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Validation of the method for hydrochlorothiazide assay in extemporaneous preparations

Extemporaneous preparations that contain hydrochlorothiazide are widely prescribed and used in different countries for treating adults and children. The feature of the preparation of such dosage forms is the use of substances and commercial drugs as a source of the active pharmaceutical ingredient.

Aim. To validate the UV-spectroscopic assay method for determining hydrochlorothiazide in extemporaneous syrups and powders.

Results and discussion. For method proposed the conditions of analysis, sample preparation and validation characteristics were determined. The samples of syrups and the powder were dissolved in 0.01 M sodium hydroxide solution and assessed by spectrophotometry in the ultraviolet region of light at the wavelength of 273 nm. The samples comply with the Beer-Lambert Bouguer law within the concentration range of 8 × 10-3-1.2 × 10-2 mg/ml with the the correlation coefficients ≥ 0.9992. The uncertainty of the methods was within the critical value of the error (the powder – 1.14 %, the syrup – 0.72 %) for both samples of the syrup containing the pure substance and commercial tablets. The assay method of hydrochlorothiazide in the extemporaneous preparations meets the acceptance criteria for the assay limits of ± 7.5 % and ± 10 % by such validation parameters as specificity, linearity, precision, accuracy within the range of 80-120 % of the nominal content.

Experimental part. For research the volumetric glassware Class A, an UV-spectrophotometer (Thermoscientific Evolution 60S), analytical balances (AXIS ALN220), reagents and solvents corresponding to the requirements of the State Pharmacopoeia of Ukraine were used.

Conclusions. The validation results have proven that the method can be reproduced correctly and is suitable for use in pharmaceutical analysis.

Key words: Hydrochlorothiazide; UV-spectrophotometry; validation of the analytical method; extemporaneous preparations

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Валідація методики кількісного визначення гідрохлоротіазиду в екстемпоральних лікарських засобах

Екстемпоральні лікарські засоби, що містять гідрохлоротіазид, досить часто прописуються лікарями та використовуються у різних країнах для лікування дорослих і дітей. Особливістю виготовлення таких лікарських форм є використання як субстанцій, так і лікарських засобів комерційного виробництва у якості джерела активного фармацевтичного інгредієнта.

Метою дослідження є валідація методики кількісного визначення гідрохлоротіазиду методом УФ-спектрофотометрії в екстемпорально виготовлених сиропах і порошку.

Результати та їх обговорення. Для запропонованої методики були визначені умови аналізу, пробопідготовка і валідаційні характеристики. Зразки сиропів і порошку розчиняли в 0,01 М розчині натрію гідроксиду і оцінювали спектрофотометрично в ультрафіолетовій області світла за довжини хвилі 273 нм. Зразки відповідають закону Бугера-Ламберта-Бера в діапазоні концентрацій 8 × 10^{-3}-1.2 × 10^{-2} мг/мл, коефіцієнти кореляції – ≥ 0.9992. Невизначеність методів не перевищує меж критичного значення похибки (порошок – 1,14 %, сироп – 0,72 %) для обох зразків сиропу, що містять субстанцію і комерційні таблетки. Досліджувана методика кількісного визначення гідрохлоротіазиду в екстемпоральних лікарських засобах відповідає критеріям прийнятності для діапазонів визначення ± 7,5 % і ± 10 % за валідаційними характеристиками: специфічність, лінійність, прецизійність, точність – у межах 80-120 % від номінального вмісту.

Експериментальна частина. Для дослідження використовували мірний посуд класу А, УФ-спектрофотометр (Thermoscientific Evolution 60S), аналітичні ваги (AXIS ALN220), реактиви та розчинники, які відповідають вимогам Державної фармакопеї України.

Висновки. Результати перевірки показали, що методика може бути правильно відтворена і підходить для використання у фармацевтичному аналізі.

***Ключові слова*:** гідрохлоротіазид; УФ-спектрофотометрія; валідація аналітичних методик; екстемпоральні лікарські засоби

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Валидация методики количественного определения гидрохлортиазида в экстемпоральных лекарственных средствах

Введение. Экстемпоральные лекарственные средства, содержащие гидрохлортиазид, достаточно часто прописываются врачами и используются в разных странах для лечения взрослых и детей. Особенностью приготовления таких лекарственных форм является использование как субстанций, так и лекарственных средств коммерческого производства в качестве источника активного фармацевтического ингредиента.

