CRIMSON PUBLISHERS
Wings to the Research

Research in
Medical & Engineering Sciences

ISSN: 2576-8816

Review Article

A Brief Review on Importance of DFT In Drug Design

Hiteshi Tandon*, Tanmoy Chakraborty and Vandana Suhag

Department of Chemistry, Manipal University Jaipur, India

***Corresponding author:** Hiteshi Tandon, Department of Chemistry, Manipal University Jaipur, India

Submission: February 04, 2019; **Published:** February 26, 2019

Abstract

Density Functional Theory (DFT) is progressively becoming vital for the drug designing process. Since past few years DFT has appeared as a Quantum Mechanical (QM) method which is satisfactorily meticulous as well as competent to be employed in pharmaceutical studies. Biologically important molecular systems can be exactly described using DFT at a lesser computational cost than other methods making it a highly utilized technique. Current review presents prospective applications of DFT in drug design. To begin with, the basis of DFT is discussed. Next, accuracy of DFT for the analysis of drug design is discussed followed by applications of DFT for molecular modeling in drug chemistry. In the end, a summary of all the sections has been presented.

Keywords: Density functional theory (DFT); Drug design; Molecular modeling; Molecular recognition; Drug-Receptor interactions; Biological system

Abbreviation: DFT: Density Functional Theory; QM: Quantum Mechanical; CI: Configuration Interaction; HF: Hartree-Fock; MPn: Møller-Plesset Perturbation Theory

Introduction

There has been a constant rise in the need for growing efficiency in the field of medicinal chemistry and drug designing. When working at quantum mechanical level, the study of biological system requires selection of a technique which provides significant amount of information in a limited time period. As electron correlation is excluded in Hartree-Fock (HF) methods [1-4], thus it may not be able to describe certain properties precisely. Møller-Plesset perturbation theory (MPn) [5] and Configuration Interaction (CI) [6,7] are post-HF methods which consider electron correlation, but their high computational costs limit their use. Consequently, Density Functional Theory (DFT) has come into light which offers excellent level of accuracy with lesser computational time and is cost effective in comparison to other existing methods. The present review focuses on the application and potentiality of DFT for the study of pharmaceutically relevant molecules. Initially an introduction to DFT will be made. Next, an overview of the ability of DFT to determine drug properties will be presented followed by applications of DFT in drug design. Finally, conclusion would summaries the importance of DFT in medical and drug design chemistry.

Density Functional Theory (DFT)

In theoretical medicinal chemistry, DFT-based computations are budding as a significant methodological substitute. The central idea of DFT is that electronic density, ρ, exclusively determines the ground state energy and other molecular properties [8]. For a system, a density functional is represented by the ground state energy and is used to map a function to a value. It is expressed by equation 1 where square brackets denote a functional [9].

$$E0[\rho] = T[\rho] + V[\rho] + EXC[\rho] \quad (1)$$

A value for E0 is related with each density function, ρ. The ground state energy functional is comprised of three terms, i.e., T[ρ], V[ρ] and EXC[ρ]. T[ρ] gives information regarding the kinetic energy of the system while V[ρ] is a potential energy component which consists of Coulomb interaction amongst the electron distributions and the nuclei-electron interaction. The third term, EXC [ρ], corresponds to the exchange correlation energy, which involves exchange as well as correlation effects. The utilization of Schrödinger equation and complex wave function is replaced by electron density due to which the calculation of electronic structure of bigger molecules becomes easy through DFT as compared to HF, CI and MPn methods. The expressions for the first and second terms are available; however, the exact form of third term is unknown. DFT would have become an accurate technique if the true exchange correlation functional was known. As a result, different approximations, i.e. generalized gradient approximations (GGA), local-density approximations (LDA) and hybrid functionals, are used for the exchange correlation functional. B3LYP is a hybrid functional, introduced by Stephens et al. [10], wherein B3 stands for Becke's 3-parameter exchange [11] which consists of three empirical parameters while LYP includes four parameters. It is a highly accepted functional of all existing modern functionals and

very successful [12]. Since the functionals are selected empirically, there is no standardized method for increasing the preciseness of DFT computations. Regardless of this fact, DFT is an extensively used method for electronic structure computations due to its accuracy and efficiency.

Accuracy of DFT for Examination of Drug Properties

The accuracy of DFT for the study of diverse molecular properties has been studied extensively. In general, geometries of smaller organic molecules have been accurately predicted by DFT demonstrating its efficacy to predict geometries of drug molecules. Various studies have been performed comparing DFT calculations and experimental values which reveal the suitability of DFT technique [13-18]. The BP86 functional has been most widely studied in this field.

The energetic properties of drug molecules are also of significant interest in drug designing. Ionization energies, relative energies, electron affinities and metal ligand bond strengths can be effectively studied through DFT, however, no satisfactory information is provided for atomization energies. Molecular structure governs the properties as well as interaction of drug molecules with their receptors. Thus, the basis of any computational drug study is the prediction of the lowest energy conformation of that drug molecule. Numerous studies exist that utilize DFT technique for computation of relative conformational energies [19-21].

