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Form Selection of Pharmaceutical Compounds

Ann W. Newman and G. Patrick Stahly
SSCI, Inc., West Lafayette, Indiana

I. INTRODUCTION

The drug development process involves a number of activities which are carried out simultaneously, as shown by the oversimplified depiction in Fig. 1. Once a molecule is discovered that has desirable biological activity, the process of creating a pharmaceutical drug product from this molecule begins. As toxicology and efficacy studies are undertaken, methods for manufacture of the active molecule and for its delivery in therapeutic doses are sought. Critical to the latter effort is finding a form of the active molecule which exhibits appropriate physical properties. The form ultimately selected, called the active pharmaceutical ingredient (API), or drug substance, must be stable and bioavailable enough to be formulated into a drug product, such as a tablet or suspension. This formulation must be effective at delivering the active molecule to the targeted biosystem.

This chapter describes methodology useful in selection of the appropriate solid form of a drug substance for inclusion in a drug product. Form selection is commonly considered among the primary goals of a preformulation study. However, the investigative techniques discussed herein also have application in early drug substance and drug product development activities (shown by the circled area in Fig. 1).

Solid form selection involves the preparation and property evaluation of many derivatives of an active molecule. Drug substance properties of importance in the drug development process may be categorized as shown in Table 1. These properties depend on the nature of the drug substance and the final formulation. Many bioactive organic molecules contain ionizable groups such as carboxylic

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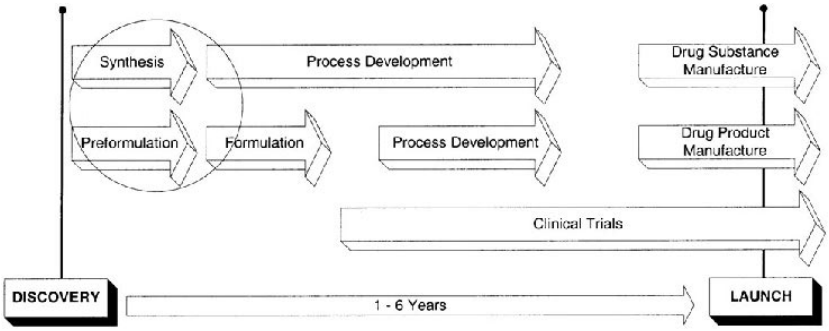

Fig. 1 The drug development process.

acid or amino groups. Reaction of these compounds with acids or bases produce salts, which have much different physical properties than the neutral parents. A single molecular entity, be it a salt or a neutral molecule, often exists in multiple solid forms, each of which exhibits unique physical properties. The properties of many such forms need to be evaluated relative to the intended formulation. A lyophilized product that will be dissolved and injected needs to be chemically stable in the dry state and adequately soluble in the carrier. On the other hand, the drug substance in a tablet formulation needs to be processable, chemically stable, and physically stable in the dry state, as well as having adequate solubility for delivery.

Form selection activities should be started as early in the development process as material availability allows. Salt selection, including preparation and eval-

Table 1 Some Important Properties of Drug Substances

Bioavailability	Chemical and physical stability	Processibility
Dissolution rate	Excipient compatibility	Color
Solubility	Hygroscopicity	Compactibility
Toxicity	Oxidative stability	Density
	Photostability	Ease of drying
	Thermodynamic stability	Filterability
	Crystal form	Flowability
		Hardness
		Melting point
		Particle size

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uation of samples, and polymorph screening can be carried out with as little as half a gram of active compound. Results of form selection include information that can be used in planning the final step of the manufacturing process (often crystallization) as well as information that is critical to formulation development.

The nature and extent of work to be performed during development can be modeled after the draft International Committee on Harmonization (ICH) Q6A document on specifications, which can be found on the Food and Drug Administration (FDA) website (www.fda.cder.gov). This document outlines the specifications needed for a New Drug Application and contains several decision trees to guide the selection of specifications. The Q6A decision tree 4 (Fig. 2) describes

