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Theoretical Investigation of Inclusion Complex between Omeprazole Enantiomers and Carboxymethyl-β-Cyclodextrin

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Abstract. Host-guest inclusion complexes between R/S-Omeprazole (R/S-OME) enantiomers with Carboxymethyl-β-Cyclodextrin (CM-β-CD) is proposed to predicts the separation of its enantiomers that considering the interaction energy and inclusion geometry. The inclusion complex structures were built into two orientations i.e. 1: 1 and 2: 1 as the ratio of host to guest. All structures were optimized by two methods i.e. molecular mechanic docking and quantum semi empiric PM3. Based on the value of binding energy obtained from the computational modelling, it was found that inclusion complex of S-Omeprazole with Carboxymethyl-β-Cyclodextrin (S-OME/CM-β-CD) is more stable than the inclusion complex of R-Omeprazole with Carboxymethyl-β-Cyclodextrin (R-OME/CM-β-CD). Moreover, R/S-Omeprazole can form stable inclusion complexes with Carboxymethyl-β-Cyclodextrin by the ratio of host: guest equal to 2: 1. Other thermodynamic parameter values, i.e. Enthalpy (ΔH), Entropy (ΔS), and Gibbs free energy (ΔG) show that the inclusion complex of S-OME/CM-β-CD is more exothermic, more spontaneous, and preferably formed when compared to inclusion complex of R-OME/CM-β-CD. In addition, the formation of the R/S-OME inclusion complex with Carboxymethyl-β-Cyclodextrin (CM-β-CD) is an enthalpy driven process based on these values.

1. Introduction

Cyclodextrin is a modified starch, cyclic non-reducing oligosaccharide that composed by D-glucopyranose units connected with α-(1,4)-glicocydic bonding [1]. Thus, cyclodextrin can be classified into α- cyclodextrin, ß-cyclodextrin, and γ-cyclodextrin [2]. Ability of cyclodextrin to separate isomers is not good, because it has weak interactions [2]. The interactions were be improved by modify to hydroxyl groups and cyclodextrin cavity, which can improves adjust to guest molecule and interactions of formed inclusion complex [3].

This study uses carboxymethyl-β-cyclodextrin (CM-β-CD) as host molecule, because it was widely used to more applications and flexible to form complex inclusion with various guest molecules [4]. Previously, several studies have been examined relating to cyclodextrin derivatives, that CM-β-CD has

good ability to separate enantiomers [5]. CM-β-CD can be improves to stability with guest molecules, increases to electrophoresis mobility for enantiomers separation, and its carboxymethyl group does not interfere with the hydrophobic cavity [6].

Proton Pump Inhibitor (PPI) is a type of drugs relates to gastrointestinal diseases that used to inhibit gastric acid release. PPI compounds worked by forming to proton pump bonding (H^+/K^+-adenosine triphosphates) inside gastric parental cell [7,8]. These compounds are widely used to treat the gastrointestinal diseases i.e. Pantoprazole (PAN), Omeprazole (OME), Lansoprazole (LAN) and Rabeprazole (RAB). Each of these compounds have R - and S - enantiomers. However, these enantiomers have different work to inhibit the gastric acid release [7].

Previously, computational studies to predict chirality separation by using CM-β-CD has been studied, i.e. molecular mechanics [9], molecular dynamics [12], semi empiric methods (AM1[10], PM3[6,11], PM6[12]), ONIOM[11], and DFT[12]. The cyclodextrin system studies with PM3 method have been widely performed to getting the results with good accuracy [6,11]. Nascimento et al was done to calculate the CM-β-CD/Hydroxypropanolol system by using PM3 and DFT methods [6]. Chunli Yan et al.[10] was calculated the system by using PM3 and ONIOM2 methods. From previous studies, the calculation of PM3 method was a good result to predicting the separation of enantiomers by carboxymethyl-β-cyclodextrin [6,11]. The aims of this study were done to calculate the inclusion complexes between R/S-omeprazole (R/S-OME) enantiomers with various CM-β-CD system by using mechanical molecular docking and quantum semi empiric PM3 methods.

