[Chem. Pharm. Bull. 27(6)1441—1447(1979)]

UDC 543.241.06 : 541.454.04.08

Solubility Characteristics of Weak Bases and Their Hydrochloride Salts in Hydrochloric Acid Solutions[1)]

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(Received January 29, 1979)

The pH-solubility profiles of four basic drugs were studied at 37°. The solubility of papaverine hydrochloride in acetate buffer showed a typical pH-profile, which increased with decrease in pH. On the other hand, the pH-solubility profile of the hydrochloride in HCl-sodium acetate buffer was not as simple as that in acetate buffer, showing a solubility maximum at approximately 3.7. Similar pH-profiles of solubility were observed for trihexyphenidyl hydrochloride, isoxsuprine hydrochloride, and oxyphencyclimine hydrochloride. The decrease in the solubility of these drugs at more acidic pH values could be rationalized on the basis of the common ion effect.

The dissolution behavior of the free bases and that of the hydrochloride salts of papaverine, trihexyphenidyl, and isoxsuprine were compared in dilute hydrochloric acid solutions, in the pH range from 1.0 to 1.8. It was confirmed that a much higher solution concentration and dissolution rate could be obtained using the free bases than from the hydrochloride salts in the pH range of the stomach (pH 1.0—1.2 for papaverine, and pH 1.2—1.4 for trihexyphenidyl and isoxsuprine) due to the common ion effect. It is suggested that salt formation does not always result in an enhancement of solubility characteristics.

Keywords——papaverine; trihexyphenidyl; isoxsuprine; pH-solubility profile; common ion effect; salting-out; dissolution behavior; free base and hydrochloide salt

Salt formation is one of the first approaches considered as a means of increasing drug solubility and dissolution rate.[3)] Salt formation, however, does not necessarily result in an enhancement of the solubility characteristics and the bioavailability.[4—9)]

In the previous paper,[9a)] it was confirmed that the free bases of chlortetracycline (CTC), demethylchlortetracycline (DMCT), and methacycline (MOTC) were more soluble than the corresponding hydrochloride salts at the gastric pH values due to the common ion suppression of the solubility product equilibrium. Furthermore, gastrointestinal absorption of CTC and its hydrochloride was studied in rats and human subjects.[9b)] Following oral administration, the free base produced higher CTC levels in the body fluids than the hydrochloride. Similar results were also noted for MOTC and its hydrochloride.

The solubility characteristics of four additional basic drugs, which are generally used as the hydrochloride salts, are discussed in this communication to substantiate further the contention that salt formation is n t always associated with improved solubility character-

1) Studies on Pharmaceutical Salts, Part I. This work was presented at 97th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April, 1977.
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3) S.M. Berge, L.D. Bighley, and D.C. Monkhouse, *J. Pharm. Sci.*, **66**, 1 (1977).
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6) R.A. O'Reilly, E. Nelson, and G. Levy, *J. Pharm. Sci.*, **55**, 435 (1966).
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istics. Basic drugs studied were papaverine, trihexyphenidyl, isoxsuprine, and oxyphencyclimine. These drugs were chosen for this investigation because they are known to have sparingly soluble hydrochloride salts.

Experimental

Materials——Isoxsuprine hydrochloride, trihexyphenidyl hydrochloride, and oxyphencyclimine hydrochloride were gifts from Daiichi Seiyaku Co., Yamanouchi Seiyaku Co., and Chas. Pfizer Co., respectively. Papaverine hydrochloride was purchased from Tokyo Kasei Kogyo Co. The drugs were used without further purification. Crystals of trihexyphenidyl and papaverine free bases were prepared by dissolving the hydrochloride in water, and adding NaOH to attain a basic pH. Isoxsuprine base was prepared by dissolving the hydrochloride in water and then adjusting the pH to 7 with aqueous ammonia. The resulting precipitate was filtered off and dried *in vacuo* at 50—60°. In the case of oxyphencyclimine it was difficult to prepare a crystalline form of the free base.

The size of the crystals in the dissolution studies was not controlled. The melting point and the results of elemental analysis of drugs used are shown in Table I.

