Precaution on Use of Hydrochloride Salts in Pharmaceutical Formulation

SHOZO MIYAZAKI ˣ, MIDORI OSHIBA, and TANEKAZU NADAI

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Abstract □ Previous reports suggested that the formation of hydrochloride salts does not always enhance solubility due to the common ion effect. The extent of the common ion effect seems to be related to aqueous solubility, with slightly soluble hydrochlorides being more sensitive to the common ion, *i.e.*, chloride ion. The relationship between solubility in water and the extent of the common ion effect was examined, and a high correlation was found, suggesting that hydrochlorides possessing solubilities in water at least of the order observed for papaverine and demeclocycline hydrochlorides (~32 mg/ml at 25° and 42 mg/ml at 37°) are less soluble than the corresponding free base at gastric pH.

Keyphrases □ Hydrochlorides—effect on solubility, common ion effect □ Solubility—effect of hydrochlorides, common ion effect □ Common ion effect—effect of hydrochlorides on solubility □ Physicochemistry—effect of hydrochlorides on solubility, common ion effect

Salt formation is one of the first approaches used to modify drug solubility and dissolution rates. Because of simple availability and physiology, the monohydrochloride salts have been the most frequent choice of the available salts of basic drugs (1). However, previous reports (2–5) showed that hydrochloride salt formation does not necessarily enhance solubility and bioavailability. This finding is based on the common ion effect of chloride on the solubility product equilibrium of hydrochloride salts (6), which often is overlooked. Hydrochloride salts of the drugs frequently exhibit less than desirable solubility in gastric fluid because of the abundance of chloride ion.

BACKGROUND

Unusual pH–solubility profiles containing maxima at pH 2–3 were reported previously (2) for chlortetracycline, demeclocycline, 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 product equilibrium of the hydrochloride salts. The apparent dissolution rates and solubilities of these hydrochloride salts were less than those of the respective free base forms in chloride-containing media. Evidence was presented for greater bioavailability from the chlortetracycline and methacycline free bases compared to the hydrochloride salts (3). The common ion effect also influenced the solubilities and dissolution rates of the hydrochloride salts of papaverine, trihexyphenidyl, isoxsuprine, phenazopyridine, cyproheptadine, and bromhexine (4, 5).

On the other hand, tetracycline hydrochloride solubility, which increased with a pH decrease, showed a usual pH profile in chloride-containing buffers (2). Tetracycline hydrochloride exhibited a greater solubility than its free base in hydrochloric acid at pH 1.2 since the hydrochloride exhibited a low sensitivity to the chloride ion. The differences between tetracycline and the other drugs in sensitivity to the chloride ion may result because the aqueous solubility of tetracycline hydrochloride is much higher than that of the others.

The addition of a common ion often reduces the solubility of a slightly soluble electrolyte. Although the concept of solubility product equilibrium originated in inorganic chemistry, this principle can be applied to slightly soluble organic salts (7). The drugs under study are basic amino compounds and form slightly or sparingly soluble hydrochloride salts. Since the salt in solution is partially dissociated, further solubility suppression may be caused by the common ion effect. The equilibrium involved is shown in Scheme I.

From previous results, it seems that the extent of the common ion effect

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

Scheme I

is related to aqueous solubility, with slightly soluble salts being more sensitive to the chloride ion. In this study, an attempt was made to determine the relationship of solubilities in water and their sensitivities to the chloride ion of nine hydrochloride salts that showed unusual solution properties. The salting-out constant with sodium chloride, based on the Setschenow equation (8), was taken as the parameter of the extent of the common ion effect, *i.e.*, sensitivity to chloride ion. The Setschenow equation was found to be applicable to an amine hydrochloride (9).

EXPERIMENTAL

The drugs studied are listed in Table I. Solubility measurements in distilled water were made at 25 and 37°. An excess of the drugs was placed into each vial containing the solvent, and the vials were equilibrated by shaking overnight. Equilibrated mixtures were filtered[1], and the filtrates were assayed spectrophotometrically.

The solubility of each drug in sodium chloride solutions also was determined as already described. Experimental salting-out constants were calculated according to the Setschenow equation (8):

$$\log S_0/S = kC \qquad \text{(Eq. 1)}$$

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

RESULTS

Table I summarizes the solubility data obtained for each hydrochloride salt and their experimentally determined salting-out constants with sodium chloride at 25 and 37°; the solution pH is also given. Setschenow plots for these drugs in sodium chloride at 25° are shown in Fig. 1. There appears to be a distinct relationship between the solubility in water and the salting-out constant with sodium chloride; as the solubility in water increased, the salting-out constant decreased. Thus, phenazopyridine, cyproheptadine, and bromhexine hydrochlorides, which had the smallest solubilities, were sensitive to the chloride ion to the greatest extent. The most soluble drugs, papaverine and demeclocycline hydrochlorides, were the least sensitive to the chloride ion.

