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Prediction of fraction of dose absorbed based on *in vitro* solubility and flux measurements

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PURPOSE

In formulation development traditional (USP) dissolution tests have been used to compare performance of different drug formulations before conducting in vivo studies. Although dissolution tests provide a simple way of testing formulations, the *in vivo* predictive power of these tests are questionable [1]. When a poorly water-soluble API is formulated to enhance its dissolution additives, such as surfactants, polymers and cyclodextrins have an effect not only on dissolution profile, but on flux through the membrane. The aim of this study was to compare 2 generic formulations of telmisartan (TEL) to its brand name product, Micardis using simultaneous dissolution-permeation apparatus (BioFLUX™). Furthermore we aimed to investigate the effect of formulation additives on the amorphous solubility and permeability of the drug in order to gain a better understanding of the in vitro behavior of the marketed formulations.

METHOD(S)

Drug Products

API	Drug Product	Dose (mg)	Formulation additive
Telmisartan (TEL)	Micardis (referens)	40	Sorbitol
	Telmisartan Actavis (test)	40	Mannitol
	Telmisartan Sandoz (test)	40	Lactose

Flux Measurements

BioFLUX™ device was used for flux measurements. The schematic of the experiments is shown on Figure 1. Concentration in both chambers were monitored in real time using *in situ* fiber optic dip probes connected to the Rainbow instrument (Pion Inc.).

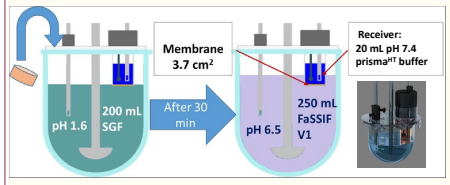

Figure 1. A dosage form was added to 200 mL of SGF and dissolution profile was monitored. After 30 min the medium was changed to 250 mL of FaSSIF continuing the concentration monitoring in both dissolution and receiver chambers. An insert shows BioFLUX™device.

RESULTS

Modelling Approach

Flux through the membrane was calculated based on concentration – time profiles in the receiver chamber

$$J_{invitro} = \frac{1}{A} \cdot \frac{dm}{dt} \quad (1)$$

where A is the area of the membrane in the BioFLUX™ device and dm/dt (μg/min) is the rate of absorption into receiver chamber.

Fraction of dose absorbed ratio (Fa ratio) for the prediction of bioequivalence was calculated using Eq.2.

$$F_a \text{ ratio} \approx \frac{J_{test}}{J_{reference}} \quad (2)$$

where test and reference are related to the flux measured for the test and reference drug product correspondingly.

Flux results

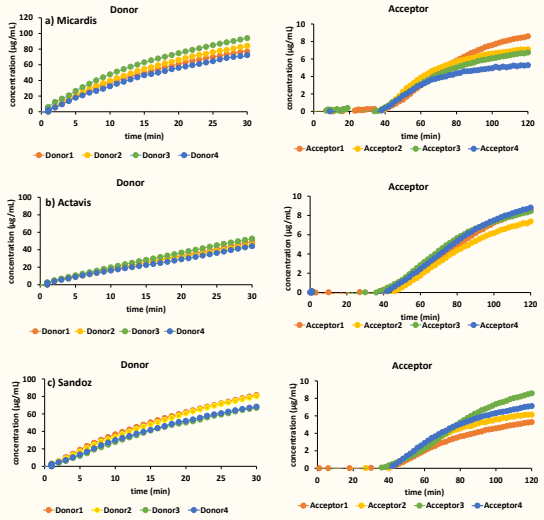

Figure 2. Dissolution in SGF (left) and appearance profile (right) of TEL from Micardis (a), TEL Actavis (b) TEL Sandoz (c).

