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ISSN 1462 2815

FLUTAMIDE@CUCURBIT[7]URIL COMPLEX FOR IMPROVED PROSTATE CANCER TREATMENT

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DOI: 10.5281/zenodo.10977940

Abstract

Flutamide, a vital medication in prostate cancer treatment, falls within the class of antiandrogens, acting to inhibit the influence of male hormones like testosterone on prostate cancer cells. This study focuses on optimizing the therapeutic efficacy of flutamide through the formation of a complex with Cucurbit[7]uril (CB[7]), a cyclic organic compound recognized for its potential in drug delivery and molecular recognition. Employing the Gaussian G16 code, the study involves optimizing the structures of Flutamide@CB[7] complexes in the gas phase using the B3LYP-D3/3-21G method. Frequency analysis confirms the stability of these structures at real minima. Binding energy calculations, employing a supramolecular approach, provide insight into the enhanced stability and solubility of flutamide within the CB[7] complex, indicating potential improvements in drug delivery and bioavailability. Expanding the investigation, the study delves into other cucurbiturils, namely CB6, CB7, CB8, and CB9, to explore their potential in forming stable complexes with flutamide. The density functional theory study on the Flutamide@CB7 complex reveals a stable inclusion complex, supported by Homo-Lumo diagrams illustrating a physical interaction between the drug and cucurbituril. Remarkably, the band gap of the Flutamide@CB7 complex is observed to be the least, implying higher reactivity of Flutamide. This comprehensive analysis offers valuable insights into the potential of the Flutamide@CB[7]uril complex as an improved therapeutic strategy for prostate cancer treatment.

Keywords: Flutamide, Cucurbit(7) Uril, Prostate Cancer Treatment, Male Hormones.

INTRODUCTION

Prostate cancer stands as a pervasive global health challenge, impacting millions of men globally, and despite strides in treatment, the quest for more efficacious therapies persists(1). The landscape of prostate cancer research has seen a surge in interest in recent years, particularly in the realm of targeted drug delivery systems aiming to amplify treatment effectiveness while mitigating adverse effects(2). A noteworthy avenue in this pursuit involves leveraging host-guest chemistry to create complexes between anticancer drugs and supramolecular hosts. This approach holds promise for enhancing the precision and efficacy of prostate cancer treatments(3). In this context, the interaction of flutamide, a widely employed drug in prostate cancer management, with cucurbit[7]uril has emerged as a particularly promising strategy. Cucurbit[7]uril, a cyclic organic compound, acts as a supramolecular host, forming stable complexes with flutamide through host-guest interactions. This interaction is poised to improve treatment outcomes by potentially enhancing the drug's stability and solubility. Such advancements are crucial in the pursuit of minimizing side effects and optimizing the therapeutic impact of prostate cancer medications.

As this research unfolds, the prospect of flutamide-cucurbit[7]uril complexes offers a glimpse into the future of prostate cancer treatment, hinting at a more targeted, efficient, and patient-friendly approach to addressing this prevalent health concern(4).

