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The Study of Delivery Medicine Using ENDS Device: A Bromhexine Study Case

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ABSTRACT

Electronic Nicotine Delivery Systems (ENDS) have been used over the last decade as substitutes for conventional cigarettes. The delivery of active pharmaceutical ingredients (APIs) using these devices has been reported in the literature; however, many puffs are required to achieve a therapeutic dose. This study aimed to deliver and measure bromhexine hydrochloride (BRM) as an API via inhalation using an e-liquid formulation. The e-liquid was obtained by trapping the aerosol and measuring the concentration using high-performance liquid chromatography–mass spectrometry (HPLC-MS) in multiple reaction monitoring (MRM) mode. Our study demonstrated that five puffs accumulated 3.3156 ng/mL of BRM, and the efficiency of the ENDS device was calculated to be 99.8%. In addition, computational simulations were performed, resulting in a binding affinity of BRM of −7.3 kcal mol^{-1}, compared with −8.1 kcal mol^{-1} for salbutamol. Nevertheless, BRM formed a hydrogen bond between the amine group and Ser204, π-alkyl bonds with Ala200 and Val114, and alkyl interactions with Phe289 and Phe290. However, the BRM interaction with the protein did not form a stable complex in the dynamic simulation, although it may act as an allosteric modulator or partial agonist. The results of this study corroborate previous findings that ENDS technology may offer broad innovations for inhaled medicines.

INTRODUCTION

Inhaled active pharmaceutical ingredient (API) administration is one of the non-invasive drug delivery methods that is highly desirable for the treatment of respiratory disorders due to its low systemic adverse effects and efficient pulmonary targeting (Banat et al., 2023; Yue et al., 2023). However, the patient's physiology, the device, and the formulation must work in synergy to achieve optimal aerosol delivery. These devices should be capable of producing appropriately sized particles, be simple to use, affordable, portable, and, most importantly, "personalized" to meet individual patient needs. Alternative aerosol-generating drug delivery systems have been widely investigated in recent years (Buonocore et al., 2023; Pourchez et al., 2017).

The Study of Delivery Medicine Using ENDS Device: A Bromhexine Study Case Electronic Nicotine Delivery Systems (ENDS) have been established as a smoking cessation aid and are often perceived as a less harmful alternative to conventional cigarettes (Sahoo & Priyadarshini, 2019). The number of ENDS users was projected to reach approximately 90

million in 2023. Over the past decade, ENDS technology has evolved into advanced generations capable of temperature regulation, low-resistance (low-ohm) heating elements, and adjustable airflow systems (Sala & Gotti, 2023). ENDS-generated aerosols are complex mixtures of droplets and vapors that undergo dynamic physicochemical processes such as evaporation, condensation, and coagulation during transport through the respiratory tract (Schroeter et al., 2024). These devices can generate submicron particles and deliver relatively consistent doses of active substances per puff. The potential of ENDS as an alternative drug delivery platform has therefore attracted increasing scientific interest. Modern ENDS are also considered potentially more acceptable to patients, which may improve adherence (Buonocore et al., 2023).

Recent studies suggest that the familiar design and user-friendly operation of ENDS may enhance patient adherence compared to conventional inhalers, which often require precise coordination and inhalation technique for effective drug delivery (Steinberg et al., 2014). The ability of ENDS to generate submicron aerosols enables efficient deposition of active substances in the lower respiratory tract, potentially improving therapeutic outcomes (Mansour et al., 2024; Negi et al., 2023). Additionally, features such as adjustable airflow and temperature control allow for more individualized dosing strategies, thereby enhancing usability and compliance (Labiris & Dolovich, 2003; Ram et al., 2009). Furthermore, modeling studies indicate that ENDS constituents are primarily absorbed in the pulmonary region, where gas exchange with the bloodstream is most efficient, supporting their potential for systemic drug delivery. Moreover, compounds with lower volatility are mainly absorbed through droplet deposition, while higher-volatility compounds are absorbed through vapor-phase uptake, enabling relatively high overall retention of inhaled substances and suggesting suitability for a broad range of therapeutic formulations (Asgharian et al., 2024).

While these advantages position ENDS as promising alternatives to traditional inhalers—particularly for individuals with poor inhaler technique—further research is required to establish their safety and efficacy for delivering medications beyond nicotine. This remains controversial due to concerns regarding their potential misuse as unintended or illicit drug delivery systems (Breitbarth et al., 2018).

Several studies have demonstrated the capability of ENDS to deliver active pharmaceutical ingredients (APIs). Herbert et al. (2021) used fluorine-18 for radiolabeling applications, while Khaled et al. (2022) investigated the administration of fluticasone propionate via ENDS. Research also indicates that methamphetamine can remain stable in ENDS e-liquids at detectable concentrations (Breitbarth et al., 2018). Additionally, cannabinoids and 3,4-methylenedioxymethamphetamine (MDMA) have been successfully delivered using ENDS (Steinberg et al., 2014). For pulmonary applications, ENDS have been shown to deliver salbutamol with consistent dosing that is not significantly affected by device power variations (Labiris & Dolovich, 2003). Similarly, terbutaline delivery via ENDS produces a respirable dose with an aerosol size distribution comparable to that of a jet nebulizer over approximately 120 puffs (Labiris & Dolovich, 2003). Given these findings, ENDS may have therapeutic potential for respiratory diseases such as chronic obstructive pulmonary disease (COPD), where exposure to noxious particles, gases, and tobacco smoke contributes to progressive airflow limitation (Breitbarth et al., 2018; Ram et al., 2009).

