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Research Article

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Molecular Modeling study of the Chiral Recognition of Celiprolol Enantiomers by a β-Cyclodextrin

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Abstract Molecular dynamic docking simulations for 100 pico-seconds were performed for all the possible alignments of Celiprolol in complex with β-cyclodextrin "Celiprolol-β-CD" complexes on the level of molecular mechanics and calculations of interaction energies were performed. The computational calculations for the inclusion complexes of the S- and R-β-CD rationalized the reasons for the different migration times between the Celiprolol enantiomers. These calculations allowed determining the mode of binding of Celiprolol enantiomers to β-CD and explaining the stereoselectivity enantioselectivity. (S) isomer forms complex with β -CD that different from the corresponding (R) isomer, as judged from the binding energy difference in interaction energy; Molecular modeling calculations suggested that the total chiral selectivity action by β-CD favors the (R) Celiprolol enantiomer.

Keywords Enantioselective separation; Celiprolol-β-CD complexes, Molecular dynamics

Introduction

Cyclodextrins are cyclic (α-1, 4)-linked oligosaccharides of α-D-glucopyranose, containing a relatively hydrophobic central cavity and hydrophilic outer surface [1]. Owing to lack of free rotation about the bonds connecting the glucopyranose units, the cyclodextrins are not perfectly cylindrical molecules with toroidal or cone shape as seen in Figure 1-3.