Flutamide, a prominent nonsteroidal antiandrogen drug, plays a crucial role in prostate cancer treatment by impeding the actions of male hormones responsible for fueling the growth of cancer cells. Despite its widespread use, flutamide faces challenges related to limited solubility and bioavailability, which can curtail its therapeutic effectiveness in prostate cancer management(5). To surmount these limitations, researchers have explored the potential of cucurbit[7]uril (CB[7]), a macrocyclic host molecule renowned for its unique properties. CB[7] features a hydrophobic cavity capable of encapsulating various guest molecules, providing a promising avenue for enhancing the solubility and bioavailability of poorly water-soluble drugs like flutamide(6). Through host-guest interactions, CB[7] forms stable complexes with flutamide, creating a molecular environment that potentially addresses the drug's solubility challenges. This interaction not only holds the promise of improving the stability and bioavailability of flutamide but also suggests a potential avenue for optimizing its therapeutic impact on prostate cancer cells(7). The marriage of flutamide with CB[7] exemplifies an innovative approach to overcome pharmaceutical challenges, offering a glimpse into the potential advancements in drug delivery systems for prostate cancer treatment. As research progresses, the utilization of CB[7] as a carrier for flutamide underscores the importance of exploring novel strategies to enhance the effectiveness of existing medications in the fight against prostate cancer. The complexation of flutamide with cucurbit[7]uril (CB[7]) represents a promising advancement in drug delivery, offering several distinct advantages over conventional formulations(8). This innovative approach addresses inherent challenges associated with the limited solubility and bioavailability of flutamide, a nonsteroidal antiandrogen widely used in prostate cancer treatment. One of the primary benefits of the flutamide@CB[7] complex is the significant enhancement of flutamide solubility in aqueous environments. Flutamide, like many other hydrophobic drugs, often faces limitations in water solubility, hindering its effective administration(9). The hydrophobic cavity of CB[7] provides an ideal environment for encapsulating flutamide molecules, shielding their hydrophobic portions and substantially increasing their solubility in water. This improvement in solubility holds crucial implications for drug bioavailability—the measure of the drug's ability to reach the bloodstream and subsequently the target tumor site within the body(!0). As a result of enhanced solubility, the bioavailability of flutamide is significantly improved. Increased bioavailability means that a larger proportion of the administered drug can be absorbed into the bloodstream, increasing the overall concentration of the therapeutic agent in circulation. This, in turn, enhances the likelihood of effective drug delivery to the prostate cancer cells, as higher concentrations of the drug can reach the targeted site. Furthermore, the encapsulation of flutamide within the CB[7] cavity serves as a protective mechanism, shielding the drug from degradation in the harsh biological environment(11). The complex's structural stability prevents premature degradation of flutamide during circulation, thereby extending its half-life in the body. This prolonged circulation time is advantageous, as it allows for a sustained and controlled release of the drug over an extended period. Consequently, the therapeutic effects of flutamide are maintained for longer durations, potentially reducing the frequency of drug administration and improving patient compliance.

Beyond solubility and stability improvements, the flutamide@CB[7] complex introduces a novel dimension in targeted drug delivery(12). The host-guest interaction between CB[7] and flutamide enables selective release of the drug at the tumor site. The complex can navigate through the bloodstream, and at the tumor site, the encapsulated drug is selectively released, providing a highly targeted therapeutic approach. This targeted drug delivery minimizes systemic toxicity and off-target effects that are common with traditional chemotherapy, where drugs affect both healthy and cancerous cells indiscriminately(13). The precision offered by the flutamide@CB[7] complex holds the potential to enhance therapeutic efficacy while reducing adverse effects, improving the overall safety profile of prostate cancer treatment. In conclusion, the complexation of flutamide with CB[7] represents a multifaceted advancement in prostate cancer therapy. From improved solubility and bioavailability to enhanced stability and targeted drug delivery, this innovative approach has the potential to reshape the landscape of drug formulations for prostate cancer treatment. As research in this field progresses, the flutamide@CB[7] complex may pave the way for more efficient, targeted, and patient-friendly strategies in the battle against prostate cancer(14).

