Utilization of pH-Metric Titration to Evaluate the Supersaturation Behavior of Weakly Basic Drugs

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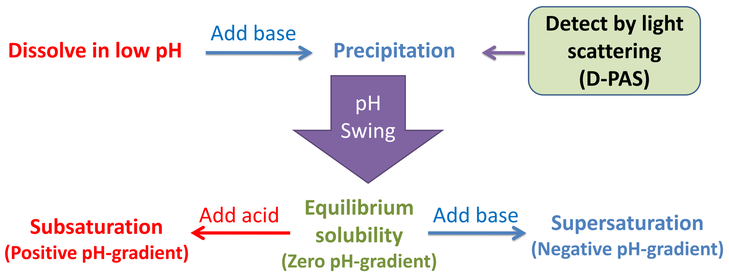
ABSTRACT

Ionizable compounds, especially weakly basic drugs, are susceptible to precipitation in the gastrointestinal (GI) region due to physiological pH changes. Supersaturation may arise in vivo upon entering higher pH intestinal regions for weakly basic and poorly soluble compounds after solubilization in the acidic environment in the stomach. The goal of this study is to investigate the supersaturation behavior of different basic compounds and evaluate their tendency to precipitate during acidic-to-neutral pH transition in solution using the pH-metric titration method. Two types of behavior were observed: type I compounds have short-lived supersaturation due to precipitation of a crystalline form, whereas type II compounds precipitate as an amorphous form upon pH increase which results in prolonged supersaturation. This study shows the feasibility of utilizing pH-metric titration for evaluating the supersaturation behavior of ionizable pharmaceutical compounds in real time as well as measuring the amorphous solubility of type II compounds.

INTRODUCTION

Basic compounds which represent almost 2/3 of the ionizable drugs surveyed in the World Drug Index in 1999 [1] are prone to precipitation in the GI tract due to supersaturation induced by physiological pH differences. The duration of supersaturation as well as the solubility of the precipitate are important since they can affect the extent of absorption across the luminal membrane.

An attempt to gain insight into supersaturation behavior of different drugs has been made previously using pH-metric titration [2, 3]. A Sirius GLpKa pH titrator coupled with ultraviolet/visible fiber optic dip probe (D-PAS) was utilized in this study. The experimental set up can be described by the following schematic:



Kinetic solubility is measured at the point where precipitation of the free base is first observed, while equilibrium solubility at the saturation point can be attained by slight supersaturation and subsaturation induced by titration of base and acid respectively (pH swing). The concentration of neutral (free base) species in solution can be calculated by mass and charge balance equations at different time points during the titration process. Two types of behavior were observed: type I compounds with significantly higher kinetic solubility than the equilibrium solubility and type II compounds with similar kinetic and equilibrium solubility. However, based on crystallization theory, supersaturation is required prior to precipitation and therefore type II behavior needs to be rationalized.

In this study, we investigate the supersaturation behavior based on the crystalline or amorphous nature of the precipitate induced by pH changes and therefore provide a more rational explanation for these observations.

MATERIALS AND METHOD

Bifonazole and pyrimethamine were purchased from Spectrum Chemical (Gardena, CA). Dipyridamole, droperidol, clotrimazole and papaverine HCl were purchased from Sigma-Aldrich (St. Louis, MO). Papaverine free base was prepared by dissolving the salt in water and titrating to pH 10. Carvedilol and loratadine were purchased from Attix (Ontario, Canada). Ketoconazole and clozapine were purchased from Hawkins, Inc (Minneapolis, MO) and Euroasia (Mumbai, India) respectively.

The pH-metric titration method is described above and additional details can be found in previous publications [2, 3]. For measuring equilibrium solubility by HPLC, the drug powder was equilibrated in buffer at least two units higher than its pKa for 72 hours. The supernatant and precipitate were obtained by using ultracentrifugation at 40,000RPM. The precipitate was then dried overnight in vacuum oven at room temperature.

RESULTS

Type I compounds (Dipyridamole)

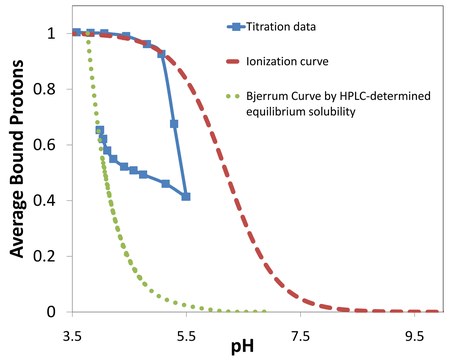


Figure 1: Bjerrum profile displaying crystallizing behavior upon precipitation

Type II compounds (Loratadine)

