A PROJECT REPORT ON

“STUDY OF ELECTRONIC & CHEMICAL PROPERTIES OF CLARITHROMYCIN USING DENSITY FUNCTIONAL THEORY”

SUBMITTED TO THE

DEPARTMENT OF PHYSICS

FACULTY OF SCIENCE

INTEGRAL UNIVERSITY, LUCKNOW,

226026

IN PARTIAL FULFILMENT OF REQUIREMENTS

FOR THE DEGREE OF

MASTER OF SCIENCE

IN PHYSICS

SUBMITTED BY-

TANVEER FATIMA RIZVI

M.Sc. PHYSICS (IV SEMESTER)

ROLL NO: 2001080007

UNDER THE SUPERVISION OF

Dr. ANURADHA SHUKLA

DEPARTMENT OF PHYSICS

INTEGRAL UNIVERSITY, LUCKNOW

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TO WHOM IT MAY CONCERN

This is to certify that **TANVEER FATIMA RIZVI** is a bona fide student of M.Sc. (II Year /IV semester) Session 2020-21 to 2021-22 at Integral University, Lucknow. She completed her project entitled **"STUDY OF ELECTRONIC & CHEMICAL PROPERTIES OF CLARITHROMYCIN USING DENSITY FUNCTIONAL THEORY"** successfully under the supervision of **Dr. Anuradha Shukla**, Assistant Professor, Department of Physics, Integral University.

I wish her good luck and a bright future.

Date:

Place: Lucknow

(Dr. Seema Srivastava)
Head Department of Physics
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CERTIFICATE

This is to certify that **TANVEER FATIMA RIZVI**, a student of M.Sc. (Physics-IV Semester) has completed the project on **"STUDY OF ELECTRONIC & CHEMICAL PROPERTIES OF CLARITHROMYCIN USING DENSITY FUNCTIONAL THEORY"** under my supervision during the year 2021-2022.

I wish her good luck and a bright future.

Date: **(Dr. Anuradha Shukla)**

Place: Lucknow

Supervisor
Assistant Professor
Department of Physics
Integral University,
Lucknow-226026

ACKNOWLEDGEMENT

In the accomplishment of this project successfully, many people have best owned upon me the blessings and the heart pledged support, this time. I am utilizing this to thank all the people who have been concerned with this project.

Primarily, I would thank God for being able to complete this project with success. Then, I would like to thank my project teacher **DR. ANURADHA SHUKLA**, whose valuable guidance has been the ones that helped me patch this project and make it full proof of success. Her suggestions and her instructions have served as the major contributor to the completion of the project. Then I would like to thank my parents and friends who have helped me with their valuable suggestions and guidance has been very helpful in various phases of the completion of the project. Having an idea and turning it into a book is as hard as it sounds. The experience is both internally challenging and rewarding. I especially want to thank the individual that helped make this happen. Lots of thanks to Ms. Sarita Yadav, a Ph.D. scholar who gave her precious time to my project. Last but not least I would like to thank my classmates who have helped me a lot.

TANVEER FATIMA RIZVI

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ABSTRACT

The present project is concerned with the study of the chemical and electronic properties of clarithromycin using Density Functional Theory, by comparing its form 1 and 2. Clarithromycin ($C_{38}H_{69}NO_{13}$) is a macrolide drug that is somehow different from other antibacterial drugs in its chemical structure.

The expected outcomes of this project are to view which form of Clarithromycin is better by analyzing its electro-static potential and total density.

KEYWORD

- **Density functional theory (D.F.T.)**
- **Basis Sets**
- **Electro-static potential**
- **Total density**
- **Clarithromycin**
- **Polymorphism**
- **Active pharmaceutical ingredients (A.P.I)**
- **Pharmaceutical Compounds (P.C.)**

LIST OF SYMBOLS AND ABBREVIATIONS

- **D.F.T. = Density Functional theory**
- **P.C. = Pharmaceutical Compounds**
- **A.P.I.= Active Pharmaceutical Ingredients**
- **H.F.= Hartee-Fock**
- **S.T.O.= Slatter Type Orbitals**
- **G.T.O.-= Gaussian Type Orbitals**

CHAPTER 1. INTRODUCTION

1. BACKGROUND: A SHORT INTRODUCTION

Generally, a solid can sustain in two forms i.e., crystalline or amorphous. In which, the development of drugs, the crystalline form of solids is preferred most. In the crystalline form, the solids can appear as co-crystals, salts, polymorphs, hydrates, etc. as dictated in the following figure1.1

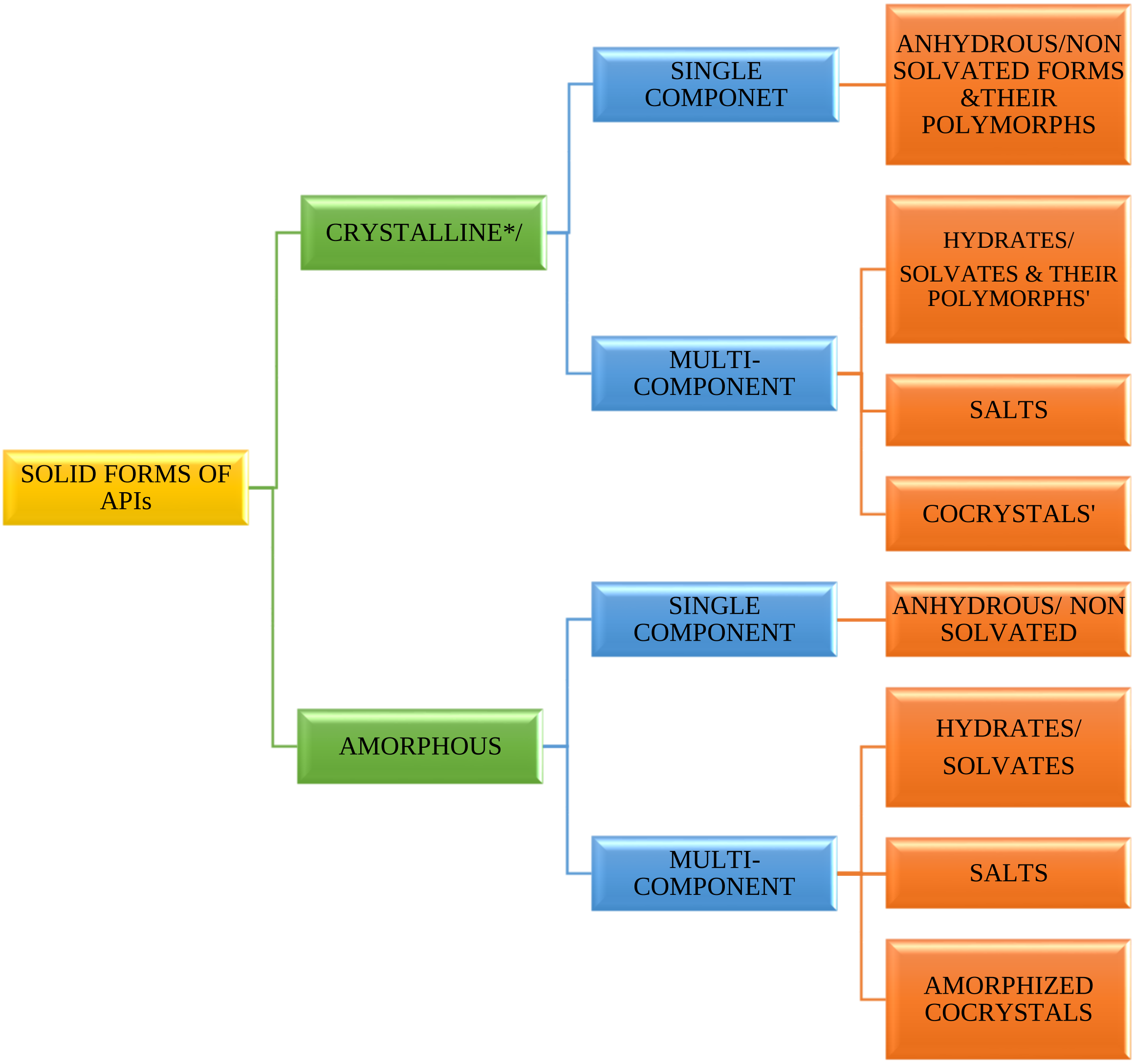


Figure 1.1: API solid form structure and composition

Drugs are the chemical components that react with the body of any organism while consumed. The major step in the formation of any drug or pharmaceutical compound is sharply based on the selection of correct Active Pharmaceutical

Ingredients (A.P.I). The active ingredients of the pharmaceutical compound play different roles in the development of desired drugs. such as solubility, stability, reactivity, and other chemical properties. The bodies of human beings are controlled by proteins. Which exists in so many forms & does different functioning. Each protein must have a specific function and is quite specific to the type of cell that acts on it. They act as drug targets. In the current era, researchers prefer crystalline form as an active ingredient in the pharmaceutical compound due to its lasting property of stability, solubility, reactivity, etc.

