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PHYSICO-CHEMICAL ASPECTS OF THE COMPLEXATION OF SOME DRUGS WITH CYCLODEXTRINS

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INTRODUCTION

The three major cyclodextrins consist of six, seven and eight units of glucose, respectively (1). Cyclodextrins readily form inclusion complexes with a wide range of organic compounds. The complexation of drugs with cyclodextrins has been shown to have great potential for the pharmaceutical industry (2). Potential Pharmaceutical advantages of the drug-cyclodextrin complex formation include: a) enhancement or organoleptic properties; b) stabilization of the drug; and c) improvement of the solubility, dissolution and bioavailability of drugs.

However, relatively little attention appears to have been directed by pharmaceutical scientists to the thermodynamic parameters controlling the interaction.

The objectives of this paper are: to report the effect of pH and temperature on the phase-solubility of three drugs on complexation with cyclodextrins and to determine the thermodynamic parameters of complexation using a novel computer approach based on a non-linear program.

EXPERIMENTAL SECTION

Reagents and Chemicals - All solvents and reagents were of analytical grade and were used as received. Hydrochlorothiazide and diazepam were obtained from Sigma Chemical Co. (St. Louis, MO). Ibuprofen was received from Whitehall Laboratories. The cyclodextrin materials used were generously given by American Maize (Hammond, IN).

Methods - The solubility method used was based on that described by Higuchi and Connors (8). An excess of solid drug was added into screw-capped tubes containing solutions of cyclodextrins at various known concentrations. The tubes were rotated in a waterbath at constant temperature ($\pm$ 0.05°C) until saturation was reached. The filtration and dilution steps were conducted in a walk-in oven. The complexation of ibuprofen, diazepam and hydrochlorothiazide were studied at various temperatures from 20°C to 50°C, and at different pH values. The

solubility isotherms were obtained by plotting the solubility of the drug as a function of cyclodextrin concentration.

Computer treatment of Data - The thermodynamic parameters of complexation were determined using a computer method based on non-linear regression. Three programs were used: 1) a datafile: 2) a subroutine; and 3) a JCL program which links the datafile and the subroutine; and 3) a JCL program which links the datafile included a full set of data consisting of drug concentration, cyclodextrin concentration and temperature at a given pH value and the initial estimates of the thermodynamic parameters. The three major parameters considered were the enthalpy (ΔH) and entropy (ΔS) of complexation, and the heat of solution (ΔH_s). The subroutine program contained the following mathematical equation:

$$[AH]t = e^{A+B} / (1+e^{A+B}) [CD]t + e^{B} \quad (1)$$

where: $[AH]t$ = total concentration of drug in solution

$[CD]t$ = total concentration of cyclodextrin

$A = \Delta H/RT - \Delta S/R$

$B = Hs (T-T_o) /RTT_o - \ln \gamma$

with: ΔH = enthalpy of complexation

ΔS = entropy of complexation

ΔHs = heat of solution

R = gas constant

T = absolute temperature (^oK)

T_o = melting point

γ = activity coefficient

This equation is based on the following assumptions: 1) the stoichiometry of the drug/cyclodextrin complex was 1:1; (2,) the change of the free energy of complexation with temperature obeyed the Gibbs equation; 3) the complexing ability of the cyclodextrins was pH independent between pH 2 and pH 9; and 4) the free drug solubility could be described by the general Van't Hoff equation. The output of the NONLIN program used gave the final estimates of the thermodynamic parameters, their standard deviation and their 95% confidence limits.

Statistical Analysis - An analysis of variance (ANOVA) was performed on the slope of the solubility isotherms using a SAS statistical package. Temperature and pH were the two experimental variables. A SASGRAPH program was used to plot the solubility of the drug as a function of cyclodextrin concentration and pH. A G3D grid technique was used in all cases.

RESULTS AND DISCUSSION

Determination of pKa - The Benet and Peck approach was used to calculate the apparent pKa of each drug from the intercept data of the solubility isotherms built at a given temperature (9). The solubility C varies as a function of pH according to the following equation:

$$\log (C/C_o - 1) = pH - pKa \qquad (2)$$

where C_o = solubility of the unionized species

This assumption is supported by previously published data originating from the University of Rhode Island Department of Pharmaceutics. The pKa value corresponds to the pH at which the solubility is twice that of the unionized species. The apparent pKa determined from the data available were 4.8, 3.6 and 8.0 for ibuprofen, diazepam and hydrochlorothiazide respectively. These values are in good agreement with the values available in the literature. In the case of diazepam, which is a weak base, 3.6 is the pKa of the conjugated acid.

Determination of Heat of solution - The heat of solution (ΔH_s) of the free drug represents the intercept of the solubility isotherm.

The Van't Hoff and Hildebrand equations can be used to show the solubility-temperature relationship (10). Although both equations have the same theoretical basis, the plot of the log solubility expressed in mole fraction as a function of the reciprocal of the absolute temperature is referred to as the Van't Hoff plot (11,12).

$$\log x = -(\Delta H/2.303\ R)\ (1/T) + ct \qquad \text{(eq. 3)}$$

The Van't Hoff plots for ibuprofen, diazepam and hydrochlorothiazide are shown in Figures 1, 2 and 3 respectively. Each straight line represents a set of data at a given pH value. The slope of the linear plots varied with pH

