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Original Article

Molecular docking and molecular dynamics study of 3-hydroxybutyrate with polymers for diabetic ketoacidosis-targeted molecularly imprinted polymers

[Estudio de acoplamiento molecular y dinámica molecular de 3-hidroxibutirato con polímeros para polímeros de impresión molecular dirigidos a cetoacidosis diabética]

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Abstract

Context: Molecularly imprinted polymers (MIPs) are promising materials with tailored binding sites that can selectively recognize and bind target molecules. The combined approach of molecular docking and molecular dynamics (MD) simulation provides valuable insights into the interactions between 3-hydroxybutyrate (3HB) and the designed MIPs, shedding light on the intricate details of their binding mechanisms. This information is crucial for designing MIPs with high selectivity and affinity for 3HB, which is a key biomarker of diabetic ketoacidosis (DKA).

Aims: To examine the interactions and dynamic behavior of 3HB in a complex with ten polymers by employing molecular docking and MD simulations.

Methods: Initially, molecular docking was employed to predict the binding orientations and affinities of the 3HB molecule within the active sites of the polymers. Subsequently, molecular dynamics simulation was utilized to explore the dynamic behavior, stability, and interactions within these complexes for 100 ns. Metabolic and toxicological properties of 3HB using SwissADME were also predicted.

Results: *N*-(hydroxymethyl)acrylamide (NHMAm), hydroxyethyl methacrylate (HEMA), itaconic acid (ITA), and N-[tris(hydroxymethyl)methyl]acrylamide (TrisNHMAm) displayed the strongest interactions with 3HB, with binding affinities of -2.64, 2.523, 2.469, and 2.305 kcal/mol, respectively. Various kinds of molecular interactions influence ligand-polymer binding in a variety of ways, as illustrated by the four polymers with the lowest binding affinities. In molecular dynamics, 4-vinylpyridine (4VP), *N*,*N*-dimethylacylamide (DMAm), *N*-(hydroxyethyl)acrylamide (NHEAm), and hydroxyethyl methacrylate (HEMA) suggest a strong stable complex with 3HB with an overall ΔTOTAL of -0.56, -0.35, -0.32, and -0.27 kcal/mol, respectively. The ADME prediction indicated that 3HB has favorable pharmacokinetic properties.

Conclusions: HEMA shows the ability to interact well with 3HB both by molecular docking and molecular dynamics.

Keywords: 3-hydroxybutyrate; diabetic ketoacidosis; interaction; molecularly imprinted polymers; polymer.

Resumen

Contexto: Los polímeros impresos molecularmente (MIPs) son materiales prometedores con sitios de unión a medida que pueden reconocer y unir selectivamente moléculas diana. El enfoque combinado de acoplamiento molecular y simulación de dinámica molecular (MD) proporciona información valiosa sobre las interacciones entre el 3-hidroxibutirato (3HB) y los MIPs diseñados, arrojando luz sobre los intrincados detalles de sus mecanismos de unión. Esta información es crucial para diseñar PIM con alta selectividad y afinidad por el 3HB, que es un biomarcador clave de la cetoacidosis diabética (CAD).

Objetivos: Examinar las interacciones y el comportamiento dinámico de la 3HB en un complejo con diez polímeros mediante docking molecular y simulaciones MD.

Métodos: Inicialmente, se empleó docking molecular para predecir las orientaciones y afinidades de unión de la molécula de 3HB dentro de los sitios activos de los polímeros. Posteriormente, se utilizó la simulación de dinámica molecular para explorar el comportamiento dinámico, la estabilidad y las interacciones dentro de estos complejos durante 100 ns. También se predijeron las propiedades metabólicas y toxicológicas del 3HB mediante SwissADME.

Resultados: La N-(hidroximetil)acrilamida (NHMAm), el hidroxietil metacrilato (HEMA), el ácido itacónico (ITA) y la N-[tris(hidroximetil)metil]acrilamida (TrisNHMAm) mostraron las interacciones más fuertes con el 3HB, con afinidades de unión de -2,64, 2,523, 2,469 y 2,305 kcal/mol, respectivamente. Varios tipos de interacciones moleculares influyen en la unión ligando-polímero de diversas maneras, como ilustran los cuatro polímeros con las afinidades de unión más bajas. En dinámica molecular, la 4-vinilpiridina (4VP), la N,N-dimetilacilamida (DMAm), la N-(hidroxietil)acrilamida (NHEAm) y el metacrilato de hidroxietilo (HEMA) sugieren un fuerte complejo estable con el 3HB con un ΔTOTAL global de -0,56, -0,35, -0,32 y -0,27 kcal/mol, respectivamente. La predicción ADME indicó que el 3HB tiene propiedades farmacocinéticas favorables.

Conclusiones: HEMA muestra la capacidad de interaccionar bien con 3HB tanto por acoplamiento molecular como por dinámica molecular.

Palabras Clave: 3-hidroxibutirato; cetoacidosis diabética; interacción; polímeros molecularmente impresos; polímeros.

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INTRODUCTION

Diabetes and ketones are closely related, and the presence of ketones in the blood can be a sign of diabetic ketoacidosis (DKA), which is a serious complication of diabetes (Peters et al., 2016). Ketones are alternative fuels for the body that are made when glucose is in short supply. However, in an individual with diabetes, dangerous and life-threatening levels of ketones can develop. DKA is a serious complication of diabetes that can be life-threatening. DKA develops when the body does not have enough insulin to allow blood sugar into cells for use as energy (Karrar et al., 2022).

DKA is most common among people with type 1 diabetes, but people with type 2 diabetes can also develop DKA (Ooi et al., 2021). Nearly a third of all deaths from DKA occurred in individuals who had no known history of diabetes, highlighting the significance of DKA as the initial manifestation of type 1 diabetes or as a result of increased insulin requirement in type 1 diabetic patients (O'Reilly et al., 2020). Mortality rates in DKA patients increased with advancing age, with an estimated 492.8 deaths per 10,000 DKA cases among patients aged 85 years and above (Ramphul and Joynauth, 2020). DKA is a serious complication of diabetes that can be life-threatening.

The presence of ketones in the blood can be a sign of DKA. 3-hydroxybutyrate (3HB), also known as β-hydroxybutyrate, is a type of ketone that is produced in the liver from the breakdown of fats. Monitoring 3HB levels can aid in the diagnosis and monitoring of DKA. It is a type of ketone that can be monitored to help detect the development of DKA. Increases in blood BHA above 3.5 mmol/L should prompt clinicians to start more aggressive treatment. Point-of-care 3HB testing has been evaluated in various studies for its ability to detect patients with DKA. The cut-off value for DKA diagnosis ranges from 1.5-3.5 mmol/L, and the blood volume necessary for 3HB measurement is 5-10 µL. A 3HB level of more than 1.5 mmol/L has high sensitivity and specificity for the diagnosis of DKA in diabetic patients presenting to the emergency department with blood glucose levels of more than 250 mg/dL (Wallace et al., 2001). Elevated ketones are a sign of DKA, which is a medical emergency and needs to be treated right away.

The provided search results suggest that there are some weaknesses in the sample preparation of 3HB in urine for the diagnosis and monitoring of DKA. Ketones in the urine are not a precise estimation of blood ketones, and the most abundant ketone body during DKA is 3HB, with a concentration of 3-10 times higher than that of acetoacetate (Dhatariya et al., 2020). Not all patients with DKA can provide a urine sample upon presentation, and ketones in urine are not a precise estimation of blood ketones (Wallace et al., 2001). Numerous studies have demonstrated the superiority of blood 3HB versus urine ketones in patients with diabetes and hyperglycemia with possible DKA. The direct measurement of 3HB in blood has been shown to enhance the management of DKA in children and reduce the time and costs of treatment (Vanelli et al., 2003).

Molecularly imprinted polymers (MIPs) have been widely used in sample preparation due to their selective molecular recognition abilities. MIPs are tailor-made, stable polymers with molecular recognition abilities, making them excellent materials for providing selectivity in sample preparation (Martín-Esteban, 2013). MIPs have been applied in various sample preparation formats, including solid-phase extraction, solid-phase microextraction, and stir-bar sorptive extraction (Hu et al., 2013). The synthesis of MIPs involves the copolymerization of a functional monomer and a crosslinker around a selected template molecule. MIPs provide selectivity to sample preparation by creating specific binding sites for target analytes (Martín-Esteban, 2009).

