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Research Article

Possible kinetic Equilibria of 5-Fluorouracil Drug with Anionic and Cationic Micelles

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Abstract

Initially, anionic (SDS) and cationic (TBAB) micelles were prepared with a suitable concentration (0.1 mM) in potassium phosphate buffer at physiological conditions (pH=7.4 and T=37°*C*). The followed method of micelles molecules was distinguished by fixed its molecules as a monomer, unclouded and clarity solutions as well as agreement with an ideal linearity of Beer-Lambert law. Then, the spectral checkup of 5-FU drug (0.1 mM; with =0.673 at λ=266 nm) and the micelles solutions (as blank solution; without any interferences) were achieved in a phosphate buffer at physiological conditions. This matter was encouraged on complete assessment of the equilibrium state between chemotherapy compound (5-FU) with micelles, which it can be accompanied into formation processes of molecular complexes. The produced spectral lines of molecular complexes were followed as first order interactions for SDS (at 268 nm; k^*=7.60× 10^{-3} min^{-1}; $t_{1/2}$= 91.20 min) and TBAB micelles (at 267 nm; k^*=17×10^{-3} min^{-1}; $t_{1/2}$= 40.76 min). mathematically, the same obtained results were treated as a reversible equilibrium from first order interaction; with same physicochemical parameters for TBAB micelles (with; Keq=17.72). But, the opposite properties of SDS micelles were extracted (k_1=15.17 × 10^{-3}; k_{-1}= 1.22 × 10^{-3} min^{-1}; τ^*= 42.25 min; Keq=12.38) as result of complicated interactions involved the relaxation equilibrium processes. The molecular complexes interactions (5-FU drug and micelles) were occurred spontaneously, with free energies favourable for van der Waals forces or hydrogen bonding (ΔG^0<10 kJ/mol).

1. Introduction

Cancer is one of the largest dangerous diseases that led to mortality worldwide. The global Cancer Statistics 2020 reports is estimated of 19.3 million new cancer cases [1, 2]. 5-fluorouracil (5-FU) chemotherapy compound (5-fluoro-1H-pyrimidine-2,4-dione) is considered the most common cancer treatment method. The various antineoplastic drugs are used to remove cancer cells and prevent the tumor growth in human body [3]. The targeted delivery of cancer drugs to their action sites with optimal concentration and suitable bioavailability by selectively into tumor tissues has been considered an effective strategy to improve their chemotherapeutic activities [4, 5]. 5-FU is phase specific drug that is a pyrimidine analog used in cancer treatment, it interferes with nucleic acids synthesis by substituting for the normal building blocks of RNA and DNA [6, 7]. This agent (trade names: Adrucil, Carac and Efudex) damages the cells during the S phase (involved DNA replication in cell cycle of human body; Figure 1) for at least about 18 to 20 h [8].

Generally, a circulating conventional treatment is less efficient and causes side effects because it is non selective of drug distribution in tissue. For example, 5-FU drug might include diarrhea, nausea, vomiting, stomach/abdominal pain and general weakness [2, 9].

