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Finding the right excipients for generic drug formulations – a retrospective study using *in vitro* dissolution-absorption tests

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PURPOSE

For generic formulation development, traditional (USP) dissolution tests provide primary input parameters for predicting *in vivo* performance of different drug formulations before conducting bioequivalence studies. Although USP dissolution tests are relatively simple to conduct for testing formulations, the *in vivo* predictive power of these tests is questionable[1]. Namely, 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 also on flux through the membrane.

OBJECTIVE(S)

The aim of this study was to represent how simultaneous dissolution-absorption studies using MacroFLUX™ apparatus can be used for comparing brand and generic formulations containing different excipients.

METHOD(S)

Absorption chamber for bioequivalence prediction ✓

USP 2 dissolution vessel for dissolution characterisation. ✓

Real time concentration monitoring in both compartments ✓

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

Brand and 4 generic formulations of Telmisartan, an antihypertensive drug, were tested using MacroFLUX™. Receiver chamber integrated with permeation membrane, overhead stirrer and fiber optic UV probe was inserted in the standard 900 mL vessel of USP 2 apparatus. A filter-supported artificial membrane with 3.8 cm^2 area was separating the dissolution (donor) compartment from the absorption compartment containing 13 mL of pH 7.4 buffer. Real time concentration monitoring in both dissolution and absorption chambers was enabled through fiber optic UV probes connected to the Rainbow Dynamic Dissolution Monitor instrument (Pion Inc).

RESULT(S)

I. MacroFLUX results for sorbitol containing formulations

Does same qualitative tablet composition mean same dissolution and absorption profile?

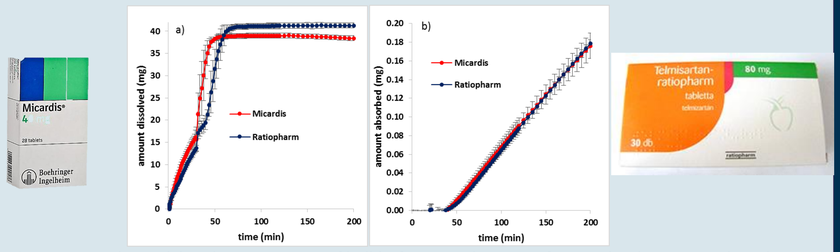

Figure 2. Dissolution (a) and appearance profile (b) of 40 mg telmisartan from sorbitol containing brand (Micardis) and sorbitol containing generic (Ratiopharm) formulations showing matching flux results for formulations with identical qualitative composition.

II. MacroFLUX results for lactose monohydrate containing formulations

Does changing one excipient make a difference in dissolution and absorption profile?

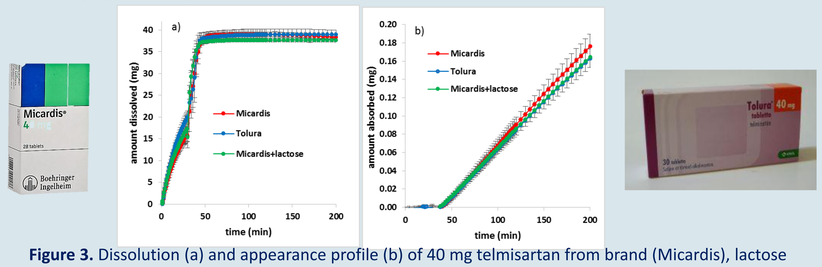

Figure 3. Dissolution (a) and appearance profile (b) of 40 mg telmisartan from brand (Micardis), lactose monohydrate containing generic formulation (Tolura), and Micardis in presence of additional lactose monohydrate showing the flux-decreasing effect of lactose monohydrate

III. MacroFLUX results for mannitol containing formulations

Does changing one or more excipients make a difference in dissolution and absorption profile?

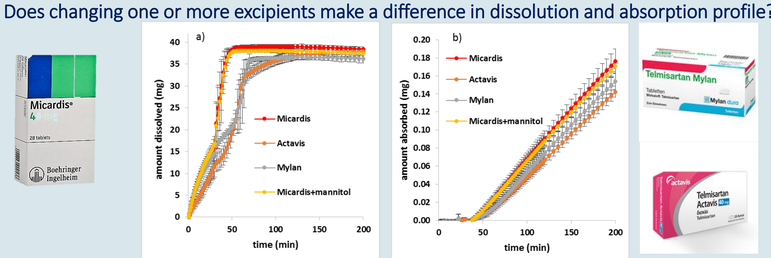

Figure 4. Dissolution (a) and appearance profile (b) of 40 mg telmisartan from sorbitol containing brand (Micardis), mannitol containing generic formulations (Actavis, Mylan) and Micardis in presence of additional mannitol showing the flux-decresing effect of mannitol

IN VIVO VS *IN VITRO* RESULTS

What can we predict based on *in vitro* results?

Name	Characteristic filler	Flux ratio (%)	Lower 90 % CI in %	Upper 90 % CI in %	Prediction based on *in vitro* result	*In vivo* result of bioequivalence study	***In vitro* prediction matches *in vivo* results**
Ratiopharm	Sorbitol	100.1	97.3	103	Going to be accepted	Accepted	✓
Tolura	Lactose monohydrate	91.4	87.3	95.8	Going to be accepted	Accepted	✓
Actavis	Mannitol	81.6	79.2	84.2	Borderline of acceptance	Borderline of acceptance	✓
Mylan	Mannitol	92.1	85.7	99.4	Going to be accepted	Accepted	✓

Table 1. *In vitro* flux ratios of generic formulations of telmisartan compared to brand name product and comparison of *in vivo* and *in vitro* results

CONCLUSION(S)

In contrast with traditional (USP) dissolution tests in case simultaneous dissolution-absorption studies the effect of formulation excipients on dissolution and also on membrane transport can be measured. This knowledge is essential for generic formulation development for finding the right additives to be able to meet the bioequivalence criteria.

REFERENCE

1. Buckley, S.T., Fischer, S.M., Fricker, G., Brandl, M., 2012. In vitro models to evaluate the permeability of poorly soluble drug entities: Challenges and perspectives. Eur. J. Pharm. Sci. 45, 235–250. doi:10.1016/j.ejps.2011.12.007

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