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Turbidimetric determination for promethazine hydrochloride and codeine phosphate in pharmaceutical preparation using sodium tungstate as precipitating reagent

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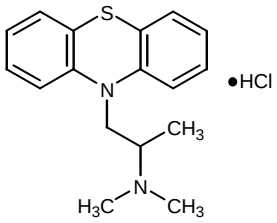
ABSTRACT

New turbidimetric methods were developed for the determination of Promethazine Hydrochloride and Codeine Phosphate in pharmaceutical preparation. The procedure is based on the precipitation of Promethazine and Codeine as ion pair complex by reaction with sodium tungstate in acidic media to formation a white precipitate. The experimental parameters such as reagent concentration, colloid protection, time effect…etc, have been investigated in this paper. The results show that the calibrations graph were constructed to form linear range (0.03-2.0) and (0.05-3.5) mmol.L^{-1} while the correlation coefficient are 0.9985 and 0.9951 for Promethazine and Codeine respectively. Also, Limit of Detections for stepwise dilution of minimum concentration in the linear range of the calibration graph is 1×10^{-5} (PMH) and 2.5×10^{-5} (COP) mol.L^{-1}. While repeatability (RSD%) of the proposed method < 2.5% for both of Promethazine and Codeine. A comparison was achieved between the developed procedures and the official method via use the paired t-test. The proposed methods were successfully applied in the determination of drugs in different pharmaceutical tables.

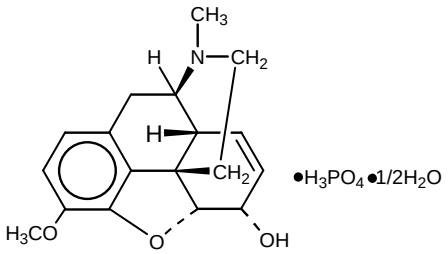
INTRODUCTION

Promethazine (PMH) is a one of phenothiazine derivatives, which considered as first-generation antihistamine [1]. Chemically, knowns as (2RS)-N,N-dimethyl-1-(10H-phenothiazin-10-yl)propan-2-amine hydrochloride. It is characterized as a white or faintly yellowish crystalline powder, odorless powder form, very soluble in water, freely soluble in alcohol and methylene chloride. The molecular formula of PMZ is $C_{17}H_{20}N_2S$,HCl and the molecular weight 320.9 g.mol^{-1} [2]. PMH acts as anti-histamine, sedative, and antiemetic [3]. The chemical structure was shown in Scheme (1-A). Numerous methods in the literature have been used in order to analysis of PMH in pharmaceutical formulations like spectrophotometry [4-6], turbidimetry [7], HPLC [8-9], and Voltametric method [10].

Codeine is a morphine derivative, obtaining from naturally alkaloid such as opium or other poppy saps. Recently, it is obtained by synthesis and available as a salt forms like phosphate or hydrochloride [11]. Codeine is used for the treatment of analgesic, antidiarrheal, antitussive, antihypertensive and to relieve cough [3]. Codeine phosphate (COP) chemically known as 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate hemihydrate. It is characterized as White or almost white crystalline powder or small, freely soluble in water, slightly soluble or very slightly soluble in ethanol [2]. The molecular formula of COP is $C_{18}H_{21}NO_3$,H_3PO_4,1/2H_2O. The molecular weight of COP is 406.4 g.mol^{-1}. The chemical structure was shown in Scheme (1-B).



Scheme (1-A):Chemical structure of Promethazine Hydrochloride



Scheme (1-B):Chemical structure of Codeine phosphate

Codeine phosphate in combination with other drugs have been determined using many techniques like HPLC [12-13], spectrophotometric [14], Chemiluminescence [15], derivative spectrophotometry [16], Gas chromatographic-mass and spectrometric methods [17].

