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Dissolution Behavior of Solid Drugs. VII.[1] Dissolution Rates of Sulfanilamide in Aqueous Carboxymethylcellulose Sodium Solutions with or without Sodium Chloride[2]

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The dissolution rates of sulfanilamide in the solutions of two kinds of carboxymethylcellulose sodium (CMC–Na) in the presence or absence of NaCl were measured by the fixed disk method. At the same time, viscosities of these solutions were determined at various rates of shear with a cone and plate viscometer.

In the case of simple CMC–Na solutions, it was found that the dissolution rate of sulfanilamide depends almost only upon the viscosity of the solution, irrespective of the degree of polymerization of CMC–Na. Also, it is supposed that the decrease in the dissolution rate occurs by different mechanisms according to whether the solution belongs to the Newtonian or to the non-Newtonian fluid.

On the other hand, additional influences due to the actions by NaCl become more or less evident in the mixed solutions of CMC–Na and NaCl. One of them is the salting-out effect and has a tendency to decrease the dissolution rate, while the second acts to increase the rate through viscosity decrease of the solutions by shrinking CMC–Na molecules.

Keywords——sulfanilamide; dissolution rate; carboxymethylcellulose sodium; polyelectrolyte solution; sodium chloride; molecular shrinkage; viscosity change; Newtonian fluid; non-Newtonian fluid; flow curve

Hydrophilic high polymers such as cellulose derivatives are widely employed as pharmaceutical ingredients for preparing or stabilizing various dosage forms. Since these polymers are usually incorporated in close contact with other substances and exhibit characteristic viscosities when dissolved, they will exert great influences upon dissolution of an active ingredient. Therefore, it is natural that the absorption and biological availability of the drug are markedly changed by the nature and the amount of the hydrophilic polymer employed.

Recently, the importance of the dissolution behavior of a drug from its dosage forms has been fully recognized and a number of pilot tests and studies have been carried out on this subject. However, they are mainly concerned either with dissolution of the drug itself or with its release from the whole dosage forms. Such being the case, we have little knowledge about how pharmaceutical ingredients, especially those belonging to hydrophilic high polymers, modify the dissolution rates of a drug.

In the present investigation, the authors examined the dissolution patterns of sulfanilamide in various concentrated solutions containing either one of two different specimens of carboxymethylcellulose sodium with or without addition of sodium chloride. At the same time, viscosity characteristics of these solutions were determined. Then, they tried to make comprehensive interpretation of these results and thus acquired informations that would hitherto be unavailable for formulating drug dosage forms.

Experimental

Materials——1) Carboxymethylcellulose Sodium (CMC–Na): Two different specimens of CMC–Na obtained from Tokyo Kasei Co., Ltd. were used. The mean degrees of polymerization were 500 and 1050; therefore, they are denoted by CMC-P500 and CMC-P1050, respectively.

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[1] Part VI: K. Sekiguchi, Y. Tsuda, and M. Kanke, *Chem. Pharm. Bull.* (Tokyo), 23, 1353 (1975).

[2] Presented partly at the 96th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, 1976.

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2) Sulfanilamide: The β-form of sulfanilamide was obtained by crystallization from methanol solution[1] and was used after confirmation of purity by X-ray powder diffractometry and by infrared spectroscopy.

3) Sodium Chloride (NaCl): NaCl used for dissolution and solubility studies was of J.P. VIII grade.

Preparation of Solutions used for Dissolution Measurements——Various amounts of CMC-P500 or CMC-P1050 were dissolved in laboratory distilled water for making up solutions with or without addition of specified amount of NaCl. These solutions were used for dissolution measurements within one hour after preparation.

Measurements of Viscosities——Flow curves of the solutions were measured at 37±0.5° with a cone and plate viscometer (type 832, made by B.E.E. Co., Ltd.) exactly five minutes after setting each sample solution between the cone and the plate. Throughout the measurements, a cone with a diameter of 100 mm was used, and the rotating speed was varied up to 100 rpm.

Solubility Measurements of Sulfanilamide——Solubilities of sulfanilamide in NaCl, CMC-P500, and CMC-P1050 solutions were measured at 37.0±0.1°. The apparatus and the procedure employed were the ones described in the preceding papers.[1,4] At fixed intervals, the concentrations of sulfanilamide dissolved were assayed spectrophotometrically after appropriate dilution of the filtered sample solutions.