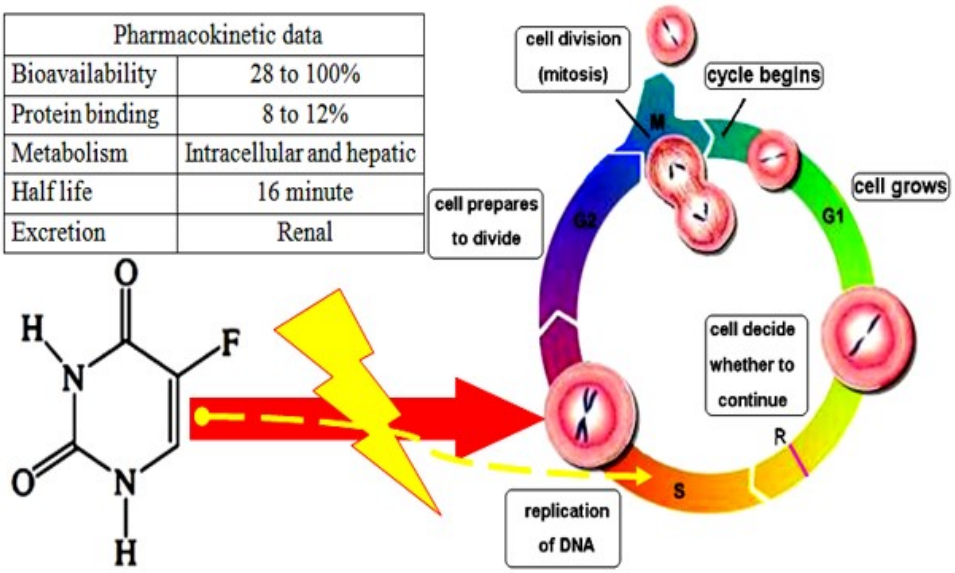

Figure 1: Diagram of pharmacokinetic data and effect of 5–FU on the cell cycle in human body

The micelles are act as delivery vehicles of drug, so it necessary their existence for enhanced bioavailability of drugs in the body. Extensively, natural surfactant micelles in gastrointestinal fluid were used to increase solubility and drugs delivery such as lecithin, bile salts, cholesterol and its esters [10]. The surfactant consist of two parts are hydrophobic (tail; which can direct its self at the core) and hydrophilic (polar head; it is periphery exposed to surrounding solvent) [11–13]. The shape and size of surfactant (spherical, cylindrical, bilayer or the reverse structure in nonpolar media) are controlled by factors such as surfactant concentration, composition, solution pH, ionic strength and temperature [14, 15].

Generally, surfactant is behaving in diluted aqueous solutions as a strong electrolyte (it appears as monomer); but at concentrated solutions (by excess about critical micelles concentration) would be formed aggregation (known as a micelles) [2, 15]. Many drugs are need to bind and cross the cellular membrane to perform their action, and the surfactant can be considered similar to simple membrane systems [16–18]. In order to overcome these problems, kinetics of chemotherapeutic drug should be known by easily accurate pattern at the molecular level [19]. Therefore, assessment of the drug-membrane interactions behavior of anticancer drug 5-FU at physiological conditions in aqueous solution was investigated in presence of some surfactants.

2. Methods

2.1. Materials

All chemicals used in the present investigation were obtained from commercial sources, with highest available purity. 5-FU was purchased from Sigma Aldrich, USA, with purity of 99.99%. KH_2PO_4 and K_2HPO_4 of phosphate buffer solution (has pH=5∼8) were obtained from Sdfine chemical limited-Mumbai, India.Sodium dodecyl sulphate (SDS:$CH_3(CH_2)_{11}OSO_3Na$; anionic surfactant), Tetra butyl ammonium bromide (TBAB; cationic surfactant) were supplied by GCC-England with the purity of 99.99 %.

2.2. Instruments and method

The all electronic absorption spectra of ultraviolet-visible spectroscopy (UV-Vis) were recorded by Shimadzu (Japan) 1800PC-computrace spectrophotometer, version 2.42, by using 1cm matched quartz cells in aqueous solution of potassium phosphate buffer as a solvent. Measurements of pH were adjusted by using WTW (Germany) Inolap720 pH meter with electrode Sentix41. The distilled water produced by GFL (Germany) apparatus was purified via SG ionic exchangers. The prepared deionized water was measured in WTW (Germany) Inolap720 Conductivity meter. The temperature of all prepared solutions was regulated within 37°*C*, by using Julabo (Germany) circulator water bath. All weights were taken by Mettler Toledo (Switzerland) SAB204S, sensitive electronic balance. The some apparatus are used in preparation of micelles compounds such as sonifier; model 150D for liquid processor (ultrasonic waves) with probe (Branson; USA), heater with magnetic stirrer (IKA; India), cooling centrifuge (15,000 rpm;USA) and Oven with controlled temperature (Heidolph; Germany).

All glassware was thoroughly cleaned with aqua region, and rinsed with distilled water as well as deionized water prior its use. The deionized water (has conductivity = 0.5 ∼ 0.7 μ S/cm) was used to prepare all the solutions.

