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Review Article

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The Significance of FT-IR, FT-Raman spectroscopic studies and quantum chemical methods in exploring physicochemical properties of paclitaxel

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ABSTRACT

This review presents the importance of vibration spectroscopy and the quantum chemical methods in the elucidation of paclitaxel. Paclitaxel, the most well-known natural-source cancer drug derived from the bark of the Pacific yew tree (Taxus brevifolia) and is used in the treatment of breast, lung, and ovarian cancer, as well as Kaposi's sarcoma. Infrared spectroscopy is a mature research tool, which has enjoyed a renaissance in recent years due to the introduction of Fourier transform techniques. Raman spectroscopy is also an important spectroscopic technique, which provides exquisite structural insights into the molecular structures. The introduction of FT–Raman spectroscopy has brought a new impetus to Raman spectroscopy. It has allowed the study of materials that were previously "impossible" because of fluorescence and provides ready access in the extensive data handling facilities that are available with a commercial FTIR spectrometer. Computational chemistry generates data which complements experimental data obtained by chemical experiments. It is widely used in the design of new drugs and materials. Computational chemistry can assist the experimental chemist or it can challenge the experimental chemist to find entirely new chemical objects. So this article reviews the elaborate elucidation of paclitaxel through vibrational spectroscopic techniques and quantum chemical methods

Key words: Paclitaxel, DFT, HF, FT-IR, FT-Raman

INTRODUCTION

Paclitaxel (Taxol) has a broad activity spectrum and is clinically used, often in combination with carboplatin, to treat breast, ovarian and lung cancer [1]. The response to treatment and the severity of adverse drug reactions after chemotherapy varies greatly among individuals, and one of the most important factors responsible for these differences is now recognized to be the genetic variability.

Figure.1.Pacific Yew Tree (Taxus brevifolia) [22]

Taxol has a lot of importance, both on a national and global scale. It is one of the most effective anti-cancer drug that has been developed from plants in the recent years. It also happens to be the most controversial natural product in recent years. As for its ability to fight cancer itself it not only stops the tumor from growing, it also shrinks it. This phenomenon is only the second of its kind. It also proved to be one of the most effective agents in treating breast cancer. It is shown to be highly effective even in patients with advanced cancer. Taxol was obviously seen as a drug with huge potentials, which is why even though it took nearly 22 years for it to be tested on humans, scientists still pursued its' research. The disadvantages of paclitaxel is

- Many times the taxol drug just bounces off the cancer tumour, doing little or no damage to it.
- It decreases your blood cells, which puts you at risk of infection or other diseases.
- As with almost any other type of chemotherapy, use of taxol is also results in hair loss.
- Use of taxol may also result in nausea, vomiting or diarrhea.

Taxanes bind to the interior surface of β-microtubule chain and enhance tubulin polymerization, thereby stabilizing microtubules. This inhibits mitosis, motility and intracellular transport within (cancer) cells, leading to apoptotic cell death. Taxanes also block anti apoptotic effects of BCL2 gene family, induce TP53gene activation with resultant mitotic arrest leading to cell death. [2]. Paclitaxel was first approved in 1992 for clinical use. The structure of paclitaxel is shown in Figure.2

Cremaphor EL (CrEL), a non ionic surfactant poly-oxy-ethylated castor oil mixed 1:1-with dehydrated ethanol was recognized to be the most feasible option to solubilise paclitaxel for intravenous administration. Being biologically and pharmacologically active, these solvents are associated with several major side effects such as hypersensitivity reactions and neuropathies. They also impair tumour penetration, limiting the clinical effectiveness of solvent-based taxanes [3, 4]

To address these limitations of solvent-based taxanes and to improve their therapeutic index, various solvent-free formulations and delivery systems such as liposomal encapsulated paclitaxel, paclitaxel vitamin E emulsion and polymer microsphere formulation of paclitaxel were investigated but with limited success.[4,5]

In order to understand the water-solubility and anti cancer activity of paclitaxel prodrugs, it is inevitable to study the physicochemical properties of them.

