ELSEVIER

International Journal of Pharmaceutics 195 (2000) 71–79

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Interaction of *p*-hydroxybenzoic esters with beta-cyclodextrin

L.W. Chan *, T.R.R. Kurup, A. Muthaiah, J.C. Thenmozhiyal

Department of Pharmacy, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260, Singapore

Received 22 July 1999; received in revised form 15 October 1999; accepted 15 October 1999

Abstract

In the present investigation, the complex formation of beta-cyclodextrin (βCD) with *p*-hydroxybenzoic esters (parabens) was studied by mixing βCD with methyl, ethyl, propyl and butyl parabens, respectively, in aqueous solutions and subjecting the resultant mixtures individually to the following processes: occasional shaking for 24 h at 25°C, continuous shaking using shaker bath for 24 h at 25°C, intermittent ultrasonification for 90 min at 25°C, autoclaving at 115°C for 30 min and freeze-drying followed by reconstitution with distilled water. The degrees of interaction between βCD and the parabens subjected to the various processes were evaluated, using the membrane dialysis method. The difference in the method of processing did not affect the degree of interaction significantly. However, the degree of interaction was found to increase proportionally with the concentration of βCD. The alkyl group of the parabens was also found to affect the extent of interaction. Compared to methyl paraben, the degree of interaction of ethyl paraben was observed to be lower. Interestingly, further increase in the size of the alkyl group significantly enhanced the extent of interaction. Studies using ^{1}H-NMR showed that the extent of interaction depended on how well the parabens could fit into the βCD cavity.

Keywords: Beta-cyclodextrin; Parabens; Interaction

1. Introduction

Beta-cyclodextrin (βCD) is a cyclic oligosaccharide made up of seven alpha-1,4-linked D glucose units. An important feature of cyclodextrin concerns the distribution of hydrophilicity around the wider rim and hydrophobicity in the cavity, thereby facilitating the inclusion of non-polar molecule into the hydrophobic cavity (Szejtli, 1988).

The extensive application of cyclodextrins in various fields is attributed to the ability of cyclodextrins to form complexes with many types of compounds. In pharmaceutical products, cyclodextrins act as drug carriers (Szejtli, 1983), improve dissolution (Montassier et al., 1997; Veiga et al., 1998), and enhance absorption of drugs (Iwaoku et al., 1982). It is believed that the same complexation effect exists with preservatives, which are present in pharmaceutical products (Loftsson et al., 1992). The complexation between preservatives and other pharmaceutical

* Corresponding author.

0378-5173/00/$ - see front matter
PII: S0378-5173(99)00393-2

ingredients has been reported to affect the antimicrobial activity of the preservatives (Kurup et al., 1992, 1995). Hence, the aim of this study was to investigate the interaction of βCD with various preservatives and the effect of various processing methods on the extent of the interaction.

Parabens are often employed as preservatives in pharmaceutical products. Occasional manual shaking, agitation in shaker bath, ultrasonification, autoclaving and freeze-drying are common processing methods in use. These preservatives and processing methods were therefore chosen for investigation in this study.

2. Materials and experimental methods

2.1. Materials

The preservatives used were methyl paraben, ethyl paraben, propyl paraben and butyl paraben. Dimethyl-d_6 sulfoxide (DMSO.d_6) was used as the solvent while tetramethylsilane (TMS) as the internal reference in the ^{1}H-NMR studies. All these materials and βCD were procured from Sigma, USA. The semipermeable cellulose acetate membrane (SPECTRA/POR® No. 6) was supplied by Spectrum Medical Industries, USA.

