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SELECTION AND VERIFICATION OF THE METHOD FOR PHYNELEFRINE HYDROCHLORIDE ASSAY IN SIMANOVSKY OINTMENT

© L. Savchenko, K. Uminska, N. Bevz, V. Georgiyants

Фенілефрину гідрохлорид – симпатоміметик з вираженою місцевою судинозвужувальною дією. Його здатність зменшувати набряк і гіперемію слизової оболонки носа використана в складі мазі Симановського, яка готується про запас в аптеках України. Для кількісного визначення фенілефрину гідрохлориду в багатьох одно- та багатокомпонентних лікарських формах запропоновано використовувати метод спектрофотометрії. Однак, в літературних джерелах не зустрічається прикладів використання спектрофотометричних методик кількісного визначення фенілефрину гідрохлориду в досліджуваній мазі.

Мета. *Метою роботи був вибір та верифікація оптимальної методики кількісного визначення фенілефрину гідрохлориду в мазі Симановського з доведенням можливості її подальшого використання для аналізу стабільності лікарської форми в процесі зберігання.*

Методи. *Метод прямої УФ-спектрофотометрії для кількісного визначення фенілефрину гідрохлориду в складі досліджуваної мазі.*

Результати дослідження. *Для кількісного визначення фенілефрину гідрохлориду в складі мазі Симановського обрано метод прямої спектрофотометрії після його екстракції з мазі 0.1 М розчином кислоти хлористоводневої. Для доведення можливості його використання в аналізі мазі проведено визначення валідаційних характеристик. Отримані результати свідчать, що виконуються вимоги до специфічності методики (δ_{noise}, %=0.47≤1.02), параметрів лінійної залежності, правильності (δ,%=0.20≤1.02) та прецизійності (Δ_Z=0.39≤3.20). Дослідження робасності методики свідчить про стабільність розчинів протягом години. Методика була апробована на досліджуваній мазі. Визначені метрологічні характеристики способів розрахунку кількісного вмісту фенілефрину гідрохлориду методом стандарту та питомого показника поглинання. Отримані результати свідчать про можливість використання обох методів.*

Висновки. *Для кількісного визначення фенілефрину гідрохлориду в складі мазі Симановського обрано метод прямої спектрофотометрії. Валідаційні характеристики методики свідчать про можливість її використання для аналізу мазі та вивчення її стабільності в процесі зберігання. Доведено, що розрахунок кількісного вмісту фенілефрину гідрохлориду в мазі може бути проведений з використанням як методу стандарту, так і методу питомого показника поглинання*

Ключові слова: *мазь аптечного виготовлення, фенілефрину гідрохлорид, метод спектрофотометрії, верифікація*

1. Introduction

Phenylephrine hydrochloride (Fig. 1) – a synthetic substitute for adrenaline that has vasoconstrictive and α-adrenomimetic action [1, 2].

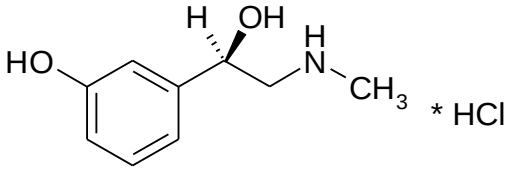

Fig. 1. Phenylephrine hydrochloride structure

It is part of the eye drops [1, 3], solution for injection [3], nasal drops [2, 3], and powders and tablets for the treatment of colds [1, 2].

Often it is introduced into the anti-inflammatory drugs as nasal decongestant. It acts by vasoconstriction, reducing swelling and congestion of the nasal mucosa [3–8]. Such its action was used in the Symanovsky ointment, which is being prepared for stock in many pharmacies of Ukraine. The ointment composition can vary slightly, but more often it is prepared by the following prescription: phenylephrine hydrochloride 0.02; menthol 0.04; zinc oxide 0.24; wool fat 4.0; white soft paraffin 6.0.

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

Since the ointment is being prepared for stock, in accordance with the requirements of the State Pharmacopoeia of Ukraine (SPhU) necessary to develop a technological instruction of the ointment preparation with a description of the methods for assay of its active components. In addition, the methods of quantitative determination are necessary to increase the ointment shelf life during the analysis of its stability.

3. Analysis of recent studies and publications

Monographs on phenylephrine hydrochloride are part of many pharmacopoeias. SPhU [9], European [10] and British [11] Pharmacopoeias are recommending using alkalimetric titration with a potentiometric determination of the equivalence point for its quantitative determination. According to the Chinese [12], Japanese [13] and USP [14] Pharmacopoeias requirements assay of the phenylephrine hydrochloride substance is carried out using bromatometric reverse titration.

