A new drug application (NDA) can be approved primarily on the basis of the results from pivotal safety and efficacy studies conducted in the indicated patient population. The knowledge of drug absorption is necessary to ensure safe and effective use of an oral dosage form. As mentioned earlier, drug oral absorption and subsequently oral bioavailability can be impacted by many factors. It has been known for some time that the rate and extent of oral drug absorption can be influenced, and even significantly altered, by the presence of food (Welling, 1977) or coadministration with an agent that can alter the GI motility (Greiff and Rowbotham, 1994) or gastric pH (Yago et al., 2014; Zhang et al., 2014). It could become clinically significant if substantial interactions exist for an insoluble drug with narrow therapeutic window.

EFFECTS OF FOOD INTERACTIONS ON PHARMACOKINETICS OF INSOLUBLE DRUGS

Food–drug interaction mechanisms are variable and drug-specific (Toothaker and Welling, 1980; Welling and Tse, 1984). Better understanding of food–drug interactions for an insoluble drug is especially important for optimizing patient management and streamlining drug development.

The food–drug interactions for water-insoluble drugs usually manifest themselves either in alteration in absorption rate or in absorption extent. Herein several case examples are selected to further illustrate the food-drug interactions for water-insoluble drugs.

CASE STUDY 1

Compound A was developed for acute pain management. It has fascinating pharmacology, and was positioned as a first-in-class pain reliever under clinical development.

Compound A is insoluble in water over a wide pH range, and it has large molecular weight (>700). Numerous attempts had been made to improve its oral absorption and minimize its food effect through tedious preformulation and formulation works. However, no substantial improvement in terms of formulation performance and mitigated food effect had been achieved. Significant food interactions (about 2-fold) were observed in dog models, although different formulations were tested. When Compound A was moved into the clinical phase, food effect was the most outstanding pharmacokinetic concern, and the team recognized it could eventually hamper its further clinical development.

A food-effect cohort was incorporated into the first-in-human single ascending dose study to preliminarily evaluate food effect of Compound A. An approximately 5- to 8-fold increase in oral bioavailability under fed condition was observed when Compound A was ingested with a high-fat meal in this food-effect cohort with a small number of subjects. Realizing that such a significant food effect could be a great hurdle to the further clinical development for Compound A, the team decided to conduct a formal food-interaction study with both a Food and Drug Administration (FDA)–recommended high-fat meal and a low-fat meal. Intensive and identical pharmacokinetic samples were collected in each of the three study treatments (i.e., fasted, fed with a low-fat meal, and fed with a high-fat meal) in a crossover manner. A high-fat meal resulted in the highest mean plasma concentration profile of Compound A, followed by a low-fat meal, as shown in Figure 5.1. Consistent with the preliminary findings in the first-in-human study in a small number of subjects, an approximately 2- to 3-fold increase in oral bioavailability with the low-fat meal was observed, while an approximately 5-fold increase was observed with a high-fat meal. Apparently, the oral bioavailability enhancement was related to the percentage of fat content in the test meal, as illustrated in Figure 5.2 for

(*Continued*)