2. Methods

In this study, structure and frequency of inclusion complex between R/S-Omeprazole (R/S-OME) and Carboxymethyl-β-Cyclodextrin (CM-β-CD) was optimized using PM3 method implemented in Games-US version December 5, 2014 R1 for 64 bit (x86_64 compatible) under Linux with gnu compilers. The initial molecule structure of R/S-OME was created using Avogadro software package [13]. The CM-β-CD molecular structure was created by modify the original β-CD using carboxymethyl group. The original geometry of β-CD was obtained from CSD (Cambridge Structural Database).

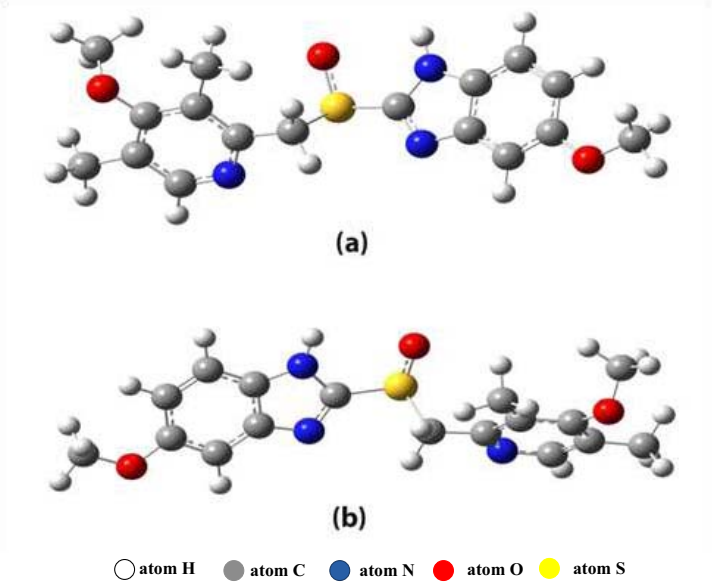

Figure 1. Molecular structure of free R/S-Omeprazole optimized by PM3 method.

The guest molecule structures distinguished into two enantiomers i.e. R-Omeprazole (R-OME) and S-Omeprazole (S-OME), which showed as Figure 1(a) and 1(b), respectively. The host molecule structure was modeled by considering the ratio of host to guest i.e. 1: 1 and 2: 1 that known as monomer and dimer,

respectively. A monomer form was symbolized to CM-β-CD that showed by Figure 2(a). Thus, dimer forms divided into three orientations i.e. head to head (CM-β-CD-HH), tail to tail (CM-β-CD-TT), and head to tail (CM-β-CD-HT) that showed by Figure 2(b), 2(c), and 2(d), respectively. These dimer forms were built by adjusting the orientation between two CM-β-CD cavity.

Briefly, the calculation of inclusion complex structures divided into three general steps. Initially, the host and guest compounds were calculated by PM3 method to get optimized structures. Next, the host-guest inclusion complex created by docking process with considering the best conformation of guest. Finally, the docking results were calculated using PM3 method taking frequency calculation to get thermodynamic property of host-guest inclusion complex.