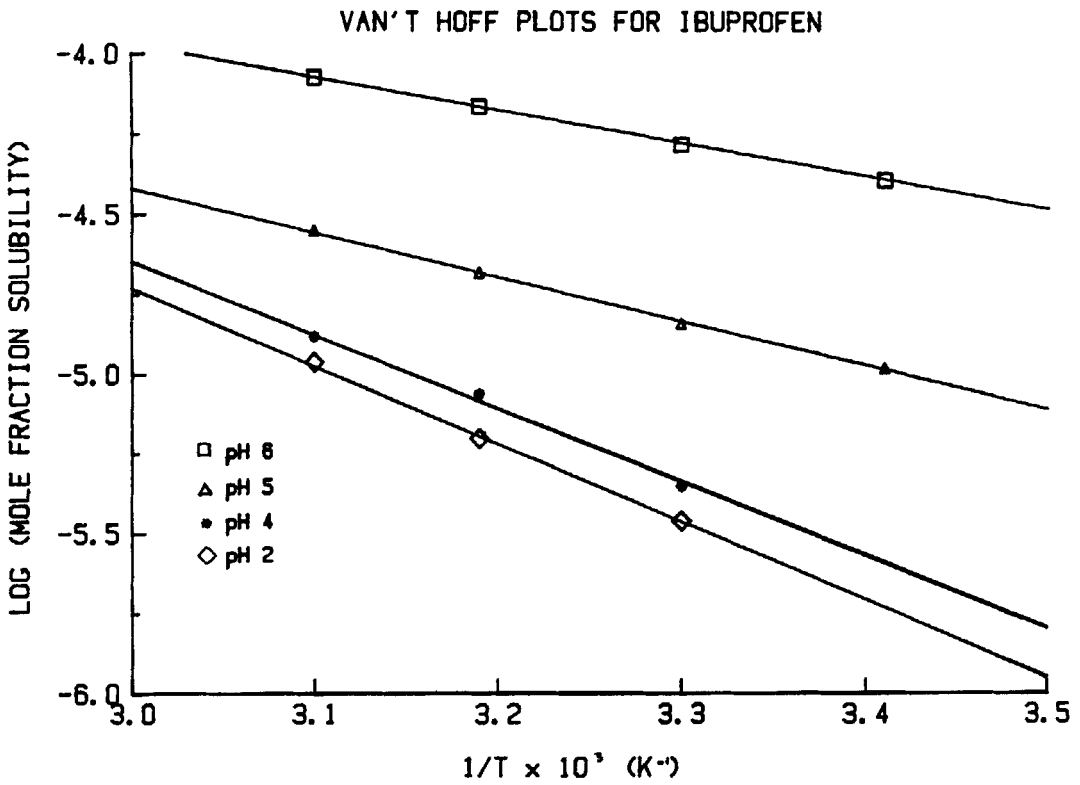

Figure 1

Van't Hoff plots for Ibuprofen

indicating that the heat absorbed by the system during dissolution varied with the extent of ionization.

Table I shows the values for the heat of solution of the three drugs determined by both the manual method using equation 2 and linear regression and the computer method using non-linear regression. The advantage of the computer approach is that each parameter is estimated with a 95% confidence interval. An

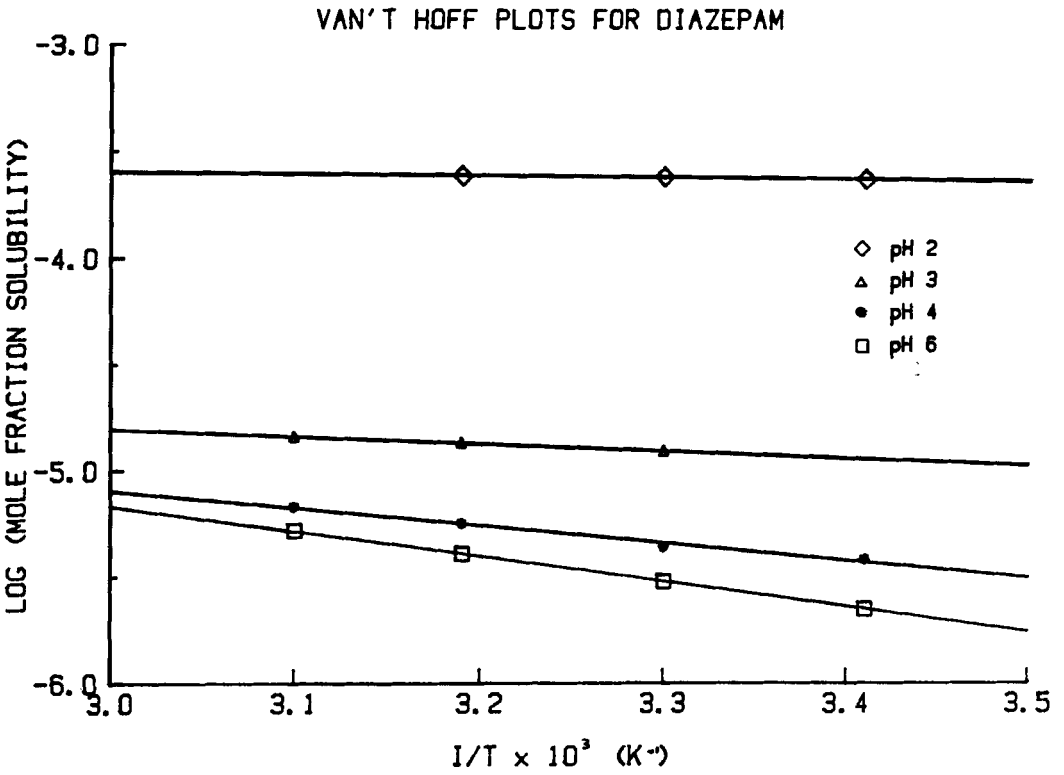

Figure 2

Van't Hoff plots for Diazepam

excellent correlation was observed between the results obtained from the two different methods for all three drugs tested. In the case of ibuprofen and hydrochlorothiazide, which are both weak acids, an increase of pH resulted in lower heat of solution because of the increased ionization of the drug. The lack of variation in the ΔH_s with pH for hydrochlorothiazide can be correlated to the almost parallel lines observed in Figure 3.

