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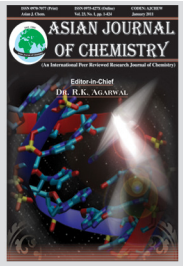

Spectrophotometric Determination of Centrophenoxine Hydrochloride with Alkalinity Potassium Permanganate Method

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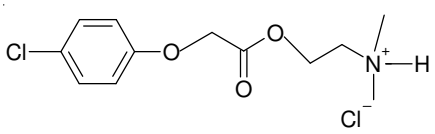
The simple, senstitive spectrophotometric methods have been developed for the assay of centrophenoxine hydrochloride in pure and pharmaceutical formulations. This method is based on oxidation of centrophenoxine hydrochloride by potassium permanganate in alkalinity media with the maximum wavelength of colour reaction at 430 and 610 nm, of fading reaction at 525 nm. Reaction conditions were optimized to obtain the maximum colour intensity and maximum fading intensity. The absorbance was found to increase linearly in concentration of centrophenoxine hydrochloride, which was corroborated by the calculation coefficient values (0.9997, 0.9993 and 0.9995, respectively). The system obeyed Beer's law in the range of 2.5-15 μg/mL for centrophenoxine hydrochloride. Various analytical parameters have been evaluated and the results have been validated by statistical data.

Key Words: Centrophenoxine hydrochloride, Spectrophotometric determination, Potassium permanganate.

INTRODUCTION

Centrophenoxine hydrochloride or meclofenoxate hydrochloride is designated chemically as 4-chlorophenoxy-acetic acid 2-(dimethylamino)ethyl ester hydrochloride or (*p*-chlorophenoxy)acetic acid 2-(dimethylamino)ethylester hydrochloride (**Scheme-I**), which is an ester of dimethyl aminoethanol and *p*-chlorophenoxy acetic acid. It is a known antiaging drug, which enables its passage through the blood brain barrier easily and can stimulate brain metabolism, can increase lifespan and improve learning capacity. Therefore, it is a psychostimulant in the nootropic agent group available in capsule and tablet formulations approved for traumatic cataphora, alcoholic poisoning, anoxia neonatorum and children's enuresis in China[1-5]. Centrophenoxine hydrochloride (CH) is official in Ch.P.[5]. The reported method is high performance liquid chromatography method[6-9], whose instrument is expensive, the H_2SO_4 titrimetric method after distillation is of less sensitivity and trouble procedure[10]. Spectrophotometric methods are the most popular methods employed in medicine. Therefore, the development of a low-cost, simple, sensitive and precise spectrophotometric method for the determination of centrophenoxine hydrochloride (CH) in pharmaceutical formulations is desirable. $KMnO_4$ is a cheap reagent, employed to spectrophotometric determination of nizatidine and ranitidine[11], norfloxacin[12], isoxsuprine[13] and tramadol hydrochloride[14]. Therefore, the spectrophotometric method has been proposed based on oxidization of centrophenoxine hydrochloride by $KMnO_4$ in NaOH media for its dimethylaminoethyl group similar to dimethylamino-methyl group of tramadol hydrochloride[14].



Scheme-I: Structure of centrophenoxine hydrochloride

EXPERIMENTAL

All chemical reagents used were of analytical or pharmaceutical grade and distilled water was used throughout the experiments. Pharmaceutical grade centrophenoxine hydrochloride (99.95 % pure) was obtained as gift sample from Nanjing Haichen Pharma. Ltd., China. A stock solution of CH containing 100 μg/mL was prepared in distilled water. 0.005 mol/L $KMnO_4$ solution and 0.75 mol/L NaOH solution were prepared separately in high purity water. Different dosage forms of centrophenoxine hydrochloride such as Jiannaoling injection, Surueisu injection, Zhengsu injection and Teweizhi Capsules were obtained commercially from different firms in china.

A Shimadzu UV-250PC model UV-Visible spectrophotometer (Tokyo, Japan) with 1 cm matched quarz cells was used for the absorbance measurements.

