The drug saturation solubility is $C_s = [B]$ when the drug is totally unionized in an aqueous solution. Therefore,

$$C_h = C_s\left(1+\frac{[H]}{K_b}\right) \tag{22.6}$$

Ideally, the release of an ionizable compound from a sustained-release product should be programmed in accordance with the variation in physiological pH along different segments of the GI tract. Thus, theoretically, the amount of the absorbed (uncharged) species and the plasma concentration can be kept approximately constant throughout the time course of drug release and action.

Another important factor that may influence solubility, dissolution rate, and therefore absorption of water-insoluble compounds is the contents of the GI fluids. The GI fluids contain various materials, such as bile salts, enzymes, and mucin. Bile salts are surface active and as such could potentially enhance the rate or extent of absorption of water-insoluble drugs. Thus, the increased absorption of a water-insoluble compound, griseofulvin (GF), after a fatty meal may be facilitated by bile salt secretion into the gut resulting in solubilization (Crounse 1961; Kraml et al. 1962).

In Vitro and *In Vivo* Evaluations

The rational development of a drug delivery system can be timely and costly. Formulation development and optimization requires a step-wise approach by first screening and evaluating various formulations *in vitro* before one initiates formulations/dosage forms testing *in vivo.*

The drug release or dissolution rate is considered one of the most important *in vitro* characteristics as the *in vivo* absorption for BCS Class II compounds can be significantly affected by these parameters. Identifying a discriminating and predictive *in vitro* dissolution/drug-release test method is important in the cost-effective development of oral solid dosage forms. The ability of using an *in vitro* dissolution test to predict the *in vivo* performance and correlate with the resulting absorption profile, that is, establishment of *in vitro/in vivo* correlation (IVIVC), has been an ongoing industrial effort with the ultimate goal being a validated *in vitro* test and IVIVC model that can be used for multifarious purposes including (Skelly et al. 1990; Food and Drug Administration 1997a, b; Yu et al. 1998; Sunkara and Chilukuri 2003):

- Facilitating screening, monitoring, and optimization of dosage forms
- Providing product quality and process control
- Assisting in certain regulatory determinations and judgments when there are minor formulation and process changes, and sometimes, a change in manufacturing equipment, methods, or sites

Over the last decade, it has been increasingly reliable to use the *in vitro* dissolution or drug release rate test as an indication of the *in vivo* absorption characteristics and PK behavior for the oral solid dosage form based on a well-established IVIVC (Hwang et al. 1995; Food and Drug Administration 1997b; Modi et al. 2000). In particular, the application of IVIVC studies for supporting regulatory submissions is gaining currency. As a result, the Food and Drug Administration (FDA) has published guidance for the industry regarding development, evaluation, and application of IVIVCs for extended-release oral dosage forms (Food and Drug Administration 1997).

In Vitro Methods

Several known *in vitro* dissolution/release-rate test methods have been reported for assessing *in vitro* performance of MR dosage forms. The selection of a particular *in vitro* dissolution test method for a product is often dependent on the type and/or design of the dosage form. These commonly used tests are summarized in the following: