

Research Article

Qualitative Assessment for Kinetic Interactions of Caffeine Drug with Copper and Zinc Ions

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Abstract

Practically, caffeine drug is checking as pure material by melting point and solubility for ensuring from purity of compound, before complete progress to known properties of caffeine. Then, the behave of caffeine drug in selected solvents was achieved, and the extension coefficient was determined depending on the obtained absorbance. The mathematical calculations were shown presence relationship between dielectric constant (ϵ_0) of solvents with extension coefficient (ϵ) of caffeine drug. Caffeine drug has the highest value of extension coefficient (ϵ) in ethanol and the least value in hexane; as well as the electronic interactions in different solvents were π - π^* transitions. The experimental data of caffeine drug in different acidity function were shown good solubility in acidic media (pH=5.0 – 6.0) compared with relative stability in basic media (pH=7.0 – 8.0), although the little change in maximum wave length (λ_{max}). The spectral analysis of reactant molecules (caffeine drug and elements ions) at pH=7.4 and T=37°C were showed identical values for the standards (λ_{max} = 273; 242, 376 nm for caffeine, copper and zinc ions respectively). The spectral measurements of molecular complexes between caffeine drug and elements ions (at λ_{max} = 238 and 270 nm for copper and zinc complexes respectively) were regularity, and the spectral lines were followed as first order interactions. The mathematical calculations showed that, rate constant and half time of interaction caffeine drug with elements ions did not differ largely (for molecular complex of Cu^{2+} ions; $k^* = 28.40 \times 10^{-3} \text{ min}^{-1}$; $t_{1/2} = 24.401$ min, and for complex Zn^{2+} ions; $k^* = 24.00 \times 10^{-3} \text{ min}^{-1}$; $t_{1/2} = 28.875$ min). Therefore, interactions between caffeine drug and elements ions occurred spontaneously by van der Waals forces; and resulted molecular complexes forming and deforming continuously in aqueous solution.

1. Introduction

Caffeine has the stimulant property for central nervous system, it is considering the most widely consumed in world's as a psychoactive drug and used legally unlike many other psychoactive substances [1, 2]. The most mechanism prominent to explain the effect of caffeine was reversibly block the action of adenosine on its receptors and consequently prevents the onset of drowsiness induced by adenosine. Also, caffeine can be stimulating certain portions of the autonomic nervous system. The caffeine has a bitter taste, white crystalline purine, methylxanthine alkaloid and chemically it can relate to nitrogen bases (A and G) of DNA and RNA (this matter was encouraged to understanding interactions of caffeine). It is existence in the seeds, nuts and leaves of number of plants native to Africa, East Asia and South America, and almost people may drink beverages containing caffeine [1–3]. Commonly, the drinks are containing caffeine such as coffee,

tea, and cola which be as a daily drink. In 2014, American adults (about 85%) were consumed some form of caffeine daily by consuming average 164 mg [4, 5].

Caffeine have effects both positive and negative health Figure 1. It can be treating and prevent the infant breathing disorders of prematurity. Caffeine citrate is considered as the essential medicines on model list of WHO [6], it may confer a modest protective effect against some diseases [7] including Parkinson's disease [8]. In the other side, some medical authorities were recommended that pregnant women must be limit caffeine into the equivalent quantity of two cups of coffee per day or less [9, 10]. The autonomic effects of beginning take caffeine may be led into increased blood pressure, heart rate and increased urine output, then it develops with chronic use (i.e., the symptoms which be dominating would become less pronounced or do not occur at following consistent use) [11]. Generally, caffeine is classified by US Food and Drug Administration as recognized as safe; and the toxic doses would be over 10 grams per day for an adult. So, the human body requires roughly 50 – 100 ordinary cups of coffee to reach the toxic dose, since cup of coffee contains 80 – 175 mg of caffeine [12].

The elements ions (such as iron, zinc, copper, and manganese) were represent important part for human body health, because it has antioxidant properties and another functions. For example, Zinc plays an important role in the activation of over 300 enzymes, it is influence on the efficiency of immune system, the sense of taste and smell, fertility and proper development of children. Zinc has a crucial role in maintaining (so known as a redox balance in cells of human body), It is an inducer of metallothionein, and compete with pro-oxidative metals (iron and copper) in prevent the formation of reactive oxygen species.

