anocobalamin. The results are indicative of an interaction between these two substances and the formation of a new compound. The interaction is apparently enhanced by elevated temperatures. When the mixture was kept at room temperature for a long period, a small amount of a new compound was formed, suggesting a very low rate of deterioration of cyanocobalamin at room temperature.

Methylparaben and sodium chloride had no effect on cyanocobalamin in the same conditions, which rules out the effect of sodium ion in deterioration of cyanocobalamin.

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Enhancement of Solubility of Drug Salts by Hydrophilic Counterions: Properties of Organic Salts of an Antimalarial Drug

S. AGHARKAR, S. LINDENBAUM [x], and T. HIGUCHI

Abstract □ Judicious choice of the salt form of a drug can greatly affect the aqueous solubility and formulation of the compound. The objective of this work was to demonstrate the effect of various counteranions on the aqueous solubility of the antimalarial agent α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol. Several organic salts of this drug were studied. The methods of synthesis, the apparent aqueous solubilities, and *in vitro* dissolution tests for these salts are reported. The lactate salt was 200 times as soluble as the hydrochloride salt. This enhanced solubility suggests that parenteral administration of this drug may now be feasible.

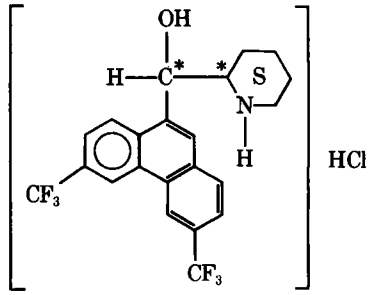
Keyphrases □ Solubility, aqueous—salts of substituted phenanthrenemethanol antimalarial agent, effect of hydrophilic counterions □ Salts—substituted phenanthrenemethanol antimalarial agent, effect of hydrophilic counterions on aqueous solubility □ Counterions, hydrophilic—effect on aqueous solubility of substituted phenanthrenemethanol antimalarial agent □ Antimalarial agents—α-(2-piperidyl) -3,6- bis(trifluoromethyl) -9- phenanthrenemethanol, salts, effect of hydrophilic counterions on aqueous solubility

It has been shown that organic acid salt forms of basic drugs, such as amines, have higher aqueous solubilities than their corresponding halide salts (1). This technique has found important application in the development of more soluble salt forms of drugs to improve their bioavailability and ease in formulation.

The objective of this work was to utilize previous findings (1) for α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol (I). The principles employed in choosing counterions to render a high molecular weight hydrophobic drug more water soluble are generally applicable.

Compound I has been shown to exhibit significant activity against infections with strains of *Plasmodium falciparum* resistant to chloroquine, quinine, and pyrimethamine (2). Because of two optically active centers, it can exist as any one of four possible stereoisomers or mixtures thereof. The absolute configuration of all of the isomers has been established (3). The work reported here was done with one racemic pair, referred to as "isomer a" by Carroll and Blackwell (3). They also showed that all four enantiomers are potent antimalarials and, therefore, no attempt was made to resolve the racemic mixture.

The apparent solubility of the hydrochloride salt of I and its free base was measured in water at 25°. Compound I, being large and hydrophobic, is only sligtly soluble as the hydrochloride salt (Table I). This poor solubility was suspected to be the main reason for its poor bioavailability. In all previous work, I was administered orally as the hydrochloride



I

* = optically active centers

Table I—Apparent Solubilities and Melting Points of Salt Forms of I

Salt Form	Melting Point	Apparent Solubility[a]	pH of Saturated Solutions[a]
Hydrochloride	331°	12–15 mg/liter	5.79
Free base (I)	215°	7–8 mg/liter	
dl-Lactate	172° dec.	1.8–1.9 g/liter	3.8
l-Lactate	192–193° dec.	0.9–0.95 g/liter	
2-Hydroxyethane-1-sulfonate	250–252° dec.	0.62 g/liter	5.0
Methanesulfonate	290° dec.	0.3 g/liter	2.4
Sulfate	270° dec.	20 mg/liter	5.1
Sulfate		8 mg/liter[b]	

[a] At 25° in water. [b] At 25° in 0.1 *N* HCl.

