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Determining binding free energy by computational modelling: A theoretical approach for selection of stationary phase in chromatographic studies

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Abstract: HPLC is one of the most widely used analytical method for determination of pharmaceuticals in pharmaceutical industry. Because of wide range availability of columns, it is difficult to choose the column while optimization and it consume lot of time. To reduce the time and solvent consumption for optimizing the column in HPLC method the best alternative is computational approach. Computational chemistry is a subfield of chemistry that employs computer modelling as a means of assisting in the resolution of difficult chemical issues. The computation of molecular structures, interactions, and properties is accomplished by the utilization of theoretical chemistry techniques that are integrated into efficient computer programs. In the current investigation, the objective was to implement a computational strategy with the purpose of optimizing the chromatographic column for the detection of certain pharmaceuticals. For the purpose of this experiment, the Avogadro with orca software was utilized to calculate the Gibbs free energy between the stationary phase and the pharmaceutical of choice for different columns, including C8 and C18. Relative binding free energies between the analyte and column were calculated and applied for selection of column. The tool was utilized for the purpose of optimizing the column in order to minimize the amount of solvent that was utilized and time to lessen the complexity of the procedure. Overall, this computational approach serves as preliminary screening phase for selection of the best column through binding free energy guided process that ensures efficient elution of analyte from stationary phase and supports sustainable development goals (SDGs) through responsible consumption of solvent.

Keywords: Chromatography, Column optimization, Computational modelling, Gibbs free energy, Analytical method, Eco-friendliness, Sustainability

1. Introduction

Chromatography is a versatile method of separation that examines and separates components of a mixture based on the manner in which they interact with a stationary phase and a mobile phase in a manner that is distinct from one another. Forensic science, chemistry, biochemistry, medicine, and environmental studies are just few of the scientific disciplines that make substantial use of this chromatography. The chromatographic technique utilized depends on the analytical goals, analytes, and separation mechanism. Chromatography is essential for qualitative and quantitative analysis, purification, separation, and characterization of chemicals in complex mixtures in analytical labs. It is useful for research, quality control, and other applications since it separates and identifies individual components. [1] High-performance liquid chromatography (HPLC) is a common analytical method for separating mixture components. In HPLC, the sample is placed in the mobile phase, which is forced through the column at high pressure. The physicochemical properties of sample components affect how they interact with the stationary phase. These include size, charge, binding free energy, and polarity. Uneven interactions divide components as they flow along the column. This occurs as they move through the

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column. [2] HPLC is divided into several types based on the stationary phase and separation procedure. Reverse-phase chromatography (RPC) requires a nonpolar stationary phase like C18 or C8 and a polar mobile phase like water and organic solvents like acetonitrile or methanol. It is ideal for pharmaceutical, environmental, and biological material separation because to its hydrophobicity-based separation. [3] For example, bare silica or diol are examples of polar stationary phases that are used in normal-phase chromatography (NPC). When using high-performance liquid chromatography (HPLC), it is essential to optimize both the mobile phase and the stationary phase in order to accomplish the required separation and increase the overall performance of the chromatographic process. [4,5].

1.1. Column Optimization

Column technology innovations including hybrid and superficially porous particles have improved RPC analysis speed and efficiency. Reversed-phase chromatography is a powerful technique used in chemical, environmental, and medicinal analysis. Most RPC systems use C18 and C8 bound silica stationary phases. [6]

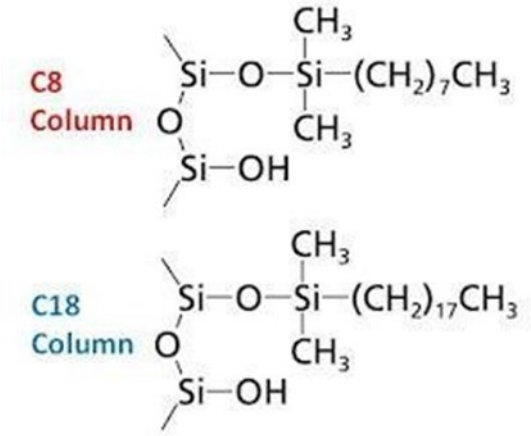

Figure 1. Structure of C8 (octyl) and C18 (octadecyl)