Copper have important roles as a cofactor of antioxidant enzymes, catalysis the oxidation of iron, participate in the production of energy in cells and contribute in the proper functioning of thyroid gland [13, 14]. Deficiency of copper levels have been clearly concerned in genetic diseases, cancer, and neurodegeneration. Copper is absorbed from the food, and human body can excretion of excess amounts through liver (by bile glands) [14]. Therefore, the assessment of interactions caffeine with copper and zinc ions is represented maximal importance for health of human body.

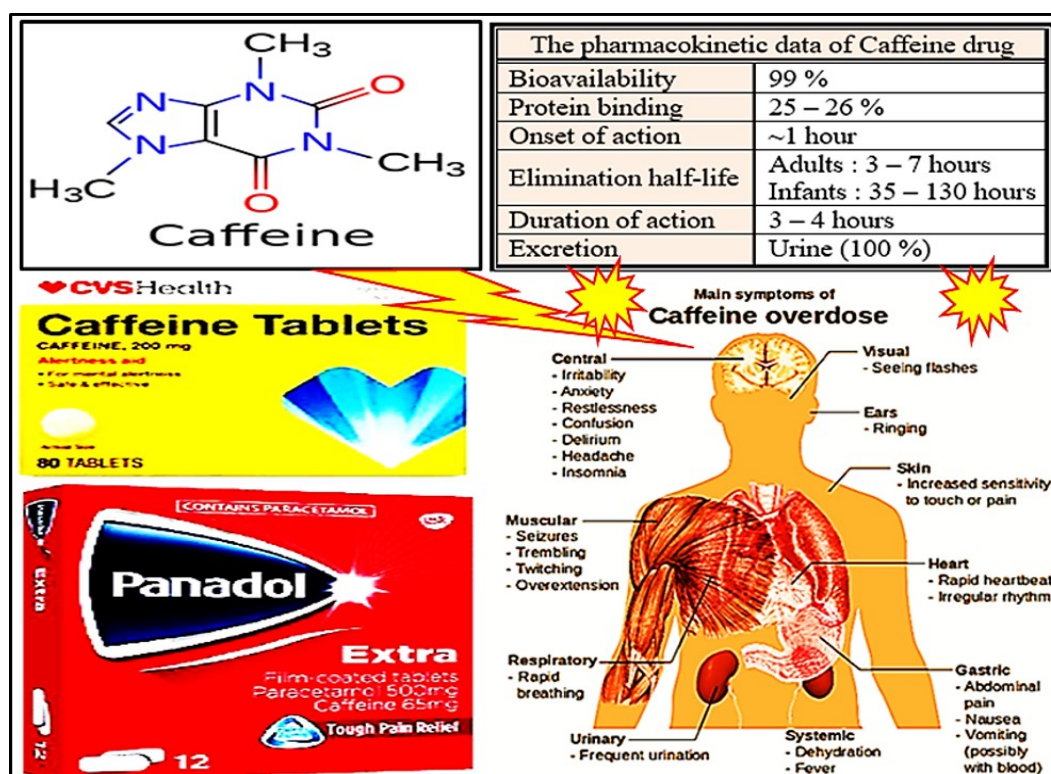


Figure 1: Diagram shown some caffeine properties: Chemical structure, pharmacokinetic data, symptoms of overdoses and pharmaceutical shapes [7, 10, 12, 15–17]

2. Experimental

2.1. Materials

The all chemicals were obtained from commercial sources, with a highest purity. Caffeine anhydrous [Cas No. 58-08-2, $C_8H_{10}N_4O_2$, $M=194.19$ g/mol] was purchased from Sigma Aldrich, USA, with purity of 99.99%. KH_2PO_4 and K_2HPO_4 of phosphate buffer solution (has $pH=5 \sim 8$) were obtained from Sdfine chemical limited-Mumbai, India. Cupric Chloride anhydrous [$CuCl_2$, $M=134.45$ g/mol]; Zinc Oxide [ZnO , $M=81.38$ g/mol]; Absolute Ethanol [C_2H_5OH]; Methanol [CH_3OH]; n-Hexane [C_6H_{14}] were all 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. Some apparatus was used in different preparation processes such as heater with magnetic stirrer (IKA; India) and Oven with controlled temperature (Heidolph; Germany).

