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Potential Pharmaceutical Applications of a New Beta Cyclodextrin Derivative

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INTRODUCTION

The three major natural cyclodextrins viz alpha, beta and gamma, consist of six, seven or eight glucose units, respectively (1). In addition to the natural cyclodextrins, numerous new products have been shown to have potential for the pharmaceutical industry (2,3). A clear distinction has to be made between cyclodextrin polymers, which are mainly used as separation materials in analytical chemistry (4) and cyclodextrin derivatives, which are monomers of substituted cyclodextrins (5). In the synthesis process of the latter, both the C(2) and C(3) secondary and the C(6) primary hydroxyl groups have been the target of many chemical substitutions (6), leading to the development and the characterization of cyclodextrin derivatives of pharmaceutical interest (7). Such derivatives have been successfully used in the design of new drug carrier systems (3,5). Hence, in addition to their increased solubility,

these chemically modified cyclodextrins exhibit excellent complexing abilities (8). The different possibilities of modifying cyclodextrins have been reviewed by Sebille (2), Szejtli (1) and Uekama (3). Szjetli also published an extensive list of the major cyclodextrin derivatives under investigation until 1982 (1).

The chemical considerations of the substitution of cyclodextrins have been investigated by Harata et al., who examined the macrolytic conformation of permethylated cyclodextrins (6). The main factor is the loss of the ability to form hydrogen bonds upon substitution. Further studies dealing with the properties of cyclodextrin derivatives have been recently published (9).

The stability of prostaglandins was improved by complexation with methylated cyclodextrins (10). On the other hand, an ammonium beta cyclodextrin derivative was shown to catalyze the hydrolysis of nitrophenyl ester (11). Nakai et al. studied the effect of a tri-methyl beta cyclodextrin on the partition of nitrophenol, and interpreted the data as the formation of a 1:1 complex (12). The use of cyclodextrin derivatives as agents of solubilization has been reported in the literature (13). Muller and Brauns have investigated the complexation of diazepam, hydrocortisone and digitoxin with methyl beta cyclodextrin (14), as well as the effect of the derivatization of gamma cyclodextrin on the phase-solubility of progesterone (15). Otagiri et al. have also studied the complexation of several drugs with tri-methyl cyclodextrin.

In most of the studies, the critical factor to be carefully considered in the interpretation of the data is the degree of substitution (DS) of the cyclodextrin derivatives (16). Muller and Brauns have established a relationship between the average degree of substitution and the complexing ability (14). From the data obtained, the lower the degree of substitution, the more extensive the complexation phenomenon. This result was attributed to the steric blockage of the cyclodextrin cavity by the substituents.

Several researchers have published data regarding specific dosage forms of complexes of drug/cyclodextrin derivatives. Dimethyl beta cyclodextrin has been proposed as a parenteral drug carrier for such drugs as progesterone and hydrocortisone (17). The dissolution of flurbiprofen suppositories was shown to be greatly improved by complexation with dimethyl and trimethyl beta cyclodextrin (18). Also, a comparative study of the complexation of flurbiprofen with both beta cyclodextrin and its derivatives showed that the mode of inclusion was quite different, due to the different number of free hydroxyl groups on the cyclodextrin ring (18). In-vivo studies in rats suggested that the complexation of ketoprofen with methyl beta cyclodextrin could lead to high plasma levels (19). It was also proposed that the surface active properties of methyl beta cyclodextrins could facilitate drug absorption through membranes. However, as discussed further in this paper, the same surface active properties may well be responsible for negative toxic effects on the cells, causing hemolysis (3). Pitha et al. investigated the oral administration of

steroidal hormones. The study showed that the complexation of progesterone and testosterone with beta cyclodextrin derivatives allowed for the correction of serum levels and could efficiently be used for therapeutic applications (17).

Even though the hydrophilic cyclodextrins have been the focus of the attention of many researchers, Uekama recently published data showing that ethylated beta cyclodextrins could be used as hydrophobic drug carriers. An in-vivo study in rats showed that these hydrophobic derivatives produced a sustained release of diltiazem (21). It is very likely that more work will be done in the future to establish the exact potential of cyclodextrin derivatives in sustained release.

The purpose of this paper is to evaluate the complexing ability of hydroxyethyl beta cyclodextrin, a new beta cyclodextrin derivative. Furthermore, the complexation of several drugs with both the natural beta cyclodextrin and its new derivative was investigated in order to establish a possible comparison of the data and to propose a valid prediction of the overall increase in drug solubility upon complexation.

EXPERIMENTAL

Materials

Hydroxyethyl beta cyclodextrin (batch #CDM108) was obtained from American Maize (Hammond, IN). Table 1 shows some of its basic physico-chemical properties, compared to those of the natural cyclodextrins.