Figure 1 shows an octyl (C8) chain linked to silica as an extra hydrophobic stationary phase. Its intermediate hydrophobicity gives some compounds a unique selectivity and elution order compared to C18. For faster elution or better separation selectivity than C18, the C8 stationary phase is often used. Pharmaceutical analysis, natural product analysis, and environmental research are among its many uses. Particle sizes and pore diameters for C18 and C8 stationary phases vary, allowing for optimization of separation efficiency, resolution, and analysis time. The analyte, separation requirements, and selectivity determine whether C18 or C8 is superior. RPC also uses polymeric or hybrid stationary phase materials to increase selectivity and performance. RPC stationary phase selection depends on analyte hydrophobicity, chemical properties, and separation goals. Screening many stationary phases during method development and optimization may be essential to maximize analyte separation and peak resolution. [7] C18 is a hydrophobic stationary phase that is made up of an octadecyl (C18) chain that is attached to the surface of the silica (Fig.1). Strong hydrophobic interactions with analytes are provided by it, and it affords good retention for molecules that are neither polar nor moderately polar. [8] In the fields of pharmaceutical analysis, environmental analysis, and natural product analysis, C18 stationary phase is frequently utilized. It has a high degree of selectivity when it comes to the separation of hydrophobic substances, such as medicines, lipids, and hydrophobic biomolecules. Cyano, which is a strong dipole, has the ability to interact with other dipoles on solutes.

Figure 2. Structure of Cyano bonded phase

Figure 2 shows that the alkyl ligands that are present in cyano phases give them a somewhat hydrophobic property. There is presently no other type of HPLC phase that is more stable than the more recent Cyano phases. [9] Lewis bases, or electron donors, interact with electron-deficient compounds, or Lewis's acids. Phenol is a Lewis base. Gradient-elution chromatography in normal-phase systems concentrates polar solvents in non-polar solvents. One downside of reversed-phase gradient elution is the potential of preferential adsorption of more polar solvents on the polar

adsorbent. Because of this, the gradient profile may differ greatly from the mobile phase composition program specified. [10,11].

1.2. Problems while optimization of stationary phase/ columns

As reversed phases become more available for trade, column selection may become problematic. Analysts must pick from several choices. These characteristics, together with packaging facilities and column manufacturers' unique testing methods, cause misunderstanding. [12,13] The availability of a large number of column brands, chemistries, particle sizes, and diameters might make it challenging to select the column that is specifically designed to meet the requirements of a particular separation. Selectivity, efficiency, and durability are some of the features that may be unique to each column. These qualities might have an effect on the overall analysis as well as the performance of the separation process. [14] It's crucial to remember that choosing the right column could need some trial and error because it depends on the particular separation criteria and analytes being examined. Making well-informed judgements on column selection can also be aided by routinely examining and becoming current with developments in chromatography literature and column technology. [15] Several Problems are encountered during column optimization in HPLC such as selectivity, retention and resolution, stability and robustness of columns, sample matrix effects etc. [16]

1.3. Computational approaches for column optimization

Pharmaceutical HPLC separation optimization has advanced greatly in recent decades. Gaussian is used to screen columns to find the optimal one for eluting the analyte faster based on intermolecular interactions. To study the degree of intermolecular interactions between chemicals and stationary phases, computer modelling and theoretical studies have been applied. Computational calculations and chemical modelling can greatly minimize the number of feasible columns for the optimal chromatographic separation technique. [17] Computational methodologies can assist build methods by anticipating appropriate column designs and offering separation process insights. However, they need specific input parameters and assumptions that may not reflect real-world chromatographic system complexity and complexities. HPLC column optimization, especially for medicines or complex compounds, requires empirical optimization and experimental validation. Computational methods may be effective. To achieve the desired chromatographic performance, column selection, mobile phase composition, and operating conditions must be carefully examined and tested. [18]

Abinitio, density functional, and semiempirical computational chemistry theories may study molecular geometries, rates, equilibria, spectra, and other physical properties. Pharmaceutical companies use computational chemistry to study biomolecule-drug interactions. Computational chemistry is often used to dock drugs into enzyme active sites. It can compute molecular Gibbs free energy and bond free energy between molecules. Materials science uses it to study solids like plastics and catalysts in crucial lab and industrial activities. It cannot replace experimentation, which is the last judge of nature. [18], [19]

