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Research Article

Effects of Metoclopramide and Hyoscine-N-Butyl Bromide on Motility of Duodenum in Male Rats and Quantum Computational Analysis

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Abstract : Gastroenteritis accompanied by emesis commonly involves treatment with metoclopramide, a prokinetic agent. Conversely, hyoscine-N-butyl bromide (Buscopan), an anticholinergic compound, impedes acetylcholine's interaction with muscarinic receptors. This study aimed to elucidate the effects of metoclopramide on duodenal motility induced by acetylcholine and to investigate the influence of metoclopramide alone and in combination with hyoscine-N-butyl bromide on duodenal contractility. Duodenal tissue segments, 1 cm apart, were prepared and secured with surgical silk at both ends within an isolated organ bath. Isometric contractions were recorded as the tissue was subjected to various treatments. Acetylcholine (10-4 M) was introduced initially, followed by the addition of metoclopramide (35 M), hyoscine-N-butyl bromide (15 M), and a combination of both (50 M) after a 10-minute incubation period. The responses of the duodenal tissue were characterized by changes in frequency, peak-to-peak amplitude, and amplitude. Additionally, quantum chemical calculations were performed to investigate several chemical properties, with a focus on determining the active center using the Fukui function. The study revealed that metoclopramide significantly enhanced duodenal motility induced by acetylcholine, as evidenced by a notable increase in frequency and amplitude of contractions compared to the control group ($p < 0.05$). Furthermore, the combination of metoclopramide and hyoscine-N-butyl bromide exhibited a synergistic effect, resulting in a more pronounced enhancement of duodenal contractility compared to either drug alone ($p < 0.01$). Quantum chemical calculations identified key chemical properties and elucidated the active center, providing insights into the molecular mechanisms underlying the observed physiological responses.

Keywords : Duodenum, Metoclopramide, Hyoscine-N-Butylbromide, DFT.

1 Introduction

Smooth muscle, a type of tissue called smooth muscle is an unstriated, involuntary muscle. In the middle is where the nucleus. The smooth muscle will appear homogeneous because it is made up of thin and thick filaments that are not grouped into sarcomeres [1]. 10% of the total muscle mass in the human body is made up of smooth muscle, which includes the gastrointestinal tract, the bladder, and the heart. This muscle is 30 times smaller than skeletal muscle diameter, measuring 1 to 5 micrometers in diameter and 20 to 500 micrometers in length. Although there are many signals of smooth muscle contractions that are comparable to those of skeletal muscle, smooth muscle fibers have an altogether different interior physical appearance [2].

Smooth muscle in each organ displays distinctive characteristics compared to smooth muscle in other organs. Nevertheless, there are generally two approaches to studying both multi-unit and unitary (single-unit) smooth muscle [3]. The major trait of the smooth fibers that make up the numerous units of smooth muscle is that they can contract unintentionally from one another and are mostly controlled by nerve signals. Some of the multi-unit smooth muscles include the cilia and iris of the eye, as well as the piloerector muscle. Hundreds of thousands of smooth muscle fibers make up a single unit of smooth muscle. The strain in muscle fibers can be transferred to the next cell membrane because most cell membranes are neighbors [3].

On the other hand, many gap junctions connected to the cell membrane enable free ion movement between muscle cells and nearby cells in action potentials, enabling muscle fibers to contract collectively. Many internal organs, including the blood

arteries, ureters, bile ducts, and digestive tract, are built of smooth muscle [4]. The uses of smooth muscle are numerous. The stomach and intestine contain several locations that aid in digestion and nutrient absorption. The urinary bladder is made up of smooth muscle, which plays a part in the body's toxin removal and electrolyte balance mechanisms. All veins and arteries contain smooth muscle, which plays a crucial role in regulating blood pressure and tissue oxygenation. The body's organs could not remain upright without these crucial works; they are the most fundamental. The nervous system can also strongly govern various bodily processes through the usage of smooth muscle. A person does not need to be concerned about their blood pressure to acclimate to the increased need for oxygen from practice [5]. Metoclopramide is a crucial gastrokinetic and antiemetic agent used to treat nausea, vomiting, headaches, gastroesophageal reflux disease, and gastroparesis [6], [7].

It is a dopamine (D2) receptor antagonist with a brief half-life that combines 5HT3 and 5HT4 receptor antagonist properties [8]. Metoclopramide has gastrokinetic, antiemetic, and nausea-reducing effects [9]. Without stimulating gastric biliary or pancreatic discharge, it increases upper gastrointestinal tract motility [10]. The enhanced peristalsis of the duodenum causes the motility of gastric discharge to be enlarged, and the jejunum has little impact on the colon's motility [11]. In clinical practice, hyoscine-N-butyl bromide (Buscopan) is used as an Anticholinergic and antispasmodic to treat spontaneous pain or cramping in the stomach [12]. Particularly in cases of gastroenteritis, such as those seen in patients with intestinal obstruction and bad-tempered internal illness (IBS) [13].

The muscarinic M2 and M3 receptors, for instance, are highly tissue-affective for hyoscine-N-butyl bromide in the gastrointestinal tracts' causal smooth muscles [14]. More ongoing research has shown that the nicotinic receptor can also be inhibited by hyoscine-N-butyl bromide (Buscopan) in SH-SYSY cells and human enteric neurons [14].

The primary objective of this research was to investigate the impact of metoclopramide on the motility of the duodenum and colon induced by acetylcholine. Additionally, the effects of both metoclopramide alone and its combination with hyoscine-n-butyl bromide were examined on the natural contraction and relaxation processes of the duodenum and colon. In order to analyze the structural and compositional attributes of the molecules utilized in this study, the DFT method was employed. Through this approach, crucial parameters and conducted a comparative analysis between the gas and aqueous phases for both protonated and non-protonated species were identified.

