193. Hisashi Nogami, Shoji Awazu, Keiichi Watanabe, and Kazuhiko Sato :Studies on Decomposition and Stabilization of Drugs in Solution. VII.*¹

Stabilization of Methantheline Bromide in Aqueous Solution

by Surface-active Agents.*²(Faculty of Pharmaceutical Sciences, University of Tokyo*³)

When a solubilize is solubilized by a surface-active agent, it is a widely adopted assumption that the solubilize is distributed between aqueous and micellar phases. The resultant solubilization and other phenomena which occur in the surfactant solution have been explained on such assumption.¹⁾ Alexander, *et al.*²⁾ for example, found the decrease of antibacterial activity of phenol solutions in the presence of a surfactant and gave the interpretation that phenols, being active in aqueous phase, transfer into the micellar phase and became inactive. Decrease in antifungal activities of fungicides, e.g. Parabens, with the addition of nonionic surfactants was found by Aoki, *et al.*³⁾ and the phenomenon was explained in the same way. McBain⁴⁾ examined the hydrolysis of nitrosotriacetoneamine in a soap solution, found the change in hydrolysis rate to occur at the critical micelle concentration, and stated that the slower rate above the critical micelle concentration was due to the move of a part of the amine from the aqueous phase to the micelles.

Consequently, when a surfactant is added to the aqueous solution of hydrolytic drugs, it may be expected that a part of the drug will move from the aqueous to micellar phase, the hydrolysis will be prevented, and the solution of drugs will be stabilized.

It has been reported that the oxidation of benzaldehyde in solution⁵⁾ is repressed by a surfactant, but there has been no report on hydrolysis other than McBain's.⁴⁾ Very recently, however, and after completion of the present work, Riegelman⁶⁾ reported that the rate of hydrolysis of benzocaine is decreased by a surfactant (his study was based on the similar assumption as in this work). Surfactants are added to many pharmaceutical preparations, but the reactivity of drugs in such a system has scarcely been studied. Therefore, the present work was instituted in order to study the possibility of stabilization and to examine the reactivity of drugs in an aqueous solution containing surfactants.

Methantheline bromide (Banthine) was selected as the object in this investigation. As reported previously,⁷⁾ methantheline bromide is a quaternary amine which has an ester linkage hydrolyzed in aqueous solution by acid-base catalysis. As methantheline bromide is positively ionized and freely soluble in water, it may be considered that methantheline bromide hardly transfers into the micelle interior which is said to be composed of higher hydrocarbon chains. It may therefore be expected that a cationic surfactant does not repress the hydrolytic decomposition of methantheline bromide in water or stabilize its aqueous solution. When a nonionic surfactant is added, on the basis of the above discussion, the

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2) A. E. Alexander, A. J. H. Tomlinson : "Surface Chemistry," 317(1949). Interscience Publishers Inc., New York.

3) M. Aoki, *et al.* : Yakugaku Zasshi, **76**, 939(1956); *ibid.*, **77**, 410, 1071(1957).

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5) J. E. Carless, J. R. Nixon : J. Pharm. Pharmacol., **9**, 963(1957).

6) S. Riegelman : J. Am. Pharm. Assoc., Sci. Ed., **49**, 339(1960).

7) H. Nogami, *et al.* : This Bulletin, **6**, 277(1958).

8) R. Goto, *et al.* : Nippon Kagaku Zasshi, **75**, 73(1954).

surfactant may not distinctly stabilize the methantheline bromide solution. However, it has been reported that the critical micelle concentration of nonionic surfactant is determined with an ionic dye so that ionic substances may interact with a nonionic surfactant, and it cannot be predicted easily whether nonionic surfactants may stabilize the methantheline bromide solution or not. The effect may be complicated when an anionic surfactant which has the opposite charge to methantheline bromide is added. Since Hartley,⁹⁾ many investigators have studied interaction between ionic dyes and ionic surfactants which are oppositely charged. According to Mukerjee,¹⁰⁾ a dye and a surfactant form a complex and the complex is solubilized in micelles which are formed by the excess surfactant. Provided that ionic drugs behave like ionic dyes, methantheline bromide will form a complex with an anionic surfactant and, according to Mukerjee,¹⁰⁾ the complex will move from the aqueous to micellar phase, and consequently methantheline bromide will be stabilized.

