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Comparison of the Complexation of Cosmetical and Pharmaceutical Compounds with γ-Cyclodextrin, 2-Hydroxypropyl-β-cyclodextrin and Water-Soluble β-Cyclodextrin-co-epichlorhydrin Polymers

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Abstract

The ability of different cyclodextrins (CDs): γCD, 2- hydroxypropyl βCD to complex drugs like 3-β-hydroxy-11-oxoolean-12-en-30-oic acid, 2-ethylhexyl-3-(4-methoxyphenyl)-2-propanoate and menthol was compared to that of water-soluble polymers: βCD-co-epichlorhydrin polymer (pβCD/EP) and βCD-co-epichlorhydrin polymer partially modified with trimethylammonium groups (pβCD/EPN$^+$). 3-β-Hydroxy-11-oxoolean-12-en-30-oic acid was poorly solubilized by γCD compared with other CD derivatives, however the determination of the complexation constants was possible for pβCD/EP, K_{11} = 740, K_{12} = 4, for pβCD/EPN$^+$, K_{11} = 681, for γCD, K_{11} = 16 and for hydroxypropyl βCD, K_{11} = 114, K_{12} = 3.4. A significant increase of the solubility was observed for 2-ethylhexyl-3-(4-methoxyphenyl)-2-propanoate with all host molecules, it was 916 times its solubility in pure water with pβCD/EPN$^+$, 1116 and 1300 times with 2-hydroxypropyl βCD and pβCD/EP respectively. The association constants are K_{11} = 7970, K_{11} = 4700, K_{11} = 1470, K_{11} = 230 and K_{12} = 200 with pβCD/EP, pβCD/EPN$^+$, γCD, 2-hydroxypropyl βCD respectively. An increase of the solubility of menthol was observed with all CD derivatives, up to 36–37 times, except for γCD. The complexation constants are similar equal to about 200.

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides composed of six, seven or eight glucose units, with α-l,4 linkages. They have a torus shape with a central void of 5.7 Å, 7.8 Å and 9.5 Å diameter for α, β and γ-CD respectively. The internal surface is relatively hydrophobic so that CDs can form inclusion complexes with a variety of organic and inorganic guest molecules or ions [1]. The formation of inclusion complexes increases the bioavailability and stability of poorly soluble drugs. Further, CDs can be used to reduce or prevent some gastrointestinal or ocular irritation, reduce or eliminate unpleasant smells or tastes and prevent drug–drug interactions. However, large amounts of CDs must frequently be used to complex small amounts of drug.

Previous work [2–5] showed that the complexing abilities of CDs were enhanced when small amounts of water soluble polymers were added, by increasing the complexation constants of the drug-CD complexes. The mixtures of water soluble polymers, CD and drug must be heated to enhance the availability of drugs. Addition of polymers increases the apparent stability constant of the drug-CD complex and the entropy variation becomes more negative, indicating a more ordered complex structure [2]. Bibby *et al.* [6] described recently the modification of drug release from a polymeric system in which CD was incorporated. In aqueous solutions the polymers reduce the mobility of the CD molecules and enhance the solubility of the complex formed [7].

The limited applications of CDs in the pharmaceutical field seems to be related to the relatively low aqueous solubility (1.8%, w/v at 25 °C) [8]. Albers *et al.* reviewed some pharmaceutical relevant applications of CD-derivatives [9].

The purpose of the present work is to examine the effect of using water-soluble β-CD epichlorhydrin polymers: a β-CD-co-epichlorhydrin polymer (pβCD/EP) and a βCD-co-epichlorhydrin polymer, partially modified with trimethylammonium groups (pβCD/EPN$^+$) of low molecular weight, to enhance the solubilization of some compounds in comparison with 2-hydroxypropyl βCD (HPβCD) and γ-CD. We hope that it will be possible to solubilize higher amounts of drugs with βCD polymers than with HPβCD or with γCD, based on their higher solubility in water. Further, we will determine also the stability constants of the drug-cyclodextrin complexes.

