Advanced Pharmaceutical Bulletin

Adv Pharm Bull, 2015, 5(2), 289-291
doi: 10.15171/apb.2015.040
http://apb.tbzmed.ac.ir

TUOMS Publishing Group

Short Communication

Host-guest Inclusion Complexes between Mitiglinide and the Naturally Occurring Cyclodextrins α, β, and γ: A Theoretical Approach

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Article info
Article History:
Received: 4 May 2014
Revised: 9 July 2014
Accepted: 21 July 2014
ePublished: 1 June 2015

Keywords:
· Host-guest inclusion
· Mitiglinide
· Cyclodextrins
· PM3 method
· Semi-empirical

Abstract
Purpose: The present study is aimed to study the host-guest inclusion complexation of the naturally occurring cyclodextrins (CDs), namely; (α-CD,β-CD, and γ-CD) with mitiglinide (MIT).
Methods: Host-guest inclusion complexation was simulated using semi-empirical PM3 method.
Results: The obtained results clearly indicate that the complexes formed are energetically favored in the presence of γ-CD (E_{comp} = -17.884 kcal/mol) of the optimal configurations of (1:1) MIT/γ-CD inclusion complexes. Moreover, the results obtained reveal that the formation of more stable MIT/γ-CD complex compared to MIT/α-CD or MIT/β-CD complexes is primarily due to differences in intermolecular hydrogen bonding.
Conclusion: The present theoretical results may be informative to scientists who are devoting themselves to developing effective methods for enhancing the drug solubility.

Introduction

The inclusion complexation with cyclodextrins (CDs) is an attractive and widely used technique for solubility/dissolution enhancement of poorly water-soluble drugs. CDs, are naturally occurring cyclodextrins that commercially available cyclic oligosaccharides containing 6, 7, 8-glucopyranose units and are referred to as α-, β- and γ-CDs, respectively.[1] The inclusion complexation of drug molecules with CDs usually accompanied in favorable changes in the physicochemical properties of the drug, such as solubility, dissolution rate, stability and bioavailability, thus making them more suitable for oral drug delivery.[2]
Mitiglinide (MIT), (2S)-benzyl-4-(cisperhydroisoindol-2-yl) butyric acid (Figure 1). It is a novel insulinotropic agent of the glinide class with rapid onset.[3] Analogous to other glinide group members, MIT acts by stimulating the secretion of insulin from pancreatic-beta cells by closing the ATP-sensitive K^+ [$K_{(ATP)}$] channels.[4] MIT is hydrophobic and has a low aqueous solubility, possibly limiting its range of applications.[5]
In the current paper, we have investigated the inclusion processes of MIT with the naturally occurring CDs using PM3 method in order to get some insight into the conformation of this complex. Furthermore, to investigate and predict the interaction energies (E_{comp}) of the optimal configurations of (1:1) mitiglinide/CDs inclusion complexes by employing molecular simulations using molecular mechanics methods with Autodock to determine the mode of inclusion of MIT within the CD. The obtained structures were further optimized by the semiempirical method PM3 to obtain the binding energies of the studied inclusion complexes.

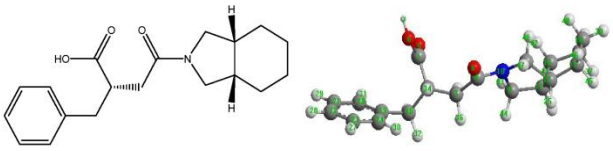

Figure 1. The chemical and 3D structures of mitiglinide (MIT) optimized using the PM3 method.

Computational method

The starting geometries of MIT and the host structures (α-CD,β-CD, γ-CD,) were built based on the structures that are generated from the crystallographic parameters provided by the Drug,[6] and the Cambridge Structural Database (CSD).[7,8] Each of the starting geometry was separately optimized using the semi empirical method, PM3 available in the Gaussian03 software package.[9] The starting geometries of the inclusion complexes were constructed using HyperChem (Version 7.0, Hypercube, Gainesville, FL, USA). The previously optimized structures of MIT and host molecules were allowed to approach each other along the symmetric axis (the X-axis) passing through the center of the host cavity. For example, in the β-CD case, the coordinate system used to define the process of complexation is based on constructing the CD with the seven identical glucose units positioned symmetrically around the Z-axis, such that all the glycosidic oxygens are in the XY plane and

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their center was defined as the center of the coordination system.[10] MIT molecule was docked into the cavity of the CD with the central oxygen atom connecting the two rings coincide with the Z-axis. Multiple starting points were generated by moving the guest molecules along the – and +Z-axis from 10 to -10 Å, at 1 Å intervals, and by rotating the guest molecules from 0° – 360° at 45° intervals. Different inclusion orientations, i.e the pyrrolidine group facing down, the benzene ring facing down into the cavity of the CDs and the carboxylic group facing up and down horizontally into the cavity of the host, were considered for all cases.