Table I. Compositions of the Drugs tested

Drugs	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	mp
Trihexyphenidyl[a]	$C_{20}H_{31}NO$	79.66	10.38	4.65	79.50	10.64	4.65	114—115°
Trihexyphenidyl·HCl	$C_{20}H_{31}NO \cdot HCl$	71.08	9.55	4.15	71.28	9.75	4.12	235—238°[c]
Papaverine[b]	$C_{20}H_{21}NO_4$	70.78	6.24	4.13	70.59	6.28	4.41	150—152°
Papaverine·HCl	$C_{20}H_{21}NO_4 \cdot HCl$	63.91	5.90	3.73	64.01	5.89	3.53	223—224°
Isoxsuprine[a]	$C_{18}H_{23}NO_3 \cdot 1/2H_2O$	69.65	7.81	4.51	69.90	7.78	4.29	90— 92°
Isoxsuprine·HCl	$C_{18}H_{23}NO_3 \cdot HCl$	63.99	7.18	4.15	63.84	6.90	4.63	200—202°
Oxyphencyclimine–HCl	$C_{20}H_{28}N_2O_3 \cdot HCl$	63.06	7.69	7.36	62.95	7.51	7.49	228—231°[c]

a) Samples were recrystallized from methanol and dried *in vacuo* at 50—60° over P_2O_5.
b) recrystallized from ethanol.
c) decomposition.

Solubility Determination——Solubility measurements of the drugs at various pH's were made in 1 M HCl–sodium acetate buffer and 0.2 M acetate buffer solutions at 37°. Excess amounts of the drugs were suspended in buffer solution (2 ml). These suspensions were shaken horizontally for about an hour and aliquots filtered through a Millipore filter (0.45 μ) were assayed spectrophotometrically. The pH of each aliquot was measured with a combination pH electrode (type 6028-10T, Horiba Ltd.).

The solubility of each drug in salt solutions was also determined as described above. Experimental salting-out constants were calculated according to the Setschenow equation.[10]

$$\log S_0/S = kC$$

where S and S_0 are the solubility in the salt solution and in pure water, respectively; C the molar concentration of the electrolyte, and k the empirical salting-out constant.

Procedure for Dissolution Studies——The dissolution behavior of crystalline powder was determined at 37° as described previously,[11] except that the volume of dissolution medium in individual flasks was increased to 2 ml.

The dissolution behavior of compressed disks was also studied in the case of papaverine and its hydrochloride. The disks, 13 mm in diameter, were prepared by direct compression using a die and hydraulic press for KBr disks. Three hundred milligrams of mixed powder containing a drug (10%), potato starch (5%), talc (1%), and Avicel PH101 (84%) was accurately weighed and compressed at 100 kg/cm². The dissolution rates of compressed disks were measured with the USP dissolution apparatus with a stirring speed of 50 rpm. In one exception, the volume of the dissolution medium was reduced to 100 ml in a 100 ml beaker. Sample solutions were filtered through a Millipore filter (0.45 μ).

In both cases, the sample solution was analyzed spectrophotometrically.

10) F.A. Long and W.F. McDevit, *Chem. Rev.*, **51**, 119 (1952).
11) S. Miyazaki, T. Arita, R. Hori, and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **22**, 638 (1974).

Results and Discussion

pH-Solubility Profile

An increase in solubility is usually observed for basic drugs at more acidic pH values.[12] On the other hand, a decrease in the solubility of some tetracycline antibiotics (CTC·HCl, MOTC·HCl, and DMCT·HCl) was found in HCl–sodium acetate buffer solution at more acidic pH values.[9a]

Initially, the pH-solubility profiles of the drugs in 1 M HCl–sodium acetate buffer and 0.2 M acetate buffer solutions at 37° were determined.

The results of these studies are shown in Figs. 1 and 2. The solubility of papaverine hydrochloride in the acetate buffer, which increased with decrease in pH, shows a usual pH-profile within the range of experimental pH values (Fig. 1A). On the other hand, the pH-solubility profile of the drug in the HCl-sodium acetate buffer was not as simple as that in the acetate buffer, and showed a solubility maximum at approximately pH 3.7.

