

COMPUTATIONAL AND POLAROGRAPHIC STUDY ON DRUG-RECEPTOR INTERACTION FOR CARVEDILOL

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ABSTRACT

Objective: The aim of this study was to evaluate Carvedilol-receptor binding using computational and polarographic methods.

Methods: Differential pulse polarographic (DPP) wave was measured for carvedilol, serine, and aspartic acid in phosphate buffer solution pH 7.4 at 37 °C. Interaction of drug receptors with two amino acids serine and aspartic acid was studied by linking the thermodynamic (K_{eq}) and kinetic behavior. The forward reaction rate constant (k₁) and reverse reaction rate constant (k₋₁) was calculated for carvedilol-receptor complexes and through the half-life time was also calculated.

Results: The study found that carvedilol, serine and aspartic acid electrical active agents and have E_{1/2} 0.148, 0.127 and 0.119 V respectively. After formation of drug-receptor molecular complexes, a negative displacement in carvedilol half-wave potential value. Gibbs, free energy was calculated and found to be a negative value for all the molecular complexes indicate that spontaneous interaction occurred. The chemical affinity was also calculated which gave a positive result and indicated a high tendency of molecules to associate with each other. A computational study using the Gaussian software, DFT-6311G on carvedilol-receptor molecular complexes gave significant agreement of complex behavior in the theoretical study with the polarographic study, depending on the values of the energy gap between HOMO-LUMO.

Conclusion: the study showed that there is a good rapprochement between theoretical and experimental results allows the possibility of evaluated drug-receptor interaction in Subsequent studies theoretically, also showed the possibility to determine the spontaneously and chemical affinity of drug-receptor molecular complex formation based on polarographic results

Keywords: Carvedilol, Drug-receptor, HOMO-LUMO gap, Differential pulse polarography, DFT-6311G and E_{1/2}

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INTRODUCTION

Carvedilol (±)-1-(carbazol-4-yloxy)-3-((2-(o-methoxy-phenoxy) ethyl) o)-2-propanol is a racemic lipophilic aryloxy propanolamine. Noncardioselective β-adrenergic blocking agent with blocking activity against blocks α₁ - and β-adrenergic receptors.

It is considered as an effective treatment for mild and moderate congestive heart failure [1]. The vasodilatation which results from blocking of α₁-receptors significantly decreases systemic blood pressure, pulmonary capillary wedge pressure, and pulmonary artery pressure. While a reduction in the heart rate and increasing in diastolic filling time are all considered as an outcome of blocking of β-receptors. The combined effects of blocking both α- and β-adrenergic receptors also have an impact by reducing the preload, afterload, and myocardial oxygen consumption [2].

The ability of drugs to exert a biochemical and/or biophysical modification in cellular activity depend mainly on its ability to interact with cellular receptors (macromolecular structures located intracellularly or on the cell surface). This interaction could be achieved by binding of drugs to the cellular surface receptors, nucleic acids or enzymes, which will be reflected the formation of drug-receptor complex which leads to a biologic response. The selectivity of the receptor is mainly determined by the drug receptors interaction involves the formation of chemical bonds, mainly electrostatic and hydrogen bonds, as well as weak interactions involving van der Waals forces. These bonds are important in determining the selectivity of receptors because the strength of these noncovalent bonds is related inversely to the distance between [3]. In DPP the current is measured in two intervals of about (15 ms), the first immediately prior to the potential pulse and the second during but towards the end of the potential pulse. The final current signal displayed is, in fact, the difference of these two current values [4]. The two current values

represent the current at two potential values separated by about 10-100 mV (the pulse amplitude). This difference in current will be greatest on the steep rising part of the polarographic wave around the half wave potential, where a small change in potential produces a large change in current.

Thus, this technique in fact produces not a wave, but a peak with the highest current signal at roughly the half-wave potential of the classical DC and NP). Since the output signal increases with the steepness or slope of the conventional current potential curve, this final curve approximates to a derivative or differential of the classical polarographic current potential curve [5, 6].

Computational chemistry has become a useful way to investigate materials that are too difficult to find or too expensive to purchase. It also helps chemists make predictions before running the actual experiments so that they can be better prepared for making observations [7].

MATERIALS AND METHODS

All chemicals used in this investigation were obtained from commercial sources. The device used was Polarographic analyzer model 797VA supplied from Metrohm made in Switzerland

Which have two electrodes rotating disk electrode RDE and Multi-Mode Electrode MME having three modes: Dropping mercury electrode DME, Static mercury drop electrode SMDE and Hanging mercury drop electrode HMDE

Polarographic cell consisting of three electrodes:

1. **Working Electrode:** the dropping mercury electrode which is normally a cathode of the Polarographic cell
2. **Reference Electrode:** silver-silver chloride electrode immersed in a solution of potassium chloride 3M. (Ag/AgCl/KCl).

3. **Auxiliary Electrode:** it is an inert electrode consist of platinum rod

Also, there is a tube in which the nitrogen gas passes through it into the Polarographic cell.

Preparation of buffer phosphate

Preparation of aqueous solutions of phosphate buffer was occurred by mixing a given volume of mono potassium phosphate solution 0.0667 M and then complete the volume up to 100 ml with sodium phosphate dibasic dehydrate solution 0.0667M, and then pH was adjusted using pH meter.

Preparation of carvedilol, aspartic acid and serine solutions

Aqueous solutions of carvedilol M. Wt=406.5 g/Mol, serine M. Wt=105. 1g/Mol and aspartic acid MW. t=133. 1g/Mol were prepared with concentrations of 0.98×10^{-4} , 0.98×10^{-4} and 0.99×10^{-4} M of carvedilol, serine and aspartic acid, respectively by

weighing 0.004g, 0.0003g and 0.0004 g respectively in 100 ml as a stock solution.

RESULTS AND DISCUSSION

Carvedilol was electrochemically oxidized using glassy carbon electrode (GCE) [8]. In this study the reduced polarographic wave was determined using HMDE as a working electrode, the optimized condition was determined listed in table 1, Polarographic wave recorded before and after optimization (fig.1), showed a peak at $E_{1/2}$ 0.148 V and id 36.4 μ A.

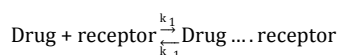
Determination of drug-receptor interaction

β 1-adrenoceptor (β 1AR) is the site of action of beta blockers, β 1-adrenoceptor, having an Amino acid Side-Chain includes Leu, Trp, Thr, Asp, Val, Cys, Phe, Tyr, Ala, Ser, Asn[9], Coupled amino acids, serine, and aspartic acid has been suggested as a receptor for carvedilol, based on literature information [10, 11]

Table 1: Optimal instrumentation, condition to determined polarographic wave of carvedilol

Instrumental conditions	Value
Initial purges Time	300 Sec.
Drop Size	9 mm ³
Deposition Time	70 Sec.
Equilibrium Time	25 Sec.
Voltage Step	0.008 V
Voltage Step Time	1 Sec.
Pulse Amplitude	0.05 V
Pulse Time	0.02 Sec.
Initial potential	-0.4 V
Final potential	+0.4V

From the polarographic study noted that the amino acids suggested as receptors have a polarographic wave with $E_{1/2}$ value different from those of pharmaceutical compounds, the polarographic behavior of amino acids studied by the DPP in the phosphate buffer pH=7. 4 with a concentration of 0.98×10^{-5} and 0.99×10^{-5} M for serine and aspartic acid respectively, at 37° C. Serine, shows polarographic wave at $E_{1/2}$ 0.127 V with id 35.8 μ A. While aspartic acid shows polarographic wave at $E_{1/2}$ 0.119 V and id 37.8 μ A. The interaction between drug and receptor could be represented as:



The concentrations of reactants or product could be follow through a physical property change (as a function of concentration) during the course of the reaction, such as limiting current (Diffusion current) in a Polarography. Thus, the interaction electrochemical kinetic equation can be written as follows [12]:

$$\ln \frac{id(eq)}{id(eq) - id(x)} = (k_1 + k_{-1})t$$

$$id_{(x)} = id_{(0)} - id_{(t)}$$

Where:

$id_{(0)}$: Diffusion current measured in different time t

id : Diffusion current at time $t = 0$

So, by plotting $\ln [id_{(eq)}/id_{(eq)} - id_{(x)}]$ against t and calculate the value of slope which equal to $k_1 + k_{-1}$ we could calculate the rate

Constants and equilibrium constant of the drug-receptor interaction

Determination of ser and asp interaction with carvedilol

The effect of added Ser and Asp on the half-wave potential of carvedilol studied in phosphate buffer pH 7.4 at 37°C by using a different mole ratio (1: 1and 1: 2) to the drug-receptor. It has been noted that half-wave potential of carvedilol shifted in different values with changing times and type of additive.

Carvedilol-Serine interaction

Study of carvedilol-serine interaction given a clear shifting to the polarographic wave of the drug after complication, which was at $E_{1/2} = 0.148$ V, $id = 36.4\mu$ A before interaction and become at $E_{1/2} = 0.132$ V, $id = 27.7\mu$ A after interaction, while the polarographic wave of serine was $E_{1/2} = 0.127$ V, $id = 35.8\mu$ A, (fig. 2, fig. 3, fig. 4), (table 2, table 3, table 4, table 5).