The aim of this research is development a new, accurate and selective method for the determination both of Promethazine HCl (PMH) and Codeine phosphate in pharmaceutical formulations. The method used Sodium Tungstate as Precipitating reagent to form a white precipitate as ion pair complexes. The proposed methods were successfully applied for analysis of these compounds in cold pharmaceutical preparations.

EXPERIMENTAL SECTION

Chemicals

All of chemical materials were used from analytical grade and distilled water throughout this work. Stock solutions of PMH (SDI) (0.05 mol.L^{-1}) was prepared by dissolving 1.6045 g in 50 mL distilled water and was stored in a refrigerator. Sodium tungstate (BDH) ($Na_2(WO_4).2H_2O$, 329.93 g.mol^{-1}), (0.05 mol.L^{-1}) was prepared by dissolving 4.1241 g in 250 mL distilled water. Hydrochloric acid (BDH) (1 mol.L^{-1}) was prepared by diluting 44.15mL of 35% HCl (1.18 g.mL^{-1}) with distilled water in 500 mL and standardized with Na_2CO_3 solution.

Apparatus

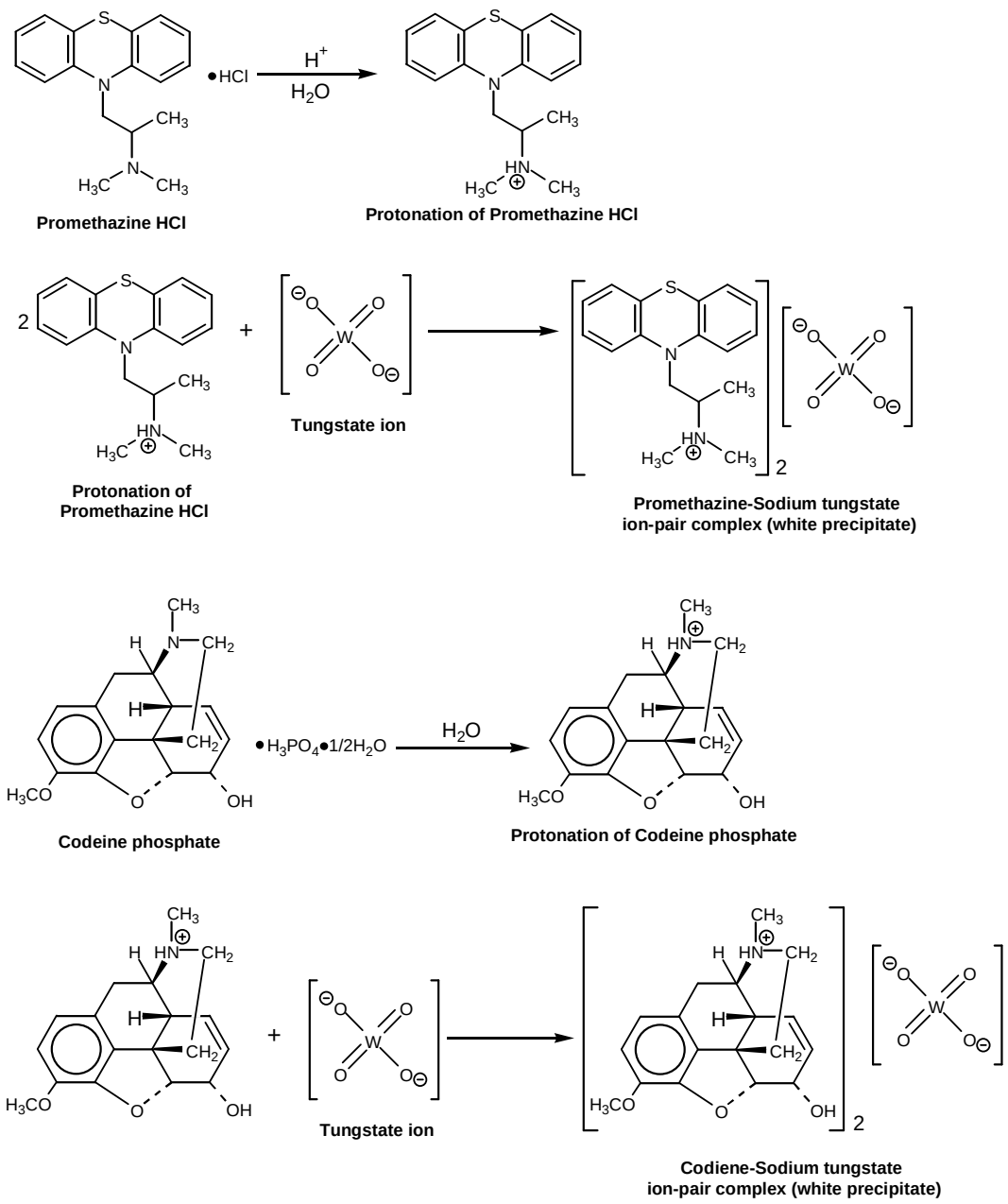
A Hanna bench (LP2000) turbidimeter (Italy) with 1 cm path length was used for the turbidity measuring. Magnetic stirrer was used to mix the solutions. pH adjustment by using Hanna bench type pH meter.

