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ДУШАНБЕ – 2018

ИЛМ ВА ФАНОВАРЇ

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Дар як сол 4 шумора нашр мегардад.

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DIRECT SPECTROPHOMOMETRIC DETERMINATION OF DESLORATADINE IN TABLET FORMULATION

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Introduction. Desloratadine (DES), 4-(8-chloro-5,6-dihydro-11H-benzo-[5,6]cyclohepta [1,2b]pyridin-11-ylidene)-1-piperidine, is a selective, potent, peripheral H_1-receptor antagonist. It is the primary active metabolite of loratadine. It inhibits the release of histamine and leukotriene C4 from mast cells, prevents the development and facilitates allergic reactions. This substance reduces the permeability of blood vessels, eliminates spasms of smooth muscles and prevents tissue swelling. It exhibits a comprehensive anti-allergic, antiexudative and antipruritic activity. DES has a long-lasting effect and doesn‘t cause drowsiness because it is difficult for the compound to pass through the blood–brain barrier [1] (Fig.1).

Figure 1. Structural formula of desloratadine (DES).

As a result of the high demand for DES drugs in the pharmaceutical market, the importance of the improvement of existing and development of new methods for the quantitative determination of this active substance in the pharmaceutical formulation is undeniable.

Due to the relatively recent advent of DES in the market of medicines, only EPh has a monograph to it and recommends the use of HPLC method for quantitative analysis [2]. However, the high demand for this drug has induced researchers to develop other analytical techniques, primarily using HPLC. As mobile phase the authors use mixture of methanol:phosphate buffer (70:30) [3], gradient mixture of citrate buffer and acetonitrile [4], methanol:0.03 M sodium heptanesulfonate: anhydrous acetic acid (70:30:4) [5]. Moreover, a range of these type methods are described for the analysis of biological fluids [6, 7].

Among others, spectrophotometric techniques which are based on the formation of colored complexes with organic reagents are of severe importance. For example, Ayman A. Goudaa and Mohamed Kassem proposed to use Alizarin, Alizarin Red S and Quinalizarin as reagents. The absorbance of the reactions products is measured at a wavelength of 528, 505 and 560 nm, respectively.

Submission of Beer's law for these reactions is observed in a fairly wide range and the correlation coefficient of linear dependence is 0.9993 [8]. Another one of the methods is based on the reaction of DES with Eosin resulting in the formation of a complex with an absorption maximum at a wavelength of 549 nm. In this technique, researchers have been able to avoid the extraction step by the use of a non-ionic surface active agent, such as methylcellulose [9]. In addition, a direct spectrophotometric method has been developed, in which the authors have

proposed a new model of computing the UV spectra. It has reduced the molecule protonation effect on the results of analysis [10].

Materials and methods.

Chemicals. All solvents (methanol, acetone, acetonitrile, chloroform and ethyl acetate) used in this work were of analytical grade.

DES reference standard was supplied from Morepen Laboratories Ltd.

The dosage forms of DES were provided by various pharmaceutical companies – ‒Edem‖ pills 5.0 mg from PJSC ‒Farmak‖; ‒AlerhoMaks‖ pills 5.0 mg from LLC ‒Pharmaceutical company‖ Health‖; «Trexyl Neo» pills 5.0 mg from ‒Ranbaksi Laboratories Limited‖; ‒Alersis‖ pills 5.0 mg from ‒Normon Laboratorios SA‖; ‒Alerhostop‖ pills 5.0 mg from JSC ‒Fitofarm‖; ‒Desloratadine‖ pills 5.0 mg from JSC «Technology».

Bromocresol green, 2,6-Dibromo-4-[7-(3,5-dibromo-4-hydroxy-2-methyl-phenyl)-9,9-dioxo-8-oxa-9λ6-thiabicyclo[4.3.0]nona-1,3,5-trien-7-yl]-3-methyl-phenol, was a Synbias product and used without further purification. A stock 0.2 % solution was prepared by weighing the appropriate weight of the reagent, transferring it to a 100 mL volumetric flask, dissolving it in acetone and diluting to the mark with the same solvent.