TABLE I

BASIC PROPERTIES OF CYCLODEXTRINS

CD	# GLUCOSE UNITS	MW	# WATER MOLECULES	SOLUBILITY gm/100ml
α	6	972	6	14.5
β	7	1135	11	1.8
γ	8	1297	17	23.2
β'	7	1300	11	60.0

Three of the drugs viz phenytoin, diazepam and hydrochlorothiazide were obtained from Sigma Chemical Co. (St. Louis, MO). Ibuprofen was generously given by Whitehall Laboratories. All drugs were used as received. All solvents and reagents used in the study were of analytical grade and were used as received.

Methodology

The complexation of the drugs with the new modified beta cyclodextrin was studied using the solubility method described by Higuchi and Connors (21). An excess of drug was placed into screw-capped vials containing various concentrations of cyclodextrins. The vials were then rotated at constant temperature (±0.05°C) in a waterbath, until the maximum solubility was reached. The samples of drug solutions were then filtered using glasswool, diluted and assayed for drug concentration using a diode-array

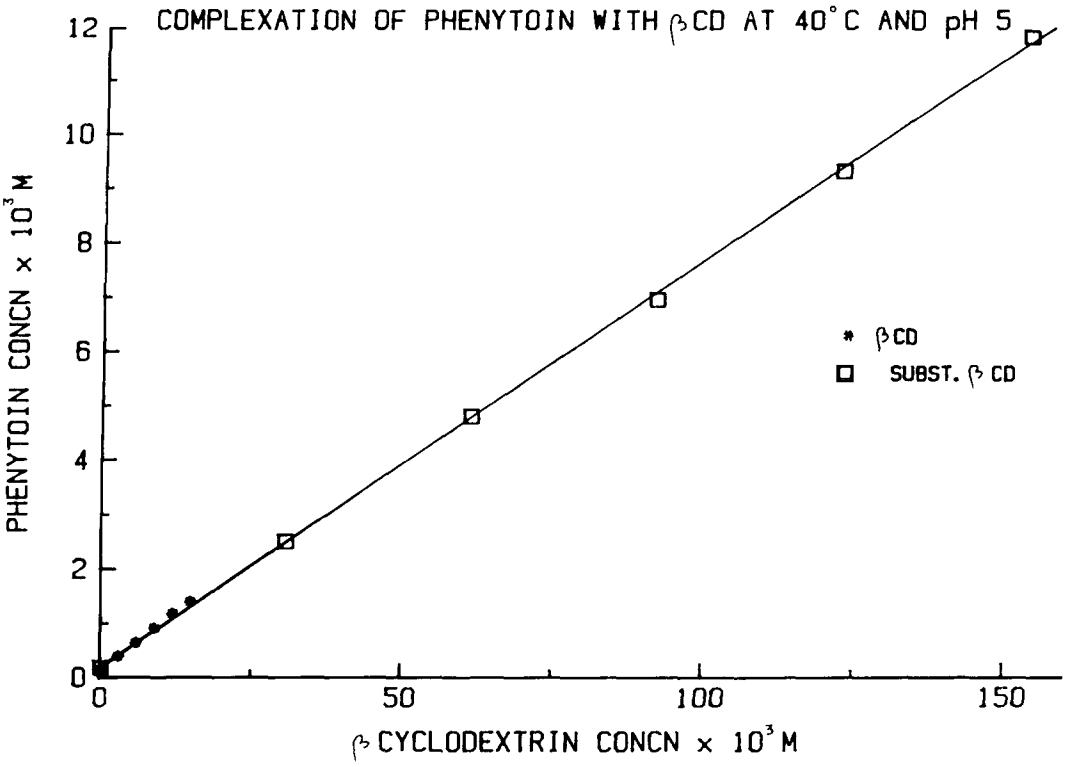

Figure I

Complexation of phenytoin with β CD at 40°C and pH 5

ultra-violet spectrophotometer (Hewlett-Packard HP 8451A). The drug standards obeyed the Beer's law in all cases, and cyclodextrin was shown not to interfere with the assay.

RESULTS AND DISCUSSION

The solubility isotherms were obtained by plotting the total drug concentration as a function of total cyclodextrin concentration. In all cases the plots were linear, suggesting a type A phase solubility (21). The

