Computational Study of Inclusion Complexes Between Omeprazole Enantiomer with Hydroxypropyl-β-Cyclodextrin

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**Abstract.** Computational study of inclusion complexes between R/S-omeprazole as Proton Pump Inhibitor (PPI) compound with hydroxypropyl-β-cyclodextrin in three of its dimeric structure configurations (head to head, head to tail and tail to tail) has been carried out. All calculations were performed using PM3 quantum semiempirical method. Computational results showed that total binding energy (BE) of R-omeprazole complex is more exothermic than total binding energy of S-omeprazole complex. The calculated binding energy of R-omeprazole complex was -74.65 kcal/mol, while for S-omeprazole complex was -64.09 kcal/mol. This results indicate that R-omeprazole inclusion complex has higher stability compared to S-omeprazole inclusion complex. The value of ΔH, ΔS, and ΔG for R-omeprazole inclusion complex formation were -77.02 kcal/mol, -0.24 cal/mol.K and -2.62 kcal/mol, respectively, while the value of ΔH, ΔS, and ΔG for S-omeprazole inclusion complex formation were -66.47 kcal/mol, -0.29 cal/mol.K and 19.29 kcal/mol respectively. These values indicate that the formation of inclusion complexes between R/S-omeprazole with hydroxypropyl-β-cyclodextrin is enthalpy driven process.

1. **Introduction**

PPI (Proton Pump Inhibitor) is a class of drugs used to inhibit gastric acid release. The PPI compound works by forming a covalent bond in the H+/K⁺ ATPase enzyme system present in the gastric parietal cell [1]. PPI compounds that are often used in treating gastric acid problems include lansoprazole, omeprazole, pantoprazole and rabeprazole [1]. Each of these PPI compounds has R- and S-
enantiomer, in which has different pharmacological characteristics in treating gastric acid excessive secretion. For example, both R- and S-enantiomer of omeprazole have the same function, i.e. treating excess gastric acid, but their effectiveness in treating the disease is different. S-omeprazole is more effective in treating gastric acid excessive secretion compared to R-omeprazole and its racemic mixture [2]. To obtain effective results in the treatment of the disease, separation of both enantiomers of PPI drugs was performed. The most common separation method used in this enantiomeric separation is HPLC (high performance liquid chromatography) and CE (capillary electrophoresis). To separate S-omeprazole enantiomer from the mixture, chiral stationary phase in HPLC or chiral selector in CE have important role.

One of the materials that can be used as chiral stationary phase and chiral selector is cyclodextrin. Cyclodextrin is cyclic oligosacharide which composed of glucose molecules connected with α-1,4-glycocydic bonding. The molecular geometry of cyclodextrin is similar with a truncated cone. Cyclodextrin has an ability to form inclusion complex with various guest molecule depends on its polarity and size because the inner cavity of cyclodextrin molecule is hydrophobic and the outer surface is hydrophilic. Due to this ability, cyclodextrin and its derivatives has been utilized in the field of pharmacy, cosmetic industry, agrochemical industry and analytical chemistry, especially in the separation of chiral compounds. One of cyclodextrin derivative used for this application is hydroxypropyl-β-cyclodextrin [3,4]. In the understanding of microscopic phenomena of chiral separation between PPI compound and hydroxypropyl-β-cyclodextrin, molecular modeling is one of the best method used so far. There are several level of theories which is used in molecular modeling, such as DFT, ONIOM, Semiempiric Quantum, Molecular Dynamics, and Molecular Mechanics. Even though DFT is the level of theory with high accuracy for molecular modeling [5-8], semiempiric quantum method using PM3 is one of the method that has good cost-performance ratio which has been used by some researchers to perform host-guest inclusion complex modeling [9-12]. In this research, molecular modeling calculation has been performed using semiempiric quantum PM3 to learn about microscopic phenomena in the inclusion complex between R,S-omeprazole and hydroxypropyl-β-cyclodextrin. This research aimed to study the inclusion complexes between R/S-omeprazole and hydroxypropyl-β-cyclodextrin to understand chiral separation process of R/S-omeprazole compound by hydroxypropyl-β-cyclodextrin.

