Application of MacroFLUX™ Apparatus for Screening Formulations before Bioequivalence Studies

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.

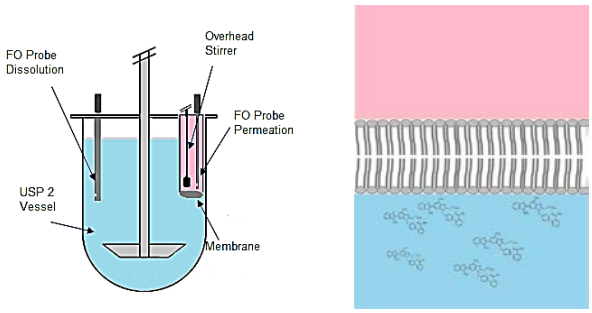
Materials and Methods

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 containing 15 mL of pH 7.4 (Prisma™ HT, Pion Inc.). The experiment began in 850 mL at pH 1.6 simulating gastric conditions. After 30 minutes, 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).

$$J = dm/(A*dt) \qquad (1)$$

A schematic of the experimental setup is depicted on Figure 1.

Figure 1. Schematic of MacroFLUX™ (Dissolution – Flux) device used in this study.

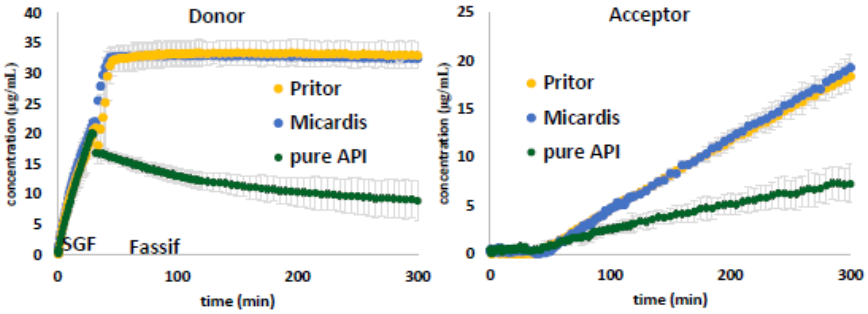


Results

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

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 conversion 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 (approximately 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/(cm^2*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.

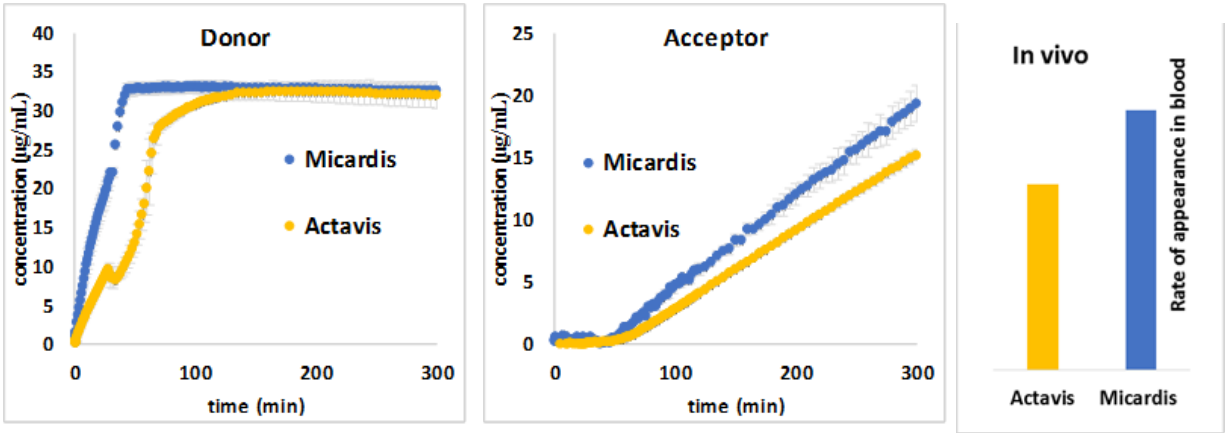
Figure 2. Dissolution profile (on the left) and appearance profile (on the right) of Telmisartan from Micardis and Pritor drug products and pure API.



II. Brand name compared to generic formulation containing different excipients

The dissolution and flux results of the brand name (Micardis) and generic (Actavis) Telmisartan 40 mg tablets were compared (Figure 3). Actavis showed slower-release kinetics than Micardis, though reached the same maximum concentration after 110 minutes. 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 appearance rate or the drug in blood from Actavis was 72% of the rate from Micardis.

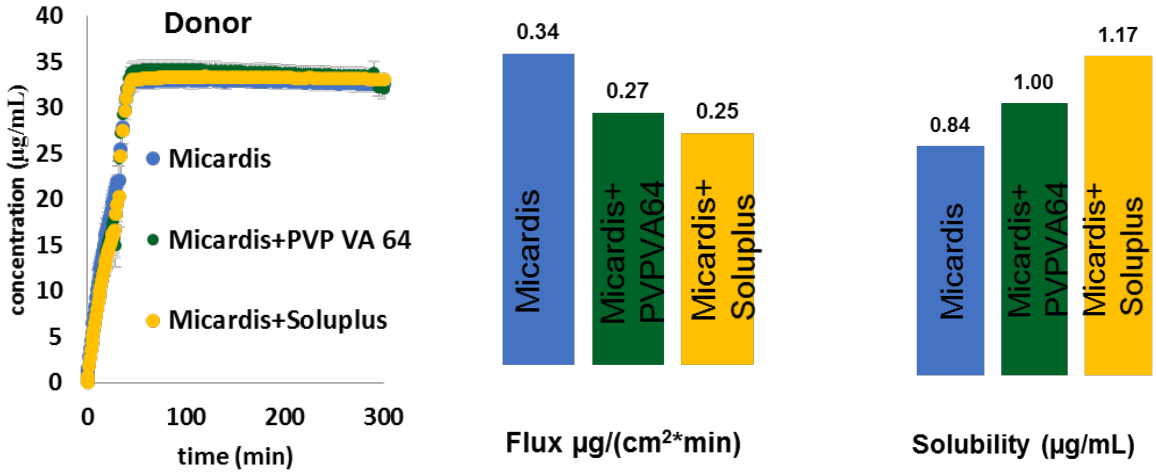
Figure 3. Dissolution profile (on the left), in vitro appearance profile (in the middle) and *in vivo* appearance rate presented as a ratio of C_{max} and T_{max} (on the right) of Telmisartan from Micardis and Actavis products.



III. Brand name with additional solubility modifier formulation additives

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 the 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 in corresponding media as shown in Figure 4.

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



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 emphasize 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 performance of the generic product was 71% of the brand *in vitro*, while 72 % *in vivo*, showing excellent *in vitro-in vivo* correlation.

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References

1. Public Assessment Report 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).