Conductivity and Spectrophotometric Study of Drugs and their Complexes with Some Metal ions in Aqueous Solution

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Abstract:

This research is used to study of some antibiotics (Cephelaxine ,Amoxicillin**,** and Chloramphenicol) by Conductivity & U.V. in aqueous solution at pH 7 at a wide range of concentration and also to study their complexes with some metal ions (Fe , Cu , Ca). The complexes were identified and studied using the techniques of electrical conductivity and spectrophotometric (U.V.) methods to determine their behaviour at (37 ^{o}C) and at pH 7 . The equivalent conductivity at infinite dilution (Λ_o), the ion association constant (K_A) and the main distance between ions (R) at the best fit values of standard deviation ($\sigma\Lambda$) are calculated for each antibiotic and also the conductivity parameters for the complexes. This method is then compared with the spectrophotometric method by studying the complexes by measuring the absorbance in the (U.V.) region.

Key word: Conductivity , Lee-Wheaton equation , Cephelaxine , Amoxicillin **,** Chloramphenicol

Introduction:

The physiochemical properties of compounds are measured and characteristics by which the compound may interact with other system. Biological response to drug is consequence of the interaction of that drug with the living system, causing some change in the biological processes present before the drug was admintered(1). Since physiochemical properties determine the processes by which drugs reach and interact with this sites of action , it is important to examine the extent to which any one property correlates with the observed biological activity. The possible importance of such properties as solubility , partition coefficients , surface activity , degree of dissociation of the pH at the body fluid ,interatomic distances between functional groups, redox potential (reduction-oxidation),hydrogen bonding,dimensional factor chelation and the spatial configuration of the molecule are worthy of consideration .

A classic electroanalytical technique that finds application in a variety of chemical and biochemical studies is a measurement of solution conductance. For example determination of ionic strengths of solutions, monitor dissolution, kinetics and the approach to equilibrium for partially soluble salts , determine critical micelle concentration , follow the course of some enzymatic reaction , as well as to provide basic thermodynamic data of other electrolyte solution (2) .

An other electrochemical technique for determination of for example Cephelaxine and its determination in pharmaceutical and human serum was by polarography where Cephelaxine gives a reduction wave in 0.3 mol/L HCl medium at 1.24 volt while Cephelaxine concentration higher than 2.5 x 10^{-5} mol/L , another reduction wave is observed at -0.90 volt. These reduction waves are attributed to the reduction of ethylenic bond of a six membered dihydrothiazine(3).

The complexes formed by the interaction of the amphiphilic drug amitripyline hydrochloride and human serum albumin (HAS) in aqueous solution at pH 3.2 , 4.9 , and 6.0 .were investigated at 25 ^{o}C using a range of physico chemical technique .The complexation process was investigated by conductometric measurements on HAS amitriptyline solution of increasing drug concentration from which values of the critical concentration at which adsorption of drug commenced and also the critical micelle concentration of amitriptyline in the presence of protein were determined(4).

The electrical conductivities of 5-(p-substituted) phenylazo barbituric acid compounds and their complexes were measured .The results illustrate faint semi-conducting behavior for these system .The conductivities were found to depend on the structure of the compounds. The metal ion forms a bridge between the ligands to facilitate the transfer of current carriers with some degree of delocalization in the excited state(5).

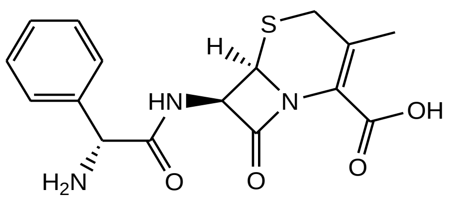
Experimental:

Purification of solvent:

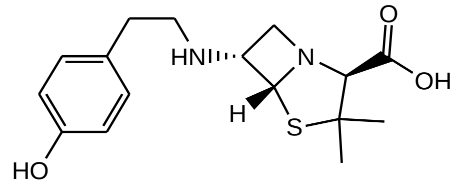
Conductivity water was prepared by redistilling water three times with the addition of a little amount of potassium permanganate and small pellets of (KOH) (6) , the specific conductance of this water was less than 1.2 x 10^{-6} siemens cm^{-1}.

