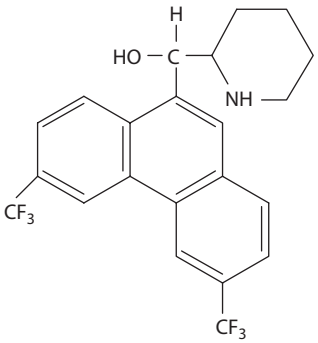
**TABLE 15.1**
**Melting Point and Solubility of Salts of an Antimalarial Drug α-(2-Piperidyl)-3,6-bis(Trifluoromethyl)-9-Phenanthrenemethanol**




| Chemical | Melting Point (°C) | Solubility (mg/L)[a] |
|---|---|---|
| Free base | 215 | 7 |
| Hydrochloride | 331 | 12 |
| *d,l*-Lactate | 172, dec.[b] | 1800 |
| *l*-Lactate | 192, dec. | 900 |
| 2-Hydroxyethane-1-sulfonate | 250, dec. | 620 |
| Methanesulfonate | 290, dec. | 300 |
| Sulfate | 270, dec. | 20 |

*Source:* From Agharkar, S. et al., Enhancement of solubility of drug salts by hydrophilic counterions: Properties of organic salts of an antimalarial drug. *J. Pharm. Sci.* 1976. 65. 747–749. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

[a] Apparent solubility in water at 25°C.

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

This enhanced aqueous solubility was attributed in part to the decrease in crystal lattice energy as attested by the reduction in melting point between the hydrochloride salt and the lactate salt (Motola and Agharkar, 1984). This has proved true in other studies comparing physicochemical properties of salts with inorganic counterions with those of salts formed using organic counterions (Creasey and Green, 1959). The enthalpies of fusion, however, were not investigated to support this hypothesis.

On the contrary, Surov et al. (2015) reported a lower solubility for the adipate, maleate, and fumarate salts of ciproflaxicin in acidic pH when compared to the hydrochloride salt of the antibiotic. This has been attributed to the differences in their lattice energies due to the formation of hydrates and the type of hydrate formed. When methanedisulfonate, ethanedisulfonate, or camphorsulfonate is employed as the counterion, the product is referred to as a mesylate, edisylate, or camsylate salt, respectively (Miller and Heller, 1975). Miller and Heller (1975) concluded combinations with monocarboxylic acids are usually poorly soluble in water, whereas those of dicarboxylic acids above oxalic acid, which itself is considered toxic, can be water soluble if one carboxylic acid group is still free to dissociate. Examples of di- and tricarboxylic acids that have been used in marketed products include citric, tartaric, succinic, and glutamic acids (Berge et al., 1977; Fiese and Hagen, 1986).

The aqueous solubility of the salt of a drug has also been considered a function of the acid–base strength and aqueous solubility of the counterion employed in the salt formation (Nelson, 1957). As an example, choline itself is considered strongly basic because of the hydroxide counterion, and choline salts of acidic drugs can be readily prepared. The choline cation, being a quaternary amine,