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HPLC Chiral Analysis and Stereo-Bioactivity of Repaglinide Enantiomers

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ABSTRACT

In this study a rapid chiral High performance Liquid Chromatography (HPLC) method has been developed and validated for the enantiomeric separation of Repaglinide, with the molecular docking study of Repaglinide against carbonic anhydrase II (CA2). The method was carried out on a chiralcel® OD-RH column using a mixture of n-hexane: 2-propanol (95:5, v/v), The flow rate was 1.0 ml/min and the eluent was monitored at 240nm. The software used in this molecular docking is PyRx-Virtual Screening Tools (for molecular docking process) and Discovery Studio (for pose visualization and data analysis). According to the study's findings, for HPLC two peaks with a 2.074- and 3,258-min retention time was achieved and the resolution, capacity and selectivity factors obtained were Rs = 0.773; k′1= 1.074, k′2 = 2.258 respectively and α =2,1. The result of molecular docking showed the binding energy of repaglinide to CA2 was found to be -6.8 kcal/mol with RMSD of 1.55 Å, indicating a higher binding affinity compared to native ligand (dansylamide).The method was found to be fast, simple, precise and suitable for analysis of Repaglinide in drug substance.

Keywords: *Repaglinide*, HPLC, Chiralcel®OD-RH, molecular docking, antidiabetic, chiral separation.

1. INTRODUCTION

Diabetes mellitus (DM) is one of the oldest diseases that has recently gained popularity and become a serious health concern for human [1,2]. It is a long-term metabolic condition defined by pancreatic β-cell dysfunction, decreased insulin production and resistance [3,4], with insulin being the major hormone directing intermediate metabolism [5]. Diabetes mostly affects the liver and kidney. Type 2 diabetes (non-insulin-dependent) can now be treated with orally administered hypoglycemic medications that help to lower blood sugar levels [1,2]. Carbonic anhydrase II (CAII) is a zinc metalloenzyme that is involved in numerous physiological processes in the human body, including pH regulation, electrolyte balance, ionic transport, carboxylation or decarboxylation reactions, biocalcification, and tumorigenesis. It catalyzes the reversible conversion of CO2 into bicarbonate, which is required for respiration, pH regulation, ion exchange, and bone resorption [6-9].

Repaglinide is an oral meglitinide-class antidiabetic medication used to treat type II diabetes mellitus. It reduces blood glucose levels by increasing insulin secretion from the pancreas by inhibiting the sulfonyl urea receptor on KATP channels in pancreatic β-cell membranes [10-14]. *Repaglinide* structure, binding profile, duration of action, and excretion method set it apart from other antidiabetic drugs because it is easily absorbed from the gastrointestinal tract after oral administration. [15,16]. Chemically, *Repaglinide* is a novel carbomoxylmethyl benzoic acid derivative, also referred to as (S)-2-ethoxy 4-[[3-methyl-1-[2-(1-piperidinyl) phenyl]butyl]amino]-2-oxoethyl][17-19], as illustrated in Figure1. Repaglinide has the molecular formula $C_{27}H_{36}N_2O_4$ and is soluble in methanol and methylene chloride but practically insoluble in water [20].

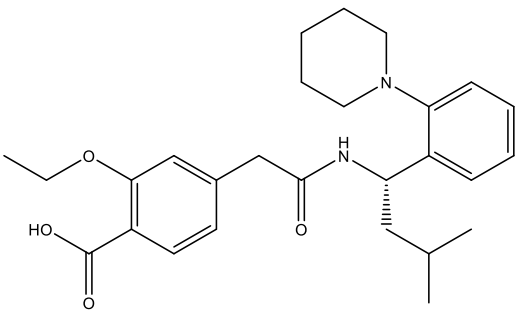
Over several decades, researchers have grown increasingly interested in and focused on the separation of chiral enantiomers of medications [21,22]. In the field of medicine, pharmacology, and chemical research, determining enantio-separation, absolute configuration, and chiral recognition mechanism is crucial for the production of safe and efficient medicines during the drug development process. Chiral medications enantiomers may differ in their biological activity as well as in their potential therapeutic effects [23-25]**.** Several methods have been reported in the literature for determination of Repaglinide in pharmaceutical formulations and in human serum and other biological fluids, these methods include HPLC [26-29], HPLC/ tandem mass spectrometry [11,30,31], visible spectrophotometric [32-34], HPTLC [35-36] and electrochemical methods [16,37]. HPLC is the most commonly used method for chiral analysis because it offers greater

