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Effect of Additives on the Cloud Point of Polyethylene Glycols

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Abstract □ Polyethylene glycol 20,000 and 6,000 were found to have an upper consolute temperature, called "cloud point", and the effects of various additives on the polyethylene glycols were investigated in this study. Electrolytes lowered the cloud point in proportion to their concentrations through dehydration and electrostriction. It was found that anions played a more important role than cations and the effects of both the cations and the anions clearly followed the classical Hofmeister series. However, the Schultze-Hardy rule holds for the effect of anions, and fails for the effect of cations. Salts of large polarizable anions such as iodide and thiocynate rather raised the cloud point, and their effects were ascribed to the fact that they break the water structure and weaken hydrophobic bonding of the polyoxyethylene moiety. Nitrates of polyvalent cations also raised the cloud point. This was ascribed to the complex formation between the polyvalent cations and ether oxygens of the polyoxyethylenes. This explained the failure of the Schultze-Hardy rule for cations. Uncharged aromatic compounds drastically lowered the cloud point, while aliphatic alcohols slightly lowered the cloud point. This result suggests that there might be some interaction between ether oxygens and aromatic nucleus.

Keywords □ Additives, Cloud point, Polyethylene glycols, Electrolytes, Hofmeister series, Schultze-Hardy rule, Aromatic compounds.

When an aqueous solution of some organic compounds such as polyoxyethylated nonionic surfactant is heated, it suddenly turns cloudy at the specific temperature.[1] This kind of clouding is not a unique phenomenon observed in aqueous solutions of polyoxyethylated nonionic surfactants. It is rather a common property of aqueous solutions of organic compounds, of which hydrogen bonding is the main driving force for solution. However, the existence of this upper consolute temperature in aqueous solutions of polyethylene glycols is relatively unknown, because it is usually beyond the boiling point of the solution and consequently, seldom observed. The hydration of the ether oxygens of the polyethylene glycols makes the compounds water-soluble. However, the hydrophilic properties of polyethylene glycols gradually change to be more hydrophobic at elevated temperature, and consequently, they become insoluble in water at some elevated temperature. The reason for this change is the reduced interaction between the polyoxyethylene and water at elevated temperature. Clouding phenomena were also reported in the system of polyoxyethylenes of molecular weight more than about millions,[2] polyvinylpyrroidone,[3] and some proteins.[4,5] However, any cloud points of lower homologs of polyethylene glycols have not been reported.

It has been reported that additives may raise or lower the cloud point of polyoxyethylated nonionic surfactants. Their effects may be linear or nonlinear, and theoretically complicated phenomenon. Electrolytes usually lower the cloud point through dehydration and electrostriction.

[6-8] On the other hand, electrolytes of cations which form stable solid complexes with model ether such as dioxane raise the cloud point.[6,9] They salt in through complexation with the ether oxygens of polyoxyethylene moiety. Hydrogen ion also salt in through protonation of the ether oxygens.[6] Urea and inorganic electrolyets such as sodium iodide, sodium thiocyanate and sodium perchlorate, raise the cloud point.[6] This is ascribed to the increased hydration and weakenedh ydrophobic bonding due to the water-structure breaking by urea and the large polarizable anions such as iodide, thiocyanate and perchlorate. The cloud point shift values of individual ions follow the classical Hofmeister series. Symmetrical tetraalkylammonium halides and n-alkylammonium chlorides are also reported to raise the cloud point through hydrotropy or the formation of mixed micelles of tetraalkylammonium or n-alkylammonium cations with the nonionic surfactants.[10,11] Organic additives have been known to have drastic effects on the cloud point of polyoxyethyated nonionic surfactants, and their effects are known to be related to the locus of solubilization in the micellar system.[12,13] Uncharged aromatic compounds and aliphatic hydrocarbons with a polar head group usually lower the cloud point, whereas aliphatic hydrocarbons lower it to some degree but may raise it again at higher concentration.[1,12] With the regard to the effect of organic additives on the cloud point, no general theory has yet emerged. The effect of electrolytes, ureas and phenols on the cloud point of polyvinylpyrrolidone was investigated by Sekikawa *et al.*[3] and it was found that the effect was similar to that of these compounds on the cloud point of nonionic surfactants.

