -mobility, i.e. dry/hydrated tablet and dissolution medium. This enables quantification of dimensional properties (thickness/area/volume) associated with the movement of water and its effect on the matrix (e.g. gelation/swelling and/or erosion).

3. Bulk relaxometry and diffusion measurements

'Bulk' NMR measurements, particularly of T_2 and self-diffusion coefficients, can be used to probe the microscopic spatial heterogeneity in what are otherwise macroscopically homogeneous samples. Since these measurements are taken from the whole sample, signal-to-noise is not usually a limitation, thus are typically carried out at low field.

Metz and Mäder [7] described a variety of applications for NMR relaxometry studies, particularly on food systems, and their relevance to drug delivery. The T_2 decay, in particular, can be fitted to either discrete or continuous distribution of exponentials such that the population and corresponding T_2 relaxation time of each component represents the amount and physicochemical state of water and/or lipid. As described previously (see Section 2), T_2 relaxation can be affected by a variety of physicochemical properties (e.g. molecular viscosity, pore size, interaction with polymers) which in this case was used to characterise different ingredients and formulations, which had undergone different processing conditions.

In contrast, Baumgartner et al. [8] used T_1 and T_2 relaxation times to study the water distribution in hydrogels made from cellulose ethers with different substituents and molecular weights. Measurements were made on equilibrated systems of hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC) K4M and K100M grade polymers with water at room temperature. The relaxation rate $1/T_1$ was sensitive to polymer substituent but insensitive to polymer molecular mass, whereas the rate $1/T_2$ was much less sensitive to polymer substitution. Using these values, they calculated the average number of water molecules bound to a polymer repeating unit, which was found to correlate well with the degree of hydrophilic substitution of the polymer chains.

Collins et al. [9] used CPMG and PFG-NMR experiments to measure the T_2 and diffusion properties of water in partially soluble pharmaceutical pellets, either drug loaded or placebo, at different immersion times. T_2 decays were fitted to a distributed exponential model, then subsequent analysis was used to calculate the pore-size distributions. Data from the PFG-NMR experiments were used to observe the restricted diffusivity of water.

Ferrero et al. [10] used PFG-NMR to measure the self-diffusion coefficient of 1% w/w sodium salicylate, a model solute, in different cellulose ethers, with varying polymer weight fraction and molecular weight, to investigate the drug release mechanism in these swellable systems. Given the low concentration and specificity of

the analyte, diffusion measurements were acquired from an NMR spectrum at high field (11.75 Tesla).

4. High-field imaging

Most studies of tablet dissolution carried out using superconducting magnets at high field (2.35–11.75 Tesla) have been covered in previous reviews [1,2], consequently, an overview of the different types of MRI experiments used to investigate tablet dissolution will be described here.

Some studies have quantified water ingress into tablets using a diffusion front defined by a sharp gradient in signal intensity as well as the subsequent physical changes that take place, for example, swelling or erosion. For instance, a set of studies used MRI to measure the swelling and water uptake of tablets made from cross-linked high-amylase starch [11] in order to investigate the effect of tablet size [12], initial diffusion and temperature [13]. A 50:50 H_2O/D_2O mixture was used as the dissolution media to better discriminate between water inside and outside the tablet. Another study by the same group investigated the effect of drug loading [14]. Water uptake was found to be faster for the drug-loaded tablets and a membrane at the water/tablet interface was observed. Subsequently, they used diffusion-weighted MRI to obtain better contrast between regions and show formation of the highly hydrated membrane at the water–tablet interface, which was essential to maintain tablet integrity. They proposed that membrane formation was based on reorganisation and retrogradation of the starch chains, which also contributes to restricted swelling of the tablet.

Black et al. [15] used NMR imaging to compare the dissolution of a sleep aid/analgesic tablet with an analgesic-only formulation which exhibited faster drug release. The former exhibited faster water penetration but formed a gel layer, which was proposed to act as a diffusional barrier to the drug release. They subsequently separated the two active ingredients by creating a bilayer tablet from which the release of the analgesic was improved.

Given that the MRI signal intensity can be based on a number of sample and experimental parameters, other studies mapped water T_2 relaxation times and self-diffusion coefficients to obtain better distinction between the gel layer and the dissolution media. Kojima et al. [16] used two-dimensional (2D) maps of water T_2 and self-diffusion coefficient to characterise the mobility and diffusivity of water absorbed on a variety of water soluble, swellable cellulose derivatives (HPC, HPMC and LH41, a micronized low-substituted HPC). These images were not only used to measure the overall swelling but they also observed different expansion rates in different directions, which may have been a result of the compression of the original tablet. Subsequently, they mapped T_2 and the apparent diffusion coefficient in 1D to investigate the water mobility across the interface between the aqueous phase and the non-hydrated tablet core and found a relationship between T_2 of the gel layer and the drug release rate [17].