Preparation of solutions :

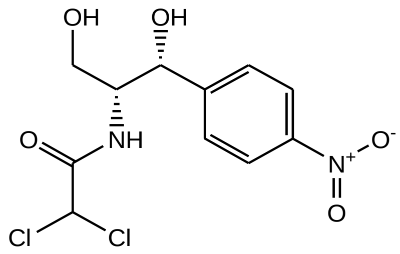
A solution of 1 x 10^{-3} M of each drugs (Amoxicillin , Cephelaxine , Chloramphenicol) were prepared from standard drugs from SDI by weighting a known amount of each drug in deionized water. The salts of metal ions($FeCl_2$, $CaCl_2$, $CuCl_2$ from BDH) also prepared (1 x 10^{-3}M) by the same way in deionized water.



cephalexin



Amoxicillin



Chloramphenicol

General procedure:

All stock solutions were prepared freshly by weighing and using freshly prepared solvents. Conductivity measurements were made using Jenway PCM3 conductivity meter with frequency range of 50 HZ-1KHZ and accuracy of 0.01 μS. The cell constant of the conductivity cell was measured using the method of Jones and Bradshaw[7]. A standard addition method has been used for measuring the conductance of electrolyte solutions. The conductivity cell was washed , dried , and then weighed empty and kept at (37 ^oC) ±0.1 ^oC using a water – circulating ultra thermostat type VH5B radiometer. A certain amount of solution was injected into the conductivity cell and the conductivity of the solution was measured, Another known amount of the solution was added and the measurement was repeated as before. Generally (15) additions have been made throughout each ran.

For the mixed solution ,the addition was made by kept the concentration of the drugs and change the concentration of the salt added (by standard addition method).

Results and Discussion:

The conductometric data for each complex and antibiotics were treated using (LW) in which a wide dielectric range for electrolytes solution can give detailed information concerning ion-ion and ion-solvent interaction. For unsymmetrical electrolyte 2:1 a program (RM1) is used to analyze the concentration conductivity measurement in which the input data are (T , D , η) where T is temperature in Kelvin , D and η are the dielectric constant and viscosity (poise) of the solvent at (37 ^oC).

Lee and Wheaton obtained an equation of symmetrical 1:1 and unsymmetrical 2:1 electrolytes of the form[8].

$$\lambda i = \lambda i^o \left[1+Z_j \sum_{P=2}^{S} X_j^{\,P} \sum_{V=1}^{S} tvX_V^{\,P} \; [A^P_v(t)(\beta k)+B^P_v(t)(\beta k)^2 + C^P_v(t)(\beta k)^3\right] - \frac{Z_j(Kt)}{2(I+t)} \left[I+ V_j^{(1)}(t)(\beta k) + V_j^{(2)}(t)(\beta k)^2 + \Pi_j^{(5)}\, t/6\right]$$

For unsymmetrical electrolyte 2:1

$$\Lambda=\Lambda_o[\,1+ C_1(KR)(\varepsilon K) + C_2(KR)(\varepsilon K)^2 + C_3(KR)(\varepsilon K)^3\,] - PK/1+KR \;\; \{ C_4(KR)(\varepsilon K) + C_5(KR)(\varepsilon K)^2 + KR/12\}$$

for Symmetrical electrolyte 1:1

all the terms are define in details[9] (Lee and Wheaton (1978). The program (RM1) is used to determine values of $K_A^{(1)}$, $K_A^{(2)}$, $\lambda^o_{MX^-}$, $\lambda^o_{M^{2+}}$, R where K_A is the association constant , R is the average centar to centar distance for the ion pairs , λ^o, is the ionic equivalue conductance of each ion in solution , Amulti parameter " Least square " curve fitting procedure is used to give the lowest value of curve fitting parameter σ(Λ) between the experimental and calculated points. An iterative numerical method which was found to be very successful has been used to find the minimum σ(Λ).

