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Spectrophotometric Study of Complexation between Trimethoprim and Sulfamethoxazole and Pd(II) and Cu(II) and the Determination of Thermodynamic Parameters with Kinfit Software

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Abstract
The complexation reactions between Cu^{2+} and Pd^{2+} ions with trimethoprim (TMP) and sulfamethoxazole (SMX) in N,N-Dimethylformamide (DMF) were studied by the spectrophotometric methods at [(15, 25, 35 and 45±0.1) °C]. The complexation process was optimized in terms of pH, temperature and time. The stoichiometry of the complexes was found to be 1:2 (metal ion/ligand). The formation constants of the resulting complexes were determined from computer fitting absorbance-mole ratio data and emphasized by the *KINFIT* program. The values of the thermodynamic parameters for complexation reactions were obtained from the temperature dependence of the stability constants. In all cases, the complexes were found to be enthalpy stabilized but entropy destabilized. SMX and TMP could be determined by measuring the absorbance of each complex at its specific λ_{max}. The proposed method was successfully applied for the determination of these compounds in their dosage forms.

Keywords
Trimethoprim; Sulfamethoxazole; Metal Complexes; Thermochemistry; KINFIT.

1. INTRODUCTION

Metal ions are known to accelerate drug actions. The efficacies of some therapeutic agents are known to increase upon coordination [1]. Some metal complexes are known to exhibit remarkable antitumour, antifungal, antiviral and special biological activities. Therefore, complexations of chemotherapeutic agents are applicably useful in medicine and pharmacy.

Many studies have recently stressed the role of metal ions in important biological processes [2,3], whereas the inorganic pharmacology started to be an important field with more than 25 inorganic compounds being used in therapy as antibacterial, antiviral and anticancer drugs [3,4] also targeted against Human immunodeficiency (HIV) in the form of combinations called Co-trimoxazole [5] etc. It has also been demonstrated that chelation/complexation tend to make nonbiologically active compounds biologically active [3, 6–9] and already biologically active compounds to be more active [10].

The most widely studied metal in this respect is copper (II) which has proved beneficial in diseases such as tuberculosis, gastric ulcers, rheumatoid arthritis and cancers [10]. These reencouraged us to investigate the coordination chemistry of antibiotics with transition metal ions in an attempt to examine the modes of binding in the solid state.

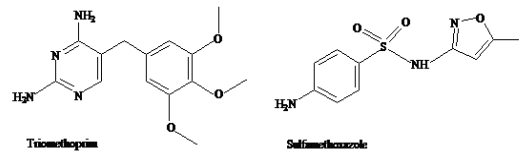

Fig.1. Chemical structures of TMP and SMX.

The binary mixture of SMX and TMP (Fig.1) has been widely studied and numerous spectrophotometric methods for the simultaneous determination in mixtures and pharmaceutical preparations have been developed [11–18]. However, most of these methods require a lot of data manipulation, which makes it difficult for their application as standard transferable methods. Thus, it is highly desirable to develop even simpler methodologies with minimal sample and data manipulation.

In the present study was investigated the complexation reactions of SMX and TMP with some metal ions. For evaluation of the formation constants of complexes, K_f, from the absorbance-mole ratio data, the nonlinear least-squares curve-

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fitting program *KINFIT* was used [19-21]. Also, a simple and sensitive spectrophotomertic method was developed for the simultaneous determination of TMP and SMX in pharmaceuticals. This procedure was based on complexation of SMX with Pd(II) or Cu(II), without being interfered by TMP.

2. EXPERIMENTAL

2.1. Apparatus

A JASCO model V-530 UV–Vis spectrophotometer with 1 cm matched cell was used for electronic spectral measurements. SPECTRA MANAGER software was used for all absorbance measurements. A Horiba D-14 pH meter was employed for pH measurements.

2.2. Solutions

A standard palladium (II) chloride solution (2×10^{-3} M) was prepared as described previously [22] and then standardized gravimetrically [23]. Walpole,s acetate buffer 22 was prepared by mixing appropriate quantities of 0.2 M acetic acid with 0.2 M sodium acetate to get the desired pH that were obtained with addition of their different proportions. A 0.2% (w/v) of sodium lauryl sulfate in DMF.