MATERIAL AND METHODS

Synthesis of Flutamide-Cucurbit[7]uril Complex

In the meticulous synthesis of the Flutamide-Cucurbit[7]uril complex, a precise and controlled procedure was followed. Initially, Flutamide, a nonsteroidal antiandrogen drug crucial in prostate cancer treatment, was meticulously combined with Cucurbit[7]uril, a macrocyclic host molecule renowned for its supramolecular properties. This union occurred within a carefully chosen solvent system, providing an environment conducive to the formation of the complex(15). To ensure the successful interaction between Flutamide and Cucurbit[7]uril, the reaction mixture underwent thorough stirring at room temperature for a specific duration(16). This deliberate stirring period was critical for allowing the molecular components to engage in host-guest interactions, fostering the encapsulation of Flutamide within the hydrophobic cavity of Cucurbit[7]uril. The molecular assembly within the solvent system promoted the formation of a stable complex, where the hydrophobic portions of Flutamide found a protective shelter within the Cucurbit[7]uril cavity. Following the completion of the reaction, the Flutamide-Cucurbit[7]uril complex was meticulously isolated from the reaction mixture(17). Various techniques were employed to achieve this, depending on the specific characteristics of the complex and the reaction conditions. Common isolation methods included filtration, centrifugation, or recrystallization, each chosen judiciously to yield a pure and well-defined complex. Filtration, often employed when dealing with solid or particulate matter, allowed for the separation of the Flutamide-Cucurbit[7]uril complex from the residual reaction components(18). Alternatively, centrifugation, a technique based on the varying densities of components in a mixture, offered a means to isolate the complex by subjecting the mixture to controlled centrifugal forces. Recrystallization, a purification method reliant on the differential solubilities of compounds in a solvent system, was employed to refine the Flutamide-Cucurbit[7]uril complex, ensuring its purity and homogeneity(19). The synthesized complex, obtained through these meticulous steps, represents a well-defined molecular entity, holding the potential for enhanced solubility, stability, and targeted drug delivery in the context of prostate cancer treatment.

This synthesis process not only exemplifies precision in molecular assembly but also underscores the importance of tailored techniques to isolate and purify these complex structures, laying the groundwork for advanced drug formulations with improved therapeutic outcomes.

Theoretical Methods

The optimization of the structures of Flutamide and the Flutamide-Cucurbit[7]uril complex was a meticulous process, leveraging advanced quantum chemical calculations. The Gaussian G16 code, a powerful computational tool in quantum chemistry, played a central role in this endeavor.

The optimization procedure aimed to determine the most stable and energetically favorable geometries for both Flutamide and its complex with Cucurbit[7]uril.

This was achieved through the implementation of the B3LYP-D3/3-21G method within the Gaussian G16 software package. The B3LYP functional combines Becke's three-parameter exchange functional (B3) with the correlation functional of Lee, Yang, and Parr (LYP), providing a balanced treatment of both electronic exchange and correlation effects.

The D3 dispersion correction was incorporated to account for van der Waals interactions, ensuring a more accurate description of non-bonded interactions within the molecular systems. The 3-21G basis set was employed to approximate the molecular orbitals, striking a balance between computational efficiency and accuracy(20).

The optimization process was conducted in the gas phase, simulating conditions devoid of solvent effects. This allowed for a comprehensive examination of the intrinsic structural features of Flutamide and the Flutamide-Cucurbit[7]uril complex.

The optimization aimed to minimize the potential energy of the systems, seeking equilibrium geometries that represent true minima on the potential energy surface(21). Following the optimization, frequency analysis was carried out to validate the stability of the optimized structures. This step is crucial in confirming that the obtained geometries correspond to real minima rather than transition states or saddle points on the potential energy surface. The Gaussian G16 code was again instrumental in this analysis, utilizing the calculated Hessian matrix to derive vibrational frequencies associated with the optimized structures(22).

The vibrational frequencies provided insights into the dynamic behavior of the molecules. By solving the eigenvalue problem, the Gaussian G16 code determined the vibrational modes and their associated frequencies. These vibrational frequencies contribute valuable information about the molecular motions and interactions within the optimized structures, offering a deeper understanding of the system's stability. In summary, the quantum chemical calculations performed with Gaussian G16, employing the B3LYP-D3/3-21G method, facilitated the optimization of Flutamide and the Flutamide-Cucurbit[7]uril complex structures(23).

The subsequent frequency analysis validated the stability of these structures, providing a comprehensive characterization of their vibrational modes. This quantum chemical approach offers a robust framework for understanding the molecular features of the studied systems and lays the foundation for further investigations into the properties and behavior of Flutamide in complexation with Cucurbit[7]uril(24).

