### 6.8.2 Melting Point

Solubility is increased when the melting point of the salt is lower or where there is improved hydrogen bonding (with water), and as a result, the hydroxyl groups in the conjugate acid improve the solubility and the hydrophobic groups reduce the solubility. Often, it is desired to prepare salts with a lower solubility to mask taste, provide slower dissolution, and increase its chemical stability. An increase in the melting point results in process problem and reduced solubility; this can be achieved by the use of more flexible aliphatic acids with aromatic bases. Move to more highly substituted acids that destroy the crystal symmetry. A decrease in the melting point generally improves the solubility and allows the formation of oil, and it can be achieved by using small counterions, for example, chloride and bromide, or aromatic conjugate anions in case of aromatic base or by using small hydroxyl acids if the drug has good hydrogen bonding potential. The melting point is generally decreased by increasing the hydroxylation of the conjugate acid and, in the cases of common ion dependence, by moving small organic acids. In the case of the sodium salt of drugs, the logarithm of aqueous solubility is often inversely related to melting point.

### 6.8.3 Dissolution

The factors described above affecting the solubility are important to select a salt form or a specific crystalline or polymorphic form that may affect dissolution rate, the most critical parameter. The first step in the commencement of dissolution is the wettability of solid particles—there is a direct correlation between wettability and bioavailability. As the milieu of drug administration sites is mostly aqueous in nature, low wettability makes the particles less hygroscopic.

The dissolution of the salts leads to a change in the pH of the dissolution media because of the buffering effect. A base dissolved in the acidic media increases the pH, because the acidic counterions are trapped into salt forms. Similarly, as the salts dissolve, the pH shift depends on whether it is the acid or the basic component that is weaker. The final balance is always dependent on the relative p$K_a$ of the acidic and alkaline components. This is an important consideration, as it explains the difference in the results obtained when the studies are conducted in water or buffer. When enteric protection is desired, the dissolution rates should be determined in 0.1 N HCl, wherein many differences in the dissolution rates between water and buffer are obviated.

## 6.9 Study Methods

At the preformulation stage, the limitations of the quantity of the sample available determines to a great degree the type of the study to be conducted. Some physical properties are fundamental in nature, whereas others are a manifestation of these basic properties. For example, melting point determination reveals much about the internal structure of crystals and the solubility and dissolution characteristics; the latter properties are the derived properties. As a result, techniques available to study the aforementioned properties are categorized by the U.S. FDA in a decreasing order of