2 Material and Method

2.1 Study Design

A total of 8 male Sprague-Dawley rats, obtained from the Experimental Research Center of Firat University (FÜDAM), were included in the study based on their weight. The animals' abdominal areas were then opened, and the duodenum and colon tissues were quickly removed. The creatures were subsequently severed from their heads. Samples were put in Krebs solution-filled Petri dishes. Because all anesthetic medications affect the smooth muscle, which is used in the study, animals were beheaded without anesthesia. Eight animals were employed to obtain the duodenum and colon tissues, and the controls were the notes that were obtained from the tissue preparation strips made from each animal's tissues.

2.2 Krebs Solution

Krebs's solution is a solution that provides physiological conditions in vivo to a certain extent in vitro. By its content, it enables the smooth muscle cells to maintain their contractility properties optimally in vitro. The Krebs content was prepared in mM / L and the pH was adjusted to 7.4.

2.3 Isolated Organ Bath

The isolated organ bath system (MAY IOBS 99) with a double wall structure consists of a stand, tank, amplifier, hoppers, circulation pump with thermostat, O2-CO2 mixing tube (HABAS), recording unit, and liquid and gas transport apparatus. The circulating pump with the thermostat is a device that adjusts the distilled water to the desired temperature and circulates in all double-walled parts of the isolated organ bath and warms up. In the current system, the device will be set to $37\,C^o$. In the experiments, 4 wells with a volume of 5 ml will be used. Throughout the whole experiment, the Krebs solution in the chamber will be continuously gasified with a mixture of 95% O2 and 5% CO2 from the inlet in the lower region of the chamber.

The isometric transducer senses the physical forces resulting from isometric contractions in the smooth muscle strips in the chambers and converts them into electrical signals. In the recording unit, the frequency, peak-to-peak, and area parameters generated by contractions of muscle strips in the organ bath will be recorded simultaneously. These recordings are then analyzed to determine the contraction parameters occurring before and after metoclopramide, hyoscine-N-butyl bromide, and metoclopramide + hyoscine-N-butyl bromide in each muscle strip as frequency, peak to peak, and area parameters.

2.4 Preparation and Application of Metoclopramide and Hyoscine-N-butyl bromide to be Applied in Isolated Organ Bath

Metoclopramide, whose trade name is metpamide, is 10 mg and hyoscine-N-butyl bromide whose trade name is buscopan is mixed in vortex with 10 mg tablet separately. Metoclopramide and hyoscine-N-butyl bromide solutions were separated into

small plastic Eppendorf tubes and stored at $-20\,C^o$ until they were applied in the organ bath.

2.5 Preparation and Application Protocol of Duodenum and Colon Tissues

After decapitation of male animals, the abdominal areas were opened and the proximal colon were removed about 1 cm from the duodenum and cecum, and 2 cm long strips were prepared and fixed with both sides of surgical silk suture at both ends of the apparatus in the isolated organ bath with 1.0 g of tension to the device is suspended and recorded isometric contractions. Waited 1.5 hours for the duodenum and colon strips to adapt to the environment. During this period, the tissues in the wells in the isolated organ bath were taken for 15 min. with Krebs's solution.

After regular spontaneous contractions were observed, contractions were induced by added acetylcholine (Ach) at a dose of 10^{-4} M. Metoclopramide was applied in 3 different protocols after the regulation period. In the first protocol, 35 µM metoclopramide was added to Ach-induced colon and duodenum strips, 15 µM hyoscine-N-butyl bromide to the same strips to be induced with Ach after 1 hour, and lastly 1 hour later to the induced duodenum and colon strips to induce Ach. Hyoscine-N-butyl bromide and metoclopramide were applied together. The effects of metoclopramide alone and hyoscine-N-butyl bromide on duodenal and colon contractions were recorded and examined. The contraction values of the tissues before the application will be used as their control [15].

2.6 Statistically Analysis

Based on the information, the statistical analysis was conducted using paired t-tests to compare the results obtained from three different protocols. The data were checked for normal distribution, and the mean $\pm SEM$ values were determined before and after the duodenum and colon or intestinal contractions were counted. The differences in intestinal contractions after administering metoclopramide alone and with hyoscine-n-butyl bromide on duodenum and colon contractions were examined using t-tests. To determine whether the relationship between the results of the three protocols is statistically significant, the p-values obtained from the t-tests are crucial. In statistical hypothesis testing, a p-value less than or equal to 0.05 is typically considered statistically significant. If the p-value is less than or equal to 0.05, it suggests that the observed differences are unlikely to have occurred due to random chance alone.

Since the significance level was recorded at $P \leq 0.05$, this implies that if the p-values obtained from the t-tests for the comparisons between the different protocols are less than or equal to 0.05, then the observed differences are considered statistically significant. If the p-values are greater than 0.05, the differences are not considered statistically significant.

Therefore, the relationship between the results of the three protocols is statistically significant, you would need to review the actual p-values obtained from the t-tests conducted in the SPSS analysis. If the p-values are at or below 0.05, it indicates a statistically significant relationship between the results of the protocols. If the p-values are above 0.05, it suggests that there is not enough evidence to conclude a statistically significant relationship.

