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Determination of chemical potential for carvedilol, atenolol and Propranolol diffusion through SDS micelle solution

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ABSTRACT

Spectroscopic measurements of pharmaceutical compounds in phosphate buffer solution was conducted, compounds gave clear absorption peaks at 241 nm, 224.6 nm 289nm for carvedilol, atenolol and Propranolol respectively ,which is consistent with the standard values. The study of the spectroscopic properties of these compounds in polar and non-polar medium showed that the value of the extension coefficient and Λ_{max} reduced in the non-polar medium. The compounds showed a high stability with time in pH 7.4. Decomposition constants were calculated for each compound, and from which the half-life was calculated. Diffusion rate of pharmaceutical compounds through SDS micelles solution (an alternative model for cell membranes) with a concentration of 0.2 $\times 10^{-2}$ M was studied, and the chemical potential of each case was calculated and showed that Carvedilol can diffuse from the aqueous medium to inside micelle in a rate constant of 16.56$\times$ 10^{-3} min^{-1}, for Atenolol it is 18.913$\times 10^{-3}$ min^{-1} and 15.789 $\times 10^{-3} min^{-1}$ for Propranolol. The equilibrium constants for diffusion rate were determined and found to be 3.04109, 1.102039 and 1.923079 $min^{-1}$for Carvedilol, Atenolol and Propranolol respectively. The chemical potential also detected for the diffusion of each pharmaceutical compound, were found to be -2.8667,-0.25043 and -1.68547KJ.mol^{-1} respectively, which mean that the diffusion process was spontaneous for all compounds.

Keywords: Chemical potential, diffusion, carvedilol, atenolol, Propranolol, SDS, lipophilicity.

INTRODUCTION

Carvedilol, atenolol and Propranolol classified as Beta blocker compounds which are chemical substance having the ability to block the action of endogenous catecholamine such as adrenaline and noradrenalin upon β-adrenergic receptor, resulting in modifying the sympathetic nervous system activity [1]Self-organized assemblies such as micelles can change the rates of chemical and enzymatic reactions. anionic surfactants, such as sodium dodecyl sulfate (SDS), contain anionic functional groups at their head, that is, sulfate, sulfonate and phosphate.[2] Recently, surfactants have been of tremendous scientific importance because of their many promising applications in detergents, cosmetics, material fabrication, and drug delivery, among other areas.[3] The main property of surfactant systems is that their aggregation phenomena arise from various non-covalent interactions (such as π-π stacking, H-bonding, van der Waals interactions) operating at the molecular level.[4], therefore it has been adopted as an alternative model for cell membranes

MATERIALS AND METHODS

All chemicals used in the present investigation were obtained from commercial sources.

Electronic spectra were obtained on a Shimadzu 1800 UV-spectrometer using phosphate buffer as a solvent in the 400-200 nm range.

Preparation of buffer phosphate:
Preparation of aqueous solutions of phosphate buffer was occur by mixing a given volume of Mono potassium phosphate solution 0.0667 M and then complete the volume to 100 mL with Sodium phosphate dibasic dehydrate solution 0.0667M and then it was adjusting pH values by using pH meter.

Preparation of drugs solutions:
Aqueous solutions of Carvedilol (M. Wt.=406.5 g/mol.), Atenolol (M. Wt.=266.336 g/mol.) and Propranolol (M. Wt.=259.34 g/mol.) were prepared with a concentration of 0.98×10^{-4} M , 1.12×10^{-4} M and 1.15×10^{-4} M by weighing0.004, 0.003 and 0.003 g respectively in 100 mL , as a stock solutions .

Spectroscopic measurement of drugs solutions:
Spectroscopic measurements was performed to analyze the prepared drugs solution with concentration of 0.9×10^{-5}, 1.12×10^{-5} and 1.15×10^{-5} M for carvedilol, atenolol and Propranolol respectively in aqueous solution and cyclohexane using an equal pair of quartz cells with absorption lane of 1 cm, measurements were recorded at 37^0C.

Drugs diffusion measurement through SDS:
Spectroscopic measurements was performed for each drug solution in SDS micelle solution with a concentration of 2×10^{-2} M, using an equal pair of quartz cells with absorption path length of 1 cm, measurements were recorded at 37 ^{0}C.

RESULTS AND DISCUSSION

Spectroscopic properties of carvedilol:
Spectroscopic properties of Carvedilol with a concentration of 0.98×10^{-5} M at 37 C° have been measured in a different polarity media, figure (1). The study showed a deviation in the ʎmax and molar extension coefficient values when the media change from polar to nonpolar ,as in the buffer phosphate solution ʎmax = 241 nm agree with literature [5][6] while ʎmax = 240.1 nm in cyclohexane , these clarified in detail in table (1) below.

Spectroscopic properties of Atenolol:
Spectroscopic properties of Atenolol with a concentration of 1.12×10^{-5}M at 37 C° has been measured in a different polarity media , figure (2)The study showed a deviation in the ʎmax and molar extension coefficient values as the media change from polar to nonpolar ,as in the buffer phosphate solution ʎmax = 224.6 nm agree with literature[7], while ʎmax = 219 nm in cyclohexane , these clarified in detail in table (2) below.

Spectroscopic properties of Propranolol:
Spectroscopic properties of Propranolol with a concentration of 1.15×10^{-5} M at 37 C° has been measured at different polarity media , figure (3) The study showed a deviation in the ʎmax and molar extension coefficient values when the media change from polar to nonpolar , as in the buffer phosphate solution ʎmax = 289 nm agree with [8][9] while ʎmax = 285nm in cyclohexane, table (3) .