Similar solubility behavior in the pH-profile was observed for trihexyphenidyl hydrochloride (Fig. 1B), isoxsuprine hydrochloride (Fig. 2A), and oxyphencyclimine hydrochloride (Fig. 2B). Usual pH profiles were obtained in the acetate buffer; the solubility increased with decrease in pH. In the HCl-sodium acetate buffer, however, a decrease in the solubility at more acidic pH values was found for these drugs. There were no solubility maxima within the range of experimental pH values.

The maximum solubility of papaverine hydrochloride at acidic pH may be due to the common ion effect.[9a] This view is based on the results obtained by Dittert *et al.*[13] in their study on the pH-solubility profile of triamterene in hydrochloric acid. They reported that the decline at more acidic pH values in the pH-solubility profile was due to common ion suppression of the solubility product equilibrium. The pH-solubility profiles of trihexyphenidyl hydrochloride, isoxsuprine hydrochloride, and oxyphencyclimine hydrochloride may also be explained in a similar manner.

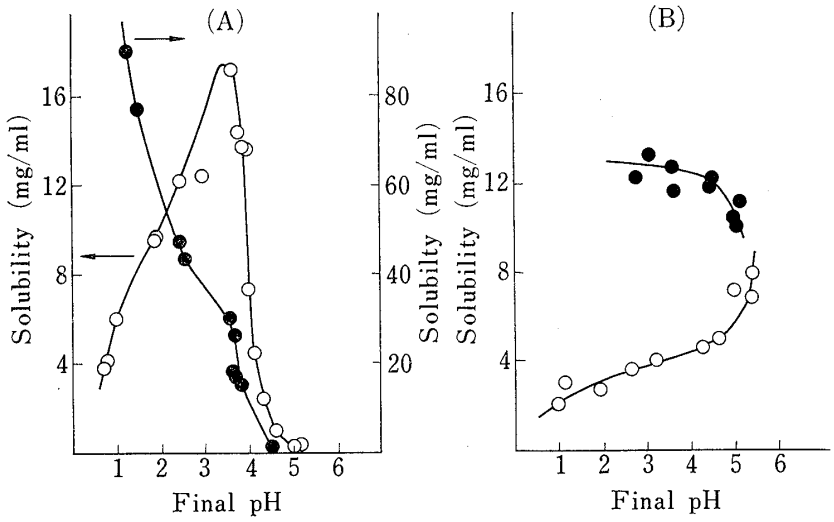

Fig. 1. The pH-Solubility Profiles of Papaverine Hydrochloride (A) and Trihexyphenidyl Hydrochloride (B) at 37°

All data are expressed in terms of the free base equivalent.
—○—: 1M HCl-CH_3COONa buffer.
—●—: 0.2M CH_3COOH–CH_3COONa buffer.

12) M. Gibaldi, "Introduction to Biopharmaceutics," Lea and Febiger, philadelphia, 1971, pp. 21—26.
13) L.W. Dittert, T. Higuchi, and D.R. Reese, *J. Pharm. Sci.*, 53, 1325 (1964).