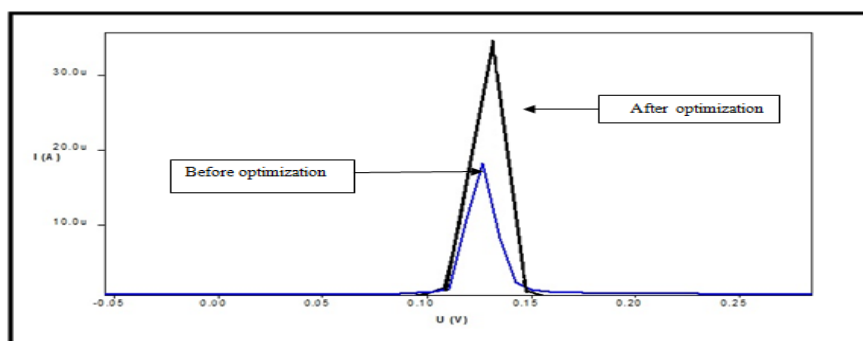


Fig. 1: Carvedilol DPP polarogram before and after optimization

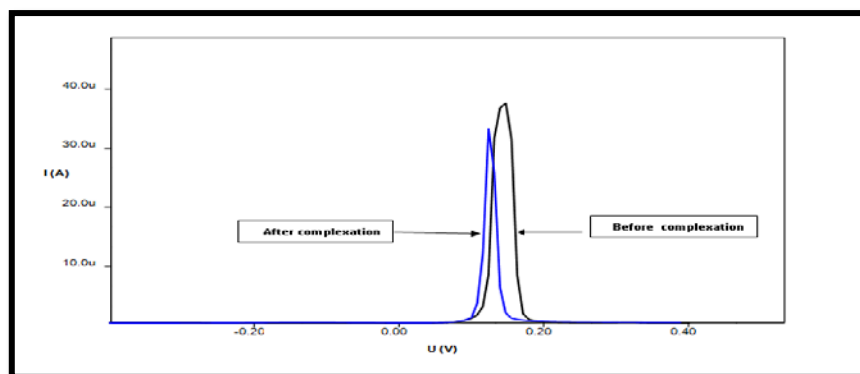


Fig. 2: Polarographic wave potential for carvedilol-Serine interaction

As noted, the interaction between carvedilol and Serine negatively shifted the polarographic peak of carvedilol in a magnitude of 0.016V which indicating of drug-receptor interaction, diffusion current slightly decrease from the value carvedilol for both mole ratios, In both cases, $E_{1/2}$ magnitude is the same shifting with a little difference in i_d value.

Carvedilol-aspartic acid interaction

The interaction study of carvedilol-aspartic acid gave a clear shifting to the polarographic wave of the drug after complication, which was

at $E_{1/2} = 0.148$ V, $i_d = 36.4\mu\text{A}$ before interaction and become at $E_{1/2} = 0.124$ V, $i_d = 20.4\mu\text{A}$ after interaction, while the polarographic wave of Aspartic acid was $E_{1/2} = 0.119$ V, $i_d = 37.8\mu\text{A}$, (fig. 5, fig. 6, fig. 7). And (table 6, table 7, table 8, table 9).

As noted, the interaction between carvedilol and aspartic acid negatively shifted the polarographic peak of carvedilol in a magnitude of 0.024 v that is a proof of drug-receptor interaction, the diffusion current for both mole ratio decreasing than the original value, In both cases the magnitude of $E_{1/2}$ shifting is the same with a difference in i_d value.

Table 2: Carvedilol-serine interaction at molar ratio (1: 1)

Time/min	$E_{1/2}/V$ carvedilol	$E_{1/2}/V$ mixture	$\Delta E_{1/2}$	$i_d/\mu\text{A}$
5	0.148	0.132	-0.016	33.4
10	0.148	0.132	-0.016	31.7
20	0.148	0.132	-0.016	27.9
30	0.148	0.132	-0.016	26.1
40	0.148	0.132	-0.016	24
50	0.148	0.132	-0.016	22.3
60	0.148	0.132	-0.016	21.4
120	0.148	0.132	-0.016	19.3
1440	0.148	0.132	-0.016	18.5

Table 3: The gradual increase in the diffusion current of carvedilol-Serine (1: 1) molecular complex with time

Time/min.	$i_d(x)/\mu\text{A}$	$\frac{i_d(\text{eq})}{i_d(\text{eq}) - i_d(x)}$	$\ln \frac{i_d(\text{eq})}{i_d(\text{eq}) - i_d(x)}$
5	3	1.193548	0.176931
10	4.7	1.34058	0.293102
20	8.5	1.85	0.615186
30	10.3	2.256098	0.813637
40	12.4	3.032787	1.109482
50	14.1	4.204545	1.436166
60	15	5.285714	1.665008
120	17.1	13.21429	2.581298
1440	17.9	*(indeterminate)	*

