INTRODUCTION

The advent of high-throughput screening technologies, combinatorial chemistry, computational modeling, and proteomics has resulted in many more targets and compounds during the drug discovery stage (Venkatesh and Lipper, 2000). However, many of these compounds are highly lipophilic and have a high molecular weight. This is because compounds with these properties tend to have high potency (*in vitro* binding activity) due to additional hydrophobic interactions with enzyme or receptor surface (Lombardino and Lowe III, 2004). These compounds are usually not drug-like because of their low water solubility, a major cause for poor pharmacokinetics (PK) and oral bioavailability. As a result, they may falter in further development, resulting in a higher attrition rate and lost productivity.

Because how the drug is delivered has a direct impact on the PK behavior and the availability of the compound in efficacy studies and toxicological studies, identification of an appropriate formulation is crucial for an accurate assessment of a compound's suitability for pharmaceutical development. Formulations in early stages of development face an additional set of challenges such as time and material limitation. Adding to the challenges is the requirement for supra-pharmacological exposures (and hence high doses) in toxicology studies. Therefore, it is important to have phase appropriate formulation strategies in order to balance formulation challenges, stringent timelines, and cost. Good formulations should aid the establishment of structure–activity relationships (SARs); maximize the efficacy of the compound, while minimizing side effects in an animal model; and enable identification of potential development challenges by evaluating biopharmaceutical properties.

FORMULATION NEEDS AND CHALLENGES IN DISCOVERY SETTING

In the early development stages, there are mainly three studies that require formulations: *in vivo* efficacy studies, PK studies, and toxicology studies. Because of the large numbers of compounds involved and the very low amounts of each compound available, several high-throughput formulation development platforms have been developed to enable efficient formulation development. For poorly water-soluble compounds, multiple formulation options often need to be evaluated. Depending on the study purpose, exotic vehicles sometimes have to be used without considering the commercial viability of the formulation. Typically, the materials from the medicinal chemistry laboratories tend to be less controlled and might vary from batch to batch with high impurity levels (Gardner et al., 2004); therefore, the physical parameters such as solid state form (Huang and Tong, 2004), morphology, and particle size are not optimized (Kerns and Di, 2002; Pritchard et al., 2003; Balbach and Korn, 2004; Chaubal, 2004). Solubility/dissolution rate of material with different quality may vary, which can result in variable PK performance.

FORMULATION STRATEGIES AND DRUG DELIVERY OPTIONS

Several recent publications reviewed the formulation development aspects of drug candidates at the discovery stage (Chen et al., 2006; Neervannan, 2006; Maas et al., 2007; Timpe and Forschung, 2007). Amidon et al. (1995) first developed a system that groups drug molecules on the basis of their different solubility and/or permeability, known as the Biopharmaceutics Classification System (BCS). This classification has been widely used as a guide to assess the formulation development challenge. However, lack of the dose information at this early stage makes the assessment difficult. This is because the minimum solubility requirement is dependent on dose and permeability (Lipinski, 2002). In addition, BCS does not account for drug metabolism, another important factor affecting drug bioavailability. The molecular parameters, such as H-bond donors, H-bond acceptors, molecular weight, and calculated log *P* (Clog *P*), can also serve as a guide to understand the challenge in formulation development (Lipinski et al., 1997). Lee et al. (2003) presented a high-throughput