Cloud points of polyethylene glycols and the effect of additives on them are of practical importance in pharmaceutical technology. Pharmaceutical preparations stabilized by polyethylene glycols tend to coagulate or coalesce, when the systems are heated to temperature in the vicinity of the cloud point. The studies on the effects of additives on the cloud point of polyethylene glycols are very limited in spite of their necessity. Bailey and Callard reported the effects of electrolytes on the cloud point of polyoxyethylene with a molecular weight of $4\times10.$[3-6] The electrolytes lowered the cloud point in proportion to their concentration. They show similar trends in their effects as in the effects of electrolytes on the cloud point of polyoxyethylated nonionic surfactants. However, the studies on the effects of organic additives on the cloud point of polyethylene glycols have been lacking.

This kind of studies would make the hydrodynamic properties of polyethylene glycols better understood. Moreover it is necessary for predicting pharmaceutical incompatibility of polyethylene glycols in the drug formulation.

EXPERIMENTAL METHODS

Material

The polyethylene glycols employed were PEG 20,000 and 6,000 supplied from Wako Pure Chemical Industry Co. (Japan), and used without further purification. Electrolytes, ureas and organic compounds were reagent grade and used as received. Water was double distilled.

Measurement of Cloud Point

The cloud point was measured according to the method described in ref. (6). The concentration of polyethylene glycols employed was 1% (w/w) based on the amound of water present.

The flask containing the solution, immersed in a water bath, was heated or cooled at a rate of 1°C every 1-2 min. while being stirred by

Teflon magnetic stirring bar. Each cloud point was obtained by observing the onset of cloudiness on heating and then its disappearance on cooling. These two temperatures were fairly reproducible and always agreed within a degree or less.

RESULTS AND DISCUSSION

The Inverse Solubility- Temperature Relationship of PEG's

The existence of the inverse solubility- temprature relationship in aqueous solutions of PEG 20,000 and 6,000 was ascertained as expected; the aqueous solutions of PEG 20,000 turned cloudy athigher temperature than 70.5°C in the presence of 0.2M Na_2SO_4, and PEG 6,000 at higher temperature than 72.5°C in the presence of 0.4M Na_2SO_4. Without any additives, their cloud points are expected to exist above the boiling points of the solutions. By extrapolation, the cloud point of PEG 20,000 is expected to be around 105°C. The lower the molecular weight of PEG's, the higher the cloud point.

This result suggests that there is the possibility of existence of cloud points in aqueous solutions of PEG's of lower molecular weight in the presence of some additives.

Effect of the Concentration of PEG on the Cloud Point

The effect of the concentration of PEG on the cloud point was investigated. The cloud point of aqueous solution of varing concentrations of PEG 20,000 was measured in the presence of 0.2M Na_2SO_4, and the result is shown in Fig. 1. It shows that the cloud point of PEG 20,000 is rather insensitive to the concentration itself over the range from 0.5% to 10%. However, in the solution of concentration lower than

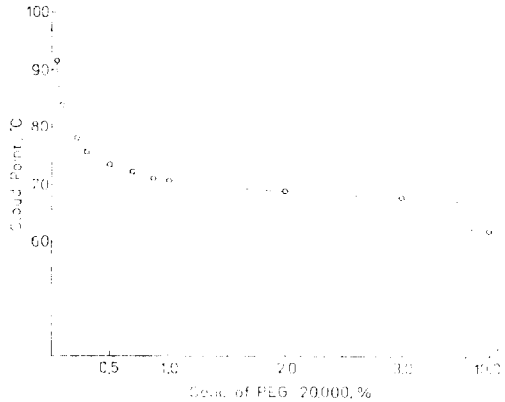

Fig. 1 : Effect of the concentration of PEG 20,000 on the cloud point in the presence of 0.2M Na_2SO_4.