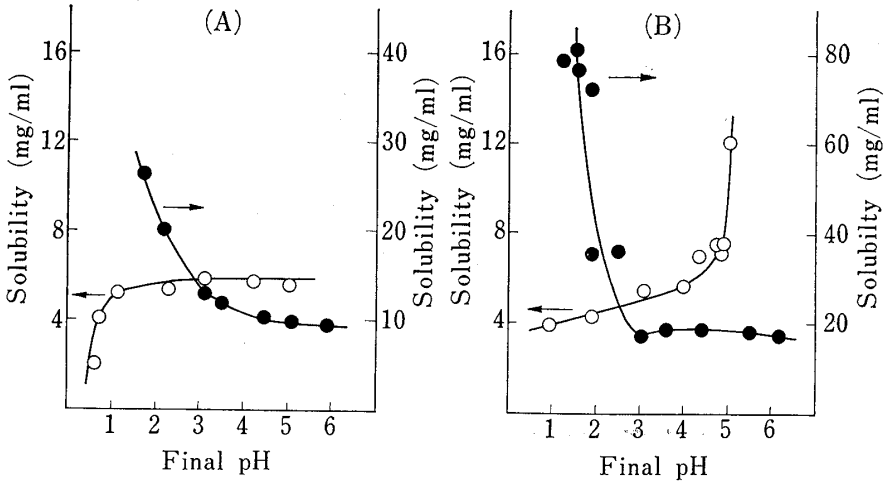

Fig. 2. The pH-Solubility Profiles of Isoxsuprine Hydrochloride (A) and Oxyphenycyclimine Hydrochloride (B) at 37°

key: as in Fig. 1.

Effect of Salts on the Solubility

The addition of a common ion often reduces the solubility of a slightly soluble electrolyte. The principle of this common ion effect can also apply to slightly soluble organic salts. Since the salt in solution is partially dissociated, further suppression of the solubility may be caused by the common ion effect. Swintosky *et al.* reported this effect with penicillin G procaine on adding procaine hydrochloride to the preparation in order to enhance its stability.[14]

The significant decrease in the solubility of the drugs at more acidic pH values (Figs. 1 and 2) may indeed be attributable to the common ion effect; the experimental evidence is shown in Figs. 3 and 4, and Table II, based on the Setschenow equation. As shown in

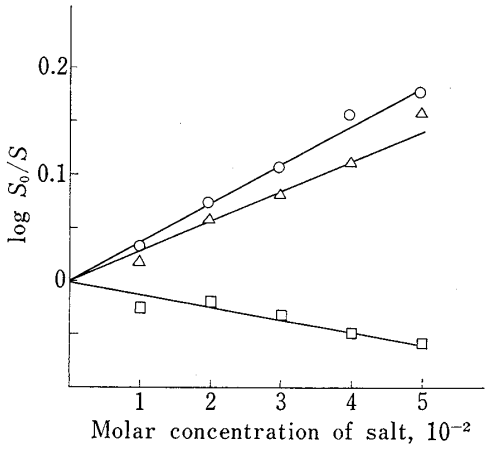

Fig. 3. Setschenow Plots for Papaverine Hydrochloride in Salt Solutions at 37°

—○—: NaCl.
—△—: NH_4Cl.
—□—: Na_2SO_4.

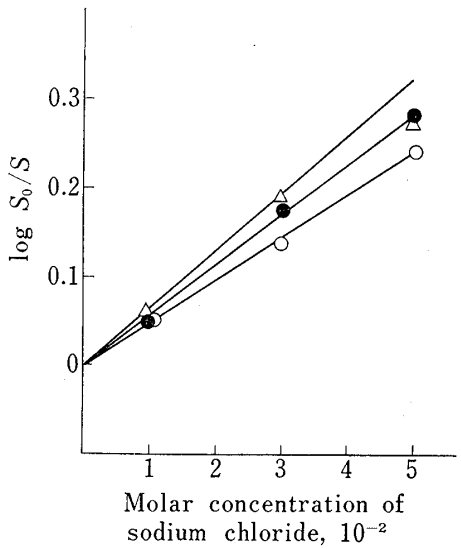

Fig. 4. Setschenow Plots for Drugs in Sodium Chloride Solutions at 37°

—●—: trihexyphenidyl hydrochloride.
—△—: isoxsuprine hydrochloride.
—○—: oxyphencyclimine hydrochloride.

14) J.V. Swintosky, E. Rosen, M.J. Robinson, R.E. Chamberlain, and J.R. Guarini, *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 34, 37 (1956).

Table II. Salting-out Constants of Drugs[a] at 37°

Salt	Papaverine	Trihexyphenidyl	Isoxsuprine	Oxyphencyclimine
NaCl	3.60(−0.867)[b]	5.66	6.30	4.90
NH_4Cl	2.70	7.43	4.62	3.02
Na_2SO_4	−1.10	*c*)	1.00	0.180

a) hydrochloride salts.
b) free base.
c) not determined.

