Small Scale Biphasic Dissolution Testing of Itraconazole (ITZ) Formulations with a pH Shift.

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PURPOSE

The use of an organic layer, such as octanol or decanol, on top of an aqueous layer can be used to incorporate an absorption step into a dissolution experiment. Unionised drug can partition from the aqueous layer into the organic layer, thus mimicking the absorption step in the small intestine. This allows the dynamic dissolution process incorporating dissolution, supersaturation, precipitation and absorption to be observed simultaneously.

The aim of this study was to assess the release of five formulations of the weakly basic drug itraconazole (ITZ) (pKa = 3.7)[1] using a biphasic assay on the inForm (Pion Inc.) platform. As supersaturation of weakly basic drugs can be induced by changes in pH across the gastrointestinal tract, a pH shift from an acidic gastric environment to an almost neutral intestinal environment was incorporated into the method. The effect of an elevated gastric pH on itraconazole concentrations was also evaluated.

METHOD(S).

- Stirring speed 100 rpm
- Temperature 37°C
- Initially, samples (all equivalent to a dose of 5 mg ITZ API) were introduced into an acetate phosphate buffer at pH 2 or pH 4.5 to simulate normal and elevated gastric pH respectively

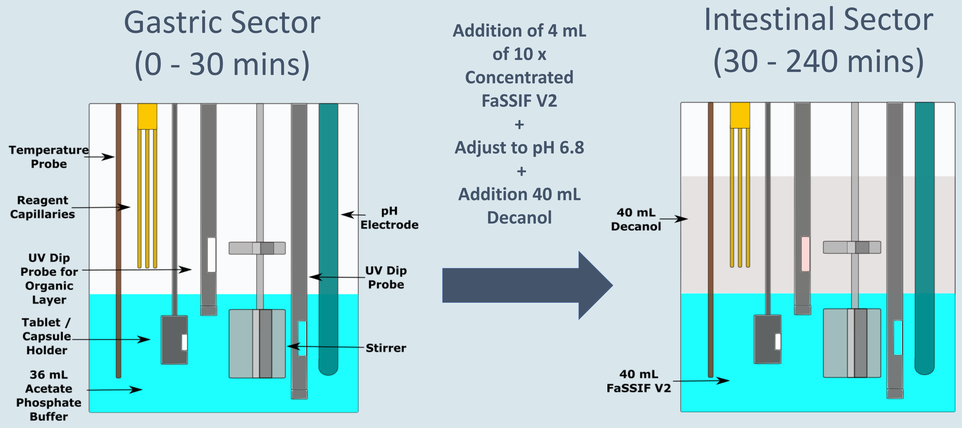
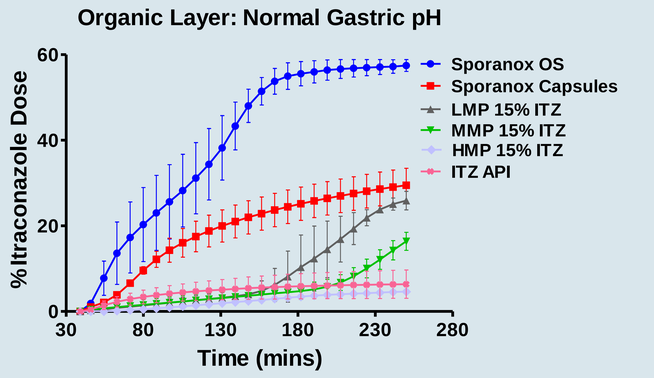