Preparation of buffer phosphate

The phosphate buffer was prepared by mixing a suitable volume of potassium dihydrogen phosphate (0.0666M) with dipotassium hydrogen phosphate (0.20M). Continuously, the prepared solution of phosphate buffer was adjusted by using a calibrated pH meter.

Preparation of the different micelle (surfactants)

The different types of micelles [SDS and TBAB at 0.1 mM, for fixed molecules as a monomer] were prepared by phosphate buffer solution at physiological conditions (pH=7.4 and T=37°*C*) directly. All the prepared solution of micelles is mixing by heater magnetic stirrer (40°*C*,15 min), and it exposure to the ultrasonic waves as discontinuous pulses (by; sonicator; 10 min). End step, all the solutions of surfactants are treatment by cooling centrifuge (2,000 rpm, 10 min, 37°*C*); to ovoid aggregate of molecules and guaranty the solve all molecules of micelles [2, 20, 21]. the resulted solutions were structural directing agents (distinguished by unclouded and clarity), it was stored in vacuum oven in closed dark volumetric flask at controlled temperature.

Preparation of drug solutions

The solution of 5-FU drug (M.wt.=130.08 gm/mol) was prepared with concentration of 0.1 mM in micelles solution that prepared previously by phosphate buffer (at pH=7.4 and T=37°*C*) by weight of 0.0013 gm in 100 mL calibrated flask. The prepared method of 5-FU drug was used with a different types of surfactants with simple continuous shaking through the preparation process.

3. Results and Discussion

At the beginning, investigation of 5-FU drug in the phosphate buffer solution was performed at physiological conditions to get on absorption peak corresponded to a standard value Figure 2. The electronic wave of 5-FU drug has spectral distinguished data involved a maximum wave length (λ=266 nm) with absorption (A =0.673) [2, 3]. In all spectral measurements that a this study, the test solution of 5-FU drug has constant parameters such as concentration (0.1 mM); temperature (T=37°*C*); acidity function (pH=7.4). As well as, the blank solution (without any signal or absorption peak) in each time was surfactants solution which prepared previously by a potassium phosphate buffer (at pH=7.4; T=37°*C* and same concentration of 5-FU drug 0.1 mM). Therefore, the experimental applied studies between 5-FU drug with a different micelles can be summarized as follow:

3.1. Assessment interaction of 5-FU drug with SDS (as an anionic surfactant)

Experimentally, after certainty an empty phosphate buffer, SDS micelle and 5-FU drug from any possible spectral problems; 5-FU drug (0.1 mM) was prepared by direct mixing with SDS micelle at physiological conditions (pH=7.4 and T=37°*C*). The obtained experimental spectral data for interaction 5-FU drug with SDS micelle in potassium phosphate buffer (at pH=7.4, T=37°*C*) are presented easily without any complicated as shown in Figure 2 and Table 1.

The comparison of resulted data in this work for interaction 5-FU drug with SDS micelles in literature is achieved, but detailed kinetic equilibrium report don't founded. Previously scientific studies, it suggests that small molecules (such as; 5-FU drug and paracetamol) interact with SDS micelles by an exothermic process (ΔH_m^0=-ve). It is noticed too, the partition of SDS micelles can be tuned by controlling hydrophobic character of drug spontaneously (ΔG_m^0=-ve) in a presence or without NaCl salt at T=25°*C* [19, 22, 23].