Целью исследования является валидация методики количественного определения гидрохлортиазида методом УФ-спектрофотометрии в экстемпорально приготовленных сиропах и порошках.

Результаты и их обсуждение. Для предложенной методики были определены условия анализа, пробоподготовка и валидационные характеристики. Образцы сиропов и порошка растворяли в 0,01 М растворе натрия гидроксида и оценивали спектрофотометрически в ультрафиолетовой области света при длине волны 273 нм. Образцы соответствуют закону Бугера-Ламберта-Бера в диапазоне концентраций 8×10^{-3}-$1{,}2 \times 10^{-2}$ мг/мл, коэффициенты корреляции – ≥ 0,9992. Неопределенность методов не превышает пределов критического значения погрешности (порошок – 1,14 %, сироп – 0,72 %) для обоих образцов сиропа, содержащих субстанцию и коммерческие таблетки. Исследуемая методика количественного определения гидрохлортиазида в экстемпоральных лекарственных средствах соответствует критериям приемлемости для диапазонов определения ± 7,5 % и ± 10 % по валидационным характеристикам: специфичность, линейность, прецизионность, точность в пределах 80-120 % от номинального содержания.

Экспериментальная часть. Для исследований использовали мерную посуду класса А, УФ-спектрофотометр (Thermoscientific Evolution 60S), аналитические весы (AXIS ALN220), реактивы та растворители, которые отвечают требованиям Государственной фармакопеи Украины.

Выводы. Результаты проверки показали, что методика может быть правильно воспроизведена и подходит для использования в фармацевтическом анализе.

***Ключевые слова*:** гидрохлортиазид; УФ-спектрофотометрия; валидация аналитических методик; экстемпоральные лекарственные средства

Extemporaneous preparations of hydrochlorothiazide are common in a number of countries [1-2]. They are prescribed for both adults and children in the treatment of hypertension, congestive heart failure, symptomatic edema and when preventing kidney stones [3-5]. Syrups and powders serve as dispersion media for individually dosed prescriptions [6-12, 15]. These medicines can be used by pediatric patients or by those who are unable to swallow solid dosage forms. The UV-spectroscopic method is proposed because it is relatively cheap compared to the HPLC method and can be used during in-pharmacy quality control.

The aim of this study was to develop and validate a simple, economic, accurate and sensitive UV method for determination of hydrochlorothiazide in compounded suspensions and powders.

Results and discussion

The *validation criteria* (Tab. 1) for the tolerance content ± 10 % and ± 7.5 % were determined according to the requirements of the SPhU and the work on development and validation of quality assurance methods for compounded preparations [16].

Table 1

Critical values for systematic error, total uncertainty of the analysis and parameters for the linear dependence

Range, %	B, %	max Δ_{As},%	max δ_{max},%	RSD_0, %	min R^2_c	max a,%	max δ_{abs}, % (λ = 273 nm)
Syrup							
80-120	± 10	3.2	2.3	1.81	0.9924	4.7	2.72
	± 7.5	2.4	1.7	1.35	0.9957	3.5	
Powder							
80-120	± 10	3.2	2.3	1.2	0.9924	4.7	2.72
	± 7.5	2.4	1.7	0.90	0.9957	3.5	

Notes: B – permitted deviation in the content; $\max\Delta_{As}$ – critical value of the error; δ_{max} – maximum systematic error; R^2_c – coefficient of determination; a – y-intercept on the calibration graph; δ_{abs} –uncertainty of absorbance.

Based on recommendations from the European (Euph), Japanese (JP) and British Pharmacopoeia(BP) 0.01 M sodium hydroxide was selected. For our method, the value for dilution is:

$$D = \frac{100}{50} \times \frac{100}{2} = \frac{10000}{100}.$$

The prognosis (Tab. 2, 3) took into consideration the maximum permissible errors during operations associated with use of glassware [14] and the value of uncertainty in the final analytical operation, Δ_{FAO}(0.49) [16]. The uncertainty of the method (powder – 1.14 %, syrup – 0.72 %) was within the limits of $\Delta_{As} \le \max\Delta_{As}$.