2.3. Procedure for calibration curve

Metal ions standard solution were pipetted into a 10 ml volumetric flask and then the specified volumes of Walpole's acetate buffer and sodium lauryl sulfate (SLS) (for palladium chloride) were added. Aliquots of SMX and TMP within the concentration range cited in Table 1, were transferred each into its corresponding set. The solutions, were diluted in a 10 ml standard flask with DMF.The absorbance of the complexes were measured at corresponding λmax for the studied drugs, against a reagent blank similarly prepared without drug solution.

2.4. Procedure for the determination of SMX and TMP in pharmaceutical formulations

Twenty tablets of were weighed and powdered and transferred to a 100 ml conical flask and extracted by shaking with 60 ml water for 20 min. Prepared solution was filtered and the filtrate was made up to 100 ml with water. An aliquot of this solution was treated by the same procedure as described for the calibration curve. Final estimated concentration was 100 ppm.

3. RESULTS AND DISCUSSION

The reactions of SMX and TMP with Palladium (II) chloride and Copper (II) acetate were investigated over different pHs in acetate buffer solutions at [(15, 25, 35 and 45±0.1) °C]. It was found that complexes of with Palladium (II) chloride or Copper (II) acetate are DMF-soluble. The complexes of SMX-Pd, SMX-Cu, TMP-Pd and TMP-Cu gave an absorption peak at 400, 766 418 nm and 780, respectively, which were used for the analytical determination. Under the same conditions, SMX, TMP, Pd (II) and Cu (II) does not absorb significantly over the investigated wavelength range. Formation of stable complexes depends largely on the reaction conditions. The stoichiometry of complexes were determined with the classical methods of continuous variations and molar ratio. For evaluation of the formation constants of complexes, were used from *KINFIT* program.

3.1. Pd(II)- SMX and Pd- TMP complexes

The absorption spectra of SMX-Pd and TMP-Pd were recorded over the wavelength range 350–450 nm. It was found that SMX and TMP with palladium (II) chloride form DMF-soluble 2:1 complexes. The complexes gave an absorption peak at 400, 418 which were used for the analytical determination (Fig.2). Formation of stable complex depends largely on the reaction conditions.

3.1.1. Effect of pH

The most suitable pH for formation of Palladium (II) complexes were determined by mixing 3 ml 2 $\times10^{-4}$ M drug and 2 ml 2 $\times10^{-3}$ M Palladium (II) chloride,1 mL SLS, 4 mL 0.2 M acetate buffer solutions of pH 2.5-6.5. The spectra of the formed coloured complex were scanned over the range of 350-450 nm against a reagent blank. The results for SMX are represented in Fig. 3. Starting from pH 2.5 a yellow-brown colour appears and the intensity of this colour increases with increase of pH of the solution up to pH 4.5 (for SMX) and 5.0 (TMP).

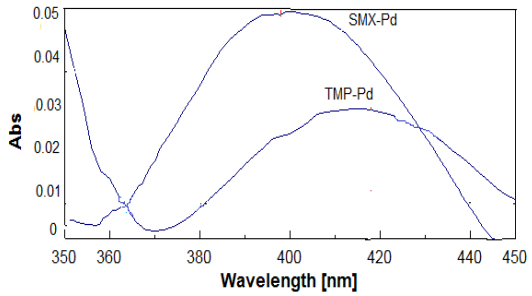

Fig. 2. Absorption spectra of the complexes of SMX and TMP with Pd (II) in the range of 350-450 nm.

3.1.2. Effect of SLS concentration

The chelates were found to be soluble only in the presence of a surfactant. An investigation of the effects of the SLS concentration on the formation of the SMX-Pd and TMP-Pd complexes showed that a 1.0 mL volume is appropriate for maximum complexes formation.

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3.1.3. Effect of Palladium (II) concentration

An investigation of the effect of Palladium (II) chloride concentration on the complex formation showed that the drug (2×10^{-4} M) was converted quantitatively into the complex in the presence of a relatively large excess of Palladium (II) chloride (2×10^{-3} M), i.e. an increasing concentration of Palladium (II) chloride produced an increase in the absorbance of the complex. A suitable volume 2 for SMX-Pd and 1 for TMP-Pd was selected, in which the absorbance of the complex reached a maximum (Fig. 1). With further increasing the effect of Palladium (II) concentration the absorbance remained constant.