Table 4: Carvedilol-serine interaction at molar ratio (1: 2)

Time/min.	$E_{1/2}/V$ carvedilol	$E_{1/2}/V$ mixture	$\Delta E_{1/2}$	$i_d/\mu\text{A}$
5	0.148	0.132	-0.016	33.9
10	0.148	0.132	-0.016	32.5
20	0.148	0.132	-0.016	30.4
30	0.148	0.132	-0.016	27.9
40	0.148	0.132	-0.016	26.2
50	0.148	0.132	-0.016	24.7
60	0.148	0.132	-0.016	22.8
120	0.148	0.132	-0.016	21.5
1440	0.148	0.132	-0.016	19.8

Table 5: The gradual increase in the diffusion current of carvedilol-Serine (1: 1) molecular complex with time

Time/min.	$I_d(x)/\mu A$	$\frac{id(eq)}{id(eq) - id(x)}$	$\ln \frac{id(eq)}{id(eq) - id(x)}$
5	2.5	1.144509	0.134975
10	3.9	1.245283	0.219363
20	6	1.434783	0.361013
30	8.5	1.752212	0.560879
40	10.2	2.0625	0.723919
50	11.7	2.444444	0.893818
60	13.6	3.193548	1.161133
120	14.9	4.040816	1.396447
1440	16.6	(Indeterminate)	*

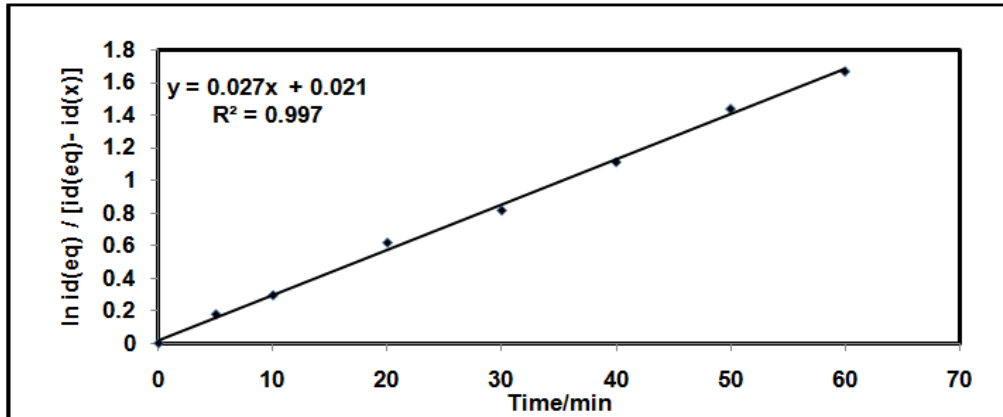


Fig. 3: Consequence of the rate of irreversible equilibrium interaction of CRV-Ser1: 1 vs. time

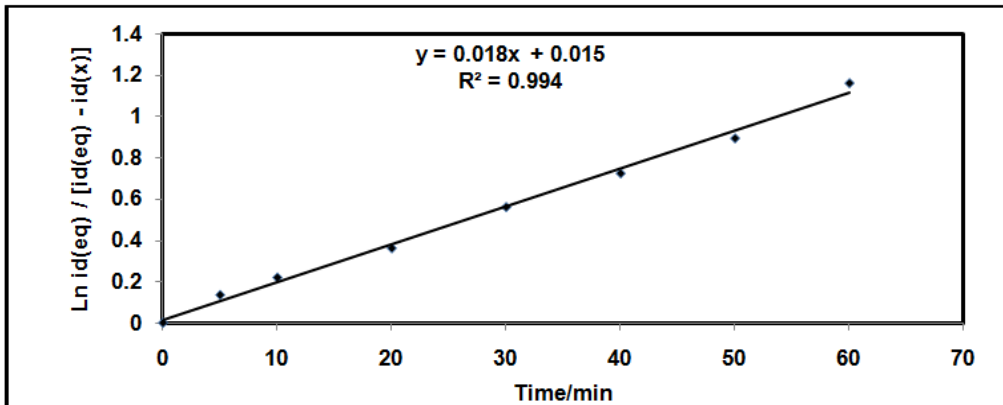


Fig. 4: Consequence of the rate of irreversible equilibrium interaction of CRV-Ser1: 2 vs. time