The compounds of interest (Scheme 1) are 3-β-hydroxy-11-oxoolean-12-en-30-oic acid, (glycyrrhetinic acid) , 2-ethylhexyl-3-(4-methoxyphenyl)-2- propanoate

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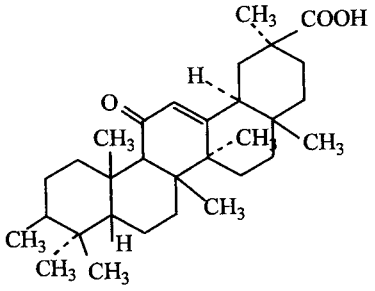
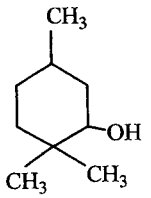
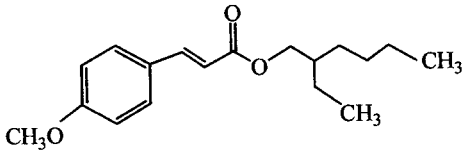


3–β-hydroxy-11-oxoolean-12-en-30-oic acid



levo-menthol



2-ethylhexyl-3(4-methoxyphenyl)-2-propanoate

Scheme 1.

(Parsol MCX) and levomenthol, which are poorly water soluble compounds. Glycyrrhetinic acid is used in cosmetical formulations for its anti inflammatory properties. 2-Ethylhexyl-3-(4-methoxyphenyl)-2-propanoate is one of the most tested and the most frequently used anti UVB filters worldwide. Emulsions containing 2-ethylhexyl-3-(4-methoxyphenyl)-2-propanoate are most commonly used. The most important characteristic of an effective UV filter is high photostability [10–13]. The photochemical decomposition of the sunscreen agent under sunlight irradiation, not only reduces the photoprotective power of the sunscreen during use, but can also lead to degradation products which might promote phototoxic or photoallergenic contact dermatitis [10, 13–17]. The complexation of this sunscreen agent by CD derivatives can stabilize it and prevent or reduce its photodegradation. Menthol is used as an ingredient of pharmaceutical products for its fragrance and flavor, moreover it is widely used in foods, beverages, tooth paste, cigarettes and food flavor for its particularly refreshing taste. 1-Menthol is more commonly used than d,l-menthol or d-menthol.

Materials and methods

Materials

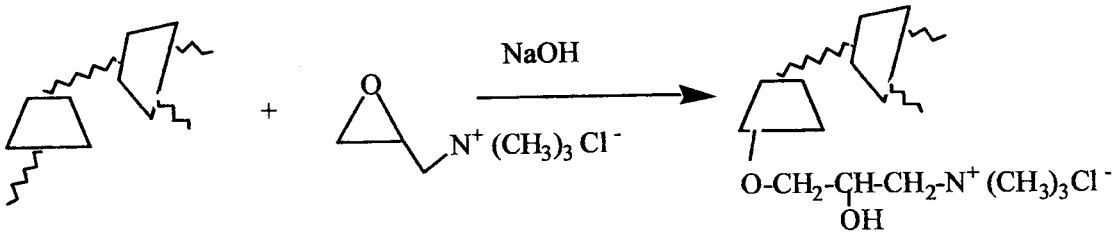
βCD was a gift from Roquette (France). 2-Hydroxypropyl βCD (HPβCD) with a molar substitution 0.6–0.95 and γCD were purchased from Wacker-Chemie (Burghansen, Germany). 3-β-Hydroxy-11-oxoolean-12-en-30-oic acid (glycyrrhetinic acid) was from Laderson (Etampes, France). Levo-menthol and 2-ethylhexyl-3-(4-methoxyphenyl)-2-propanoate (Parsol MCX) were purchased from International Express Service (Allauch, France). 2,3-Epoxypropyltrimethyl ammonium was from Aldrich. Ultra pure water (Milli-Q system, Millipore) was used for this study. A Zeta-sizer N°3 (Malvern, USA) was used for the determination of the size of some particles. The ^{1}H NMR spectra were recorded on a Brucker 200 MHz instrument.