0.5%, the cloud point was elevated as the concentration decreased. This result coincides with that obtained with polyoxyethylated nonionic surfactants.[1,12]

Effect of pH on the Cloud Point of PEG

The effect of pH on the cloud point of PEG 20,000 was examined employing 1% aqueous solution containing 0.2M Na_2SO_4, and the pH was adjusted with 10%HCl or 10%NaOH. The pH profile of the cloud point is shown in Fig. 2. It reveals that the cloud point was relatively

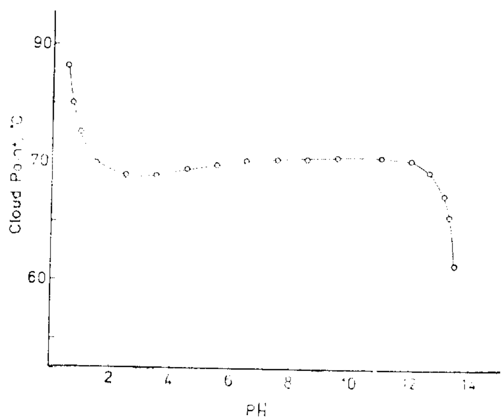

Fig. 2 : Effects of pH on the cloud point of 1% aqueous solution of PEG 20,000 containing 0.2M Na_2SO_4.

independent of pH over the range between pH 2 to 12. However, below pH 2 the cloud point was elevated as the pH decreased. This should be due to the protonation of the ether oxygens of the polyoxyethylene moiety, and the electric charge increased the solubility of the solute. Over pH 12 the cloud point was drastically lowered. This effect should be due to the effect of hydroxyl ion, which is known to be an effective lowering agent of the cloud point, and will be included and discussed in the effect of electrolytes on the cloud point. This profile is also almost identical with the pH profile of the cloud point of nonionic surfactant.[12]

Effect of Electrolytes on the Cloud Point of PEG 20,000

1. Effect of Electrolytes of Monovalent Cations

The cloud point of 1.0% aqueous solution of PEG 20,000 in the presence of sodium salts of various anions was measured, and the results are shown in Fig. 3-5. They lowered the cloud point in almost linear proportion to their concentrations within concentration ranges tested. The effectiveness of anions to lower the cloud point was in the following order; PO_4^{-3}>HPO_4^{-2}>SO_4^{-2}> IO_3^->$H_2PO_4^-$>OH^->F^->BrO_3^->Cl^->Br^->NO_3^->SCN^->I^-. However, sodium iodide and sodium thiocyanate decreased the cloud point at lower concentration, levelled off, and then rather raised the cloud point at higher concentrations. Because sodium iodide and sodium thiocyanate increased the cloud point, the cloud point of PEG 20,000 in the presence of these electrolytes was measured in the presence of 0.2M Na_2SO_4 to lower the cloud point. This order of anions clearly follows the classical Hofmeister series with some minor exceptions. The Schultze- Hardy rule also holds for the effect of anions; trivalent anion》 divalent anion》 monovalent anion.

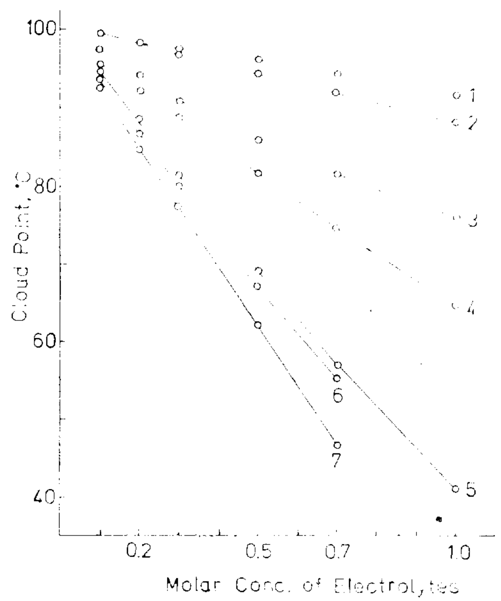

Fig. 3 : Effects of electrolytes on the cloud point of PEG 20,000.
1. $NaNO_3$ 2. NaBr 3. NaCl 4. $NaBrO_3$
5. NaF 6. NaOH 7. $NaIO_3$