The goal of a theoretical model built to do calculations is to compute the quantum heat of a body that might be gained or provided during a thermal change of its quantum states. Because of its potential to provide substantial accuracy while utilizing less computer resources, density functional theory (DFT) simulations are frequently employed in the domains of chemistry and materials. [20], [21],[22], [23], [24] The total energy of quantum systems is frequently created in density functional theory (DFT) models, and the model is largely directed at the electronic structure of matter. It is important to define an entropy functional S in order to optimize the free energy G of the quantum system at constrained temperatures. The latter may also be used to a variety of first principles computational codes, which are scenarios in which ab initio quantum matter modelling is necessary. [25], [26] The Gibbs free energy, or chemical potential in fundamental theoretical physics, is crucial in chemical and biological processes. Studying the free energy behavior of systems like protein ligand binding constants, permeability coefficients, conformational equilibrium constants, membrane-water partition coefficients, electron transfer, solvation, and others can help us understand their

structural, kinetic, and dynamic properties. [27–31] Recent developments in computation theory, computing power, and statistical mechanics have made Gibbs free energy change determination more reliable, efficient, and well-organized. Protein-ligand binding constants and membrane-water partition coefficients are important for rational drug design. Without knowing the free energy changes, these properties are hard to evaluate. Analyte-stationary phase interaction structural and thermodynamic studies require accurate free energy computation. We also studied the most accurate, low-cost, and reliable approaches to pick the best column for analyte elution by assessing Gibbs free energy. We believe calculating free energy is essential to augment experimental values in the literature. [32] The current work used a computational technique to optimize the chromatographic column for the detection of chosen medicines. Tapinarof, Elacestrant, and Bexagliflozin were chosen for this investigation. The medications were chosen based on a review of the literature since no HPLC techniques for estimating them have been developed too far. As a result, the created technique will serve as a reference for analysts when constructing a chromatographic method, reducing the time required for optimization.

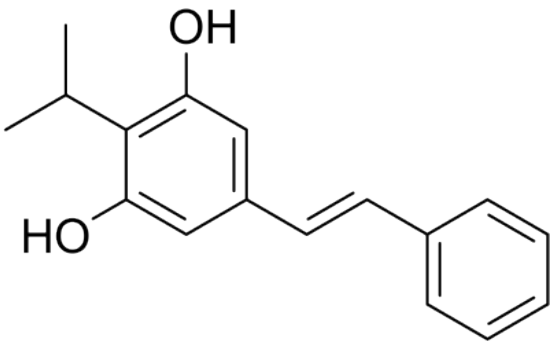

Figure 3. Structure of Tapinarof

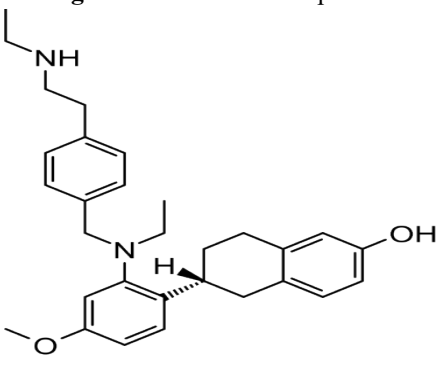

Figure 4. Structure of Elacestrant

Tapinarof (TAP) is chemically 5-[(E)-2-Phenylethen-1-yl]-2-(propan-2-yl) benzene-1,3-diol (Fig.3) and has shown promise as a potential treatment for various inflammatory skin conditions, particularly psoriasis and atopic dermatitis (eczema). It belongs to a class of compounds known as Aryl hydrocarbon receptor modulators (AhR modulators). [33] Elacestrant (ECT) is (6R)-6-{2-[Ethyl({4-[2-(ethylamino) ethyl] phenyl} methyl) amino]-4- methoxyphenyl}-5,6,7,8-tetrahydronaphthalen-2-ol (Fig.4). It's an antineoplastic and a selective estrogen receptor degrader (SERD). [34] Bexagliflozin (BXG) is chemically (2S,3R,4R,5S,6R)-2-[4-Chloro-3-[[4-(2-cyclopropyloxyethoxy) phenyl] methyl] phenyl]-6-(hydroxymethyl) oxane-3,4,5-triol (Fig.5).

