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Water Soluble Cyclodextrin Polymers: Their Interaction with Drugs

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Abstract. The complex forming ability of a water-soluble β-cyclodextrin epichlorohydrin polymer (CDPS) and its different molecular weight fractions was studied and compared with the complexing properties of β-cyclodextrin (βCD) and dimethyl-βCD (DM-βCD). CDPS was separated into two main fractions. CDPS and its fractions formed well soluble inclusion compounds with the studied drugs. The low molecular weight fraction formed rather stable complexes with small guest molecules, the high molecular weight fraction was found to be more efficient in binding larger substrates. Structural studies of furosemide-CD complexes were attempted by NMR spectroscopy.

Key words: Cyclodextrin polymer, solubility method, complex stability, NMR spectroscopy.

1. Introduction

The water soluble cyclodextrin polymers [1, 2, 3] form amorphous, well soluble complexes with drugs [4, 5]. Sublingual/buccal administration of such steroid complexes resulted in improved absorption [6]. These CD derivatives have no known undesirable or toxic effects, and they neither enter nor damage oral tissue [6]. The simplest way to prepare such polymers is crosslinking CD molecules with epichlorohydrin. The degree of polymerization depends on the preparative procedure [3]. The present work deals with the complex forming ability of a water-soluble β-cyclodextrin epichlorohydrin polymer [CDPS] and its different molecular weight fractions with some drug molecules. The results have been compared to the efficacy of βCD and dimethyl-βCD (DM-βCD).

2. Materials and Methods

CDPS is a pilot product of Chinoin Pharm. Chem. Works Ltd. (Hungary) [3], a white powder with the following characteristics: βCD content – 52.6%; average molecular weight – 4150. The following other materials were used, βCD (Nihon Shokuhin Kako Co., Ltd.) DM-βCD (Toshin Chemical Co., Ltd.), butylparaben (Tokyo Kasei T.C.I.) hydrocortisone (Nakarai Chemicals Ltd.), cinnarizine (Eisae Co. Ltd),

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furosemide (Hoechst Japan Co. Ltd), acetohexamide (Shionogi Pharm. Co. Ltd.), NaOD and D_2O (Merck).

Chromatographic separation: Column: Ultrogel AcA 54 gel, eluent: water containing 0.02% w/v NaN_3, the separation was monitored by Sepa-200 High Sensitive Polarimeter (Horiba). The chromatogram was evaluated on the basis of the relationship between the relative elution volumes and molecular weight [3]. Two main fractions were collected, dialyzed (1–7/8 DM cellulose tubing, Union Carbide Corp.) and freeze dried. The apparent βCD content of the samples was determined by the acidic hydrolysis method [1].

The observed stability constants were calculated from the phase solubility diagrams [7, 8], which were determined in water at 25 °C. ^{1}H-NMR spectroscopy was carried out in 0.02M NaOD solution at 24.5 ± 0.5 °C using a JEOL FX-100 spectrometer. ^{1}H chemical shifts were referred to tetramethyl silane external standard.

3. Results and Discussion

CDPS could be separated into two main fractions (Figure 1). The lower molecular weight fraction, CDPS-L is a mixture of different isomers of CD glyceryl ethers, its average molecular weight is about 1600, and its apparent CD content is 51.7%. The other peak represents the real polymer fraction (CDPS-H) which consists of 4–5 or more CD rings interconnected with longer or shorter glyceryl ether chains. The average molecular weight of this fraction, CDPS-H, is more than 9000, and its apparent βCD content is 51.4%. The weight ratio of separated fractions was found to be about 1:1.

The complex forming ability of CDPS and its fractions was studied with small and large drug molecules (Table I).

Butylparaben (BPB), a small guest molecule can fit well into the βCD ring. The βCD derivatives, DM-βCD, CDPS and its fractions formed more stable complexes with BPB than the parent βCD. CDPS and its fractions resulted in relatively low