Figure 2 shows the salting-out constant with sodium chloride as a function of solubility in water at 25 and 37°. A least-squares line was fitted to all points in each log–log plot. A high correlation coefficient (r) was obtained at both 25 (r = 0.902) and 37° (r = 0.946), indicating that the smaller the solubility in water, the larger the salting-out constant.

Furthermore, the data are interesting with regard to their general applicability to other slightly soluble organic hydrochlorides. For all drugs listed in Table I, much greater solubility and dissolution rates were obtained by the free bases than by hydrochloride salts in hydrochloric acid solution at pH 1.2. Perhaps this phenomenon applies to hydrochloride salts having water solubilities less than ~32 mg/ml at 25° and 42 mg/ml at 37°, which are the solubilities of papaverine and demeclocycline hydrochlorides.

DISCUSSION

Comparison of the solubilities in water to the salting-out constant revealed an inverse relationship between these quantities. Although it would be desirable to develop this relationship further, a general statement concerning hydrochloride salt formation within the solubility range found in this study may be possible: hydrochloride salts having solubil-

[1] Millipore 0.45-μm filter.

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Table I—Solubility in Water and Salting-Out Constant with Sodium Chloride at 25 and 37° [a]

Hydrochloride (Molecular Weight)	Temperature	Solubility[b], mg/ml	pH[c]	Salting-Out Constant, k[d]
Phenazopyridine (249.7)	25°	2.81 (4, 0.03)	3.35	18.06
	37°	4.03 (6, 0.06)	3.28	11.57
Cyproheptadine[e] (350.9)	25°	2.98 (3, 0.02)	5.74	21.18
	37°	4.56 (3, 0.05)	5.29	14.80
Bromhexine (412.6)	25°	3.85 (5, 0.05)	4.00	20.00
	37°	4.85 (9, 0.03)	3.83	16.78
Trihexyphenidyl (337.9)	25°	5.17 (5.04, 5.29)	5.51	8.24
	37°	11.34 (7, 0.37)	5.23	5.66
Isoxsuprine (337.9)	25°	8.86 (8.84, 8.88)	5.45	6.32
	37°	11.60 (5, 0.85)	5.10	6.30
Chlortetracycline (515.4)	25°	10.72 (10.67, 10.77)	2.39	9.60
	37°	11.74 (7, 0.34)	2.28	6.52
Methacycline (478.9)	25°	16.89 (3, 0.04)	2.26	8.24
	37°	19.49 (3, 0.89)	1.94	6.36
Papaverine (375.8)	25°	31.78 (4, 0.29)	2.90	5.09
	37°	41.74 (41.73, 41.75)	3.13	3.60
Demeclocycline[f] (519.4)	25°	32.55 (32.06, 33.04)	2.11	3.73
	37°	41.49 (40.64, 42.34)	1.86	2.68

[a] As reported in Refs. 2, 4, and 5. [b] The averaged result is reported where there were more than two determinations, followed by parentheses containing the number of determinations and the standard error. For two determinations, the average is followed by parentheses containing the individual values. All data are expressed as the free base equivalent. [c] The pH of a saturated solution. [d] Estimated from the initial slope. [e] Contained 3/2 mole of water. [f] Monohydrate.

ities in water at least of the order observed for papaverine and demeclocycline hydrochlorides are less soluble than the corresponding free base at gastric pH. This finding may be useful in predicting the most soluble form of similar drugs from known or readily determined water solubility values.

Lin *et al.* (9) illustrated a similar phenomenon that decreases the dissolution rate of the salt below that of its free base form. The free base of an experimental antihypertensive exhibited a greater dissolution rate

