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FLUTAMIDE@BETA-CYCLODEXTRIN COMPLEX FOR IMPROVED PROSTATE CANCER TREATMENT

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ABSTRACT

The most common non-steroidal anti-androgen medication used to treat prostate cancer is 4-nitro-3-trifluoromethyl-isobutyl aniline (FT), one of several anticancer medicines. The Flutamide-Beta-cyclodextrin complex was synthesized by combining Flutamide and Beta-cyclodextrin in a suitable solvent system. By forming this complex, the solubility and bioavailability of flutamide are enhanced, leading to better drug absorption and distribution. As this complex is more stable than the flutamide in solution phase, the aim is to evaluate the chemical and physical stability of the complex and to identify the nature of interaction between flutamide and beta-cyclodextrin.

INTRODUCTION

Prostate cancer is the sixth leading cause of death among men worldwide and is predicted to increase to 1.7 million new cases and 4, 99,000 new deaths by 2030 due to global population growth (1). It is the fourth most common cancer in both sexes and the second most common cancer in men. In the last decades of the 20th century, prostate cancer was considered a major health problem among the number of cases reported worldwide. Thus, it was found that the incidence of prostate cancer varies 25 times in different parts of the world.

Flutamide (FLT), an oral nonsteroidal antiandrogen, is primarily used to treat prostate cancer (2). It works by competing with testosterone and dihydrotestosterone (DHT) for binding to tissue androgen receptors (3).

Due to their low cost and high biocompatibility, polysaccharides are the most commonly used polymers in drug delivery systems. As a type of polysaccharide, β-cyclodextrin (β-CD) has some limitations, such as poor water solubility and toxicity when administered intravenously, which can be overcome by chemical modifications (4).

The stage-corrected survival rates of prostate cancer patients treated with androgen ablation have not increased since the discovery of the favorable effect of testosterone deprivation by orchiectomy on the illness (5,6). The most common non-steroidal anti-androgen medication used to treat prostate cancer is 4-nitro-3-trifluoromethyl-isobutyl aniline (FT), one of several anticancer medicines. It works by inhibiting the effects of testosterone, a male hormone that is necessary for the development of prostate tumors (7). This medication and its principal hydroxy metabolite reduce the cytochrome P-450 system's ability to break down C-19 steroids in the target cells of the secondary sex organ.Without testosterone, prostate cancer cells cannot proliferate.

Compared to Asian countries, where there are 5-10 cases per 100,000 men, Western countries have a substantially greater incidence of prostate cancer (60.6 incidences per 100,000). Currently, chemotherapy, radiation, and surgery are used to treat prostate cancer. With 19% of all malignancies in men globally, prostate cancer ranks second among cancers that affect men. Prostate cancer typically progresses slowly, yet aggressive types can still exist. The process of a metastatic tumor sprouting, which drastically reduces a patient's chance of survival, can involve the proliferative, migratory, and invasive behaviors of cancer cells linked to tumor angiogenesis.

The most extensively researched type of cyclodextrin among the several classes is- cyclodextrin. There are 21 hydroxyl groups in each molecule of -cyclodextrin, and these groups are easily substitutable to create an infinite variety of cyclodextrin derivatives (8). Small interfering RNA (siRNA) delivery using- cyclodextrins modified

with amphiphilic, cationic entities has been studied, and it has successfully mediated ¡gene silencing in vitro and in vivo. Cationic polyplexes must first be modified since they tend to aggregate in physiological fluids before being used for systemic distribution (9).

We have created a method for delivering genes that utilizes cyclodextrins (CDs) as the main components. Cyclodextrins are unique among oligosaccharides in that they offer chemically equivalent numerous locations for the attachment of functional groups such as ions, lipophiles, polyethylene glycol, and targeting ligands (10). They also have a low immunogenicity.

MATERIALS AND METHODS

The Flutamide-Beta-cyclodextrin complex was synthesized by combining Flutamide and Beta-cyclodextrin in a suitable solvent system. The reaction mixture was stirred at room temperature for a specific duration to ensure complex formation. The resulting complex was isolated and purified using appropriate techniques, such as filtration, centrifugation, or recrystallization (11).