Measurements of Dissolution Rate——The apparatus used was the same as in the previous papers.[1,5] A compact disk of sulfanilamide was prepared in a die with a diameter of 20 mm by hard compression (3 tons/cm^2) in a vacuum. All measurements were done at 37.0±0.1° under agitation at 240 rpm. During the measurement, the bulk solution was circulated through the flow cell of the spectrophotometer at a rate of 250 ml/min.

As shown in the following equation, the experimental conditions were so adopted that the dissolution rate was always proportional to the rate of changes in absorbance, so that the former was represented by the latter without recalculation.

$$\frac{dE}{dt} = \varepsilon\frac{dC}{dt} = \varepsilon K(C_s - C) = \varepsilon KC_s \qquad (\because C_s \gg C) \tag{1}$$

dE/dt: rate of change in absorbance of the bulk solution,
dC/dt: dissolution rate,
ε : molar extinction coefficient,
K : constant of the Noyes–Whitney equation,
C_s: solubility of the dissolving substance,
C : concentration of the bulk solution

Results and Discussion

Dissolution Rates of Sulfanilamide in Simple Aqueous CMC-Na Solutions

Sulfanilamide is known to be dissolved in water by diffusion controlled mechanism.[1] Accordingly, the authors supposed before the experiments that its dissolution rates would be decreased in CMC–Na solutions as the concentration and the degree of polymerization of CMC–Na is increased. As shown in Fig. 1, the experimental curves meet the above expectations; however, it should be noted that the rates fall distinctly in relatively dilute solutions of both CMC–Na specimens but become nearly constant at higher concentrations.

In order to find the influencing factors, solubility data of sulfanilamide from Fig. 2 were introduced into Eq. (1) assuming that the dissolution rate constant is independent of viscosity of the medium and is equal to the value in pure water. The hypothetical curve thus obtained is represented by a dotted line in Fig. 1 and is quite different from the experimental ones. The fact indicates that the assumption is inadequate and the solubility decrease has a minute or a negligible contribution to the decreased dissolution. It is supposed, therefore, that the viscosity of the medium is most influencing. Accordingly, flow curves of various solutions were determined as shown in Fig. 3 and 4. From parallelism of the curves to the abscissa, convertion from Newtonian to non–Newtonian fluids occurs in each series of CMC–Na solutions at a certain viscosity value of about 5 centipoises. It is also evident from the viscosity–concentration curves in Fig. 5 that the viscosity increases not proportionally but

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[4] K. Sekiguchi, K. Shirotani, M. Kanke, H. Furukawa, and M. Iwatsuru, *Chem. Pharm. Bull.* (Tokyo), **24**, 1621 (1976).

[5] K. Sekiguchi, K. Shirotani, and M. Kanke, *Yakugaku Zasshi*, **95**, 195 (1975).

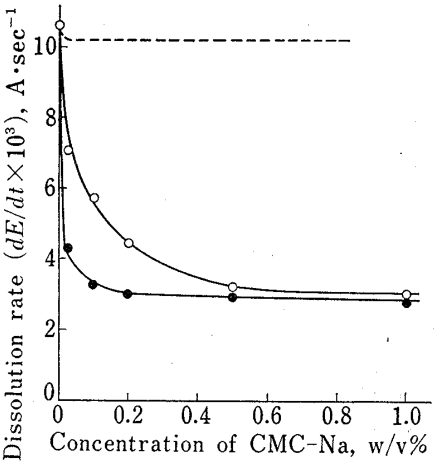

Fig. 1. Plots of dE/dt against CMC-Na Concentration for Sulfanilamide in Each CMC-Na Specimen Solution at 37.0±0.1°

The dotted line represents the hypothetical curve obtained by assuming that the dissolution rate constant, K, is a constant.
○, in CMC-P 500 solutions;
●, in CMC-P 1050 solutions.

