Non-Steroidal Anti-Inflammatory Drugs' Complexes with Cyclodextrins – Molecular Modelling Study

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Objectives: Association of non-steroidal anti-inflammatory drugs with cyclodextrins is a largely used method to increase their stability and water solubility. The aim of our study was to clarify the interactions between seven nonsteroidal anti-inflammatory drugs and HP-β-CD and the spatial geometry of these inclusion complexes by using molecular modelling.
Methods: From the non-steroidal anti-inflammatory class seven representatives were chosen: ibuprofen, ketoprofen, piroxicam, meloxicam, tenoxicam, mefenamic acid and flufenamic acid. Computational study on host-guest complexes was carried out using molecular mechanics in Hyperchem software, both in vacuum and water periodic box condition.
Results: The obtained results show that all NSAIDs form inclusion complex with HP-β-CD. The spatial geometry of complexes was established by molecular mechanics computation and the complex formation energies were calculated.
Conclusions: Intermolecular hydrogen bonds and hydrophobic interactions play an important role in the binding of NSAIDs to HP-β-CD. The results show good correlation with literature data.

Keywords: non-steroidal anti-inflammatory drugs, molecular modelling, cyclodextrin, inclusion complex

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are some of the most commonly prescribed medications, effective at pain relief and to reduce swelling. These drugs belong to class II of Biopharmaceutical Classification System (BCS), being low soluble in water and highly permeable. The solubility of drugs in water is essential for their bioavailability, therefore their association with cyclodextrins could improve the drugs' biopharmaceutical properties [1,2].

Cyclodextrins (CD) are cyclic (α-1,4)-linked oligosaccharides of a-D-gluco-pyranose containing a relatively hydrophobic central cavity and hydrophilic outer surface with the capacity to form inclusion compounds (so-called host-guest complexes) with different pharmaceutical substances. The primary hydroxyl groups are located on the narrow side of the torus, while the secondary hydroxyl groups are located on the wider edge.

The most common CDs are α-CD, β-CD, and γ-CD, which consist of six, seven and eight glucopyranose units, respectively [3,4]. The aqueous solubility of these main CDs is much lower than that of comparable linear dextrins, most probably due to relatively strong binding of the CD molecules in the crystal state, therefore various semisynthetic derivatives have been synthesized. The most commonly used of them is 2-hydroxypropyl-β-cyclodextrin (HP-β-CD), which is about 30 times more soluble in water than β-CD [5].

There are literature data on CD-NSAIDs complexation [4,6,7], related to solubility-, stability- and bioavailability increment of these drugs. The aim of our study was to investigate the complexation capacity of HP-β-CD, with molecular modelling and docking study, in vacuum and in water periodic box, using molecular mechanics (MM+) method. This method uses the classical laws of physics to calculate the interactions and the corresponding energies, considering a molecule as a collection of atoms held together by elastic forces and taking into account potential energy functions of various structural features such as bond length, bond angle, non-bonded interactions, etc (so-called force-field) [8,9].

Material and methods

Seven representative compounds from the NSAID class were chosen: two of propanoic acid derivates (ibuprofen – IBU and ketoprofen – KETO), three of enolic acid derivates (piroxicam – PX, meloxicam – MX and tenoxicam – TX) and two of fenamic acid derivates (mefenamic acid – MA and flufenamic acid – FA). The initial structures were generated through SMILES (Simplified Molecular Input Line Entry System) using Chem3D software.

The geometry of the guest molecules, host molecules and the complexes were optimized using the MM+ method of the HyperChem software. In order to minimize the energy of the structures and to obtain the most stable conformations 0.01 kcal/moleÅ RMS gradient and Polak-Ribiere algorithm were used. At the docking studies, the starting model was built by positioning the guest molecules at the larger or narrower side of the HP-β-CD molecules, building complexes in 1:1 molar ratio. The distance between the guest and host molecules was set up at ~5Å. In the case of determinations in water environment, the dimension of the water periodic box was set at 21Å × 21Å × 21Å, containing 306 water molecules.