Baumgartner et al. [18] quantified the polymer concentration profile during swelling of hydrophilic matrix tablets made from HPC, HPMC K4M, and HPMC K100M polymers. They quantified both the T_1 and T_2 parameters for equilibrated samples with a range of polymer concentrations and then calculated the signal intensity for each polymer concentration (as per the parameters in Fig. 2), which relate to the images acquired during swelling.

In general, MRI is used to measure only liquids. However, there are some protocols that allow imaging of solid materials although they may still suffer from signal-to-noise issues and, by their nature, long acquisition times and therefore tend to be carried out in 1D. Dahlberg et al. [19] used a constant time, or single point, imaging experiment of tablets immersed in D_2O, thus enabling imaging of the solid material as it was being hydrated. Alternatively, one can indirectly image the density of a solid tablet by filling the voids with liquid. Nebgen et al. [20] determined the porosity distribution, cracks and cavities inside physically intact tablets by filling the tablet cavities with silicone oil under vacuum. Similarly, Djemai and Sinka [21] imaged the density distributions in tablets, by filling the pores with an inert oil-based filler fluid, to investigate the effect of tablet geometry and die wall friction on the relative density distribution at various stages during compaction.

In general, measurement of the active pharmaceutical ingredient (API) itself is not possible unless at high field (for signal-to-noise), and it is highly fluorinated for specificity [22]. The dissolution of ion-releasing tablets can be measured indirectly by passing pulses of electric current through the media during MRI acquisition and measuring the changes in conductivity, which is proportional to the ion concentration [23].

5. Low-field imaging

The use of low-field MRI (typically 0.5 Tesla) for pharmaceutical research, and specifically for tablet dissolution, has been limited partly due to the availability of instrumentation and also the perceived lack of sensitivity. Nevertheless, they have found value in many non-medical applications especially in water-rich systems such as foods where they have been used to follow processes such as hydration and freeze drying. Given similarities with the food industry in terms of the materials and processes used, it is not surprising that the technique lends itself to the pharmaceutical sector. Low-field MRI is also used for porous systems such as rock, cores and even concrete since the NMR signal of oil and/or water decays faster at higher field strengths due to the magnetic susceptibility gradients within the pores, which counteract any potential gain in signal-to-noise. An analogous effect would be observed for ferromagnetic iron oxide, commonly used for tablet coatings, which is minimised at low field.

Strübing et al. used a bench-top MR imager based on a 0.5 Tesla permanent magnet to study the hydration and swelling mechanisms of different floating tablet formulations. Buoyancy of one formulation was based on CO_2 formation inside coated tablets [24], whereas the other was based on hydration and swelling of matrix tablets [25] made from poly(vinyl acetate) giving them lower apparent densities.

Malaterre et al. [26] used a bench-top MR imager to investigate the effect of composition on the hydration and swelling of osmotic push–pull release systems. They were able to relate the drug release performance to the hydration and subsequent release mechanism and were, therefore, able to optimise the formulation accordingly.

6. Dissolution during flow

Although measurement of hydration in static media provides useful information on various polymer systems, studies of tablet dissolution and the subsequent drug release are only meaningful to the formulation/dissolution scientist if they are carried out under controlled conditions with flow or another form of agitation.

Abrahmsén-Alami et al. [27] constructed a small release cell in the form of a rotating disc to study the dissolution of poly(ethylene oxide) tablets at 25 °C. The aim was to be able to make quantitative measurements of polymer concentration during hydration, swelling and erosion processes under conditions that simulate stirring. A subsequent study investigated the impact of the solubility of additives (mannitol and dicalcium phosphate) on the swelling