Fig. 3, NaCl showed a salting-out effect in papaverine hydrochloride solution, suggesting that NaCl depressed the solubility of the drug. A similar effect was noted with NH_4Cl, while Na_2SO_4 appeared to exhibit a salting-in effect. In addition, the solubility of the free base was only slightly affected by the addition of NaCl, as shown in Table II, which summarizes the salting-out constants obtained. Figure 4 shows Setschenow plots for the hydrochlorides of trihexyphenidyl, isoxsuprine, and oxyphencyclimine in the presence of NaCl. In every drug solution, NaCl showed a salting-out effect.

These results indicate that every drug is salted-out of a solution containing a common ion, that is, the chloride ion. Thus, the decrease in the solubility of the drugs at more acidic pH values can be rationalized on the basis of common ion suppression of the solubility product equilibrium.

Dissolution Behavior in Hydrochloric Acid Solutions

The dissolution behavior of the free bases and that of the hydrochloride salts of papaverine, trihexyphenidyl, and isoxsuprine were compared in hydrochloric acid solutions at pH's corresponding to that of gastric fluid, since the behavior in hydrochloric acid solutions is relevant to the bioavailability after oral administration.

Figure 5 illustrates the dissolution curves of papaverine and its hydrochloride in hydrochloric acid solutions at pH 1.0, 1.2 and 1.4 at 37°. The free base of papaverine showed greater solubility than the hydrochloride in hydrochloric acid solution at pH 1.0 and gave a greater concentration at pH 1.2 in the initial stage of dissolution. The solubility of papaverine as the free base is twice that of the hydrochloride at pH 1.0. On the other hand, at pH 1.4 the hydrochloride has higher solubility than the free base.

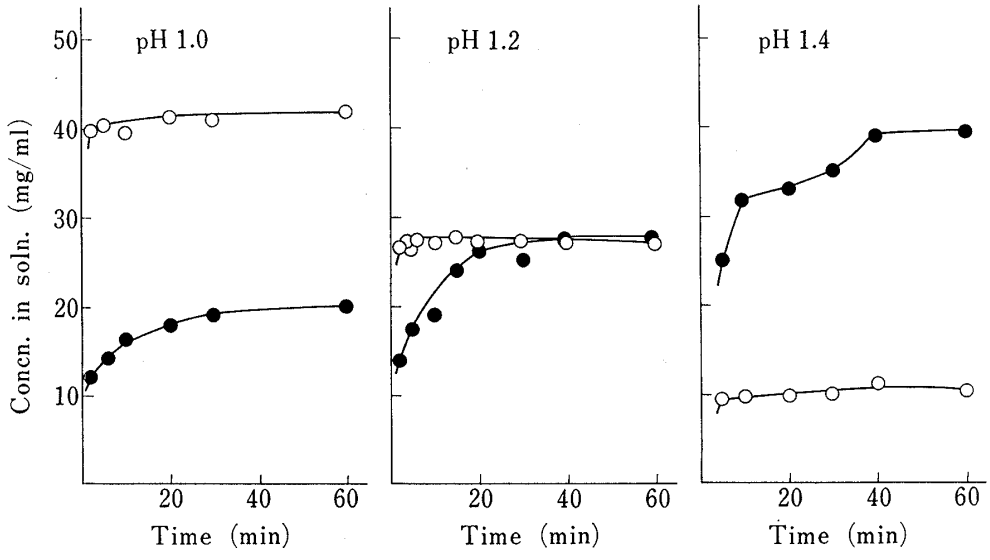

Fig. 5. Dissolution Curves of Papaverine (○) and Its Hydrochloride (●) from Crystalline Powder in Dilute Hydrochloric Acid Solutions at 37°

All data are expressed in terms of the free base equivalent.

