BACKGROUND OF DRUG ABSORPTION

In 1937, the pioneering paper "Kinetics of Distribution of Substances Administered to the Body" was published (Teorell, 1937). Since then, pharmacokinetics has been well developed and matured as an independent discipline. Nevertheless, the characterization of drug absorption usually is assumed empirically and lacks sufficient physiological basis. Even to date, some absorption processes are still not well understood and adequately defined.

Most drugs on the market today are taken orally. As long as a drug is well absorbed, oral administration is considered as the safest and most economical way of delivering drugs and brings effective and convenient means for treating patients. Some disadvantages to oral administration include limited absorption of some drugs owing to their physicochemical characteristics (e.g., water solubility, pK_a), emesis as a result of irritation to the gastrointestinal (GI) mucosa, disintegration and destruction of some drugs by digestive enzymes or low gastric pH, irregularities in absorption or propulsion in the presence of food or other drugs such as gastric pH modulating agents, and necessity for cooperation on the patient's side (Goodman & Gilman's 10th ed., 2001). For some drugs that are insoluble or sparingly soluble in water, the oral absorption could be limited or erratic, and this in turn may give rise to inconsistent efficacy or impose safety concerns.

Hellriegel et al. (1996) observed a significant inverse linear relationship between the bioavailability of a drug and its coefficient of variation. An insoluble drug with very low oral bioavailability usually has a very large intersubject variability in its absorption pharmacokinetic parameters, which may result in a worrisome safety profile or unfavorable efficacy profile.

A number of insoluble NCEs may not survive long before they can enter clinical testing. Nevertheless, under some special situations, for example, if an NCE is first-in-class or first-in-therapy, even if it has unfavorably poor water solubility, its entrance into further clinical testing is not unimpossible.

Factors Affecting Drug Absorption

Absorption from the GI tract is governed by many factors. Broadly, it can be categorized into three classes: physicochemical properties, biopharmaceutical factors, and physiological and pathophysiological factors (Mojaverian et al., 1985, 1988; Nomeir et al., 1996). Since this chapter focuses on the pharmacokinetic perspectives, the main factors that could affect drug absorption are merely listed in the following, and will be discussed in detail in other chapters.

Physicochemical Properties of a Drug

- pK_a, solubility, permeability
- Crystal forms
- Rate of dissolution

Biopharmaceutical Factors of a Dosage

- Excipients
- Tablet compression parameters
- Coating and matrix

Physiological and Pathophysiological Factors

- GI transit and pH microenvironment
- Presystemic metabolism
- Transport mechanism/efflux
- Absorption window
- Diseases, demographics including gender, age, ethnicity, and so forth