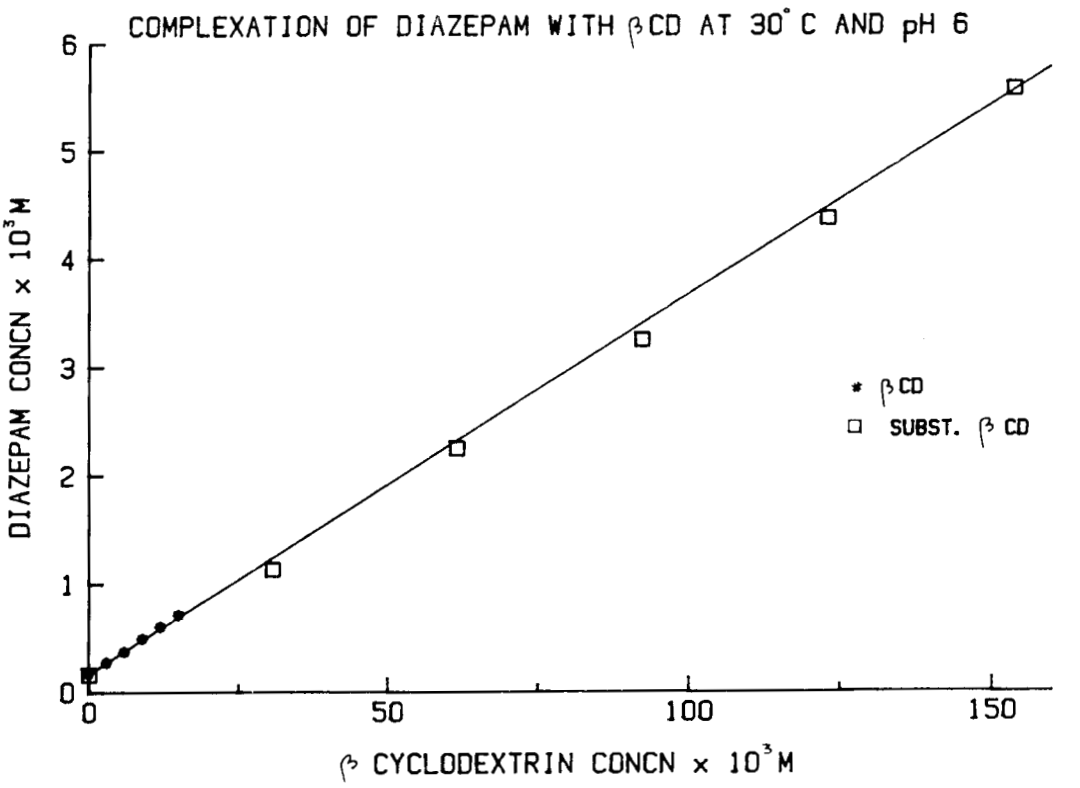

Figure II

Complexation of diazepam with β CD at 30°C and pH 6

intercept represents the concentration of the free drug, while the slope represents the solubilization power of the complexing agent. Figures 1, 2, 3 and 4 show the solubility isotherms of phenytoin, diazepam, ibuprofen and hydrochlorothiazide, respectively. Each plot shows the complexation data with both beta cyclodextrin and the hydroxyethyl derivative. The maximum concentration of beta cyclodextrin used was 15 x 10^{-3} M, except in the case of ibuprofen, where a maximum concentration of 5.0 x 10^{-3} M was