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, initial maintenance treatment for COPD typically includes bronchodilators, such as long-acting β2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs), or short-acting β2-agonists (SABAs) such as salbutamol and short-acting muscarinic antagonists (SAMAs) as reliever medications. As adjunct therapy, mucolytics may be used in selected patients, particularly those with chronic bronchitis, productive cough, or frequent exacerbations (Global Initiative for Chronic Obstructive Lung Disease [GOLD], n.d.). Thiol-based mucolytics such as erdosteine, N-acetylcysteine (NAC), and carbocysteine are commonly used, particularly in patients with moderate COPD (FEV_1 50–79% predicted) (Calverley et al., 2019; Papi et al., 2020). In addition, bromhexine hydrochloride (BRM) has also been evaluated in COPD. Prabhu Shankar et al. (2010) conducted a multicenter, double-blind, randomized trial involving 426 patients with productive cough, including those experiencing acute exacerbations.

BRM is a mucolytic drug commonly administered orally. It has been shown to modify mucus properties and has demonstrated therapeutic benefits in various conditions, including xerostomia, nephropathy, asthma, and bronchitis (Bhagat & Bhagat, 2018). BRM has been reported to alter sputum characteristics in vitro; however, clinical trial outcomes have been inconsistent (Bhagat & Bhagat, 2018; Hughes, 1978). Orally administered bromhexine is rapidly absorbed but undergoes extensive first-pass metabolism, resulting in low absolute bioavailability of approximately 20–27%. Lung tissue concentrations of bromhexine two hours post-dose were 1.5 to 3.2 times higher in bronchial tissues than in plasma, while pulmonary parenchyma concentrations were 3.4 to 5.9 times higher than plasma levels (DrugBank, n.d.). Although these pharmacokinetic properties are promising, the effectiveness and safety of inhaled BRM delivered via ENDS have not yet been extensively evaluated in clinical settings, and further studies are required to establish its clinical utility.

The urgency of this research stems from the growing need for alternative drug delivery systems that improve patient compliance and therapeutic outcomes. Despite the potential of ENDS technology for drug delivery, significant gaps remain in the literature. Most studies have focused on nicotine delivery, with limited exploration of therapeutic agents such as mucolytics via ENDS. Furthermore, integrated evaluations combining experimental quantification of drug delivery with computational modeling of molecular interactions and ADMET properties remain scarce. This study addresses these gaps by investigating the potential of ENDS to deliver BRM as an inhaled mucolytic therapy.

The novelty of this study lies in its integrated approach, combining experimental quantification of BRM delivery via ENDS using HPLC-MS analysis with computational molecular docking, molecular dynamics simulations, and ADMET predictions to evaluate BRM interactions with the β2-adrenergic receptor. This multidisciplinary framework provides both empirical evidence of drug delivery feasibility and mechanistic insight into receptor-level interactions, offering a comprehensive evaluation of ENDS-based BRM delivery potential.

This study aimed to investigate the feasibility of delivering free-base BRM via inhalation using e-liquid formulations aerosolized through ENDS technology as a mucolytic therapy. This objective was achieved through mass spectrometry analysis to confirm the presence of BRM and quantify its concentration under different experimental conditions. In addition, molecular

docking simulations were conducted to compare the interaction of BRM with salbutamol, as a standard inhaled drug.

METHOD

Materials

Bromhexine hydrochloride (BRM) (purity 99.83%) was purchased from Merck (Darmstadt, Germany). The solvents (propylene glycol and vegetable glycerin) used for the formulation of e-liquid were obtained as food-grade supplied by local suppliers. Hypergrade solvents (acetonitrile and methanol) for HPLC-MS analysis were purchased from Merck.

Instrumentation

Waters Xevo-G2 XS QToF (Waters, Milford, Massachusetts, USA) equipped with C18 BEH column (2.1 × 50 mm, 1.7 μm) as the stationary phase was used for Multiple Reaction Monitoring (MRM) analysis. The acetonitrile (B) and ultrapure water (A) supplemented with 0.1% formic acid were used as the mobile phase. A gradient system starting from 5% B held for 1 minute, followed by increasing to 100% B in 12 minutes and holding for 3 minutes at 100%, and finally bringing back to the initial conditions in 3 minutes was applied.