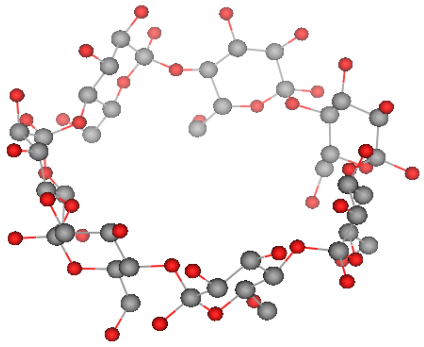


Figure 1: Cone shaped cyclodextrin β-CD

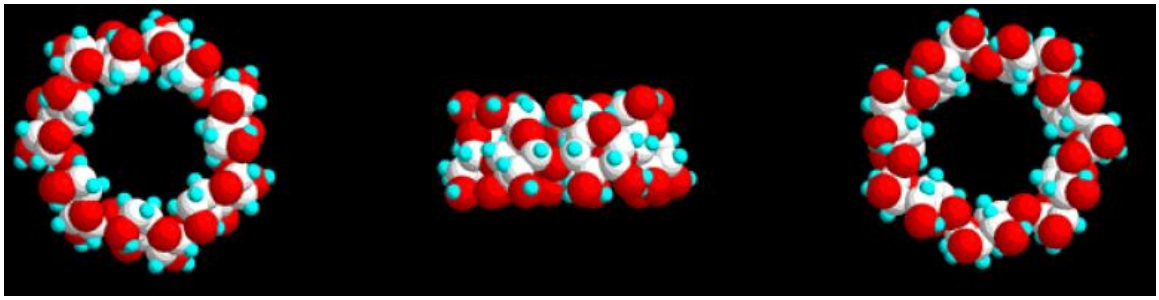


Figure 2: 3D Molecular model of β-CD

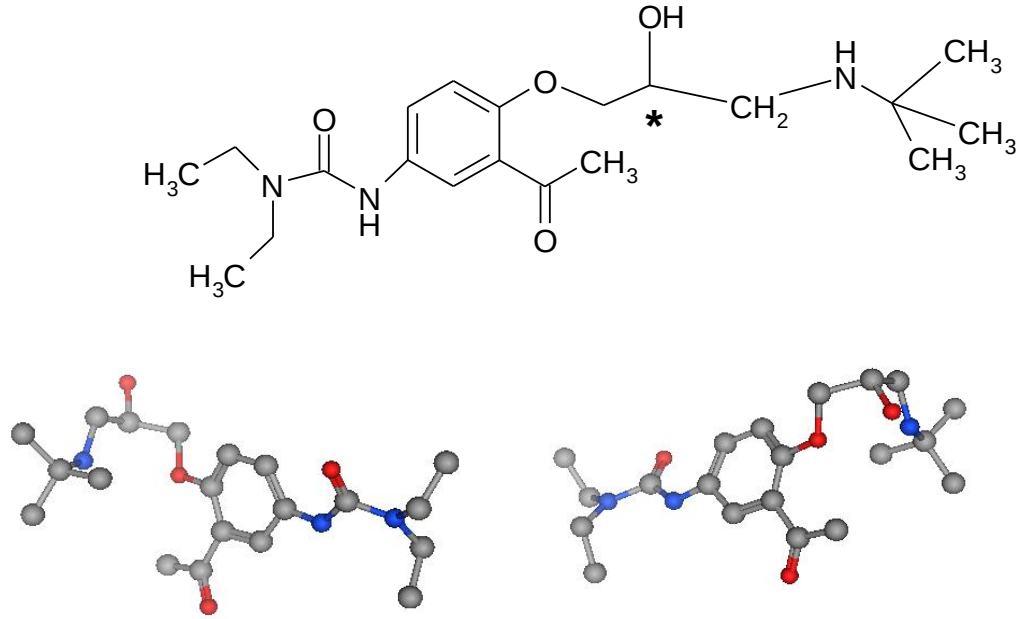


Figure 3: chemical structure of Celiprolol and the molecular model R , S-chiral forms

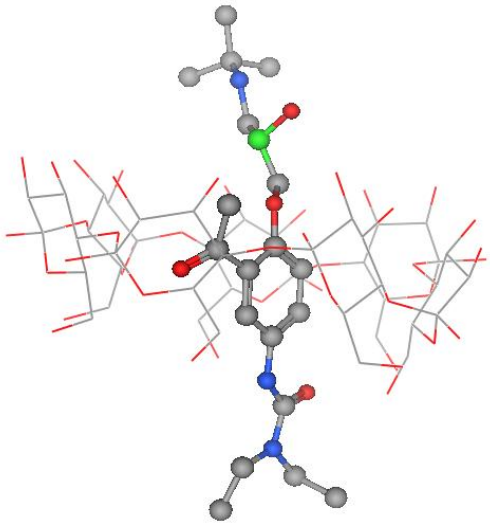
Based on this architecture, the primary hydroxyl groups are located on the narrow side of the torus, while the secondary hydroxyl groups are located on the wider edge. When cyclodextrins are used to solubilize water insoluble drugs, it is generally assumed that the solubilization proceeds through inclusion complex formation. The hydrophobic cavity of cyclodextrins is capable of trapping a variety of molecules within to produce inclusion compounds [2].

β-CD is a cyclic oligomer made of seven α-D-glucose residues arranged in a donut shaped ring. The specific coupling and conformation of these glucose units give the cyclodextrin a rather rigid, toroidal molecular structure with a hollow interior of specific volume [3].

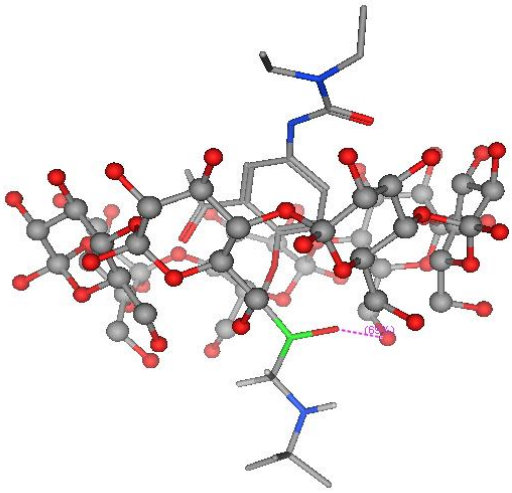
The lining of the cavity is formed by hydrogen atoms and glycosidic bridging oxygen atoms; consequently this surface is fairly hydrophobic. The unique shape and physical–chemical properties of the cavity allows the formation of inclusion complexes with organic molecules, where the extent of the complex formation depends on the polarity of the absorbed molecules. The hydrophilic characteristic of β-CD is provided by its two different rims: one narrower (N) or primary hydroxyl rim and another wider (W) or secondary hydroxyl rim.

