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β-Cyclodextrin as the suitable molecular container for isopulegol enantiomers

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ABSTRACT

Isopulegol, an insoluble in water and highly volatile compound, due to its neuroactive properties is a potentially important agent for medical applications. Formation of "host–guest" molecular complexes with cyclodextrins would lead to the increase of its water solubility and bioavailability. Interactions between native cyclodextrins (α, β and γ) and isopulegol enantiomers were studied in solution proving the formation of inclusion complexes for β- and γ-cyclodextrins. For the more stable complexes with β-cyclodextrin crystal structures were obtained showing the formation of molecular capsules forming molecular container able to accommodate two guest molecules.

1. Introduction

Active pharmaceuticals usually applied in solid dosage formulations appear as a crystalline, which is highly preferred to the amorphous forms, due to its better stability and usually, higher purity. The main problem for solid formulations is the occurrence of polymorphism, leading to the change in physiochemical properties of the molecule, which may cause change in its bioavailability (Bernstein, 1989). One of the means of better control over crystallization process and thus elimination of polymorphism is the usage of co-crystallization. Crystal engineering and supramolecular synthesis of active pharmaceutical ingredients (API)-based co-crystals is now being incorporated in the drug design process (Maiwald, 2006; Weyna et al., 2012).

Several volatile terpenoids, among them isopulegol, are reported to have neuroactive properties. The studies of experimental animal models revealed their possible usefulness against anxiety (Silva et al., 2007) and seizures (de Almeida et al., 2008; de Sousa, Quintas, & Almeida, 2007). Lately, some reports concerning experiments involving essential oils, which can lead to their usage as anti-tumour agents in hepatocellular carcinoma therapy, were published. Paik, Kork, Beak, Paek, and Kim (2005) demonstrated that essential oils from *Zanthoxylum schinifolium* pericarp, containing isopulegol, could induce apoptosis of HepG2 Human Hepatoma Cells. Hepatocellular Carcinoma (HCC) is the fifth most widely occurring cancer (targeting around a million people a year) (Marrero, 2006; Motola-Kuba, Zamora-Valdes, Uribe, & Mendez-Sanchez, 2006). It affects mostly people with viral hepatitis B or C (Blum, 2005). Unfortunately, surgery involving liver transplantation seems to be the only remedy for HCC (Singhal, Jayaraman, Dhanasekaran, & Kohli, 2012); which leads to the extensive search for the alternative cure.

Isopulegol, which belongs to the class of terpenoids, is highly volatile compound, insoluble in water. The formation of "host–guest" complex would lead to the increase of its water solubility and bioavailability. The choice of cyclodextrins as a "carrier" compound was motivated by their general non-toxicity (Irie & Uekama, 1997) and previous incorporations of cyclodextrins into some drug formulations (e.g. β-cyclodextrin/proxicam β-cyclodextrin/omeprazole tablets) (Loftsson & Duchene, 2007). Moreover, there is a linear correlation between solubility of the guest compound and concentration of the cyclodextrin solution (Stella & Rajewski, 1997). To date there are not many examples of API-based crystalline complexes involving native cyclodextrins, due to the problems with crystallization process. Nevertheless, some crystal structures of inclusion complexes of β-cyclodextrin with drugs are known, e.g. with quinine (Fan et al., 2006) and sulfonylurea hypoglycemic drugs (Paulidou, Maffeo, Yannakopoulou, & Mavridis, 2010). In this paper we will show that, by changing the size of host cyclodextrins from α-cyclodextrin, containing 6 glucose units to β-cyclodextrin, containing 7 glucose units, the process of complex formation may be induced (Fig. 1). Moreover, we show that the largest γ-cyclodextrin may also be able to form inclusion complexes with isopulegol, but based on stability constants

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measured in solution, β-cyclodextrin seems to be a better host for isopulegol molecules. Isopulegol exists in the form of two enantiomers, differing in configuration on C1, C3 and C5 stereogenic centres. For the most efficient β-cyclodextrin complexes with (+)- and (−)-isopulegol were obtained in crystalline form and crystals structures were solved. Unfortunately, despite many attempts to get analogous crystals with γ-cyclodextrin, we were not able to obtain them.

