

dissolution testing

USING LOW-FIELD MRI TO IMPROVE TABLET DISSOLUTION TESTING

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This article describes a study that GlaxoSmithKline (GSK) conducted to determine the feasibility of using low-field magnetic resonance imaging (MRI) to improve dissolution testing. The company used a dissolution apparatus from Oxford Instruments [1] and analyzed the drug release of modified-release (MR) and immediate-release (IR) tablets.

The FDA's Quality by Design initiative has spurred pharmaceutical regulators and manufacturers to demonstrate better scientific understanding of drug products prior to approval. In February 2008, a pharmaceutical development team at GSK began a 10-month study to determine the feasibility of using low-field MRI to improve the dissolution testing of MR and IR tablets. The study was conducted at the company's R&D facility in Harlow, UK, using a dissolution apparatus from Oxford that combines a low-field MRI scanner at 0.5 tesla and a USP-4 flow-through cell.

Current techniques

Dissolution testing is the standard technique for studying drug release. One dissolution test method—USP 4—

suspends a tablet (or other dosage form) in a flow-through cell while dissolution media flows continuously around it. The drug content of the outflow is measured to generate a drug-release profile, expressed as the percentage of drug released over time.

It is difficult to directly observe how a tablet swells or erodes during dissolution. Instead, behavior is usually inferred from the tablet's drug-release profile. Inference, however, is unreliable when testing tablets with several different layers or coatings, which are increasingly used to modify drug release. The complex behaviors of these tablets are difficult to deduce from a drug-release profile alone. That's where MRI is helpful.

MRI shows how a tablet breaks down in real time, as has been done with simple monolithic hydroxypropyl methylcellulose (HPMC) matrix extended-release tablets [2-5]. The technique captures images of a cross-section, or slice, of a tablet during hydration that show differences in water content and water binding in different areas (e.g., dissolution media, gel layer, and dry core).

While high-field MRI scanners at 2.35 to 9 tesla are expensive and require specialist operators and a dedicated, controlled environment, low-field MRI scanners are fairly inexpensive, easy to use, and operate safely in a conventional environment.

Equipment, method

The purpose of the study was to discover whether a low-field MRI dissolution apparatus could provide useful, new information about the behavior of standard MR and IR tablets.

The study was conducted using Oxford's apparatus integrated with a Hewlett-Packard HP8453 ultraviolet spectrophotometer for measuring drug concentration during image acquisition. Figure 1 shows a schematic diagram of the apparatus. The flow-through cell operated in a closed loop, circulating dissolution media at 16 milliliters (ml) per minute for MR tablets and at 8 ml per minute for IR tablets.

The flow-through cell kept the tablet in place using a holder, which positions a small, medium, or large tablet horizontally or vertically (Figure 2). The holder minimizes contact with the tablet during dissolution and replaces the metal holder typically found in a USP-4 flow-through cell.

MRI acquisition rates varied depending on the tablet being tested. Typically, the apparatus captured five to 25 images during dissolution tests that lasted 20 minutes to 20 hours. Contrast between the tablet and the dissolution media in the images was improved by varying image acquisition parameters to accentuate the differences in water mobility and, when necessary, by reducing signals from the dissolution media. Subsequently, the apparatus's software quantitatively measured the tablet's behavior over time. Two methods were used to analyze the images. When a clear distinction existed between the tablet's hydrated and dry areas, the tablet's hydrated, dry, and total areas were measured (Figure 3). When a clear distinction did not exist between the tablet's hydrated and dry areas, the image intensity of a cross-section of the tablet was plotted (Figure 4).

The performance of the apparatus was tested by comparing the drug-release profiles of USP-standard, 16-milligram (mg) chlorpheniramine maleate tablets against those generated by a standard USP-4 flow-through cell.

Simple MR tablets. Data were collected for two simple HPMC matrix MR tablets, chlorpheniramine maleate and once-daily nifedipine. The tablets were selected because they had similar formulations but differed in drug solubility and drug load, which are factors that might alter the drug-release mechanism. The chlorpheniramine

FIGURE 1

Schematic of MRI scanner and flow-through cell, integrated with a third-party ultraviolet spectrophotometer