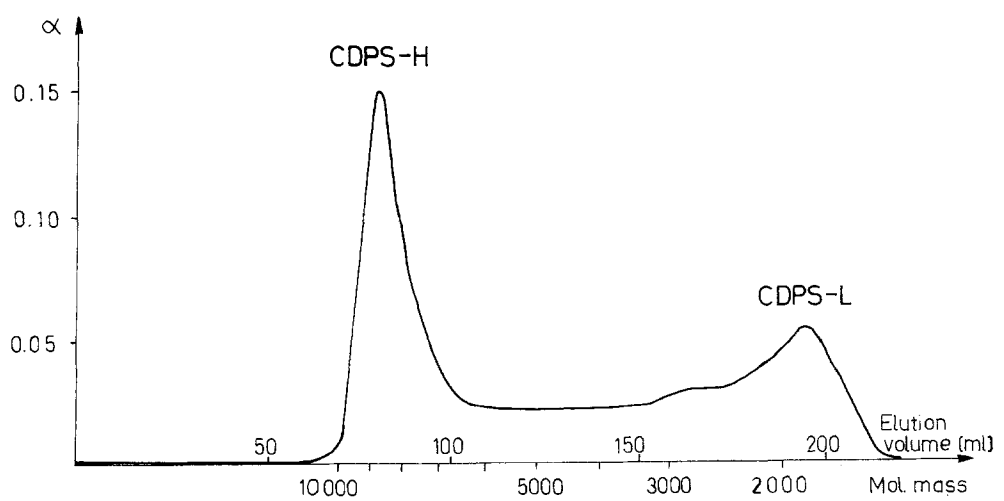
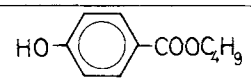
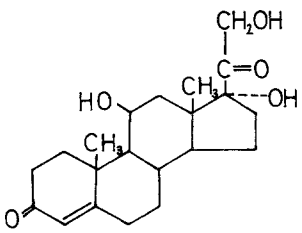
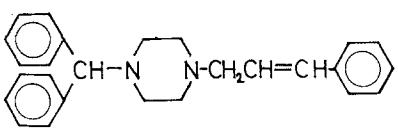
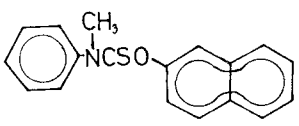
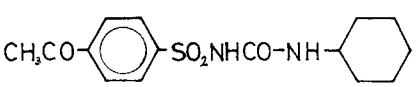
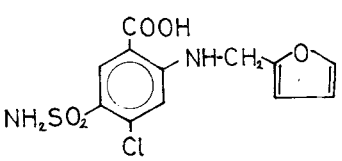


Fig. 1. Elution profile of the CDPS on Ultrogel ACA 54.

Table I. Apparent stability constants, type of solubility curves and increase of solubility of some drugs with βCD and CD derivatives in water at 25 °C

Drug	CD	Apparent stability constant (M^{-1}) $K'_{1:1}$	$K'_{1:2}$	Type of sol. curve	Increase of sol. c_x/c_0 [a]
Butylparaben 	β-CD	2130	–	B_S	3.6
	CDPS	7260	–	A_N	90
	CDPS-H	8160	–	A_L	95
	CDPS-L	8160	–	A_L	95
	DM-β-CD	7260	–	A_N	70
Hydrocortisone 	β-CD	4170	–	B_S	5.5
	CDPS	990	–	A_L	45
	CDPS-H	1250	–	A_L	50
	CDPS-L	1250	–	A_L	50
	DM-β-CD	5910	–	A_L	70
Cinnarizine 	β-CD	4510	–	B_S	7.5
	CDPS	2490	3.4	A_P	300
	CDPS-H	5200	–	A_L	330
	CDPS-L	2190	85	A_P	500
	DM-β-CD	8640	13	A_P	2500
Tolnaftate 	β-CD	7140	–	B_S	70
	CDPS	17000	–	A_L	3000
	CDPS-H	42000	–	A_L	4000
	CDPS-L	17000	–	A_L	3000
	DM-β-CD	17000	29.5	A_P	45000
Acetohexamide 	β-CD	890	–	B_S	4.1
	CDPS	1900	–	A_L	190
	CDPS-H	890	–	A_L	90
	CDPS-L	890	–	A_L	90
	DM-β-CD	810	9.5	A_P	125
Furosemide 	β-CD	62	–	B_S	8.8
	CDPS	590	–	A_L	45
	CDPS-H	330	–	A_L	32
	CDPS-L	330	–	A_L	32
	DM-β-CD	160	26	A_L	70

[a] c_0: water solubility of drug. c_x: solubility in 0.1M solution of the respective CD, (molarity of CDPS relates to the actual CD content of the polymer) in βCD solutions the maximally obtained solubility.

stability constants with hydrocortisone (HC), probably because of the steric hindrance caused by the hydrophilic substituents on the βCD rings. In spite of this fact the increase of solubility is about 10 fold compared to βCD, because the CDPS and its complexes are much more soluble. In the case of cinnarizine (CN), which is also a relatively large guest molecule, CDPS and CDPS-L were less effective than βCD or DM-βCD. The observed stability constant (K') of the CN-CDPS-H system is higher than the K' of CN-βCD but lower than the K' of the CN-DM-βCD. A_p type solubility isotherms were obtained with DM-βCD, CDPS and CDPS-L because they are overlapped by a micelle formation.

The largest complex stability was observed for the high molecular weight CDPS-H

fraction and tolnaftate (TN) system, but as a means of increasing the solubility of TN, the DM-βCD was the most effective, because of its A_p type solubility curve. Acetohexamide (AH) formed complexes of similar stability with βCD and its derivatives, except the unfractionated CDPS, which resulted in the best solubilization of AH. Similar results were found with furosemide (FS). The highest complex stability was obtained with the CDPS, and both its fractions form more stable complexes with FS than the βCD or DM-βCD.

