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

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SUMMARY

Drug release from immediate release (IR) and extended release (ER) metformin products was investigated using the Dow Chemical Company's FloVitroTM biorelevant dissolution instrument. This was complemented by using the Sirius SDi2 (Surface Dissolution Imaging) platform to investigate mechanistic differences accounting for drug release. Level A IVIVC was demonstrated for metformin IR dosage forms, using FloVitroTM, whilst ER tablets demonstrated lower Cmax and Tmax using the same method. The SDi2 showed disintegration as the main release mechanism for IR tablets, whilst swelling and drug diffusion was observed for ER tablets. FloVitroTM and SDi2 technologies can be used to compare behaviour of formulations during dosage form selection

INTRODUCTION

Data from traditional dissolution tests are notoriously difficult to correlate with in vivo outcomes. This is a key challenge in formulation development. 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 level A IVIVC 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 imaging using the Sirius SDi2.

MATERIALS AND METHODS

Experiments were carried out at 37°C using 500 mg Metformin HCl IR and ER tablets. Dilute HCl, pH 1.2 and phosphate buffer, pH6.8 were used as dissolution media.

The FloVitro™ system consists of three chambers representing gastric, intestinal and systemic absorption compartments. FloVitro™ dissolution was studied using flow rates of 1 and 2 mL/min for HCl and phosphate buffer, respectively.

FloVitro™ drug concentration was measured over 16 or 24 hours using inline spectrophotometry (247 nm). The results were compared to in-vivo data from a previous clinical trial (Idkaidek, 2011).

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Sirius SDi2 experiments were performed using a USP IV type flow cell at a flow rate of 8.2 mL/min. The SDi2 is designed for whole dosage imaging of tablets or capsules. Absorbance data at 255 and 520 nm wavelengths were collected over 3 hours for the Metformin IR tablets and for 10 hours for the Metformin ER tablets. The dual-wavelength capability allows discrimination between the dissolved API, the dosage form and excipients.

RESULTS AND DISCUSSION

FloVitro™ results for the IR dosage form are shown in Figure 1 (top panel). Superimposed is the scaled in-vivo data. Level A IVIVC was achieved for IR Metformin with R2 = 0.945 (Figure 1B).

Results for an ER dosage form using the same method demonstrated lower in vitro c_{max} and later t_{max} (Table 1, and Figure 1A).

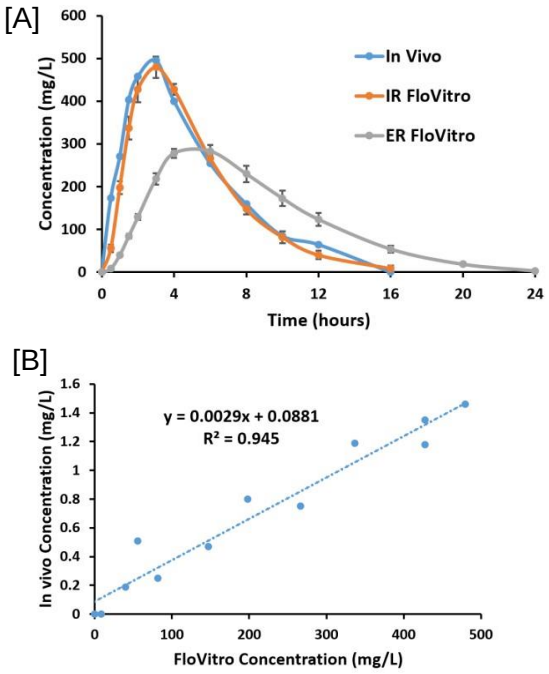

Figure 1[A] *FloVitro™ concentration profile (IR and ER Metformin) with superimposed scaled in vivo data.* ***[B]*** *IVIVC plot showing Level A correlation.*

Mechanistic details accounting for the observed differences were obtained using the Sirius SDi2: The IR tablet disintegrated, leading to rapid onset of drug release. The ER tablet swelled in acid and only after a transition into pH6.8 phosphate buffer did the drug diffuse gradually into solution from the hydrogel matrix, while the dosage form remained intact (Figure 2).

Table 1. *Mass dissolved and IDR of free base and salts.*

Dosage Form	C_{max} (ng/mL)	t_{max} (h)
IR formulation	479	3
ER formulation	283	6

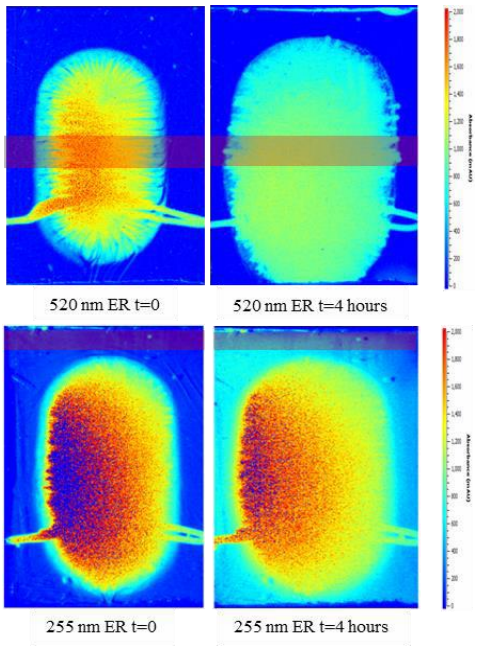

Figure 2. *Sirius SDi2 images at 255 nm and 520 nm detection wavelengths for ER metformin tablets. Red zones indicate quantification region.*

CONCLUSIONS

FloVitro™ and the Sirius SDi2 are novel, complementary techniques which provide detailed in vitro discrimination between IR and ER dosages of metformin. These technologies may also be used to rank comparative performance of formulations of other drugs, providing invaluable information to assist dosage form selection.

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