Fifteen determinations were made for each NSAID compound, the mean of the interaction energies (E_{bond}) and standard deviations were calculated, upstairs the most stable conformations were stated based on the highest value of the E_{bond}.

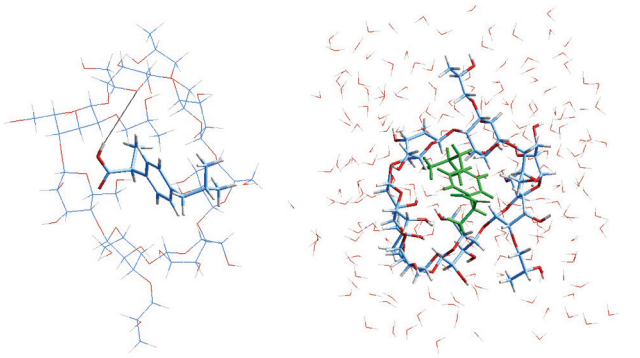

Fig. 1. The most stable conformation of IBU-HP-β-CD complex in vacuum and in water periodic box (C, O, H)

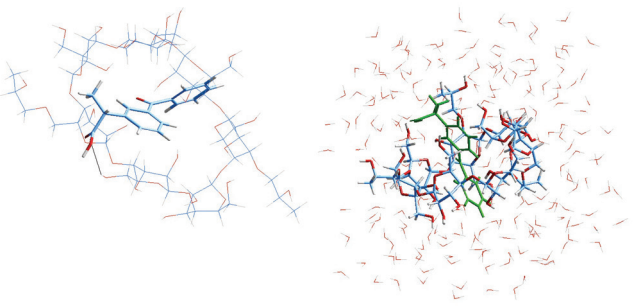

Fig. 2. The most stable conformation of KETO-HP-β-CD complex in vacuum and in water periodic box (C, O, H)

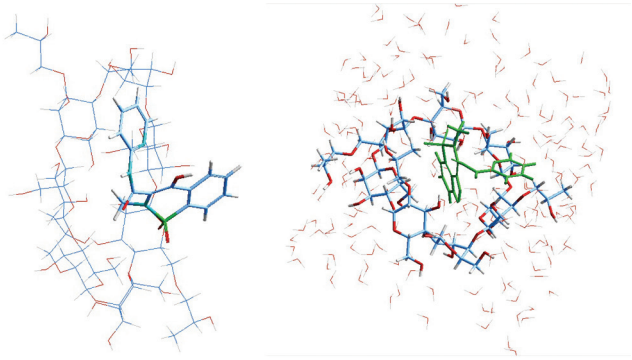

Fig. 3. The most stable conformation of PX-HP-β-CD complex in vacuum and in water periodic box (C, O, H, S)

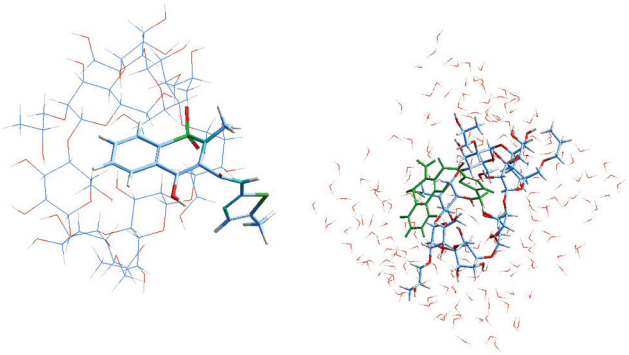

Fig. 4. The most stable conformation of MX-HP-β-CD complex in vacuum and in water periodic box (C, O, H, N, S)

