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Common Ion Effect of Chloride on the Dissolution Properties of Papaverine Hydrochloride[1]

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The effect of chloride ion on the dissolution properties of papaverine-HCl was studied. The solubility and dissolution rate of papaverine-HCl were decreased by the common ion effect in a medium rich in chloride ion. The effect of chloride ion on the plasma levels of papaverine-HCl was also tested in rats, and lower plasma levels were observed when the drug was administered with 0.9% NaCl than in its absence. The results suggest that it may be possible to formulate sustained release preparations of papaverine-HCl by combination with NaCl.

Keywords——common ion effect; hydrochloride salts; papaverine hydrochloride; solubility; dissolution rate; oral administration; plasma concentration; sustained release

Many pharmaceutical techniques have been developed to achieve sustained release of drugs.[3] Most often, sustained release is achieved by coating of tablets or granules, by embedding the drug in a slowly eroding matrix, by the use of ion exchange resins, or by the formation of slightly soluble salts or complexes. Sustained release oral products employing dissolution as the rate-limiting step are in principle the simplest to prepare. A previous report[4] showed that solubility product equilibria involving chloride ion were a major factor affecting the aqueous solubility of some pharmaceutical hydrochloride salts. The apparent dissolution rates and solubilities of the hydrochloride salts were reduced in chloride-containing media. This characteristic can be applied to the formulation of sustained release preparations of the drugs. The addition of the common ion, *i.e.*, chloride ion, to the formulation can alter the rate of dissolution and enhance the sustained release of the hydrochloride salts. Common ion effects have been applied to slightly soluble organic salts, in order to enhance the stability[5] and improve the taste[6]

In the present work, we attempted to investigate the effect of chloride ion on the dissolution properties of pharmaceutical hydrochloride salts. In addition, a study was undertaken to determine the effect of chloride ion on the GI absorption of papaverine hydrochloride (papaverine-HCl),[7] used as a model drug. A recent review article provides general information on sustained release of papaverine-HCl.[8]

Experimental

Materials——Papaverine-HCl was of J.P. IX grade and was used without further purification. All other materials were of reagent grade.

Solubility Studies——An excess of the drug was placed in each vial containing the solvent, and the vials were equilibrated by shaking overnight at 37°C. Equilibrated mixtures were filtered through a Millipore filter (0.45 μm), and, after appropriate dilution with 0.1 N HCl, the filtrates were assayed for the drug spectrophotometrically at 251 nm employing a Jasco UVIDEC-2 spectrophotometer. The pH of each aliquot was measured with a combination pH electrode (Type 6028-10T, Horiba, Tokyo).

Dissolution Studies——A weighed sample of the drug (2.5 g) was added to 100 ml of dissolution medium maintained at 37°C in a water-jacketed beaker. The solution was agitated by means of an overhead stirrer (3-cm blade) with a stirring speed of 50 rpm. At suitable intervals, 1 ml of the medium was taken with a syringe and an aliquot of the filtrate was assayed for the drug in the same manner as in the solubility studies.

The volume of the dissolution medium was kept constant throughout the dissolution experiment by the addition of 1 ml of fresh dissolution medium after each sampling.

Absorption Studies——Male Wistar rats, weighing 160—230 g, were fasted for 20—24 h before the experiment. At the time of dosing, the fasted rats were lightly anesthetized with ether. The drug (50 mg suspended in 2 ml of water or 0.9% NaCl) was administered orally to rats *via* a stomach tube. The animals were sacrificed by decapitation and the plasma was separated immediately by centrifugation. Plasma samples were analyzed by the spectrophotometric method introduced by Axelrod *et al.*[9]

Results and Discussion

Solubility of Papaverine-HCl in Chloride-Containing Media

The effect of added chloride ion on the solubility of papaverine-HCl in water and 0.1 N HCl was first investigated. Sodium chloride was used in the 0.1—0.5 M concentration range. As shown in Fig. 1, the solubility decreased sharply with increasing concentration of sodium chloride.

The solubilities of papaverine-HCl in various solvents of interest are shown in Table I. In 0.1 N HCl, the amount of papaverine-HCl dissolved was less than half that in pure water. Reduction of the hydrochloric acid concentration from 0.1 to 0.01 N caused a two-fold increase in the solubility. Increase in sodium chloride concentration caused the solubility to decrease. The solubility in water and in 0.1 N HCl decreased to half when 0.5% (0.09 M) NaCl was present and to about one-third when 0.9% (0.154 M) NaCl was present.

It is known from the pK_a of the papaverine cation (6.4)[10] that the ionic nature of papaverine does not change appreciably as the pH is increased from 1.18 (0.1 N HCl) to 3.80 (0.9% NaCl in water). Hence, increasing chloride ion concentration probably caused precipitation of papaverine-HCl by a common ion effect.

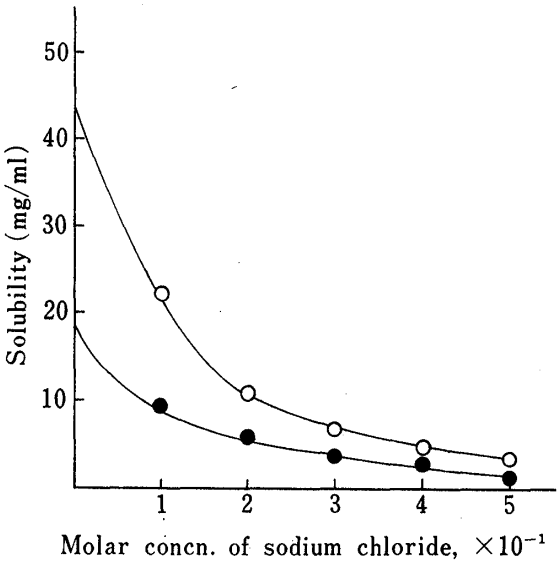

Fig. 1. Effect of Sodium Chloride Concentration on the Aqueous Solubility of Papaverine–HCl at 37°C

—○—: water, —●—: 0.1 N HCl.
Each point represents the mean of 3 or 4 experiments.

