International Journal of Pharmaceutics, 98 (1993) 239–242

IJP 03247

Increase in temperature enhances solubility of drugs in aqueous solutions of hydroxypropylcyclodextrins

Teruhiko Hoshino [a], Kaneto Uekama [b] and Josef Pitha [a]

[a] *National Institutes of Health, NIA / GRC, 4940 Eastern Avenue, Baltimore, MD 21224 (USA) and* [b] *Faculty of Pharmaceutical Sciences, Kumamoto University, Kumamoto 862 (Japan)*

(Received 16 June 1992)
(Modified version received 1 March 1993)
(Accepted 12 March 1993)

Key words: Hydroxypropylcyclodextrin; Drug solubilization; Drug preparation; Hydroxypropylcyclodextrin complex; Temperature effect

Summary

The solubilities of carbamazepine, dexamethasone, and griseofulvin in aqueous media were synergistically increased with increasing hydroxypropylcyclodextrin concentration and with increasing temperature. The results suggest that the increase in free drug concentration from solution heating counterbalances the simultaneously occurring dissociation of the drug-hydroxypropylcyclodextrin complexes. From a practical point of view, the results show that heating or heat-sterilization may be useful steps in the preparation of hydroxypropylcyclodextrin-based pharmaceutical formulations.

Hydroxypropylcyclodextrins efficiently solubilize some non-polar drugs in aqueous solutions through the formation of inclusion complexes (Muller et al., 1985; Pitha et al., 1985; Brewster et al., 1989: Loftsson et al., 1991; Mesens et al., 1991; Uekama et al., 1991). Since hydroxypropylcyclodextrins are nontoxic and their complexes with drugs dissolve fully and rapidly in water, they are useful both in parenteral preparations (Brewster et al., 1989) and in solid dosage forms such as tablets (Pitha et al., 1986).

Correspondence to: J. Pitha, National Institutes of Health, NIA/GRC, 4940 Eastern Avenue, Baltimore, MD 21224, U.S.A.

Since a limiting factor in the production of hydroxypropylcyclodextrin complexes of drugs is the dissolution of drugs in aqueous solutions of hydroxypropylcyclodextrins, we investigated whether the addition of organic solvents or an increase in temperature may produce some improvements. The effects of solvent have already been described (Pitha et al., 1990, 1992). In the present paper, we describe effects of temperature manipulations.

Carbamazepine, dexamethasone and griseofulvin were purchased from Sigma Chemical Co, St. Louis, MO. Hydroxypropyl-β-cyclodextrin and hydroxypropyl-γ-cyclodextrin were purchased from Pharmatec Inc., Alachua, FL and from Research Biochemicals Inc., Natick, MA, respectively. Both had an average degree of substitution

between 4.9 and 6.1 of hydroxypropyl groups per molecule.

In order to measure solubility, a slight excess of drug was added to an aqueous solution of hydroxypropylcyclodextrin and the suspension vigorously stirred, at the given temperature, for 2 h. The saturated solution was then sampled using a syringe equipped with an ultracleaning filter unit (Millex-HA 0.45 μm, Millipore Co., Bedford, MA). An aliquot of the filtrate was removed, promptly diluted and the concentration of drug present was then measured spectrophotometrically (for carbamazepine at 285 nm, dexamethasone at 240 nm and griseofulvin at 288 nm). All concentration data given in the figures are in terms of room temperature.

The circular dichroic and ultraviolet spectra were recorded using a J-500C spectropolarimeter (Jasco Co.) and a Lambda 3 spectrophotometer (Perkin Elmer Co.), respectively.

Elevation of the temperature increased the solubility of the drugs investigated, carbamazepine, dexamethasone and griseofulvin. For carbamazepine, the data obtained are plotted in Fig. 1; for dexamethasone and griseofulvin, the solubility data observed can be described by the relations $-684T^{-1} + 1.208$ and $-443T^{-1} + 0.460$, respectively (solubility, expressed in mg/ml; temperature, in K). Addition of hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin at room temperature increased the solubility of all three drugs; the increase was proportional to the amount of solubilizer added, as may be expected for solubilization through the formation of 1 : 1 inclusion complexes (Fig. 1 and Table 1). At elevated temperatures (investigated range: 23–60°C), when inclusion complexes are expected to dissociate, the solubilization of all three drugs was also enhanced by both hydroxypropyl-β- and -γ-cyclodextrins (Fig. 1 and Table 1). At elevated temperatures dissolution proceeded noticeably faster in every case.