resolution, sensitivity, broad applicability, and compatibility with a wide range of detection techniques. It is crucial to determine the validity, pharmacokinetics, and pharmacodynamics of chiral medications at various stages of drug development [23,24].

The literature provides an HPLC method for the enantio-separation of *Repaglinide* using a Chiralpack®AD-H (amylose-based stationary phase) column [26], Chiralpack®IA (immobilized amylose based stationary phase) [27]and C18 column [10-20, 28-35].

Molecular docking is a widely used tool in drug discovery and development to investigate protein-ligand interaction configurations [38-40]. This method entails docking a molecule with a certain macromolecule and determining the binding free energy between the ligand and receptor. Molecular docking can save time, effort, and environmentally harmful solvents or chemicals [6,41].

The current study addresses with a fast, effortless, precise, robust enantioselective, and isocratic chiral LC technique for the enantio-separation of *Repaglinide* employing a Cellulose tris (3, 5 Dimethylphenyl carbamate) based chiral stationary phase (chiralcel®OD-RH) (Fig.2) and Molecular docking simulations were done using PyRx and Discovery Studio software to assess the binding affinity and mechanism of interaction between *Repaglinide* and the CA2 enzyme (Fig.3).The availability of highly sensitive and selective HPLC technology will be very useful in the determination of *Repaglinide* in pharmaceutical dosage forms.



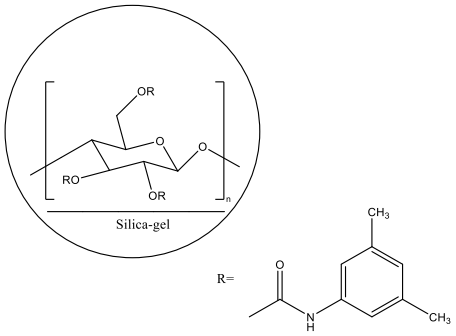


Fig.1. Chemical structure of *Repaglinide* **Fig.2.** Chemical structure of chiralcel®OD-RH column

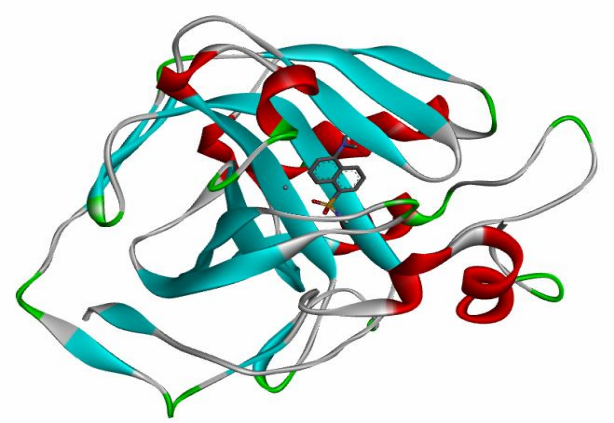


Fig.3. 3D structure of CAII

2. RESULTS AND DISCUSSION

2.1.Chiral Separation Study:

The mechanism of separation in direct chiral separation methods is the interaction of chiral stationary phase (CSP) with enantiomers that are analytes to form short-lived, transient diastereomeric complexes [26] [42,43]. Chiral separation of *Repaglinide* can be achieved using chiral stationary phases (CSPs) such as chiralcel®OD-RH column which is Cellulose tris (3, 5-dimethylphenylcarbamate) coated on 5µm silica-gel.The Cellulose-based stationary phase in Chiralcel®OD-RH column has higher selectivity being suitable for the enantioselective separation and accurate quantification of (R)-*Repaglinide*. The results of the chiral liquid chromatographic method are presented in table 1.

