DISSOLUTION MEDIA

Quality Control Dissolution Media

The choice of dissolution medium will depend on the purpose of the dissolution test. For batch-to-batch quality control testing, selection of the dissolution medium is based, in part, on the solubility data and the dose range of a drug product to ensure that sink conditions are met. However, under certain circumstances, a medium that fails to provide sink conditions may be justifiable (Brown et al. 2004). If the pH-dependent solubility indicates that the drug has a low solubility only in a particular pH range, the most likely media for an appropriate quality control dissolution test is an aqueous buffer at pH values that lead to high solubility. This approach becomes problematic when the pH with high solubility is greater than 6.8, because this condition is not relevant to *in vivo* dissolution. Nevertheless, in FDA OGD's dissolution database [http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm], out of about 300 dissolution methods, 19 use a pH higher than 7.2 and 10 use pH greater than 6.8 but less than or equal to 7.2. The use of pH outside physiologically relevant pH should be strongly discouraged.

Surfactants can be used in a biorelevant manner by choosing a surfactant that matches solubility in more expensive simulated biological fluids. However, surfactants are more often used in a quality control setting for drugs whose solubility (even *in vivo* solubility) is too low to establish the sink condition. Noory et al. (2000) discuss some method development strategies and provide justification for the use of particular surfactants. Surfactants that have been used in the FDA-approved dissolution methods include Tween, CTAB, and Tris buffer, with SLS being by far the most commonly used surfactant. In general, it is desirable to use as little surfactant as possible to reach sink conditions. If too much surfactant is used, a dissolution test may not be able to detect changes in polymorphic form or particle size, as suggested in International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Biorelevant Dissolution Media

Although dissolution testing is currently used primarily for quality control, it is desirable to have a dissolution test that is predictive of *in vivo* performance. Therefore, there has been recent interest in developing biorelevant media whose properties match those of human gastric or intestinal fluids (Kalantzi et al. 2006). Vertzoni et al. (2005) proposed a fasted state simulating gastric fluid (FaSSGF), as shown in Table 6.1. The use of FaSSGF improves the predictability of dissolution for a weak base, but not for a neutral drug. Table 6.1 also describes Dressman's proposed biorelevant dissolution media that simulate intestinal fluid for the fasted state as well as fed state. A comparison of the *in vitro* dissolution data in biorelevant media with *in vivo* data shows that it is possible to simulate food effects and shows differences in absorption between products of the same drug with the physiologically relevant media (FaSSIF, FeSSIF, and milk) (Nicolaides et al. 1996).

TABLE 6.1
Biorelevant Media to Gastric and Intestinal Conditions

Ingredient	FaSSGF: Stomach (Fasted State)	FaSSIF: Small Intestine (Fasted State)	FeSSIF: Small Intestine (Fed State)
NaH_2PO_4 (mg/mL)	—	3.95	—
Acetic acid (mg/mL)	—	—	8.65
Pepsin (mg/mL)	0.1	—	—
Sodium taurochorate (mM)	0.08	3	15
Lecithin (mM)	0.02	0.75	3.75
NaCl (mM)	34.2	0.068 g	0.20