1.2 PHARMACEUTICAL COMPOUNDS(PCs)

The term pharmacy comes from the Greek word pharmakon, which means medicine or remedy. So, pharmaceutical compounds (PCs) are those types of chemical elements that can be used in the medicinal field. Pharmaceutical compounds are chemicals that are combined as a single active ingredient or in a combination with other Pharmacology active substances that may be packed in a single unit or combination products. The main objective of the pharmaceutical analysis is to observe the molecules with their medicinal reactivity. The pharmaceutical compounds should have the features like medicinal efficacy, security profile, medicinal activity, and stability. Many pharmaceutical drugs fail or are withdrawn (rejected) from the market after approval due to severe effects.

Crystallization processes that are done in the field of pharmaceutical compounds are usually mapped out to received crystals with controlled shape, purity, and polymorphic form.

The schematic diagram of the drug development process is depicted in Figures 1.2(a) & 1.2(b)

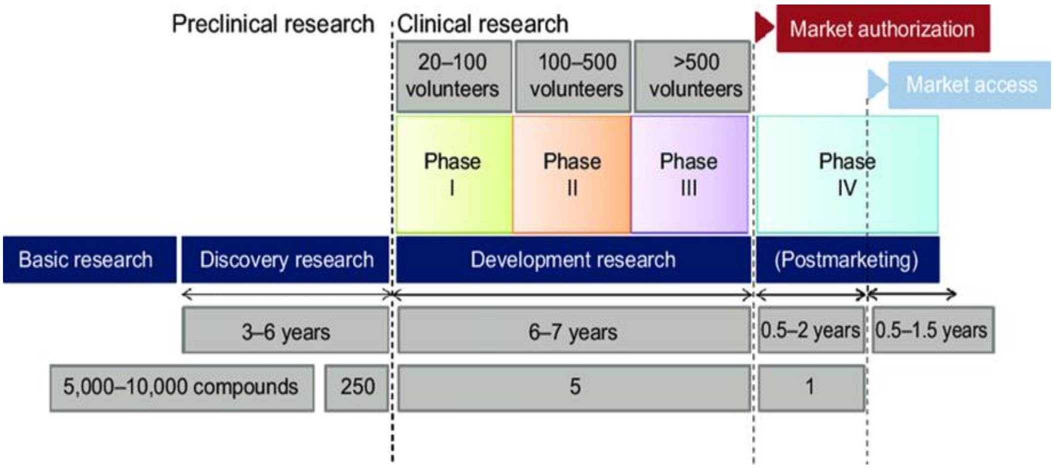


Figure 1.2(a): The schematic diagram of the drug development process

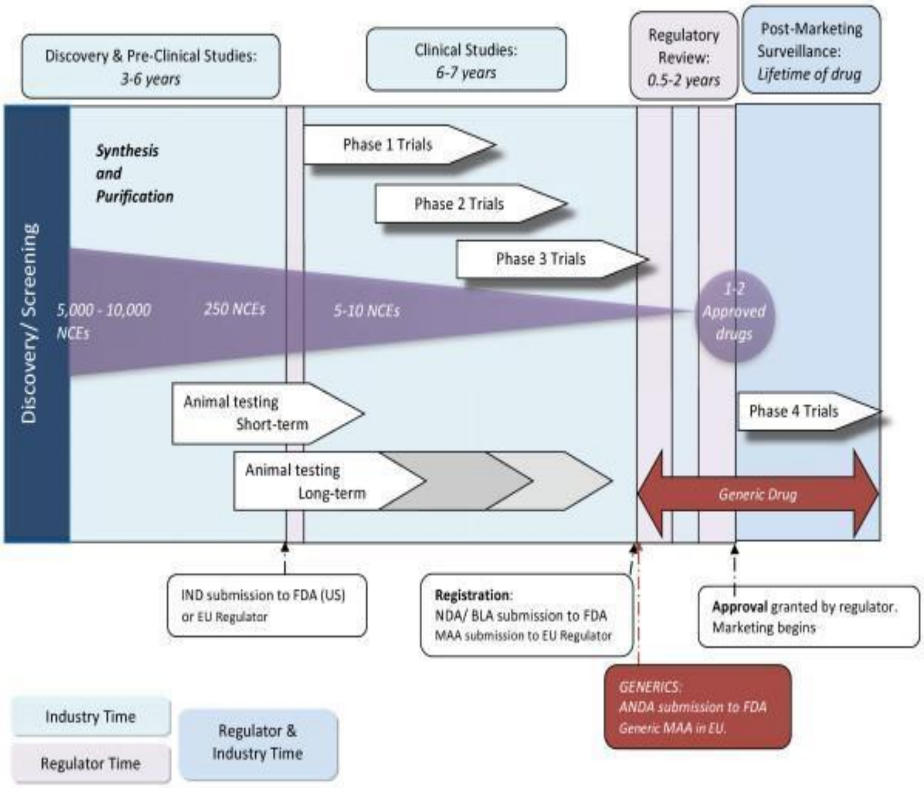


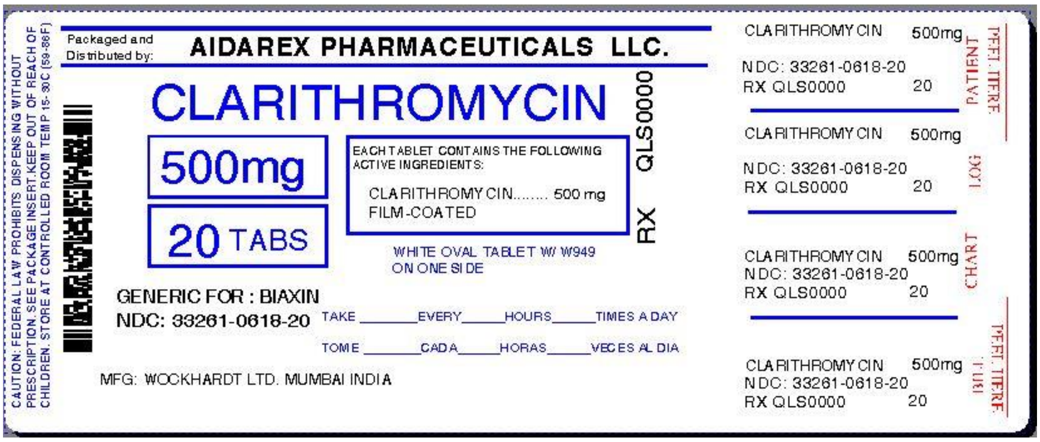
Figure 1.2(b): Schematic of the Drug development process.

1.3 ACTIVE PHARMACEUTICAL INGREDIENTS(APIs)

All drugs are composed of two major components one is active pharmaceutical ingredients & the other is excipients. Where API is the main (central) ingredient and excipient is the reactionless component other than the drug that helps in the binding of pharmaceutical compounds. Excipients are considered the inactive part of the drug as mineral oil in the pill for lactose etc. The active ingredient of a pharmaceutical compound is the part of any pharmaceutical drug that gives rise to the aimed effect. API plays a vital role in making any pharmaceutical compound. As if the quality of the active ingredient of any drug is poor then it can cause severe damage to the body of the composer or even can cause death too. So, one should be very careful while using the drug's active ingredient for making pharmaceutical compounds or medicine.

