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Degree and Extend of Supersaturation of Amorphous Pharmaceuticals and Their Flux Lipophilic Membrane

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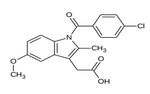
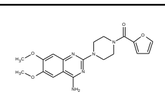
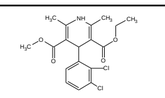
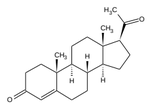
PURPOSE

Amorphous Solid Dispersions (ASD) of low soluble drugs has become one of the favorite technologies in attempt for improving gastro-intestinal (GIT) absorption and as a result bioavailability of insoluble compounds. The goal of this study was to apply *in situ* concentration monitoring for quick assessment of degree and extent of supersaturation that can be achieved by amorphization of the drug. In addition the comparison of the flux through artificial lipophilic membrane from drug loaded below and above their amorphous solubility threshold was investigated.

METHOD

Indomethacin (IND, weak acid), prazosin hydrochloride (PRZ, HCl salt of a weak base), felodipine (FLD, neutral) and progesterone (PGN, neutral) were selected as model drugs. The *in situ* concentrations were determined at ambient temperature at various pH values by using µDISS Profiler™ (Pion Inc). Amorphous solubility of the model compounds were measured using solvent shift method [1]. The extent of supersaturation was studied by *in situ* concentration monitoring at the drug loads below, at, and above their amorphous solubility.The flux through GIT mimicking membranes was studied using µFLUX apparatus (Pion Inc.) Precipitation kinetic parameters were determined by fitting concentration time profile to the empirical model where precipitation rate was proportional to the degree of supersaturation. Zero Intercept Method (ZIM) [2] was used to recognize spectroscopic changes due to liquid-liquid phase separation (LLPS) or spontaneous nanoparticle formation.

Table 1. Model compounds used in this study

Compound	Structure	MW	pK_a	Log P	T_m, ºC
Indomethacin (IND)		357.8	4.45(A)	3.5	161
Prazosin Hydrochloride (PRZ)		383.4	8.3(B)	1.2	279
Felodipine (FLD)		384.3	NA	5.6	147
Progesterone (PGN)		314.5	NA	3.5	121

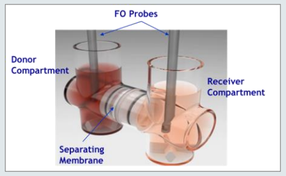


Figure 1. A schematic of the µFLUX apparatus showing a pair of the donor and receiver chambers. FO probes attached to the µDISS Profiler monitor concentrations in the donor (left) and receiver (right) compartments. The chambers can be separated by artificial, cell-based, size exclusion, or other types of membranes mounted in the Membrane Holder.

RESULTS

Amorphous solubility of IND at pH 2.0 was 26.8 ± 0.7 µg/mL (Figure 2) while it's equilibrium solubility determined from the powder dissolution experiment was ~ 1 µg/mL. Precipitation began after about 20 min and the induction time did not depend on the load. The rate of precipitation, however, was proportional to the degree of supersaturation (Figure 3).

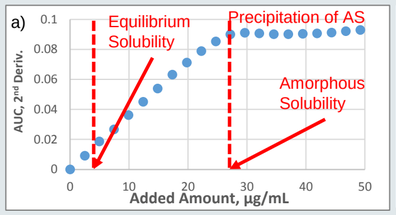


Figure 2. Derivative absorbance versus amount of added IND: area under 2nd derivative curve (a); value at one of the ZIM points (b).

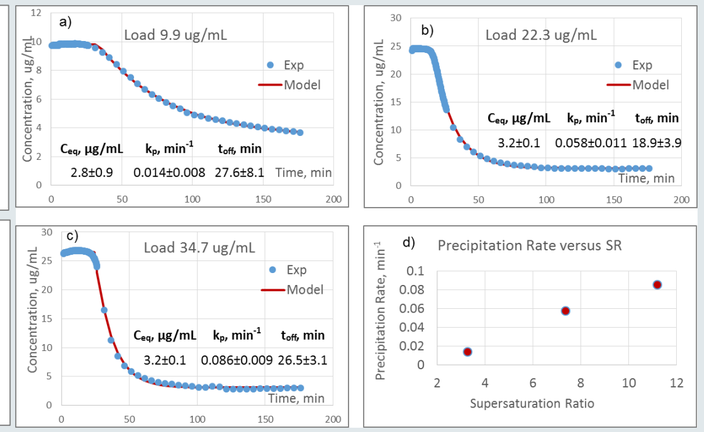


Figure 3. Precipitation kinetic modelling for different loads of IND (a – c). Dependence of the precipitation rate on the supersaturation ratio (d).