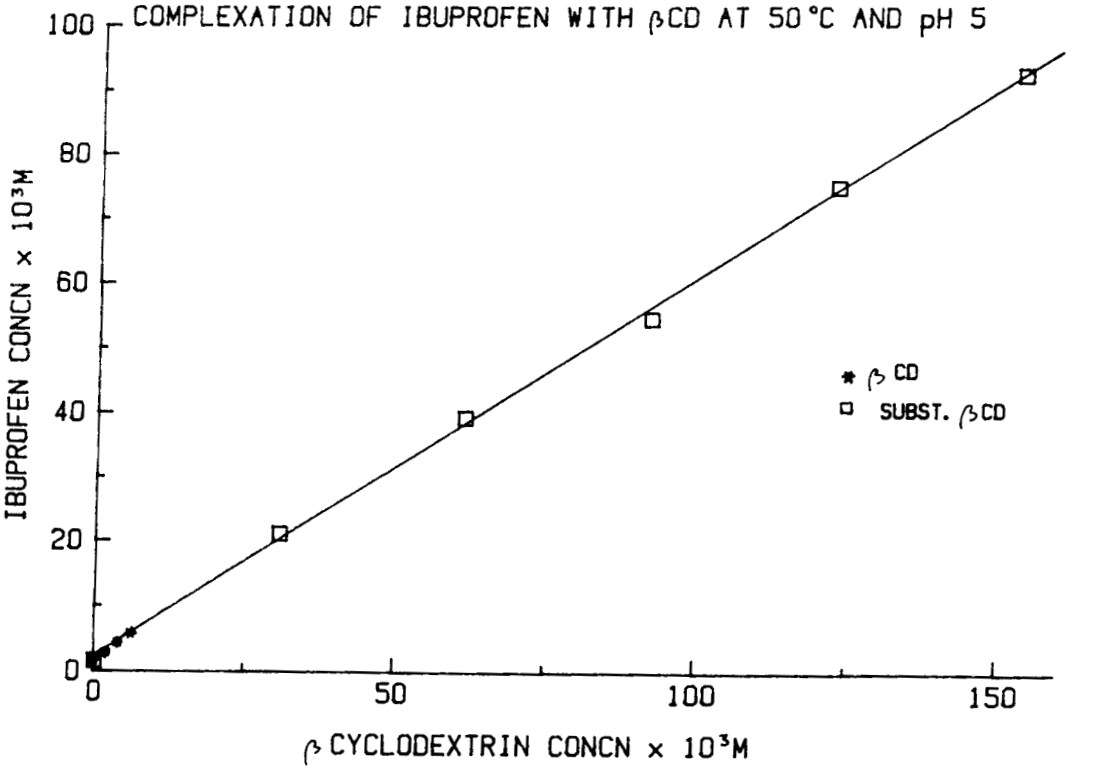

Figure III

Complexation of ibuprofen with β CD at 50°C and pH 5

used ,due to the low solubility of the ibuprofen/beta cyclodextrin complex. The concentration of hydroxyethyl derivative varied from 0 to about 150 x 10^{-3} M (20% w/w) (although, according to the supplier, solutions of up to 60% solids could actually be prepared). The molar concentration was calculated using a molecular weight of 1300, value obtained from the average value of the degree of substitution. The concentrations of both complexing agents are plotted on the X-axis using the same scale; the use of

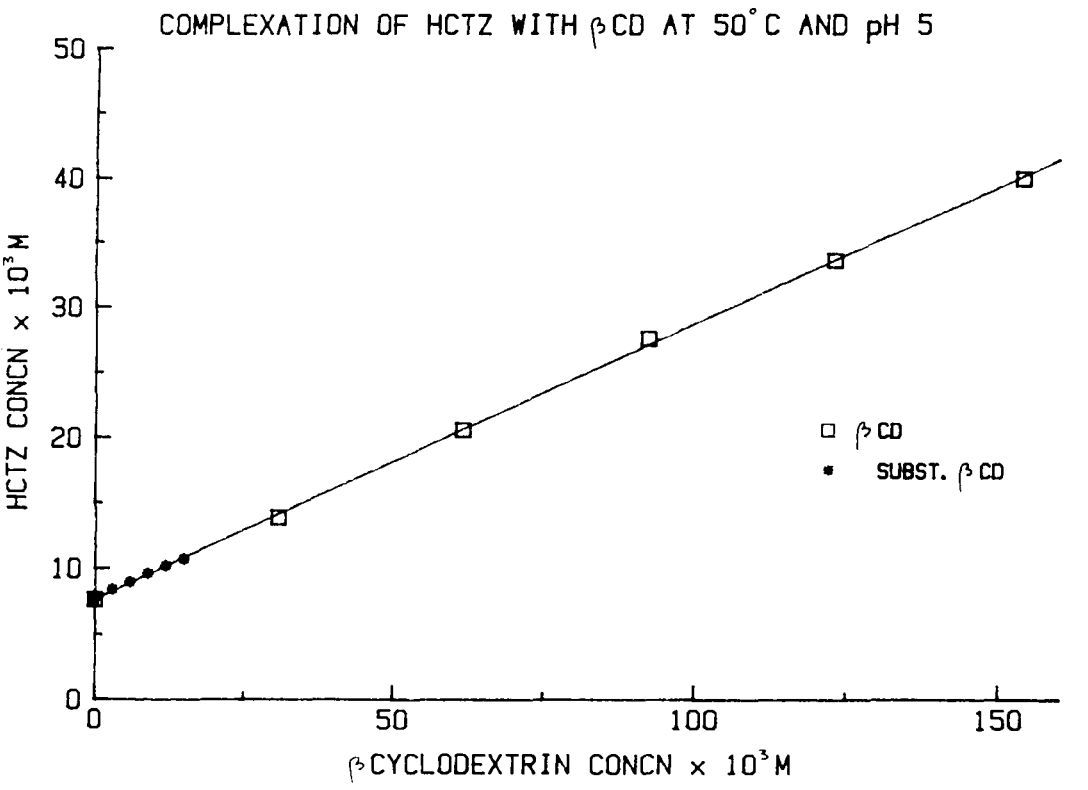

Figure IV

Complexation of HCTZ with β CD at 50°C and pH 5

the derivative thus corresponds to an extension of the X-axis.

From Figures 1 to 4, it appears that the slope of the solubility isotherms remained identical for both complexing agents. This result was confirmed statistically using a SAS program. The results thus suggest that even though the overall increase of drug solubility was much higher in the case of the derivative, the solubilizing power was

unchanged. This observation confirms the "hand and glove" theory used to describe how the steric factors control the extent of complexation. Some researchers have reported that the complexation of drugs with cyclodextrin derivatives was associated with a lower solubilizing power (14). These results were obtained in the case of hydroxypropyl beta cyclodextrin, with high degrees of substitution. The decrease of complexing ability was therefore suggested to be due to steric hindrance. In the case of hydroxyethyl beta cyclodextrin, it seems that the low degree of substitution presents the unique advantage of preserving the complexing ability of the cyclodextrin.