Specificity. Fig. 1 shows that neither sucrose nor the excipients in tablets significantly interfered with the result from spectrophotometric determination of hydrochlorothiazide. There was also the correspondence in peaks at the wavelength of 273 nm and 323 nm for both the substance and tablets. Thus, the method is specific for hydrochlorothiazide. The effect of placebo (only the syrup) was taken by repeating the procedure in the section method with just the dispersion agent (85 % syrup, USP). Its effect was calculated with the formula:

$$100 \cdot A_{blank}/A_{st},$$

where: its absorbance, A_{blank} = 0.006; A_{st} = 0.520.

Contribution of placebo to the total absorbance of the analyte is:

- A_{nom} = A (1 %, 1 cm) × C_{nom} = 520 × 0.001 % = 0.520 (syrup).
- A_{nom} = A (1 %, 1 cm) × C_{nom} = 520 × 0.001 % = 0.520 (powder).
- $\delta_{noise} = A_{sucrose}/A_{nom} \times 100\ \% = 0.006/0.520 \times 100\ \% = 1.15\ \%$.
- $\delta_{glucose} = A_{glucose}/A_{nom} \times 100\ \% = 0.004/0.520 \times 100\ \% = 0.77\%$.

Its effect was within the limits of the criteria: ($\le \delta_{max}$ = 1.7 %, $\le \delta_{abs}$ = 2.72).

Table 2

The uncertainty of the analytical method assessment (syrups)

Stages of the sample preparation	Parameter	Uncertainty, %
Test solution for the hydrochlorothiazide substance in the syrup		
Weighing on the analytical balance, g	13.05	0.0015
Volumetric dilution, ml	100	0.12
Taking an aliquot, ml	2	0.5
Volumetric dilution, ml	100	0.12
The total uncertainty of the sample preparation $\Delta_{SP} = \sqrt{0.0015^2 + 0.12^2 + 0.5^2 + 0.12^2} \approx 0.53$ %		
Uncertainty of the method $\Delta_{As} = \sqrt{\Delta^2_{SP} + \Delta^2_{FAO}} = \sqrt{0.53^2 + 0.49^2} \approx 0.72$ %		
Test solution for the crushed hydrochlorothiazide tablets in the syrup		
Weighing on the analytical balance, g	13.26	0.0015
Volumetric dilution, ml	100	0.12
Taking an aliquot, ml	2	0.5
Volumetric dilution, ml	100	0.12
The total uncertainty of the sample preparation $\Delta_{SP} = \sqrt{0.0015^2 + 0.12^2 + 0.5^2 + 0.12^2} \approx 0.53$ %		
Uncertainty of the method $\Delta_{As} = \sqrt{\Delta^2_{SP} + \Delta^2_{FAO}} = \sqrt{0.53^2 + 0.49^2} \approx 0.72$ %		

The maximum uncertainty of absorbance for our preparations was calculated using the formula:

$$\delta_{abs} = \sqrt{2} \times \frac{100 \times \Delta A}{A_{пот}} = \sqrt{2} \times \frac{100 \times 0.01}{0.520} = 2.72,$$

where: ΔA – is the tolerance for absorbance, ± 0.01 (Fig. 1) [17].

Table 3

The uncertainty of the analytical method assessment (powder)

Stages of the sample preparation	Parameter	Uncertainty, %
Test solution		
Weighing on the analytical balance, g	0.025	0.8
Volumetric dilution, ml	50	0.17
Taking an aliquot, ml	1	0.6
Volumetric dilution, ml	50	0.17
The total uncertainty of the sample preparation $\Delta_{SP} = \sqrt{0.8^2 + 0.17^2 + 0.6^2 + 0.17^2} \approx 1.03$ %		
Uncertainty of the method $\Delta_{As} = \sqrt{1.03^2 + 0.49^2} \approx 1.14$ %		

Linearity and range. The absorbance of aliquots at a concentration range of 8×10^{-3}-1.2×10^{-2} mg/ml corresponding to 80-120 % of the nominal concentration of hydrochlorothiazide was measured. The values in the linearity graphs were converted to nominal coordinates using the formula [16]:

$$X_i = \frac{C_i}{C_i^{st}} \times 100\ \%,\ Y_i = \frac{A_i}{A_i^{st}} \times 100\ \%,$$

where: C_i^{st}, A_i^{st}, – are the standard nominal concentration and absorbance; C_i – is the concentration of the analyte introduced; A_i – is the absorbance read on the spectrophotometer.