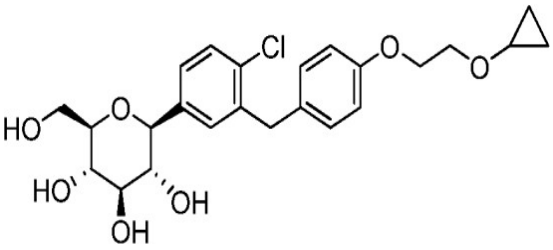

Figure 5. Structure of Bexagliflozin

It works in the kidneys to stop glucose (blood sugar) from being absorbed. This aids in lowering blood sugar levels. A sodium-glucose co-transporter 2 inhibitor called Bexagliflozin is used to assist those suffering from type 2 diabetes in controlling their blood sugar levels. A powerful and extremely selective inhibitor of sodium-glucose co-transporter 2 (SGLT2) is Bexagliflozin. [35]

2. Computational Method

2.1. Tools

The tools used in the present work include Chemsketch [36], Avogadro software[37], Orca software [38].

2.2. Column Optimization in HPLC method development

Column optimization is a key step in HPLC technique development for identifying analytes in a given sample. Many solvents and time will be spent during the optimization process, which contradicts the principles of Green Analytical Chemistry (GAC). [39–43] The computational

technique is one of the greatest ways to optimize the column in order to decrease solvent use and prevent the laborious procedure. The ORCA tool was used in the current investigation to determine Gibbs free energy between the stationary phase and the selected medication for different columns such as C8 and C18. The study's complete methodology is as follows.

2.3. Procuring 3D structure of the molecule

The 2D structures of the compounds used for this work were obtained from authorized sources such as PubChem, Drug Bank, Med Chem Express, and others, or were sketched using Chem sketch and transformed into a 3D structure. The 3D structures of molecules were then stored in 'cml' format in a separate folder labelled XYZ. If the molecule is downloaded directly, it will be in 'mol' format and must be converted to 'cml' using Avogadro Software.

2.4. Computational approach by Avogadro with ORCA

First, a 'cml' file containing selected substances from the chem sketch was opened. To open the file, choose Open from the File menu. Looking through the files on the disc yielded an acceptable drug file. After opening the relevant drug file, the geometry of the chosen molecule was optimized by selecting Optimize Geometry from the Extensions toolbar. "Optimize Geometry" gave a rapid, realistic representation of a molecule using molecular physics. [44] An input file was prepared once the geometry was optimized in the Avogadro program, where the software is accessible, in order to commence computational computations. The settings shown in Table 1 were used to build an orca input file with Avogadro by selecting Extensions > Orca > build Orca Input. Figure 6 depicts the dialogue with the autogenerated command after selecting the relevant parameters for the investigation. [45,46]

Table 1. Parameters selected for generation of input file

PARAMTER	SELECTED LEVEL
Calculation	Frequency
Method	DFT (Density Functional Theory)
Charge	0
Format	Cartesian
Basic Set	Def2-Svp
Multiplicity	1

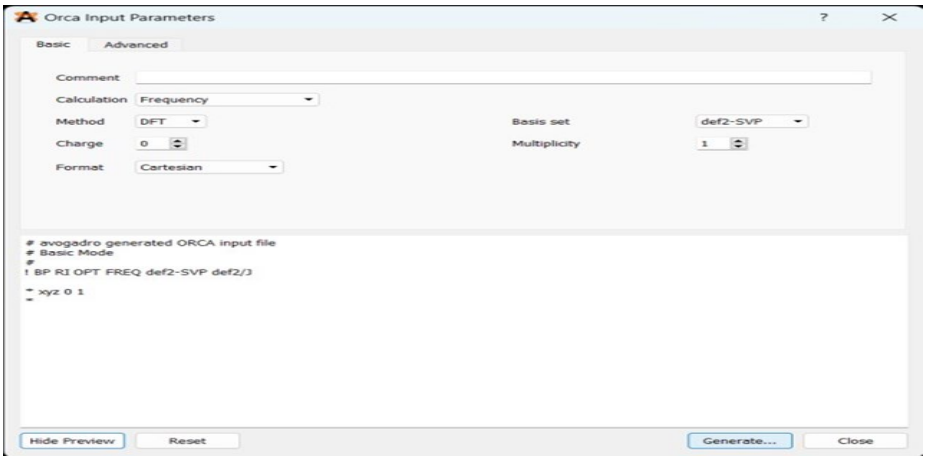

Figure 6. Orca input parameters

The input file was titled "xyz.inp" and was saved in the same folder as the xyz. cml. The Run app was used to launch cmd, and the following command was entered to browse the location of the Orca input file and tell it to make an output file. Figure 7 depicts a picture of the command supplied in the run app. "C:\Users\91807\OneDrive\Desktop\XYZ>C:\orca\orca xyz.inp > xyz.out". Following the command, geometry optimization cycles were done during the

