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A New Approach to the Preparation of Inclusion Complexes with Cyclodextrins: Studying Their Stability Using 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. The 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 the nimesulide inclusion complex in β-, γ-cyclodextrin cavity. The experimental results were confirmed using 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 via one of the most innovative methods, the molecular dynamics method, using NAMD V2.14 and Gaussian 09W 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 that promotes selective COX2 (cyclooxygenase-2) inhibition; however, it does not affect other isozymes, such as COX1 (cyclooxygenase-1), thereby reducing the risk of ulceration and gastrointestinal bleeding and exhibiting a more favorable safety profile [1,2]. Nimesulide was suggested as a multifactorial approach to inflammation; thus, it serves as a promising therapeutic agent in the management and treatment of a large spectrum of pathologic conditions associated with acute pain [3]. Since it was first authorized and launched in Italian healthcare in 1985 [4,5]

as a drug with potent analgesic, anti-inflammatory, and antipyretic properties, the indications of the application of nimesulide were expanded. In recent decades, several in vitro investigations, accompanied by animal models, provided insights into the promising impact of nimesulide in such pathologic conditions as dry eye syndrome (DES) and malignant tumors via carrier-mediated drug delivery. It is widely known that drug delivery systems (DDSs) are used in order to provide a proper site for drug release, to enhance the 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, the success of which was confirmed by both in vivo and in vitro studies due to the percentage of edema inhibition. These investigations shed light on the ability of a noisome-based transdermal drug delivery system of nimesulide to effectively inhibit fluid retention in rodent animal models and 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 its anti-inflammatory effect in the benzalkonium chloride-induced experimental dry eye rabbit model. Chen TY and coworkers have developed a rabbit model of dry eye—a severe condition that is a characteristic sign 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]. The raw 264.7line, which is the derivate of monocyte/macrophage-like cells [10], was exposed to hyaluronic acid-nimesulide conjugates and was evaluated for several biomarkers representing inflammation. Raw 264.7 is the eukaryotic cell line, which originated from BALB/c male mice with a tumor induced by Abelson leukemia virus. Raw 264.7 cells have been widely used as a myeloid cellular model for several decades. A significant reduction in nitric oxide biosynthesis was observed after the cell culture was treated using nimesulide conjugated with hyaluronic acid, as well as IL-6 and TNF-α, which were considerably decreased. The 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 in dry eye patients in contrast to the Optive Fusion® and Restasis®eye drops. In the animal model, HA-NIM improves the density of goblet cells and inhibits the infiltration of the cornea via $CD11b^{+}$cells [11]. The significant tumoricidal activity of nimesulide conjugates, such as HAL-nimesulide and HAH-nimesulideis, have also been reported in the HT-29 cell line of colorectal cancer together with HT-29 xenografted mice via the initiation of apoptosis [12].Together with niosomely entrapped and HA-conjugated nimesulide, several other delivery systems were suggested. Among them, the nimesulide–β–cyclodextrin complexation serves as both a clinically and experimentally approved delivery system for nimesulide. The inclusion complex of β-cyclodextrin and nimesulide demonstrates a more favorable therapeutic profile compared to non-conjugated nimesulide drugs. The main therapeutic advantages of the β–CD–nimesulide complex over non-conjugated nimesulide demonstrate a better analgesic and anti-inflammatory effect together with better tolerability with an enhanced drug solubility and dissolution rate [13–16].

Numerous investigations conducted both in a “wet lab” and in silico indicate the many benefits of β-CD as a drug carrier; it can overcome the low water solubility and low bioavailability of therapeutic agents [17–21]. At the same time, limited data concerning the molecular dynamics simulation of the β–CD–nimesulide inclusion complex are available to the best of our knowledge. Thus, one of the aims of the present study was dedicated to in silico investigations of the β–CD–NIM complexes’ stability and its hydrophobic–hydrophilic characterization. The main distinguishing feature of any molecular dynamic simulation lies in its high accuracy and in the fact that it might reproduce events observed experimentally. In our work, we performed an experiment to obtain the inclusion complex of nimesulide in β–cyclodextrin under laboratory conditions. This 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, and methanol were also used (Chemistry: CAS68-12-2, CAS 67-64-1, CAS 67-56-1).