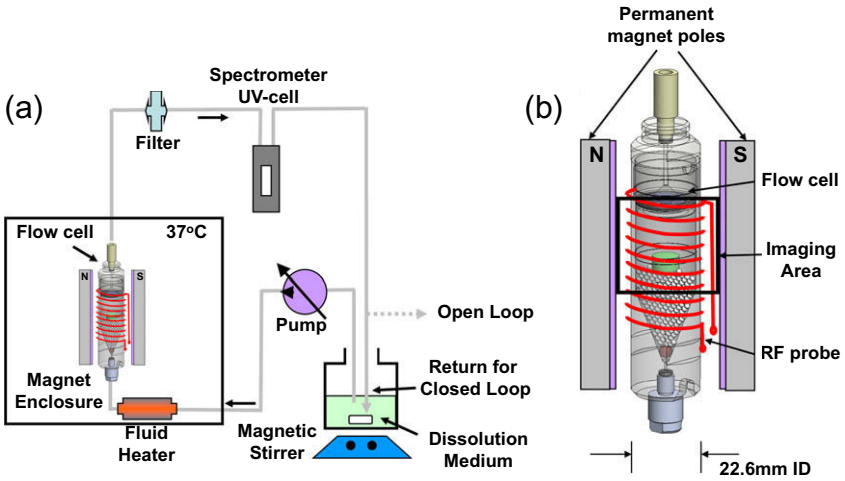

Fig. 3. Schematic diagram of (a) the MARAN-iP, a low-field magnetic resonance imager with an integrated USP-4 dissolution circuit, (b) the MRI-compatible flow cell containing a ruby bead at the apex of the entry cone and glass beads used primarily to produce laminar flow and also, in this case, to centre the tablet in the active imaging area.

and erosion fronts of HPMC tablets [28]. Madhu et al. [29] used NMR imaging to map the T_2 and self-diffusion coefficient of water during continual flow over an erodible tablet at 37 °C.

In contrast, other studies have attempted to create an environment equivalent to the standard USP dissolution testing, particularly apparatus 4, which consists of a flow-through cell, inside the bore of the magnet. This arrangement is challenging because of the inaccessibility of superconducting magnets, which are typically 1½ m high; the necessity to manufacture accessories using MRI compatible, typically non-metallic materials; and the need to keep electronic devices away from the strong magnetic field to prevent either it being interfered with or causing interference. Fyfe et al. [30] incorporated a modified USP apparatus 4 flow-through cell design within a 9 Tesla vertical superconducting magnet to study the hydration of HPMC and elementary osmotic pump tablets. UV spectroscopy was employed to measure the total drug released during the dissolution.

In contrast, Dorożyński et al. [31] developed a USP apparatus 4 design flow-through cell to fit inside a 4.7 Tesla horizontal superconducting magnet. They imaged the hydration of 1:1 and 1:3 mixtures of L-Dopa/HPMC in FaSSGF and FeSSGF (Fasted and Fed State Simulated Gastric Fluid) at 37 °C and obtained dissolution profiles by sampling the media reservoir. In a subsequent study [32], they also quantified areas of different regions in the tablet (dry core, hydrogel and diffusion front) since the hydration was non-uniform around its circumference.

Recent developments have enabled the integration of USP apparatus 4 with a low field 0.5 Tesla MRI instrument optimised for dissolution studies at 37 °C [33] as summarised in Fig. 3. Although it cannot compete against the signal-to-noise and spatial resolution produced by high-field superconducting magnet systems, it is sufficient to measure the hydration rate and to visualise the release mechanism of commonly available tablets, as well as to provide a dedicated system for reproducible dissolution measurements.

For example, MR images were acquired during dissolution of a USP standard gel matrix tablet with chlorpheniramine maleate as the active ingredient using water flowing at 16 ml/min and 37 °C (Fig. 4). A bed of glass beads were placed in the cone of the flow cell to ensure laminar flow further upstream and also to position the tablet without restricting the swelling. The rate of water ingress and swelling was quantified by calculating the areas of the non-hydrated core and whole tablet, respectively (Fig. 5); the gel layer can also be quantified by subtracting one from the other. The boundary between the gel layer and the dissolution media was chosen by varying the contour intensity to highlight the tablet for a series of images until the gel layer becomes so diffuse that it becomes impossible to define; in practice, this was a narrow window. The boundary between hydrated and non-hydrated regions was chosen by using a contour intensity that was half way between the highest (gel) and the lowest (non-hydrated core) intensities for the first image, which was used throughout the series. Fortunately, this determination ignores the apparent increase of water content in

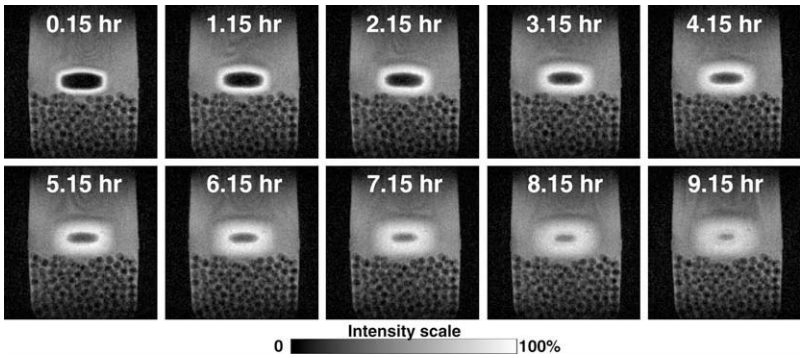

Fig. 4. A set of images acquired during dissolution of a chlorpheniramine maleate, USP standard tablet in water flowing at 16 ml/min at 37 °C in a closed loop configuration. Time stated is the start of a 4.3 min scan at 250-μm isometric pixel resolution and 3-mm slice (other image parameters: 12 ms echo time, 1 s repetition time and 2 averages).