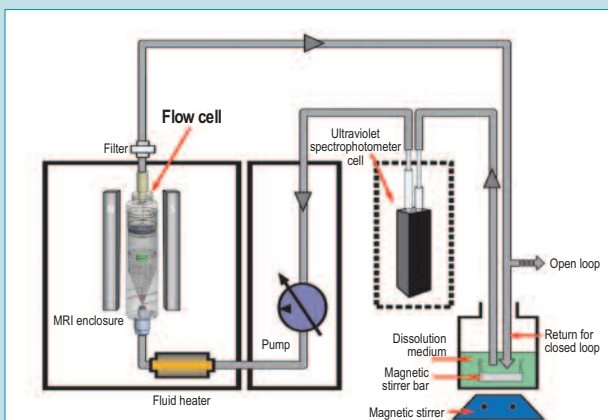


FIGURE 2

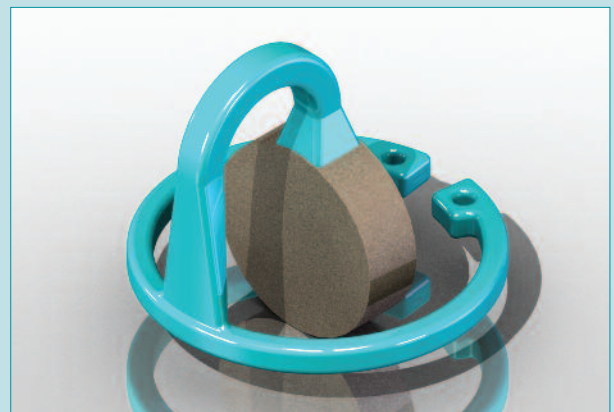
Tablet holders



a. Retaining band holds a tablet in place, used in early experiments.



b. Two plastic hooks hold a small or medium tablet in place horizontally.



c. Adhesive holds a large tablet in place.

maleate tablets had good water solubility (less than 10 mg per ml) and contained a 16-mg dose. The nifedipine tablets were insoluble (less than 0.01 mg per ml) and contained a 60-mg dose. Both comprised HPMC, which is a water-soluble, gel-forming polymer commonly formulated as a matrix to slow the release of drugs taken orally.

The chlorpheniramine maleate tablets were tested using water as the dissolution media. Image analysis, taking into account the time frame of drug release, showed that the mechanism for drug release was hydration of the core, followed by diffusion (Figure 5). Erosion of the matrix did not significantly contribute to drug release.

FIGURE 3

Image analysis of a USP-standard chlorpheniramine maleate tablet showed a clear distinction between the steadily wetting gel layer and dry core.

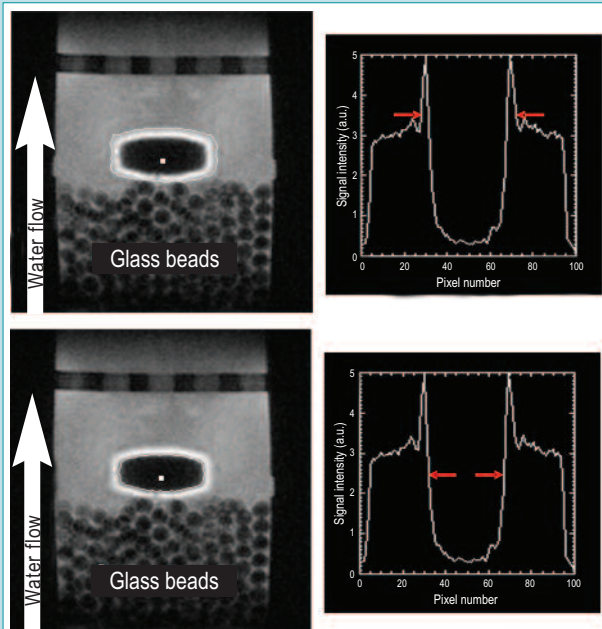
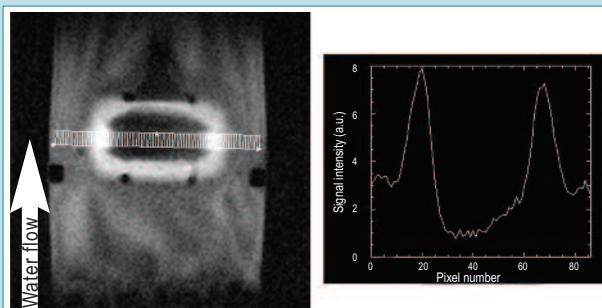


FIGURE 4

Image analysis of a tri-layer tablet showed no clear distinction between the steadily wetting or eroding area and dry core.



Since nifedipine is insoluble, the dissolution media contained 0.5 percent sodium lauryl sulfate. Image analysis showed that the tablet's total area decreased as the drug release progressed, while the tablet's dry core disappeared relatively quickly, taking into account the rate of drug release (Figure 6). The drug-release profile showed that 15 percent of the drug was released during hydration of the core and that the rest of the drug was released during erosion.

Complex MR tablets. Two relatively complex MR tablets were also tested. One was a bi-layer, osmotic, "push-pull," once-daily nifedipine tablet. The other was a tri-layer tablet that contained GSK's Drug A in the center.

No image analysis was performed on the MRI data of the nifedipine tablet. However, Figure 7 shows the change in the tablet's key features during dissolution. As the water-soluble "push" layer swelled in liquid, it forced the drug in the upper "pull" layer through a hole in the top of the tablet.

FIGURE 5

A simple HPMC matrix MR chlorpheniramine maleate tablet predominantly released its drug via hydration of the core during the first 400 minutes.