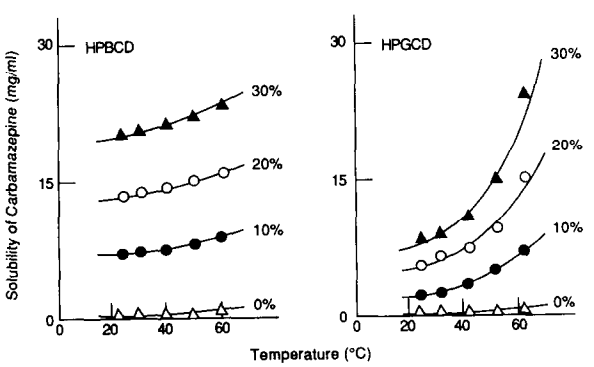

Fig. 1. Temperature dependence of the solubility of carbamazepine in water and in aqueous solutions of hydroxypropylcyclodextrins. The concentrations of hydroxypropylcyclodextrin are given beside the respective curves (data refer to room temperature; w/w). (Left) Hydroxypropyl-β-cyclodextrin; (right) hydroxypropyl-γ-cyclodextrin.

TABLE 1

Apparent stability constants (K) for complex of drugs with hydroxypropyl derivatives of β or γ-cyclodextrin in water [a]

System	K (M^{-1})				
	23°C	30°C	40°C	50°C	60°C
Carbamazepine/					
HPBCD	600	600	590	470	350
HPGCD	350	310	270	260	270
Dexamethasone/					
HPBCD890	840	770	660	590	
HPGCD	6100	5400	5090	4750	4000
Griseofulvin/					
HPBCD	20	20	20	15	20
HPGCD	70	60	60	55	60

[a] Calculated from the data in Fig. 1 and unpublished results; compare the Discussion part for factors which are neglected when such approach is used.

This enhancement of solubilization prompted us to attempt to reconfirm the expected dissociation of inclusion complexes as a result of a temperature increase for the achiral drug carbamazepine. Alone, an achiral compound does not show any circular dichroism (CD) but on inclusion into a cyclodextrin cavity, the latter compound being chiral, a CD spectrum may be induced, which is related to the absorption spectrum of the achiral compound that has been included (Harata, 1991; Kodaka, 1991). The addition of hydroxypropyl-β-cyclodextrin (10% w/w) to the solution of carbamazepine (4.1×10^{-5} M) at room temperature resulted in the induction of a CD spectrum. The minimum in the CD spectrum of carpamazepine at 285 nm was clearly related to the absorption maximum at the same

wavelength in the ultraviolet spectrum. On heating this solution to 60°C, the intensity of the induced CD spectrum of carbamazepine was reduced by about 50%. In spite of this decrease in inclusion complexation, the results in Fig. 1 demonstrate that the solubility of carbamazepine in hydroxypropyl-β-cyclodextrin of the same concentration is increased by about 13% when the temperature is elevated from room temperature to 60°C.

The solubility of a drug, D_t in a solution containing hydroxypropylcyclodextrin at a concentration of C_t is a function of the apparent association constant K of the complex formed and of the solubility of the drug in water D_o, as expressed by Eqn 1:

$$D_t = D_o + \frac{D_o K}{1 + D_o K} C_t \qquad (1)$$

The solubility in water, D_o, of all the drugs investigated in the present paper increased with temperature, as observed previously for many other organic compounds (Sokolski, 1985). Since D_t increases with D_o, the increase in D_o should make a positive contribution to the heat-assisted preparation of the solutions. On the other hand, the apparent association constants, K, of all inclusion complexes studied decrease with increasing temperature (Szejtli, 1988; Tong et al., 1991; Table 1). Since D_t decreases with decreasing K (Eqn 1), this will make a negative contribution to the heat-assisted preparation of the solutions. The final effects of temperature on D_t are determined by the manner in which the product $D_o K$ changes with temperature. For carbamazepine, the temperature dependences of all parameters involved are plotted in Fig. 2. Obviously, for this drug and the other two, a greater increase in water solubility with temperature leads to an increase in concentration of complexed drug despite the lower stability of the complex.

In the above experiments, hydroxypropylcyclodextrins were used at concentrations where the solutions cannot be considered as dilute or ideal nor the properties of water to be unaffected by the solute. Consequently, there are other factors involved in the heat-assisted preparation of the solutions of drugs in aqueous hydroxypropylcyclodextrins. After the importance of these factors has been separately assessed, all the data may possibly be regressed into thermodynamic parameters in a manner which recently has been established for ideal solutions (Rhodes et al., 1992). The practical consequences of the present results nevertheless are clear: when drugs are of suitable stability, heating facilitates the preparation of drug-cyclodextrin complexes.