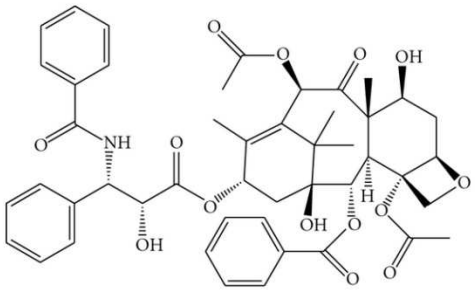

Figure.2. Paclitaxel

2. Approaches in the study of Paclitaxel drugs:

2.1. Vibrational Spectroscopy

Vibrational spectroscopy is an important tool for the elucidation of molecular structure and gives a dynamical picture of the molecule. The study of vibrational spectroscopy provides affluence of data on the vibrations of polyatomic molecules, which, when properly interpreted, yields information regarding the molecular structure, bonds, forces behind the bonds, molecular dynamics etc [6].

Infrared spectroscopy is a fully grown research tool, which has enjoyed revitalization in recent years due to the introduction of Fourier transform techniques. Raman spectroscopy is also an important spectroscopic technique, which provides exquisite structural insights into the molecular structures. In conventional Raman spectroscopy, the strongly interfering fluorescence has always been a great nuisance and obscures the Raman signal. The introduction of FT–Raman spectroscopy has brought a new impetus to Raman spectroscopy. It has allowed the study of materials that were previously "impossible" because of fluorescence and provides ready access in the extensive data handling facilities that are available with a commercial FTIR spectrometer. Thus, Raman scattering has been proved to be a powerful technique, complementary to inelastic neutron scattering and infrared spectroscopy.

2.2. Quantum Chemical Methods

The computational chemistry methods outcome data is complement to the experimental data of chemical experiments. The calculations are based primarily on Schrodinger's equation. The properties such as structure (i.e. the expected positions of the constituent atoms), absolute and relative (interaction) energies, electronic charge distributions, dipoles and higher multipole moments, vibrational frequencies, reactivity or other spectroscopic quantities, and cross sections for collision with other particles can be evaluated. In some cases, it can predict hitherto unobserved chemical phenomena too. It is widely used in the design of new drugs and materials. Computational chemistry can assist the experimental chemist or it can challenge the experimental chemist to find entirely new chemical objects.

Computational quantum chemistry is principally concerned with the numerical computation of molecular electronic structures by ab initio and semi–empirical techniques. Hartree–Fock (HF) and Density functional theory (DFT) are ab initio methods for determining the molecular electronic structure. The HF and DFT methods of analysis of molecular vibrations have been of great service in the study of molecular dynamics. The computational analysis is the universally accepted approach for interpretation of the spectral data of the molecules [7].

The ab initio HF and DFT theories have proved to be highly successful in describing structural and electronic properties in a vast class of materials, ranging from atoms and molecules to simple crystals to complex extended systems. These work falls mainly into three classes: those dealing with the theory, those concerned with the technical aspects of the numerical implementations, and vast majority of presenting results.

The Gaussian program developed for HF and DFT calculations endow with vast number of data such as the harmonic vibrational frequencies, optimized molecular parameters (bond length, bond angle, dihedral angle), dipole moment, rotational constants, Non linear optical parameters (first and second order Polarizability, anisotropy) and thermodynamical parameters (zero point energy, entropy, enthalpy and specific heat capacity[8].