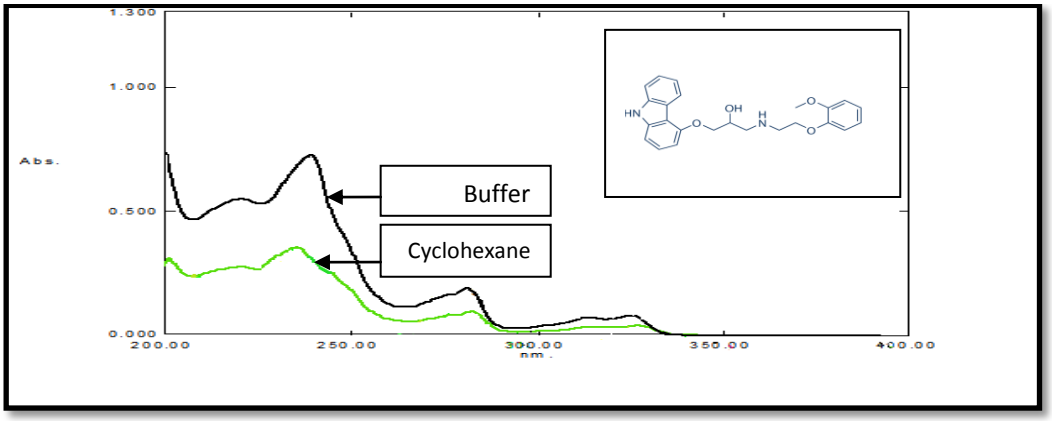

Figure (1): Absorption spectrum of carvedilol 0.98×10^{-5} M at 37 C° in phosphate buffer pH=7.4 and cyclohexane

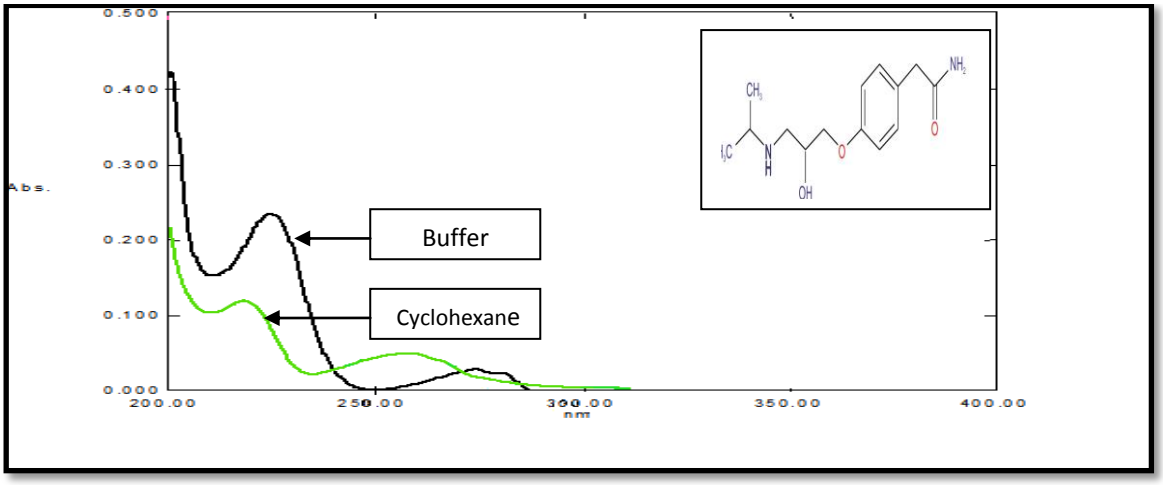

Figure (2): Absorption spectrum of atenolol1.12 ×10^{-5} M at 37 C° in phosphate buffer pH=7.4 and cyclohexane

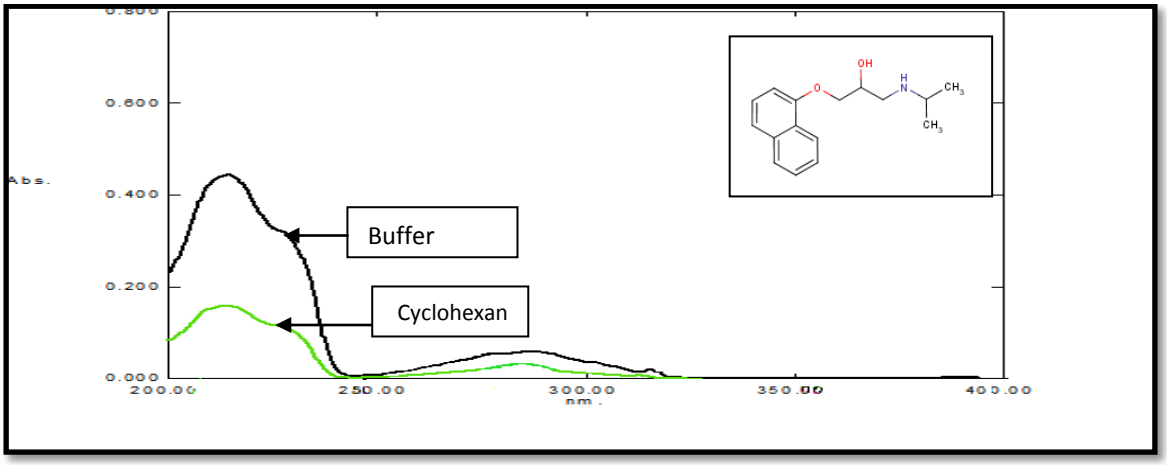

Figure (3): Absorption spectrum of Propranolol 1.15 ×10^{-5} M at 37 ^{0}C in phosphate buffer pH=7.4 and cyclohexane