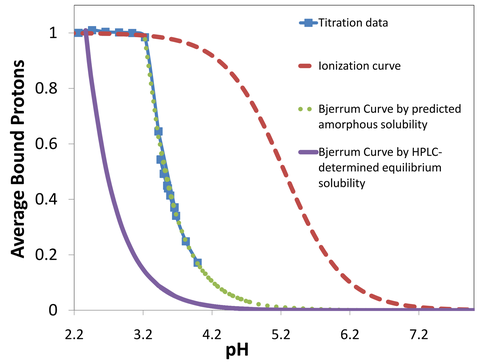


Figure 2: Bjerrum profile for compound precipitating as amorphous form

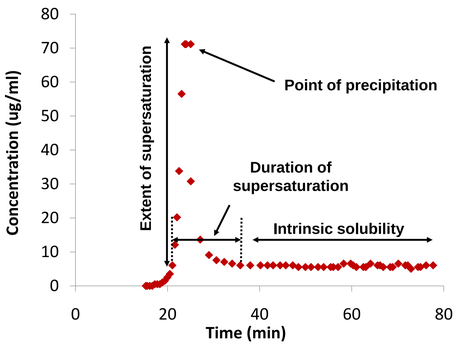


Figure 3: Neutral species concentration for dipyridamole upon pH increase

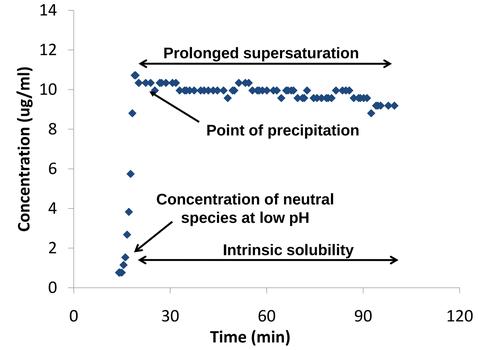


Figure 4: Concentration of neutral species for loratadine upon pH increase

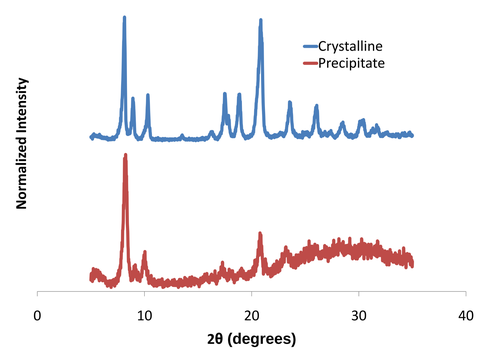


Figure 5: PXRD results indicate crystalline form for dipyridamole precipitate

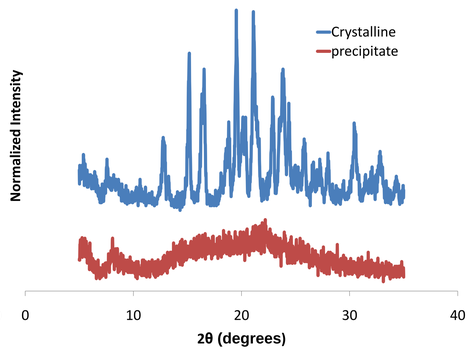


Figure 6: PXRD results indicate amorphous form for loratadine precipitate

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SUMMARY AND CONCLUSION

The intrinsic solubility and post-precipitation solution concentrations for type II compounds determined from HPLC measurements showed that solution concentrations following precipitation **were significantly higher than the intrinsic solubility of the most stable crystalline form.** Moreover, the predicted amorphous solubility values were in good agreement with the solution concentrations observed after precipitation for type II compounds.

Compounds	Supersaturation behavior	Precipitate Solid state	C(pH-Metric)* / C(HPLC)	Theoretically estimated Amorphous/Crystalline solubility ratio [4-6]
Bifonazole	I	Crystalline	N/A	-
Dipyridamole	I	Crystalline	1.4	-
Droperidol	I	Crystalline	0.7	-
Papaverine	I	Crystalline	0.8	-
Pyrimethamine	I	Crystalline	1.0	-
Carvedilol	II	Amorphous	18.5	12.3
Clotrimazole	II	Amorphous	14.1	9.8
Clozapine	II	Amorphous	19.4	16.7
Ketoconazole	II	Amorphous	22.9	15.3
Loratadine	II	Amorphous	6.3	4.3

*C (pH-Metric) = concentration determined from pH titration
C (HPLC) = Crystalline solubility determined by using HPLC

The supersaturation behavior of several compounds was thus found to have a significant correlation with the solid state properties of the resultant precipitates. Compounds that precipitate as amorphous forms have prolonged supersaturation profiles (type II), while short-lived supersaturating profiles were observed from compounds that precipitate as the crystalline form (type I). In conclusion, pH-metric titration is an effective approach for evaluating supersaturation behavior of ionizable compounds as well as for measuring amorphous solubility in conjunction with solid state analysis.

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