Application note 307/16

Using the Pion SDi2 to characterise the swelling and drug release profiles of an extended release formulation of Metformin

The Pion SDi2 surface dissolution imaging system provides unique insights into physical phenomena that occur at the interface of a drug product and dissolution medium. These phenomena are by necessity overlooked using compendial dissolution techniques, because concentration measurements are usually taken downstream of the dissolution process, yet they are key to understanding the full picture of how a formulation will perform in vivo. The SDi2 is used to observe and measure such effects of erosion, swelling, disintegration and drug release from API compacts or formulated whole dosages in a single experiment, enabling rapid, informed decisions to be made during dosage form selection/optimization.

Background

Metformin is commonly used to treat type II diabetes. Several generic formulations have been approved, for both immediate release (IR) and extended release (ER). An ER formulation of Metformin (500 mg Glucophage SR, Merck) used in this study was designed to swell under gastric conditions whilst retaining Metformin within the formulation's polymer matrix in the stomach, then subsequently release Metformin in the upper GI tract over an extended duration. The SDi2 was used to:

1) Quantify the extent of swelling of an ER formulation of Metformin at gastric pH
2) Measure local drug concentration over time after a gastric to intestinal pH shift.

Experimental

SDi2 experiments were carried out over 10 hours using the open loop configuration. The flow rate was set to 8.2 mL/min, equivalent to 1.3 cm/min linear velocity (bioequivalent linear velocity in the small intestine[1]). The flow cell was initially pumped with simulated gastric fluid. After 2 hours, the media was switched to simulated intestinal fluid to simulate gastric emptying into the small intestine. Tablets were held vertically with respect to the flow cell using a commercially available wire tablet holder. The chosen instrument configuration is depicted in Figure 1. The SDi2 flow cell was illuminated using alternate pulsing of 520 and 255 nm LEDs.

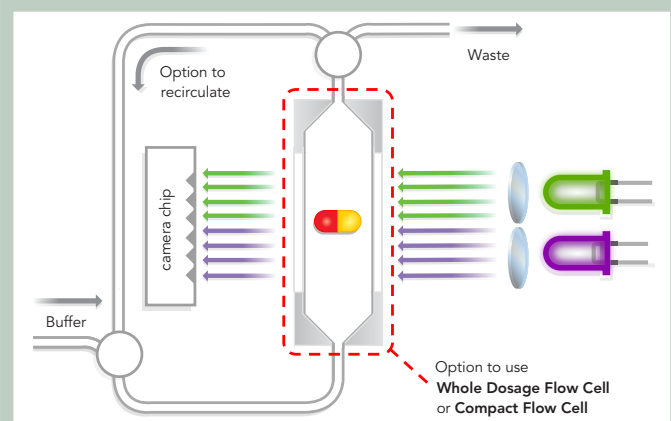

Figure 1. Schematic of the SDi2 configuration. 520 and 255 nm LEDs alternately illuminate Metformin ER in the whole dosage flow cell. Open loop fluidics were employed with the fully automated pH shift.

Patented Actipix™ imaging technology recorded intensity reaching each individual pixel. These data were used to create an image per wavelength every 25 seconds, with lower intensity in regions where either the detector is physically blocked by the dosage form (520 nm), or where dissolved drug is absorbing light (255 nm) . Images can be converted into false colour images, in which regions of equal intensity are displayed using the same colour (iso-absorbance regions). Unparalleled spatial resolution (13.75 µm effective pixel size) is achieved, enabling highly accurate detection of subtle changes during dissolution.

SDi2 Fasted state media
Simulated Gastric Fluid (SGF): 0.1M HCl, 2g/L NaCl, pH 1.2
Simulated Intestinal Fluid (SIF): 6.8g/L KH_2PO_4 at pH 6.8

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Results and Discussion

1) Swelling

Data used to measure swelling were obtained from 520 nm images (Figure 2). A measurement zone was placed horizontally across the centre of the imaging area (Figure 2A). Obscuration data across the width of the flow cell was quantified and plotted as a function of time using the SDi2 data analysis software (Figure 3A). Absolute tablet width was then calculated over the duration of the experiment (Figure 3B). The Metformin ER tablets swelled rapidly in SGF (pH1.2), then continued to swell at a slower rate in SIF (pH6.8).

