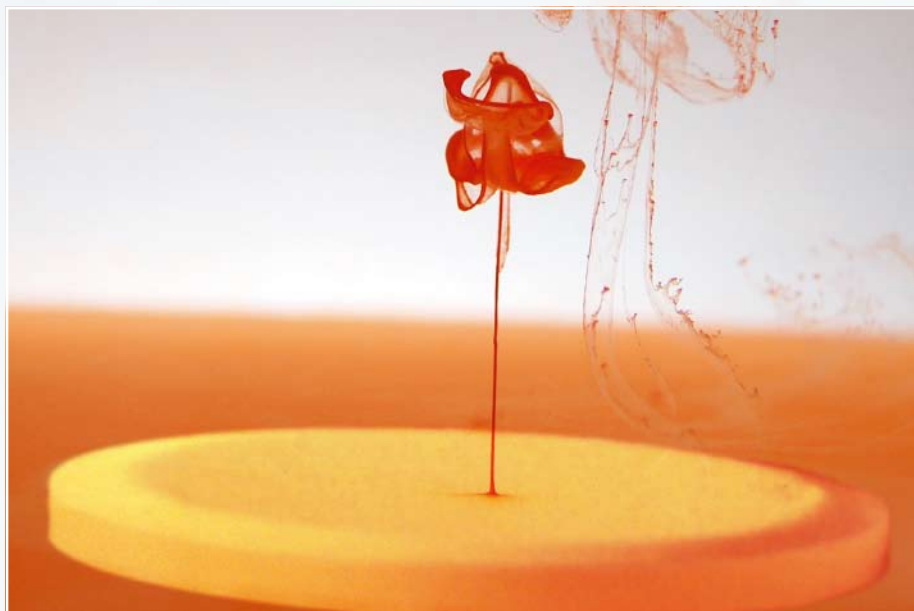


Visualising Tablet Dissolution

Measurement of Hydration and Drug Release

Magnetic Resonance Imaging (MRI) measures the hydration of tablets during dissolution by non-invasively mapping ^1H nuclei associated with "mobile" water. Images acquired on the PharmaSense Tablet Dissolution Imager with integrated US Pharmacopeia 4 apparatus, provide key data for the formulation chemist. Furthermore, simultaneous measurement of the drug concentration in the outflow by on-line UV analysis allows comparison of the drug release profile against the rate of water ingress.



Most studies of tablet dissolution are characterised by a drug release profile which is determined by collecting aliquots of the outflow, usually analysed off-line for the active pharmaceutical ingredient (API). However, controlled release pharmaceuticals are being developed with an increasing degree of complexity and are difficult to characterise using API analyses alone. They are typically a composite and therefore the rate of drug release could be dependent on a number of different factors including the excipients and coatings used as well as the geometry of the tablet.

There are various imaging techniques that map the physical and/or chemical properties of a dry tablet. For example, terahertz imaging can be used to measure coating thickness and uniformity, as well as structural imaging [1]. Chemical imaging techniques based on infra red and Raman spectroscopy [2] can also be used to visualise the heterogeneity of tablets, however, these techniques are destructive since samples have to be sectioned to analyse inside the tablet. As such, it is impractical to monitor processes such as hydration, particularly under conditions that are meaningful to the formulation chemist.

There are numerous examples of the use of MRI for pharmaceutical applications [3] and, especially, studies of tablet hydration which are

fundamental to understanding the subsequent drug release. Unlike most other imaging techniques, MRI can non-invasively and non-destructively obtain data from the whole tablet and, since it is not an optical technique, measurements can be made on opaque systems such as poorly water soluble drugs. However, its use is constrained by the availability of MRI systems for long experiments, the high running costs (i.e. helium and nitrogen for superconducting magnets) and a requirement for expert users.

This application note presents imaging data acquired on a low field MRI system based on compact permanent magnet technology combined with a dissolution apparatus [4] where the tablet is placed in a flow-through cell. Imaging data is presented which allows measurement of the rate of hydration inside a gel matrix tablet during the dissolution process. In addition, UV analysis of the outflow simultaneously measures the drug concentration. The insight that this valuable combination of data provides is discussed.