Standard solutions. A standard stock solution containing 0.004% DES was prepared by dissolving 10 mg of pure drug in an approximate amount of acetone in a 250 ml measuring flask and subsequently adding the same solvent up to the mark for achieve the desired concentration of solution. The resulting solution is stable at room temperature.

Apparatus. All the absorption spectral measurements were made using Analytic Jena UV-visible spectrophotometer model Specord 200 equipped with 10 mm matched quartz cells. The weighing of the samples was done with Kern electronic scales ABT-120-5DM.

Procedure.

General procedure. Aliquots of acetonic solutions containing 0.5 – 1.2 mg of a standard solution of DES were transferred to separated 10 mL measuring flasks. To each flask 1.0 mL of 0.2 % BCG solution was added. Afterward, the volume was completed to the mark with acetone. The contents were shaken well and left at room temperature for a minute. The absorbance of this final yellow colored solution was measured at 407 nm respectively against a reagent blank. A calibration graph was plotted by performing a linear regression analysis using absorbance data vs. concentration of the drug.

Procedure for Pharmaceutical Preparations. The content of ten tablets was weighed and powdered using a mortar. A portion of the powder equivalent to 0.5 – 1.2 mg of DES was accurately weighed into a 25 ml volumetric flask and dissolved in 20 ml of acetone by 15–20 min of thorough shaking. The content was diluted to the mark with acetone, mixed well and filtered into a 50 mL volumetric flask through a filter paper to remove the insoluble matter. 2 ml of the filtrate were used for analysis using the procedure given above. The active substance content was calculated using the standard formulas.

Results and discussion. At the initial stage of this research, it was established that DES has a heterocyclic nitrogen atom with an unshared pair of electrons. It gives to the matter weakly basic properties and the ability to form ionic associate with BCG.

At optimum conditions, an ionic associate formed in the acetone medium immediately after mixing of reagents and showed maximum absorption at 407 nm. Thus, this wavelength was chosen for all further measurements in order to obtain highest sensitivity for the proposed method. It is important to point out that a reagent blank exhibits negligible maximum absorption at 407 nm respectively (Fig.2).

