6.2

ROLE OF PREFORMULATION IN DEVELOPMENT OF SOLID DOSAGE FORMS

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Contents

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6.2.1 INTRODUCTION

The advent of combinatorial chemistry and high-throughput screening (HTS) has exponentially increased the number of compounds synthesized and screened during the drug discovery phase. However, the overall efficiency of the drug discovery process is still exceedingly low (only 1 in 10,000 makes it to the market). Drug discovery is mostly driven by "activity screens" with little emphasis on "property screens." This is exemplified by the fact that 40% of attrition in drug discovery and development is attributed to poor biopharmaceutics and pharmacokinetic properties [1], which in turn are related to poor physicochemical properties. As a result, pharmaceutical companies have started to redesign their strategies by including property screens quite early in the discovery stage [2]. Preformulation is the study of fundamental properties and derived properties of drug substances. In other words, preformulation is the first opportunity to learn about the drug's physicochemical properties from the perspective of transforming a biologically active molecule to a "druggable" molecule. The type and extent of preformulation activities vary in a discovery and generic setting.

The main goal of a drug discovery program is to develop an orally deliverable molecule for obvious reasons of ease of manufacture and convenience of drug administration. More than 75% of the drug products in the market are oral formulations, of which more than half are solid dosage forms [3]. The "rule of five" developed by Christopher Lipinski [4] is one of the "physicochemical screens" to weed out molecules with poor physicochemical properties very early in the drug discovery process. According to Lipinski's rule, a drug will show poor oral absorption if it does not conform to any of the two physicochemical requirements listed in Table 1. The rule of five is applicable only to small molecules and it relates the chemical properties of the drug to its solubility and permeability characteristics. During the initial stages of drug discovery, the preformulation activities are mainly focused on developing a water-soluble compound for early activity studies and preclinical testing in animals. At this stage, the preformulation scientist is faced with the challenge of working with a limited quantity of compound (few milligrams) for testing a long list of physicochemical parameters. On the other hand, developing preclinical formulations can be quite a daunting task given the fact that toxicological studies require a high dose of drug (10–100 times above the effective dose) to be delivered in a small volume of the formulation. Preformulation activities increase as the molecule proceeds through the development phase. The "discovery and development phar-

TABLE 1 Lipinski Rule of Five for Orally Active Compounds

Physicochemical Parameter	Lipinski rule
Molecular weight	Not more than 500 Da
log *P*	Not more than 5
Hydrogen bond donors	Not more than 5 hydrogen bond donors expressed as the sum of OH's and NH's
Hydrogen bond acceptors	Not more than 10 expressed as the sum of OH's and NH's

maceutics" documentation forms a significant portion of the investigational new drug application (IND) application and new drug application (NDA) filed to the U.S. Food and Drug Administration (FDA). In a generic setting, preformulation studies are mainly focused on developing a formulation that is bioequivalent to the innovator's product with the main objective of filing an abbreviated new drug application (ANDA). A strong preformulation team can generate intellectual property in the form of new salts, solid-state forms, or new stabilized formulations of the drug for an innovator and/or a generic manufacturer.

In the present chapter, the discussion is mainly focused on preformulation testing for oral solid dosage forms in a drug discovery setting. The chapter address the following goals of preformulation: (i) to gain knowledge about the physicochemical characteristics of the drug, (ii) to define the physical characteristics of the drug, (iii) to understand the stability characteristics of the drug, and (iv) to determine the compatibility of excipients with the drug. In this chapter, we have grouped all the parameters under three sections and discussed in a logical sequence for the convenience of the reader.