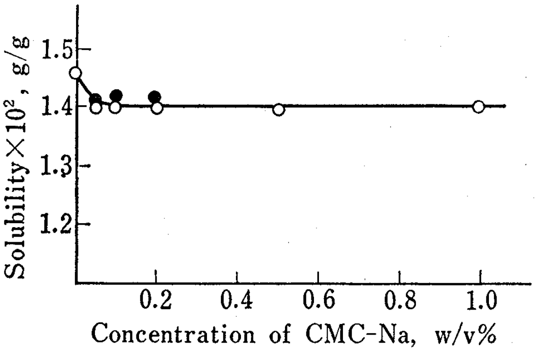

Fig. 2. Solubilities of Sulfanilamide in Various CMC-Na Solutions at 37.0±0.1°

○, in CMC-P 500 solutions;
●, in CMC-P 1050 solutions.

Table I. Dissolution Rates of Sulfanilamide and Viscosities of CMC-Na Solutions

	CMC-Na concentration (w/v %)	Viscosity[a] (Centipoise)	Dissolution rate ($dE/dt\times10^3$), A·sec^{-1}
CMC-P 500	0.05	1.1	7.07
	0.1	1.6	5.69
	0.2	2.8	4.40
	0.5	5.3	3.22
	1.0	15.5	2.99
CMC-P 1050	0.05	2.7	4.23
	0.1	3.7	3.23
	0.2	5.3	2.99
	0.5	16.0	2.90
	1.0	53.0	2.73

a) At a constant rate of shear of 1800 sec^{-1}.

progressively and that the discrepancy due to the degrees of polymerization becomes more pronounced with the increase in concentration of the two CMC–Na specimens.

Combining the data in Fig. 1, 3, and 4, dissolution rates of sulfanilamide were plotted against viscosities at various fixed rates of shear. As is illustrated in Fig. 6, all points are seemingly located on one curve irrespective of the two different CMC–Na specimens, and the dissolution rates attain to nearly constant value in the non–Newtonian region of viscosity where the solutions behave as non–Newtonian fluid, whereas a marked decrease in the rate occurs by a slight increase in viscosity in the Newtonian range.

Based on these results, especially on the rheological data, a possible explanation for reduced dissolution of sulfanilamide was drawn by the authors as follows. In the lower range of concentrations where the solution shows no structural viscosity, the CMC–Na molecules may assume extended forms; accordingly migration of sulfanilamide molecules through the diffusion layer may be strongly disturbed probably because of frequent interaction with unrestricted groups on the polyelectrolyte molecules. Thus, a marked fall in the dissolution rate may be caused by a slight increase in CMC–Na concentrations.

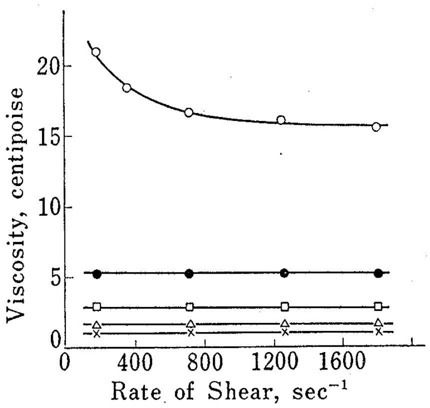

Fig. 3. Flow Curves for Five Concentration of CMC-P 500 Solutions at 37 ± 0.5°

Concentration of CMC-P 500: ×, 0.05 %; △, 0.1%; □, 0.2%; ●, 0.5%; ○, 1.0%.

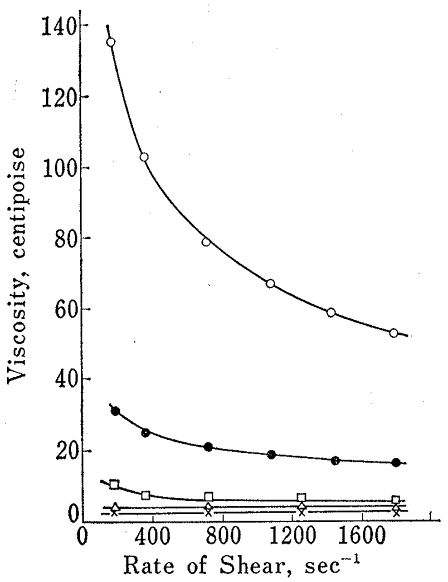

Fig. 4. Flow Curves for Five Concentration of CMC-P 1050 Solutions at 37 ± 0.5°

Concentration of CMC-P1050: ×, 0.05%; △, 0.1%; □, 0.2%; ●, 0.5%; ○, 1.0%.