APIs - Proposed Regulatory Changes

The Active Ingredients must be registered proximately below the brand name, with the primary letter of the active ingredient directly below the first letter of the brand name. The active ingredients must have an equal reputation with the brand name on the front/main panel of the label. For better-quality distinction between the brand name and the active ingredient, there should



CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. SEE PACKAGE INSERT. KEEP OUT OF REACH OF CHILDREN. STORE AT CONTROLLED ROOM TEMP 15- 30C (59-86F)

Packaged and Distributed by: **AIDAREX PHARMACEUTICALS LLC.**

CLARITHROMYCIN

500mg

20 TABS

EACH TABLET CONTAINS THE FOLLOWING ACTIVE INGREDIENTS:

CLARITHROMYCIN........ 500 mg
FILM-COATED

WHITE OVAL TABLET W/ W949 ON ONE SIDE

RX QLS0000

GENERIC FOR : BIAXIN
NDC: 33261-0618-20

TAKE ______EVERY_____HOURS_____TIMES A DAY

TOME ______CADA_____HORAS_____VECES AL DIA

MFG: WOCKHARDT LTD. MUMBAI INDIA

CLARITHROMYCIN 500mg
NDC: 33261-0618-20
RX QLS0000 20

PATIENT

PEEL HERE

CLARITHROMYCIN 500mg
NDC: 33261-0618-20
RX QLS0000 20

LOG

CLARITHROMYCIN 500mg
NDC: 33261-0618-20
RX QLS0000 20

CHART

CLARITHROMYCIN 500mg
NDC: 33261-0618-20
RX QLS0000 20

BILL

PEEL HERE

Fig 1.3: Show the details of Active Pharmaceutical Ingredients present in the tablet of clarithromycin.

be a difference in font style or letter spacing, or font color. The active ingredient should begin with an uppercase letter but the remainder should be in lower case. Products containing day and

night preparations, different preparations, and the composition of each tablet must be provided immediately below the brand name, and the font size must be less than 2mm in height on the main/front panel.

1.4 CLASSIFICATION OF ACTIVE PHARMACEUTICAL COMPOUNDS (APIs)

Active Pharmaceutical Ingredients are widely classified in two ways that are-

1. **INORGANIC COMPOUNDS**
2. **ORGANIC COMPOUNDS**

Inorganic Compounds of APIs are also called synthetic active pharmaceutical ingredients. They are further classified into generic and innovative synthetic APIs, based on the way synthetic is used. Inorganic compounds of APIs, also called tiny molecules are made up a large part of the pharmaceutical market, with many small molecule drugs commercially available in the market.

Organic compounds of APIs are also called natural APIs. They are Isolated from materials of animal or human origin. And can be used as synthetic or semi-synthetic or isolated from herbal sources or microorganisms. Natural APIs are utilized in making biologics, which are becoming the top-selling drugs in day-to-day marketing. Based on the solubility, Active Pharmaceutical compounds are categorized into soluble and insoluble drugs.

1.5POLYMORPHISM

The term polymorphism is taken from the Greek words 'polus' & 'morphs' which mean 'so many' & 'shape' respectively. Thus, polymorphism can be defined as the component consisting of two or more crystal phases in the crystal's lattice.

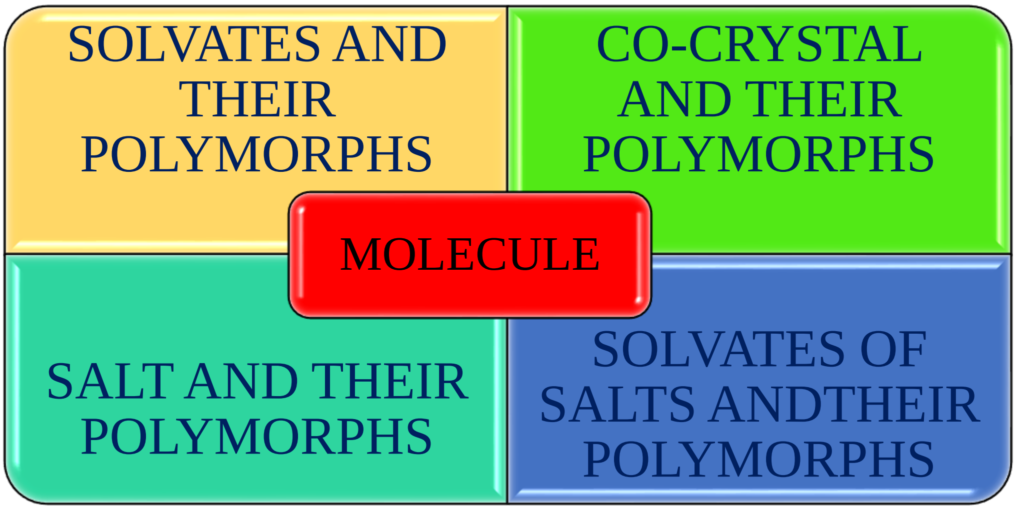


Fig 1.5: a different form of a polymorph of the molecule

It can be further understood by the fact that it is making some new drug compounds in different shapes or crystalline forms which possess different properties. Like, if polymorphism occurs due to the packing of crystalline phases, then it is called packing polymorphism on the other hand if it occurs due to differences in confirmation then it is called conformational polymorphism[4]. With the help of polymorphism, we can tune different properties like thermodynamics properties, melting points, chemical properties tableting commerce stability, tensile strength, free energy, etc.

1.6POLYMORPHISM OF CLARITHROMYCIN

It has been observed that the physicochemical properties of pharmaceuta ical drugs are concerned with the type of polymorphic crystalline form of pharmaceutical drugs. In this project, claarithromycin is taken which rests in at least two forms i.e clarithromycin form 1, and clarithromycin form 2.

Clarithromycin of form O is also known as 6-O-methylerythromycin A. Its structural formula is shown in the following diagram-

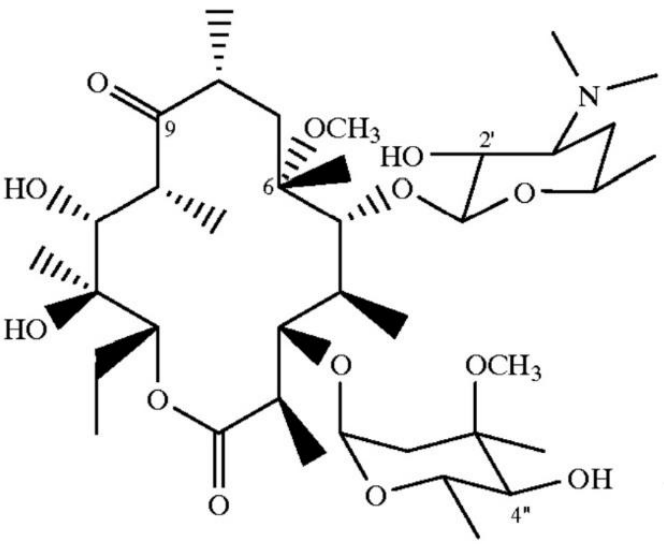


Fig 1.6 (a) 6-O-methyl erythromycin A

6-O-methylerythromycin A exhibits excellent antibacterial activity contrary to gram-positive bacteria, Some gram-negative bacteria, anaerobic bacteria, Mycoplasma, and Chlamidia. It is steady under the tart conditions and is too worthwhile when administered verbally. It is a useful treatment for infections of the upper respiratory expanse in children and adults. 6-O-methylerythromycin A is available as tablets and as an oral Suspension. Drugs currently on the market are formulated using the thermodynamically more stable 6-Omethylerythromycin A form II. Drugs currently on the market are framed from thermodynamically more stable Form II crystals. Therefore, the preparation of the current commercial entity requires converting the Form I crystals to Form II. Typically, this is done by heating the Form I crystals under a vacuum at a temperature of greater than 800C. Therefore, the discovery of a novel form of methyl erythromycin A which can be prepared without the high-temperature treatment results in substantial processing cost savings. In addition, the favorable dissolution characteristics of Form I relative to Form II increase the bioavailability of the antibiotic and provides significant formulation advantages. The present invention also provides pharmaceutical compositions which comprise a therapeutically effective amount of 6-O-methylerythromycin A Form I, exhibiting an exothermic transition at 132.2°C, in combination with a pharmaceutically acceptable carrier. The invention further relates to a method of treating bacterial infections in a host mammal in need of such treatment comprising administering to the mammal a therapeutically effective amount of 6-0-methylerythromycin A Form I.