Sample Preparation

Twenty tablets of each drug were randomly selected from different strips, and packets. Each tablet consist of 5 mg of Promethazine HCl and 8 mg Codeine phosphate. The tablets were crashed and grinded then weighing 3.9797 g and 2.8744 g which are equivalent to 0.0320 g and 0.5664 g active ingredient for PMH (Coldin, Ninawa Drug Iraqi (NDI)) and COP (Co-codamol, Bristol) respectively. Finally, each weighted material was transferred into a 50 mL volumetric flask to prepare 2 mmol.L^{-1}.

Procedure

A series of 10 mL calibrated flasks, were placed two mL of distilled water. Then suitable volumes of the standard solution of drugs were transferred into the flasks. Three mL of the sodium tungstate was also added to the flask then 1 mL of 1M HCl was added. The remainning volume of flask was filled by distilled water. The turbidity of complexes was recorded against the distilled water as blank. A proposed mechanism of ion pair complexes is presented in Scheme (2).



Scheme (2): Probable proposed mechanism for the reaction Promethazine HCl and Codeine phosphate with Sodium tungstate

RESULTS AND DISCUSSION

A number of important factors were investigated in order to obtain smaller and homogeneous precipitate particles to have successful turbidimetric analysis. These factors include reagent concentrations, surfactant, pH, time …etc.

Effect of Sodium Tungstate Concentration

A series of the precipitating reagent solutions (1-5) mmol.L^{-1} were prepared using preliminary concentration of PMH (2 mmol.L^{-1}) and COP (1 mmol.L^{-1}). The results show that there is an increase in turbidity values combining with increase of sodium tungstate concentration up to 3, 2.5 mmol.L^{-1} for PMZ and COP respectively, after this concentration there was a slightly decrease in turbidity values, probably due to many of particle assemble together (aggregation process), therefore, 3, 2.5 mmol.L^{-1} for PMH and COP was selected as the optimum concentration, Figure (1).

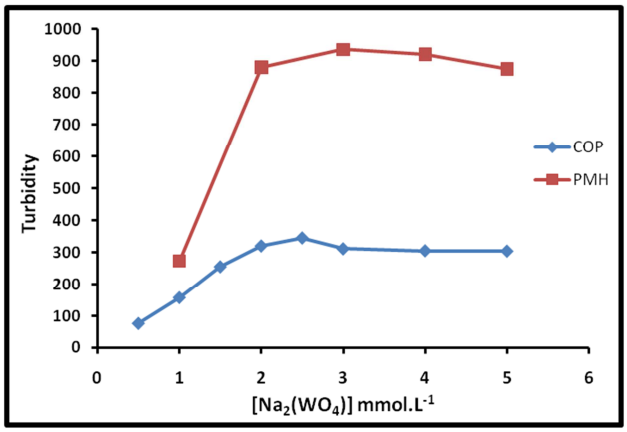


Figure (1): Effect of sodium tungstate concentration on precipitation of PMH and COP

