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Application of MacroFLUX™ apparatus for screening formulations before bioequivalence studies

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PURPOSE

For **generic drug development** traditional (USP) dissolution tests have been used in the pharmaceutical industry to compare performance of different drug product formulations before or instead of conducting bioequivalence studies. Although **dissolution tests** provide a simple way of testing formulations, the ***in vivo* predictive power** of these tests are questionable. Namely, when a poorly water-soluble API is formulated to enhance its dissolution, additives, such as surfactants and polymers have an effect not only on dissolution profile, but also on flux through the membrane. The aim of this study was to represent the importance of simultaneous dissolution-absorption studies using **MacroFLUX™** apparatus before conducting **bioequivalence studies**.

MATERIALS and METHODS

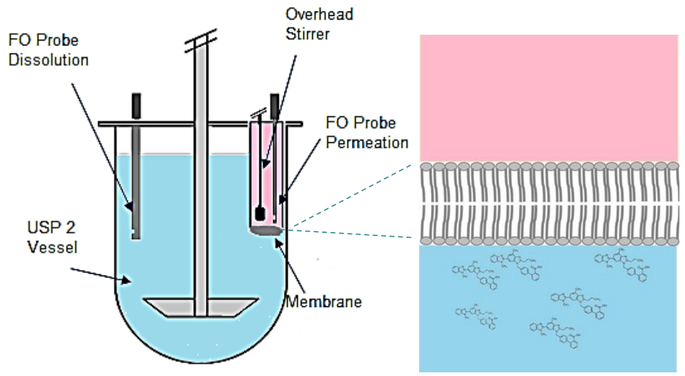

Figure 1. Schematic of Dissolution – Flux device used in this study.

Brand and generic formulations of **Telmisartan**, an antihypertensive drug, were tested using **MacroFLUX™**. Receiver chamber integrated with permeation membrane, overhead stirrer and fiber optic (FO) UV probe was inserted in the standard **900 mL** vessel of **USP II** apparatus. A filter-supported **artificial membrane** with 3.8 cm^2 area was separating the dissolution (donor) compartment from the receiver compartment contained 15 mL of pH 7.4 (Prisma™ HT, Pion Inc). The experiment began in 850 mL at pH 1.6 simulating gastric conditions and then after 30 min media in the dissolution vessel was converted to **FaSSIF** by adding 212 mL of specially formulated concentrate containing SIF powder. The integrated fiber-optic UV probes were positioned in the donor and receiver compartments allowing **real time concentration monitoring** in both chambers. Concentration monitoring was enabled through **fiber optic UV probes** connected to the Rainbow Dynamic Dissolution Monitor instrument (Pion Inc). **Flux** (J) of a drug through a membrane is defined as the amount of drug (m) crossing a unit area (A) perpendicular to its flow per unit time (t).

$$J=\frac{dm}{A*dt} \qquad (1)$$

RESULTS

I. Brand name compared to generic formulation containing the same excepients

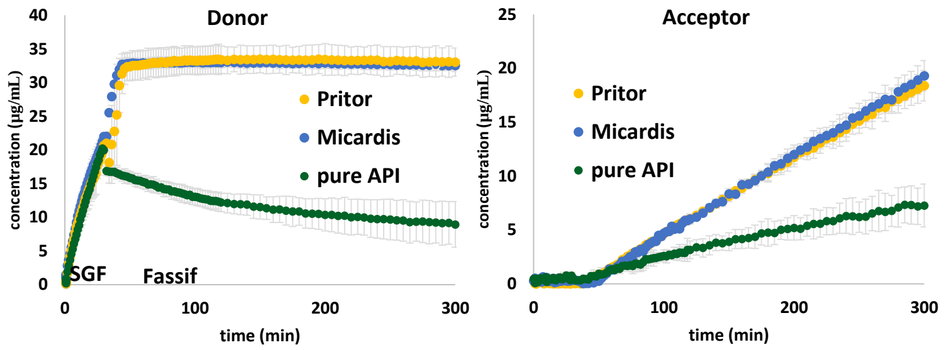

Figure 2. Dissolution profile (on the left) and appearance profile (on the right) of telmisartan from different formulation and pure API.

The dissolution and flux results of the **brand name** (Micardis) and **generic** (Pritor) Telmisartan 40 mg tablets were compared (Figure 2). Both formulations showed slow release kinetics in SGF and instant dissolution after media convertion to FaSSIF full with the final concentration around 35 µg/mL (more than 90% of the API dissolved). In the first 30 minutes of the experiments the concentration of the API in the acceptor chamber was under the detection limit (~ 0.1 µg/mL). After media change in the time interval of 50-120 minutes the flux through membrane was found to be **0.337 ± 0.028** µg/(cm^2*min) in case of the brand and **0.308 ± 0.014** µg/(cm2*min) in case of the generic product. In comparison the initial flux from unformulated API at the same load in the donor compartment was **0.120 ± 0.016** µg/(cm^2*min) and it was decreasing due to **precipitation** of API in FaSSIF.