Procedure

Formulation of e-liquid

The e-liquid was prepared by accurately weighing 1 gram of BRM (98.7% purity) and dissolving it in a mixture of propylene glycol (PG) and vegetable glycerin (VG). The solvents were combined in a 1:1 (v/v) ratio, after which the active compound was gradually introduced under continuous stirring to ensure complete dissolution. The final solution volume was adjusted to 100 mL, corresponding to a concentration of 1% (w/v) active ingredient.

Preparation of standard bromhexine hydrochloride (BRM)

The stock solution of BRM 1000 μg/mL was prepared by weighing 5 mg of BRM and dissolving it in 5 mL of methanol (hypergrade) under gentle vortexing until complete dissolution was achieved. From this stock, two independent sets of standard BRM samples were freshly prepared, covering concentration ranges between 2 to 6 ng/mL and 10 μg/mL to 50 μg/mL, and were used to establish the standard calibration curve.

Sample preparation

The available ENDS devices (MOVI® MARK ZERO) in the market were purchased, including the cartridge (0.8 ohm). An aliquot of the formulated e-liquid (1 mL) was carefully dispensed into the cartridge. The generated aerosol from the ENDS device was collected using a free-fat cotton (size and mass will be checked) trapping system to capture the vaporized matrix. After five puffs, the BRM from entrapped aerosol residue was extracted from the matrix by dissolving the cotton in 2 mL of methanol (hypergrade) with the aid of sonication for 5 minutes to ensure complete leaching of the analyte. After sonication, the methanol was concentrated under vacuum to 1 mL.

Determination of the Limit of Detection (LoD) and Determination of the Limit of Quantification (LoQ)

The sensitivity of the HPLC-MS method was assessed by calculating the limit of Detection (LoD) and the limit of Quantification (LoQ). Both values were estimated from replicate analyses of low-concentration standards under the same experimental conditions. The LoD was calculated according to Equation (1).

$$LoD = 3.3\ x\ \left(\frac{SD\ of\ intercept}{slope}\right) \quad (1)$$

While the LoQ was calculated according to equation (2)

$$LoQ = 10\ x\ \left(\frac{SD\ of\ intercept}{slope}\right) \quad (2)$$

Computational Simulations

Molecular docking was performed using Autodock Vina run through the WSL system. The receptor protein target chosen was β-2 adrenergic receptor (β2AR), covering anti-inflammatory response at the bronchial smooth muscle when binding with its agonist. The full-length human β2AR structure was obtained from the Protein Data Bank (PDB) database (ID: 2RH1). The ligands BRM and salbutamol (as standard) were obtained from PubChem. Proteins were prepared by removing non-protein components (such as water, carbohydrates, lipids, etc.), and protein residues were inserted using a Modeler 10.5 based on their FASTA files. The polar hydrogens and charges were then added using AutodockTools. Similarly, the ligands were prepared using AutodockTools in flexible mode.

Molecular Dynamics (MD) simulation was conducted utilizing the open secure shell (SSH) connected to HPC BRIN Mahameru, as the national research and innovation agency in Indonesia.

The simulations were carried out on the B2AR protein, B2AR with BRM, and B2AR with SBM, and ran for 100 nanoseconds (ns) in duration with a trajectory graph spanning 105 picoseconds (ps). During the preparation, the docking results were taken, and the ionization state was adjusted using PROPKA calculation and pH conditions to 7.4 with the PDB2PQR website (https://server.poissonboltzmann.org/pdb2pqr). This study utilized the Gromacs MPI 2023.3 software with the Amber forcefield (ff99SB-ILDNP) owned in the system. The Protein topology file was made by the Gromacs Mpi 2023.3 program with SPC/E as water molecules. BRM and SBM were preprocessed by adding General AMBER Force Field 2 (GAFF2) from Antechamber using AmberTools23. The ligand topology files were aligned to adapt at the Gromacs environment using ACPYPE (AnterChamber Python Parser Interface). The parameter conditions of the system were regulated by equilibrating the temperature to 310.15 K and the pressure to 1 atm in the NVT and NPT scripts. The script was run for 1 ns with a velocity rescaling thermostat with a time constant of 0.1 ps and the pressure parameters with Parrinelo-Rahman barostat at a time constant of 2 ps. The Particle Mesh Ewald (PME) method was utilized to regulate the electrostatic interaction.

Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET) Prediction

Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET) Prediction was conducted using machine learning https://biosig.lab.uq.edu.au/deeppk/prediction. This website was run by entering SMILES of SBM (CC(C)(C)NCC(C1=CC(=C(C=C1)O)CO)O) and BRM (CN(CC1=C(C(=CC(=C1)Br)Br)N)C2CCCCC2).

RESULT AND DISCUSSION

Method Development and Validation Results

Since the ENDS relied on its properties to convert the e-liquid into an aerosol state, most of the experiments on measuring the concentration were conducted using the next-generation impactor (NGI) (Khaled et al., 2022). The device was set to aerosolize the e-liquid, then trapped with cotton puffs and measured the concentration using high-performance mass

spectrometry (HPLC). Two sets of standard bromhexine Hydrochloride (BRM) were prepared as the representative e-liquid. These two standards were chosen to accommodate the low dose of puffs and the large dose of puffs after the e-liquid of the pod was empty and needed to be refilled.