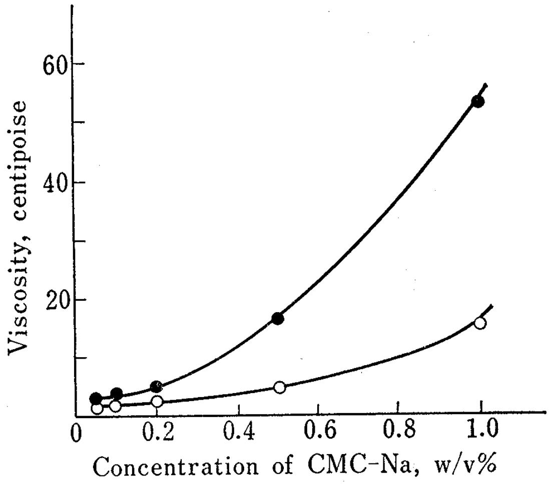

Fig. 5. Relationship between Viscosity and CMC-Na Concentration in Each Series of CMC-Na Solution at a Constant Rate of Shear of 1800 sec^{-1}

○, CMC-P 500 solution; ●, CMC-P 1050 solution.

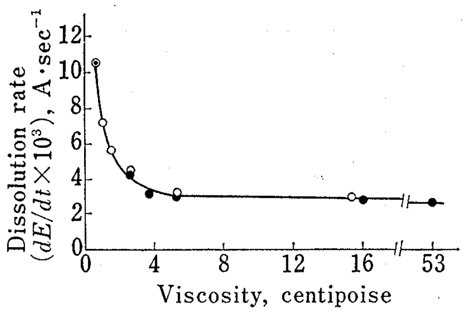

Fig. 6. Relationship between Dissolution Rates of Sulfanilamide and Viscosities of Solutions at a Constant Rate of Shear of 1800 sec^{-1}

⊙, in water;
○, in CMC-P 500 solution;
●, in CMC-P 1050 solution.

On the other hand, a much less variation in the rate in the non-Newtonian range of viscosity means that the passage of such small molecules of sulfanilamide through the network in the diffusion layer is maintained nearly constant. In other words, even if the network formed by entanglement of CMC-Na molecules becomes more dense by further increase in CMC-Na concentration, the effective space for molecular transfer or the resistance to diffusion will remain almost unchanged. The fact will be explained qualitatively by the reason that the network structure is the denser, the interaction between sulfanilamide and CMC-Na molecules is supposed to become the weaker, since attracting forces of the groups in the network will be increasingly dissipated for molecular aggregation.

Dissolution Rates of Sulfanilamide in the Aqueous Mixed Solutions of CMC-Na and NaCl

In order to obtain basic informations on drug release from some kinds of dosage forms, systems were chosen that were composed of solid sulfanilamide and the solutions containing one of the two CMC–Na specimens and NaCl in various compositions, and the dissolution patterns of the former were investigated in connection with viscosities of the dissolving media.

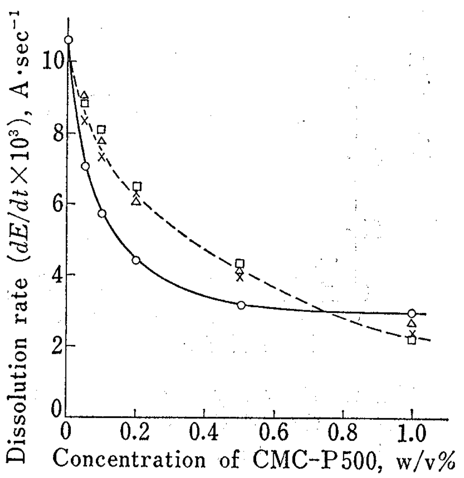

Fig. 7. Relationship between Dissolution Rates of Sulfanilamide and CMC-P 500 Concentrations in Solutions together with Sodium Chloride at 37.0±0.1°

○, no NaCl; △, 0.05 M NaCl; □, 0.2 M NaCl; ×, 0.5 M NaCl.