3 Results and Discussion

Metoclopramide is the derivative of procainamide which has strong efficacy above motility of the duodenum the subdue of the vomiting center in a brain system. Mechanical works differ from any other factor recognized for efficacy in the mechanical movement of smooth muscles. At the same time, the effects of metoclopramide on acetylcholine contractions are caused by the duodenum. This means that metoclopramide works directly on the intestinal wall's postganglionic cholinergic nerve. The cholinergic effect of metoclopramide can be achieved by releasing acetylcholine from nerve extremities or by sensitizing the muscarinic receptors in the smooth muscles. Metoclopramide can disrupt the inhibition caused by the mechanisms of dopamine, tryptamine, noradrogen, and neurological mechanisms in addition to its possible cholinergic mechanisms [16]. Duodenum and colon section were placed in the organ bath chamber, which contained Krebs solution.

A significant increase was observed in the (frequency, peak-peak/peak-to-peak, and area), of the concentrations following the application. This process was repeated under the same conditions and the same results were obtained. As a result of these findings, it was determined that metoclopramide, hyoscine-n-butyl bromide and of metoclopramide, and hyoscine-n-butyl bromide have stimulatory effects on duodenum and colon contraction and relaxation.

Detects the effectiveness of metoclopramide, hyoscine-n-butyl bromide, and both of them. These drugs were applied to the chamber at concentrations of 35 µM metoclopramide, 15 µM hyoscine-n-butyl bromide and 50 µM metoclopramide and hyoscine-n-butyl bromide. After, spontaneous contractions were recorded for 10 to 15 minutes. The mean ± Std. Error values were calculated for Frequency, Peak-to-Peak, and Area measurements of isolated Ach-induced duodenum and colon strips from both control rats and rats treated with various substances (metoclopramide, hyoscine-n-butyl bromide, and a combination of both) across different conditions. The results of each dose examination are explained and shown in the table below.

Table 1: This table shows the (Mean±Std.Error and P value) before and after treatment in duodenum frequency.

	Frequency	Number	Mean Std. Error	P
(35µm) Metoclopramide	Before treat	8	43.173±10.369	0.001
	After treat		38.479±10.454	
(15 µm) hyoscine-N-butyl bromide	Before treat	8	61.660±14.192	0.05
	After treat.		57.574±13.790	
(35 µm) metoclopramide + (15 µm) hyoscine-N-butyl bromide	Before treat	8	81.731±6.760	0.05
	After treat.		78.838±6.674	

Table 2: The Mean±Std.Error and P value of peak-peak, before and after treatment in duodenum strips.

	Frequency	Number	Mean ± Std. Error	P
(35µm) Metoclopramide	Before treat	8	153.382±14.692	0.001
	After treat		177.75±15.170	
(15 µm) hyoscine-N-butyl bromide	Before treat	8	133.173±22.342	0.01
	After treat.		366.633±75.831	
(35 µm) metoclopramide + (15 µm) hyoscine-N-butyl bromide	Before treat	8	173.127±48.847	0.13
	After treat.		189.237±52.989	

3.1 Effects of Metoclopramide and Hyoscine-N-butyl bromide on Frequency of Smooth Muscle Contraction and Relaxation in Duodenum

Hyoscine-N-butyl bromide has a significant anticholinergic effect on the human duodenum of smooth muscle by antagonizing the muscarinic receptors M_2 and M_3, especially in cholinergic spasticity. The specific reduction effectiveness of hyoscine-N-butyl bromide on different parts of the gastrointestinal tract may provide potentially useful information for medical use in the treatment of craps-related visceral pain. Because metoclopramide and hyoscine-n-butyl bromide are anticholinergic, when used for the treatment of intestinal spasms, or abdominal pain was blocked acetylcholine in the duodenum contraction and relaxation [17]. The first table explains the mean ± Std. error effects of metoclopramide alone, hyoscine-n-butyl bromide only, and metoclopramide and hyoscine-n-butyl bromide together on the mechanisms of contraction and relaxation of smooth muscle frequency in the duodenum before and after treatment.

In this analysis, the Mean $\pm Std$. error for the frequency of the isolated Ach-induced duodenum strips control and treated rats with 35 µM metoclopramide, 15 µM hyoscine-N-butyl bromide, and 50 µM metoclopramide and hyoscine-N-butyl bromide concentration respectively. The results recorded as following 34.47 ± 10.45 $(n = 8)$, 57.57 ± 13.79 $(n = 8)$, 78.83 ± 6.67 $(n = 8)$. All of the frequencies of the dose are statistically significantly decreased compared to the control. Respectively, it was observed this metoclopramide only and with hyoscine-n-butyl bromide applied at concentrations of 35 Mm, 15 µM and 50 µM significantly decreased the frequency of contractions. However, the 35 µM drugs showed significantly the highest decreasing frequency $(P < 0.05$ and$P < 0.001)$ in comparison to other drugs as shown in Table 1.

Table 1. This table shows the (Mean±Std.Error and P value) before and after treatment in duodenum frequency.

3.2 Effects of Metoclopramide and Hyoscine-N-butyl Bromide on Peak-Peak (Peak to Peak) of Smooth Muscle Contraction and Relaxation in Duodenum

Table 2 shows the mean±Std. error Isolated Ach peak-to-peak decreases or increases in muscle contraction before and after application of metoclopramide alone, hyoscine-n-butyl bromide only, and metoclopramide and hyoscine-n-butyl bromide together influence the mechanisms of contraction and relaxation of duodenal smooth muscle. In this examination, the Mean ± Std. error for the peak-peak of the isolated Ach reduced duodenum strips control and treated rats with 35 µM metoclopramide, 15 µM hyoscine-N-butyl bromide, and 50 µM of mixed (metoclopramide and hyoscine-N-butyl bromide) concentration separately. The results detected as follows 177.71 ± 15.17 $(n = 8)$, 366.63 ± 75.83 $(n = 8)$, 189.23 ± 52.98 $(n = 8)$. The results determined significance for 35 µM metoclopramide (P < 0.001) increased peak to peak compared to the control and showed a significant increase in 15 µM hyoscine-N-butyl bromide $(P < 0.05)$ determined compared to the control. Whereas, 50 µM both of them (metoclopramide and hyoscine-N-butyl bromide) showed no significance $(P < 0.05)$, while these drugs were not effective on the peak-peak as can be seen in Table 2.