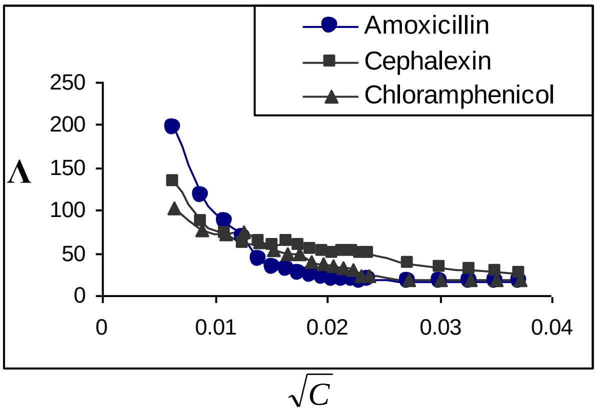
$$\sigma\Lambda = \left\{ \sum_{n=1}^{NP} \left(\Lambda_{calc.} - \Lambda_{exp.}\right)^2 /NP \right\}^{1/2}$$

Amoxicillin is used as a ligand, from its reaction with some metal salts as ($CaCl_2$,$FeCl_2$,$CuCl_2$)to form complexes which identified spectrophotometrically to know the metallic binding with lighand and their equilibrium constant under standard condition by using molar percent method which gives values of formation constant between (10^7 – 10^{14}) and to know more information about Gibbs free energy which conferm with the high stability of the complexes [10] .

The following are the results of typical conductivity runs , it is shown in Table (1) and Figure (1) for antibiotics only (Amoxicillin , Cephelaxine , Chloramphenicol) at 37 ^oC and pH 7.

Table (1): The molar conductivity ($\Omega^{-1}.cm^2.equiv^{-1}$) with molar concentration of the antibiotics in water at 37 °C and pH 7.

Concentration x 10^{-5} mol/L	Λ Amoxicillin	Λ Cephelaxine	Λ Chloramphenicol
3.98	197.13	133.13	102.40
7.94	116.95	87.39	77.11
11.85	86.88	72.25	73.11
15.74	68.65	59.58	74.48
19.60	41.56	62.42	62.94
23.43	32.08	58.31	53.09
27.23	30.28	62.91	48.68
31.00	25.58	58.55	48.35
34.74	22.85	54.30	40.31
38.46	21.65	51.44	37.51
42.14	19.80	49.61	35.18
45.80	18.60	50.55	33.01
49.43	17.89	51.17	30.09
53.03	17.38	49.23	23.68
56.60	18.17	48.29	22.32
74.07	16.65	38.00	19.80
90.90	16.01	33.77	18.60
107.14	15.66	30.65	18.48
122.80	15.73	27.74	18.05
137.93	15.35	24.84	18.54



Figure(1): The plot of equivalent conductivities($\Omega^{-1}.cm^2.equiv^{-1}$) against square root of concentration for the antibiotics in water at 37 °C and pH 7.

From the results of each of Table(1) and the Figure (1) it is clear that the antibiotics behave as a weak electrolytes, the equivalent conductivity follow the sequence:

Λ Amoxicillin > **Λ** Cephelaxine > **Λ** Chloramphenicol

This may be attributed to the polarization and structure effect of each one of them toward water.

Table(2) Shows the analysis of the results of the antibiotics by using Lee-Wheaton equation for symmetrical electrolytes.

Table(2): Values of K_A (association constant) Λ_o (equivalent conductivity at infinite dilution) R(distance parameter) , λ and σ(standard deviation) of the three antibiotics at 37 °C and pH 7.

