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# COMPUTATIONAL INSIGHTS INTO SOLUBILITY ENHANCEMENT OF KETOCONAZOLE VIA COMPLEXATION WITH β-CYCLODEXTRIN AND HYDROXYPROPYL-β-CYCLODEXTRIN

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**ABSTRACT**
Ketoconazole is a widely used antifungal drug with poor aqueous solubility, which limits its bioavailability and therapeutic efficacy. Cyclodextrins like β-cyclodextrin (BCD) and its derivative 2-hydroxypropyl-β-cyclodextrin (HPBCD) are recognised for their ability to improve the solubility and stability of drugs. The objective of this research was to explore the binding strength, structural integrity, and solubility improvements of ketoconazole complexes with BCD and HPBCD through the use of molecular docking and molecular dynamics simulations. Molecular docking was performed using AutoDock 4.2, followed by 100 ns molecular dynamics simulations in a water/octanol mixture using Amber 16. The assessments included binding energies, hydrogen bonds, hydrophobic interactions, radius of gyration, and solvent-accessible surface area (SASA) to examine the behaviours of the complexes. Docking results showed stronger binding of ketoconazole–BCD (ΔG_bind = –4.56 kcal/mol) compared to ketoconazole–HPBCD (ΔG_bind = –3.05 kcal/mol). MD simulations revealed that BCD formed a compact and stable complex with a lower radius of gyration, while HPBCD exhibited higher SASA and stronger interactions with water molecules. Trajectory analyses confirmed that ketoconazole remained more stable in aqueous solution when encapsulated by HPBCD. The results indicate a trade-off between structural compactness and solubility enhancement. Although BCD forms a tighter and more rigid complex, HPBCD's hydrophilic substituents promote greater solvent accessibility and water affinity, leading to improved solubility of ketoconazole. These findings align with previous reports on cyclodextrin derivatives improving dissolution and suggest HPBCD as the more suitable excipient for aqueous formulations. While BCD forms a tighter inclusion complex, HPBCD provides superior solubility enhancement through increased solvent interactions. These results indicate that HPBCD may be a useful additive to enhance the solubility and bioavailability of ketoconazole.
**Keywords:** Ketoconazole, B-Cyclodextrin, 2-Hydroxypropyl-B-Cyclodextrin, Molecular Dynamics, Solubility Enhancement.
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## INTRODUCTION

Ketoconazole is an imidazole-derived antifungal drug that has been widely used in the treatment of systemic and superficial fungal infections.[1] Despite its therapeutic potential, the clinical application of ketoconazole is limited by its poor aqueous solubility and low bioavailability, which reduce its effectiveness in oral and topical formulations. Improving the solubility and stability of ketoconazole, therefore, remains a critical challenge in pharmaceutical development.[2]

Though ketoconazole shows promise in therapy, its use in clinical settings is hindered by inadequate solubility in water and a low rate of absorption when taken orally, leading to variable absorption and diminished exposure throughout the body. Additionally, ketoconazole falls under the Biopharmaceutics Classification System (BCS) class II category, which is defined by its poor solubility yet favourable permeability.[4] This means its dissolution rate is the rate-limiting step in oral absorption, posing a significant barrier to achieving adequate therapeutic plasma concentrations. The poor solubility also hampers its effectiveness in topical formulations, where drug penetration into deeper skin layers is often insufficient.[5] An additional constraint related to ketoconazole treatment is its risk of liver toxicity and

interactions with other medications because it inhibits human cytochrome P450 enzymes, especially CYP3A4.[6]

These safety concerns, combined with its solubility-related challenges, have led to restrictions on its systemic use in many countries, with topical formulations being preferred for superficial infections. Nonetheless, the search for innovative formulation strategies to overcome these issues remains crucial, especially since ketoconazole continues to serve as a reference drug for the development of new antifungal agents and drug delivery systems. One promising approach to address these limitations is the use of cyclodextrins, a family of cyclic oligosaccharides capable of forming host–guest inclusion complexes with hydrophobic drugs.[7] β-Cyclodextrin (BCD) has been extensively studied as a drug carrier due to its hydrophobic cavity, which allows the encapsulation of poorly soluble molecules, thereby enhancing their solubility and stability.