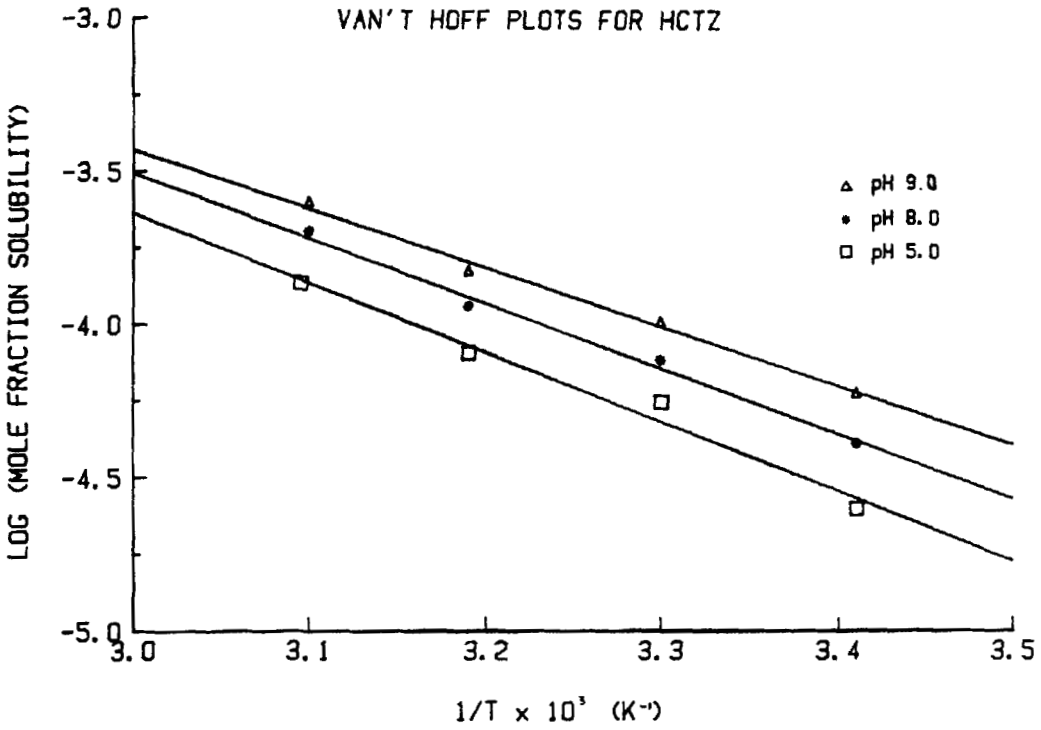

Figure 3

Van't Hoff plots for Hydrochlorthiazide

For diazepam, the unionized species at pH 6 required more energy to go into solution. In al cases, the solubility process was endothermic as indicated by the positive values of heat of solution.

Effect of pH on complexation - the solubility isotherms of the complexation of the three drugs with β cyclodextrin at various pH values and constant temperature are presented in Figures 4, 5 and 6. As the pH increased, the intercept

TABLE I: Heat of solution of the drugs at various pH values

DRUG	pH	ΔH_s (linear) ($cal.mol^{-1}$)	ΔH_s (non-linear) ($cal.mol^{-1}$)
	2	11,158.8	8,718.9 ± 1,266.2
	4	10,534.1	9,447.9 ± 1,223.0
IBUPROFEN	5	6,287.5	6,207.5 ± 375.7
	6	4,685.9	4,157.7 ± 385.8
	2	311.2	1,246.8 ± 543.2
DIAZEPAM	3	1,565.2	1,459 ± 289.6
	4	3,724.9	5,368.5 ± 716.0
	6	5,381.4	6,509.3 ± 565.4
	5	10,392.2	9,420.3 ± 327.4
HYDROCHLORO-	8	9,756.2	10,313.4 ± 332.2
THIAZIDE	9	8,808.9	9,157.6 ± 330.3

increased for ibuprofen and hydrochlorothiazide and decreased for diazepam due to the ionization of the drug. The solubility plots obtained for diazepam (Figure 5) indicate that there is an increase of the slope as the pH decreased. Since diazepam is completely ionized at pH 2, the observed increase of the slope