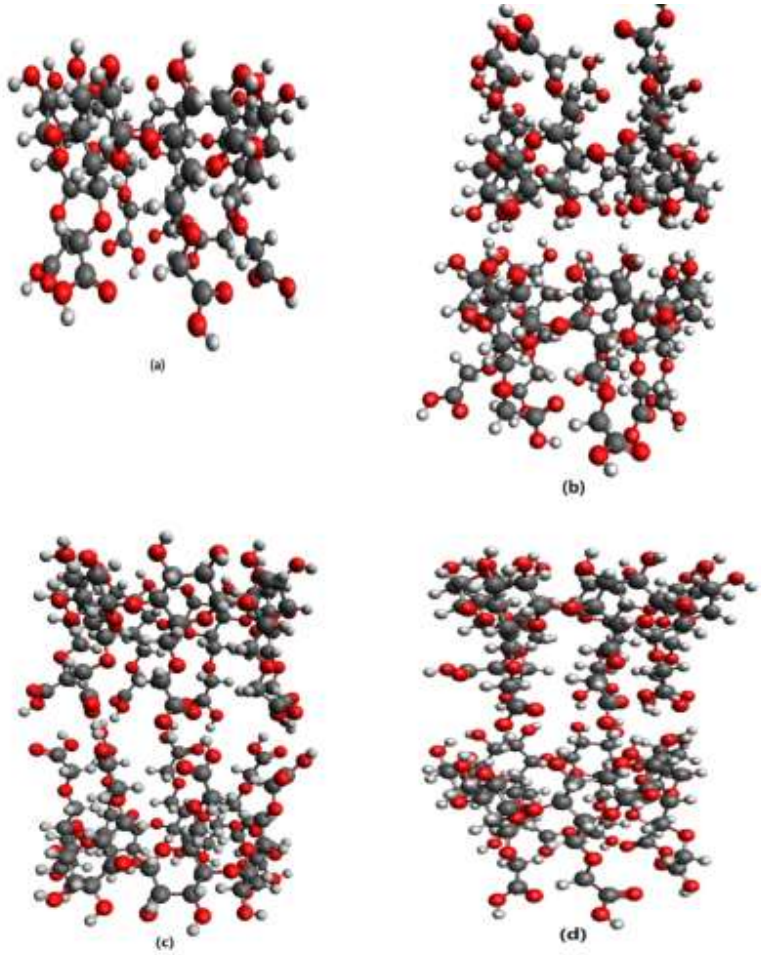

Figure 2. Molecular structure of free Carboxymethyl-β-Cyclodextrin (a) CM-β-CD, (b) CM-β-CD-HH, (c) CM-β-CD-TT and (d) CM-β-CD-HT.

3. Results and discussion

3.1. Binding energy calculation using molecular mechanics docking method from carboxymethyl-β-cyclodextrin/omeprazole inclusion complex

Binding energy of inclusion complex between omeprazole with carboxymethyl-β-cyclodextrin that calculated using molecular mechanics docking method was summarized by Table 1. The results have a positive and negative values for each of binding energy (ΔE). The positive value of binding energy show that R-OME enantiomer will be eluted first than S-OME and otherwise. By overall, binding energy of S-

OME/CM-β-CD inclusion complex is more negative (ΔE(S) = -26.50 kcal/mol) than R-OME/CM-β-CD inclusion complex (ΔE(R) = -26.17 kcal/mol). This case implied that non-covalent interaction resulted between R-OME with host molecule was weak, so that R-OME will be eluted first than S-OME. From these considerations show that S-omeprazole enantiomers more stable to form inclusion complex with carboxymethyl-β-cyclodextrin.

Table 1. Binding energy (kcal/mol) of inclusion complex of Omeprazole/Carboxymethyl-β-Cyclodextrin calculated using Docking method

Omeprazole						
Complex	**%frequency**	**ΔE**	**ΔΔE**	**ΔE(R)**	**ΔE(S)**	**ΔΔE(R)-(S)**
R-OME/CM-β-CD	96.0	-5.43	0.21			
S-OME/CM-β-CD	100.0	-5.64				
R-OME/CM-β-CD-HT	98.0	-6.88	0.10			
S-OME/CM-β-CD-HT	100.0	-6.98		**-26.17**	**-26.5**	0.33
R-OME/CM-β-CD-HH	54.0	-7.59	0.31			
S-OME/CM-β-CD-HH	85.5	-7.90				
R-OME/CM-β-CD-TT	96.0	-6.27	-0.29			
S-OME/CM-β-CD-TT	50.0	-5.98				

3.2. Molecular structure of carboxymethyl-β-cyclodextrin/omeprazole inclusion complex optimized using semiempiric quantum pm3 method

A stable structure was resulted through optimization the molecular structure until obtained minimum energy. Figure 3 shows the optimized structure of carboxymethyl-β-cyclodextrin/Omeprazole inclusion complex were calculated using molecular mechanics docking and PM3 methods. In the figure seem that geometry resulted by PM3 method is more random than molecular mechanics docking method. This case indicates that occurred relaxation toward the inclusion complex structures due to PM3 calculation.