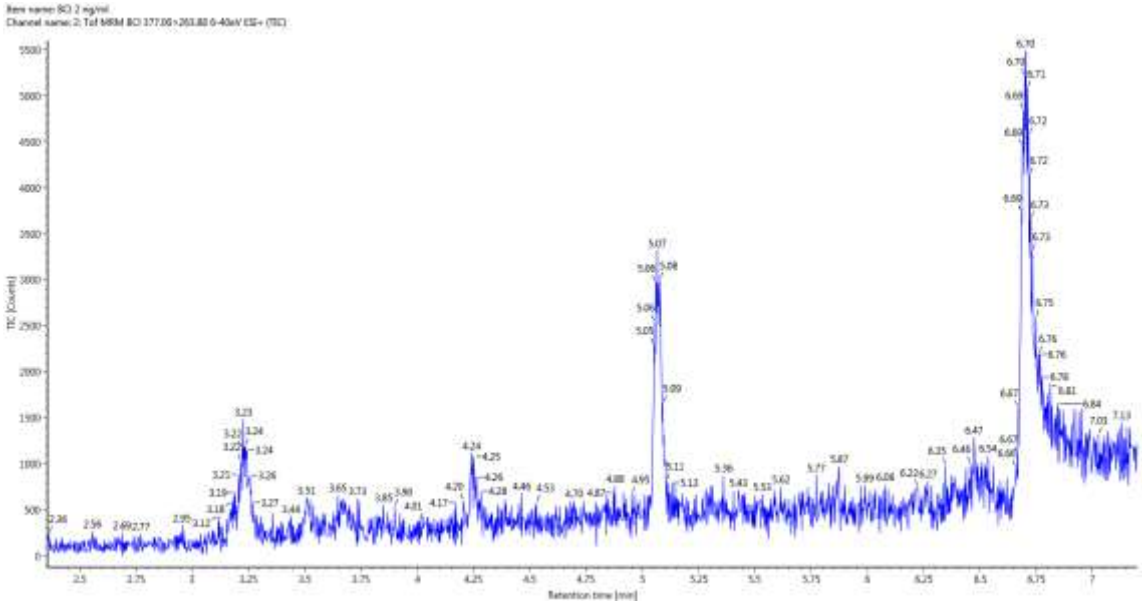

Figure 1. The example of the mass chromatogram of BRM (2 ng/mL) in MRM mode. The BRM was eluted at 5.06 minutes

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The quantification of BRM samples followed the method from El-Naem and Saleh (2021) by using multiple reaction monitoring techniques. The first set of standards ranged from 2 to 6 ng/mL and had a correlation coefficient (r^2) of 0.9931, as shown in Figure 2a. The limit of detection (LoD) is the lowest analyte concentration likely to be reliably distinguished from the limit of blank (LoB), and the limit of quantification (LoQ) is the lowest analyte concentration that can be quantitatively detected with a stated accuracy and precision (Handbook of Immunoassay Technologies, n.d.) were tabulated in Table 1. The LoD and LoQ of the instrument were found to be 0.3014 ng/mL and 0.9138 for standard set 1, which is in agreement with the results from El-Naem and Saleh (2021). The initial measurement of the first sample with only one puff was unsuccessful (data not shown); this could have happened due to the concentration of the sample being lower than the LoD. Analysis of the sample after five puffs revealed that the content of the BRM was found to be 3.3156 ng/mL.

Table 1. The limit of detection (LoD) and limit of quantification of the two sets of standards

No.	Standard set 1 (2 to 6 ng/mL)		Standard set 2 (10 to 50 µg/mL)	
	LoD (ng/mL)	LoQ (ng/mL)	LoD (µg/mL)	LoQ (µg/mL)
1	0.3015	0.9138	1.1718	3.5510

After successfully detecting the BRM in the trapped aerosols e-liquid, the calculations of the efficiency of the ENDS were performed by measuring the leftover e-liquid in the pod after the cartridge was empty. To do this experiment, the second set of BRM standards was established at a higher concentration i.e., 10 to 50 µg/mL, for comparison.