Table 1
R-values of different parabens subjected to various processes

Preservatives	*R*-values at 0.25% w/v βCD					Analysis of variance		
	OS	SB	UB	AC	FD	*F*-value	*F* critical	*P*-value
Methyl paraben	1.65 ± 0.10	1.60 ± 0.12	1.64 ± 0.09	1.79 ± 0.09	1.74 ± 0.06	2.20	3.48	0.10
Ethyl paraben	1.84 ± 0.34	1.98 ± 0.30	1.89 ± 0.08	2.24 ± 0.55	2.14 ± 0.18	1.04	3.06	0.42
Propyl paraben	2.04 ± 0.17	2.08 ± 0.10	1.95 ± 0.12	1.99 ± 0.15	2.07 ± 0.37	0.29	3.06	0.88
Butyl paraben	1.86 ± 0.05	2.56 ± 0.77	1.89 ± 0.59	1.91 ± 0.67	2.09 ± 0.36	0.84	3.48	0.53
	R-values at 0.50%w/v βCD							
	OS	SB	UB	AC	FD			
Methyl paraben	2.32 ± 0.06	2.04 ± 0.33	2.18 ± 0.55	2.16 ± 0.24	2.31 ± 0.10	0.42	3.48	0.79
Ethyl paraben	2.75 ± 0.22	2.63 ± 0.41	3.29 ± 0.20	2.68 ± 0.54	3.32 ± 0.62	2.50	3.06	0.09
Propyl paraben	3.13 ± 0.08	3.37 ± 0.62	3.08 ± 0.47	2.68 ± 0.21	3.36 ± 0.28	2.16	3.06	0.12
Butyl paraben	3.88 ± 0.57	3.91 ± 0.90	4.34 ± 0.28	4.19 ± 0.40	5.11 ± 0.65	2.09	3.48	0.16
	R-values at 0.75%w/v βCD							
	OS	SB	UB	AC	FD			
Methyl paraben	3.71 ± 0.17	3.45 ± 0.31	3.92 ± 0.26	3.68 ± 0.22	3.53 ± 0.34	1.40	3.48	0.30
Ethyl paraben	3.07 ± 1.06	5.51 ± 2.53	3.66 ± 0.10	5.08 ± 0.77	4.44 ± 0.33	2.42	3.06	0.09
Propyl paraben	4.13 ± 0.24	3.77 ± 0.57	4.64 ± 0.94	4.26 ± 0.43	3.83 ± 0.30	1.61	3.06	0.22
Butyl paraben	6.49 ± 0.46	6.55 ± 0.94	7.33 ± 0.32	7.20 ± 0.87	7.55 ± 0.60	1.48	3.48	0.28
	R-values at 1.00%w/v βCD							
	OS	SB	UB	AC	FD			
Methyl paraben	7.23 ± 0.71	6.27 ± 0.75	7.27 ± 0.41	6.63 ± 0.42	6.68 ± 0.65	1.50	3.48	0.30
Ethyl paraben	4.51 ± 0.26	5.65 ± 1.09	4.75 ± 0.54	5.30 ± 0.32	4.69 ± 0.25	2.67	3.06	0.07
Propyl paraben	7.03 ± 1.29	5.17 ± 1.19	5.34 ± 0.96	5.05 ± 0.50	5.78 ± 0.33	3.00	3.06	0.05
Butyl paraben	10.92 ± 1.17	12.24 ± 1.44	10.50 ± 0.61	12.24 ± 1.44	12.24 ± 1.44	1.20	3.48	0.37

Table 2
Average *R*-values of the preservatives

Preservatives	*R*-values at different concentrations (%w/v) of βCD				*S*-values
	0.25%	0.50%	0.75%	1.00%	
Methyl paraben	1.68 ± 0.08	2.20 ± 0.12	3.66 ± 0.18	6.82 ± 0.43	6.75
Ethyl paraben	2.02 ± 0.17	2.93 ± 0.34	4.35 ± 1.00	4.98 ± 0.48	4.12
Propyl paraben	2.03 ± 0.06	3.12 ± 0.28	4.13 ± 0.35	5.67 ± 0.81	4.77
Butyl paraben	2.06 ± 0.29	4.29 ± 0.50	7.02 ± 0.48	11.63 ± 0.85	12.58