run, culminating in the generation of the result file. The entire Gibbs free energy of the optimized medication was recorded in the output file. The same approach was used for all compounds in the research, including chosen medications Tapinarof (TAP), Bexagliflozin (BXG), and Elacestrant (ECT); column molecules C8, C18, and drug-column complexes. The binding free energy of pharmaceuticals with columns was calculated by taking into account the previously described molecules' Gibbs free energy. The following formula was used to determine the binding free energy values:

$$\Delta E = E_{A-B} - [E_A + E_B]$$

Where, ΔE is Binding free energy between drug and stationary phase (column). E_{A-B} is Gibbs free energy Drug-column complex. E_A is Gibbs free energy of Drug. E_B is Gibbs free energy of stationary phase (column)

The binding free energy of the complex between the drug and the column reflects the stability of the complex. The greater the binding free energy, the lower the stability. If the complex is not stable, the analyte which interacted with the stationary will be eluted faster and so the retention time of the analyte. The process of optimizing chromatographic settings for column selection include selecting the column that elutes the analyte the fastest which results in less retention time. As a result, the current study proposes selecting a column with a high binding free energy value of the drug-column combination.

3. Results and discussion

Chemists can quantitatively detect numerous unique components in a mixture using high-performance liquid chromatography (HPLC) in a single analytical step. By extensively examining the aspects impacting chromatographic performance, the optimum chromatographic parameters required for drug separation and quantitative determination were established. To assure proper separation of the substances under investigation, every HPLC method should be optimized by testing with multiple columns. Computational study was conducted to determine which was the best fit. The structures of TAP, ECT, and BXG, as well as the main unit of C18 and C8 columns and the complexes generated between them, were sketched in chem sketch software and converted to 3D form, as shown in Figs 8, 9, and 10.