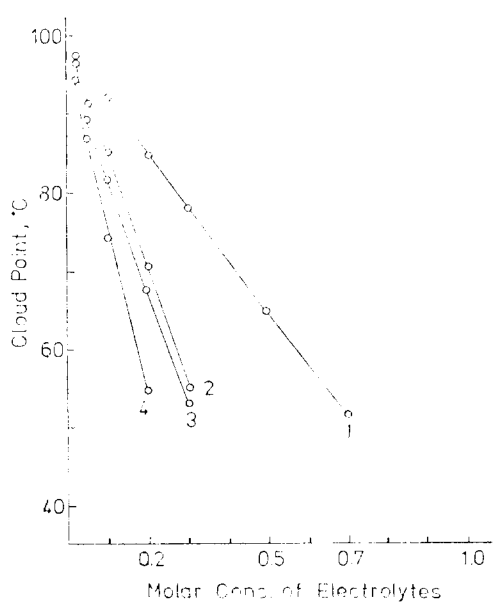

Fig. 4 : Effects of electrolytes on the cloud point of PEG 20,000.
1. NaH_2PO_4 2. Na_2SO_4
3. Na_2HPO_4 4. Na_3PO_4

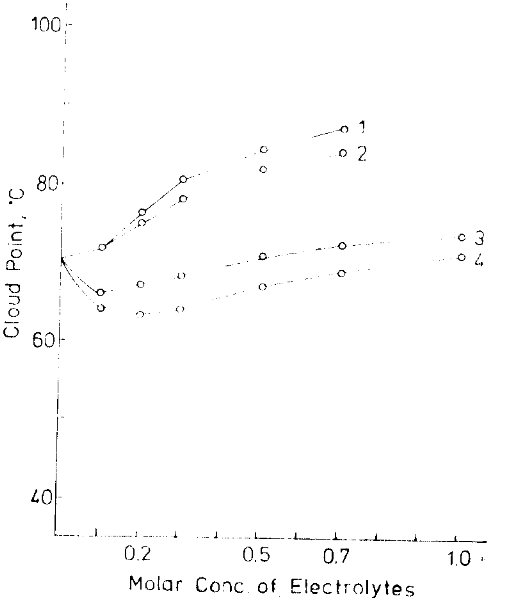

Fig. 5 : Effects of electrolytes on the cloud point of PEG 20,000 containing 0.2M Na_2SO_4
1. $Cu(NO_3)_2$ 2. $Mg(NO_3)_2$
3. NaI 4. NaSCN

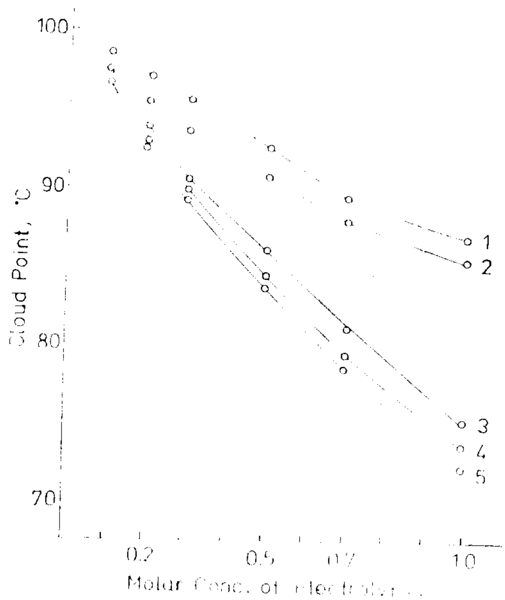

Fig. 6 : Effects of electrolytes on the cloud point of PEG 20,000.
1. LiCl 2. NH_4Cl 3. NaCl
4. KCl 5. CsCl

Fig. 6 shows the effect of chlorides of monovalent cations on the cloud point. They also lowered the cloud point in proportion to their concentrations. The effectiveness of monovalent cations to lower the cloud point was in the following order; $Cs^+ > K^+ > Na^+ > NH_4^+ > Li^+$. This order also follows the Hofmeister series with exception of ammonium ion. Ordinarily, ammonium cation should be placed between cesium and potassium ion. Cations exhibited not so much variation in their effects compared with the effects of anions. This result shows that anions play a more important role than cations in lowering the cloud point.