The linear graphs below show their corresponding linear dependence. The regression line equations obtained were y = 0.9911x + 0.738 for the powder sample (Fig 2); y = 0.9905x + 0.512 and y = 0.9968x + 0.152 for the substance and tablets suspended in the syrup, respectively (Fig 3, 4), in conformity with Beer-Lambert's law. The coefficients of determination were > 0.9992 for all samples.

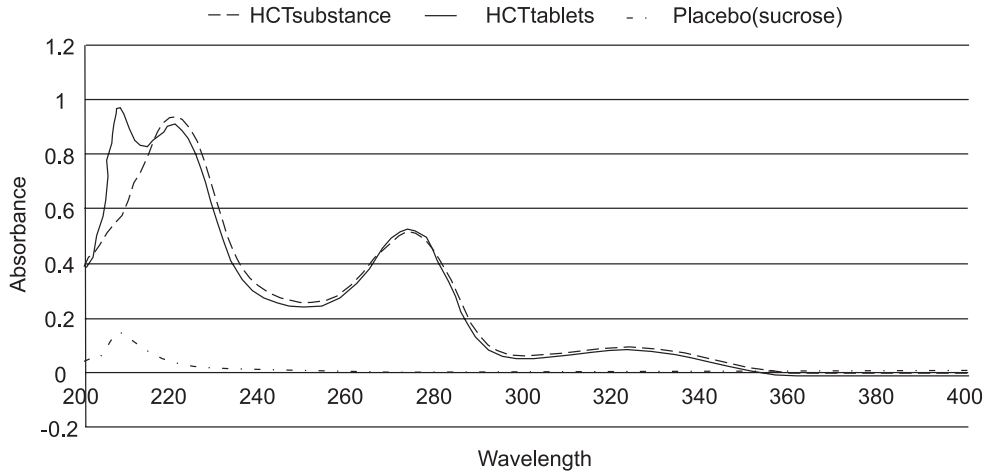

Fig. 1. The spectrum for hydrochlorothiazide in analytical solutions of the substance (in the syrup), tablets (in the syrup) and placebo (sucrose – no analyte)

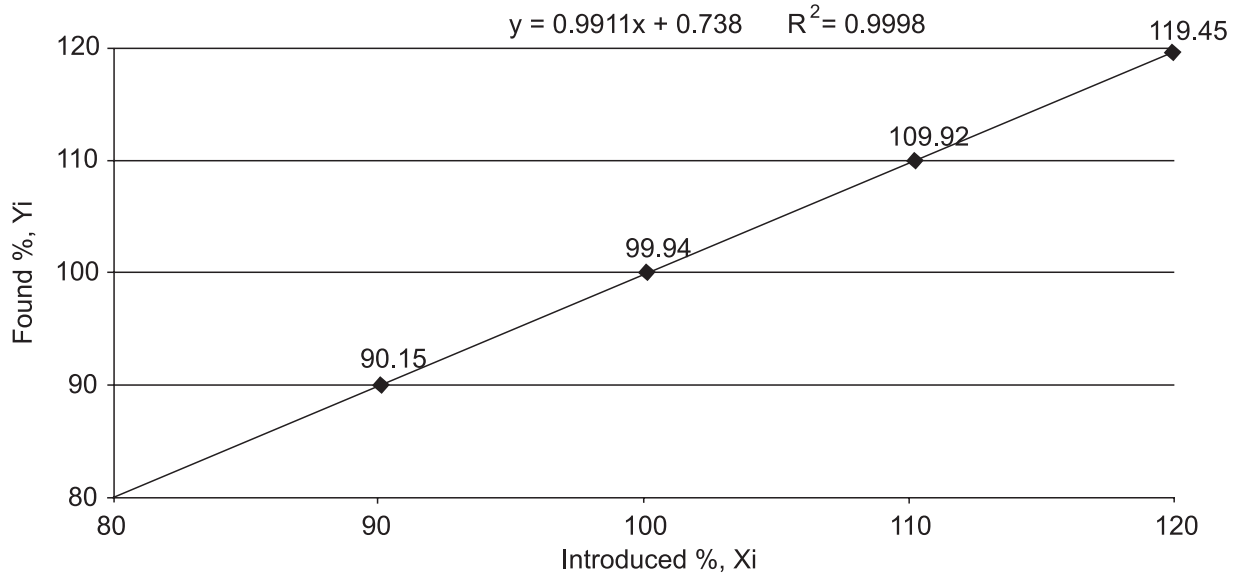

Fig. 2. The linear dependence in the percentage recovery of hydrochlorothiazide on the powder sample in the normalized coordinates