Drugs	R (A°)	K_A	Λ_o	σ
Cephelaxine	2×10^{-8}	8530.10	136.31	0.081
Chloramphenicol	3×10^{-8}	4095.82	88.16	0.071
Amoxicillin	5×10^{-8}	1361.80	37.46	0.070

From table (2) the analysis also show the difference in Λ_o for each antibiotic as shown in the series above, in the same manner The association constant (K_A) follow the sequence:

K_A Cephelaxine > K_A Chloramphenicol > K_A Amoxicillin

This conclusion is due to Bjeerum theory since the theoretical expression of K_A is due to formation of CIP as

$$K_A = \frac{4\pi N_A}{3000} a^3 e^b \ , \quad b = \frac{\beta}{R}$$

where β is Bjeerum constant and equal to the ratio between the electrostatic forces eiej /Da for the ions i , j which have a distance a between them , e^b is the long energy forces . and when solvent separated ion pair formed (SSIP) so (R= a + ds) but when (CIP) (R=a). so the value of $e^{\beta/R}$ for CIP >SSIP and the value of K_A(SSIP) less than K_A(CIP) because the value of K_A depend on (CIP) and (SSIP) and this as shown from the values of K_A and R.

The standard devotion (σ) are very small for the three drugs indicate that Lee-Wheaton equation is applicable for each drugs in solution.

Complexation of Antibiotics (drugs) with metal ions

Different spectra were measured using shimadzu (U.V.-1650PC) with two microcuvettes operating in the U.V. visible region with full scale expansion of 0.0 – 2 units for absorbance spectra, One microcuvett was filled with the drug solution (1×10^{-4} M) , the other was filled with distilled water , other measurements are for the drug and metal ion (1×10^{-4} M) with distilled water .The results of complexation of different metal ions with drugs by conductivity method are shown in table 3 (A-C) and fig 3 (A-C) .

These complex solutions behave as a weak electrolytes and obeys Kolarosh equation for weak electrolytes. The equivalent conductivity of the complex solutions against the square root of concentration are shown in figures and tables 3 (A- C).

Table (3-A): The equivalent conductivities ($\Omega^{-1}.cm^2.equiv^{-1}$) with molar concentration for Cephelaxine (1.6×10^{-4} M) with metal ions.

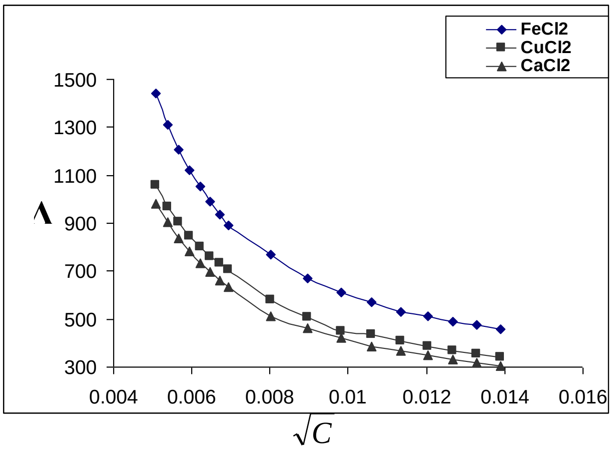
Conc. x 10^{-5} mol/L	Λ Cephelaxine +$FeCl_2$	Λ Cephelaxine +$CuCl_2$	Λ Cephelaxine +$CaCl_2$
2.57	1443.35	1058.72	983.38
2.89	1311.17	969.28	905.83
3.21	1208.60	904.07	837.46
3.53	1121.80	847.84	784.39
3.85	1052.11	800.98	734.89
4.18	988.26	761.32	695.44
4.50	935.79	731.87	661.63
4.82	892.44	704.22	634.44
6.43	767.67	578.92	513.89
8.03	669.96	508.82	463.14
9.64	610.11	447.28	420.84
11.20	569.18	434.13	387.00
12.86	531.34	406.04	367.18
14.46	513.19	383.48	349.64
16.09	490.42	366.70	331.17
17.68	474.67	352.40	318.37
19.29	458.38	338.36	306.64

Table (٣-B): The equivalent conductivities ($\Omega^{-1}.cm^2.equiv^{-1}$) with molar concentration for Amoxicillin (1.6×10^{-4} M) with metal ions.