Molecular docking simulations have been employed in the field of MIPs to investigate the interactions between template molecules and the polymer matrix. Molecular docking studies have been conducted to explore the interactions between proteins, such as human serum albumin (HSA), and common monomers and crosslinkers used in MIPs (Kryscio et al., 2011). These docking simulations provide insights into the binding mechanisms and the formation of hydrogen bonding between the template molecules and the functional monomers and crosslinkers. MD simulations have been utilized in the study and development of MIPs. MD simulations of pre-polymerization mixtures can provide detailed insights concerning the molecular-level mechanisms underlying the formation of MIPs (Elsonbaty et al., 2023). Comprehensive MD simulations of MIPs pre-polymerization mixtures have been highlighted as an effective approach in the study and development of MIPs (Nicholls et al., 2022). Theoretical calculations and simulations of various MIP designs have been conducted using molecular mechanics (MM), MD, and quantum methods (Liu et al. 2021). Molecular modeling and simulations are valuable tools for the polymer science and engineering community, providing insights into the structure and properties of polymers (Gartner and Jayaraman, 2019).

This study aimed to investigate the interactions and dynamic behavior of 3HB in a complex with ten polymers, each consisting of its seven monomers, using molecular docking and MD simulations. In the beginning, molecular docking was utilized so that predictions could be made regarding the binding orientations and affinities of the molecule containing 3HB within the active sites of the polymers. Following that, an MD simulation was carried out for a duration of one hundred nanoseconds in order to investigate the dynamic behavior, stability, and interactions that occurred inside these complexes.

MATERIAL AND METHODS

Materials

The workstation was equipped with a double processor of Intel® Xeon E5-2673v2 20 core 40 Thread 2.3 GHz, 64 GB of RAM, and RTX 4060 Ti with dual operating system: Windows 10 Pro-64-bit and Ubuntu 22 for molecular docking and MD simulation.

Preparation of ligand and polymer structures

The input structures for 3HB (Fig. 1) and the polymers (4VP, HEMA, ITA, MAA, TFMAA, AAm, NHMAm, NHEAm, DMAm, and TrisNHMAm) each consist of 7 monomers (Table 1) were created using Avogadro 1.2.0 (Snyder and Kucukkal, 2021). The 2D chemical structures of 3HB and polymers were converted into 3D molecular structures using Avogadro 1.2.0. Hydrogens were added to the molecular structures using Avogadro's built-in tools. Charges were assigned using MMFF94 force field parameters based on the molecular composition and functional groups. The prepared structures were subjected to energy minimization within Avogadro to alleviate steric clashes and optimize bond lengths and angles. The steepest descent was selected for the energy minimization method. The ligand and polymer structures were saved in *.pdb file formats.

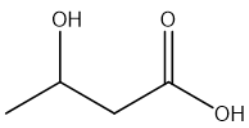

Figure 1. The 2D structures for 3-hydroxybutyrate (3HB).

Grid box generation

A grid box was defined around the active site of the polymer where the ligand was expected to bind. The grid box size and coordinates were determined based on the binding pocket dimensions and ligand positions.

Running AutoDock Vina

The ligand and polymer structures were specified as input files, along with grid box coordinates. The docking calculations were performed using AutoDock Vina 1.2.3 (Butt et al., 2020) to predict the binding poses and binding affinities of the ligand-polymer complexes.

Analysis of docking results

The output files generated by AutoDock Vina 1.2.3 were analyzed to identify the potential binding modes of 3HB with each polymer. The docking scores and binding energies were extracted to rank the binding affinities of different polymers.

Visualization of results

The docking results were visualized using the BIOVIA Discovery Studio Visualizer 2021. The binding poses of 3HB within the binding pockets of the polymers were analyzed for interactions, including hydrogen bonds, hydrophobic interactions, and other relevant interactions.

Selection of promising polymers

Based on the docking scores, binding affinities, and interactions observed, a subset of polymers showing favorable binding interactions with 3HB was selected as potential candidates for further investigation.

Molecular dynamics simulation

Molecular dynamics simulations were conducted using the GROMACS 2022.4 program (Kutzner et al., 2022). The initial structures of 3HB and the polymers (4VP, HEMA, ITA, MAA, TFMAA, AAm, NHMAm, NHEAm, DMAm, and TrisNHMAm) were obtained from the previous molecular docking simulation. These best-pose structures were prepared using the BIOVIA Discovery Studio Visualizer 2021 and saved in *.pdb.

Topology and parameter generation

The structures of 3HB and the polymers were processed to generate topology and parameter files suitable for molecular dynamics simulations. The Acpype tool was utilized to convert the input structures into formats compatible with the AMBER force field (Bernardi et al., 2019).

System solvation and ionization

The generated topology and parameter files were used to create molecular systems by placing the ligand of 3HB and polymer structures in a TIP3P solvent

box. Appropriate counter ions were added to ensure system neutrality. The system was then energy minimized to remove steric clashes.

Equilibration

The equilibration process involved a series of gradual heating, equilibration, and relaxation steps to allow the system to reach a stable state. During equilibration, the solvent and ions around the polymer-ligand complex were allowed to relax through short simulations.

Production molecular dynamics

The equilibrated system was subjected to a 100 ns production molecular dynamics (MD) simulation. The simulation was performed using a molecular dynamics software package of the GROMACS 2022 on an RTX 4060 Ti GPU for enhanced computational efficiency.

Trajectory analysis

The trajectory generated during the 100 ns MD simulation was analyzed using various analysis tools available in GROMACS. The analysis included monitoring the root mean square deviation (RMSD), root mean square fluctuation (RMSF), solvent accessible surface area (SASA), and MMGBSA (Asnawi et al., 2023; Febrina and Asnawi, 2023).

Visualization and interpretation

Molecular visualization software was used to visualize the MD trajectory and gain insights into the dynamic behavior of the 3HB-polymer complexes. The visualization aided in understanding the conformational changes, interactions, and stability of the complexes over the simulation period. Key data points, such as RMSD, RMSF, and binding interactions, were extracted from the MD trajectory for further analysis. The results were interpreted to conclude the stability, dynamics, and potential binding modes of 3HB with the different polymers.

ADME and toxicity

The predictive evaluation of the metabolic and toxicological profiles of 3HB using SwissADME (Bakchi et al., 2022) involved several steps. The chemical structure of 3HB (SMILES: CC(O)CC(O)=O) was initially inputted into the SwissADME web portal. The tool was used to forecast numerous pharmacokinetic aspects, such as absorption, distribution, metabolism, and excretion (ADME). The features encompassed parameters such as gastrointestinal absorption, blood-brain barrier permeability, cytochrome P450-mediated metabolism, and renal excretion.

In silico data analysis

The study employed various approaches to validate the docking technique, examine predicted absorption and distribution features, and evaluate potential toxicity. Studied chemical interactions between ligands and target proteins by molecular docking and MD simulations. The free energy of each ligand was calculated using methods like molecular mechanics generalized born surface area (MMGBSA). The study analyzed specific species or compounds in relation to natural ligands on target proteins to evaluate their potential as therapeutic drugs. Data was examined and conveyed using tables, figures, and charts. Reference compounds were used as standards for comparison and validation to provide context and assess effectiveness.

RESULTS

In silico study on the relationship between DKA and molecularly imprinted polymers (MIPs) is an emerging field that holds promise for improving the detection and management of this life-threatening condition. DKA is a severe complication of diabetes, primarily affecting individuals with type 1 diabetes but occasionally occurring in those with type 2 diabetes. It is characterized by high blood glucose levels (hyperglycemia), the presence of ketones in the blood and urine, metabolic acidosis, and dehydration. Prompt diagnosis and treatment of DKA are critical to prevent life-threatening complications.

MIPs are synthetic polymer materials that have been designed to recognize and selectively bind to specific target molecules, known as templates. These polymers are created through a process known as molecular imprinting, where the template molecule is incorporated during polymerization and then removed, leaving behind cavities or "imprints" with a shape and chemical functionality that matches the template. This allows MIPs to selectively bind to and capture the template molecule or molecules with similar structural features.

The choice of polymers for molecularly imprinted polymers (MIPs) of 3HB was based on a number of factors, such as the monomers' ability to make specific binding sites for 3HB (Table 1). Polymers formed from 4VP monomers have been used for various molecular imprinting applications, and their pyridine groups can be tailored for specific molecular recognition. The 4VP monomer contains a pyridine ring, which can form hydrogen bonds and electrostatic interactions with 3HB. It provides a suitable functional group to create recognition sites for 3HB. Polymers derived from HEMA monomers are known for their biocompatibility and have been applied in biomedical

Table 1. The molecular docking simulation results of 3HB with various polymers.