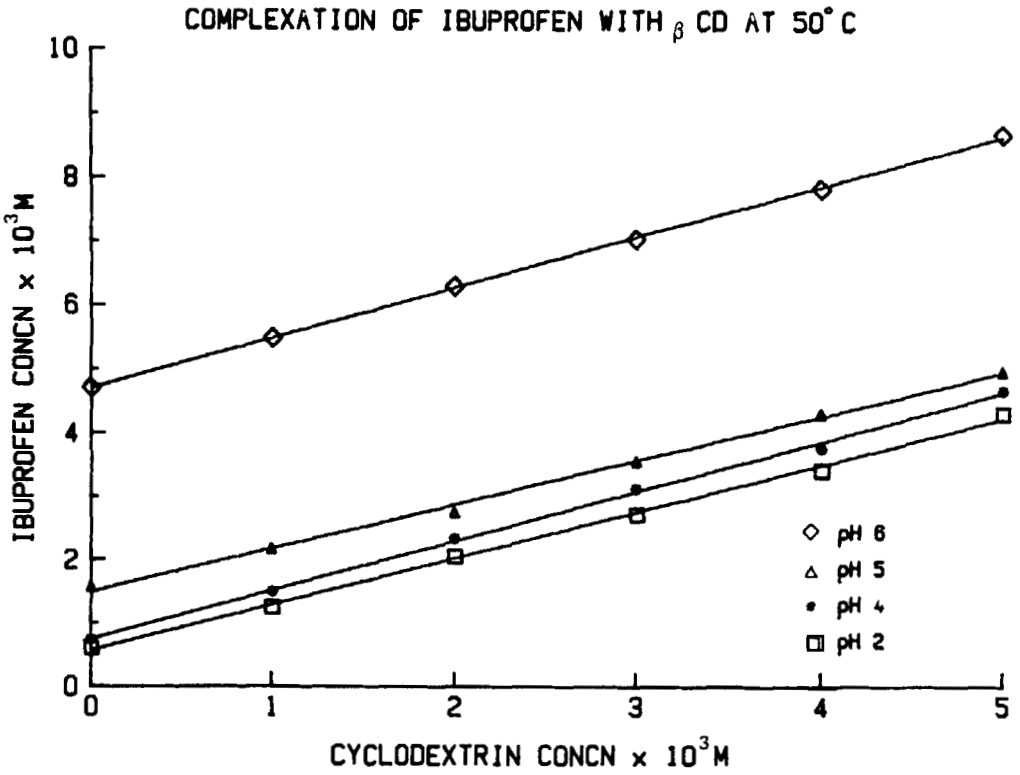

Figure 4

Complexation of Ibuprofen with cyclodextrin at 50°C

corresponds to the interaction of β cyclodextrin with the ionized species. Without such interaction, the pH 2 line should have been parallel to those obtained at the other pH values. However, in the case of ibuprofen and hydrochlorothiazide, the SAS treatment showed that there was no significant difference in the slope as a function of pH i.e. for these two drugs the ionized species does not interact significantly with β cyclodextrin.

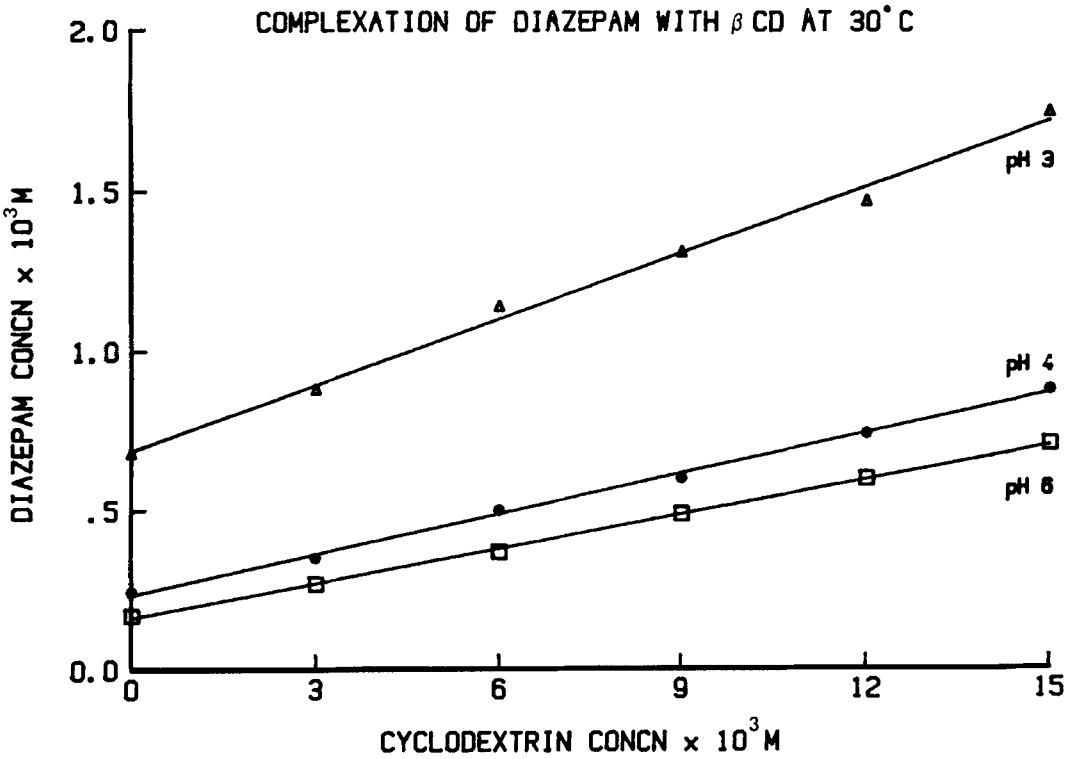

Figure 5

Complexation of Diazepam with cyclodextrin at 30°C

In order to rationalize the differences in complexation behavior, one has to consider the basic mechanism of inclusion complex formation. The cavity of cyclodextrin is an hydrophobic environment that can host an hydrophobic molecule. It seems that B cyclodextrin can fit a group similar in size to the benzene ring, which is one of the groups present in diazepam and phenytoin that has previously been shown to form a complex at the ionized state. For these two molecules the complexing group