6.2.2 PHYSICAL/BULK CHARACTERISTICS

The bulk or physical characteristics of a drug substance are mainly dictated by its solid-state properties. Purity of the drug substance is a fundamental property that is characterized at the beginning of preformulation studies. In the initial stages of drug development, the drug is usually not very pure. Nevertheless, it is essential to know the purity of the material at hand using simple measurements such as melting point. This would serve to set drug specifications during later stages of drug development. Differential scanning calorimetry (DSC) requires very little sample (1–5 mg) and is a useful tool to estimate the purity of the compound. The drug sample is heated in a crucible, where the difference in heat between the sample and a reference crucible is seen as an endotherm or exotherm in the thermogram depending on whether heat is taken up or given up, respectively, by the sample. The integrated area under the endotherm or exotherm gives a measure of the heat or enthalpy involved in this process. Melting is seen as an endothermic event and the purity of the sample will govern the peak position, shape, sharpness, and heat of fusion (ΔH_f). DSC is sensitive in detecting impurities to the extent of 0.002 mol % [5]. The DSC findings should be substantiated by a stability-indicating high-performance liquid chromatography (HPLC) assay. On the other hand, thin-layer chromatography (TLC) may be used to qualitatively detect the number of impurities in the drug sample. Impurity profiling is an important aspect of the drug development process, particularly for optimizing the synthetic process. The impurities can originate from many sources, including starting materials, intermediates, synthetic processes, or degradation reactions [6]. The regulatory guidelines stipulate that any impurity >0.05% of total daily dose (for drugs with a dose <2 g/day) or >0.15% of total daily dose (for drugs with a dose >2 g/day) should be evaluated for its safety [6]. Organoleptic properties such as color, taste, and odor are assessed qualitatively to set bulk drug specifications. If the drug has an unacceptable taste or odor, the chemistry group is advised to make a suitable salt form of the drug.

6.2.2.1 Crystallinity and Polymorphism

The majority of the drugs exist in crystalline form and are characterized by their crystal habit and crystal lattice. The crystal habit describes the external morphology of the crystal, including shape and size, while the crystal lattice describes the internal arrangement of molecules in the crystal (Figures 1*a* and *b*). Drug molecules arrange in more than one way in a crystal, and this difference in the internal arrangement of crystals is known as polymorphism. The polymorphs have the same elemental composition but differ in their physical, chemical, thermodynamic, stability, and spectroscopic properties. A crystal lattice represents the space in which molecules arrange in different ways. Organic molecules arrange in one or more of the seven possible crystal systems: triclinic, monoclinic, orthorhombic, tetragonal, rhombohedral, hexagonal, and cubic [7]. Each crystal system is characterized by its three-dimensional geometry and angles between the different crystal faces. The crystal lattice geometry is obtained using single-crystal X-ray diffractometry (XRD) and the details can be found elsewhere [7]. The difference in the crystal lattice of a drug arises as a result of the difference in packing of the molecules if the molecules are conformationally rigid (e.g., chlordiazepoxide) or due to the differences in conformation for flexible drug molecules (e.g., piroxicam). Although polymorphs differ in their internal crystal lattice, it may not be necessarily reflected in their external crystal habit (Figure 1*b*). In other words, a drug can exist in different crystal habits without any change in the internal crystal lattice (isomorphs).

Crystal habit is mainly dependent on crystal growth conditions [8]. For example, Figure 1*a* shows two different crystal habits for a given crystal lattice. A prismatic crystal habit will result if the growth is equal in all directions, while plates are formed if the growth is slow in one direction. Alternatively, needle-shaped crystals (acicular) are formed when the growth is slow in two directions. Thus, the crystal habits can