No.	Polymer	Binding affinity (kcal/mol)	Classical hydrogen bond	Non-classical hydrogen bond	pi-pi interaction
1	Poly(4-vinylpyridine), (4VP)	-1.761	0	0	4
2	Poly(hydroxyethyl methacrylate), (HEMA)	-2.523	0	0	1
3	Poly(itaconic acid), (ITA)	-2.469	2	0	0
4	Poly(Methacrylic acid), (MAA)	-2.018	2	0	0
5	Poly(trifluoromethyl acrylic acid), (TFMAA)	-2.270	2	0	1
6	Poly(acrylamide), (AAm)	-1.990	1	0	0
7	Poly(*N*-(hydroxymethyl)acrylamide), (NHMAm)	-2.643	2	0	0
8	Poly(*N*-(hydroxyethyl)acrylamide), (NHEAm)	-2.189	2	1	0
9	Poly(*N*,*N*-dimethylacylamide), (DMAm)	-1.719	0	1	0
10	Poly(*N*-[tris(hydroxymethyl)methyl]acrylamide), (TrisNHMAm)	-2.305	1	4	0

and pharmaceutical fields. The HEMA monomer contains hydroxyl groups that can participate in hydrogen bonding interactions with 3HB. The presence of these groups can enhance the selectivity of 3HB. Polymers based on ITA monomers have been used for the imprinting of various analytes, and their carboxylic acid functionalities offer tunable binding sites. The ITA monomer includes carboxylic acid groups that can form hydrogen bonds and electrostatic interactions with 3HB. These groups can enable selective binding. Polymers derived from MAA monomers are well-suited for molecular imprinting due to the presence of carboxylic acid groups and their versatility. The MAA monomer, like the ITA monomer, contains carboxylic acid groups that can form hydrogen bonds and electrostatic interactions with 3HB. This helps create selective binding sites. Polymers from the TFMAA monomer provide a specific type of binding site suitable for hydrophobic molecules. The TFMAA monomer offers unique functionality due to its trifluoromethyl group. This group can participate in hydrophobic interactions and enhance the affinity for hydrophobic analytes like 3HB. The remaining monomers (AAm, NHMAm, NHEAm, DMAm, and TrisNHMAm) can be classified similarly based on the functional groups they contain and their compatibility with the desired molecular interactions for 3HB.

Molecular docking and molecular dynamics (MD) simulations of pre-polymerization mixes can provide precise information about the molecular-level mechanisms behind the performance of MIPs and can be utilized for the *in silico* screening of potential polymer systems (Olsson et al., 2021). Important for the development of MIPs for the diagnosis and treatment of DKA, simulations can also be used to evaluate the stability of the polymer-ligand combination.

In molecular docking or molecular dynamics simulations, one of the most important steps in computational chemistry research is finding the active site for each polymer. The active site is the part of a molecule where interactions happen, like when it binds to a ligand or substrate. In this research, blind docking was used. When it's not known where the active site is, blind docking or molecular dynamics simulations can be run over the whole polymer surface to find possible binding regions. The active site is the area that has the highest binding affinity or stability.

Polymer-ligand interaction

In the field of molecular computational, docking simulations play a crucial role in understanding the interactions between small molecules and larger macromolecules. Binding affinity, hydrogen bonding, non-classical hydrogen bonding, and pi-pi interactions are key factors that influence the stability and strength of these interactions. The analysis of the docking simulation results of 3HB with various polymers focuses on the relationship between binding affinity, classical and non-classical hydrogen bonds, and pi-pi interactions (Table 1 and Fig. 2).

Binding affinity, measured in kcal/mol, quantifies the strength of interaction between a 3HB and a polymer. A more negative binding affinity indicates a stronger binding interaction. The docking simulation results reveal that different polymers exhibit varying binding affinities with 3HB. For instance, the polymer HEMA has the most negative binding affinity of -2.523 kcal/mol, suggesting a strong interaction.

Hydrogen bonding is a fundamental intermolecular interaction that plays a significant role in molecular recognition and binding. Classical hydrogen

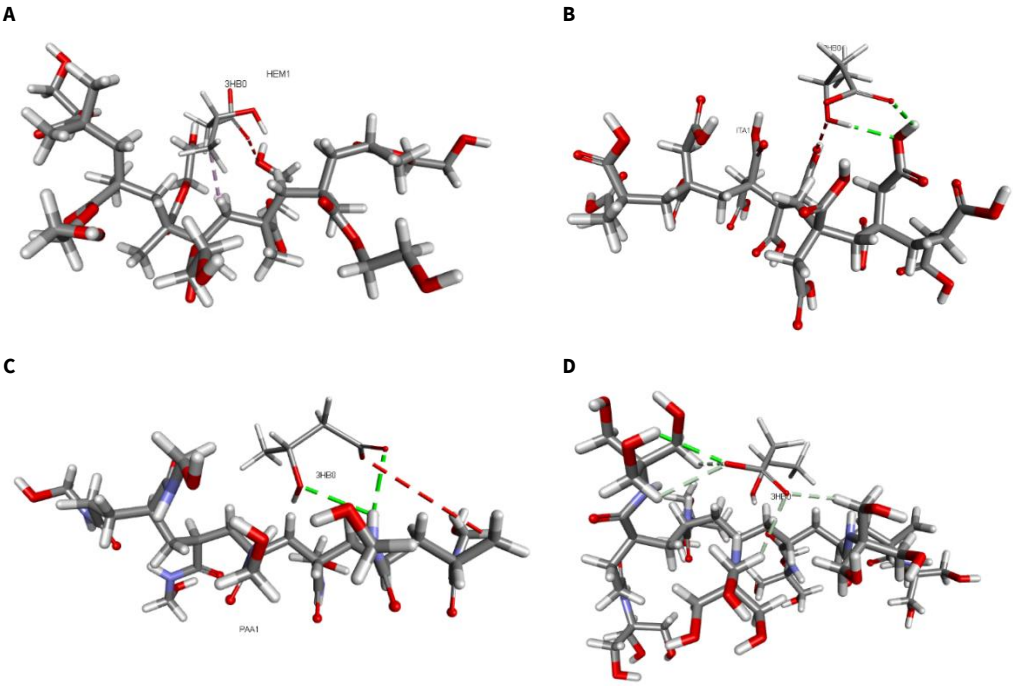

Figure 2. Typical polymer-ligand interaction of 3HB with various polymers.

(A) Poly(hydroxyethyl methacrylate), (HEMA); **(B)**Poly(itaconic acid), (ITA); **(C)**Poly(*N*-(hydroxymethyl)acrylamide), (NHMAm); and **(D)**Poly(*N*-[tris(hydroxymethyl)methyl]acrylamide), (TrisNHMAm).

bonds involve a hydrogen atom bonded to an electronegative atom (such as oxygen or nitrogen) in the ligand interacting with another electronegative atom in the polymer. Among the polymers studied, MAA, TFMAA, ITA, and NHMAm form classical hydrogen bonds with 3HB. This interaction contributes to the stabilization of the ligand-polymer complex.

Non-classical hydrogen bonds involve a more complex interaction pattern compared to the traditional hydrogen bond definition. In this study, NHEAm and DMAm polymers exhibit non-classical hydrogen bonding with 3HB. Non-classical hydrogen bonds often involve interactions with functional groups that might not traditionally participate in hydrogen bonding. The presence of non-classical hydrogen bonds could influence the overall stability of the complex.

A low binding affinity in docking studies (for example, -1 to -2) means that the 3HB and its polymers do not bind very well or at all. A low binding affinity indicated that the polymer had a low tendency to bind strongly to the target. This could be due to limited favorable interactions, such as hydrogen bonds, van der Waals forces, or electrostatic interactions, between the 3HB and the polymers.

Pi-pi interactions involve the stacking of aromatic rings, typically found in molecules containing conjugated double bonds or aromatic systems. These interactions are weaker than traditional hydrogen bonds but can still contribute significantly to molecular recognition. Among the polymers studied, 4VP and TFMAA exhibit pi-pi interactions with 3HB. The presence of pi-pi interactions may lead to additional stabilization of the ligand-polymer complex.

