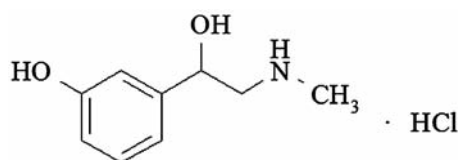


The use of 2,6-dichloroquinone-4-chlorimide for quantitative determination of phenylephrine hydrochloride in combined tablets with paracetamol and chlorpheniramine maleate

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Introduction

Phenylephrine hydrochloride (mesaton) belongs to the group of α -agonists – α -adrenergic stimulants; it has a little effect on β -adrenergic receptors of the heart. Due to its vasoconstrictive action it reduces edema and hyperemia of the mucous membranes of the upper respiratory tract and paranasal sinuses, increases blood pressure, but it has almost no effect on the cardiac output value. Thanks to these properties mesaton has found application in medicine with paracetamol and chlorpheniramine maleate in the symptomatic treatment of influenza, acute respiratory viral infections and cold in order to reduce temperature, eliminate headaches, pain in muscles and joints, edema of the mucous membranes of the respiratory tract.



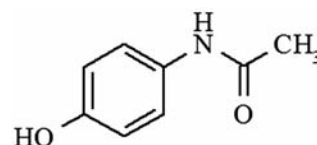
phenylephrine hydrochloride

The literature describes methods for quantitative determination of phenylephrine hydrochloride in combined dosage forms by HPLC^{1, 2}; they are characterized by high efficiency, selectivity, but are not always suitable for routine analysis.

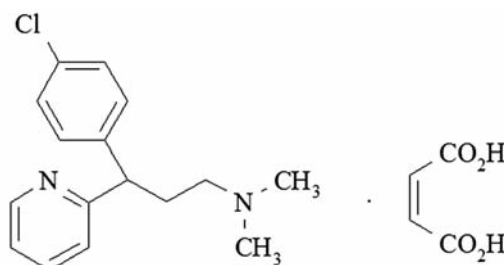
The given method is based on the chemical properties of phenols. Phenols with the unsubstituted *para*-position are characterized by formation of indophenols with Gibbs reagent (2,6-dichloroquinone-4-chlorimide) in the alkaline medium³.

As the object of research, Antiflu tablets containing 325 mg of paracetamol, 5 mg of phenylephrine hydrochloride, 2 mg of chlorpheniramine maleate and such excipients as microscopic cellulose, croscarmellose sodium, colloidal anhydrous silica, stearic acid, magnesium silicate, magnesium stearate, hypromellose,

polyethylene glycol, mineral oil, D & C yellow varnish dye No. 10 (E 104) were chosen.



paracetamol



chlorpheniramine maleate

The presence of a large amount of paracetamol in the composition of the dosage form impedes determination of a small amount of phenylephrine hydrochloride by direct spectrophotometry. Therefore, it is advisable to use other accurate and selective methods in routine analysis.

Experimental methods

When developing the method for quantitative determination of phenylephrine hydrochloride, reagents meeting the requirements of the State Pharmacopoeia of Ukraine^{4, 5} were used: the standard samples of phenylephrine hydrochloride (Unichem Laboratories Ltd, India, batch number)/paracetamol (Anqui Lu'an Pharmaceutical Co. Ltd, China, batch number PPPH 1410746) and chlorpheniramine maleate (Anqui Lu'an Pharmaceutical Co. Ltd, China, batch number SLL/P/1113052), Antiflu tablets (Contract Pharmacal Corporation, USA, batch number 028011213).

The following analytical equipment was used: an Evolution 60s spectrophotometer, an «AXIS» ANG 200 laboratory balance (Poland), and measuring glassware of class A.

Assay (absorption spectrophotometry)

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Test solution

Weigh and powder 20 tablets. Shake the quantity of the powder containing the equivalent of 0.025 g of phenylephrine hydrochloride with 30 ml of 0.1 M hydrochloric acid for 15 minutes, dilute the same solvent to 50 ml and filter. Add 1 ml of the filtrate, 7 ml of 0.1 M hydrochloric acid, 1 ml of water, 5 ml of isopropyl alcohol, 2 ml of ammonia buffer with pH 10 and 1 ml 0.25% solution of 2,6-dichloroquinone-4-chlorimide and dilute to 25 ml with 0.1 M hydrochloric acid and mix.