3.3 Effects of Metoclopramide and Hyoscine-N-butyl bromide on Area of Smooth Muscle Contraction and Relaxation in Duodenum

Tytgat, Guido N. In this experiment, the antispasmodic hyoscine-n-butyl bromide is an anticholinergic that acts on smooth muscle cells in the gastrointestinal tract locally at the muscarinic receptor. As such causes relaxation and reduction in the smooth muscle. Pathologically stimulated gut motility is the basis for spasmolytic special effects and uses in the treatment of abdominal cramping and pain. This dose is available for >50 years [18]. Leslie A. Samuels (2009), in this paper, after proved Hyoscine-N-Butylbromide (HBB) means a quaternary ammonium compound that blocks the effect of acetylcholine at parasympathetic sites (both muscarinic and nicotinic receptors) in smooth muscle, and in secretory glands. It reduces the motility of the gastrointestinal tract and the urogenital tracts and is helpful in the treatment of spasms that regions [19].

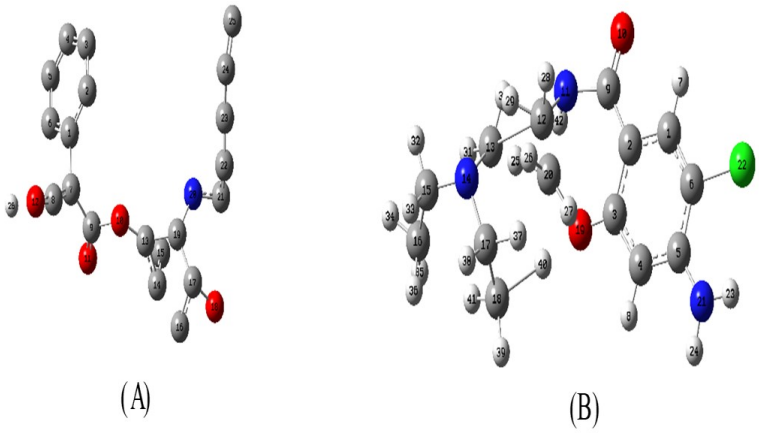

Figure 1: The optimized molecule structure of (A) hyoscine-N-butyl bromide (B) metoclopramide, is strictly associated with procainamide based on DFT at 6-311G++(d,p) basis set.

The Mean ± Std. error for the amplitude/area of the isolated Ach-induced duodenum strips controls and treated rats how the amounts of muscle before and after the administration of metoclopramide alone, hyoscine-n-butyl bromide alone, and metoclopramide and hyoscine-n-butyl bromide combined affect the mechanisms of contraction and relaxation of duodenal smooth muscle. In this study, the Mean ± Std. error for the amplitude/area of the isolated Ach-induced duodenum strips control and treated rats with 35 µM metoclopramide, 15 µM hyoscine-N-butyl bromide, and 50 µM of metoclopramide and hyoscine-N-butyl bromide concentration respectively. The following results determined 370.55 ± 129.89 ($n = 8$), 311.36 ± 85.23 ($n = 8$), 494.27 ± 145.67 ($n = 8$). The result of 50 µM of mixed (metoclopramide and hyoscine-N-butyl bromide) compared to the control significantly increased area ($P < 0.05$). On the other hand, the 35 µM metoclopramide, and 15 µM hyoscine-N-butyl bromide were statistically not significant ($P < 0.05$), while these drugs were not effective on the amplitude as shown in Table 3.

Table 3: The Mean±Std.Error and P value shows amplitude, before and after treatment in duodenum strips.

	Frequency	Number	Mean ± Std. Error	P
(35µm) Metoclopramide	Before treat After treat	8	355.43± 120.33 370.555±129.891	0.092
(15 µm) hyoscine-N-butyl bromide	Before treat After treat.	8	276.333±110.11 311.361±85.326	0.056
(35 µm) metoclopramide + (15 µm) hyoscine-N-butyl bromide	Before treat After treat.	8	410.974±125.079 494.272±145.272	0.03

4 Electronic Structures

The molecular structures of the studied compounds were optimized using the Density functional theory (DFT) method, the B3LYP hybrid functional, which is a combination of Becke's three parameters (B3) exchange functional with the Lee, Yang, and Parr (LYP) correlation functional, and the 6-311G(d, p) basis set, to speed up the calculations [20]. The Gaussian 09 software package was used to complete all computations [21]. Gauss09 view was used to visualize the optimal structures of the compounds (Fig. 1). The HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) frontier molecular orbitals, as well as the molecular electrostatic potential (MEP) of all optimized compounds, were displayed from a gauss perspective. This MEP outlines to illustrate the main size of the molecule, and the color-coded surface shows the position of negative and positive electrostatic potentials as a consequence of drug compound attraction or repulsion.