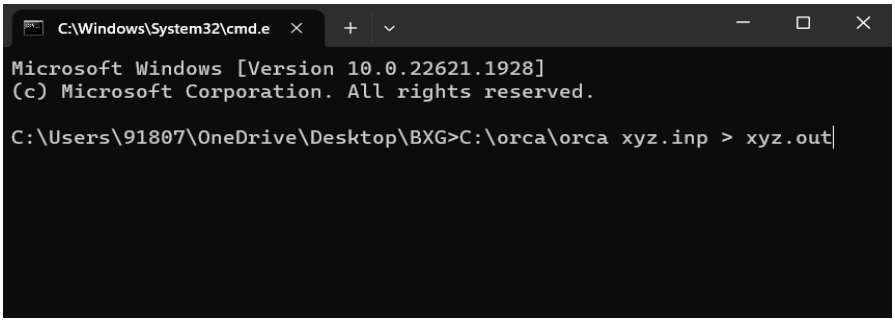

Figure 7. Run display of command

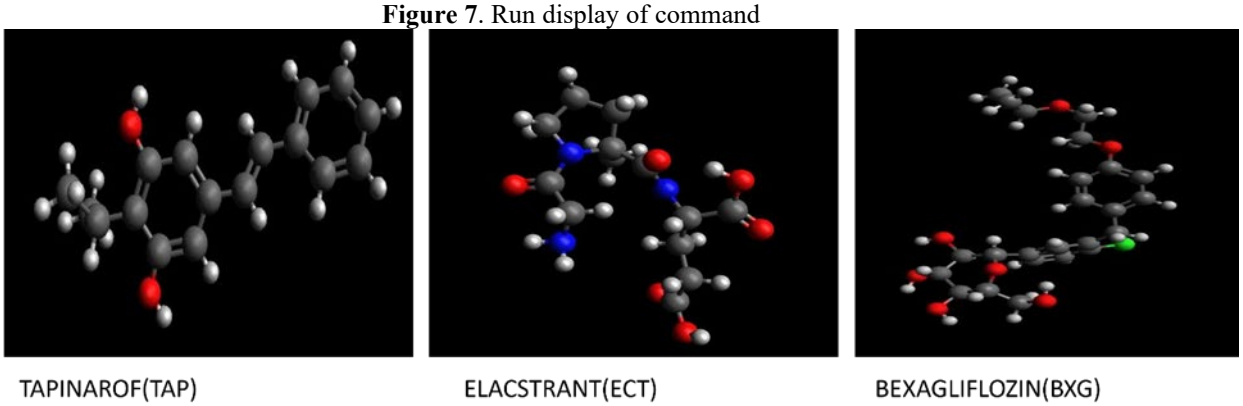

Figure 8. 3D Structure of selected drugs

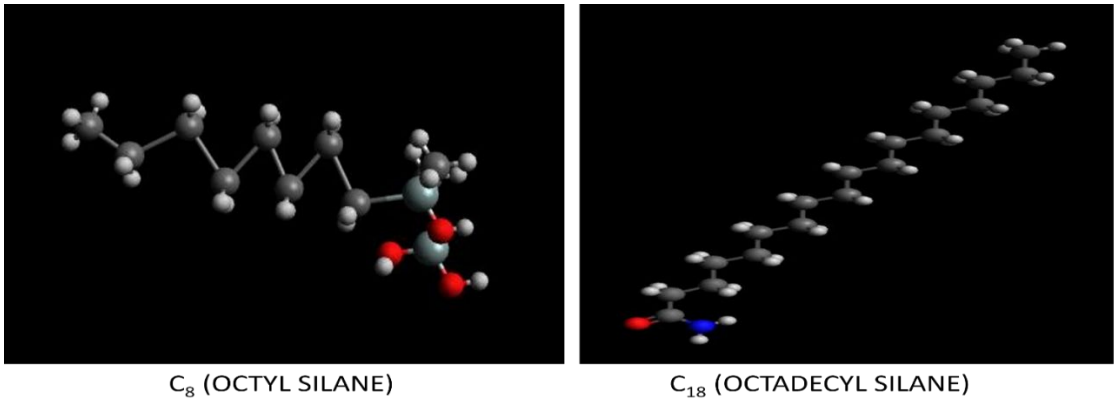

Figure 9. 3D Structures of selected columns

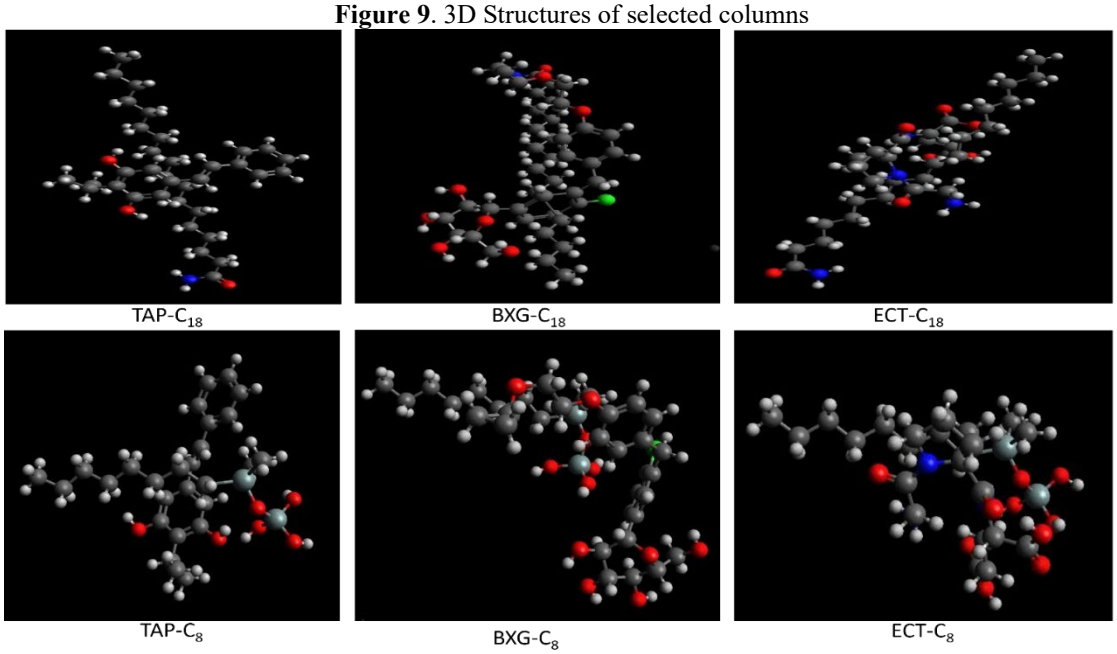

Figure 10. 3D-Structures of Drug-Column Complexes

Table 2. The Gibbs free energies of the selected drugs, C_8 and C_{18} columns

MOLECULE	GIBBS FREE ENERGY (HATREE)
TAPINAROF (TAP)	-808.26 Eh
BEXAGLIFLOZIN (BXG)	-1917.12 Eh
ELACSTRANT (ECT)	-1122.61 Eh
C_8	-1275.93 Eh
C_{18}	-1668.49 Eh