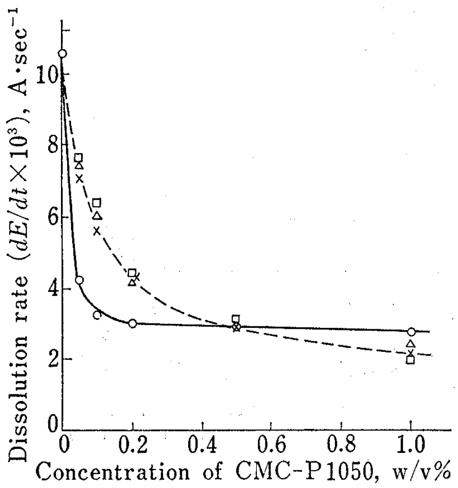

Fig. 8. Relationship between Dissolution Rates of Sulfanilamide and CMC-P 1050 Concentrations in Solutions together with Sodium Chloride at 37.0±0.1°

○, no NaCl; △, 0.05 M NaCl; □, 0.2 M NaCl; ×, 0.5 M NaCl.

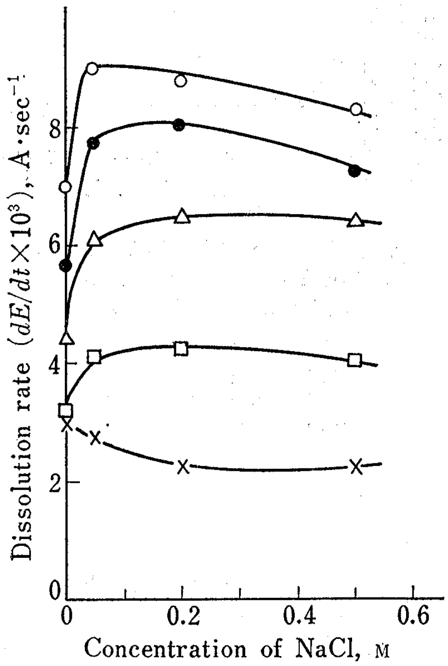

Fig. 9. Relationship between Dissolution Rates of Sulfanilamide and Sodium Chloride Concentrations in CMC-P 500 Solutions at 37.0±0.1°

Concentration of CMC-P 500: ○, 0.05%; ●, 0.1%; △, 0.2%; □, 0.5%; ×, 1.0%.

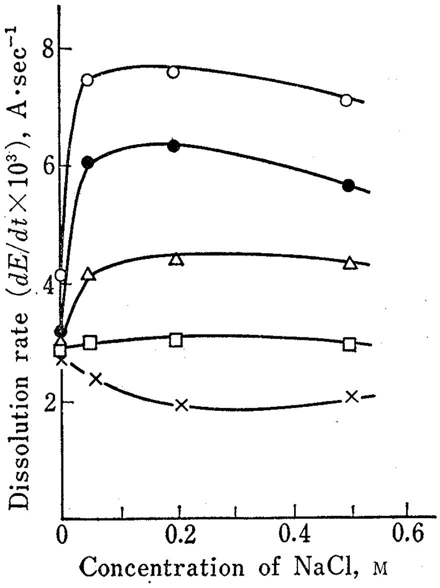

Fig. 10. Relationship between Dissolution Rates of Sulfanilamide and Sodium Chloride Concentrations in CMC-P 1050 Solutions at 37.0±0.1°

Concentration of CMC-P 1050: ○, 0.05%; ●, 0.1%; △, 0.2%; □, 0.5%; ×, 1.0%.

In Fig. 7—10, initial dissolution rates of sulfanilamide measured by the fixed disk method are plotted against concentrations of both ingredients. Also, viscosities of the mixed solutions were determined with a cone and plate viscometer and the flow curves in Fig. 11 and 12 were thus obtained. In addition, viscosity or fluidity variations of the solutions due to addition of NaCl are represented by the curves in Fig. 13 and 14 in which abscissas are taken as the concentrations of CMC–P500 and CMC–P1050, respectively.

It is evident from Fig. 7 and 8 that up to certain CMC–Na concentrations, the dissolution rates of sulfanilamide in the mixed solutions are significantly greater than the rates in the corresponding simple CMC–Na solutions. However, the relations are reversed at higher CMC–Na concentrations. Although the curves in Fig. 9 and 10 indicate the fact that considerable rate changes occur by adding NaCl, it is certain that the influence due to NaCl is not simple but complicated and is supposed to be rather weak as compared with that by CMC–Na.

