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Solution and Partition Behaviors of Colchicine

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Dissolution curves of colchicine in water, carbon tetrachloride, and benzene revealed that solvates are formed after initial dissolution of ansolvate with a resultant decrease in concentration in solution. An aqueous solubility-temperature profile exhibited a minimum in 25—45° range. Addition of trichloroethanol and chloroform to benzene resulted in increase in benzene/water partition coefficient of colchicine. Benzene/water and carbon tetrachloride/water partition coefficients were greater at higher temperature. Salt effects on benzene/water partition coefficient followed the Hofmeister series and the Setshenow relationship.

Keywords——colchicine; dissolution and precipitation; partition coefficient; solvates; effect of temperature; salt effect; DSC-TGA

Although colchicine has been used for the therapy of acute gout since 1763, its physicochemical properties in solution have not been completely elucidated. Approximate solubility of colchicine in water is listed to be 1 g in 25 ml solvent.[2] On the other hand, it has been noted by Loudon and Speakman[3] that the drug dissolved completely in only 3 parts of cold water and that the solution on standing deposited a sesquihydrate, the solubility of which was less than 1 in about 70 parts of water. Since molecular structure of colchicine is unique among therapeutic agents, it may be worthwhile to explore its properties in solution. Results obtained as to its solution and partition behaviors are reported here.

Experimental

Materials——Colchicine obtained from Nakarai Chemicals, Ltd., Kyoto contained no solvent of crystallization as determined by differential scanning colorimetry and thermal gravimetric analysis. Its purity was checked with thin-layer chromatography employing three solvent systems.[4] Organic solvents and inorganic salts were of reagent grade (Wako Pure Chemical Industries, Ltd., Osaka). Trichloroethanol (Tokyo Kasei Kogyo Co., Tokyo) was vaccum-distilled before use.

Measurement of Solution Behavior——A small amount of solvent was placed in the water-jacketed beaker and agitated by a magnetic stirrer at the speed of about 60 rpm. Circulating water was connected to Taiyo Thermo Unit C-550. A known amount of the drug powder was added to the solvent after temperature equilibrium had been reached. At appropriate time intervals, a small portion of the suspension was withdrawn, quickly filtered through a sintered-glass disk, diluted with an appropriate solvent, and assayed for the drug concentration at 352 nm with Hitachi Spectrophotometer Model 139. For the measurement of equilibrium solubility, more than 5 hours were usually allowed for the attainment of equilibrium before filtration was made.

Measurement of Partition Coefficient——Two milliliters of aqueous solution of the drug and the same volume of an immissible solvent were placed in a test tube which was immersed in water within a water-jacketed beaker and the liquid layers were agitated by a magnetic stirring bar (10 mm long). Following 20 min of agitation, stirring was stopped and the solution was left for about 30 min before pipetting the aqueous solution for the measurement of concentration of the drug remained in the aqueous layer.

When effect of chloroform or trichloroethanol on partition coefficients was examined, chloroform or trichloroethanol dissolved in benzene was used as an organic layer. On the other hand, an aqueous solution

1) Location: *Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan.*
2) The Pharmacopeia of the United States of America, 19th Rev., Mack Publishing Co., Easton, Pa., 1974, p. 775.
3) J.D. Loudon and J.C. Speakman, *Research* (London), 3, 583 (1950).
4) A. Norfalise and G. Mees, *J. Chromatogr.*, 31, 594 (1967).

containing various salts was used as an aqueous layer for the examination of the effect of salt on partition coefficient.

For the determination of benzene/water partition coefficient at various temperature, solvents mutually saturated (*i.e.* benzene saturated with water and water saturated with benzene) at each temperature were employed.

Differential Scanning Colorimetry and Thermal Gravimetric Analysis——Melting and desolvation behaviors of colchicine samples were examined with Rigaku Denki Thermal Gravimetry-Differential Scanning Colorimeter, Thermoflex Model M8085. Heating rate of 10°/min was employed.

Results and Discussion

Solution Behaviors

Dissolution and Precipitation——The solution behavior of colchicine in water is shown in Fig. 1. The drug dissolved quickly in the solvent but the amount of drug in solution subsequently decreased to attain the equilibrium solubility. The similar solution curves were obtained with carbon tetrachloride and benzene as solvents. Such dissolution curves as these have been reported for theophylline, glutethimide,[5] phenobarbital,[6] and testosterone.[7]

The solid phase obtained after equilibration contained an evaporable substance (solvent) as observed by differential scanning colorimetry and thermal gravimetric analysis. Dehydration of colchicine hydrate is illustrated in Fig. 2. Similar desolvation behaviors were obtained with carbon tetrachloride (Fig. 3) and chloroform solvates of colchicine. Thus it is apparent that decrease in the amount of drug in solution observed in Fig. 1 is due to precipitation of the colchicine solvate after initial dissolution from colchicine ansolvate.