Docking of the guest molecule was initially done to maximize the electrostatic interaction and hydrophobic interaction between the host and the guest molecules using the Autodock4.2 software.[11] The Kollman and Gasteiger charges were assigned on the host while the charges on MIT were added automatically. For the autogrid calculation, the grid map of 40 x 40 x 40 $Å^3$ was used for α-CD and β-CD while 50 x 50 x 50 $Å^3$ dimension of grid box was set on γ-CDs. Grid point spacing of 0.375 Å was used and centered on the macromolecule. A total of 21 rigid docking tests in vacuo were constructed using Autodock4.2 software and a total of 100 runs adopting the Lamarkian Genetic Algorithm were performed. The results of cluster ranked in the order of increasing in energy and ranked in the order of increasing energy with 2.0 Å tolerance. The configurations obtained were ranked in clusters which list from the lowest to highest binding energy.

The results from docking study were then again submitted to further optimization at the PM3 level. The inclusion interactions were simulated in vacuum and the presence of water molecules were ignored to save computational time especially for large molecules. Comparisons were made between the conformation from the semi empirical method and the optimized docking results to determine the lowest energy conformation which is then taken as the final structure. The complexation energy, ΔE_{comp}, was calculated for the minimum energy structures by the following equation:

$$\Delta E_{comp} = E_{comp} - E_G - E_H \qquad (1)$$

where, E_{comp}, E_G, and E_H represent the total energy of the host-guest complex, the free guest molecule and the free host molecule, respectively. The magnitude of the energy change would be an indication of the driving force towards complexation. The more negative the complexation energy change is the more thermodynamically favorable is the inclusion complex.

Results and Discussion

To further understand how molecular recognition takes place at the atomic level, we use two different molecular modeling techniques that are the quantum mechanics calculation using the PM3 semi empirical method as well as the docking calculation to complement the experimental studies. Overall the PM3 semiempirical method proved to be more efficient to locate the minimum energy conformations when compared to docking calculation. The final complexation energies (E_{comp}) of the MIT/α-CD, MIT/β-CD, and MIT/γ-CD inclusion complexes were -13.571 kcal/mol, -9.696 kcal/mol and -17.884 kcal/mol, respectively.

The optimized geometries for the lowest energy conformation for the inclusion complexes of MIT with the different CDs are shown in Figure 2. In general, the inclusion of MIT into the cavity of γ-CD results in the most stable conformation when compared to α- and β-CDs and the overall lowest binding energies upon complexation with the different hosts decrease in the order of: γ-CD > α-CD > β-CD. In general the results from the lowest rank structure produced via docking calculation needs to be further optimized through the PM3 calculation and the results after closed comparison between the two methods produced an almost similar inclusion site as shown in Figure 2.

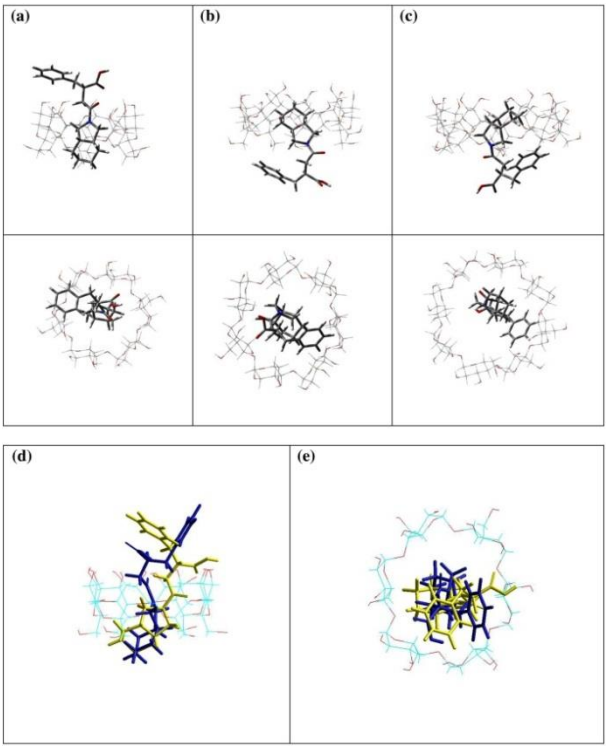

Figure 2. Energy minimized structures obtained from PM3 calculations for the front side and top views of (a): MIT/α-CD; (b): MIT/β-CD; (c): MIT/γ-CD and the Autodock calculations for the (d): side and (e): top views of the MIT/α-CD inclusion complexes.

The dominant driving force for the complexation is evidently H-bondings interaction. Close observation on the structure of the inclusion complexes shows that γ-CD complexes have more H-bonding interactions compared to the β-CD complexes. Various authors have also reported that intermolecular hydrogen bondings between the host-guest interactions resulting from the fitting of small molecules into the cyclodextrin cavities play an important role in the binding energies of a number of cyclodextrin inclusion complexes.[12]

In all three hosts, the pyrrolidine group of the MIT was included into the cavity leaving the benzene ring to move freely outside the cyclodextrin cavity. Almost a complete inclusion of the pyrrolidine ring was observed for the MIT/γ-CD and MIT/α-CD. However, the inclusion the pyrrolidine ring in the β-CD is shallow and consistently, no H-bondings were observed. A slightly more positive complexation energy displayed for the MIT/β-CD inclusion complex, shows that inclusion complex between the two molecules are less favorable from the theoretical point of view.

