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DEVELOPMENT OF METHODOLOGY FOR THE DETERMINATION CETIRIZINE HYDROCHLORIDE IN MEDICINES

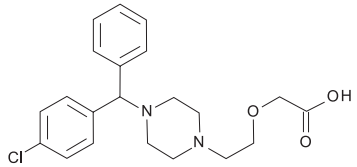
Methods for identification and quantification of cetirizine hydrochloride in medicines have been developed. Developed and validated characteristics have been studied of methods for identification and quantitative determination by the standard method. Validation methodology did not exceed the critical error and is characterized by qualitative analytical performance.

Key words: cetirizine hydrochloride; thin layer chromatography; UV-spectrophotometry; validation

INTRODUCTION

The current pharmaceutical analysis has got more emphasis to satisfy our query for better understanding of physico-chemical properties of pharmaceutical compounds, by the use of advanced instrumental methods. It also plays an important role for quality assurance of pharmaceutical product throughout the shelf life. The pharmaceutical industry is under increased scrutiny to constrain costs and yet consistently deliver to market safe, efficacious products that fulfill medical needs. As a part of this, drug analysis also plays an important role. Analytical methods must be validated to provide reliable data for regulatory submissions. These methods are essential for a number of purposes, including testing for QC release, testing of stability samples, testing of reference materials and to provide data to support specifications. Standard analytical procedure for newer drugs or formation may not be available in Pharmacopoeia; it is essential to develop new analytical methods which are accurate, precise, specific, linear, simple and rapid.

Cetirizine ((±)-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic acid) is piperazine derivative and metabolite of hydroxyzine, is an antihistamine, reported to be a long action and with mast-cell stabilizing activity.



Cetirizine (trade names Zyrtec, Reactine) is a second-generation antihistamine used in the treatment of hay fever, allergies, angioedema, and urticaria. Second-generation antihistamines like cetirizine are less able to cross the blood-brain barrier and therefore have diminished effects on the central nervous system compared to first-generation drugs: for instance they are less likely to induce drowsiness or to interfere with memory formation. Formerly prescription-only in the US and Canada, cetirizine is now available over-the-counter in both countries as Zyrtec and Reactine, respectively. Zyrtec was the highest-grossing new non-food product of 2008 in the US, generating sales of $315.9 million. It is also available as a generic drug. In Turkey, Iran, Australia and New Zealand, Zyrtec is available over-the-counter in pharmacies and in the UK, Norway and The Netherlands cetirizine can be sold in limited quantities off-the-shelf in any outlet and is often available in supermarkets. From 2009 Germany made many generic drugs containing cetirizine available in pharmacies without prescription. Sweden, Finland, Poland, and Israel also recognize Cetirizine as an over-the-counter medicine. In India, it is sold over-the-counter as brand-name "CTZ" (formerly called "Cetzine"), even though it remains classified as a Schedule H (prescription) drug. India also classifies Cetirizine as an OTC drug, and uses it as an alternative to Pheniramine (Avil) which is no longer provided OTC in India. In Ireland, cetirizine is known as Zirtek (as well as under generic names), and is available OTC in limited quantities (usually no more than seven tablets per pack). Cetirizine crosses the blood–brain barrier only slightly, reducing the sedative side-effect common with older antihistamines. It has also been shown to inhibit eosinophil chemotaxis and LTB4 release. At a dosage of 20 mg, Boone et al. found that it inhibited the expression of VCAM-1 in patients with atopic dermatitis. Unlike many other antihistamines, Cetirizine does not exhibit anticholinergic properties. The levorotary enantiomer of cetirizine, known as levocetirizine, is the more active form. Analysis of ceti-

Table 1

CHROMATOGRAPHIC CHARACTERISTICS OF CETIRIZINE HYDROCHLORIDE IN DIFFERENT SOLVENT SYSTEMS

Mobile phase	Color zone	Stationary phase (plate) Rf on "Sorbfil"	The limit of detectio, micrograms
	View in ultraviolet light with a wavelength of 254 nm		
Ammonia R-methanol R-methylene chloride R (1:10:90)	fluorescence	0.55	0.2
Ethanol R-solution ammonia R (16:4,7)	fluorescence	0.63	0.4
Ammonia R-propanol R(30:70)	fluorescence	0.64	0.4
Formic acid R-isopropanol R-water R (40:2:10)	fluorescence	0.75	0.4
Formic acid R-water R(1:4)	fluorescence	0.94	0.4
Aceton R-benzene R (35:65)	fluorescence	0.90	0.4
Ethanol R-acetic acid R-water R (17:2:2)	fluorescence	0.66	0.6
Chloroform R-methanol R-ammonia R (4:4:2)	fluorescence	0.79	0.6

rizine hydrochloride in substance is described in British Pharmacopoeia (alkalimetry in acetone solution potentiometric titration) but this method can not be used for pharmaceutical dosage forms contain of cetirizine hydrochloride [1, 3]. Therefore, the development of new methods for identification and quantification of active pharmaceutical ingredients in medicines is an important task of pharmaceutical chemistry and standardization of medicines.