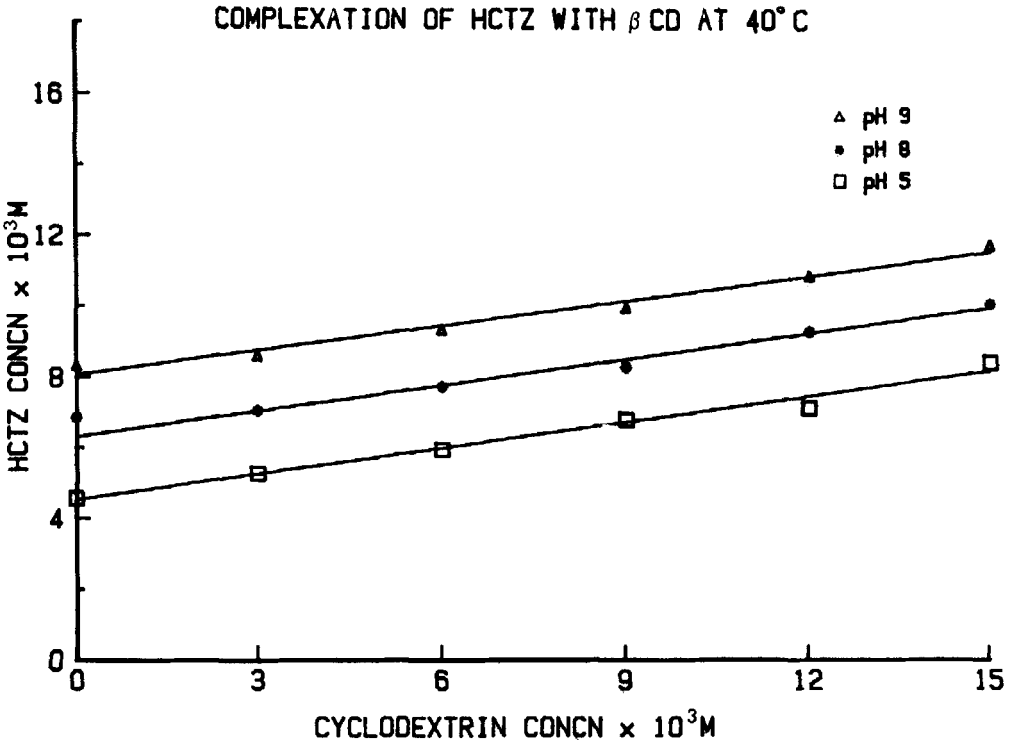

Figure 6

Complexation of Hydrochlorothiazide with cyclodextrin at 40°C

may remain mostly unaffected by the ionization and therefore the ionized species is still able to form a complex with cyclodextrin. Ibuprofen and hydrochlorothiazide do not form such a complex after ionization and the slope of the solubility isotherms is pH independent. It is possible that the ionization of both drugs greatly affects the polarity or the hydrophobicity

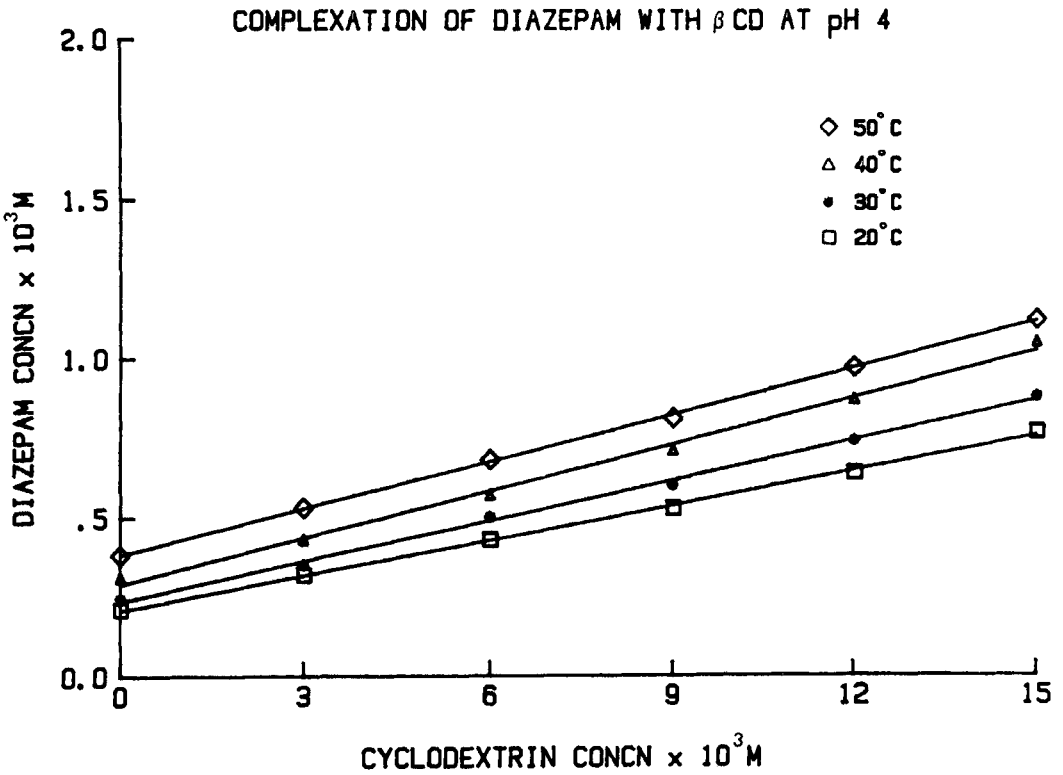

Figure 7

Complexation of Diazepam with cyclodextrin at pH4

of the complexing group, thus preventing the formation of a complex at higher pH values.

Effect of temperature on complexation - The solubility study was also conducted at different temperatures for each of the three drugs studied. Figure 7 shows an example of the plots obtained at each pH value. The analysis of variance using SAS did not show any significant difference of the slopes tested, which means that the solubilization power was essentially

temperature-independent. Three-dimensional plots obtained at given pH values using SASGRAPH are shown in Figures 8, 9 and 10 for ibuprofen, hydrochlorothiazide and diazepam, respectively.

Determination of thermodynamic parameters - The classical method to detemrine thermodynamic parameters of complexation is based on the temperature dependence of the complexation constant. However, this method based on two sequential steps of linearization of data, does not allow a precise determination of the enthalpy and entropy of complexation, which can make difficult further comparisons. The computer method developed in this study utilized datafiles that contained a set of solubility data at one pH value similar to that plotted in Figures 8 to 10.