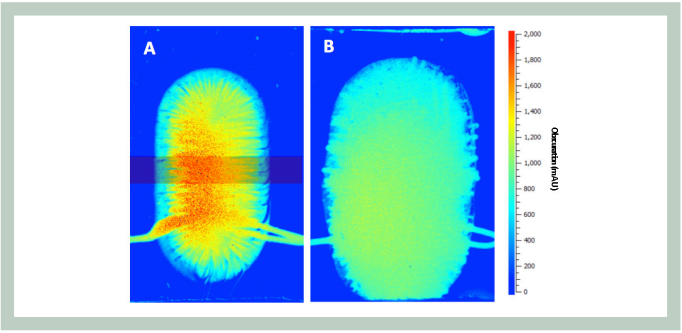
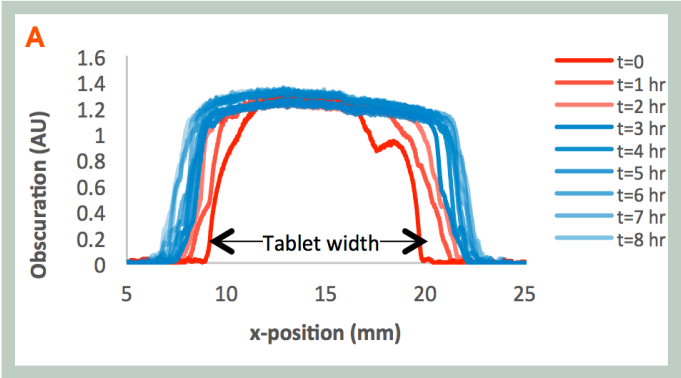


Figure 2. False colour images of Metformin dosage form in dissolution medium using 520 nm LED at A) t=0 and B) t=10 hours.



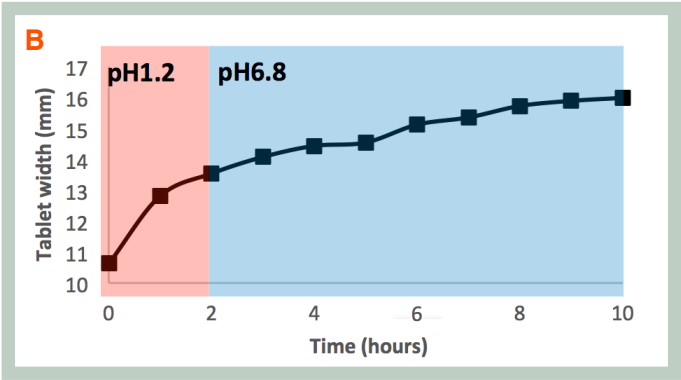


Figure 3. A) Raw obscuration data using 520 nm LED exported from SDi2 software. Red and blue profiles represent data at pH1.2 and pH6.8 respectively. B) Calculated absolute tablet width over duration of experiment.

2) Drug release

False colour images created using the 255 nm LED pulses were used to detect drug release. The colour transition of the dissolution medium from dark to light blue (Figure 4) indicates an increase in absorbance and hence drug release from the dosage into solution. Local metformin concentration was calculated in a region above the tablet (Figure 4B) using a previously measured extinction coefficient of metformin at the same wavelength (Figure 5). These results highlight the ER formulation release mechanism, with drug release occurring over 8 hours in SIF.

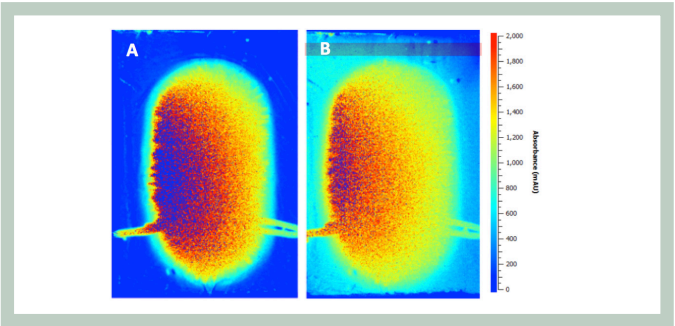


Figure 4. Absorbance images obtained from illuminating flow cell with 255 nm LED. A) t=2 hours in gastric pH buffer. B) t=8 hours in intestinal pH buffer, with measurement zone present above tablet.

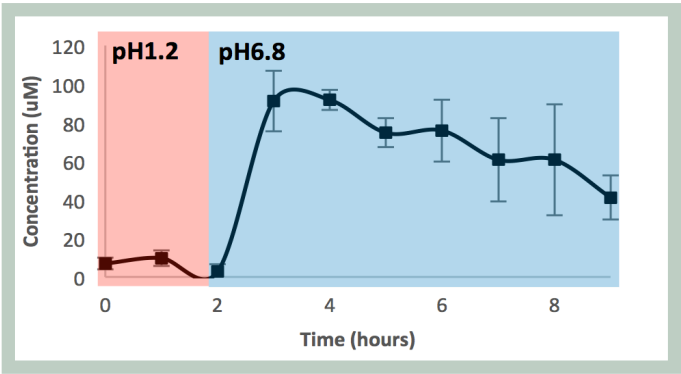


Figure 5. Average metformin concentration in measurement zone with standard deviation.

Conclusion

The Pion SDi2 is a powerful analytical tool, used to measure physical phenomena and drug concentration during dissolution from a single experiment. The SDi2 has been implemented to quantify 1) dosage form swelling and 2) local dissolved concentration of Metformin from a generic ER formulation. The technology is primarily aimed at formulation development use, offering detailed insights into processes often overlooked using conventional techniques.

Reference 1) Fotaki, N. and Reppas, C., The flow through cell methodology in the evaluation of intraluminal drug release characteristics, Dissolution Technologies, 2005, 17-21.

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