Assay procedure for pure drug: An aliquot of the solution containing 25-150 µg of centrophenoxine hydrochloride was transferred into a series of 10 mL volumetric flasks, 2.00 mL of 0.005 mol/L $KMnO_4$ solution and 2.00 mL of 0.75 mol/L NaOH solution were added successively. The each flask was made up to volume with distilled water. The absorbance of the solution containing centrophenoxine hydrochloride was measured at 430 and 610 nm against a reagent blank or the absorbance of the reagent blank at 525 nm against the solution containing centrophenoxine hydrochloride.

Assay procedure for dosage forms: For injections, the contents of five ampoules were mixed, 100 mg of the drug was dissolved to the 1000 mL volumetric flasks and the flask was made up to volume with distilled water. Aliquots of the solution were then treated as described above under the assay procedure for pure drug. For capsules, the contents of five capsules were mixed, 100 mg of the drug was dissolved to the 1000 mL volumetric flasks and the flask was made up to volume with distilled water. Aliquots of the solution were then treated as described above under the assay procedure for pure drug.

RESULTS AND DISCUSSION

Absorption spectra and reaction mechanism: $KMnO_4$ has been used in pharmaceutical analysis for the determination of specific functional groups such as dimethylaminomethyl group of tramadol hydrochloride in aqueous alkalinity media[12]. In present work, $KMnO_4$ reacts with centrophenoxine hydrochloride to produce the green MnO_4^{2-}, which of dimethylaminoethyl group similar to dimethylaminomethyl group of tramadol hydrochloride, the reaction was proposed in **Scheme-II**. $KMnO_4$ was used as oxidant in aqueous alkalinity media to produce green MnO_4^{2-} with the absorption peak at 430 and 610 nm and fading red colour of $KMnO_4$ at 525 nm (Fig. 1 absorption spectra).

Optimization of reaction condations: The reaction was investigated on effect of the reaction time, the reaction temperature and the volume of NaOH solution as well as the volume of $KMnO_4$ solution. From Table-1, the optimum volumes of 0.75 mol/L NaOH solution were found to be at the range from 1.50 mL to 3.00 mL to give the maximum colour intensity at 430 or 610 nm and maximum fading intensity at 525 nm. From Table-2, effects of the reagent on colour development and fading development were also studied where it was found that 0.005 mol/L $KMnO_4$ solution was at the range from 1.50 to 3.00 mL

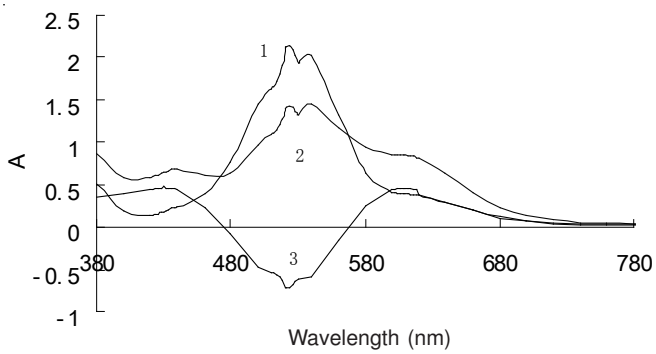


Fig. 1. Absorption spectra (curve 1: The reagent blank *vs.* water; curve 2: The reaction solution *vs.* water curve 3: The reaction solution *vs.* the reagent blank