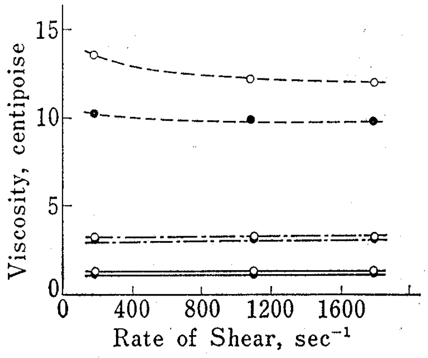

Fig. 11. Flow Curves for Solutions with Three Levels of CMC-P 500 and Two Levels of Sodium Chloride at 37±0.5°

--------, 1.0% CMC-P 500 solution;
-·-·-, 0.5% CMC-P 500 solution;
——, 0.2% CMC-P 500 solution;
○, 0.1 M NaCl; ●, 0.5 M NaCl.

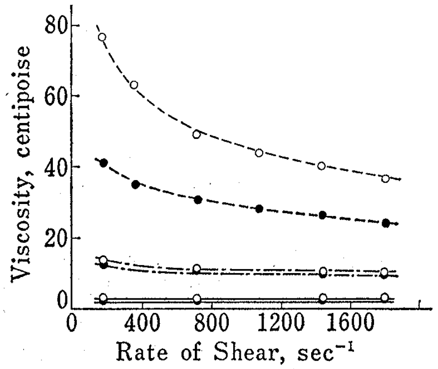

Fig. 12. Flow Curves for Solutions with Three Levels of CMC-P 1050 and Two Levels of Sodium Chloride at 37±0.5°

--------, 1.0% CMC-P 1050 solution;
-·-·-, 0.5% CMC-P 1050 solution;
——, 0.2% CMC-P 1050 solution;
○, 0.1 M NaCl; ●, 0.5 M NaCl.

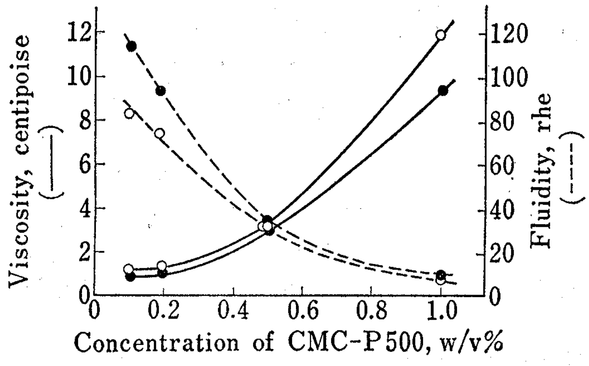

Fig. 13. Viscosity and Fluidity Curves of CMC-P 500 Solutions with Two Levels of Sodium Chloride at a Constant Rate of Shear of 1800 sec^{-1}

○, 0.1 M NaCl in CMC-P 500 solution;
●, 0.5 M NaCl in CMC-P 500 solution.

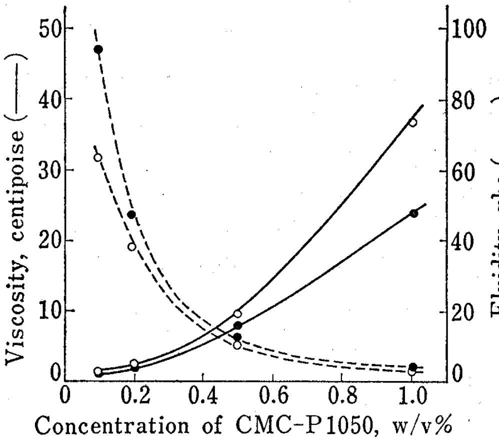

Fig. 14. Viscosity and Fluidity Curves of CMC-P 1050 Solutions with Two Levels of Sodium Chloride at a Constant Rate of Shear of 1800 sec^{-1}

○, 0.1 M NaCl in CMC-P 1050 solution;
●, 0.5 M NaCl in CMC-P 1050 solution.

