PHASE BEHAVIOR AND TRANSFORMATION KINETICS OF A POORLY WATER SOLUBLE WEAKLY BASIC DRUG UPON TRANSIT FROM LOW TO HIGH pH CONDITIONS

M1330-10-074

Tu V. Duong[1], David B. Turner[2], Lynne S. Taylor[1]

[1]Purdue University, College of Pharmacy, West Lafayette, Indiana 47907, United States

[2]Certara UK Limited, Simcyp Division, Sheffield, S1 2BJ, United Kingdom

CONTACT INFORMATION: vduong@purdue.edu

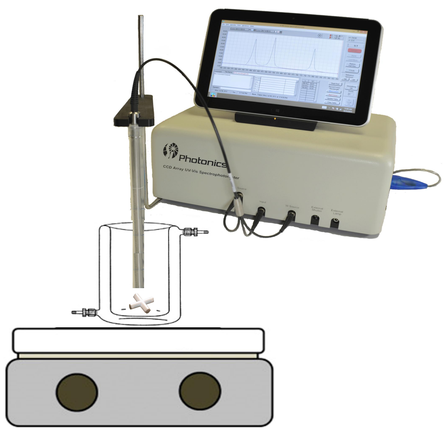
aaps PharmSci 360 ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

PURPOSE

- Weakly basic compounds, which account for nearly 75% of marketed drugs, have an inherent tendency to undergo supersaturation *in vivo* upon transit from stomach to intestine.
- Phase behavior of a given compound can currently only be experimentally determined.
- We design *in vitro* experiments to define phase diagram of a model, poorly water soluble compound, posaconazole (PCZ), and evaluate its phase behavior and transformation kinetics.

METHODS

- Crystalline solubility: shake flask approach.
- Amorphous solubility: ultraviolet (UV) extinction method.
- Induction time: monitor the concentration and turbidity of a solution as a function of time using an *in situ* UV probe.



RESULTS

I. PHASE DIAGRAM

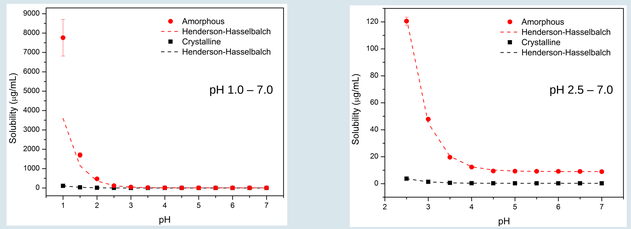


Figure 1. pH-solubility phase diagram of PCZ in phosphate buffer.

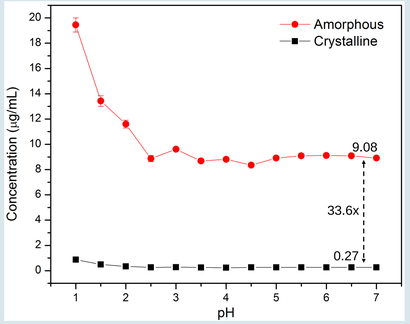


Figure 2. Concentration of unionized form as a function of pH comparing crystalline and amorphous forms for PCZ.

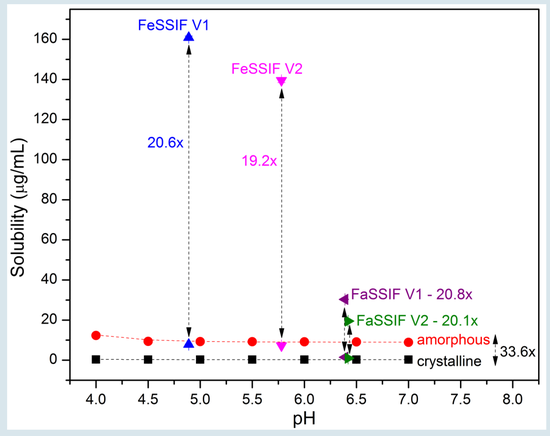


Figure 3. Modified pH-solubility phase diagram of PCZ.

II. INDUCTION TIME

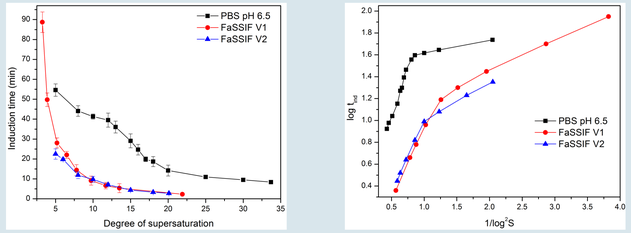


Figure 4. Nucleation induction time of PCZ as a function of supersaturation in phosphate buffer and biorelevant media.

III. MEDIUM COMPOSITION

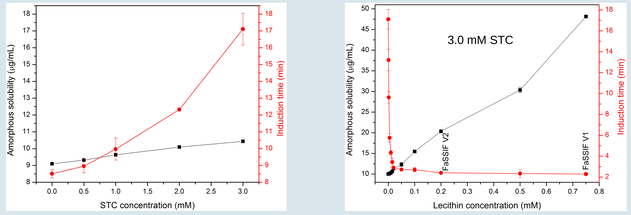


Figure 5. Influence of sodium taurocholate (STC) and lecithin on the solubility and induction time of PCZ.

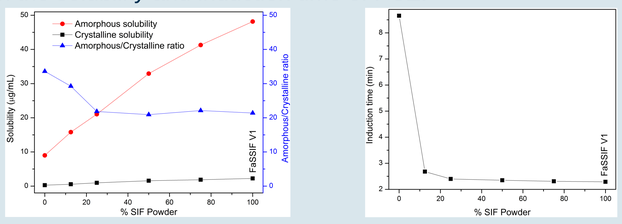


Figure 6. Influence of the amount of SIF powder on the solubility and induction time of PCZ.

IV. RESIDUAL CONCENTRATION

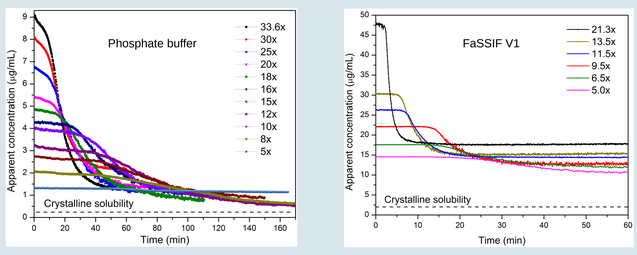


Figure 7. Residual concentration of PCZ upon crystallization in phosphate buffer and FaSSIF V1.

CONCLUSIONS

- Solubility of posaconazole as a function of pH follows the Henderson-Hasselbalch equation.
- pH-solubility phase diagram is constructed to define possible phase transformations, namely crystallization or liquid-liquid phase separation.
- Nucleation induction time varies as a function of degree of supersaturation.
- Nucleation mechanism can change from homogeneous at high supersaturation to heterogeneous at low supersaturation.
- Medium composition significantly affects phase boundaries and nucleation induction time.
- Findings for posaconazole could be broadly applicable to other weakly basic compounds, after taking into consideration differences in pK_a, solubility and molecular structure.

FUNDING

The authors would like to acknowledge the financial support from U.S. Food and Drug Administration via a GDUFA regulatory research contract (HHSF223201710137C).

PURDUE UNIVERSITY®

FDA U.S. FOOD & DRUG ADMINISTRATION

CERTARA

Simcyp