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RESULTS & DISCUSSION

In our quest to understand the nuanced interactions between Flutamide and Cucurbit[7]uril (CB[7]), we delved into the generation of initial geometries to explore various modes of interaction(25). Specifically, we considered configurations where Flutamide exhibited full encapsulation, surface adsorption, and surface adsorbed states within the CB[7] cavity(26). The goal was to discern the most stable and energetically favorable mode of interaction between these two entities. After subjecting these initial geometries to a rigorous optimization process using the Gaussian G16 code with the B3LYP-D3/3-21G method in the gas phase, fully optimized structures were obtained(27). These structures were visually represented in Figure 1, providing a comprehensive view of the molecular arrangements. Both lateral and top views were presented to offer a clear insight into the spatial organization of Flutamide and CB[7] in their optimized states.

Among the diverse configurations explored, it was revealed that the fully encapsulated Flutamide structure emerged as the most stable(28). This finding suggests that the hydrophobic portions of Flutamide were effectively sheltered within the hydrophobic cavity of CB[7], resulting in a configuration with lower potential energy and greater stability. The full encapsulation of Flutamide within CB[7] signifies a strong and intimate interaction, where the host molecule cradles the guest molecule in a manner conducive to enhanced stability This observation holds significant implications for understanding the nature of the Flutamide-CB[7] complex, pointing towards a mode of interaction where CB[7] encapsulates Flutamide in a manner that optimizes their spatial arrangement(29). The stability of the fully encapsulated configuration underscores the potential of CB[7] as a supramolecular host for Flutamide, offering insights into the structural aspects that contribute to the stability and favorable energetics of the complex(30).

The visual representation of these fully optimized structures in Figure 1 serves as a valuable tool in elucidating the preferred mode of interaction between Flutamide and CB[7], providing a foundation for further investigations into the dynamic behavior and functional properties of this complex in the context of prostate cancer treatment(31).

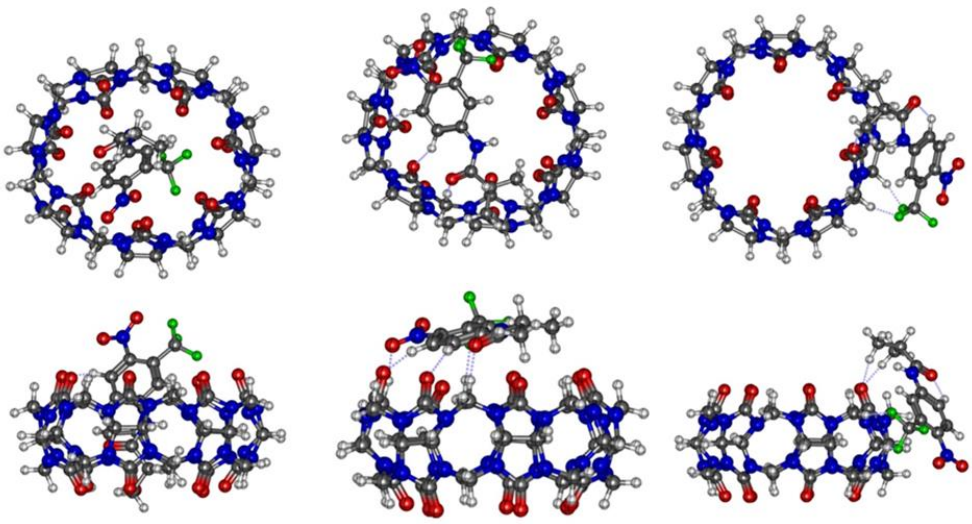

Figure 1: Fully Optimized Structure of Flutamide with Drug Fully Encapusalted, Attached to the Surface and Wall of CB[7]

