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Short Communication

Molecular Modeling of Inclusion Complex of Aceclofenac with β-Cyclodextrins

KAMAL DUA*[,1], KAVITA PABREJA[2],VINNY LATHER[3]

[1]Department of Pharmaceutical Technology, School of Pharmacy and Health Sciences, International Medical University, Kuala Lumpur, MALAYSIA-57000.

[2]Department of Life Sciences, School of Pharmacy and Health Sciences, International Medical University, Kuala Lumpur, MALAYSIA-57000.

[3]Centro de Quimica da Madeira, Universidade da Madeira, Campus da Penteada, Funchal 9000390, Madeira, PORTUGAL

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ABSTRACT

Aceclofenac (AF) is a new generational non-steroidal anti-inflammatory drug showing effective anti-inflammatory and analgesic properties with a good tolerability profile in a variety of painful conditions like ankylosing spondylitis, rheumatoid arthritis and osteoarthritis. Aceclofenac is very slightly soluble in water and therefore an attempt has been made to prepare inclusion complexes of aceclofenac with β-cyclodextrin (β-CD) and to explore the possibility of its molecular arrangement using molecular modeling and structural designing. The results indicated the relative energetic stability of the β-CD dimer-AF complex as compared to β-CD monomer-AF. Such molecular-modeling studies can be employed as an additional tool to support the formation of stable molecular inclusion complexation of any water insoluble drug complexed with cyclodextrins.

INTRODUCTION

Cyclodextrin are well-known cyclic oligomers composed of several D-glucose units bonded by linkages providing a hydrophobic internal cavity able to include various drug molecules, thus forming non-covalent inclusion complexes [1, 4]. Cyclodextrin complexation has been widely used in the pharmaceutical field to improve properties of drugs, such as solubility, dissolution rate, chemical and physical stability, and, as consequence, bioavailability, as well as to reduce their irritancy and toxicity [2, 3, 4, 5].The fit of the entire or at least a part of the guest molecule in the cyclodextrin-host cavity determines the stability of the inclusion complex and the selectivity of the complexation process. Therefore, the stability constant value of drug–cyclodextrin complexes is a useful index of the binding strength of the complex and is of great importance for the understanding and evaluation of the inclusion complex formation [6].

Author for Correspondence:
Email: kamalpharmacist@gmail.com

It is important to accurately determine this parameter, in order to predict changes in the physico-chemical properties of the drug after inclusion in the cyclodextrin cavity and to select the most suitable cyclodextrin-host molecule for a given drug-guest, so that inclusion complexation may be successfully exploited at its best [7].

Aceclofenac (AF) is a new generational non-steroidal anti-inflammatory drug showing effective anti-inflammatory and analgesic properties and a good tolerability profile in a variety of painful conditions like ankylosing spondylitis, rheumatoid arthritis and osteoarthritis. Aceclofenac is very slightly soluble in water [8] and hence an attempt has been made to prepare inclusion complexes of aceclofenac with β-cyclodextrin (β-CD) and to study the formation of AF-β-CD inclusion complexes using Fast Rigid Exhaustive Docking (FRED) docking software. β-CD was used for the study, as it has bigger cavity size of (7.5 A°) and it is the least toxic among all the other natural cyclodextrins [9].

