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Study of Danazol Cocrystal Using Trans-Membrane Flux Measurements

O.Tsinman[1], K.Tsinman[1]*, R. Lingamaneni[1], Y. Chen[2], and N. Rodríguez-Hornedo[2]
*presenting author; ktsinman@pion-inc.com
[1]Pion Inc., 10 Cook Str., Billerica, Ma 01821, USA; [2]University of Michigan, Department of Pharmaceutical Sciences, 428 Church St., Ann Arbor, MI 49109, USA

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PURPOSE

Pharmaceutical cocrystals have emerged as one of the potential strategies to provide supersaturation for poorly soluble drugs and as a result to improve their oral absorption and bioavailability[1]. Flux across a membrane provides a better understanding of passive absorption of solutes from supersaturated solutions, since solute activity rather than concentration is the driving force[2]. This study was aimed at investigating how supersaturation of model drug danazol released from its cocrystal in biorelevant media affects the trans-membrane flux of this low soluble compound.

METHOD

Danazol powder (DNZ), DNZ cocrystal (DNZ-CC) with 4-hydroxybenzoic acid (HBA, coformer) prepared by reaction crystallization method[3] and DNZ/HBA physical mixture (DNZ+HBA) were used in this study. Ionization constant (pK_a) of HBA was measured using UV titration (Pulse™, Pion Inc., Figure 2).

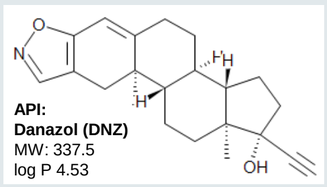

Figure 1. Danazol (API) and 4-hydroxybenzoic acid were selected for this study.

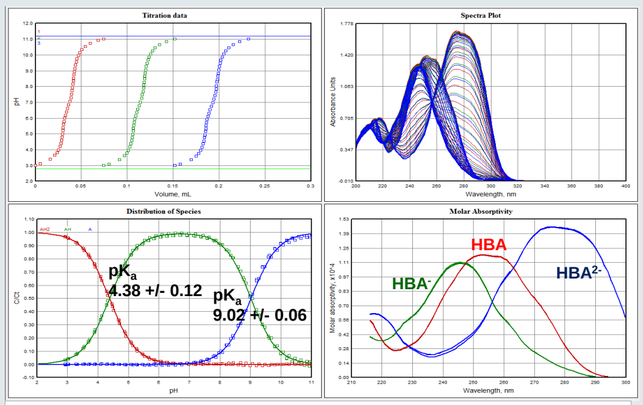

Figure 2. A group analysis of 3 UV titrations that determined pK_a values for HBA

All solid forms were introduced as powders to the donor compartment of µFLUX apparatus (Pion Inc., Figure 3) containing either FeSSIF media or corresponding aqueous buffer ($FeSSIF_{blank}$, pH 5.0). The receiver solution contained acceptor sink buffer (ASB, pH 7.4). Donor and receiver chambers were separated by lipophilic artificial membrane (Double-Sink™ PAMPA type, Pion Inc.). The real time concentration monitoring was provided by using µDISS Profiler (Pion Inc.).

RESULTS

COMPARATIVE FLUX of DANAZOL from DRUG and COCRYSTAL

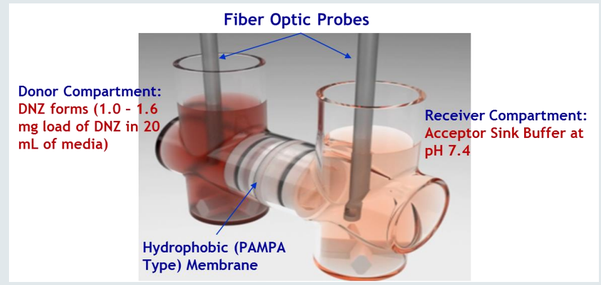

Figure 3. Schematic of µFLUX setup with some details of the assay setup.

In FeSSIF media concentration of DNZ released from the DNZ-CC reached c_{max}=46.1±1.8 µg/mL and sustained ~ 1.8 times higher than concentration of DNZ released from either a DNZ (c_{max}=26.2±1.2 µg/mL) or DNZ+HBA (c_{max}=24.9±0.4 µg/mL) through the duration of the experiment (Figure 4, a). This higher concentration in the donor compartment translated to a similar increase in flux of DNZ from DNZ-CC 0.41±0.04 µg $min^{-1}cm^{-2}$ versus 0.24±0.05 µg $min^{-1}cm^{-2}$ (DNZ) and 0.26±0.04 µg $min^{-1}cm^{-2}$ (DNZ+HBA). The flux for all solid forms was nearly constant for the duration of the experiment (Figure 5, a).

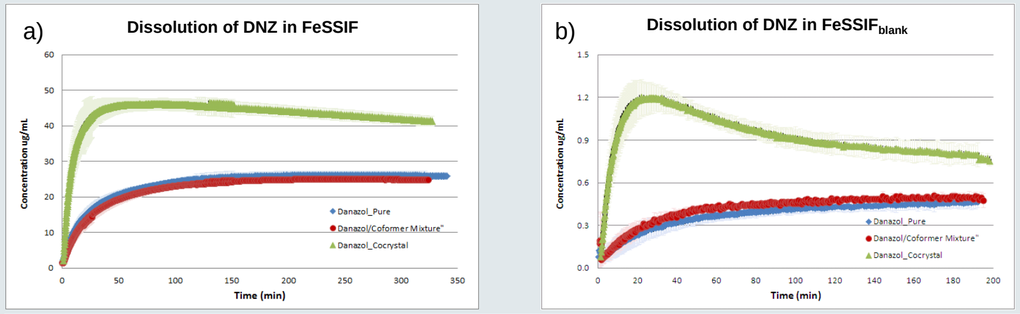

Figure 4. Dissolution profile of different forms of DNZ in full FeSSIF media (a) and in FeSSIF blank media (b)measured in the donor compartments of µFLUX system.

