A miniaturized instrument for rapid in vitro release testing of semi-solid formulations in pharmaceuticals: application to ibuprofen gel

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ABSTRACT SUMMARY
This study describes a miniaturized instrument for in vitro release of semi-solid pharmaceutical formulations, imaging transfer of ibuprofen from a topical gel through a membrane developed for transdermal testing.

INTRODUCTION
Current methods for permeation testing are slow, resource intensive, require relatively large amounts of sample and analyses are done in the the bulk media. With semi-solid creams or gels designed for topical application there are no methods for direct monitoring of the donor layer in a standard or miniature Franz cell set up. The aim of this work was to develop a novel application of Paraytec's unique 2-dimensional UV imaging technology, to provide direct imaging of both the semi-solid donor layer and the receptor compartment and address shortfalls in current methodology.

Imaging through a thin layer of donor material allows direct probing of sample depletion. The method uses only small amounts of material, typically 100 μg API in 1 μL donor sample volume, and partitioning into 1-2 mL of receptor media. The small volumes used mean results can be obtained in minutes rather than hours. This will allow probing of early stage, transient and burst effects as well as longer term steady state diffusion. Future benefits of this technique with real time spatially resolved 2D images should include monitoring local effects such as pore transfer with skin samples.

EXPERIMENTAL METHODS
The experimental setup consists of an ActiPix™ D100 detector system (Paraytec Ltd) illuminated alternately by UV and visible light sources at ~ 1 Hz repetition rate. The semi-solid sample (1 μL) was inserted using a positive displacement pipette into the bottom of a narrow sample holder (200 μm optical path length), with fused silica windows. To start the experiment the sample holder is pushed down to contact a membrane which is attached to the base of a rectangular fused silica cell. This is contained within a standard 1 cm path length UV cuvette, containing 1.5 mL of receptor fluid. A miniature magnetic stir-bar driver is positioned underneath the cell, allowing the receptor fluid to be stirred if required using a magnetic follower.

Image data files (ActiPix™ software) are processed to allow spatially-resolved intensity distributions at UV and visible wavelengths to be viewed separately and the corresponding absorbance changes calculated. The software is flexible in placement of detection zones to allow different sample types to be used.

Figure 1. Experimental setup
RESULTS AND DISCUSSION

The gel sample used as donor phase was 5% ibuprofen gel (Boots plc, UK). 1 μL of the gel was inserted into the sample holder. The membrane (Strat-M™, EMD Millipore) is a synthetic, non-animal based model for transdermal diffusion testing. A cut section of this was attached by glue bonding to the base of a Paraytec SDI cell. Figure 2 shows the vertical (z direction) zone spanning the donor phase, the membrane and the acceptor phase (top to bottom). It was found that the active pharmaceutical ingredient, ibuprofen, could be imaged in the UV at 255 nm, and time dependent changes in its spatial distribution monitored. The visible image data track physical phenomena such as any changes to boundaries and movement of bubbles.

CONCLUSION

We have demonstrated a sensitive, spatially-resolved technique to image transfer of a drug across a synthetic membrane simulating transdermal skin diffusion. This is the first time imaging a donor phase has been carried out.

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