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Original Research Paper

A practical guide to pharmaceutical polymorph screening & selection

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ARTICLE INFO

Article history:
Received 1 April 2014
Received in revised form
29 April 2014
Accepted 3 May 2014
Available online 16 May 2014

Keywords:
Polymorphs
Polymorph screening
Polymorph selection
Polymorph preparation

ABSTRACT

Prevalence and importance of polymorphism occurring in pharmaceutical compounds are well recognized. It is of great importance to prepare and select the right form from the beginning during drug discovery and development. This review introduces the basic concepts of "What is polymorphism?", addresses a fundamental question of "Why do polymorphs form?", and provides practical guidelines of "How to prepare polymorphs?" "How to evaluate the relative thermodynamic stability between polymorphs?", and "How to analyze polymorphs?". Moreover, case studies of pharmaceutically important polymorphs are provided.

1. Introduction

The importance of polymorphism in pharmaceutical, pigment, electrical industry is mainly due to two reasons. The first one is because the existence of polymorphism is inevitable. In other words, polymorphism unavoidably occurs during discovery, development, and/or manufacturing process. As Ostwarld stated in 1899, "*Almost every substance can exist in two or more solid phases provided the experimental conditions are suitable.*" The other reason is because one may want it to happen. In other words, one can change the physicochemical properties of a given compound by using different polymorphs. Jean-Paul Garnier, CEO of GlaxoSmithKline said that "*About 50 % of drug candidates that enter clinical trials fail due to efficacy and safety concerns, and the remaining 40% fizzle due to patent concerns and issues like solubility and drug interaction.*" [1,2] This statement emphasizes the importance of manipulating the desired physicochemical properties during drug development.

Improvements in physicochemical properties can be achieved by altering the physical forms of a given compound such as polymorphs, solvates, amorphous, salts, cocrystals, and/or hydrates, etc. [3] Singhal et al. well summarized the physicochemical properties shown by different polymorphs with examples [4]. The physicochemical properties that can be

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Peer review under responsibility of Shenyang Pharmaceutical University

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.ajps.2014.05.002

Table 1 – Properties that can be altered by choosing different polymorphic forms [7–9,12].

Thermodynamic properties	**Kinetic properties**
• Melting and sublimation temperatures, and vapor pressure	• Dissolution rate
• Enthalpy, entropy, and heat capacity	• Rates of solid state reaction
• Free energy, chemical potential, and solubility	• Physical/chemical Stability
	• Rate of nucleation/crystal growth
Packing properties	**Surface properties**
• Molar volume and density	• Surface free energy
• Conductivity, electrical and thermal	• Interfacial tensions
• Refractive index	• Habit
• Particle morphology	**Mechanical properties**
• Hygroscopicity	• Hardness
• Color	• Tensile strength
	• Compactibility and tableting
	• Handling, filtration, flow and blending
	• Cleavage

altered by choosing different polymorphs are summarized in Table 1. The most important properties during drug discovery and development include solubility, dissolution, bioavailability, and physical/chemical stability. The best known polymorphs showing a significantly different bioavailability in human study are chloramphenicol palmitate [5] and mefenamic acid [6]. As the amount of the metastable form B present in suspension formulation increases, the peak plasma concentration of chloramphenicol palmitate in human increases linearly.

Over the past two decades, the importance of pharmaceutical polymorphism has been arising in scientific community and industry as well as regulatory agencies. Numerous reviews, book chapters, and literatures related to pharmaceutical polymorphism have been published [1,4,7–13]. This review introduces basic concepts of "What is polymorphism?", address fundamental questions of "Why do polymorphs form?", and provide practical guidelines of "How to prepare polymorph?", "How to evaluate the relative stability between polymorphs?", and "How to analyze polymorphs?". Moreover, case studies of pharmaceutically important polymorphs are provided.

2. What is polymorphism?

Polymorphism occurs when a chemical compound crystallizes with different internal structures. ICH Q6A defines polymorphism as "*some new drug substances exist in different crystalline forms which differ in their physical properties. Polymorphism may also include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms.*" [14] In a strict sense, polymorphs have to retain the same chemical composition and therefore, solvates or hydrates are defined as pseudopolymorphs. Polymorphs can be categorized into two subtypes: (1) conformational polymorphism and (2) packing polymorphism. Conformational polymorphs occur when conformationally different molecules exist in the crystalline state. Since pharmaceutical compounds generally contain flexible moieties in their molecular structures, there are numerous examples of conformational polymorphs. In packing polymorphism, the molecules share the same molecular conformations, but are packed differently in three-dimensional space. Form I and II of acetaminophen are the example of the most well known packing polymorphs [15,16].

In many known cases, several polymorphs crystallize concomitantly. *Concomitant polymorphism* is headache for pharmaceutical industry which seeks for polymorphic purity or blessing for those who seeks for several polymorphic forms. There are numerous examples of showing concomitant polymorphism. Extensive study of concomitant polymorphism was conducted by Bernstein et al. [17].

Another interesting and frustrating phenomenon related to polymorphism is "*disappearing polymorphism.*" [18–20] It is generally believed that "*any authentic crystal form should be capable of being re-prepared, although selection of the right conditions may require some time and trouble.*" [21] In contrast to the previous statement, "*disappearing polymorphism*" refers to a situation where the previously prepared form no longer appears after obtaining the more stable form. There are quite a few examples showing disappearing polymorphism including benzylidene-dl-piperitone, benzocaine picrate, mannose, etc. [18] "God-only knows where" seeds may play a role in crystallization of *disappearing polymorph* similar to *Dr. Breed* case for seeding phenomena [22].

3. Why do polymorphs form?

System tends to move toward thermodynamically equilibrated state. In other words, the system eventually transforms to the most stable state. However, the routes to the final state depend on kinetics as well as other factors as shown below. Several mechanisms were proposed why the metastable form appears first.

3.1. *Ostwald's rule of stages*

Ostwald in 1897 stated, "…beim Verlassen irgend eines Zustandes und dem Übergang in einen stabileren nicht der unter den vorhandenen Verhältnissen stabilste aufgesucht wird, sondern der nächtsliegende," and "*die Form, welche unter moglichst geringem Verlust an freier Energie erreicht werden kann.*" [23] When the system leaves any state, the transition occurs to a more stable one, not the most stable one but the nearest one under a given condition (Fig. 1). According to the theory, one has to observe all metastable forms before one finally observes the stable form. However, it is not always true. We often observe the direct crystallization of the stable form from a solution.

3.2. *Kinetic nucleation theory*

In this theory, the rate of nucleation of metastable form and the stable form are compared. In classical nucleation theory, the rate of nucleation is derived using Arrhenius equation [24].

$$J_{meta} = A_{meta} \exp\left(-\frac{\Delta G_{meta}}{kT}\right) \quad \text{Eq. 1}$$