3.1.4. Effect of temperature and heating time

The amount of the complexes produced are considerably influenced by the temperature of the reaction mixture and by the effect of heating time. Heating the solutions up to 75 ºC for 40 min was found to contribute significantly to the complete development of the palladium complexes.

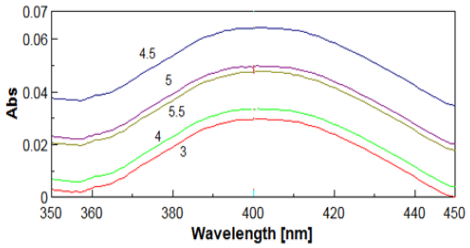

Fig. 3. Absorbance spectra of SMX-Pd complex in different pHs.

3.2. Cu(II)- SMX and Cu(II)- TMP complexes

The problem of resistance to antimicrobial activity is being addressed by medicinal chemists and various strategies have been devised and attempted in order to enhance the activity or broaden the spectrum of the drugs [24]. It has been demonstrated that transition elements play a very important role in of various medicinal compounds [25, 26]. In the present work we report derivatives of sulfamethoxazole and trimethoprim with copper with greater medicinal value. The drug molecules used in the present study contain $-NH_2$, and other donor groups; construction of molecular models indicates that the structures are suitable for chelate formation. Trimethoprim has four nitrogen atoms which can donate electron pairs, two nitrogens of pyrimidine ring and two nitrogens of amine groups. The absorption spectra were recorded over the wavelength range 750-800 nm and the absorption maxima are recorded in Fig. 3. It was found that formed copper complexes are blue and DMF-soluble. The complexes were formed in base pHs. As it is shown in Fig. 5, the maximum absorption of Cu(II)- SMX and Cu(II)- TMP complexes are at 766 and 780 nm, respectively that were used for the analytical measurements. The stoichimetry of the complexes were obtained 2:1.

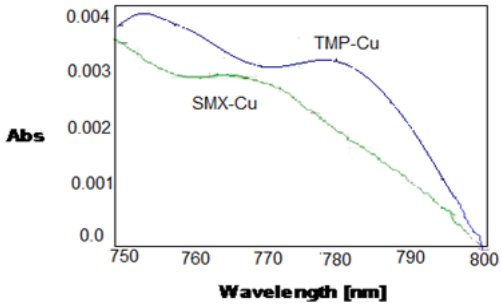

Fig. 4. Absorption spectra of complexes of SMX and TMP with Cu (II) in the range of 750-800 nm.

3.3. The composition of the complexes and stability constants

Job's method of analysis corresponds well with the analogous values obtained using mole ratio method of analysis [27,28]. When SMX and TMP react with metal ions, in solution, they form 1:2 metal ion to ligand complexes. The mass balance equation for formation of ML_2, should be solved in order to calculation of the free ligand concentration [L].

The formation constant (K_f) and the molar absorptivity ($\mathcal{E}$) of the resulting 2:1 complex between the SMX and TMP and different metal ions at different temperatures were calculated by fitting the observed absorbance, A_{obs}, at various metal ion/ligand mole ratios to the previously derived equations, which express the A_{obs} as a function of the free and complexed metal ions and the formation constant evaluated from a non-linear least-squares program *KINFIT*. The free metal ion concentration, [M], was calculated by, a Newton-Raphson procedure. When the value of [M] had been obtained, the concentration of all other species involved are calculated from the mass balance equations by using the estimated value of the formation constant at the current interaction step of the program. The output of the program *KINFIT* comprises the refined parameters, the sum of squares and the standards deviation of the data.