3. Spectroscopic and quantum chemical studies of paclitaxel

Spectroscopic investigations on pharmaceutical samples are of importance in the present. Vibrational spectral studies of many pharmaceutical drugs are extensively studied by many scientists. Pharmaceutical and physicochemical analyses of various drugs- membrane complexes have been studied by various analytical methods. Thermodynamic, spectroscopic and microscopy approaches were used for structural characterization of these macromolecular associations. Among these, vibrational spectroscopy (Infrared and Raman spectroscopy) provide useful information on dynamic changes occurring after complex formation of various biomolecules, FTIR and Raman spectroscopic methods are being extensively used to identify the structural groups present in a compound [9-11]. Many research suggested an interesting method of assigning group frequencies observed in vibrational spectra. Spectroscopic studies of the Paclitaxel binding and proximity relationships with cisplatin and adriamycin are done by Lilianna TryndaLemiesz [12], FTIR and NMR spectroscopy studies on the interaction of paclitaxel with lipid bilayers are studied by Dhanikula Anand[13], conformation of microtubule bound paclitaxel by fluorescence spectroscopy and NMR were given by Yankun Li[14]., however the vibrational spectral analysis of polymeric nanoparticle Paclitaxel drug have not carried out before. An attempt has been made in this work to study the vibrations of the functional derivatives in the drug. The optimized molecular structure, atomic charges, vibrational frequencies, natural bond orbital analysis and ultraviolet-visible spectral interpretation of rosmarinic acid have been studied by performing HF and DFT/B3LYP/6-31G(d,p) level of theory and the FT-IR (solid and solution phase), FT-Raman (solid phase) by Mariyappan[15]. The structure and relative energies of the tautomers of the anti cancerous drug dichloroacetate are predicted using Hartree Fock and density functional theory by Singh [16].

FTIR and FT-Raman spectra of the pure paclitaxel drug [17], castor oil solvent-based paclitaxel drug and polymeric nanoparticle paclitaxel drug showed the specific functional groups of the polymeric nanoparticle drug material and solvent based paclitaxel drug have almost the same chemical characteristics of the pure paclitaxel drug.

Folate decorated paclitaxel loaded PLA–TPGS nanoparticles were prepared by a modified emulsification/solvent evaporation method [18]. The obtained nanoparticles were characterized by Field Emission Scanning Electron Microscopy (FESEM), Fourier Transform Infrared (FTIR) and Dynamic Light Scattering (DLS) method. PTX loaded nanoparticles exhibit great advantages compared to free PTX and the folate decoration significantly improve the targeted delivery of drug to cancer cell in both *in vitro* and *in vivo.*

Quantum chemistry, a sub-discipline of computational chemistry, is the weapon of choice when detailed knowledge of a chemical reaction is required and when it is impractical or even impossible to experimentally obtain the sought information. Density functional Theory (DFT) and Hartree Fock calculation were applied to study some

physicochemical properties of Taxol and its complexes. Taxol conjugated with this polymer can be utilized to improve the biological and anti cancer activity of Taxol [19].

The concept of utilizing polymers in drug delivery has been extensively explored for improving the therapeutic index of small molecule drugs. In general, polymers can be used as polymer-drug conjugates or polymeric micelles. The physicochemical properties of a novel amphiphilic polymer–paclitaxel conjugate monomethoxy-poly(ethylene glycol)-b-poly(lactide) (MPEG-PLA) and a cyclic small peptide c(RADfK)-paclitaxel containing the arginyl-glycyl-aspartic acid (RGD) amino acid sequence using Density Functional Theory (DFT) and Hartree Fock (HF) calculations[20] showed that these carrier paclitaxel complexes mentioned above can be used to improve anti cancer activity and water-solubility of paclitaxel.

DISCUSSION

From the above it is seen that though number of reported cases of cancer is steadily increasing, the study on paclitaxel which is very important anticanerous drug is inadequate. Paclitaxel is very effective in the treatment of various cancers especially ovarian and breast cancer, but it demonstrates poor aqueous solubility, which results in the difficulty challenging the development of paclitaxel parenteral formulations, so its clinical application is greatly restricted. Nanotechnology has been widely exploited in the field of antitumor research, and paclitaxel is no exception. In recent decades, a series of novel formulations of paclitaxel based on nanotechnology have been developed, including albumin-bound paclitaxel, polymeric micelle-formulated paclitaxel, polymer-paclitaxel conjugates, liposome encapsulated paclitaxel etc. The common advantage shared with these novel injectable formulations is that they are developed based on nanotechnology and Cremophor EL-free. In addition, these nanoformulations can significantly reduce toxicities of paclitaxel and greatly promote its antitumor efficiency [21].

CONCLUSION

The study about the efficient anticanerous drugs such as paclitaxel in nanoform can be studied powerfully using Quantum chemical calculations of ground state energy, geometrical structure and vibrational wavenumbers using DFT, HF quantum chemical methods and FT-IR and FT-Raman spectroscopic methods.

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