However, the limited aqueous solubility of BCD itself has encouraged the development of modified derivatives, such as 2-hydroxypropyl-β-cyclodextrin (HPBCD)[8], which exhibit improved solubility and biocompatibility, making them more suitable for pharmaceutical applications. Among the various cyclodextrins, β-cyclodextrin (BCD) has been extensively studied as a drug carrier due to its optimal cavity size, which is particularly suitable for accommodating many pharmaceutical agents.[9,10] The encapsulation of hydrophobic molecules within BCD can protect drugs from degradation, mask undesirable odours or tastes, and improve their dissolution rate, ultimately leading to better therapeutic performance.[10] However, despite these advantages, the clinical use of native BCD is restricted by its own limited water solubility and potential nephrotoxicity at higher concentrations, which can compromise its safety profile. To overcome these limitations, chemically modified cyclodextrin derivatives have been developed. One of the most widely studied derivatives is 2-hydroxypropyl-β-cyclodextrin (HPBCD), which exhibits superior aqueous solubility, reduced toxicity, and enhanced biocompatibility compared to native BCD.[11,12] These modifications not only broaden the pharmaceutical applicability of cyclodextrins but also enable their use in parenteral formulations and targeted drug delivery systems.[13,14] Earlier experimental research has shown that cyclodextrin inclusion complexes can notably enhance the dissolution characteristics, stability, and bioavailability of antifungal medications[15,16], including ketoconazole. Nevertheless, a deeper molecular-level understanding of the interactions between ketoconazole and cyclodextrins is essential to elucidate the mechanisms governing complex formation and to rationalise the observed improvements in drug solubility. Computational techniques like molecular docking and molecular dynamics (MD) simulations serve as effective instruments for exploring these interactions. They yield understanding regarding binding strength, structural integrity, exposure to solvents, and the dynamic characteristics of drug-carrier complexes.[8,17]

Currently, molecular dynamics (MD) simulations are essential for investigating how the solubility of ketoconazole can be improved.[11] While molecular docking offers initial predictions of potential binding poses, MD simulations capture the dynamic and flexible nature of host–guest interactions under conditions that mimic the physiological environment.[18] These computational insights not only help clarify why modified cyclodextrins such as HPBCD often outperform native BCD in improving solubility and biocompatibility, but also guide the rational design of optimised cyclodextrin-based formulations. Recent studies have highlighted the effectiveness of this approach, molecular docking and MD simulations were employed to investigate the encapsulation of α-mangostin in β-cyclodextrin and HPBCD,T and demonstrated that HPBCD formed a more stable and favorable complex, characterized by lower binding energy.

In this way, Molecular dynamics simulations are essential for connecting the structural and energetic characteristics of inclusion complexes with the experimentally observed enhancement of ketoconazole solubility and bioavailability. [19] In this research, molecular docking along with molecular dynamics (MD) simulations were conducted to explore the encapsulation of ketoconazole within BCD and HPBCD. This study concentrated on assessing the stability, density, and solvent exposure of the inclusion complexes in water-octanol environments by employing MD parameters. The results are anticipated to deliver molecular-level insights that bolster the potential of cyclodextrin-based carriers, specifically HPBCD, as an effective approach to improve the solubility and therapeutic efficacy of ketoconazole.

## EXPERIMENITAL

### Ketoconazole Structure Preparation

The construction and optimisation of the ligand structure are essential steps that must be completed before proceeding with the docking process. The selected ligand, ketoconazole, was obtained from the PubChem database.[20,21] Its two-dimensional (2D) structure was drawn using ChemDraw Ultra 12.0 and saved in .mol format. The three-dimensional (3D) structure was then generated from the 2D structure using ChemBio 3D Ultra.[22]

### Cyclodextrin Structure Preparation

The cyclodextrins analysed in this research were β-cyclodextrin (BCD) and 2-hydroxypropyl-β-cyclodextrin (HPBCD). The three-dimensional conformation of BCD was sourced from the Protein Data Bank (http://www.rcsb.org/pdb), identified by PDB ID: 1Z0N, featuring a resolution of 1.49 Å. Meanwhile, the HPBCD structure was created in ChemBio 3D 16.0 by introducing seven hydroxypropyl groups to BCD, followed by optimisation utilising Gaussian, applying DFT calculation utilising the B3LYP approach and the 3-21G basis set.[23]

