bioavailability is not a very important factor, particularly when safe plasma concentrations well above the target efficacious concentrations are achievable by the intended clinical route. Nevertheless, a comparison of absolute bioavailabilities in different animal species could provide important information with regard to permeability, absorption, and drug metabolism across species.

Poor bioavailability may sometimes also be the result of extensive hepatic clearance and/or hepatic metabolism rather than poor absorption. In such cases, permeability data in Caco-2 cells and in vitro metabolism studies in liver microsomes/hepatocytes could help guide the preclinical programs.

3.3.1. Formulation Selection for Preclinical Toxicology Studies

Often, bioavailability studies in animals are very useful for appropriate design of preclinical toxicology studies. For a poorly bioavailable drug, even when the compound is highly potent, it is important to achieve sufficient plasma concentrations and exposure in order to achieve measurable toxicity and to calculate the margin of safety. Early preclinical toxicology studies are generally conducted with escalating doses usually up to MTD, in some cases as high as 2000 mg/kg. Unfortunately, in most cases, drugs are insoluble at those high doses and, therefore, are poorly absorbed. As a result, a dose–response relationship up to MTD may not be achieved. Therefore, it is critical to use a vehicle that solubilizes the drug at high doses, before toxicology studies are conducted. It is now routine practice in early drug development to use common vehicles that solubilize the drug to desired concentrations. Several formulation additives (e.g., PEG-400, hydroxypropyl β-cyclodextran, Tween, propylene glycol, cremophere, and VitaminE-TPGS) are known to enhance the solubility of compounds (60,61). These agents can be utilized to enhance drug absorption, resulting in a dose-dependent increase in drug exposure and toxicity. In addition, some of these formulations also increase drug absorption by inhibiting Pgp-dependent efflux, as described previously in this chapter.

4. MECHANISMS OF SMALL MOLECULE DISTRIBUTION

Distribution is one of the two critical determinants of drug disposition, the other being clearance. Once a compound reaches the systemic circulation, it is available for distribution throughout the body. While the therapeutic effect of the drug will depend on its ability to access its site of action or ''biophase,'' drug distribution to other organs and tissues can result in adverse or toxic effects. Additionally, sequestration of drug in an organ or tissue may result in a prolonged residence time in the body (i.e., a long elimination half-life).