The formation constants of the resulting 1:2 metal ion to ligand complexes were obtained at different temperatures by absorbance measurements of solutions in which varying concentrations of metal ions were added to fixed amounts (5.0×10^{-5} M) of ligand solution , at λ_{max} of ligand. The mass balance equation of used in computer program KINFIT should be solved in order to obtain Eq. (1) for the free ligand concentration [L].

$$K_1K_2[L]^3 + K_1\big(1 + K_2(2C_M - C_L)\big)[L]^2 + (1 + K_1(C_M - C_L)[L] - C_L) \quad (1)$$

The formation constants ($K_f = K_1 + K_2$) of the resulting 1:1 and 1:2 (metal ion to drug) were calculated. For evaluation of the formation

constant from molar absorbance vs C_L/C_M mole ratio data (C_{drug}/C_{metal}), the *KINFIT* program a non-linear leastsquares curve fitting program KINFIT was used. All of the logkf values evaluated from the computer fitting of the corresponding absorbance – mole ratio data are listed in Table 1. A sample computer fit of the absorbance- mole ratio data for metal ion and SMX and TMP at 25°C is shown in Fig. 5.

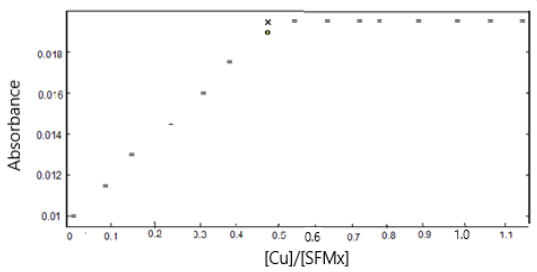

Fig. 5. Computer fits of the plots of absorbance vs. [Cu]/[SFMx] mole ratios at 25 ˚C: (x) experimental point, (o) calculated point, (=) experimental and calculated points are the same within the resolution of the plots.

The trend of the stability of the complexes follows the order Cu (II)>Pd (II). This order agrees with the conclusions reached by Irving and William [29]. The Cu (II) complexes is the most stable of the studied complexes, probably due to its $3d^9$ configuration and well-known Jahn–Teller effect [30-31].

3.4. Thermodynamic parameters

The thermodynamic parameters were calculated from the temperature dependence of the complexation constants (Vant Hoff plot). The formation constants were measured as a function of temperature (288, 298,305 and 315 K).

The stability of the complexes increases with increasing the temperature. In all cases, the plots of log K_f versus $1/T$ were linear and the ΔH° and ΔS° values were determined in the usual manner from the slope and intercept of the plots, respectively. The calculated thermodynamic parameters for all systems are listed in Table 1.

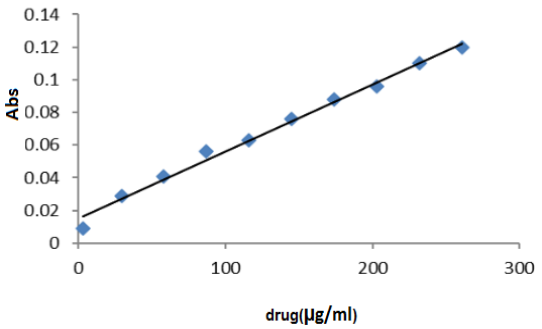

Fig. 6. Calibration curve of TMP with Palladium (II) chloride.

3.5. Quantification and application to dosage forms

Molecules that absorb in the visible region, usually absorb very strongly so that absorbances can readily and accurately be determined.

Metal complexing ability of SMX and TMP is a very important character of this group of compounds. This character was utilized to develop a method for determination of SMX and TMP in bulk powder and pharmaceutical formulations. The proposed method based on complexes formation between SMX and TMP with Palladium (II) chloride and copper (II) acetate.

Table 1. Average values of *logKf*, ΔG° and ΔS° of metal ions with SMX and TMP with standard deviations (0.01) at different temperatures.

Complex	logKf	ΔS°,J/mol.k	-ΔG°,J/mol
	15° C		
Pd (II) /SMX	4.95	94.63	27260.59
Pd (II) /TMP	4.05	77.42	22304.12
Cu (II)/SMX	7.1	135.72	39101.05
Cu (II)/TMP	9,46	180.8	52098.02
	25° C		
Pd (II) /SMX	5.015	96.93	28890.89
Pd (II) /TMP	4.08	77.99	23249.47
Cu (II)/SMX	7.2	137.64	41028.48
Cu (II)/TMP	9.7	185.43	55274.48
	35° C		
Pd (II) /SMX	5.07	96.93	29860.27
Pd (II) /TMP	4.18	79.91	24618.53
Cu (II)/SMX	7,47	142.8	43995.31
Cu (II)/TMP	9.87	188.69	58130.35
	45° C		
Pd (II) /SMX	5.12	97.89	31133.70
Pd (II) /TMP	4.27	81.63	25965.02
Cu (II)/SMX	7.57	144.71	46031.66
Cu (II)/TMP	10.01	191.37	60868.81

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Table 2. Optical characteristics and statistical data of the regression equations for the complexes of Cu(II) and Pd(II) with SMX and TMP.