Table 3. Gibbs free energies of the complexes of drug and columns

COMPLEX	GIBBS FREE ENERGY (HATREE)	BINDING FREE ENERGY (KJ/Mol)
TAP-C_8	-2084.18 Eh	-26.59 KJ/mol
TAP-C_{18}	-2476.77 Eh	-31.04 KJ/mol
BXG-C_8	-3193.16 Eh	-268.63 KJ/mol
BXG-C_{18}	-3585.57 Eh	-149.34 KJ/mol
ECT-C_8	-2398.54 Eh	-16.25 KJ/mol
ECT-C_{18}	-2791.30 Eh	-520.62 KJ/mol

After optimization, the relative energy of these molecules in their ideal form was found. The computations were carried out using the Avogadro and orca software, with the density functional

theory approach used at the level B3LYP/6-31G (d) basis set as this level is widely used for studying molecular properties including Gibb's free energy as it makes a balance between accuracy and computational efficiency. [47] TAP, ECT, BXG, and the columns under consideration all had their Gibbs free energy estimated (Figure 11). The theoretical binding energy of complexes produced between TAP, ECT, and BXG with columns such as C8 and C18 was estimated using the above mentioned formula. TAP, ECT, and BXG have high affinity and will significantly interact with the C8 and C18 columns in particular, owing to their larger binding free energy. As a result, we anticipated that peaks would arise over a long period of time and a significant analytical run time. ORCA's computational calculations yielded the Gibbs free energy of the specified molecules, which was recorded in the output file. The output file contains the Gibbs free energy in the form of Hartree energy. The above formula was used to calculate the binding energies of the chosen medicines with C8 and C18.

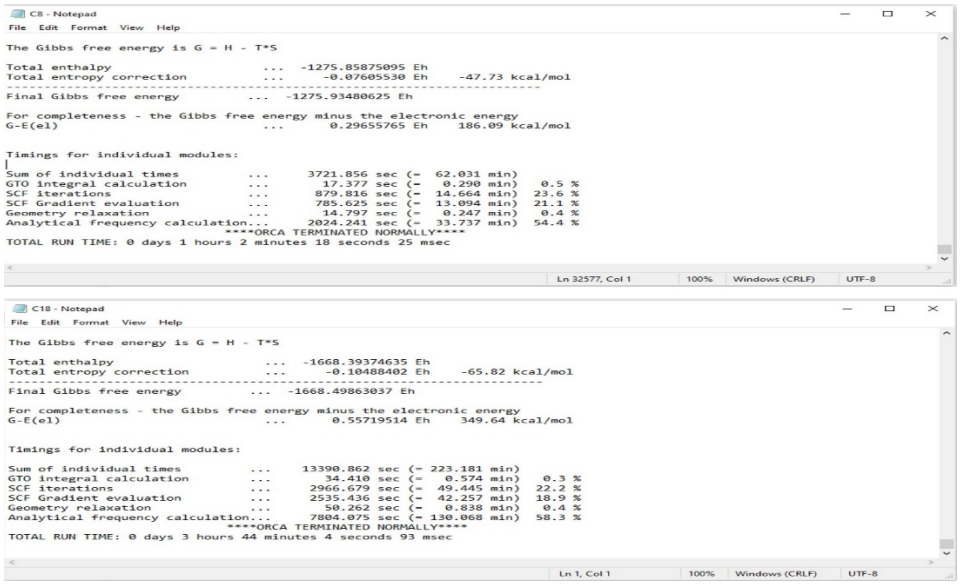

Figure 11. Output file showing Gibb's free energies of C8 and C18

Table 2 displays the computed Gibbs free energy values. Table 3 shows the findings of the binding free energy between the chosen medicines and columns. The computed binding free energy was translated to KJ/mole, with one Eh equaling 2625.5002KJ/mol. Because binding free energy and stability are inversely related, a high binding free energy between the drug and the stationary phase suggests a less stable complex, and thus the drug elutes faster, which is an important factor to consider when selecting a column. According to the preceding phrases, the binding free energy was chosen for the medication with their specific column, i.e. TAP and C8 were discovered to have greater binding free energy, i.e., -26.588466780402 KJ/mol, which elutes quickly. BXG and C18 were discovered to have a higher binding free energy, -149.338451376 KJ/mol, which elutes quickly. ECT and C8 were discovered to have a higher binding free energy, -16.251399902966 KJ/mol, which elutes quickly.

