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Historical Perspectives

A material science perspective of pharmaceutical solids

Yong Cui *

Small Molecule Pharmaceutical Sciences, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, United States

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Abstract

This review introduces the basic material science concepts and principles behind some common topics in the development of pharmaceutical solid formulations. The physiochemical properties of small organic pharmaceutical materials are summarized. Common phases, differences in phases, phase transitions, and their relation to pharmaceutical development are reviewed. The characteristics and physical nature of solid phases, including crystalline and amorphous solids, are presented in conjunction with some pharmaceutically relevant phenomena, such as polymorphism, phase transition kinetics, and relaxation. Mesophases, including liquid crystals and condis crystals, are introduced. The potential energy states of different phases are highlighted as the key connection between the physical nature of the materials and their pharmaceutical behavior, and energy landscape is employed to enhance the understanding of this relation.

Keywords: Material science; Physical property; Phase; Solid; Crystalline; Amorphous; Mesophases; Liquid crystals; Energy landscape

Contents

* Tel.: +1 650 467 1402; fax: +1 650 225 3613.
E-mail address: ycui@gene.com.

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1. Introduction

In modern drug discovery environment, it is crucial to build "drug-like" properties in the candidate molecules to ensure successful late-stage product development. Nevertheless, this goal has been proven challenging, particularly in many new drug discovery organizations, where pharmaceutical functionalities and procedures have not been well established. The challenge results partly from the lack of understanding among the discovery teams on the basic principles, technologies, and limitations of formulation development. Consequently, the "late-stage concerns" have not been given sufficient consideration at the early compound screening stage. To solve this problem, formulation scientists not only need to provide early formulation support, but also should serve as counselors to the discovery teams and ensure that "late-stage concerns" are well understood and addressed. To help achieve this goal, this article is targeted to provide an educational review on formulation strategies for drug discovery scientists with a diverse set of background.

Formulation of drug products has long been recognized as a multidisciplinary field. Material science is one of the pivotal branches that continuously provide important insights, theories, and technologies to formulation sciences. As an introduction to this broad topic, this article should necessarily be general, selective, and somewhat superficial. The focus is on early-stage solid formulation development strategy. Additionally, mesophases were given considerable attention in the text. This attention, however, highlighted the solid formulation considerations of mesogenic drug substances. The liquid crystalline drug delivery systems, on the other hand, have not been incorporated in this discussion. Although pharmaceutical implications and formulation strategies were underlined as the key topics, they were approached from a material science perspective and the underlying physical nature is the focus of this paper. The emphasis was given to energy states of various phases that are commonly encountered in pharmaceutical field due mainly to the rationale that the energy states impact directly to the pharmaceutical behaviors. Potential energy landscape was introduced to delineate the energy states in a topographic fashion. While maintaining the text straightforward and qualitative, attempt was made to keep the content consistent with the current scientific understanding, insights, and opinions in this broad area. In order to provide a general and broad overview, the literature cited has an emphasis on classical monographs and review papers.

2. Molecules and phases

Molecules are aggregates of atoms that are connected together through strong chemical bonds, most commonly covalent bonds. Molecules can generally be divided into two categories based upon their size: small molecules refer to molecules consisting of less than 1000 atoms or a molecular weight (MW) less than 10,000 Da; while large molecules (or macromolecules) consist of more than 1000 atoms (Wunderlich, 1999). This division is generally correct in many areas. In pharmaceutical environment, however, it may be more appropriate to set the division line at 1500 Da. One of the reasons to make this change is the difference in absorption of the molecules between these two ranges. In fact, Lipinski pointed out that those molecules with MW higher than 500 Da may already see significant reduction in absorption (Lipinski et al., 1997). Currently, most pharmaceutically significant small molecules indeed have MWs below 1500 Da.

Macroscopically, molecules exist in the form of phases. Molecules, either a single type or a mixture of different types, can aggregate together in different macroscopic forms with different states of thermodynamic energies. These macroscopic forms, which are uniform and homogeneous in chemical composition and physical state within the boundary of the forms, are called "phases" (Tilly, 2005).

When defining a phase, a couple of points should be kept in mind:

1. Phases should have well-defined boundaries or interfaces.
2. The boundaries or interfaces should have negligible influence on the phase properties. This requirement restricts the phases at the macroscopic scale because the interfaces will have significant impacts on the properties of "phases" if the size of the "phases" reduces to a sufficiently small scale.
3. The size or scale, within which the homogeneity is maintained, is crucial in defining a phase. In general, the composition and physical state become more and more heterogeneous as the scale goes smaller. For example, a solution consisting of two different types of molecules is homogeneous when observed at a macroscopic scale (e.g., of micrometers or above). It is therefore defined as ONE phase. However, when the scale reduces to one molecule, we either see molecule A or molecule B, which are obviously different and heterogeneity is observed. Therefore, homogeneity, and thereby phases, is really scale-dependent. Sometimes, when the scale reduces to a critical size, a clear definition of a phase is somewhat difficult. An example in pharmaceutical field is the difference between microemulsions and micellar systems containing solubilized oil in the core. Both systems contain dispersed oil "droplets" surrounded by surfactant layers. Microemulsons are viewed as two-phase systems, while micellar systems are generally believed to have only one phase (Attwood, 1994). These phases are sometimes called "microphases" or even "nanophases", with some ambiguity in their meanings.

Phases are one of the most crucial topics in pharmaceutical sciences. This is partly due to the following reasons:

1. Phases are the macroscopic existence of molecules. In practical applications, molecules are always utilized in the form of their phases. Therefore, the phase properties always play a role in the applications.
2. When molecules aggregate together in different ways, e.g. with different intermolecular distances or molecular orientations, different phases are produced, often at different energy levels. These energy differences, although in general are quite "weak", often generate pharmaceutically significant impact on the compound behaviors, including solubility, bioavail-