The aim of our study was to develop rapid, more accurate, precise, reliable, less expensive methods of identification and quantification of cetirizine hydrochloride in medicines.

MATERIALS AND METHODS

At carrying out research using the substance of cetirizine hydrochloride, according to the SPU. We made analysis of tablets three different manufacturers.

Analytical equipment: UV spectrophotometer Carry 50 and Lambda 25, Scales AVT-120-5D, measuring vessel glass and reagents, that meet the SPU requirements. TLC test was carried out using Silica gel, chromatographic plates 60 F254 (company "Merck", Germany) and "Sorbfil" (Russia).

In developing the technique of identification and assay data as part of cetirizine hydrochloride in medicines was chosen by UV-spectrophotometry and TLC.

Validation procedures carried out in accordance with the requirements of SPU [2, 4].

Methodology of Identification

Thin layer chromatography

Test solutions tablets "Allercet", tablets "Цетиризин-нортон", tablets "Цетиризин ГЕКСАЛ". To sample powder of tablets, equivalent to 10 mg of *cetirizine hydrochloride*, add *water R* and dilute to 5 ml with the same solvent. Mix and filtrate.

Reference solution. Dissolve 10 mg of *cetirizine hydrochloride CRS* in water R and dilute to 5 ml with the same solvent.

Plate: TLC silica gel GF_{254} plate R.

Mobile phase: ammonia R, methanol R, methylene chloride R (1:10:90 V/V/V).

Application: 5µl.

Drying: in a current of cold air.

Detection: examine in ultraviolet light at 254 mn.

Results: the principal spot in the chromatogram obtained with the test solution in position and size to the the principal spot in the chromatogram obtained with the reference solution.

Methodology of Quantitative Determination

Absorption spectrophotometry in the ultraviolet region (standard method).

Test solutions tablets "Allercet", tablets "Цетиризин-нортон", tablets "Цетиризин ГЕКСАЛ". To sample powder of tablets, equivalent to 20 mg of *cetirizine hydrochloride*, add 50 ml of a 10.3 g/l solution of *hydrochloric acid R* and dilute with the same acid. Dilute 10 ml of the solution to 100.0 ml with the same solvent. Mix and filtrate.

Reference solution. Dissolve 20 mg of *cetirizine hydrochloride CRS* in 50 ml of a 10.3 g/l solution of *hydrochloric acid R* and dilute with the same acid. Dilute 10 ml of the solution to 100.0 ml with the same solvent.

Compensation solution. Solution a 10.3 g/l of *hydrochloric acid R.*

Optical density of the test solution and reference solution was measured at 231 nm wavelength relative to compensation solution.

RESULTS AND DISCUSSION

We had investigated various mobile phases (solvent system) in order to identify the optimal choice of cetirizine hydrochloride investigation by TLC in medicines. The factors of mobility in the studied systems of cetirizine hydrochloride solvents, are listed in Table 1.

Therefore, to identify cetirizine hydrochloride in tablets TLC method could be used. It is established that, the most optimal values of the coefficient of mobility is ob-