Tables II, III and IV summarize the results of the treatment of the solubility data for the three drugs. The thermodynamic parameters of complexation can be used as a basis for discussion of the mechanism of complexation. The driving forces of complexation have long been a subject of controversy (13,14). The different possibilities proposed include hydrophobia interaction, hydrogen bonding, Van der Waals interaction, release of enthalpy rich water molecuels and release of conformational strain (15). The contribution of each of these factors depends upon the nature of the drug. The overall thermodynamic parameters, namely enthalpy (H) and entropy (S) are related to the apparent free energy (G) by the

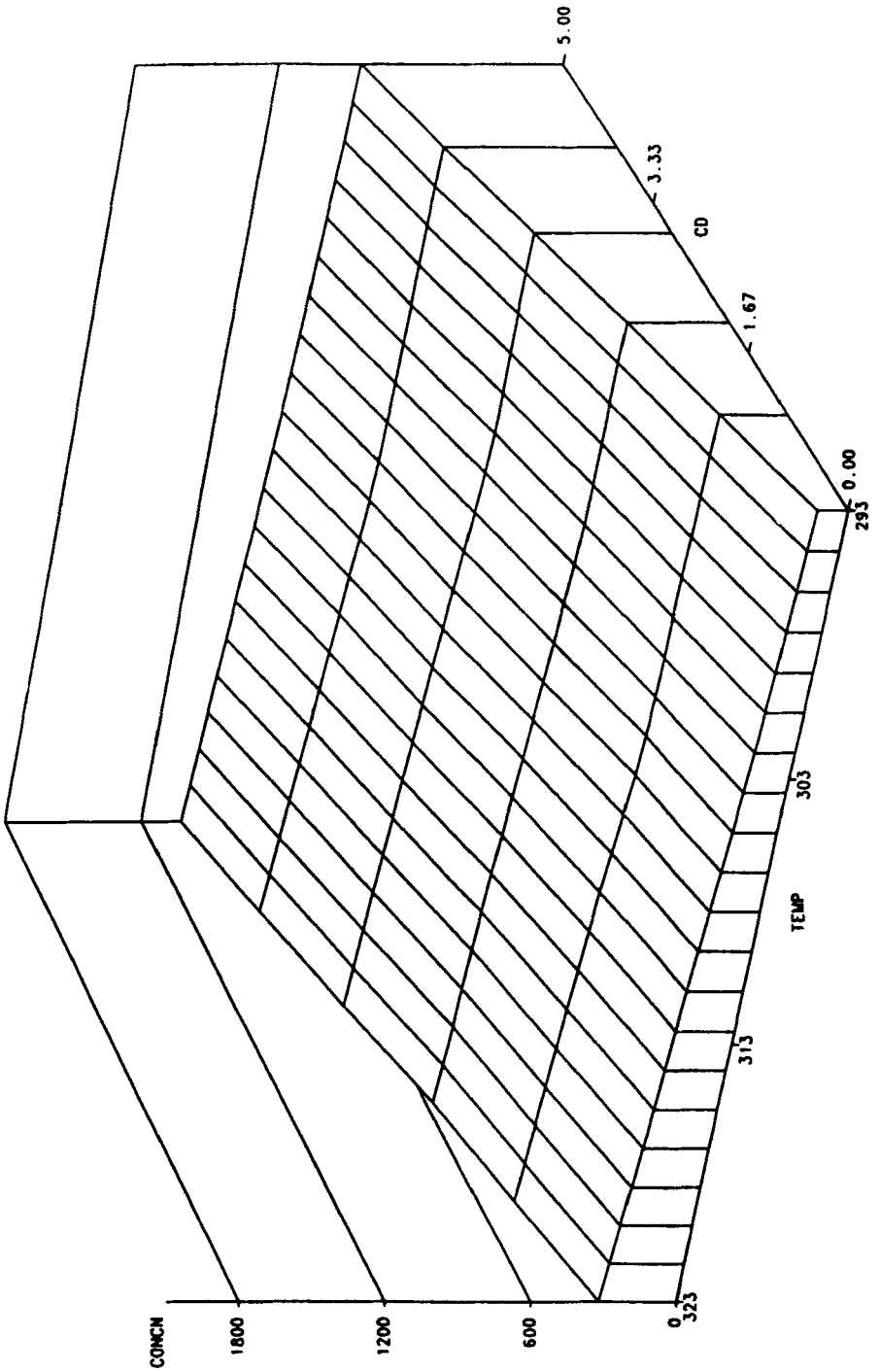

Figure 8 Solubility response surface diagram for Ibuprofen

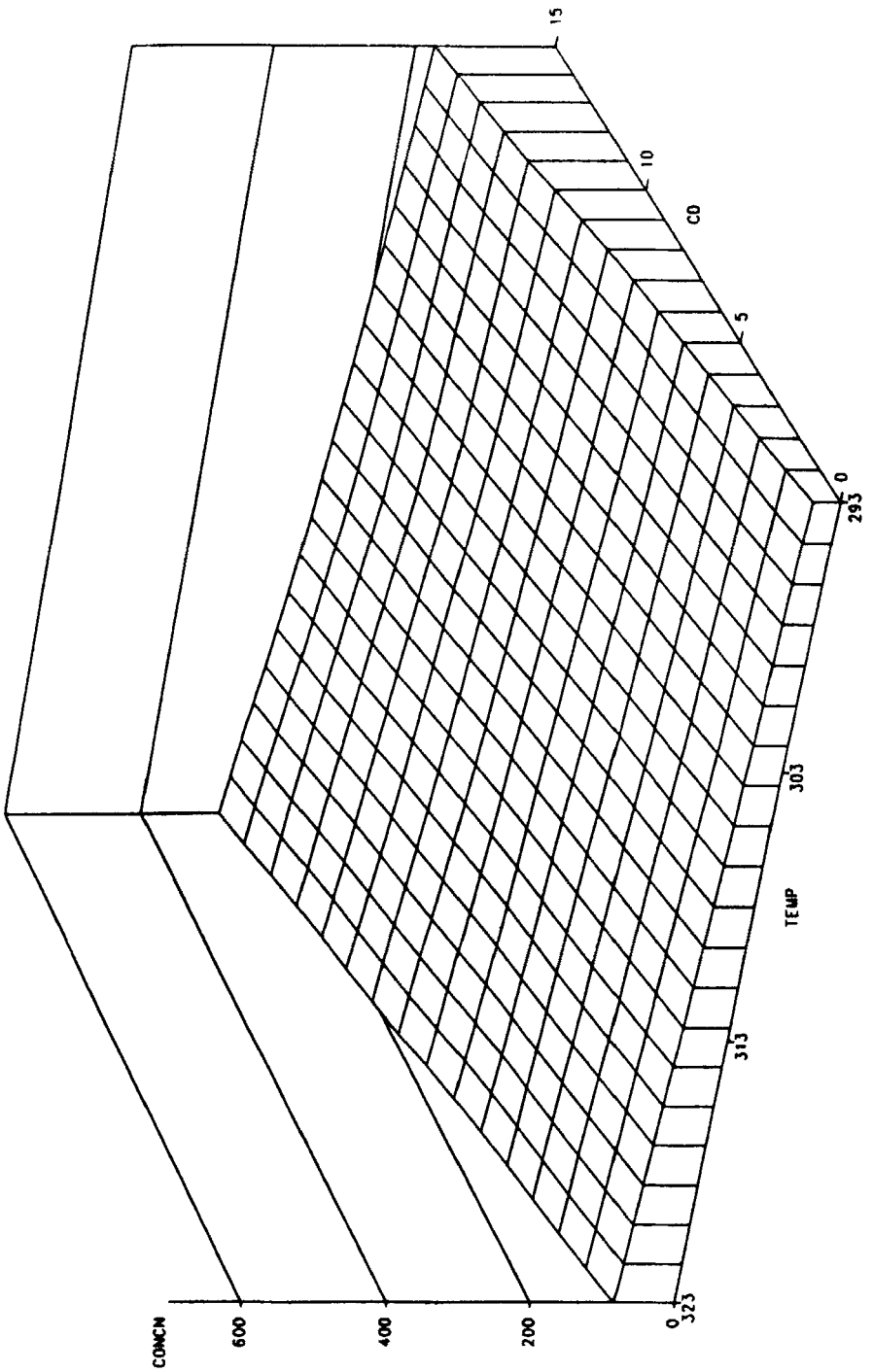

Figure 9 Solubility response surface diagram for Diazepam

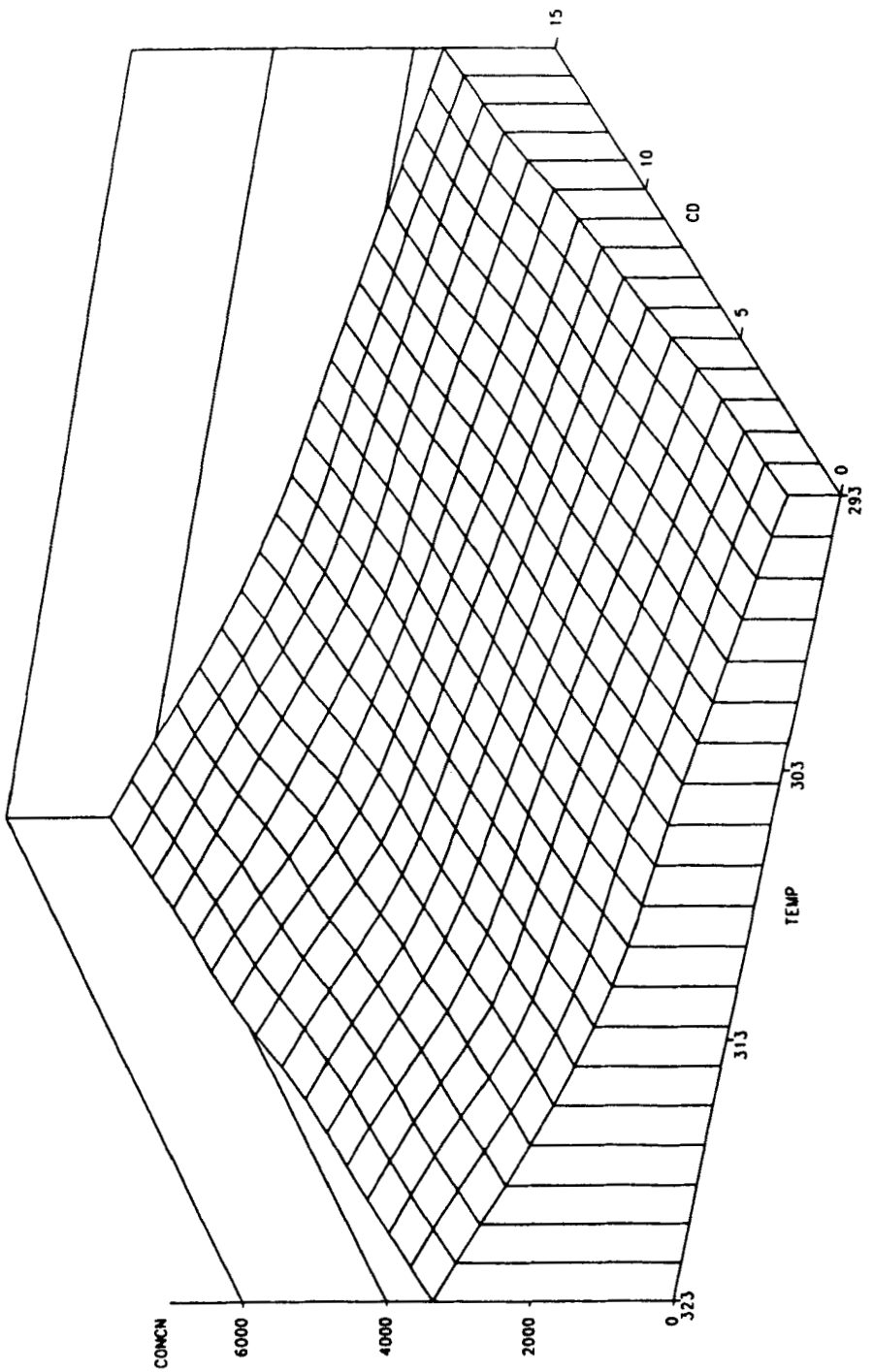

Figure 10

Solubility response surface diagram for Hydrochlorothiazide

TABLE II: Ibuprofen/β cyclodextrin complexation thermodynamic parameters

pH	r	Δ H (cal.mol^{-1})	std. dev.	ΔS	std. dev. (e.u.)
2	0.999	-6,925.5	324.9	+3.49	1.06
4	0.999	-7,797.9	321.7	+0.88	1.05
5	0.999	-7,045.5	300.0	+0.72	0.97
6	0.991	-4,036.4	1,246.6	+8.15	4.06

TABLE III: Diazepam/β cyclodextrin complexation thermodynamic parameters

pH	r	Δ H (cal.mol^{-1})	std. dev.	Δ S	std. dev. (e.u.)
2	0.960	-51.4	1502.4	+16.63	4.89
3	0.998	-797.9	145.7	+16.50	0.47
4	0.998	-4,070.7	184.2	+ 5.22	0.60
6	0.999	-4,416.4	104.3	+ 4.44	0.34

TABLE IV: Hydrochlorothiazide/β cyclodextrin complexation thermodynamic parameters

pH	r	Δ H (cal.mol^{-1})	std. dev.	Δ S (e.u.)	std. dev.
5	0.997	-9,642.3	432.3	+ 14.7	1.4
8	0.997	-9,322.1	574.1	+ 14.1	1.9
9	0.996	-10,012.2	715.9	+ 16.7	2.3

Gibbs equation:

$$\Delta G = \Delta H - T\Delta S \quad (4)$$

The free energy can be considered as the sum of the energy changes due to each of the factors listed earlier. Therefore, the values given in Tables III to IV can be seen as overall thermodynamic parameters, that indicate which factors may be predominant in the mechanism of complexation.