Table I. Aqueous Solubility of Papaverine–HCl in Various Media at 37°C

Composition of media	Solubility[a] (mg/ml)	pH[b]
Water	43.80(11, 0.52)	3.18
0.01 N HCl	38.47(3, 0.09)	2.08
0.05 N HCl	28.41(3, 0.09)	1.32
0.1 N HCl	19.31(14, 0.40)	1.18
0.5% NaCl and water	20.12(3, 0.12)	3.58
0.5% NaCl and 0.1 N HCl	9.72(9.77, 9.68)	1.32
0.9% NaCl and water	11.93(5, 0.07)	3.80
0.9% NaCl and 0.1 N HCl	6.57(4, 0.14)	1.27

a) The averaged result is reported when 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 hydrochloride salt equivalent.
b) The pH of a saturated solution.

These results indicate that the solubility of papaverine-HCl is decreased by the common ion effect in media rich in chloride ion.

Dissolution of Papaverine-HCl in 0.1 N HCl Containing Chloride Ion

The dissolution behavior of papaverine-HCl was examined in 0.1 N HCl, since the behavior in hydrochloric acid solution is more relevant to the bioavailability after oral administration. Fig. 2 shows the dissolution curves of papaverine-HCl in 0.1 N HCl and media containing 0.5% and 0.9% NaCl. In contrast to the rapid dissolution of the drug in 0.1 N HCl, slow dissolution was obtained in the media containing the chloride ion. As the chloride ion concentration was increased, the apparent dissolution rate decreased.

Chloride ion, a common constituent of the contents of the stomach and duodenum, significantly reduced the concentration of papaverine-HCl in solution by a common ion effect. The decrease in the apparent dissolution rate of papaverine-HCl in the presence of chloride ion also supports the view that the common ion equilibria with chloride ion can strongly suppress the rate of dissolution in GI fluids.

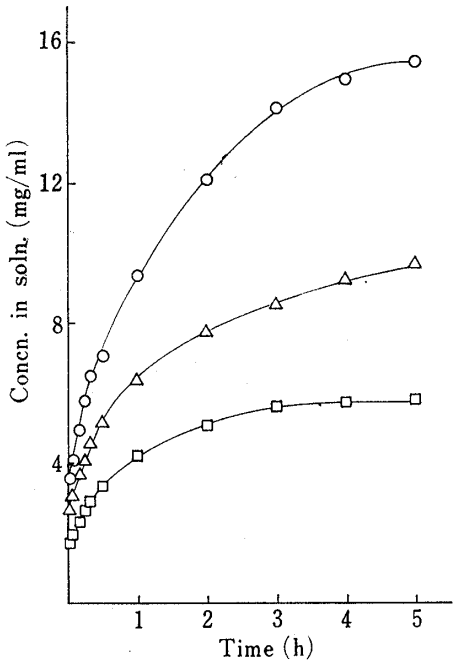

Fig. 2. Dissolution Behavior of Papaverine–HCl in 0.1 N HCl at 37°C, in the Presence and Absence of Sodium Chloride

—○—: 0.1 N HCl.
—△—: 0.5% NaCl in 0.1 N HCl.
—□—: 0.9% NaCl in 0.1 N HCl.
Each point represents the mean of three experiments.

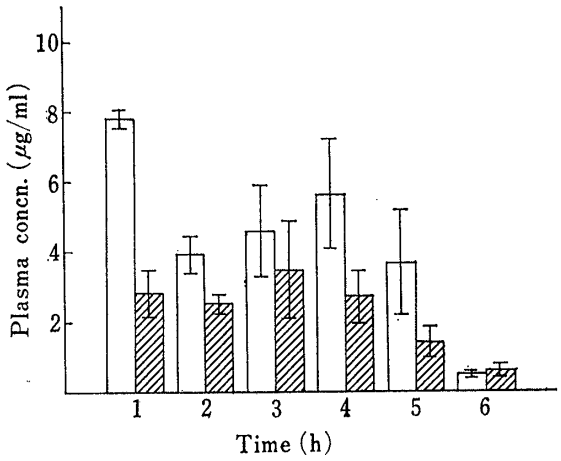

Fig. 3. Effect of Chloride Ion on the Plasma Drug Levels following Oral Administration of Papaverine–HCl Suspensions to Rats

□: water, ▨: 0.9% NaCl.
Each point represents the mean of between 4 and 9 experiments and is shown with the standard error.

***In Vivo* Study in Rats**

A plasma level study was conducted in rats to determine whether or not chloride ion affects the plasma levels of papaverine-HCl. Plasma concentrations of papaverine-HCl were determined after oral administration of the drug as a suspension in pure water or in 0.9% NaCl. The average blood level-time profiles are shown in Fig. 3. It is apparent that papaverine-HCl concentrations in the presence of 0.9% NaCl were lower than those in its absence. The data obtained in this study are in accord with the dissolution data. The decrease in papaverine-HCl plasma levels in the presence of the physiological saline may be explained

by the dissolution retarding effect, which decreases the amount of papaverine-HCl available for absorption.[11)]

A second peak was observed in the plasma drug concentration profile after administration of the drug with pure water, but no attempt was made to determine the reason for this.

From a pharmaceutical point of view, the above results suggest that a combination of drug hydrochloride salts with chloride ion may be useful for the preparation of sustained release dosage forms. Further work is necessary to investigate the applicability of this approach to a variety of drugs.

References and Notes

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