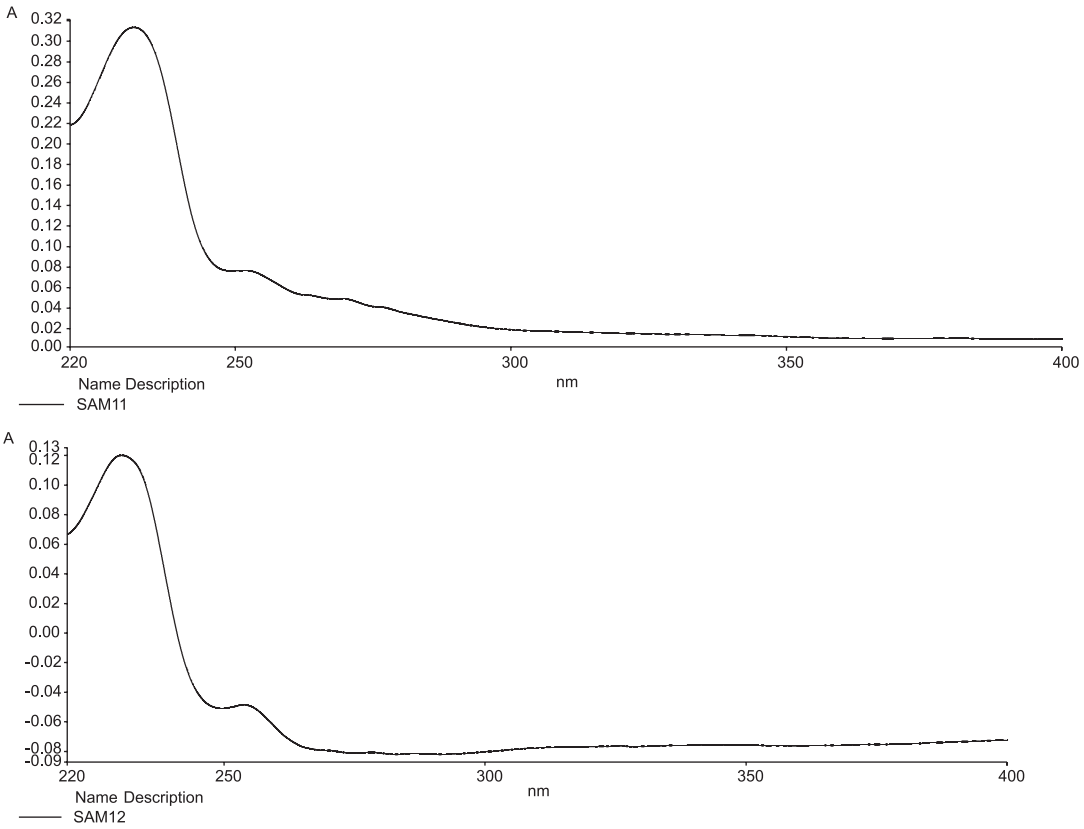


Fig. *Electronic absorption spectra for: 1 – solution from tablets "Allercet" (in 0.1 mol/l solution of hydrochloric acid); 2 – solution standard sample of cetirizine hydrochloride.*

served, when using mobile phase ammonia R – methanol R – methylene chloride R (1:10:90). The limit of detection in this systems, cetirizine hydrochloride solvents is 0.2 micrograms. However, it is express solvent system. Thus, identification of cetirizine hydrochloride in medicines we offer TLC – method using solvent system ammonia R – methanol R – methylene chloride R (1:10:90) and stationary phase – plate "Sorbfil".

According to the SPU and Note for guidance on validation of analytical procedures: text and methodology (CPMP/ICH/381/95) to test the "Identification" must be validated, to determine such characteristics as specificity and suitability of the chromatographic system. To investigate the specificity, it is necessary to confirm the selected mobility of cetirizine hydrochloride system to ensure proper Rf stability of solutions in time. The maximum difference of Rf values in the same plate (for two series of plates) must not exceed the value of 0.02. Originally, plates were tested according to the requirements of SPU on chromatographic resolution.

When checking for the stability of the solution at the time we started chromatography of cetirizine hydrochloride freshly prepared test solution sustained, over time for 30 min. Visual assessment of spots on the size and intensity of staining confirms that they clearly appear as freshly cooked and seasoned in time solutions (for plates of different series). The solutions were stable over time and new areas, had been identified.

Thus, we explored the validation characteristics – specificity and suitability of the chromatographic system that met, the eligibility criteria established by the SPU. The objective of any analytical measurement is to obtain consistent reliable and accurate data. Validated analytical methods plays a major role in achieving this goal. The results obtained from method of validation can be used to judge the quality, reliability and consistency of analytical results. It is an integral part of any good analytical practice. Validation of analytical methods is also required by most regulations and quality standards that impact laboratories. Analytical methods of validation is essential for adherence to Current Good Manufacturing Practice and Good Laboratory Practice regulations. Thus, validation studied characteristics - specificity and suitability of chromatographic systems to meet the eligibility criteria established by the SPU.

We had previously studied the behavior of cetirizine hydrochloride in the UV spectrum using in different solvents (ethanol, purified water, 0.1 mol/l solution of hydrochloric acid). The behavior of cetirizine hydrochloride in the UV spectrum in different solvents showed that all drugs have characteristic absorption bands in the wavelength range (220-360 nm). Thus in various solvents observed different absorption maxima. UV spectrum of cetirizine hydrochloride in all investigated solvents was characterized by the same absorption maximum at 231 ± 2 nm (Fig.). It makes it possible for the use of UV-spectropho-

Table 2

THE RESULTS OF THE DETERMINATION OF THE CONTENT OF CETIRIZINE HYDROCHLORIDE IN MEDICINES

Name of medicine	Company	A_i	$A_{average}$	X_i, mg	X_i, %	Conclusion
"Цетиризин-нортон"	"Unimax Laboratories" для "Norton International Pharmaceutical Inc.", India/Canada	0.562 0.562 0.562	0.562	9.98	99.82	Correct
"Цетиризин ГЕКСАЛ"	"Salutas Pharma GmbH" підприємство компанії "Hexal AG", Germany	0.562 0.564 0.562	0.563	9.99	99.95	Correct
"Allercet"	"Micro Labs Limited", India	0.561 0.561 0.561	0.561	9.96	99.64	Correct

tometry for analysis of cetirizine hydrochloride in medicines. The results of determination of the content of cetirizine hydrochloride in tablets and methrological characteristics are given in tables 2-3.