The technique may be used to estimate analytes simultaneously by comparing their binding free energy. If the analytes have a lower binding free energy, it implies that they interact strongly with the column, hence elution will be delayed, increasing the run time. Furthermore, if the binding free energies of the analytes under investigation are very near, it implies that peaks will be closer, resulting in reduced resolution and symmetry. To achieve higher elution and resolution, both the binding free energy between analyte and column, as well as the binding free energies of the analytes under research, should be compared while selecting an appropriate column for the study. Earlier investigations compared theoretical and experimental methodologies, concluding that the computational approach produces comparable results. [17]

This technique also helps to accomplish sustainable development goals by reducing environmental impact and encouraging responsible consumption. Companies may help prevent climate change, safeguard natural resources, and maintain biodiversity by implementing sustainable practices and minimizing waste. Furthermore, by encouraging responsible consumption, businesses may encourage customers to make educated decisions and choose products and services with a lesser environmental imprint. This can assist to limit waste creation and the utilization of scarce resources. Overall, the implementation of such a plan improves not just the company's bottom line but also aligns with global efforts to create a more sustainable and resilient future for everybody. [48], [49] As there are no HPLC methods till date for the selected drugs, this study can give a clear idea on column selection while optimizing the chromatographic conditions without wasting much time, solvent and energy for the selection of column during HPLC method development. Despite these advantages, the computational approach has limitations where the selection of functional is an approximation and DFT calculations varies with choice of basic set. By considering its advantages and disadvantages, the computational approach is a powerful tool which minimizes the time, energy and solvent utilization during column selection process thereby supporting sustainable development goal 12 of responsible consumption and production.[50]

4. Conclusions

Computational chemistry is a new area of study in chemistry. As a result of the substantial amount of time, chemicals, and energy that is saved with the application of computational approaches to chromatographic processes, Green Analytical Chemistry receives more support. This work utilized a computational method to column optimization for the high-performance liquid chromatography (HPLC) technology. Both the Avogadro and ORCA tools were utilized in the research project. These tools make use of density functional theory with a basis set of def2-SVP in order to estimate Gibbs free energies through the utilization of a frequency computation mode. TAPINAROF (TAP), BEXAGLIFLOZIN (BXG), ELACSTRANT (ECT), and columns C8 and C18 were made to run by delivering commands in ORCA to acquire Gibbs free energies. A determination of the Gibbs free energy of drug-column complexes was made with the use of the same software. Once everything was said and done, the drug binding free energies were calculated using C8 and C18 columns. Due to the fact that binding free energy is a reflection of the stability of the drug-column combination, the complex that possessed the greatest binding free energies was picked as the column for the drugs that were chosen. This made it possible for the drug to be eluted from the stationary phase in a more expedient manner. Based on the findings of the investigation, the column C8 is the most suitable for TAP and ECT, whereas the column C18 is the most suitable for BXG. The research encourages the utilization of a computational approach in the development of analytical procedures, which reduces the amount of solvent that is used and the amount of energy that is consumed. This technique may be used as a preliminary screening phase for selecting the column during the optimization of chromatographic conditions in the process of developing an HPLC method, and an experimental procedure should be carried out in order to detect the analytes. By reducing the amount of damage done to the environment and encouraging responsible consumption, this strategy also contributes to the promotion of sustainable growth.

ABBREVIATIONS

AhR- Aryl hydrocarbon Receptor
B3LYP- Becke's Three-parameter hybrid functional with Lee-Yang-Parr correlation
BXG- Bexagliflogin
C8- Octyl silane column
C18- Octadecyl silane column
DFT- Density Functional Theory
ECT- Elacestrant
GAC- Green Analytical Chemistry
HPLC- High Performance Liquid Chromatography
KJ- Kilo Joule
NPC- Normal Phase Chromatography
RPC- Reverse Phase Chromatography
SERD- Selective Estrogen Receptor Degrader
TAP- Tapinarof

CONSENT FOR PUBLICATION

Not Applicable

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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