solution, thus increasing the chance of interaction. If ΔpK_a lies between 3 and zero then knowledge of ΔpK_a *per se* is not predictive of whether salt formation will occur and if ΔpK_a is less than zero then co-crystal formation is the more likely outcome.

Thus, selection of a salt-forming entity starts with knowledge of the pK_a of the entity and the pK_a of the drug. The pK_a values of some of the most common salt forming acids and bases in water are given in Tables 23.9 and 23.10.

The top ten anions and cations by frequency for drugs in the 2006 USP are shown in Table 23.11. For basic drugs, the hydrochloride salt is the most common form. In part this is because the pK_a of hydrochloric acid is so low it is very likely that it will form a salt with a weak base. Hydrochloride salts are also widely understood and form physiologically common ions and so are acceptable from a regulatory perspective. However, they do have some disadvantages, including the fact that the drop in pH upon dissolution may be significant (which is not good for parenteral formulations). There are also risks of corrosion of manufacturing plant and equipment, instability during storage (especially if the salt is hygroscopic) and reduced dissolution and solubility in physiological fluids because of the common ion effect.

Stahl (2011) organizes salt-formers into three categories, which may be used as a guide to selection.

First class salt-formers are those that form physiologically ubiquitous ions or which occur as

Table 23.9 Values of pK_a for selected pharmaceutical acids

Acid	Anion	pK_a	Example
Hydrobromic	Hydrobromide	<−6.0	Galantamine
Hydrochloric	Hydrochloride	−6.0	Clindamycin
Sulphuric	Sulphate	−3.0, 1.92	Salbutamol
p-Toluenesulphonic	Tosylate	−1.34	Sorafenib
Methanesulphonic	Mesylate	−1.2	Benztropine
Naphthalene-2-sulphonic	Napsylate	0.17	Levopropoxyphene
Benzenesulphonic	Besylate	0.7	Amlodipine
Oxalic	Oxalate	1.27, 4.27	Escitalopram
Maleic	Maleate	1.92	Fluvoxamine
Phosphoric	Phosphate	1.96, 7.12, 12.32	Fludarabine
Pamoic	Pamoate	2.51, 3.1	Amitriptyline
Tartaric	Tartrate	3.02, 4.36	Metoprolol
Fumaric	Fumarate	3.03, 4.38	Formoterol
Citric	Citrate	3.13, 4,76, 6.40	Sildenafil
Hippuric	Hippurate	3.55	Methenamine
Benzoic	Benzoate	4.19	Emamectin
Succinic	Succinate	4.21, 5.64	Metoprolol
Acetic	Acetate	4.76	Megestrol
Carbonic	Carbonate	6.46, 10.3	Lithium

(Stahl and Wermuth, 2011).