Reference solution

Dissolve 50 mg of phenylephrine hydrochloride RS in 30 ml of 0.1 M hydrochloric acid and dilute the solution to the volume of 50 ml with the same solvent. To 0.5 ml of the solution obtained add 7 ml of 0.1 M hydrochloric acid, 1 ml of water, 5 ml of isopropyl alcohol, 2 ml of ammonia buffer with pH 10 and 1 ml of 0.25% solution of 2,6-dichloroquinone-4-chlorimide, dilute the solution to the volume of 25 ml with 0.1 M hydrochloric acid and mix.

Compensation solution

Dilute 7 ml of 0.1 M hydrochloric acid, 1 ml of water, 5 ml of isopropyl alcohol, 2 ml of ammonia buffer with pH 10 and 1 ml of 0.25% solution of 2,6-dichloroquinone-4-chlorimide with 0.1 M hydrochloric acid to the volume of 25 ml.

Measure the absorbance at the maximum at 615 nm.

Preparation 0.25% solution of 2,6-dichloroquinone-4-chlorimide

Dissolve 0.125 g of 2,6-dichloroquinone-4-chlorimide in 30 ml of isopropyl alcohol and dilute the solution to the volume of 50 ml with the same solvent.

Results and discussion

A method based on the properties of phenylephrine hydrochloride to form a blue colour with 2,6-dichloroquinone-4-chlorimide in the alkaline medium has been proposed.

To develop the method for the quantitative determination of phenylephrine hydrochloride by absorption spectrophotometry, the solutions of phenylephrine hydrochloride, paracetamol, chlorpheniramine maleate and the test solution of Antiflu tablets were prepared dissolving them in acid and adding the necessary reagents specified above. Their absorption was studied in the range from 550 nm to 650 nm (Fig. 1). As can be seen from the spectra obtained, the maximum of phenylephrine hydrochloride (Curve 1) is observed at 615 nm. The absorption spectrum of the tablet weight of Antiflu (Curve 4) after the reaction with 2,6-dichloroquinone-4-chlorimide almost coincides with the absorption spec-

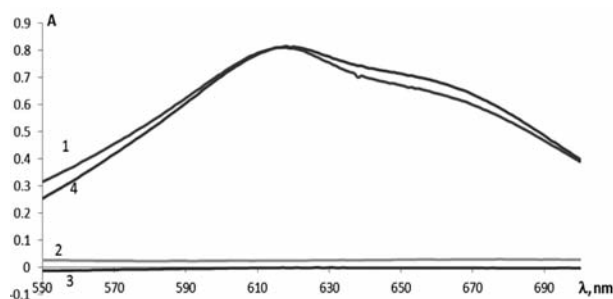


Fig. 1. The absorption spectra of: 1 – phenylephrine hydrochloride, 2 – paracetamol, 3 – chlorpheniramine maleate and 4 – Antiflu tablets after reaction with 2,6-dichloroquinone-4-chlorimide solution

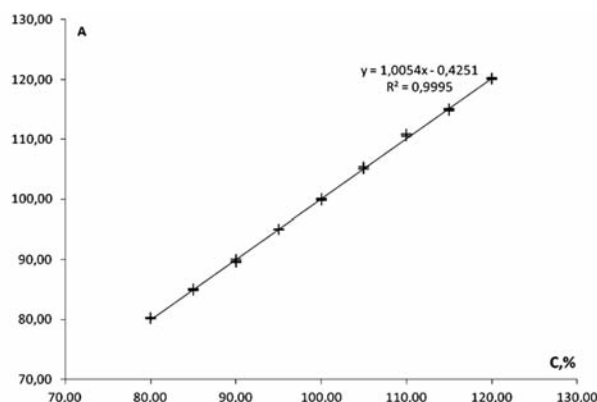


Fig. 2. The linear dependence of optical density on the concentration of phenylephrine hydrochloride in the normalized coordinates

trum of the reference solution, but it is slightly more intense. This suggests the effect of other APIs (Curve 2 and 3). When calculating the effect of paracetamol and chlorpheniramine maleate it has been found that this value is about 3%, and only slightly affects the results of the quantitative determination of phenylephrine hydrochloride with tolerances of $\pm 10\%$.

According to standardized procedures, such validation characteristics of the spectrophotometric method as robustness, linearity, accuracy and precision were studied^{6,7)}.