Table (1) : Extension coefficient values of carvedilol 0.98 × 10^{-5}M solutions in different media

Wave length /nm	Extension coefficient/mol^{-1}.L.cm^{-1}	
	Buffer	Cyclohexane
223	41836.73	27551.02
225	43061.22	28469.39
227	44897.96	29183.67
229	48163.27	29591.84
231	52653.06	31836.73
233	58061.22	36122.45
235	61224.49	36734.69
237	63367.35	37346.94
239	67959.18	37857.14
240	68673.47	38571.43
241	70714.29	38061.22
243	66122.45	29591.84
245	57244.9	19183.67
247	52346.94	13775.51
249	47040.82	12755.1
251	38469.39	12244.9
253	21224.49	9183.673

Table (2): Extension coefficient values of Atenolol1.12× 10^{-5} M solutions in different media

Wave length /nm	Extension coefficient/$mol^{-1}.L.cm^{-1}$	
	Buffer phosphate	Cyclohexane
211	14107.14	9910.714
213	14821.43	10357.14
215	15446.43	10803.57
217	17142.86	11607.14
219	18125	11785.71
221	20000	11517.86
223	20535.71	11339.29
224	20892.86	11071.43
224.6	21339.29	10803.57
227	19642.86	8928.571
229	17232.14	8214.286
231	13125	5714.286
233	10446.43	5089.286

Table (3): Extension coefficient values of Propranolol 0.98 × 10^{-5} M solutions in different media

Wave length /nm	Extension coefficient/$mol^{-1}.L.cm^{-1}$	
	Buffer phosphate	Cyclohexane
255	1130.43	347.82
260	2000	782.6
265	2782.6	1130.43
270	3565.21	1391.3
275	4347.82	1739.13
280	4782.6	1739.13
285	5130.43	2000
289	5217.39	1913.04
290	4956.52	1826.08
295	4000	1391.3
300	3130.43	956.52
305	2608.69	782.6
310	1639.13	521.73
315	1391.3	521.73
320	347.82	173.91

Recapitulation of all above, the solvatochromism phenomenon is clearly observed in this study. This phenomenon is ascribed to a solvent-induced change in the ground-state structure from a less dipolar to a strongly dipolar one. Solvatochromatic effect has been used to determine the magnitude of the solute-solvent interactions such as the polarizability/polarity parameter, π*, of the solvent, as well as giving information about hydrogen bond. [10]

It has been noted that the peak Exposure to a blue shift toward the lower wave length in the non-polar solvent (cyclohexane) , that is refer to change in the geometry of the molecule due to the influence of the solvent which cause a significant change in the energy level of molecular orbital's .

So, decreasing in the energy level of the molecular orbital π caused shifting toward the lower wave length (hypsochromic shift). The effect in the spectrum of pharmaceutical compounds from solvent to another, Due to the difference in dielectric constant of solvents (it is 2.02 Debye for cyclohexane compare with 80 Debye for water) in addition to the difference in solvent –solute interaction in the ground and excited state .

It is noted here that the increase in the polarity of the media lead to an increase in the intensity of absorption band , returns to that the polar solvent increases the polarity of excited state that leads to increasing in the value of extinction coefficient .[11][12]

Usually, the spectral shifts are attributed to specific solute-solute and solute-solvent interaction in form of hydrogen bonding or bulk solvent properties.

For the molecular systems without intermolecular hydrogen bond, the spectral shifts are sensitive to the solvent polarity. Thus, in many molecules the bands (π-π*) are shifted bathochromically when the solvent polarity increases. [10][13]

Study the stability of pharmaceutical compounds in aqueous media at different pH:
Stability study of carvedilol showed a higher stability in acidic media [14], with a decomposition rate constant of (0.595, 0.824, 1.38 and 4.171) $\times 10^{-5}$ S^{-1} at pH 5, 6, 7.4 and 8 respectively.

The stability decrease with increasing the alkalinity of media as in table (4), rate constants and half- life time has been calculated as shown in table (5)

Table (4): Absorbedat241nm of carvedilol 0.98 $\times$ 10^{-5} M solutions with pH change at different duration time

pH	Absorbance		
	1 min	10 min	60 min
5	0.575	0.569	0.563
6	0.661	0.655	0.642
7.4	0.694	0.679	0.661
8	0.896	0.813	0.773

Table (5) :Dissociation rate constant and half-life times of carvedilol aqueous solutions at different pH

pH	K/ 10^{-5} min^{-1}	$t_{1/2}$ / hr.	Log K
5	0.595	32.31	-5.22
6	0.824	23.36	-5.08
7.4	1.38	13.17	-4.86
8	4.171	4.61	-4.38

The stability study of Atenolol showed a higher stability in acidic media [15]. With decomposition rate constant of 1.619, 1.978, 3.043 and 7.222 $\times 10^{-5}$ S^{-1} at pH 5, 6, 7.4 and 8 respectively. The stability decrease with increasing the alkalinity of media, table (6), dissociation rate constants and half- life time has been calculated as shown in table (7)

