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UNUSUAL SOLUBILITY AND DISSOLUTION BEHAVIOR OF PHARMACEUTICAL HYDROCHLORIDE SALTS IN CHLORIDE-CONTAINING MEDIA *

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SUMMARY

The pH–solubility profiles of 3 pharmaceutical hydrochloride salts were determined in sodium acetate–hydrochloric acid buffer. Unusual pH–solubility profiles containing maxima at pH 4–6 were observed for phenazopyridine hydrochloride, cyproheptadine hydrochloride and bromhexine hydrochloride. The decrease in solubility at lower pH values was attributed to the common ion effect of chloride on the solubility product equilibrium of the hydrochloride salts. The dissolution behavior of the free bases and that of the hydrochloride salts of these drugs were compared in dilute hydrochloric acid solutions, in pH range from 1.0 to 3.0. The apparent dissolution rates and solubilities of these hydrochlorides were less than those of the respective free base forms in the pH range of the stomach (pH 1.0–2.0). These results substantiated further the contention that the salt formation does not always result in an enhancement of solubility characteristics.

INTRODUCTION

In the previous paper (Miyazaki et al., 1975a), unusual pH–solubility profiles containing maxima at pH 2–3 were reported for chlortetracycline, demethylchlortetracycline, and methacycline hydrochlorides in sodium acetate–hydrochloric acid buffers. The decrease in solubility at lower pH values was attributed to the common ion effect of chloride on the solubility .o produce equilibrium of the hydrochloride salts. The apparent dissolution rates and solubilities of these hydrochlorides were less than those of the respective free base in chloride-containing media. Evidence was presented for greater bioavailability from the chlortetracycline and methacycline free bases compared to the hydrochloride salts (Miyazaki et al., 1975b). Common ion effect also influenced the solubil-

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ities and dissolution rates of the hydrochlorides of papaverine, trihexyphenidyl, and isoxsuprine (Miyazaki et al., 1979).

These results indicate that formation of the hydrochloride salts does not necessarily result in an enhancement of the solubility characteristics. Others (Lin et al., 1972; Bogardus and Blackwood, 1979b) have illustrated a similar phenomenon that decreases the dissolution rate of the salt below that of its non-ionized form. These findings seem to be important in the development of more soluble forms of drugs to improve their bioavailability and ease in formulation.

Solubility and dissolution behavior of 3 additional basic drugs, which are generally used as the hydrochloride salts, are discussed in this communication to substantiate further the contention that hydrochloride salt formation is not always associated with improved solubility characteristics. The drugs selected for this study were phenazopyridine, cyproheptadine, and bromhexine, which are basic amino compounds. They have slightly soluble hydrochloride salts.

MATERIALS AND METHODS

Materials

Phenazopyridine hydrochloride, cyproheptadine hydrochloride (contained 3/2 mol of water), and bromhexine hydrochloride were gifts from Eisai, Tokyo, Banyu Pharmaceuticals, Tokyo, and Taito Koeki, Osaka, respectively. The drugs were used without further purification. Free bases were prepared by dissolving the hydrochlorides in water, and adding NaOH to attain a basic pH. The resulting precipitates were filtered and recrystallized from ethanol. Each free base was identified by melting point and elemental analysis. The size of the crystals in the solubility and dissolution studies was not controlled.

Solubility studies

Solubility measurements of the drugs at various pHs were made in 1 M sodium acetate–hydrochloric acid buffer at 25°C and 37°C. Excess amounts of the drugs were suspended in 2 ml buffer. These suspensions were shaken horizontally overnight. It had been established previously that equilibrium was attained within this period. Aliquots were filtered through a Millipore filter (0.45 μm) and assayed spectrophotometrically. The pH of each aliquot was measured with a combination pH electrode (Type 6028-10T, Horiba, Tokyo). The solubility of each drug in salt solutions was also determined as described above.

Dissolution studies

The dissolution behavior of crystalline powder was determined at 37°C as described previously (Miyazaki et al., 1979). The experiments were performed at pH 1.0 (0.1 N HCl), 2.0 (0.01 N HCl), and 3.0 (0.001 N HCl) in dilute hydrochloric acid. Two milliliter portions of the solvent previously kept at 37°C were added into individual 10 ml Erlenmeyer flasks, which were immersed in an incubator (M-100T, Taiyo Kagaku Kogyo, Tokyo) and contained an excess amount of samples, and they were immediately started to be mechanically shaken horizontally at a rate of 60 ± 2 strokes/min. Sample solutions were filtered quickly and assayed.