Experimental

The Oxford Instruments PharmaSense Tablet Dissolution Imager is based on a 0.5 Tesla permanent magnet stabilised at 37°C, which contains the radio frequency (RF) probe and 22.6 mm I.D.



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flow cell (fig. 1). The dissolution media, also regulated at 37°C, is pumped into the flow-through cell at 16 ml/min, in this case, in a closed loop circuit containing 250 ml water. The USP 4 cell is filled, almost to the centre, with 2 mm glass beads to position the sample in the centre of the probe and also to produce laminar flow. The latter is a requirement for MRI measurements to avoid spatial mis-registration of the MRI signal.

At an appropriate time the flow is stopped, the flow cell opened and fluid from above the glass beads removed to allow insertion of the sample. After positioning of the sample, the flow cell is closed, and flow restarted; this point is

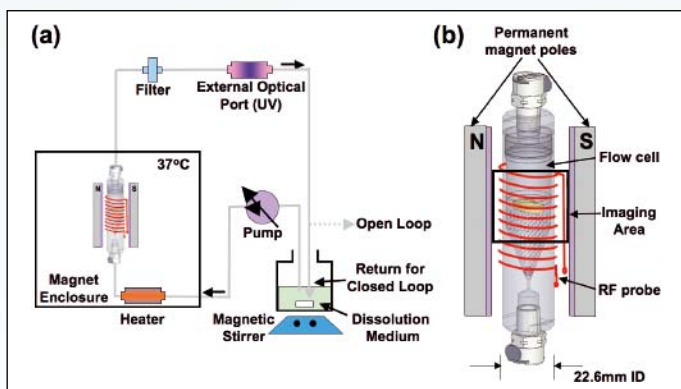


Fig. 1: (a) Schematic diagram of the PharmaSense, low field Magnetic Resonance Imager combined with USP 4 apparatus, and (b) expanded view inside magnet enclosure

time = 0 in the experiment. As soon as the flow cell is filled with water, a short "Preview" scan is acquired consisting of three orthogonal 2-dimensional images from which an Image with a 3 mm slice is accurately positioned. Subsequently, images from this same slice are automatically acquired at regular intervals throughout the entire experiment.

UV measurements are acquired simultaneously using a Thermo Evolution 300 spectrometer with a 10 mm path length, 80 μ l, flow cell (Hellma, Germany) which was in-line with the dissolution circuit.

Results

Figure 2 shows a set of images acquired during dissolution of a gel matrix tablet. The high intensity area in these images corresponds to the gel layer that forms when the water ingresses into the tablet which provides a barrier to further hydration and as a consequence

drug release. The zero intensity region within the gel layer corresponds to the non-hydrated region which represents the undissolved drug. The dissolution media has intermediate intensity and highlights voids caused by the glass beads which give no signal.

The contrast between the different features allows use of image analysis tools for quantification of the non-hydrated tablet and gel layer areas (fig. 3). Contours are drawn outside the gel layer to quantify the whole tablet, and inside to quantify the non-hydrated tablet. The gel layer area is then determined by subtracting the area of non-hydrated tablet from the total area of the tablet.

In open loop mode, UV analysis was insensitive to the drug dissolved at 262 nm; only 16 mg of the active ingredient was present in a 300 mg tablet. However, a noticeable increase in the absorbance at 262 nm was observed in closed loop mode using a 250 ml stirred

