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METHODS FOR EVALUATING THE QUALITY AND QUANTITATIVE INDICATORS OF "CLARIN" TABLETS COVERED WITH A COATING

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ABSTRACT

This article analyzes the main approaches to assessing the quality indicators of "Clarin" 250 mg and 500 mg coated tablets. The appearance, purity, disintegration time, solubility, average mass, amount of impurities, quantitative composition, and microbiological purity of the preparations were comprehensively studied. The results obtained showed that the use of modern analytical methods and standard samples is important for accurate quality assessment. At the same time, the studies have provided the necessary practical and theoretical basis for further improving the requirements for tablet dosage forms and scientifically justifying regulatory documents.

Relevance of the topic. Today, when the incidence of infectious diseases is increasing, drugs with antibacterial activity are the main choice for treating these diseases. Bacterial infections have been a serious threat to human health and life for years [1].

The discovery of antibiotics not only ushered in a new era of treatment, but also led to improved quality of life for millions of people and a reduction in deaths due to possible complications [2].

Inappropriate dosing of antibiotic tablets can lead to reduced therapeutic efficacy and the development of antibiotic resistance [6].

In this regard, the development and improvement of modern approaches to assessing the quality indicators of antibiotic tablet dosage forms, as well as a thorough study of the scientific basis for the use of standard samples, is an urgent issue. In this process, the physicochemical and pharmacotechnological parameters of tablets, such as disintegration, solubility, quantitative content, dose uniformity, and microbiological purity, are important [3,4,6].

This study analyzed the methods for evaluating the quality indicators of antibiotic-coated tablet dosage forms and the importance of using standard samples. The results of the research are of significant theoretical and practical importance for determining modern requirements for the quality of antibiotic tablets, improving them, and scientifically substantiating regulatory documents.

Research objective. The main purpose of this study is to carry out a

comprehensive assessment of the quality indicators of clarithromycin storage tablets 250 mg and 500 mg in composition, covered with a shell under the trade name “Clarin”, produced by Novugen Pharma, based on Pharmacopoeia requirements[7,9].

Clarithromycin belongs to the macrolide antibiotic group and is a broad-spectrum semi-synthetic derivative of erythromycin. It is used to treat streptococcal pharyngitis, pneumonia, skin and soft tissue infections, Helicobacter pylori-related diseases, and Lyme disease. Therefore, the clinical significance of this drug requires a reliable assessment of its quality, safety, and efficacy [6].

Within the framework of the study, the main quality indicators of “Clarin” shell-coated tablets were found, including appearance, validity, average mass and deviation from it, microbiological purity, quantitative composition, decay time, solubility, dose uniformity [5,7,8].

The obtained results were evaluated in accordance with the requirements of the State Pharmacopoeia of the Republic of Uzbekistan, 1st edition, and it was determined that the quality indicators of the drug comply with the requirements of the current regulatory documents.

Indicators of microbiological purity, fragmentation and authenticity (identification) of shell-coated “Clarin” tablets were determined with the participation of qualified specialists in the laboratory of “quality control and standardization of medicines” of the state institution “Center for the safety of pharmaceutical products” under the Ministry of health of the Republic of Uzbekistan.The results are presented in Table 1.

Based on the results of the study, the appearance of the 250 mg and 500 mg tablets was visually evaluated. The tablet samples were found to be round, biconvex in shape, coated, and white in color. It was observed that the tablets had the mark "53" on one side and "N" on the other.

Table 1.