Experiments were duplicated or triplicated, and the mean values were obtained. The results were satisfactorily reproducible. All data were expressed as free base equivalent.

RESULTS AND DISCUSSION

pH–solubility profile

Organic bases are generally soluble in low pH where they exist in ionized form, but have very low solubility at higher pH, depending upon the pK_a of the drug. On the other hand, a decrease in the solubility of some drugs with basic nature was found in sodium acetate–hydrochloric acid buffer at lower pH values (Miyazaki et al., 1975a, 1979). Therefore, the pH–solubility profiles of 3 amine hydrochlorides in sodium acetate–hydrochloric buffer were initially determined at 25°C and 37°C.

The results of these studies are shown in Figs. 1–3. The solubility of phenazopyridine hydrochloride showed a unusual pH-profile in the chloride-containing buffer (Fig. 1). A maximum solubility was observed at approximately pH 4.2 at 37°C (solid circles), which is the result of simultaneous equilibration of crystal forms of free base and hydrochloride (Bogardus and Blackwood, 1979a). The melting point and the result of elemental analysis of solid phase isolated from the medium after equilibrium showed that the free base was the solid phase in equilibrium with solution above the maximum point and the hydrochloride salt was the solid phase below this point. The degradation of the drug during

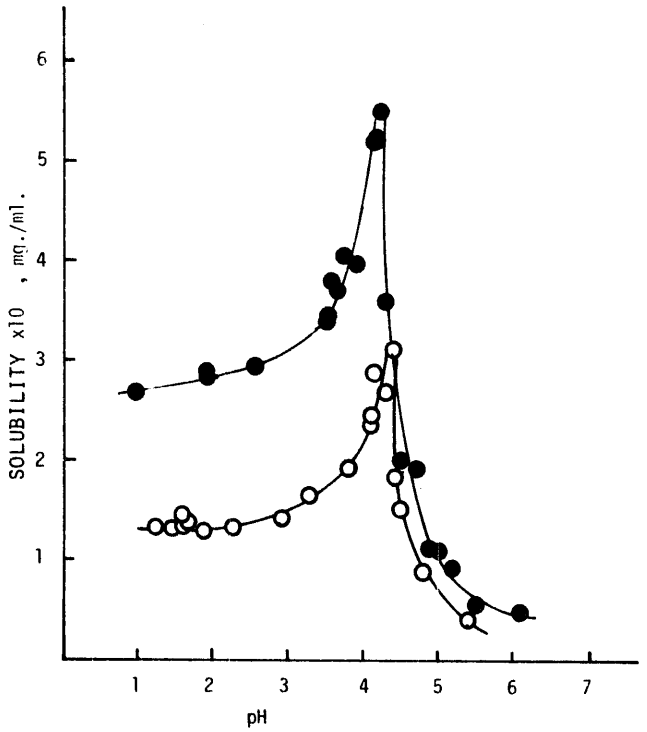

Fig. 1. The pH–solubility profiles of phenazopyridine hydrochloride in 1 M sodium acetate–hydrochloric acid buffer at 25°C (○) and 37°C (●).