The effect of electrolyte on solutions of nonelectrolytes is a very complex phenomenon, and theories have not satisfactorily explained the experimental results. The general problem of the salting out of nonelectrolytes by inorganic electrolytes has been extensively investigated and reviewed.[15,16] It is generally accepted that added electrolytes cause dehydration of nonelectrolytes and electrostriction of water and increase the internal pressure of the solution. The precipitation of PEG from aqueous solution when the temperature is increased can be considered as a result of an increase in activity of the polymer. In a medium such as water, neutral salts increase the activity of neutral molecules, and in this light it is possible to consider the effect of salts on PEG. From the Debye-McAulay equation it is expected that the upper temperature limit of solubility of polyoxyethylene in water should lowered in a manner proportional to the salt concentration and the valencies of the ions of the salts.[15] Also, small hydrated ions should be more effective than large hydrated ions in salting out the polymer.

In their effect on the cloud point of PEG 20,000, electrolytes should salt out the PEG through dehydration and electrostriction. However, sodium iodide and sodium thiocyanate depolymerize the water structure and salt in the PEG through better hydration of polyoxyethylene moiety and weakened hydrophobic bonding due to the water- structure breaking. It is remarkable that anions exerted more pronounced effect than cations. These results might be ascribed that in the effects of electrolytes on the cloud point of PEG the hydraton and electrostriction effects might be minor, while the effect of the water-structure breaking by anions is major.

2. *Effect of Electrolytes of Divalent Cations*

The effects of salts of divalent cations on the clond point of PEG 20,000 are shown in Fig. 5 and 7. Magnesium chloride, barium chloride and calcium chloride showed almost the same salting- out effects. This is contrary to the electrostriction theory. Their effects were far less

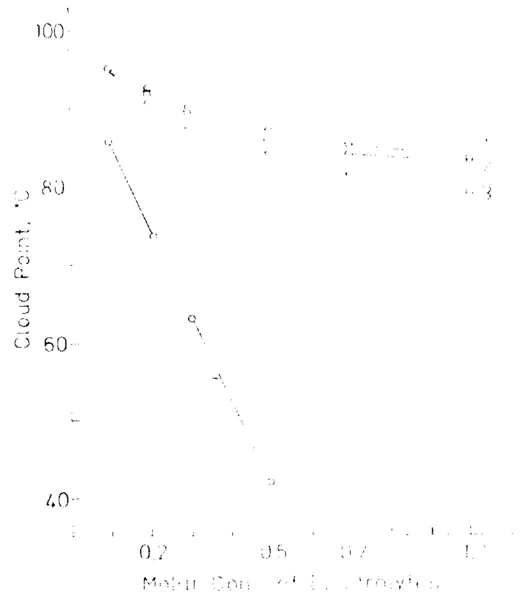

Fig. 7 : Effects of electrolytes on the cloud point of PEG 20,000.
1. $MgCl_2$ 2. $BaCl_2$
3. $CaCl_2$ 4. $MgSO_4$

than those expected on hydration and electrostriction theories, and levelled off at higher concentration. Clearly, the Schultze-Hardy rule fails to predict the effect of cations; salts of divalent cations showed less cloud-point lowering than salts of monovalent cations. Magnesium sulfate drastically lowered the cloud point in linear proportion to its concentration. On the other hand, cupuric nitrate and magnesium nitrate significantly raised the cloud point. Salts of these divalent cations are known to form stable adduct complexes with model ether such as dioxane. Consequently, the salting-in by magnesium nitrate and cupuric nitrate should be due to the complex formation of the cations with the ether oxygens of polyoxyethylene moiety of PEG. This also explains the small effects of chlorides of magnesium, barium and calciumt cation in lowering the cloud point. The effectiveness of magnesium sulfate to lower the cloud point could be explained by great role of sulfate anion in its effect. The complex formation between divalent cations and polyoxyethylene moiety in polyoxyethylated nonionic surfactants has been already confirmed.[9]