Polymer-ligand interaction stability

RMSD

In molecular dynamics simulations, we began with the polymer's and 3HB's initial structure or conformation, which served as the reference or starting point for the simulation. This first structure was derived from a docked result. The starting configuration of the molecule was represented by the reference structure. The RMSD was computed by measuring how much the atoms of the 3HB and polymer migrated or departed from their starting positions in the reference structure on average. The reference structure serves as a baseline for evaluating structural changes and polymer variations during the simulation.

The examination for the fluctuations in RMSD over a 100 ns MD simulation was performed for ten different polymers: 4VP, HEMA, ITA, MAA, TFMAA, AAm, NHMAm, NHEAm, DMAm, and TrisNHMAm (Fig. 3).

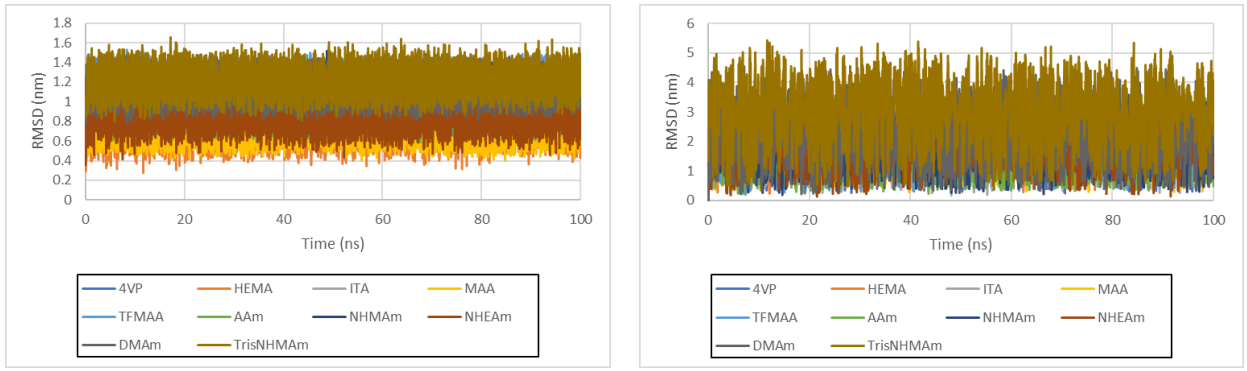

Figure 3. The RMSD of polymer-ligand complexes.

RMSD for various polymers **(A)** and 3HB **(B)**. 4VP: Poly(4-vinylpyridine); HEMA: poly(hydroxyethyl methacrylate); ITA: poly(itaconic acid); MAA: poly(methacrylic acid); TFMAA: poly(trifluoromethyl acrylic acid); NHMAm: poly(*N*-(hydroxymethyl)acrylamide); NHEAm: poly(*N*-(hydroxyethyl)acrylamide); DMAm: poly(*N*,*N*-dimethylacylamide); TrisNHMAm: poly(*N*-[Tris(hydroxymethyl)methyl]acrylamide); and Aam: poly(acrylamide) (reference compound).

RMSD for polymers

RMSD values for polymers (Fig. 3A) represent the average distance between corresponding atoms in the reference and current structures of the polymer. Higher RMSD values indicate greater structural deviation from the starting structure. The RMSD values for 4VP (4-vinylpyridine) show fluctuations ranging from around 0.65 to 1.23 Å, suggesting some degree of structural flexibility. However, the fluctuations were relatively moderate, indicating a relatively stable interaction with the ligand. Hydroxyethyl methacrylate (HEMA) exhibits fluctuations from approximately 0.37 to 0.9 Å. These fluctuations were relatively small, suggesting a stable binding interaction with the ligand throughout the simulation. Itaconic acid (ITA) displays fluctuations ranging from about 0.93 to 1.27 Å. The RMSD values are higher compared to HEMA, indicating more flexibility in the ITA-ligand complex. HEMA and methacrylic acid (MAA) exhibit the lowest average RMSD values (0.8036 Å and 0.7485 Å, respectively), suggesting relatively stable interactions with the ligand. On the other side, HEMA and MAA also exhibit the lowest bottom RMSD values (0.2766 Å and 0.3515 Å, respectively), indicating minimal structural changes at certain points in the simulation.

MAA's RMSD fluctuations vary from approximately 0.35 to 1.0 Å. Similar to ITA, MAA shows moderate fluctuations, implying dynamic interactions with the ligand. Trifluoromethyl acrylic acid (TFMAA) demonstrates fluctuations in the range of 1.08 to 1.42 Å. These fluctuations are relatively higher, indicating more pronounced conformational changes over time. Among the PAM polymers, AAM, NHMAm, and NHEAm show fluctuations around 1.0 Å, while DMAM and TrisNHMAm display fluctuations ranging from around 1.04 to 1.34 Å. These variations suggest varying degrees of flexibility in the complexes, with DMAm and TrisNHMAm exhibiting slightly more conformational changes.

ITA, NHEAm, and DMAm show moderate average RMSD values, indicating a moderate degree of flexibility. TFMAA, AAM, NHMAm, TrisNHMAm, and 4VP demonstrate higher average RMSD values, suggesting greater conformational fluctuations and dynamic interactions. However, the TrisNHMAm displays the highest top RMSD value (1.6479 Å), indicating significant structural deviations.

Overall, the fluctuations in RMSD over the 100 ns MD simulation provide insights into the stability and flexibility of the polymer-ligand complexes. Polymers with lower RMSD fluctuations, such as HEMA and MAA, maintain relatively stable interactions with the ligand. In contrast, polymers with higher RMSD fluctuations, such as TFMAA and some of the polymers, exhibit more dynamic behavior, potentially indicating conformational changes in the complex over time.

RMSD for 3HB

RMSD values for polymers (Fig. 3B) represent the average distance between corresponding atoms in the reference and current structures of the 3HB. At time zero (0 ns), the RMSD values are quite small for all polymers, indicating that the complexes begin the simulation in close structural alignment with the initial configuration. As the simulation progresses, all complexes experience fluctuations in RMSD. The fluctuations of the complexes show varying patterns. The 4VP, HEMA, ITA, MAA, and TFMAA exhibit relatively consistent fluctuations, indicating a balance between stability and flexibility. The AAm and NHMAm complexes show increasing fluctuations, suggesting dynamic interactions between 3HB and these polymers. The NHEAm and DMAm show more stable fluctuations with some increase toward the end of the simulation. The TrisNHMAm displays an unu-

sual behavior with extremely high RMSD values at 0 ns, indicating an initial structural deviation.

The 3HB in TFMAA and TrisNHMAm complexes have the lowest and highest average RMSD values, respectively. The "Top" RMSD values, representing the highest deviations from the initial structure, vary significantly among the complexes. TrisNHMAm exhibits the highest top RMSD value (4.6946 Å). The "Bottom" RMSD values, representing the lowest deviations from the initial structure, are generally small for most complexes, indicating certain points of stability during the simulation.

Gyration

Gyration (Rg) is a key measure of the size and shape of a polymer chain in a molecular system. Understanding the fluctuations in Rg over time provides insights into the conformational changes and structural dynamics of these polymers. The analysis of the fluctuations in Rg over a 100,000 ps (100 ns) molecular dynamics simulation for ten polymers, 4VP, HEMA, ITA, MAA, TFMAA, AAm, NHMAm, NHEAm, DMAm, and TrisNHMAm, within complexes with 3HB (Fig. 4). The Rg fluctuations will shed light on the stability and flexibility of the polymer-ligand complexes.

At time zero (0 ps), the initial Rg values are indicative of the starting conformations of the polymer-ligand complexes. The Rg fluctuations over the simulation timeframe exhibit varying patterns among different polymers. Polymers like 4VP, HEMA, ITA, MAA, and TFMAA display moderate fluctuations in Rg, suggesting a balance between stability and flexibility. The AAm, NHMAm, NHEAm, DMAm, and TrisNHMAm exhibit more diverse patterns of fluctuations, with some undergoing considerable conformational changes.

Some polymers, such as TrisNHMAm, exhibit relatively higher Rg values throughout the simulation, suggesting greater structural expansion and flexibility. Others, like HEMA and MAA, demonstrate relatively consistent Rg values, indicating more stable interactions with the ligand. Among the polymers, TrisNHMAm demonstrates the highest Rg values, indicating the largest conformational changes. HEMA, ITA, and MAA exhibit relatively lower Rg fluctuations, suggesting more confined structural variations. Polymers like 4VP, TFMAA, AAm, NHMAm, NHEAm, and DMAm display moderate Rg fluctuations, implying moderate flexibility.