The host-guest inclusion complex was created by the intermolecular hydrogen bonding between the nitrogen and oxygen at omeprazole with hydrogen atoms of the host hydroxyl group. The hydrogen bonding given as the distance of $d_{H\text{-}O}$. If the $d_{H\text{-}O}$ distance is less than 3.00 Å, then intermolecular hydrogen bonding on the inclusion complex was created. All geometry of inclusion complex show that the guest molecules position located into the host cavity. Based on amount hydrogen bonding was created, that head to head (HH) dimer orientation of the inclusion complex is more stable than head to tail (HT) and tail to tail (TT) dimer orientations. This case was also corresponding toward the thermodymic analysis result from Table 2 i.e. ΔE = -49.49 kcal/ mol, ΔH = -55.92 kcal/mol and ΔG = -47.55 kcal/mol, which referenced by the inclusion complex S-OME/CM-β-CD-HH. The stability of inclusion complex interaction is also determined by the steric factor between host and guest molecules.

The output data of host-guest inclusion complex from docking process is recalculated using semi empiric quantum PM3 method to get result with more accuracy. By overall, binding energy from Table 2 shows that the interaction of inclusion complex between S-OME with host molecule are more negative than R-OME interaction. From these considerations show that S-OME is more stable than R-OME to form inclusion complex with host molecules.

3.3. Thermodynamic analysis from frequency calculation using PM3 method

Thermodynamic parameters that calculated using PM3 method were summarized by Table 2. The parameters were obtained from the output data due to frequency calculation. The thermodymics calculation was assumed at 1 atm and 289.15 K. The resulted thermodymics values were binding energy (ΔE), Gibbs free energy (ΔG), enthalpy (ΔH), and entropy (ΔS).

From binding energy (ΔE) show that S-OME enantiomer is more stable than R-OME to form inclusion complex with all host molecules. From enthalpy (ΔH) seem that S-OME enantiomer is more exothermic than R-OME to form inclusion complex with all host molecules. From Gibbs, free energy (ΔG) and entropy (ΔS) show that S-OME enantiomer is more spontaneous than R-OME to form inclusion complex

with the host molecules at low temperature. The thermodymic analysis shows that R/S-omeprazole can form stable inclusion complexes with carboxymethyl-β-cyclodextrin by the ratio of host: guest equal to 2: 1 as dimer form.

