and light stability are all measured before development of potential formulations. Physicochemical interactions with typical excipients should be evaluated at this stage of the investigation. Using results from force displacement curves, differences in compaction properties were evident in the different salt forms, including the hydrochloride, methanesulfonate, oxalate, and tartrate salts, of S (–)-*N*-[(1-ethyl-2- pyrrolidinyl)methyl]-2-hydroxy-, 3,5-diethyl-, 6-methoxysalicylamide (Graffner et al., 1985). The oxalate and methanesulfonate salts, for example, exhibited a higher elasticity. The methanesulfonate salt did not form coherent compacts. Results indicated that the methanesulfonate salt was far more hygroscopic than the oxalate salt, and yet each demonstrated reversible water sorption. The difference could not be explained in terms of surface area exposed because the oxalate salt possessed the greater surface area.

Different salts can impart different stability characteristics depending on the degradation mechanism. Differences in hygroscopicity, for example, will largely influence the salt choice for a drug that degrades by hydrolysis. Hygroscopicity can also result in handling and flow problems (Morris et al., 1994). Lithium chloride is an example of a salt that is too hygroscopic to allow tableting (Greene, 1975).

The influence of pH on salt solubility has already been discussed in the previous section. Since the salt forms of drugs involve the ionized form of the drug, the pK_a will largely determine the incidence of precipitation of uncharged drug. The pH of an aqueous medium, then, will be critical to drug solubility (Amidon, 1981; Anderson and Conradi, 1985). Bioavailability of salt forms, then, will depend on the absorption rate for the unionized form from a solution that has a high ionized form reserve present in it. The pH of the medium and the pK_a of the parent drug will determine the ratio of ionized and unionized form concentrations present in the solution at any time, is given by

$$\frac{\left[\mathrm{A}^-\right]}{\left[\mathrm{HA}\right]} = 10^{\mathrm{pH}-\mathrm{p}K_a} \tag{15.37}$$

and

$$\frac{\left[\mathrm{B}\right]}{\left[\mathrm{BH}^+\right]} = 10^{\mathrm{pH}-\mathrm{p}K_a} \tag{15.38}$$

for acidic and basic drugs, respectively. As the unionized form of the drug is absorbed, its concentration drops and the charged form generates the uncharged form by acceptance or release of a proton to increase the concentration of the uncharged form in an attempt to reestablish equilibrium between the two forms.

For many poorly soluble drugs, the dissolution rate best reflects the bioavailability of the salt (Juncher and Raaschou, 1957; Berge et al., 1977). Indeed, solubility might affect absorption only to the extent that it affects the dissolution rate. Since absorption is a dynamic process, the solubility of a drug might be of limited consequence if the absorption rate is so rapid that solubility is not attained in the fluid from which the drug is absorbed. The dissolution rate in this instance would be critical since it could establish the effective absorption rate (Berge et al., 1977).

Fortunately, in most cases, the salt form under serious consideration exhibits a faster dissolution rate than the corresponding parent drug at an equivalent pH. This dissolution phenomenon can be explained in light of the parameters that govern the dissolution rate, as found in the diffusion layer model of Brunner (1904):

$$\frac{\mathrm{d}M}{\mathrm{d}t} = \frac{DS}{h}\left(C_s - C_b\right) \tag{15.39}$$

where dM/dt is the dissolution rate representing the mass of drug, M, dissolved in a period of time, t, from a solid dosage form possessing a surface area of S, where the drug has a diffusivity D in the dissolving fluid and a solubility C_s in the dissolution medium, and the drug concentration in the bulk of that medium at time t is C_b. The parameter h refers to the thickness of a stagnant diffusion