pH-Solubility Profiles of Organic Bases and Their Hydrochloride Salts

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Abstract: Knowledge of comparative solubility profiles of a base and its hydrochloride salt is important in selecting one form over the other for dosage form design. The studies with two model bases, namely, tiaramide and papaverine, showed that, except during phase transition from a base to a salt or *vice versa,* the pH-solubility profiles are identical whether a base or a salt are used. The solubilities were determined by equilibration after addition of hydrochloric acid or sodium hydroxide solutions to suspensions of bases and salts. With the addition of hydrochloric acid solution, the pH values of the suspensions of tiaramide and papaverine dropped to 5.0 ±0.1 and 4.0 ±0.1, respectively, and then remained constant until supersaturated solutions were formed. After nucleation of supersaturated solutions with the addition of hydrochloride salt or the reduction of temperature, the precipitation of hydrochloride salt occurred. The solubilities of salts decreased at low pH due to common ion effect. The K°_{sp} values, however, did not remain constant and the solubility profiles showed positive deviations from the theoretical ones. These may be due to a possible self-association and the resultant difference between the solubilities and activities of the compounds in solutions. The reported differences between the solubilities of bases and their respective hydrochloride salts at a particular pH and the lack of common ion effects on the solubilities and dissolution rates of bases are explained.

The solubilities of organic bases and their salts are highly dependent on pH, ionic strength, and the nature of the anions used in forming the salts and adjusting the pH. Kramer and Flynn (1) investigated the solubility behavior of organic hydrochloride salts and observed that the pH-solubility profile was not a continuous one. They defined two equations to express the profile; each of the equations described an independent curve which was limited by the solubility of either the ionized or the unionized species. The point where the two curves intersected was designated pH_{max}, the pH of maximum solubility. Bogardus and Blackwood (2) also observed an essentially similar nature in the pH-solubility profile of a hydrochloride salt. In addition, they observed a very sharp decline in the solubility of the salt due to the common ion effect at pH below 2.5. Kramer and Flynn (1) did not extend the solubility profiles below pH 4 and so no common ion effect on the saturation solubility of the hydrochloride salts was observed.

The above-mentioned studies were conducted by using only hydrochloride salts as the starting materials. When a basic drug, triamterene, was used as the starting material, Dittert et al. (3) observed that the nature of the pH-solubility profile depended on the type of acid used to adjust the pH. The compound formed complex salts and exhibited supersaturated solutions under certain pH conditions. Common ion equilibria were observed at low pH.

In studies where free bases as well as their hydrochloride salts were used, Miyazaki et al. (4–6) observed that at pH < 3, the solubilities of a wide variety of free bases were higher than those of their hydrochloride salts, sometimes by a factor of three to five. Unlike hydrochloride salts, the solubilities and dissolution rates of bases were also not affected by common ions.

Either a base or its salt may be used in pharmaceutical dosage forms. Knowledge of the pH-solubility profiles obtained when a base or its salt form are used as the starting materials is, therefore, very important in selecting one form over the other. In this report, the pH-solubility profiles of two organic bases determined by using the base forms as starting materials are presented. These profiles are then compared with those determined by the use of their hydrochloride salts. In addition, the reported differences in the solubility and the dissolution rate of an organic base from those of its hydrochloride salt are explained on the basis of the present study.

Materials and Methods

The pH-solubility profiles of tiaramide, tiaramide hydrochloride (Fujisawa, Japan), and papaverine (USV Pharmaceutical Corp., Tuckahoe, N.Y.) were determined by the phase-solubility technique of Dittert et al. (3). The saturated solution of each base was prepared by stirring an excess of solid with about 25 ml of water in a beaker for 2 h by using an overhead stirrer. The temperature was controlled by placing the beaker in a water bath at 37 ±0.1 °C. The solubilities at pH values less than that of the saturated solution was determined by titrating dropwise with 1N or 6N HCl, as necessary, stirring for 1 h after each addition, recording the pH (Digital 110, Corning Instruments, Medfield, Mass.) and then collecting a suitable aliquot. To attain a pH higher than that of the saturated solution in water, dilute sodium hydroxide solutions were used similarly. Throughout the titration, care was taken to maintain an excess of solid in equilibrium with the solution.