In the case of ibuprofen, the apparent enthaply of complexation is negative at all pH values indicating that the system is releasing energy upon complexation. The extent of the energy released decreases as the drug becomes more ionized. There is no definite trend in the change in enthalpy from pH 2

to pH 5. However, the large negative enthalpies probably indicate a strong involvement of dipoles and Wan der Waals interaction during complexation. Also this loss of heat upon complexation could correspond to the energy released by the enthalpy rich water molecules trapped within the cyclodextrin cavity. The entropy factor is positive at all pH values, showing that the order of the systems decreases upon complexation. At pH 6, the entropy increase is particularly significant despite the high standard deviation. Ibuprofen is substantially ionized at pH 6 and it is likely that some water molecules of solvation are still in contact with the drug molecule. If one considers that the change in entropy corresponds to the difference in hydrogen bonds before and after complexation, one could suggest that the larger overall balance is due to the smaller number of hydrogen bonds broken.

The thermodynamic parameters of complexation for the diazepam/β cyclodextrin interaction are presented in Table III. The enthalpy of complexation is again negative at all pH values. As pH decreases and drug ionization increases, the absolute value of H decreases. This lower value of ΔH indicates a weaker binding and a lower loss of heat upon complexation. It has also been proposed that the complexation of an ionized species would occur on a more random fashion than for the ionized species (16). The entropy value is positive and increases as the pH is increased. As for ibuprofen, the entropy can be correlated to

the forming and breaking of hydrogen bonds upon complexation. The ionized form of diazepam probably retaining a shroud of water solvation gains hydrogen bonding without loosing such a great amount as in pH 6. The overall result is a larger entropy upon complexation. Also, as the pH decreases the water molecules are more tightly bound to the drug molecule and therefore are only slowly removed, partially explaining the high entropy values.