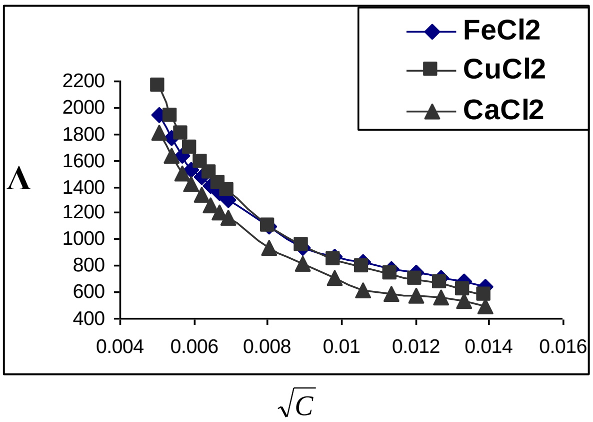
Conc. x 10^{-5} mol/L	Λ Amoxicillin $+FeCl_2$	Λ Amoxicillin $+CuCl_2$	Λ Amoxicillin $+CaCl_2$
2.57	1942.10	2156.99	1812.36
2.89	1767.89	1937.81	1637.74
3.21	1641.79	1795.20	1507.96
3.53	1532.92	1693.65	1425.76
3.85	1472.50	1579.24	1338.39
4.18	1404.00	1505.37	1259.55
4.50	1352.60	1423.42	1201.53
4.82	1295.06	1365.78	1171.30
6.43	1093.95	1102.36	940.79
8.03	941.72	956.76	811.87
9.64	865.84	846.192	709.78
11.20	826.46	784.23	615.32
12.86	781.83	737.20	585.48
14.46	744.31	694.42	576.14
16.09	712.36	663.16	558.87
17.68	677.01	618.12	533.05
19.29	637.24	575.24	499.91

Table (٣-C): The equivalent conductivities ($\Omega^{-1}.cm^2.equiv^{-1}$) with molar concentration for Chloramphenicol (1.6×10^{-4} M) with metal ions

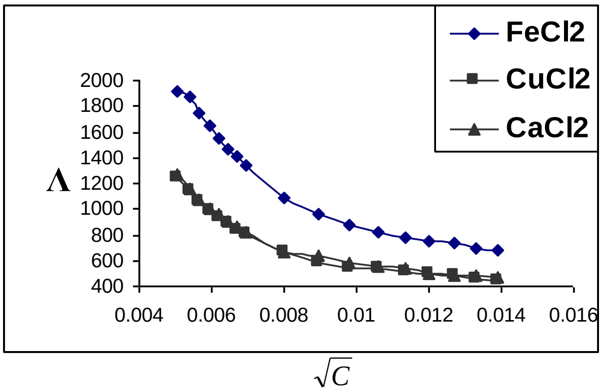
Conc. x 10^{-5} mol/L	Λ Chloramphenicol $+FeCl_2$	Λ Chloramphenicol $+CuCl_2$	Λ Chloramphenicol $+CaCl_2$
2.57	1917.77	1248.78	1265.00
2.89	1879.97	1138.83	1153.29
3.21	1749.50	1060.80	1070.59
3.53	1643.05	991.18	997.14
3.85	1549.14	930.58	955.21
4.18	1469.89	887.00	904.74
4.50	1404.54	835.64	856.88
4.82	1343.68	802.23	824.33
6.43	1093.95	666.46	663.10
8.03	960.86	582.25	634.195
9.64	877.40	538.69	583.78
11.20	819.42	535.89	548.96
12.86	782.72	516.75	539.07
14.46	747.53	503.72	501.30
16.09	729.99	480.29	481.03
17.68	697.68	457.33	480.69
19.29	676.26	446.76	468.792



Fig(٣ –A): The plot of equivalent conductivities ($\Omega^{-1}.cm^2.equiv^{-1}$) against square root of concentration for Cephelaxine s with ($FeCl_2$,$CuCl_2$,$CaCl_2$) in water at 37 °C and pH 7.