Effect of Acidity

The precipitation of PMH and COP were studied in acidic media using optimum concentration of sodium tungstate. A range of diluted solutions of hydrochloric acid HCl (0-40) mmol.L^{-1} were prepared. Table (1) summarized all obtained data. It can be seen that an increase in turbidity values for PMH during increase of acidic medium up to 10 mmol.L^{-1}, while decrease of the obtained values during increase of HCl concentration for COP due to may be dissolving of particles in acid.

Table (1): Variation of HCl concentration on precipitation reaction

Drug complex	Concentration of HCl mmol.L^{-1}	Average of turbidity reading	Standard Deviation σ_{n-1}	%RSD
PMH-Na_2WO_4	5	983.33	6.50	0.66
	10	994.00	3.46	0.34
	20	758.33	16.62	2.19
	30	580.33	6.65	1.14
	40	531.66	5.50	1.03
COP-Na_2WO_4	0.2	349.66	2.51	0.71
	0.3	351.66	3.51	0.99
	0.5	356.00	3.60	1.01
	0.7	314.00	1.73	0.55
	1	257.33	1.15	0.44
	1.5	250.33	0.57	0.23

Effect of Colloid Protector

Turbidimetric procedures in literature [18] have been used a colloid protectors as stabilizers of suspensions and used to avoid adherence of the precipitate in the inner walls of the cell. The effect of colloid protectors Glycerin and 2-propanol was studied at three different concentrations (0.2, 1.0 and 2.0% v/v) of each compound using the previously optimum conditions. Table (2) shows that the turbidity values decrease continuously with increases concentration of colloid protector, probably due to decrease of precipitation nucleation. Also an increase of the induction period. Thus, water was chosen as the optimum medium in the further experiments.

Table (2): Effect of colloidal protector in the precipitation procedure

Drug complex	Colloidal protector	Turbidity readings			
		Without 0.0%	0.2% v/v	1.0% v/v	2.0% v/v
PMH-Na_2WO_4	Glycerin	996	960	752	743
	2-propanol	994	794	693	687
COP-Na_2WO_4	Glycerin	360	352	322	310
	2-propanol	359	329	304	291

Effect of time

In order to investigate the effect of time on precipitation process, all of previously optimum parameters and preliminary concentrations for both of PMH (2 mmol.L^{-1}) and COP (1 mmol.L^{-1}) are applied to do so. Then, the turbidity of ion-pair complexes were recorded after adding precipitating reagent and acid media at the intervals of 1 to 20 min. The obtained results plotted in Figure (2). From the results it can clearly see that, at time 1 min of reaction of PMH with precipitating reagent, the reaction completes and the turbidity values stopped to increase, wherever, after 1 min of reaction the turbidity values decrease and that probably due to ion- pair complex is not

stable for long time and starts to dissociate. While turbidity values of COP continue increasing with time up to 10 min., then turbidity slightly decreases with time goes.