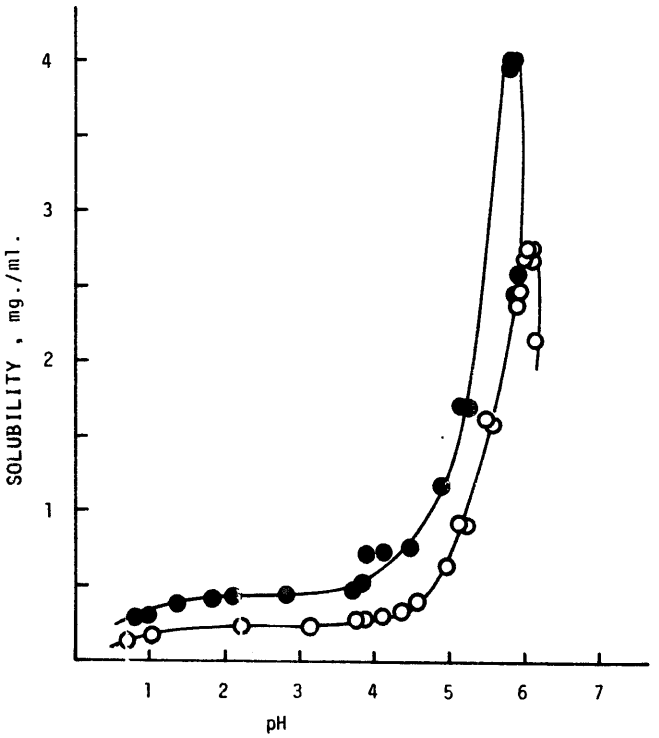

Fig. 2. The pH–solubility profiles of cyproheptadine hydrochloride in 1 M sodium acetate–hydrochloric acid buffer at 25°C (○) and 37°C (●).

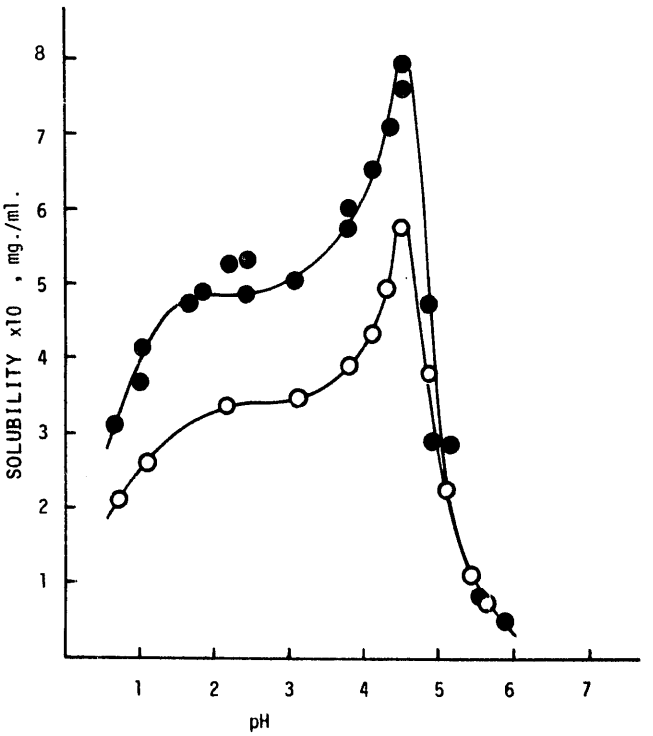

Fig. 3. The pH–solubility profiles of bromhexine hydrochloride in 1 M sodium acetate–hydrochloric acid buffer at 25°C (○) and 37°C (●).

equilibration could be negligible since no significant change in UV spectra was observed. Unusual pH–solubility profile was also obtained at 25°C (Fig. 1, open circles).

Similar solubility maxima were observed for cyproheptadine hydrochloride (Fig. 2) and bromhexine hydrochloride (Fig. 3) in the pH-profile.

Solubility maxima at lower pH values may be due to the common ion effect. This view is based on the results obtained by Dittert et al. (1964) in their study on the pH–solubility profile of triamterene in hydrochloric acid. They reported that the decline at lower pH values in the pH–solubility profiles was due to common ion suppression of the solubility product equilibrium.

Effect of chloride ion on the solubility

The addition of a common ion usually reduces the solubility of a slightly soluble electrolyte. The principle of this common ion effect can also apply to slightly soluble organic salts (Swintosky et al., 1956). To provide evidence for the decrease in solubility of the hydrochloride salts due to the common ion effect, it was decided to measure the solubility of these hydrochlorides as a function of chloride ion concentration. The empirical Setschenow equation (Long and McDevit, 1952) to express the extent of salt effect on the solubility of non-electrolytes was found to adequately express the effect of chloride ion concentration on the the solubilities of these hydrochlorides; i.e.

$$\log S_0/S = kC$$

Where S and S_0 are the solubility in the salt solution and in pure water, respectively; C is the molar concentration of the salt solution. The overall salting-out constant, k, can be obtained from the slope of a plot of log S_0/S vs C. Lin et al. (1972) have also observed that the Setschenow equation was applicable to an amine hydrochloride.

