5 Water-Insoluble Drugs and Their Pharmacokinetic Behaviors

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With the great advances in high-throughput chemical synthesis and bioactivity identification, more and more new chemical entities (NCEs) gush into the pharmaceutical pipelines in this postgenomic era. Many of these NCEs in the pipelines are water insoluble, and pose great challenges not only to the preformulation and formulation endeavors but also to the *in vivo* assessment of their pharmacokinetic characteristics.

On the basis of Biopharmaceutics Classification System (BCS), water-insoluble drugs fall into two broad categories: BCS Class II (low solubility and high permeability) and BCS Class IV (low solubility and low permeability). Given the inherent low aqueous solubility and slow dissolution rate of water-insoluble drugs, a large intersubject variability in their pharmacokinetics, sizable and sometimes unmanageable food effects, erratic absorption patterns, unfavorable oral bioavailability in high gastric pH environment, difficulties in development of sustained-release formulations, and serious hurdles in establishing IVIVC may be anticipated. Since the impact of poor water solubility on pharmacokinetics mostly occurs at the dissolution and absorption levels, this chapter focuses only on the absorption aspect. Other aspects of the pharmacokinetics, that is, distribution and elimination, are considered less important and thus are not covered in this chapter.

To help investigators overcome these hurdles, several case studies will be presented in this chapter from a pharmacokinetic perspective. Some pharmacokinetic strategies in the drug development will also be discussed to mitigate or overcome the inherent caveats of water-insoluble drugs.