5 Quantum Chemical Parameters

Using LUMO and HOMO orbital energies, the electron affinity and ionization energy can be expressed as $A = -E_{LUMO}$, $I = -E_{HOMO}$, respectively. Softness (S) is a molecular attribute that indicates the degree of chemical reactivity. The reciprocal of softness is called hardness η [22]. The electronegativity can calculate as $\chi = -\mu$, the first time proposed by Parr et al and the global electrophilicity power of a ligand as $w = \mu^2/2\eta$ [23]. When the system receives an additional electronic charge from the environment, this index evaluates the energy stability. Electrophilicity refers to an electrophile's capacity to acquire more electronic charge as well as the system's resistance to exchanging electronic charge with the environment. It is a better description of global chemical reactivity since it comprises information on both electron transport (chemical potential) and

Table 4: Theoretical calculation of electronic parameters for compound A at protonated and non-protonated species in gas and aqueous phases.

A	Non-protonated gas phase	Protonated gas phase	Non-protonated aqueous phase	Protonated aqueous phase
EHOMO (eV)	-7.20639506	-7.18054423	-5.74922459	-7.91634049
ELUMO (eV)	-6.570736758	-6.60910483	-5.21996286	-7.42190935
Dipole moment (Debye)	10.6328	17.7123	15.7043	23.1631
Total energy a.u	-1116.8279	-1117.0173	-1116.8121	-1116.8919
Ionization energy (eV)	7.2063	7.1805	5.7492	7.9163
Electron affinity (eV)	6.5707	6.6091	5.2199	7.4219
Band-gap energy (eV)	0.6356	0.5714	0.5292	0.4944
Hardness (eV)	0.31782	0.2857	0.2646	0.2472
Softness (eV)	3.1463	3.4999	3.7788	4.045
Electronegativity (eV)	6.8885	6.8948	5.4845	7.6691
Chemical potential (eV)	-6.8885	-6.8948	-5.4845	-7.6691
Electrophilicity (eV)	74.6507	83.1909	56.8353	118.955
Nucleophilicity (eV)-1	0.0133	0.012	0.0175	0.0084
Transfer electrons	-0.0794	-0.07142	-0.066	-0.0618
ΔE Back-donation (eV)	0.1753	0.184	2.8632	-1.3533
ΔN	-0.0097	-0.0096	-2.1694	-0.4527
E_{MEI}	68.0799	76.5818	51.6153	111.5339
Nucleophugality	81.857	90.3715	62.5845	126.8721
Electrphugality	7.2063	7.18054	5.7492	7.9163

stability (hardness). This equation yields the maximum electron flow between donor and acceptor (Nmax) [24]:

$$\Delta N_{max} = -\mu/\eta \tag{1}$$

To examine the influence of electronic and structural characteristics on the efficiency of the researched medicines attributes, quantum chemical simulations were done using DFT/B3LYP at the 6-311G (d, p) basis set level. The examined inhibitors' geometric and electronic structures were computed by optimizing their bond lengths, bond angles, and dihedral angles. Fig. 1 shows the optimal molecule structures with the lowest energy generated from quantum chemical computations.

Quantum chemical characteristics acquired from DFT calculations, such as the energy of the highest occupied molecular orbital (EHOMO), the energy of the lowest unoccupied molecular orbital (ELUMO), and the energy gap, may be responsible for the inhibitors' inhibitory efficacy. The dipole moment (DM), ionization potential (IP), electron affinity (EA), electronegativity (χ), chemical potential (μ), softness (σ), hardness (η), electrophilicity index (ω), maximum electron flow from donor to the acceptor (ΔN_{max}), are collected in Table 4 and 5. Frontier molecular orbital electron densities of the compounds are responsible for charge-transfer complexes and provide a helpful technique for the comprehensive analysis of donor-acceptor interactions. Frontier orbital energies are significant features in a variety of chemical and pharmacological activities [25], [26].

The energy of the HOMO level is proportional to the ionization potential and describes the molecule's sensitivity to electrophile attack. The energy of the LUMO level, on the other hand, is proportional to the electron affinity and indicates the sensitivity to nucleophile attack [27].

Frontier molecular orbital electron density of the compounds is responsible for charge transfer complexes and provides a helpful means for the comprehensive analysis of donor-acceptor interactions [28], [29]. Frontier orbital energies are significant features in a variety of chemical and pharmacological activities. The energy of the HOMO level is proportional to the ionization potential and describes the molecule's sensitivity to electrophile attack [30]. The energy of the LUMO level, on the other hand, is proportional to the electron affinity and indicates the sensitivity to nucleophile attack [31].

ΔE is a reactivity function; reducing the value of ΔE enhances the inhibitors' reactivity. The narrow energy difference between HOMO and LUMO allows for electron transport and exchange, increasing the reactivity of these molecules (Fig. 2,3). The compound (A) had lower separation energies, ΔE $(0.63, 0.57, 0.52 \text{ and } 0.59eV)$, than compound (B) $(0.905, 0.53, 0.68 \text{ and } 1.24eV)$ which suggests the strongest reactivity of these compounds, as shown in Table 4 and 5. Polar compounds dissociate more readily than non-polar compounds, with the polarity of the structure being described in terms of dipole moment. It's a physicochemical feature of a drug candidate that's commonly employed in medicinal chemistry as a measure of lipophilicity and the drug's ability to pass different biological membranes. When the dipole moment of a pharmacological ingredient rises, so does its solubility in water.

