CASE STUDY 7 (*Continued*)

pretreatment with metoclopramide decreased the systemic exposure by about a half, and shortened t_{max} by 2.7 h. However, for griseofulvin formulated in polyethylene glycol (PEG) 600, the pretreatment of metoclopramide could increase the systemic exposure to griseofulvin by approximately 2.5-fold. The underlying mechanism of the contrary results that were observed with different formulations of griseofulvin has not been well defined. The potential role of PEG 600 in facilitating the oral absorption of griseofulvin cannot be excluded.

CASE STUDY 8

Cyclosporine A, an immunomodulating agent, has poor water solubility (19 nM at 25°C). It has very large molecular weight (1203). Its oral absorption is incomplete and variable from the GI tract, and its absolute bioavailability was found to be less than 10% in liver transplant patients, but was more than 89% in some renal transplant patients. The pretreatment with metoclopramide could significantly shorten t_{max} of cyclosporine A owing to the increase in the absorption rate of cyclosporine A by metoclopramide. Meanwhile, its oral bioavailability was also enhanced by 29% with this GI prokinetic agent (Wadhwa et al., 1987).

Effects of Gastric Emptying-Slowing Agents

Gastric emptying-slowing agents, another class of GI motility modifying agents, include (but are not limited to) opioids (such as morphine, pethidine [Wood, 1991]), anticholinergics, β-adrenoreceptor agonists, omeprazole (Cowan et al., 2005), and exenatide (Kolterman et al., 2003). This class of agents is anticipated to increase total bioavailability of a coadministered drug by decreasing its rate of absorption owing to decreasing gastric emptying.

One example is the examination of the effect of a gastric emptying-slowing agent, propantheline, on the bioavailability of ciglitazone (Cox et al., 1985). The coadministration of propantheline resulted in 20% increase in ciglitazone bioavailability, and this increase might be explained by the absorption window hypothesis. An increase in the residence time by a gastric emptying agent may have allowed more of the drug to dissolve at absorption sites. Though supported by very limited data, in theory, the increase in the residence time of a drug with poor water solubility by a gastric emptying agent may facilitate dissolution in the GI tract before absorption occurs, and subsequently augment its oral bioavailability (Zhou, 2003).

Although many effects reported in the literature are of limited clinical importance, they may be significant when prescribing a drug with a narrow therapeutic window, especially if it is absorbed poorly owing to its poor water solubility.

CHARACTERIZATION OF ABSORPTION PROCESSES VIA MODELING APPROACHES

Over the last several decades, modeling and simulation techniques have become more widely used to characterize the *in vivo* dissolution and subsequent absorption characteristics of orally administered drugs. These modeling and simulation approaches can help the formulation development and optimization for water-insoluble drugs. The understanding and characterization of the absorption kinetics is an important step in a successful absorption modeling endeavor.