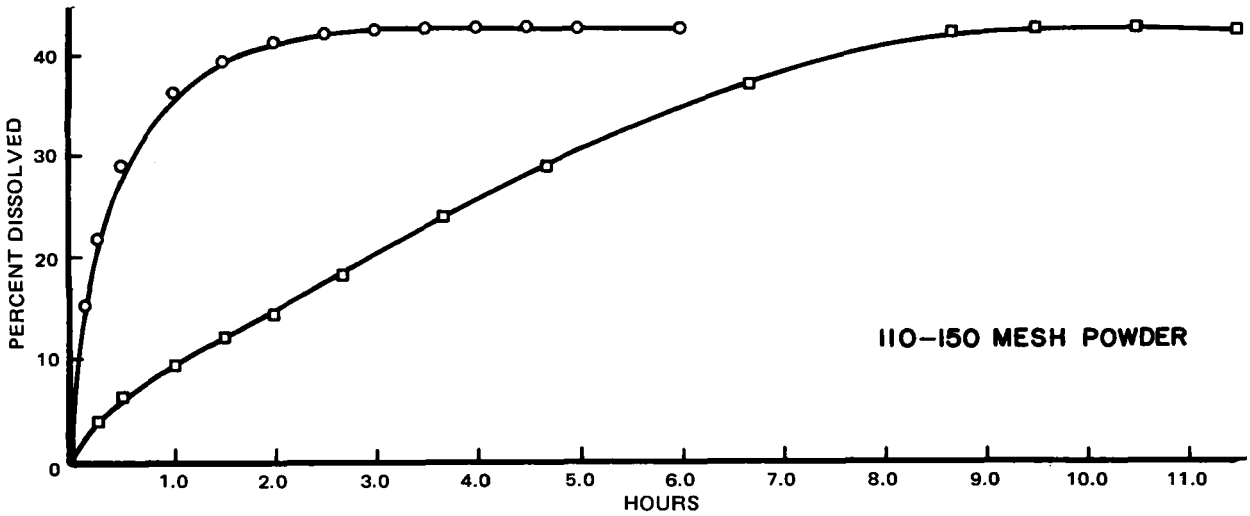


Figure 1—*Dissolution rate of hydrochloride salt of I in 0.1 N H_2SO_4 (○) and 0.1 N HCl (□) at 37°. Some of the solid was still floating on the surface after the rate of dissolution had leveled off, which may explain why the percent dissolved did not reach a value of 100.*

salt. Since stomach contents are rich in chloride ions, it is expected that the equilibrium represented by Scheme I will remain farther to the left, thus decreasing the solubility and the rate of solubilization of the hydrochloride salt of I, represented as BH^+Cl^-

$$BH^+Cl^-_{(solid)} \overset{K_{sp}}{\rightleftharpoons} (BH^+)_{aq} + (Cl^-)_{aq}$$

Scheme I

EXPERIMENTAL

The free base of I was prepared by the method of Carroll (4).

All salts were prepared by mixing a solution of I in 95% ethanol and a 50% excess of the stoichiometric amount of acid required for neutralization. The solution was stirred for about 2 hr. Excess solvent was evaporated, and the precipitated salt was filtered and recrystallized from methanol–water.

Salts were identified using IR[1], UV[2], and elemental analyses. Physicochemical properties of these salts are given in Table I. Apparent solubilities of these salts were measured by shaking excess salt at 25° in water for 3 days.

The equilibrium solutions were tested for the presence of decomposition products by TLC using silica plates. The solvent system was benzene–methanol–concentrated ammonium hydroxide (79:19:2). The freshly prepared solution and equilibrated solutions of salts of I showed a single spot (R_f 0.45) as detected by UV light and iodine vapor, thus indicating that the salt forms of I did not undergo any detectable degradation in the aqueous solutions over the equilibration period. A single spot was also observed using ethyl acetate–propyl alcohol–acetic acid–water (10:10:5:2) with an R_f of 0.68.

Aqueous concentrations were determined using a previously constructed Beer's law plot in the UV region at λ_{max} 252.5 nm. Dissolution tests were carried out on pure powder using an equivalent amount of each salt equal to 6.30 mg of I free base. A sample of 100–150-mesh powder in 500 ml of dissolution medium was used. The dissolution rate of the powder was monitored continuously at 252.5 nm using a flowcell. The USP dissolution test apparatus was employed without the basket, and the dissolution medium (Figs. 1 and 2) was maintained at 37° and stirred at 100 rpm.

RESULTS AND DISCUSSION

From Table I it can be seen that the lactate salt is approximately 200 times as soluble as the hydrochloride salt of I, the form used in the past.

