Evaluating Drug Salt Dissolution and Precipitation Processes for Rational Formulation Strategies

Richard Winnike [1], Chris Spancake [2], Konstantin Tsinman [3] and Alex Avdeef [3]

[1] Winnike Consulting LLC, 110 Fieldstone Ct, Chapel Hill NC 27754, USA, [2] GlaxoSmithKline, 5 Moore Dr, Research Triangle Park, NC 27709, USA, [3] pION INC, 5 Constitution Way, Woburn, MA 01801, USA

Introduction

The salt form of an API (active pharmaceutical ingredient) may dissolve, partially or completely, to transient concentrations far above equilibrium solubility levels. The supersaturated solution may then precipitate as the free acid/base, sometimes coating the remaining input API or formulation, thus significantly modifying the subsequent dissolution rate. The timeframe of supersaturation and potential precipitation events may have profound effects on bioavailability *in vivo*.

Purpose

The aim of this study was to develop a practical and predictive *in vitro* powder and formulation dissolution method to monitor dissolution and concomitant precipitation processes in biorelevant media.

Material

A1 Na salt: API powder (neat), IR capsules (250 mg), API/PEG 8000 capsule granulation and tablet (compressed granulation). Granulation produced by a hot melt extrusion process with 10% PEG 8000.

A1B2 Na salt: micronized and unmicronized API powder (neat).

A1 Na salt is a relatively fast dissolving sodium salt of a weak acid with low intrinsic solubility. A1B2 Na salt is a relatively slow dissolving sodium salt of an ampholyte with extremely low intrinsic solubility.

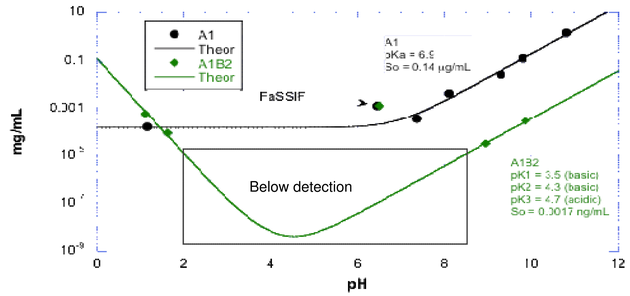


Figure 1. pH solubility profile for A1 free acid and A1B2 free ampholyte. Note that the solubility in FaSSIF pH 6.5 is approx. 12 µg/mL for both A1 and A1B2.

Equipment and Methods

µDiss Profiler™ apparatus (37°C, 250 RPM; *p*ION INC, Figure 2) and USP dissolution apparatus 2 (37°C, 75 RPM) were used in this study.

The powder dissolution kinetics were evaluated at biorelevant loads in 0.03N HCl, SGF pH 1.6 or FaSSIF pH 6.5.

The amount of API dissolved versus time is also monitored for A1 Na salt formulations and A1B2 Na salt API in 0.03N HCl (pH 1.6) using a Na^+ ion sensitive electrode.

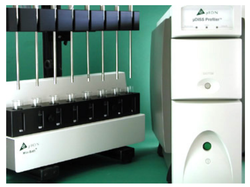


Figure 2. µDISS Profiler from *p*ION INC uses a temperature controlled Mini-Bath and 8 integrated diode array spectrometers to collect full UV spectra as often as once per one second.

The A1 Na salt formulations were further evaluated in SGF pH 1.6; after approx. 30 min, appropriate quantities of concentrated phosphate buffer and concentrated lecithin/taurocholate were added to the SGF to transform the media *in situ* to FaSSIF pH 6.5 (increasing the media volume 25%).

The drug solution concentration versus time is evaluated *in situ* using fiber optic UV and a 2nd derivative analysis technique. No sample manipulation which could compromise accurate quantitation of supersaturated solutions was performed.

Results

A1 Na salt

The powder dissolution profile of A1 Na salt (neat) in SGF pH 1.6 is depicted in Figure 3. The A1 Na salt shows a very quick dissolution spike followed by free acid precipitation within a few minutes. The precipitation process is quite reproducible with the 1 mg/mL load spike marginally higher than that for the 0.5 mg/mL load.

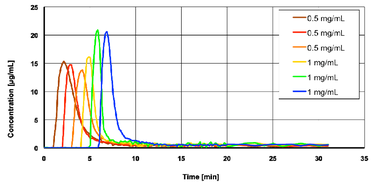


Figure 3. A1 Na salt powder in SGF pH 1.6 with 0.5 and 1 mg/mL loads in 16 mL (µDiss). Sample start times staggered at 1 min intervals.

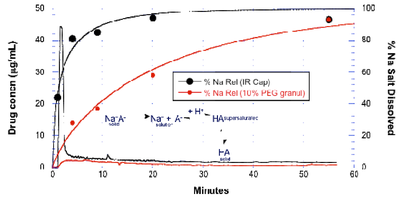


Figure 4. A1 Na salt formulation dissolution (IR capsule contents and 10% PEG 8000 granulation) 250 mg in 500 mL 0.03M HCl pH 1.6, 37°C (USP 2).

Similarly, immediate release capsules of A1 Na salt dissolved quickly in 0.03 N HCl followed by free acid precipitation within 1-2 minutes (Figure 4). However, it took around 20 minutes for the entire input A1 Na salt to dissolve from the IR capsules. A capsule granulation of A1 API/PEG 8000 (90:10) dissolved much slower in (no spike) with some undissolved input A1 Na salt remaining around 1 hour. Free acid precipitation appears to be coating the PEG 8000 granulation, slowing API release.