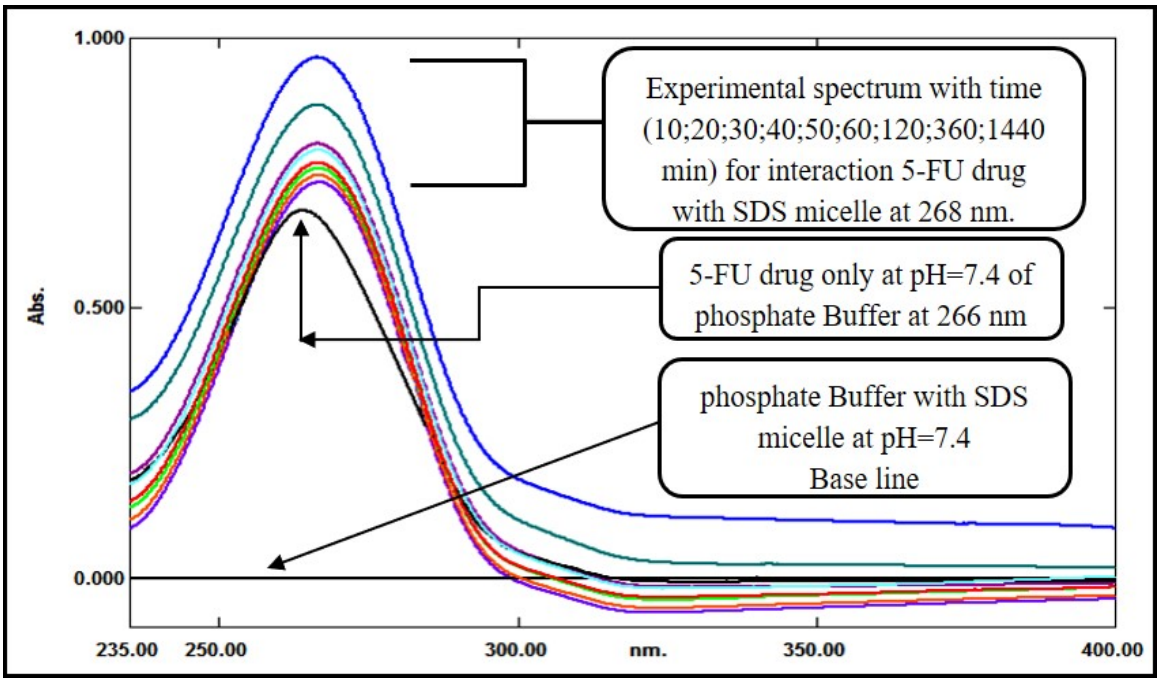

Figure 2: The experimental spectral for interaction 5-FU drug with SDS micelle in phosphate buffer at same concentration, acidity function and temperature (conc.= 0.1 mM, pH=7.4, T=37°*C*)

As shown results, The wave of 5-FU drug shifts slightly into the visible spectrum region after interaction with SDS micelle. The new obtained wave (at 268 nm) may be formed as a result as transient molecular complex (it is re formatted continuously) between 5-FU drug and SDS micelle in the aqueous solution. This matter is encouraged following the interaction between 5-FU drug and another micelle at same physiological conditions in potassium phosphate buffer.

3.2. Assessment interaction of 5-FU drug with TBAB (as a cationic surfactant)

By the same followed mode in SDS micelle, interaction between 5-FU drug and TBAB micelle is studied at a physiological conditions (conc.= 0.1 mM, pH=7.4, T=37°C). The experimental spectral data for this interaction in potassium phosphate buffer are achieved as fixed in Figure 3 Table 1.