2. Materials and methods

2.1. Materials

(+)- and (−)-Isopulegols were obtained from Sigma–Aldrich and used without further purification. α-, β- and γ-Cyclodextrins were purchased from Cyclolab and used as received. Distilled water was used for aqueous solutions.

2.2. Preparation of the complexes

To the 0.01 M solution of β CD (10 mL) (+)- or (−)-isopulegol [15.4 mg (16.9 μl), 0.01 mM] was added. The formed precipitation was filtered off, added to water and stirred at 60 °C until complete solution, and later left for slow cooling. Monocrystals appropriate for X-ray measurement were obtained after 1 week.

2.3. Methods

2.3.1. Chromatography – apparatus and procedures

HPLC experiments were performed using a Waters Acquity *UPLC* system equipped with a vacuum degasser, a high pressure binary pump, a column oven, and *refractive index* detector (Waters, Milford, MA, USA). The mobile phases consisted of a solvent mixture of 20% ethanol in water, containing different amounts of β-cyclodextrin, depending on the experiment. The column used was: symmetry 5 μm C18 4.6 mm × 250 mm (Waters, USA). Flow rate was 0.8 ml/min. All chromatographic measurements were performed at the temperature 25 °C.

2.3.2. X-ray crystallography

Colourless crystals of approximate dimensions 0.20 × 0.13 × 0.08 (β-cyclodextrin/(+)-isopulegol complex) and 0.18 × 0.13 × 0.05 (β-cyclodextrin/(−)-isopulegol complex) were used. Diffraction data were collected at 100 K using Bruker Kappa CCD diffractometer with graphite monochromated Mo Kα radiation. Structure were solved by direct methods (SHELXS-97) and refined on F^2 by full-matrix least-squares method (SHELXL-97) (Sheldrick, 1997). Non-hydrogen atoms of β-cyclodextrin, (+)- and (−)-isopulegols and water were refined with anisotropic thermal displacement parameters. All hydrogen atoms were placed in geometric positions and treated as riding on their parent atoms with C—H = 0.95 Å and O—H = 0.84 Å.

2.3.2.1. Crystal data for β-cyclodextrin/(−)-isopulegol complex. $C_{42}H_{70}O_{35}{\cdot}C_{10}H_{18}O{\cdot}11.22H_2O$, $M = 1491.45$, colourless plate, 0.18 mm × 0.13 mm × 0.05 mm, triclinic, space group $P1$ (No. 1), $a = 15.1663(2)$, $b = 15.4856(2)$, $c = 17.9084(2)$ Å, $\alpha = 113.311(1)$, $\beta = 99.226(1)$, $\gamma = 102.367(1)^\circ$, $V = 3629.39(8)$ Å^3, $Z = 2$, $D_c = 1.365$ g/cm^3, $F_{000} = 1601$, KappaApexII, Mo$K\alpha$ radiation, $\lambda = 0.71073$ Å, $T = 100(2)$ K, $2\theta_{max} = 57.4^\circ$, 52,137 reflections collected, 25,723 unique ($R_{int} = 0.047$). Final $GooF = 1.06$, $R = 0.085$, $wR = 0.219$, R indices based on 22,719 reflections with $I > 2\sigma(I)$ (refinement on F^2), 1860 parameters, 3 restraints. Lp and absorption corrections applied, $\mu = 0.121$ mm^{-1}.

2.3.2.2. Crystal data for β-cyclodextrin/(+)-isopulegol complex. $C_{42}H_{70}O_{35}{\cdot}C_{10}H_{18}O{\cdot}12.38H_2O$, $M = 1512.17$, colourless plate, 0.20 mm × 0.13 mm × 0.08 mm, triclinic, space group $P1$ (No. 1), $a = 15.2569(4)$, $b = 15.3507(4)$, $c = 17.7940(4)$ Å, $\alpha = 113.184(1)$, $\beta = 99.141(1)$, $\gamma = 102.100(1)^\circ$, $V = 3608.17(16)$ Å^3, $Z = 1$, $D_c = 1.153$ g/cm^3, $F_{000} = 1264$, KappaApexII, Mo$K\alpha$ radiation, $\lambda = 0.71073$ Å, $T = 100(2)$ K, $2\theta_{max} = 55.2^\circ$, 47,878 reflections collected, 29,075 unique ($R_{int} = 0.075$). Final $GooF = 1.07$, $R = 0.084$, $wR = 0.185$, R indices based on 24,165 reflections with $I > 2\sigma(I)$ (refinement on F^2), 1878 parameters, 27 restraints. Lp and absorption corrections applied, $\mu = 0.104$ mm^{-1}.