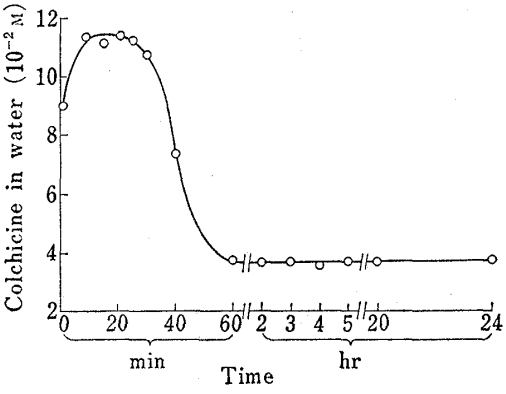

Fig. 1. Dissolution Behavior of Colchicine in Water at 26.5°

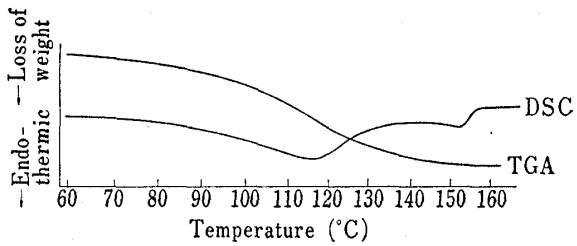

Fig. 2. Differential Scanning Colorimetry (DSC) and Thermal Gravimetric Analysis (TGA) Curves for Colchicine Hydrate

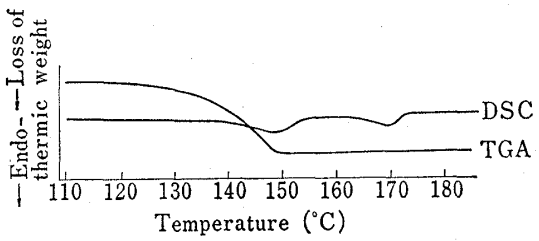

Fig. 3. Differential Scanning Colorimetry (DSC) and Thermal Gravimetric Analysis (TGA) Curves for Possible Carbon Tetrachloride Solvate of Colchicine

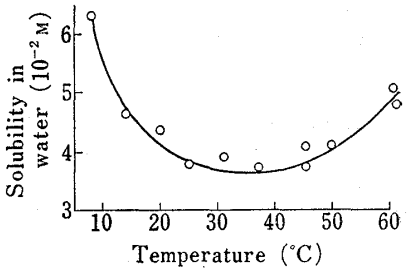

Fig. 4. Solubility of Colchicine in Water as a Function of Temperature

5) E. Shefter and T. Higuchi, *J. Pharm. Sci.*, **52**, 781 (1963).
6) H. Nogami, T. Nagai, and T. Yotsuyanagi, *Chem. Pharm. Bull.* (Tokyo), **17**, 499 (1969).
7) A.L. Thakkar and N.A. Hall, *J. Pharm. Sci.*, **58**, 68 (1969).

Effect of Temperature on Solubility———The aqueous solubility-temperature relationship is shown in Fig. 4. The solubility profile is unique in that a U-shaped curve with a minimum value in 25—45° was obtained. The effect of temperature on solubility in benzene could not be determined because high drug solubility in the solvent rendered the solution gelly.

Partition Behaviors

Effect of Solvent on Partition Coefficient——Studies on the effect of solvents on organic solvent/water partition coefficient indicated that the partition coefficient is generally increased as polarity of solvent is increased. Exceeding large partition coefficient observed for chloroform, however, may be rationalized in terms of complex formation of colchicine with the solvent chloroform. The examination on the effect of chloroform concentration in benzene on partition coefficient of colchicine has demonstrated an increase in partition coefficient with an increase in chloroform concentration. From the examination of molecular structures, it may be stated that chloroform acts as a proton donor in benzene phase, colchicine acting as a proton acceptor.

The effect of a stronger proton donor, trichloroethanol, on the partition coefficient is shown in Fig. 5. Upward curve indicates possible formation of higher-order complex as well as 1:1 complex.[8] This is expected from the fact that both conjugated carbonyl group and amide group in colchicine molecule can participate in hydrogen bonding with the proton donor.