Effect of Ureas on the Cloud Point of PEG 20,000

The cloud point of PEG 20,000 in the presence of different concentrations of urea, methylurea and thiourea was measured and showed in Fig.8. Urea and methylurea raised the cloud point in proportion to their concentration. It is interesting to note that methylurea was more effective in its effect than urea, and thiourea brought about slight lowering of the cloud point. Urea was well known for its ability to break the water structure and to weaken hydrophobic bonding. The cloud-point raising by urea and methylurea should be ascribed to the better hydration and weakened hydrophobic bonding due to the water-structure breaking. This result suggests that methylurea might be more effective in breaking water structure than urea, and thiourea might not have any significant effect on the water structure.

Effect of Organic Solubilizates on the Cloud Point of PEG 20,000

It was found that uncharged aromatic solubilizates such as phenols, anisole, nitrobenzene and benzoic acid had a drastic ability to lower the cloud point of PEG 20,000, whereas aliphatic alcohols slightly lowered the cloud point. These results are shown in Fig. 9, 10 and 11. In the effect of aromatic compounds on the cloud point, apparent correlation among their cloud-point lowering ability, number of substituents and the position of the substituents can not be found. In the effect of aliphatic alcohols, the larger the hydrophobic chain, the more lowering they exhibited. It is remarkable to note that 1, 3, 5-trihydroxybenzene, phloroglucinol was the most effective among phenolic compounds tested, while its isomer, 1, 2, 3-trihydroxybenzene, pyrogallol was the least effective. Anisole showed far less effective than phenol, and it might be possible that phenolic hydrogen plays an important role, which suggests there is hydrogen bonding between the solubilizates and the PEG, and the hydrophobicity of the solubilizates does not seem to play a critical role. These results suggest that steric problem in hydrogen bonding between polyoxyethylene and phenols might play crucial role in lowering the cloud point. In general, aromatic compounds lowered the cloud point more drastically than aliphatic alcohols. This indicates that in addition to the hydrogen bonding there might be some kind of interaction between aromatic ring and ether oxygens of polyoxyethylene moirety, which might be a $n \rightarrow \pi$ interaction. The

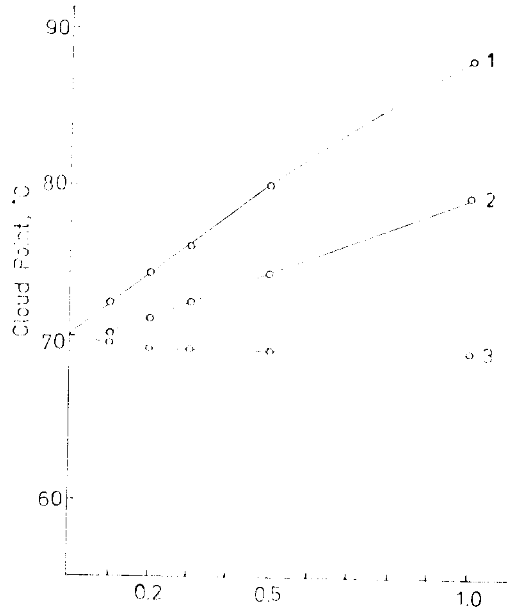

Fig. 8 : Effects of ureas on the cloud point of PEG 20,000 containing 0.2M Na_2SO_4.
1. methylurea 2. urea 3. thiourea

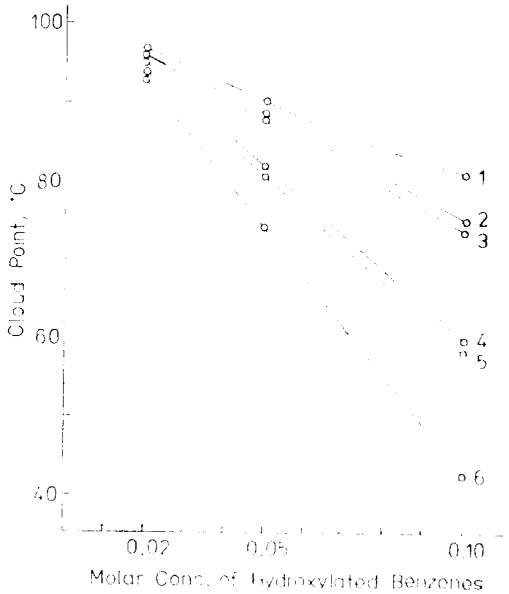

Fig. 9 : Effects of hydroxylated benzenes on the cloud point of PEG 20,000.
1. pyrogallol 2. pyrocatechol
3. hydroquinone 4. resorcinol
5. phenol 6. phloroglucinol