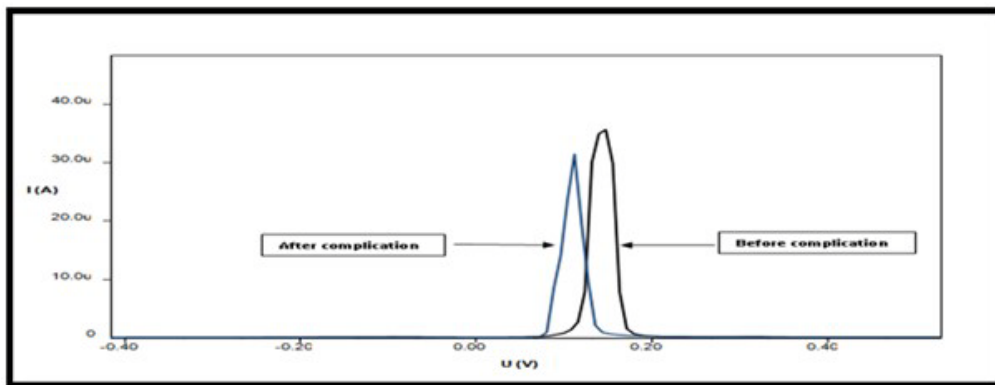


Fig. 5: Polarographic wave potential carvedilol-aspartic acid interaction

Table 6: Carvedilol-aspartic acid interaction at molar ratio (1: 1)

Time/min	$E_{1/2}/V$ carvedilol	$E_{1/2}/V$ mixture	$\Delta E_{1/2}$	Id/ μ A
5	0.148	0.124	-0.024	32.1
10	0.148	0.124	-0.024	28.2
20	0.148	0.124	-0.024	26.7
30	0.148	0.124	-0.024	23.3
40	0.148	0.124	-0.024	21.9
50	0.148	0.124	-0.024	20.5
60	0.148	0.124	-0.024	19.8
120	0.148	0.124	-0.024	18.9
1440	0.148	0.124	-0.024	17.8

Table 7: The gradual increase in the diffusion current of carvedilol-aspartic acid (1: 1) molecular complex with time

Time/min.	Id (x)/ μ A	$\frac{id(eq)}{id(eq) - id(x)}$	$\ln \frac{id(eq)}{id(eq) - id(x)}$
5	4.3	1.318519	0.276509
10	8.2	1.854167	0.617435
20	9.7	2.197531	0.787334
30	13.1	3.787234	1.331636
40	14.5	5.393939	1.685276
50	15.9	9.368421	2.237345
60	16.6	14.83333	2.696877
120	17.5	59.33333	4.083171
1440	18.6	(Indeterminate)	*

Table 8: Carvedilol-aspartic acid interaction at molar ratio (1: 2)

Time/min	$E_{1/2}/V$ carvedilol	$E_{1/2}/V$ mixture	$\Delta E_{1/2}$	Id/ μ A
5	0.148	0.124	-0.024	32.9
10	0.148	0.124	-0.024	30.1
20	0.148	0.124	-0.024	28.6
30	0.148	0.124	-0.024	25.9
40	0.148	0.124	-0.024	23.7
50	0.148	0.124	-0.024	21.7
60	0.148	0.124	-0.024	20.2
120	0.148	0.124	-0.024	19.9
1440	0.148	0.124	-0.024	18.9

Table 9: The gradual increase in the diffusion current of carvedilol-aspartic acid (1: 2) molecular complex with time

Time/min.	Id (x)/ μ A	$\frac{id(eq)}{id(eq) - id(x)}$	$\ln \frac{id(eq)}{id(eq) - id(x)}$
5	3.5	1.227273	0.204794
10	6.3	1.5	0.405465
20	7.8	1.702703	0.532217
30	10.5	2.25	0.81093
40	12.7	3.048387	1.114613
50	14.7	4.5	1.504077
60	16.2	7	1.94591
120	16.5	7.875	2.063693
1440	17.5	*(indeterminate)	*

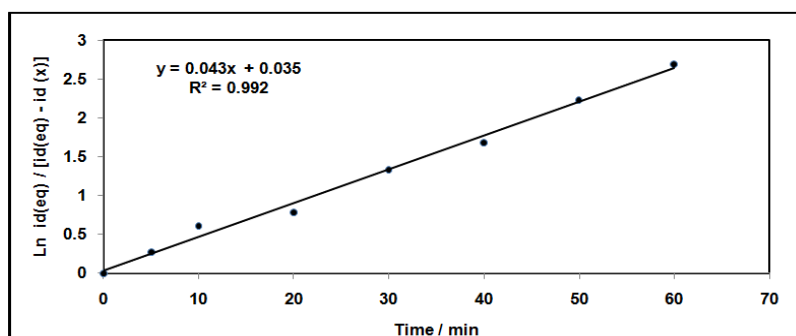


Fig. 6: Consequence of the rate of irreversible equilibrium interaction of CRV-Asp1: 1 vs. time

