1 Introduction

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"These new compounds, like rocks, never dissolve in water." It sounds so familiar to you, does it not? Product development scientists often encounter significant difficulties in solving the problem of poor water solubility of drug candidates in the development of pharmaceutical dosage forms (Sweetana and Akers, 1996; Yamashita and Furubayashi, 1998; Willmann et al., 2004; Di et al., 2006). Poor *drug-like* properties of lead compounds led to ineffective absorption in the site of administration, which has been designated as an important part of the high clinical failure due to poor pharmacokinetics (Caldwell et al., 2001; Kerns and Di, 2003; Hartmann et al., 2006). However, these kinds of compounds represent an increasing proportion of newly discovered drug candidates. It is commonly recognized in the pharmaceutical industry that on average more than 40% of newly discovered drug candidates are poorly water soluble. Recently, it was reported that the percentage could be as high as 90% for new chemical entities (Kalepu and Nekkanti, 2015) and 75% for compounds under development (Rodriguez-Aller et al., 2015). As a matter of fact, poorly soluble compounds represent 40% of the top 200 oral drugs marketed in the United States, and more than one-third of the drugs listed in the U.S. Pharmacopeia fall into the poorly water-soluble or water-insoluble categories (Pace et al., 1999; Takagi et al., 2006; Rodriguez-Aller et al., 2015).

Interpretations of the term *water-insoluble drug* can vary depending on an individual's definition. According to USP 40/NF 35, *slightly soluble* means that "one part of solute can be solubilized by 100 to 1000 parts of solvent." If water is the solvent, then the water solubility of a *slightly soluble* drug can range from 10 mg/mL down to 1 mg/mL. If the same assumption is applied, *very slightly soluble* and *practically insoluble or insoluble* can be translated to 1 mg/mL down to 100 μg/mL, and equal to or less than 100 μg/mL, respectively. Therefore, in the broader definition, the term *water-insoluble drug* in this book is defined as the aqueous solubility of a drug that falls into the range of *slightly soluble* and below (i.e., <10 mg/mL). In the narrower definition, the term *water-insoluble drug* in this book indicates that the aqueous solubility of a drug belongs to the category of *practically insoluble or insoluble* (i.e., <100 μg/mL).

In the past two decades, with the applications of genomics, high-throughput screening, robotics, combinatorial chemistry, computational modeling, informatics, and miniaturization to the drug discovery area, far more drug candidates than ever have been generated for development (Lipper, 1999; Hann and Oprea, 2004). However, as a result of the preferred pharmacological activity process of drug discovery, which attempts to maximize the activity, biopharmaceutical or *drug-like* properties of new drug candidates, including water solubility, tend to suffer (Yamashita and Furubayashi, 1998; Lipinski, 2000; Caldwell et al., 2001). Although the incompatible work partnership between the preclinical groups and the discovery groups has been improved in many companies in the recent years (Alanine et al., 2003), it is noteworthy that a compound with great receptor affinity and selectivity, but with poor *drug-like* properties for formulation or delivery, is still rarely regarded as ineligible to enter development. This viewpoint has prevailed in industry despite the potential for a compound's poor *drug-like* properties to be a major delay on the development timeline (Lipper, 1999; Kola and Landis, 2004). Compounds optimized solely on the basis of receptor-based potency, depending on the nature of the receptor, are usually hydrophobic or water insoluble. Therefore, many problems have recently been experienced in the early formulation development of drugs (Sweetana and Akers, 1996; Corswant et al., 1998; Pace et al., 1999; Di et al., 2006). Water insolubility can postpone or completely halt new drug development, and can prevent the much needed reformulation of currently marketed products (Pace et al., 1999; Caldwell et al., 2001; Hartmann et al., 2006).