INTERPLAY BETWEEN KETOCONAZOLE COCRystal SUPERSATURATION AND TRANS-MEMBRANE FLUX

INTRODUCTION

It was demonstrated recently that cocrystals of ketoconazole could lead to enhanced aqueous solubility. However, the absorption of the drug from gastro-intestinal tract (GIT) depends also on dissolution rate and permeability that could be altered by cocrystal constituents. This study was aimed at investigating how cocrystal coformers affect the trans-membrane flux in the in vivo relevant dissolution – permeability setup.

MATERIALS AND METHODS

API: Ketoconazole

Cocrystals

Adipic Acid

Sucinic Acid

Fumaric Acid

Concentration of KTZ released from KTZ-AA and KTZ-SA cocrystals was about 20% higher than one from KTZ powder or KTZ-FA cocrystal.

RESULTS AND DISCUSSION

Dissolution and Flux of KTZ-CC in FeSSIF

Dissolution of KTZ-CC (Figure 3, a) was studied in parallel with pure KTZ and physical mixtures of KTZ and coformers (Figure 3, b).

All three studied cocrystals sustained supersaturated state of KTZ in FeSSIF media. It is noted that extent (duration) of supersaturation depended on the stirring speed. With increased stirring speed precipitation occurred faster. Supersaturation of KTZ-CC led to higher flux of KTZ as evident from the initial slopes of concentration-time profile of KTZ in the receiver chambers of µFLUX system (Figure 4).

There was no increase in the flux from physical mixtures of KTZ and coformers.

Dissolution and Flux of KTZ-CC in FeSSIF

Figure 5 below is analogous to Figure 3, but for full FeSSIF media. There was no precipitation observed within first 250 min of dissolution process. It has to be noted that solubility of KTZ powder increased ~ 4 times comparing to the blank media.

Initial flux values obtained for different forms of KTZ in the both studied media are combined on Figure 7.

CONCLUSIONS

• Initial flux of KTZ was only about 1.6 times higher for co-crystals than for pure KTZ in FeSSIF, despite of up to 7 times difference in initial concentration. There was no significant difference between flux values from different co-crystals.

• KTZ cocrystals form supersaturated solutions in aqueous buffer at pH 5.0 with kinetic solubility up to 7 times higher than equilibrium solubility of KTZ.

• Physical mixtures of KTZ and co-formers led to faster dissolution rates, but no supersaturation. The effect requires additional investigation and could be due to the in situ cocrystal formation or to other solution phase interactions.

• The extent of supersaturation depends among other factors on the concentration of KTZ, rate at which supersaturation is generated, and stirring speed.

• In full FeSSIF medium KTZ-AA and KTZ-SA cocrystals seemed to reach ~30% higher concentration than KTZ or KT-FA cocrystal. However, experimental errors have to be confirmed to assess the significance of this observation.

• Flux of KTZ-SA and KTZ-FA cocrystals was slightly higher than other forms, but this has to be confirmed by more measurements.

• FA coformer has its own UV spectrum that could potentially interfere with results and its influence has to be further studied.

REFERENCES