For the quantitative determination of phenylephrine hydrochloride in a variety of dosage forms it

is proposed to use the method of spectrophotometry. Direct spectrophotometry method recommended for its quantitative determination in solution for injection [1], drops for the nose [3], in capsules with chlorpheniramine maleate [2], in combined drops with dimethindene maleate [4]. It is also recommended to carry out a spectrophotometric determination of phenylephrine hydrochloride by reaction with diazotized metoclopramide hydrochloride [7], after interaction with 4-aminoantipyrine followed by the formation of a complex with copper (II) [8], by using haematoxylin [15], with alizarine dyes [16], by reaction with ninhydrin [17], with iron (III) ions and subsequent addition of 2,2'-bipyridyl [18]. Indirect spectrophotometric methods after adding of chloramine-T and rhodamine-B [19] and after adding of N-bromosuccinamide and indigo carmine for its assay were also proposed [20].

In addition, for the simultaneous quantitative determination of phenylephrine hydrochloride with other components of dosage forms, it is recommended to use the method of derivative spectrophotometry. For example, to determine it in combination with tropicamide in eye drops [21], cetirizine hydrochloride by simultaneous equation method and first order derivative spectroscopy [5], dual wavelength, absorbance ratio and mean centering of ratio spectra methods [22], absorbance ratio and area under curve methods [23], paracetamol by the graphical, simultaneous equation, first order derivative and absorbance ratio methods [6], paracetamol and chlorpheniramine maleate by simultaneous equation, absorbance ratio and area under curve methods 24], chlorpheniramine maleate [25] in combined dosage forms.

4. Allocation of unsolved parts of the general problem, which is dedicated to the article

Literature review of the developed methods for phenylephrine hydrochloride assay showed that there is no description of the methods for its quantitative determination in the composition of the Simanovsky ointment.

5. Formulation of goals (tasks) of the article

The task of the work was to select and verify the optimal method for phenylephrine hydrochloride assay in the Simanovsky ointment with the possibility of its further use for the analysis of the dosage form stability during storage.

6. Presentation of the main material of the research (methods and objects) with the justification of the results

Class A volumetric glassware, reagents which meet the requirements of the SPhU, analytical balance AXIS ANG 200 (Poland), spectrophotometer Evolution 60s (USA) with 1 cm cell, phenylephrine hydrochloride substance (series PPHLP60001 produced by Unichem Laboratories LTD, India) were used for the analysis.

Tested solution. 1.0000 g of ointment was heated in a water bath with 10 ml of 0.1 M hydrochloric acid, carefully mixed with a glass rod, cooled and filtered in the volumetric flask of 25.0 ml. The operation was repeated two more times, using 5 ml of 0.1 M hydrochloric acid. The volume of the solution was adjusted to the mark 25.0 ml with a 0.1 M hydrochloric acid and stirred.

Reference solution: 0.0200 g of phenylephrine hydrochloride standard sample was dissolved in 0.1 M hydrochloric acid in the 25.0 ml volumetric flask, diluted to the mark 25.0 ml with the same solvent. 1.0 ml of this solution was placed into the 10.0 ml volumetric flask and adjusted to the mark with 0.1 M hydrochloric acid.

Compensation solution. 0.1 M hydrochloric acid.

The method of direct spectrophotometry was chosen for the phenylephrine hydrochloride assay in the studied ointment. Due to the fact that compound is a salt of weak base and strong acid, phenylephrine hydrochloride can be extracted from the ointment with 0.1 M hydrochloric acid. The possibility of using this solvent has been proven in the analysis of the solution for injections of phenylephrine hydrochloride [1], so it was chosen for extraction procedure. The optical density of the test and the reference solutions was measured at a wavelength of 273 nm relative to the compensation solution (Fig. 2).

