with a narrow neck, and the closed hysteresis loop, which may be closed owing to compounds having capillary pore sizes.

A large uptake of moisture often indicates a phase change. In this case, the desorption phase is characterized by only small decreases in the moisture content (depending on the stability of the hydrate formed), until at low RH, when the moisture is lost. In some cases, hydrated amorphous forms are formed on desorption of the hydrate formed on the sorption phase. In this case, the sorption of moisture causes the sample to crystallize as a hydrate, which at higher RH crystallizes into a higher hydrate. The higher hydrates are generally more stable to decreasing RH until the humidity level reaches to less than 10%, when most of the sorbed moisture can be lost to regenerate the amorphous forms.

In terms of salt selection procedure, the critical relative humidity (CRH) of each salt should be identified. This is defined as the point at which the compound starts to sorb moisture. Clearly, compounds or salts that exhibit excessive moisture uptake should be rejected. The level of this uptake is debatable, but those exhibiting deliquescence (where the sample dissolves in the moisture that has been sorbed) should be automatically excluded from further consideration.

The automation of moisture sorption measurements is a relatively recent innovation. Prior to this, moisture sorption of compounds (~10 mg) was determined by exposing weighed amounts of compound in dishes placed in sealed desiccators containing saturated solutions of salts. Saturated solutions of salts that give defined RH (as a function of temperature) have long been in use. The RH of a saturated solution at 25°C ranges between 0% for silica gel and 100% for water, potassium acetate (20%), calcium chloride (32%), sodium bromide (58%), potassium bromide (84%), and dipotassium hydrogen phosphate (92%). The test samples are placed in chambers containing these salts and then, after saturation sorption, analyzed using methods such as TGA, HPLC, and so on, to ascertain if there had been any phase change owing to sorption in the solid state; this may require additional testing using scanning electron microscopy (SEM), DSC, or XRPD.

6.9.11 Dissolution Testing

During the preformulation stage, an understanding of the dissolution rate of the drug candidate is necessary, as this property of the compound is recognized as a significant factor involved in drug bioavailability. Dissolution of a solid usually takes place in two stages: salvation of the solute molecules by the solvent molecules, followed by transport of these molecules from the interface into the bulk medium by convection or diffusion. The major factor that determines the dissolution rate is the aqueous solubility of the compound; however, other factors, such as particle size, crystalline state (polymorphs, hydrates), pH, and buffer concentration, can affect the rate. Moreover, physical properties, such as viscosity and wettability, can also influence the dissolution process.

Ideally, dissolution should simulate in vivo conditions. To do this, it should be carried out in a large volume of dissolution medium, or there must be some mechanism whereby the dissolution medium is constantly replenished by fresh solvent. Provided this condition is met, the dissolution testing is defined as taking place under sink conditions. Conversely, if there is a concentration increase during dissolution testing, such that the dissolution is retarded by a concentration gradient,