API Polymorph Screening and Separation by Crystallization Process

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Many chemical substances, especially pharmaceuticals, can be crystallized in different crystal forms, a phenomenon known as polymorphism. Polymorphic forms can exhibit different chemical and physical properties, which has directed and significant influence on the product performance in pharmaceutical, chemical and food industry and continues to pose a challenge to scientist in producing product of consistent quality. Concurrently, it provides a unique opportunity, to engineer solid to get new valued materials. Knowledge of solid-state properties and the identification of polymorphic forms are hence critical in the pre-clinical stage, due to the biopharmaceutical, regulatory and intellectual property implication. In new development trend, polymorphism screening which provides a general overview of polymorphic forms, is a very necessary and potential technology. This paper reviewed the control and screening of polymorphs in crystallization process.

The purpose of the screening is to find the different solid forms the API may exhibit and choose the form most suitable for further development. Even though the screening is called polymorph screening, other solid forms (hydrate/ solvates and amorphous form) cannot be neglected, which make them the best for development. In general, the polymorph was defined as the ability of the same substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Different solid-form can be profoundly influenced on the solubility, bioavailability and stability.

Unfortunately to crystallize complex molecules, such as active pharmaceutical ingredients (APIs), leads to problems on the formation of polymorphism and controlling polymorphism is a very complicated and unsolved problem in particular pharmaceutical crystallization research[1,2]. Due to these limitations, solid form discovery remains an experimental exercise, where manual screening methods are employed to explore form diversity of a compound.

Polymorph is determined by the kinetic of nucleation and growth rate which are function of supersaturation. The combination of generating different conditions and characterization methods can complete the screen of polymorphism. There are many factors, which can control polymorphic crystallization, including primary factors (eg, supersaturation, temperature, stirring rate, mixing rate of reactant solution, seed crystals) and secondary factors (eg, solvent, additives, interface, pH, Host-Guest composition). Different generating, controlling these factors in specially supersaturation can establish variety crystallization conditions and as the result, the different polymorphic forms may take place. Coordinating the identify and characterization polymorphism via analysis technique such as X-ray diffraction, microscopy, thermal analysis, vibrational spectroscopy (FTIR, Raman spectroscopy) and NMR can have a general observation of polymorphs. Currently, the application of in-situ measurement such as ultrasonic technique, FBRM aids to monitor polymorphs during crystallization process[3,4]. High throughput screening and high throughput experiment have also been desirable for polymorphism screening

References

[1] Haleblian J, McCrone W. Pharmaceutical applications of polymorphism. *J Pharm Sci* **58**. 1969. 911-929.

[2] Laird T. Special feature section: Polymorphism and crystallization. *Org Process Res Dev* **4**. 2000. 370-371.

[3] H.J. Kim, K.J. Kim, In-situ monitoring of polymorph transformation of clopidogrel hydrogen sulfate using measurement of ultrasonic velocity. J. *Pharm. Sci*. 97(10), 4473-4484. 2008.

[4] Nguyen, T.N.P., Kim, K.J. Kinetic Study on Hemipenta Hydrate Risedronate Monosodium in batch crystallization by cooling mode. International Journal of Pharmaceutics 364. 1-8, 2008