### Molecular Docking Simulation

The optimised structures of ketoconazole, BCD, and HPBCD were used in molecular docking simulations with AutoDock 4.2.[24,25] The grid box dimensions were established at 60 × 60 × 60, maintaining a spacing of 0.375 Å to ensure optimal coverage. The simulation utilised the Lamarckian Genetic Algorithm, performing 100 conformational searches. The analysis of docking outcomes was conducted using BIOVIA Discovery Studio Visualizer 2017.[26,27]

### Molecular Dynamics Simulation

#### Solvent Box Preparation

Two solvent boxes were constructed by combining water and octanol using the PACKMOL program for initial simulation configurations.[28,29] The preparation included free ketoconazole, ketoconazole–BCD complex, ketoconazole–HPBCD complex, water molecules, and octanol molecules. Six pre-calculated coordinate points were used for each complex in the mixed solvent system.

#### Molecular Dynamics Simulation Process

Molecular dynamics simulations were conducted on three distinct systems: free ketoconazole, ketoconazole–BCD, and ketoconazole–HPBCD. This was achieved utilising Amber 16 and AmberTools 17 alongside the General Amber Force Field (GAFF).[28,30,31] Topology and molecular parameters for ketoconazole, octanol, BCD, and HPBCD were generated using the antechamber program.[32] The setup for the simulation involved several steps: first, energy minimisation was conducted, followed by heating the system to a temperature of 25 °C (298 K). This was succeeded by temperature equilibration, then pressure equilibration, and finally, a production phase that utilised a timestep of 2 fs.[33] Simulations were carried out for a duration of 100 nanoseconds until the systems achieved stability as assessed through energy, pressure, temperature, and Root Mean Square Deviation (RMSD) evaluations. The findings were examined utilising VMD version 1.9.3 and BIOVIA Discovery Studio Visualizer 2017, and post-MD stability evaluations were assessed

## RESULTS AND DISCUSSION

### Docking Analysis of Cyclodextrins Complex

The molecular visualisation outcomes illustrated in Fig.-1 indicate that ketoconazole can interact with the internal cavity of β-CD and HP-β-CD. In the Keto-BCD complex depicted in Fig.-1A, ketoconazole is found to be more securely encapsulated within the cavity. In contrast, in the Keto-HPBCD complex shown in Fig.-1B, ketoconazole assumes a more flexible conformation, with various sections of the molecule being exposed to the surrounding solvent. This variation suggests that the hydroxypropyl modification on β-CD influences both the inclusion efficacy and stability of the resultant complex. The binding energy (ΔG_bind) values presented in Table-1 further validate these visualisation results. The Keto-BCD complex has a binding energy of –4.56 kcal/mol, which is lower compared to the Keto-HPBCD complex's value of –3.05 kcal/mol. The more negative binding energy of the Keto-BCD complex

implies a stronger affinity for binding and greater stability of the complex. Additionally, the Keto-BCD complex establishes one hydrogen bond along with three hydrophobic interactions that enhance the overall stability of the complex. Conversely, the Keto-HPBCD complex lacks significant hydrogen bonding or hydrophobic interactions, which diminishes its binding affinity for ketoconazole.

Table-1: Determined Binding Energies (ΔG_bind) of Ketoconazole in Association with β-CD and HP-β-CD Acquired from Molecular Docking Simulations

| Complex | Binding Energy (kcal/mol) | Total Hydrogen Bond | Total Hydrophobic Bond |
|---|---|---|---|
| Ketoconazole-beta-CD | -4.56 | 1 | 3 |
| Ketoconazole-HP-beta-CD | -3.05 | 0 | 0 |