Chiral cyclodextrin (CD) hosts have been used extensively as models for investigating chiral and molecular recognition. However, despite intense efforts, the mechanism of the recognition is not fully understood and many

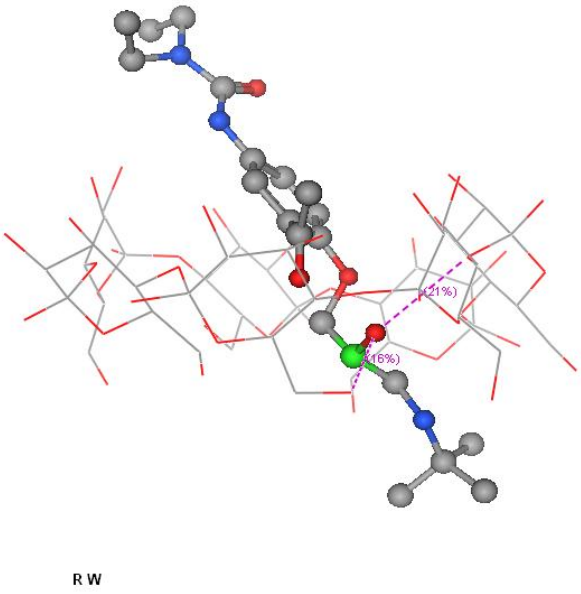
essential data are missing. In this study, we used β-cyclodextrin (β-CD) as the chiral host and the two Celiprolol isomers as the chiral guests.