All glassware was thoroughly cleaned with aqua regia, and rinsed with distilled water as well as deionized water prior its use. The deionized water (has conductivity= $0.5 \sim 0.7 \mu\text{S/cm}$) was used to prepare all the solutions.

2.3. Preparation of caffeine drug and elements solutions

The solution of potassium phosphate buffer was prepared by mixing suitable volume of potassium dihydrogen phosphate (0.0666M) with dipotassium hydrogen phosphate (0.2M). The prepared solution of phosphate buffer was adjusted by using a calibrated pH meter continuously. Then, the solution of caffeine drug was prepared with concentration of 1.0 mM in potassium phosphate buffer solution which prepared previously by weight of 0.0194 gm in 100 mL calibrated flask. Then, the elements under study (Copper and Zinc ions as a standard materials with concentration 1.0 mM) were prepared in same potassium phosphate buffer solution which it used to prepared caffeine drug (at $\text{pH}=7.4$ and $T=37^{\circ}\text{C}$). The followed prepared method of caffeine drug with a different types of elements ions were achieved by simple continuous shaking through the preparation process. As well as, the acidity function and temperature of the all prepared solutions were be measured continuously (for guarantee, the achieved of work at a physiological conditions; $\text{pH}=7.4$ and $T=37^{\circ}\text{C}$).

3. Results and Discussion

The checking of caffeine drug (as a pure material) was occurred primarily by the electro apparatus and deionized water to determining melting point and solubility of compound respectively. The calculated melting point of caffeine was corresponded of standard value ($236 - 238^{\circ}\text{C}$), and it was soluble completely with a clear solution (non coloured) [18]. This is matter encouraged into complete progress to known properties of caffeine in details.

3.1. The behave of caffeine drug in some solvents

The solubility of caffeine drug was taken the required time for complete the homogenous process in different solvents, it was putting in circulator water bath for half hour at $T=37^{\circ}\text{C}$. The caffeine drug was prepared as a stock solution (with concentration 1.0 mM), then a dilution process was used into diluted solutions (0.1 – 0.01 mM) in different polarity solvents at same temperature.

Therefore, the behave of caffeine drug (0.01 mM) was studied with different solvents to determine some spectral data of the analyte. The selected solvents were hexane, ethanol, methanol, and aqueous solution of potassium phosphate buffer at $\text{pH}=7.4$ as shown in Table 1.

Table 1: Experimental spectral data of caffeine (0.01 mM and $T=37^{\circ}\text{C}$) in the various solvents

Solvents	Hexane	Ethanol	Methanol	*H ₂ O
Dielectric constant (ϵ_0)	1.88	24.85	32.63	~ 78.35
$\lambda_{\text{max}} / \text{nm}$	275	273	272	273
Absorbance	0.399	1.990	1.864	1.012
$\epsilon / (M.cm)^{-1}$	33900	199000	186400	101200

Note : ϵ = Extension coefficient; *H₂O =Aqueous solution of phosphate buffer at $\text{pH}=7.4$.

The absorbance of caffeine drug was varied depending on the different solvents (it has least value in hexane and highest in ethanol). Especially, absorbance in the inert solvents have high dielectric constants; ethanol and methanol as protic solvent was larger compared with the aqueous solution of phosphate buffer at $\text{pH}=7.4$ and $T=37^{\circ}\text{C}$ [19, 20]. According to experimental obtained values, the relationship between absorbance and dielectric constant was inversely for solvents ethanol, methanol and aqueous solution. Although varying in maximum wave length didn't large, but the change of extension coefficient was cleared as shown in the Figure 2. Therefore, the relationship between dielectric constant (ϵ_0) with extension coefficient (ϵ) of caffeine in different solvents can be represented as the follows:

3.2. The behave of caffeine drug in acidic functions

The hydrolysis rate of caffeine drug (0.01 mM) was studied in aqueous solution of potassium phosphate buffer at different acidity functions ($\text{pH}=5.0, 5.5, 6.0, 6.5, 7.0, 7.4$, and 8.0). The all solutions at different acidity functions were prepared by the diluted method from a stock solution (by the same method followed in different polarity solvents) [20]. As well as, the prepared solutions of caffeine drug were putting in a water bath at 37°C for 8 – 10 min at least to complete thermal homogenous before the spectral measurement.