p-βCD/EP synthesis

The polymer pβCD/EP was synthesized in the laboratory according to the procedure described previously [18]. This polymer was obtained from the polycondensation of epichlorhydrin and βCD (5eq/1eq) in sodium hydroxide medium after deprotonation of βCD at 33 °C for 4 hours in order to obtain a polymer of low molecular weight. The weight of cavities (%) in the polymer was determined from ^{1}H NMR.The polymer pβCD/EP was fractionated by ultrafiltration for 48 hours on a membrane of cut off 1000 in order to discard the unreacted βCD molecules and the oligomers of pβCD/EP. It was then freeze dried. The molecular weight was determined by S.E.C. on TSK SW columns (4000 + 3000) and it is given in equivalent pullulan (Table 2).

pβCD/EPN$^+$ synthesis

pβCD/EPN$^+$ (Scheme 2) was obtained by chemical modification of pβCD/EP. Firstly deprotonation of the OH groups occurred at room temperature for 24 hours (5eq. NaOH/1eq. cage of βCD). 2,3-Epoxypropyltrimethyl-ammonium chloride was then added (5 eq./1 eq. cavities of βCD) the reaction left at 50 °C for 24 hours, and HCl 6 mol.L^{-1} was added for neutralization. The pβCD/EPN$^+$ was then purified for 5 days on a membrane of cut off 1000 and freeze dried. The characteristics of this polymer are reported in Table 2.



Scheme 2.

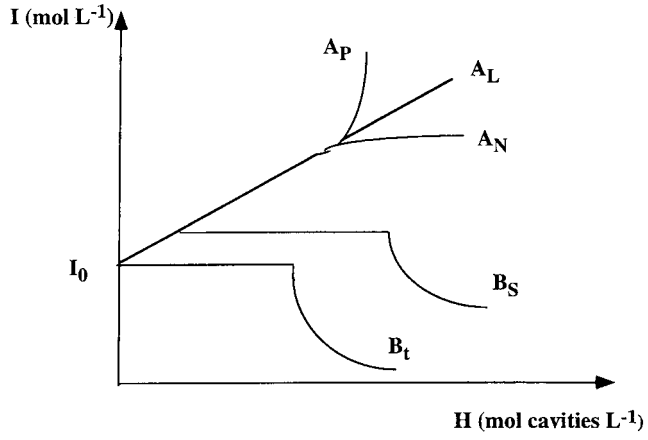


Figure 1. Solubility diagram of a guest in a host molecule according to Higuchi and Connors [19].

Solubility studies

An excess amount of compound to be tested was added to aqueous solutions containing various concentrations of the CD derivative. This excess amount of compound corresponded to twice the number of cavities of the most concentrated CD solution. These samples were prepared in duplicate or triplicate. These Solutions were magnetically stirred at 25 °C for variable durations depending on the drug. After equilibration, the suspension was centrifuged for 1 hour and then filtered through a cellulose acetate membrane (0.45 μm, AIT filter) to obtain a clear drug-cyclodextrin solution. A portion of sample was adequately diluted in the eluent used in high performance liquid chromatography (HPLC). The stability constants of the drug-cyclodextrin complexes were calculated from the phase-solubility diagrams obtained according to the method of Higuchi and Connors [19].

These authors describe two major classes of phase-solubility diagrams corresponding to soluble complexes (class A) and insoluble complexes (class B) respectively (Figure 1).

For class A three diagrams exist. The curve A_L corresponds to a stoichiometry of complexation 1:1. The equation of the straight line is:

$$S = S_0 + K_{11}S_0H,$$

where S is the concentration of guest, S_0 the concentration of guest without host, H is the concentration of host; K_{11} is the constant of complexation of the guest:host 1:1 complex. The curve A_P corresponds to a simultaneous stoichiometry of complexation of 1:1 and 1:2. The equation of the curve is:

$$S = S_0 + (K_{11}S_0H) + (K_{11}K_{12}S_0H^2)$$

where K_{12} is the constant of complexation of the 1:2 guest: host complex. The curve A_N expresses a 1:1 complexation for low concentrations of host and then reaches a critical point corresponding to a limiting solubilization.