Each aliquot was filtered immediately after collection. The ultraviolet absorbance of a tiaramide solution was recorded at 295 nm after suitable dilution of an aliquot with water. The absorbance of papaverine was recorded at 310 nm by diluting the aliquot with 0.1N HCl. The solubilities are reported on the basis of hydrochloride salts.

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Results

pH-Solubility Profile of Tiaramide – The pH-solubility profiles of tiaramide and its hydrochloride salt are given in Fig. 1. A saturated solution of tiaramide in water at 37 °C had a pH of 7.51 and a drug concentration of 1.84 mg/ml. With a lowering of the pH of this solution, the solubility of the base increased gradually until pH 5.0 was reached. On further addition of hydrochloric acid solution in an attempt to decrease the pH, the pH remained constant at 5.0 ±0.1, and the solubility increased sharply from less than 25 mg/ml to over 300 mg/ml. As long as the solid phase was in equilibrium with the solution, there was no further decrease in pH even with the addition of 6N HCl. Filtration of excess base from a solution having over 300 mg/ml concentration of tiaramide followed by seeding with tiaramide hydrochloride or cooling of the solution to 5 °C resulted in the precipitation of the hydrochloride salt. The temperature of this system was raised again to 37 °C and water was added to dilute the suspension. With the addition of hydrochloric acid solution, the pH of this suspension decreased gradually. The solubility decreased between pH 5 and 4 and then remained practically constant down to pH 1.8. A drop in solubility due to the common ion effect was observed at pH lower than 1.8. Elemental analysis (C, H, N and Cl) confirmed that the solid phase present in equilibrium with the solution at pH 5 and higher was tiaramide base, and at pH < 5, the solid phase was the hydrochloride salt.

A saturated solution of tiaramide hydrochloride in water at 37 °C had a pH of 3.24 and a solubility of 195 mg/ml. On lowering of pH of this system, the solubility of the salt, as shown in Fig. 1, followed a profile identical to that of the base. With the addition of alkali, there was a slight increase in solubility at pH above 4 prior to the precipitation of base at pH 5. The solubility profile of the salt at pH 5 and higher was identical to that of the base. For both tiaramide and its hydrochloride salt, the apparent pH_{max} was 5.0.

Common Ion Effect – Assuming that the concentration and the activity are equal, Bogardus and Blackwood (2) showed that the solubility product, K^{o}_{sp}, of a saturated hydrochloride salt may be expressed as

$$K^{o}_{sp} = [BH^+]_s[Cl^-] \quad \text{(Eq. 1)}$$

where $[BH^+]$ and $[Cl^-]$ are concentrations of ionized species and chloride ion, respectively, and the subscript s indicates saturation. However, the apparent solubility product, K'_{sp}, may be expressed as

$$K'_{sp} = S_T[Cl^-] \quad \text{(Eq. 2)}$$

where S_T is the total solubility and is equivalent to $[BH^+]_s$ + [B]. Since the concentration of the base, [B], was very low in comparison with $[BH^+]_s$, in the present investigation $[BH^+]_s$ was assumed equal to S_T and the K^{o}_{sp} was calculated according to Eq. 2. The K^{o}_{sp} values of tiaramide hydrochloride, as calculated from the pH solubility profile determined by using tiaramide base as the starting material, are tabulated in Table I. The total chloride concentration in Table I was calculated according to

$$[Cl^-] = \Sigma[M^+Cl^-]_i \quad \text{(Eq. 3)}$$

where, in the absence of any added cations, M^+ represents ionized tiaramide and hydrogen ion.