Robustness was investigated by studying stability of the solution of phenylephrine hydrochloride standard sample relative to the test solution for one hour. It was found that the test solution of Antiflu tablets was stable within the time studied.

Linearity of the method was studied within the range of concentrations from 80% to 120% in relation to the nominal value of mesaton in Antiflu tablets. Nine solutions with the known concentration were prepared by taking the desired aliquot of the model solution. The

Table 1. The results of studying the stability of the solution

	Time of the stability studies t, min					Average	RSDt %	Δt %	Max. δ %
	0	15	3	0	45	60			
Test solution	0.497	0.497	0.496	0.497	0.497	0.496	0.11029	0.152	0.51
Reference solution	0.514	0.513	0.514	0.514	0.514	0.514	0.08704	0.124	

Table 2. Metrological characteristics of linear dependence for quantitative determination of phenylephrine hydrochloride

Parameter	Value	Criteria of the linear dependence parameters (SPhU, 1 st ed., Supplement .2 (p. 85)	Conclusion
$B, \%$	1.005404	–	–
s_b	0.0046	–	–
α	$ -0.4251 $	≤ 5.1	satisfied
s_a	0.4673	–	–
s_0	0.3109	≤ 1.69	–
s_0/β	0.16567		
r	0.9995	≥ 0.98236	satisfied

Table 3. Accuracy and reproducibility of the results when determining phenylephrine hydrochloride

No. of the test solution	Concentrations of the components		
	Introduced in % to the concentration of the reference solution, % X_i	Found in % to the concentration of the reference solution, % Y_i	Found in % to the introduced, $Z_i = Y_i/X_i \cdot 100 \%$
1	80.00	80.22	100.28
2	85.00	85.02	100.02
3	90.00	89.75	99.72
4	95.00	95.01	100.01
5	100.00	100.00	100.00
6	105.00	105.19	100.18
7	110.00	110.77	100.70
8	115.00	114.98	99.98
9	120.00	120.10	100.08
Mean, $Z\%$			100.11
Relative standard deviation, $RSD_z \%$			0.97
Relative confidence interval $\Delta_z \%$ = $t(95\%, 8) \cdot RSD_z = 1.8595 - 0.97 =$			1.804
Critical value for convergence of results $\Delta_z \leq \Delta_{As} \%$			satisfied
Systematic error $\delta = Z - 100$			0.11
Criterion of the systematic error insignificance $\delta \leq 0.32 - \Delta_{As} \%$			satisfied (0.11 < 1.536)
The overall conclusion of the method:			correct

Table 4. The results of quantitative spectrophotometric determination of phenylephrine hydrochloride in Antiflu tablets

No.	The amount of phenylephrine hydrochloride in the dosage form, mg	A	A_{at}	Found of phenylephrine hydrochloride, mg
1	5 mg	0.498	0.514	4.84
2		0.497		4.83
3		0.497		4.83

results are given on the graph in the normalized coordinates (Figure 2).

The calculation of the linear dependence parameters (Table 2) was performed by the least square method (according to the data of Table 3); its results were com-

pared with the acceptance criteria given in the State Pharmacopoeia of Ukraine.

The data obtained satisfy all requirements.

The method proposed was used for quantitative determination of phenylephrine hydrochloride Antiflu tablets.

The content of phenylephrine hydrochloride (mg) in tablets was calculated according to the formula:

$$x = \frac{A \cdot m \cdot 50 \cdot 0,5 \cdot 25 \cdot m_{average} \cdot 1000}{A_{st} \cdot m_{sample} \cdot 50 \cdot 25},$$

where: m_{sample} – is the sample weight of the tablet powder, $m_{average}$ – is the average weight of one tablet, A – is the optical density of the test solution, A_{st} – is the optical density of the reference solution.

The results of quantitative spectrophotometric determination of phenylephrine hydrochloride in Antiflu tablets are shown in Table 4.

Conclusions

1. The method for quantitative determination of phenylephrine hydrochloride in tablets in the presence of other APIs has been developed by visible absorption spectrophotometry after the reaction with the solution of 2,6-dichloroquinone-4-chlorimide.

2. The validation characteristics of the method (linearity, accuracy, precision, convergence) have been studied. The results obtained indicate the possibility for using this method for analysis of multicomponent dosage forms with phenylephrine hydrochloride.

Conflicts of interest: none.

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