For class B, two types of diagrams exist. The curve B_S corresponds to a linear variation in the beginning corresponding to the formation of a soluble 1:1 complex, then a plateau appears indicating that the solubility of the complex is limited, the addition of host involving the precipitation of complex, finally, a decrease of solubility is observed which becomes inferior to S_0 The curve B_t corresponds to an immediate precipitation of complex.

Quantitative determination

Quantitative determination of the compounds were performed on a reversed-phase HPLC. Two columns were used: a Chromosorb RP8 (Merck, Germany) column 10 μm (150 × 5 mm) for studying the complexes of the compound and γCD, HPβCD or pβCD/EP, and a polystyrene/divinylbenzene column (Interchrom) 5 μm (150 × 4.6 mm) (PVB/DVB) for studying the complexes of the compound and pβCD/EPN$^+$. The system consisted of one pump (Beckman) or two pumps (Beckman, Chromatem) for studies on the PVP/DVB column and a valve permitting changing the nature of the delivered eluent. The flow rate was fixed at 1 mL min^{-1}. A Rheodyne 7125 injector was used, a SPD-6A (Shimadzu) variable-wavelength detector or a differential refractometer (Waters) for the detection of menthol and a recorder (1 cm min^{-1}, Enraf Nonius). For quantitative studies of 3-β-hydroxy-11-oxoolean-12-en-30-oic acid, or 2-ethylhexyl-3-(4-methoxyphenyl)-2-propanoate and pβCD/EPN$^+$ two eluents were successively used for the elution of filtered samples on the PS/DVB column. The first one permitted elution of the pβCD/EPN$^+$ polymer, the second one to elute the drug. For other experimental conditions see Table 1. Each injection was realized in duplicate.

Table 1. Conditions of quantitative drug determination by HPLC

Drug	Mobile phase	Wavelength (nm)	Retention time (min)
Glycyrrhetinic acid	RP8: CH_3OH/H_2O (70/30)	250	16
	PS/DVB:		
	1-CH_3OH/H_2O (70/30)		
	2-CH_3OH		9.6
Parsol MCX	RP8: CH_3OH/H_2O (85/15)	310	6.35
	PS/DVB:		
	1-CH_3CN/H_2O (70/30)		13.6
	2-CH_3CN		
Menthol	RP8: CH_3OH/H_2O (65/35)	(Detection by	9.5
	PS/DVB: CH_3OH/H_2O (80/20)	differential refractometry)	11.8

Table 2. Characteristics of βCD polymers

Polymer	Mn	Mw	Weight of cavities (%)	$-N^+$ groups/mol. cavities Elemental Analysis	$-N^+$ groups/mol. cavities ^{1}H NMR
pβCD/EP	6180	14900	76.4		
pβCD/EPN$^+$	6180	14900	76.4	1.2	1.7

Results and discussion

Drug solubilization

β-hydroxy-11-oxoolean-12-en-30-oic acid (glycyrrhetinic acid)

The time of equilibration of complexes was first determined for a mixture of βCD/EP polymer 100 g L^{-1} and glycyrrhetinic acid, 2 equivalents of drug/equivalent of cavity number. The solubility reached a plateau after about 7 days so this time of equilibration was chosen for all the experiments. All determinations of solubility in the presence of CD derivatives were done in water , except the one in the presence of pβCD/EPN$^+$, which was done in sodium acetate 10^{-1} mol L^{-1}, pH 5.6.

Figure 2 shows experimental points and theoretical curves for the solubilization of glycyrrhetinic acid by pβCD/EP and by pβCD/EPN$^+$. The best correlation corresponds to a second order equation which led to the constant values: K_{11} = 740, K_{12} = 4 for pβCD/EP. In the case of pβCD/EPN$^+$, the best correlation corresponds to an equation of first order, the complexation constant K_{11} is 681.