2. Computational Method
The initial molecular structure of R/S-omeprazole was built using Avogadro 1.1.0 [13] software package. The molecular structure of hydroxypropyl-β-cyclodextrin used in this calculation was originated from the initial geometry of β-cyclodextrin obtained from the CSD (Cambridge Structural Database). Modification has been done by replacing the H- atom in the 6’-hydroxyl functional groups with a hydroxypropyl functional group. Furthermore, R/S-omeprazole compound and hydroxypropyl-β-cyclodextrin were optimized and the frequencies were calculated using semiempiric quantum PM3 method implemented in Gamess-US version December 5, 2014 R1 for 64 bit (x86_64 compatible) under Linux with gnu compilers [14].

The structure of hydroxypropyl-β-cyclodextrin in the dimer forms was also made by adjusting the orientation of two hydroxypropyl-β-cyclodextrinnmolecule, i.e. head to tail, head to head and tail to tail orientation. Then, molecular mechanics docking calculation was performed from the optimization result of each host and guest compound. In this process, host and guest compounds form the host-guest inclusion complex. The results of the docking process were extracted by taking the guest molecules that have the most excellent conformation. Then, the host-guest inclusion complexes from the docking results were optimized using semiempiric quantum PM3 method and the frequency calculation was also performed on them to determine the thermodynamic properties of host-guest inclusion complex.

3. Results and Discussion
3.1. Binding energy calculation
Docking can be assumed as lock and key process to the interaction of enzymes and substrates [15]. The inclusion complex itself is a guest compound surrounded by host compound. Figure 1 shows that the overall binding energy of R-omeprazole and hydroxypropyl-β-cyclodextrin inclusion complex is more negative ($\Delta E_R = -26.1$ kcal/mol) than S-omeprazole and hydroxypropyl-β-cyclodextrin inclusion...
complex ($\Delta E_S = -23.7$ kcal/mol). The more negative binding energy indicates the stronger binding between guest molecule and host molecule by non-covalent interaction. It implied that S-omeprazole is going to be eluted first in HPLC, because R-omeprazole was bound stronger to hydroxypropyl-$\beta$-cyclodextrin than S-omeprazole.

Figure 1. Binding energy comparison on chiral separation of R/S-Omeprazole using hydroxypropyl-$\beta$-cyclodextrin (Hp-cyd is hydroxypropyl-$\beta$-cyclodextrin in monomeric form; while Hp-cyd-hh, Hp-cyd-hh, and Hp-cyd-tt are dimeric form with orientation: hh = head to head, ht = head to tail and tt = tail to tail).

3.2. Molecular structure and hydrogen bonding
Optimization step forms the most stable structure of each guest, host, and host-guest compound with minimum energy. Figure 2 shows the optimized geometry of each free guest compound, figure 3 shows the optimized geometry of each free host compound, and figure 4 shows the optimized geometry of hydroxypropyl-$\beta$-cyclodextrin/omeprazole inclusion complex.

The intermolecular hydrogen bonding between the hydrogen atoms of the host hydroxyl group with the nitrogen and oxygen in omeprazole were defined as the distance of $d_{H-O}$ or $d_{H-N}$ that is less than 3.00 Å. If the $d_{H-O}$ or $d_{H-N}$ distance is more than 3.00 Å, it will be concluded that there are no intermolecular hydrogen bonding on the inclusion complex.

Figure 2. Optimized molecular structure of free R/S-omeprazole guest molecule

Figure 4 shows the hydrogen bonding on the interaction between R-omeprazole and hydroxypropyl-$\beta$-cyclodextrin which has $d_{HN}$ distance of 2.970 Å between the nitrogen in the pyridine group at R-omeprazole with the hydrogen in the secondary hydroxyl group at hydroxypropyl-$\beta$-cyclodextrin; R-omeprazole with hp-cyd-hh has $d_{H-O}$ distance of 1.782 Å between oxygen in sulfonyl group with a hydrogen in secondary hydroxyl group; R-omeprazole with hp-cyd-hh has $d_{H-O}$ distance of 1.787 Å between oxygen in sulfonyl group with a hydrogen in the primary
hydroxyl group; R-omeprazole with hp-cyd-tt has a $d_{H,N}$ distance of 1.811 Å between nitrogen in the benzimidazole group with a hydrogen in the primary hydroxyl group. The total hydrogen bonding on the inclusion complex between R-omeprazole and hydroxypropyl-$\beta$-cyclodextrin. Thus, there are 4 hydrogen bondings.

