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In vitro dissolution-permeation study to characterize Itraconazole formulations: The effect of formulation additives, food and dose

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PURPOSE

For formulation development traditional (USP) dissolution tests have been used in the pharmaceutical industry 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 also on flux through the membrane.

OBJECTIVE(S)

The aim of this study was to investigate the effect of formulation additives, food and dose on the in vitro dissolution-permeation profile of Itraconazole (ITRA), and compare the results to *in vivo* data.

METHOD(S)

3 formulations of ITRA: Sporanox solution (100 mg ITRA, hydroxypropyl-beta-cyclodextrin (HPβCD) as additive), Sporanox capsule (100 mg ITRA, hydroxypropyl methylcellulose (HPMC 2910) as additive) and Lozanoc capsule (50 mg ITRA, hydroxypropyl methylcellulose-phtalate (HPMC-P) as additive) (Figure 1), were tested using BioFLUX™. Receiver chamber integrated with permeation membrane, overhead stirrer and fiber optic UV probe was inserted in the short 250 - 500 mL vessel of USP 2 apparatus (Figure 2). A filter-supported artificial membrane (Double-Sink™ PAMPA) with 3.69 cm^2 area was separating the dissolution compartment from the receiver compartment containing 20 mL of Acceptor Sink Buffer at pH 7.4 (ASB, Pion Inc). Real time concentration monitoring in both dissolution and absorption chambers was enabled through fiber optic UV probes (Pion Inc).

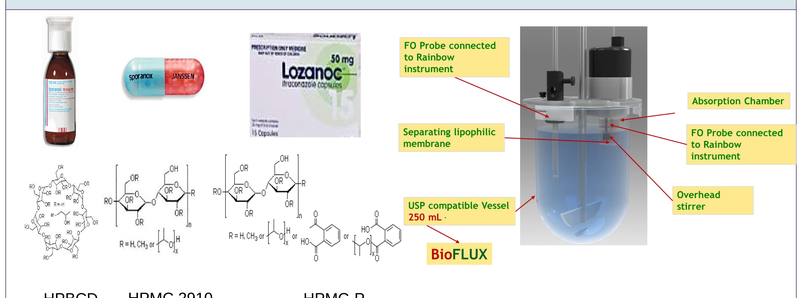

Figure 1. Itraconazole containing formulations and their characteristic formulation additives

Figure 2. A fragment of the BioFLUX apparatus showing a pair of the donor and receiver chambers

RESULT(S)

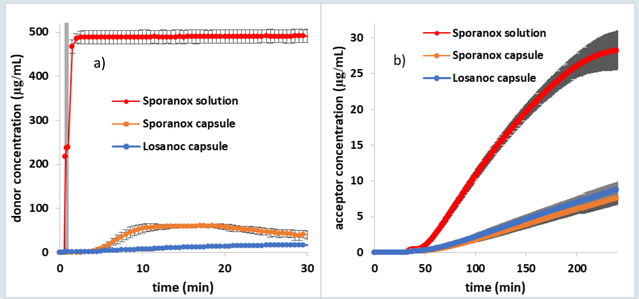

Figure 3. Dissolution (a) and appearance profile (b) of ITRA from Sporanox solution (100 mg), Sporanox capsule (100 mg) and Lozanoc capsule (50 mg) in Fasted state

For simulating the fasted state media change from simulated gastric fluid (SGF) to fasted state simulated intestinal fluid (FaSSIF) was carried out after 30 minutes. During this protocol in the case of Sporanox solution Itraconazole stayed fully dissolved in SGF (400 µg/mL) (Figure 3), while changing the pH triggered its immediate precipitation. In the case of Sporanox capsule the API created a supersaturated solution and already started precipitating in SGF (Figure 3). Lozanoc formulation, containing HPMC-P, a polymer with pH dependent dissolution, only started releasing the API in a significant amount after media change was conducted.

Although the dissolution and precipitation kinetics of the two capsules were quite different, the flux results obtained showed no significant difference (Figure 3). These flux results were found to be in agreement with *in vivo* c_{max} results [2]. The flux of ITRA from Sporanox solution was found to be ca 4 times higher than from any of the capsule forms. This is in agreement with the statement of FDA, that the bioavailability of ITRA is greater from Sporanox solution, therefore the solution and the capsule are not bioequivalent products [3].

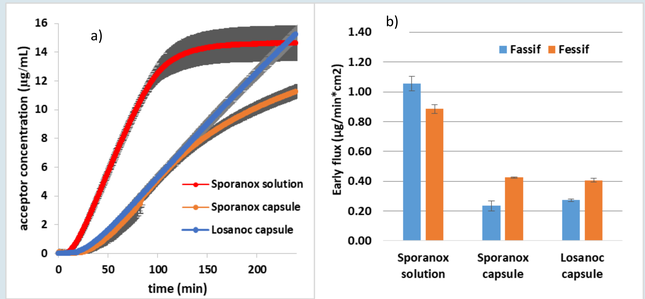

Figure 4. Appearance profile (a) of ITRA from Sporanox solution (100 mg), Sporanox capsule (100 mg) and Lozanoc capsule (50 mg) in Fed state; Summery of fluxes in fasted and fed state(b)

For simulating the conditions after food intake in the gastrointestinal tract, fed state simulated intestinal fluid was used in the donor compartment. While in the case of capsules similar flux results were obtained (Figure 4a), which predict well the similar *in vivo* c_{max} values [2]; the flux result of the API from its cyclodextrin-based solution was found superior to the capsule formulations (Figure 4b).

Table 1. Comparison of *in vivo* and *in vitro* results

Name	Characteristic formulation additive	Food effect prediction based on in vitro flux result	In vivo food effect	In vitro prediction matches in vivo results
Sporanox solution(100 mg)	HPβCD	Negative	Negative	✓
Sporanox capsule(100 mg)	HPMC 2910	Positive	Positive	✓
Lozanoc capsule (50 mg)	HPMC-P	Reduced	Reduced or no food effect	✓

CONCLUSION(S)

The dissolution and flux results of three marketed Itraconazole formulations were compared in fasted and fed state to each other and to the *in vivo* study results published by the manufacturers. The *in vitro* test was found to be sensitive enough to show differences between formulations caused by the use of different excipients and produce the same rank order the formulations in fasted and fed state as *in vivo* results do. Interestingly in the case of Sporanox solution negative while in case of Sporanox capsule positive food effect was observed (Table 1). These results are in agreement with *in vivo* data and the recommendation for taking the solution before and the capsule after meal.

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