Results of the qualitative and quantitative analysis of the “Clarin” tablets coated with a shell

Studied indicators	Requirements according to the regulatory document	Result of the analysis	
		250 mg	500 mg
Appearance	250 mg tablets are round, biconvex, white or almost white, film-coated tablets with the inscription “53” on one side and “N” on the other. 500 mg tablets are round, biconvex, white or almost white, coated with a film coating, with the inscription “54” on one side and “N” on the other.	It matches	It matches
Validity	The retention time of the main peak in the chromatogram of the test solution obtained during the quantitative analysis should be the same as the retention time of the corresponding peak in the chromatogram of the standard solution (HPLC)	It matches	It matches

Decomposi-tion	Not more than 30 minutes	5 min, 9 sec	7 min, 5 sec
Dissolution	Clarithromycin tablets should dissolve at least 75% in a phosphate buffer medium with a pH of 6.8 for 45 minutes.	97,72%	96,91%
Average weight and deviation from it	For 250 mg dosage tablets, the average mass was 495.0 mg, with an allowable deviation of ±5% (470.3–519.8 mg). For 500 mg dosage tablets, the average mass was 750.0 mg, with an allowable deviation of ±5% (712.5–787.5 mg).	494,5± 2,39%	750± 3,76%
Impurities	The amount of any individual impurity must not exceed 1.0%. The total amount of impurities must not exceed 3.5%..	It matches	It matches
Microbiolo-gical purity	In 1 g of the preparation, the total number of aerobic mesophilic microorganisms (TAMC) must not exceed 10^3 CFU. The total number of yeasts and molds (TYMC) must not exceed 10^2 CFU. In addition, pathogenic microorganisms such as *Escherichia coli*, *Salmonella spp.*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* must not be detected in the preparation.	It matches	It matches
Loss on drying	Not more than 2.0 %	1,04%	1,05%
Quantitative analysis	When determined using the HPLC method, the content of the active substance must be within the permitted limits of the specified value (usually 90.0–110.0%).	101,12%	104,45%

The purity of clarithromycin was determined by high-performance liquid chromatography (HPLC) (State Pharmacopoeia of the Republic of Uzbekistan, 2.2.29). It was noted that the retention time of the main peak of clarithromycin observed in the chromatogram of the test solution obtained during the quantitative analysis corresponded to the retention time of the corresponding peak in the chromatogram of the working standard solution [6].

The average mass and deviation of the “Clarin” tablets coated with a shell were evaluated based on the requirements of the pharmacopoeia. According to the results of the study, the average mass for tablets with a dose of 250 mg was 494.5 mg, with a relative deviation of ±2.39%; these values were noted to be in the permissible ±5% (470.3–519.8 mg) range.

For tablets with a dose of 500 mg, however, the average mass was 750.0 mg with a relative deviation of ±3.76%; these results were also observed at the permissible limit of ±5% (712.5–787.5 mg).

The obtained results comply with the requirements of the State

Pharmacopoeia of the Republic of Uzbekistan (O'zR DF 2.9.5).

The disintegration time of the "Clarin" tablets coated with a shell was determined in a disintegration apparatus at a temperature of 37 ± 0.5 °C, in accordance with the requirements of the State Pharmacopoeia of the Republic of Uzbekistan (UzR DF 2.9.1).

According to the research results, 250 mg tablets completely disintegrated in 5 minutes and 9 seconds, while 500 mg tablets disintegrated in 6 minutes and 56 seconds. These results were found to be within the established limit for film-coated tablets (not exceeding 30 minutes).

The content of heavy metals in "Clarin" tablets coated with a shell was assessed using the sulfate ash method. When the residue from 1 g of the drug was tested for the presence of heavy metals, it was found that their content did not exceed 0.001%, in accordance with the requirements of the State Pharmacopoeia of the Republic of Uzbekistan.

The determination of impurities was performed using the high-performance liquid chromatography (HPLC) method. All solutions used in the analysis were freshly prepared or, when necessary, stored at 2–8 °C for no longer than 24 hours.

The microbiological purity of film-coated "Clarin" tablets was evaluated in accordance with the requirements of the State Pharmacopoeia of the Republic of Uzbekistan. According to the study results, in 1 g of the preparation, the total aerobic microbial count (TAMC) did not exceed 10^3 CFU, and the total combined yeasts and molds count (TYMC) did not exceed 10^2 CFU [7].