Fig(٣ –B): The plot of equivalent conductivities ($\Omega^{-1}.cm^2.equiv^{-1}$) against square root of concentration for Amoxicillin with ($FeCl_2$,$CuCl_2$,$CaCl_2$) in water at 37 °C and pH 7.



Fig(٣ –C): The plot of equivalent conductivities ($\Omega^{-1}.cm^2.equiv^{-1}$) against square root ofconcentration for Chloramphenicol with ($FeCl_2$,$CuCl_2$,$CaCl_2$) in water at 37 °C and pH 7.

Table (4) shows the results of analysis of the mixed of each antibiotic with each metal ion by using Lee-Wheaton equation for unsymmetrical electrolytes by conductivity method.

The result of analysis (table ٤) show that the association constant of all complexes with the metal ions show a decrease in the series :

$K_A [Ca(X)_3]Cl_2 < K_A [Cu(X)_3]Cl_2 < K_A [Fe(X)_3]Cl_2$

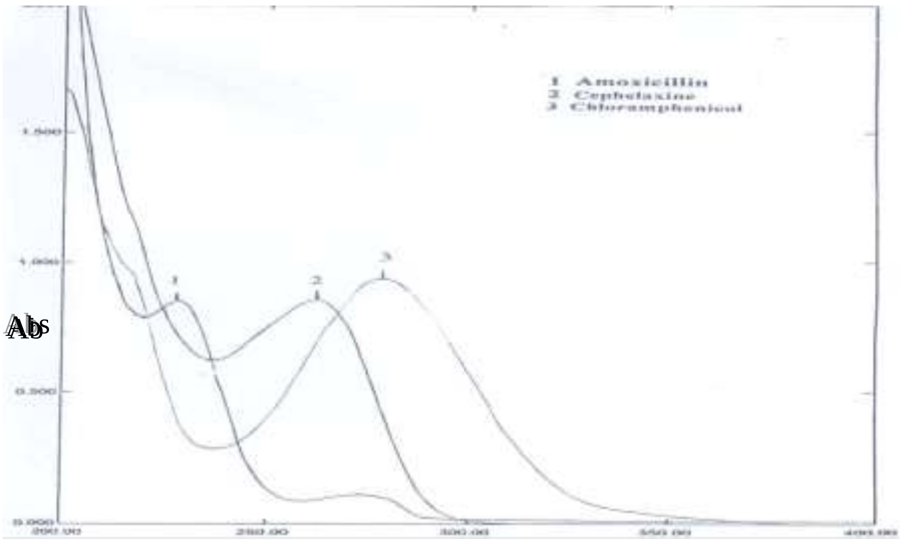
X: Chloramphenicol or Cephelaxine or Amoxicillin

This because of the increase of the ionic radius of the metals in the series $Ca^{+2} > Cu^{+2} > Fe^{+2}$ which lead [11] to form salvation shell and small ion with high molar equivalent conductance and low value of K_A as ionic radius increase and absorbance is also increase due to this fact, so there is a relationship between the equivalent conductance (Λ) and the radius of metal ion and the absorbance at which the complexes can be studied .

The study of spectral properties of complexes provides much information which usually sheds considerable light on structure and bonding , spectral properties are concerned with the difference between the ground state and the excited state of molecules . Direct evidence of orbital energy levels can be obtained from electronic spectra[12]. Fig (4) Shows the absorbance of the antibiotics only and the absorbance of the antibiotics complexes and their wave length.

Table(٤): Values of K_A (association constant) λM^{+2} , λMX^{+}(ionic concentration)and R(distance parameter) of the complex solutions at 37 °C and pH 7.