Intraday (repeatability) and Interday (reproducibility) precision. The absorbance of 10 μg/ml solutions from commercial tablets were observed at different times of the day (intraday) on different days (interday) by different analysts for two brands (Tab. 4). The coefficient of variance (RSD, %), being the measure of precision, was < 1 % for both intraday and interday results. The method was found to be precise (Tab. 4).

Robustness. According to the International conference on Harmonization deliberate variations in the wavelength and the extraction time were made to show the reliability of the method. Syrups containing 50 mg of hydrochlorothiazide were shaken with 10 ml *0.1 M sodium hydroxide* and allowed to stand for 20, 40 and 60 min before further procedures for sample preparation. The method was found to be robust (Tab. 5). The analytical solutions of two brands of hydrochlorothiazide prepared in accordance with the sample preparation for the UV-identification test for hydrochlorothiazide in the European Pharmacopeia were stable for 1 hour (Tab. 6). Time zero of minutes was counted from the moment the final dilution. There was no significant change in pH or absorbance (solvent – *0.01 M sodium hydroxide).*

Accuracy. Accuracy of the method (Tab. 7) was determined at 5 levels with 3 repetitions at each level. The quantity equivalent to 80 %, 90 %, 100 %, 110 % and 120 % was added to samples. The mean percentage recoveries ($p \leq 0.05$) of the substances against theoretical values were found to be 99.57 ± 0.23 for the hydrochlorothiazide substance, 99.84 ± 0.18 for the hydrochlorothiazide tablets in the syrup, and 99.86 ± 0.13 for tablets in the powder, indicating that the method was accurate.

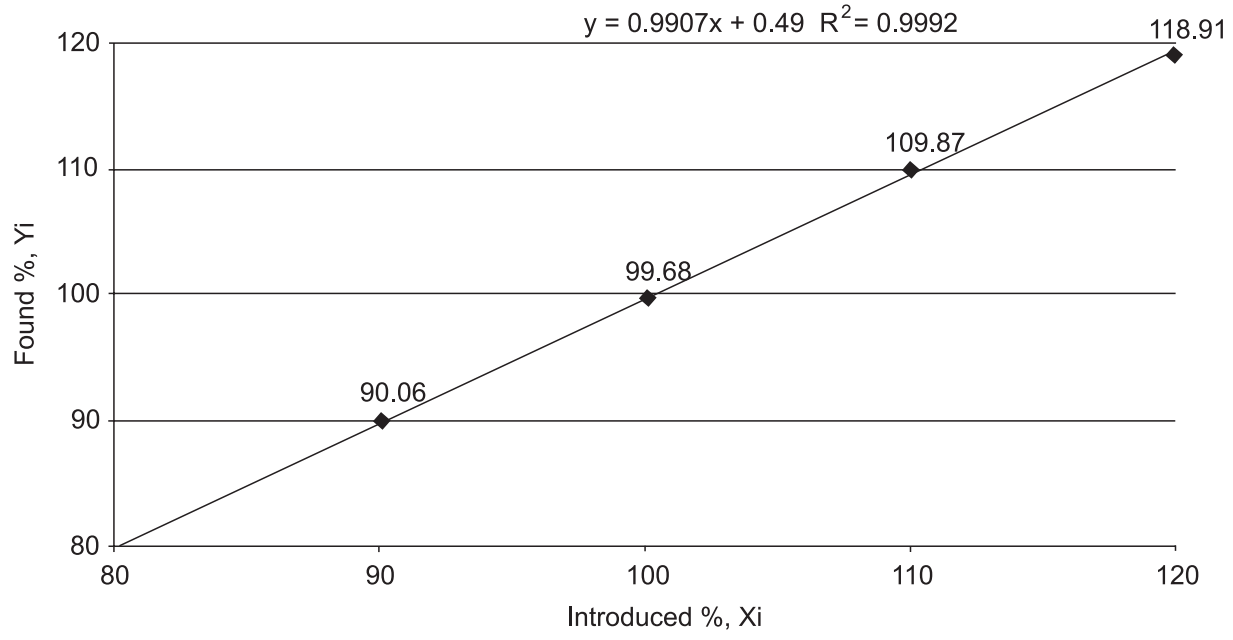

Fig. 3. The linear dependence in the percentage recovery of hydrochlorothiazide on the substance in the syrup sample in the normalized coordinates