1.7 CURRENT SCENARIO OF THE STUDIES IN PHARMACEUTICAL COMPOUNDS (PCs)

Pharmaceutical industries play a vital role in the supply of medicinal products in the world at a reasonable cost and super quality. In recent years, we observed that due to covid-19 the demand for pharmaceutical drugs has increased and changed the overall situation of the world. The pandemic that happened in the year 2020 gave rise to many pharmaceutical industries that never occurred previously.

Today estimated that about 80% of people in developing countries still relays on traditional medicine based largely on species of plants and animals for their primary health care. India has one of the richest plant traditions in the world. These are estimated to be around 25,000 effect plant-based formulations, used in folk medicine and known to rural communities in India. India̓s share in the export of herbals is USD 63 billion which is just 0.2% of the global herbal market. So there is obviously vast scope for Indian manufacturers for entering the growing worldwide opportunity of business in the herbal pharmaceutical field. We also have to focus on the standardization of herbal products. The pharmaceutical export promotion council i.e clarithromycin is ready to play a key role in this regard. Currently, a majority of the adverse events related to the use of herbal products and herbal medicines that are reported are attributable either to poor product quality or to improper use. Inadequate regulatory measures, weak quality control systems, and largely uncontrolled distribution channels may have been a contribution to the occurrence of such events. So Pharmacovigilance of herbal medicines is required.

Nowadays, the pharmaceutical industries and companies are trying hard to fulfill the demand of the people to make their health good in a very short time. For this, it is necessary to have accurate knowledge of pharmacy. Moreover, higher health authorities like W.H.O should take some major steps and plan a strategy to increase the production of pharmaceutical drugs. Proper use of active pharmaceutical ingredients (APIs) is also very important. Currently, salt formation plays a dominant role to improve the physical properties of APIs & it is forecasted that many medicinal drugs on the markets are governed by salts.

In the present circumstances, India is the number one exporter of generic medicine over 20% and the value of export of pharmaceutical compounds from the Indian market is around US$ 14 billion with a growth of 30% yearly. India exports medicines to more than 200 countries globally, and the U.S.A is one of the biggest markets for it.

1.8 RESEARCH OBJECTIVE

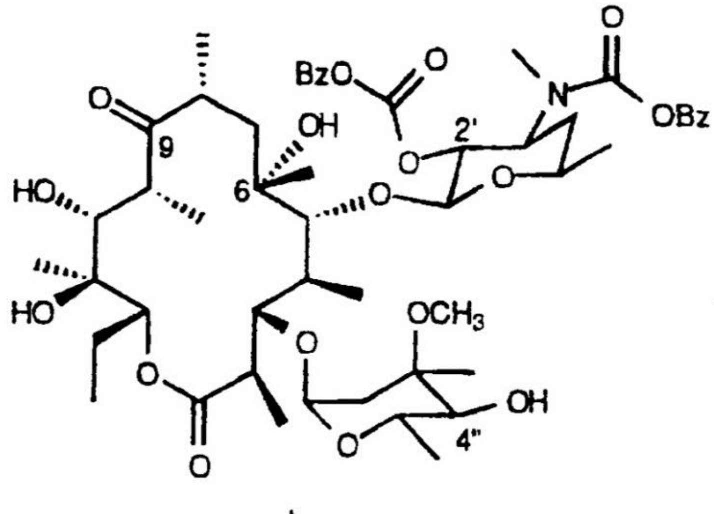
The objective of the current study is to understand the electronic and chemical properties of form 1 and form 2 of clarithromycin by calculating its electro-static potential and total density with the help of the Gaussian 09 software package.

In this proposed project work we focused on the structural properties of the forms of selected drugs and this work yielded essential information about new/novel compounds.

1.9 MODEL COMPOUNDS

Clarithromycin form1 and form2 were chosen as the model drug in this study. General information about the model compounds is as follows-

CLARITHROMYCIN FORM 1



I

Fig 1.9 (a) Form 1 of clarithromycin drug

The present invention in one characterization provides a process for the production of 6-0-methylerythromycin A Form I by conversion of erythromycin A to 6-0-methylerythrornycin A with inter-mediate protection and deportation reactions and subsequent crystallization or recrystallization of the 6-0-methylerythromycin A to 6-0-methylerythroniycin A Form I, that step comprising crystallizing 6-0-methylerythromvcin A Form I from a syrup or semisolid containing at least one residual solvent from the exclusion reaction.

In a yet further embodiment, there is provided the use of such 6-0-methylerythromycin A Form I as an antibiotic and also in the manufacture of an antibiotic medicament, as well as 6-O-methylerythromycin A Form I when prepared by the process of the contemporaneous development.

In another quintessence, the above-mentioned intermediary protection and unprotected reactions are carried out on an erythromycin A 9-oxime derivative.

In a further embodiment, in the aforementioned crystallizing step, at least one solvent added the residual solvent is utilized. Preferred additional solvents are selected from one or more or combinations of ethanol, isopropyl acetate, isopropanol, tetrahydrofuran, a hydrocarbon of from 5 to 12 carbon atoms, a ketone of from 3 to 12 carbon atoms, a carboxylic ester of from 3 to 12 carbon atoms, an ether of from 4 to 10 carbon atoms, benzene, benzene substituted with one or more substituents selected from the group consisting of alkyl of from 1 to 4 carbon atoms.

CLARITHROMYCIN FORM 2

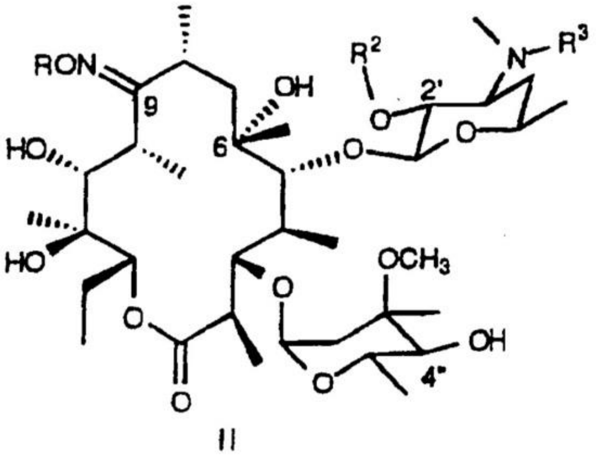


Fig 1.9 (b) Form 2 of clarithromycin drug

Another feature of the creation of the pharmaceutical drug, there is provided 6-O-methylerythromycin A Form II was produced from the aforementioned 6-0-methylerythromycin A Form I by heating the latter.

In a further embodiment, there is provided an antibiotic pharmaceutical composition comprising the aforesaid 6-O-methylerythromycin A Form II together with a pharmaceutically acceptable carrier. Preferred is a solid pharmaceutical dosage form for oral administration comprising such 6-O-methylerythromycin A Form II in combination with one or more pharmaceutically acceptable excipients, selected from one or more fillers, binders, humectants, disintegrating agents, solution retarding agents, absorption accelerators, wetting agents, and emollients. In a further personification, there is delivered the use of such 6-0-methyl erythromycin A Form II as an antibiotic and also in the production of an antibiotic pharmaceutical.

Detailed Description 6-0-methylerythromycin A is prepared by methylation of the 6-hydroxy group of erythromycin A.

We observed in fewer cases that in order to delay the effect of the drug, it is required to slow the absorption of the drug from a hypodermal or intramuscular injection. This may be consummated by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. The form 1 of clarithromycin can’t resist in a desirable state due to its dipole moment. Whereas form 2 plays vital role in the field of pharmaceutical industry as it can stay in a better form for a long time.

CHAPTER 2. METHODOLOGY

2.1 COMPUTATIONAL DETAILS

All computations used in this project were carried out using the Gaussian 09, Gauss view program package, and mercury software. The molecular structure and optimized geometry of all the selected molecules were computed by the DFT method employing cc-pvt, correlation consistent polarized valence triple-ζ, basis set, and B3LYP functional and 6311-G(d,p) basis set is used. In this project, with the help of gauss view software electro-static potential and total density are converted into ".cub file" and then after mapping out the function it was seen. Theoretical methods and basis sets have to be merged to meet up the necessities of both exactness and computation. For this DFT has been verified to be particularly beneficial in handling the electronic structure of molecules. The complete vibrational spectra, molecular geometry optimizations, and molecular electrostatic potential calculations of form1 and form 2 of clarithromycin were achieved using Gaussian 09 software package.