From Fig. 11 and 12, non–Newtonian flows are found in relatively high concentration of CMC–Na solutions; however, when the more NaCl is added, the tendency of the polyelectrolyte to form structure becomes the weaker. As for viscosity in the Newtonian range, it is also evident from Fig. 11—14 that the mixed solutions are less viscous than the corresponding simple CMC–Na solutions.

Table II. Dissolution Rates of Sulfanilamide and Viscosities of the Mixed Solution of CMC-Na with 0.05 M Sodium Chloride

	CMC-Na concentration (w/v %)	Viscosity[a)] (Centipoise)	Dissolution rate ($dE/dt \times 10^3$), A·sec^{-1}
CMC-P 500	0.1	1.0	7.80
	0.2	1.5	6.09
	0.5	4.2	4.14
	1.0	14.6	2.74
CMC-P 1050	0.1	1.7	6.06
	0.2	3.5	4.20
	0.5	12.7	2.99
	1.0	43.8	2.44

a) At a constant rate of shear of 1800 sec^{-1}.

Table III. Dissolution Rates of Sulfanilamide and Viscosities of the Mixed Solution of CMC-Na with 0.5 M Sodium Chloride

	CMC-Na concentration (w/v %)	Viscosity[a)] (Centipoise)	Dissolution rate ($dE/dt \times 10^3$), A·sec^{-1}
CMC-P 500	0.1	0.9	7.07
	0.2	1.1	6.40
	0.5	2.9	4.02
	1.0	10.0	2.25
CMC-P 1050	0.1	1.2	5.60
	0.2	2.1	4.33
	0.5	8.5	2.92
	1.0	24.0	2.08

a) At a constant rate of shear of 1800 sec^{-1}.

When all of the above dissolution and viscosity data are considered collectively, it can be said that the mixed solutions behave as Newtonian fluids up to a viscosity value of about 5 centipoises (at a rate of shear of 1800 sec^{-1}), and the corresponding dissolution rates are found to be larger than the nearly constant value of the rate ($dE/dt = 3 \times 10^{-3}$ absorbance·sec^{-1}) found in the simple CMC–Na solutions in the non–Newtonian range. On the contrary, if the viscosities of the mixed solutions exceed the limit of 5 centipoises, the dissolution rates become equal to or less than the constant value. Moreover, if curves in Fig. 7 and 8 are compared with those in Fig. 13 and 14, it is found that the dissolution rates decrease gradually, while the fluidities of the solutions fall rapidly as the concentration of CMC–Na is increased.

It is certain from these results that viscosities of the mixed solutions are very influential in reducing dissolution of sulfanilamide. The influence of viscosity is thought to be similar to the influence in the simple CMC–Na solutions and is ascribed to two kinds of mechanisms, according to whether the mixed solutions behave as Newtonian or non–Newtonian fluid. One is due to individual CMC–Na molecules, while the other is due to molecular network of CMC–Na in the diffusion layer.

In spite of a rough similarity of the dissolution patterns in the mixed solutions to those in the simple CMC–Na solutions, significant differences are still observed as seen in Fig. 7 and 8. Further, the relation between the dissolution rate and the viscosity of the mixed solution can not be represented by a single curve. Therefore, as mentioned above, additional factors caused by the presence of NaCl will also be included in determining dissolution of sulfanilamide. The first one is the salting-out effect by NaCl. Since the curves in Fig. 15 indicate that the solubilities and thereby the dissolution rates decrease significantly in simple NaCl solutions, it will be reasonable that the same decrease of the dissolution rate would also occur in the mixed solution. However, contribution by this factor becomes obscure by the influence of the second effect of NaCl described in the following.

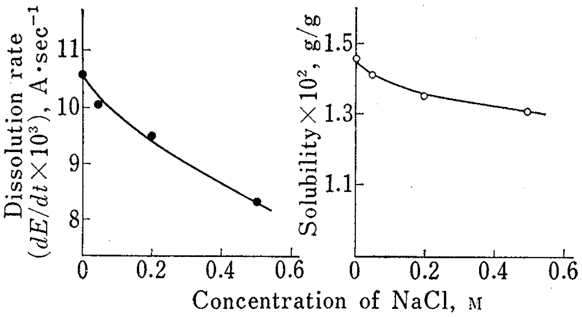

Fig. 15. Plots of Dissolution Rates and Solubility Values for Sulfanilamide against Sodium Chloride Concentrations in Solutions at 37.0±0.1°