To simulate the *in vivo* conditions, media change from simulated gastric fluid (SGF) to fasted state simulated intestinal fluid (FaSSIF) was carried out after 30 minutes. In case of all formulation TEL started dissolving in the SGF stage of procedure, while changing the pH triggered supersaturation and fast precipitation making the solution so turbid that it disabled the concentration monitoring via UV probe. During the first 30 minutes of the experiment no flux across the membrane was detected because of the charged state of the API, after media change TEL started to permeate through the membrane (Figure 2).

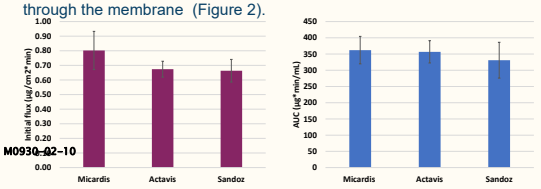

Figure 3. Initial flux of TEL (a), AUC of TEL (40-120 min) (b) calculated from measured concentration-time curve in the receiver chamber after conversion of the donor to FaSSIF .

Both initial flux and area under the concentration curve ($AUC_{40\text{-}120\ min}$) values were calculated from the concentration-time curve of the acceptor chambers. (Figure 3.)

Bioequivalence prediction based on in vitro flux and AUC results

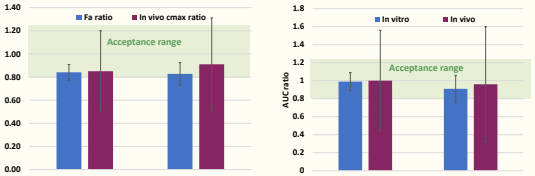

Figure 4. Comparison of *in vitro* Fa ratios and *in vivo* c_{max} ratios (test/referens) (a) comparison of *in vitro* and *in vivo* AUC ratios (test/referens) (b).

In case of AUC values no significant difference was seen between the reference product and generic formulations. These AUC results were found to be in agreement with *in vivo* AUC values, where the results of the generic products were well within the acceptance range of the bioequivalence criteria (Figure 4.b). [2-3] The initial flux results on the other hand showed significant difference between Micardis and the generic products. These flux results were found to be in agreement *with in vivo* c_{max} results [2-3], where the c_{max} values only fell on the borderline of the acceptance criteria (80-125%) for bioequivalence (Figure 4.a).

Effect of additives on amorphous solubility and permeability

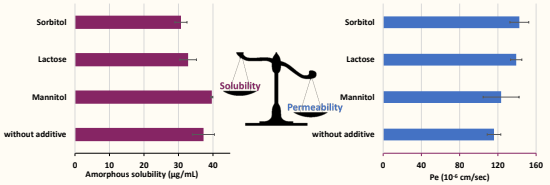

Figure 5. Amorphous solubility of TEL (a) and permeability of TEL (b) in FaSSIF full media with and without additives

Amorphous solubility of TEL was measured using zero intercepts method [4] in FaSSIF full media. From the results it can be seen that while mannitol did not influence the solubility, sorbitol, often used as tablet filler, caused a significant decrease in amorphous solubility (Figure 5.a). Permeability measurements were carried out using 96-well PAMPA setup. The addition of sorbitol resulted in significant increase of the permeability, while lactose only slightly effected this property and mannitol had no effect on it.

CONCLUSION(S)

The dissolution and flux results of three marketed TEL formulations were compared in fasted state to each other and to the *in vivo* study results published by the manufacturers. The flux of TEL from the Telmisartan Sandoz and Telmisartan Actavis was found to be significantly lower than from the brand name, Micardis. The *in vitro* test was found to be successful in predicting differences between formulations caused by using different excipients.

The effect of formulation additives was investigated in depth with amorphous solubility and permeability studies. Results clearly showed the interplay between amorphous solubility and permability, namely these two were inversely proportional to one another. The *in vivo* superior bioavalability of the brand name Micardis tablet (containing sorbitol) can be interpreted with the highest permeability measured in case of sorbitol present in the dissolution media.

REFERENCES

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