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Interaction of Nonylphenyl and Tributylphenyl Ethylene Oxide Ionic Surfactants with Highly Soluble Cyclodextrin Derivatives

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Abstract. The modification of the hydrophobicity of some ethoxylated nonylphenol and tributylphenol surfactants with various soluble β-cyclodextrin polymers has been studied by reversed-phase chromatography. Stepwise regression analysis proved that the complex forming capacity of surfactants decreases with increasing diameter of the hydrophobic moiety of surfactants, the properties of the crosslinking agent used for preparation of the polymers has no significant effect on the host-guest interaction, the presence of carboxyl groups in the polymer considerably improved the complex stability.

Key words. Water soluble cyclodextrin polymer, alkylphenol ethylene oxide surfactants, reversed-phase thin-layer chromatography

1. Introduction

Nonionic surfactants display numerous biological effects [1-4], they can inhibit or stimulate many enzymatic processes [5-8]. However, nonionic surfactants also have marked toxic effects [9-10].

Recently, reversed-phase thin-layer chromatography has been applied to study the interaction of cyclodextrins and cyclodextrin polymers with a wide variety of bioactive compounds such as barbiturates [11,12] and chlorophenol derivatives [13,14].

Cyclodextrins are cyclic oligosaccharides that are well known for their ability to form inclusion complexes [15]. Surfactants are appropriate guest molecules for complex formation: the hydrophobic moieties of the surfactant molecules can be entrapped by the apolar cyclodextrin cavity. As a consequence of complex formation the critical micelle concentration is shifted in the presence of cyclodextrins [16,17]. Beta cyclodextrin forms predominantly 1:1 inclusion complexes with ionic surfactants. The formation constant characterizing the stability of the complex remains practically unchanged by alteration of the head group of the surfactant. When the hydrophobicity of the surfactants is increased by replacing hydrogen with fluorine or by inserting aromatic groups, the value of the complex formation constant increases [18-21].

The properties of cyclodextrins can be improved by certain chemical modifications, e.g. by coupling the rings with proper crosslinking agents (e.g. epoxy compounds). These products containing at least two cyclodextrin rings in a molecule are called

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polymers. Those with 2-5 cyclodextrin rings in a molecule are well soluble in aqueous solutions and their complexes do not precipitate, either. Therefore these polymers are good solubilizers for poorly soluble substances, e.g. drugs. The bioavailability of some drugs was also improved: the adsorption promoting effect of these polymers was proved in oral, as well as in sublingual and percutaneous administration [22-24]. No studies, however, have so far been reported on their interaction with surfactants.

As the practice of including both surfactants and hydrophilic cyclodextrin polymers in pharmaceutical, cosmetic and agrochemical formulations is expected in the future, studies on the interaction of cyclodextrin polymer and nonionic surfactants is of practical and theoretical importance.

The objective of our study was to investigate the interaction of alkylphenol ethylene oxide surfactants with hydrophilic β-cyclodextrin polymers by reversed phase thin-layer chromatography and to find any relationship between molecular structure and the relative strength of interaction between some nonionic surfactants and hydrophilic β-cyclodextrin polymers.

2. Materials and Methods

Reversed-phase thin-layer chromatography was performed on Kieselgel 60 plates (Merck) impregnated with *n*-hexane : paraffin oil 95:5 v/v. The nonionic surfactants (Table I) containing a hydrophobic moiety and a hydrophilic polyethyleneoxy chain were commercial products purchased from Hoechst AG (Germany). Each nonylphenol derivative is a mixture of compounds with various lengths of polyethyleneoxy chain [25]. Moreover, the hydrophobic moiety of the tributylphenol derivatives contained various isomers.

Table I. Chemical Structures of the non ionic surfactants, R-$(CH_2CH_2O)_{ne}H$

R = *p*-nonylphenyl		R = tributylphenyl (isomer mixture)	
No.	Average value of n_e	No	Average value of n_e
1	4	11	4
2	5	12	6
3	6	13	8
4	8	14	10
5	9	15	11
6	10	16	13
7	11	17	18
8	15	18	30
9	23	19	50
10	30		

The polymers used in the present study were prepared by crosslinking β-cyclodextrin or its carboxymethylated derivative with epichlorohydrin (ep), ethylene glycol bis(epoxypropyl)ether (2-diep) or butylene glycol bis(epoxypropylether) (4-diep) in aqueous alkaline solution. The reaction mixture was purified by dialysis. The cyclodextrin content of the lyophilized products was measured by iodometric titration of the reducing end groups after hydrolysis. The carboxyl group content was measured by acid-alkalimetric titration and related to the cyclodextrin content. The molecular weight distribution of the products measured by gel permeation chromatography on Ultrogel ACA 34 columns is similar to each other. It falls in the range from 1600 to *ca* 12000 with a weight average molecular weight of about 3500-4000. The main parameters of the soluble β-cyclodextrin polymers are compiled in Table II.