The results (Table 3) show that at equal concentration (mol cavities L^{-1}) the solubilizing properties of pβCD/EP are superior to those of pβCD/EPN$^+$, the enhancement of solubility is 150 times for pβCD/EP and 103 times for pβCD/EPN$^+$. This can be explained by the more restricted accessibility to the cavity of βCD due to the pendent charged chain of pβCD/EPN$^+$. However, we observed that the filtered solutions containing complexes with pβCD/EP

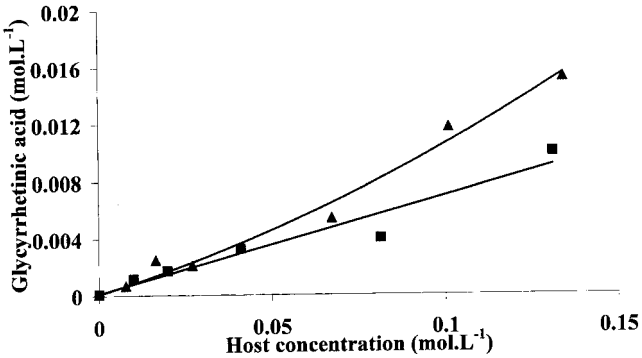


Figure 2. Solubilization of 3-β-hydroxy-11-oxoolean-12-en-30-oic acid versus host concentration. Experimental points: (▲): pβCD/EP, (■): pβCD/EPN$^+$. (__): theoretical curves: $y = 3.3039x^2 + 0.0743x + 10^{-4}$, r^2 = 0.9862 (pβCD/EP); $y = 0.0681x + 0.0001$; r^2 = 0.9486 (pβCD/EPN$^+$).

or pβCD/EPN$^+$ were not clear but whitish, corresponding to colloidal solutions. The radius of these particles is around 200 nm as determined by static light diffusion measurement with a zetasizer. The occurrence of colloidal particles makes difficult the accuracy of the analysis at high polymer concentration.

Figure 3 reports the variation of the solubility of glycyrrhetinic acid in the presence of HPβCD and γCD. The theoretical curves correspond to an equation of second order for HPβCD and of first order for γCD. The calculated constants are respectively: K_{11} = 114, K_{12} = 3 and K_{11} = 16 for hydroxypropyl βCD and γCD. We can compare the enhancement of the solubility (Table 3) of these two hosts

Table 3. Comparison of solubilizing properties of hosts molecules for glycyrrhetinic acid

	Concentration of guests (mol L^{-1})	Concentration of CD hosts (mol L^{-1})	K	Enhancement of solubility (CD/water)
pβCD/EP	1.5×10^{-2}	1.3×10^{-1}	$K_{11} = 740 \pm 110$ $K_{12} = 4 \pm 0.6$	150
pβCD/EPN$^+$	1.0×10^{-2}	1.3×10^{-1}	$K_{11} = 681 \pm 102$	103
γCD	3×10^{-4}	1.2×10^{-1}	$K_{11} = 16 \pm 2.4$	3
HPβCD	2.7×10^{-3}	1.3×10^{-1}	$K_{11} = 114 \pm 14$ $K_{12} = 3.4 \pm 0.5$	23

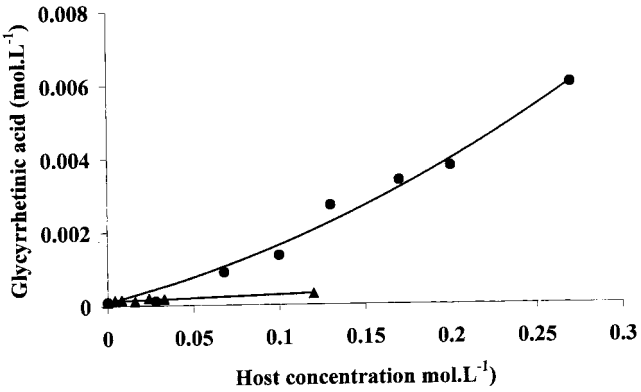


Figure 3. Solubilization of 3-β-hydroxy-11-oxoolean-12-en-30-oic acid versus host concentration. Experimental points: (●): 2-hydroxypropyl βCD, (▲): γCD. (__): theoretical curves: $y = 0.392x^2 + 0.0114x + 10^{-4}$; $r^2 = 0.9865$ (hydroxypropyl βCD); $y = 0.0016x + 10^{-4}$, $r^2 = 0.8514$ (γCD).