A crucial step in drug designing involves understanding the type of interactions taking place between the drug-like molecule and its target. Possible interactions between a drug and target consist of covalent bonds, dipole-dipole interactions, ion-dipole interactions, ionic interactions, hydrogen bonding, hydrophobic interactions and charge transfer. Prediction of hydrogen, ionic and covalent bonds has been successful through DFT, although no reasonable prediction has been possible for weaker bonds. Since the attachment of receptors to drugs is not permanent, there is rare existence of covalent bonds in drug action; inhibition of certain enzymes and antimicrobial cancer therapy are exceptions to this. Ions with unlike charge are found to form ionic bonds very commonly. Ionic interactions have a key role in the mechanism of drug action as at physical pH condition several functional groups undergo ionization. Unionized molecules may have dipole moments and can form ion-dipole or dipole-dipole bonds by interacting with ions or other dipoles respectively. Both these interactions are weaker than ionic interactions; nevertheless, they are very significant in drug-receptor binding. Weak interactions include hydrogen bonds, hydrophobic interactions and charge transfer interactions and these exist between drug and receptor to provide stability to drug-receptor complex. DFT is often utilized to study the ionic and covalent bond strengths [22-24]. It can predict the strength of hydrogen bonds very accurately [25,26]. As regards to dispersion interactions, DFT calculations are unable to predict them as they have influences ranging from hydrogen bonds to hydrophobic interactions [27]. In fact, systems with low energy forces, of the order of 1-5 kcal/mol, cannot be reliably described by DFT calculations. Hence, there should not be a complete dependence on DFT while studying such interactions between a drug and target.

DFT study is often utilized to explicate reaction mechanisms of the drug molecule. It can precisely calculate the transition state which is vital for drug design. The hybrid functional B3LYP has offered excellent insight into the mechanism of drug action [28-35]. In spite the broad success of DFT in transition structure computation, other instances of failure also exist [36-38].

Applications of DFT in Drug Design

DFT offers promising applications in the realm of drug design and a number of such applications are currently being employed. This review very briefly discusses the scope and applicability of DFT in the study of drug-like molecules and its properties.

Modelling interactions between drug and receptor

As per the basic supposition in logical drug design, molecular recognition followed by the binding of a ligand to the active site of a target molecule produces the drug effect. As a result, structure elucidation and binding interaction strength determination between drug molecule and its target holds immense importance in the drug design process. Numerous examples can be found in the literature that utilizes DFT to study potential drug-target interactions demonstrating the suitability of DFT for drug property studies [39-46].

Drug action mechanism modelling

Since enzymes act by decreasing the activation barrier of a reaction, the information of the transition state of a reaction between potential drug and receptor is of paramount importance to understand the mechanism of action of potential drug molecule. Mechanism based inhibitors can be designed using DFT that are able to imitate the transition state [47]. Several studies of neuraminidases exemplify the development of such transition state inhibitors [48-51]. A lot of other studies also present employment of DFT for deducing the enzyme action mechanism to aid in enhanced drug design [52,53] or determining drug action mechanism [54].

Organometallic drugs modelling

Biological systems comprise of organometallic complexes in the form of metalloenzymes and organometallic drugs. DFT has been fairly proficient at modeling metal-containing systems and thus has been utilized to study inorganic therapeutics [54,55]. The information regarding the structure of a drug molecule has been often deduced using DFT [56-64]. It is apparent that DFT is turning out to be extremely popular in the study of drug design. As a consequence, it is very much essential to find out the appropriateness of DFT to describe properties significant to the study of drugs.

Conclusion

The use of DFT for studying the properties of various biomolecules has been promoted by a number of studies [45], however, there also exist some other studies which point out its limitations [27,65]. DFT is undoubtedly a promising method for

How to cite this article: Hiteshi T, Tanmoy C, Vandana S. A Brief Review on Importance of DFT In Drug Design. Res Med Eng Sci. 7(4). RMES.000668. 2019. DOI: 10.31031/RMES.2019.07.00068

numerous problems and must be taken into account. The superior results of DFT, in general, make it an attractive method to be used for medicinal studies. When exact functional and basis sets are used for the study of potential drug molecules, DFT can be utilized to predict relative conformational energies, binding energies, electron affinities, ionization energies, drug molecule geometries, transition barriers, metal-ligand bond strengths and transition metal reaction pathways precisely. Although, the limitations of DFT in successfully determining some properties such as atomization energy, as discussed formerly, must not be ignored. It is crucial to be aware of the exactness of DFT for a specific issue in an attempt to identify the extent to which its predictions can be depended upon. For every system under examination, the performance of DFT must be calibrated in order to assess whether DFT meets required preciseness. An essential point to note while carrying out a DFT analysis is the selection of the exchange correlation functional. Owing to the extensive use and availability of broad validation studies, the B3LYP hybrid functional is commonly alluring. Nevertheless, more exact functionals may be accessible [63-71] and must be taken into account. With continuous development of new functionals, issues persisting with existing functionals will be resolved. Concluding, when suitable validity analyses are executed and appropriate functionals are implemented, DFT has a lot of potential to become a very valuable tool for challenging problems existing in medicinal chemistry.

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