Precipitation Behavior of Ionizable Weak Acids and Bases: Amorphous Potential and Implications for Drug Development

J. Mole[1], K. Box[1], L. Taylor[2], Y-L. Hsieh[2]
[1]Sirius Analytical Ltd., [2]Purdue University

Purpose

Poorly soluble weak bases may be susceptible to precipitation when travelling through the gastrointestinal tract following an increase of pH. Likewise, acidic compounds when dosed as salts may show initial rapid dissolution followed by precipitation at gastric pH values. The outcome for oral absorption may depend on the nature of the precipitate: amorphous versus crystalline. In this study we evaluate the precipitation behaviour of ionisable weak acids and bases following pH change

Methods

A SiriusT3 titration instrument coupled with UV spectroscopy and a fiber optic dip probe was used to perform pH titrations and detect turbidity during the titration process. Several ionisable weak acids and bases were selected (e.g., ketoprofen, warfarin, dipyridamole, ketoconazole, loratadine). Each compound was solubilised and then titrated towards the samples pKa in order to induce precipitation of the poorly soluble free form. After turbidity was detected by the UV probe, the free form concentration in solution was calculated by mass and charge balance equations at different time points to follow the precipitation process. The impact of polymers on solubility was also studied. Solid state characterization on precipitates was performed using polarized microscope, differential scanning calorimetry (DSC), synchrotron wide angle x-ray scattering.

Results

Monitoring of the solution concentration profiles with time allowed for classification of the precipitation behaviour and could be rationalized based on the crystallization tendency of the compounds. Some compounds displayed a ready tendency to crystallize after precipitation and free form concentrations reduced rapidly towards the equilibrium solubility as the process of crystal growth occurred. Polymers (e.g., PVP, HPMC) could be used to inhibit crystallization of some of these compounds but could not prevent crystallisation of others. Other compounds precipitated as long lived amorphous solids with solution concentrations significantly higher than the intrinsic solubility of the crystalline form.

Conclusion

We have described a technique for evaluating amorphous potential and directly measuring amorphous solubility of a compound. The study showed that some compounds had a long lived amorphous form that could exist in solution for prolonged time periods without crystallization. The implication for drug development is that amorphous precipitates will be readily dispersed and easily re-absorbed on transit along the gastrointestinal tract leading to higher than expected oral absorption.