These compounds have a smaller dipole moment (10.63, 17.71, 15.7 and 23.16 D) than Metoclopramide, according to calculations (8.9873, 9.7832, 12.86 and 18.5133 D). This indicates that the inhibitor (A) is more hydrophobic (lipophilic) than the inhibitor (B), which might explain why their biological activities are higher. Electrophilicity is a reactivity descriptor that may be used to define the toxicity of these compounds. It also includes a direct link between reaction rates and the ability to determine an electrophile's function or capacity. The inhibitor (A) had higher electrophilicity indices (74.65, 83.19, 56.83 and 118.95 eV) in gas and aqueous phases for protonating and non-protonated states than Metoclopramide (55.63, 96.73, 76.98 and 22.85 eV), indicating that they have more biological activity. In addition, the calculations revealed that the Hyoscine butyl bromide molecule has a low electronegativity (6.88, 6.89, 484 and 7.66 eV) in gas and aqueous phases for protonating and non-protonated states,

Table 5: Theoretical calculation of electronic parameters for compound B at protonated and non-protonated species in gas and aqueous phases.

B	Non-protonated gas phase	Protonated gas phase	Non-protonated aqueous phase	Protonated aqueous phase
EHOMO (eV)	-7.55089139	-7.42789586	-7.60857955	-5.95902449
ELUMO (eV)	-6.64529599	-6.89754567	-6.92285227	-4.71328659
Dipole moment (Debye)	8.9873	9.7832	14.6734	18.5133
Total energy a.u	-1320.7281	-1320.44	-1320.4521	-1320.7801
Ionization energy (eV)	7.5508	7.4278	7.6085	5.959
Electron affinity (eV)	6.6452	6.8975	6.9228	4.7132
Band-gap energy (eV)	0.9055	0.5303	0.6857	1.2457
Hardness (eV)	0.4527	0.2651	0.342	0.6228
Softness (eV)	2.2084	3.771093238	2.9166	1.6054
Electronegativity (eV)	7.098	7.162720765	7.2657	5.3361
Chemical potential (eV)	-7.098	-7.1627	-7.2657	-5.3361
Electrophilicity (eV)	55.6351	96.7371	76.9848	22.8575
Nucleophilicity (eV)-1	0.0179	0.0103	0.0129	0.0437
Transfer electrons	-0.1131	-0.0662	-0.0857	-0.1557
ΔE	-0.10831	-0.3068	-0.3874	1.33562
ΔN	-0.00531	-0.0249	-0.05148	-1.1111
E_{MEI}	48.9898	89.8396	70.062	18.1442
Nucleophugality	63.186	104.165	84.5934	28.8166
Electrphugality	7.5508	7.4278	7.6085	5.959

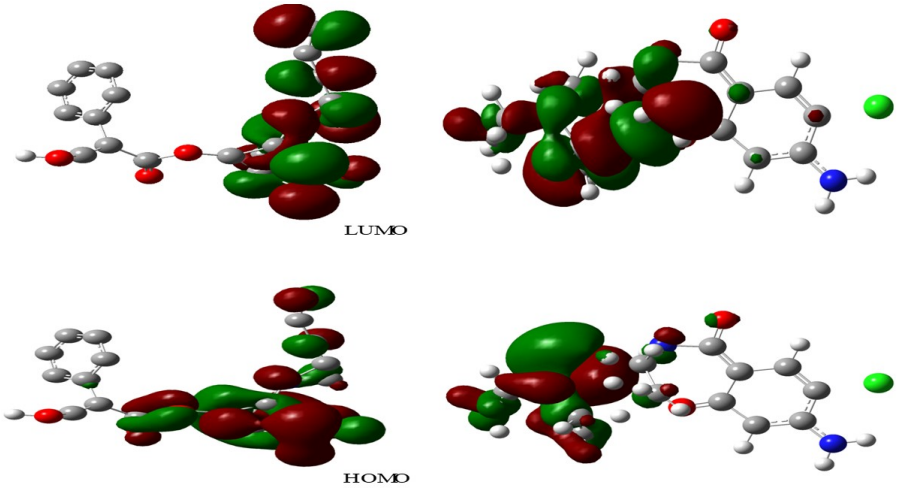

Figure 2: HOMO and LUMO of A and B compounds in gas phase

which increases the electron releasing the power of Metoclopramide to the enzyme and, as a result, increases Metoclopramide capacity to be oxidized. A novel reactivity indicator that measures the stability in the energy of the complex is the maximum amount of electronic charge (N_{max}) obtained by an inhibitor (acceptor) from the environment (donor). The inhibitor (A) has a larger electron transport, according to the calculations (-0.079, -0.0714, -0.0661, -0.0618) than Metoclopramide (-0.113, -0.066, -0.0857, -0.155). Softness is a molecular attribute that indicates the degree of chemical reactivity. The contact takes place where the softest region of the molecule is [32]. The compounds have higher softness (3.14, 3.49, 3.778 and 4.045 eV) in gas and aqueous phases for protonated and non-protonated states respectively) than Metoclopramide, according to the estimates (2.2, 3.77, 2.91 and 1.6 eV). The computed quantum chemical characteristics of Hyoscine butyl bromide revealed that they had a high biological activity equivalent to Metoclopramide inhibitors, which is in excellent accord with the experimental data. Metoclopramide alone and in combination with hyoscine-n-butyl bromide exhibited different effects depending on the concentration used. Additionally, metoclopramide alone and in combination with hyoscine-n-butyl bromide have an impact on duodenal contractions since these doses block Ach and decrease intestinal motility.