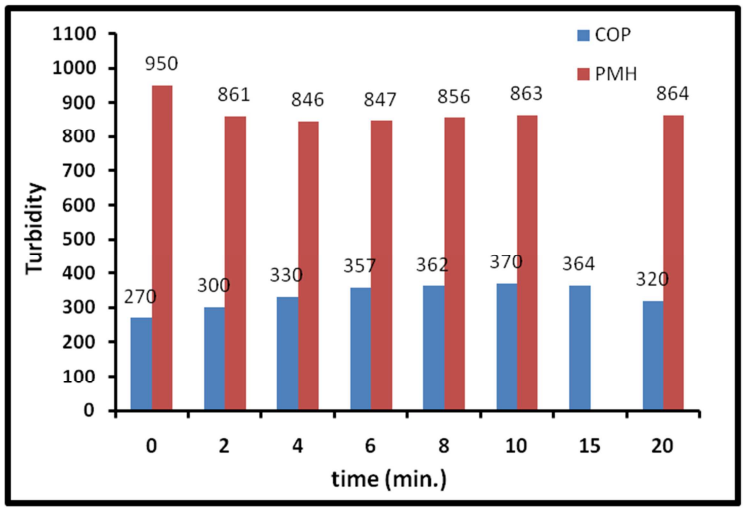


Figure (2): Dependence of turbidity of ion-pair complex on time

Stirring Effect

Stirring speed and time influence on the particle size of the precipitate. For this studied, a series of the preliminary concentrations of PMH (2 mmol.L^{-1}) and COP (1 mmol.L^{-1}) were prepared. The turbidity values of these samples were recorded immediately and also, at (0-10) min of stirring (200 rpm) after adding sodium tungstate and acid. The results show in Figure (3).

From the turbidity values, It can observed that the stirring process has no effect on the complex (size) of PMH with sodium tungstate, therefore it is not necessary. Turbidity values were decreased due to dissociation of ion-pair complex during stirring time. While turbidity of COP is slightly increased with stirring time up to 10 min. Therefore, 10 min was adopted as stirring time for COP.

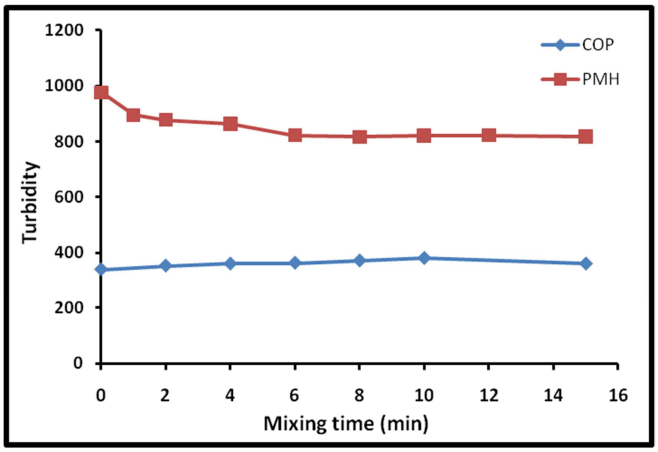


Figure (3): Effect of stirring time on the turbidity of ion-pair complexes

Calibration graph

The proposed turbidimetric method under the experimental conditions was applied to determine linear dynamic range of Promethazine HCl and Codeine phosphate. A series of variable concentrations of PMH and COP that ranged from 0.03-4 mmol.L^{-1} were prepared for the purpose of using them for the preparation of scatter plot diagram followed by the choice of calibration graph. Figure (4) shows the linear correlation between the turbidity and both of PMH and COP concentrations were obtained over the range 0.03-2 mmol.L^{-1} and 0.05-3.5 mol.L^{-1} for PMH and COP respectively. Linear dynamic range, correlation coefficient, the calculated t-value at 95% confidence interval and linear percentage display in Table (3).