The analysis of Rg fluctuations over a 100 ns MD simulation provides insights into the dynamic behavior of polymers in complexes with 3HB. The fluctuations in Rg offer valuable information about the flexibility, stability, and conformational changes of the polymer chains. Polymers with consistent Rg values may maintain stable interactions, while those with diverse Rg patterns undergo varying degrees of structural changes. These findings contribute to a better understanding of the behavior of these polymer-ligand complexes and can guide further investigations in drug delivery, material science, and molecular recognition studies. Comparing the Rg fluctuations across different polymers enhances our comprehension of their distinct interactions and behavior within the complex molecular environment.

SASA

The solvent-accessible surface area (SASA) is a crucial parameter for understanding the exposure of a molecule to its surrounding solvent environment. In this discussion, we analyze the fluctuations in SASA over a 100,000 ps (100 ns) molecular dynamics (MD) simulation for ten polymers, 4VP, HEMA, ITA, MAA, TFMAA, AAm, NHMAm, NHEAm, DMAm, and TrisNHMAm, interacting with 3HB (Fig. 5). The SASA fluctuations provide insights into the dynamic behavior and conformational changes of the polymer-ligand complexes during the simulation.

The SASA values for all polymers show temporal fluctuations over the 100 ns simulation period. Each polymer exhibits distinct patterns of fluctuations, indicating their unique interactions with 3HB. TrisNHMAm consistently displays the highest SASA values, suggesting greater exposure to the solvent environment compared to other polymers.

Most polymers experience an initial drop in SASA during the first few nanoseconds, indicating rearrangements in the complex structures. NHEAm and DMAm show relatively consistent SASA values, implying stable interactions with 3HB. Polymers like ITA and MAA exhibit noticeable fluctuations in SASA, suggesting dynamic interactions with the ligand throughout the simulation.

The average SASA values across all polymers provide a measure of their typical exposure to the solvent environment. Among the polymers, TrisNHMAm exhibits the highest average SASA, indicating its larger exposure to the solvent, which is consistent with its bulky structure. The maximum SASA values represent the peak solvent exposure experienced by the polymers during the simulation. NHEAm and DMAm have the highest maximum SASA values, suggesting instances where these polymers experience substantial solvent interactions. Polymers like MAA and TFMAA show relatively low minimum SASA values, implying that they tend to maintain a more compact structure during the simulation.

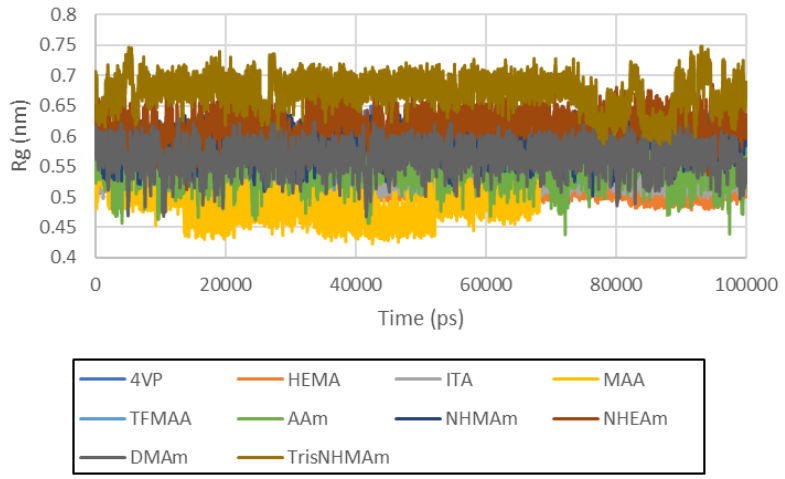

Figure 4. The gyration fluctuation of polymer-ligand complexes.

4VP: Poly(4-vinylpyridine); HEMA: poly(hydroxyethyl methacrylate); ITA: poly(itaconic acid); MAA: poly(methacrylic acid); TFMAA: poly(trifluoromethyl acrylic acid); NHMAm: poly(*N*-(hydroxymethyl)acrylamide); NHEAm: poly(*N*-(hydroxyethyl)acrylamide); DMAm: poly(*N*,*N*-dimethylacylamide); TrisNHMAm: poly(*N*-[Tris(hydroxymethyl)methyl]acrylamide), and Aam: poly(acrylamide) (reference compound).

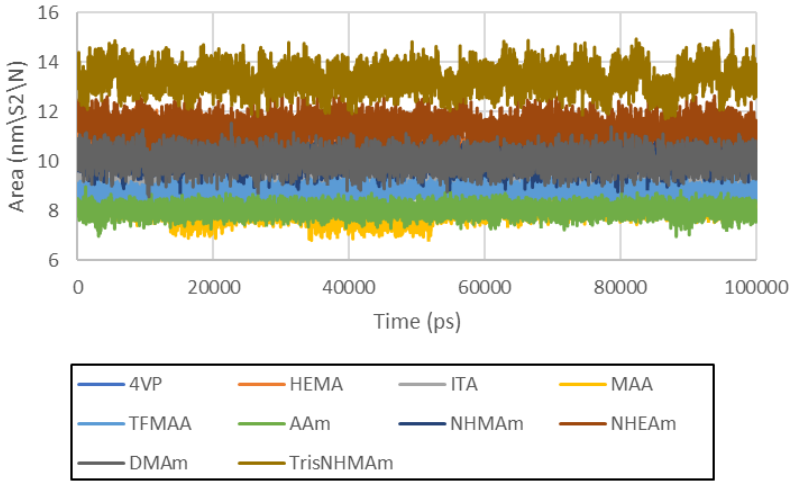

Figure 5. The SASA fluctuation of polymer-ligand complexes.

4VP: Poly(4-vinylpy ridine); HEMA: poly(hydroxyethyl methacrylate); ITA: poly(itaconic acid); MAA: poly(methacrylic acid); TFMAA: poly(trifluoromethyl acrylic acid); NHMAm: poly(*N*-(hydroxymethyl)acrylamide); NHEAm: poly(*N*-(hydroxyethyl)acrylamide); DMAm: poly(*N*,*N*-dimethylacylamide); TrisNHMAm: poly(*N*-[Tris(hydroxymethyl)methyl]acrylamide), and Aam: poly(acrylamide) (reference compound).

Energy component

Molecular dynamics simulations provide a powerful tool for understanding the interactions and energy contributions within polymer-ligand complexes. This discussion focuses on the energy components, ΔVDWAALS, ΔEEL, ΔEGB, ΔESURF, ΔGGAS, ΔGSOLV, and ΔTOTAL, involved in the interactions between the ligand 3HB and ten different polymers: 4VP, HEMA, ITA, MAA, TFMAA, AAm, NHMAm, NHEAm, DMAm, and TrisNHMAm (Fig. 6).

The ΔVDWAALS represents the van der Waals interaction energy, while ΔEEL corresponds to electrostatic interaction energy. In general, negative values for both ΔVDWAALS and ΔEEL indicate attractive interactions between the ligand and polymers. Polymers with more negative ΔVDWAALS and ΔEEL values, such as 4VP and MAA, tend to have stronger van der Waals and electrostatic interactions with the ligand.

ΔEGB represents the polar solvation energy, while ΔESURF accounts for the nonpolar solvation energy.

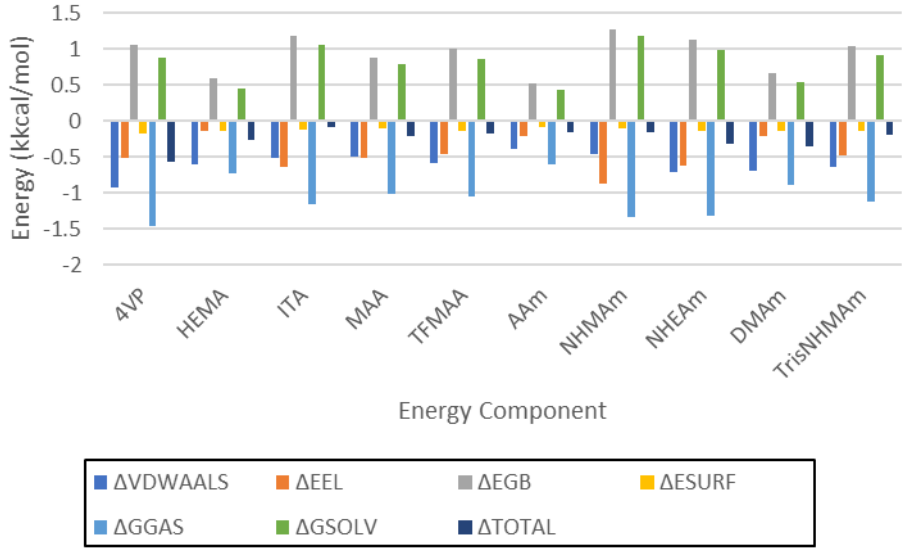

Figure 6. The energy component (ΔTotal) of polymer-ligand complexes.