We next investigated the dissolution behavior in the initial stage. The dissolution curves of the free base and the hydrochloride of papaverine obtained from compressed disks in hydrochloric acid solutions are illustrated in Fig. 6. As would be expected, the dissolution

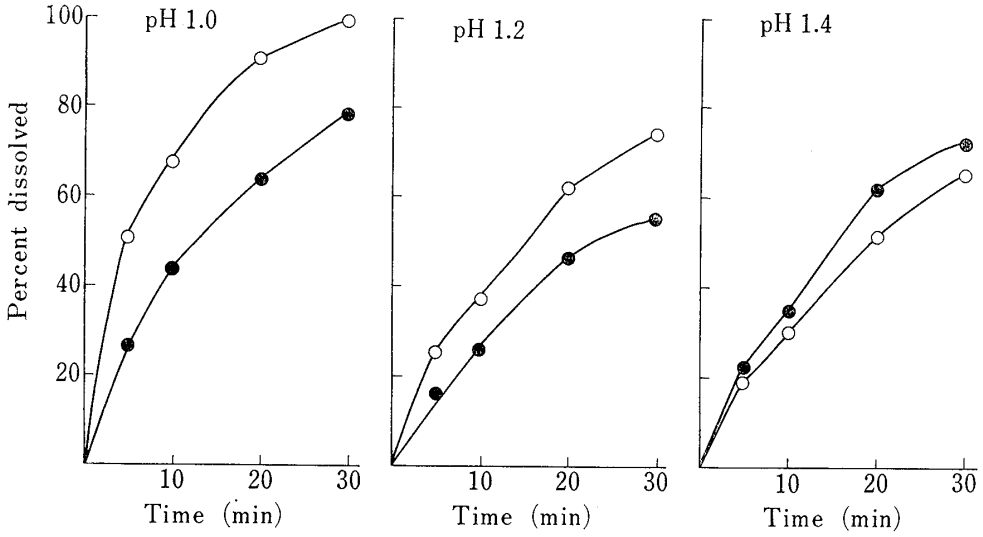

Fig. 6. Dissolution Curves of Papaverine (○) and Its Hydrochloride (●) from Compressed Disks in Dilute Hydrochloric Acid Solutions at 37°

Points are the mean values of three experiments.

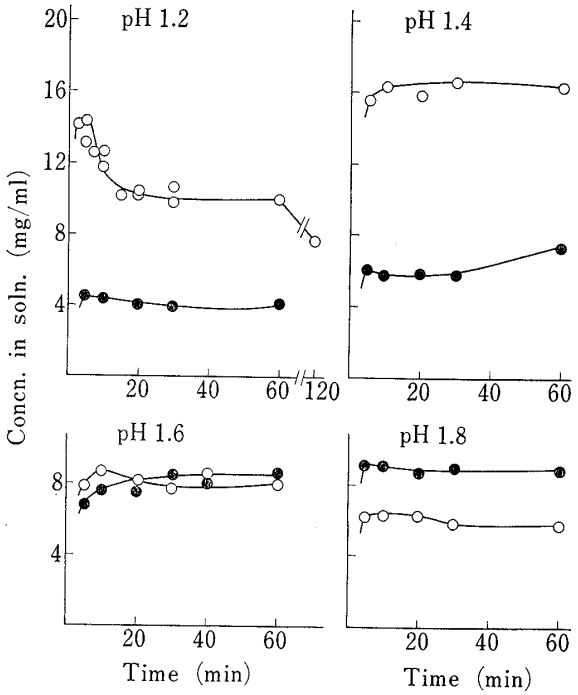

Fig. 7. Dissolution Curves of Trihexyphenidyl (○) and Its Hydrochloride (●) in Dilute Hydrochloric Acid Solutions at 37°

All data are expressed in terms of the free base equivalent.

of the free base from compressed disks was found to be faster than that of the hydrochloride at pH 1.0 and pH 1.2. Compressed disks used in this study were prepared in a manner which resulted in their rapid disintegration in order to minimize the effect of differences in disintegration rates.

The dissolution curves of trihexyphenidyl and its hydrochloride in dilute hydrochloric acid solutions in the pH range from 1.2 to 1.8 are shown in Fig. 7. A distinct difference in dissolution behavior was observed between the two species at pH 1.2, the free base yielding a much greater concentration than the hydrochloride. However, a decreace in the concentration of the free base was observed during actual dissolution studies due to conversion of the free base to the hydrochloride. Confirmation of the conversion was provided by elemental analysis and by the melting point of the solid phase isolated from the medium after 2 hr. A similar difference in dissolution behavior was found at pH 1.4. On the other hand, at pH 1.6 the free base and the hydrochloride are equally soluble. The observed order was reversed when the pH of the dissolution medium was raised to pH 1.8.