Table II. Characteristics of some soluble β-cyclodextrin polymers.

No of polymer	Crosslinking agent	COO^-/CD (molar ratio)	CD content (%)
1	ep	-	64
2	ep	-	51
3	ep	1.3	61
4	ep	2.0	54
5	2-diep	-	59
6	2-diep	1.6	57
7	4-diep	-	66
8	4-diep	2.0	58

Surfactants were dissolved in methanol (20 mg/mL) and 4 μL of solutions were spotted separately on the plates and the surfactant : β-cyclodextrin polymer ratio was identical for each surfactant. The eluent was aqueous methanol with methanol concentrations between 50 - 80 vol. % in steps of 5 vol. %. The concentration of β-cyclodextrin polymers in the eluent was 7.5 and 10 mg/mL. After development the plates were dried at 105° and the surfactants were detected with the modified Burger reagent [26]. Each determination was run in quadruplicate. The R_M value given by $\log(1/R_f - 1)$, which characterizes the molecular lipophilicity in reverse-phase thin-layer chromatography was calculated for each surfactant and eluent. The influence of the various experimental parameters on the R_M value of surfactants was calculated with stepwise regression analysis [27]. The R_M values were the dependent variables. The independent variables were the average number of ethylene oxide groups per molecule (x_1), the methanol concentration in the eluent (vol. %) (x_2), the concentration of β-cyclodextrin polymer in the eluent (mg/mL) (x_3) and the methanol concentration multiplied with the polymer concentration ($x_2.x_3$). The inclusion of the last independent variable was motivated by the supposition that the methanol concentration may influence the strength of interaction between the surfactants and β-cyclodextrin polymers (n = number of the determined R_f values; n between 128 - 185 per series). The number of

accepted independent variables was not limited and the acceptance limit was set to the 95% significance level. The calculation was carried out separately for each β-cyclodextrin polymer and for nonylphenol and tributylphenol derivatives.

Stepwise regression analysis was used to find the physico-chemical parameters of surfactants and cyclodextrins accounting for the stability of surfactant-cyclodextrin inclusion complexes. The dependence of the lipophilicity of surfactants on the polymer concentration (b_3 value in Tables III and IV) related to the strength of complexes was taken as dependent variables. The independent variables were

- the diameter of the hydrophobic moiety of surfactants,
- the COO^-/CD molar ratio,
- the β-cyclodextrin content of the polymers,
- the lipophilicity and
- length of the crosslinking agent.

The other conditions were the same as before.

3. Results and Discussion

Both methanol and cyclodextrin polymer No 1 concentrations decrease the retention of nonylphenyl and tributylphenyl surfactants (Figure 1). This finding indicates that the surfactants interact with the water-soluble polymer and the complex is less lipophilic than the uncomplexed surfactant.

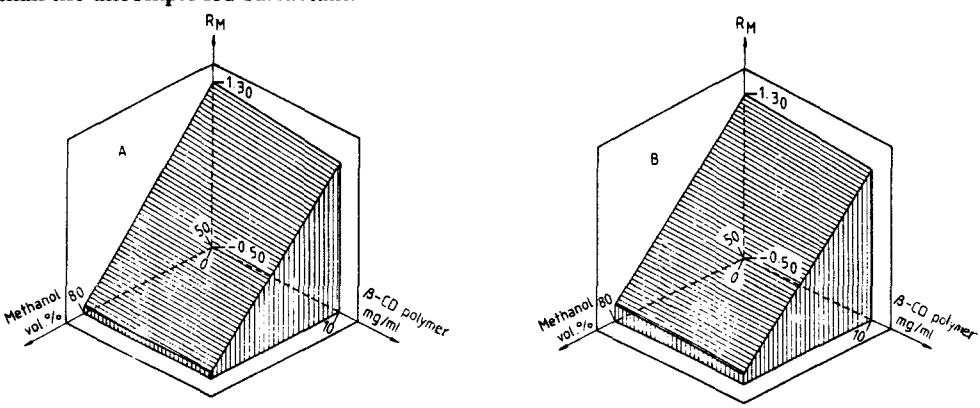

Fig. 1. Effect of methanol and β-cyclodextrin polymer No 1 concentration on the R_M value of nonylphenyl (A) and tributylphenyl (B) ethylene oxide surfactants. R_M = 1.30 - 0.50; x_2 = methanol concentration (50 - 80 vol. %); x_3 = concentration of β-cyclodextrin polymer 1 (0 - 10 mg/mL).