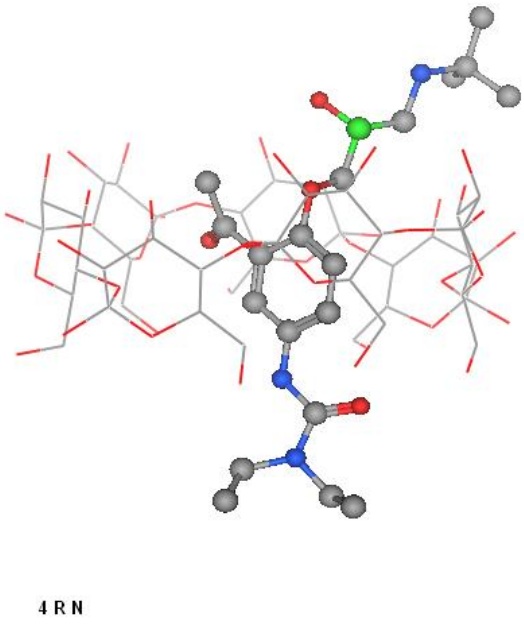
a) S-1



b) S-2



c) R-1

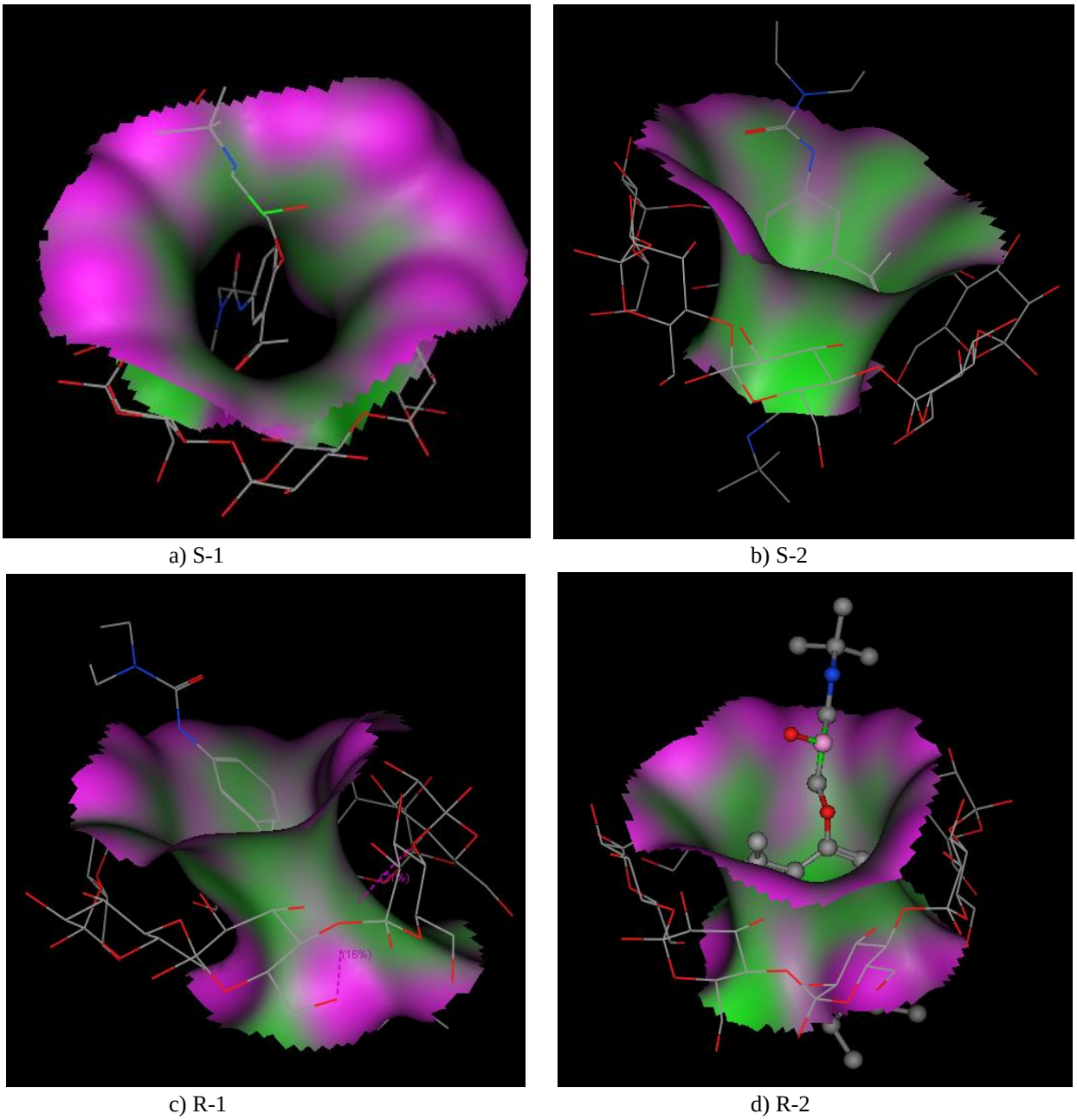


d) R-2

Figure 4: Schematic representation of the possible penetration modes (a-d) of Celiprolol into β-CD. The corresponding minimized geometries are used as the starting points for the MD simulations.

Celiprolol is a drug molecule containing a single chiral center, a phenyl urea chain (PU) and aminoalkane (AA) end; properties that are useful for constructing a simple and good model to illustrate the chiral discrimination [4]. Molecular dynamic studies suggest that features such as guest fit to the CD cavity, hydrogen bonding of the guest molecules, and binding energy combine to play a significant role in chiral discrimination [5-7].