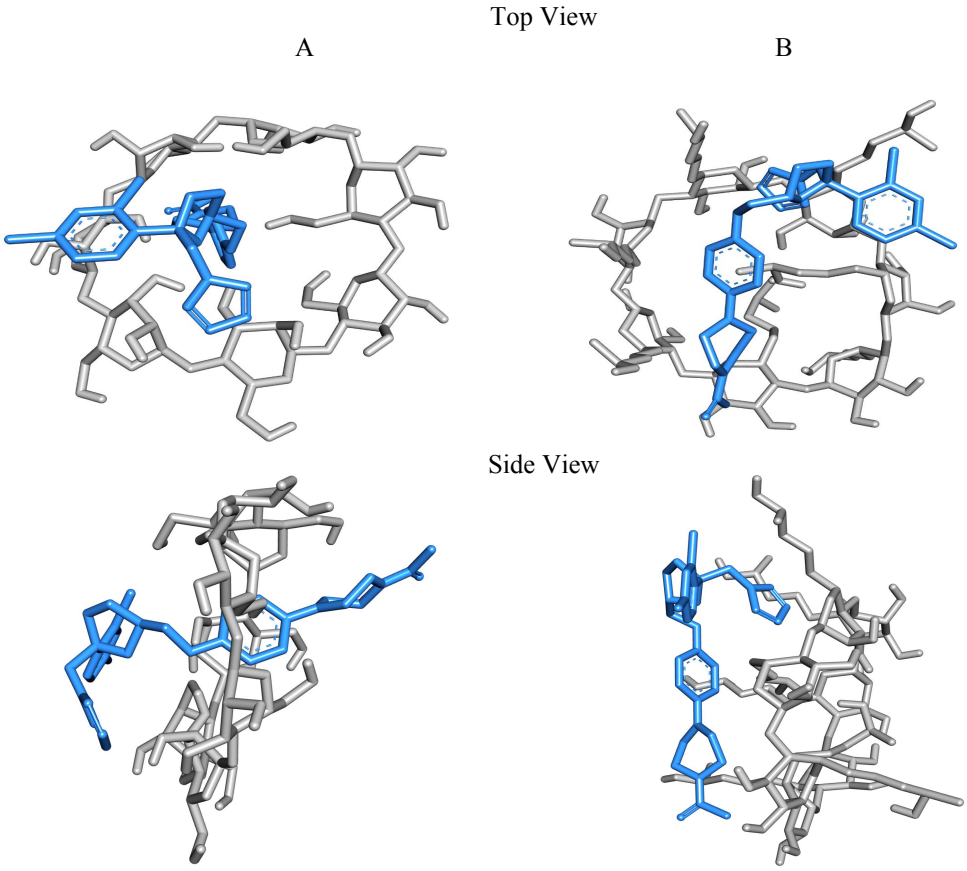


Fig.-1: Top View Visualization of Ketoconazole-beta-CD (A) and Ketoconazole-HP-beta-CD (B)

**MD Simulation**

**RMSD Analysis**

MD trajectory analysis showed the highest structural stability for Keto–β-CD with an average RMSD of 0.647 Å, whereas Keto–HP-β-CD exhibited an average RMSD of 1.861 Å and free Keto had 1.440 Å. In the water/octanol biphasic simulation, although docking and RMSD results indicated that β-CD forms a more stable complex with ketoconazole, the simulation in the water/octanol system suggests that HP substitution on β-CD enhances the complex's interaction with water molecules. This model highlights two distinct mechanisms: β-CD provides strong binding through hydrophobic and hydrogen-bond interactions that enclose the molecule within its cavity, whereas HP-β-CD, although forming weaker specific interactions, increases the host's hydrophilicity, resulting in a more hydrated complex that is more likely to enhance experimental solubility. Therefore, the hypothesised solubility enhancement by HP-β-CD can be attributed not to stronger binding but to increased solvation and predisposition toward the aqueous phase.

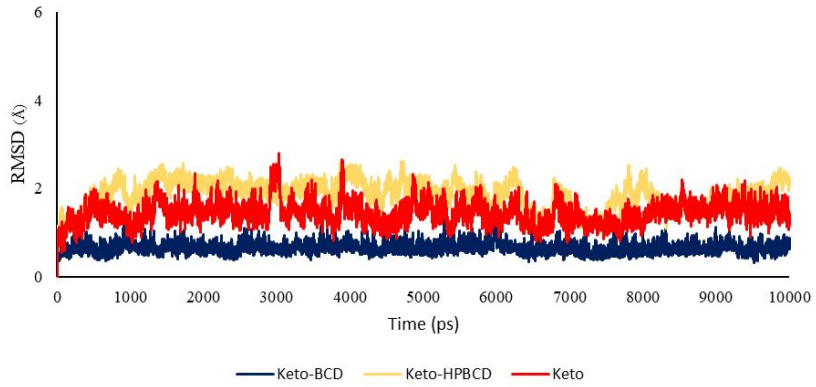


Fig.-2: The Root Mean Square Deviation (RMSD) of Ketoconazole when Paired with β-CD and HP-β-CD Throughout the Molecular Dynamics Simulation. The Stable RMSD Profiles Indicate that Both Complexes Maintain Structural Stability, With Slightly Lower Fluctuations Observed in Keto-HPBCD, suggesting a Stable Yet Flexible Complex that Supports Enhanced Solvent Exposure