The reactions of complexation can be written as following:

$$\text{Drug} + \beta\ \text{CD} \rightleftharpoons \text{Drug}/\beta\ \text{CD} \quad (1)$$

$$\text{Drug} + \beta'\text{CD} \rightleftharpoons \text{Drug}/\beta'\text{CD} \quad (2)$$

The slope of the solubility isotherm corresponds to the concentration of the complexed drug over the total concentration of cyclodextrin, as shown in Figure 5. Therefore:

$$S = [\text{Drug}/\beta\ \text{CD}] / [\beta\ \text{CD}] \quad (3)$$

$$S' = [\text{Drug}/\beta'\text{CD}] / [\beta'\text{CD}] \quad (4)$$

where S and S' represent the slope for the complexation of drugs with β and β' cyclodextrins respectively.

Figure V
Complexation of drugs with both βCD and β'CD

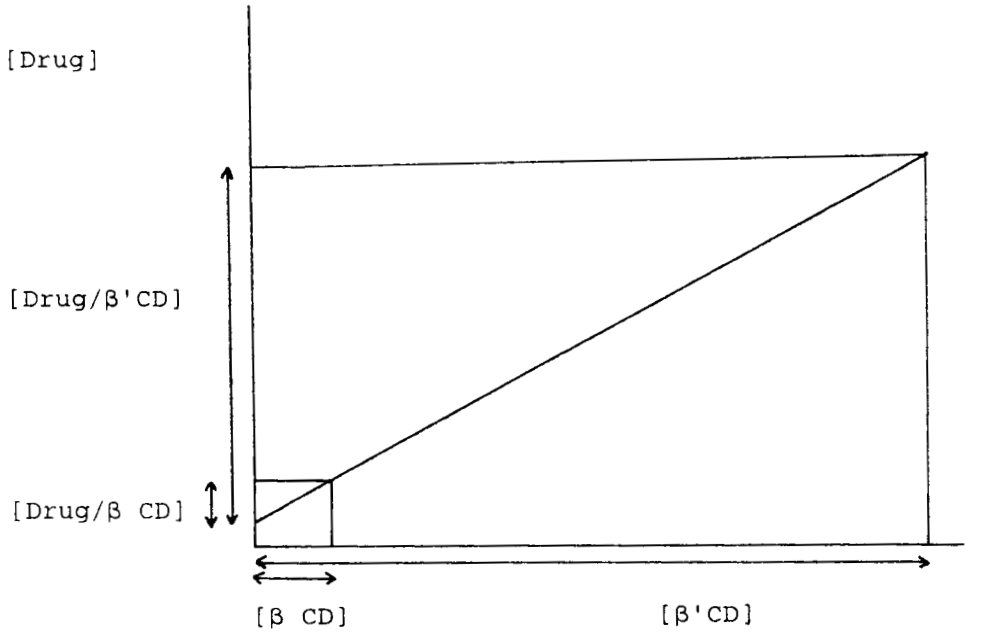

Figure V

Complexation of drugs with β and β' cyclodextrins

Assuming that the slope remains unchanged, the following equality can be written:

$$S = S' \quad (5)$$

$$[\text{Drug}/\beta\ \text{CD}] / [\beta\ \text{CD}] = [\text{Drug}/\beta'\text{CD}] / [\beta\ \text{CD}] \quad (6)$$

$$\text{and} \quad [\beta'\text{CD}] = 10 \times [\beta\ \text{CD}] \quad (7)$$

$$\text{Therefore:} \quad [\text{Drug}/\beta'\text{CD}] = 10 \times [\text{Drug}/\beta\ \text{CD}] \quad (8)$$

According to this model, the concentration of the complexed drug obtained upon complexation with the beta

cyclodextrin derivative should be about ten times that observed in the case of the natural product. Both concentrations were calculated at different temperatures and at various pH values. The ratio was then computed and the results are reported in Table 2. The ratios are in good agreement with the theory; values were in the range of 8.6 to 11.0. Two values were calculated for phenytoin and diazepam, since for these drugs both the ionized and the non-ionized species have been shown to interact with cyclodextrins. In the case of ibuprofen, the value was found to be 26.6. Once the adjustment of the concentration ratio is made, this value corresponds to 8.9. It should be mentioned that the values of concentration of complexed drug reported in Table 2 represent almost the total concentration for ibuprofen, for which the interaction is very extensive. However, in the case of hydrochlorothiazide, the value represents merely half of the concentration of the free drug, suggesting a very weak interaction.