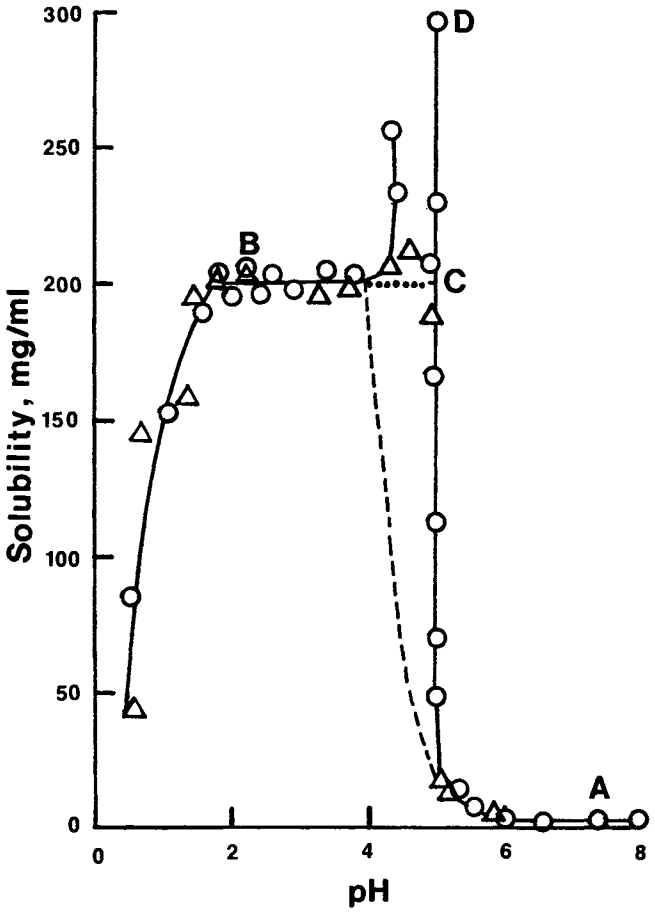

Fig. 1 pH-Solubility profiles of tiaramide (O) and tiaramide hydrochloride (△) at 37 °C. Solubilities are expressed as hydrochloride salt equivalents. Lower pH values than that of a saturated solution of tiaramide in water (Point A) were adjusted by stepwise addition of HCl solution; higher pH value was obtained by the addition of NaOH solution. Similarly, pH values lower and higher than that of a saturated solution of the salt in water (Point B) were adjusted by the addition of HCl and NaOH solutions, respectively. Point C is the apparent pH_{max}. The dashed curve was fitted theoretically (1) by using 1.80 mg/ml as unionized tiaramide solubility and 6.1 as the pKa. Curve CD represents supersaturation.

Table I. The Effect of Chloride Ion on the Solubility of Tiaramide.

pH	S_T, M	$[Cl^-]^a$, M	K^{o}_{sp}, M^2
4.38	0.594	0.594	0.353
4.32	0.653	0.653	0.426
4.00	0.518	0.518	0.268
3.82	0.515	0.515	0.265
3.38	0.524	0.524	0.275
2.90	0.501	0.502	0.252
2.20	0.521	0.523	0.273
2.00	0.496	0.506	0.251
1.83	0.519	0.533	0.277
1.58	0.482	0.508	0.245
1.04	0.388	0.479	0.186
0.52	0.218	0.520	0.113

[a] Calculated by adding molar concentrations of tiaramide and hydrogen ion.

The solubility product remained constant, within experimental error, at pH between 4.0 and 1.5. Above this pH range K°_{sp} increased, and a decrease in value was observed when the pH was lowered below this range.

pH-Solubility Profile of Papaverine – Fig. 2 gives the pH-solubility profile of papaverine. The solubility of the base increased gradually with the decrease in pH until pH 4.0 was reached. At pH 4.0 ±0.1 an increase in solubility from less than 10 mg/ml to over 120 mg/ml was observed. When a solution with a drug concentration of 123 mg/ml was nucleated with papaverine hydrochloride crystals, precipitation of the hydrochloride salt ensued and the solubility decreased. After the precipitation of the salt, the pH could be lowered easily by the addition of HCl solution. The identity of the solid phase at pH < 4 as the hydrochloride salt was confirmed by elemental analysis.