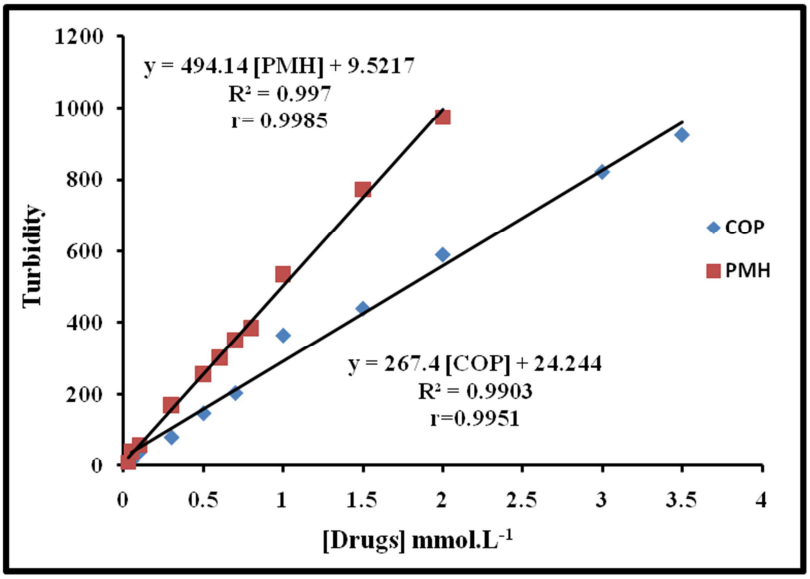


Figure (4): Linear calibration graph for the determination Promethazine HCl and Codeine phosphate in mmol.L^{-1}

Table (3): Summary of linear calibration graph [19, 20] for the analysis of Promethazine HCl and Codeine phosphate using simple regression line ($\hat{Y}$ = a+bx) at experimental conditions

Drug complex	Measured range mmol.L^{-1}	Linear range mmol.L^{-1}	y^(mV)=a±S_at+b±S_bt [X]mmol.L^{-1} at confidence interval 95%, n-2	r, r^2, r^2%	$t_{tab.}$	$t_{cal} = \frac{\lvert r\rvert\sqrt{n-2}}{\sqrt{1-r^2}}$ at 95%, n-2
PMH-Na_2WO_4	0.03-3.5	0.03-2.0 (n=11)	9.52 ± 18.61 + 494.14 ± 20.47 [PMH] mmol.L^{-1}	0.9985 0.9970 99.70	2.262	<< 54.59
COP-Na_2WO_4	0.05-5	0.05-3.5 (n=10)	24.24 ± 36.92 + 267.39 ± 21.55 [COP] mmol.L^{-1}	0.9951 0.9903 99.03	2.306	<< 23.71

The calculated t-value at 95% confidence for two drugs which larger than tabulated t-value indicating clearly that the linearity is accepted.

Limit of Detection

Limit of detection were achieved in three different approaches, first, gradual dilution of lowest concentration in the calibration graph, second, detection based on the numerical value of slope and finally, from the linear regression. Table (4) tabulated all these calculation value.

Table (4): Limit of detection of PMH and COP at optimum parameters

Drug complex	Gradual dilution for the minimum concentration in calibration graph	Based on the value of slope $x = \frac{3S_B}{slope}$	Linear equation y^(mV) = y_B+3S_B
PMH-Na_2WO_4	1×10^{-5} M 32.1 µg/sample	18.2×10^{-5} M 0.58 mg/sample	1.0×10^{-4} M 0.34 mg/sample
COP-Na_2WO_4	2.5×10^{-5} M 0.10 mg/sample	3.37×10^{-4} M 1.37 mg/sample	3.8×10^{-4} M 1.23 mg/sample

x= value of L.O.D. based on slope. *S_B = standard deviation of blank solution*
y_B= average response for the blank solution (equivalent to intercept in straight line equation)

The Repeatability

The repeatability was carried out for six successive samples and repeated measurements. The obtained data are tabulated in Table (5) which displays that, the percentage relative standard deviation %RSD is less than 1%.

Table (5): Repeatability result

Drug complex	[drug] mmol.L^{-1}	Number of measuring (n)	$\overline{y_i}$ (n=6) mV	σ_{n-1}	Repeatability R.S.D.%	Confidence interval of the mean $\overline{y_i} \pm t_{(\alpha=0.05/2)} \frac{\sigma_{n-1}}{\sqrt{n}}$
PMH-Na_2WO_4	0.1	7	59.85	1.46	2.44	59.85 ± 1.35
	1.0	7	540.42	2.22	0.41	540.42 ± 2.05
COP-Na_2WO_4	0.7	6	202.33	2.33	1.15	202.33 ± 2.45
	2.0	6	528.50	6.47	1.22	528.50 ± 6.79

