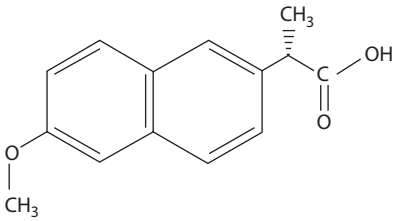
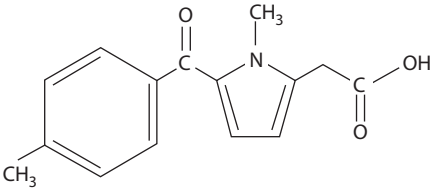
TABLE 15.2
Thermal Properties and Aqueous Solubility of Naproxen, Tolmetin, and Their Salts





Chemical	Melting Point (°C)	Enthalpy of Fusion (kJ/mole)	Solubility (mg/mL)[a]
Naproxen	157	24.8	0.07
Naproxen sodium	261, dec.[b]	35.8, dec.	266
Naproxen choline	146	30.2	472
Tolmetin	162. dec.	47.2, dec.	0.10
Tolmetin sodium	314, dec.	54.7, dec.	163
Tolmetin choline	143	19.7	795

Source: Data from Murti, S. K., On the preparation and characterization of water-soluble choline salts of carboxylic acid drugs, PhD dissertation, University of Missouri–Kansas City, 1993. Reprinted with permission of the author.

[a] Solubility is based on apparent solubility in water at 25°C.

[b] dec. indicates that the solid decomposed on melting.

is insensitive to pH effects on solubility, and is considered highly water soluble. Short-chain (up to C16) monoalkyl quaternaries (the nitrogen bearing one alkyl chain and three methyl groups) and ethoxylated quaternaries of even greater chain lengths are water soluble in general, whereas most dialkyl and trialkyl quaternary ammonium compounds are water dispersible at best (Juczyk et al., 1991). When the nitrogen bears four aliphatic groups, the cation is soluble in water except when two or more of the groups contain more than eight carbons (Shibe and Hanson, 1964).

The choline salts of naproxen and tolmetin yielded marked solubility enhancements, even over that of the sodium salts. The aqueous solubility of the choline salt of naproxen was 6700 times the solubility of naproxen and almost twice that of naproxen sodium. The choline salt of tolmetin was almost 8000 times as soluble as the parent drug and almost 5 times as soluble as its sodium salt (Murti, 1993). Table 15.2 shows that the melting point and the enthalpy of fusion are both affected by the formation of the choline salt, and in fact, the choline salt proved to be more thermally stable.

Quaternary ammonium salts of dantrolene and clodanolene have been prepared, and the effect of the organic cation on the aqueous solubility has been reported (Ellis et al., 1980). It was reasoned that since the hydantoin moiety in each drug is weakly acidic, a strong base should be found for salt formation. The 13 different quaternary ammonium compounds were therefore used in the hydroxide salt form. The acid–base reaction proceeded rapidly, and the salt products were stable during recrystallization steps. Of the four salts for clodanolene, the aqueous solubilities ranged from 2- to 100-fold that of clodanolene sodium, on a mass basis. Of the 11 salts for dantrolene, the benzyltrimethyl ammonium salt exhibited comparable solubility to that of dantrolene sodium. Among the other 10 salts were several examples that yielded enhanced solubilities of up to 1000-fold that of the sodium salt. Twelve of the 15 salts successfully demonstrated muscle relaxant activity when administered orally.

Tris(hydroxymethyl)aminomethane (THAM) has been used to form salts with drugs that bear a carboxylic acid group. Gu and Strickley (1987) reported that, for ketorolac and two investigational nonsteroidal anti-inflammatory drugs, the solubility of the THAM salt was greater than the