Table 1: Result of chiral analysis of *Repaglinide* by HPLC on chiralcel®OD-RH column

Csp	Peak	Rt (Rt)	K′	α	Rs	%
Chiralcel®OD-RH	**1**	2.074	1.074	2.1	0.773	13
	2	3,258	2.258			87

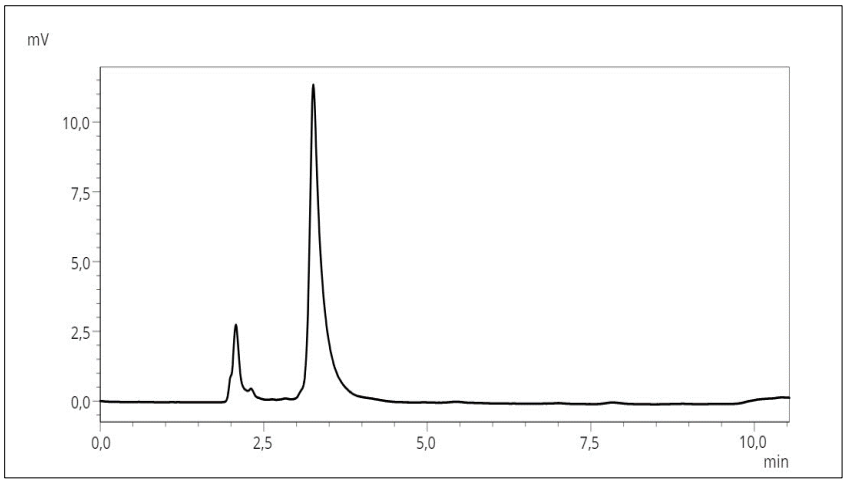


Fig.4. A Typical HPLC chromatogram of Repaglinide on chiralcel®OD-RH column. Mobile phase consisted of n-hexane: 2-propanol (95:5v/v), flow rate 1.0 mL min, UV-240 nm; column ambient temperature

A representative chromatogram of the enantiomeric resolution of *Repaglinide* is shown in figure 4. In chiralcel®OD-RH, the retention times of Repaglinide were found at 2.074 and 3.258 min. A good resolution (Rs = 0.773) between two enantiomers was obtained, with adequate system suitability parameters (enantioselectivity α= 2.1, Capacity Factor K_1=1.074 and K_2=2.258). In C18 column, the retention time of *Repaglinide* was found at 1.95 min.Chiral separation of *Repaglinide* using Chiralcel®OD-RH column is an efficient way to isolate the two enantiomers of drug. Following the results obtained, chiral separation of *Repaglinide* using a Chiralcel®OD-RH column was an effective method to isolate the two optical isomers of the drug.

1. Molecular docking study

Molecular docking study was performed to investigate the binding affinity of *Repaglinide* and dansalymide to CII enzyme. The obtained RMSD results were good with a value of less than 2 Å, indicating accurate prediction according to the literature [44–46]. Table 2 summarizes the binding energy of the study (kcal/mol), RMSD values (Å) and type of interaction with 1OKL.

Table 2. The results of molecular docking

Compounds	Binding Energy	RMSD	Interactions residues and type interaction
Native ligand	-5.5 Kcal /mol	1.95Å	hydrophobic pi alkyl interactions (VAL121, PHE 130, LEU197) Pi sigma (LEU197) Pi sulfur (THR198) Hydrogen bond (LEU197, THR198)
S-repaglinide	-6.8 Kcal /mol	1.55Å	pi-pi T-shaped (TRP244, PHE230) pi alkyl (PRO13, LYS9) attractive charge (ASP242) unfavorable negative-negative (GLU238) Hydrogen bonds (THR7, LEU239) Pi sigma (PHE230)

Table 2 indicates that *Repaglinide* has a low affinity binding value of -6.8 kcal / mol compared to dansalymid -5.5 kcal / mol has a binding value, with respective RMSD values of 1.55 and 1.95 Å.