Sodium laurylsulfate, cetyledimethylammonium bromide, and Emulgen 120*⁴ were used in this study, respectively as anionic, cationic, and nonionic surfactants.

The prevention of the hydrolysis of drugs by the addition of an organic solvent and complex formation were studied, respectively by Ikeda¹¹⁾ and Higuchi,¹²⁾ but the complex compound studied by Higuchi differs from that studied here in the state of solution.

Methantheline bromide is determined with Bromocresol Purple (anionic dye) as previously reported.⁷⁾ In the presence of a surfactant, however, this determination cannot be used, because the complex is formed between a dye and a surfactant, or the normal extraction of the complex with an organic solvent is prevented. A new spectrophotometric determination of methantheline bromide was developed. As the ultraviolet absorption of methantheline bromide is almost due to the acid (xanthene-9-carboxylic acid) portion, methantheline bromide is determined at the absorption maximum after separation of the decomposed acid substance. The acid is extracted with an organic solvent (Method 1). In the presence of sodium laurylsulfate, the ultraviolet absorption disappears from the aqueous layer with Method 1. Mukerjee¹³⁾ extracted the complex between surfactant and oppositely charged dye with an organic solvent and determined ionic surfactants colorimetrically. Therefore, it seems probable that the disappearance of the ultraviolet absorption is due to the formation of methantheline bromide-sodium laurylsulfate complex. In the presence of sodium laurylsulfate, it was possible to determine methantheline bromide when the methantheline bromide-sodium laurylsulfate complex is extracted with an organic solvent and the acid remains in the pH 8 buffer solution (Method 2).

Experimental

Materials—1) Methantheline bromide and ethylene dichloride were same as reported previously.⁷⁾
2) Sodium Laurylsulfate : A commercial product of Tokyo Chemical Industry Co., recrystallized from EtOH after extraction of higher alcohols with Et₂O.

Cetyledimethylammonium Bromide : A commercial product of Eastman Kodak Co., washed with Et₂O as in sodium laurylsulfate and recrystallized from Me₂CO and benzene.

3) Emulgen 120, Carbowax 4000, and polyethyleneglycol 400 were all commercial products, used without any purification.

4) Buffer : Since hydrolytic rates changed with buffer concentration in the presence of sodium laurylsulfate, as will be described later, all hydrolysis was studied with the following buffer solutions.

*⁴ Polyoxyethylene lauryl ether, Kao Soap Co. Ltd. product (HLB : 15.5)

9) G. S. Hartley : Trans. Faraday Soc., **30**, 444(1934).

10) P. Mukerjee, K. J. Mysels : J. Am. Chem. Soc., **77**, 2937(1955). Mukerjee showed the complex to be a simple stoichiometric salt of dye and surfactant.

11) K. Ikeda : This Bulletin, **8**, 504, 510(1960).

12) T. Higuchi, *et al.* : J. Am. Pharm. Assoc., Sci. Ed., **44**, 521(1955); *ibid.*, **45**, 290(1956); *ibid.*, **46**, 32, 36(1957).

13) P. Mukerjee : Anal. Chem., **28**, 870(1956).

The reagents used were of extra pure grade.

Na_2HPO_4 0.0614 mole + KH_2PO_4 0.00534 mole/L. $\times 1$ Buffer

Na_2HPO_4 0.123 mole + KH_2PO_4 0.0107 mole/L. $\times 2$ Buffer

Na_2HPO_4 0.246 mole + KH_2PO_4 0.0214 mole/L. $\times 4$ Buffer

pH values were determined with the Beckman Model G pH-meter.

Kinetic Procedure—100 mg. methantheline bromide and accurately weighed additive were placed in a 100-cc. volumetric flask and made to 100 cc. with the buffer solution. When sodium laurylsulfate was added, a white turbidity appeared at first but disappeared with subsequent addition. The volumetric flask was immersed in a thermostatically controlled water bath maintained at $T \pm 0.1^\circ$. Samples were taken from the flask at given intervals and methantheline bromide was determined as follows.

