Gram-positive lactic acid bacteria possess several MDRs that excrete out of the cell a wide variety of mainly cationic lipophilic cytotoxic compounds, as well as many clinically relevant antibiotics. These MDRs are either proton/drug antiporters belonging to the major facilitator superfamily of secondary transporters or ATP-dependent primary transporters belonging to the ATP-binding cassette superfamily of transport proteins.

It is increasingly recognized that efflux transporters play an important role, not only in chemo protection, for example, MDR, but also in the absorption, distribution, and elimination of drugs. The modulation of drug transporters through inhibition or induction can lead to significant drug–drug interactions by affecting intestinal absorption, renal secretion, and biliary excretion, thereby changing the systemic or target tissue exposure of the drug. Few clinically significant drug interactions that affect efficacy and safety are due to a single mechanism. and there is a considerable overlap of substrates, inhibitors, and inducers of efflux transporters and drug-metabolizing enzymes, such as CYP3A. In addition, genetic polymorphisms of efflux transporters have been correlated with human disease and variability of drug exposure.

3.6.2 In Vitro–In Vivo Correlation

The in vitro–in vivo correlation (IVIVC) is an extremely useful exercise at the preformulation level that determines how scale up and postapproval changes or Biowaiver principles would be exploited. Conceptually, IVIVC describes a relationship between the in vitro dissolution or release versus the in vivo absorption. This relationship is an important item of research in the development of drug delivery systems. In vitro dissolution testing serves as a guidance tool to the formulator regarding the product design and in quality control. Especially, it is of specific importance for modified-release dosage forms, which are intended for the purpose of prolonging, sustaining, or extending the release of drugs. By applying mathematical principles, such as linear system analysis and moment analysis, the data describing in vitro and in vivo processes can be obtained. Developing a predictable IVIVC depends on the complexity of the delivery system, its formulation composition, method of manufacture, physicochemical properties of the drug, and the dissolution method. Several sophisticated commercial dissolution methods are available, along with the software to develop IVIVC models; these will be discussed elsewhere in the book.

3.6.3 Caco-2 Cell Studies

Caco-2 monolayer, a model for human drug intestinal permeability, is of great interest. Kinetics of intestinal drug absorption, permeation enhancement, chemical moiety, structure–permeability relationships, dissolution testing, in vitro–in vivo correlation, and bioequivalence are studied using Caco-2. The Caco-2 cell line is heterogeneous and is derived from a human colorectal adenocarcinoma. Caco-2 cells are used as in vitro permeability models to predict human intestinal absorption, because they exhibit many features of absorptive intestinal cells. This includes their ability to spontaneously differentiate into polarized enterocytes that express high levels of brush-border hydrolases and form well-developed junctional complexes. Consequently, it becomes possible to determine whether passage is transcellular or paracellular, based on a compound's transport rate. Caco-2 cells also express a variety of transport systems, including dipeptide