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A new approach to the preparation of inclusion complexes with cyclodextrins and study of their stability by molecular dynamics methods †

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Abstract: One of the key characteristics of pharmaceutical substances is their solubility in pharmaceutically relevant media. This characteristic reflects the quality of the drug and the rate at which the pharmaceutical substance is released from its dosage form. Reduced efficacy and difficulties in the medical use of pharmaceutical substances are often associated with their low solubility in aqueous solutions. It is worth noting that about 40% of pharmaceuticals are practically insoluble, given that 85% are intended for oral administration, which is the simplest and most convenient form. Encapsulation of drug substances can solve this problem. The modern pharmaceutical industry uses molecular containers such as cyclodextrins for this purpose. The incorporation of the target component occurs on a host-guest basis and is driven by weak intermolecular interactions, the nature of which is not yet fully understood. Encapsulation has been shown to promote stability during storage, improve palatability, enhance pharmacological activity and bioavailability, reduce side effects and, most importantly, increase the solubility of these substances. Our study presents the synthesis of nimesulide inclusion complex in β-, γ-cyclodextrin cavity. The experimental results were confirmed by TLC, HPLC, UV- and IR spectroscopy, and X-ray diffraction analysis. The theoretical justification of the stability of the β-cyclodextrin/nimesulide complex was performed by one of the most innovative methods, the molecular dynamics method, using NAMD software with a simulation step of 2 femtoseconds and a duration of 5 nanoseconds. A modified CHARMM36 force field was used as the MD force field. The ability to enhance drug solubility and maintain drug stability is a promising area in the field of pharmaceutical chemistry.

Keywords: Bioavailability; inclusion complex; molecular dynamics; cyclodextrins; stability and elasticity of organic compounds

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1. Introduction

Nimesulide is a non-steroid anti-inflammatory agent which promotes selective COX2 (cyclooxygenase-2) inhibition, whereas it does not affect another isozyme COX1 (cyclooxygenase-1), thereby reducing risk of ulceration and gastrointestinal bleeding and exhibiting more favorable safety profile [1, 2]. Nimesulide was suggested as a multifactorial approach to inflammation, thus it serves as a promising therapeutic agent in management and treatment of a large spectrum of pathologic conditions, associated with acute pain [3]. Since it was firstly authorized and launched in Italian healthcare in 1985 [4, 5] as

a drug with potent analgesic, anti-inflammatory, and antipyretic properties, the indications for application ofnimesulide were expanded. In recent decades several in vitro investigations, accompanied with animal models provided insights into the promising impact of nimesulide in such pathologic conditions as dry eye syndrome (DES) and malignant tumors by carrier-mediated drug delivery.It is widely known that drug delivery systems (DDSs) are used in order to provide a proper site of drug release, to enhance bioavailability of a therapeutic agent, to keep it stable etc [6]. Several DDSs were developed and suggested as carriers of nimesulide. Among them niosomely entrapped nimesulide, which success was confirmedboth in vivo and in vitro studies by percentage of edema inhibition. These investigations shed light on ability of a niosome based transdermal drug delivery system of nimesulide to effectively inhibit fluid retention in rodent animal models and in ex mortem studies of human cadaver skin (HCS) [7]. Another delivery system of hyaluronic acid, conjugated with nimesulide (HA-NIM) in the form of eye drops was studied for anti-inflammatory effect in benzalkonium chloride-induced experimental dry eye rabbit model. Chen TY and coworkers have developed a rabbit model of dry eye — severe condition which is a characteristicsign of primary and secondary Sjögren syndrome, Stevens–Johnson syndrome, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis and numerous other autoimmune and non-autoimmune abnormalities [8,9]. Raw 264.7 line which is the derivate of monocyte/macrophage-like cells [10], exposed to hyaluronic acid-nimesulide conjugates, was evaluated for several biomarkers, representing inflammation. Raw 264.7 is the eukaryotic cell line, which was originated from BALB/c male mice with a tumor, induced by Abelson leukemia virus. The Raw 264.7 cells are widely used as a myeloid cellular model for several decades. Significant reduction in nitric oxide biosynthesis was observed after the cell culture was treated by nimesulide conjugated with hyaluronic acid, as well as IL-6 and TNF-α were considerably decreased. Therapeutic effects of HA-NIM were evaluated in dry eye patients. According to commonly accepted data, the average thickness of their corneal epithelium might be greater than that of normal people.It was revealed that HA-NIM maintains the average thickness of corneal epithelium indry eye patients in contrast to the Optive Fusion® and Restasis®eye drops. In animal model HA-NIM improves the density of goblet cells and inhibits infiltration of cornea by $CD11b^+$ cells[11]. Significant tumoricidal activity of nimesulide conjugates, such as HAL-nimesulide and HAH-nimesulideis also reported in the HT-29 cell line of colorectal cancer together with HT-29 xenografted mice by initiation of apoptosis [12].Together with niosomely entrapped and HA-conjugated nimesulide several other delivery systems were suggested. Among them,nimesulide-β-cyclodextrin complexation, which serves as both clinically and experimentally approved delivery system for nimesulide. Inclusion complex of β-cyclodextrin and nimesulide demonstrates more favorable therapeutic profile, comparing to non-conjugated nimesulide drugs. The main therapeutic advantages of β-CD-nimesulide complex over non-conjugated nimesulide are in better analgesic and anti-inflammatory effect together with better tolerability, enhanced of drug solubility and dissolution rate [13-16].