2.2 TYPES OF THEORETICAL CALCULATIONS

The electronic structure theory (E.S.T.) is concerned with theoretically defining the properties of the molecules. Under the determination of the electronic structure of atoms, computation focuses precisely on the equations and approximations resultant from the postulates of quantum mechanics and solves the Schrodinger equation for gaining the properties of the molecular system. There are two major models for the determination of the electronic structure of atoms proposed in computational chemistry.

a. **Semi-Empirical Method**
b. **ab-initio method**

The semi-empirical method consisted of experimental parameters and interpretation of Schrodinger's equation. This method uses experimental data to parametrize equations. (example- structure-property relationship (SPR)). This method is less accurate than ab initio but much faster. The equations are parametrized to reproduce specific results, usually the geometry and heat of formation instead of total energies. Whereas the Ab- initio method indicates that the calculations are grounded on fundamental principles. This method does not include any empirical parameters or experimental data. Ab initio is a Latin term which denotes “from the beginning” Ab initio quantum mechanics provides an energy function that can be exact in principle and works for any molecule, but it is calculated within the framework of Born-Oppenheimer approximation namely, the electrons are much lighter than nuclei, and so they move much faster and adjust adiabatically to any change in nuclear configuration.

The ab-initio calculations are of so many forms which few of them are mentioned below-

- **a.** Hartree-Fock (HF)
- **b.** Moller-Plesset-Perturbation Theory (MP)
- **c.** Density functional theory (DFT)
- **d.** Configuration Interaction (CI)

2.3 DENSITY FUNCTIONAL THEORY (D.F.T.)

Density Functional Theory was first developed theoretically by Pierre Hohenberg and Hohenberg Kohn in the composition of the Hohenberg-Kohn theorem (HK) in the year 1964, which stated that-The ground-state energy from the Schrodinger’s equation is a unique functional of the electron density. This signifies that the ground-state electron density uniquely determines all the properties consisting of energy and wave function of the ground-state. This method got notable success in forecasting, rebuilding, and explaining a wide range of materials phenomena. It is a quantum mechanical method used mainly in the field of Physics and Chemistry to determine the structure of electrons of an atom or molecules in form of solid crystals of many-body systems and to provide a quantitative understating of the properties from the fundamental laws of quantum mechanics.

The electronic wave function of a polyatomic molecule depends on several parameters—

the bond distances, bond angles, and dihedral angles of rotation about single bonds (these angles define the molecular conformation). A full theoretical treatment of a polyatomic molecule involves the calculation of the electronic wave function for a range of each of these parameters. The equilibrium bond distances, bond angles, and dihedral angles are then found as those values that minimize the electronic energy including nuclear repulsion.

The four main approaches to calculating molecular properties are ab initio methods, semi-empirical methods, the density-functional method, and the molecular-mechanics method. Semi-empirical molecular quantum-mechanical methods use a simpler Hamiltonian than the correct molecular Hamiltonian and use parameters whose values are adjusted to fit experimental data or the results of ab initio calculations. An example is the Hückel MO treatment of conjugated hydrocarbons, which uses a one-electron Hamiltonian and takes the bond integrals as adjustable parameters rather than quantities to be calculated theoretically. In contrast, an ab initio (or first principles) calculation uses the correct Hamiltonian and does not use experimental data other than the values of the fundamental physical constants.

In density functional theory, the properties of many-electron systems can be determined by using functionals (function of some other function). It does not provide information about the molecular wave function, but it can calculate the electron probability density and electronic energy.

DFT forecasts a great variability of ground-state molecular properties such as molecular structures and physicochemical properties, vibrational frequencies, thermodynamic properties, potential barriers and reaction paths, hydrogen bonding, etc. It has been applied in different situations; for example, in the study of spin-polarized systems, multicomponent systems, free energy at finite temperatures, superconductors with electronic pairing mechanisms, relativistic electrons, time-dependent phenomena, excited states, MD, etc. In materials science, it has found applications in the study of structural properties (such as lattice parameters, elastic constants, equilibrium geometry, and structural defects), lattice dynamics, electron density, electronic structure, and in different areas of spectroscopy such as Raman and Compton scatterings, photoemission spectroscopy, optical absorption spectroscopy, and magnetic resonance spectroscopy. The presentation of the DFT depends upon the choice of the exchange-correlation functional and hence utmost care is taken in its selection. The selection is made based on their performance for a wide range of properties from energetics and geometries of molecules to reaction barriers and van der Waals interactions.

The density-functional method does not attempt to calculate the molecular wave function but calculates the molecular electron probability density r and calculates the molecular electronic energy from r.

The molecular-mechanics method is not a quantum-mechanical method and does not use a molecular Hamiltonian operator or wave function. Instead, it views the molecule as a collection of atoms held together by bonds and expresses the molecular energy in terms of force constants for bond bending, stretching, torsion, and other parameters.

This chapter discusses the general principles of electronic structure calculations for polyatomic molecules and discusses the Hartree–Fock calculation method. As noted the Hartree–Fock method does not take account of electron correlation. Electronic Terms of Polyatomic Molecules

Ab initio and density-functional methods that take account of electron correlation are discussed in this project discuss semi-empirical methods and the molecular-mechanics method.

The case of hydrogen bonds, where there is a reasonable overlap of electron density as well as some electrostatic interactions between the fragments, has been a difficult challenge for functionals. Hydrogen bonds are of the order of 1–10 kcal/mol and are much weaker than normal covalent and ionic bonds. Yet they are still much stronger than the weak dispersion and van der Waals interactions found between nonpolar closed-shell fragments. A wide difference in the performance of functionals that show good results for thermochemistry and geometries has been found in the case of hydrogen bonds.

Three modes of calculation exist in density functional theory. They are:

1. Local Density Approximation (L.D.A.)

(i) Fastest method

(ii) Provides good band structures

(iii)Gives less accurate geometry

2. Gradient corrected functionals

(i) Provides more accurate geometries

(ii) Resulted in improvements for the calculated values of the total energies of atoms and molecules.

3. Hybrid functionals

(i) Gives more accurate geometries

(ii) Gives approximation to the exchange-correlation energy functional in D.F.T.

Despite several successes, the Density Functional theory possesses certain limitations that need to be flabbergasted (resolve) before it can be preserved as an exact theory rather than a semi-empirical theory. Following are a few limitations-

(a) Defaulting or negligence of strong correlations- Many transitio9n metal compounds can transfer charge in the insulator, but D.F.T. predicts a metallic state.

(b) Band Gap problems- The Hohenberg-Kohn Sham theorem is invalid for atoms in the excited state. The band gaps in semiconductors and insulators are constantly undervalued.

(c) Over-binding problems are often seen in density functional theory.

(d) Van der Waal's interactions do not include any functionals of Density Functional Theory.

2.4 BASIS SET

A basis set is a scientific depiction of the molecular orbitals within a molecule. The basis set can be understood as containing each electron in a section of space. Superior basis sets impose rarer constraints on electrons and more accurately approximate the molecular orbitals. Linear grouping of basis function approaches whole electronic wave function. Basis functions are linear arrangements of Gaussian functions

Basis sets are classified into STO and GTO forms i.e, Slater-Type Basis Sets and Gaussian-Type Basis Set. In Slater-Type Basis Sets three forms to occur are- Minimal Basis Sets, Split-Valence Basis Sets, and Polarization Basis Sets. In minimal basis sets very small functions are used to run the program. The minimal basis sets are not bendable enough for an exact depiction of orbitals and to describe the electron supply between the nuclei to form chemical bonds.

Slater Type Orbitals (STO):

$function \rightarrow S\ (\zeta, \boldsymbol{r}) = Cx\ ny\ mz\ le\ {-\zeta r}$............... (2.41)

It characterizes electron density in the valence region and beyond. But, the valuation of these integrals is difficult Gaussian Type Orbitals (GTO):

$function \rightarrow g\ (\alpha, \boldsymbol{r}) = Cx\ ny\ mz\ le\ -\alpha r$ 2............ (2.42)

where α is a constant determining the size of the function. It is easy to evaluate but does not represent electron density well. This can be overcome by using the actual basis function as a linear combination of such primitive Gaussian-

$$\chi\mu = \sum p\ d\mu pgp \text{ ………………………………… } (2.43)$$

In split valence basis sets.