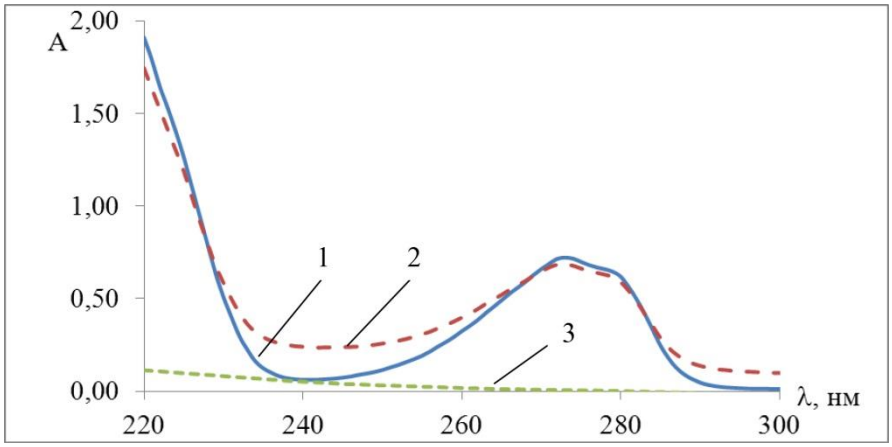

Fig. 2. Absorption spectra of solutions absorbance: 1 – standard sample of phenylephrine hydrochloride, 2 – ointment extract, 3 – placebo in 0.1 M hydrochloric acid

For study the specificity of the method (δ_{noise}, %), a solution of placebo was made using the method of the test solution preparing. During preparation the ointment without phenylephrine hydrochloride was used. The optical density of the placebo solution was determined three times with the removal of the cuvette with a paral-

lel measurement of the reference solution optical density. The resulting spectrum (Fig. 2) indicates the absence of influence of the other ointment components on the results of phenylephrine hydrochloride assay. Contribution of placebo was calculated by the following formula (1) and found that it has a negligible effect on the total absorption of the medicine.

$$\frac{A_{blank}}{A_{st}} \times 100 = \frac{0.002}{0.429} \times 100 = \quad (1)$$
$$= 0.47\ \% \le \max \delta \le 1.02\ \%$$

The next stage of the study was the verification of the robustness of the method. The stability of solutions in time has been studied for this purpose.

The optical density of the ointment test and reference solutions in the maximum absorption at a wavelength of 273 nm was measured. Measurements were carried out immediately after preparation of solutions, and then after 15, 30, 45 and 60 minutes. The obtained results indicate that the solution is stable for an hour (Table 1).

Linearity, accuracy and precision of the method in the concentration range of 80–120 % of the nominal concentration of the test substance in the ointment were also studied. In the chosen range, nine concentrations were investigated with a 5 % step. According to the results of the research, the parameters that characterize the linear dependence (Table 2) were calculated. The criteria for linear dependency parameters were calculated according to tolerances in the content of compounding ointments components (±10 %).

The obtained values indicate that the requirements for all parameters of linear dependence are met. According to the results of the linearity study, a calibration curve was constructed in normalized coordinates (Fig. 3).

Table 1

Stability study of the analytical solutions

Solution	The term of the stability study (t, min.)					Mean	RSD_t, %	Δt, %	max δ, %
	0	15	30	45	60				
Tested	0.435	0.435	0.435	0.436	0.435	0.435	0.103	0.219	1.02
Reference	0.428	0.429	0.429	0.428	0.428	0.428	0.128	0.273	

Table 2

Results of study of linear dependence parameters of the spectrophotometric method of phenylephrine hydrochloride assay

Validation characteristic	*Value*	*Permissible criteria*	*Conclusion on compliance*
b	0.98	–	–
S_b	0.012	–	–
(b-1)	0.020	–	correspond
a	2.31	statistical insignificance $a \le t(95\%, n-2) \times S_a$ *(a≤2.32)* practical insignificance *a≤5,12*	fulfilled by both criteria
S_a	1.22	–	–
S_0	0.47	*max S_0=1.69*	correspond
S_Y	13.69	–	–
r	0.9994	*min r=0.9924*	correspond

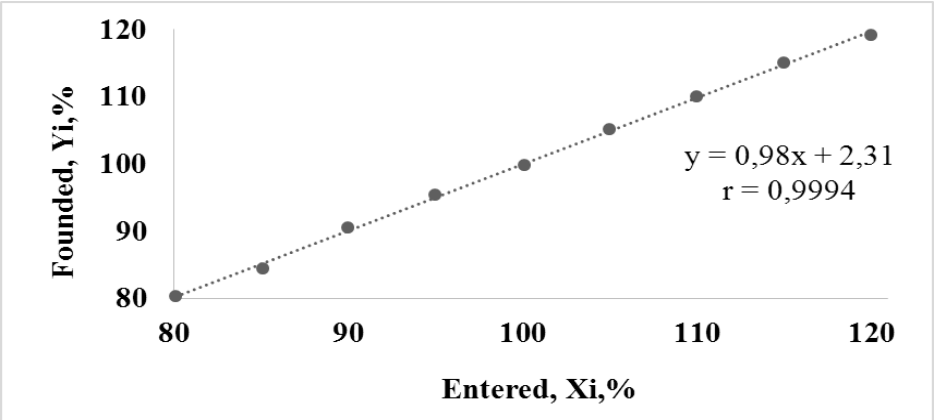

Fig. 3. Graph of the linear dependence of optical density of the phenylephrine hydrochloride concentration in normalized coordinates

Simultaneously with the study of linearity, the study of the accuracy and precision parameters was performed. It was done using the obtained data during the study of the method linearity according to the standardized procedure (Table 3).