4VP: Poly(4-vinylpyridine); HEMA: poly(hydroxyethyl methacrylate); ITA: poly(itaconic acid); MAA: poly(methacrylic acid); TFMAA: poly(trifluoromethyl acrylic acid); NHMAm: poly(*N*-(hydroxymethyl)acrylamide); NHEAm: poly(*N*-(hydroxyethyl)acrylamide); DMAm: poly(*N*,*N*-dimethylacylamide); TrisNHMAm: poly(*N*-[Tris(hydroxymethyl)methyl]acrylamide); and Aam: poly(acrylamide) (reference compound).

Positive ΔEGB values imply that the polar solvation of the complex is unfavorable, which might indicate that these polymers have hydrophobic regions interacting with the ligand. Small negative ΔESURF values indicate minimal favorable nonpolar solvation, suggesting that these complexes tend to exclude nonpolar solvent molecules from their interfaces.

ΔGGAS represents the Gibbs free energy change upon going from gas phase to solution, and ΔGSOLV is the solvent contribution to the Gibbs free energy. Negative ΔGGAS values indicate that the complexes are more stable in solution compared to the gas phase. Positive ΔGSOLV values suggest that the solvent has a stabilizing effect on the complexes.

ΔTOTAL represents the overall energy change upon ligand binding. Negative ΔTOTAL values suggest favorable interactions between the ligand and polymers, contributing to the stability of the complexes. ΔTOTAL values near zero or positive values might indicate weaker or less favorable interactions between the ligand and certain polymers.

Overall, the energy components analysis provides valuable insights into the interactions and stability of 3HB complexes with different polymers. The results indicate that some polymers exhibit stronger van der Waals and electrostatic interactions, while others might rely on solvation energies for stability. The balance between polar and nonpolar solvation, as well as the gas phase to solution transition, contributes to the overall stability of these complexes. By understanding these energy components, researchers can gain deeper insights into the molecular recognition processes and guide the design of polymer-ligand interactions for various applications, such as drug delivery or material design.

The relationship between the ability to form hydrogen bonds and pi-pi interactions of the functional groups that make up the listed monomers and the results of molecular docking and molecular dynamics simulations was investigated. The molecular docking results showed that different types of interactions, such as classical hydrogen bonds, non-classical hydrogen bonds, and pi-pi interactions, can contribute to the stability of the polymer-ligand complex. The ability of the functional groups in the monomers to form these interactions affected their binding affinity to a polymer (Table 1 and Fig. 2).

4-Vinylpyridine (4VP) contains a vinyl group (-CH=CH_2) and a pyridine ring, which is a heterocyclic aromatic ring containing a nitrogen atom. The pyridine ring in 4VP is a polar functional group due to the presence of a nitrogen atom with a partial negative charge. The vinyl group is nonpolar. The pyridine ring in 4VP can form hydrogen bonds with hydrogen bond acceptors, such as oxygen and nitrogen atoms. The vinyl group can participate in pi-pi interactions with other aromatic rings. The molecular docking results show that 4VP forms four pi-pi interactions with a polymer, which contributes to its binding affinity. It has been shown to have a high ability to form pi-pi interactions due to the presence of an aromatic pyridine ring, which could be useful for the development of MIPs for glucose monitoring in DKA

(Caldara et al., 2023). 4-VP has a pyridine ring that can engage in pi-pi interactions, as indicated by the negative ΔGGAS (-1.45), which represents the gas phase energy of interaction between the molecule and itself. Additionally, it has a positive ΔEGB (1.06), suggesting that it can form hydrogen bonds with the surrounding environment (such as water). The negative ΔTOTAL (-0.56) indicated that the molecule has an overall favorable interaction with its environment.

Hydroxyethyl methacrylate (HEMA) contains a methacrylate group (-COOCH=CH_2) and a hydroxyethyl group (-CH_2CH_2OH). The hydroxyethyl group in HEMA is polar due to the presence of an electronegative oxygen atom. The methacrylate group is also polar due to the presence of a carbonyl group. The hydroxyethyl group in HEMA can form hydrogen bonds with hydrogen bond acceptors, such as oxygen and nitrogen atoms. The methacrylate group can participate in pi-pi interactions with other aromatic rings. The molecular docking results show that HEMA forms one pi-pi interaction with a polymer, which contributes to its binding affinity. It does not form any classical or non-classical hydrogen bonds or pi-pi interactions, which could limit its potential for the development of MIPs for glucose monitoring in DKA (Olsson et al., 2021). HEMA does not exhibit strong pi-pi interactions (ΔGGAS was only -0.73), indicating minimal interaction between aromatic rings. It has a modest ΔEGB (0.59), suggesting some ability to form hydrogen bonds with its environment. The negative ΔTOTAL (-0.27) implies a relatively favorable interaction.

Itaconic acid (ITA) contains a carboxylic acid group (-COOH) and a carbon-carbon double bond (-C=C-). The carboxylic acid group in ITA is polar due to the presence of an electronegative oxygen atom. The carbon-carbon double bond is nonpolar. The carboxylic acid group in ITA can form hydrogen bonds with hydrogen bond acceptors, such as oxygen and nitrogen atoms. The carbon-carbon double bond does not participate in pi-pi interactions. The molecular docking results show that ITA forms two classical hydrogen bonds with a polymer, which contributes to its binding affinity. It has been shown to form two classical hydrogen bonds, which could be useful for the development of MIPs for glucose monitoring in DKA (Seong et al., 2002). The molecular dynamics simulations show that ITA has a negative ΔGGAS (-1.15), suggesting the potential for pi-pi interactions. It also exhibits a substantial ΔEGB (1.19), indicating a strong propensity to form hydrogen bonds with the surrounding environment. The overall ΔTOTAL was close to zero (-0.09), indicating a relatively balanced interaction.

Methacrylic acid (MAA) contains a methacrylate group (-COOCH=CH_2) and a carboxylic acid group (-COOH). The carboxylic acid group in MAA is polar due to the presence of an electronegative oxygen atom. The methacrylate group is also polar due to the presence of a carbonyl group. The carboxylic acid group in MAA can form hydrogen bonds with hydrogen bond acceptors, such as oxygen and nitrogen atoms. The methacrylate group can participate in pi-pi interactions with other aromatic rings. The molecular docking results show that MAA forms two classical hydrogen bonds with a polymer, which contributes to its binding affinity. It has been shown to form two classical hydrogen bonds, which could be useful for the development of MIPs for glucose monitoring in DKA (Seong et al., 2002). MAA exhibits a negative ΔGGAS (-1.01), indicating potential pi-pi interactions. It also has a significant ΔEGB (0.89), suggesting a strong ability to form hydrogen bonds. The overall ΔTOTAL was negative (-0.21), indicating a favorable interaction with its environment.

Trifluoromethyl acrylic acid (TFMAA) contains a methacrylate group (-COOCH=CH_2), a carboxylic acid group (-COOH), and a trifluoromethyl group (-CF3). The trifluoromethyl group in TFMAA is highly polar due to the presence of three electronegative fluorine atoms. The methacrylate and carboxylic acid groups are also polar. The trifluoromethyl group in TFMAA can form hydrogen bonds with hydrogen bond acceptors, such as oxygen and nitrogen atoms. The methacrylate and carboxylic acid groups can participate in pi-pi interactions with other aromatic rings. The molecular docking results show that TFMAA forms two classical hydrogen bonds and one pi-pi interaction with a polymer, which contributes to its binding affinity. It has been shown to form two classical hydrogen bonds and one pi-pi interaction, which could be useful for the development of MIPs for glucose monitoring in DKA (Seong et al., 2002). The molecular dynamics simulations show that TFMAA has a negative ΔGGAS (-1.04), suggesting pi-pi interactions. It also has a substantial ΔEGB (1), indicating a strong propensity to form hydrogen bonds. The overall ΔTOTAL was negative (-0.18), indicating a favorable interaction.