Determination—a) Method 1: Ten cc. of dil. HCl solution (pH 1.4), 10 cc. of ethylene dichloride, and 1 cc. of sample were pipetted into a glass-stoppered centrifugal bottle. The bottle was shaken for 10 min. and centrifuged for 10 min. The aqueous layer was assayed spectrophotometrically with Hitachi EPU-II spectrophotometer at 281 m μ . This method was used for the control (in the absence of any additives) and in the presence of Emulgen 120, cetyldimethylammonium bromide, Carbowax 4000, and polyethyleneglycol 400.

b) Method 2: Ten cc. of buffer solution of pH 8 (0.5 cc. of 2M/15 KH_2PO_4 + 9.5 cc. of 2M/15 Na_2HPO_4 ; buffer solution was previously adjusted to contain 1 mg./cc. of sodium laurylsulfate when a sample was added), 20 cc. of ethylene dichloride, and 2 cc. of sample were pipetted into the above-mentioned bottle. The bottle was shaken for 10 min. and centrifuged for 15 min. The ethylene dichloride layer was assayed spectrophotometrically at 283 m μ .^{*5}

Results and Discussion

Test of the Determination Methods 1 and 2

To examine the propriety of the Methods 1 and 2, hydrolytic decomposition of methantheline bromide in the control solution at 38° was compared by the two methods. As illustrated in Fig. 1, the coincidence of results is satisfactory and both methods can be used in this study.

Fig. 1.
Test of the Determination Methods 1 and 2

× Method 1
• Method 2

Effect of Various Surfactants on Stabilization

Hydrolysis of methantheline bromide at 38° in 0.5% cetyldimethylammonium bromide, Emulgen 120, 0.1% sodium laurylsulfate, and control solutions is illustrated in Fig. 2. In Emulgen 120, cetyldimethylammonium bromide, and control solutions, the hydrolysis followed a pseudo-first order course, but not in sodium laurylsulfate solution. This was observed in all sodium laurylsulfate concentrations studied in the present work and a characteristic feature of methantheline bromide hydrolysis in the sodium laurylsulfate solution. Therefore, half lives were compared and are tabulated in Table I. Effective stabilization was observed in 0.1% sodium laurylsulfate solution.

*5 The absorption maximum was different in water and in ethylene dichloride.

Fig. 2.
Decomposition of Methantheline Bromide in
the Control and Surfactant
Buffer Solution

- 1) Sodium laurylsulfate (0.1% in $\times 2$ Buffer)
- 2) Emulgen 120 (0.5%)
- 3) Control
- 4) Cetyledimethylammonium bromide (0.5%)

TABLE I. Half Lives of Methantheline Bromide in the Control Solution and in the Solution with Additives at 38°

	Control		0.5% CD ^{a)}	0.5% Em-120 ^{b)}
Buffer concn.	$\times 4$	$\times 1$	$\times 2$	$\times 2$
Half life (min.)	315	320	295	382
pH	7.75	7.75	7.77	7.77
	0.5% PEG ^{c)} 400		0.5% Carbowax 4000	
Buffer concn.	$\times 2$		$\times 2$	
Half life (min.)	325		332	
pH	7.76		7.75	

- a) Cetyledimethylammonium bromide
b) Emulgen 120
c) Polyethyleneglycol 400

Effect of Polyethyleneglycol on the Stabilization

As illustrated in Fig. 2, Emulgen 120 somewhat stabilizes methantheline bromide but it is not obvious whether the stabilizing effect is a specific feature of Emulgen 120 or not. It might be a kind of a solvent effect, or methantheline bromide might be stabilized by polyethyleneglycol which remained unreacted in Emulgen 120. The hydrolytic rate of methantheline bromide was determined in 0.5% solution of polyethyleneglycol 400 and Carbowax 4000 to examine the above description. The decomposition followed a pseudo-first order course in both cases. The rates are not different from the rate in the control (Table I). It was ascertained, therefore, that Emulgen 120 stabilized methantheline bromide only slightly. Methantheline bromide, an ionic substance, seems to interact with a nonionic surfactant to a small extent.