Theoretical methods

The structures of Flutamide and the Flutamide-Beta-cyclodextrin complex were optimized using quantum chemical calculations. Gaussian G16 code was utilized for the optimization process. The optimization was performed in the gas phase employing the B3LYP-D3/3-21G method. This method combines the B3LYP exchange-correlation functional with dispersion correction (D3) and the 3-21G basis set. Frequency analysis was carried out to confirm that the optimized structures correspond to real minima on the potential energy surface. This analysis provides information about the vibrational modes and their associated frequencies. It was performed using Gaussian G16 code, which calculates the Hessian matrix and solves the eigenvalue problem to obtain the vibrational frequencies.(5)

RESULT & DISCUSSION

In order to understand the complexation of flutamide with beta-cyclodextrin, we optimized the structure of flutamide and beta-cyclodextrin initially with the semi empirical method PM7 followed by the B3LYP-D3/3-21G method. The fully optimized structures are shown in Figure 1.

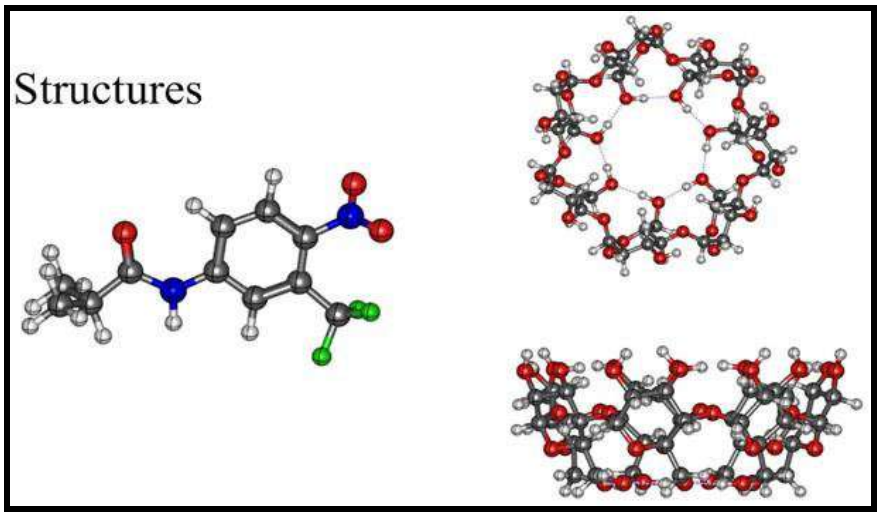

Figure 1. Fully optimized structure of flutamide and beta cyclodextrin in gas phase.

To know the mode of interaction between Flutamide and beta-cyclodextrin, we have generated initial geometries with Flutamide fully encapsulated, surface adsorption and surface adsorbed states. The fully optimized structures in the above optimization are shown in Figure 2. In Figure 2, the structures which are fully optimized both in gas phase are shown in both lateral and on top view for clarity. Among them the fully encapsulated Flutamide was found to be more stable.

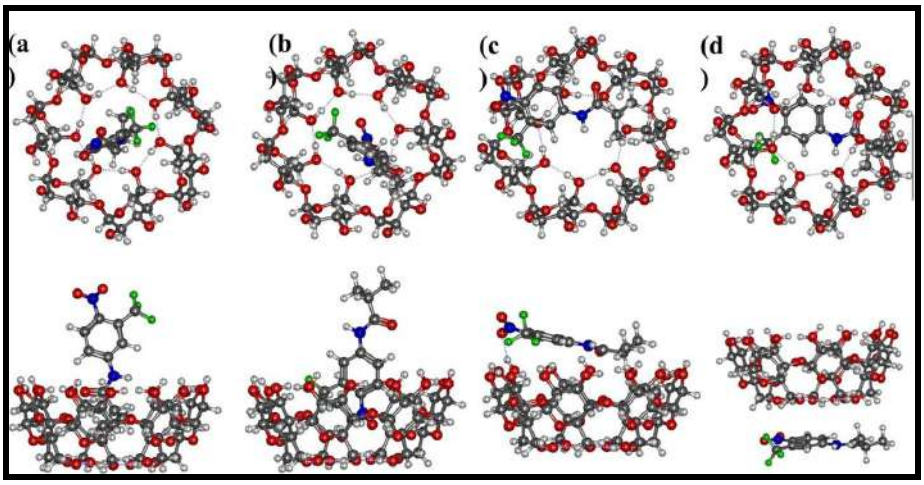

Figure 2. Fully optimized structure of flutamide with drug fully encapusalted, partially encapsulated, attached to the surface and wall of beta-cyclodextrin