Aqueous solutions of salts were prepared in concentrations up to 0.05 M and the equilibrium solubility of the hydrochlorides in these solutions was studied at 37°C. The results are shown in Fig. 4 and Table 1. As shown in Fig. 4, NaCl showed a salting-out effect in phenazopyridine hydrochloride solution, indicating a significant common ion effect owing to the addition of excess chloride, which significantly reduces the dissociation of the hydrochloride salt, and thus reducing its solubility. A similar salting-out effect was noted with NH_4Cl, as shown in Table 1, which summarizes the salting-out constant obtained. Since the data for the two salts are similar, specific effects due to the

TABLE I

SALTING-OUT CONSTANTS OF DRUGS AT 37°C

Drugs	Salts	Salting-out constant, k
Phenazopyridine hydrochloride	NaCl	11.57
Phenazopyridine hydrochloride	NH_4Cl	12.28
Phenazopyridine base	NaCl	0.84
Cyproheptadine hydrochloride	NaCl	14.80
Bromhexine hydrochloride	NaCl	16.78

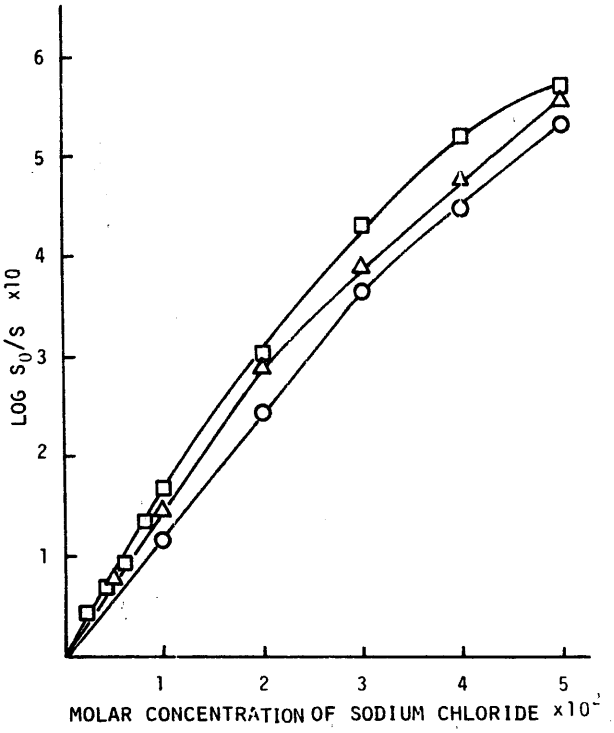

Fig. 4. Setschenow plots for phenazopyridine hydrochloride (○), cyproheptadine hydrochloride (△), and bromhexine hydrochloride (□) in sodium chloride solutions at 37°C.

cation are considered negligible. In addition, the solubility of the free base was only slightly affected by the addition of NaCl. Fig. 4 also shows Setschenow plots for cyproheptadine hydrochloride and bromhexine hydrochloride in the presence of NaCl. In each drug solution, NaCl showed a salting-out effect. In every case, the presence of higher level of salts, for example 0.9% (0.154 M) NaCl, reduced the solubility of hydrochloride salts to a great extent (roughly, by a factor of 10, unpublished data).

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 lower 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 phenazopyridine, cyproheptadine, and bromhexine were compared in hydrochloric acid solutions at pHs corresponding to that of gastric fluid, since the behavior in hydrochloric acid solution is relevant to the bioavailability after oral administration.

