Since the drug preferentially transports across biological lipid membrane in a unionized form, the relationship between drug properties such as pK_a, solubility, and the physiological environment of GI tract is of significant importance. In general, the nature of drug solubility is one of the most important factors for the design of the MR dosage forms as it limits the choice of release mechanism available. In some cases, low drug solubility may make some delivery platforms better candidates than others. Application of solubilization techniques enables design and development of oral MR dosage forms for poorly water-soluble drugs and can provide more choices and options in designing such a delivery system.

The biological half-life, $t_{1/2}$, is an important biopharmaceutical parameter quantitatively describing the elimination rate of the drug from the body and is one of the criteria for consideration in MR dosage form design. To maintain plasma levels of a therapeutic agent over a prolonged period of time, the rate of drug absorption must be approximately equal to the rate of drug elimination, which is determined by the $t_{1/2}$. Typically, therapeutic compounds with very short $t_{1/2}$ and high volume of distribution undergo rapid clearance making prolonged delivery and action difficult. On the other hand, the compounds that do have a relatively long $t_{1/2}$ exhibit by definition extended plasma levels. In general, compounds with $t_{1/2}$s shorter than 2 h or greater than 8 h are not good candidates for sustained-release dosage forms. In some unique cases, however, development of a controlled-/sustained-release oral dosage form may be considered for the drugs with $t_{1/2}$ longer than 8 h as the controlled release of these compounds can still offer reduced *C*max, thereby leading to elimination of *C*max associated side effects. For the compounds that show short half-life (<2 h), a MR dosage form design combining an immediate-release (IR) component and a controlled-release portion could mitigate the low bioavailability issue caused by extensive first pass metabolism.

The absorption window and characteristics of a compound also affect the suitability of a drug as a MR candidate. Enzymatic processes in the gut may cause significant drug loss even before the drug is absorbed, and compounds that are poorly metabolized either in the lumen or tissue of the intestine presystemically may not be suitable for MR dosage forms. Designing a once daily, zero-order, controlled-release product, for example, requires the drug to demonstrate good absorption in the lower GI tract, including the ascending colon, since the transit time of a delivery system is very limited at the upper GI tract.

Physiological Environment of GI Tract

Successful drug release from an oral dosage form, either an immediate release or a MR dosage form, and uptake into the general circulation will be dependent upon several key factors: delivery of the drug to the absorption site, providing a stable solubilized form of the drug, transport of the drug molecule across the membrane of GI tract, and delivery of the drug to its site of action. Notably, the physiological environment of the GI tract plays an important role in determining the solution state and bioavailability of the drug after it is released from the dosage form.

The Biopharmaceutics Classification System (BCS) is a drug development tool that allows estimation of the contribution of three fundamental factors of the drug including dissolution, solubility, and intestinal permeability, which govern the rate and extent of drug absorption from solid oral dosage forms. The dissolution is the process by which the drug is released, dissolved, and becomes ready for absorption. Permeability refers to the ability of the drug molecule to permeate through a membrane into the systemic circulation. According to BCS definition, drugs are classified into four categories: BCS Class I drugs are those with high drug solubility and permeability, BCS Class II drugs are ones having low solubility and high permeability, the BCS Class III drugs have high solubility and low permeability, and BCS Class IV compounds are poorly soluble and permeable. In the case of water-insoluble drugs discussed in this chapter, which are typically BCS Class II compounds, the drug dissolution and solubilization may be a serious limitation to oral drug absorption.