This inhibition of release was exacerbated in SGF for a tablet made from the A1/PEG 8000 granulation (Figure 5a). Almost no drug is released from the tablet in SGF. The tablet subsequently showed rapid dissolution in FaSSIF, functioning like an enteric coated formulation (Figures 5a and 5b).

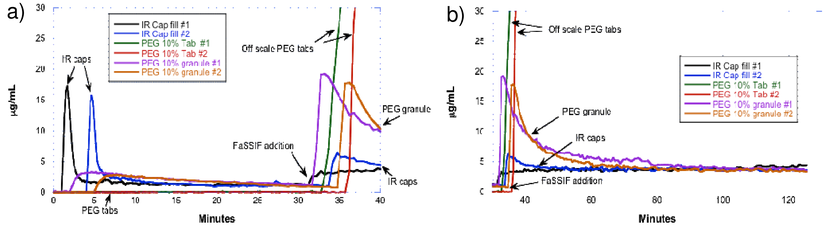


Figure 5. A1 Na salt formulation dissolution profile in SGF pH 1.6 [0 - 30 min] (a) and FaSSIF pH 6.5 [after 30 min] (b). Note: 250mg/400 mL SGF → 500 mL FaSSIF (USP 2).

A1B2 Na salt

Powder dissolution was profiled for micronized and unmicronized A1B2 Na salt in Figures 6, 7a, and 7b. In 0.03N HCl or SGF, dissolution of the A1B2 Na salt occurred over several hours (>16) with free ampholyte precipitating after 1-2 hours.

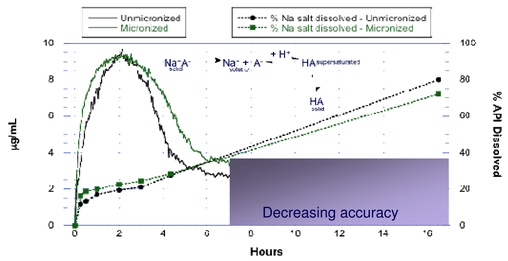


Figure 6. A1B2 Na salt (API powder) in 0.03N HCl (pH 1.6, 0.2 mg/mL load; USP 2): Amount of salt dissolved vs. amount of drug remaining in solution.

Results (continued)

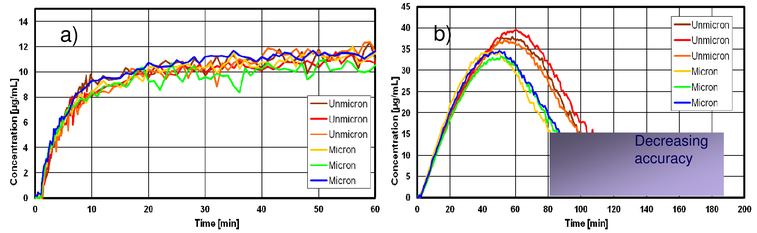


Figure 7. Dissolution profile of A1B2 Na salt (API powder) in SGF pH 1.6 (a) and FaSSIF pH 6.5 (b). The load is 0.2 mg/mL (µDiss).

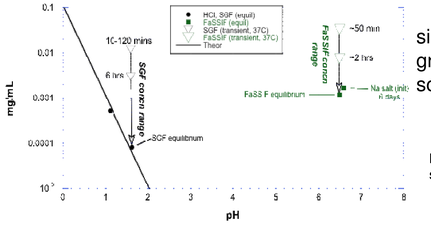
Powder Dissolution Summary of A1B2 Na Salt

SGF / 0.03N HCl

- Only ~20% of API dissolved at 2 hours
  - Most of the Na salt could be expected to pass through the stomach undissolved
- No significant dissolution difference observed between unmicronized and micronized API

FaSSIF

- Unmicronized API achieved only slightly higher C_{max} and sustained somewhat higher concentration
- *In vitro* concentrations peak ~1 hour at 30-40 µg/mL and fall ~5 fold over the next hour



The transient drug concentrations in simulated GI fluids are depicted graphically with the equilibrium solubilities in Figure 8.

Figure 8. A1B2 Na salt: Transient simulated GI fluid solution concentrations versus equilibrium solubility.

Contrasting Na Salt Dissolution Kinetics in SGF and Formulation Strategies

A1 Na salt

- Kinetic processes
  - Fast (minutes)
    - Dissolution: over several minutes
    - Precipitation: 1-2 minutes
- Formulation strategies
  - May benefit from enteric delivery
  - Dissolution enhancement of API by particle size reduction may be detrimental

A1B2 Na salt

- Kinetic processes
  - Slow (hours)
    - Dissolution: over several hours
    - Precipitation: 1-2 hours
- Formulation strategies
  - Dissolution/solubility enhancement of API
  - Enteric delivery dubious

Conclusions

- This novel yet simple *in situ* monitoring approach to *in vitro* powder and formulation dissolution/precipitation can provide a fundamental understanding of processes that may be relevant *in vivo* thus providing a rational approach to formulation design and development.
- Transient concentrations at supersaturation may be more relevant for understanding and/or predicting *in vivo* performance.
- Dissolution profiling with fiber optic probes provides a means of *in situ* monitoring of kinetic processes (at supersaturation) unachievable by other sampling and analysis procedures.