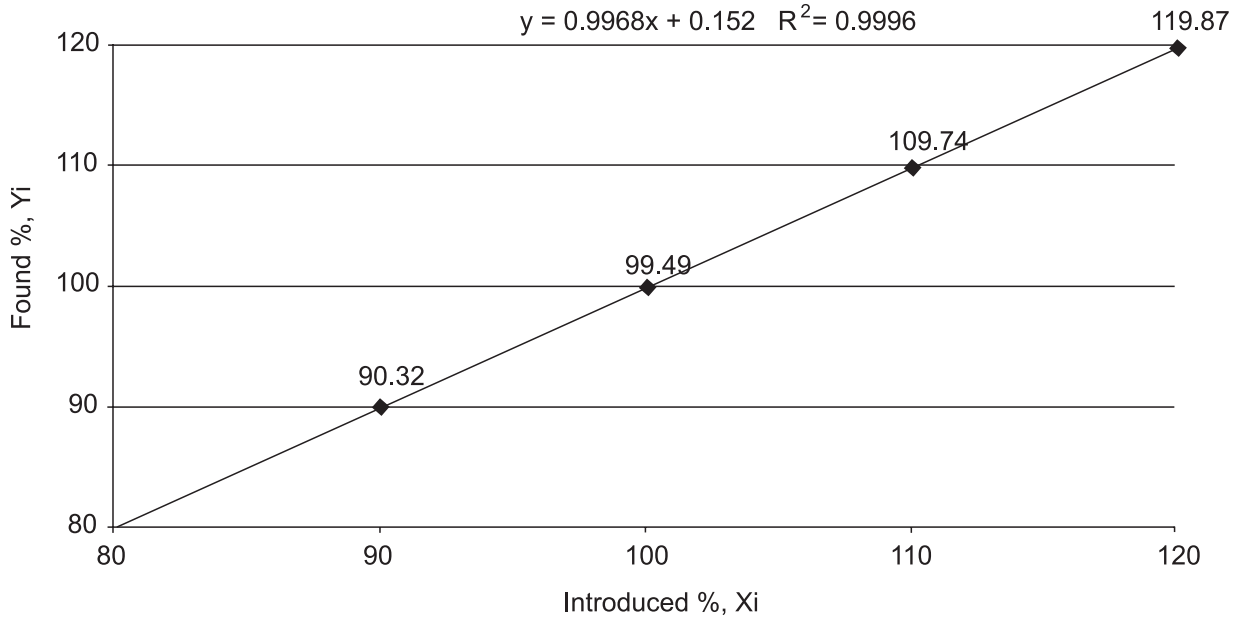

Fig. 4. The linear dependence in the percentage recovery of hydrochlorothiazide on tablets in the syrup sample in the normalized coordinates

Metrological characteristics of the method do not exceed the critical value of the error (2.4 %) and are characterized by the qualitative analytical indicators. This method can be correctly reproduced in the laboratory (Tab. 1 and 7).

Table 4

Repeatability and reproducibility of the method

	DAY 1	DAY 2
No.	Zi (Content, %)	
1	99.52	99.04
2	99.76	99.04
3	99.76	99.28
4	100.21	100.21
5	100.43	100.00
6	100.43	100.00
7	99.42	99.62
8	99.62	99.81
9	99.42	99.62
10	99.83	99.83
11	99.65	100.00
12	99.83	99.83
13	99.84	99.20
14	100.00	99.04
15	99.84	99.04
Mean (Z, %)	99.84	99.57
Z_{intra}, %	99.70	
S_z, %	0.35	0.45
SD_z, %	0.40	
Δ_{intra} (t (95 %, n-2) · SDz), %	0.68	

Notes: Z_{intra} – cumulative mean; S_z – standard deviation; SD_z – relative standard deviation; Δ_{intra} – relative confidence interval.