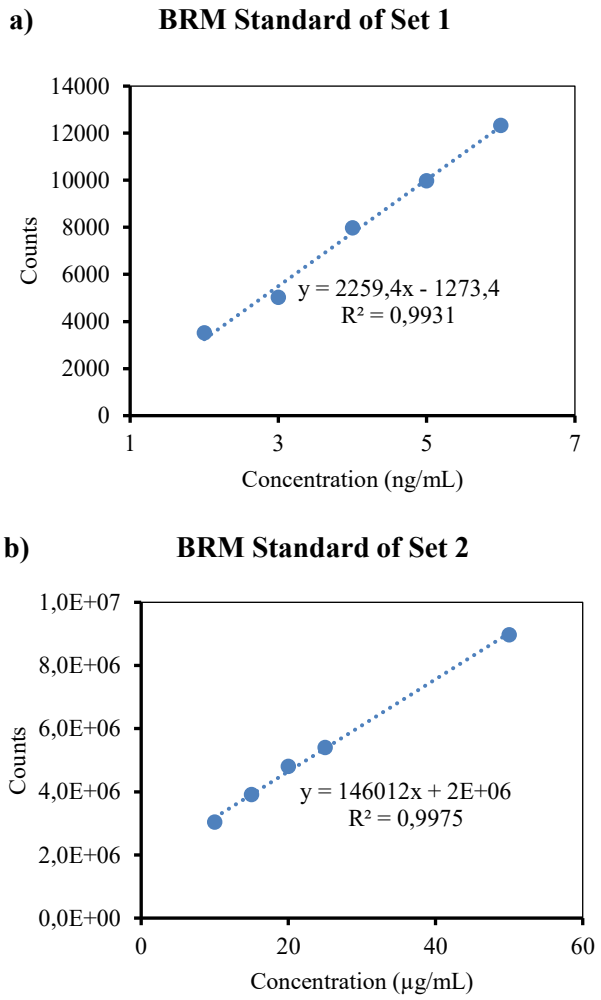


Figure 2. Calibration curve of a) the BRM standard samples of set 1 with the lowest concentrations ranged from 2 to 6 ng/mL and b) the BRM standard samples of set 1 with the highest concentrations ranged from 10 to 50 µg/mL.

After discharging the pod from the cartridge, preparing and measuring the sample, the residue of the BRM in the pod was calculated to be 19.3029 µg/mL. According to our experimental setup, the theoretical concentration in the BRM for each mL of e-liquid was 10.000 µg/mL. By applying the calculation of the BRM residue in the pod, the efficiency of the ENDS devices was calculated to be 99.80%. The experiment demonstrated that ENDS was able to deliver aerosolized BRM by detecting it using a mass spectrometer. The pharmacokinetic data for BRM obtained during the COVID-19 pandemic revealed that the oral administration of 8 mg of BRM shows the blood concentration of 22.50 ± 7.50 µg/mL, while the cough syrup normally contains about 4 mg of BRM in each 5 mL. Whereas in our ENDS-based experiment, five puffs produced only 3.3156 ng/mL, which means below therapeutic exposure. This discrepancy becomes the challenge of achieving pharmacologically relevant dosing through ENDS. Previous studies on nicotine have shown that aerosol deposition and systemic absorption are sensitive to flux and puff topography. A study by Bono et al. (2025) explained that low-flux ENDS required more puffs and functioned as substitutes for cigarettes, while high-flux ENDS delivered greater suppression of withdrawal but were less tolerable because of irritancy. These results implied that in order to maximize ENDS function as a therapeutic drug delivery will require balancing device parameters and patient usability to

achieve both efficacy and adherence. Regarding this capability, the in-vivo experiment on delivering the API rather than using nicotine as a model, which has been done in several publications, is necessary to prove the possibility of using ENDS as an alternative device for drug delivery systems.