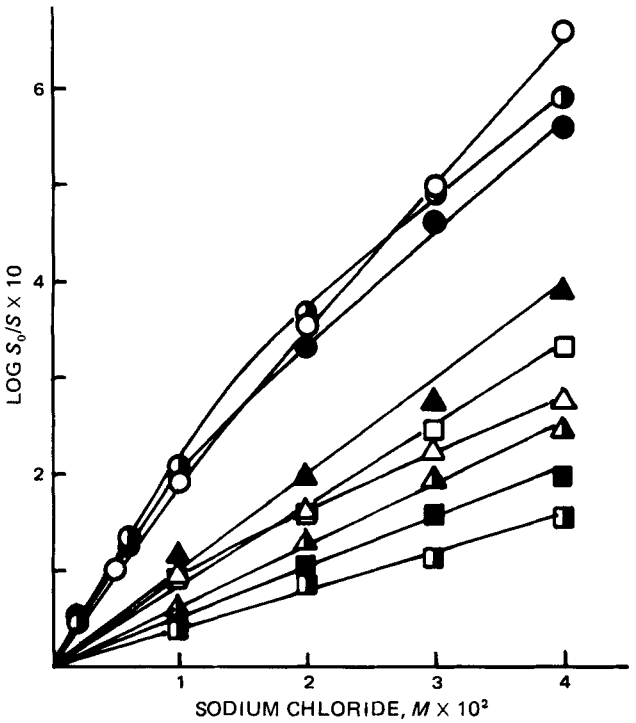

Figure 1—*Setschenow plots for hydrochloride salts in sodium chloride solutions at 25°. Key: ○, phenazopyridine; ◑, cyproheptadine; ●, bromhexine; △, trihexyphenidyl; ▲, isoxsuprine; ▲, chlortetracycline; □, methacycline; ■, papaverine; and ◨, demeclocycline.*

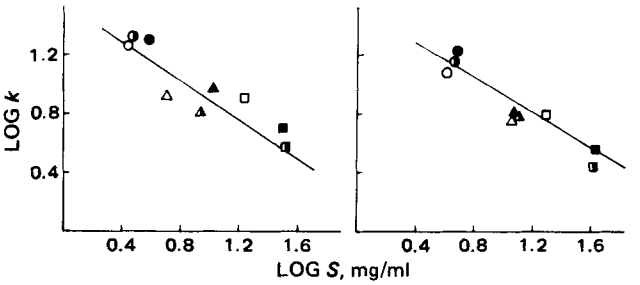

Figure 2—*Relationship between solubility in water and salting-out constant at 25 (left) and 37° (right). Key: see Fig. 1.*

than the monohydrochloride salt in 0.1 *N* HCl, and this finding was attributed to the common ion effect. The equilibrium solubility of the monohydrochloride at 37° was 16 mg/ml in water.

Because of the high aqueous solubility (133.7 and 164.4 mg/ml at 25 and 37°, respectively) and low sensitivity of tetracycline hydrochloride to the chloride ion (k = 0.94 and 0.85, respectively), this antibiotic showed unusual solubility characteristics (2). The freely soluble hydrochlorides normally exhibit no serious problem.

Although doxycycline hydrochloride solubility in water at 25° is 50 mg/ml (10), the free base dissolved from the compressed pellet form about sixfold faster than the hydrochloride in 0.1 *N* HCl (11). Common ion equilibrium with chloride strongly reduces the dissolution rate of doxycycline hydrochloride from the pellet, while the free base is not affected. Dissolution of hydrochloride salts from crystalline powder in chloride-containing media probably represents a problem only with slightly or sparingly soluble hydrochlorides, but dissolution certainly may be a problem with the tablet dosage form when the hydrochloride is soluble.

The solubility of solids is a very useful parameter since an orally administered drug in solid dosage form must dissolve in the GI tract prior to absorption. The GI absorption of chlortetracycline and its hydrochloride was studied in rats and humans (3), and the results indicated that the free base was more efficiently absorbed than the hydrochloride from the GI tract. Similar results also were noted for methacycline and its hydrochloride. The differences between the bioavailability of the free base and the hydrochloride were attributed mainly to differences in solubility at gastric pH.

Since the absorption of basic drugs occurs chiefly from the intestine, these drugs should reach the intestine in a dissolved or readily soluble form. The solubility of the drugs in the stomach is of decisive importance for absorption since basic drugs have very low solubility in the alkaline environment of the intestine. Drug particles that do not dissolve in the stomach are emptied into the intestine and generally will be unabsorbed.

The pH of the gastric fluid usually ranges from 1 to 3; fasting tends to decrease the pH to 1.2–1.8 (12). In addition, the chloride ion is present in body fluids at a high level, which also is unfavorable for dissolution of the hydrochloride due to the common ion suppression of the solubility product equilibrium. These factors create conditions less favorable for hydrochloride dissolution in gastric fluid, thus affecting bioavailability. In such cases, selection of an alternative salt form or free base may improve dissolution and bioavailability.

Special precautions should be taken when drugs are used as hydrochloride salts in pharmaceutical formulation. Consequently, extensive and systematic preformulation studies of the physicochemical properties, including salt formation, of each new drug entity are necessary to determine the most suitable form for drug formulation by the pharmaceutical industry.