2.3.3. Calculations of intermolecular interactions and crystal energies

An OPIX computer program package (Gavezzotti, 2007) was used for the calculation of intermolecular interactions and crystal energies. The functional form for the *i–j* atom–atom potential in the OPIX code is

$$E(ij, kJ/mole) = A\ \exp(-BR_{ij}) - CR_{ij}^{-6} + 1389.36\, q_i q_j / R_{ij}$$

with R in angstrom and q in electrons. The A, B and C parameters set used describe the Williams potentials (Williams & Houpt, 1986) for C, H, N, O, F atoms. Charge parameters (if applied) must be determined by separate quantum chemical calculations.

3. Results and discussion

The cyclodextrin/isopulegol complexes formation in solution was studied by High Performance Liquid Chromatography. The retention behaviour in a reversed-phase chromatographic system containing natural cyclodextrin as a mobile phase additive for complexes of 1:1 stoichiometry is described by the following equation (Asztemborska, Bielejewska, Duszczyk, & Sybilska, 2000; Walhagen & Edholm, 1991).

$$\frac{1}{k'} = \frac{1}{k'_R} + \frac{K_1[CD]}{k'_R} \quad (1)$$

where k'_R and k' are the retention factors. The first retention factor was observed in the system without the cyclodextrin and the second with cyclodextrin dissolved in the same system. K_1 means the stability constant for the analyte. The reverse of the retention factor is linearly related to the concentration of cyclodextrin. The ratio of slope provides directly a value for K_1. This is guaranteed by small adsorption of cyclodextrin at the surface of the stationary phase, negligible adsorption of its complex with solute on the stationary phase and adsorption of solute molecule at the surface of the stationary p and its complexation by appropriate cyclodextrin in the bulk phase (Asztemborska et al., 2000).

Fig. 2 shows the plot of the reversal of retention factor ($1/k$) of enantiomers of isopulegol against the β-cyclodextrin concentration. As predicted by Eq. (1), the linear relationship of $1/k$ versus cyclodextrin concentration exists for the investigate compound. This behaviour indicates a 1:1 stoichiometry of the complexes β-cyclodextrin/isopulegol. The stability constant for β-cyclodextrin/isopulegol complex is 246.355 ± 17.196 ($R^2 = 0.997$) (see Fig. 2).

The same observations were made for the complexes of the largest γ-cyclodextrin with (+)- and (−)-isopulegol proving the formation of 1:1 complexes with stability constant of 62.667 ± 2.841 ($R^2 = 0.997$) (Fig. 3).

The cavity of the smallest α-cyclodextrin is not large enough for the incorporation of the isopulegol molecules and in this case no complex formation is observed. For the most stable β-cyclodextrin/isopulegol complexes crystal structures of the complexes with both enantiomers of isopulegol were obtained.