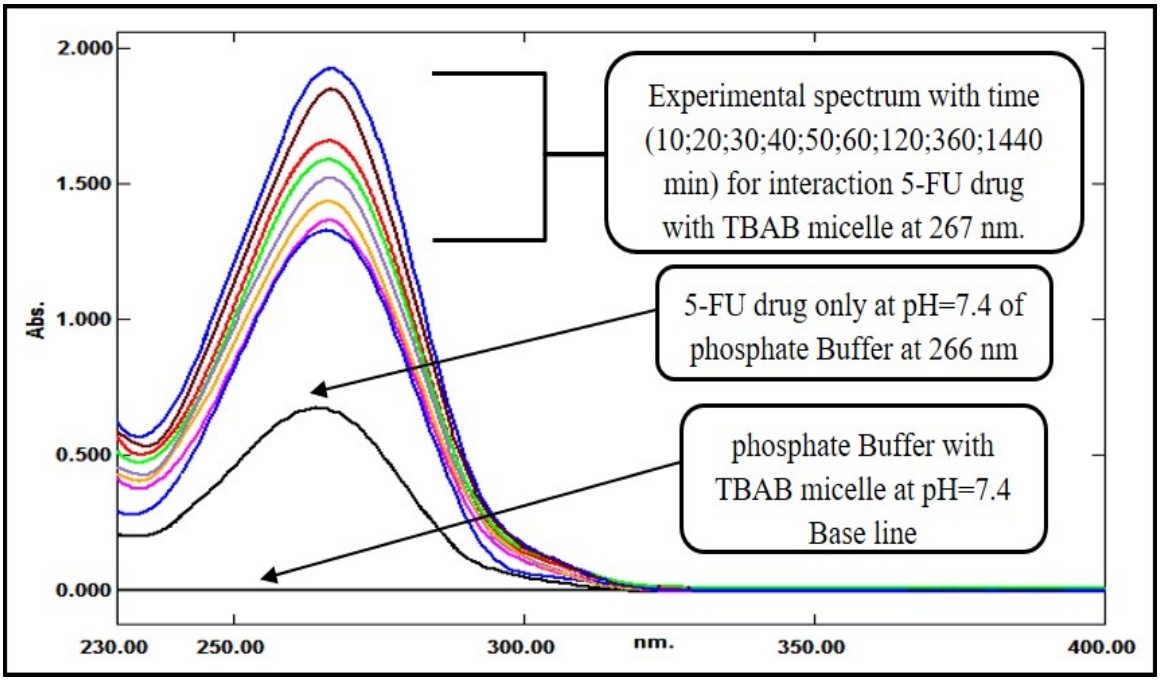

Figure 3: The experimental spectral for interaction 5-FU drug with TBAB micelle in phosphate buffer at same concentration, acidity function and temperature (conc.= 0.1 mM, pH=7.4, T=37°C)

3.3. Kinetic stability of 5-FU drug with different micelles

According to previous studies, the almost interactions are followed equation of first-order reaction Equation (1) kinetically. So, the rate constant of interaction between 5-FU drug and micelles molecules can be calculated by plotting ln (At) versus time (slope = k^*) [3, 5] as follows.

$$\ln(A_t) = \ln(A_0) - k^* t \tag{1}$$

where,
$A_t = (A_\infty - A_x)$ absorbance of molecular complex with time.

Mathematically, the absorbance value of molecular complexes at origin time (A_o) can be extracted by intercept of straight line either from equation of first-order reaction or the direct plot of (A_x) versus time (as fixed in Table 1; A_x at origin time = 0.724; 1.304 of SDS and TBAB respectively). For attention, the absorbance values that used in calculations the rate constant of interaction (5-FU drug with micelles) graphically are limited between 10-120 min only. As well as, the absorbance at time 360 min is equivalent to equilibrium (A_e), and 1440 min as a primary concentration of molecular complex (A_∞), and all spectral measurements were repeated for three times without any change in absorbance values.

The below results showed that interactions between reacted molecules (5-FU drug and micelles) in TBAB micelle case are more regulated and stability. The half time of TBAB micelle was smallest (40.76 min) and rate constant faster ($17 \times 10^{-3} min^{-1}$) when the compared with obtained resulted of SDS micelle. The regular and rapid interactions in TBAB micelle (as a cationic molecules) may be back into the negative charge that located on 5-FU drug, which it thought presence as a result as the fluoro atom in structure of drug Figure 1.

If suggested that 5-FU drug interaction with micelles molecules in aqueous solutions of phosphate buffer as a complicated process from first order reaction, instead of as a simple interaction as assumed previously. It will be required rearrangement of the same data for 5-FU drug interaction with micelles Table 1 according to a reversible equilibrium equation of first order reaction.