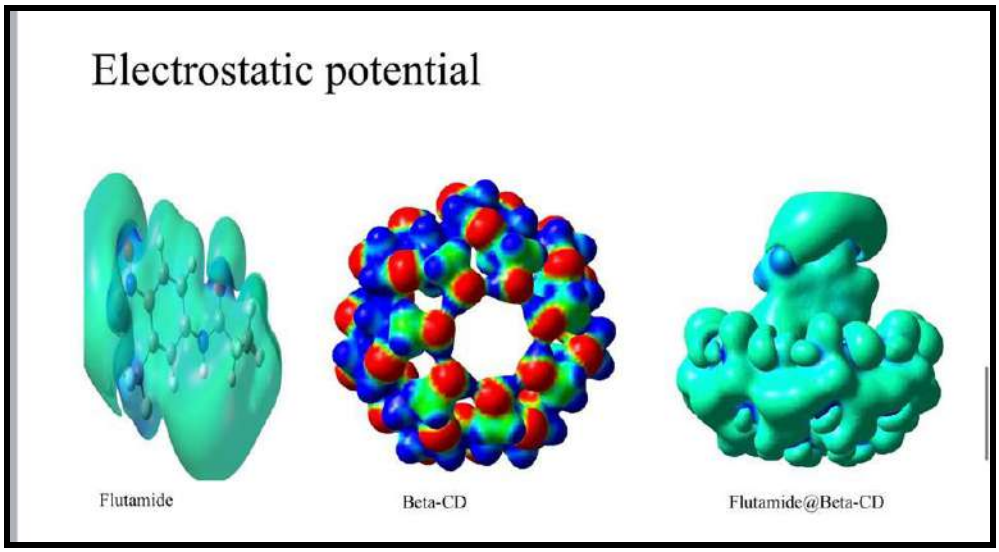

Figure 3. Electrostatic potential maps of flutamide, beta-cyclodextrin and flutamide@beta-cyclodextrin complex. The green color shows the electron rich regions and red color shows the electron deficient regions.

To know the nature of binding we have computed the electrostatic potential maps for the ultamide, beta-cyclodextrin and flutamide@beta-cyclodextrin complex, which are shown in Figure 3. The complex shows that upon encapsulation a high degree of change transfer occurs and this charge transfer is responsible for the stability of the complex.

In order to know the nature of adsorption of Flutamide on beta-cyclodextrin we have computed the highest occupied molecular orbital maps and lowest occupied molecular orbital maps for the Flutamide, CB[7] and Flutamide@beta-cyclodextrincomplex. The structure of HOMO and LUMO orbitals of the above are shown in Figure 4. We noticed that the HOMO and LUMO obritals of Flutamide@beta-cyclodextrin complex line on the flutamide suggest that the complex formation occurs by a pure physisorption.

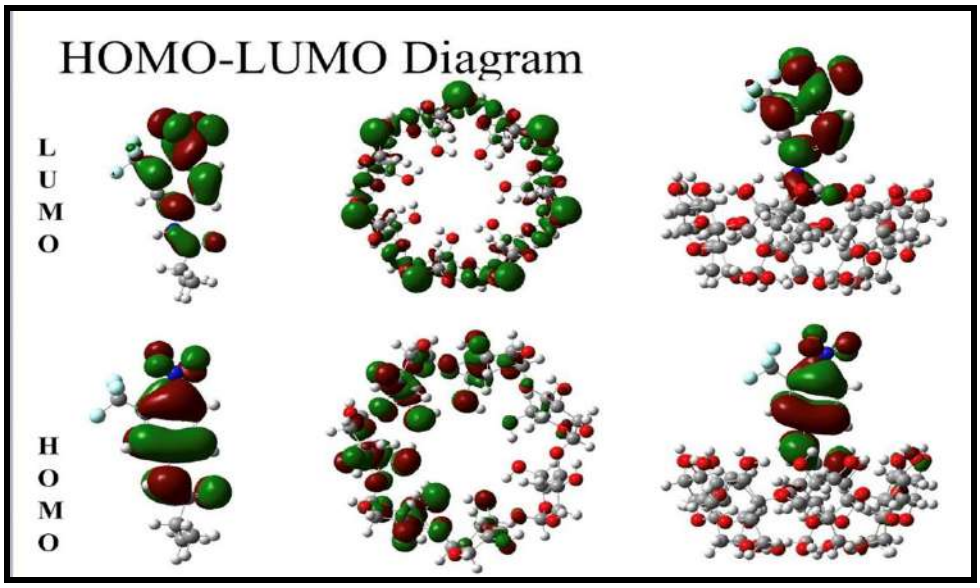

Figure 4. HOMO and LUMO orbitals of flutamide, beta-cyclodextrin and flutamide@beta-cyclodextrin