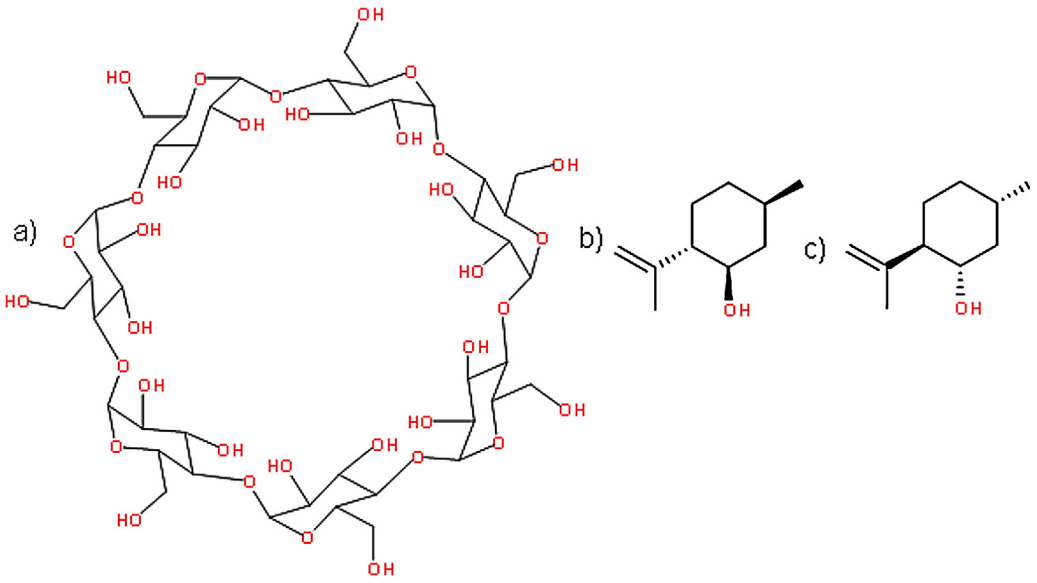

Fig. 1. Molecular structures of (a) β-cyclodextrin, (b) (−)-isopulegol, and (c) (+)-isopulegol.

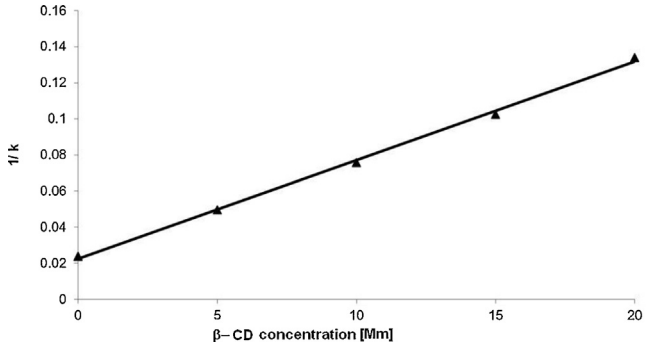

Fig. 2. Relation between the retention factors 1/*k* of (+)- and (−)-isopulegol versus β-cyclodextrin concentration.

In solid state both enantiomers of isopulegol form with β-cyclodextrin inclusion complexes of stoichiometry 2:2 (host:guest) where the cyclodextrin molecules are arranged in molecular capsules by forming head-to-head dimers stabilized by 8 O—H···O hydrogen bonds. Two isopulegol molecules occupy the internal space in the capsules (Figs. 4 and 5). The isopulegol molecules within the cavities are oriented head-to-head and are in van der Waals contact only. No specific directional interactions between guest molecules in the same cavity nor between the guest molecules from the adjacent (top and bottom) cavities were detected. The cyclodextrin molecules are involved in a number of O—H···O and C—H···O hydrogen bonds to adjacent cyclodextrin molecules as well as to water molecules present in large quantity in both crystals and located between the capsules. Most of the water molecules are disordered over several positions.

Each of individual isopulegol/cyclodextrin complexes is slightly different while looking at the host–guest interactions (Table 2). There are no specific interactions between cyclodextrin and isopulegol molecules, except for one. In the (−)-isopulegol/cyclodextrin complex the molecule A forms 1 week C—H···O hydrogen bond [C6A—H2A1···O 14, $d_{C\cdots O}$ = 3.543 Å, $<_{C-H\cdots O}$ = 174°]. The differences between the host–guest, host–host and guest–guest interactions within molecular capsule by means of interaction energy

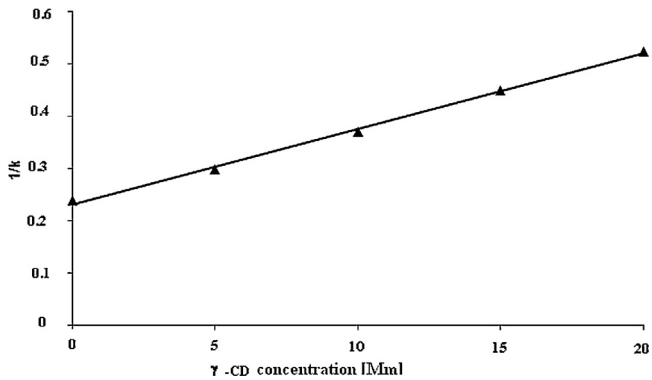

Fig. 3. Relation between the retention factors 1/*k* of (+)- and (−)-isopulegol versus γ-cyclodextrin concentration.