3.4. Kinetic Equilibrium of 5-FU interaction as a reversible first order reaction

The apparent repeated values of absorption after six hours (360 min) for 5-FU drug interaction with micelles although re measurement for more than three times; led to assume the equilibrium state occurred between interacted molecules. Therefore, the results obtained could be applied in the equation of reversible equilibrium from first order reaction Equation (2) of 5-FU drug interaction with micelles Table 2. Also, it can binding between kinetic and thermodynamic behavior in order to determine the equilibrium constant (Keq) for interaction of 5-FU drug with micelles as a parameter in thermodynamic mode according to Equation (3) [24, 25] Table 3. By the same postulated, the equilibrium absorbance (A_e; at 360 min) and infinite absorbance of molecular complex (A_∞; at 1440 min). it can represent reversible

Table 1: Experimental interaction results of 5-FU spectrums with SDS and TBAB micelles at the same concentration, acidity function and temperature (conc.= 0.1 mM, pH = 7.4, T = 37°*C*)

Molecular complex of 5-FU drug with micelles molecules						
	SDS micelle			TBAB micelle		
t / min	A_x	A_t=A_∞-A_x	$\ln(A_t)$	A_x	A_t=A_∞-A_x	$\ln(A_t)$
0	0.724	0.240	– 1.42711	1.304	0.681	– 0.38419
10	0.740	0.224	– 1.49610	1.328	0.657	– 0.42007
20	0.746	0.218	– 1.52326	1.391	0.594	– 0.52087
30	0.758	0.206	– 1.57987	1.432	0.553	– 0.59239
40	0.771	0.193	– 1.64506	1.524	0.461	– 0.77435
50	0.782	0.182	– 1.70374	1.589	0.396	– 0.92634
60	0.793	0.171	– 1.76609	1.655	0.33	– 1.10866
120	0.866	0.098	– 2.32278	1.879	0.106	– 2.24431
360	0.892	——	——	1.879	——	——
1440	0.964	——	——	1.985	——	——
Property	(R^2)	$k^*(\text{min}^{-1} \times 10^{-3})$	$t_{1/2}$ (min)	(R^2)	$k^*(\text{min}^{-1} \times 10^{-3})$	$t_{1/2}$ (min)
Value	0.9734	7.60	91.20357	0.9871	17.00	40.76470

Note: k^*=Apparent forward rate constant; $t_{1/2}$=(0.693/k^*) half time; R^2=Correlation factor.

equilibrium first order equation as a function to absorption within a limited time period (10 – 120 min) as following:

$$\ln(A_e - A_x) = \ln(A_e) - (k_1 + k_{-1})t \tag{2}$$

$$Keq = \frac{A_e}{A_\infty - A_e} \tag{3}$$

where;
A_e: absorbance of complex at equilibrium (360 min), A_x: absorbance of complex produced with time, k_1 : forward rate constant, k_{-1}: backward rate constant, t: time of measurement (min), and A_∞ : absorbance of molecular complex at infinite time.

Table 2: Time effect on absorbance of 5-FU spectrums with SDS and TBAB micelles (0.1 mM) at the same conditions (pH = 7.4 and T = 37°*C*), as a reversible equilibrium of first order reaction

Molecular complex of 5-FU drug with micelles molecules as a reversible equilibrium						
	SDS micelle			TBAB micelle		
t / min	A_x	A_e-A_x	**ln** (A_e-A_x)	A_x	A_e-A_x	**ln** (A_e-A_x)
10	0.740	0.152	– 1.88387	1.328	0.551	– 0.59602
20	0.746	0.146	– 1.92414	1.391	0.488	– 0.71743
30	0.758	0.134	– 2.00991	1.432	0.447	– 0.80519
40	0.771	0.121	– 2.11196	1.524	0.355	– 1.03563
50	0.782	0.110	– 2.20727	1.589	0.29	– 1.23787
60	0.793	0.099	– 2.31263	1.655	0.224	– 1.49610
120	0.866	0.026	– 3.64965	1.879	——	——
Equilibrium	0.892	——	——	1.879	——	——
Infinite	0.964	——	——	1.985	——	——

The plotting of ln ($A_e - A_x$) versus time must produce straight line with slope represents kinetic behavior equal to [– (k_1 +k_{-1})], as shown in Figure 4.