PRZ demonstrated very peculiar solubility-pH behavior where its HCl salt solubility at pH 1.2 was lower than amorphous solubility of free base at pH 6.5. The ZIM analysis indicated that at pH 1.2 after exceeding ~ 40 µg/mL a new phase was formed in the solution of PRZ while its standard curve remained linear until ~ 80 µg/mL. Amorphous solubility of FLD 8.2±0.8 µg/mL determined by the ZIM analysis was close to one reported earlier [3] (Figure 4). Spectral shape comparison showed that after reaching amorphous solubility a **new phase** was formed with absorbance at ZIM points increasing linearly with concentration up to 20 µg/mL (Figure 4, b). Crystalline solubility of FLD was reported to be ~ 1.1 µg/mL [3] and confirmed during this study (Figure 5).

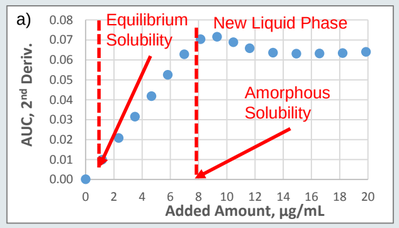


Figure 4. Derivative spectroscopy analysis for serial addition of concentrated FLD stock to pH 6.5 buffer. After reaching its amorphous solubility (a) ZIM method indicated new absorbing phase forming (b).

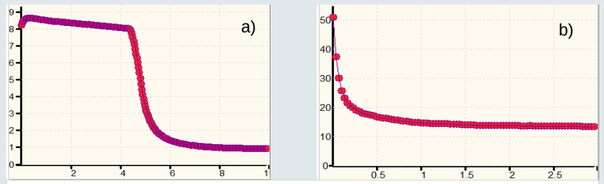


Figure 5. Concentration (µg/mL) versus time (hours) monitoring of FLD (a) and PGN (b)

Table 2. Amorphous (kinetic) and equilibrium solubility for studied compounds.

Compound	pH	Am. Sol. µg/mL	Eq. Sol. µg/mL
IND	2.0	26.8±0.7	0.9±0.2*
PRZ	8.5	208**	5.8±0.5
FLD	6.5	8.2±0.8	0.9±0.1
PGN	6.5	59.0±3.0	12.2±1.0

*Equilibrium solubility determined using precipitation monitoring was 3.1 µg/mL (Fig. 3) which was higher than one measured by powder dissolution.
**Only one replicate was stable up to this concentration.

RESULTS

Flux experiments conducted at various loads of FLD in the donor compartment showed a linear changes in flux at the loads below amorphous solubility. However, at the load approximately two times higher than amorphous solubility of FLD the increase of flux was still ~1.3 times comparing to the flux at amorphous solubility. Figures 6 and 7 below show flux – load dependency for FLD and PRZ respectively.. The dashed line line indicates expected values if flux kept being proportional to the load.

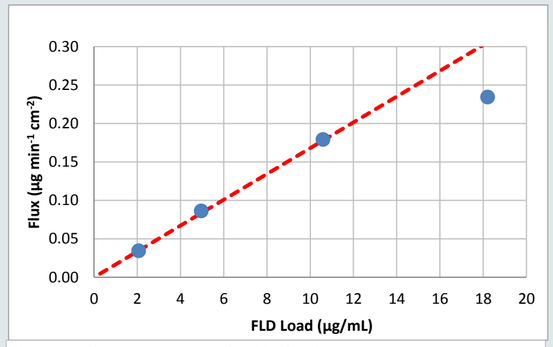


Figure 6. Flux of FLD versus load in the donor.

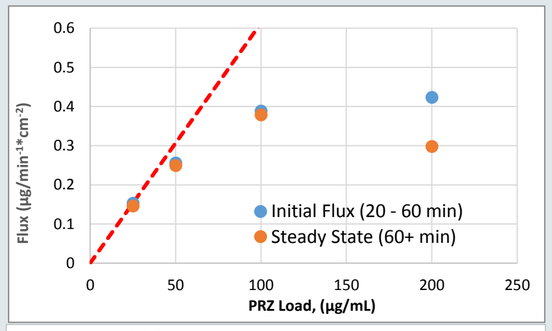


Figure 7. Flux of PRZ versus load in the donor

CONCLUSION

The data suggested that for IND the extent of supersaturation did not depend on the supersaturation ratio.

PRZ precipitation behavior was counterintuitive showing lower solubility of the HCl salt than amorphous solubility of free base and required additional investigation.

The flux experiments using lipophilic membrane showed that FLD flux could increase even after its load exceeded amorphous solubility although this increase was not linear in respect to the loads above amorphous solubility.

REFERENCES

1. Eardenbrugh BV, et al. Classification of the Crystallization Behavior of Amorphous Active Pharmaceutical Ingredients in Aqueous Environments. Pharm. Res. 2014, 31(4), 969-82.
2. Tsinman K, et al. Comparison of Naproxen Release from Nano- and Micro-Suspensions with Its Dissolution from Untreated and Micronized Powder. Poster presented at AAPS Annual Meeting and Exposition. October 14 -18, 2012, Chicago, IL.
3. Shweta A, et al. Impact of Solubilizing Additives on Supersaturation and Membrane Transport of Drugs. Pharm Res. 2015, 32: 3350-3364