Dissolution and Precipitation Monitoring of Crystalline Salts

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Introduction

For Active Pharmaceutical Ingredients (API) that have dissolution or solubility limited absorption, salt formation is commonly used to improve the dissolution/solubility characteristics and enhance oral bioavailability. A critical factor in utilizing a salt form to increase absorption is the degree to which it can maintain supersaturation before precipitating out as the thermodynamically stable form. The level of supersaturation as well as the duration of supersaturation need to be assessed to guide salt form selection and formulation design (Figure 1).

Theoretical Concentration Vs. Time Curves

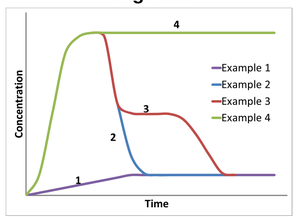
Example 1. Absorption limited by dissolution rate and/or solubility.

Example 2. Rapid dissolution followed by rapid precipitation of thermodynamic form.

Example 3. Rapid dissolution followed by rapid precipitation to a metastable form followed by conversion to the thermodynamic form

Example 4. Rapid dissolution followed by prolonged supersaturation.

Figure 1



Each example above would require a different formulation strategy to either improve or maintain the dissolution and solubility properties inherent in the crystal form to be developed. Simultaneous monitoring of dissolution and crystal form present in dissolution media provides unique insight into the behavior of solid forms and can be a valuable tool in guiding formulation development.

The ability to identify dissolution and solubility limited absorption during the discovery phase of development presents an opportunity to provide optimized formulations early on. Optimized formulations in turn enable more consistent dosing, higher exposures and thus the ability to make better decisions on higher quality animal data.

One of the key challenges facing salt screening and formulation optimization during discovery is the scarcity of material for testing. Use of micro dissolution testing enables dissolution assessment with only small quantities of API.

Purpose

The aim of this study was to evaluate the practicality of combining real-time concentration monitoring with fiber optic spectroscopy and powder x-ray diffraction (PXRD) to provide an assessment of salt disproportionation and precipitation utilizing a minimum amount of API.

Materials

API powder, neutral form, 98.9% purity by HPLC.

API powder prepared as the mono HCl salt.

Simulated gastric fluid, 0.2% (w/v) NaCl in 0.7% (v/v) HCl (RICCA Chemical Company. Arlington, TX)

Simulated intestinal fluid, USP XXII, without pancreatin (RICCA Chemical Company. Arlington, TX)

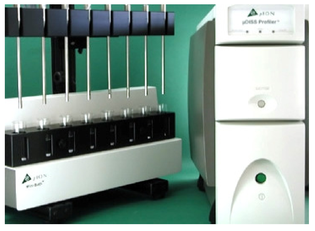
Equipment and Methods

Dissolution measurements were performed using a Pion Inc. µDISS Profiler™ fiber optic dissolution monitor (Figure 1). Prior to analysis of samples, the instrument was normalized on USP simulated intestinal fluid (USP-SIF) media and standardized with a known concentration of the API. Quantitation was accomplished by integrating from 268-350 nm and using baseline correction at 400 nm. USP-SIF media (20 mL) was added to each vessel and allowed to equilibrate at 37°C with magnetic stirring. To each of seven vessels was added 18-20 mg of the HCl salt. UV spectra were collected at the following time intervals:

50 UV spectra at 20 second intervals
10 UV spectra at five minute intervals
Total run time of 1 hour 7 minutes.

Based on the concentration versus time curve, six sample aliquots were removed and filtered as shown in Figure 2 to obtain a real-time assessment of the solid forms present at various points in the dissolution experiment. A total of six µDISS Profiler™ channels were used for the solid state analysis and an additional channel was used to obtain the complete dissolution curve.

Figure 2
µDISS Profiler includes a temperature controlled Mini-Bath and 8 integrated diode array spectrometers to simultaneously collect full UV spectra as often as once per one second vessel.



Filtered solids were air dried and crystallinity was studied with a Bruker-D8 Advance X-ray powder diffractometer using Cu Ka radiation (Bruker, Madison, WI). The instrument was equipped with a long fine focus X-ray tube. The tube voltage and amperage were set to 40 kV and 40 mA, respectively. The divergence and scattering slits were set at 1° and the receiving slit was set at 0.15 mm. Diffracted radiation was detected by a Lynxeye detector. A θ-2θ continuous scan from 3 to 39° 2θ with 0.016°/min steps and a 0.5 sec/step dwell time was used. Samples were prepared for analysis by placing them on a zero background plate.

Results

Sample points 1 and 2 in Figure 3 represent the rising and plateau phases of the dissolution curve respectively. At these early time points, it would be expected that the HCl salt form would predominate in the undissolved solids. PXRD spectra for time points 1 and 2 confirms this assumption and also demonstrates the presence of an amorphous component as evidenced by the non-linear baseline. As the measured concentration falls during time points 3 and 4, a mixture of undissolved HCl salt, more pronounced amorphous content and the appearance of crystalline freebase are observed. As the concentration reaches steady state at time points 5 and 6 only the crystalline free base (neutral form) is observed with little evidence of amorphous content and no evidence of the HCl salt. Based on these observations it would appear that the HCl salt exhibits the behavior noted in example 3 of Figure 1; the HCl salt rapidly dissolves in intestinal media but the free base rapidly precipitates as an amorphous form that in turn crystallizes to the thermodynamically stable form

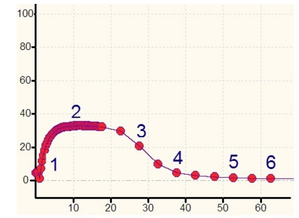


Figure 3
Dissolution Plot of API HCl salt. % dissolved vs. time

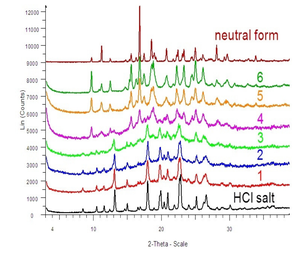
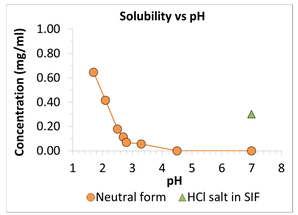


Figure 4
Stack Plot of PXRD Spectra

Figure 5
pH dependent solubility curve of neutral form of API compared to the kinetic solubility of the HCl salt at pH 7



Conclusions

Based on these observations, a formulation strategy that takes advantage of the rapid dissolution behavior of the HCl salt while inhibiting precipitation of the freebase should provide the largest window for drug absorption. Additionally, the high solubility of the HCl salt relative to the neutral form at elevated pH (Figure 5) allows for the possibility of an enteric coated formulation which protects the soluble form from dissolving in the stomach and allows it to dissolve at the site of absorption.

Combination of µDISS Profiler™ dissolution data with real time solid state characterization provides the preformulation/formulation scientist with a powerful tool with which to design effective formulation strategies to improve the oral absorption window for a poorly soluble API. In addition, the minimal API required to run the experiment makes it an analysis that is feasible for even early formulation optimization during the discovery phase of development.