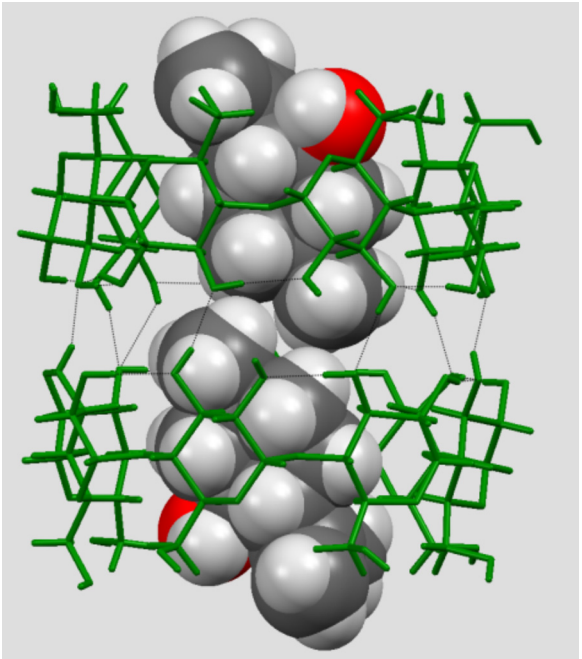

Fig. 4. [2:2] Inclusion complex of β-cyclodextrin with (+)-isopulegol.

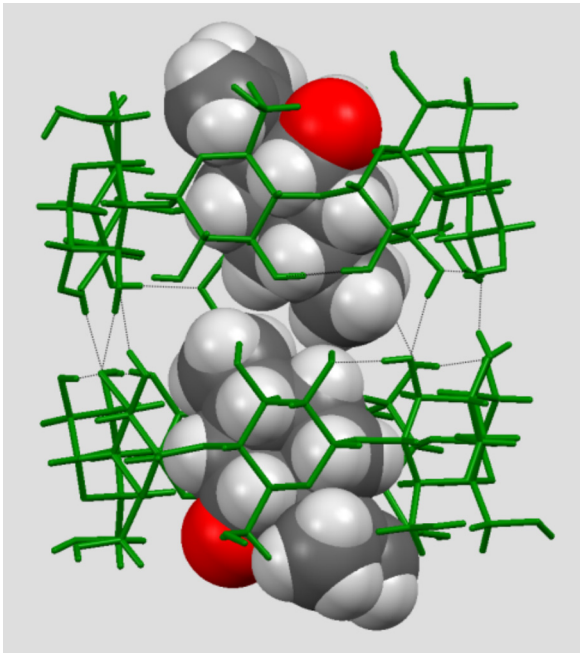

Fig. 5. [2:2] Inclusion complex of β-cyclodextrin with (−)-isopulegol.

Table 1A
Analysis of hydrogen bonds in the 2:2 host:guest dimer.