Table 2: Experimental spectral data of caffeine (0.01 mM and $T=37^{\circ}\text{C}$) in the various solvents

pH	5.0	5.5	6.0	6.5	7.0	7.4	8.0
$\lambda_{\text{max}}/\text{nm}$	271.0	271.45	272.0	272.51	273.0	273.0	273.0
Absorbance	1.609	1.580	1.446	1.219	1.021	1.012	1.011

The experimental data of caffeine drug Table 2 were shown good solubility in acidic media ($\text{pH}=5.0 - 6.0$) compared with relative stability in basic media ($\text{pH}=7.0 - 8.0$), although the little change in maximum wave length (λ_{max}). Therefore, it can represent the

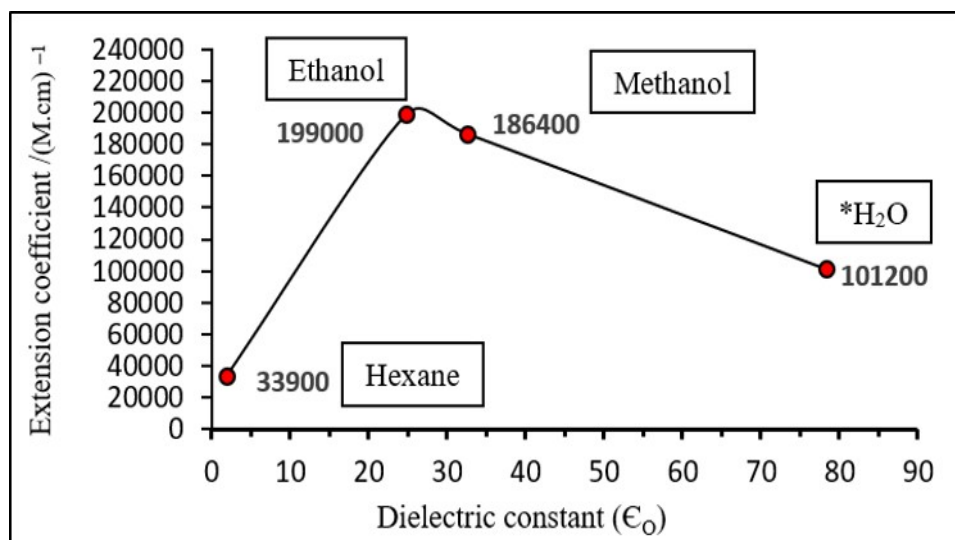


Figure 2: Diagram shown relationship between dielectric constant (ϵ_0) with extension coefficient (ϵ) of caffeine (0.01 mM) in different solvents at $T = 37^\circ\text{C}$

relationship between all these parameters (pH, λ_{max} , and Abs.) of caffeine drug in potassium phosphate buffer by one simplified diagram Figure 3 as following:

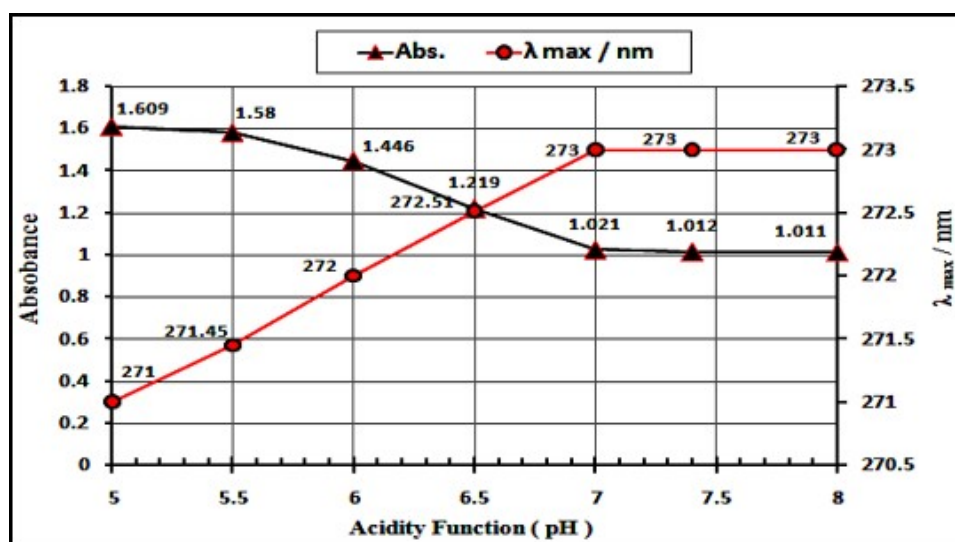


Figure 3: Diagram shown relationship between acidity function with absorbance and maximum wave length of caffeine drug (0.01 mM) in potassium phosphate buffer at $T = 37^\circ\text{C}$

The materialized results in Figure 3, it can observe cross point at pH=6.5 between absorbance and wave length that may be appear importance of caffeine drug (in another researching field). As well as, the stability of caffeine drug in basic media and solubility in acidic media was expected fact; because it has basic property [21, 22].

3.3. The behave of caffeine drug with some element's ions

The spectral analysis of caffeine drug (0.1 mM) in the phosphate buffer solution was performed (three times) at the physiological conditions (pH=7.4 and $T=37^\circ\text{C}$), for confirming absorption peak corresponded to a standard value. The drug of caffeine has distinguished spectral signal involved a maximum wave length ($\lambda=273$ nm) with absorption ($A=1.141$) [23–25].

Therefore, the interaction of caffeine drug was studied in aqueous solution of potassium phosphate buffer at the physiological conditions with some necessary elements for human body as shown in Table 3. Practically, the interaction between caffeine drug (0.1 mM) with elements ions (1.0 mM) was occurred by mixing the equivalent volumes of reactants in the potassium phosphate buffer solution at pH=7.4 and 37°C .

As shown Table 3, the spectrophotometer scans were giving evidence that elements ions have wave lengths differ from caffeine drug as starting material. As well as, the formed complexes between caffeine and elements have maximum wave lengths did not similarities of reactants. This matter was encouraged for follow the interactions between caffeine drug and elements kinetically.

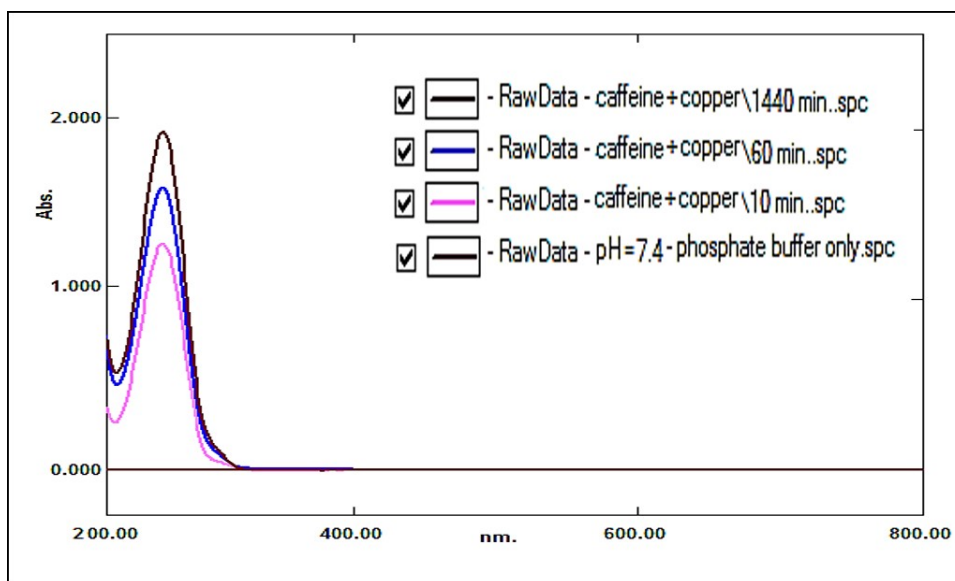
3.4. The interactions of caffeine drug with copper ions

The solutions of starting reactants materials (caffeine drug and copper ions) were mixing with equal volumes, then the mixture was putting in circulator water bath with simple shaking continuously through all measurements. The absorbance of formed complexes between caffeine