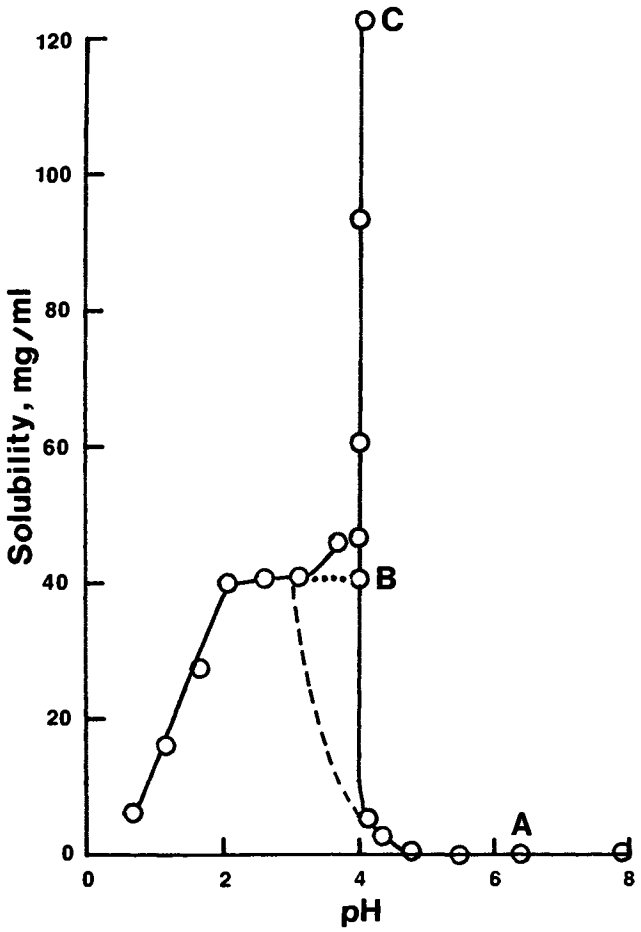

Fig. 2 pH-Solubility profile of papaverine at 37 °C. Solubilities are expressed as hydrochloride salt equivalents. Lower pH values than that of a saturated solution in water (Point A) were adjusted by stepwise addition of HCl solution; higher pH value was obtained by the addition of NaOH solution. Point B is the apparent pH_{max}. The dashed curve was fitted theoretically (1) by using 0.015 mg/ml as unionized papaverine solubility and 6.5 as the pKa (7). Curve BC represents supersaturation.

The solubility product of papaverine hydrochloride under various pH conditions are given in Table II. The K°_{sp} values remained practically constant at pH between 3.2 and 2.2. A higher value was observed at a higher pH, and the values decreased gradually with a lowering of pH below this range.

Table II. The Effect of Chloride Ion on the Solubility of Papaverine.

pH	S_T, M	$[Cl^-]^a$, M	K°_{sp}, M^2
3.7	0.123	0.123	15.1×10^{-3}
3.2	0.110	0.111	12.2×10^{-3}
2.7	0.109	0.111	12.1×10^{-3}
2.2	0.106	0.112	11.9×10^{-3}
1.7	0.073	0.093	6.8×10^{-3}
1.2	0.043	0.106	4.6×10^{-3}
0.7	0.017	0.217	3.7×10^{-3}

[a] Calculated by adding molar concentrations of papaverine and hydrogen ion.

Discussion

pH-Solubility Profile – The pH-solubility profiles of organic bases have been studied by using either a salt (1, 2) or a free base (3) as the starting material; a comparison between the pH-solubility profiles of a base and its hydrochloride salt has not been possible from these studies. The results of the present investigation show that the pH-solubility profiles of tiaramide and its hydrochloride salt, with the exception of supersaturation at apparent pH_{max}, are identical. The pH-solubility profile of papaverine is also essentially similar to that of its hydrochloride salt (7).

The results of the present investigation do not agree with the reported (4–6) difference between the solubilities of a base and its hydrochloride salt at a particular pH. This discrepancy is due to consideration by Miyazaki et al. (4–6) that the pH values of the saturated solutions of bases and hydrochloride salts are the same as the initial pH of the solvents used. The 0.1N, 0.01N and 0.001N HCl solutions were, for example, used to study the solubilities at pH 1, 2, and 3, respectively, and no mention of the pH conditions of the final solutions was made. It is observed in the present investigation that when a hydrochloric acid solution is added, the pH of a saturated solution of a base decreases to the apparent pH_{max}, and it is difficult to lower the pH below this level. On the other hand, the pH of a saturated solution of a hydrochloride salt in water or in hydrochloric acid solution remains below the apparent pH_{max}. It is thus possible that, when a base and its hydrochloride salt are added to any of the HCl solutions used in the reported studies (4–6), the pH of the solution of the base would remain above the apparent pH_{max} and that of the hydrochloride salt would have a value lower than the apparent pH_{max}. Such differences in the pH of final solutions explain the reported differences in solubilities.

