Application Note

AN: 166-1 Rev 1.

Rational Drug Formulation: Evaluating Potential Drug Availability *in vivo*

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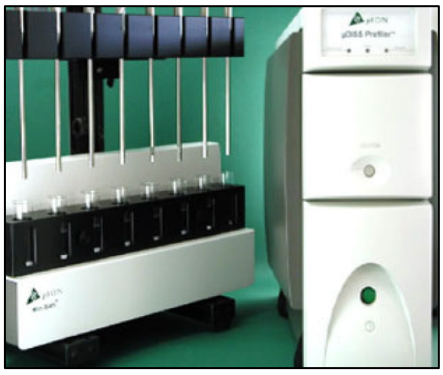
Summary

Solubility is critical to the availability of new drug compounds. Dynamic solubility- pH studies of precipitation behavior in artificial stomach-duodenum models better assess *in-vivo* solubility. When these studies are conducted with the UV-based µDISS Profiler™, real-time transient drug concentrations not achievable with liquid sampling based methods are obtained. Studies using the µDISS Profiler allow the drug developer to quickly evaluate, better understand API supersaturation and evaluate preformulation performance in biorelevant media.

Introduction

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



A Break from Tradition

The µDISS Profiler™ rapidly acquires UV spectra (200-450 nm) every 5 seconds using photo diode arrays dedicated to each of its 6-8 fiber optic dip probes. Each probe can be independently standardized with entirely different APIs to maximize sample throughput and flexibility. A second derivative algorithm effectively reduces many spectral effects associated with turbidity produced by insoluble matter.

Case Study: A Fast Dissolving, Low Solubility Acid

A fast dissolving sodium salt of a weak acid with low solubility has been studied. The API was prepared as instant release capsules (IR caps), granules and tablets (compressed granules). The granules were produced by hot melt co-extrusion with 10% polyethylene glycol (PEG 8000).

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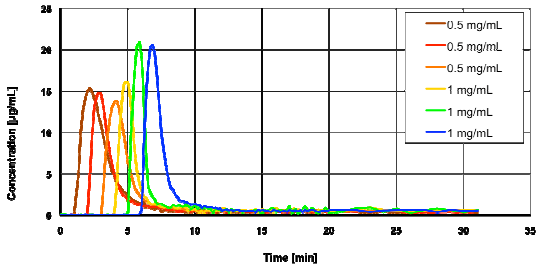

Figure 1. API salt powder in SGF pH 1.6 with 0.5 and 1 mg/mL loads in 16 mL. Sample start times staggered at 1 min intervals.

The powder dissolution profile of the neat sodium salt in simulated gastric fluid is depicted in Figure 1. A rapid dissolution spike is followed by free acid precipitation within a few minutes in which a larger spike corresponds to greater API loading.

As shown in Figure 2, the formulations were also evaluated in SGF at pH 1.6. After about 30 min, concentrated phosphate buffer-lecithin-taurocholate was added to transform the SGF media into FaSSIF at pH 6.5. Drug concentration was determined using the second derivative of the spectra. No sample manipulation was performed which could compromise accurate quantitation of the supersaturated solutions.

Tablets made from the PEG 8000 granulation displayed inhibited release in SGF, with a subsequently rapid dissolution in FaSSIF, functioning like an enteric coated formulation (Figures 2a and 2b).

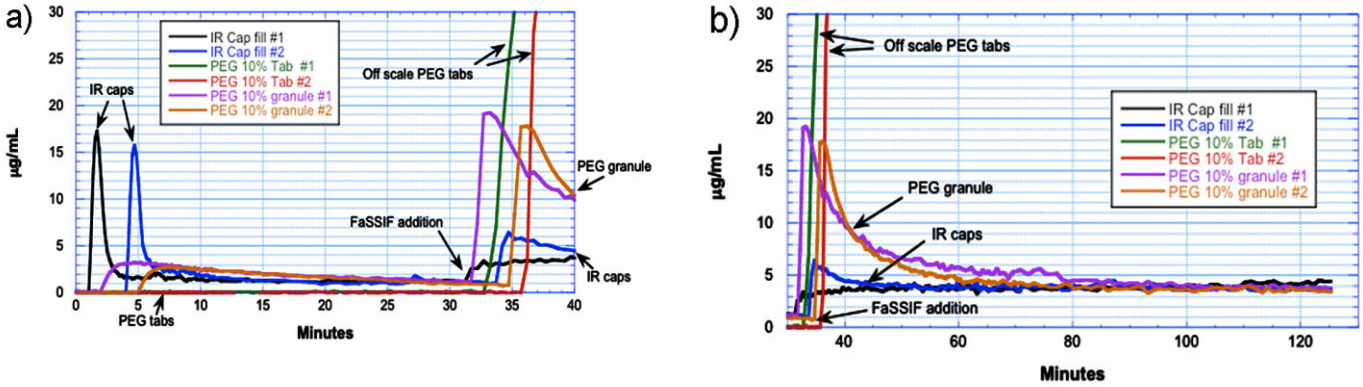

Figure 2. Dissolution profile in SGF pH 1.6 [0 - 30 min] (a) and FaSSIF pH 6.5 [after 30 min] (b).
Note: 250mg/400 mL SGF -> 500 mL FaSSIF (USP 2).

Rational

Conclusions

Real time dissolution/precipitation monitoring of API powder and formulations can provide an improved, fundamental understanding of *in vivo* relevant processes, thus providing a rational approach to formulation and development. Most notably, the µDISS Profiler™ provides a convenient and reliable means of *in situ* monitoring of kinetic processes and transient effects at supersaturation unachievable by traditional liquid sampling and analysis procedures.

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