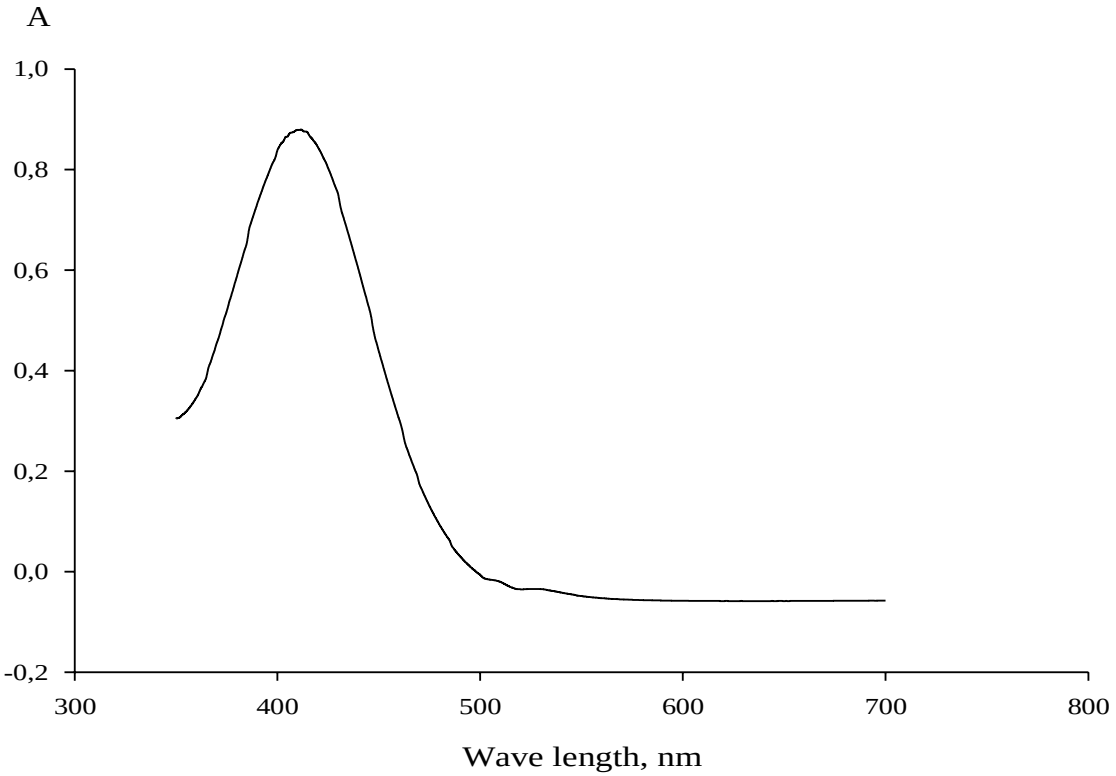

Figure 2. Absorption spectra of ionic associate of DES with BCG in acetone medium measured against a reagent blank

Optimum reaction conditions. Optimal reaction conditions for the quantitative determination of ion-pair complex were established using a series of preliminary experiments. After analyzing information on the solubility of reagents and reactivity of BCG, we studied the effect of the nature and composition of the solvent for a reaction. Acetone was chosen as the most appropriate reaction medium, which allowed a fairly high and stable in time optical density (Fig.3).

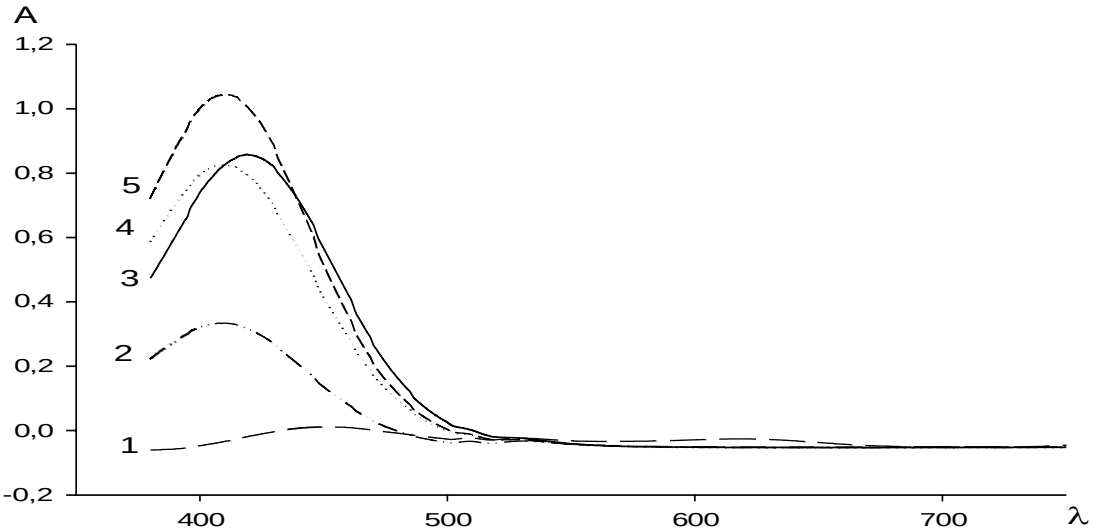

Figure 3. Effect of different solvents on the ionic associate of DES with BCG obtained against reagent solutions in each solvent. Absorption spectra of reaction products DES with BCG in methanol (1), ethyl acetate (2), chloroform (3), acetonitrile (4) and acetone (5).

In spectrophotometric analytical methods determining the reagent concentration in a solution is an important task to achieve a complete reaction. In order to assess this parameter, an experiment was performed during which various volumes of BCG solution (0.2%) in the range of 0.5–2.5 mL were added to a fixed drug concentration (0.8 mg/mL). The results showed that 1.0 mL of the reagent solution was enough to develop the full intensity color. As it can be seen in Fig. 4, a remarkable increase of absorbance was obtained by adding 1.0 mL of BCG solution, but it did not suffer any significant increase after adding more than 1.0 mL.