Also in the drug Escherichia coli, Salmonella spp., No pathogenic microorganisms such as Staphylococcus aureus and Pseudomonas aeruginosa were detected.The results obtained confirm that the microbiological purity of the drug is fully consistent with the established Pharmacopoeia standards.

The amount of the active substance, clarithromycin, in film-coated "Clarin" tablets was determined in accordance with the requirements of the State Pharmacopoeia of the Republic of Uzbekistan (UzR SP 2.2.29) using high-performance liquid chromatography (HPLC) [7].

In the analysis process, test and standard solutions were prepared and evaluated in the chromatographic system by comparing their peak areas. The preparation of the solutions was carried out in accordance with the relevant methodology.

Preparation of buffer solution (pH 4.0): for the quantitative analysis of clarithromycin, a buffer solution with a pH of 4.0 was prepared as follows. A precisely weighed 9.12 g of potassium dihydrogen phosphate was transferred into a 1000 mL volumetric flask. Approximately 800 mL of purified water was added, and the mixture was treated in an ultrasonic bath until the substance was completely dissolved.

After that, the volume of the solution was reached to the mark line with purified water and thoroughly mixed. The pH environment of the solution was precisely adjusted to 4.0 using orthophosphoric acid. The prepared buffer solution was filtered

through a 0.45 μm membrane filter and prepared for chromatographic analysis.

Preparation of the mobile phase: the mobile phase consisted of a buffer solution with pH 4.0 and methanol mixed in a ratio of 35:65 (v/v) (350 mL of buffer and 650 mL of methanol). The prepared mixture was thoroughly homogenized and degassed in an ultrasonic bath for 2 minutes to remove dissolved gases. If necessary, the solution was filtered through a 0.45 μm membrane filter to ensure the stability of the chromatographic system.

Preparation of the diluent and standard solutions: methanol was used as the diluent. Standard solutions for “Clarin” film-coated tablets with doses of 250 mg and 500 mg were prepared in accordance with the relevant methodology.

Preparation of Standard Solution–1 (~2500 ppm):

Approximately 62.5 mg of a standard sample of clarithromycin (accurately weighed) was placed in a 25 mL volumetric flask. Methanol was added to the mixture, and the solution was treated in an ultrasonic bath for 5 minutes to ensure complete dissolution of the substance (the temperature during the ultrasonic process was controlled not to exceed 25 °C).

After that, the volume of the solution was brought to the mark line with methanol and thoroughly mixed. The result was a standard solution with a concentration of approximately 2,500 ppm.

Preparation of Standard Solution–2:

5 mL of Standard Solution–1 was accurately measured using a volumetric pipette and transferred into a 25 mL volumetric flask. The solution was then diluted to the mark with the mobile phase and thoroughly mixed. As a result, Standard Solution–2 with the working concentration was obtained.

Preparation of test solutions (for 250 mg tablets):

Test solution–1 (~5000 ppm): for analysis, 5 coated "Clarin" tablets were weighed with analytical precision and placed in a 250 ml dry measuring flask. 100 ml of methanol was added to the mixture and mixed for 20 minutes using a magnetic stirrer.

Afterwards, the solution volume was made up to the mark with methanol and treated in an ultrasonic bath under intermittent shaking conditions for 20 minutes (the temperature was strictly controlled not to exceed 25 °C). The resulting solution was then centrifuged at 5000 rpm for 10 minutes, and a clear supernatant was collected.

The standard solution was taken using a 1 to 5 ml graduated pipette and transferred to a 25 ml volumetric flask. The solution was then brought to the mark line with the mobile phase and mixed thoroughly.

Preparation of test solutions (for 250 mg tablets):

Test solution–1 (~5000 ppm): for analysis, 5 coated “Clarin” tablets were weighed with analytical precision and placed in a 250 ml dry measuring flask. 100 ml of methanol was added to the mixture and mixed for 20 minutes using a magnetic stirrer.

