development. This decision will not depend on solubility alone. The prevalence of salt forms of drugs in practice (estimated at around 50%) suggests that the benefts often outweigh the drawbacks. Salt selection should preferably be made before commencement of toxicity testing, because of the associated cost and potential time delay in development of switching to a different salt form. Each is treated by regulatory authorities as a new entity.

Salt formation

A salt is formed when an acid reacts with a base, resulting in an ionic species held together by ionic bonds. In principle, any weak acid or base can form a salt, although in practice if the pK_a of the base is very low, the salt formed is unlikely to be stable at physiological pHs. Stephenson et al (2011) note that no marketed salt exists for a drug with a pK_a below 4.6. They suggested that 5 is a general value below which salt formation is unlikely to be effective. Because salts usually dissociate rapidly upon dissolution into water, they are considered electrolytes. Sometimes a drug sounds from its name that it is a salt, but it may in fact be a single entity bound via covalent bonds, in which case electrolytic behaviour does not apply (e.g. fluticasone propionate).

Acids and bases can be classifed as strong through to extremely weak, based on their pK_a (Table 23.8). When strong acids react with strong bases the reaction tends to completion, as both species will be fully ionized, and this is known as *neutralization*. For example:

$$HCl + NaOH \rightarrow NaCl + H_2O \tag{23.28}$$

In this instance, the salt formed will precipitate once it is present at a concentration beyond its solubility. However, most drug candidates are either weak acids or bases, in which case their character is usually based on the Brønsted-Lowry definition: an acidic compound is a proton donor and a basic compound is a proton acceptor. The removal of a proton from an acid produces a *conjugate base* (A^-) and addition of a proton to an acceptor produces a *conjugate acid* (BH^+).

$$HA \rightleftharpoons H^+ + A^- \tag{23.29}$$

$$B + H^+ \rightleftharpoons BH^+ \tag{23.30}$$

Note that the Brønsted-Lowry definition requires acidic species to have an ionizable proton but does not require basic compounds to possess a hydroxide group; simply that they can accept a proton (thus the theory does not consider KOH and the like to be a base but a salt containing the basic OH^- moiety). In the case of a weak base (B) reacting with a strong acid, the conjugate acid and conjugate base may then form a salt:

$$B + HCl \rightleftharpoons BH^+ + Cl^- \rightleftharpoons BH^+Cl^- \tag{23.31}$$

When a salt dissolves in water it will dissociate. Assuming dissolution of a basic salt then the species in solution is the conjugate acid. The conjugate acid can donate its proton to water, reforming the free base:

$$BH^+ + H_2O \rightleftharpoons B + H_3O^+ \tag{23.32}$$

All of the reasons for the change in solubility of salts are encompassed in Equation 23.32. A basic salt contains the conjugate acid of the drug. Upon dissolution, the conjugate acid donates its proton to water and the free base is formed. The solute is thus the free base, but the pH of the solution in which it is dissolved has reduced because of the donated proton. Recall that the solubility of weak bases increases as the pH of solution reduces. Thus, dissolution of a basic salt increases solubility because there is a concomitant reduction in pH of the solution.

Table 23.8 Descriptions of acid and base strength

Description	pK_a	
	Acid	Base
Very strong	< 0	> 14
Strong	0–4.5	9.5–14
Weak	4.5–9.5	4.5–9.5
Very weak	9.5–14	0–4.5
Extremely weak	> 14	< 0