The obtained results testify the compliance of the validation parameters with the requirements of the SPhU. Thus, the method can be used to analyze the researched ointment and study its stability.

Table 3

Results of study of precision and accuracy of the spectrophotometric method of phenylephrine hydrochloride assay

Validation characteristics	*The obtained value*
$\overline{Z}$	100.20
S_Z	0.21
Δ_Z	0.39
Criterion of one-sided confidence interval $\Delta_Z \leq \Delta_{As}$ ($0.39 \leq 3.20$)	
δ	0.20
Criterion of statistical insignificance δ, %≤0.13	
Criterion of practical insignificance δ, %≤$0.32\Delta_{As}$=1.02	

An ointment analysis using this method was conducted. Calculation of the quantitative content of phenylephrine hydrochloride in mg was carried out in two ways: by the standard method (2) and by the specific absorption index method (3) for determine the optimal method of calculation.

$$X, mg = \frac{A \cdot m_{SS} \cdot V_{v.f.} \cdot V_{pSS} \cdot m_{oint} \times 1000}{A_{SS} \cdot m_{ointsample} \cdot V_{v.f.SS}} \quad (2)$$

$$X, mg = \frac{A \cdot V_{v.f.} \cdot m_{oint} \times 1000}{A^{1\%}_{1sm} \cdot m_{oint\,sample} \cdot 100} \quad (3)$$

where: A – optical density of the tested solution;

A_{SS} – optical density of the reference solution;

m_{SS} – sample weight of the phenylephrine hydrochloride standard sample, g;

$m_{ointsample}$ – the weight of the ointment sample for the analysis, g;

m_{oint} – total mass of the ointment by prescription, g;

$V_{v.f.}$ – volume of the volumetric flask, ml;

$V_{v.f.SS}$ – volume of volumetric flask for dilution of the standard sample, ml;

V_{pSS} – volume of the pipette, ml;

$A^{1\%}_{1sm}$ – specific absorption index (equal to 92).

Results of determination of the phenylephrine hydrochloride quantitative content in the ointment by the standard method calculation (Table 4) and by the specific absorption index method (Table 5) testify that both methods give almost identical results. Thus, to reduce the analysis time and the cost of phenylephrine hydrochloride assay by spectrophotometry, the calculation of its quantitative content can be carried out by the method of specific absorption index.

Table 4

Results of determination of phenylephrine hydrochloride quantitative content in ointment (calculation by standard method (P=95; t (P, ν)=2.0150))

Sample No.	A_{SS}	A	$m_{oint\ sample}$, g	Found, mg	Metrological characteristics
1.	0.722	0.676	1.0018	20.02	$\overline{x}$ =19.73; S^2=0.12
2.		0.682	1.0032	20.17	S=0.34; $S_{\overline{x}}$ =0.14
3.		0.678	1.0102	19.92	$\Delta\mathbf{x}$ =0.69
4.		0.663	1.0097	19.48	$\Delta\overline{\mathbf{x}}$ =0.28
5.		0.659	1.0073	19.41	$\overline{\varepsilon}, \%$ =1.42
6.		0.657	1.0048	19.40	

Table 5

Results of determination of phenylephrine hydrochloride quantitative content in ointment (calculation by specific absorption index method (P=95; t (P, ν)=2.0150))

Sample No.	$A^{1\%}_{1cm}$	A	$m_{oint\ sample}$, g	Found, mg	Metrological characteristics
1.	92	0.676	1.0018	18.89	$\overline{\mathbf{X}}$ =18.62; S^2=0.11
2.		0.682	1.0032	19.03	S=0.32; $\mathbf{S}_{\overline{\mathbf{x}}}$ =0.13
3.		0.678	1.0102	18.79	$\Delta\mathbf{x}$ =0.65
4.		0.663	1.0097	18.38	$\Delta\overline{\mathbf{x}}$ =0.27
5.		0.659	1.0073	18.31	$\overline{\varepsilon}, \%$ =1.45
6.		0.657	1.0048	18.30	

7. Conclusions and prospects for further research

The method of direct spectrophotometry was chosen as an optimal method for phenylephrine hydrochloride assay in the composition of the Simanovsky compounding ointment.