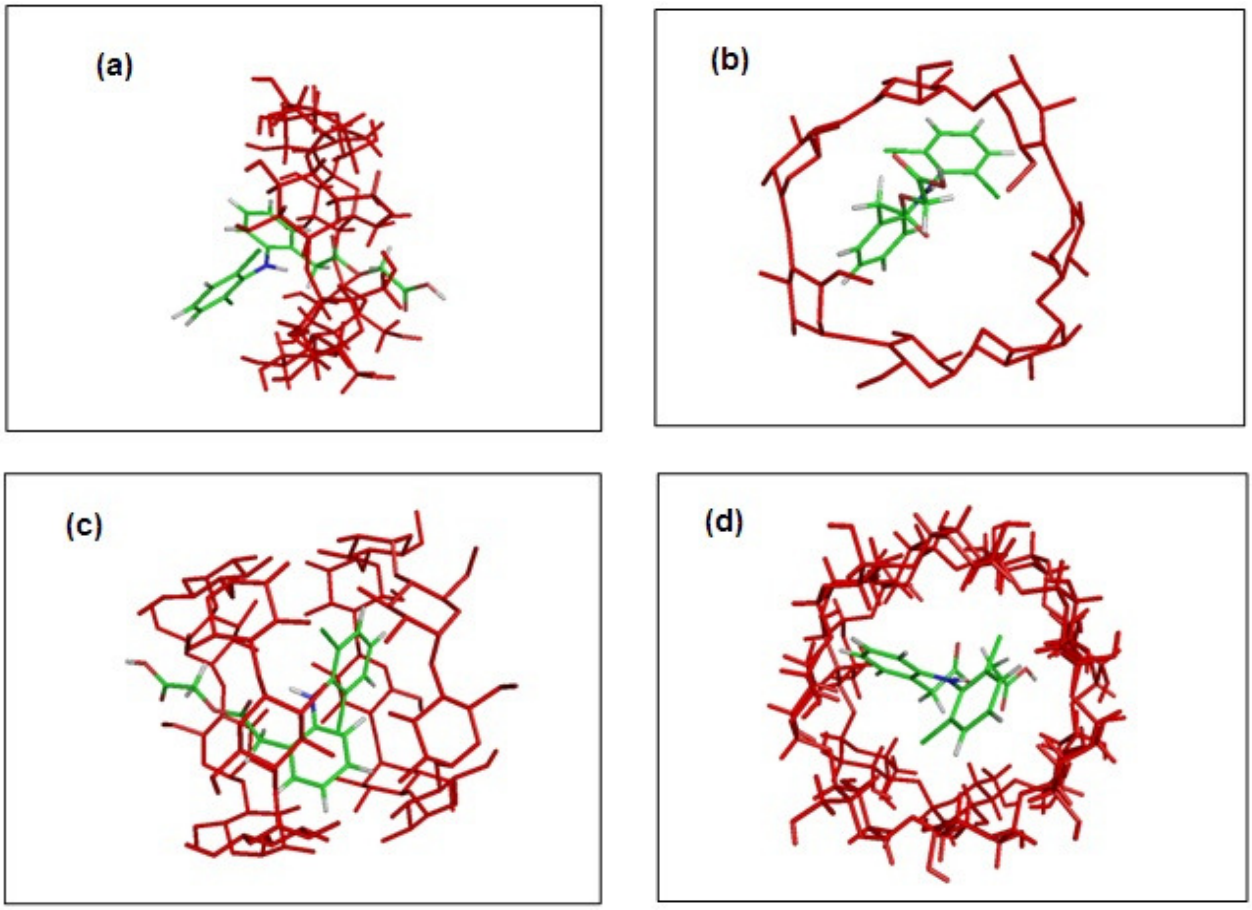

Figure 1: Relative host-guest geometry corresponding to the minimum of the energy of the formation of AF-β-CD complex (a) side view of AF in monomeric β-CD; (b) top view of AF in monomeric β-CD; (c) side view of AF in dimeric β-CD; (d) top view of AF in dimeric β-CD

MATERIALS AND METHODS

Experimental

Aceclofenac (Ipca laboratories, India), β-cyclodextrin was obtained (Cerestar, USA Inc.Hammond Indiana) of commercial purity grade were used. All other chemicals used were of analytical reagent grade.

The solid complexes of aceclofenac and β-cyclodextrin were prepared in 1:1 and 1:2 molar ratios using kneading method as described by Patel and Rawat [10, 11]. Molecular modeling studies involved the docking studies and were carried out using Fast Rigid Exhaustive Docking (FRED) docking software, version 2.2.2, Open Eye Scientific Software, Inc. The structures of ligand, namely AF were drawn using Marvin Sketch and the structures were then minimized using molecular mechanics force field (MMFF) in Omega version 2.2.1, Open Eye Scientific Software, Inc. until the derivatives were less than 0.01kcal/mol.

FRED performs an exhaustive docking by enumerating possible poses of ligand around the binding site by rigidly rotating and translating each conformer within the site followed by filtering the pose ensemble by rejecting the poses that do not fit within the larger of the two volumes specified by the receptor file's shape potential grid and an outer contour. With the aim of testing the ability of FRED to converge into solutions that are possible inside the β-CD, a box of volume, 657Å^3 was set up in such a way that it covered the internal cavity of monomeric β-CD. Docking studies were carried out in both monomeric and dimeric form of β-CD. The structures of β-CD in monomeric and dimeric form were taken from the Cambridge Structural Database (Reference code PIJGIY) [12, 13].

The following procedure was employed on the β-CD docking simulations: Lowest energy conformers for AF molecules were docked in monomeric and dimeric forms of β-CD and scored by Chemgauss Scoring function of FRED. The binding energy for the ligand-β-CD complex was calculated in terms of Chemgauss Score.

RESULTS AND DISCUSSION

The possible ways of formation of AF-β-CD complexes as obtained by molecular modeling using FRED docking software are shown in Figure 1. The energy values of β-CD monomeric and dimeric form calculated as single point energy using molecular mechanics (MM), as obtained from Cambridge structural database were 1194.214 and 1003.499 kcal/mol. The calculated energy value for lowest energy conformer of AF using molecular mechanics was found to be 71.822kcal/mol. The obtained docking score (Chemguass score) using FRED docking software for AF in β-CD monomer and dimer was -18.48 and -51.44 respectively.

The results indicated the relative energetic stability of the β-CD dimer-AF complex (-51.44) compared with β-CD monomer-AF (-18.48). A possible molecular arrangement for the energetically favorable dimer-inclusion complex is that the ligand AF is buried in the cavity of β-CD dimer in a configuration in which half of the molecule is lying in one monomer and other half is lying in the other monomer (Figure 1c). AF is possibly being held in the position due to H-bond as well as the hydrophobic interactions more tightly in the dimeric β-CD than the monomeric form, in which the H-bond were found to be absent.

CONCLUSION

The present work unambiguously determined the geometrical inclusion of aceclofenac with β-CD and indicated the relative energetic stability of the β-CD dimer-AF complex as compared with β-CD monomer-AF. Such molecular-modeling studies can be employed as an additional tool to support the formation of stable molecular inclusion complexation of any water insoluble drug complexed with cyclodextrins.

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