2.2. Experimental methods

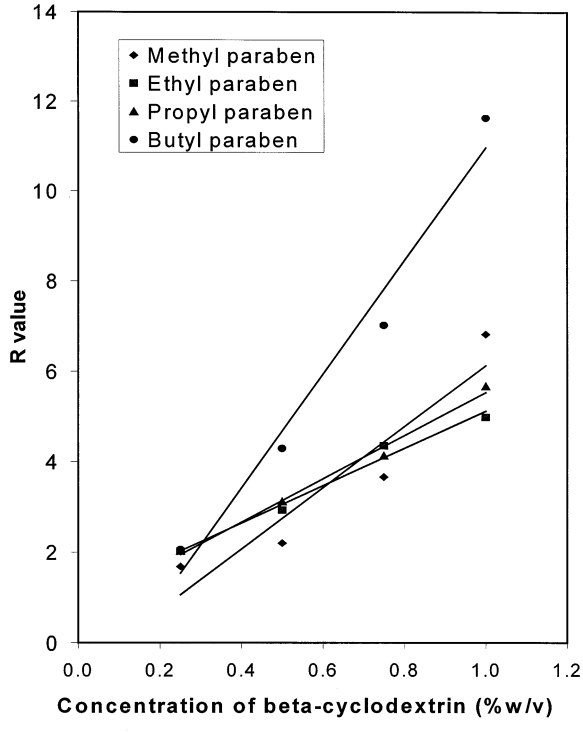
2.2.1. Preparation of test mixtures

The mixtures, consisting of 0.25, 0.50, 0.75 and 1.00% w/v βCD were prepared by dissolving the required amounts of βCD in the preservative solutions of methyl paraben (0.05% w/v), ethyl paraben (0.05% w/v), propyl paraben (0.01% w/v) and butyl paraben (0.01% w/v), respectively. The mixtures were then subjected to the following processes individually:

- Occasional shaking (once in 30 min) for 24 h at 25°C (OS).
- Continuous shaking using shaker bath for 24 h at 25°C (SB).
- Intermittent ultrasonification for 90 min at 25°C (UB).
- Autoclaving at 115°C for 30 min (AC).
- Freeze-drying followed by reconstitution with distilled water just before evaluation (FD).

2.2.2. Interaction of preservatives with βCD

The degree of interaction between βCD and the preservative was determined by the membrane dialysis method (Patel and Kostenbauder, 1958). The method essentially consisted of fixing a semipermeable cellulose acetate membrane between the two arms of a dialysis cell (Bellco Glass, USA). The two arms were held together by fastening plates to ensure that no leakage of the content through the interface of the arms occurred. Then 10 ml of test mixture was put in one arm and an equal volume of distilled water in the other arm. The two arms were capped to prevent evaporation of the contents. The whole system was equilibrated for 5 days at 25°C and the contents in the distilled water arm were assayed for the preservative spectrophotometrically (Shimadzu UV-1201, Japan), at 257 nm for methyl paraben and 256 nm for ethyl, propyl and butyl parabens, using distilled water as the reference. The *R*-value, which is the ratio of total preservative to free preservative in the test mixture arm, was calculated using the equation:



Methyl paraben : y = 6.75x – 0.63 (r^2 0.889)

Ethyl paraben : y = 4.12x + 1.00 (r^2 0.981)

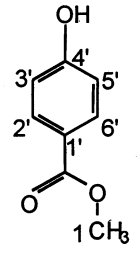
Propyl paraben : y = 4.77x + 0.76 (r^2 0.990)

Butyl paraben : y = 12.58x – 1.61 (r^2 0.970)

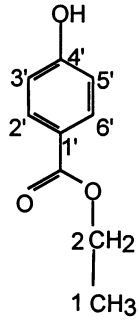
Fig. 1. Interaction of βCD with parabens.

Table 3
^{1}H-NMR chemical shifts (ppm) of alkyl parabens with ($\delta_{complex}$) and without (δ_{free}) beta-cyclodextrin

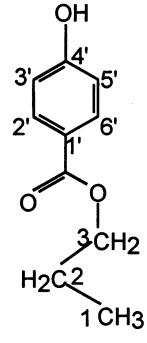
Parabens	Protons	Free (δ_{free})	Complex ($\delta_{complex}$)	$\Delta\delta$ ($\delta_{complex}-\delta_{free}$)	Effect
Methyl paraben	H1	3.79	3.78	−0.01	Shielded
	H6′, H2′	6.85	6.84	−0.01	Shielded
	H5′, H3′	7.81	7.81	0	–
	OH	10.33	10.33	0	–
Ethyl paraben	H1	1.29	1.29	0	–
	H2	4.25	4.25	0	–
	H6′, H2′	6.85	6.84	−0.01	Shielded
	H5′, H3′	7.81	7.80	−0.01	Shielded
	OH	10.38	10.31	−0.07	Shielded
Propyl paraben	H1	0.95	0.96	0.01	Deshielded
	H2	1.69	1.69	0	–
	H3	4.16	4.16	0	–
	H6′, H2′	6.85	6.84	−0.01	Shielded
	H5′, H3′	7.82	7.81	−0.01	Shielded
	OH	10.31	10.30	−0.01	Shielded
Butyl paraben	H1	0.93	0.93	0	–
	H2	1.42	1.43	0.01	Deshielded
	H3	1.66	1.66	0	–
	H4	4.20	4.21	0.01	Deshielded
	H6′, H2′	6.85	6.84	−0.01	Shielded
	H5′, H3′	7.81	7.80	−0.01	Shielded
	OH	10.31	10.33	0.02	Deshielded