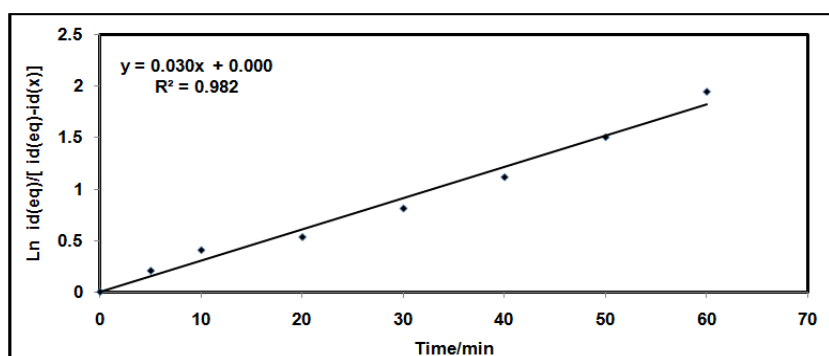


Fig. 7: Consequence of the rate of irreversible equilibrium interaction of CRV-Asp 1: 2 vs. time

Drug-amino acid interaction is due to the formation of the molecular complex between σ bonds or weak van der Waals attractive interaction or Dispersion Forces. A large group of complexes formed by the weak interaction of organic substances. Functioning as electron donors with other substances which act as electron acceptors, these complexes are formed by non-covalent interaction [12].

The extra heterocyclic ring in carvedilol, due to van der Waals contact with β 2AR, pushes the ligand more deeply into the binding site. Hydrogen bond has a significant role in the binding between the ligand (drug) and Asp, Asn and Ser [13]. The existence of carbonyl and NH groups of amino acids plays an important role in the formation of intermolecular hydrogen bonds with pharmaceutical compounds.

The interaction between pharmaceutical compound and additives was an irreversible reaction; therefore it has importance extremely by linking between the kinetic behavior of the reaction and thermodynamic properties [14].

When serine and aspartic acid add to carvedilol, it has been noted a negatively shifted to the polarographic wave, meaning that these additives reduced the energy level of the lowest unoccupied molecular orbital (LUMO) of the carvedilol, which direct proportion to the half wave potential, and raising the energy level of LUMO. The additives, so the potential of carvedilol will be reduced, because of linearity relation between the potential of the unsaturated hydrocarbon compound and the LUMO of the molecule [15].

Rate constants and equilibrium constants account or the formation of molecular complexes

The rate constants of the reaction are of great importance in various chemical reactions because it represents the number of particles generated or consumed during a given period of time. The rate constants depend greatly on the temperature, Accordingly, the increase since the higher the temperature, due to an increased number of collisions so should maintain the reaction temperature while the

calculation of rate constants of reaction [16,17]. On this basis, it can be account the rate constant of the front and reverse account depending on the value of the equilibrium constant (K_{eq}) and the value of the slope (k_1+k_{-1})resulting from drawing the equation of equilibrium reversible reaction vs. time, shown in (fig. 3, fig. 4, fig. 6 and fig. 7)

$$\text{slop} = k_1 + k_{-1}$$

$$k_{eq} = \frac{id_{eq}}{id_0 - id_{eq}} = \frac{k_1}{k_{-1}}$$

It has been noted, for all interaction (except those of carvedilol-serine 1: 1 and carvedilol-aspartic acid 1: 1), that's the rate constants of the forward molecular complex interaction are larger than those for reversible interaction, which mean that the interaction moving towards products formation, even for the above-excluded cases when the mole ratio increase to 1: 2 drug-receptor, the rate constant of the forward interaction became larger than those of reversible one, it is may be due to le-chatelier's principle [18]. The value of $t_{0.5}$ has been calculated depending on the slop value and from the below equation [18], table 10:

$$t_{0.5} = \frac{0.693147}{k_1 + k_{-1}}$$

Chemical affinity is the tendency of a molecule to associate with another. The affinity of a drug is its ability to bind to its biological target (receptor, enzyme, transport system, etc.) For pharmacological receptors, it can be thought of as the frequency with which the drug, when brought into the proximity of a receptor by diffusion, will reside at a position of minimum free energy within the force field of that receptor [19]. Chemical affinity having a positive value for the spontaneous process and vice versa:

$$A = -(\Delta G^\circ)_{T,P,n}$$

All molecular complexes had high affinity to interact unless of Carvedilol-Aspartic 1: 1.