Marked differences were observed between the interactive capacity of polymers (Figure 2), in some cases no interaction can be detected. This result indicates that the interaction between the corresponding surfactant and polymer pair is nonexistent or it is so weak that it is below the detection limit of the method. The parameters (independent variables and their coefficients) of equation describing the dependence of R_M value of nonylphenol and tributylphenol derivatives on the experimental conditions, are compiled

in Tables III and IV respectively. The equations selected by the stepwise regression analysis fit well to the experimental data, the significance level was in each case over 99.9% (See F values). The independent variables account for about 96% of the change of the lipophilicity of nonionic surfactants (see r^2 values).

Table III. Values of coefficients of the independent variables (by stepwise regression analysis) which determine the R_M values for a homologous series of nonylphenyl ethylene oxide derivatives in the presence of soluble hydrophilic β-cyclodextrin polymers and methanol. Variables: x_1 = average number of ethylene oxide group per molecule; x_2 = methanol concentration in the eluent (vol. %); x_3 = concentration of β-cyclodextrin polymer in the eluent (mg/mL); n = number of experimentally determined R_M values.

$$R_M = a + b_1.x_1 + b_2.x_2 + b_3.x_3 + b_4.x_2.x_3$$

Parameters	No of β-cyclodextrin polymer							
	1	2	3	4	5	6	7	8
n	147	154	156	185	152	156	159	159
a	4.14	4.13	4.18	4.24	4.18	4.21	4.13	4.20
b_1	-	-						
s_{b1}	-	-	-	-	-	-	-	-
path coeff.(%)	-	-	-	-	-	-	-	-
b_2	-5.71	-5.70	-5.77	-5.87	-5.78	-5.82	-5.69	-5.80
s_{b2}	0.09	0.08	0.09	0.09	0.09	0.08	0.10	0.09
path coeff.(%)	97.05	94.48	93.41	88.57	75.61	-	87.90	-
b_3	-0.37	-	-0.82	-0.87	-3.04	-	-1.55	-
s_{b3}	0.19	-	0.18	0.22	0.29	-	0.19	-
path coeff.(%)	2.95	-	6.59	7.65	19.20	-	12.10	-
b_4	-	-0.04	-	0.03	-0.05	-	-	-
s_{b4}	-	0.01	-	0.01	0.02	-	-	-
path coeff.(%)	-	5.02	-	3.78	5.19	-	-	-
r^2	0.9698	0.9684	0.9661	0.9668	0.9668	0.9690	0.9596	0.9644
F	2312.97	2317.66	2181.76	1759.94	1435.91	-	1854.16	4251.52

The intercept (a value) is related to the lipophilicity of the hydrophobic moiety of the surfactant at zero methanol and zero CD polymer concentrations. This value is slightly higher for nonylphenol than for tributylphenol surfactant series.

The majority of polymers form complexes with the surfactants (see b_3 values), however, the strength of interaction depends on the type of surfactant and polymer.

The equation correlating the strength of surfactant - cyclodextrin polymer interaction with the physico-chemical parameters of the interacting molecules fits well to the experimental data, the significance level was over 99% (see F value in Table V). The physico-chemical parameters selected by the stepwise regression analysis account for 52% of the change of the strength of interaction (see r^2 value). The strength of inclusion

complexes depended both on the diameter of the hydrophobic moiety of surfactants (62.8 Å for nonylphenyl and 186.2 Å for tributylphenyl group) [28] and on the COO^-/CD ratio and was independent of the β-cyclodextrin content of the polymers, the lipophilicity and length of the crosslinking agent. These findings stress the importance of steric parameters in the interaction. The negligible influence of the crosslinking agent on the inclusion complex forming capacity of β-cyclodextrin polymers supports the suggestion that epichlorohydrin forms longer chains (bridges and side-chains) by self-condensation [29].