Acrylamide (AAm) contains an amide group (-$CONH_2$) and a vinyl group (-CH=CH_2). The amide group in AAm is polar due to the presence of an electronegative oxygen atom and a nitrogen atom with a partial negative charge. The vinyl group is nonpolar. The amide group in AAm can form hydrogen bonds with hydrogen bond acceptors, such as oxygen and nitrogen atoms. The vinyl group does not participate in pi-pi interactions. The molecular docking results show that AAm forms one classical hydrogen bond

with a polymer, which contributes to its binding affinity. It has been shown to form one classical hydrogen bond, which could be useful for the development of MIPs for glucose monitoring in DKA (Seong et al., 2002). In molecular dynamics, the negative ΔGGAS (-0.6) suggested a weak gas-phase interaction, likely due to the absence of significant pi-pi interactions. The positive ΔEGB (0.52) indicated some ability to form hydrogen bonds. The overall ΔTOTAL (-0.16) suggested a slightly favorable interaction.

N-(Hydroxymethyl)acrylamide (NHMAm) contains an amide group (-$CONH_2$), a vinyl group (-$CH=CH_2$), and a hydroxymethyl group (-CH_2OH). The hydroxymethyl group in NHMAm is polar due to the presence of an electronegative oxygen atom. The amide and vinyl groups are also polar. The hydroxymethyl group in NHMAm can form hydrogen bonds with hydrogen bond acceptors, such as oxygen and nitrogen atoms. The amide and vinyl groups can participate in pi-pi interactions with other aromatic rings. The molecular docking results show that NHMAm forms two classical hydrogen bonds with a polymer, which contributes to its binding affinity. It has been shown to form two classical hydrogen bonds, which could be useful for the development of MIPs for glucose monitoring in DKA (Seong et al., 2002). The molecular dynamics simulations show that the negative ΔGGAS (-1.33) suggested potential pi-pi interactions. The substantial positive ΔEGB (1.28) indicated a strong propensity to form hydrogen bonds. The overall ΔTOTAL (-0.15) suggested a favorable interaction.

N-(Hydroxyethyl)acrylamide (NHEAm) contains an amide group (-$CONH_2$), a vinyl group (-$CH=CH_2$), and a hydroxyethyl group (-CH_2CH_2OH). The hydroxyethyl group in NHEAm is polar due to the presence of an electronegative oxygen atom. The amide and vinyl groups are also polar. The hydroxyethyl group in NHEAm can form hydrogen bonds with hydrogen bond acceptors, such as oxygen and nitrogen atoms. The amide and vinyl groups can participate in pi-pi interactions with other aromatic rings. The molecular docking results show that NHEAm forms two classical hydrogen bonds and one non-classical hydrogen bond with a polymer, which contributes to its binding affinity. NHEAm has been shown to form two classical hydrogen bonds and one non-classical hydrogen bond, which could be useful for the development of MIPs for glucose monitoring in DKA (Seong et al., 2002). In molecular dynamics, the negative ΔGGAS (-1.31) suggested potential pi-pi interactions. The positive ΔEGB (1.13) indicated a strong ability to form hydrogen bonds. The overall ΔTOTAL (-0.32) suggests a favorable interaction.

N,*N*-Dimethylacylamide (DMAm) contains an amide group (-$CON(CH_3)_2$) and a vinyl group (-$CH=CH_2$). The amide group in DMAm is polar due to the presence of an electronegative oxygen atom and two nitrogen atoms with partial negative charges. The vinyl group is nonpolar. The amide group in DMAm can form hydrogen bonds with hydrogen bond acceptors, such as oxygen and nitrogen atoms. The vinyl group does not participate in pi-pi interactions. The molecular docking results show that DMAm forms one non-classical hydrogen bond with a polymer, which contributes to its binding affinity. DMAm has been shown to form one non-classical hydrogen bond, which could be useful for the development of MIPs for glucose monitoring in DKA (Seong et al., 2002). The molecular dynamics simulations show that the negative ΔGGAS (-0.89) suggested a weak gas-phase interaction, possibly due to the absence of pi-pi interactions. The positive ΔEGB (0.67) indicated some ability to form hydrogen bonds. The overall ΔTOTAL (-0.35) suggested a slightly favorable interaction.

N-[Tris(hydroxymethyl)methyl]acrylamide (Tris NHMAm) contains an amide group (-$CONH_2$), a vinyl group (-$CH=CH_2$), and a tris(hydroxymethyl) methyl group (-$C(CH_2OH)_3$). The tris(hydroxymethyl) methyl group in TrisNHMAm is polar due to the presence of multiple electronegative oxygen atoms. The amide and vinyl groups are also polar. The tris(hydroxymethyl)methyl group in TrisNHMAm can form hydrogen bonds with hydrogen bond acceptors, such as oxygen and nitrogen atoms. The amide and vinyl groups can participate in pi-pi interactions with other aromatic rings. The molecular docking results show that TrisNHMAm forms one classical hydrogen bond and four pi-pi interactions with a polymer, which contributes to its binding affinity. It has been shown to form one classical hydrogen bond and four non-classical hydrogen bonds, which could be useful for the development of MIPs for glucose monitoring in DKA (Seong et al., 2002). In molecular dynamics, the negative ΔGGAS (-1.11) suggested potential pi-pi interactions. The positive ΔEGB (1.04) indicated a strong propensity to form hydrogen bonds. The overall ΔTOTAL (-0.19) suggested a favorable interaction.

However, based on general knowledge of functional groups, aromatic interactions, such as π-π stacking, are important for the stability of the polymer-ligand complex and can be used to develop docking scoring functions (Brylinski, 2018). Hydrophobic interactions, hydrogen bonds, and π-stacking are the most common interactions between ligands and macromolecules (Patil et al., 2010). These interactions are important for the stability of the polymer-ligand

complex and can be used to develop MIPs for the detection and treatment of DKA.

ADME prediction

SwissADME provides important information on the Absorption, Distribution, Metabolism, and Excretion (ADME) prediction of 3-hydroxybutyrate (3HB), giving vital insights into its pharmacokinetic features. The results show that 3HB has a low molecular weight of 104.1 g/mol, suggesting it may be efficiently absorbed. With just seven heavy atoms and no aromatic heavy atoms, 3HB has a straightforward molecular structure that could aid its passage through biological membranes.

A Csp3 score of 0.75 indicates a mostly aliphatic nature, which may impact its solubility and metabolic stability. The presence of two rotatable bonds and three hydrogen bond acceptors in this feature may enhance its favorable pharmacokinetic profile. The TPSA of 57.53 Å² indicates a likelihood of interacting with biological targets, perhaps affecting its distribution and metabolic processes.

3HB exhibits a negative XLOGP3 score of -0.53, suggesting a tendency towards hydrophilic settings due to its lipophilicity. The observation aligns with the experimentally determined ESOL Log P value of -0.19, indicating favorable aqueous solubility. The ESOL solubility data shows high solubility, which is beneficial for drug-like compounds as it can improve bioavailability and aid in formulation development.

3HB demonstrates excellent gastrointestinal absorption capability and is expected to permeate the blood-brain barrier. These traits indicate that 3HB is likely to easily pass through biological barriers, making it beneficial for medications aimed at central nervous system illnesses or needing widespread dispersion in the body. The lack of P-glycoprotein (Pgp) substrate activity suggests a lower chance of efflux-mediated medication resistance, which increases its potential as a treatment.

The absence of inhibition against major cytochrome P450 (CYP) isoforms (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4) suggests a low risk of drug-drug interactions mediated by these enzymes. This prediction aligns with the relatively low lipophilicity and simple molecular structure of 3HB, which may limit its metabolic transformation by hepatic enzymes. Overall, the ADME prediction highlights 3HB as a molecule with favorable pharmacokinetic properties, suggesting its potential utility as a drug candidate or pharmacological tool in biomedical research.