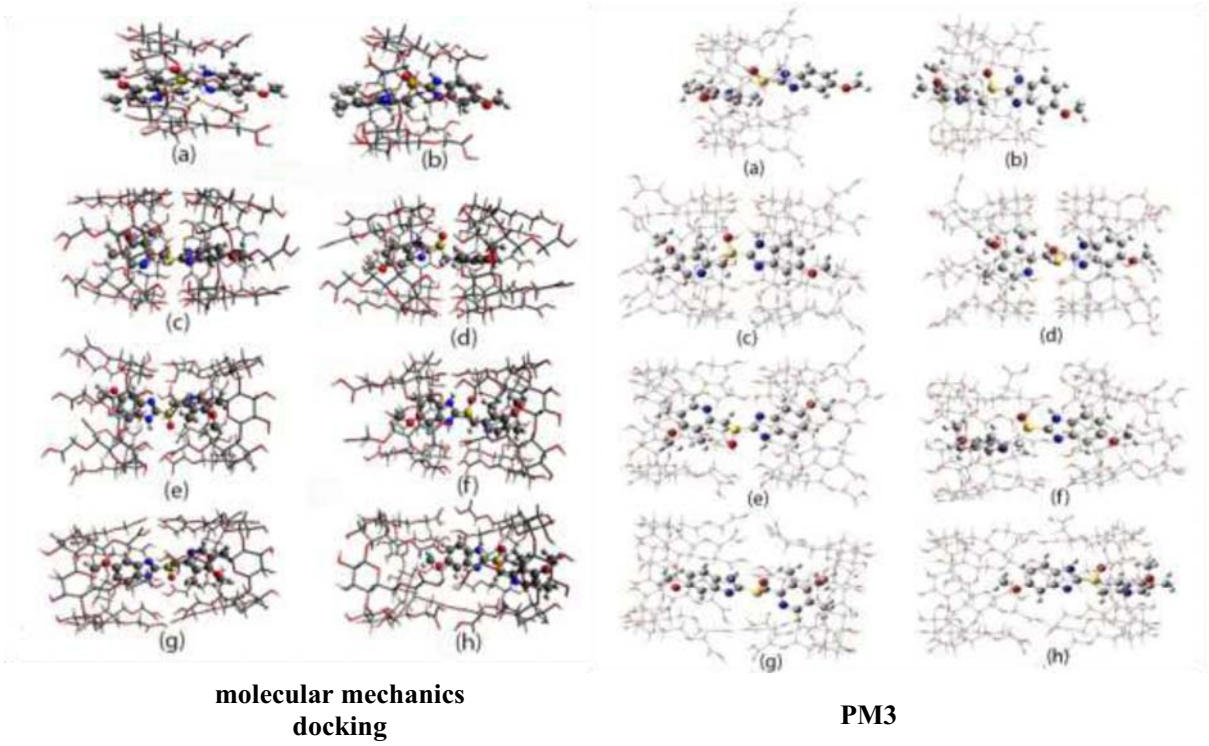

Figure 3. Structure of inclusion complex optimized using molecular mechanics docking and PM3 methods (a) R-OME/CM-β-CD, (b) S-OME/CM-β-CD, (c) R-OME/CM-β-CD-HH, (d) S-OME/CM-β-CD-HH, (e) R-OME/CM-β-CD-HT, (f) S-OME/CM-β-CD-HT, (g) R-OME/CM-β-CD-TT and (h) S-OME/CM-β-CD-TT.

Table 2. Thermodynamic parameters of inclusion complex of Omeprazole/Carboxymethyl-β-Cyclodextrin calculated using PM3 method

Inclusion Complex	ΔE (kcal/ mol)	ΔH (kcal/mol)	ΔG (kcal/mol)	ΔS (kcal/ mol K)
R-OME/CM-β-CD	-23.43	-26.35	-26.35	-95040
S-OME/CM-β-CD	**-25.89**	-28.21	-28.21	-90003
R-OME/CM-β-CD-HH	-47.17	-56.28	-40.25	-185391
S-OME/CM-β-CD-HH	**-49.49**	-55.92	-47.55	-146843
R-OME/CM-β-CD-HT	-39.92	-43.96	-43.96	-120198
S-OME/CM-β-CD-HT	**-40.16**	-44.49	-44.49	-119201
R-OME/CM-β-CD-TT	-38.41	-41.62	-41.62	-107312
S-OME/CM-β-CD-TT	**-44.05**	-47.26	-16.35	-103696

4. Conclusion

Computational calculation of inclusion complex between R/S-Omeprazole and Carboxymethyl-β-Cyclodextrin has been studied. Host-guest inclusion complexes between enantiomers of R/S-Omeprazole (R/S-OME) enantiomers and carboxymethyl-β-cyclodextrin (CM-β-CD), has been modeled using molecular mechanic docking and quantum semiempiric PM3 methods. The result from both method have

similar tendency which implied that R-Omeprazole will be eluted first than S-Omeprazole. This case was indicated that the formed interaction between S-Omeprazole with Carboxymethyl-β-Cyclodextrin more stable than R-Omeprazole, which is stabilized by hydrogen bonding. The formation of the inclusion complex between R/S-Omeprazole with Carboxymethyl-β-Cyclodextrin is an enthalpy driven process.

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