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Salt selection for development - solubility & bioperformance advantages from salts made by weaker acidic counterions explained by thermodynamic equilibria

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Salt formation is an old and yet still very useful strategy in improving developability of new chemical entities in pharmaceutical pipeline and optimizing bioperformance of drug products. When a suitable salt form can be identified for a synthetic compound, it often is the most cost-efficient approach in improving aqueous solubility/dissolution, stability, and physical quality or purity. Salt formation can also facilitate optimizing chemical process, reduce oxicity, alter absorption in the GI tract, or enhance organoleptic properties. For these reasons, about 50 % of FDA approved synthetic drugs are made by salt forms of active pharmaceutical ingredients (APIs). A roadmap for the selection of a pharmaceutical salt form for a development candidate is laid out in this presentaiton. In this study, the free base form of the development candidate has poor developability because its benzylamine moiety is highly susceptible to autoxidation. Salt formation was identified as a vital approach to protecting this moiety. Although improving solubility was not the initial goal, the unexpected high solubility from the salt made by a weak acidic counterion provided extraordinary benefits in preclinical toxicology studies. The solubility advantages were explained by the intertwined thermodynamic equilibria between the solid and solution phases and meanwhile the equilibria among all API species in the solution, which include the charged and the uncharged species of the original salt formed with weaker acidic counterion, and the in-situ salts formed with the stronger acidic counterion in the dissolution buffer or in the gastric fluid. This study demonstrates that the selection of the salt made by a weaker counterion can have advantages in driving the solubility of the API to a higher API concentration in the GI tract, in the case that the K_{sp} of the HCl salt of the API is high, although the HCl salt may not have preferrable developability. With biopharmaceutical performance being the key of developing a formulation for a new medicine, this research sheds light on how the acid strength of the pharmaceutical salt form counterion can affect this performance.

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