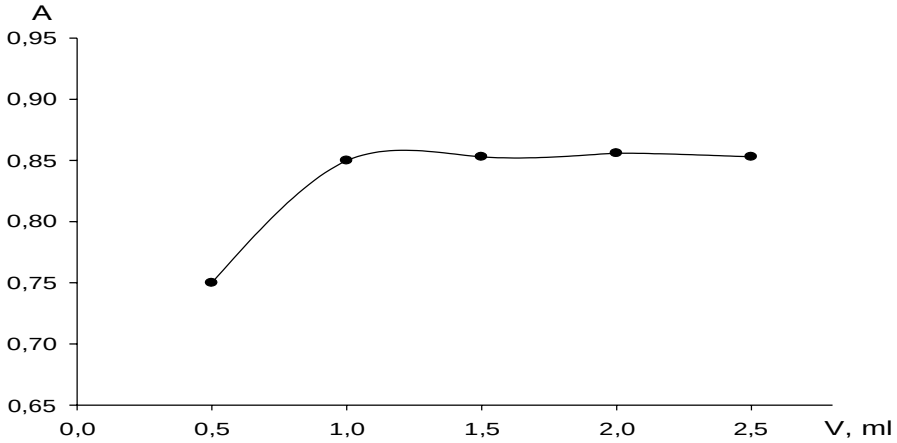

Figure 4. Effect of reagent concentration on the absorbance of ion-associate complex formed between DES and the reagent at the optimum wavelength.

The optimum reaction time was determined by continuous monitoring of the absorbance of the solution, containing 0.8 mg/mL DES and 1.0 mL of 0.2% BCG, at optimum wavelength and at Laboratory ambient temperature (22 ± 2 °C). The temperature and time regimes in this case did not require correction because the reaction proceeds rapidly at room temperature (Fig.5) [11].

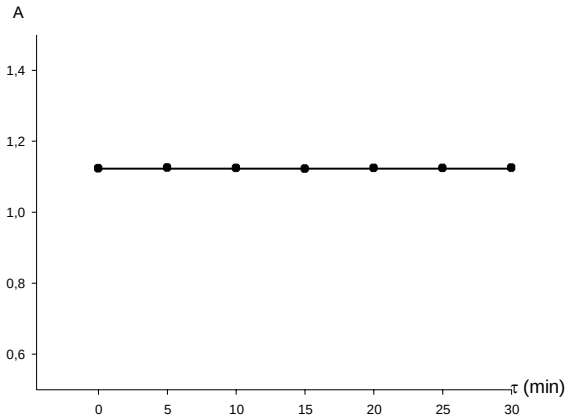

Figure 5. The dependence of the optical density of the solution on time after the reaction of DES with BCG.

Validation of the proposed method. The validity of the method was tested regarding linearity, accuracy, precision and robustness according to requirements of the Ukrainian Pharmacopoeia [12].

Linearity. For each dependence the linear regression equation was calculated by the method of the minimal squares, which has the general form: $y = a + b \times x$. Here y is the measured value (absorption), x is the concentration of the tested substance, a is the free member of the linear regression and b is the angular coefficient. In addition, for further analysis of the obtained linear dependencies, other indications were calculated: the coefficient of correlation r,

the residual standard deviation of the abscissa axis S_{x0}, (%) and the point of intersection with the axis of the ordinate *a*.

A calibration graph was constructed by measuring the absorbance at five concentration levels. It showed linear response of absorbance in relation to concentration of DES over the range of 0.5 – 1.2 mg (Fig. 6).