Table (6): Absorbedat224.6 nm of Atenolol 1.12 $\times$ 10^{-5} M solutions with pH change at different duration time

pH	Absorbance		
	1 min	10 min	60 min
5	0.323	0.318	0.305
6	0.207	0.199	0.193
7.4	0.235	0.222	0.211
8	0.164	0.149	0.127

Table (7): Dissociation rate constant and half-life times of Atenolol in aqueous solutions

pH	K/ 10^{-5} min^{-1}	$t_{1/2}$ / hr.	Log K
5	1.619	11.89	-4.79
6	1.978	9.73	-4.703
7.4	3.043	6.33	-4.516
8	7.222	2.66	-4.141

Table (8): Absorbedat289 nm of Propranolol 1.15 $\times$ 10^{-5} M solutions with pH change at different duration time

pH	Absorbance		
	1 min	10 min	60 min
5	0.153	0.153	0.151
6	0.09	0.09	0.088
7.4	0.07	0.07	0.068
8	0.082	0.079	0.075

Table (9): Dissociation rate constants and half-life times of Propranolol aqueous solutions

pH	K/ 10^{-5} min^{-1}	$t_{1/2}$ / hr.	Log K
5	0.371	51.88	-5.43
6	0.634	30.36	-5.198
7.4	0.818	23.5	-5.086
8	2.52	7.638	-4.598

The stability study of Propranolol shown a higher stability in acidic media , the drug is stable at acidic pH only; decomposes rapidly when alkaline solutions, Propranolol decomposes with oxidation of the isopropyl amine side-

chain.[16] ,with a decomposition rate constant of (0.371, 0.634, 0.818 and 2.52) $\times 10^{-5}$ S^{-1} at pH 5, 6 ,7.4 and 8 respectively. Table (8), rate constants and half- life time has been calculated as shown in table (9).

All of the above results shown that the pharmaceutical compounds hydrolyses depending on the pH value Vis the dissociation is alkaline stimulation**.**

Since, for all pharmaceutical compounds under study, the acidic stability was the dominant behavior.

The study also revealed that the absorbance value was un stable in different pH , That is may be due to the effect of pH on the dielectric constant of solvents and increasing a polarity of excited state that leads to increasing in the value of extinction coefficient in a different value depending on the nature of intra molecular between solvent-solute .

Diffusion study of pharmaceutical compounds through SDS micelle solutions:
Diffusion rate of pharmaceutical compounds through SDS micelles (an alternative model for cell membranes with a concentration of 0.2 $\times 10^{-2}$ M was studied, and the chemical potential of each case was calculated.

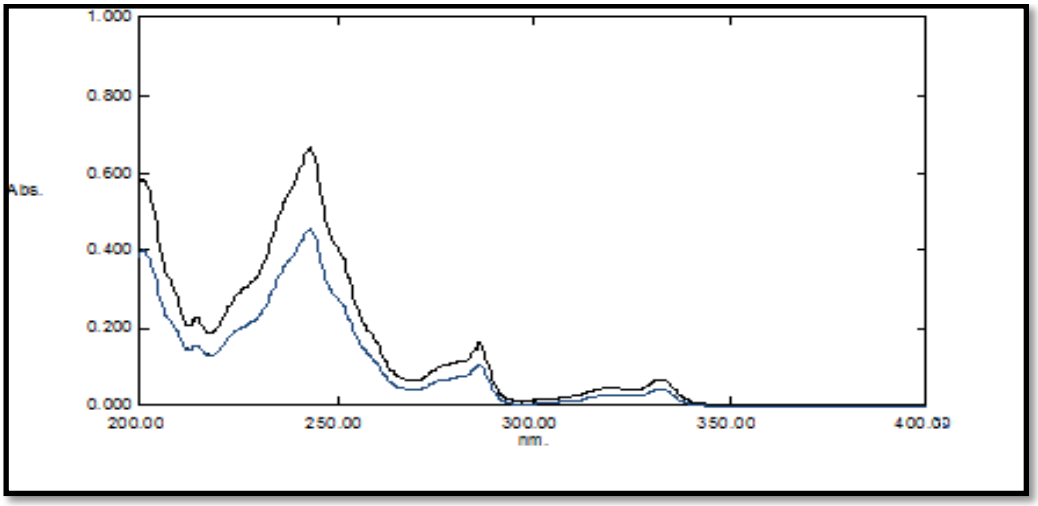

Figure (4): Initial and final absorption spectrum of carvedilol diffusion through SDS solution.

Table (10): Absorbance with time for carvedilol 0.98 $\times$ 10^{-5} M solution in SDS

Wave length/ nm	Time/min										
	1	10	20	30	40	60	80	100	120	160	1440
223	0.3	0.272	0.239	0.222	0.189	0.172	0.149	0.14	0.126	0.126	0.126
225	0.321	0.293	0.252	0.23	0.198	0.18	0.162	0.153	0.139	0.139	0.139
227	0.339	0.31	0.278	0.26	0.224	0.211	0.184	0.174	0.161	0.161	0.161
229	0.382	0.349	0.321	0.299	0.263	0.245	0.222	0.213	0.2	0.2	0.2
231	0.451	0.414	0.382	0.36	0.328	0.314	0.283	0.269	0.256	0.256	0.256
233	0.512	0.475	0.438	0.412	0.375	0.358	0.339	0.326	0.312	0.312	0.312
235	0.564	0.527	0.481	0.464	0.427	0.414	0.383	0.373	0.356	0.356	0.356
237	0.616	0.583	0.546	0.52	0.484	0.453	0.435	0.417	0.403	0.403	0.403
239	0.637	0.609	0.572	0.546	0.514	0.501	0.478	0.46	0.447	0.447	0.447
240	0.644	0.615	0.585	0.567	0.532	0.509	0.487	0.473	0.451	0.451	0.451
241	0.641	0.605	0.563	0.56	0.522	0.507	0.48	0.471	0.442	0.442	0.442
243	0.586	0.544	0.507	0.473	0.417	0.405	0.37	0.343	0.321	0.321	0.321
245	0.464	0.432	0.39	0.364	0.328	0.306	0.274	0.261	0.247	0.247	0.247
247	0.421	0.38	0.338	0.321	0.289	0.271	0.253	0.243	0.221	0.221	0.221
249	0.382	0.345	0.312	0.291	0.254	0.236	0.214	0.2	0.183	0.183	0.183
251	0.313	0.28	0.252	0.222	0.185	0.167	0.145	0.134	0.118	0.118	0.118