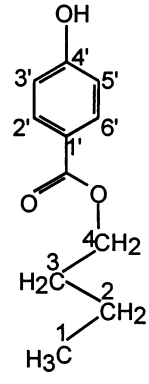
Methyl paraben



Ethyl paraben



Propyl paraben



Butyl paraben

$$R = \frac{P_T - P_F}{P_F}$$

where P_T is the total concentration of preservative and P_F is the concentration of preservative in the distilled water arm of the dialysis cell. The determination was carried out in triplicate and the mean R-value obtained. The same procedure was employed for all the test mixtures.

2.2.3. ^{1}H-NMR studies of complex formation between βCD and preservatives

The complex formation between βCD and the preservatives was investigated by ^{1}H-NMR. A

total of 6.5 mg of paraben and 13.5 mg of βCD were dissolved in DMSO.d_6. The ^{1}H-NMR spectra were recorded at 25°C on a Bruker Ultrashield-dpx 300 spectrophotometer operating at 300 MHz with a sweep width of 6172.84 Hz. ^{1}H-NMR chemical shifts were measured using TMS as the internal reference.

2.2.4. Molecular modeling of complexes formed between βCD and preservatives

The hypothetical structures of the complexes were determined using the molecular modeling package SYBYL Ver. 6.3 (SYBYL (a)) (Tripos, 1994). A docking procedure was performed, employing the DOCK command of SYBYL (SYBYL (b)) and the Tripos 5.2 force field. The paraben was introduced into the βCD cavity and the interaction energy (steric energy) computed. The most likely structure of the complex was the one with minimum interaction energy.

3. Results and discussion

The extent of interaction between βCD and each paraben was expressed by the *R*-value, which is the ratio of total preservative to free preservative. The total preservative consisted of the free preservative as well as the preservative bound to βCD. Hence, an *R*-value greater than unity indicates interaction. A greater extent of interaction will result in a smaller amount of free preservative and consequently a greater *R*-value. The *R*-values of the preservatives subjected to the various processes are given in Table 1.

Table 4
Steric energy of the preservative in complex state

Preservatives	Steric energy (kcal/mol) when entrapped	
	Alkyl chain	Phenyl ring
Methyl paraben	−12.00	−10.56
Ethyl paraben	−13.81	−8.54
Propyl paraben	−16.94	−8.77
Butyl paraben	−18.90	−13.66

The processing methods employed in this study represented significantly different conditions. Ultrasonification provided markedly rapid vibration of the test mixture compared to occasional shaking and agitation in the shaker bath. In autoclaving, the test mixture was subjected to a high temperature of 115°C while in freeze-drying, it was exposed to sub-zero temperature and low pressure. The results seemed to suggest that the extent of interaction was dependent on the processing method (Table 1). The effect of the processing methods appeared to be relatively complex as the same method could result in interaction of different ranking orders when the concentration of βCD was varied. For example, the greatest extent of interaction between methyl paraben and 0.25% βCD was produced by autoclaving. However, intermittent ultrasonification produced the greatest extent of interaction when the concentration of βCD was increased to 1.00%. The complex effect of the processing method was also observed when different types of preservatives were employed. For example, at 0.75% w/v βCD, ultrasonification produced the greatest extent of interaction for methyl paraben while continuous shaking in shaker bath produced the maximum effect for ethyl paraben.

However, ANOVA single factor analysis of the results showed that the different processing methods had insignificant effects on the degree of interaction between βCD and the preservatives. Although the processing methods were significantly different in conditions, the present finding based on *R*-values showed that the degree of interaction between βCD and the parabens was likely to be instantaneous.