It is generally known that molecules of a linear polyelectrolyte are shrunk by adding an inorganic salt.[6] In other words, the mean distance between both ends of the molecule is shortened by the electrostatic effect of ions from the salt. Thus, the extended molecules change to more spherical shape and the solution becomes less viscous than that in the absence of the salt.[7-10] Therefore, it is natural that similar decrease in viscosity can be expected in the present system. However, the mechanisms of dissolution rate changes due to this factor should be considered on a molecular level. In addition, the mechanism will differ according to whether the solution belongs to the Newtonian or to the non–Newtonian fluid.

In the Newtonian range of viscosity, groups on the CMC–Na molecules which are present separately in the diffusion layer will have less possibility to interact with molecules of sulfanilamide due to shrinkage of the CMC–Na molecules under an atmosphere of increased ionic strength. Namely, diffusion of sulfanilamide will be less obstracted, so that the dissolution rate in the mixed solution will be increased as compared with the rate in the corresponding simple CMC–Na solutions. However, it is known that the extent of molecular shrinkage is not proportional to the amount of the inorganic salt.[6] Therefore, as seen in upper four curves in Fig. 9 and 10, the salting-out effect upon the dissolution rates of sulfanilamide becomes gradually evident by increasing the NaCl amount in the mixed solution.

On the other hand, when the mixed solution exhibits structural viscosity, the shrunk CMC–Na molecules will form a denser and thicker network in the diffusion layer. Thus, it is considered that the transfer of sulfanilamide molecules will be more strongly suppressed and thereby the dissolution rates will become less than the nearly constant value found in the non–Newtonian range of the simple CMC–Na solution.

Conclusion

Up to the present, a few investigations have been undertaken concerning the decreased dissolution of some drugs in hydrophilic polymer solutions.[11,12] However, almost none has

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6) P.J. Flory, "Principles of Polymer Chemistry," Cornell University Press, Ithaca, N.Y., 1953.
7) G. Sitaramaiah and D.A.I. Goring, *J. Polym. Sci.*, **58**, 1107 (1962).
8) N. Nishida, *J. Phys. Soc. Japan*, **17**, 532 (1962).
9) N. Nishida, *J. Phys. Soc. Japan*, **16**, 2062 (1961).
10) H. Fugita and T. Homma, *J. Polym. Sci.*, **15**, 277 (1955).
11) R.J. Braun and E.L. Parrot, *J. Pharm. Sci.*, **61**, 175 (1972).
12) D.E. Wurster and G.P. Polli, *Farmacia* (Bucharest), **12**, 265 (1964).

discussed the mechanisms presumably because they lacked detailed viscosity data. Moreover, no investigation was hitherto undertaken about the combined effect of a polyelectrolyte and an inorganic salt upon the dissolution rate of a third substance.

For this reason, the present study was started as the first one of a series in order to solve these problems. Results so far are limited and are not sufficient to derive generalizations, but it will at least be possible to reach tentative conclusions as summarized in the following.

In simple CMC–Na solutions, the effect of CMC–Na upon the dissolution rates of sulfanilamide can be divided into:

1. viscosity difference due to the degrees of polymerization of CMC–Na,
2. decreased diffusion due to non–structured CMC–Na molecules in the Newtonian range of viscosity,
3. decreased and nearly fixed diffusion due to structured CMC–Na molecules in the Newtonian range of viscosity.

Although the solubility decrease of sulfanilamide in CMC–Na solutions may be included in the influencing factors, its contribution is thought to be practically negligible.

On the other hand, effects of additional factors below, which is ascribed to the presence of NaCl becomes more or less evident in the mixed solutions of CMC–Na and NaCl:

4. decrease in solubility of sulfanilamide due to salting-out,
5. viscosity decrease due to shrinking of CMC–Na molecules,
6. formation of denser structure by shrunk CMC–Na molecules in the non–Newtonian range of viscosity.

The mechanisms of actions by these factors are complicated and are mutually related; therefore, it will be very difficult to estimate quantitatively the extent of contribution of each factor. However, the above findings will offer informations that are hitherto unsettled and are useful for formulating dosage forms containing solid drugs.

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