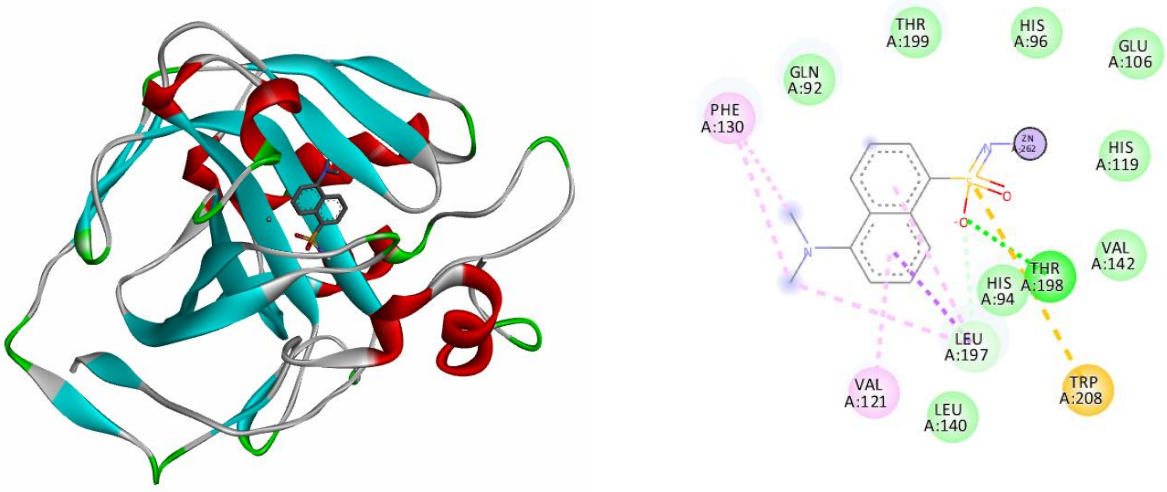


Fig.5. 3D and 2D docked pose depiction of dansylamide

The native ligand (dansylamide) formed hydrophobic pi alkyl interactions with VAL121, PHE130 and LEU197. Pi sigma interaction was constructed from the benzene ring to LEU197 amino acid, while pi sulphur interaction binding was achieved with THR198.The LEU197 and THR198 residues formed H bonds towards oxygen atom in the dansylamide molecule (Figure 5).