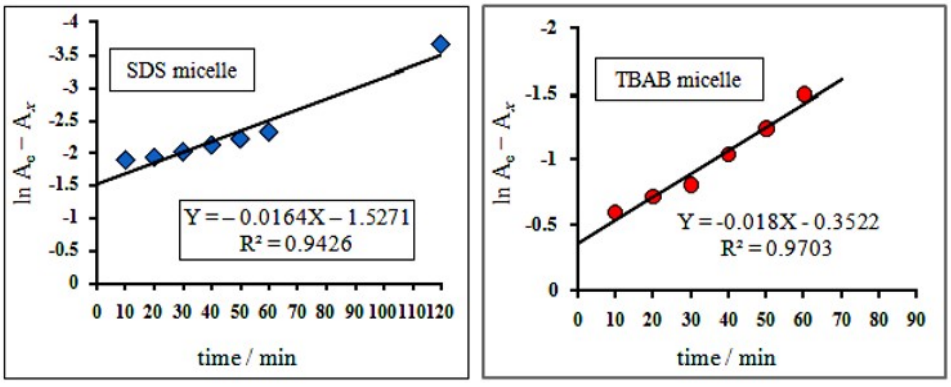

Figure 4: Diagrams show the rates of reversible equilibrium interaction of 5-FU with micelles at the same concentration, acidity function and temperature (conc.= 0.1 mM, pH = 7.4, T = 37°*C*)

Then, behavior between the thermodynamic and kinetic modes (represented by Equation (2) - (3)) could be combined to calculate the rate constants k_1 and k_{-1}, respectively according to equation of reversible first order reaction; by helping calculation of equilibrium constant Table 3.

Table 3: Thermodynamic and kinetic parameters of 5-FU drug with micelles (0.1 mM; at pH =7.4 and T = 37°C)) as a reversible equilibrium first order interaction

5-FU with Micelles	**Y = a X – b**	R^2	$k_1 \times 10^{-3}$ (min^{-1})	$k_{-1} \times 10^{-3}$ (min^{-1})	**Keq**
SDS	Y = – 0.0164X – 1.5271	0.9426	15.17510	1.22489	12.38888
TBAB	Y = – 0.018X – 0.3522	0.9703	17.03879	0.96120	17.72641

Note: k_1= forward rate constant; k_{-1}= backward rate constant; Keq= equilibrium constant.

The compares of kinetic physicochemical properties obtained for same data; but in different treatment methods mathematically (Table 1; as a simple interaction and Table 3; as a complicated pattern). The first idea would be focus on, the interactions between SDS were less regular than those in TBAB micelle with 5-FUdrug molecules. This is conclusion led to confirmation the belief that 5-FU drug may be considered as a polar molecule with a net negative charge, with respect the all interactions between reactants (5-FU and micelles) as the physiochemical forces. In addition, the interactions between molecules of resulting molecular complexes were proceeded in forward direction more than backward direction; with a conserve that the best for TBAB micelles being largest. The equilibrium constant (as a thermodynamic parameter of stability; Table 3) of 5-FU with micelles interaction was ensured the acceptability of this assumption.

The half time of equilibrium 5-FU interaction with micelle could be determined exactly :

$$(t_{1/2})_{\text{total}} = \frac{0.693}{k_1 + k_{-1}}$$

where; A_x=0.5 A_e in Equation (2), since the both two patterns were assume that physicochemical processes as a first order. Then, the forward half time $(t_{1/2})_f = \frac{0.693}{k_1}$ and the backward half time $(t_{1/2})_b = \frac{0.693}{k_{-1}}$ could be extracted respectively, by the same method and assumption Table 4 [24–26].

Table 4: Half time of 5-FU drug with micelles (0.1 mM) in aqueous solution of phosphate buffer at pH = 7.4 and T = 37°C, as a reversible equilibrium from first order interaction

5-FU with Micelles	**Equilibrium interaction** $(t_{1/2})_{\text{total}}$ **(min)**	**Forward interaction** $(t_{1/2})_f$ **(min)**	**Backward interaction** $(t_{1/2})_b$ **(min)**
SDS	42.256	45.666	565.762
TBAB	38.500	40.671	720.967

By re sight into the half time in SDS state was as a simple interaction [Table 1; $(t_{1/2})$=91.20357 min] with same value as an equilibrium complicated interaction [Table 4; $(t_{1/2})_{total}$ = 42.256 min] show's important different evidence. It was differed when comparison with the similarity values whose calculated of resulted molecular complex in TBAB state (the values didn't differ largely).