Salts of many organic bases undergo micellar and nonmicellar self-association depending on their amphiphilic nature and hydrophobic interactions of the ring systems present in the molecules (8, 9). In the present investigation, positive deviations of experimental pH-solubility profiles in Figs. 1 and 2 from theoretical ones and the changes in K°_{sp} in Tables I and II indicate changes in activity coefficients and possible self-association of the compounds in solution. Bogardus and Blackwood (2) also suggested that the deviations of pH-solubility profiles and K°_{sp} of doxycycline hydrochloride from ideality are due to self-association.

Deviations of pH-solubility profiles of tiaramide and papaverine from ideality indicate that the activity coefficients at higher concentrations are less than 1. The variations in K°_{sp} (Tables I and II), in turn, show that the activity coefficients do

not remain constant. As mentioned earlier, solubilities and activities were assumed equal in calculating the K_{sp}^{o} values. Since the activity coefficient is the ratio between the activity and the concentration, calculation of K_{sp}^{o} based on Eq. 1 in case of a decrease in activity coefficient of BH^{+} would give a higher K_{sp}^{o}. Thus the gradual increase in K_{sp}^{o} as the pH increases from 0.52 to 1.83 in Table I and from 0.7 to 2.2 in Table II shows a gradual decrease in activity coefficient. The same may also be true in case of an increase in K_{sp}^{o} near the apparent pH_{max}. Such a decrease in activity coefficient may be related to a gradual increase in the aggregation number of the possible self-association complex. The nature of the self-association was not studied in the present investigation. However, Tables I and II show that K_{sp}^{o} of a drug does not change significantly with pH if the solubility remains constant. This suggests that the change in saturation solubility of a drug has more pronounced effect on the change in activity coefficient and the possible self-association than a change in pH. This also agrees with the earlier findings of Attwood and Natarajan (10) that, under constant ionic strength and at pH well below pKa, there was no significant effect of pH on the micellar properties of chlorpromazine hydrochloride.

The similarity in solubility profiles obtained when a base or its salt are used as starting materials indicate that the deviation in pH-solubility profile, except for the supersaturation at pH_{max}, is not due to nonequilibrium conditions. Also, the solubility remained unchanged when the equilibration period was extended beyond one hour.

Many bases are solubilized by adding acidic solutions during dosage formulation. The formation of supersaturated solutions in this study indicates that special care must be taken to ensure that the dosage form is not supersaturated by such a solubilization. A supersaturated solution is inherently unstable, and the drug may precipitate out as a salt.

Common-Ion Effect – The results of the present investigation also explain the reported (4–6) lack of common ion effects on the solubilities of bases. Both Figs. 1 and 2 show that the solubility of a base decreases with an increase in hydrochloric acid concentration only after the conversion from a base to a salt. Prior to such a phase transition at the apparent pH_{max}, the solubility of a base only increases with an increase in hydrochloric acid concentration until a supersaturated solution is formed. As the highest concentration of a hydrochloric acid solution used in most of these studies was only 0.1N, it is possible that the base to hydrochloride salt phase conversion did not take place. On the other hand, when a hydrochloride salt was used as the starting material, the solid phase was a salt to begin with and the solubility in hydrochloric acid solutions was, therefore, susceptible to a common ion effect.

Dissolution – The lack of common ion effects on the dissolution rates of bases may also be explained on the basis of the results presented in this paper. The dissolution rate of a solid depends on its solubility in the diffusion layer (11) and, particularly, on the solubility when the diffusion layer thickness approaches zero (12). The possible increase in the solubility of a base in the diffusion layer leading to a supersaturated solution at high HCl concentrations is thus in agreement with the increase in dissolution rate of a base with the increase in hydrochloric acid concentration (4–6). As mentioned earlier, the solubility is susceptible to a common ion effect only after the conversion of the solid phase from base to salt. Unless such a phase transition takes place in the diffusion layer, the solubility in the diffusion layer and therefore the dissolution rate of the base, will continue to increase with the increase in hydrochloric acid concentration. From the nature of bases and the concentrations of hydrochloric acid solutions used in the reported studies, it appears that no base to hydrochloride salt phase transition occurred in the diffusion layer of any of the bases.

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