Computational Simulation Analysis

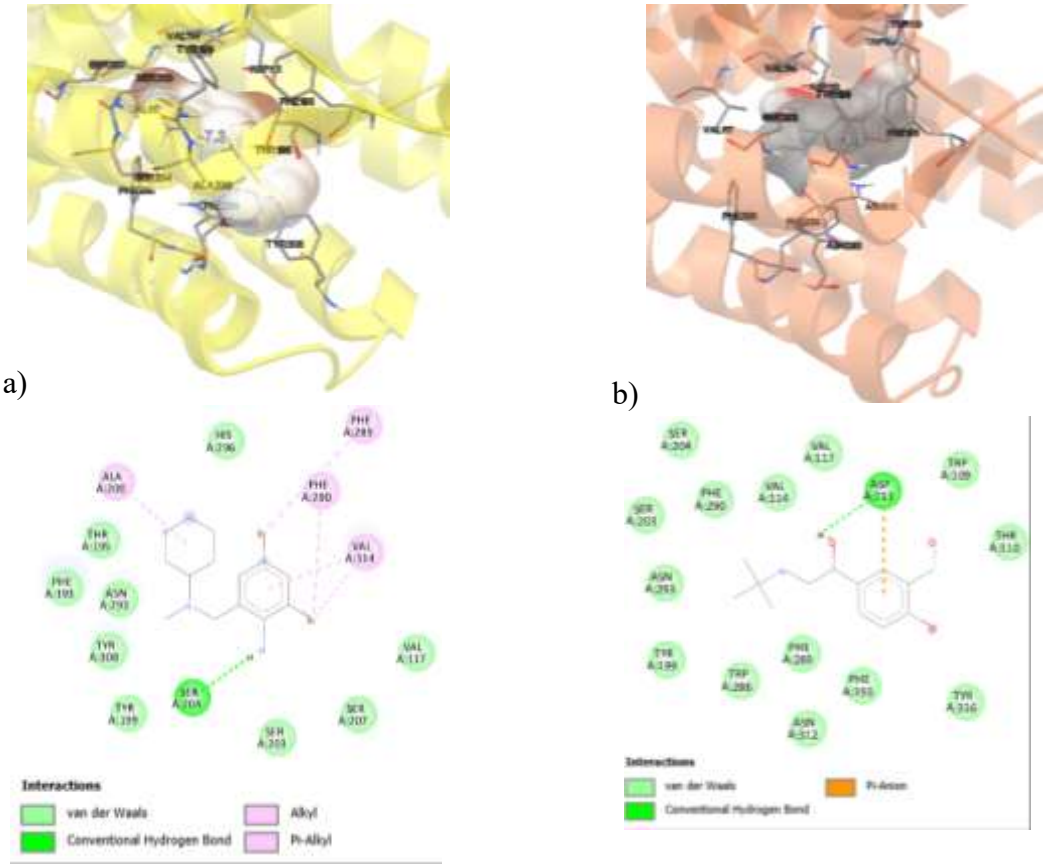


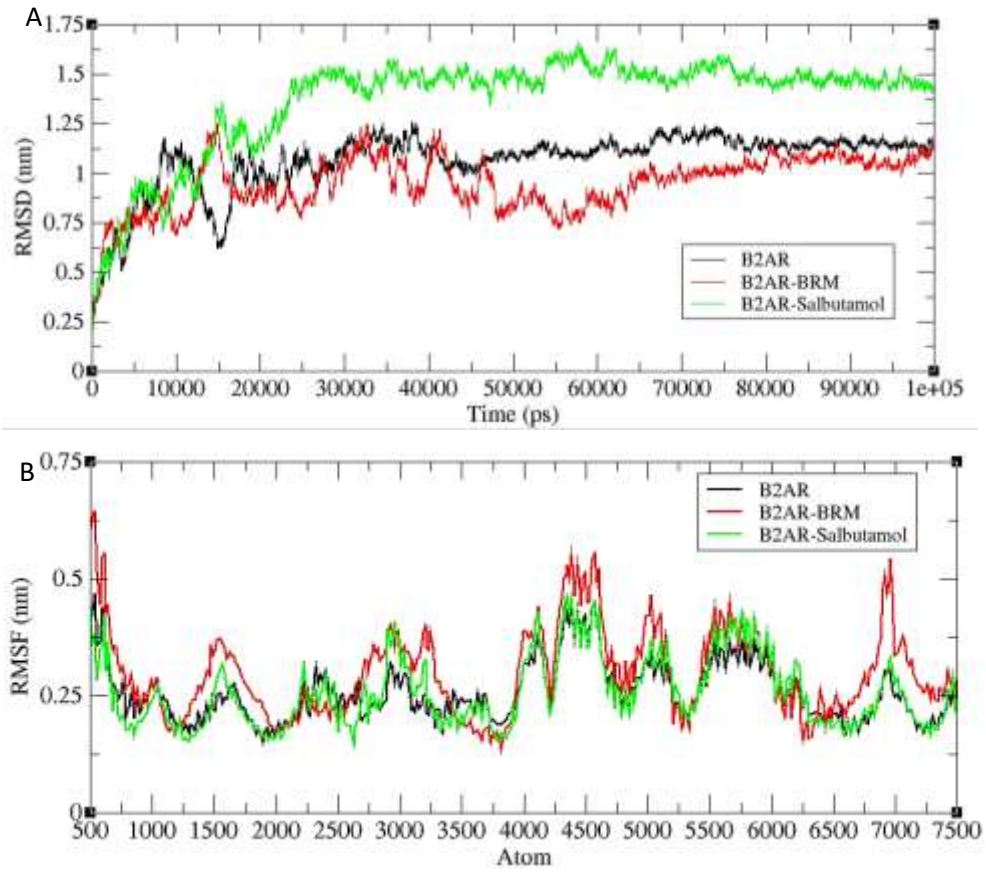
Figure 3. Molecular docking visualizations of a) BRM and b) Salbutamol

Understanding the interaction between the ligand and the protein is necessary to determine the therapeutic effect of a drug on the body [22]. This simulation analysis was conducted using a molecular docking method targeting the active receptor site, which is approximately one-third of the protein sequence [23]. The interaction between β2AR and the ligand involves several amino acid residues that modulate the agonist effect. It has been reported that agonists tend to bind with amino acids, including Asp113 from TM3, Ser203, Ser204, and Ser 207 located on TM5, Asn293, Phe259, and Phe290 in TM6, and Tyr 308 in TM7 [23–25]. In addition, there are also interactions with His93, Trp109, Val114, Val117, Asn312, Ser316, Trp313, Asn312, and Tyr316 interact [26].