Fig. 5 shows the dissolution curves of phenazopyridine and its hydrochloride in hydrochloric acid solution at pH 1.0, 2.0 and 3.0 at 37°C. The distinct difference in dissolution behavior was observed between the two species at pH 1.0, the free base yielding much greater concentrations than the hydrochloride. The drug concentration in solution

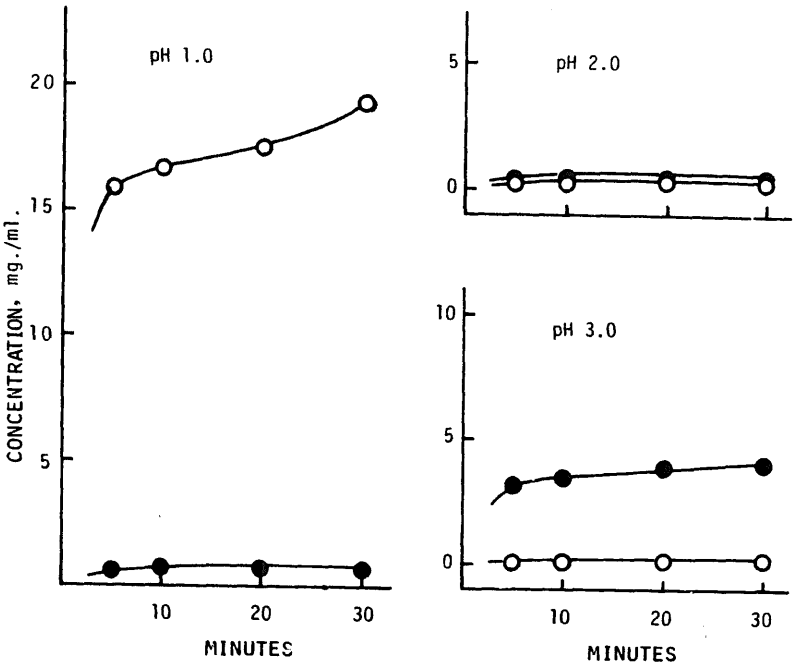

Fig. 5. Dissolution curves of phenazopyridine free base (○) and its hydrochloride (●) in dilute hydrochloric acid solutions at 37°C.

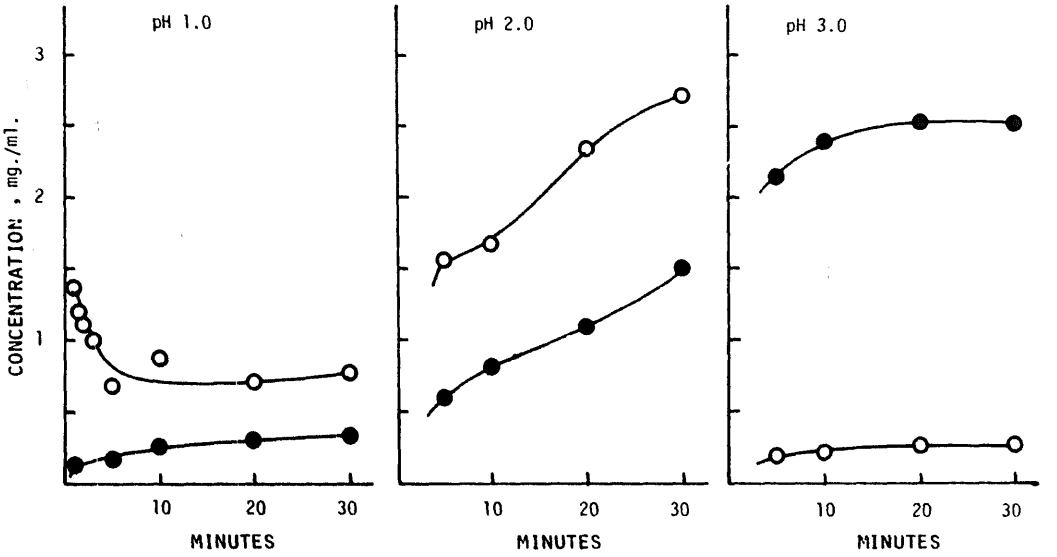

Fig. 6. Dissolution curves of cyproheptadine free base (○) and its hydrochloride (●) in dilute hydrochloric acid solutions at 37°C.

attained approximately 19 mg/ml for 30 min by its free base. On the other hand, at pH 2.0 the free base and the hydrochloride are equally soluble. The hydrochloride exhibits a greater apparent solubility than the free base at pH 3.0.

As shown in Fig. 6, cyproheptadine base is more soluble than its hydrochloride at pH 1.0. For example, at 1 min the concentration of the drug in solution was more than 10 times higher for the free base than the hydrochloride. However, a decrease 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 melting point and elemental analysis of the solid phase isolated from the medium after 30 min. In addition, the dissolution of the free base was found to be faster than that of the hydrochloride at pH 2.0. At pH 3.0 the hydrochloride has higher apparent solubility than the free base.