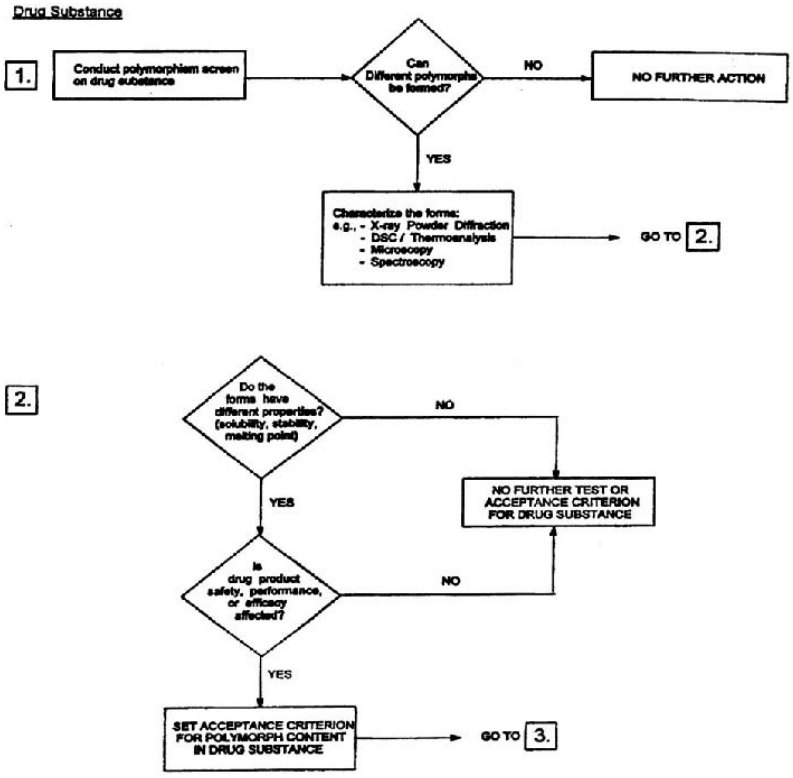

Fig. 2 Flow chart 4 from the ICH Q6A document (www.fda.cder.gov).

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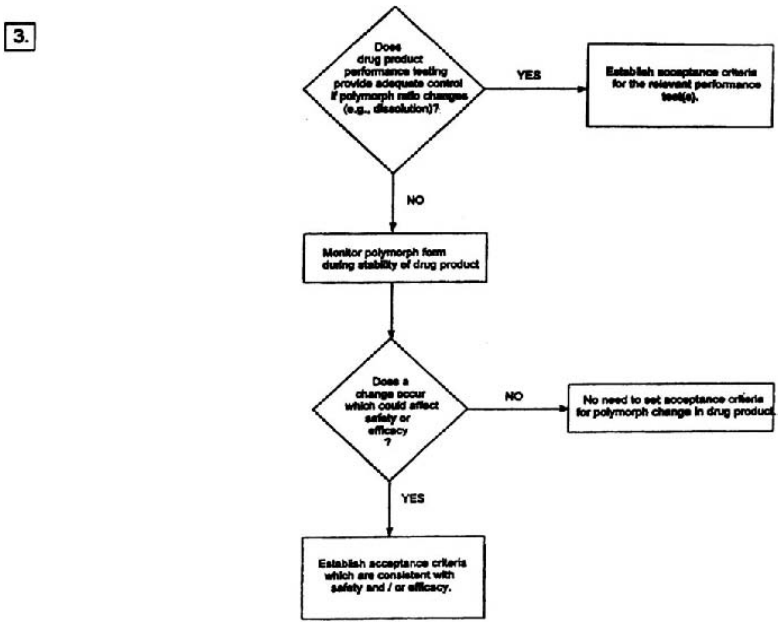

Fig. 2 Continued

methods for the study of solids for a polymorph screen as well as characterization of the drug substance in the drug product. Other decision trees have also been reported in the literature (1).

In this chapter we describe the form selection process. A short review of the analytical techniques commonly employed is followed by sections covering salt and solid form selection. Form selection should be approached in a planned, rational manner, but it is important to realize that not all compounds will allow adherence to a single experimental plan. The exercise is a scientific one, and it will yield the best results only if carried out with judgment and flexibility.

II. ANALYTICAL TECHNIQUES

A number of analytical techniques are commonly used in form selection studies. Various publications (2–4) and books (5,6) describe physical characterization

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of solid-state pharmaceuticals. A brief description of common methods will be presented in this section.

A. X-Ray Diffraction

Crystalline organic solids are made up of molecules which are packed or ordered in a specific arrangement. These molecules are held together by relatively weak forces, such as hydrogen bonding and van der Waals interactions. The arrangement of the molecules is defined by a unit cell, which is the smallest repeating unit of a crystal. The unit cell can be divided into planes, as shown in Fig. 3.

X-ray diffraction techniques used for characterizing pharmaceutical solids

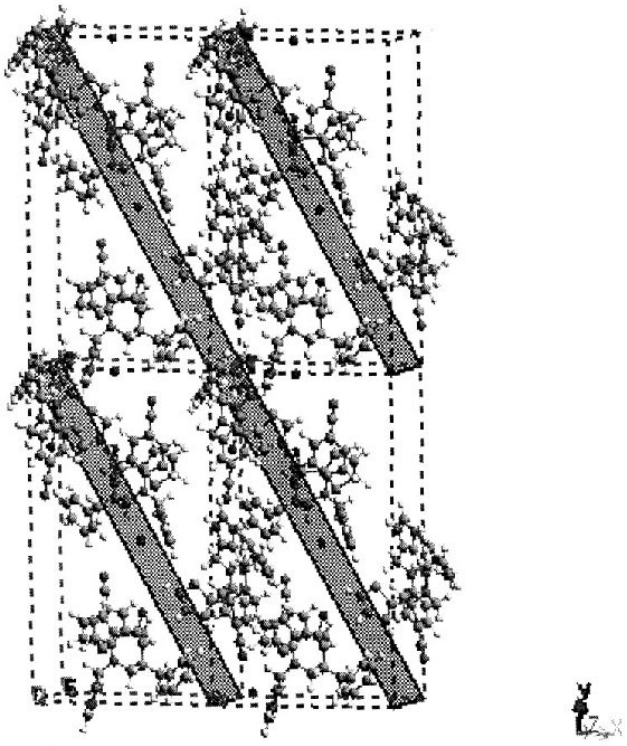

Fig. 3 A packing diagram of unit cells divided into planes.

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