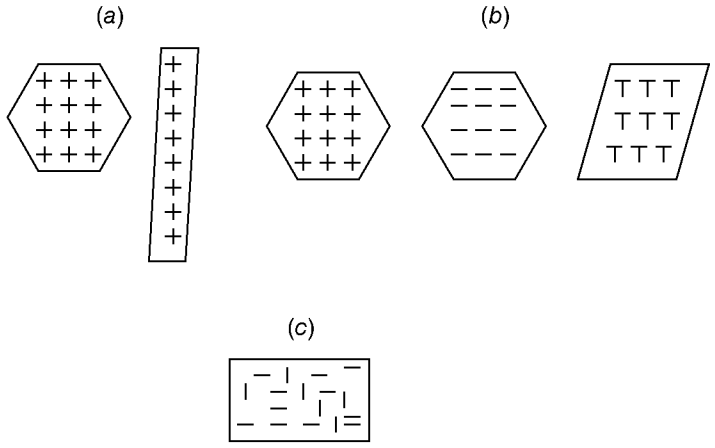
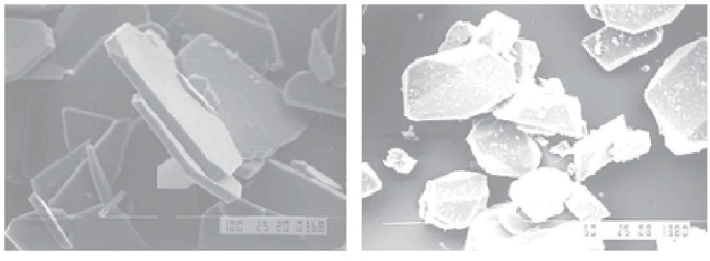
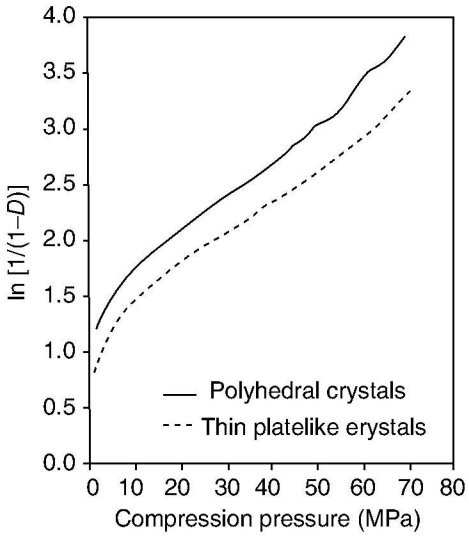


FIGURE 1 Schematic of crystal habits, polymorphs and amorphous drug forms. (*a*) Two crystal habits are shown. The internal crystal lattice is the same while the external morphology is different. (*b*) In a crystal the molecules are arranged in a regular fashion. However, the arrangement may vary depending on how the molecules orient themselves in the internal crystal lattice. The internal crystal lattice is different in all the three polymorphic forms. The polymorphs may or may not differ in their external morphology. (*c*) Random arrangement of molecules in amorphous form.

be altered without any change in the internal crystal lattice by varying the crystallization conditions. The polarity of the crystallizing solvent mainly influences the crystal habit by preferentially adsorbing to one surface of the crystal face. Similarly, surfactants or additives are added to the crystallization medium to prevent or promote the growth of a specific crystal habit [8]. Crystal habits mainly differ in physicomechanical properties such as packing, flow property, compressibility, and tablettability. Acetaminophen crystallizes as polyhedral crystals when crystallized from water and as plates when crystallized from ethanol–water (Figure 2*a*). Both these crystal habits are isomorphic [9], that is, have the same internal crystal arrangement, since their melting points and heats of fusion were similar (melting point 178 °C and ΔH_f = 177 kcal/mol). The polyhedral crystals have better flow and



(*a*)



(*b*)

FIGURE 2 Difference in crystal habit of acetaminophen and resultant difference in compressibility (*a*) Acetaminophen crystallizes as either platy crystals or polyhedral crystals depending on the solvent of crystallization. Both crystal habits have the same internal crystal lattice since they showed the same melting point. (*b*) Difference in compression behavior of two crystal habits. The *x* axis represents the compression pressure while the *y* axis represents the densification of the drug sample on compression. This plot is known as Heckel plot. The polyhedral crystal habit shows a higher densification implying better compressibility than plate like crystals. [From Garekani, H. A., Ford, J. L., Rubinstein, M. H., and Rajabi-Sahboomi, A. R., *International Journal of Pharmaceutics*, 187, 77–89, 1999. Reproduced with permission from Elsevier.)

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