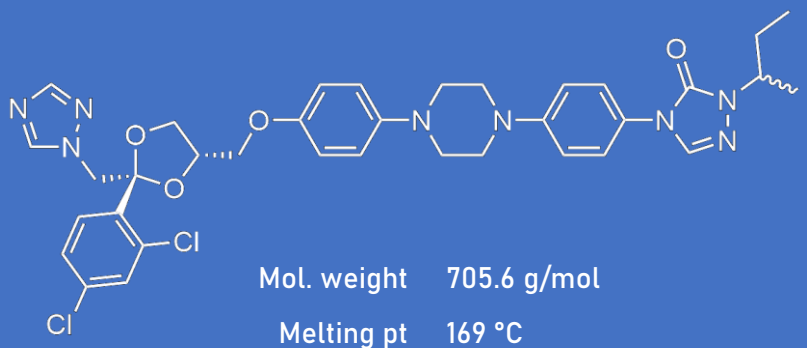
Designing a high-payload liquid formulation for the poorly water-soluble compound Itraconazole using SeraNovo's Deep Eutectic Solvent technology

Itraconazole

The antimycotic compound itraconazole is extremely poorly water-soluble, which is mainly driven by its high lipophilicity. The oral solution as developed by the originator (Sporanox®, Janssen Pharmaceutica) contains hydroxypropyl-β-cyclodextrin (40%), propylene glycol and hydrochloric acid (pH 2) as solubilising excipients. In spite of the cocktail of solubilisation strategies employed in this product (cyclodextrin complexation, cosolvency and pH-adjustment), the total itraconazole concentration is only 10 mg/ml. In general, developing a high-payload solubilised formulation is difficult, given itraconazole's low solubility in excipients.



Mol. weight	705.6 g/mol
Melting pt	169 °C
logP	6.2
pKa	2.0 (b), 3.7 (b)

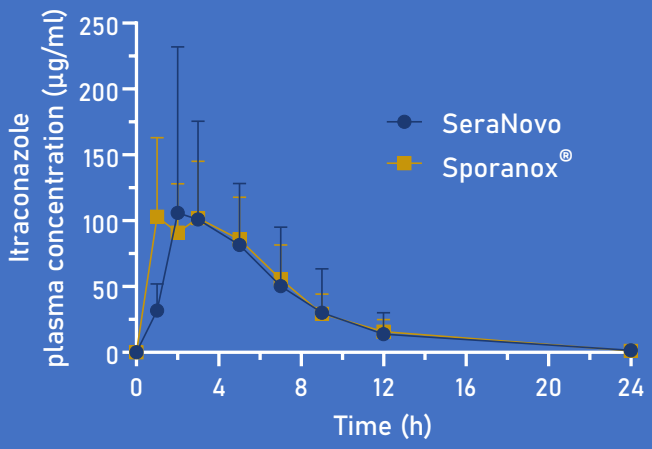
Itraconazole solubility in water and a range of solubilising excipients

Solvent	Solubility (mg/ml)
Water pH 7	0.000004
PEG400	2.1
Propylene glycol	0.2
Transcutol® P	5.2
Tween® 20	1.2
Poloxamer 188	4.5
Corn oil	0.2

Designing a high-payload liquid formulation

Using our deep eutectic solvent technology, we have designed a liquid formulation that contains 140 mg/ml itraconazole. This formulation was based on two small organic molecules that served to form the deep eutectic solvent with itraconazole, and one polymer that acted as a precipitation inhibitor.

The loading level in our formulation is 14-fold higher than that in the Sporanox® oral solution and two orders of magnitude higher than the solvent capacity in most traditional solubilising excipients (see table above). Oral gavage administration of our formulation to rats resulted in equivalent bioavailability to the Sporanox® oral solution.



Itraconazole plasma concentration vs time profiles Rats, n=3 (mean + standard deviation), 1.25 mg dose

Conclusion

Harnessing the potential of our our deep eutectic solvent platform, we have designed a formulation that has equivalent biopharmaceutical performance but 14-fold higher itraconazole loading than the marketed oral solution Sporanox®. These findings illustrate the potential of our technology for the formulation of lipophilic, poorly soluble weak bases.

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