The interactions between 5-FU drug and SDS micelles may be passed by the relaxation processes, according to first belief which assumes that the two reactants molecules have the negative charges. Therefore, the half time of SDS interaction would correspond to relaxation time (τ^*); and all the physiochemical forces which binding with 5-FU drug as a complicated interaction involved the relaxation equilibrium processes.

But, the binding forces in TBAB state were described as a simple reversible equilibrium from first order interaction; and the molecular complex didn't involve any complicated and relaxation processes. This conclusion was depended on the obtained results of rate constants and half time which showed similar values closely for a simple or reversible equilibrium interaction.

3.5. Gibbs free energy and chemical affinity of 5-FU interaction

Generally, the physicochemical parameter of free energy is considered as a thermodynamic gauge for spontaneously of chemical reaction, it has zero value at equilibrium state (ΔG=0). So that, the standard Gibbs free energy (ΔG^0) consider is more useful in biophysicochemical processes, which can be calculated depending on equilibrium constant value.

$$\Delta G^0 = -RT\ ln\ Keq \tag{4}$$

where;
R : gas constant (8.314 J/K.mol), and T : absolute temperature (310°K).

Then, chemical affinity (A_h; or Helmholtz constant) can be extracted depend on free energy but with different sign, this means A_h; +ve of spontaneous processes (ΔG^0; –ve) and vice versa as shown in Table 5 [3, 25].

$$A_h = (\Delta G^0)_{T,P,n} \tag{5}$$

Table 5: Gibbs free energy and chemical affinity of 5-FU drug (0.1 mM) with micelles molecules as reversible equilibrium from first order interaction in phosphate buffer at pH = 7.4 and T = 37°C

5-FU with Micelle	**Keq**	**ln Keq**	ΔG^0 **(J/mol)**	A_h **(J/mol)**
SDS	12.38888	2.51679	– 6486.62353	6486.62353
TBAB	17.72641	2.87505	– 7409.98136	7409.98136

The high obtained values of ΔG^0 were ensure occurrence presence interactions between 5-FU drug with both the micelles molecules (SDS and TBAB). The only difference, the molecular complexes obtained from interactions between 5-FU molecules with TBAB micelles were more regular and formed easier at comparison with its similarities in SDS micelles.

In SDS micelles, the interactions between reactants molecules are less facile (as with TBAB), and resulted molecular complexes may be exposure into relaxation processes through the formation. This believe was based on absorbance values at the equilibrium (360 min) and infinite (1440 min) states Table 1; which it shown presence rapid equilibrium state individually after pass two hours (120 min) in TBAB micelles. But in the opposite direction, SDS micelles were suffer instability through interaction with 5-FU drug at period times between 360 min and 1440 min especially. Although, the molecular complexes formed from interactions between 5-FU and SDS (as a anionic surfactant) and TBAB (as a cationic surfactant) micelles may be occurred spontaneously by van der Waals forces or by hydrogen bonding respectively depend on the calculated values of standard free energy (ΔG^0).

4. Conclusions

Technically, selection of a suitable concentration for micelles molecules (0.1 mM) was important step in phosphate buffer at pH=7.4 and T=37°*C*. To ensure, excess critical micelle concentration, guarantee fixed molecules as monomer in micelles and obey the Beer-Lambert law that required to prepare 5-FU drug. The experimental measurements between anionic (SDS) and cationic (TBAB) micelles with 5-FU drug showed formation of molecular complexes; as a reversible equilibrium from first order interaction. The molecular complex of SDS micelles was less regular and required more time to form; because the relaxation processes occur through interaction process especially after 120 min. While, the molecular complex of TBAB exhibits simple regular equilibria without any complications in completing the interaction with 5-FU drug. So, a mathematical treatment of calculated data ensured that interactions occurred spontaneously by van der Waals forces or by hydrogen bonding.

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Conflict of Interest: The authors declare no conflict of interest.

Data Availability Statement: Data are available from the corresponding author upon reasonable request.

Disclaimer (Artificial Intelligence): The author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc).

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