**RDF Analysis**

Radial Distribution Function (RDF) Analysis provided insights into the spatial organisation of water molecules around the target compounds. For Keto-BCD, the RDF peaks were relatively moderate and well-defined, indicating that water molecules around the complex were structured and stable. This finding correlates with RMSD analysis, which showed low fluctuations and high structural stability for the Keto-BCD complex. The β-cyclodextrin acts as a protective host, encapsulating the hydrophobic regions of Keto and limiting excessive exposure to the aqueous environment. Consequently, although the direct water–Keto interactions are reduced, the complex maintains conformational stability over the simulation period. In contrast, the Keto-HPBCD complex exhibited higher RDF peaks compared to Keto-BCD, suggesting a greater number of water molecules interacting with the complex. The 2-hydroxypropyl substituents on HPBCD introduce additional hydrophilic groups, which enhance solvent accessibility and increase hydration of the encapsulated Keto. This higher degree of water interaction is consistent with the hypothesis that HPBCD can improve the apparent solubility of Ketoconazole. Despite slightly higher RMSD values indicating modestly reduced structural stability, the hydrophilic modifications in HPBCD facilitate stronger interactions with the aqueous phase, thereby promoting solubility enhancement. The RDF profile of free Keto displayed a sharp first peak followed by a rapid decrease in probability at larger distances, consistent with its hydrophobic nature. The water molecules initially interact directly with Keto but do not form a sustained hydration shell. This limited solvation explains the well-known poor aqueous solubility of Ketoconazole and emphasises the advantage of cyclodextrin-based inclusion for solubility improvement.

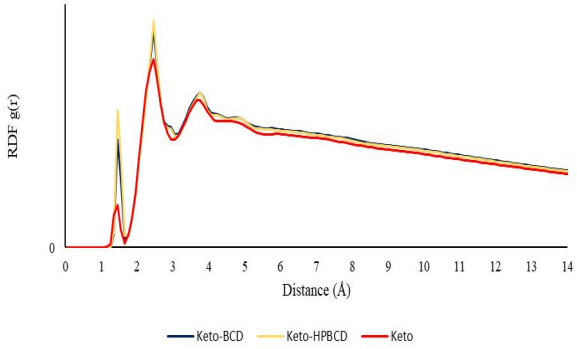


Fig.-3: Radial Distribution Function (RDF) Shows how Water Molecules Are Arranged Around Ketoconazole when it FORMS COMPLEXES with β-CD and HP-β-CD. The Taller RDF Peak for Keto-HPBCD Indicates that There are Stronger Interactions with the Solvent, Which Suggests that the Drug is More Soluble in this Combination.

**Radius of Gyration Analysis**

Radius of gyration (Rg) analysis gives insights into how tightly packed and stable the structure of molecular complexes is throughout molecular dynamics simulations. In the displayed graph, the Rg for Keto-BCD (blue line) is around 23.44 nm, while Keto-HPBCD (yellow line) is slightly higher at 23.54 nm, consistent with the averages calculated from the simulation trajectories This small difference indicates that Keto-BCD maintains a more compact structure compared to Keto-HPBCD. This is consistent with the hypothesis that β-cyclodextrin forms a more stable complex through hydrophobic interactions and hydrogen bonds that enclose the ketoconazole molecule within its cavity. Meanwhile, the slightly higher Rg for Keto-HPBCD indicates greater flexibility in this complex, possibly due to the hydroxypropyl substitution on β-cyclodextrin, which increases the molecule's exposure to the solvent. This flexibility allows for more interactions with water molecules, which may contribute to the experimentally observed increase in ketoconazole solubility in the HP-β-CD complex.