The average *R*-value for each preservative subjected to the different processing conditions was calculated to determine the effect of varying concentrations of βCD on the extent of interaction with the respective preservatives (Table 2). All the *R*-values obtained were greater than unity, indicating complex formation between βCD and the preservatives. For methyl paraben, the *R*-values obtained were 1.68, 2.20, 3.66 and 6.82 for 0.25, 0.50, 0.75 and 1.00% w/v βCD, respectively. It is clearly seen that the degree of interaction increased with the concentration of βCD. The same

trend was observed for ethyl paraben, propyl paraben and butyl paraben. Linear regression analysis of the results showed that the R-values varied with the concentration of βCD according to the following relationship:

$$R = SC + K$$

where S is the slope of the graph and K is the Y-intercept (Fig. 1). The S-value is a constant, which represents the effect of changing βCD concentration on the degree of interaction with the preservatives, with a high S-value indicating a greater effect. The S-values of the preservatives are given in Table 2.

For each concentration of βCD, the R-values were also found to vary with the type of preservative. At 0.25, 0.50 and 0.75% w/v of βCD, the R-values generally increased in the following order: methyl paraben < ethyl paraben < propyl paraben < butyl paraben. However, at 1.00% w/v of βCD, the trend was different and more complex as the R-values were 6.82 for methyl paraben, 4.98 for ethyl paraben, 5.67 for propyl paraben and 11.63 for butyl paraben. Similarly, the S-values were observed to vary for the different parabens. These findings clearly showed that the extent of interaction was affected by the types of preservatives. Other workers had reported the effects of the electronic nature and the position of certain functional groups on the interaction between compounds (Blaug and Ahsan, 1961; Patel and Foss, 1965). Since the difference between the preservatives used in this study lies in the alkyl group, it was postulated that the size, shape and