Donor—H···acceptor	D—H	H···A	D···A	D—H···A
β-Cyclodextrin/(−)-isopulegol complex				
Host–host interactions				
O16—H16H···O20[a]	0.82	1.93	2.7260	165
O18—H18H···O15[b]	0.82	2.16	2.9803	176
O23—H23H···O60	0.82	2.39	3.1215	149
O24—H24H···O62	0.82	2.33	2.7800	115
O28—H28H···O66	0.82	1.95	2.7132	154
O29—H29H···O59[b]	0.82	1.99	2.8002	170
O51—H51H···O54[c]	0.85	1.92	2.7622	169
O56—H56H···O52[d]	0.82	2.03	2.8522	178
O58—H58H···O34	0.82	1.96	2.7586	164
O60—H60···O22	0.82	1.96	2.7648	166
O61—H61···O8W[a]	0.82	2.34	2.6544	104
O64—H64H···O26	0.82	2.04	2.8336	163
O68—H68H···O30	0.82	2.01	2.8008	161
O70—H70···O32	0.82	1.93	2.7438	175
C9—H9A···O31[a]	0.98	2.45	3.2533	139
C10—H10···O32[a]	0.98	2.39	3.3455	166
C22—H22A···O22[b]	0.98	2.33	3.2817	164
C53—H53···O66[c]	0.98	2.37	3.2995	157
C79—H79···O63[d]	0.98	2.53	3.3594	143
C83—H83···O62[d]	0.98	2.38	3.3012	157
Host–guest interaction				
C6A—H2A1···O14	0.97	2.58	3.5433	174

[a] Symmetry equivalent positions: $1+x, y, z$.
[b] Symmetry equivalent positions: $x, 1+y, z$.
[c] Symmetry equivalent positions: $x, -1+y, z$.
[d] Symmetry equivalent positions: $-1+x, y, z$.

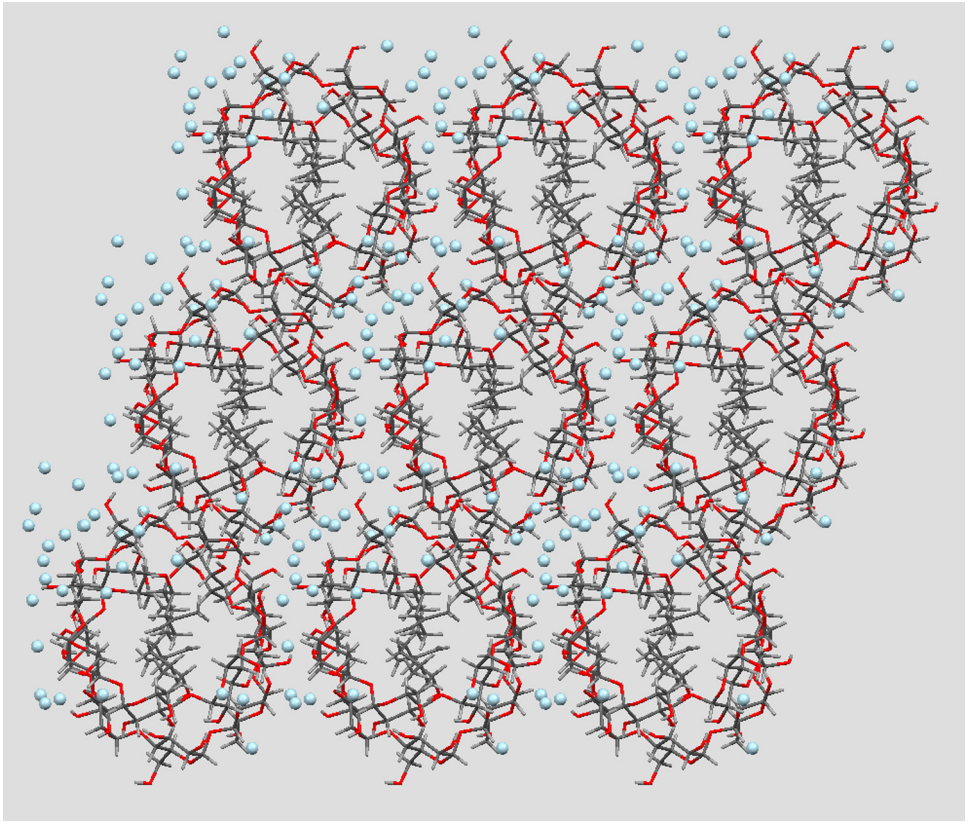

Fig. 6. Packing diagram for (−)-isopulegol/β-cyclodextrin complex. View down the *c* crystallographic axis. Water molecules represented by pale blue balls. Due to the high degree of disorder of most of the water molecules the hydrogen atoms were not located during the crystal solution and refinement. (For interpretation of the references to color in text, the reader is referred to the web version of this article.)