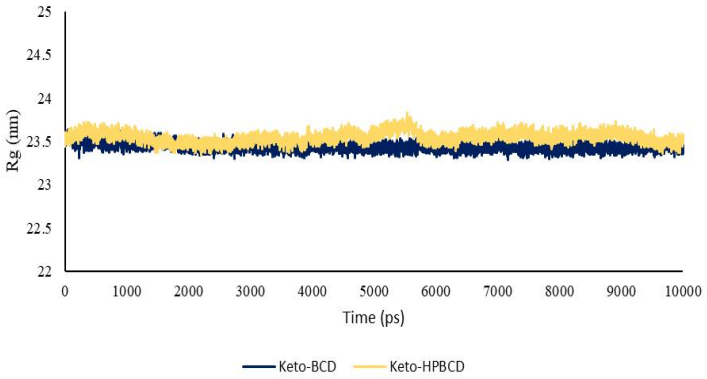


Fig.-4: Average Gyrate Values of Ketoconazole in Association with β-CD and HP-β-CD. The Marginally Elevated Gyrate in Keto-HPBCD Suggests Enhanced Molecular Flexibility, Probably Attributable to the Hydroxypropyl Modification

**SASA Analysis**

Solvent Accessible Surface Area (SASA) is a crucial factor in molecular dynamics research that indicates the surface area of a molecule that can be reached by solvent molecules, such as water. SASA provides insight into how much of a molecule is exposed to a polar environment, correlating with polarity, solubility, and the potential for interactions with solvent molecules. In this study, the average SASA values of both complexes were analyzed to assess changes in drug surface accessibility after complexation. Simulation results showed that Keto-BCD has an average SASA of 691.51 Å², whereas Keto-HPBCD has a higher average SASA of 1188.20 Å². The increased SASA in Keto-HPBCD compared to Keto-BCD indicates that the HPBCD complex has a more open surface with more parts of the molecule exposed to the solvent.

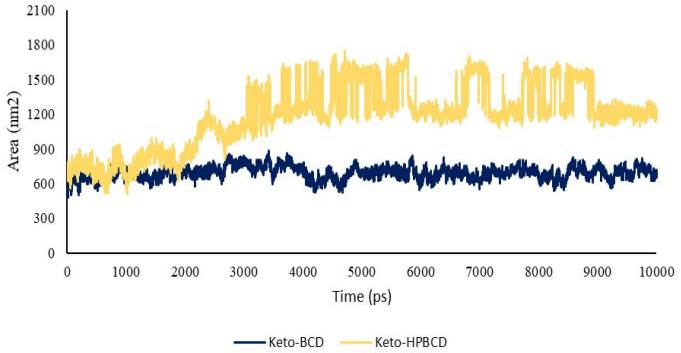


Fig.-5: Time Evolution of SASA Analysis of Both Complex β-CD and HP-β-CD. The Average SASA Values Indicate that Keto-HPBCD Exhibits a Larger Solvent-Exposed Surface, Suggesting Enhanced Solubility Compared to Keto-BCD

This is likely due to the hydroxypropyl chains, which enhance flexibility and facilitate interactions with solvent molecules. Conceptually, this increased SASA supports the potential for improved ketoconazole solubility in aqueous systems, as more of the drug surface can interact with solvent molecules. Additionally, the higher SASA in Keto-HPBCD may also suggest better stability of the complex in polar media, as HPBCD can encapsulate ketoconazole more efficiently while maintaining interactions with the solvent. In contrast, the lower SASA in Keto-BCD indicates that more of the drug is buried inside the BCD cavity, limiting solvent accessibility and potentially reducing relative drug solubility.

**Molecular Motion**

Molecular dynamics (MD) simulations are essential to more accurately predict and validate molecular interactions, offering an advantage over molecular docking, which is limited to evaluating structural orientations and restricted rotations at specific points. Unlike docking, MD allows compounds to be modelled in a non-rigid form, enabling them to move according to their natural flexibility, including rotational and translational motions. Molecular motions were analysed through the generated trajectories, as illustrated in Fig.-6. Snapshots taken at 0 ns, 50 ns, and 100 ns revealed that free ketoconazole molecules tended to migrate toward the octanol phase. Notably, at the final conformation (100 ns), the ketoconazole–HPBCD complex demonstrated greater stability in the aqueous environment compared to the ketoconazole–BCD complex. This suggests that encapsulation of ketoconazole within HPBCD enhances its solubility, thereby promoting stronger interactions with water molecules.