Table 10: Rate constant and half time of molecular complexes

S. No.	Molecular complex	K_{eq}	Slop	$t_{0.5}/\text{min}$	k_1/min^{-1}	k_{-1}/min^{-1}
1	CRV+Ser 1: 1	9.402	0.0277	25.1	0.025	0.0026
2	CRV+Ser 1: 2	1.193	0.018	37.9	0.0099	0.0083
3	CRV+Asp 1: 1	0.957	0.043	15.9	0.0213	0.0222
4	CRV+Asp 1: 2	1.08	0.0303	22.87	0.016	0.0145

Table 11: Gibbs free energy and chemical affinity of molecular complexes

S. No.	Molecular complex	K_{eq}	$\Delta G^\circ/\text{KJ. mole}^{-1}$	$A/\text{KJ. mole}^{-1}$
1	CRV+Ser 1: 1	9.40247	-5.77603	5.77603
2	CRV+Ser 1: 2	1.19277	-0.45435	0.45435
3	CRV+Asp1: 1	0.95699	0.113314	-0.11331
4	CRV+Asp1: 2	1.08	-0.19836	0.19836

The above results showed a positive value of chemical affinity for all molecular complex (except carvedilol-aspartic acid 1: 1 complex)

meaning that, the interaction displaced towards equilibrium, the formation of a stable molecular complex between pharmaceutical

compounds and additives. As they begin with a physical operations (move a substance towards the other) in addition to a simple equilibrium process leading to complex systems (particles collected and interact and the formation of molecular complexes) and the occurrence of some molecular changes that characterize the chemical process, such as the driving force influencing the processes (A) and standard free energy (ΔG°) from which the system tends to move from any state to another, right up equilibrium state. As a result, the molecular complex carvedilol-serine 1: 1 is the fastest-balanced, and therefore the fastest formation, while the rest of the complex is observed a gradient positive value of A. This excludes a complex carvedilol-aspartic acid 1: 1 who have a low chemical affinity toward interaction and the formation of the molecular complex.

Computational study

Computational modeling has become a powerful tool in understanding detailed protein-ligand interactions at the molecular level and in rational drug design. To study the binding of a protein with multiple molecular species of a ligand, one must accurately determine both the relative free energies of all of the molecular species in solution and the corresponding microscopic binding free energies for all of the molecular species binding with the protein [20].

Many computational approaches, at different levels of complexity, have been developed and applied to different ligand-target systems. They essentially differ in the accuracy and resolution level of structural description and in the derived description of ligand-target interactions [21-24].

Carvedilol was studied theoretically to make a true based scientific comparison between theoretical and experimental complication study. However, carvedilol has a HOMO molecular orbital figure. 8, which indicate that HOMO orbital is at the core of the compound. So, the interaction with the receptor is certainly from the core.

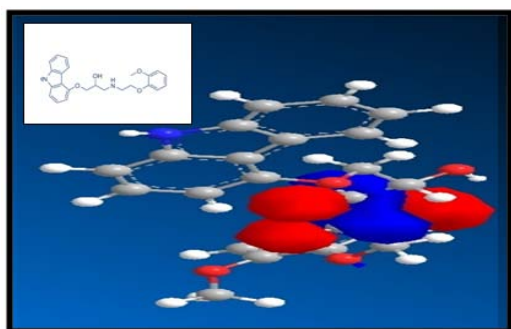


Fig. 8: HOMO molecular orbital of carvedilol

CRV-ASP Interaction

Carvedilol interaction with aspartic acid, which has HOMO orbital shown in (fig. 9), hydrogen bonds were made between CRV and Asp. (fig. 10), to achieve the interaction, (fig. 11)