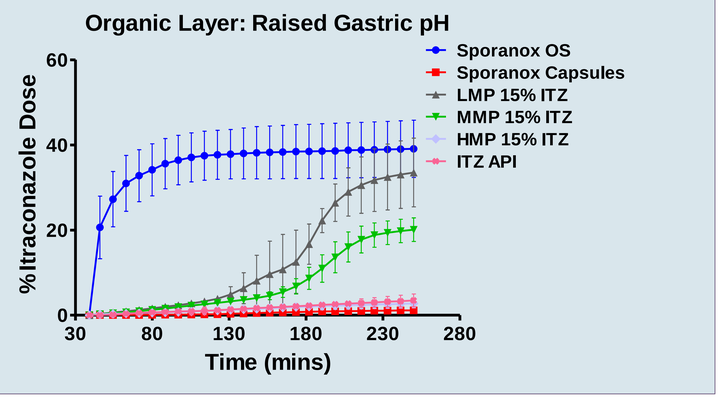
Table 1. Overview of Itraconazole Formulations.

Formulation Name	Formulation Design / Release Mechanism
Sporanox Oral Solution (OS)	Hydroxypropyl-β-cyclodextrin acts as a solubilizer of ITZ [2]
Sporanox Capsules	Amorphous dispersion of ITZ and HPMC (hydroxypropylmethylcellulose) on surface of inert sugar cores [2]
LMP (Low Acetate Content) HPMCAS (Hypromellose Acetate Succinate)	Polymer soluble above pH 5.5
MMP (Medium Acetate Content) HPMCAS	Polymer soluble above pH 6.0
HMP (High Acetate Content) HPMCAS	Polymer soluble above pH 6.5

RESULT(S)

- ITZ concentrations in the organic phase were significantly higher (two tailed t-test P<0.05) for the Sporanox OS compared to the Sporanox Capsules. Greater drug exposure is observed *in vivo* for the OS versus the capsule when the same dose of drug is administered.[3]
- Release from the HPMCAS amorphous solid dispersions (ASDs) was controlled by the pH at which the polymers dissolve. The dissolution results from the HPMCAS ASDs showed greatest release from the LMP grade HPMCAS and the lowest release from the HMP grade HPMCAS.
- A decrease in ITZ concentrations at elevated gastric pH for Sporanox OS was likely due to precipitation in the gastric sector as observed by UV blackout in the aqueous layer.
- ITZ concentrations were markedly decreased for Sporanox capsules at elevated gastric pH compared to normal gastric pH (29.50% ± 3.96 vs 1.14% ± 0.61 at t = 240 mins). Lim *et al.* found a 52.9% and a 51.1% decrease in Cmax and AUC respectively after Sporanox capsules were administered with famotidine compared to Sporanox alone.[4]





CONCLUSION(S)

- This small-scale dissolution test acts as a convenient method to screen different prospective formulations.
- Differences in bioavailability and issues associated with raised gastric pH were identified using this setup.
- While these clinically significant effects are overestimated relative to *in vivo,* the results from this small scale dissolution test serve as an early warning indicating that further investigation is warranted.

REFERENCES:

1. Locher K, Borghardt JM, Frank KJ, Kloft C, Wagner KG. Evolution of a mini-scale biphasic dissolution model: Impact of model parameters on partitioning of dissolved API and modelling of in vivo-relevant kinetics. Eur J Pharm Biopharm [Internet]. 2016;105(Supplement C):166–75.
2. Peeters J, Neeskens P, Tollenaere JP, Van Remoortere P, Brewster ME. Characterization of the interaction of 2-hydroxypropyl-β-cyclodextrin With itraconazole at pH 2, 4, and 7. J Pharm Sci. 2002;91(6):1414–22.
3. Brouwers J, Geboers S, Mols R, Tack J, Augustijns P. Gastrointestinal behavior of itraconazole in humans – Part 1: Supersaturation from a solid dispersion and a cyclodextrin-based solution. Int J Pharm [Internet]. 2017;525(1):211–7.
4. Lim SG, Sawyerr AM, Hudson M, Sercombe J, Pounder RE. Short report: the absorption of fluconazole and itraconazole under conditions of low intragastric acidity. Aliment Pharmacol Ther. 1993;7(3):317–21.

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