	Ionic radius for metals ion(A°)	**K_A mol/l**	**λM^{+2}**	**λMX^{+}**	**R(A°)**	**σ**
Chloramphenicol+ $FeCl_2$	٠,٧٦	800	٣٠٠	1×10^{-3}	8.9×10^{-7}	٠,٠١٢
Chloramphenicol+ $CuCl_2$	٠,٩٦	٧٥٠	٣٥٠	1×10^{-3}	8.9×10^{-7}	٠,٠٦
Chloramphenicol+ $CaCl_2$	٠,٩٩	٥٠٠	٤٥٠	1×10^{-3}	8.9×10^{-7}	٠,٠٦
Cephelaxine+ $FeCl_2$	٠,٧٦	٨٠٠	٢٠٠	2×10^{-3}	11×10^{-7}	٠,٠١
Cephelaxine+ $CuCl_2$	٠,٩٦	900	١٥٠	2×10^{-3}	12×10^{-7}	٠,٠٥
Cephelaxine+ $CaCl_2$	٠,٩٩	٦٥٠	٢٨٠	2×10^{-3}	11×10^{-7}	٠,٠٤
Amoxicillin+ $FeCl_2$	٠,٧٦	٦٥٠	٢٠٠	2×10^{-3}	9.9×10^{-7}	٠,٠١٧
Amoxicillin+ $CuCl_2$	٠,٩٦	600	٢٠٠	2×10^{-3}	9.9×10^{-7}	٠,٠٢٣
Amoxicillin+ $CaCl_2$	٠,٩٩	٥٠٠	٣٠٠	2×10^{-3}	8.9×10^{-7}	٠,٠١٦



Wavelength(nm)

Fig(٤): The absorbance against the wavelength of the antibiotics

The electronic spectra for the studied complexes have been measured to give new bands when these bands may be due to the formation of charge transfer complex . and the bands mentioned in Table (5) for ligand are shifted to longer wavelength in the complex spectra which indicate the formation of complexes[13].

Table (5): The value of the Wavelength and Absorbance for the antibiotics(1×10^{-4}) only and the complexes of antibiotics with ($FeCl_2$,$CuCl_2$,$CaCl_2$)

	Wavelength	Absorbance
Chloramphenicol only	278	0.940
Chloramphenicol+ $FeCl_2$	274	0.751
Chloramphenicol + $CuCl_2$	274	0.778
Chloramphenicol + $CaCl_2$	272	0.810
Cephelaxine only	262	0.858
Cephelaxine + $FeCl_2$	262	0.689
Cephelaxine+ $CuCl_2$	260	0.800
Cephelaxine + $CaCl_2$	262	0.790
Amoxicillin only	228	0.855
Amoxicillin + $FeCl_2$	228	0.973
Amoxicillin + $CuCl_2$	226	0.998
Amoxicillin+ $CaCl_2$	228	1.126

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دراسة التوصيلية وطيف الأشعة فوق البنفسجية لبعض الأدوية ومعقداتها مع بعض ايونات الفلزات في المحلول المائي

عمر عادل شريف

قسم الكيمياء، كلية العلوم، جامعة الموصل، الموصل، جمهورية العراق

الملخص:

أجريت هذه الدراسة لمعرفة طريقة تقدير بعض المضادات الحيوية في المحلول المائي عند الدالة الهيدروجينية (٧) وفي مدى تركيز واسع ودراسة معقدات بعض ايونات المعادن وتشخيصها ودراستها بطريقة التوصيل الكهربائي وبالأشعة فوق البنفسجية (U.V.) لمعرفة سلوك هذه المعقدات في درجة (٣٧) مئوية ولمعرفة بعض الثوابت مثل التوصيل المكافئ عند التخفيف الى اللانهائي (Λ_o) ، وثابت التجمع ألايوني (K_A) والمسافة بين الايونات في المحلول (R) عند قيم (σ_Λ) معدل انحراف قليلة جداً لكل مضاد حيوي بمفرده فضلاً عن معطيات التوصيلية لمزيج من كل مضاد حيوي مع ايونات املاح كل من كلوريد الحديد والنحاس والكالسيوم، ولمقارنة هذه الطريقة مع الطريقة الطيفية لتشخيص معقدات الأدوية.