The behavior of the Gaussian exponential factor is shown where the origin is at nucleus b. A Gaussian function does not have the desired cusp at the nucleus and hence gives a poor representation of an AO for small values of rb. To accurately represent an AO, we must use a linear combination of several Gaussians. Therefore, an LC-GTF SCF MO calculation involves the evaluation of very many more integrals than the corresponding LC- STO SCF MO calculation, since the number of two-electron integrals is proportional to the fourth power of the number of basis functions. However, Gaussian integral evaluation takes much less computer time than Slater integral evaluation. This is because the product of two Gaussian functions centered at two different points is equal to a single Gaussian centered at a third point. Thus all three- and four-center two-electron repulsion integrals are reduced to two-center integrals.

Let us discuss some of the terminology used to describe STO basis sets. A minimal (or minimum) basis set consists of one STO for each inner shell and valence-shell AO of each atom (Section 14.3). For example, for C2H2 a minimal basis set consists of 1s, 2s, 2px, 2py, and 2pz AOs on each carbon and a 1s STO on each hydrogen. There are five STOs on each C and one on each H, for a total of 12 basis functions. This set contains two s-type STOs and one set of p-type STOs on each carbon and one s-type STO on each hydrogen.

Such a set is denoted by (2s1p) for the carbon functions and (1s) for the hydrogen functions, a notation that is further abbreviated to 12s1p>1s2.

Gaussian-Type Basis Sets are also categorized into minimal basis sets, split valence basis sets, and polarization functions.

Minimal Basis sets hold the lowest number of basis functions required for each atom. It uses fixed-size atomic kind orbitals. A common naming convention for a minimal basis set is STO-XG where X is an integer. This X value represents the number of Gaussian primitive functions including a single basis function. In these basis sets, the comparable number of Gaussian primitives comprises core and valence orbitals. Minimal basis sets typically give rough results that are insufficient. Commonly used minimal basis sets are STO-2G, STO-3G, STO-6G, and STO-3G*(polarized). STO-3G basis set means that the linear combination of 3Gaussian type orbitals fitted to one Slater type orbital. Some of the usually used split-valence basis sets with or without polarization and diffuse functions are –

- 3-21G
- 3-21G*- polarization function on heavy atoms

- 3-21G**- polarization functions on heavy atoms and hydrogen
- 3-21+G- Diffuse functions on heavy atoms
- 3-21++G- Diffuse functions on heavy atoms and hydrogen
- 3-21+G*- Polarization and diffuse functions on heavy atoms
- 3-21+G**- Polarization functions on heavy atoms and hydrogens, as well as diffuse functions on heavy atoms
- 4-21G
- 4-31G
- 6-21G
- 6-31G
- 6-31G*
- 6-31+G*
- 6-31G(3df,3pd)
- 6-311G
- 6-311G*
- 6-311+G*

2.5 TOOLS USED IN THE PROJECT

In recent years, the use of software in research activity gains much popularity. Computational researches and information are much valuable as they can produce required data in a more accurate form. In this project, three software plays the dominant role that is Mercury, Gaussian 09 and Gauss view 06.

Gaussian is software that is used in the computers which support the windows. This software is mainly used by researchers, physicists, chemists, etc. It employs fundamental laws of quantum mechanics to predict the molecular structure and to know the electro-static properties, thermal properties, etc. of the required compound.

Gaussian09 offers new features and performance enhancements that will enable you to model molecular systems of increasing size, with more accuracy, under a broader range of real-world conditions. Some of these features include;

- Model Reactions of Very Large Systems with ONIOM.
- Study Excited States in the Gas Phase and Solution.
- Additional Spectra Prediction.
- New and Enhanced Methods and Algorithms

- Ease-of-Use Features.
- Performance Improvements.

Gauss View is a graphical user interface designed to help you prepare input for submission to Gaussian and to examine graphically the output that Gaussian produces. Gauss View is not integrated with the computational module of Gaussian, but rather is a front-end/back-end processor to aid in the use of Gaussian. Gauss View provides three main benefits to Gaussian users.

- Gauss View offers you an advanced visualization facility.
- Gauss View makes it easy to set up many types of Gaussian calculations.
- Gauss View lets you examine the results of Gaussian calculations using a variety of graphical techniques.

CHAPTER 3. RESULTS AND DISCUSSION

3.1 GEOMETRY OPTIMIZATION

The chemical structure of Clarithromycin in form 1 and form 2 has been shown in the following figure.

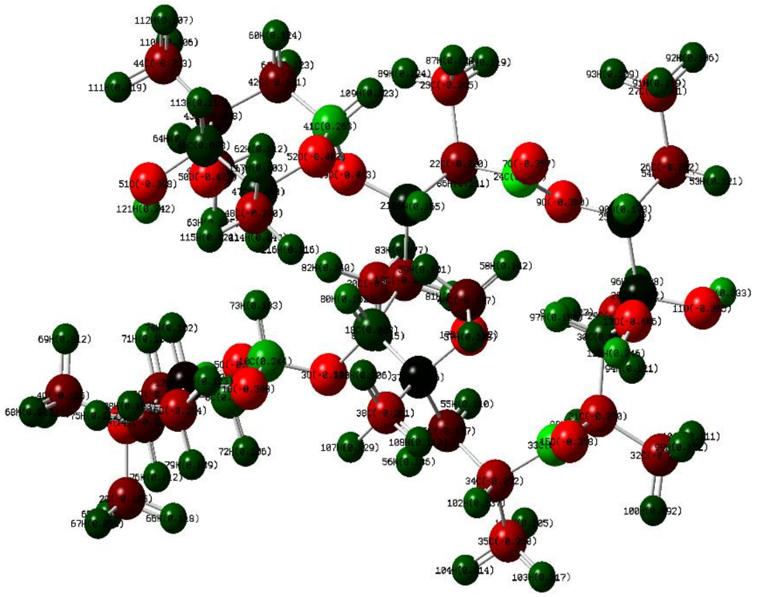


Fig 3.1 (a): Geometrically Optimized structure of clarithromycin form1

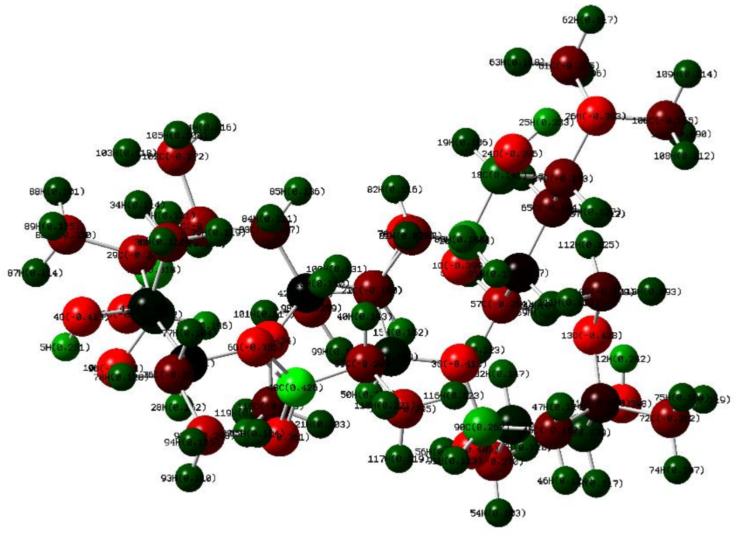


Fig 3.1 (b): Geometrically Optimized structure of clarithromycin form 2

The table obtained by the geometrical optimization of form 1 and form 2 of clarithromycin is shown below:

CLARITHROMYCIN FORM 1

FILENAME	CLARITHROMYCIN FORM 1
FILE TYPE	.fch
CALCULATION TYPE	FREQ(RAMAN)
CALCULATION METHOD	B3LYP
BASIS SET	6-311G(d,p)
CHARGE	0
SPIN	SINGLET
TOTAL ENERGY	-2522.89994295
RMS GRADIENT NORM	0.00000310
DIPOLE MOMENT	8.1832

Table 3.1 (a) shows the geometry optimization details of form 1 clarithromycin

CLARITHROMYCIN FORM 2

FILENAME	CLARITHROMYCIN FORM 2
FILE TYPE	.fch
CALCULATION TYPE	FREQ(RAMAN)
CALCULATION METHOD	B3LYP
BASIS SET	6-311G(d,p)
CHARGE	0
SPIN	SINGLET
TOTAL ENERGY	-2522.91280126
RMS GRADIENT NORM	0.00000154
DIPOLE MOMENT	7.787

Table 3.1 (b) shows the geometry optimization details of form 2 clarithromycin

Geometry optimization was carried out in unessential internal coordinates and the ground state optimized structure of forms 1 and 2 of clarithromycin as shown in the above figures respectively. Initial geometry for forms 1 and 2 of clarithromycin was diminished at DFT employing B3LYP using a basis set 6-311G (d,p). The molecular energy of the optimized structures of form 1 and form 2 of clarithromycin is obtained to be -2522.89994295 and –2522.91280126 respectively. The dipole moment obtained in form 1 was 8.81832 Debye and in form 2 was 7.7877 Debye respectively.