Table 3: The interaction of caffeine drug (0.05 mM) with some elements ions (0.5 mM) in aqueous solution of potassium phosphate buffer at pH=7.4 and 37°C

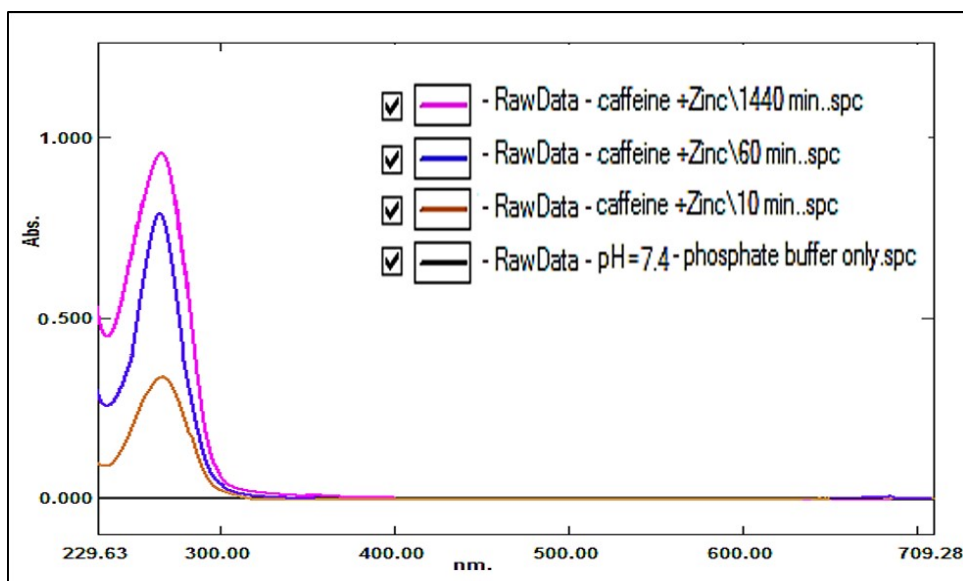
The interaction of caffeine with elements in pH = 7.4 and 37°C			Maximum wave length with Absorbance of elements only [26, 27]		
Substance	λ_{max} / nm	Abs.	Elements (1.0 mM)	λ_{max} / nm	Abs.
Caffeine (CAF) only (0.1 mM)	273	1.141	pH=7.4	— line base —	
CAF—Cu	238	1.578	CuCl ₂	242	0.287
CAF—Zn	270	0.539	ZnO	376	0.432

drug (0.1 mM) with copper ions (1.0 mM) was measured with time in the potassium phosphate buffer solution at physiological conditions (pH=7.4 and T=37°C). The distinguished experimental spectra of formed complex between caffeine and copper ions at pH=7.4 and T=37°C were recorded as shown in the Figure 4.

**Figure 4:** The interaction caffeine drug (0.05 mM) and copper ions (0.5 mM) with time in potassium phosphate buffer solution at physiological conditions (pH=7.4 and T=37°C)

3.5. The interactions of caffeine drug with zinc ions

The interaction between caffeine drug (0.1 mM) with zinc ions (1.0 mM) was achieved at physiological conditions (pH=7.4 and T=37°C). This means, the same followed conditions and procedures in copper ions experimental would be repeated in zinc ions case. Therefore, the obtained results of formed complex between caffeine drug with zinc ions was recorded as shown in Figure 5 at pH=7.4 and T=37°C.

**Figure 5:** The interaction caffeine drug (0.05 mM) with zinc ions (0.5 mM) with time in potassium phosphate buffer solution at physiological conditions (pH=7.4 and T=37°C)

3.6. The kinetic interactions of caffeine drug as a first order

The spectral measurements of interaction caffeine drug with elements ions (Cu^{2+} and Zn^{2+} ions) in the phosphate buffer solution at pH=7.4 and $T=37^{\circ}C$ were achieved with regularity manner each ten minute for one hour (10 – 60 min). Then, the same spectral measurement was repeating overnight (at 1440 min) for same prepared solution stored at $T=37^{\circ}C$. as well as, the apparent values of absorption for caffeine interaction with elements ions were repeated more than two times, in order to ensure the interactions state occurred between interacted molecules.