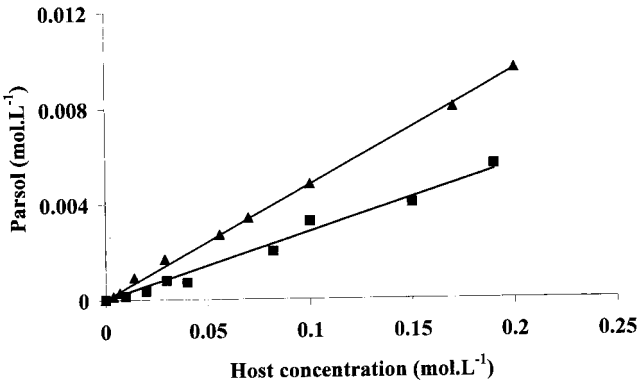


Figure 4. Solubilization of Parsol MCX versus host concentration. Experimental points: (▲): pβCD/EP, (■): pβCD/EPN$^+$. (__): theoretical curves: $y = 0.0478x + 6.10^{-6}$; $r^2 = 0.9982x + 6.10^{-6}$; $r^2 = 9.9803$ (pβCD/EPN$^+$).

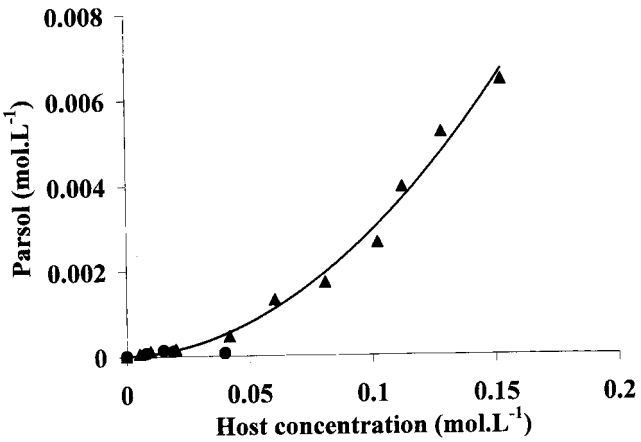


Figure 5. Solubilization of Parsol MCX versus host concentration. Experimental points: (▲): 2-hydroxypropyl βCD, , (●): γCD. (__): theoretical curves: $y = 0.2797x^2 + 0.0014x + 6.10^{-6}$; $r^2 = 0.9893$ (2-hydroxypropyl βCD); $y = 0.0088x + 6.10^{-6}$; $r^2 = 9.9978$ (γCD).

with that of pβCD/EP at equal concentration of host (1.3×10^{-1} mol L^{-1}) which are 150, 28 and 3 for pβCD/EP, HPβCD and γCD respectively. γCD is a poor solubilizing agent of glycyrrhetinic acid. The best results are obtained with both polymers, with pβCD/EP giving the highest K_{11} inclusion constant.

2-Ethylhexyl-3-(4-methoxyphenyl)-2-propanoate (Parsol MCX)

The solubility S_0 of Parsol determined after 24 hours at 25 °C by reversed phase HPLC was $S_0 = 6 \times 10^{-6}$ mol L^{-1}.

The time of solubilization was determined for a mixture of pβCD/EP (100 g L^{-1}) and Parsol MCX (2 equivalents drug/equivalent cavity number). The equilibration time was 4 hours. An equilibration time of 24 hours was chosen for easier experiments.

The variation of solubility of Parsol versus host concentration is reported in Figure 4 for both polymers and shows the best solubilizing power for pβCD/EP. The theoretical curves correspond to a linear variation and give the complexation constants: $K_{11} = 7970$ and $K_{11} = 4700$ for pβCD/EP and pβCD/EPN$^+$ respectively. Figure 5 shows the solubilizing properties of HP βCD and γCD. Analysis of curves which correspond to a second order equation for HPβCD and a first order equation for γCD lead to the values $K_{11} = 230$, $K_{12} = 200$ and $K_{11} = 1470$ respectively. The calculation of the complexation constant for γCD was made with the lowest concentrations because the solubility decreases for host concentration greater than 1.9×10^{-2} mol L^{-1}.