A SASGRAPH software was used to plot the drug solubility as a function of cyclodextrin concentration and temperature. The three dimensional plots obtained are shown in Figures 6, 7, 8 and 9, for phenytoin, diazepam, ibuprofen and hydrochlorothiazide respectively. The overall volume of these plots allows a good visualization of the extent of complexation.

The practical implications of the results of this study can be discussed at two levels. Firstly, it appears that it may be possible to predict the solubility of drug upon

TABLE II

Concentrations of drug complexed with β and β' cyclodextrins at 50°C

DRUG	pH	[DRUG]f (mM)	[Drug/βCD] (mM)	[Drug/β'CD] (mM)	Ratio*
Phenytoin	5.0	0.26	1.28	12.69	9.9
	8.0	0.68	1.62	13.98	8.6
Diazepam	3.0	0.80	1.12	12.32	11.0
	6.0	0.29	0.71	7.82	11.0
Hydrochlo-thiazide	5.0	7.65	3.05	32.30	10.6
Ibuprofen	5.0	0.16	0.34	9.08	8.9**

* Ratio = [Drug/β'CD] / [Drug/βCD]

** The value of 8.9 was obtained by dividing 26.6 by 3 The maximum concentration of β CD was 5.0×10^{-3} M in the case of ibuprofen and 15.0×10^{-3} M for the other drugs

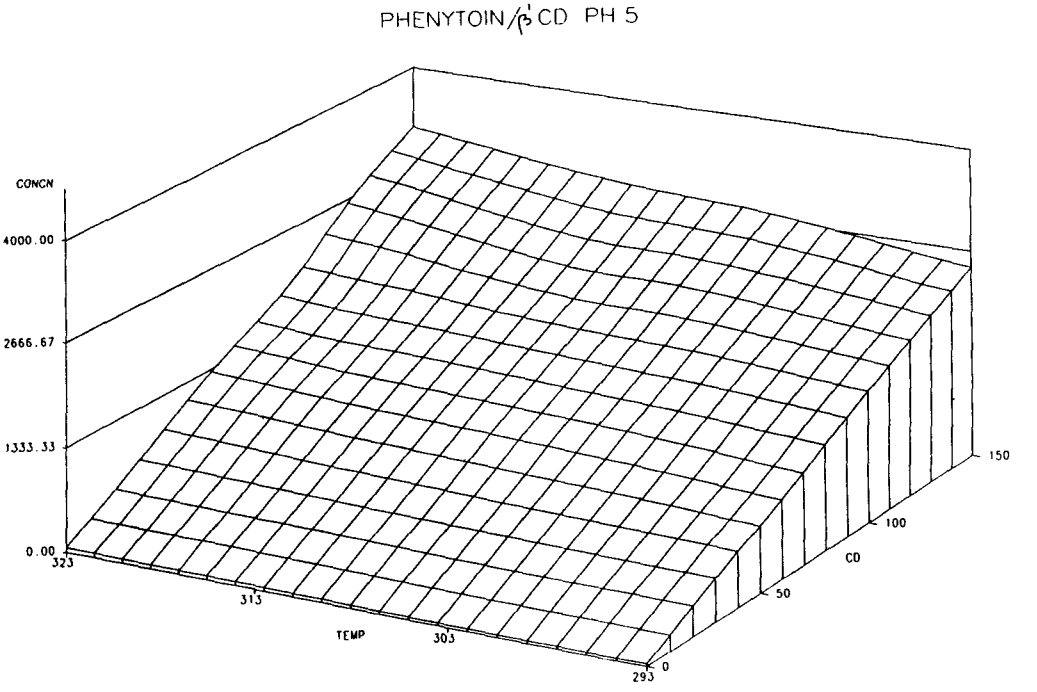

Figure VI

Solubility of phenytoin as a function of temperature and β' CD concentration at pH 5

complexation with hydroxyethyl beta cyclodextrin, based on the data obtained with the natural form. Beta cyclodextrin, which is a much more readily available material, could be used as a model to evaluate whether a drug concentration in the range desired could be achieved through beta cyclodextrin derivative complexation. The empirical rule suggested here corresponds to the multiplication of the solubility observed with beta cyclodextrin by the ratio factor between the solubility of beta cyclodextrin and its