The results shown in Figure IV for the complexation of hydrochlorothiazide with β cyclodextrin are less dramatic but possibly easier to interpret. Hydrochlorothiazide is a weak acid with a pKa around 8.0. It seems that the ionization of the drug has very little effect on the thermodynamic parameters of complexation. This result also confirms the fact that hydrochlorothiazide does not form a complex with β cyclodextrin in its ionized form. The negative values of enthalpy testifies again of the strong involvement of the enthalpy rich water during complexation. The large negative values of entropy suggest that the system becomes more ordered upon complexation.

SUMMARY

From the results for the complexation of three drugs with cyclodextrins, it appears that the maind riving forces of complexation reside in the release of energy of the water molecules entrapped in the cyclodextrin cavity. Although the negative enthalpy value was a common point between the drugs

tested, the extent of the pH effect varied from one molecule to another. The entropy is probably more related to the solvent participation in the complexation phenomenon. The consideration of the interaction between water and non-polar drug, water and cyclodextrin before complexation as well as the breakage and establishment of hydrogen bonds. allows for a description of the complexation mechanism for each drug. However, this drug/cyclodextrin interaction depended on the nature of the drug and the pH of the solution. The practical biopharmaceutical implication of the results can be quite significant. A drug/cyclodextrin complex dosage form either for parenteral or oral administration, would encounter various pH conditions in vivo. The therapeutic effect might well be affected by the mechanism of complexation. Further work is still needed to fully explain the exact mechanism of drug/cyclodextrin complex formation and to eventually optimize complex formulation

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