As shown in Fig. 8, isoxsuprine base is more soluble than its hydrochloride in hydrochloric acid solutions at pH 1.2. A distinct difference in apparent solubility between these

two forms was observed at pH 1.4, whereas the hydrochloride exhibited a greater solubility than the free base at pH 1.6.

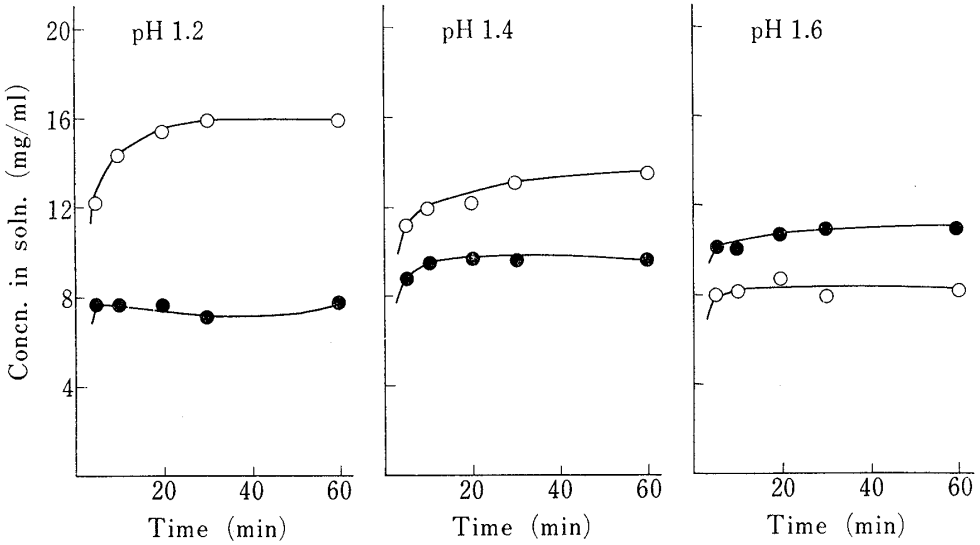

Fig. 8. Dissolution Curves of Isoxsuprine (○) and Its Hydrochloride (●) in Dilute Hydrochloric Acid Solutions at 37°

All data are expressed in terms of the free base equivalent.

Although the crystalline form of the oxyphencyclimine free base was not obtained, the free base should be more soluble than the corresponding hydrochloride salt in the more acidic pH range.

These results confirm that the free bases of papaverine, trihexyphenidyl, and isoxsuprine are more soluble than the corresponding hydrochloride salts in the pH range of the stomach (pH 1.0—1.2 for papaverine, and pH 1.2—1.4 for trihexyphenidyl and isoxsuprine) due to the common ion effect. This indicates that salt formation does not always result in an enhancement of solubility characteristics.

The pH of the gastric fluid is said to range usually from 1 to 3.[15] In addition, NaCl is present in body fluids at a high concentration, which is also unfavorable for dissolution of the hydrochlorides due to common ion suppression of the solubility product equilibrium. Thus, these factors create conditions less favorable for the dissolution of the hydrochlorides in gastric fluid, affecting the bioavailability.

Formation of the salt is known to influence a number of physicochemical properties of the parent compound, including dissolution rate, solubility, stability, and hygroscopicity. These properties, in turn, affect the bioavailability and formulation characteristics of the drug. Consequently, extensive and systematic preformulation studies of the physicochemical properties of each new drug entity are necessary to determine the most suitable form for drug formulation by the pharmaceutical industry.

Acknowledgement The authors are grateful to Daiichi Seiyaku Co., Yamanouchi Seiyaku Co., and Chas. Pfizer Co. for generous supplies of the drugs used in this study.

15) T.H. Wilson, "Intestinal Absorption," W.B. Saunders Company, Philadelphia, 1962, p. 250.