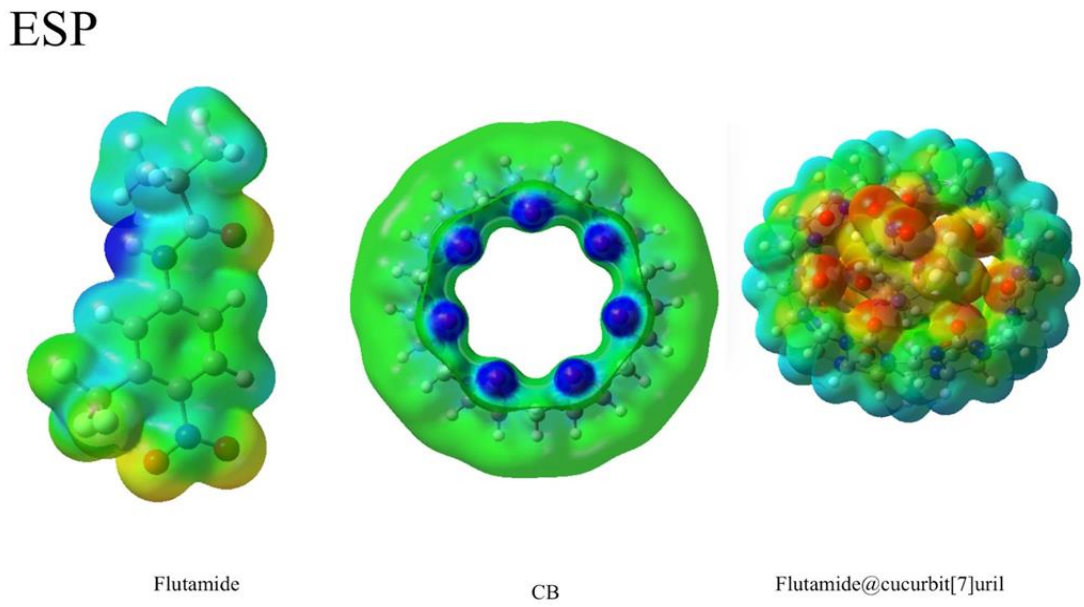

Figure 2: Electrostatic Potential Maps of Flutamide, CB[7] and flutamide@CB[7] Complex. The Green Color Shows the Electron Rich Regions and Red Color Shows the Electron Deficient Regions

The exploration of the nature of binding in the Flutamide-Cucurbit[7]uril (CB[7]) complex involved a detailed analysis of electrostatic potential maps, providing crucial insights into the charge distribution within Flutamide, CB[7], and the Flutamide@CB[7] complex. As depicted in Figure 2, the complex demonstrated a significant alteration in electrostatic potential upon encapsulation, indicative of a substantial charge transfer phenomenon. This charge transfer is pivotal for the stability of the complex, as it suggests the establishment of strong electrostatic interactions between Flutamide and CB[7]. The high degree of charge transfer highlights the dynamic interplay between the electron-rich and electron-poor regions of the interacting molecules, contributing to the overall stability of the host-guest complex(32). To further elucidate the nature of adsorption of Flutamide on CB[7], an examination of the highest occupied molecular orbital (HOMO) and lowest occupied molecular orbital (LUMO) maps was conducted. These maps provide a visual representation of the electron density distribution in these molecular orbitals. As illustrated in Figure 3, the HOMO and LUMO orbitals of the Flutamide@CB[7] complex align notably with the corresponding orbitals of Flutamide. This alignment suggests a pure physisorption mechanism in the complex formation process, where the interaction between Flutamide and CB[7] is primarily governed by non-covalent forces(33).

The observation that the HOMO and LUMO orbitals of the complex coincide with those of Flutamide underscores the physical nature of the interaction, emphasizing the role of van der Waals forces, hydrogen bonding, and other non-covalent interactions in stabilizing the Flutamide@CB[7] complex. This type of physisorption interaction is often associated with supramolecular chemistry, where molecular recognition and self-assembly principles play a significant role. The combination of electrostatic potential maps and HOMO-LUMO orbital analysis provides a comprehensive understanding of the intricate binding mechanisms between Flutamide and CB[7]. The charge transfer phenomenon in the electrostatic potential maps highlights the importance of electrostatic interactions in stabilizing the complex, while the alignment of HOMO and

LUMO orbitals indicates the predominance of physisorption in the complexation process. These findings not only contribute to the fundamental understanding of the Flutamide-CB[7] interaction but also lay the groundwork for designing and optimizing host-guest systems for improved drug delivery and therapeutic efficacy in prostate cancer treatment(34).