In the diffusion study of carvedilol , There was a noticeable change been in absorbance value with time .figures (4),(5) tables (10) , (11) The calculations was according to the equation below at a λ_{max} = 240 nm which is the maximum wave length of carvedilol diffusion through SDS

$$A_{tot} = A_{aq} + A_{org}$$
$$A_{tot} = \varepsilon_{aq} C_{aq} + \varepsilon_{org} [C_{initial} - C_{aq}]$$

$$C_{aq} \underset{}{\overset{K_{eq}}{\rightleftharpoons}} C_{org}$$

out side micelle *in side micell*

From table (1) **:**

$$A_{tot} = 68673.47\ C_{aq} + 38571.43[C_{initial} - C_{aq}]$$

Putting primary concentration and arrange the equation:

$$A_{tot} - 0.378 = 30102.04\ Caq$$

Table (11) :concentration of carvedilol in aqueous and organic media with time

Time/min	$C_{.aq}/10^{-5}$ M	$C_{.org}/10^{-5}$ M	Xe/(Xe-X)	Ln [Xe/(Xe-X)]
1	0.883661	0.096339	1.150259	0.139987
10	0.787322	0.192678	1.353658	0.302811
20	0.687661	0.292339	1.656716	0.504838
30	0.627864	0.352136	1.913793	0.649087
40	0.511593	0.468407	2.740741	1.008228
60	0.435186	0.544814	3.827586	1.342234
80	0.362102	0.617898	6.166666	1.819158
100	0.315593	0.664407	10.09091	2.311635
120	0.242508	0.737492	×	×

Where:
XP: is a concentration of drug in organic media at time t
Xe::is a concentration of drugin organic media at equilibrium
C_{eq}: a concentration of drug in aqueous media, C_{org}: a concentration of drug in organic media

From the first order equation for the reversible reaction:

$$t = 1/(k_1+k_{-1})\ \ Ln\ [Xe/(Xe-X)]$$
$$t_{0.5} = 0.693/(k_1 + k_{-1})$$
$$k_{eq} = k_1/k_{-1}$$
$$k_{eq} = X_{eq}/(a-X_{eq})$$

by plutting the relation between ***Ln [Xe/(Xe-X)]***and time figure(3-43) ,we obtained a stright line with a slop equal to($k_1 + k_{-1}$), thus :

$$Slop = 0.022$$
$$So:\ k_1+k_{-1} = 0.022\ min^{-1}$$
$$K_{eq} = k_1/k_{-1} = 3.04109$$
$$K1 = 0.016556 = 16.56*10^{-3}\ min^{-1}$$
$$K\ -1 = 0.005444 = 5.4\ *10\text{-}3\ min^{-1}$$
$$t_{0.5} = 31.5\ min = 0.00875\ hr$$
$$\Delta G^{o} = -\ RT\ ln\ Keq$$
$$\Delta G^{o} = -2.8667\ K\ J\ mol^{-1}$$

In the diffusion study of Atenolol , also a noticeable change have been shown in absorbance value with time .figures (6), (7) tables (12) , (13) The calculations was according to the equation below at a λ_{max}= 223 nm which is the maximum wave length of Atenolol diffusion through SDS

$$A_{tot} = A_{aq} + A_{org}$$
$$A_{tot} = \varepsilon_{aq} C_{aq} + \varepsilon_{org} [C_{initial} - C_{aq}]$$

From table (2):

$$A_{tot} = 20535.71\ C_{aq} + 11339.29\ [C_{initial} - C_{aq}]$$

Putting primary concentration then arrange the equation:

$$A_{tot} - 0.127 = 9196.42\ C_{aq}$$

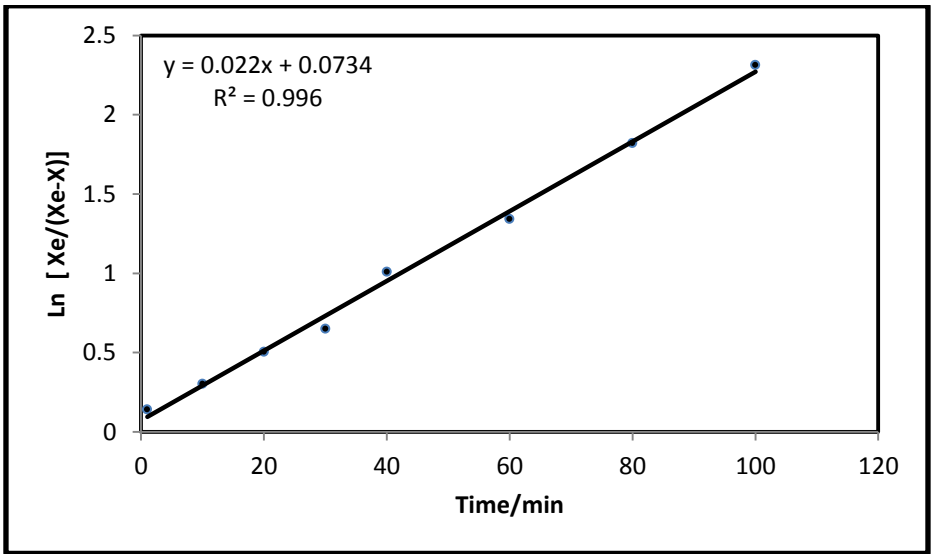

Figure (5): relation between Ln [Xe/(Xe-X)] vis. time for diffusion of carvedilol through SDS micelles

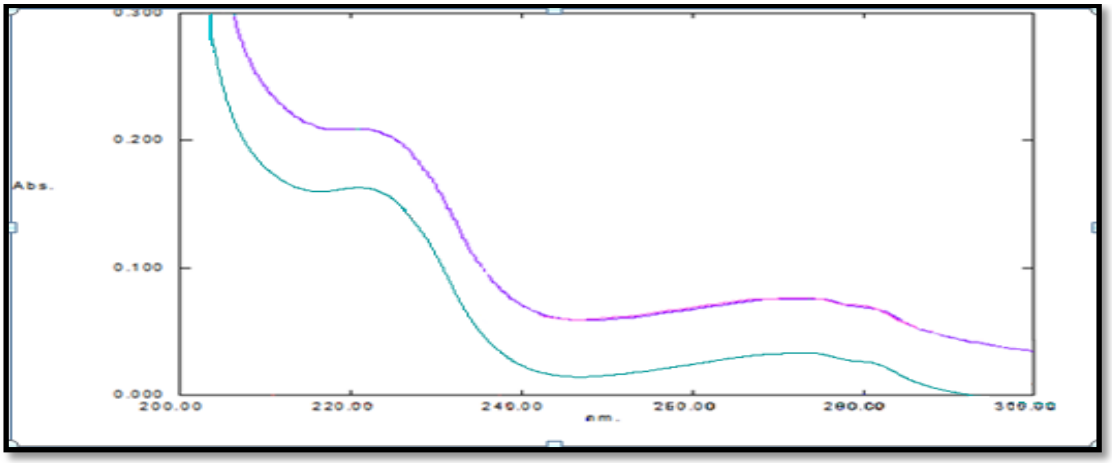

Figure (6): initial and final absorption spectrum of Atenolol diffusion through SDS solution

Table (1): Absorbance with time for Atenolol 1.12 ✕ 10^{-5} M solution in SDS

Wave length/nm	Time/min											
	1	**10**	**20**	**30**	**40**	**60**	**80**	**100**	**120**	**160**	**200**	**1440**
211	0.243	0.227	0.226	0.223	0.225	0.232	0.22	0.213	0.208	0.188	0.185	0.185
213	0.231	0.218	0.217	0.214	0.214	0.221	0.212	0.205	0.203	0.203	0.2	0.2
215	0.222	0.214	0.211	0.208	0.207	0.215	0.206	0.196	0.189	0.179	0.173	0.173
217	0.217	0.214	0.207	0.2	0.198	0.201	0.192	0.174	0.17	0.166	0.163	0.163
219	0.217	0.215	0.208	0.201	0.199	0.202	0.193	0.177	0.174	0.171	0.167	0.167
221	0.218	0.215	0.21	0.202	0.201	0.203	0.194	0.18	0.178	0.176	0.173	0.173
223	0.222	0.219	0.211	0.207	0.201	0.197	0.19	0.185	0.182	0.179	0.176	0.176
224.6	0.212	0.209	0.206	0.2	0.199	0.193	0.183	0.176	0.172	0.174	0.172	0.172
227	0.2	0.196	0.191	0.186	0.181	0.186	0.18	0.17	0.166	0.165	0.154	0.154
229	0.181	0.179	0.176	0.17	0.166	0.171	0.166	0.157	0.154	0.152	0.148	0.148
231	0.161	0.157	0.156	0.152	0.153	0.155	0.15	0.142	0.14	0.139	0.131	0.131
233	0.132	0.133	0.129	0.124	0.123	0.129	0.123	0.113	0.105	0.108	0.105	0.105

by plutting the relation between ***Ln [Xe/(Xe-X)]***and time figure(3-45) , a stright line was obtained with a slop equal to($k_1 + k_{-1}$), thus :

Slop = 0.017

So: $k_1+k_{-1} = 0.017\ min^{-1}$

$K_{eq} = k_1/k_{-1} = 1.102039$

$K_1 = 0.008913\ min^{-1}$
$K_{-1} = 0.008087 min^{-1}$
$t_{0.5} = 40.76471\ min = 0.011324 hr$
$\Delta G^o = - RT\ ln\ Keq$
$\Delta G^o = -0.25043 K\ J\ mol^{-1}$