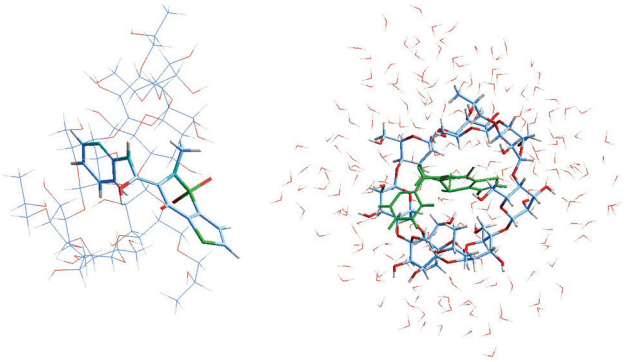

Fig. 5. The most stable conformation of TX-HP-β-CD complex in vacuum and in water periodic box (C, O, H, N, S)

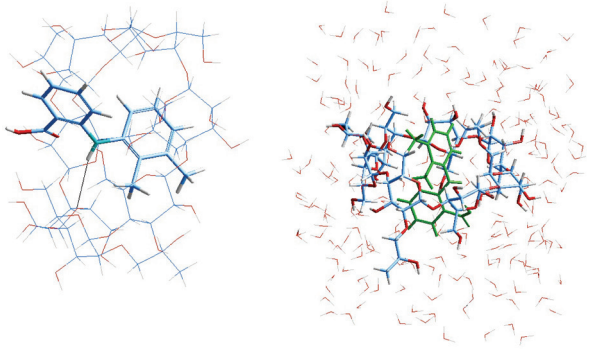

Fig. 6. The most stable conformation of MA-HP-β-CD complex in vacuum and in water periodic box (C, O, H, N)

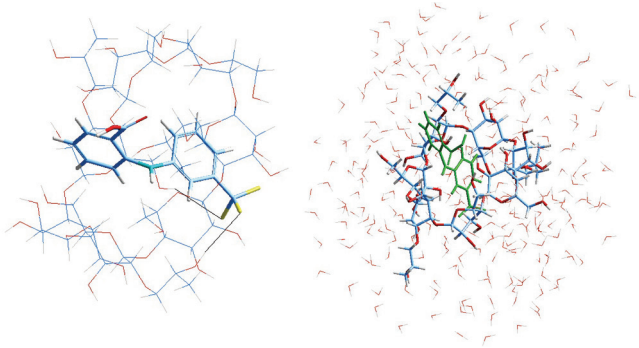

Fig. 7. The most stable conformation of FA-HP-β-CD complex in vacuum and in water periodic box (C, O, H, N, F)

Results

The calculated energies by molecular mechanics have no significance in reality, only the difference between two or more conformations. That is why, the bond energies of the CD-NSAID complexes were calculated by using the following equations:

$$E_{bond} = (E_{CD} + E_{AINS}) - E_{complex}$$

The most stable conformations in vacuum and in water periodic box of the complexes are presented in Figures 1–7.

In vacuum, according to the mean E_{bond} values KETO forms the most stable complex with HP-β-CD, the mean

Table I. Bond energies of NSAIDs-HP-β-CD complexes in vacuum

Guest molecule	Mean E_{bond} (kcal/mol)	Standard deviation	E_{bond} highest value
Ibuprofen	19.04	5.65	31.22
Ketoprofen	**32.52**	3.53	37.28
Piroxicam	24.33	5.42	35.32
Meloxicam	27.34	4.31	38.39
Tenoxicam	26.30	7.39	**45.08**
Mefenamic acid	26.02	6.16	37.25
Flufenamic acid	22.21	9.69	43.33

Table II. Bond energies of NSAIDs-HP-β-CD complexes in water periodic box

Guest molecule	Mean E_{bond} (kcal/mol)	Standard deviation	E_{bond} highest value
Ibuprofen	818.42	16.60	951.56
Ketoprofen	807.51	14.13	841.83
Piroxicam	795.96	14.53	822.48
Meloxicam	**827.31**	15.10	**961.90**
Tenoxicam	826.26	16.02	852.91
Mefenamic acid	818.62	16.47	840.20
Flufenamic acid	825.65	22.98	856.77

interaction energy being 32.52 kcal/mol, followed by MX, TX and MA. According to the bond energy value of the most stable configurations the best interaction of HP-β-CD is obtained with TX (Table I).

