Biorelevant drug release of Metformin dosage forms using complementary *in vitro* tools

Hayley Watson[1], Karl Box[1], Amie Gehris[2]

[1]**Sirius Analytical Instruments Ltd,** Forest Row, United Kingdom, [2]**The Dow Chemical Company,** Collegeville, PA, USA

Purpose

A key challenge in formulation development is correlating data from traditional dissolution tests with *in vivo* outcomes. In this study, two proprietary dissolution technologies were utilized to investigate the effect of formulation differences on drug release for immediate (IR) and extended (ER) release Metformin tablets. The Dow Chemical Company's FloVitro™ biorelevant dissolution instrument was implemented to achieve IVIVR for the IR dosage form and for *in vitro* comparison of IR and ER tablets. Mechanistic differences accounting for drug release were investigated by real-time UV/vis imaging using the Sirius SDi2 (surface dissolution imaging) platform.

Experimental

Experiments were carried out at 37°C using 500 mg Metformin HCl IR (Glucophage®, BMS) and ER (Glucophage SR®, Merck Serono) tablets. 0.1 M HCl + 2 g/L NaCl, pH 1.2 and phosphate buffer, pH6.8 were used as dissolution media.

FloVitro™ is a transfer system consisting of three cells representing gastric, intestinal and systemic absorption compartments (Figure 1). FloVitro™ dissolution was studied using flow rates of 1 and 2 mL/min for HCl and phosphate buffer, respectively. Metformin drug concentration was measured over 16 or 24 hours using inline spectrophotometry (247 nm) for the IR and ER tablets, respectively.

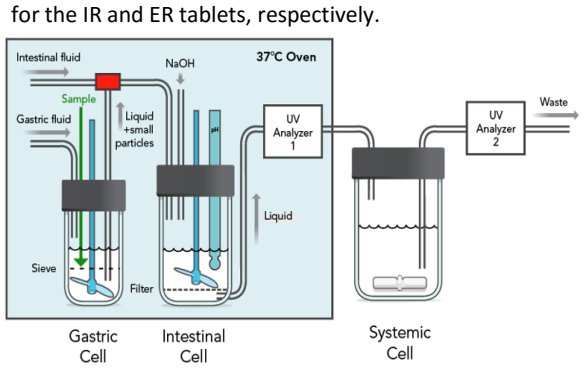

Figure 1. FloVitro™ Schematic.

The Sirius SDi2 experiments were performed over 8 hours using a USP IV type flow through cell at a flow rate of 8.2 mL/min. Metformin IR and ER tablets were held in place with a tablet holder, while HCl was pumped through the flow cell for the first two hours, followed by an automated buffer switch to phosphate buffer for a further 6 hours. Two dimensional absorbance/obscuration data at 255 and 520 nm wavelengths were collected in a single experiment using the patented detector chip. Images collectively built a high resolution video at each detection wavelength. False colouring was applied to the images to better visualize iso-absorbance regions within the flow cell.

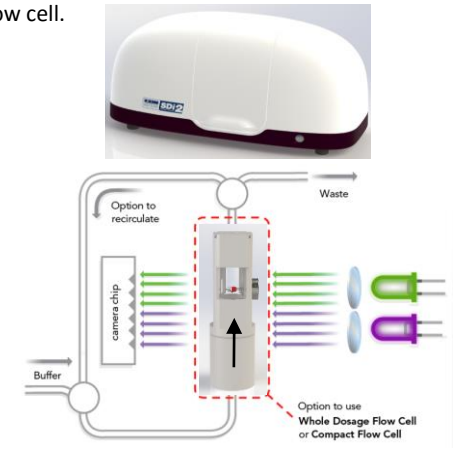

Figure 2. Top: Sirius SDi2 instrument, Bottom: SDi2 schematic.

Results and Discussion

FloVitro™ results for the IR dosage form were compared to scaled *in-vivo* data from a previous clinical trial[3] (Figure 3). IVIVR was achieved for IR Metformin with $R^2 = 0.945$, (Figure 4). Results for the ER dosage form using the same method demonstrated lower *in vitro* c_{max} and later T_{max}, as expected (Figure 3, Table 1).

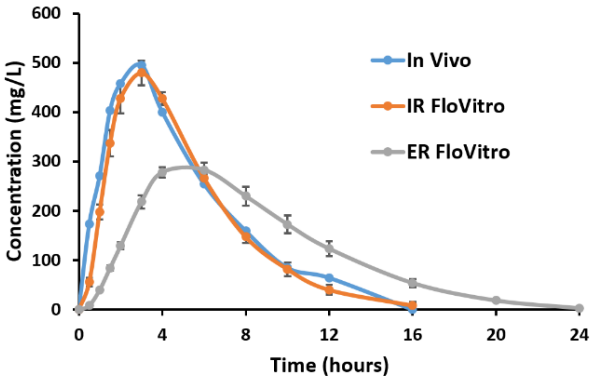

Figure 3. FloVitro™ concentration versus time data for IR and ER Metformin, and scaled in vivo data.

Dosage Form	C_{max} (ng/mL)	T_{max} (hrs)
IR metformin	479	3
ER metformin	283	6

Table 1. FloVitro™ C_{max} and T_{max} values for IR and ER Metformin

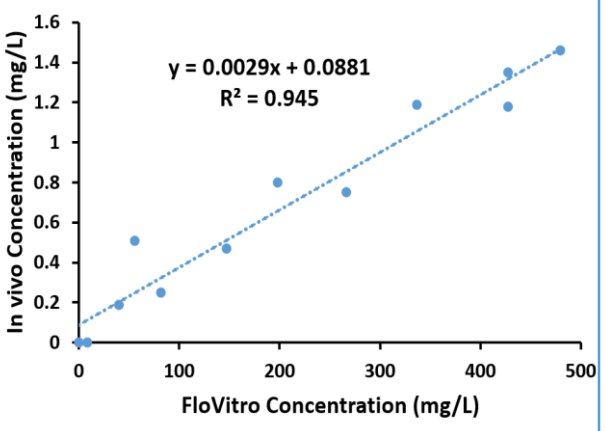

Figure 4. Levy plot for in vivo data versus FloVitro™ for IR Metformin.