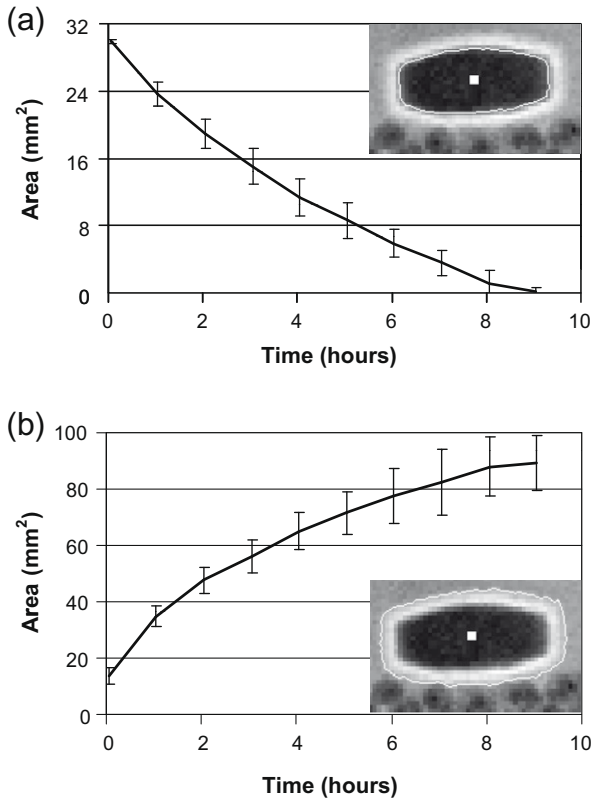

Fig. 5. Graph showing the areas of the (a) non-hydrated core and (b) whole tablet (swelling) calculated from image data acquired during six repeat dissolutions (average ± 2 × standard deviation). The images, which company each graph, show how the areas were defined.

the previously non-hydrated core after 5 h, which is due to ingress from outside the 3-mm slice. Although positioning of the non-hydrated core boundary can be debated, consistency between measurements is more important for comparison, for example, between different flow rates, dissolution media etc.

Simultaneously, the concentration of active ingredient was quantified by passing the outflow through a UV flow cell (the result is shown in Fig. 6), thus for a more complex formulation allows comparison of hydration kinetics and/or release mechanism against the rate of drug release. In this case, variability of the drug release profile was comparable to that of the batch (~12% at various time points analysed by USP apparatus 3).

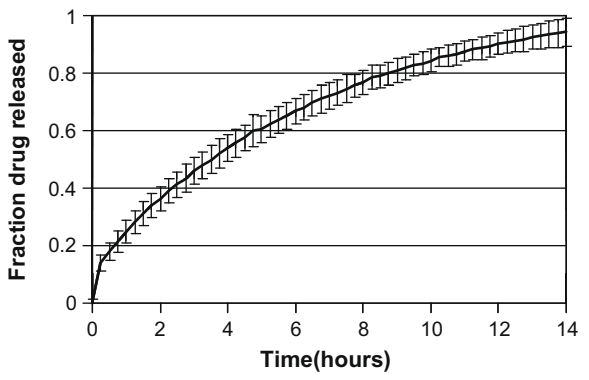

Fig. 6. Graph showing the fraction of chloropheniramine maleate released during dissolution of a USP standard tablet, measured by absorbance at 262 nm (average ± 2 × standard deviation for six repeats).

7. Summary

NMR and MRI techniques have been proven to be useful in the study of various polymer materials such as excipients for tablet formulations. The combination with USP-4 apparatus allows measurements during dissolution under conditions relevant to the formulation scientist.

Recent studies using low-field MRI show that the same benefits can be found on lower cost instrumentation that is accessible for a standard laboratory environment. These systems can be easily configured and optimised for various applications thus combined with USP-4 apparatus, MRI provides a powerful tool for investigating how the hydration of the tablet affects the dissolution mechanism, and as a consequence, the drug release profile.

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