Numerous investigations, conducted both in a “wet lab” and in silico indicate many benefits of β-CD as a drug carrier, which provides overcoming of low water solubility and low bioavailability of therapeutic agents [17-21]. At the same time not much data concerning molecular dynamics simulation of β-CD-nimesulide inclusion complex is available to the best of our knowledge. Thus, one of the aims of present study was dedicated to in silico investigations of the β-CD-NIM complex stability and its hydrophobic-hydrophilic characterization. The main distinguishing feature of any molecular dynamics simulation lies in high accuracy and in the fact that it might reproduce events, observed experimentally. In our work, we perform an experiment to obtain the inclusion complex of nimesulide in β-cyclodextrin under laboratory conditions. The theoretical approach to complexation is carried out with the help of quantum mechanical calculations and molecular dynamics.

2. Materials and methods

2.1. Instrumentation and chemical reagents

2.1.1. Chemical reagents

AcrosOrganics CAS Number: 51803-78-2 nimesulide; AcrosOrganics CAS 68168-23-0 β,-γ-cyclodextrin were used in this work. N,N-Dimethylformamide, acetone, methanol (Chemistry: CAS68-12-2, CAS 67-64-1, CAS 67-56-1).

2.1.2. Analytical equipment

Instrumentation for physicochemical methods of analysis includes:

- Shimadzu UV1800 spectrophotometer: quantitative analysis of complexation products
- FMS 1201 FT-IR spectrometer: qualitative analysis of complexation products, indirect confirmation of clath-rate inclusion complex formation.
- Waters MSD SQD - ESI chromatograph: quantitative analysis of complexation products, qualitative analysis by retention time [34]

2.2. Method for obtaining the inclusion complex

The inclusion complexes were obtained by various methods, including both the classical coprecipitation method and the more complicated co-evaporation method. The co-evaporation method consists in simultaneous evaporation of liquid from an ideal solution obtained by mixing a solution of β-CD in distilled water and a suspension of nimesulide dissolved in excess DMFA. During addition of the first portions of nimesulide solution, a white flaky precipitate may form in the reaction mixture. In this case, the addition of the nimesulide solution is slowed down or stopped until the precipitate is completely dissolved. The reaction mixture should be a homogeneous system, free of precipitate and other undissolved particles.The evaporation was carried out at 70 ◦C for 48 hours without any sudden jumps in temperature or boiling. In the case of co-precipitation and co-evaporation method, we obtained a series of products, which were further subjected to physicochemical analysis.

2.3. Software used for molecular modeling

The first step of computational part of this study lied in obtaining of topologies of β-cyclodextrin and nimesulide with further modelling the complex between them, using Gaussian software [22], fig. 1. Our simulations were completed, using NAMD package, which is known as one of the most used software for MD studies of β-cyclodextrin and molecules, resembling it [23]. In the light of absence of available parameter files which are compatible enough with such simulations, the customized CHARMM36 parameters were prepared, basing on previously published data[24]. Particularly, β-cyclodextrin as a complicate compound demonstrates a large diversity of atom types, comprising its structure. Among them, several carbon, oxygen and hydrogen atoms, which must be properly chosen.

3. Results and discussion

3.1. Instrumental methods

It was previously shown that the water-soluble complexation product is a mixture of clathrate inclusion complex and nimesulidemicrocapsules in cyclodextrin [33]. The main objectives of the complexation process with cyclodextrins is to obtain a stable clathrate complex in high yield. Therefore, a qualitative and quantitative comparison of co-precipitation and co-evaporation methods for obtaining complexes of nimesulide with cyclodextrins was carried out. It was shown that the co-precipitation method is optimal for obtaining complexes with β-cyclodextrin. In the case of γ-cyclodextrin, co-evaporation

is the best. Such conclusions are confirmed by the methods of quantitative UV-analysis and HPLC, the results are presented in Table 1

Table 1. Results of quantitative analysis.