TABLE-1
EFFECT OF 0.75 mol/L NaOH SOLUTION

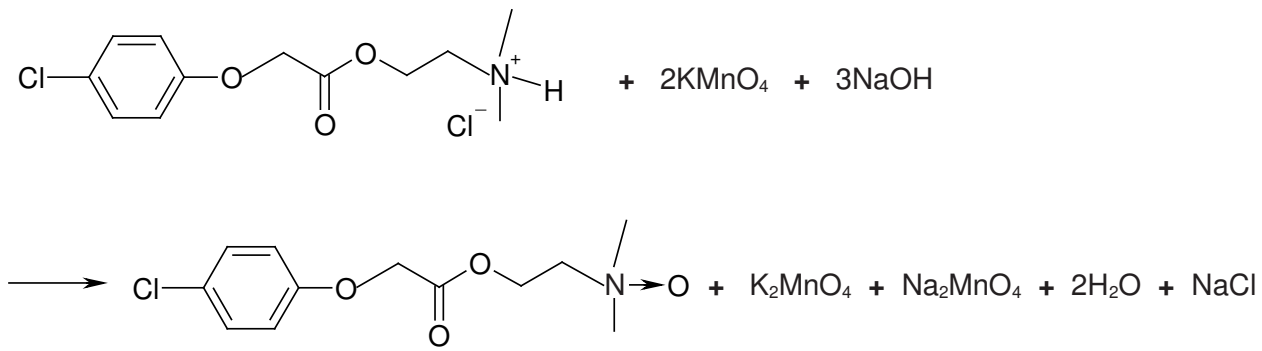
Absorbance (nm)	Volume (mL)					
	0.50	1.00	1.50	2.00	2.50	3.00
610	0.322	0.394	0.433	0.435	0.434	0.432
430	0.300	0.354	0.369	0.370	0.370	0.370
525	0.421	0.484	0.530	0.532	0.530	0.531

TABLE-2
EFFECT OF 0.005 mol/L $KMnO_4$ SOLUTION

Absorbance (nm)	Volume (mL)						
	0.20	0.50	1.00	1.50	2.00	2.50	3.00
610	0.040	0.182	0.313	0.392	0.393	0.393	0.393
430	0.082	0.198	0.300	0.428	0.430	0.429	0.430
525	0.098	0.272	0.437	0.545	0.545	0.546	0.545

sufficient to give the maximum colour intensity at 430 and 610 nm and give the maximum fading intensity at 525 nm. The reaction temperature was found at the range 25-30 ºC to give maximum colour intensity and maximum fading intensity. The reaction time was found to be 70-120 min to give the maximum values.

Validation of the method: Linear correlations were found between the absorbance values and the concentration of centrophenoxine hydrochloride over the ranges stated in Table-1. Good linearity of the calibration plots is evidenced by low variances around the slops and high correlation coefficient. Accuracy was examined by calculating the recovery of the drug spiked to the pharmaceutical preparations where good results were obtained. If a method is of low value of relative standard deviation (RSD), the method will give high precision



Scheme-II: Reaction equation of $KMnO_4$ with centrophenoxine hydrochloride

and good determined results. The solutions containing three different concentrations of centrophenoxine hydrochloride were prepared and analyzed in five replicates, the mean relative standard deviations were calculated in order to evaluate the precision of the proposed method. The detection and quantitation limits were calculated from the standard deviation of the absorbance measurement obtained from the blank solution. These results are summarized in Table-3.

TABLE-3
OPTICAL CHARACTERISTICS, PRECISION AND ACCURACY DATA

Parameter	Values		
λ_{max} (nm)	430	525	610
Beer's law limit (μg/mL)	1-15	1-15	1-15
Molar absorptivity (L mol^{-1} cm^{-1})	1.315×10^4	1.899×10^4	1.280×10^4
Sandell's sensitivity (ng cm^{-2})	22.37	15.49	22.98
Correlation coefficient (r)	0.9997	0.9993	0.9995
Regression equation (Y)[a]			
Slop, b	0.0447	0.0637	0.0435
Intercept, C	0.0038	0.0007	0.0113
RSD (%)[d]	0.93	0.97	0.89
% Range of error[d] (95 % confidence limit)	0.81	0.82	0.79
Limit of detection (ng/mL)	8.29	7.42	7.11
Limit of quantification (ng/mL)	24.16	18.37	23.86

[a]Y=bX+C, where X is the concentration of drug in μg/mL. [d]Average of five determinations.

In order to study accuracy of the proposed method, recovery studies were carried out by the standard addition method. Known quantities of pure centrophenoxine hydrochloride were mixed with definite amounts of pre-analyzed formulations such that final concentration of centrophenoxine hydrochloride was within Beer's law limits and the mixtures were analyzed as before. The total amount of the drug was then determined and the amount of the added drug was calculated by difference. The results of recovery are given in Table-4. The average recoveries obtained were quantitative, its recoveries were at range of 98.76-99.75, 98.84-99.60 and 99.64-99.83 % for different determined wavelength at 430, 525 and 610 nm, separately. These results indicated good accuracy of the proposed method for determination of centrophenoxine hydrochloride.