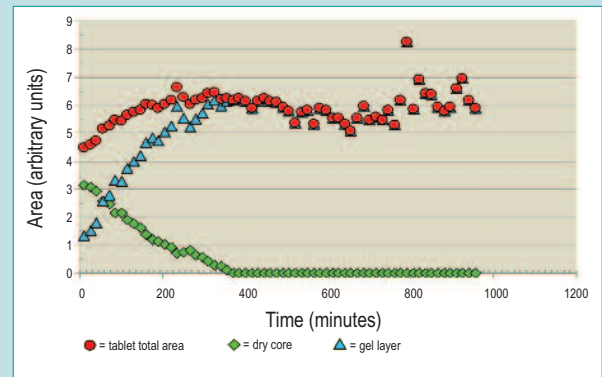
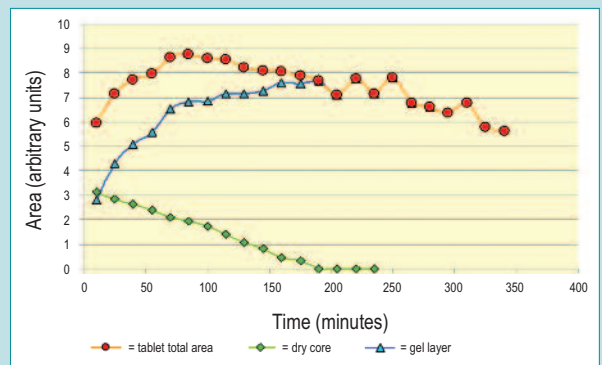


FIGURE 6

A simple HPMC matrix MR nifedipine tablet released its drug via hydration of the core during the first 20 minutes, then subsequently by erosion.



The tablet with Drug A, which is highly water soluble, comprised outer and inner layers that hydrated over time (Figure 8). The outer layers acted as barriers and slowed drug release. Image analysis was performed by plotting image intensities of the central area that contained the drug. Image analysis of the hydration of the inner layer showed a correlation between the extent of that layer's hydration and the rate of drug release. The correlation indicated that hydration and diffusion were the drug-release mechanisms.

IR tablets. IR tablets disintegrate rapidly compared to MR tablets, and therefore it's more difficult to capture MRI data.

However, a 10-millimeter-diameter, 300-mg, wet-granulated tablet with 120 mg of GSK's Drug B eroded slowly. Analysis of images taken every 5.6 minutes (see page 25) showed that the apparatus was able to measure the rate of the tablet's disintegration and the dimensions of a thin hydration layer around the disintegrating tablet.

Tests performed on several IR tablets showed that it was possible to capture images of them and produce usable quantitative data from these images, provided that the tablet's disintegration time in the flow-through cell lasted 10 to 15 minutes, sometimes longer. The tests also

showed that it was easier to obtain quantitative image analysis data from large tablets than from small tablets.

Results

The study found that low-field MRI could provide useful qualitative and quantitative information about the way MR tablets release their drug. For example, changes over time in the size of hydrated and non-hydrated areas could be clearly observed and measured. Low-field MRI was also found to be suitable for testing IR tablets, provided that the tablets were relatively large and that their disintegration was relatively slow. Therefore, low-field MRI may be useful when troubleshooting dissolution and disintegration problems associated with MR and IR tablets. T&C

Acknowledgements

The authors thank Luca Venturi, from Oxford Instruments, who conducted practical work for the study at GSK's site, and Paul Connelly, from GSK, who supervised the work.

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FIGURE 7

MRI images (taken over approximately 12 hours) show a bi-layer, osmotic, "push-pull" nifedipine tablet.

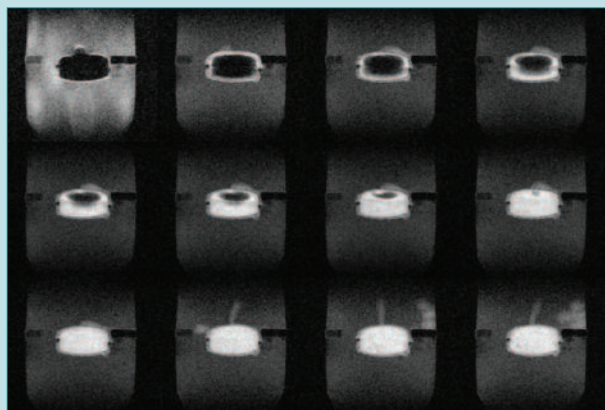
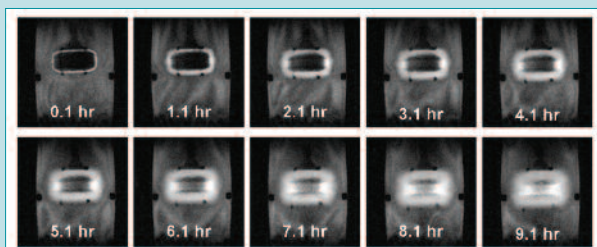


FIGURE 8

MRI images show a tri-layer tablet containing GSK's Drug A.



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