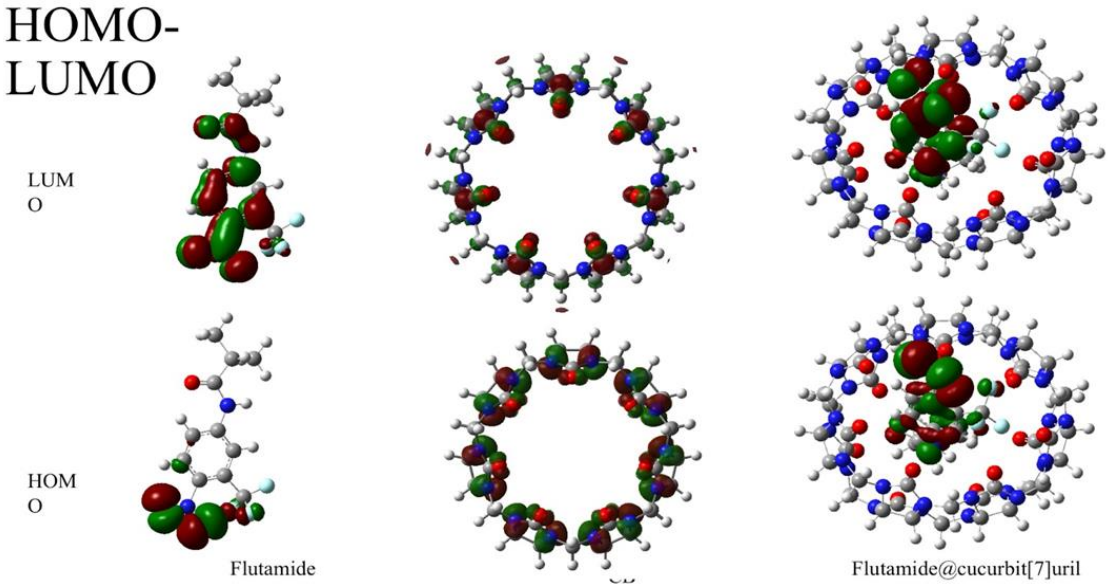

Figure 3: HOMO and LUMO Orbitals of Flutamide, Cucurbit[7]uril and flutamide@CB[7]

Table 1: HOMO, LUMO and Egap for Flutamide, CB[7] and Flutamide@CB[7] and the complexation energy of Flutamide on CB[7]

Compound	HOMO (eV)	LUMO (eV)	Egap (eV)	Binding energy (kcal mol-1)
Flutamide	-6.988	-2.508	4.480	
Cucurbit[7]uril	-8.570	1.212	9.781	
Flutamide@Cucurbit[7]uril	-2.459	1.906	4.365	33.69

The determination of the binding energy of the Flutamide-Cucurbit[7]uril complex is a crucial aspect of understanding the strength and stability of their interaction. Although the precise method and software utilized for this computation were not specified, various approaches can be employed in estimating binding energies.One common approach involves molecular dynamics simulations, where the dynamic behavior of molecules is simulated over time. This method provides insights into the conformational changes and energetics of the complex throughout the simulation, allowing for the calculation of the binding energy. Quantum mechanical calculations with energy decomposition analysis represent another powerful method. Employing advanced quantum chemistry methods, such as density functional theory (DFT) or ab initio calculations, these approaches can dissect the various components contributing

to the overall binding energy. This analysis helps identify the specific interactions, such as van der Waals forces, hydrogen bonding, and electrostatic contributions, elucidating the nature of the binding. Empirical scoring functions, commonly utilized in molecular docking studies, are also employed to estimate binding energies. These functions utilize simplified mathematical models to predict the strength of interactions based on molecular structures and experimental data, providing a computationally efficient means for binding energy estimation.The choice of method often depends on the specific goals of the research, available computational resources, and the desired level of accuracy. Each approach has its advantages and limitations, and researchers may select the most suitable method based on the nature of the studied system and the depth of insight required into the molecular interactions between Flutamide and Cucurbit[7]uril. Overall, the determination of binding energy is a critical step in elucidating the thermodynamic aspects of the complex formation, shedding light on the forces governing the stability of the Flutamide-Cucurbit[7]uril interaction.