Molecular dynamics simulations for 100 ps was carried out on four different penetration modes of the celiprolol isomers into the β-CD cavity. During the simulation time, this penetration mode produces a large number of hydrogen bonds between the amido urea group of Celiprolol and the secondary hydroxyl groups of β-CD (Figure 4)**.**
Molecular modeling data showed that for the possible penetration modes, there are evident differences in occupancy and orientation between the two Celiprolol enantiomers inside the β-CD cavity, which in turn plays an important role in maximizing hydrogen bonding.
Molecular modeling calculations suggested that the total chiral selectivity action by β-CD favors the (R)-Celiprolol enantiomer.



a) S-1 b) S-2

c) R-1 d) R-2

Figure5: Electrostatic mapping of the R-β-CD and S-β-CD complexes in the wide and narrow arrangements

Geometrical analysis of the hydrogen bond indicates that H-bonds are formed between Celiprolol and the host is considered the key element to favor the (R)-isoform. The preferred penetration mode found, corresponds to the R-isomer geometry where the phenyl urea group of Celiprolol faces the wide cavity of the β-CD. In this geometry, the (S)-Celiprolol enantiomer moves more freely inside the host cavity after insertion, while the (R)-Celiprolol enantiomer presents different configuration (Figure 5).

Moreover, the (R)-Celiprolol enantiomer forms a significant number of moderate to strong hydrogen bonds with the secondary hydroxyl groups of β-CD during the entire simulation time, while the (S)-Celiprolol enantiomer showed less hydrogen bonds; Table 2.

Table 1: Energy contribution of the lowest energy conformer of each isoform of the Celiprolol and the energy performance of the host before docking the guest.

Energy (kcal/mol)	S-Celiprolol	R-Celiprolol	β-CD
E_{electr}	-19.00	-29.00	4.2
E_{vdW}	32	52	69.00
$E_{(total)}$	42	53	315
$E_{(complex)}$	357	368	-

Table 2: Energy data of the 100 ps molecular dynamics simulations carried out on four different penetration modes of the Celiprolol isomers into the β-CD cavity.

Energy (kcal/mol)	S-β-CD	R-β-CD	S-β-CD	R-β-CD
MODEL*	A		B	
E_{electr}	-31.60	-35.00	-155.00	-138
E_{vdW}	104.00	105.00	203	181
$E_{(total)}$	325	323	249	248
$E_{(binding)}$ #	-32	-45	-108	-120
HB	4	4	7	7

* Model A: S or R-enantiomer is docked at the host where the urea group pointed out from the narrow rim.

Model B: S or R-enantiomer is docked at the host where the urea group pointed out from the wide rim.

$E_{binding} = E_{complex} - (E_{\beta\text{-CD}} + E_{celiprolol})$

Materials and methods

Molecular modeling methodology:

Molecular mechanics and dynamics calculations were performed with Hypechem and MOE package [8].The structure of β-cyclodextrin was taken from the Cambridge Structural Database (Reference code **2V8L**) [9].The Celiprolol molecule was constructed using the builder program of Hyperchem. Partial charges were defined using AM1 calculation. Energy minimization was performed using the conjugate gradient at 0.01 kcal mol^{-1}. Molecular properties were calculated using SCF Wave functions module.

Docking Studies:

Docking the Celiprolol into the cavity of β-CD was performed by means of molecular simulations. Four different inclusion orientations were considered according to the penetration modes of each enantiomer S and R-Celiprolol(A & B models); [8]. Each model has two different Celiprolol entry based on the site of penetration. (Model-A) configuration is performed by fitting the phenyl urea group from the narrow rim. Orientation of the (S) guest with phenyl urea group immersed in β-CD cavity (1:1 complexes) through the wider ring (Model-B).Similar to (S)-isomer, the other (R) enantiomer has two possible alignments within the CD cavity; Figure 5.

The low-energy structures of the docking simulations of each host-guest complex was subjected to molecular dynamics (MD) simulation for 100 ps.