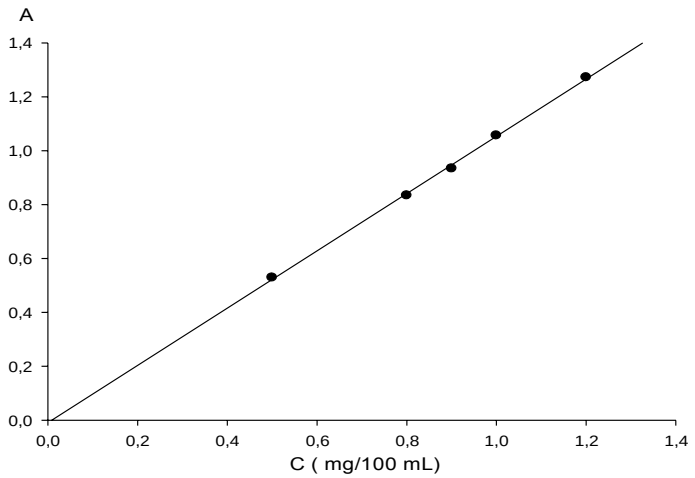

Figure 6. Linear correlation between absorbance and concentration of DES.

Precision. Precision was determined from DES samples at three different concentrations in the calibration range in three replicates (for each dosage form n = 9). The relative standard deviation (RSD) was found within 0.3 – 1.83 % for dosage forms (Table 1).

Table 1. **Precision determination results for DES dosage forms.**

Drug dosage form	$\bar{x}$	S	RSD	$\Delta_{x,r}$	$\Delta_{\bar{x},r}$	ΔAs, %
‑Edem‖ pills 5.0 mg (PJSC ‑Farmak‖, Ukraine, series 470714)	0.00499	$1.50 \cdot 10^{-5}$	0.30	0.56	0.19	3.20
«Trexyl Neo» pills 5.0 mg (‑Ranbaksi Laboratories Limited‖, India, the series 2639904)	0.00500	$3.50 \cdot 10^{-5}$	0.70	1.30	0.43	3.20
‒AlerhoMaks‖ pills 5.0 mg (LLC ‑Pharmaceutical company‖ Health‖, Ukraine, series 0020714)	0.00501	$3.60 \cdot 10^{-5}$	0.72	1.34	0.45	3.20
‑Desloratadine‖ pills 5.0 mg (JSC «Technology», Ukraine, series 10115)	0.00499	$2.96 \cdot 10^{-5}$	1.10	0.37	0.19	3.20
‒Alerhostop‖ pills 5.0 mg (JSC ‑Fitofarm‖ Ukraine, series 21014)	0.00499	$2.90 \cdot 10^{-5}$	0.58	1.08	0.36	3.20
‒Alersis‖ pills 5.0 mg (‑Normon Laboratorios SA‖, Spain, series J3RN1)	0.00499	$2.40 \cdot 10^{-5}$	0.48	0.89	0.30	3.20

Accuracy. Accuracy was checked by using the standard addition method. To previously analyzed tablet solutions known amounts of DES standard solution were added. The recovery was calculated by comparing the concentration of the spiked mixtures against the previously found value. Found recoveries were in the range 99.29 – 100.1 %. It can be seen from Table 2.

Table 2. Accuracy determination results for DES dosage forms.

Drug dosage form	$\bar{Z}$	RSD	$\Delta_{\bar{z}}$	$\lvert\bar{Z}$ -100|
–AlerhoMaks‖ pills 5.0 mg (LLC –Pharmaceutical company‖ Health‖, Ukraine, series 0020714)	100.1	0.93	0.58	0.1
«Trexyl Neo» pills 5.0 mg (–Ranbaksi Laboratories Limited‖, India, the series 2639904)	99.34	1.35	0.84	0.66
–Edem‖ pills 5.0 mg (PJSC –Farmak‖, Ukraine, series 470714)	100.0	1.25	0.78	0.00
–Desloratadine‖ pills 5.0 mg (JSC «Technology», Ukraine, series 10115)»	99.29	1.25	0.78	0.71
–Alerhostop‖ pills 5.0 mg (JSC –Fitofarm‖ Ukraine, series 21014)	99.89	0.87	0.54	0.11
–Alersis‖ pills 5.0 mg (–Normon Laboratorios SA‖, Spain, series J3RN1)	99.39	1.83	1.13	0.61

Conclusions. The proposed method has some advantages over others. It doesn't require extraction, heating, a buffer, or any other auxiliary actions and reagents. The formed complex is quite stable in time. Being simple, rapid, sensitive, accurate and economic, these characteristics make the developed method very suitable for routine analysis of DES in quality control laboratories.