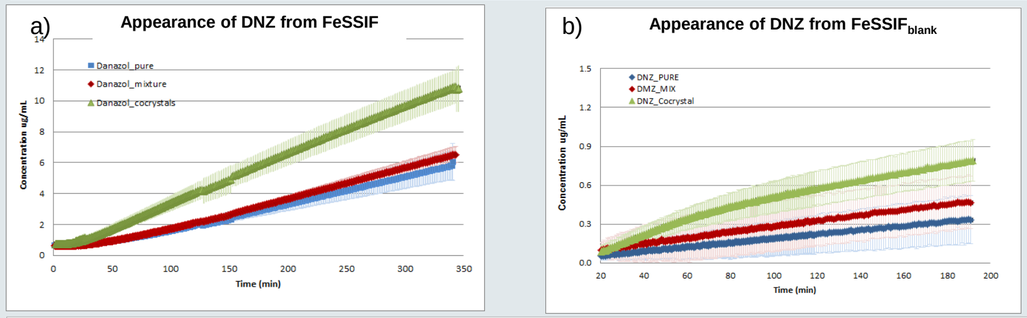

Figure 5. Appearance profile of DNZ in the receiver compartments of µFLUX system corresponding to donors presented on Figure 4.

In $FeSSIF_{blank}$ media DNZ-CC produced a brief supersaturation period, but with c_{max} reaching only 1.4±0.4 µg/mL. DNZ and DNZ+HBA showed no signs of supersaturation in the donor chamber with similar c_{max} values of 0.47±0.03 µg/mL for DNZ and 0.52±0.02 µg/mL for DNZ+HBA (Figure 4, b). The flux for these solid forms was unchanged for the duration of the experiment 0.021±0.010 µg $min^{-1}cm^{-2}$ (DNZ) and 0.028±0.003 µg $min^{-1}cm^{-2}$ (DNZ+HBA) while for DNZ-CC it decreased from 0.077±0.021 µg $min^{-1}cm^{-2}$ (30 – 60 min) to 0.039±0.006 µg $min^{-1}cm^{-2}$ (after 120 min) reflecting DNZ precipitation in the donor (Figure 5, b).

RESULTS

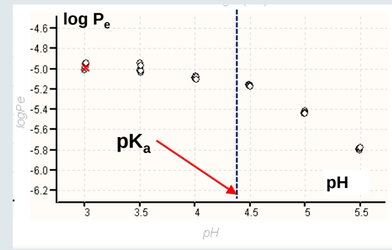

Figure 6. Logarithm permeability versus pH profile of HBA in $FeSSIF_{blank}$ buffer. Leveling off at the low pH is in agreement with measured pK_a value 4.38 (Figure 2).

Table 1. Permeability of HBA in different media

Media	pH	P_e (10^{-6} cm/s)	SD
$FeSSIF_{Blank}$	5.0	3.0	0.2
FeSSIF	5.0	2.0	0.1

It is interesting to note that HBA was also penetrating to receiver chamber (Figure 6, Table 1) but with rates ~ 20 - 50 times slower for FeSSIF media and 4 – 10 times slower for $FeSSIF_{blank}$ compared to DNZ (Figure 7).
Both fluxes for DNZ and HBA could be measured in parallel using dual component analysis implemented in Au PRO software (Version 5.1, Pion Inc.). The results are presented on Figure 7.

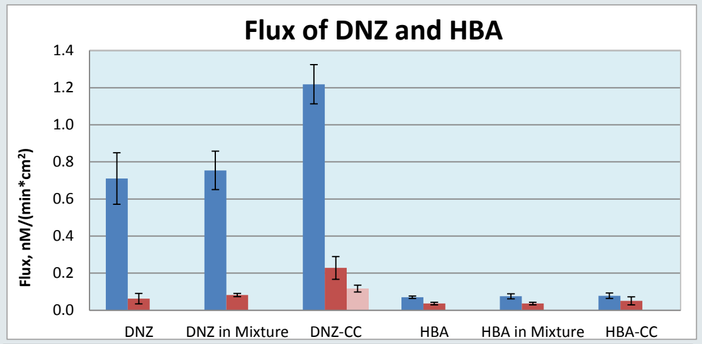

Figure 7. Flux values (in Mole related weight units) of DNZ and HBA introduced as different forms in donor having FeSSIF (blue bars) or $FeSSIF_{blank}$ (brown bars) media. Flux of DNZ from cocrystal form was decreasing to the value indicated by the pink bar.

CONCLUSION

Cocrystals of DNZ form supersaturated solutions in FeSSIF media with concentration being up to 1.8 times higher than the solubility of DNZ in the same media. Monitoring concentration in the receiver compartment revealed similar increase in flux confirming higher activity of DNZ and predicting potential increase in bioavailability of DNZ released from cocrystal.

REFERENCES

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