Experimental part

The following compositions of hydrochlorothiazide dosage forms were selected for the study:

1. *Composition of Syrup 1:*
Hydrochlorothiazide 0.5
Syrup, USP qs 100 ml
2. *Composition of Syrup 2:*
Hydrochlorothiazide
ex tab 0.5
Syrup, USP qs 100 ml
3. *Powder Composition:*
Hydrochlorothiazide
ex tab 0.005
Glucose ad 0.2

The following substances were used for preparation of model samples with hydrochlorothiazide: hydrochlorothiazide substance from Changzhou Pharmaceutical Factory, China (certificate of analysis, batch No. 120402), hydrochlorothiazide tablets, 25 mg (Sanofi-Aventis LLC, batch 5V007, Ukraine), hydrochlorothiazide tablets, 25 mg (Borshchahivskiy CPP, batch 4.823012.510864), sucrose (pharmaceutical grade), hydrochlorothiazide tablets, 25 mg (Chinoin Pharmaceutical and Chemical Works Private Co. Ltd., Hungary), and dextrose monohydrate (CARGILL S.L.U.).

Table 5

Robustness

Parameter	Absorbance		
	Minimum	Optimum	Maximum
Variation in the wavelength	272 nm	273 nm	274 nm
	0.517	0.520	0.519
Variation in the extraction time (20 min)	0.519	0.520	0.520

Table 6

Absorbance stability of analytical solutions

Brand	The period of study, min					mean	RSDt, %	Δt, %	max δ,%
	0	30	60	90	120				
Borshchahivskiy CPP batch	0.520	0,521	0.520	0.519	0.517	0.5197	0.1977	0.4215	1.02
	0.521	0.522	0.520	0.519	0.518				
	0.520	0.519	0.519	0.521	0.519				
	0.5203	0.5207	0.5197	0.5197	0.5180				
Brand	The period of study, min					mean	RSDt, %	Δt, %	max δ,%
	0	30	60	90	120				
Sanofi-Aventis batch	0.519	0.518	0.519	0.519	0.518	0.5183	0.1286	0.2742	1.02
	0.519	0.519	0.519	0.517	0.518				
	0.518	0.519	0.519	0.518	0.516				
	0.5187	0.5187	0.5190	0.5180	0.5173				

Notes: Δt = average change over the time period, maxδ- maximum error.

A simple syrup USP (85 % w/v) was compounded according to instructions for its preparation [13]. All reagents and solvents were prepared in accordance with the requirements of the State Pharmacopoeia of Ukraine (SPhU) corresponding to the European Pharmacopoeia [14].

Equipment. Volumetric glassware of class A, filter paper (FILTRAK® Acido Hydrochlorico Extraca), an UV-spectrophotometer (Thermoscientific Evolution 60S) with 10 mm quartz cells, a mortar, a pestle, analytical balance (AXIS, Poland ALN220) were used.

Compounding technology of Syrup 1 and 2. Levigate accurately weighed 500 mg of the hydrochlorothiazide substance (or an equivalent quantity of the powdered tablet mass) with a small portion of syrup to form a paste. Add the syrup gradually with stirring to form a homogenous mixture. Fill the mixture with the same base up to 100 ml to form a 5 mg/ml suspension.

Compounding technology of Powder. Weigh and pulverize the appropriate number of hydrochlorothiazide tablets in a mortar. Triturate separately approximately 5.5 g of the glucose powder in a mortar. Add gradually 0.2 g of the equivalent hydrochlorothiazide in portions from pulverized tablets. Add the remaining portion of glucose to the final weight of 8 g and mix to homogeneity [15].

Assay of hydrochlorothiazide in Syrup 1. Using the analytical balance weigh the appropriate volume of 5 mg/ml compounded suspension corresponding

Table 7

Validation characteristics of the method for quantitative determination of hydrochlorothiazide in compounded preparations