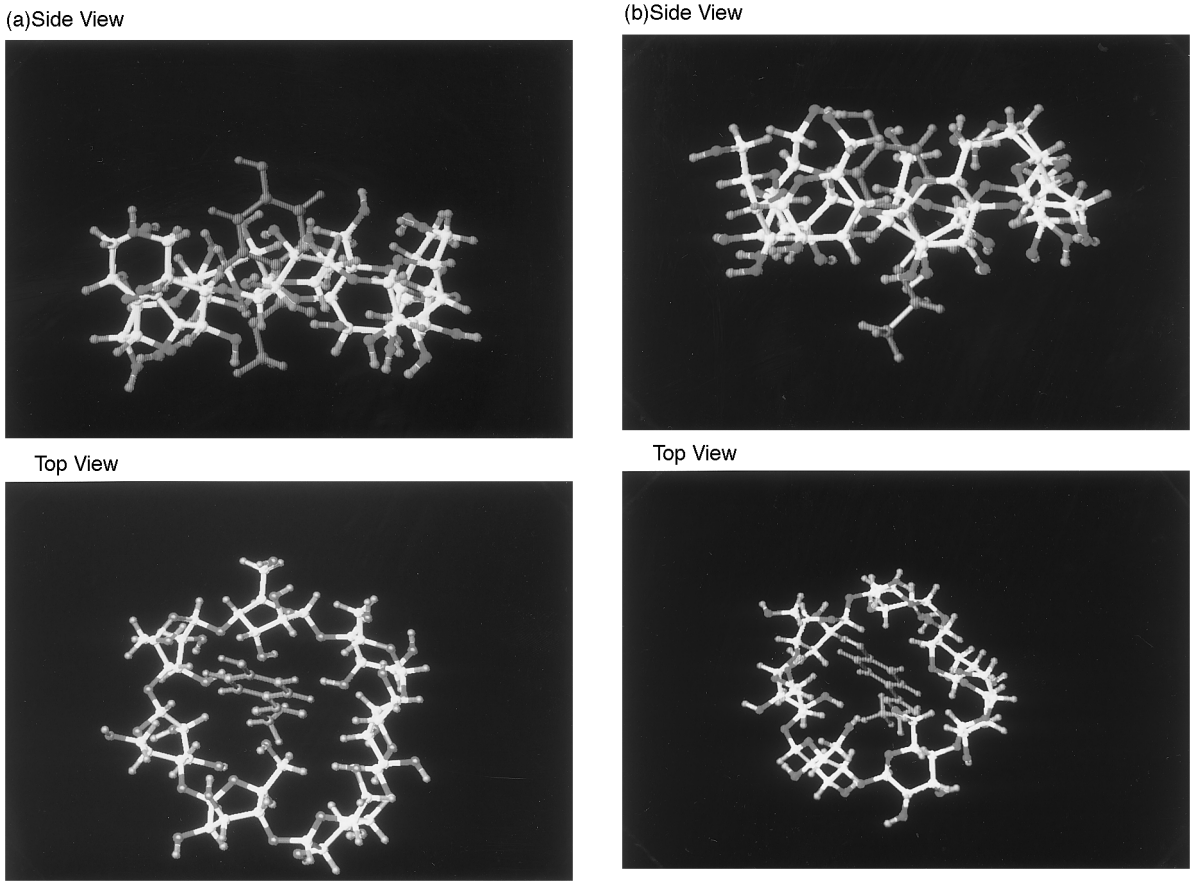


Fig. 2. Hypothetical structures of paraben-βCD complexes. (a) Methyl paraben-βCD complex (b) Ethyl paraben-βCD complex (c) Propyl paraben-βCD complex (d) Butyl paraben-βCD complex.

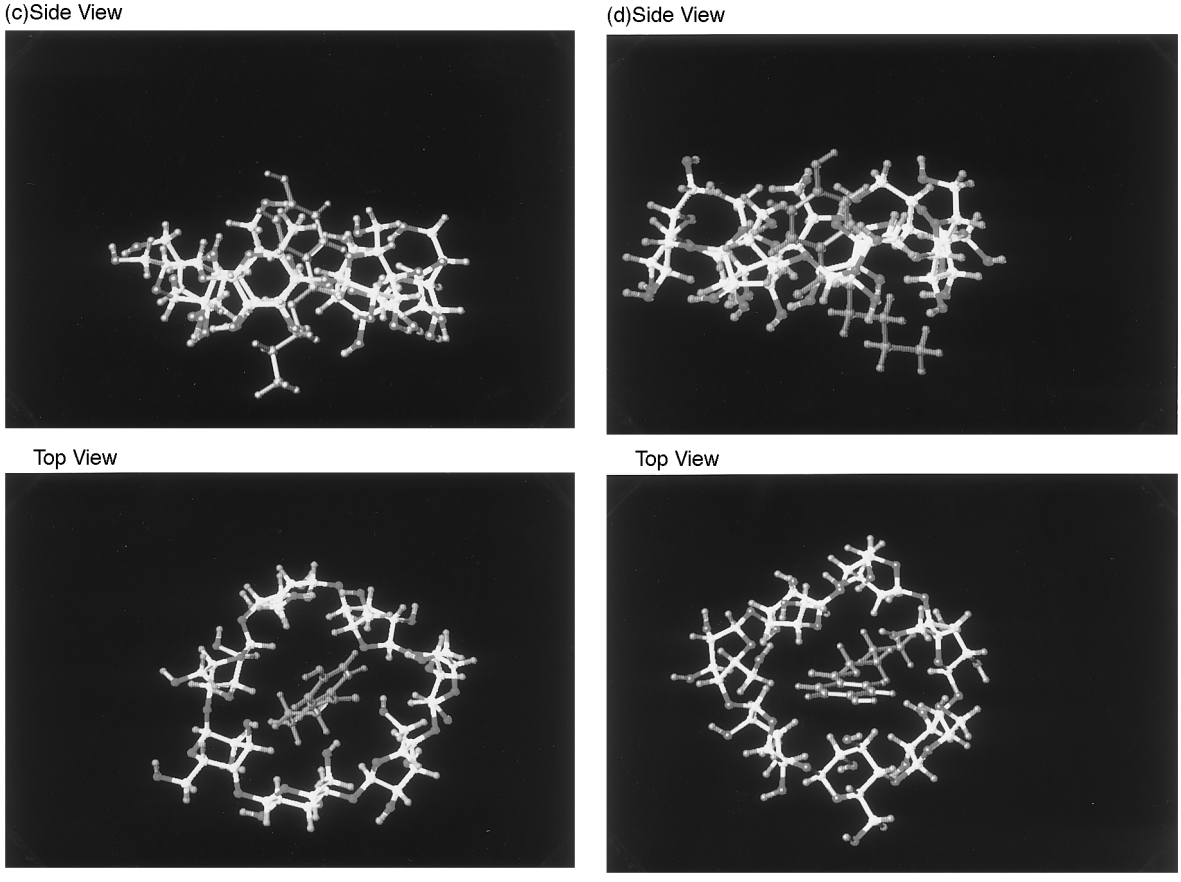


Fig. 2. (*Continued*)

degree of hydrophobicity of the alkyl group could affect the extent of interaction.