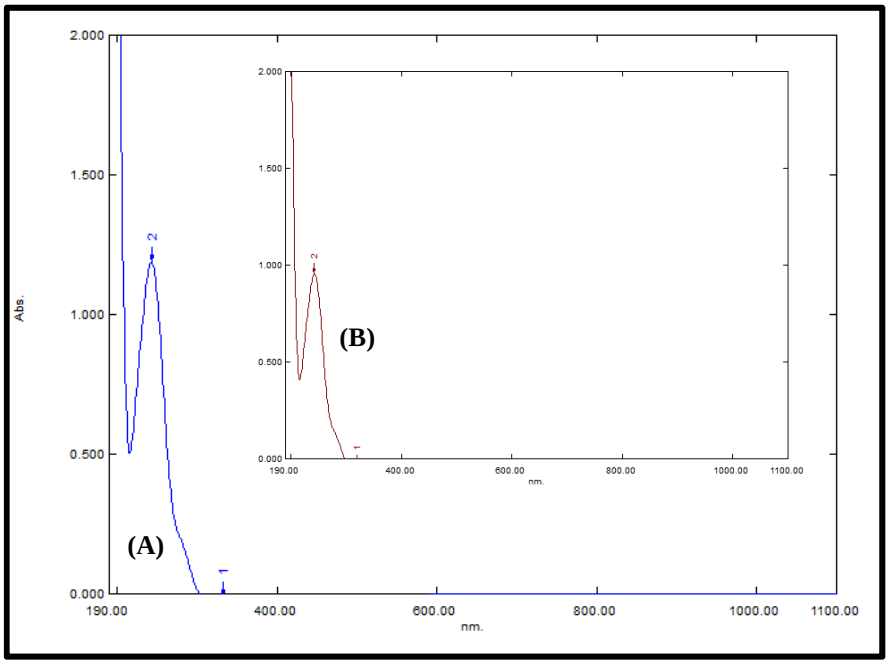


Figure (5): (A) UV-Vis spectrum of Paracetamol drug against distilled water as blank.
(B) UV-Vis spectrum of Paracetamol after addition sodium tungstate against sodium tungstate solution as blank.