**Figure 3.** Optimized molecular structure of free host molecule (a) hp-cyd; (b) hp-cyd-hh; (c) hp-cyd-ht; dan (d) hp-cyd-tt.

Figure 4 also shows the intermolecular hydrogen bonding between S-omeprazole and hp-cyd-ht has a $d_{H,O}$ distance of 1.777 Å between oxygen in the sulfanyl group with hydrogen in the primary hydroxyl group. S-omeprazole with hp-cyd-tt has a $d_{H,N}$ distance of 2.257 Å between nitrogen in the benzimidazole group with a hydrogen in the primary hydroxyl group. Total hydrogen bonding on the inclusion complex between S-omeprazole and hydroxypropyl-$\beta$-cyclodextrin is 2 hydrogen bondings. Based on the total of intermolecular hydrogen bonding in each inclusion complex, it was concluded that R-omeprazole will be bound to hydroxypropyl-$\beta$-cyclodextrin stronger than S-omeprazole and S-omeprazole will be eluted faster than R-omeprazole. This result has similar tendency with the previous result that S-omeprazole will be eluted first than R-omeprazole based on binding energy value from docking result.

3.3. Thermodynamic analysis
The thermodynamic analysis was performed using frequency calculation data obtained from the output file. The analyzed thermodynamic parameters were the binding energy (taken from total energy), enthalpy, Gibbs free energy, and entropy. Statistically, this thermodynamic calculation was performed at pressure of 1 atm and temperature of 298.15 K. The results data analysis of omeprazole was used as a validation method based on experiments that have been done by Hancu et al. In the Hancu et al study, it is known that S-omeprazole is more easily separated than the R-enantiomer [10].

The complexation reaction of omeprazole with hydroxypropyl-$\beta$-cyclodextrin is exothermic, indicated by the negative value of energy and enthalpy changes. According to table 1, the thermodynamic quantities of R-omeprazole enantiomer tend to be more negative than the S-omeprazole enantiomer, which are seen from the overall quantity data of binding energy, enthalpy
changes, Gibbs free energy change, and entropy changes. This proves that the R-omeprazole enantiomer is more stable than S-omeprazole enantiomer.

![Figure 4](image_url)

**Figure 4.** The inclusion complex structure of hydroxypropyl-β-cyclodextrin (hp-cyd) with R/S-omeprazole in the form of (a) monomer, (b) dimer head to head (hh), (c) head to tail (ht), and (d) tail to tail (tt).

| Inclusion Complex | BE (kcal/mol) | ΔH (kcal/mol) | ΔG (kcal/mol) | ΔS (kcal/mol K) |
|-------------------|---------------|---------------|---------------|-----------------|
| R-omz : hp-cyd    | -11.31        | -11.90        | 1.64          | -0.05           |
| S-omz : hp-cyd    | -2.23         | -2.82         | 14.93         | -0.06           |
| R-omz : hp-cyd-hh | -26.72        | -27.31        | -3.46         | -0.08           |
| S-omz : hp-cyd-hh | -19.11        | -19.70        | 5.16          | -0.09           |
| R-omz : hp-cyd-ht | -28.38        | -28.97        | -4.25         | -0.09           |

Table 1. Thermodynamic parameters of inclusion complex of omeprazole/hydroxypropyl-β-cyclodextrin.
S-omz : hp-cyd-ht  |  -34.69  |  -35.28  |  -12.09  |  -0.08
R-omz : hp-cyd-tt  |  -8.24   |  -8.84   |   2.07   | -0.04
S-omz : hp-cyd-ht  |  -8.08   |  -8.67   |  11.29   | -0.07

**Overall**
R-omz  |  -74.65  |  -77.02  |  -2.62   | -0.24
S-omz  |  -64.09  |  -66.47  |  19.29   | -0.29

4. Conclusion
Molecular modeling of inclusion complex between R/S-omeprazole with hydroxypropyl-β-cyclodextrin have been performed using molecular docking and semiempiric quantum PM3 method, and the result from both method have similar tendency which implied that S-omeprazole will be eluted first, faster than R-omeprazole. Computational calculation conclude that inclusion complex formed between hydroxypropyl-β-cyclodextrin with R-omeprazole is more stable than with S-omeprazole, which is stabilized by hydrogen bonding. Moreover, the formation of the inclusion complex between R/S-omeprazole with hydroxypropyl-β-cyclodextrin is an enthalpy driven process.

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