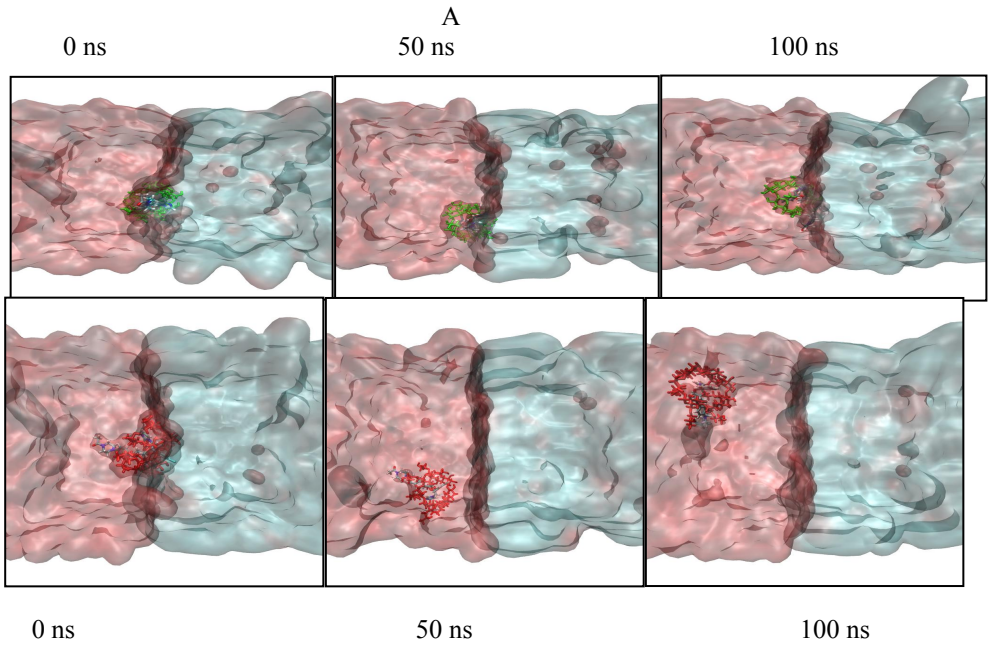


Fig.-6: Molecular Movement of Ketoconazole Confined within β-cyclodextrin (A), along with Ketoconazole Contained in 2-hydroxypropyl-β-cyclodextrin, was Observed During a 100 ns Molecular Dynamics Simulation within a Water-Octanol Environment; the Water Environment is Depicted in Red, While the Octanol Environment is Illustrated in Blue

## CONCLUSION

From the findings of molecular dynamics simulations, it can be inferred that the interaction between ketoconazole and β-cyclodextrin (BCD), alongside 2-hydroxypropyl-β-cyclodextrin (HPBCD), significantly influences the structural integrity, density, and surface exposure of the drug molecule. The Radius of Gyration (Rg) analysis indicated that the Keto-BCD complex displayed a smaller Rg value in comparison to Keto-HPBCD, suggesting that the structure of the Keto-BCD complex is denser and more stable. This observation supports the idea that BCD forms hydrophobic interactions and hydrogen bonds that encase the ketoconazole molecule within its cavity, thereby limiting the movement of the complex. In contrast, the Solvent Accessible Surface Area (SASA) assessment revealed that Keto-HPBCD presented a

greater SASA when compared to Keto-BCD, implying that the HPBCD complex featured a more accessible surface, which allowed for a larger exposure of the drug molecule to the solvent. This increase in SASA is likely attributable to the hydroxypropyl modification in HPBCD, which provides additional flexibility, facilitates more interactions with water molecules, and conceptually reinforces the improved solubility of ketoconazole in water-based environments. Ultimately, the findings related to Rg and SASA align with the hypothesis that β-cyclodextrin yields a denser and more stable complex, whereas HPBCD enhances flexibility and surface exposure, potentially leading to better drug solubility. These results form a solid molecular framework for the utilisation of HPBCD as a drug delivery mechanism to augment the solubility of ketoconazole while ensuring the stability of the complex.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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