Accepted Manuscript

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PII: S0022-3549(17)30026-6

DOI: 10.1016/j.xphs.2017.01.023

Reference: XPHS 631

To appear in: *Journal of Pharmaceutical Sciences*

Received Date: 29 August 2016

Revised Date: 13 January 2017

Accepted Date: 18 January 2017

Please cite this article as: He Y, Ho C, Yang D, Chen J, Orton E, Measurement and Accurate Interpretation of the Solubility of Pharmaceutical Salts, *Journal of Pharmaceutical Sciences* (2017), doi: 10.1016/j.xphs.2017.01.023.

Measurement and Accurate Interpretation of the Solubility of Pharmaceutical Salts

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Abstract

Salt formation is one of the primary approaches to improve the developability of ionizable poorly water soluble compounds. Solubility determination of the salt candidates in aqueous media or bio-relevant fluids is a critical step in salt screening. Salt solubility measurements can be complicated due to dynamic changes in both solution and solid phases. Because of the early implementation of salt screening in research, solubility measurements often are performed using minimal amount of material. Some salts have transient high solubility upon dissolution. Recognition of these transients can be critical in developing these salts into drug products. This minireview focuses on challenges in salt solubility measurements due to the changes in solution caused by self-buffering effects of dissolved species and the changes in solid phase due to solid-state phase transformations. Solubility measurements and their accurate interpretation are assessed in the context of dissolution monitoring and solid phase analysis technologies. A harmonized method for reporting salt solubility measurements is recommended to reduce errors and to align with the USP policy and FDA recommendations for drug products containing pharmaceutical salts.

Keywords: salt, solubility, pH, dissolution, poorly water soluble, solution phase, solid phase, equilibrium, salt dissociation, phase-transformation

Introduction

Salt formation usually is the first consideration and the primary approach in the pharmaceutical industry to address the challenges of low solubilities and/or slow dissolution rates of ionizable drug substances. It also is a commonly applied technique to rectify suboptimal drug properties, such as poor stability, physical quality, and purity, optimize process chemistry, reduce toxicity, alter absorption in the gastrointestinal (GI) tract, and enhance organoleptic palatability.[1-4] An analysis of the U.S. Food and Drug Administration (FDA) Orange Book database revealed that half of the approved active pharmaceutical ingredients (APIs) are salt forms.[5]

In today's pharmaceutical development paradigm, salt screening is implemented early in research with the aims of improving developability and maximizing *in vivo* exposure from orally administered solid dosage forms. For many poorly soluble compounds, adequate exposure could not be achieved without converting them to more soluble salt forms.[6] Salt forms with higher solubility are also often selected to develop parenteral products to prevent precipitation at the injection sites because precipitated drugs can cause adverse effects.[7] On the other hand, some highly soluble compounds have unpleasant tastes, which can be masked by converting the parent compounds to salts with lower solubility or slower dissolution rate because only dissolved molecules can elicit taste sensation.[1] In life cycle management and generic drug products, salt forms with altered solubility can offer opportunities for new dosage forms such as modified release profiles, reduced tablet or capsule sizes, or liquid forms to improve patient compliance.[8]

Abbreviations used: **API,** active pharmaceutical ingredient; **AUC,** area under curve; **C_{max}**, maximum concentration; **DSC**, differential scanning calorimetry; **FaSSIF**, fasted state simulated intestinal fluid; **FDA**, food and drug administration; **FTIR**, Fourier transform infrared spectroscopy;**GI**, gastro-intestine; **HPLC**, high performance liquid chromatography; **HT**, high throughput; ***K_a***, ionization constant; **MT**, medium throughput; **OrBiTo**, oral biopharmaceutical tools; **PAT**, process analytical technology; spectroscopy; **PLM**, polarized light microscopy; **PK**, pharmacokinetic; **SGF**, simulated gastric fluid; **SOP**, standard operating procedure; **TGA**, thermogravimetric analysis; **T_{max}**, maximum time to reach the highest concentration; **USP**, United States pharmacopeial; **UV**, ultraviolet; **XRPD**, X-ray powder diffraction