Both the 2-hydroxyethane-1-sulfonate and lactate salts of I have

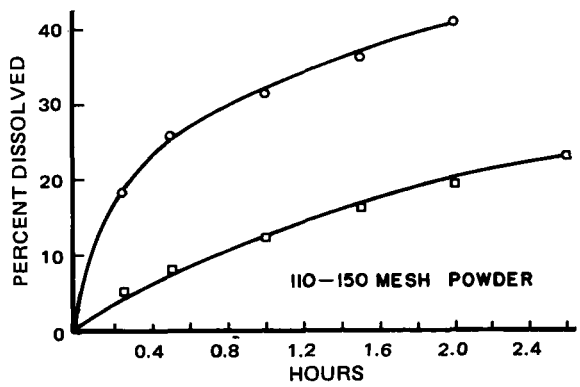


Figure 2—*Dissolution rate of the 2-hydroxyethane-1-sulfonate (○) and the hydrochloride (□) salts of I in 0.1 N HCl at 37°.*

[1] Beckman IR 33.
[2] Cary 14 or 15.

Table II—Apparent Solubility of 2-Hydroxyethane-1-sulfonate Salt of I at 25° in Commonly Used Parenteral Vehicles

Vehicle	Apparent Solubility, g/liter
20% Ethanol—20% glycerin in water	1.9
20% Propylene glycol—5% ethanol in water	0.6
10% Dextrose in water	0.75

lower melting points than the hydrochloride salt of I, suggesting that the enhanced solubility of these salts with organic anions is due in part to decreased crystal lattice energy. Also contributing to the increased solubility of these salts is the possibility of hydrogen bonding between the hydroxyl groups of the lactate and 2-hydroxyethane-1-sulfonate anions with the solvent.

The optical activity of lactic acid creates difficulties in defining the system studied due to the presence of several isomers with different physical properties. Therefore, it was decided to investigate the 2-hydroxyethane-1-sulfonate salt of I in more detail.

Since one objective of this work was to improve the aqueous solubility of I so that it could be administered parenterally, the apparent solubility of the 2-hydroxyethane-1-sulfonate salt of I in different commonly used vehicles was measured (Table II). As can be seen from Table II, the apparent solubility of I as the 2-hydroxyethane-1-sulfonate salt can be considerably increased by choice of the proper vehicle.

To provide evidence for the decrease in solubility of the hydrochloride salt of I due to the common-ion effect, it was decided to measure the apparent solubility of this salt as a function of chloride-ion concentration. When these data (Table III) were plotted as the molar concentration of the hydrochloride salt of I in solution as a function of the reciprocal of the chloride-ion concentration, a nonlinear curve was obtained. Therefore, it was not possible to calculate the solubility product constant (K_{sp}) of this salt (5).

The nonlinearity may be due to the presence of two diastereoisomers with different solubilities. Further work is required to ascertain the source of this nonlinear behavior. However, it is apparent that the solubility of the hydrochloride salt of I decreases considerably with an increase in the chloride-ion concentration.

The apparent solubility of the sulfate salt of I is slightly greater than that of the hydrochloride salt. However, in 0.1 *N* HCl, the solubility is approximately equal to that of the hydrochloride salt, probably due to the rapid conversion of the sulfate to the hydrochloride in 0.1 *N* HCl.

To substantiate the argument against the use of hydrochloride salts of amines due to the common-ion effect, dissolution rates of the hydrochloride salt of I were measured in 0.1 *N* HCl and in 0.1 *N* H_2SO_4 (Fig. 1). The study was conducted in acid solutions to avoid dissociation of the protonated base as shown in Scheme II.

The dissolution rate in 0.1 *N* H_2SO_4 is much faster than in 0.1 *N* HCl, thus supporting the hypothesis that the rate of dissolution and the solubility of the hydrochloride salt of I will be decreased by the common-ion effect in the medium rich in chloride ion.

$$(BH^+)_{aq} \rightleftharpoons B_{aq} + H^+_{aq}$$

Scheme II

Table III—Apparent Aqueous Solubility of the Hydrochloride Salt of I as a Function of Chloride-Ion Concentration at 25°

Apparent Solubility[a], moles/liter × 10^5	Total Chloride-Ion Concentration, moles/liter × 10^3
3	40.0
6.2	10.0
9.5	8.0
10.9	5.0
15.9	3.1
19.0	2.2
24.0	1.3

[a] Represents average of three measurements; range ±0.5–1%.

The dissolution rate of 2-hydroxyethane-1-sulfonate salt of I was also measured in 0.1 *N* HCl (Fig. 2). The dissolution rate of this salt is considerably greater than that of the hydrochloride salt.

The optimum oral therapeutic dose of the hydrochloride salt of I was determined to be 750 mg as a single dose (6). This high dose was probably necessary due to incomplete absorption from the GI tract. Since the organic salts of I reported in this work are considerably more soluble than the hydrochloride salt, the dose of these salts of I required to achieve the same therapeutic response as with the hydrochloride salt should be considerably reduced.

By using these newly prepared salts, it should now be possible to administer I in a parenteral dosage form for the treatment of malaria.

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