**TABLE 4.3**
**Classification of Effective Permeability**

| Effective Permeability (Pe) | Classification | Comments |
|---|---|---|
| $\leq 0.1 \times 10^{-6}$ cm/sec | *Low* | Will have permeability problems |
| $0.1 - 1 \times 10^{-6}$ cm/sec | *Moderate* | May have permeability problems |
| $\geq 1 \times 10^{-6}$ cm/sec | *High* | No permeability problem |

have been successfully extended in the Biopharmaceutics Drug Disposition Classification System (BDDCS) to explain the potential mechanism of drug clearance and understand the effects of uptake and efflux transporters on absorption, distribution, metabolism, and elimination (Varma et al. 2012).

In pharmaceutical industry, in both Caco-2 measurement and rat jejunal perfusion, if a drug has higher permeability than metoprolol, the drug is considered highly permeable. With permeability coefficient approximately $1 \times 10^{-6}$ cm/sec, metoprolol has about 95% human adsorption fraction (Regardh et al. 1974, Kim et al. 2006). Even though the *in vitro* permeability measurement may not be exact the same as *in vivo* permeability data, many publications have shown that there exists good rank order relationship between true permeation rate constant with measured permeability from Caco-2 monolayer or rat jejunal perfusion (Polli and Ginski 1998, Winiwarter et al. 1998, Kim et al. 2006). Therefore, by comparing the measured drug permeability with the measured Metoprolol permeability in the same measurement system, it is possible to evaluate whether the drug has high permeability or not.

It is worthwhile to note that BCS was designed to evaluate whether or not clinical bioequivalence can be justified based on *in vitro* dissolution tests, especially for immediate release solid oral dosage forms. However, the criteria of high solubility and high permeability in the system are higher than actual drug developability. For example, some Class IV drugs with solubility and permeability just below the criteria are still good candidates in development to achieve desired bioavailability. With permeability about $0.1 \sim 0.3 \times 10^{-6}$ cm/sec, drugs like atenolol and a-methyldopa have about 50% absorption fraction (Walter et al. 1996, Kim et al. 2006). Combining the information about the permeability and absorption fraction of metoprolol, effective drug permeability can approximately be classified into three categories as shown in Table 4.3 (Chemical Sciences 2001). The table may provide more practical evaluation on drug permeability than does BCS evaluation.

## STABILITY

Information about drug stability is important for drug synthesis, formulation, and storage to the final dosing in humans. In addition to chemical stability of drug substance reviewed in this section, physical stability will be reviewed in the section titled Solid State Properties. Table 4.4 illustrates some indicative stability studies (Chemical Sciences 2001). It is worthwhile to note that the stability of these insoluble compounds in the presence of solubilizing agents is very likely to be different from the stability in aqueous solutions. For this reason, stability in purely aqueous media may not be relevant at all and it may be difficult to determine because of the solubility limitation. Besides those solubilizing excipients, it is important to check whether the drug of interest is compatible with other excipients that may be used in formulation design and process development.

### Forced Degradation Studies

Forced degradation studies are useful not only for checking the drug stability under different conditions, but also for analytical method development and method validation (Maheswaran 2012). In the forced degradation studies, the solubilized drug is exposed to extremes of acid, base, heat,