^{1}H-NMR spectra showed differences in the mode of inclusion between CDPS, βCD and DM-βCD (Figure 2.). The inclusion of the phenyl moiety was found to

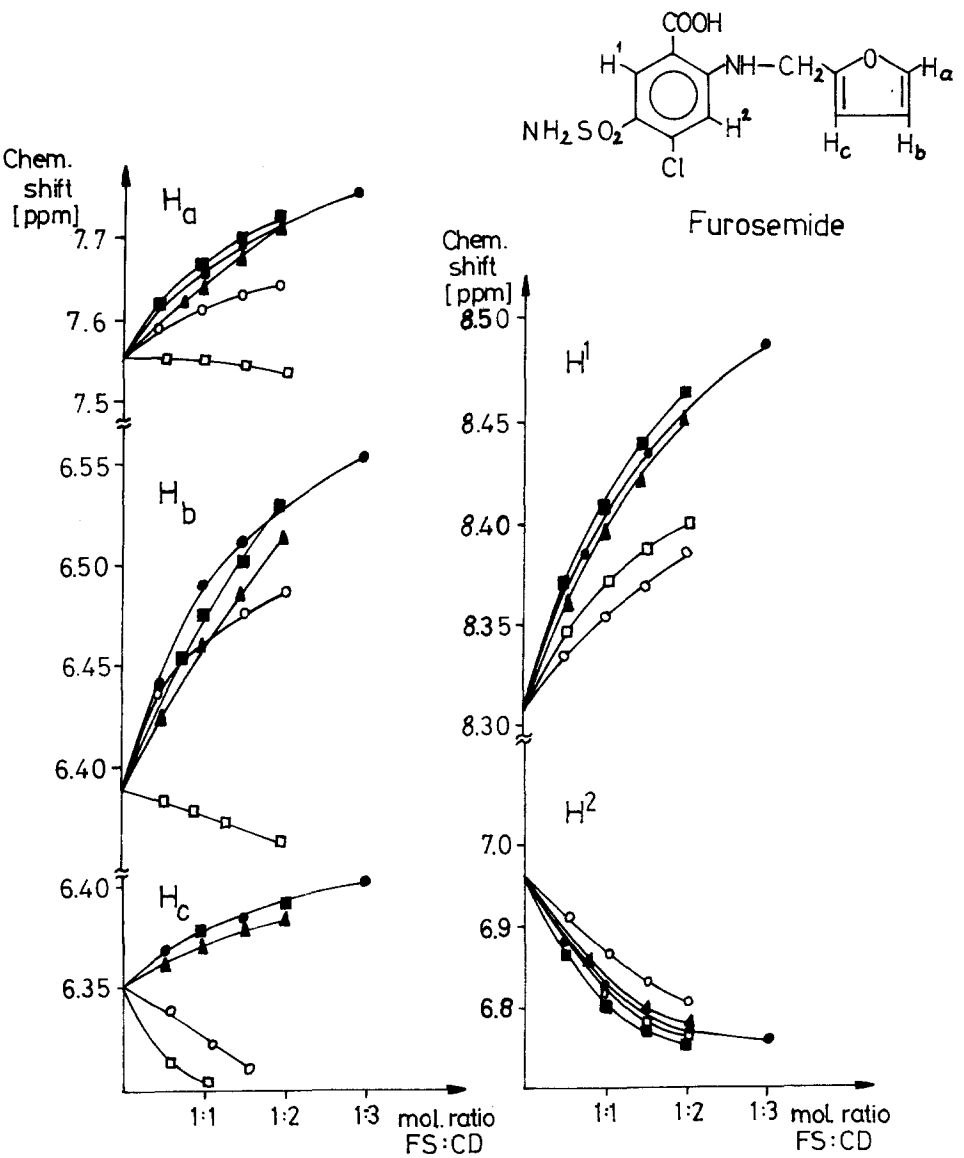


Fig. 2. Variation of chemical shifts of Furosemide with the concentration of βCD and its derivatives in NaOD solution at 24.5 ± 0.5 °C. βCD ○, DM-βCD □, CDPS ●, CDPS-H ▲, CDPS-L ■.

be similar with all CD-hosts. Both rings of furosemide were included in the CD cavity of CDPS and its fractions. Also βCD includes both rings, but the H_c proton of the furanyl group is located outside of the CD cavity. The H_a, H_b and H_c proton signals are shifted towards higher fields in the case of DM-βCD, the furanyl group of FS is not included in the CD cavity.

4. Conclusions

CDPS and its different molecular weight fractions form more or less stable inclusion complexes with several drugs. The water solubility of the CDPS complexes are considerably higher than that of the complexes of the parent βCD. The complex forming ability of CDPS and its fractions depends on the structure of the guest molecule, the hydrophilic substituents on the βCD rings may prevent or help the inclusion of guest molecules. The interaction of the studied drugs with CDPS-L was equivalent or somewhat weaker than that with CDPS. The solubilizing effect of CDPS-H was better with larger guest molecules (cinnarizine, tolnaftate), which probably can be explained by cooperativity in binding between the adjacent CD units of the polymer molecule [2].

A small fraction of CDPS was lost upon separation and dialysis. Perhaps this lost fraction plays some complementing role because the unfractionated CDPS resulted in larger stability constants with furosemide and acetohexamide, than the less heterogeneous fractions.

Mixing the separated CDPS-H and CDPS-L fractions in a 1:1 weight ratio resulted in about the same stability constant with FS, than that with the fractions.

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