2.1.2. Analytical Equipment

The instrumentation for physicochemical methods of analysis includes the following:

- Shimadzu UV1800 spectrophotometer: the quantitative analysis of complexation products.
- FMS 1201 FT-IR spectrometer: the qualitative analysis of complexation products and the indirect confirmation of clath–rate inclusion complex formation.
- Waters MSD SQD—ESI chromatograph: the quantitative analysis of complexation productsand qualitative analysis viaretention time.

2.2. Method for Obtaining the Inclusion Complex

The inclusion complexes were obtained usingvarious methods, including both the classical coprecipitation method and the more complicated co-evaporation method. The co-evaporation method consists ofthe simultaneous evaporation of liquid from an ideal solution obtained viamixing a solution of β-CD in distilled water and a suspension of nimesulide dissolved in excess DMFA. During the addition of the first portions of the 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 precipitates and other undissolved particles.The evaporation was carried out at 70 °C for 48 h without any sudden jumps in temperature or boiling. In the case of the 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 the computational part of this study lies in obtaining the topologies of β-cyclodextrin and nimesulide while further modeling the complexity between them using Gaussian software [22], Figure 1. Our simulations were completed using the NAMD package, which is known as one of the most-used forms of software for MD studies of β-cyclodextrin and molecules resembling it [23]. In light of the absence of available parameter files that are compatible enough with such simulations, the customized CHARMM36 parameters were prepared based on previously published data [24]. Particularly, β-cyclodextrin, as a complicated compound, demonstrates a large diversity of atom types comprising its structure. Among them are several carbon, oxygen, and hydrogen atoms, which must be properly chosen.

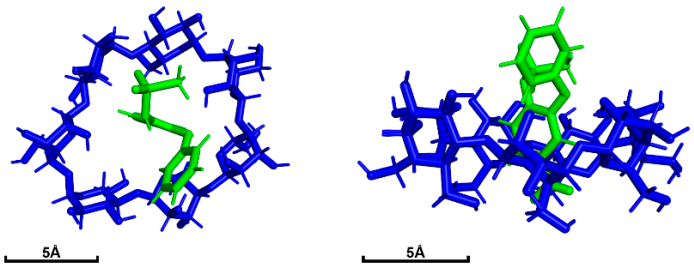

Figure 1. The β–cyclodextrin–nimesulide inclusion complex, modelled via Gaussian software. Nimesulide is highlighted in green, and β-cyclodextrin is highlighted in blue.

3. Results and Discussion

3.1. Instrumental Methods

It was previously shown that the water–soluble complexation product is a mixture of the clathrate inclusion complex and nimesulide microcapsules in cyclodextrin The main objective of the complexation process with cyclodextrins is to obtain a stable clathrate complex at ahigh 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 of which 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 losses into account.

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

3.2. Computational Chemistry Methods

Each of the seven units in the β-cyclodextrin molecule is presented using D-glucopyranose, linked by ether oxygen to the next monomer in the manner of forming a cyclic structure, which 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 clear 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); and 2 types of hydrogen—HCA1 (H1–H7) and HCP1 (H8, H9, H10)—in our simulations, see Figure 2.

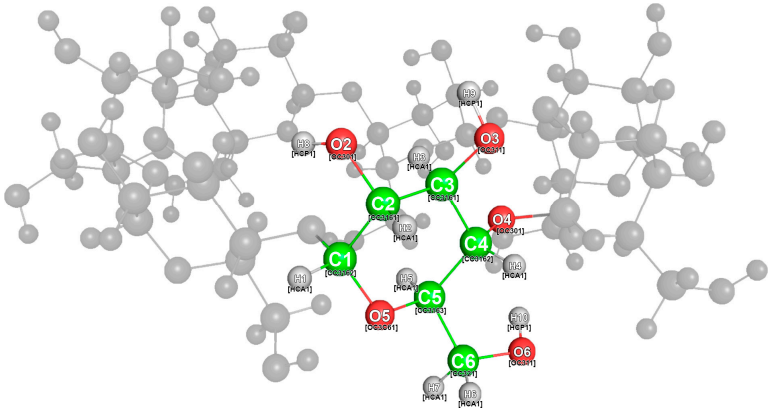

Figure 2. CHARMM atom types, used for β-cyclodextrin parametrization. One of the 7 β-CD units is highlighted.