HPβCD, pβCD/EP and pβCD/EPN$^+$ lead to significant increase of the solubility (Table 4). The solubilizing properties of HPβCD and pβCD/EP for similar CD host concentrations (1.5×10^{-1} and 1.7×10^{-1} mol cavities L^{-1}) are of the same order of magnitude, up to 1116 and 1300 times respectively. On the other hand, a small increase of solubility was observed with γCD: $S = 6.6 \times 10^{-5}$ mol

Table 4. Comparison of solubilizing properties of hosts molecules for parsol MCX

	Concentration of guests (mol L^{-1})	Concentration of CD hosts (mol L^{-1})	K	Enhancement of solubility (CD/water)
pβCD/EP	8×10^{-3}	1.7×10^{-1}	$K_{11} = 7970 \pm 1195$	1300
pβCD/EPN$^+$	5.8×10^{-3}	1.9×10^{-1}	$K_{11} = 4700 \pm 705$	916
γCD	6.6×10^{-5}	4.5×10^{-2}	$K_{11} = 1470 \pm 220$	10
HPβCD	1.9×10^{-3}	1.5×10^{-1}	$K_{11} = 230 \pm 34.5$ $K_{12} = 200 \pm 30$	1116

L^{-1} which corresponds to a solubilizing property of 1 order of magnitude (Table 4).

Parsol MCX forms 1:1 (drug: ligand) complexes with both polymers and γCD but forms 1:1 and 1:2 complexes with HP βCD. The presence of polymer seems to have a cooperative effect due to the higher values of the K_{11} complexation constant.

5-methyl-2(1-methylethyl)cyclohexanol (Menthol)

Ajisaka *et al.* [20] recently reported the solubility enhancement of menthol with βCD derivatives. In 10 mmol L^{-1} solutions of βCD, 6-O-α-maltosyl-βCD and 6-O-α-(4-O-α-glucuronyl)-D-glucosyl-βCD they observed a solubility enhancement up to 2, but up to 3 with 6-O-α-maltosyl-βCD, synthesized by a condensation reaction of maltose and a CD debranching enzyme, and with 6-O-α-(4-O-α-D-glucuronyl)-D-glucosyl-βCD, prepared by oxidation of 6-O-α-maltosyl-βCD with Pseudogluconobacter saccharoketogenes. This enhancement of solubility reached up to 21 and 22 for 6-O-α-maltosyl-βCD and 6-O-α-(4-O-α-D-glucuronyl)-D-glucosyl-βCD respectively at a concentration of 100 mmol L^{-1}. This can be explained by the formation of insoluble complexes with βCD but soluble complexes with 6-O-α-maltosyl-βCD and 6-O-α-(4-O-α-D-glucuronyl)-D-glucosyl-βCD.

We fixed the equilibration time at 24 hours based on Ajisaka's study [20] who stirred the mixtures for 17 hours. The solubility of menthol in water used in this work is 2.3×10^{-3} mol L^{-1} [21].

The solubilization of menthol with CD derivatives is shown in Figures 6 and 7. γCD does not include menthol as seen in Figure 7. On the other hand, the three other CD derivatives lead to an increase of the solubility, up to 36–37 times (Table 5). The complexes are 1:1 complexes for pβCD/EP, pβCD/EPN$^+$ and HPβCD. The values of the inclusion constants are similar, equal to about 200. These similar results can be explained by the smaller size of this drug compared to the others, which can enter easily into the different cavities, even if the entrance is restricted by a small chain as in the case of pβCD/EPN$^+$ and hydroxypropyl βCD.