A careful scanning of literature shows that several studies also used semi-empirical PM3 method and HyperChem software as reliable tools for the inclusion complexes as they yield a good estimate.[13,14] For example, in our previous work, Khaldun *et al*., 2010, we used the above mentioned methods to study the enantiomeric inclusion complexes and to rationalize the reasons for the different migration between the ofloxacin and ornidazole enantiomers with sulfated beta cyclodextrin. The results were in full agreements with the experimental part conducted. As a general conclusion, the use of such PM3 and HyperChem methods in theoretical calculations provides sufficient data for a reliable image of the inclusion process occurred.

Conclusion

The inclusion complexation of MIT with the naturally occurring CDs has been investigated theoretically by performing two different molecular modeling techniques that is the quantum mechanics calculation using the PM3 semi empirical method as well as the docking calculation to complement the experimental studies. The complexation is energetically driven by hydrogen bond interactions between the host and guest molecules. The geometry of the most stable complex shows that the pyrrolidine ring is included deeply inside in the hydrophobic cavity of γ-CD and α-CD while it is shallow in the case of β-CD.

Acknowledgments

The authors are thankful to Universiti Sains Malaysia (USM) and to Batterjee Mecical College for Science and Technology (BMC) for such work collaboration.

Ethical Issues

Not applicable.

Conflict of Interest

Authors declare no conflict of interest.

References

1. Jadhav P, Petkar B, Pore Y, Kulkarni A, Burade K. Physicochemical and molecular modeling studies of cefixime-L-arginine-cyclodextrin ternary inclusion compounds. *Carbohydr Polym* 2013;98(2):1317-25. doi: 10.1016/j.carbpol.2013.07.070
2. Doiphode D, Gaikwad S, Pore Y, Kuchekar B, Late S. Effect of β-cyclodextrin complexation on physicochemical properties of zaleplon. *J Incl Phenom Macrocycl Chem* 2008;62:43-50. doi: 10.1007/s10847-008-9435-3
3. Cai S, Huo T, Xu J, Lu X, Zheng S, Li F. Effect of mitiglinide on Streptozotocin-induced experimental type 2 diabetic rats: a urinary metabonomics study based on ultra-performance liquid chromatography-tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* 2009;877(29):3619-24. doi: 10.1016/j.jchromb.2009.08.044
4. Reimann F, Proks P, Ashcroft FM. Effects of mitiglinide (S 21403) on Kir6.2/SUR1, Kir6.2/SUR2A and Kir6.2/SUR2B types of ATP-sensitive potassium channel. *Br J Pharmacol* 2001;132(7):1542-8. doi: 10.1038/sj.bjp.0703962
5. Protein Information. Database of Therapeutics Targets in Pathogens; Available from: http://circe.med.uniroma1.it/tips/ProteinInfo.php?proteinid=Q09428&type=original.
6. Open Data Drug and Drug Target Database. DrugBank; Available from http://www.drugbank.ca/drugs/DB01252.
7. Betzel C, Saenger W, Hingerty BE, Brown GM. Topography of cyclodextrin inclusion complexes, part 20. Circular and flip-flop hydrogen bonding in .beta.-cyclodextrin undecahydrate: a neutron diffraction study. *J Am Chem Soc* 1984;106(24):7545-57. doi: 10.1021/ja00336a039
8. Harata K. The structure of the cyclodextrin complex. XX. Crystal structure of uncomplexed hydrated γ-cyclodextrin. *Bull Chem Soc Jpn* 1987;60(8):2763-7. doi: 10.1246/bcsj.60.2763
9. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, et al. Gaussian 03, Revision B.03. Pittsburgh PA: Gaussian Inc: 2003.
10. Lyng SMO, Passos M, Fontana JD. Bixin and α-cyclodextrin inclusion complex and stability tests. *Process Biochem* 2005;40(2):865-72. doi: 10.1016/j.procbio.2004.02.017
11. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, et al. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *J Comput Chem* 2009;30(16):2785-91. doi: 10.1002/jcc.21256
12. Yan C, Xiu Z, Li X, Hao C. Molecular modeling study of beta-cyclodextrin complexes with (+)-catechin and (-)-epicatechin. *J Mol Graph Model* 2007;26(2):420-8. doi: 10.1016/j.jmgm.2007.01.010
13. Haiahem S, Nouar L, Djilani I, Bouhadiba A, Madi F, Khatmi DE. Host-guest inclusion complex between β-cyclodextrin and paeonol: A theoretical approach. *C R Chim* 2013;16(4):372-9. doi: 10.1016/j.crci.2012.11.008
14. Al Azzam KM, Saad B, Adnan R, Aboul-Enein HY. Enantioselective analysis of ofloxacin and ornidazole in pharmaceutical formulations by capillary electrophoresis using single chiral selector and computational calculation of their inclusion complexes. *Anal Chim Acta* 2010;674(2):249-55. doi: 10.1016/j.aca.2010.06.046