not only in pharmacokinetic and toxicity profiles (Thackaberry, 2012) but also in processing and manufacturing include, but are not limited to, hygroscopicity, the physical stability of the crystal forms particularly under humid conditions, the chemical stability of the salt, and of course the solubility (Morris et al., 1994). Li et al. (2005) considered the biopharmaceutical properties, namely the solubility and the dissolution rate, to be just as critical in salt selection as the physicochemical properties such as crystallinity, hygroscopicity, and chemical stability. Salt formation is considered the most practical approach to maximizing the bioavailability of a poorly soluble drug (Huang and Tong, 2004).

In the case of metoprolol succinate and metoprolol fumarate, the maximum drug concentration in the plasma (C_{max}) and the area under the plasma drug concentration–time curve were statistically equivalent, based on a 90% confidence interval (Sandberg et al., 1993), indicating comparable *in vivo* performances. With fenoprofen, the C_{max} following administration of its calcium salt was reached somewhat later than the C_{max} associated with the sodium form (Rubin et al., 1971). This was attributed to the slower dissolution rate for the calcium salt. Bioavailability and the measured distribution and elimination parameters, however, were reported to be similar. It has been suggested that a pharmacokinetic study needs to be performed to allow selection of the ideal salt when two or more salt forms exhibit similar solid state characteristics (Saxena et al., 2009).

INORGANIC SALTS

It has been confirmed that the solubility of the salt depends largely on the counterion. The hydrophobicity of the counterion and the melting point of the salt both play a role in the solubility of the salt form (Anderson and Conradi, 1985). The hydrophobicity of the counterion is most often reflected in the melting point and enthalpy of fusion, in that a hydrophobic counterion is more likely to engage in weaker intermolecular bonds limited to van der Waals forces. Crystal lattice energy, solvation energy, the common ion effect, the hydrated state, and other factors also influence the solubility of a drug salt (Serajuddin and Pudipeddi, 2002). Crystal lattice and hydration energies are expected to increase with an increase in the cation or anion charge, and they should also increase with an increase in the charge density.

The most common method to produce salts involving inorganic counterions is to expose a weak base drug to an inorganic acid, or a weak acid drug to the hydroxide form of the desired counterion. Examples of inorganic acids include phosphoric, sulfuric, nitric, or hydrochloric acid (Dittert et al., 1964). Anderson and Flora (1996) pointed out that the pK_a of that acid should be lower than the pK_a of the conjugate acid formed by the protonation of the base drug. Wells (1988) and Tong and Whitesell (1998) recommended that this difference between pK_a values be at least two units.

Sodium is the most common counterion for salts of acidic drugs. It has even been successfully used in the preparation of an amorphous form of furosemide to achieve pharmaceutical objectives (Nielsen et al., 2013). Diclofenac is marketed as three different salt forms, namely its sodium, potassium, and diethylamine salt. The low solubility of the parent drug (about 0.02 mg/mL) necessitated the preparation of salt forms. Each of the three salts improved the solubility of diclofenac, with 9.7 and 4.6 mg/mL reported for the sodium and potassium salts, respectively (Kumar et al., 2007).

The weakly acidic drug *para*-aminosalicylic acid (PAS) is available as sodium, calcium, or potassium salt. The reported aqueous solubilities of the nonionized and salt forms, in terms of available PAS, are 1 g/600 mL for the nonionized form, 1 g/10 mL for the potassium salt, 1 g/7 mL for the calcium salt, and 1 g/2 mL for the sodium salt. Since the poorly soluble nonionized form of PAS passes through the gastrointestinal tract without being absorbed, it is not surprising that each of the salt forms was able to enhance the oral bioavailability of the parent drug (Wan et al., 1974). However, the bioavailability of the drug from tablets using each of the three salts was considered comparable. The anti-inflammatory properties of fenoprofen were investigated using the sodium salt, but the calcium salt was later considered because it was found to be more stable than the sodium salt (Rubin et al., 1971). The sodium salt became amorphous and darkened in certain