3.2 ELECTRO-STATIC POTENTIAL

The electrostatic potential is a very useful property or quantity to explain the charge transfer and polarization within the molecule. It is further helpful in explaining reactivity, hydrogen bonding of electrons, and analyzing the nucleophilic and electrophilic properties. In these processes, chemical reactions are likely to occur.

The electrostatic potential of clarithromycin of form 1 and form 2 are commanded by using a basis set of 6-311G(d,p) and the B3LYP method. The following figures show the electrostatic potential of form 1 and form 2 of clarithromycin

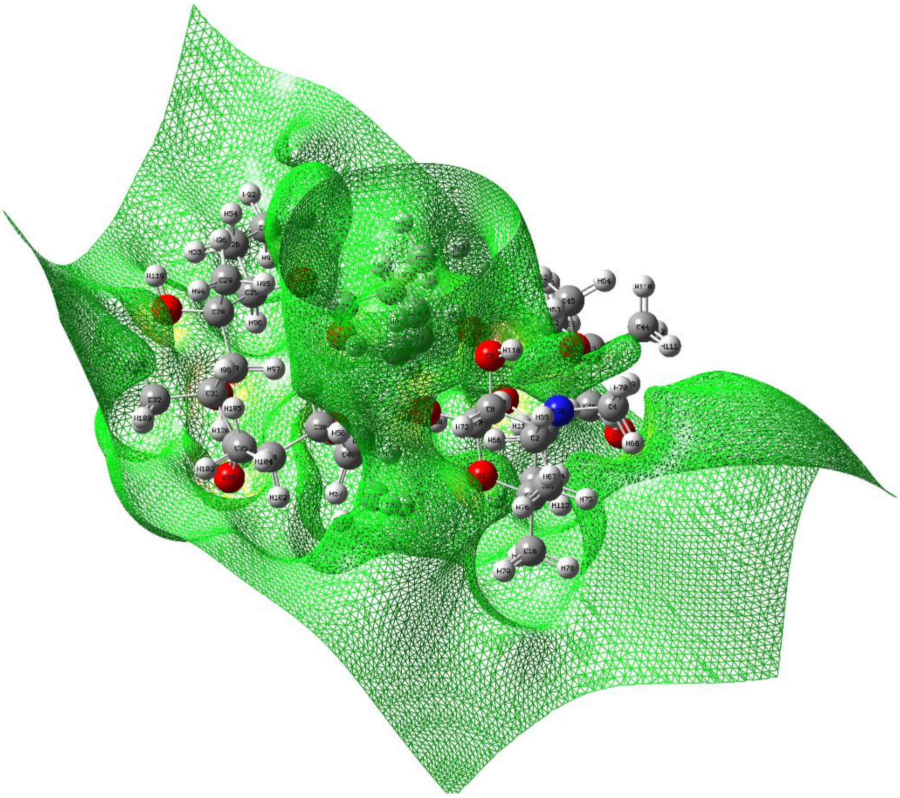


Fig 3.2 (a)- Electro-static potential of form1 of Clarithromycin using basis set 6-311g(d,p) with B3LYP method.

CLARITHROMYCIN FORM 1

FILE TYPE	.fchk
CALCULATION TYPE	FREQ (RAMAN)
CALCULATION METHOD	B3LYP
BASIS SET	6-311G(d,p)
CHARGE	0
SPIN	SINGLET
SOLVATION	NONE
ELECTRONIC ENERGY	-2522.899943 HARTREE
RMS GRADIENT NORM	0.000003 HARTREE/BOHR
DIPOLE MOMENT	8.183153 DEBYE
POLARIZABILITY (α)	473.164623 A.U.
HYPER POLARIZABILITY (β)	265.707648 A.U.

Table 3.2(a): Shows the summary of the electrostatic potential of form 1 clarithromycin using DFT B3LYP and basis set 6-311G (d,p)

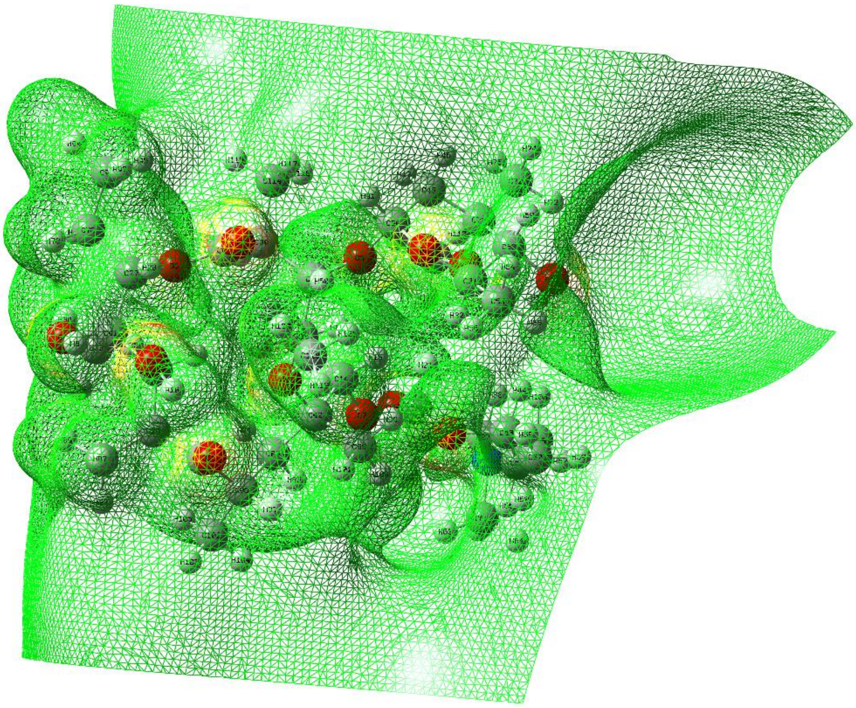


Fig 3.2 (b)- Electro-static potential of form2 of Clarithromycin using basis set 6-311g(d,p) with B3LYP method.

CLARITHROMYCIN FORM 2

FILE TYPE	.fchk
CALCULATION TYPE	FREQ (RAMAN)
CALCULATION METHOD	B3LYP
BASIS SET	6-311G(d,p)
CHARGE	0
SPIN	SINGLET
SOLVATION	NONE
ELECTRONIC ENERGY	-2522.912801 HARTREE
RMS GRADIENT NORM	0.000002 HARTREE/BOHR
DIPOLE MOMENT	7.787744 DEBYE
POLARIZABILITY (α)	472.743468 A.U.
HYPER POLARIZABILITY (β)	236.693077A.U.

