Typical Absorption

In general, it is assumed that the oral absorption process follows first-order kinetics. This assumption appears to be valid for the majority of the drugs. The first-order process can also satisfactorily describe the oral absorption process of some drugs with very poor water solubility. Sometimes, the inclusion of the absorption time lag may appear to be needed to account for the lag time for the dissolution of the drug substance from the dosage form into the aqueous media in the GI tract. However, in some cases, the absorption patterns can't be readily characterized by the first-order kinetics with or without lag time; instead, they may be described by the following atypical or erratic absorption processes.

Zero-Order Absorption

For a typical drug with zero-order absorption, the concentrations after oral administration rise to a sharp peak and then quickly decline with no intermediate plateau. Examples of insoluble drugs whose absorption processes follow zero-order kinetics are cyclosporine (Grevel et al., 1986) and griseofulvin (Bates and Carrigan, 1975).

Erratic Absorption

Sometimes, absorption can be described by sequential zero-order and first-order absorption processes. Conceptually, if the first-order rate constant is linked to the zero-order input, the model can be postulated as the consequence of dissolution-limited absorption (Garrigues et al., 1991; Holford et al., 1992).

CASE STUDY 9

Apomine™, a biophosphonate ester, has poor water solubility (<0.1 μg/mL in water) and high lipophilicity (mLog P = 6.8). In the first single-dose study in healthy male subjects under fasting condition, it was observed that saturable absorption was occurring at a high dose (150 mg). This is consistent with the low solubility of apomine because it was anticipated that apomine's absorption would be dissolution rate limited, and that increasing the dose would eventually saturate the GI fluids (Bonate et al., 2004). A population pharmacokinetic modeling approach using NONMEM was applied to characterize the pharmacokinetics of apomine in healthy males and in male and female patients with solid tumors. Given the water-insoluble characteristics of apomine, two major modeling steps were adopted to well characterize its absorption process under both fasting and fed conditions:

Modeling of food effect on apomine's pharmacokinetics: It was expected that food would affect relative bioavailability ($F1$). Hence, three models had been tested:

$$\text{Model1: } F1 = 1 - \frac{\text{Dose}}{D_{50} + \text{Dose}} \times (1 + \text{Food} \times \theta_{\text{Food}}) \tag{5.1}$$

$$\text{Model2: } F1 = 1 - \frac{(\text{Dose})^n}{(D_{50})^n + (\text{Dose})^n} \times (1 + \text{Food} \times \theta_{\text{Food}}) \tag{5.2}$$

$$\text{Model3: } F1 = [1 - \exp(-D_{50} \times \text{Dose})] \times (1 + \text{Food} \times \theta_{\text{Food}}) \tag{5.3}$$

(*Continued*)