Description/parameter		Tablets in the powder	Substance in the syrup	Tablets in the syrup
Permissible limits of the content, B, %		7.5 %	7.5 %	7.5 %
Mean recovery (p ≤ 0.05) %		99.86 ± 0.13	99.57 ± 0.23	99.84 ± 0.18
Mean absorbance, A		0.520	0.518	0.519
Relative standard deviation, Sz, %		0.24	0.42	0.32
Average content Z, %		99.86	99.57	99.84
Relative confidence interval Δz, %		0.4193	0.7462	0.5580
Critical values for convergence of results, Δas ≤ 2.4 %		1.14	0.72	0.72
Linearity	a ≤ 3.5	0.74	0.51	0.15
	$S \le RSD_0 = 1.35$ %	0.23	0.43	0.07
	$R^2 \ge 0{,}9957$	0.9998	0.9992	0.9996
		Brands		
Repeatability RSD, %		DAY I (Borshchahivskiy CPP batch)	DAY 2 (Sanofi-Aventis batch)	
		0.35	0.45	
Overall conclusion for the method		Correct		

to 50 mg of hydrochlorothiazide. Transfer the suspension into a 100 ml volumetric flask, add 10 ml of *0.1 M sodium hydroxide,* shake and allow standing for 20 min. Dilute to 100 ml with *water R*. Dilute 2 ml of the solution obtained to 100 ml with *0.01 M sodium hydroxide.* Measure the absorbance at 273 nm using *0.01 M sodium hydroxide* as the compensation solution. Calculate the content of $C_7H_8ClN_3O_4S_2$ taking 520 as the value of A (1 %, 1 cm) at the maximum at 273 nm.

Assay of hydrochlorothiazide in Syrup 2*.* Using the analytical balance weigh the appropriate volume of 5 mg/ml compounded suspension corresponding to 50 mg of hydrochlorothiazide. Transfer the suspension into a 100 ml volumetric flask, add 10 ml of *0.1 M sodium hydroxide,* shake and allow standing for 20 min. Dilute to 100 ml with *water R* and filter. Dilute 2 ml of the solution obtained to 100 ml with *0.01 M sodium hydroxide.* Measure the absorbance at 273 nm using *0.01 M sodium hydroxide* as the compensation solution. Calculate the content of $C_7H_8ClN_3O_4S_2$ taking 520 as the value of A (1 %, 1 cm) at the maximum at 273 nm.

Assay of hydrochlorothiazide in Powder*.* Transfer a portion of the powder equivalent to 5.0 mg to a 10.0 ml volumetric flask. Add 1.0 ml of *0.1 M sodium hydroxide* and shake for 20 min. Dilute with *water R* to 10 ml. Mix and filter. Transfer 1.0 ml of the resulting solution with a pipette to a 50 ml volumetric flask and dilute to the volume with *0.01 M sodium hydroxide*. Measure the absorbance at 273 nm using *0.01 M sodium hydroxide* as the compensation solution. Calculate the content of $C_7H_8ClN_3O_4S_2$ taking 520 as the value of A (1 %, 1 cm) at the maximum at 273 nm.

Placebo*:* Add 10 ml *0.1 M sodium hydroxide* to 10 ml of the syrup, USP (not active ingredient). Shake the mixture and allow it to stand for 20 min, then dilute to the volume of 100 ml with *water R*. Filter the mixture and discard the first 10 ml. Dilute 2 ml of the supernatant in a volumetric flask to the volume of 100 ml using *0.01 M sodium hydroxide* solution. Measure the absorbance at 273 nm using *0.01 M sodium hydroxide* as the compensation liquid.

The content of $C_7H_8ClN_3O_4S_2$ taking 520 as the value of A (1 %, 1 cm) and the maximum at 273 nm was calculated using the formula:

$$X(\%) = \frac{A_1}{A_{nom}} \times D \times C_s \times 100;\ D = \frac{V_D}{m_t},$$

where: A_1 – is the absorbance observed; A_{nom}($A_{nom} = A^{1\%}_{1cm} \times 0.001$ %) – is the specific absorbance (0.520) equivalent to 0.01 g/L solution; D – is dilution of the sample analyzed; C_s – is the final concentration (mg/ml) of the solution analyzed; m_t – is the mass of the analyte.

Conclusions

The non-derivative UV-spectrophotometric method is validated for the content determination of hydrochlorothiazide tablets in the syrup (USP). The method for assay meets acceptance criteria for the assay limits by such validation parameters as specificity, linearity, precision, accuracy within the range of 80-120 % of the nominal content. Based on the results of validation studies it has been substantiated and verified experimentally that this method can give reliable results, reproducible and be suitable for quality control of hydrochlorothiazide in the syrup (USP).

Conflicts of Interests: authors have no conflict of interests to declare.

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