Further studies were carried out to determine the factors contributing to the interaction between βCD and the preservatives. It had been reported that the interaction between βCD and other compounds occurred via the formation of inclusion complexes (Karl-Heinz and Szejtli, 1994; Szejtli, 1988). It was postulated that the hydrophobic part of the paraben molecule entered the hydrophobic cavity of βCD, with the phenol moiety of the preservative located at the wider region of the cavity which consisted of secondary hydroxyl groups (Matsuda et al., 1993). As the length of the alkyl chain was increased in the preservatives, the extent of interaction was found to be considerably affected (Table 2). The relatively high *S*-value of methyl paraben (6.75) showed that the methyl group could accommodate quite well into the hydrophobic cavity of βCD. Interestingly, the ethyl group was found to decrease the *S*-value while further increase in the size of the alkyl group produced the opposite effect. It is known that the cavity of cyclodextrin is hydrophobic in nature and hence the results obtained could be attributed to the increase in the hydrophobicity of the larger alkyl groups, leading to greater interaction with βCD. If that is the reason there should be a uniform increase in the extent of interaction as the length of the alkyl chain increased. However, the results obtained did not show such a trend, implying that some other factor was also playing a significant role. It appeared that the orientation of the preservatives would also con-

tribute to the extent of interaction with βCD. It was probable that the increase of steric strain due to the longer chain length of propyl and butyl parabens was overcome by the convenient twist in the chain conformation, which favored easy and compact accommodation of the preservative molecules in the hydrophobic cavity of βCD.

^{1}H-NMR spectral studies carried out for βCD and the preservatives, supported the above postulation (Table 3). During complexation, the chemical and electronic environments of protons are affected, causing them to get shielded or deshielded. This is reflected by changes in the chemical shifts (δ), which is a measure of change in the chemical and electronic environment of the respective protons. It is well-established that those protons which are inside the hydrophobic cavity of cyclodextrins experience a shielding effect and this is represented by a decrease in the δ causing negative $\Delta\delta$ value. Conversely, those protons that are outside the cavity experience a deshielding effect with positive $\Delta\delta$ value.

In the presence of βCD, the H1, H6′and H2′ protons of methyl paraben shifted upfield ($\Delta\delta = -0.01$) while the OH proton did not exhibit any change in chemical shift. This indicates the possibility of the molecule being inserted into the hydrophobic cavity, with the hydroxyl group located around the wider end of the cavity. In the case of ethyl paraben, the H1 and H2 protons belonging to the alkyl chain showed no changes in chemical shift suggesting that the ethyl group was not in the cavity. On the other hand, the H2′, H6′, H3′, H5′ and OH protons shifted to the upfield region indicating that these parts of the molecule were found in the cavity. In the case of propyl paraben, the H1 proton showed a downfield shift ($\Delta\delta = +0.01$) while the H2 and H3 protons were unaffected showing a change in the orientation of the propyl group in the presence of βCD. The phenyl and the hydroxyl group were found in the cavity, as shown by the upfield shift ($\Delta\delta = -0.01$) of the H2′, H6′, H5′, H3′ and OH protons. Interesting observations were made in the case of butyl paraben. The H2 and H4 protons of the butyl group experienced a downfield shift ($\Delta\delta = +0.01$) whereas the H1 and H3 protons were unaffected. Unlike the rest, butyl paraben has OH proton showing downfield shift ($\Delta\delta = +0.02$), probably due to the presence of the more bulky butyl group. However, the aromatic protons were shifted upfield ($\Delta\delta = -0.01$) as in the other parabens. The results of ^{1}H-NMR spectral studies showed that the phenyl ring was inserted into the hydrophobic cavity and the propyl and butyl chains were allowed to orientate themselves to assume a low energy conformation.