The ligand position was determined based on the lowest affinity value with an RMSD value of about 2 Å at the active site coordinate. BRM has a lower affinity value than salbutamol, with a value of -7.3 kcal/mol compared to -8.1 kcal/mol. Although the resulting value is weaker than salbutamol, this value is not significantly different and is still classified as a good value for protein-ligand complexes [27]. As a standard, salbutamol interacts with the agonist active side of the receptor, where two Asp113 amino acid interactions occur in the form of hydrogen bonds that bind to the hydroxyl (-OH) group on the ethanolamine chain and pi-anion interaction

with the benzene ring. Previous studies have reported several van der Waals (VDW) interactions on amino acid residues, including Trp109, Val114, Val117, Ser203, Ser204, Phe290, Asn293, Asn312, and Tyr316.

Compared with salbutamol, BRM also exhibits interactions with the active side of the receptor. As shown in Figure 3a, a hydrogen bond exists between the amine group and Ser204 in BRM, which exhibits the strongest affinity-forming bond. The two benzylamine rings have ionic interactions by forming Pi-Alkyl bonds with Ala200 and Val114, for which Val114 also has double ionic bonds with bromine groups. Alkyl interactions with Phe289 and Phe290 with bromine groups at different positions reinforced the ionic bonds. Noncovalent bonds are also supported by VDW interactions, strengthening the protein-ligand complex with Vall117, Phe193, Thr195, Ser203, Ser207, Asn293, His296, and Tyr308. The simulation demonstrated interactions between BRM and the active agonist side of β2AR, confirming the modulation of anti-inflammatory activity through the β2AR receptor on the bronchial membrane.



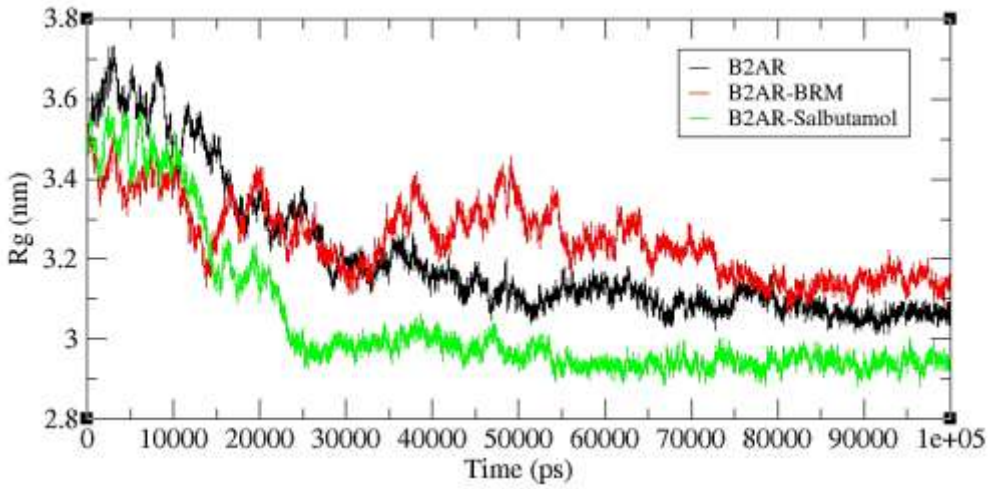


Figure 4. Trajectory analysis of B2AR, B2AR-BRM, and B2AR-SBM (A) RMSD dan (B) RMSF on 100 ns dynamics simulations.

The Root Mean Square Deviation (RMSD) in molecular dynamics simulations shows the average deviation over the simulation time (100 ns) with the backbone of the protein residues as the reference. RMSD analysis between the protein and ligand-protein complexes was performed to determine the presence or absence of deviations and the stability and similarity of the structures during the simulation. Figure 4-A shows the trajectories of the three different systems. B2AR in the black graph shows the RMSD trend of the single protein or when it does not bind to the ligand. The B2AR protein stabilizes at an RMSD of approximately 40 ns at 1 nm. The red graph shows the deviation trend in the B2AR and BRM complexes; however, the graph appears to be less stable, with a fluctuation of approximately 0.25 ns. The interaction with the salbutamol standard increased the RMSD up to 1.5 nm but tended to be more stable than that with BRM.

The Root mean square fluctuations (RMSF) determine the deviation of the atomic position from the original point; the higher the fluctuation, the more flexible the atom. A similar pattern can be observed for the B2AR and B2AR-Salbutamol complexes in Figure 4-B. Meanwhile, BRM gives a more unstable residue interaction. In the atomic number range of 1250-2000 at TM2-TM3, it occurs with fluctuations increasing by about 0.15 nm in B2AR-BRM compared to B2AR. A high fluctuation occurs in the GPCR activation region corresponding to TM5-TM6 in the atomic number around 4000-5000. Furthermore, the highest fluctuation increase was observed at TM7 around atomic number 7000. In GPCRs such as β2AR, the transmembrane regions play a crucial role in regulating conformational change that triggers receptor activation. Fluctuations in TM5 and TM6 are particularly significant because outward movement of TM6 and rearrangement of TM5 are essential steps in creating the binding pocket of the G protein and thereby stabilizing the active site of the receptor. Increased fluctuations in these helices, as observed in BRM, indicate flexibility that suggests weaker stabilization of the active conformation. In line with partial agonist behavior, decreased signaling effectiveness might result from lower stability of the active conformation (Lu et al., 2021).