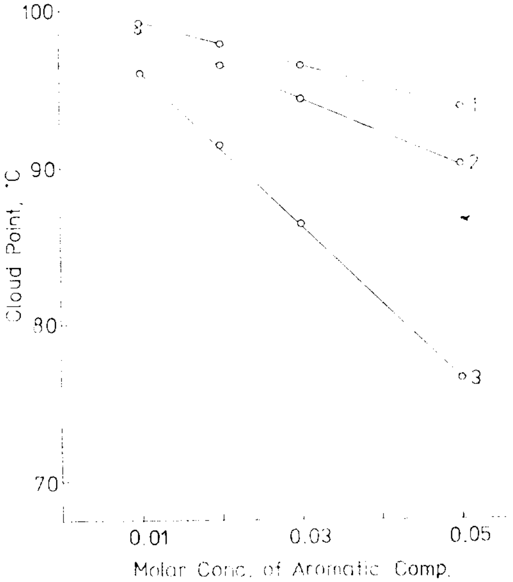

Fig. 10 : Effects of aromatic compounds on the cloud point of PEG 20,000.
1. anisole 2. nitrobenzene
3. benzoic acid

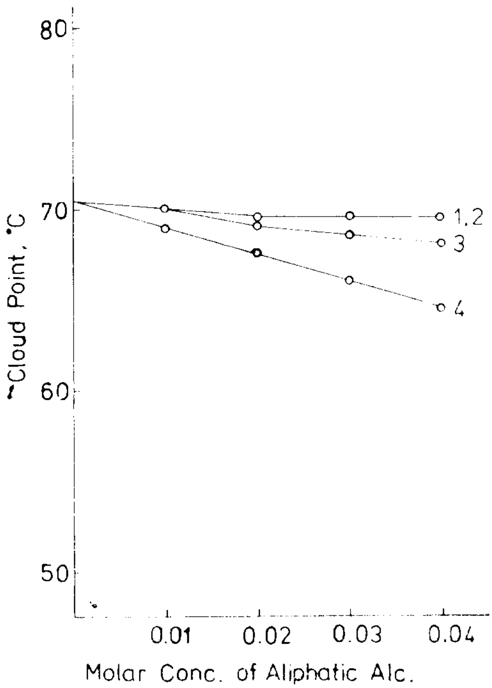

Fig. 11 : Effects of aliphatic alcohols on the cloud point of PEG 20,000.
1. n-butanol 2. n-propylalcohol
3. n-amylalcohol 4. n-heptanol

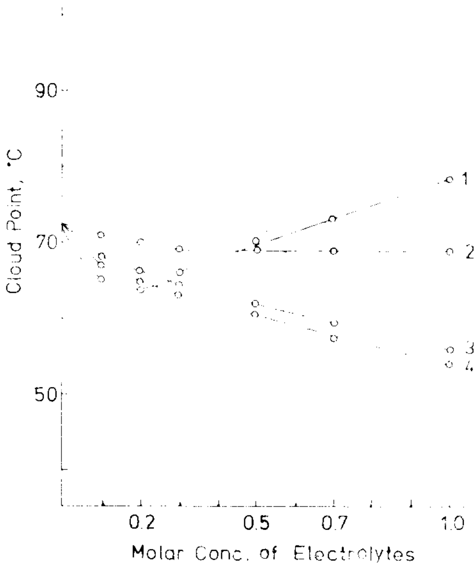

Fig. 12 : Effects of electrolytes on the cloud point of PEG 6,000 containing 0.4M Na_2SO_4.
1. NaI 2. LiCl 3. NaCl 4. KCl

fact that aromatic compounds are solubilized mainly in the polyoxyethylene mantle of the micelle of nonionic surfactant strongly back up this hypothesis.[17,18] Spectroscopical evidence of this interaction has been extensively sought in this laboratory. However, positive results have not be obtained so far.