Table 1B
Analysis of hydrogen bonds in the 2:2 host:guest dimer.

Donor—H···Acceptor	D—H	H···A	D···A	D—H···A
β-Cyclodextrin/(+)-isopulegol complex				
Host–host interactions				
O15—H15A···O19[a]	0.82	2.00	2.7961	163
O17—H17A···O21[b]	0.82	2.02	2.8205	167
O20—H20A···O51[d]	0.82	1.87	2.6841	169
O24—H24···O60	0.82	1.97	2.7499	158
O28—H28A···O64	0.82	1.98	2.7726	164
O32—H32A···O68	0.82	1.99	2.7600	157
O34—H34H···O70	0.82	1.95	2.7533	164
O51—H51A···O20[g]	0.82	2.26	2.6841	112
O56—H56A···O52[h]	0.82	1.88	2.7025	176
O58—H58A···O22	0.82	1.99	2.7883	166
O62—H62A···O26	0.82	1.95	2.7437	163
O65—H65A···O30	0.82	2.44	3.0810	136
O66—H66···O30	0.82	1.93	2.7083	158
C4—H4···O30[a]	0.98	2.38	3.2933	154
C15—H15···O33[b]	0.98	2.55	3.3932	144
C16—H16···O33[b]	0.98	2.35	3.2633	154
C24—H24B···O50[c]	0.97	2.38	3.3258	165
C71—H71···O58[e]	0.98	2.32	3.2875	170
C79—H79···O63[f]	0.98	2.52	3.2771	134
C83—H83···O626	0.98	2.36	3.3349	170

[a] Symmetry equivalent positions: $x, -1+y, z$.
[b] Symmetry equivalent positions: $-1+x, y, z$.
[c] Symmetry equivalent positions: $x, 1+y, 1+z$.
[d] Symmetry equivalent positions: $1+x, 1+y, 1+z$.
[e] Symmetry equivalent positions: $x, y, 1+z$.
[f] Symmetry equivalent positions: $1+x, y, 1+z$.
[g] Symmetry equivalent positions: $-1+x, -1+y, -1+z$.
[h] Symmetry equivalent positions: $1+x, y, z$.

Table 2
Calculated energies (kJ/mol) of intermolecular interactions.

Interaction		$E_{6\text{-exp}}$	E_{coul}
β-Cyclodextrin/(−)-isopulegol complex			
Host–guest	Molecule A	−101.0	−4.2
	Molecule B	−112.9	−1.6
Host–host		14.2	−9.5
Guest–guest		−6.5	0.3
β-Cyclodextrin/(+)-isopulegol complex			
Host–guest	Molecule A	−111.3	−4.0
	Molecule B	−107.5	−4.0
Host–host		−31.3	−22.8
Guest–guest		−7.6	0.2

components $E_{6\text{-exp}}$ and E_{coul}, for both complexes are shown in Tables 1A and 1B.

β-Cyclodextrin complexes with (−)- and (+)-isopulegol are isostructural (Table 2). Dimeric complexes are stacked one on top of another along the crystallographic *c* axis forming columns. Most of the water molecules are located between the columns playing the role of 'molecular glue' and stabilizing the structure by forming significant number of hydrogen bonds to cyclodextrin molecules as well as between themselves. Packing diagram for (−)-isopulegol/cyclodextrin crystal structure is presented in Fig. 6.

4. Conclusions

In conclusion, interactions between native cyclodextrins and the two enantiomers of highly volatile isopulegol were studied in solution by means of HPLC experiments, proving the formation of 1:1 host–guest complexes for β- and γ-cyclodextrins, while for the smallest α-cyclodextrin no complex formation was observed. Measured stability constants indicated formation of stronger complex with β-cyclodextrin. Complexes of β-cyclodextrin with (+)- and (−)-isopulegol were also obtained in crystalline form. In solid state both enantiomers of isopulegol form 2:2 inclusion complexes with β-cyclodextrin, where the cyclodextrin molecules are arranged in molecular capsules forming molecular container able to accommodate two guest molecules.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carbpol.2013.04.097.

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