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Urinary Excretion of Methenamine and Formaldehyde: Evaluation of 10 Methenamine Products in Humans

RAMACHANDER GOLLAMUDI, ARTHUR B. STRAUGHN, and MARVIN C. MEYER ˣ

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Abstract □ The urinary excretion of both methenamine and formaldehyde was measured for 48 hr after the oral administration of 10 different methenamine products to 10 human subjects in a crossover study. The following dosage forms were evaluated: a tablet of methenamine base, a methenamine hippurate tablet, and eight products containing methenamine mandelate, including six enteric-coated tablets, a suspension, and a granule dosage form. The nonenteric-coated dosage forms were absorbed more rapidly, based on maximum excretion rates that occurred within 3 hr after dosing. The enteric-coated tablets, which were designed not to release methenamine until reaching the intestinal tract, exhibited maximum excretion rates that did not occur until 7–17 hr after dosing. There were no significant differences ($p > 0.05$) among products in terms of total excretion of free formaldehyde in the urine. However, large differences ($p < 0.05$) were noted among products for urinary recovery of total methenamine, with the amount of administered dose recovered ranging from 16 to 83%.

Keyphrases □ Methenamine—evaluation of 10 products, urinary excretion of formaldehyde □ Bioavailability—methenamine in 10 products, humans □ Urinary tract antibacterials—evaluation of 10 methenamine products, excretion of formaldehyde □ Antibacterials, urinary tract—evaluation of 10 methenamine products, excretion of formaldehyde

Methenamine (hexamethylenetetramine) is a urinary tract antibacterial agent. It is absorbed from the intestinal tract, circulates unchanged in blood, and is excreted in the urine. Under acidic conditions in the urine, it undergoes hydrolysis to formaldehyde. Approximately 10–30% of the drug also is believed to be converted to formaldehyde in the acidic environment of the stomach (1). Enteric-coated preparations are designed to withstand such premature hydrolysis by releasing drug only in the intestine. With such dosage forms, drug absorption may be delayed due to slow gastric emptying or may be incomplete due to failure of the product to release methenamine in the intestine.

A crossover study was undertaken to evaluate the relative bioavailability of 10 methenamine products. The urinary excretion of both methenamine and formaldehyde was determined in 10 human volunteers who received all 10 dosage forms.

EXPERIMENTAL

Methenamine Products—The 10 methenamine products evaluated are summarized in Table I. Products 1–3 were included as reference products for comparison with the hippurate tablet and the six enteric-coated tablets. All products were supplied by the U.S. Food and Drug Administration, except Products 1 and 2, which were purchased from a local pharmacy.

Table I—Methenamine Products Tested

Product[a]	Dosage Form	Administered Dose	Calculated Methenamine Content, g
1	Methenamine tablets (0.5 g)	1 tablet	0.500
2	Methenamine mandelate suspension (50 mg/ml)	20 ml	0.480
3	Methenamine mandelate granules (0.5 g/package)	2 packages	0.480
4	Methenamine mandelate tablets (0.5 g)[b]	2 tablets	0.480
5	Methenamine mandelate tablets (0.5 g)[b]	2 tablets	0.480
6	Methenamine mandelate tablets (0.5 g)[b]	2 tablets	0.480
7	Methenamine mandelate tablets (0.5 g)[b]	2 tablets	0.480
8	Methenamine mandelate tablets (0.5 g)[b]	2 tablets	0.480
9	Methenamine mandelate tablets (0.5 g)[b]	2 tablets	0.480
10	Methenamine hippurate tablets (1.0 g)	1 tablet	0.439

[a] Manufacturer (lot number): 1, Eli Lilly (9SW09A); 2, Warner/Chilcott (8425105A); 3, Warner/Chilcott (9607055-B); 4, Warner/Chilcott (6479016A); 5, J.W.S. Delavau Co. (unknown); 6, Tablicaps (31931); 7, Standard Pharmacal (41870); 8, Vangard Laboratories (420924); 9, Heather Drug Co. (510059); and 10, Riker Laboratories (57729). [b] Enteric coated.

Study Protocol—Ten male volunteers[1], average age 26 years (range of 23–30 years), average weight 81 kg (range of 63.5–95.3 kg), and average height 179.9 cm (range of 170.1–190.5 cm) underwent a hematological and blood chemistry[2] analysis and a urinalysis to ensure inclusion of only healthy subjects. One subject was dropped after the 3rd week because of illness that was not related to the study. He was replaced by Subject 6, who received all 10 products in the order originally assigned to the dropped subject.

Each subject received one methenamine product at intervals of at least 1 week, except for Subject 6 who received doses at 4-day intervals to permit completion of the study at the same time as the other nine subjects. The administration sequence was based on a crossover matrix designed to minimize any residual or cumulative effects of the preceding dose (2).

Each methenamine product was given along with 200 ml of water after an overnight fast. Subsequent water intake was unrestricted but was

[1] Staff and students of the University of Tennessee Center for the Health Sciences. Written informed consent was obtained.
[2] SMA 12/60.

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