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Absorption Driven Drug Formulation through the example of Telmisartan

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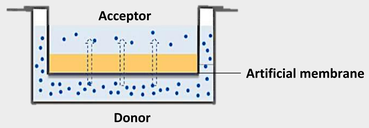
PURPOSE

The use of *in vitro* flux measurements in formulation development and bioequivalence prediction has been explored in a number of recent studies [1 - 4]. The benefits of such measurements are based on the fact that they capture the complex interplay between the effects of formulation ingredients on solubility, dissolution rate and permeability of an active pharmaceutical ingredient (API). The current work demonstrates a new aspect of generic formulation development called Absorption Driven Drug Formulation (ADDF) that investigates and considers the excipient effect on absorption from the excipient selection through the whole development process. ADDF utilizes permeability and flux assays in each development phase to be able to select the most advantageous excipients to enhance or hinder the absorption.

METHOD(S)

PAMPA assay

Each well of the top (acceptor) compartment of 96-well STIRWELL™ PAMPA sandwich was coated with 4 µL of n-dodecane. The resultant sandwich was incubated at 37°C for 30 min with the API in the donor phase with or without the excipient. Both compartments were stirred at 60 µm with Gut-Box™.

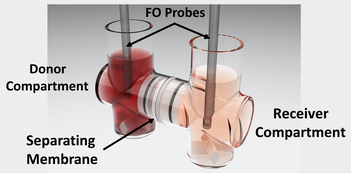


Formulation strategy

electrospinning (amorphization)

µFlux assay

Electrospun formulations of Telmisartan (TEL) were tested using MicroFLUX™ apparatus. Concentration in both chambers was monitored in real-time using in situ fiber optic dip probes connected to the Rainbow system (Pion Inc.). A PVDF membrane impregnated with 25 µL n-dodecane was applied to form a lipophilic barrier between the donor and the acceptor chamber.

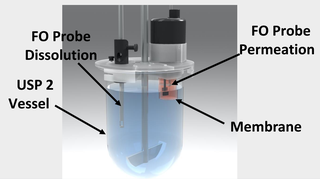


Preparation of final dosage form

Powder blending, tableting

MacroFlux assay

Final dosage forms of TEL were tested using MacroFLUX™ (Pion Inc.). The receiver chamber integrated with permeation membrane (same membrane as used in MicroFlux studies), overhead stirrer, and fiber optic UV probe was inserted in the standard 900 mL vessel of USP 2 apparatus (Erweka DT 126 Dissolution Tester).



RESULT(S)

Excipient selection

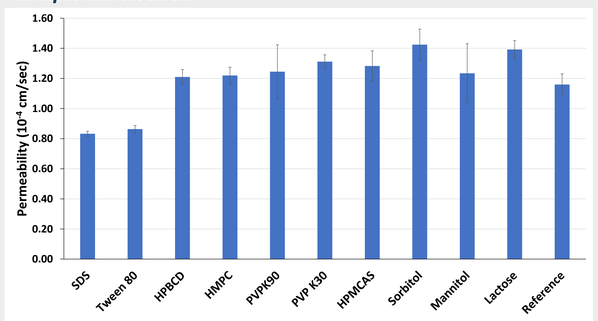


Figure 1. Permeability of TEL in FaSSIF full media with and without additives

The excipients of the available telmisartan formulations and widely used standard excipients were involved in the first API-excipient investigations. A 25% reduction in permeability was seen for the surfactants, while the polymers increased permeability by 5-10%. Mixed effects were experienced with fillers, where mannitol provided 15% lower permeability than the others.

Dissolution-permeation assay of pre-formulation with MicroFLUX apparatus

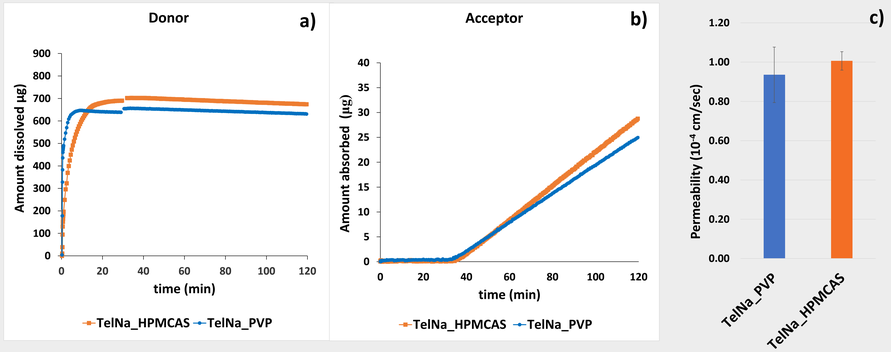


Figure 2. Dissolution in SGF (a), appearance profile (b) and permeability (c) of TEL pre-formulations

The tested pre-formulation samples confirmed that the selected polymers are suitable to maintain API supersaturation, however, no significant difference of permeability has been found between formulations of PVP and HPMC-AS.

Dissolution-permeation assay of final dosage forms with MacroFLUX apparatus

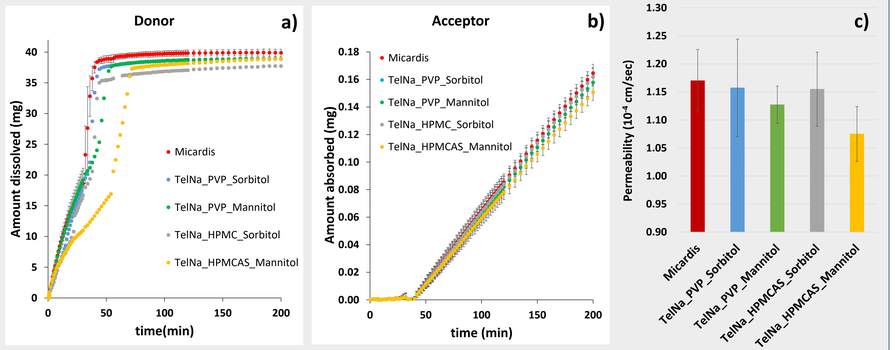


Figure 3. Dissolution in SGF (a) appearance profile (b) and permeability (c) of TEL formulations

To simulate the *in vivo* conditions, media change assay (SGF to FaSSIF) was carried out. In the case of all formulations, TEL started dissolving in the SGF stage of the procedure. During the first 30 minutes of the experiment, no flux across the membrane was detected because of the charged state of the API, while after media change TEL started to permeate through the membrane. The initial flux results showed a non-significant difference between Micardis (innovator product) and the developed formulations. In the case of HPMC-AS based formulations, the mannitol-containing ones performed more poorly (6% lower flux) compared to the sorbitol ones, in accordance with the expectations from the excipient selection study.

REFERENCE(S)

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4. Borbás E, et al. Mol. Pharmaceutics 2019, 16 (10): 4121.

CONCLUSION(S)

The described formulation development procedure demonstrated how excipients can be classified in the early stage of excipient selection and the most advantageous ones can be used in the later stages to ensure suitable behavior of the final product.

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