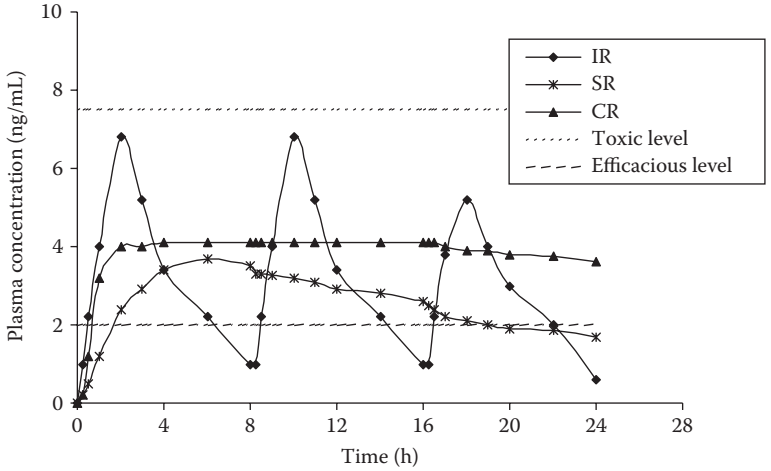

FIGURE 22.1 A typical plasma concentration profile comparing differences between immediate-release (IR), sustained-release (SR), and controlled-release (CR) oral dosage forms.

and effectiveness both by absorption enhancement as well as by focusing drug release at or near its site of action. With an ever-increasing number of water-insoluble or poorly water-soluble compounds discovered as the result of high-throughput screening (HTS), MR drug delivery of water-insoluble drugs is becoming an important product development strategy to maximize utility. In addition, these approaches are useful as a life-cycle extension tool for application to clinically proven drug molecules. In this respect, the development of such a drug delivery product may create greater value in fulfilling unmet medical needs not addressable by the marketed immediate release formulation.

Since more than 80% of candidate drugs have traditionally been developed for oral administration, this chapter will focus on a discussion of theories, delivery technologies, examples, and future perspectives regarding design of oral MR delivery systems for water-insoluble compounds. Figure 22.1 illustrates one of the classic clinical benefits of applying sustained- and controlled-release dosage forms, that is, improving the safety profile and patient compliance by reducing peak plasma concentration while at the same time providing for prolonged effective drug levels in the blood at levels sufficient for therapy, but below those that provoke unwanted side effects.

In the initial design of an oral MR drug product, a number of parameters often dictate feasibility and as such need to be critically evaluated. These important parameters include

- Physicochemical properties of the drug.
- Biopharmaceutical and pharmacokinetic (PK) information of the drug available after immediate release administration.
- Physiological factors affecting absorption, for example, gastrointestinal (GI) transit time, gastric emptying time, GI content, surface area, pH, enzymatic metabolism, and site-specific absorption.
- Desired therapeutic and PK profile.

FACTORS INFLUENCING ORAL MODIFIED-RELEASE DELIVERY SYSTEM DESIGN AND PERFORMANCE FOR WATER-INSOLUBLE DRUGS

Compound Characteristics

Physicochemical properties of the drug, such as ionization constant (pK_a), aqueous solubility, partition coefficient (log P), and chemical stability significantly influence the dosage form design.