6 Electrostatic Potential Map of Selected Molecules

Three-dimensional molecular electrostatic potentials (MEPs) overlaid on the total electron density are beneficial for interpreting long-range interactions between molecules, which benefits in understanding how a ligand binds to its receptor. MEPs consist of some different regions, a negative area can be thought of as a nucleophilic center, whilst positive electrostatic potentials can be thought of as potential electrophilic sites. Furthermore, the electron density's polarization is evident due to the electrostatic potential. They also offer information on the size and shape of molecules. The red and orange portions in these color-coded

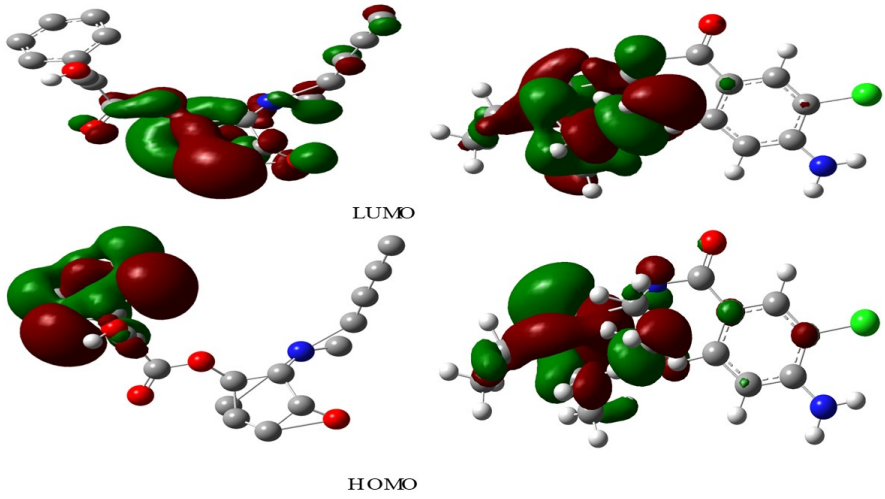

Figure 3: HOMO and LUMO of A and B compounds in the aqueous phase.

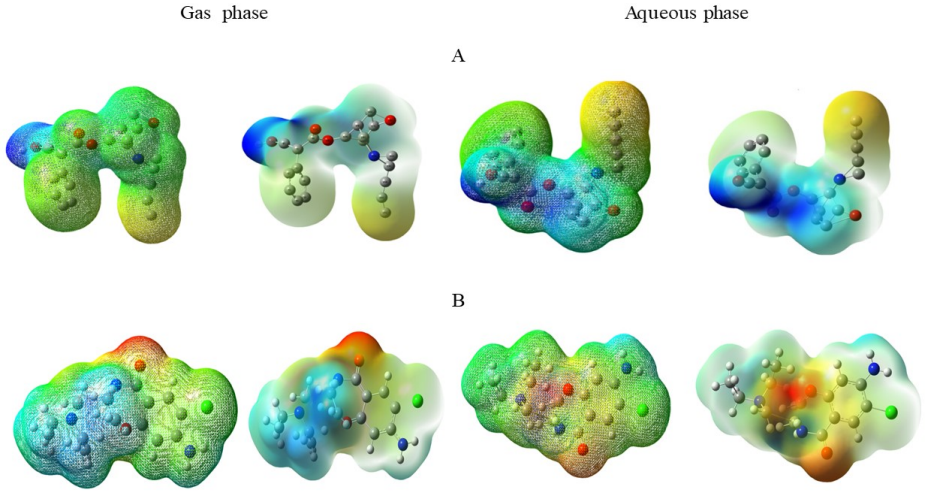

Figure 4: Electrostatic potential map of the selected molecule drugs in gas and aqueous phases.

maps show locations with high electron density, whereas the blue parts reflect electron-poor locales.

These MEP outlines offer a measurement of the molecule's overall size, while the colour-coded surface indicates the position of the positive and negative electrostatic potentials as a result of the positively charged test probe's repulsion or attraction, correspondingly [33], [34]. The oxygen and nitrogen atoms have the strongest negative potential on Hyoscine butyl bromide, as can be shown in Fig. 4. On the other hand, is particularly electron-rich in the oxygen atom regions that have been identified as important for forming a hydrogen bond with the active site of Metoclopramide. The electron-poor sites observed around the oxygen atom of the Hyoscine butyl bromide drug molecule and the rich electron sites located at the edge surface for gas and water phases in protonated and non-protonated states.

7 Fukui Function Analysis

The Fukui function defines the electron density after several electrons have been added or removed [35], [36]. It can forecast the location of the molecule's most nucleophilic and electrophilic sites. A finite charge change is used to implement the Fukui function. By default, an entire electron is deleted or added, although the computation is not limited to this value. Electrons in fractional quantities are permitted. When one electron is added, the Fukui equation for the electrophilic attack can be expressed as:

$$f^{+} = \rho\,(N+1) - \rho\,(N)\,. \tag{2}$$

Table 6: Calculated Mulliken atomic charges and Fukui functions for inhibitor A, in gas and aqueous phase.

Atom	Gas phase			Aqueous phase		
	f^+	f^-	f^0	f^+	f^-	f^0
1C	-0.005	-0.023	-0.014	0.062	-0.051	0.0055
2C	-0.01	0.021	0.0055	0.29	-0.152	0.069
3C	0.001	0.02	0.0105	0.274	-0.139	0.0675
4C	0.016	-0.048	-0.016	-0.107	0.161	0.027
5C	0.003	0.008	0.0055	0.288	-0.155	0.0665
6C	-0.016	0.041	0.0125	0.303	-0.165	0.069
7C	0	0.012	0.006	0.373	-0.38	-0.0035
8C	-0.009	-0.076	-0.0425	-0.47	0.6	0.065
9C	0.016	0.025	0.0205	-0.612	0.692	0.04
10O	0.056	-0.001	0.0275	0.025	0.011	0.018
11O	0.013	0.031	0.022	0.442	-0.383	0.0295
12O	0.021	0.03	0.0255	0.135	-0.022	0.0565
13C	0.169	0.112	0.1405	-0.426	0.32	-0.053
14C	0.069	0.042	0.0555	0.026	0.097	0.0615
15C	0.277	0.177	0.227	-0.144	0.346	0.101
16C	0.087	0.054	0.0705	-0.195	0.304	0.0545
17C	0.103	0.02	0.0615	-0.353	0.483	0.065
18O	0.086	0.017	0.0515	0.285	-0.084	0.1005
19C	0.025	0.077	0.051	0.007	0.128	0.0675
20N	0.01	0.078	0.044	-0.048	0.042	-0.003
21C	0.023	0.024	0.0235	0.034	-0.01	0.012
22C	-0.032	0.124	0.046	0.084	0.169	0.1265
23C	0.051	-0.001	0.025	0.272	-0.342	-0.035
24C	0.001	0.023	0.012	0.152	-0.263	-0.0555
25C	0.046	0.197	0.1215	0.374	-0.333	0.0205