Validation characteristics of the chosen method were studied. The obtained parameters of linearity, accuracy, precision, specificity and robustness testify to its correctness and the possibility of use in other laboratories to determine the quantitative content of phenylephrine

hydrochloride in the studied ointment and to analyze its stability.

The analysis of the studied ointment was carried out using the chosen method. An estimation of metrological characteristics was performed when calculating the quantitative content of phenylephrine hydrochloride by the standard method and the method of specific absorption index. The obtained results indicate the possibility of using both methods for determining the quantitative content of the test component in the ointment.

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Lesia Savchenko, PhD, Associate Professor, Department of Quality, Standardization and Certification of Medicines IQIP, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: savchenkolesia@gmail.com

Kateryna Uminska, Department of Quality, Standardization and Certification of Medicines IQIP, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Nataliia Bevz, PhD, Associate Professor, Department of Pharmaceutical Chemistry, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: natali.bevz.60@gmail.com

Victoriya Georgiyants, Doctor of Pharmaceutical Sciences, Professor, Department of Pharmaceutical Chemistry, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: vgeor@ukr.net

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STUDY OF EXCIPIENTS QUANTITIES INFLUENCEIN THE COMPOSITION OF THE POWDER IN SACHET PACKAGES

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При розробці порошку в пакетах саше з протизапальною дією особливим завдання є встановлення оптимального якісного та кількісного складу допоміжних речовин. Метою дослідження було вивчити вплив кількостей допоміжних речовин на фармако-технологічні показники порошку.

Методи. *З активних компонентів і допоміжних речовин були складені різні композиції з використанням методу математичного планування експерименту. Методом випадкового балансу вивчено їх вплив на фізико-хімічні, технологічні та органолептичні властивості порошку.*

Результати дослідження. *Аналіз діаграм розсіювання результатів дослідження впливу кількісних факторів на зовнішній вигляд маси показав, що найсуттєвіше на цей показник впливають вміст кальцію фосфату, натрію цитрату, куркуміну й ароматизатора лимон-лайм. Значущими факторами для насипної густини і густини після усадки є кількості кальцію фосфату, натрію цитрату, ароматизатору лимон-лайм і титану діоксиду. На результати дослідження індексу Карра найбільше впливають кількості кислоти лимонної безводної, титану діоксидута куркуміну. Експериментальні значення текучості найсуттєвіше залежать від вмісту кальцію фосфату. Кількості кальцію фосфату, натрію цитрату і титану діоксидує найбільш значущими для кута відкосу. Найбільший вплив на показники втрати в масі при висушуванні проявляють кількості куркуміну та кислоти яблучної. На основі діаграми розсіювання зовнішньоговигляду розчину встановлено визначальний вплив кількості кальцію фосфату, натрію цитрату, ароматизатору лимон-лайм і титану діоксиду. Цілком очевидним є значущість кількості ароматизатора лимон-лайм на запах розчину. Аналіз діаграми розсіювання смаку розчину показав, що найбільш значущими є вміст кальцію фосфату і кислоти лимонної безводної. Найбільш значущими факторами для pH розчину є кількості кальцію фосфату та ароматизатора лимон-лайм.*

Висновки. *Досліджено вплив кількостей допоміжних речовин на фармако-технологічніта органолептичні властивості порошку в пакетах саше склад саше*

Ключові слова: *порошок, саше, кількість допоміжних речовин, фармако-технологічні показники, випадковий баланс*

1. Introduction

Powders in packs are well appreciated by patients, because they have the combined benefits of tablets (precise dosage) and the possibility of easier ingestion (do no need to swallow the tablets) [1].

2. Statement of the problem

During developing a drug, you must take into account a number of key moments. After all, the purpose of pharmaceutical development is not only the creation of an effective and safe drug, but also the organization of appropriate conditions of the production process, which would ensure its reproducibility. The choice of the optimal composition of the drug and the development of technology makes it possible to establish a range of permissible values of the parameters of the process and components of the recipe, the observance of which guarantees the conformity of the final product to the requirements of the specification [2].

In order to develop a drug with anti-inflammatory properties, active pharmaceutical ingredients were selected, depending on the mechanisms of action. When creating powder in sachets with 0.325 g of paracetamol, 0.05 g ascorbic acid, 0.01 g of phenylep-