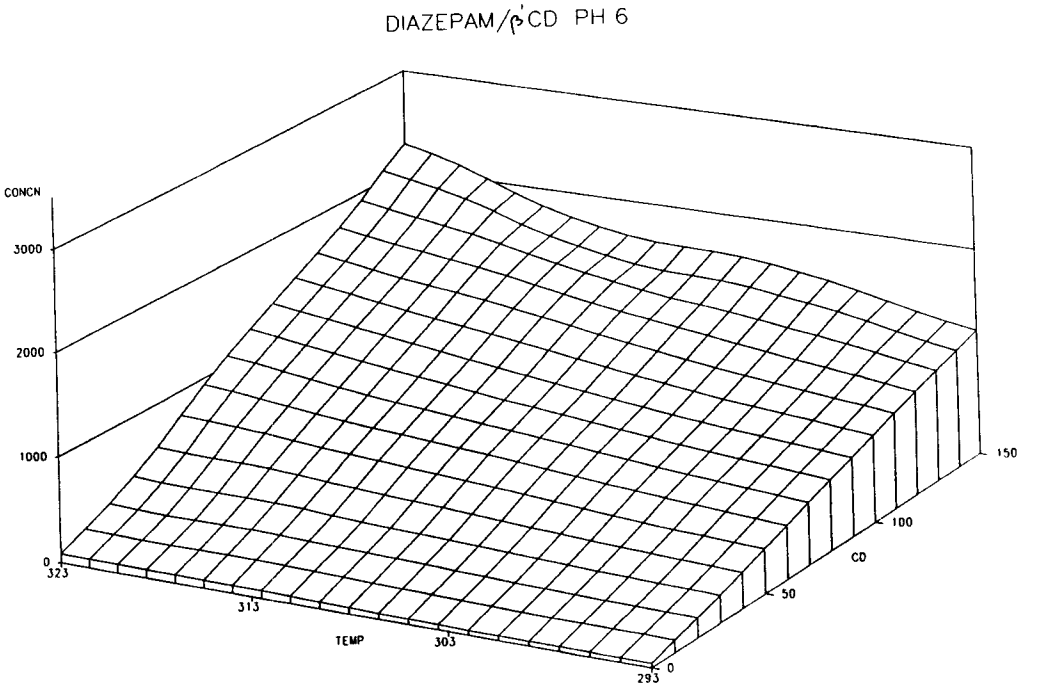

Figure VII

Solubility of diazepam as a function of temperature and β' CD concentration at pH 6

derivative. This rule has been shown here to stand very well in the case of four drugs, at different pH values and different temperatures.

The second point of interest resides in examining the range of solubility obtained after complexation. The complexation of drugs with cyclodextrins can be particularly appropriate either to improve the physico-chemical properties or the organoleptic properties of drugs. Clearly, the concentrations of ibuprofen attained in this

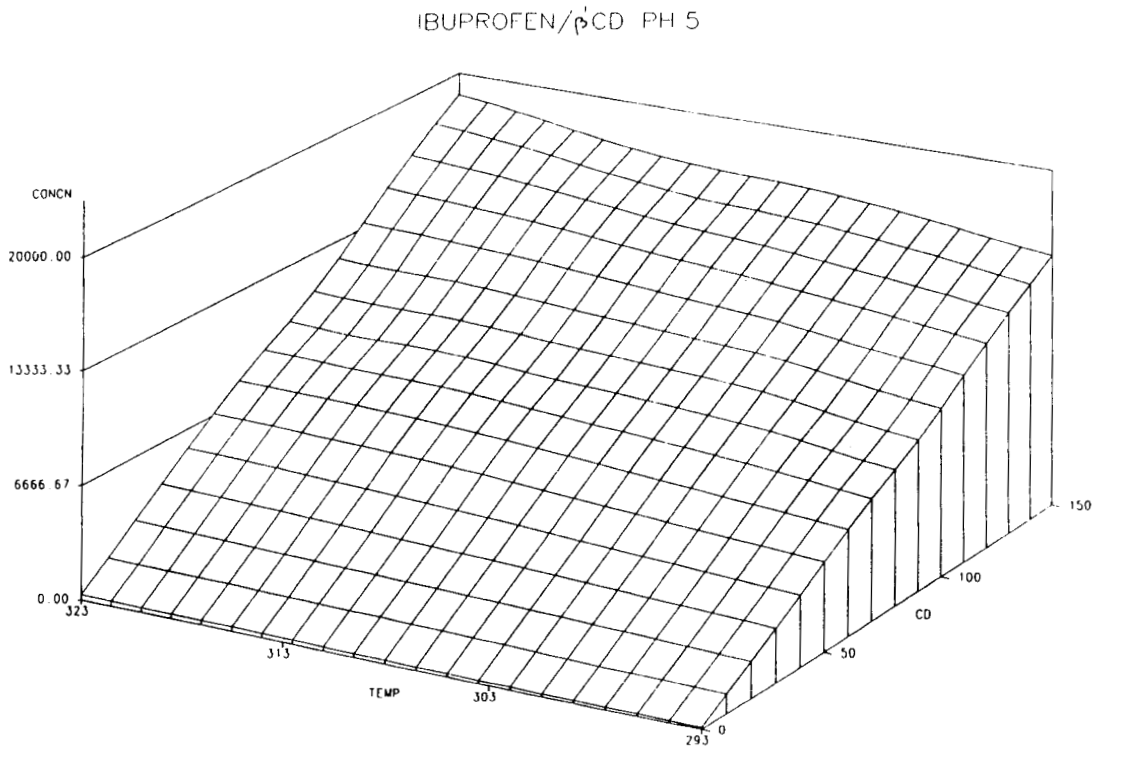

Figure VIII

Solubility of ibuprofen as a function of temperature and β' CD concentration at pH 5