Effects of Sodium Laurylsulfate Concentration on the Stabilization

Sodium laurylsulfate stabilized methantheline bromide so greatly that it would take too much time to study the decomposition of methantheline bromide at 38°. In the presence of sodium laurylsulfate all the study were accomplished at 70°. Examples of the decomposition of methantheline bromide in 0.1, 0.2, 0.3, and 0.5% sodium laurylsulfate solution are illustrated in Fig. 3. The decomposition does not follow a pseudo-first order course in every case as mentioned previously. The higher the concentration of sodium laurylsulfate, the slower the decomposition becomes. As the rate constants could not be calculated, the magnitude of stabilization is expressed by half lives which are tabulated in Table II. The half life of methantheline bromide at pH 7.75 and 70° is 5.6 min. (calculated with the equation given in the previous report⁷⁾). Comparing 5.6 min. with the half life in 0.5% sodium laurylsulfate solution of 10 hours, the life in the latter is 100 times longer.

Fig. 3.
Decomposition of Methantheline Bromide in
Sodium Laurylsulfate $\times 2$ Buffer
Solution at 70°

- 1) Sodium laurylsulfate (0.5%)
- 2) Sodium laurylsulfate (0.3%)
- 3) Sodium laurylsulfate (0.2%)
- 4) Sodium laurylsulfate (0.1%)

TABLE II. Half Lives of Methantheline Bromide in Sodium Laurylsulfate Solution at 70°

Concn. of SLS ^{a)}	0.1%	0.2%	0.3%	0.5%	0.5%	0.5%
Buffer concn.	$\times 2$	$\times 2$	$\times 2$	$\times 2$	$\times 1$	$\times 4$
Half life (min.)	78	198	322	600	>720	435
pH	7.72	7.76	7.75	7.78	7.76	7.72

a) Sodium laurylsulfate

The phenomenon that the decomposition does not follow a pseudo-first order course in sodium laurylsulfate solution may be explained as follows. Methantheline bromide decomposes into 2-diethylaminoethanol methobromide by hydrolysis. Ino¹⁴⁾ reported that the sodium salts of lower alcohol (C_4 and C_8) sulfates have less tendency to form the complex with dodecylpyridinium bromide than the salt of higher alcohol (C_{12}) sulfate. Assuming that the aminoethanol, which has a smaller hydrophobic portion than methantheline bromide is less inclined to form a complex with sodium laurylsulfate than methantheline bromide, the decomposition of methantheline bromide to the aminoethanol results in the increase of sodium laurylsulfate to interact with methantheline bromide. Hence, the rate is decreased, but experiments on this point have not yet been made.

Effect of Buffer Concentration on the Stabilization

It is a well-known fact that magnitude of solubilization is changed with various additives, such as electrolytes, alcohols, etc. Hence the stabilization of methantheline bromide with sodium laurylsulfate, if it is assumed to be parallel with solubilization phenomenon, may be affected by a buffer concentration even in the same pH. The decomposition of methantheline bromide in $\times 1$, $\times 2$, and $\times 4$ buffer solutions each containing 0.5% sodium laurylsulfate was examined. As illustrated in Fig. 4, the higher the buffer concentration, the larger was the decomposition rate. On the other hand, the half lives of methantheline bromide in the control solution were determined in $\times 1$ and $\times 4$ buffer, and the effect of buffer concentration was not noticed (see Table I). Hence, it is the specific feature in sodium laurylsulfate solution that the decomposition rate of methantheline bromide changes with buffer concentration.

As described above, the remarkable stabilization effect of sodium laurylsulfate on methantheline bromide was observed, but precipitation of sodium laurylsulfate from the solution at a low temperature (below the Kraft point) may be the undesirable point in this procedure. Hence, it may not be practical to use sodium laurylsulfate for the stabilization of methantheline bromide, but it seems certain that a new method for stabilization of hydrolytic drugs has been found by this study.

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Fig. 4.
Effect of Buffer Concentration on the
Decomposition of Methantheline
Bromide in Sodium Lauryl-
sulfate Solution at 70°

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Summary

1) The prevention of hydrolysis of ester, using methantheline bromide (Banthine) as an example, with surfactants was examined. Surfactants used were anionic, cationic, and nonionic. Anionic surfactant (sodium laurylsulfate) markedly prevented the hydrolysis (the half life becomes 100 times longer in 0.5% laurylsulfate solution) and nonionic surfactant prevents it slightly.

2) Hydrolysis in sodium laurylsulfate solution does not follow a pseudo-first order course and is influenced by a buffer concentration.

3) The higher the concentration of sodium laurylsulfate, the slower became the hydrolysis.

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