Dissolution and Precipitation Monitoring of Crystalline Salts

J. Michael MacPhee and Dana C. Lipp

1 Biogen Idec, 14 Cambridge Center, Cambridge, MA 02142, USA, 2 Pion Inc., 10 Cook Street, Billerica, MA 01821, USA

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 metastable form followed by conversion to the thermodynamic form.

Example 4. Rapid dissolution followed by prolonged supersaturation.

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 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.

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.