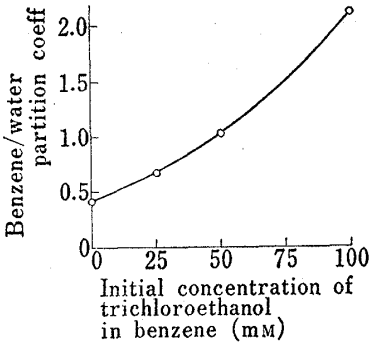

Fig. 5. Effect of Trichloroethanol on Benzene/Water Partition Coefficient of Colchicine at 25.9°

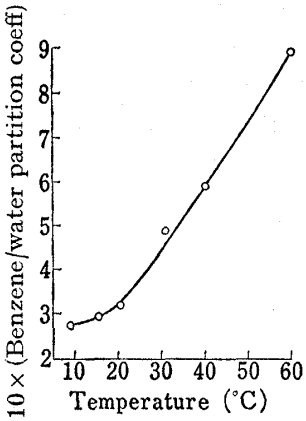

Fig. 6. Effect of Temperature on Benzene/Water Partition Coefficient of Colchicine

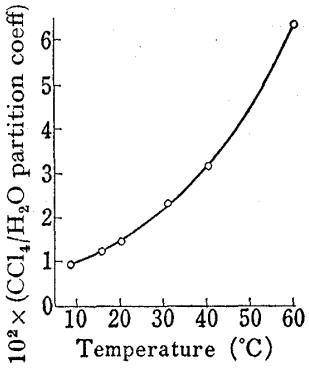

Fig. 7. Effect of Temperature on Carbon Tetrachloride/Water Partition Coefficient of Colchicine

Effect of Tempreature on Partition Coefficient——The effect of temperature on benzene/water partition coefficient of colchicine is shown in Fig. 6. Unexpectedly large dependency on temperature was observed. This is not unique in the benzene/water system. Similar temperature dependency was noted for carbon tetrachloride/water partition coefficient as shown in Fig. 7.

Effect of Salt——Effect of salt species on partition coefficient of colchicine is shown in Table I. Chloride and sulfate ions salted-out colchicine whereas iodide salted-in the drug. The rank of anions is in agreement with the Hofmeister (lyotropic) series.[9]

8) T. Higuchi and K.A. Connors, *Advan. Anal. Chem. Instr.*, **4**, 117 (1965).
9) A.N. Martin, J. Swarbrick, and A. Cammarata, "Physical Pharmacy," 2nd. ed., Lea and Febiger, Philadelphia, 1969, p. 461.

Table I. Salt Effects on Benzene/Water Partition Coefficient of Colchicine at 25°

Salt in aqueous phase	Partition coefficient
None	0.40
1.6M NaCl	1.1
0.8M $(NH_4)_2SO_4$	2.2
0.8M Na_2SO_4	3.7
1.6M NaI	0.23

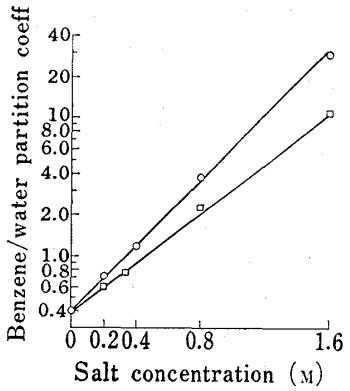

Fig. 8. Effect of Salts on Benzene/Water Partition Coefficient of Colchicine at 25.8°

key: ○; Na_2SO_4 □; $(NH_4)_2SO_4$

Plots of log (partition coefficient) against salt concentration of sodium sulfate and ammonium sulfate are shown in Fig. 8. Logarithmic dependency on salt concentration is expected from the Setshenow relationship.[10]

General Discussion——It is noteworthy that colchicine forms solvates with such nonpolar solvents as benzene and carbon tetrachloride. Desolvation from colchicine solvates with rise in temperature is not sharp, indicating their characteristic crystalline structure. In order to clarify the cause of anomalous dependency of solubility in water on temperature, complete characterization of solid phase may be required. Colchicine serves as a good proton acceptor as expected from its tropolone structure. This finding can be a clue in elucidating solute-solvent interactions in solution as well as crystalline structure of solvates. In order to clarify extremely high dependency of partition coefficient on temperature, elucidation of state of the molecules in solution may be essential.

10) F.A. Long and W.F. McDevit, *Chem. Rev.*, **51**, 119 (1952).