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The Selection of a Pharmaceutical Salt – the Effect of the Acidity of the Counterion on Its Solubility and Potential Biopharmaceutical Performance

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Abstract

A roadmap for the selection of a pharmaceutical salt form for a development candidate is presented. The free base of the candidate did not have sufficient chemical stability for development. The initially selected salt form turned out to be undevelopable because it was unstable during scale-up synthesis and storage. The rationale for the new solid form screening and the criteria for selection are discussed. Prior to the final selection, the pH solubility profiles of the two new salts, a benzoate and a besylate, were compared. Atypical solubility behavior was observed for the benzoate salt in hydrochloric acid with and without normal saline. A scheme is proposed illustrating how the pK_as of the counterion and API, the medium composition, and final pH affect the solubility and solution equilibria of the two selected salt forms. This scheme also includes the equilibria between solution and solid phases in different pH ranges. The pharmaceutical importance of this research is that it sheds light on how the acidity of the counterion can affect the solubility of the selected salt form in the gastric environment. With a well-designed formulation strategy, this property potentially can be translated to optimal biopharmaceutical performance of the drug product.

Keywords: salt, solubility, stability, biopharmaceutical, poorly water soluble, solution phase, solid phase, equilibrium, pK_a, pH

Introduction

In the pharmaceutical industry salt formation of ionizable drug substances is a common strategy to rectify suboptimal drug properties so as to improve aqueous solubility/dissolution, stability, and physical quality or purity, optimize process, reduce toxicity, alter absorption in the gastrointestinal (GI) tract, or enhance organoleptic properties.[1-6] When a suitable salt form can be identified for a small molecule entity, it often is the most cost-efficient approach in drug product development. For these reasons, not only about 50% of US Food and Drug Administration (FDA) approvals comprise active pharmaceutical ingredients (APIs) in salt forms,[7] also half of the top 200 US prescription drugs were made from pharmaceutical salts.[8]

Compound A (Figure 1) is a selective and reversible inhibitor of human β-tryptase. It was developed by Sanofi for the treatment of inflammatory and allergic disorders, such as asthma and chronic obstructive pulmonary disease (COPD).[9-11] This compound is a primary benzylic amine with pK_a and logP calculated as 9.0 and 4.9 (ACD Labs v12). Its free base form is not suitable for development because the benzylamine moiety is highly susceptible to autoxidation. Solid form selection including salt screening is implemented in early research in Sanofi because it is believed to be of utmost importance to optimize the properties and identify potential liabilities of development candidates.[12] A salt form was identified in the early stage salt screening which enabled advancement of this compound to development. However, this salt form was then deemed unsuitable for development because a major

Abbreviations[1]

[1] **AB**, acetate buffer; **ACN**, acetonitrile; **API,** active pharmaceutical ingredient; **BS**, benzoate salt; **CB**, citrate buffer; **COPD**, chronic obstructive pulmonary disease; **DSC**, differential scanning calorimetry; **DVS**, dynamic vapor sorption analysis; **FBE**, Free base equivalent; **FDA**, Food and Drug Administration; **FTIR**, Fourier transform infrared spectroscopy; **GI**, gastrointestinal; **HCl**, hydrochloric acid; **HEC**, hydroxyethyl cellulose; **HPLC**, high performance liquid chromatography; **^{1}H NMR,** proton nuclear magnetic resonance; **IV,** intravenous; **LC-MS,** liquid chromatography-mass spectrometry**;** **NOAEL**, no observed adverse effect level; **NOEL**, no observed effect level; **NS**, normal saline; **PB**, phosphate buffer; **PK**, pharmacokinetics; **PLM**, polarized light microscopy; **RH**, relative humidity; **SEM**, Scanning electron microscopy; **TFA**, trifluoroacetic acid; **TGA**, thermogravimetric analysis; **UV**, ultraviolet; **XRPD**, X-ray powder diffraction;