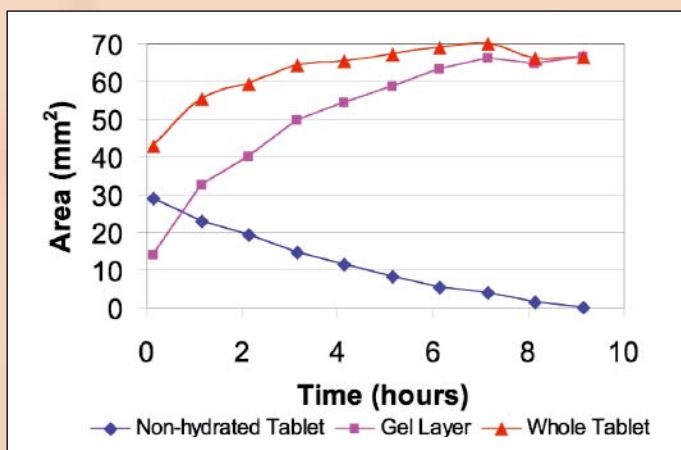


Fig. 3: Graph showing the areas of the gel layer, non-hydrated and whole tablet calculated from the images in Figure 2

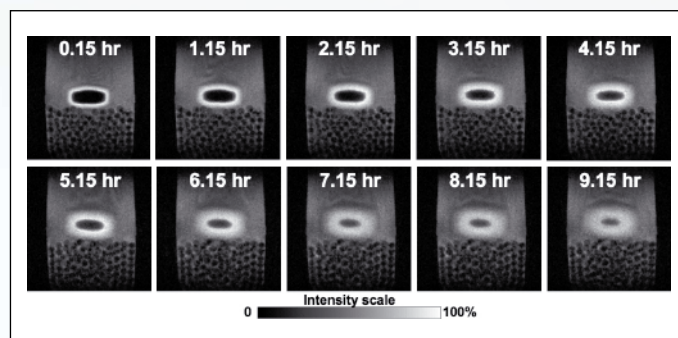


Fig. 2: A set of images acquired during dissolution of a Chlorpheniramine Maleate, USP standard tablet in water flowing at 16 ml/min at 37°C in a closed loop configuration. Time stated is the start of a 4.3 min scan. 250 μ m isometric pixel resolution and 3 mm slice (Other image parameters: 12 ms echo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

reservoir. This allows controlled build-up of the dissolved drug in the dissolution media (fig. 4).

Data generated by the USP 4 apparatus has most value using an open loop configuration to create sink conditions. This ensures that drug dissolved in the dissolution media does not alter the dissolution profile of the drug. However, where the proportion of the active pharmaceutical ingredient is low, it is possible/desirable to carry out this study in a closed loop configuration with on-line UV measurements.

Conclusions

Magnetic Resonance Imaging provides valuable data with which to characterise hydration kinetics of tablet dissolution. Image contrast allows quantification of water ingress and gel layer formation in a controlled release matrix tablet. Furthermore, it is possible to simultaneously measure the drug release

profile (% drug released over time) using on-line UV analysis without manual intervention. Since these measurements are acquired under USP 4 conditions, they will be directly relevant to other dissolution measurements, and therefore will give insight into how hydration affects the drug release profile for different formulations.

References

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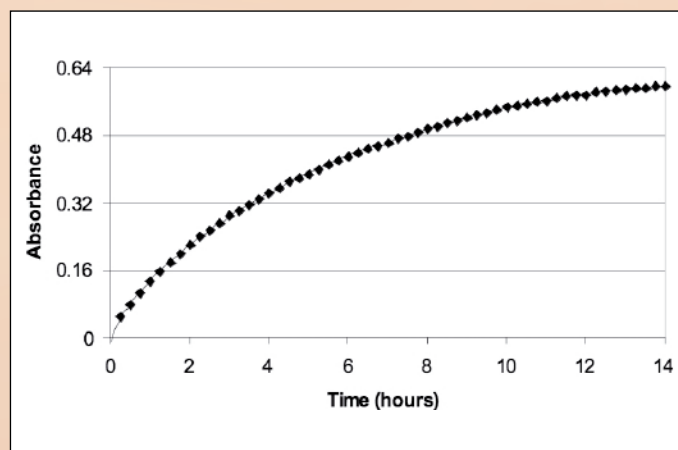


Fig. 4: Graph showing the UV absorbance at 262 nm during dissolution of a Chlorpheniramine Maleate tablet