II. Brand name compared to generic formulation containing different excepients

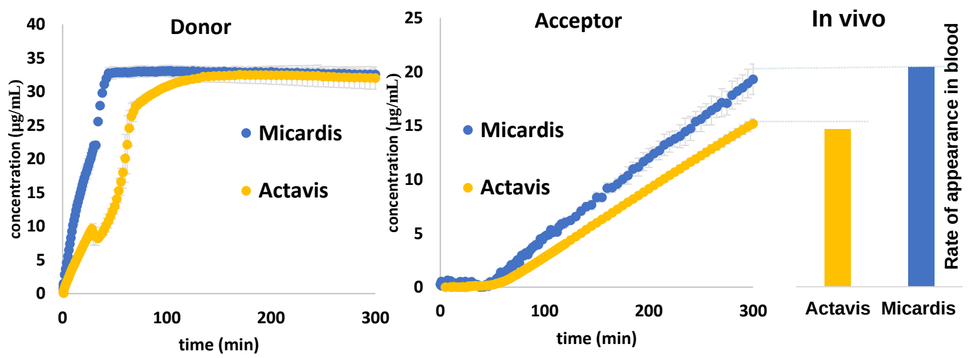

Figure 3. Dissolution profile (on the left), in vitro appearance profile (in the middle) and in vivo appearence (on the right) of telmisartan from different formulations.

The dissolution and flux results of the **brand name** (Micardis) and **generic** (Actavis) Telmisartan 40 mg tablets were compared (Figure 3). Actavis showed a slower release kinetics than Micardis, though reached the same maximum concentration after 110 min. After media change the flux from the generic product was found to be **0.240 ± 0.011** µg/(cm^2*min), which is only **71%** of the flux of the brand name (**0.337 ± 0.028** µg/(cm^2*min)). This *in vitro* result showed excellent correlation with the *in vivo* data from bioequivalence studies[1], where the appearence rate or the drug in blood from Actavis was **72 %** of the rate from Micardis.

RESULTS

III. Brand name with additional solubility modifier formulation additives

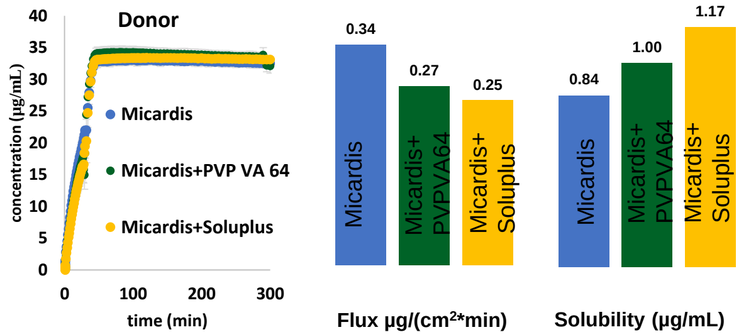

Figure 4. Dissolution profile (on the left) and flux (in the middle) and solubility (on the left) of telmisartan from Micardis tablet with additional solubility modifiers

The effect of solubility modifier formulation additives, such as **Soluplus, PVP VA 64** were studied by adding excipients (80 mg) to the donor chamber. Although the addition of excipients to the donor media had **no significant effect on the dissolution** kinetics (Figure 4) of the API resulting in more than 90% dissolved drug in FaSSIF media, the **flux** through membrane was significantly **decreasing**. In case of Soluplus containing media the flux was found to be 0.252 ± 0.017 µg/(cm^2*min) while in case of PVP VA 64 containing media 0.274 ± 0.003 µg/(cm^2*min). Flux results can be better understood considering that flux not only depends on the concentration gradient between the two chambers, but also **inversely proportional to the solubility**[2] of the API as shown in Figure 4.

CONCLUSION

The results showed that by adding **solubility modifier formulation excipients** the **dissolution** of Telmisartan was not altered, but the **flux** through the membrane was found to be **decreasing significantly**. These results point out the limitations of traditional (USP) dissolution tests and emphasis the importance of **simultaneous dissolution-absorption** studies, where the effect of formulation excipients on dissolution and also on membrane transport can be measured. This knowledge is essential for **generic formulation development** before **bioequivalence studies** are conducted.

The ***in vivo* predictive power** of the **simultaneous dissolution-absorption** test was demonstrated by comparing the *in vitro* fluxes to *in vivo* rate of appearance in blood of brand name and generic formulation of telmisartan. The preformance of the generic product was 71% of the brand *in vitro* , while 72 % *in vivo,* showing excellent ***in vitro-in vivo* correlation.**

REFERENCE

[1]Public Assessment Riport of Actavis

[2]Borbas, et al. "Investigation and mathematical description of the real driving force of passive transport of drug molecules from supersaturated solutions." Mol. Pharm. (2016)