Parameters	Pd (II) /SMX	Pd (II) /TMP	Cu (II)/SMX	Cu (II)/TMP
λ_{max} (nm)	400	418	766	780
Molar absorbitivity(l mol^{-1} cm^{-1})	2.05×10^3	4.4×10^3	52	624
$(\mu g ml^{-1})$ Beer's law rang	25-227	29.3-261	2.5-25.3	14.5-145
$(\mu g ml^{-1})$Limit of detection	0.26	0.38	0.0126	0.0074
$(\mu g ml^{-1})$Limit of quantitation	0.08	0.126	0.0381	0.0224
Slope(b)	0.0003	0.0004	0.0001	5×10^{-6}
Intercept(a)	0.0081	0.0152	0.0262	0.0125
Correlation coefficient (r)	0.9944	0.9911	0.9969	0.9991

Table 3. Evaluation of the accuracy and precision of the proposed method for SMX and TMP determination in pharmaceutical preparations

complex	Added (μg ml^{-1})	Found (μg ml^{-1})	SD	RSD (٪)	Recovery (%)
Pd (II) /SMX	31	30.83	0.0006	4.9	97.5
	46	45.99	0.0007	4.48	99.98
Pd (II) /TMP	62	61.98	0.0004	1.87	99.5
	77	76.96	0.0001	3.73	98.9
Cu (II)/SMX	18	17.999	0.0001	0.3665	99.8
Cu (II)/TMP	35	34.998	2.81×10^{-5}	0.2221	94.6

A linear relationship was obtained between the absorbance and the concentration of SMX and TMP (Table 2).A sample is shown in Fig. 6. The reproducibility of the procedure was determined by running five replicate samples. The high percentage recoveries and the values of standard deviation (Tables 2, 3) indicate the good accuracy and repeatability of the proposed method. This study describes an accurate, sensitive, more conventient, and less timeconsuming spectrophotometric method for rapid determination of SMX and TMP in raw material and in pharmaceutical formulations.

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مطالعه اسپکتروفتومتری کمپلکس‌های تریمتوپریم و سولفامتاکسازول و Cu(II) و Pd(II) وتعیین پارامترهای ترمودینامیکی با نرم افزار کین فیت

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چکیده

واکنش‌های تشکیل کمپلکس بین یون‌های Cu^{2+} و Pd^{2+} با تری‌متوپریم (TMP) و سولفامتوکسازول (SMX) در N,N دی‌متیل‌فرمامید (DMF) با روش اسپکتروفتومتری در دمای [(۱۵، ۲۵، ۳۵ و ۴۵±۰,۱) °C] مورد مطالعه قرار گرفتند. فرآیند کمپلکس‌سازی از نظرpH ، دما و زمان بهینه شد. استوکیومتری کمپلکس‌ها ۱:۲ (یون فلزی/لیگاند) تعیین شد. ثابت‌های تشکیل کمپلکس‌های حاصل از برازش کامپیوتری داده‌های نسبت جذب–مول تعیین و توسط برنامه KINFIT تأیید شدند. مقادیر پارامترهای ترمودینامیکی برای واکنش‌های کمپلکس‌سازی از وابستگی دمایی ثابت‌های پایداری به دست آمد. در همه موارد، کمپلکس‌ها از نظر آنتالپی پایدار اما از نظر آنتروپی ناپایدار بودند SMX و TMP را می‌توان با اندازه‌گیری جذب هر کمپلکس در λmax خاص آن تعیین کرد. روش پیشنهادی با موفقیت برای تعیین این ترکیبات در اشکال دارویی آن‌ها به کار گرفته شد.

کلید واژه ها

تری متوپریم؛ سولفامتوکسازول؛ کمپلکس‌های فلزی؛ ترموشیمی؛ کین فیت.

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