Because both complexes are unstable with the BRM, the residual RMSF value corresponds to the observed RMSD. This graph shows that the interaction with BRM increases

flexibility in several protein domains that allow BRM to act as a partial agonist or as an allosteric modulator. This result is supported by the radius of gyration (Rg) graph in Figure 4-C, which shows the atomic distance from the central atom with a value of approximately 2.9 nm occurring from 25 to 100 ns, where salbutamol is still superior to others in shortening the atomic distance, which makes the protein more rigid and stable. The interaction of B2AR with BRM increases Rg, indicating system instability.

ADMET Prediction

Based on the ADMET prediction results generated by https://biosig.lab.uq.edu.au/deeppk, SBM and BRM are equally absorbed through the enteric route and show efficacy of more than 50% at a bioavailability of 50%. BRM is not a P-glycoprotein (P-gp) substrate, allowing for broader biological penetration than SBM. This implies that BRM will have greater opportunities to be retained in the body's systemic tissue, affecting multiple areas. The distribution in the BBB shows extreme BRM penetration (Pr = 0.999), indicating the possibility of penetration through the barrier during the inhalation process. A plasma protein binding of 24.55 in a BRM also signifies that the drug tends to bind with protein during systemic circulation, favoring delayed movement and an increased chance of systemic side effects. Long-term use of neither drug showed mutagenicity, even at low doses (MTRD < 0.477). Both BRM and SBM were found to be toxic to the pulmonary system, even SBM is capable of alleviating bronchodilation symptoms. These compounds may be highly active in the respiratory tract and exert a deep impact.

Generally, the ADMET predictions indicate different characteristics, but both can be possible candidates for co-administration via inhalation. The SBM drug exhibits rapid action and minimal absorption into the bloodstream, making it suitable for inhaled bronchodilators, whereas the BRM possesses features that enable it to function as an inhaled mucolytic, thereby enhancing mucus removal in patients with excessive mucus production [15, 31].

Table 2. ADMET Prediction data of salbutamol and bromhexine

Compounds		Salbutamol	Bromhexine
Adsoprtion	Human Intestinal Absorption/ Pr	Absorbed/0.966	Absorbed/0.981
	Human Oral Bioavailability 50%/Pr	Bioavailable/0.529	Bioavailable/0.717
	P-Glycoprotein Substrate/Pr	Substrate/0.585	Non-Substrate/0.252
Distribution	Blood-Brain Barrier/Pr	Non-Penetrable/0.003	Penetrable/0.999
	Plasma Protein Binding	-6.89	24.55
	Steady State Volume of Distribution	2.78	5.14
Metabolism	CYP 2D6 Inhibitor	Non-Inhibitor	Inhibitor
	CYP 2D6 Substrate	Non-Substrate	Substrate
	CYP 3A4 Inhibitor	Non-Inhibitor	Non-Inhibitor
	CYP 3A4 Substrate	Non-Substrate	Non-Substrate
Excretion	Clearance	7.09	10.8
	Cation Transporter 2/Pr	Non-Inhibitor/0.099	Inhibitor/0.671
	Half-Life of Drug	< 3hs (Low Confidence)	< 3hs (High Confidence)
Toxicity	AMES Mutagenesis/Pr	Safe/0.136	Safe/0.002

Max. Tolerated Dose	-0.27	-0.07
Respiratory Disease/Pr	Toxic/0.999	Toxic/0.975

*Note: Pr = Probability

CONCLUSION

This study revealed that ENDS could deliver bromhexine hydrochloride (BRM) as an active pharmaceutical ingredient in the form of an e-liquid formulation. The HPLC-MS concentration assay detected the presence of BRM after five puffs of delivery. ENDS devices may deliver APIs by aerosolizing the drug into respirable particles for targeted pulmonary delivery. This targeted approach using ENDS is non-invasive and user-friendly, which may enhance patient compliance. The possibility of a therapeutic effect is further supported by the interaction of BRM as an API with the β2-adrenergic receptor (β2AR) at its active binding site. The binding affinity of BRM is comparable to that of salbutamol (SBM), a standard bronchodilator, and shows several hydrogen bond interactions.

However, molecular dynamics simulations indicate that the BRM–protein complex is not fully stable over time, although BRM may act as an allosteric modulator or partial agonist. The lack of a stable dynamic complex does not necessarily diminish the potential clinical relevance of inhaled BRM delivered via ENDS. Despite ongoing controversy surrounding ENDS technology, its potential application as a drug delivery platform should not be overlooked.

Additional studies are required to validate the clinical feasibility of The Study of Delivery Medicine Using ENDS Device: A Bromhexine Study Case, particularly through in vitro lung cell models and/or in vivo experiments to evaluate the effects of aerosolized BRM on the pulmonary system and to further elucidate the underlying mechanisms of action.

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