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МУАЙЯНКУНИИ БЕВОСИТАИ СПЕКТРОФОТОМЕТРИИ ТАБЛЕТКАИ ДЕЗЛОРАТАДИН

Дар маќола усули оддї, зуд, њассос ва даќиќи муайянкунии таблеткањои дезлоратадин дар шаклњои воянокшудаи таъия ва собит карда шудааст. Усул дар њосилшавии маљмуаи ранги зард дар байни дезлоратадин ва бромкрезол дар муњити атсетонї, ки фурубарии баландтаринаш дар њудуди 407 нм мебошад, асосног мегардад. Шартњои бартариятноки таомул: ба монанди навъи њалкунанда, консентратсияи реагент, ваќти таомул ва устувории маљсулоти њосилшаванда омўхта шудааст. Усули пешкашшаванда мутобиќи талаботњои валидатсиявии Доруномаи Украина њаќќонї ба њисоб меравад. Ќонуни Бера дар њудуди консентратсияњои аз 0,50 то 1,20 мг/100 мл риоя карда мешавад. Ин усул барои муайян кардани дезлоратадин дар маводи дорувории (таблеткањо) бомуваффаќият истифода бурда шуд ва мумкин аст барои назорати пурзањмати сифат љойгузин гашта, ба кор бурда шавад.

Калидвожањо: таблеткањо, дезлоратадин, спектрофотометрї, бромкрезоли сабз, атсетон.

ПРЯМОЕ СПЕКТРОФОТОМЕТРИЧЕСКОЕ ОПРЕДЕЛЕНИЕ ДЕЗЛОРАТАДИНА В ТАБЛЕТКАХ

Разработана и подтверждена простая, быстрая, чувствительная и точная спектрофотометрическая методика определения дезлоратадина в дозированных формах. Методика основана на образовании комплекса желтого цвета между дезлоратадином и бромкрезоловым зеленым в ацетоновой среде, который имеет максимум поглощения при 407 нм. Изучены оптимальные условия реакции, такие как тип растворителя, концентрация реагентов, время реакции и стабильность образующихся продуктов. Предлагаемый метод действителен в соответствии с требованиями валидации Украинской Фармакопеи. Закон Бера соблюдается в пределах концентрации от 0,50 до 1,20 мг/100 мл. Этот метод был успешно применен для определения дезлоратадина в фармацевтических препаратах (таблетках) и может быть использован для рутинного контроля качества.

Ключевые слова: таблетки, дезлоратадин, спектрофотометрия, бромкрезоловый зеленый, ацетон.

DIRECT SPECTROPHOMOMETRIC DETERMINATION OF DESLORATADINE IN TABLET FORMULATION

A simple, rapid, sensitive and accurate spectrophotometric method has been developed and validated for the estimation of Desloratadine in dosage forms. The method is based on the formation of a yellow complex between DES and the Bromocresol Green in acetone medium, which showed an absorption maximum at 407 nm. The optimization of the reaction conditions such as the type of solvent, reagent concentration, reaction time and the stability of the formed products was investigated. The proposed method is valid according to the validation requirements of the Ukrainian Pharmacopoeia. Beer‘s law is obeyed within the concentration range 0,50 – 1,20 mg / 100 ml. The method was successfully applied to the determination of DES in pharmaceutical formulations (tablets) and it is suitable for routine quality control.

Keywords: tablets, Desloratadine, spectrophotometry, Bromocresol Green, acetone.

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УДК: 615+577:541.452:546.47(575.3)

БИОЛОГИЧЕСКИЕ СВОЙСТВА КООРДИНАЦИОННЫХ СОЕДИНЕНИЙ ЦИНКА (II) С ГЛИЦИНОМ И ГЛЮТАМИНОВОЙ КИСЛОТОЙ

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Актуальность. В последние десятилетия значительно увеличилось количество лекарственных препаратов, представляющих собой синтетические аналоги природных биологически активных веществ. До настоящего времени не был разработан ни один лекарственный препарат на основе биокоординационных соединений иммунологически

НАУКА И ИННОВАЦИЯ

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