Table (7): concentration of Atenolol in aqueous and organic media with time

Time/min	C.aq/10^{-5} M	C.org/10^{-5} M	Xe/(Xe-X)	Ln [Xe/(Xe-X)]
1	1.033011	0.086989	1.173911	0.160341
10	1.000389	0.119611	1.255812	0.227782
20	0.913399	0.206601	1.542854	0.433634
30	0.869904	0.250096	1.741932	0.554995
40	0.804661	0.315339	2.159996	0.770106
60	0.761166	0.358834	2.571424	0.94446
80	0.685049	0.434951	3.857136	1.349925
100	0.63068	0.48932	5.999989	1.791758
120	0.598059	0.521941	8.999984	2.197223
160	0.565437	0.554563	17.99997	2.89037
200	1.033011	0.086989	×	×

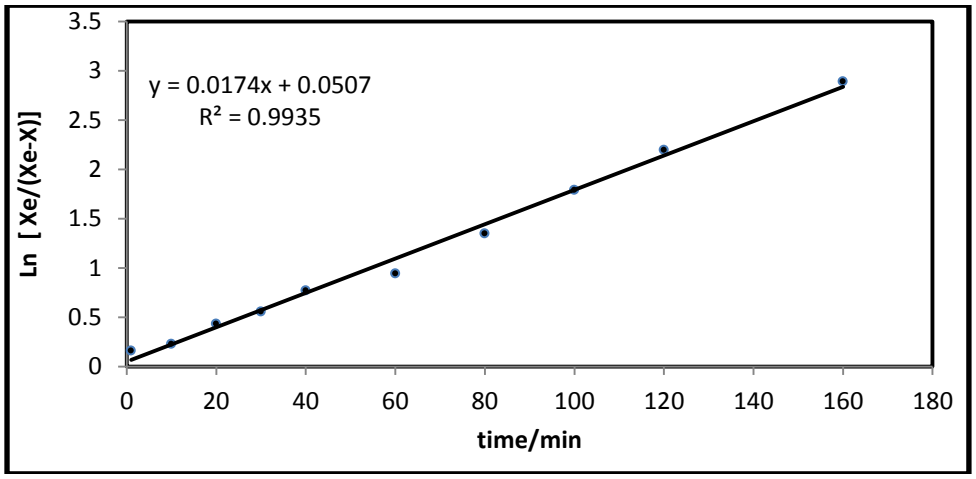

Figure (14): relation between Ln [Xe/(Xe-X)] vis. time for diffusion of atenolol through SDS micelles

Diffusion study of Propranolol showed noticeable change in absorbance value with time .figures (8), (9). Tables (15), (16) The calculations was according to the equation below at a λ_{max}= 289 nm which is the maximum wave length of Propranolol diffusion through SDS

$A_{tot} = A_{aq} + A_{org}$
$A_{tot} = \varepsilon_{aq} C_{aq} + \varepsilon_{org} [C_{initial} - C_{aq}]$

From table (3):
$A_{tot} = 5217.39\ C_{aq} + 1913.04\ [C_{initial} - C_{aq}]$

Putting primary concentration and arrange the equation:
$A_{tot} - 0.022 = 3304.35\ C_{aq}$

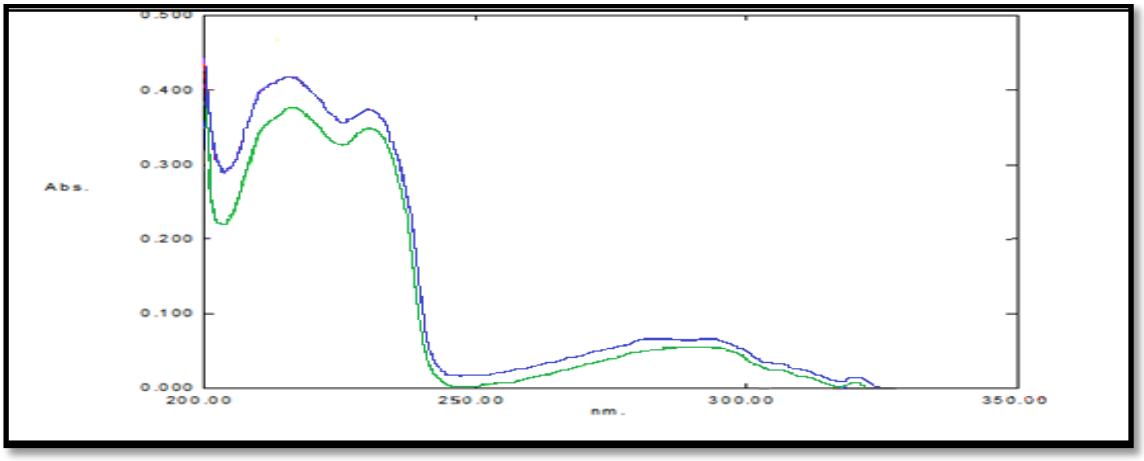

Figure (8): Initial and final absorption spectrum of Propranolol diffusion through SDS

Table (15): Absorbance with time for Propranolol 1.15 ✕ 10^{-4} M solution in SDS