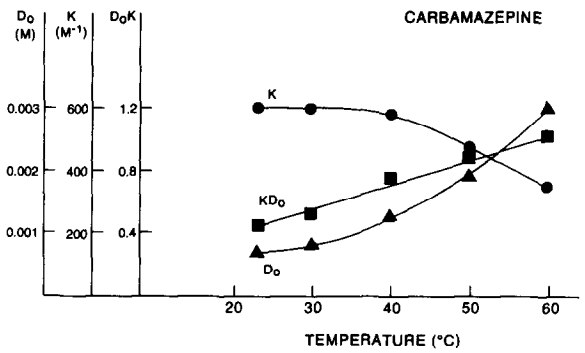

Fig. 2. Temperature dependence of the solubility of carbamazepine in water (D_o), the apparent association constant of carbamazepine with hydroxypropyl β-cyclodextrin (K) and of the product of D_o and K.

Acknowledgements

The authors are grateful to Mrs Audrey L. Brown for typing and preparation of the manuscript and to Dr M.K. Garwood-Pitha for clarifying comments.

References

Brewster, M.E., Simpkins, J.W., Hora, M.S., Stern, W.C. and Bodor, N., The potential use of cyclodextrins in parenteral formulations. *J. Parenteral Sci. Technol.*, 43 (1989) 231–240.

Harata, K., Induced circular dichroism of cycloamylose complexes with *meta* and *para* disubstituted benzenes. *Bioorg. Chem.*, 10 (1981) 255–265.

Kodaka, M., Sign of circular dichroism induced by β-cyclodextrin. *J. Phys. Chem.*, 95 (1991) 2110–2112.

Loftsson, T. Brewster, M.E., Derendorf, H. and Bodor, N., 2-Hydroxypropyl-β-cyclodextrin: properties and usage in

pharmaceutical formulations. *Pharm. Ztg. Wiss.,* 136 (1991) 5–10.

Mesens, J.L., Putteman, P. and Verheyen, P., Pharmaceutical applications of 2-hydroxypropyl-β-cyclodextrin. In Duchene, D. (Ed.), *New Trends in Cyclodextrins and Derivatives,* Editions de Sante, Paris, 1991, pp. 369–407.

Muller, B.W. and Brauns, U., Solubilization of drugs by modified β-cyclodextrins. *Int. J. Pharm.,* 26 (1985) 77–88.

Pitha, J., Harman, S.M. and Michel, M.E., Hydrophilic cyclodextrin derivatives enable effective oral administration of steroidal hormones. *J. Pharm. Sci.,* 75 (1986) 165–167.

Pitha, J. and Hoshino, T., Effects of ethanol on formation of inclusion complexes of hydroxypropylcyclodextrins with testosterone and with methyl orange. *Int. J. Pharm.,* 80 (1992) 243–251.

Pitha, J., Hoshino, T., Torres, J.L. and Irie, T., Preparation of drug: hydroxypropylcyclodextrin complexes by a method using ethanol or aqueous ammonium hydroxide as cosolubilizers. *Int J. Pharm.,* 80 (1992) 253–258.

Pitha, J. and Pitha, J., Amorphous water soluble derivatives of cyclodextrins, non-toxic solubilization enhancing excipients. *J. Pharm. Sci.,* 74 (1985) 987–990.

Pitha, J., Torres, J.L. and Irie, T., Preparation of lipophile-hydroxypropylcyclodextrin complexes by a method using cosolubilizer. *US Patent Application Serial No. 07/585 792,* Sept. 1990.

Rhodes, C.T. and Menard, F.A., Determination of the thermodynamic paramets controlling drug/cyclodextrin complexation using a non-linear regression method, Abstr. L-29, *6th International Cyclodextrin Symposium,* Chicago, IL, 1992.

Sokolski, T.D., Solutions and phase equilibria. In *Remington's Pharmaceutical Sciences,* Mack, Easton, PA, 1985, pp. 207–229.

Szejtli, J., *Cyclodextrin Technology,* Kluwer, Dordrecht, 1988.

Tong, W.Q., Lach, J.L., Chin, T.F. and Guillory, J.K., Structural effects on the binding of amine drugs with diphenylmethyl functionality to cyclodextrins. *Pharm. Res.,* 8 (1991) 951–957.

Uekama, K., Hirayama, F. and Irie, T., Modification of drug release by cyclodextrin derivatives. In Duchene, D. (Ed.), *New Trends in Cyclodextrins and Derivatives,* Editions de Sante, Paris, 1991, pp. 409–416.