According to the requirements of the SPU, methods of quantitative determination of drugs must be validated. We studied the following validation characteristics: linearity, accuracy and precision (convergence), robustness and a whole range of applications.

Linearity was determined by the method of least squares within 80-120 % of nominal concentrations of cetirizine hydrochloride. The evaluation was performed linearity across the range of application of the method of standard methods. Study nature, depending on the concentration of the absorbance was performed using 9 model solutions for accurate analysis of sample concentrations: 80, 85, 90, 95, 100, 105, 110, 115 and 120 %. Requirements for the parameters of linear dependence in our case performed on the entire range of application methods (80-120 %). Accuracy and convergence studied by "put-found" on standard solutions of cetirizine hydrochloride. For the measurement and calculation metrological evaluation convergence methodology and accuracy was obtained three values of optical densities for the reference solution and 27 values of optical densities for model solutions. Calculated actual value (*Xi*), the ratio of average values of optical densities for each of 27 solutions to the mean optical density reference solution to give value $Xi = (Ci/Cst) \times 100\ \%$, $Yi = (Ai/Ast) \times 100\ \%$, and as the value of $Zi = (Yi/Xi) \times 100\ \%$, which is found concentration as a percentage of the administered [5-8].

Thus, developed spectrophotometric method of quantitative determination of cetirizine hydrochloride in tablets containing cetirizine hydrochloride. Carried out its partial validation, namely investigated specificity, linearity, range, accuracy (convergence) and accuracy. Since executed eligibility criteria concerning the validation of these characteristics according to the requirements of SPU, the method can be used for the determination of cetirizine hydrochloride in tablets.

Table 3

RESULTS THE STATISTICALLY PROCESSED OF METROLOGICAL CHARACTERISTICS

Metrological characteristics	Critical values	The obtained values
Linearity		
Angular coefficient of linear relationship, b		0.9954
S_b		0.0067
Free member linear relationship, a	a, % = 3.8	0.5256
S_a		0.8816
Correlation coefficient, r	R_o = 0.9957	0.9998
Accuracy and convergence		
The arithmetic mean, %		100.07
The relative standard deviation, S_z%		0.2561
Relative confidence interval, Δ_z%	Δ_{As} % = 2.4	0.4762
The criterion of statistical insignificance systematic error, δ%	δ% = 0.4762	0.07
General conclusion of method		Correct

CONCLUSIONS

We developed and validated simple, accurate, rapid and economical methods of identification and quantification of cetirizine hydrochloride in medicines, which can be used for improving methods of quality control.

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РАЗРАБОТКА МЕТОДИКИ ОПРЕДЕЛЕНИЯ ЦЕТИРИЗИНА ГИДРОХЛОРИДА В ЛЕКАРСТВЕННЫХ СРЕДСТВАХ

Разработаны методы идентификации и количественного определения цетиризина гидрохлорида в лекарственных средствах. Изучены валидационные характеристики с помощью стандартного метода идентификации и количественного определения. Методика предполагает использование более быстрого, достоверного, точного, менее затратного способа идентификации и количественного определения цетиризина гидрохлорида в лекарственных средствах.

Ключевые слова: цетиризина гидрохлорид; тонкослойная хроматография; УФ-спектрофотометрия; валидация

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РОЗРОБКА МЕТОДИКИ ВИЗНАЧЕННЯ ЦЕТИРИЗИНУ ГІДРОХЛОРИДУ В ЛІКАРСЬКИХ ЗАСОБАХ

Розроблені методи ідентифікації і кількісного визначення цетиризину гідрохлориду в лікарських засобах. Вивчені валідаційні характеристики за допомогою стандартного методу ідентифікації і кількісного визначення. Методологія передбачає використання більш швидкого, достовірного, точного, менш витратного способу ідентифікації і кількісного визначення цетиризину гідрохлориду в лікарських засобах.

Ключові слова: цетиризину гідрохлорид; тонкошарова хроматографія; УФ-спектрофотометрія; валідація

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