UF			
Type of cyclodextrin	Preparation method	Amount of nimesulide in the finished product, *%mass*	Amount of nimesulide in the filtrate, *%mass*.
β-	Co-precipitation	72	21
	Co-evaporation	43	52
γ-	Co-precipitation	19	67
	Co-evaporation	87	8

HPLC				
Type of cyclodextrin	Preparation method	Amount of nimesulide in the finished product, *%mass*		Amount of nimesulide in the filtrate, *%mass*
		Nimesulide encapsulated in CD,%mass	Inclusion complex ,%mass	
β-	Co-precipitation	21	43	19
	Co-evaporation	8	35	54
γ-	Co-precipitation	5	12	65
	Co-evaporation	12	74	7

The results are given from the initial amount of nimesulide taken for the reaction, without taking into account losses.

Thus, the choice of complexation technique allows not only to increase the yield of the target product, but also to increase the proportion of nimesulide enclosed in the clathrate complex.

3.2. Computational chemistry methods

Each of 7 units in the β-cyclodextrin molecule is presented by D-glucopyranose, linked by ether oxygen to a next monomer in the manner to form the cyclic structure, β-CD is prominent for. Each unit in the β-CD molecule, in turn, is composed of both extracyclic and intracyclic carbon, several ether and hydroxyl oxygen atoms etc. Atom types, therefore, may prove to be more than is obvious at first sight. Thus, the atom types were determined in accordance with the specification, suggested by Arsiccio A et al for hydroxypropyl-β-cyclodextrin [24].In this way each monomer (D-glucopyranose) of the β-CD molecule was represented by 4 types of carbon — CC3161 (C2, C3), CC3162 (C1, C4), CC3163 (C5) and CC321(C6); 3 types of oxygen — OC301 (O2, O4), OC311 (O3, O6) and OC3C61 (O5); 2 types of hydrogen — HCA1 (H1-H7) and HCP1 (H8, H9, H10)in our simulations, see figure 2.

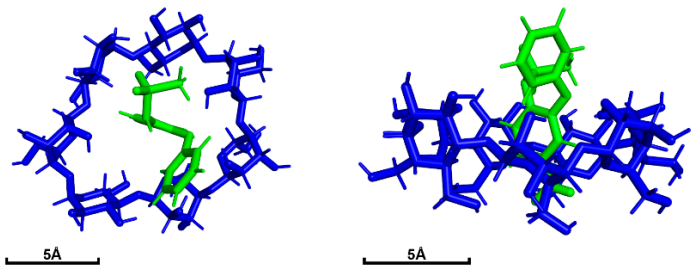

Figure 1. The β-cyclodextrin-nimesulide inclusion complex, modelled via the Gaussian software. Nimesulide is highlighted green, β-cyclodextrin is highlighted blue.

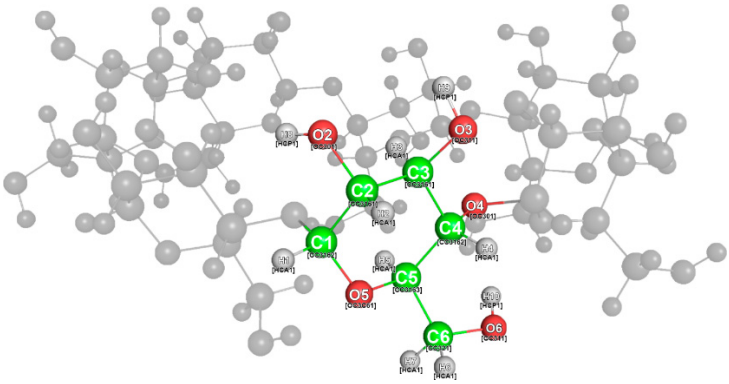

Figure 2. CHARMM atom types, used for β-cyclodextrin parametrization. One of the 7 β-CD units is highlighted.