When one electron is removed, the Fukui equation for the electrophilic attack can be expressed as:

$$f^- = \rho\,(N) - \rho\,(N) - 1. \tag{3}$$

An approach to combine the two Fukui functions is to use the Dual Descriptor. When it is electrophilic, it has a positive value, and when it is nucleophilic, it has a negative value [37]. The difference between the Fukui minus and Fukui plus functions is used to implement it.

$$f\,(r) = f^{\pm} f^-. \tag{4}$$

The Fukui function can also be used to characterize chemical reactivity in a particular region. Using the condensed Fukui function, this may even be done per atom.

$$f_k^- = q_k\,(N) - q_k\,(N) - 1, \tag{5}$$

$$f_k^- = q_k\,(N+1) - q_k\,(N)\,. \tag{6}$$

The condensed Fukui function is calculated using atomic charges. The atomic charges can be partitioned in a variety of ways. The condensed Fukui functions for Voronoi, Hirshfeld, Mulliken, and, if determined, Bader charges are published by the Fukui computation [38].

Because these atoms have a greater negative charge, Fukui function calculations show that they contain active centers and surplus charges that might serve as a nucleophilic group [39]. The large values of the nucleophilic attack obtained from Fukui function calculations indicate that the molecule has a strong capacity to take electrons. The electrophilic attack site's high score indicates the molecule's great propensity to donate electrons. The tendency of a molecule to give off electrons is represented by the high electrophilic site [40].

8 Conclusion

The study found that metoclopramide's anti-emetic effects are boosted by its ability to block dopamine receptors in both central and peripheral areas, akin to how gastrointestinal motility syndrome operates. For patients experiencing cramping-related stomach discomfort, hyoscine-n-butyl bromide is a popular treatment choice. Metoclopramide, at low and high concentrations, reduces gastrointestinal smooth muscle activity, while moderate levels enhance muscle contraction, mainly through intracellular Ca^{+2} ions. The study utilized isolated organ bath tissue strips from the duodenum and colon, measuring contractions under various drug combinations. Metoclopramide, alone and with hyoscine-n-butyl bromide, displayed concentration-dependent effects on duodenal contractions, blocking acetylcholine and reducing intestinal motility. Chemical analyses showed hyoscine-n-butyl bromide's greater reactivity due to its lower bandgap energy and higher interaction potential compared to metoclopramide. This study enhances our understanding of how these drugs affect gastrointestinal function, providing insights for potential therapeutic applications.

Table 7: Calculated Mulliken atomic charges and Fukui functions for compound B, in gas and aqueous phase.

Atom	Gas phase			Aqueous phase		
	f^+	f^-	f^0	f^+	f^-	f^0
1C	-0.014	0.031	0.0085	0.081	-0.058	0.0115
2C	-0.022	0.054	0.016	0.447	-0.42	0.0135
3C	0.003	0.026	0.0145	-0.296	0.303	0.0035
4C	0.016	-0.022	-0.003	0.404	-0.355	0.0245
5C	-0.011	0.04	0.0145	-0.247	0.257	0.005
6C	-0.017	-0.014	-0.0155	0.133	-0.106	0.0135
7H	0.006	-0.005	0.0005	-0.136	0.17	0.017
8H	0.013	-0.014	-0.0005	-0.178	0.223	0.0225
9C	0.094	-0.129	-0.0175	-0.579	0.618	0.0195
10O	0.023	-0.018	0.0025	0.324	-0.263	0.0305
11N	0.03	-0.018	0.006	0.339	-0.33	0.0045
12C	0.048	0.007	0.0275	0.154	-0.214	-0.03
13C	0.682	0.077	0.3795	0.906	-0.668	0.119
14N	-0.025	0.096	0.0355	-0.154	0.152	-0.001
15C	-0.01	0.033	0.0115	0.419	-0.462	-0.0215
16C	0.142	-0.161	-0.0095	0.65	-0.672	-0.011
17C	-0.037	0.191	0.077	0.173	-0.195	-0.011
18C	-0.064	0.18	0.058	0.687	-0.701	-0.007
19O	-0.068	0.081	0.0065	0.311	-0.298	0.0065
20C	0.357	0.127	0.242	0.157	-0.052	0.0525
21N	0.005	0.001	0.003	0.375	-0.357	0.009
22Cl	0.013	-0.006	0.0035	-0.049	0.118	0.0345

Authors' Contributions

Sleman Yousif Omar: Laboratory working at Firat University when he was MSc student and data analysis. Emine Kaçar: Supervisor on this work and plan to writing up. Dyari Mustafa Mamand: Theoretical working and data analysis. Rebaz Anwar Omer: Writing up and data analysis.

Competing Interests

The authors state that there is no conflict of interest in the printing of this manuscript.

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