The dissolution curves of bromhexine free base and its hydrochloride between pH 1.0 and 3.0 are shown in Fig. 7. The free base of bromhexine showed greater concentrations than the hydrochloride at pH 1.0 and at pH 2.0 in the initial stage of dissolution; whereas, the hydrochloride exhibited greater concentration than the free base at pH 3.0.

These results confirm qualitatively that the free bases of phenazopyridine, cyproheptadine, and bromhexine dissolve more rapidly and yield higher concentrations than the corresponding hydrochloride salts in the gastric pH and show that common ion equilibria with chloride can strongly reduce the dissolution of hydrochloride salt forms, while the free bases are not similarly affected. This indicates that formation of the hydrochloride salts does not always result in an enhancement of solubility characteristics.

Sometimes, pharmaceutical hydrochloride salts seem to exhibit less than desirable

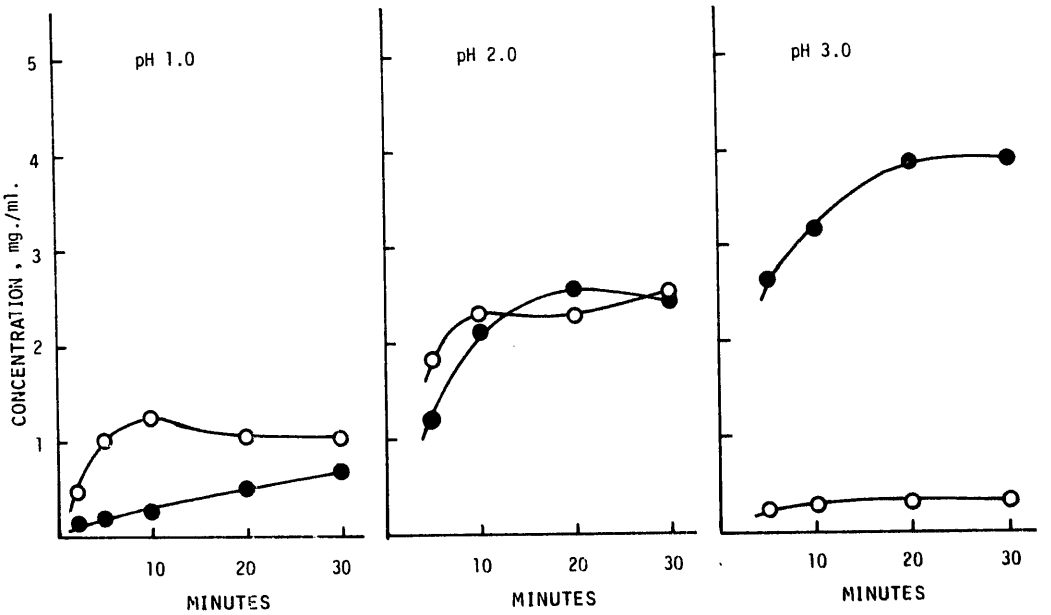

Fig. 7. Dissolution curves of bromhexine free base (○) and its hydrochloride (●) in dilute hydrochloric acid solutions at 37°C.

solubility in gastric fluid because of the abundance of chloride ion. As the absorption of basic drugs takes place chiefly from the intestine, it is important that it should reach the intestine in a dissolved or readily soluble form. It appears that the solubility of the drugs in the stomach is of decisive importance for the absorption since basic drugs have very low solubility in the alkaline environment of the intestine. Drug particles which do not dissolve in the stomach are emptied into the intestine which is much less favorable for dissolution and generally will be unabsorbed (Barr, 1972).

Bezwoda et al. (1978) showed that the normal subjects had gastric pH values below 2. In addition, the chloride is present in body fluids at high level, which is also unfavorable for dissolution of the hydrochloride due to the common ion. Thus, these factors create conditions less favorable for the dissolution of the hydrochlorides in gastric fluid, affecting the bioavailability. Since the drugs are usually administered orally, it is of interest to compare the absorption of these drugs when administered orally as the hydrochloride and as the free base.

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