Wave length/ nm	Time/min										
	1	**10**	**20**	**30**	**40**	**60**	**80**	**100**	**120**	**160**	**1440**
255	0. 018	0.016	0.01	0.008	0.008	0.004	0.004	0.001	0.001	0.001	0.001
260	0.025	0.024	0.019	0.015	0.013	0.01	0.009	0.007	0.007	0.007	0.007
265	0.032	0.031	0.026	0.024	0.023	0.02	0.018	0.016	0.016	0.016	0.016
270	0.042	0.041	0.036	0.033	0.032	0.029	0.027	0.024	0.024	0.024	0.024
275	0.05	0.046	0.042	0.04	0.039	0.034	0.035	0.032	0.031	0.031	0.031
280	0.053	0.051	0.046	0.044	0.042	0.036	0.036	0.033	0.032	0.032	0.032
285	0.055	0.052	0.048	0.046	0.043	0.038	0.037	0.034	0.033	0.033	0.033
289	0.058	0.054	0.05	0.047	0.044	0.04	0.039	0.037	0.035	0.035	0.035
295	0.055	0.051	0.047	0.045	0.042	0.039	0.036	0.033	0.032	0.032	0.032
300	0.047	0.045	0.041	0.038	0.038	0.036	0.035	0.032	0.031	0.031	0.031
305	0.031	0.029	0.025	0.023	0.023	0.02	0.021	0.019	0.019	0.019	0.019
310	0.023	0.022	0.018	0.015	0.015	0.013	0.012	0.01	0.01	0.01	0.01
315	0.012	0.01	0.006	0.004	0.004	0.002	0.001	0	0	0	0

Table (16) :concentration of Propranolol in aqueous and organic media

Time/min	C.aq/10^{-5}	C.org/10^{-5}	Xe/(Xe-X)	Ln [Xe/(Xe-X)]
1	1.089473	0.060527033	1.086958	0.083383
10	0.96842	0.181579584	1.315791	0.274438
20	0.847368	0.302632136	1.666668	0.510827
30	0.756578	0.39342155	2.083335	0.73397
40	0.665789	0.484210964	2.777781	1.021652
60	0.544736	0.605263516	5.000005	1.609439
80	0.514473	0.635526654	6.250006	1.832582
100	0.453947	0.69605293	12.50001	2.52573
120	0.393421	0.756579206	×	×

by plutting the relation between ***Ln [Xe/(Xe-X)]***and time figure(3-47) ,we obtained a stright line with a slop equal to($k_1 + k_{-1}$), thus :

Slop = 0.024
So: $k_1+k_{-1} = 0.024\ min^{-1}$
$K_{eq}= k_1/k_{-1}= 1.923079$
$K_1 =0.0157895min^{-1}$
$K_{-1}= 0.00821052min^{-1}$
$t_{0.5}=28.875\ min = 0.008021hr$
$\Delta G^o = - RT\ ln\ Keq$
$\Delta G^o = -1.68547K\ J\ mol^{-1}$

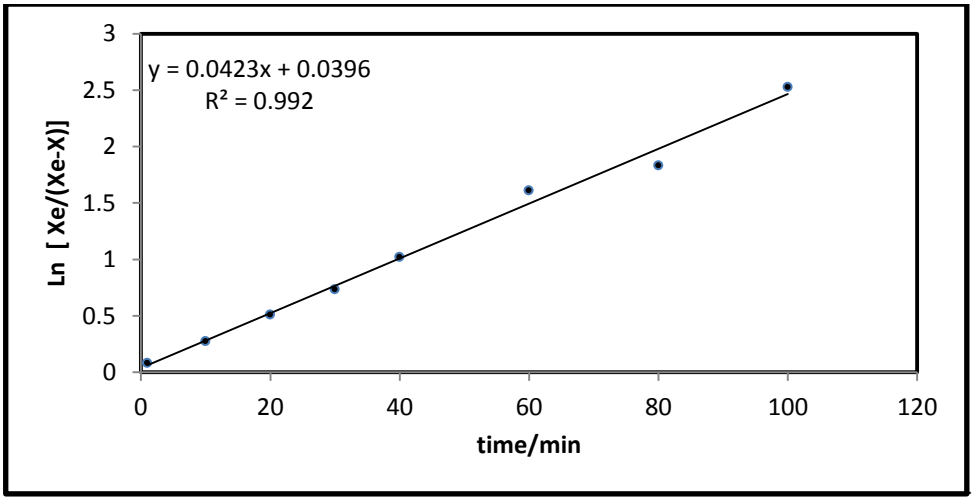

Figure (9): relation between Ln [Xe/(Xe-X)] vis. time for diffusion of atenolol through SDS micelles

As there is no reaction between carvedilol , atenolol and Propranolol with phosphate buffer component , which used as a solvent in preparation of SDS solution , taking into consideration the high value of extension coefficient of carvedilol , atenolol and Propranolol in aqueous media compare with the low value in organic non polar solvent , then , the decreasing in the absorbance of these pharmaceutical compounds in SDS solution refers to Entering them from the aqueous solution outer of micelle into the organic media inside the micelle.

The behavior of drugs agree with the fact of the difference on their lipophilicity, carvedilol a high lipophilic molecule[17][18] given the higher rate of diffusion and the highest ΔG^o value refers to spontaneously of diffusion process of carvedilol ,followed by Propranolol another lipophilic molecule with a low lipophilicity than carvedilol[19][20]Which is reflected on the value of diffusion rate and ΔG^o value , came last atenolol the hydrophilic molecule[21][22] with a lowest value of diffusion rate and ΔG^o value

In addition, by comparison between the rate constant of diffusion2200×10^{-5}, 1700×10^{-5},2400×10^{-5} min^{-1} for carvedilol , atenolol and Propranolol with that of Decomposition in aqueous media at pH=7.4 which equal to1.38×10^{-5} ,3.043×10^{-5}, 0.818×10^{-5} min^{-1} , respectively it is clearly noted the great difference in both case . the conclusion is that, The measured rate constant does not return to the speed of hydrolysis , but back to the rate of the fast entry of drugs into micelles and stability within them. The negative value of standard free energy of drugs refers to the Spontaneity of their diffusion process into the micelles.

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