Semi-empirical calculations using PM3 level were applied to define the partial charges and the molecular dynamics were carried out for the entire system for 5 ps intervals at temperatures 10, 100, 200, 300, 400, and again 300 K with velocity reassignment every 0.5 ps followed by 50 ps simulation at 300 K. After the equilibration, the main simulations were run for more 50ps.The molecular lipophilicity-hydrophilic patterns (MLHP) for complex models were calculated.

Energy of binding ($E_{binding}$), corresponding to energy minima, were computed together with their electrostatic and *van der waals* contributions. Energy of interaction between β-CD and target molecule was calculated using the following formula:

$$E_{binding} = E_{complex} - (E_{\beta\text{-}CD} + E_{celiprolol})$$

Where $E_{binding}$= energy of binding of the complex, $E_{complex}$ = total energy of the complex.

$E_{\beta\text{-}CD} + E_{celiprolol}$ are the individual total energies of the β-CD and the celiprolol molecules.

The magnitude of the energy change would be an indication of the stability of guest-host complexation. The more negative the complexation energy change is the more thermodynamically favorable is the inclusion complex.

Results and Discussion:

In this study, we used β-cyclodextrin (β-CD) as the chiralhost and the two Celiprololisomers as the chiral guests. β-CD is a cyclic oligomer made of seven a-D-glucose residues arranged in a donutshapedring. The specific coupling and conformation of these glucose units give the cyclodextrin a rather rigid, toroidal molecular structure with a hollow interior of specific volume. The lining of the cavity is formed by hydrogen atoms and glycosidic bridging oxygen atoms; consequently this surface is fairly hydrophobic. The unique shape and physical–chemical properties of the cavity allows the formation of inclusion complexes with organic guest molecules, where the extent of the complex formation depends on the polarity of the absorbed molecules.

The hydrophilic characteristic of β-CD is provided by its two different rims: one narrower (N) or primary hydroxyl rim and another wider (W) or secondary hydroxyl rim. These features are shown in Figure 3. Celiprolol is a drug molecule containing a single chiral center, a phenyl urea chain (PU) and aminoalkane (AA) end; properties that are useful for constructing a simple and good model in which study chiral discrimination.

The main theoretical results obtained for the optimized geometries are shown in Tables 1 & 2. The binding energies upon complexation with β-CD; indicates that the β-CD can form stable complexes with both S- and R-Celiprolol. The energy calculations show that the inclusion of the substituted phenyl urea group of the (R)-isomer through the wider rim (Model B) is energetically more favorable (-31) out of the four possible orientations, Table 1.

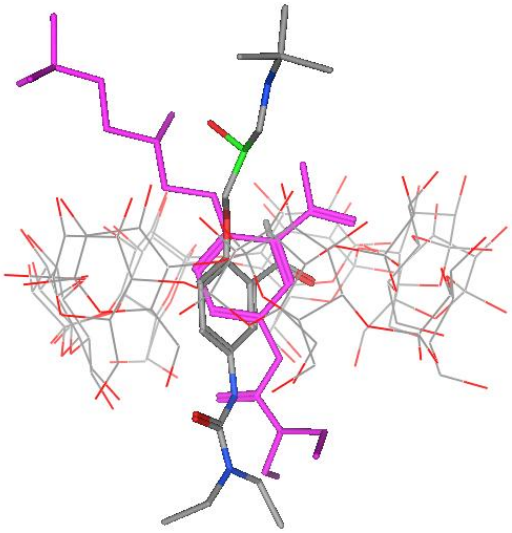
The (S-CD) inclusion complex is significantly more favorable than that of the R-CD complex by an energy difference of 2 and 6.0 kJ mol^{-1} for model A and B respectively, Tables 1 & 2. Analysis of the modeling data indicates that S-CD fits more tightly into the β-CD. Dynamic simulation for 100 ps indicated that R-CD tilt towards

the *Z*-axis in model B when it enters the cyclodextrin cavity, probably to enhance the stability of the formed complex. This phenomenon was not observed for the inclusion of R-CD in the cyclodextrin; Figure 6.