study are very high and would even make possible a liquid dosage form of the drug. However, ibuprofen has a bitter taste, that even a 60 to 70% complexation level may not totally mask. In the case of the other drugs, phenytoin is complexed at about 10% and diazepam around 20%. This percentage would be a critical factor in the development of any dosage form of a drug/cyclodextrin complex. Obviously, on a development point of view, the closer to a 100% complexation, the better. The results of the study indicate

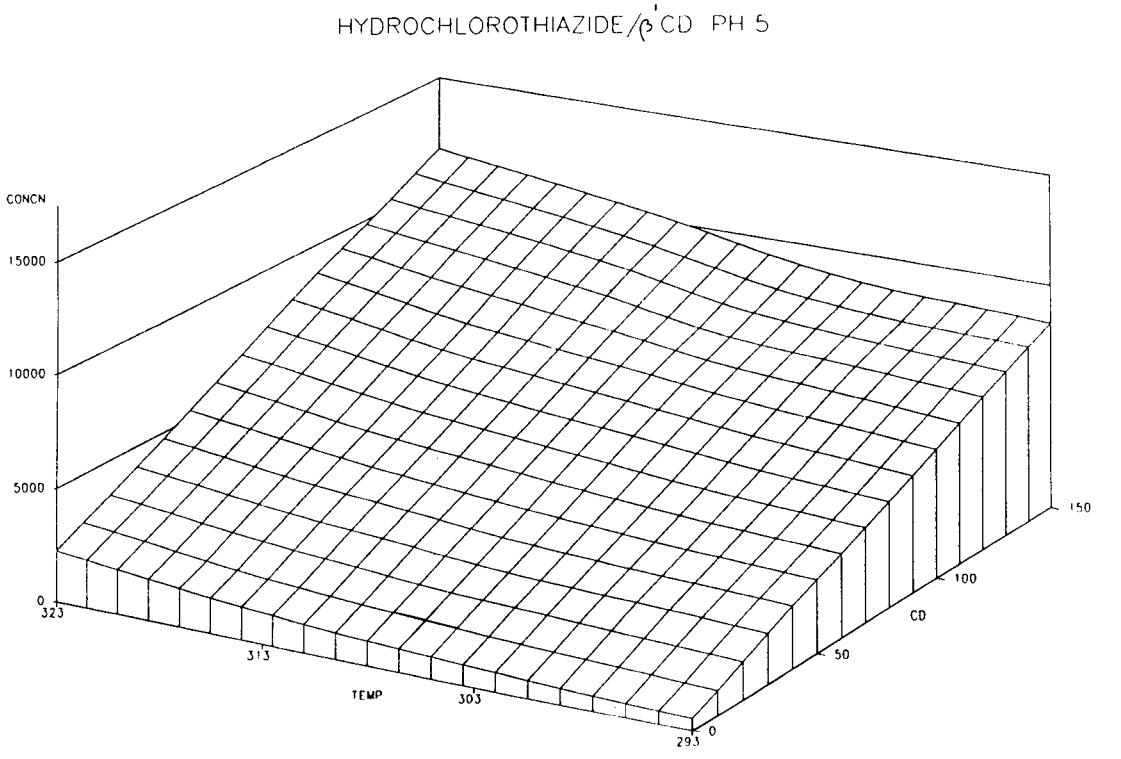

Figure IX

Solubility of hydrochlorothiazide as a function of temperature and β' CD concentration at pH 5

that the use of hydroxyethyl beta cyclodextrin may offer clear advantage to the pharmaceutical formulator.

CONCLUSIONS

The complexation ability of β'cyclodextrin has been shown to be similar to that of the natural β cyclodextrin. The slope of the solubility isotherms was indeed identical for the four drugs studied. It thus appears that the substituents do not affect the basic mechanism of

complexation. The particular advantages of β' cyclodextrin are its high solubility and its low degree of substitution. The range of drug concentrations achieved in the study suggests real new possibilities of formulation. A liquid dosage form of ibuprofen with high bioavailability could very well be developed. One of the major concerns in the pharmaceutical industry has been the toxicity of the cyclodextrin derivatives, in particular unacceptable hemolytic properties. However, it has also been shown that the lower the degree of substitution, the lower the hemolytic properties. From the preformulation data presented here in the study, hydroxylethyl β cyclodextrin seems to be an excellent candidate for future drug/cyclodextrin complex formulation.

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