The values of partial charges of atoms in the β-cyclodextrin molecule were also used as it was applied for hydroxypropyl-β-cyclodextrin, proposed by Arsiccio A et al [24]. Further parametrization of β-CD, which is essential for the simulation, including determination of corresponding values of bond strength, angles, dihedrals and impropers, was completed by similarity with existing data in various CHARMM parameter files, including CgenFF, the forcefield for drug-like molecules [25]; CHARMM27, all-atom force field for nucleic acids [26]; CHARMM36, all-atom additive protein force field [27] and several other for carbohydrates, ethers, lipids etc [28, 29]. Parametrization of nimesulide (see fig. 2) and creation of the waterbox (see fig. 3) were performed via CHARMM-GUI online server [30]. Nimesulide was represented by 2 types of carbon — CC2R1 (all carbon atoms, except C13 which is linked to sulfur) and CC331 (C13); 2 types of nitrogen — NC201 (N1) and NC311 (N2); 3 types of oxygen — eOC301 (ether O1), OC2N1 (O2, O3) and OC2P1 (O4, O5); 3 types of hydrogen — HCR61 (H1-H8), HCP1 (H9) and HCA3 (H10, H11, H12) and SC3O2 for the single serum atom.

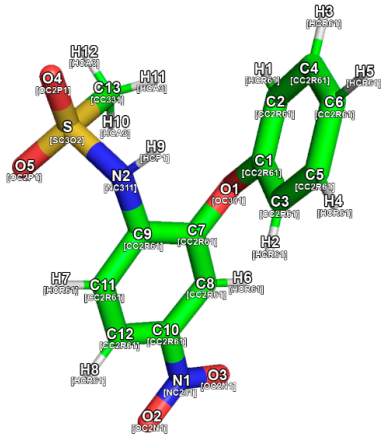

Figure 3. Molecular structure of nimesulide with specified atom types.

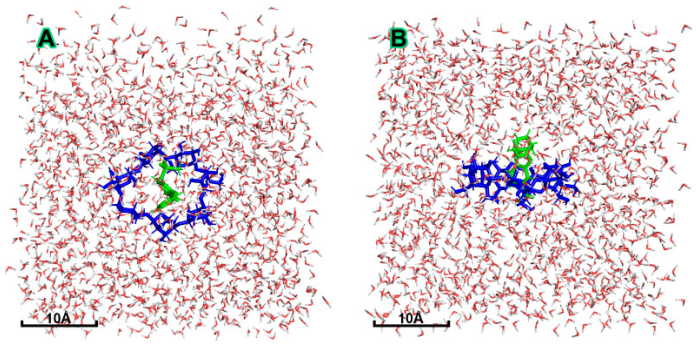

Figure 4. β-cyclodextrin-nimesulide complex in aqueous solution: A (upper view), B (side view).

Molecular dynamics simulation of the complex was performed under standard settings (310°K, enabled Langevin dynamics) of the NAMD computer program [31] for 5 ns and analyzed via VMD software [32]. The results of our in silico investigations confirm hydrophobic-hydrophilic characteristics of β-cyclodextrin as a proper drug carrier for nimesulide, having outer hydrophilicity on the one hand and lack of water molecules in the hydrophobic cavity on the other during the entire period of simulation. Such profile of interaction with water might promote enhancing of solubility of nimesulide at its release cite in vivo and improve bioavailability. We also suggest high stability of β-CD-NIM complex, as no dissociation of the complex was observed. Analysis of RMSD trajectories supports the idea of complex stability, as no drastical shifts in the RMSD curves were detected (fig. 5).

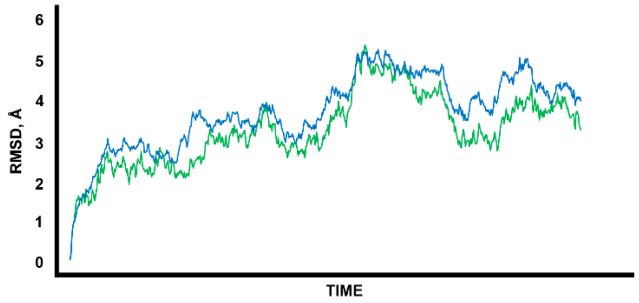

Figure 5. Diagram of RMSD trajectories. Nimesulide is represented blue and β-CD is marked green**.**

4. Conclusion

As a result of this study, it was possible to find an approach to explain the process of complexation with cyclodextrins as carriers of the active substance. This technique of synthesis of inclusion complexes can be tested on a wide class of non-steroidal drugs, as its repetition is easy to perform, does not require large material and time costs. The question of improvement of drugs and methods of their point delivery is one of the most urgent today. Complexation with cyclodextrins is successful in this field. In turn, the method of analysis by molecular dynamics and computer modeling opens wide opportunities for studying the formation of complex supramolecular associates.

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