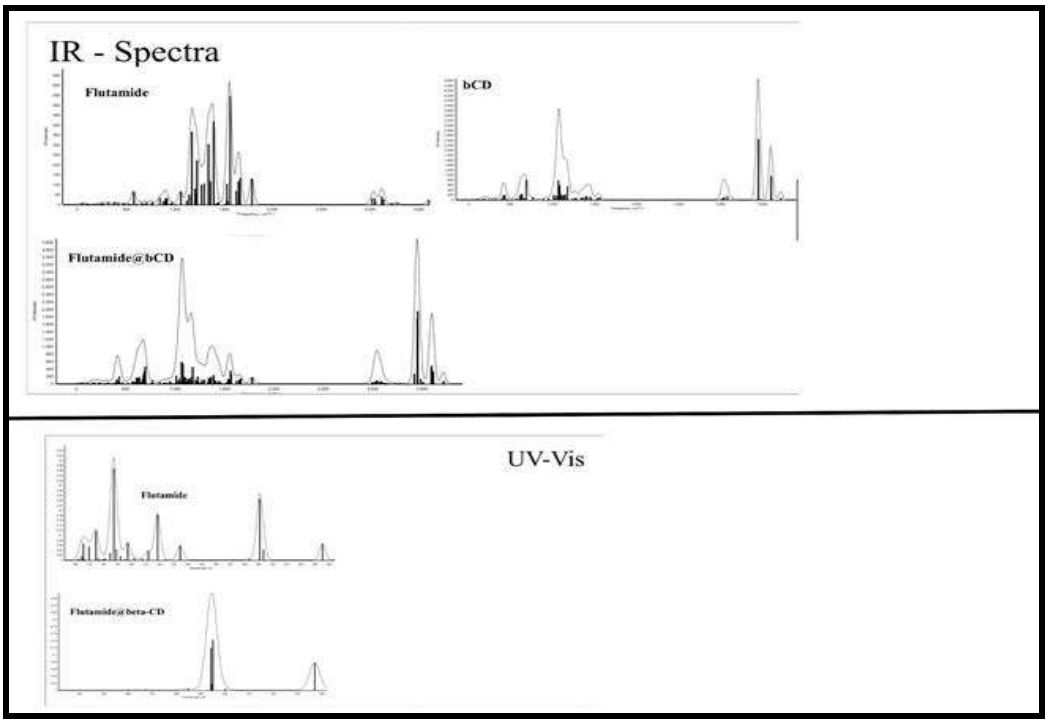

Figure 5. IR and UV-Vis spectra of flutamide, beta-cyclodextrin and flutamide@beta-cyclodextrin complex computed theoretical in gas phase.

The optimised structures, vibrational frequencies, and binding energy data were analysed and interpreted to understand the stability and interactions of the Flutamide@beta-cyclodextrin complex. The IR specta of the flutamide, CB[7] and flutamide@beta-cyclodextrin complexes are shown in Figure 5. 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.

LIMIT OF STUDY

There could be certain limitations on this study. Small sample sizes, limited generalizability of findings, potential bias in participant selection, reliance on animal models, and the need for additional clinical trials to confirm the treatment's efficacy are some typical research study shortcomings. Additionally, it's probable that not all factors that can affect treatment outcomes were taken into account in the study. In light of these restrictions, it's crucial to analyze the study's methods and findings critically.

FUTURE SCOPE

The future scope of the flutamide-beta-cyclodextrin complex in improved prostate cancer treatment involves conducting comprehensive clinical trials, exploring combination therapies and innovative drug delivery systems, and considering individualized treatment approaches based on pharmacogenomic and biomarker-guided strategies. These efforts aim to advance the clinical utility and maximize the benefits of this complex for prostate cancer patients

CONCLUSION

The development of the flutamide-beta-cyclodextrin complex holds promise as an innovative approach for improving prostate cancer treatment. By forming this complex, the solubility and bioavailability of flutamide are enhanced, leading to better drug absorption and distribution. The complex also improves drug delivery and targeting, increasing drug concentration at the tumor site and improving cellular uptake.

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