CONCLUSION

The *in silico* study of both molecular docking and molecular dynamics for the interaction of 3HB with the designed polymers has been presented. Among the polymers studied, NHMAm, HEMA, ITA, and TrisNHMAm indicated strong interactions with 3HB, with the most negative binding affinities of -2.643, -2.523, -2.469, and -2.305 kcal/mol, respectively. The four polymers with the most negative binding affinities exemplify the diverse ways in which different types of molecular interactions influence ligand-polymer binding. In molecular dynamics, 4VP, DMAm, NHEAm, and HEMA indicate a strong stable complex with 3HB with an overall ΔTOTAL of -0.56, -0.35, -0.32, and -0.27 kcal/mol, respectively. HEMA shows the ability to interact well with 3HB through molecular docking and molecular dynamics.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

Asnawi A, Nedja M, Febrina E, Purwaniati P (2023) Prediction of a stable complex of compounds in the ethanol extract of celery leaves (*Apium graveolens* L.) function as a VKORC1 antagonist. Trop J Nat Prod Res 7: 2362–2370. https://doi.org/10.26538/tjnpr/v7i2.10

Bakchi B, Krishna AD, Sreecharan E, Ganesh VBJ, Niharika M, Maharshi S, Puttagunta SB, Sigalapalli DK, Bhandare RR, Shaik AB (2022) An overview on applications of SwissADME web tool in the design and development of anticancer, antitubercular and antimicrobial agents: A medicinal chemist's perspective. J Mol Struct 1259: 132712. https://doi.org/10.1016/j.molstruc.2022.132712

Bernardi A, Faller R, Reith D, Kirschner KN (2019) ACPYPE update for nonuniform 1–4 scale factors: Conversion of the GLYCAM06 force field from AMBER to GROMACS. SoftwareX 10: 100241. https://doi.org/10.1016/j.softx.2019.100241

Brylinski M (2018) Aromatic interactions at the ligand–protein interface: Implications for the development of docking scoring functions. Chem Biol Drug Des 91: 380–390. https://doi.org/10.1111/cbdd.13084

Butt SS, Badshah Y, Shabbir M, Rafiq M (2020) Molecular docking using chimera and autodock vina software for nonbioinformaticians. JMIR Bioinform Biotech 1: e14232. https://doi.org/10.2196/14232

Caldara M, Kulpa J, Lowdon JW, Cleij TJ, Diliën H, Eersels K, Grinsven Bv (2023) Recent advances in molecularly imprinted polymers for glucose monitoring: From fundamental research to commercial application. Chemosensors 11: 32. https://doi.org/10.3390/chemosensors11010032

Dhatariya KK, Glaser NS, Codner E, Umpierrez GE (2020) Diabetic ketoacidosis. Nat Rev Dis Primers 6: 40. https://doi.org/10.1038/s41572-020-0165-1

Elsonbaty A, Attala K, Eissa MS, Abdelshakour M, Mostafa A, Abdel Salam R, Hadad G (2023) Current advances in computer-aided design of electrochemical sensors: An analytical review. Rec Pharm Biomed Sci 7: 65–96. https://doi.org/10.21608/rpbs.2023.188482.1202

Febrina E, Asnawi A (2023) Lead compound discovery using pharmacophore-based models of small-molecule metabolites from human blood as inhibitor cellular entry of SARS-CoV-2. J Pharm Pharmacogn Res 11: 810–822. https://doi.org/10.56499/jppres23.1688_11.5.810

Gartner TEI, Jayaraman A (2019) Modeling and simulations of polymers: A roadmap. Macromolecules 52: 755–786. https://doi.org/10.1021/acs.macromol.8b01836

Hu Y, Pan J, Zhang K, Li G (2013) Novel applications of molecularly-imprinted polymers in sample preparation. Trends Anal Chem 43: 37–52. https://doi.org/10.1016/j.trac.2012.08.014

Karrar HR, Nouh M, Alhendi R (2022) Diabetic ketoacidosis: a review article. World Fam Med 20: 66–71. http://dx.doi.org/10.5742/MEWFM.2022.9525062

Kryscio DR, Shi Y, Ren P, Peppas NA (2011) Molecular docking simulations for macromolecularly imprinted polymers. Ind Eng Chem Res 50: 13877–13884. https://doi.org/10.1021/ie201858n

Kutzner C, Kniep C, Cherian A, Nordstrom L, Grubmüller H, de Groot BL, Gapsys V (2022) GROMACS in the cloud: A global supercomputer to speed up alchemical drug design. J Chem Inf Model 62: 1691–1711. https://doi.org/10.1021/acs.jcim.2c00044

Liu Z, Xu Z, Wang D, Yang Y, Duan Y, Ma L, Lin T, Liu H (2021) A review on molecularly imprinted polymers preparation by computational simulation-aided methods. Polymers 13: 2657. https://doi.org/10.3390/polym13162657

Martín-Esteban A (2013) Molecularly-imprinted polymers as a versatile, highly selective tool in sample preparation. Trends Anal Chem 45: 169–181. https://doi.org/10.1016/j.trac.2012.09.023

Martín-Esteban A (2009) Molecularly imprinted polymers: Providing selectivity to sample preparation. J Chromatogr Sci 47: 254–256. https://doi.org/10.1093/chromsci/47.3.254

Nicholls IA, Golker K, Wiklander JG (2022) Molecular Dynamics in the Study and Development of Molecularly Imprinted Materials–Status Quo, Quo Vadis? Preprints 2022020154. https://doi.org/10.20944/preprints202202.0154.v1

Olsson GD, Wiklander JG, Nicholls IA (2021) Using molecular dynamics in the study of molecularly imprinted polymers. Methods Mol Biol 2359: 241–268. https://doi.org/10.1007/978-1-0716-1629-1_21

Ooi E, Nash K, Rengarajan L, Melson E, Thomas L, Johnson A, Zhou D, Wallett L, Ghosh S, Narendran P, Kempegowda P (2021) Clinical and biochemical profile of 786 sequential episodes of diabetic ketoacidosis in adults with type 1 and type 2 diabetes mellitus. BMJ Open Diabetes Res Care 9: e002451. https://doi.org/10.1136/bmjdrc-2021-002451

O'Reilly JE, Blackbourn LA, Caparrotta TM, Jeyam A, Kennon B, Leese GP, Lindsay RS, McCrimmon RJ, McGurnaghan SJ, McKeigue PM, McKnight JA, Petrie JR, Philip S, Sattar N, Wild SH, Colhoun HM (2020) Time trends in deaths before age 50 years in people with type 1 diabetes: a nationwide analysis from Scotland 2004–2017. Diabetologia 63: 1626–1636. https://doi.org/10.1007/s00125-020-05173-w

Patil R, Das S, Stanley A, Yadav L, Sudhakar A, Varma AK (2010) Optimized hydrophobic interactions and hydrogen bonding at the target-ligand interface leads the pathways of drug-designing. PloS One 5: e12029. https://doi.org/10.1371/journal.pone.0012029

Peters AL, Henry RR, Thakkar P, Tong C, Alba M (2016) Diabetic ketoacidosis with canagliflozin, a sodium–glucose cotransporter 2 inhibitor, in patients with type 1 diabetes. Diabetes Care 39: 532–538. https://doi.org/10.2337/dc15-1995

Ramphul K, Joynauth J (2020) An update on the incidence and burden of diabetic ketoacidosis in the US. Diabetes Care 43: e196–e197. https://doi.org/10.2337/dc20-1258

Seong H, Lee H-B, Park K (2002) Glucose binding to molecularly imprinted polymers. J Biomater Sci Polym Ed 13: 637–649. https://doi.org/10.1163/156856202320269139

Snyder HD, Kucukkal TG (2021) Computational chemistry activities with Avogadro and ORCA. J Chem Educ 98: 1335–1341. https://doi.org/10.1021/acs.jchemed.0c00959

Vanelli M, Chiari G, Capuano C, Iovane B, Bernardini A, Giacalone T (2003) The direct measurement of 3-beta-hydroxy butyrate enhances the management of diabetic ketoacidosis in children and reduces time and costs of treatment. Diabetes Nutr Metab 16: 312–316. https://pubmed.ncbi.nlm.nih.gov/15000443/

Wallace T, Meston N, Gardner S, Matthews D (2001) The hospital and home use of a 30-second hand-held blood ketone meter: Guidelines for clinical practice. Diabet Med 18: 640–645. https://doi.org/10.1046/j.1464-5491.2001.00550.x

AUTHOR CONTRIBUTION:

Contribution	Asnawi A	Febrina E	Aligita W	Aman LO	Razi F
Concepts or ideas	x				
Design	x	x	x	x	x
Definition of intellectual content	x	x	x	x	x
Literature search	x	x	x	x	x
Experimental studies	x	x	x	x	x
Data acquisition	x	x	x	x	x
Data analysis	x	x	x	x	x
Statistical analysis	x	x	x	x	x
Manuscript preparation	x	x	x	x	x
Manuscript editing	x	x	x	x	x
Manuscript review	x	x	x	x	x

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