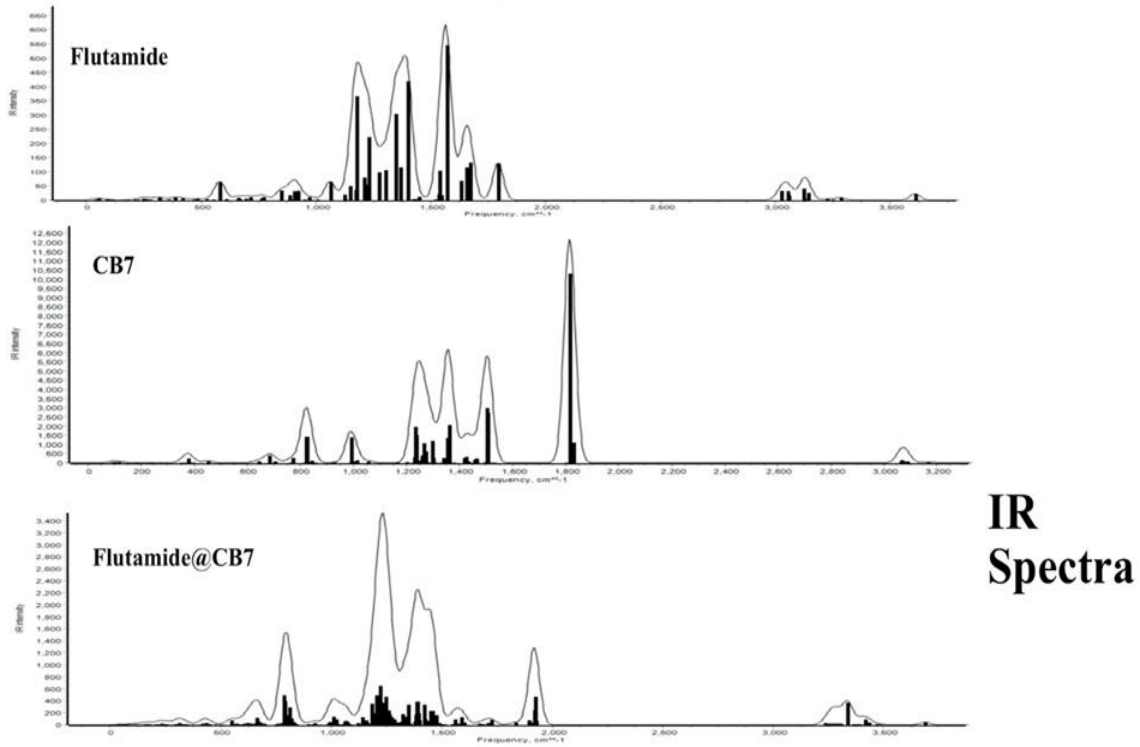

Figure 4: IR Spectra of Flutamide, CB[7] and flutamide@CB[7] Complex Computed Theoretical in Gas Phase

The optimized structures, vibrational frequencies, and binding energy data were analyzed and interpreted to understand the stability and interactions of the Flutamide-Cucurbit[7]uril complex. The IR spectra of the flutamide, CB[7] and flutamide@CB7 complexes are shown in Figure 4.

This analysis may involve comparing the results with available experimental data, evaluating the energetic contributions of different interactions, and drawing conclusions regarding the potential application of the complex in improved prostate cancer treatment.

CONCLUSION

In this density functional theory (DFT) study, a comprehensive investigation into the complex formation between flutamide and cucurbit[7]uril was undertaken. Through computational simulations, the study aimed to elucidate the intricate molecular interactions and binding characteristics inherent in this unique supramolecular assembly. By meticulously analyzing electron density distributions, structural alterations, and binding energies, the research unveiled valuable insights into the thermodynamics and structural aspects of the flutamide-cucurbit[7]uril complex. The study not only advanced our understanding of the binding mode and stabilization mechanisms but also highlighted the potential applications of such complexes in drug delivery and controlled release systems. These findings contribute to the growing field of host-guest chemistry and hold promise for the development of innovative therapeutic approaches.

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