The Sirius SDi2 data collected at 254 nm and 520 nm for both tablets are displayed in Figure 5 and 6, respectively. Dark blue regions indicate no or very little absorbance/obscuration, where no drug is present in solution. Light blue, green, yellow and red areas represent areas of low to high absorbance/obscuration. Measurement zones in the SDi2 software (overlaid on the images) were used to measure drug concentration in solution at 255 nm, and swelling/disintegration of the tablets at 520 nm.

UV data (Figure 5) show that the IR tablet rapidly released drug Metformin into solution. Dissolution was complete within 2 hours. In contrast, the ER tablet retained Metformin within the dosage form under gastric conditions. Upon the pH shift, Metformin was gradually released into solution for the remainder of the experiment.

Visible data (Figure 6) show that the IR tablet had fully disintegrated within 1 hour, whereas the ER tablet formed a hydrogel from which the drug diffused into solution at a steady rate. The ER tablet swelled by almost 5 mm in width over 8 hours.

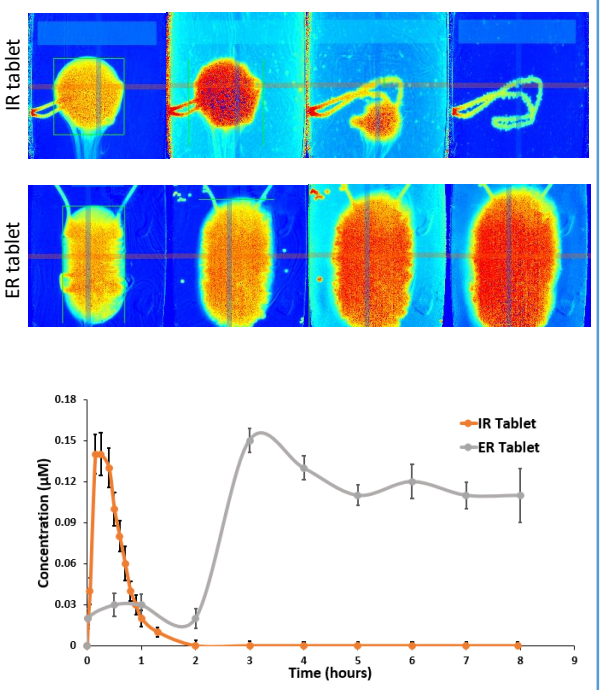

Figure 5. UV data images for IR (left to right: t=0, 10, 30 and 60 minutes) and ER (left to right: t=0, 2, 4 and 8 hours) Metformin tablets. Blue measurement zones above the tablet were used to plot the concentration versus time graph.

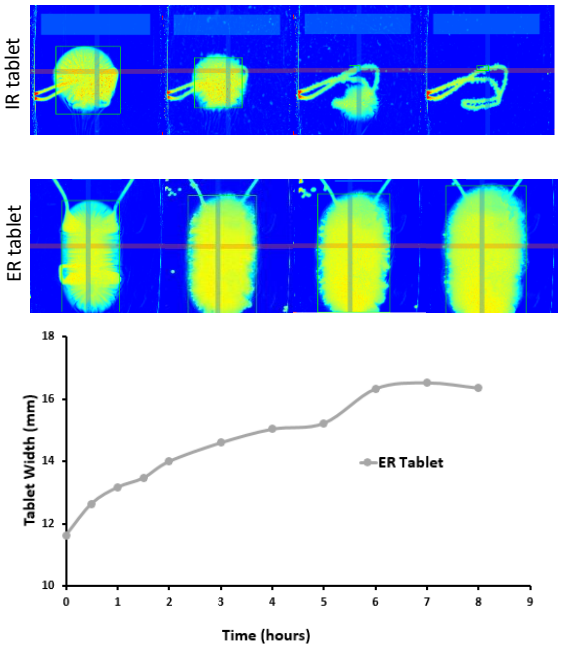

Figure 6. Visible data images for IR (left to right: t=0, 10, 30 and 60 minutes) and ER (left to right: t=0, 2, 4 and 8 hours) Metformin tablets. The cross measurement zone over the ER tablet were used to plot the tablet width versus time graph.

Conclusions

The **Sirius SDi2** and **FloVitro™** platforms offer unique, complementary techniques which provide detailed *in vitro* discrimination between IR and ER dosages of Metformin. These technologies have also been successfully used to rank comparative performance of formulations of other drugs, providing invaluable information to assist dosage form selection.

References

1) Buhse L.F., Chikhale E.G., De S.K., Doub W.H., Gehris A.S., Gao Z., Hughes L., Lu R., Mahayni H., Matura P.K., Mehta T.D., Selen A., 2008. Exploring suitability and feasibility of a novel in vitro dissolution system. American Association of Pharmaceutical Scientists Annual Meeting poster.

2) Lenke, J., Wren, S., 2011. Pharmaceutical dissolution and UV imaging. American Laboratory, February 2011.

3) Idkaidek N, Arafat T, Melhim M, Alawneh J, Hakooz N (2011) Metformin IR versus XR Pharmacokinetics in Humans. J Bioequiv Availab 3: 233-235. doi: 10.4172/jbb.1000092