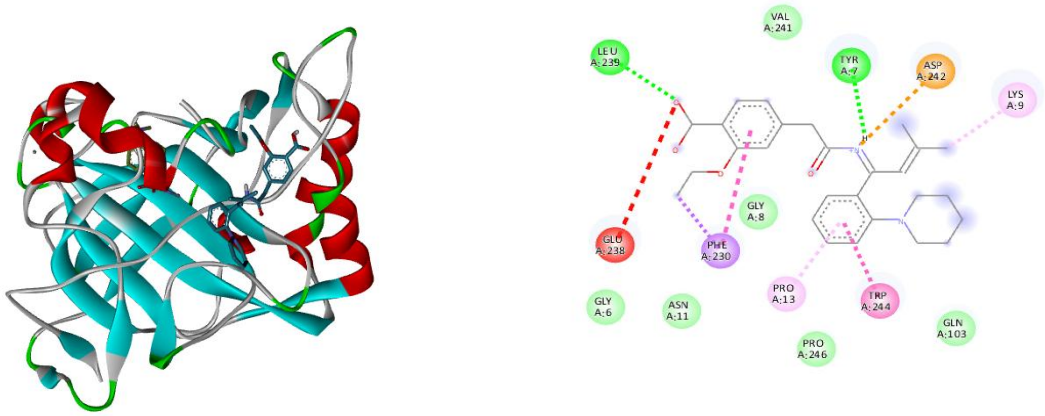


Fig.6. 3D and 2D docked pose depiction of *Repaglinide*

When the interaction of *Repaglinide* with the residues in the enzyme's active site was examined, it was observed that it made two different hydrogen bond interactions, two different pi alkyl interactions, pi sigma interaction, two different pi-pi T-shaped interactions, attractive charge and unfavorable negative-negative interaction. Two different pi-pi T-shaped interaction were constructed from the benzene ring to TRP244 and PHE230. Of the hydrophobic interactions formed, pi alkyl interactions were achieved with PRO13 and LYS9 residues, while attractive charge interaction was achieved with ASP242 and unfavorable negative-negative interaction formed with GLU238 amino acid. Accordingly, all H-bonds formed are from the S-*Repaglinide* molecule via amino acids THR7 and LEU239 and Pi sigma interaction formed with PHE230 (Fig.6).

3. EXPERIMENTAL

3.1.Apparatus:

The HPLC system used was a SHIMADZU Scientific Instruments' system LC-20A (Shimadzu, Kyoto, Japan) with an injector of 10 µl Rheodyne 1907 sample loop, a pump LC-20A, a vacuum degasser DGU-20A5, a UV detector Shimadzu SPD-20A (Kyoto, Japan), Shim-pack GIS C18

column, and Chiralcel®OD-RH coated on a 5µm silica-gel column. The LC Lab solution software (Shimadzu, Tokyo, Japan) was used to obtain, store, and evaluate chromatographic data. The chromatographic separation was performed on two mobile phases: methanol for the Shim-pack GIS C18 column and n-hexane:2-propanol (95:05, v/v) for the Chiralcel®OD-RH. The mobile phases were pumped from the solvent reservoir to the column at a flow rate of 1 ml/min. The column temperature was maintained at ambient temperature, and the eluent was monitored at a wavelength of 240 nm. The injection volume was 10 µL.

3.2.Chemicals:

Novo Norm® tablets: Each tablet contained 2 mg *Repaglinide*. Chromasolv®methanol, LiChrosolv®n-hexane and Chromasolv® 2-propanol for HPLC were purchased from Sigma Aldrich. The stock solution of *Repaglinide* (2 mg) was prepared by dissolving appropriate amount of substance in methanol.

3.3.Molecular Docking Methodology

Ligands preparation: Three-dimensional structure of S repaglinide and native ligand (dansylamide), downloaded from the site of databank zinc.docking.org in the form of mol2 code ZINC22056467 and mol2 code ZINC56543 respectively. The software utilized is PyRx-AutoDock Vina and Discovery Studio.

Protein preparation: The material comprises a three-dimensional structure of Carbonic anhydrase II (CAII) with the code of 1okl, which is downloaded from the website of protein data bank https://www.rcsb.org/structure/1OKL. The CAIIprotein is separated by water and ligand molecules with Discovery Studio version 4.5. Then, it is stored in a pdb format. Next, with Autodock Vina 4.2, the hydrogen atom of the protein is displayed and stored in a pdbqt format.

Molecular docking: After preparing the ligands and Protein, PyRx was implied with the Autodock Vina option using the new scoring function. It analyzes the docking orientations and interactions between the ligands and CAII. Determination of Grid box of all ligands is at the receptor site (CAII) with the centre X: -1.8654, Y: -2.6221, Z: 15.5964 and the large dimension with the angstrom X: 54.305, Y: 55.3329, Z: 66.9195 for molecular docking. After importing the docked data into the Discovery Studio visualizer, 2D and 3D formats of the significant interactions between the ligands and the receptor-binding sites were obtained.

4. CONCLUSION

The results of HPLC method showed that it is a flexible, simple and fast method for the chiral separation and detection of enantiomers in a pharmaceutical study. Chiralcel®OD-RH was found to be selective for the enantiomers of the drug. The mobile phase is simple to prepare and economical. The developed method is more rapid and enantioselective than reported methods. Hence, this can be conveniently adopted for routine analysis of *Repaglinide* in pure form and its dosage forms. The results of molecular docking using PyRx shows that *Repaglinide* has a more stable interaction with carbonic anhydrase II compared to *Dansylamide* based on its lower binding energies. This enables the production of highly pure and effective drugs, minimizing side effects and ensuring consistency in dosing.

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