cost-effective means to improve solubility and thus enhance the oral bioavailability of ionizable drugs (Berge et al., 1977; Gould, 1986; Serajuddin, 2007; Elder et al., 2013). The crystalline nature of the salt form can also improve processability and dosage form development, but solid state properties such as crystallinity, crystal habit, particle size, flowability, melting point, enthalpy of fusion, hygroscopicity, and the potential for solvate formation or polymorphic changes must be considered when choosing a salt form for a drug (Berge et al., 1977; Gould, 1986; Huang and Tong, 2004; Serajuddin, 2007; Guerrieri et al., 2010; Elder et al., 2013).

The physical form of the salt must be taken into account, and several issues must be considered (Serajuddin and Pudipeddi, 2002). For example, a salt form might prove to be amorphous material. Even if crystalline, the salt form might prove to be polymorphic. David et al. (2012) reported that benzylamine salts are likely to be polymorphic, whereas cyclohexylamine and t-butylamine produced salts with good physicochemical properties that are unlikely to undergo polymorphic transitions, presumably due to the lack of the ability to stack by π–π interactions. Aakeröy et al. (2007) reported that about 45% of *N*-heterocyclic salts of carboxylic acids have some tendency toward solvate formation. Formation of a hydrate or a solvate might occur on crystallization or recrystallization, and the effect of temperature and humidity on this should be investigated. In general, hydrates and solvates are more stable, but less soluble in the respective solvent, than the anhydrous or non-solvated form (Khankari and Grant, 1995), although they will be more soluble in a solvent that is not involved in the solid form (Davies, 2001). A particular counterion for a drug salt will affect the melting point, solubility, dissolution rate, and hygroscopicity (Huang and Tong, 2004). Both the physical and chemical stability of the different candidate salts in the solid state will ultimately determine the optimal form of the drug.

Miller and Heller (1975) pointed out that different salts of the same drug rarely differ in their pharmacological effect. Differences are usually limited to the physical and chemical properties exhibited by the salts that ultimately affect absorption and bioavailability. Typically, a low bioavailability of less than 20% leads to dose-to-dose differences that result in variable drug levels, pharmacological effects, and side effects (Schoenwald, 2002). Wagner (1961) stated that, although the biological response elicited by salts of the same drug might not differ qualitatively, the intensity of the response may differ markedly in relation to the time after administration. Nelson (1957) pointed out that the dissolution rate of the drug from a particular dosage form largely determines the rate of drug appearance in the blood, as well as the timing and magnitude of the maximum concentration attained. Since salt formation can increase the solubility by several orders of magnitude, this approach to improving drug solubility can have a profound effect on the dissolution rate (Serajuddin, 2007) as described by the Nernst equation (Nernst 1904; Elder et al., 2013):

$$\frac{\mathrm{d}C}{\mathrm{d}t} = \frac{DA\left(C_\mathrm{s} - C_\mathrm{b}\right)}{h} \tag{15.1}$$

where d*C*/d*t* is the dissolution rate, *D* is the diffusion coefficient of the drug in the solvent system, *A* is the surface area of the solid exposed to the solvent system, *h* is the thickness of the stagnant solvent at the interface between the solid surface and the bulk of the solvent system, C_s is the solubility of the drug in the solvent system, and C_b is the concentration of the drug in the bulk of the solution at time *t*. If the bulk concentration is very low in comparison to the solubility, this parameter is negligible in comparison to C_s and it can be dropped to simplify the equation.

With passive diffusion as the most common mechanism for drug absorption, the rate of appearance depends on the concentration of the drug dissolved, which in turn is influenced by the physicochemical properties of the drug (Amidon et al., 1995). Although the overall bioavailability of different salts of the same drug is expected to be similar, pharmacokinetic profiles likely reflect physicochemical differences found between salt forms of the same drug (Patel et al., 2009). Bighley et al. (1995) presented a summary of drug salts and the influence the salt form has on bioavailability and pharmacokinetics in general. Physicochemical characteristics that can play a profound role