Table IV. Values of coefficients of the independent variables (by stepwise regression analysis) which determine the R_M values for a homologous series of tributylphenyl ethylene oxide derivatives in the presence of soluble hydrophilic β-cyclodextrin polymers and methanol. Variables: x_1 = average number of ethylene oxide group per molecule; x_2 = methanol concentration in the eluent (vol. %); x_3 = concentration of β-cyclodextrin polymer in the eluent (mg/mL); n = number of experimentally determined R_M values

$$R_M = a + b_1.x_1 + b_2.x_2 + b_3.x_3 + b_4.x_2.x_3$$

Parameters	No. of cyclodextrin polymer							
	1	2	3	4	5	6	7	8
n	128	138	139	157	130	142	144	137
a	3.87	4.04	4.11	4.08	4.09	4.12	4.01	4.06
b_1	-	-0.16	-0.17	-0.16	-0.17	-0.17	-0.13	-0.13
s_{b1}	-	0.05	0.05	0.07	0.07	0.05	0.05	0.05
path coeff. (%)	-	4.95	4.97	4.22	4.24	4.68	4.04	3.70
b_2	-5.21	-5.44	-5.56	-5.52	-5.53	-5.57	-5.43	-5.49
s_{b2}	0.10	0.09	0.10	0.10	0.10	0.09	0.09	0.10
path coeff. (%)	92.41	95.05	91.30	83.20	80.43	84.44	95.96	89.47
b_3	0.91	-	1.03	0.85	-1.30	1.38	-	0.81
s_{b3}	0.22	-	0.19	0.26	0.32	0.18	-	0.19
path coeff. (%)	7.59	-	3.73	7.56	9.23	10.88	-	6.83
b_4	-	-	-	-0.22	-0.03	-	-	-
s_{b4}	-	-	-	0.01	0.01	-	-	-
path coeff. (%)	-	-	-	5.08	6.10	-	-	-
r^2	0.9586	0.9638	0.9664	0.9647	0.9621	0.9684	0.9614	0.9647
F	1447.88	1795.42	1295.80	1038.23	794.37	1411.88	1757.02	1210.93

Thus the crosslinking agents of different length provide a similar microenvironment to the cyclodextrin rings. However, the significant contribution of the COO^-/CD ratio to the complex stability needs some explanation. The carboxyl groups on the surface of the cyclodextrin molecule may interact with the polar ethylene oxide chain of surfactants by hydrophilic forces, possibly with hydrogen bond formation or modify the accessibility of the cyclodextrin cavity.

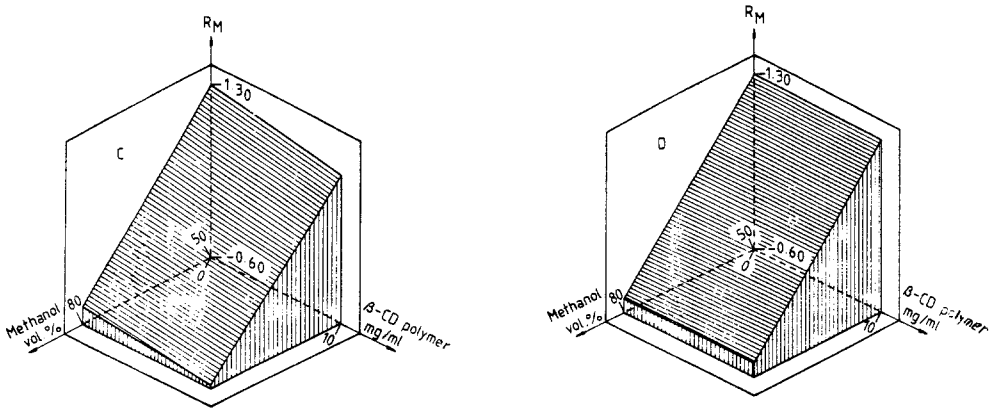

Fig. 2. Effect of methanol and β-cyclodextrin polymer No 7 (interacting polymer, C) and 8 (not interacting polymer, D) concentration on the R_M value of nonylphenyl ethylene oxide surfactants. R_M = 1.30 - 0.60; x_2 = methanol concentration (50 - 80 vol. %); x_3 = concentration of β-cyclodextrin polymer 1 (0 - 10 mg/mL).

Table V. Dependence of the strength of surfactant - β-cyclodextrin polymer interaction (b) on the physicochemical parameters of surfactants and polymers. Results of stepwise regression analysis.

$b = a + b_1$.diameter of hydrophobic moiety + b_2.COO^-/CD

n = 16 $a = 6.58.10^{-3}$ F = 7.04 $r^2 = 0.520$

Parameter	Diameter of hydrophobic moiety (A)	COO^-/CD
b	-1.29	0.53
s_b	0.42	0.24
path coeff. %	58.13	41.87

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