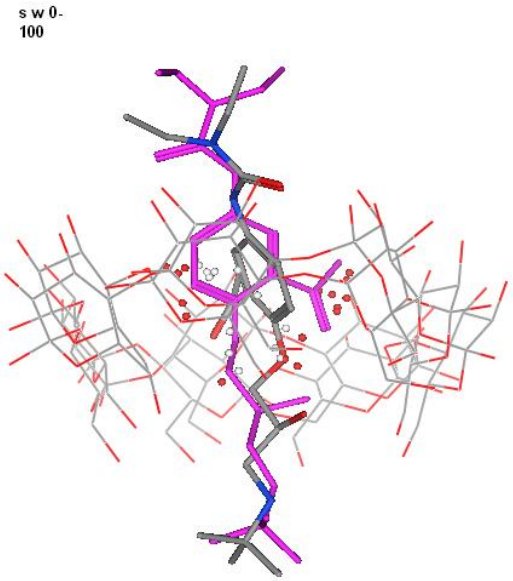
Host–guest hydrogen bonding interactions resulting from fitting small molecules in cyclodextrin cavities play an important role in the stability of the inclusion complex formation. The S-CD complex is favorable for both orientations where the S-enantiomer penetrates well into the cavity of the cyclodextrin in both alignments; Figure 4.

We also observed from Figure 5 that R-CD tilt towards the *Z*-axis in model, when it enters the cyclodextrin cavity, probably to enhance the stability of the formed complex. This phenomenon was not observed for the inclusion of R-CD in the cyclodextrin. The R-isomer was found to possess more hydrogen bonds than the S-isomer. These interactions are considered as an additional force beside the *vander waals* forces that adding extra stability of the inclusion complexes.

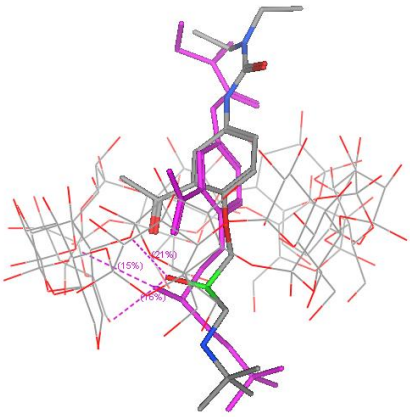
The energy of interaction determines the most stable inclusion complex between the chiral molecules and the cyclodextrin. Therefore, the enantiomeric separation using cyclodextrin is probably achieved via preferential electrostatic interaction of the host molecule with each of the enantiomers.

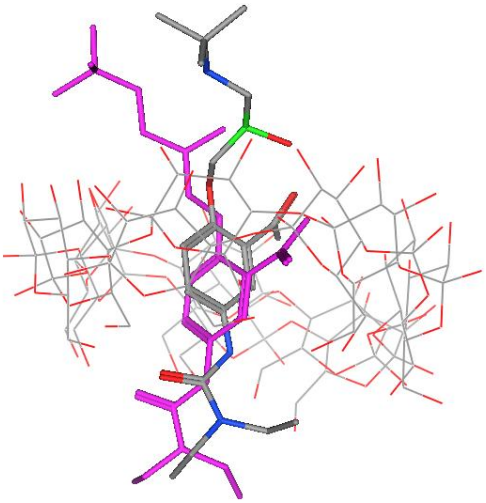


a) S1-β-CD



b) S2- β-CD





c) R1-β-CD d) R2-β-CD

Figure 6: Schematic representation of the MD simulations models of the four complexes of Celiprolol-β-CD. at 0ps (magenta) and at 100ps (colored).different penetration modes

Conclusion

The molecular dynamic results come in agreement with the experimental results revealing that the (R)-celiprolol enantiomer is more tightly bonded than the (S)-celiprolol enantiomerenlightening that among the four penetration modes, there is one that appears to possess the most predominant discriminating features, (R) isoform in wide model-B.

Acknowledgments

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