The hypothetical structures of the complexes were subsequently determined by using the molecular modeling package SYBYL (Ver. 6.3) (Table 4). When the alkyl chain was introduced into the cavity, the steric energy obtained was in the following order: methyl paraben (12.00) > ethyl paraben (−13.81) > propyl paraben (−16.94) > butyl paraben (−18.90). A reduction in the steric energy with increasing size of the alkyl chain was observed, suggesting greater interaction between βCD and parabens with larger alkyl groups. However, the latter was not always true based on earlier interaction studies. When the phenyl ring of the paraben was introduced into the cavity, ethyl paraben (−8.54) and propyl paraben (−8.77) showed higher steric energy compared to methyl and butyl parabens. This observation agreed with the *S*-values (Table 2) obtained for the various parabens. This supported the findings of the ^{1}H-NMR spectral studies, which showed that the phenyl ring of the paraben was found in the cavity of βCD. The most likely structures of the complexes are given in Fig. 2.

4. Conclusion

Subjecting the mixture of βCD and parabens to various processes had no significant effect on the extent of their interaction. Higher concentrations of βCD enhanced its interaction with the preservative. Increase in alkyl chain length also affected the degree of interaction. Ethyl, propyl and butyl parabens showed a regular trend of increase in the extent of interaction, which was attributed to the decrease in steric strain by appropriate orientation of the alkyl chain. Methyl paraben showed a higher extent of interaction than ethyl and propyl parabens. This is due to the small size of the

methyl paraben molecule that can fit well into the cavity of βCD. The extent of interaction was influenced by the hydrophobicity and steric energy of the parabens.

References

Blaug, S.M., Ahsan, S., 1961. Interaction of sorbic acid with nonionic macromolecules. J. Pharm. Sci. 50 (2), 138–141.

Iwaoku, R., Arimori, K., Nakano, M., Uekama, K., 1982. Enhanced absorption of phenobarbital from suppositories containing phenobarbital-β-cyclodextrin inclusion complex. Chem. Pharm. Bull. 30 (4), 1416–1421.

Karl-Heinz, F., Szejtli, J., 1994. Cyclodextrins in Pharmacy. Kluwer, Dordrecht, pp. 50–81.

Kurup, T.R.R., Lucy, S.C.W., Chan, L.W., 1992. Interaction of preservatives with macromolecules: part I — natural hydrocolloids. Pharm. Acta Helv. 67 (11), 301–307.

Kurup, T.R.R., Lucy, S.C.W., Chan, L.W., 1995. Interaction of preservatives with macromolecules: part II — cellulose derivatives. Pharm. Acta Helv. 70, 187–193.

Loftsson, T., Stefansdouir, O., Frioriksdouir, H., Guomundsson, O., 1992. Interaction between preservatives and 2-hydroxypropyl-β-cyclodextrin. Drug Dev. Ind. Pharm. 18 (13), 1477–1484.

Matsuda, H., Ito, K., Sato, Y., Yoshizawa, D., Tanaka, M., Taki, A., Sumiyoshi, H., Utsuki, T., Hirayama, F., Uekama, K., 1993. Inclusion complexation of *p*-hydroxybenzoic acid esters with 2-hydroxypropyl-β-cyclodextrins. On changes in solubility and antimicrobial activity. Chem. Pharm. Bull. 41 (8), 1448–1452.

Montassier, P., Duchene, D., Poelman, M.C., 1997. Inclusion complexes of tretinoin with cyclodextrins. Int. J. Pharm. 153, 199–208.

Patel, N.K., Foss, N.E., 1965. Interaction of preservatives with macromolecules I — Binding of certain benzoic acid derivatives by polysorbate 80 and cetomacrogol 1000. J. Pharm. Sci. 54, 1495–1499.

Patel, N.K., Kostenbauder, H.B., 1958. Interaction of preservatives with macromolecules I — Binding of *p*-hydroxybenzoic acid esters by polyoxyethylene 20 sorbitan monooleate (Tween 80). J. Am. Pharm. Assoc. Sci. Edn. 47, 289–293.

Szejtli, J., 1983. Dimethyl-β-cyclodextrin as parenteral drug carrier. J. Inclusion Phenomena 1, 135–150.

Szejtli, J., 1988. Cyclodextrin Technology. Kluwer, Dordrecht, pp. 79–170.

SYBYL (a) Molecular Modeling Software Version 6.3. Tripos Inc., St. Louis, MO. (b) Theory Manual. Tripos Inc., St. Louis, MO, 1994, p. 61T.

Veiga, M.D., Diaz, P.J., Ahsan, F., 1998. Interactions of griseofulvin with cyclodextrins in solid binary systems. J. Pharm. Sci. 87, 891–900.