In a previous studies, the molecular interactions are followed kinetically equation of first-order reaction Equation (1). Consequently, the rate constant of interaction between caffeine drug and elements molecules can be calculated by plotting $\ln(A_{a-x})$ versus time (slope = k^*) [20, 28] as following.

$$\ln(A_{a-x}) = \ln(A_a) - k^* t \quad (1)$$

where,

($A_{a-x} = A_{\infty} - A_x$) absorbance of molecular complex with time.

Then, the obtained results of molecular complexes between caffeine drug and elements ions were extracted from spectral charts Figures 4 and 5 and it fixed in the Table 4.

Table 4: Time effect on absorbance of caffeine drug (0.05 mM) with elements ions (0.5 mM) in potassium phosphate buffer at pH = 7.4 and $T = 37^{\circ}C$, as a first order interaction

Molecular complex of caffeine drug with elements ions as a first order interaction							
Copper ions (at 238 nm)				Zinc ions (at 270 nm)			
t / min	A_x	$A_{\infty} - A_x$	$\ln A_{\infty} - A_x$	t / min	A_x	$A_{\infty} - A_x$	$\ln A_{\infty} - A_x$
10	1.203	0.621	-0.47642	10	0.211	0.710	-0.34249
20	1.301	0.523	-0.64817	20	0.344	0.577	-0.54991
30	1.434	0.390	-0.94160	30	0.468	0.453	-0.79186
40	1.538	0.286	-1.25176	40	0.579	0.342	-1.07294
50	1.605	0.219	-1.51868	50	0.650	0.271	-1.30563
60	1.671	0.153	-1.87731	60	0.701	0.220	-1.51412
1440	1.824	—	—	1440	0.924	—	—

The kinetic behavior of interaction between the reactant molecules can be represented by plotting of $\ln(A_{\infty} - A_x)$ within a limited time period (10 – 60 min) would produce straight line with slope equal to rate constant (k^*). Mathematically, the half time of caffeine interaction with elements ions (Cu^{2+} and Zn^{2+} ions) could be determined exactly : $(t_{1/2})_{total} = 0.693 / k^*$ (where; $A_x=0.5 A_a$ in Eq.1); as shown in Table 5 [29–31]

Table 5: The parameters of kinetic of interaction caffeine (0.05 mM) with elements ions (0.5 mM) at pH=7.4 and $T = 37^{\circ}C$; as a first order interaction

Affine with elements	$Y = a X - b$	R^2	$k^* 10^{-3} (min^{-1})$	$(t_{1/2})_{total} min$
Cu^{2+} ions	$Y = -0.0284X - 0.1264$	0.9923	28.400	24.401
Zn^{2+} ions	$Y = -0.0240X - 0.0889$	0.9981	24.000	28.875

As seen, the calculated results as a physicochemical properties (k^* and $t_{1/2}$) were gave important evidence of interaction process between caffeine drug and elements ions. The rate constants and half times of interaction caffeine drug with two elements ions didn't different largely, this may be mean that caffeine drug behavior similar in interaction with di equivalent ions. As well as, the interactions between caffeine drug and elements ions may be occurred spontaneously by van der Waals forces or by hydrogen bonding; and the resulted molecular complexes forming and deforming continuously in aqueous solution [32, 33].

4. Conclusions

Practically, the checking a pure material was very important as a primary step before beginning research work (especially, melting point and solubility). The obtained experimental results of caffeine drug shown electronic interactions was $\pi - \pi^*$ transition in selected solvents depending on extinction coefficient. Then, the experimental data of caffeine drug in different acidity function were shown good solubility in acidic media compared with stability in basic media. The interactions between caffeine drug and elements ions were exhibit as a simple interaction from first order reaction proceed in forward direction in potassium phosphate buffer solution at pH=7.4 and $T=37^{\circ}C$. As well as, the interactions of molecular complexes (between caffeine drug and elements ions) at physiological conditions occurred spontaneously by van der Waals forces; and it forming and deforming continuously in aqueous solution.

Article Information

Ethical Approval: Not applicable.

Informed Consent: Not applicable.

Data Availability: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest: The author declares no conflict of interest.

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AI Use Disclosure: No generative artificial intelligence tools were used in the preparation of this manuscript.

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