TABLE-4
RECOVERY STUDY FOR THE SPIKED CONCENTRATION OF CENTROPHENOXINE HYDROCHLORIDE TO THE PRE-ANALYZED DOSAGE FORMS

Formulation	λ (nm)	Label claim (mg)	Amount (mg)		Recovery (%)	RSD (%)
			Added	Found		
Jiannaoling injection	430	100	25	124.63	99.63	0.21
	525	100	25	124.52	99.52	0.35
	610	100	25	124.81	99.81	0.28
Jiannaoling injection	430	200	50	249.50	99.75	0.20
	525	200	50	249.20	99.60	0.32
	610	200	50	249.66	99.83	0.17
Surueisu injection	430	100	20	119.54	99.54	0.37
	525	100	20	118.80	98.80	0.56
	610	100	20	119.47	99.47	0.31
Zhengsu injection	430	100	30	128.76	98.76	0.27
	525	100	30	128.96	98.96	0.61
	610	100	30	128.86	98.86	0.22
Teweizhi capsules	430	100	20	119.54	99.54	0.26
	525	100	20	118.64	98.64	0.48
	610	100	20	119.73	99.73	0.29

Analytical applications: The proposed method was successfully applied to determination of centrophenoxine hydrochloride in its pharmaceutical preparations. The results obtained were statistically compared to those of official method by students t-test for accuracy and the variance ratio F-test for precision as recorded in Table-5.The experimental values of t at 95 % confidence level did not exceed the theoretical value of 2.31, the experimental value of F for p = 0.05 also did not exceed the theoretical value of 6.39, indicating lack of significant difference between the proposed method and the official method. The results are shown in Table-5.

TABLE-5
DETERMINATION OF CENTROPHENOXINE HYDROCHLORIDE IN PHARMACEUTICAL PREPARATIONS USING THE PROPOSED METHOD

Preparation	Label amount (mg)	This method		Official method
		λ (nm)	Recovery (%) ± SD[a]	Recovery (%) ± SD[a]
Jiannaoling injection	100	430	99.45 ± 0.48 F=1.37; t=1.47	99.37 ± 0.78 F=1.25; t=1.55
		525	99.39 ± 0.65 F=1.44; t=1.28	
		610	99.48 ± 0.53 F=1.21; t=1.58	
Jiannaoling injection	200	430	100.1 ± 0.51 F=1.09; t=1.76	99.78 ± 0.57 F=1.90; t=1.89
		525	99.75 ± 0.76 F=1.63; t=1.88	
		610	99.89 ± 0.35 F=1.35; t=1.59	
Surueisu injection	100	430	100.7 ± 0.65 F=1.19; t=1.82	99.87 ± 0.61 F=1.57; t=1.73
		525	100.2 ± 0.58 F=1.77; t=1.85	
		610	100.5 ± 0.51 F=1.29; t=1.55	
Zhengsu injection	100	430	99.04 ± 0.81 F=1.29; t=1.73	98.68 ± 0.97 F=1.35; t=1.86
		525	98.87 ± 0.91 F=1.09; t=1.69	
		610	99.21 ± 0.69 F=1.55; t=1.78	
Teweizhi capsules	100	430	99.44 ± 0.28 F=1.28; t=1.53	99.31 ± 0.47 F=1.57; t=1.75
		525	99.15 ± 0.47 F=1.69; t=1.87	
		610	99.56 ± 0.25 F=1.33; t=1.56	

[a]Each value is the mean of five measurements.

Conclusion

Unlike the HPLC procedure, the instrument of the proposed method is simple and affordable. The reagents ($KMnO_4$ and NaOH) utilized in the proposed method are cheaper, readily available and the procedure do not involve any critical reaction conditions or tedious sample preparation. The proposed method was simple and can be recommended for routine quantitative determination of centrophenoxine hydrochloride.

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