Table 3.2(b): Shows the summary of the electrostatic potential of form 2 clarithromycin using DFT B3LYP and basis set 6-311G (d,p)

3.3 TOTAL ELECTRON DENSITY

The total density of the molecules of forms 1 and 2 of clarithromycin are investigated and formed by using Density Functional Theory B3LYP and basis set 6-311G(d,p) mapped out after making its cube file. The total electron density of form 1 and form 2 of clarithromycin obtained by density functional theory is mentioned in figures 3.3(a) and 3.3(b)

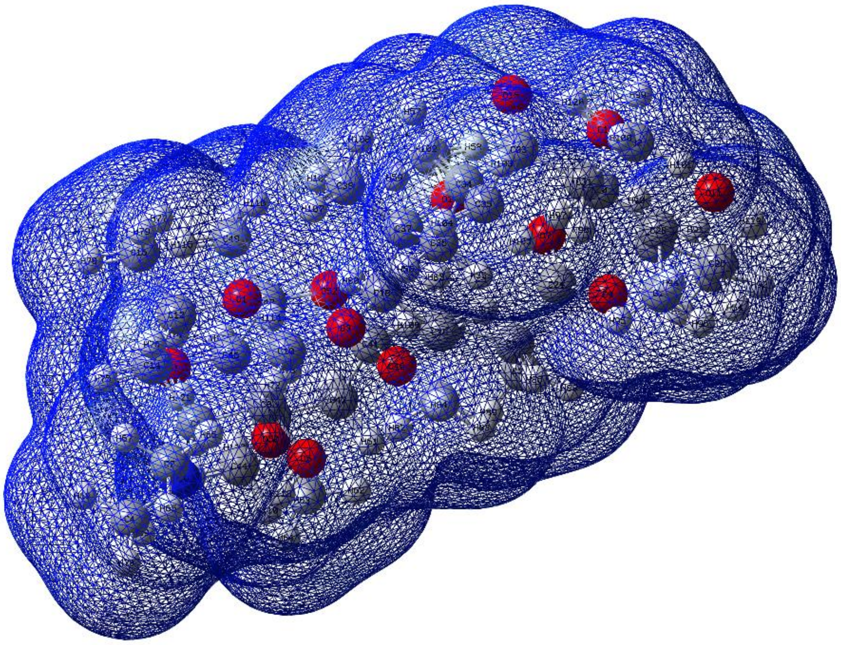


Figure 3.3 (a) Total electron density of form 1 of clarithromycin using B3LYP and basis set 6-311G(d,p)

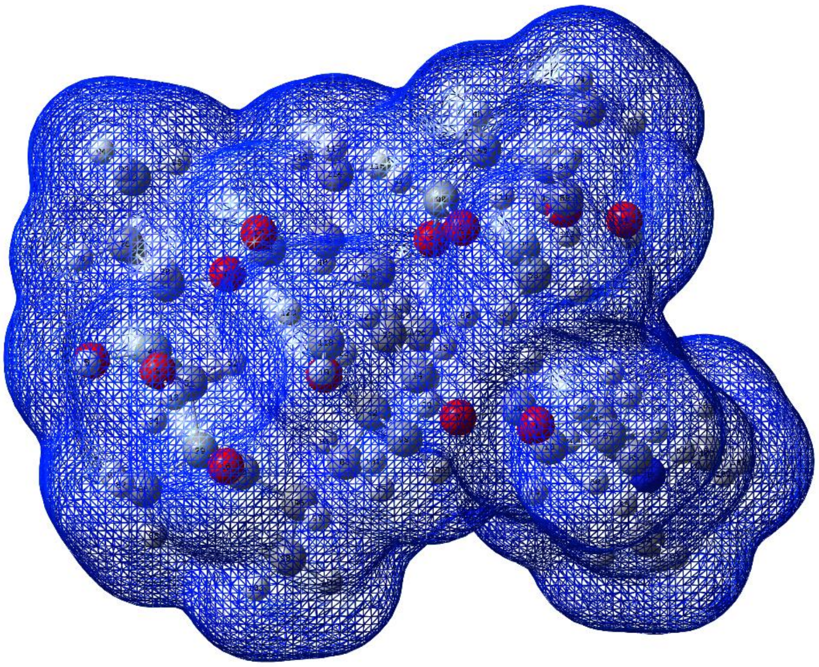


Figure 3.3 (b) Total electron density of form 2 of clarithromycin using B3LYP and basis set 6-311G(d,p)

The combined total electron density and electrostatic potential of form 1 and form 2 of clarithromycin is as depicted below:

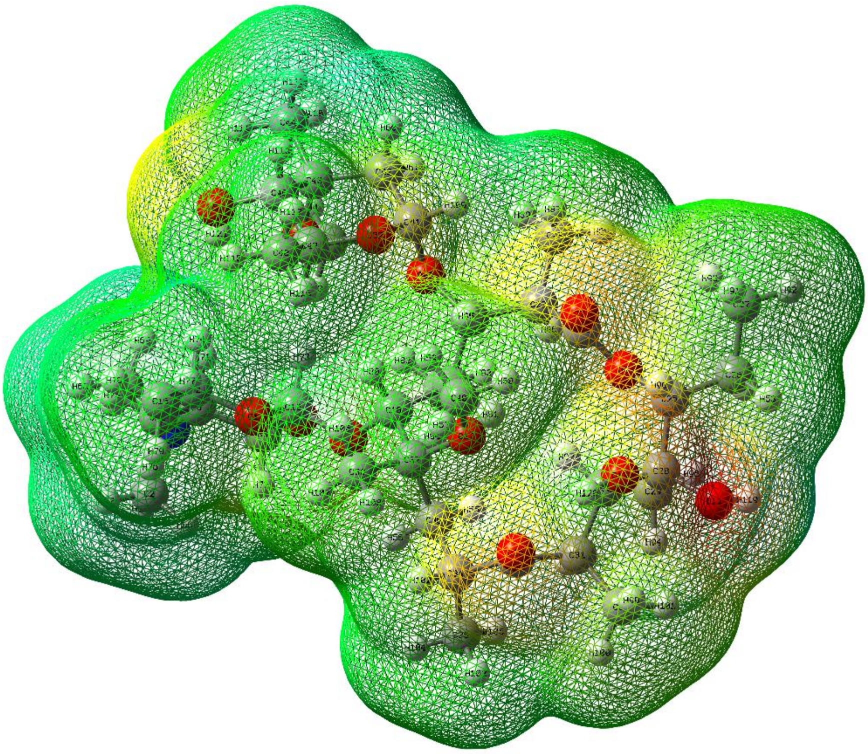


Figure 3.3 (c) combined ESP and Total electron density of form 1 of clarithromycin using B3LYP and basis set 6-311G(d,p)

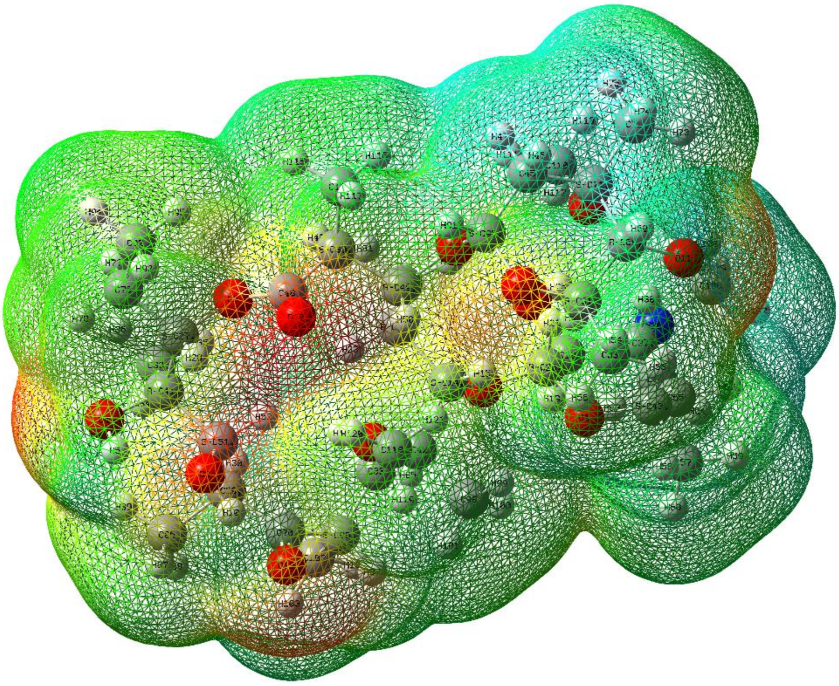


Figure 3.3 (d) combined ESP and Total electron density of form 2 of clarithromycin using B3LYP and basis set 6-311G(d,p)

CHAPTER 4. CONCLUSION

The most stable structure of clarithromycin obtained by this project is of form 2 by optimizing its electro-static potential and total density. The methodology used in this project is Density Functional Theory. The geometric optimization of the clarithromycin drug of form 1 and form 2 was obtained using Gaussian 09 software program package. As we see that Clarithromycin is available in the current world as a generic form of the drug. It can be known well that the physical and chemical properties of clarithromycin are affected by their different forms as discussed above in this project. From the result, we observed that form 2 of clarithromycin is thermodynamically more stable among its three forms.

It could be predicted that the improvement in the purity of form 2 of clarithromycin can help in the field of medical sciences in the upcoming time as the availability of this drug is easy and it is cost-friendly.

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