Effect of Electrolytes on the Cloud Point of PEG 6,000

The effect of several electrolytes on the cloud point of PEG 6,000 was investigated, and the results are shown in Fig. 12. The effects showed almost the same trend as in the effects on the cloud point of PEG 20,000. Consequently, to avoid duplication, no further experimentals were carried out.

LITERATURE CITED

1) Nagagawa, T.: *Nonionic Surfactants,* Schick, M.J., Ed., Dekker, New York, 1967, Chap. 17.
2) Bailey Jr., F.E. and Callard, R.W.: Some properties of poly (ethylene oxide) in aqueous solution. *J. Appl. Polymer Sci.* **1**, 56, (1959).
3) Sekikawa, R., Hori, R., Arita, T., Ito, K. and Nakano, M.: Application of the cloud point method to the study of the interaction of polyvinylpyrrolidone with some organic compounds. *Chem. Pharm. Bull.* **25**, 2489 (1978).
4) Shaw, A.B., Dobbie, D.N. and Harrison R.J.: Synthetic poly (pentapeptide) of elastic coacervates and forms filamentous aggregates, *Proc. Roy. Soc. Med.* **49**, 115(1956).
5) Urry. D.W., Long, M.M., Cox, B.A., Ohnishi, T., Mitchell,L.W. and Jacobs, M.: Cryoglobulinemia and lymphoid leukosis. *Biochim. Biophys. Acta.* **371**, 597(1974).
6) Schott, H. and Han, S.K.: Effect of inorganic additives on solutions of nonionic surfactants Ⅱ. *J. Pharm. Sci.* **64**, 6, 658(1975).
7) Florence, A.T., Madsen, F. and Puisieux, F.: Emulsion stabilization by nonionic surfactants. *J. Pharm. Pharmacol.* **27**, 385(1975).
8) Ward, A.J.: Ionic effects on the cloud temperatures of aqueous nonionic surfactants. *ibid.* **34**, 612(1982).
9) Schott, H.: Salting in of nonionic surfactants by complexation with inorganic salts. *J. Colloid Interface Sci.* **43**, 152(1973).
10) Schott, H. and Han, S.K.: Effect of symmetrical tetraalkylammonium salts on cloud point of nonionic surfactants. *J. Pharm. Sci.* **66**, 165(1977).
11) Han, S.K. and Kim, Y.M.: Effect of n-alkylammonium chlorides on cloud point of nonionic surfactant. *Yakhak Hoeji* **20**, 156(1976).
12) Maclay, W,N.: actorsF affecting the solubility of nonionic emusilifiers. *J. Colloid Sci.* **11**, 272 (1956).
13) Donbrow, N. and Azaz, E.: Solubilization of phenolic compounds in nonionic surfactants. *J. Colloid Interface Sci.* **57**, 20(1976).
14) Shinoda, K.: *Solvent Properties of Surfactant Solutions*, Dekker, New York, 1967, Chap. 1.
15) Harned, H. S.and Owen, B.B.: *Physical Chemistry of Electrolyte solutions*, 3rd Ed., Reinhold Publishing Corp., New York, 1958.
16) Leng, F.A. and McDevit, W.F.: Activity coefficients of Nonelectrolyte solutes in aqueous salt solutions. *Chem. Rev.* **51**, 119(1952).
17) Christenson, H. and Friberg, S.E.: Spectroscopic investigation of the mutual interactions between nonionic surfactant, hydrocarbon, and water. *J. Colloid Interface Sci.* **75**, 276(1979).
18) Miyagishi, S. and Nishida, M.: NMR study about solubilization of Phenylalkyl alcohol in sodium dodecyl sulfate micelle and in Brij 35 micelle. *ibid.* **78**, 195(1980).