Salt and Polymorph Selection: Fundamental Topics in any Pharmaceutical Development

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Modern drug substance processes involve the screening of a large number of compounds obtained by combinatorial chemistry techniques. These compounds are generally dissolved and screened by biological tests to find an eventual therapeutic activity. When new chemical entities show the desired biological activity (generally a small number of candidates), their solid state characteristics and theirs properties as pharmaceutical material have to be determined.

The first step of the material design is the selection of an appropriate salt form for the new chemical entity. The salt preparation provides the pharmaceutical scientists with the opportunity to modify the characteristics of the potential drug substance. Salts are more commonly employed for modifying aqueous solubility. When possible, a range of salts should be prepared for each new substance and their properties compared during an adequate solid state characterization and preformulation program. When the salt or the free molecule has been selected, the crystalline form has to be selected to offer a better definition of the material. Polymorphism screening consisting of exploration of the various possible recrystallization solvents or/and conditions of the material generally allows to obtain various crystalline forms further identified and characterized. The inter-relationships between the different forms of the active pharmaceutical ingredient and the definition of the most stable crystalline form have to be clearly understood.

The salt and the crystalline form selected will influence various properties such as melting point, hygroscopicity and propensity to hydration, chemical and physical stability, mechanicals properties (morphology of particles, agglomeration, flowability…) etc…

An understanding of the influence of drug, salt and crystalline form properties on the finished product is essential to ensure selection of the best salt and crystalline form.

Concrete examples will be presented to illustrate the importance of salt and crystalline form selection.

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