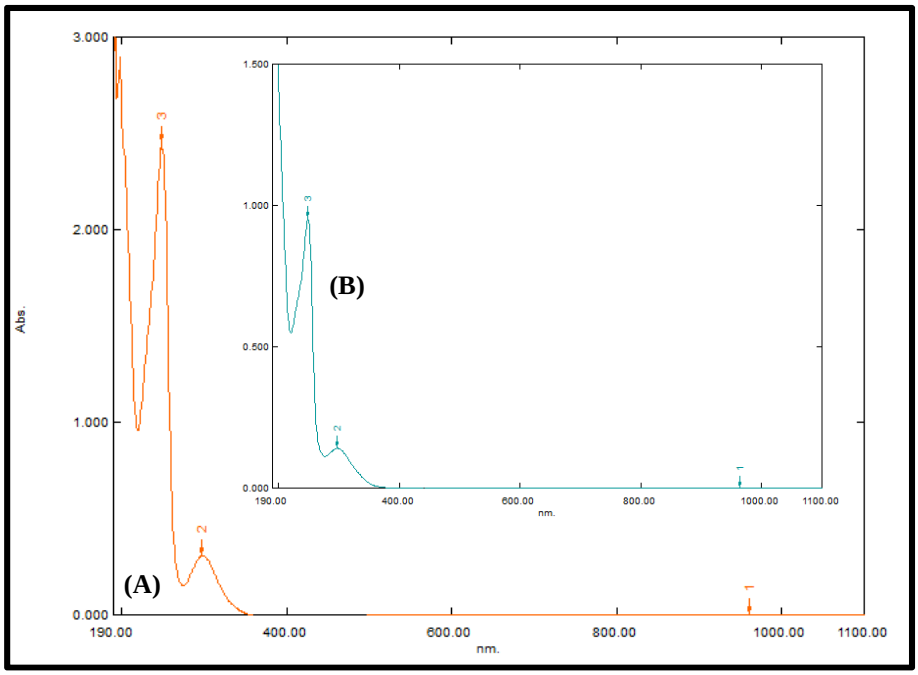


Figure (6): (A) UV-Vis spectrum of Phenylephrine HCl against distilled water as blank.
(B) UV-Vis spectrum of Phenylephrine HCl after addition sodium tungstate against sodium tungstate solution as blank.

Application

The proposed turbidimetric method under the experimental conditions was applied to selective analysis of Promethazine HCl in Coldin pharmaceutical preparation, that contents 450 mg Paracetamol, Promethazine HCl 5 mg and Phenylephrine HCl 5 mg. Also the method was applied to determine the Codeine phosphate in Co-codamol pharmaceutical preparation, which contents Paracetamol (500 mg) and Codeine phosphate (8 mg). Method selectivity was achieved through no change in color and wavelength during addition the precipitating reagent (sodium tungstate) to Paracetamol or Phenylephrine HCl as shown in the Figure (5 and 6).

The measurements were conducted by standard addition method and the results were mathematically treated. The results of the analysis of PMH and COP in pharmaceutical preparations are presented in Table (6). While Table (7) shows the value of t-test at 95% confidence intervals which used in comparison with official method [2].

Table (6): Summary of determination for Promethazine HCl and Codeine Phosphate in pharmaceutical preparation

Commercial name Content Country	**Confidence interval for average weight at 95%** $\overline{w} \pm 1.96\frac{\sigma_{n-1}}{\sqrt{n}}$ **(g)**	**Weight of sample (g) to obtain 2 mmol.L^{-1} (g)**	**Theoretical content of active ingredient at 95% n=∞ (mg)**	**found content of active ingredient at 95% n=∞ (mg)**	**% Recovery**
Coldin Paracetamol 450 mg, **Promethazine HCl 5 mg,** Phenylephrine HCl 5 mg Ninawa Drug Iraqi – Iraq	0.6200±0.0021	3.9797 g equivalence to 320 mg PMH active ingredient	5.0 ± 0.032	4.84±0.043	96.80
Co-codamol Paracetamol 500 mg, **Codeine phosphate 8 mg** Bristol - UK	0.5664±0.0062	2.8744 g equivalence to 406 mg COP active ingredient	8.0 ± 0.057	8.23±0.650	102.87

Table (7): Calculations of paired t-test for developed methods with quoted value using standard additions method

Drug	**Practical content (mg)**		**D**	$\overline{x}_d$	σ_{n-1}	**Paired t-test** $t = \frac{\overline{x}_d\sqrt{n}}{\sigma_{n-1}}$	$t_{tab.}$ **at 95% confidence interval n-1**
	Quoted value	**New method**					
PMH	5.0	4.88	0.12	0.153	0.0757	3.507 < 4.303	
	5.0	4.76	0.24				
	5.0	4.90	0.1				
COP	8.0	8.35	-0.35	-0.233	0.1069	|-3.779| < 4.303	
	8.0	8.21	-0.21				
	8.0	8.14	-0.14				

CONCLUSION

The developed turbidimetric procedures are characterized by simple, selective and inexpensive for the determination of Promethazine HCl and Codeine phosphate in pharmaceutical preparations. Sodium tungstate were used as a precipitant to forms a white precipitate of ion pair complexes. The methods do not required pretreatment to the real samples and no needing for heat or extraction. The standard addition method was used to avoid matrix effects.

A good linear dynamic range (0.03-2.0) mmol.L^{-1} for PMH, (0.05-3.5) mmol.L^{-1} for COP. The methods show a good repeatability (%RSD < 3%), which is an indication of satisfactory accuracy of the proposed methods.

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