The most stable conformation of the complexes shows that, the guest molecule IBU and KETO enters totally into the cavity of HP-β-CD. Of the propanoic acid derivates the KETO forms the most stable complex. In the case of IBU the isobutyl group is situated at the narrow side of HP-β-CD. In the case of KETO the propanoic acid moiety of the molecule is situated closer to the primary hydroxyl groups. Of the oxicams the TX-HP-β-CD's E_{bond} is the highest. In the case of PX the methyl group bound to the nitrogen from the benzothiazinic nucleus enters in the CD's cavity, at the wide side. In the case of MX the benzothiazinic nucleus enters in the HP-β-CD's cavity, at TX the pyridyl ring is enclosed into the HP-β-CD's hydrophobic cavity. Of the fenamic acid derivates the FA forms the most stable complex. Both guest molecules penetrate totally in CD's cavity. In the case of MA the aminobenzoic acid part of the molecule is located near the narrow rim of the HP-β-CD. In the case of FA the trifluormethyl tail is oriented to the primary hydroxyl groups.

The mean distance between the hydrogen atoms of the guest molecules and the oxygen atoms of the primary hydroxyls of the host molecules is situated between 2.1–5.2 Å. Considering the mean E_{bond} values and the hydrogen-oxygen distances it can be concluded that hydrogen bonds are formed between the guest and host molecules. Between the guest molecule's benzene or heterocyclic part and the CD's apolar cavity van der Waals forces or hydrophobic interactions can develop.

Conformations stabilized in water periodic box show higher values of interaction energy compared to those obtained in vacuum. In this case the MX forms the most stable complex with HP-β-CD (Table II).

The results were processed statistically comparing the mean E_{bond} values, using ANOVA test, Tukey method. The difference between the mean E_{bond} values obtained in the case of "in vacuum" analysis is statistically significant ($p < 0.05$) in the case of KETO vs FA and IBU. In the case of docking simulation in water periodic box statistically significant differences of the mean E_{bond} values were obtained in the following cases: KETO vs MX, PX vs IBU, MX, TX, MA and FA ($p < 0.05$).

Discussion

In this paper some NSAIDs complexes with HP-β-CD were studied, in order to describe the geometry and energy of these complexes, using molecular mechanics method. This method was used for molecular modelling and docking studies on different CD derivates and various pharmaceutical compounds [10,11,12,13].

The obtained results are in concordance with literature data regarding the complexes' structure. Wang et al [14] demonstrated by atomic force microscope, that the benzene and the isobutyl group from the IBU structure enter into the cavity of CD. A KETO-HP-β-CD complex was made by freeze-drying method by Tayade and Vavia [15] and by IR spectroscopy and X-ray powder diffraction was demonstrated that no crystalline drug is present in the complex due to true inclusion complexation formation or drug amorphysation. Domanska et al. [16] and Fülöp et al. [17] studied the MA and FA complexes with HP-β-CD, calculating the free energy of complex formation and similar results were obtaind with those obtained by molecular modelling in vacuum conditions. Zhang et al. [18] trough solid-state 13C NMR spectrometry assumed inclusion of PX in the HP-β-CD through the pyridine ring. Baboota and Agarwaal [7] prepared complexes using MX and HP-β-CD by freeze drying method; by differential scanning calorimetry was demonstrated that at products prepared in 1:1 molar ratio partial encapsulation of MX occurs. TX is partially incorporated in β-CD cavity [19].

Conclusion

The presented results show that cyclodextrins are good complexing agents for the studied NSAIDs. Calculated energies, using molecular modelling programs, suggest that the interactions are due to hydrogen bonds and apolar bonds.

Usually total inclusion occurs, as is the case of IBU, KETO, MA and FA. In the case of oxicams only partial inclusion was observed.

Using molecular modelling it is possible to predict interactions that will occur between host and guest molecules

since good correlations are observed with experimental methods such as: differential scanning calorimetry, atomic force microscope and NMR.

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