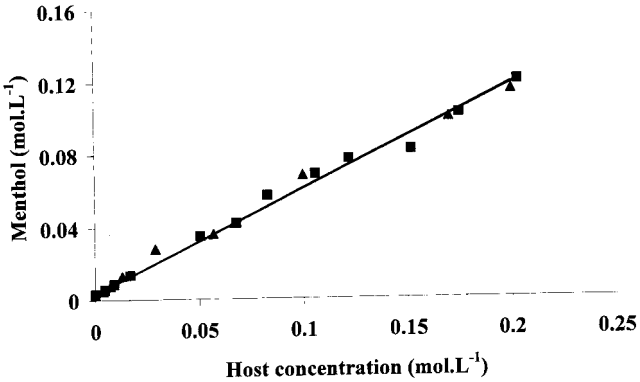


Figure 6. Solubilization of menthol versus host concentration. Experimental points: (▲): pβCD/EP, (■) : pβCD/EPN$^+$. (__): theoretical curves: $y = 0.5739x + 0.003$; $r^2 = 0.9803$ (pβCD/EP); $y = 0.5756x + 0.003$; $r^2 = 0.987$.

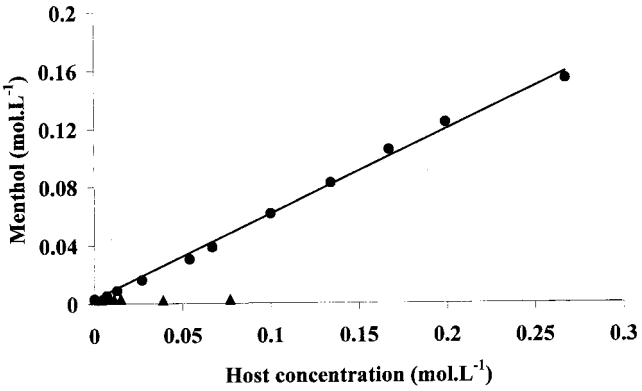


Figure 7. Solubilization of menthol versus host concentration. Experimental points: (●): hydroxypropyl βCD, (▲): γCD. (__): theoretical curves: $y = 0.5839x + 0.003$; $r^2 = 0.9959$.

Conclusion

Except in the case of γCD-menthol, we saw in all cases solubilizing properties of the CD derivatives. This effect does not depend on the nature of the βCD derivative for menthol. The complexes formed are of the 1:1 type, the inclusion constants have quite a low value of 200 due to the smaller size of menthol compared to the βCD cavity size. Differences in the solubilizing power of CD derivatives were observed in the case of glycyrrhetinic acid and Parsol MCX. The lowest solubilizing power was obtained for γCD whose cavity size is too large for these drugs. The polymer pβCD/EP is the best complexing CD derivative for glycyrrhetinic acid.

Parsol MCX solubilization is higher with pβCD/EP and hydroxypropyl βCD. The highest inclusion constant, K_{11} = 7970 was determined with pβCD/EP. Results obtained with pβCD/EPN$^+$ are inferior, due to the restricted access of mo-

Table 5. Comparison of solubilizing properties of hosts molecules for menthol

	Concentration of guests (mol L^{-1})	Concentration of CD hosts (mol L^{-1})	K	Enhancement of solubility (CD/water)
pβCD/EP	8.4×10^{-2}	1.3×10^{-1}	$K_{11} = 200 \pm 30$	37
pβCD/EPN$^+$	8.5×10^{-2}	1.5×10^{-1}	$K_{11} = 200 \pm 30$	37
γCD	2.8×10^{-3}	7×10^{-2}		1
HPβCD	8.2×10^{-2}	1.3×10^{-1}	$K_{11} = 195 \pm 29$	36

lecules to the cavities. The solubilizing power ($\times$ 1116) of Parsol MCX with HPβCD corresponds however, to a smaller value of the K_{11} inclusion constant, 230. The formation of a 1:2 complex was observed in this case with K_{12} = 200. Parsol MCX has less affinity for HPβCD. The higher solubilities are explained by the high K_{12} constant. The K_{12} constant is negligible in the case of pβCD/EP because of steric effects: cyclodextrin units being constrained to belong to a branched structure.

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