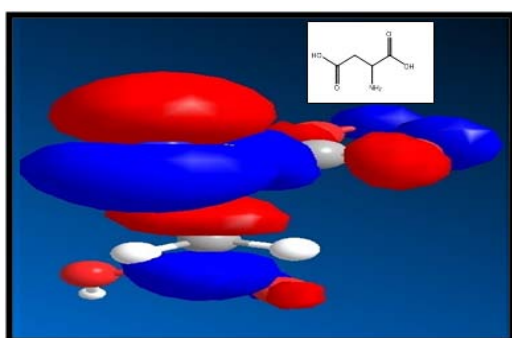


Fig. 9: HOMO molecular orbital of aspartic acid

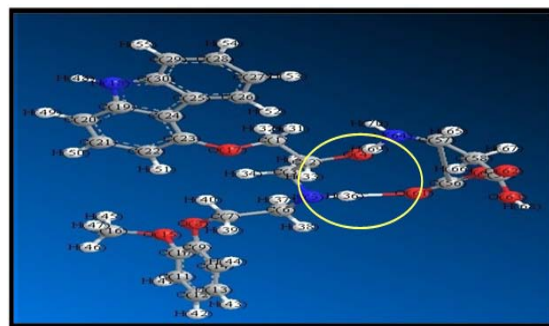


Fig. 10: Optimized structure of CRV+ASP molecular complex

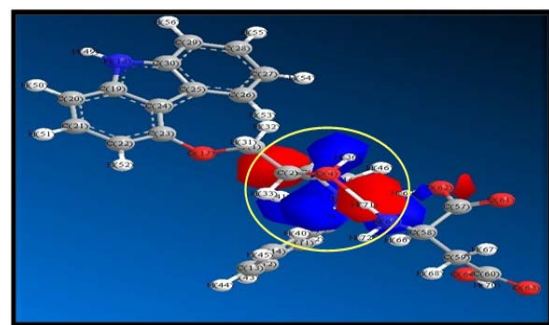


Fig. 11: HOMO molecular orbital of CRV+ASP molecular complex

CRV-ser interaction

Carvedilol interaction with serine which has HOMO orbital shown in (fig. 12), hydrogen bonds were made between CRV and Ser. (fig. 13), to achieve the interaction, (fig. 14)

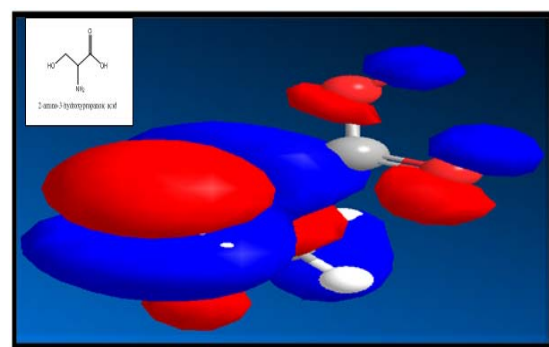


Fig. 12: HOMO molecular orbital of Ser

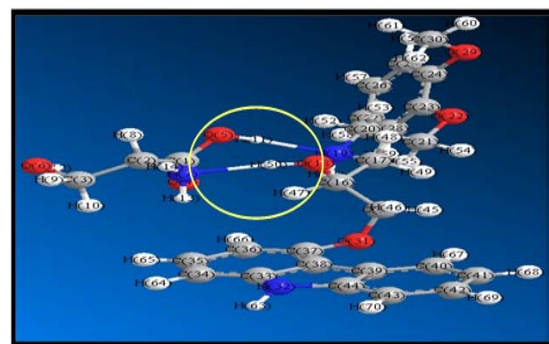


Fig. 13: Optimized structure of CRV.+Ser. Molecular complex

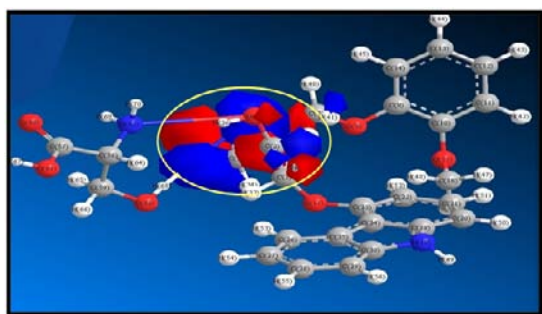


Fig. 14: HOMO molecular orbital of CRV+Ser. Molecular complex

Significant approach noted in comparison between theoretical and experimental complication results; this comparison depends on the value of HOMO-LUMO gap.(table 12, table 13) this may be summarized as below:

CRV-ASP interaction reduced HOMO-LUMO gap from 8.274 to 7.804eV, energy of HOMO

Increased after a complication with decreased of LUMO energy, which exactly agrees with experimental data, reinforce our suggested explanation.

CRV-Ser. Reduced in HOMO-LUMO gap from 8.274 to 8.132eV, the energy of HOMO increased after a complication with decreased of LUMO energy, agree with experimental data.

Table 12: Heat of formation and molecular orbital energies for each compound and its molecular complexes

Compound	HOMO/eV	LUMO/eV	Δ HOMO-LUMO/eV
CRV	-10.671	-2.397	8.274
ASP	-11.365	-0.300	11.065
CRV+ASP	-10.327	2.523	7.804
Ser	-10.888	-0.327	10.561
CRV+Ser	-10.541	-2.409	8.132

Table 13: relation between theoretical and experimental complication study

Compound	Δ HOMO-LUMO/eV theoretical	$E_{1/2}$ /V experimental	Notes
CRV	8.274	0.148	Reducing in Δ HOMO-LUMO gap that calculated theoretically, exactly agrees with negatively shifted of $E_{1/2}$, higher shifting in wave potential in CRV-ASP complex Accompanied by the highest decrease in the energy of HOMO-LUMO gap
CRV+ASP	7.804	0.124	
CRV+Ser	8.132	0.132	

CONFLICT OF INTERESTS

Declared none

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