The value of partial charges in atoms in the β-cyclodextrin molecule was also used as it was applied for hydroxypropyl-β-cyclodextrin, as proposed by Arsiccio A et al. [24]. The further parametrization of β-CD, which is essential for the simulation, including the determination of corresponding values of bond strength, angles, dihedrals, and impropers, was completed considering its similarity with existing data in various CHARMM parameter files, including CgenFF, the forcefield for drug-like molecules [25]; CHARMM27, the all-atom force field for nucleic acids [26]; CHARMM36, the all-atom additive protein force field [27] and several other for carbohydrates, ethers, lipids, etc. [28,29]. The parametrization of nimesulide (see Figure 3) and the creation of the waterbox (see Figure 4) were performed via the 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); and 3 types of hydrogen—HCR61 (H1–H8), HCP1 (H9) and HCA3 (H10, H11, H12) and SC3O2—for the single serum atom.

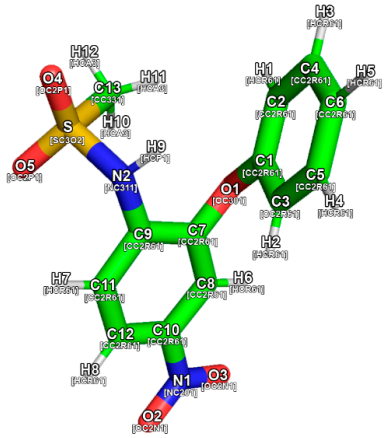

Figure 3. Molecular structure of nimesulide with specified atom types.

The 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 using VMD V1.9.4 software [32]. The results of our in silico investigations confirmed the hydrophobic–hydrophilic characteristics of β-cyclodextrin as a proper drug carrier for nimesulide, with outer hydrophilicity on the one hand and a lack of water molecules in the hydrophobic cavity on the other during the entire period of simulation. Such a profile of interaction with water might promote the solubility of nimesulide to be enhanced at its release site in vivo and improve bioavailability. We also suggest the high stability of the β–CD–NIM complex, as no dissociation in the complex was observed [32,33].

An analysis of RMSD trajectories supports the idea of complex stability, as no drastic shifts in the RMSD curves were detected (Figure 5).

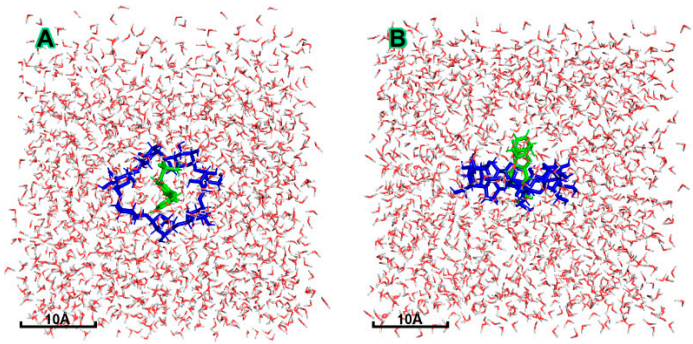

Figure 4. β–cyclodextrin–nimesulide complex in aqueous solution: (**A**) upper view, (**B**) side view.

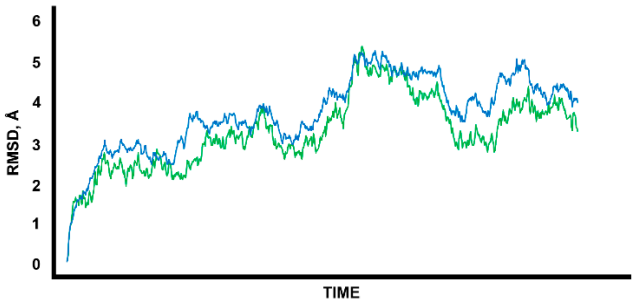

Figure 5. Diagram of RMSD trajectories. Nimesulide is represented blue and β-CD is marked in green.

4. Conclusions

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

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