After that, the volume of the solution was brought to the mark line with methanol and processed in an ultrasonic bath under intermittent

shaking conditions for 20 minutes (the temperature was controlled not to exceed 25 °C). The resulting solution was centrifuged at 5000 rpm for 10 minutes to obtain a clear supernatant solution.

To prepare the test solution–2 (~500 ppm), 5 ml of the clear supernatant solution obtained after centrifugation was taken using a clear pipette and transferred to a 50 ml volumetric flask. Then the solution was brought to the mark line with the mobile phase and mixed well.

Preparation of test solution–1 (~5000 ppm) (for 500 mg tablets):

For analysis, 5 coated "Clarin" tablets were weighed with analytical precision and placed in a 500 ml dry measuring flask. 200 ml of methanol was added to the mixture and mixed for 20 minutes using a magnetic stirrer.

After that, the volume of the solution was brought to the mark line with methanol and processed in an ultrasonic bath under intermittent shaking conditions for 20 minutes (the temperature was strictly controlled not to exceed 25 °C). The resulting solution was centrifuged at 5000 rpm for 10 minutes to obtain a clear supernatant solution. The resulting solution was also centrifuged at 5000 rpm for 10 minutes to obtain a clear supernatant solution.

Preparation of test solution–2 (~500 ppm):

After centrifugation, 5 ml of the clear supernatant was taken using a clear pipette and transferred to a 50 ml volumetric flask. Then the solution was brought to the mark line with the mobile phase and mixed well.

The analysis was performed using high-performance liquid chromatography (HPLC). The separation process was carried out in an inertial type (150 × 4.6 mm, 5 µm) colon or in a colon with an alternative property to it. The flow rate of the moving phase was set at 0.8 ml/min.

The detection was carried out in the ultraviolet (UV) field at a wavelength of 205 nm. The volume of sending the sample to the system was 20 µl. During chromatographic separation, the column temperature was held at 50 °C and the sample temperature at 25 °C. The analysis was carried out in an isocratic mode, that is, with the moving phase content kept constant [7].

Procedure:

As part of the solubility (dissolution) analysis, the chromatographic system was first injected with a single injection of the dissolution medium (blank solution). The standard solution was then injected five times in succession and the system's suitability was assessed.

In the next step, the solution of the test drug was injected into the chromatographic system in a single injection, and the results obtained were analyzed by comparing them with standard solutions.

Calculation (for 250 mg tablets):

The amount of clarithromycin in the capsule was calculated as a percentage based on the following formula:

$$X\frac{At \cdot m0 \cdot 5 \cdot 250 \cdot 50 \cdot P}{As \times 25 \times 25 \times N \times 5 \times LC}$$

Calculation (for 500 mg tablets):

The content of clarithromycin in the tablet was calculated in percentages based on the following formula:

$$X\frac{At \cdot m0 \cdot 5 \cdot 500 \cdot 50 \cdot P}{As \times 25 \times 25 \times N \times 5 \times LC}$$

At – the average area of the clarithromycin peak in the test solution chromatogram;

As – average area of the clarithromycin peak in the working/reference standard solution;

t_0 – mass (mg) of clarithromycin standard taken to prepare the standard solution;

P – standard sample the quantitative proportion of clarithromycin in the composition (%);

LC – the amount of clarithromycin in the tablet (mg) (250 mg or 500 mg);

N – the number of pills taken for analysis;

According to the results of the quantitative analysis, the amount of active substance in the “Clarin” tablets coated with a shell was found to be within the specified normal range of 90.0–110.0%.

In addition, according to the results of the solubility (dissolution) analysis, the dissolution rate of the drug exceeded the specified requirement of at least 75%. In particular, the solubility for 250 mg tablets was 97.2%, and for 500 mg tablets it was 91.62%. The results obtained confirm that the quality indicators of the drug fully meet the requirements of the current pharmacopoeia [8].

After the quantitative analysis of the clarithromycin drug substance was performed at the next stage of the study, the metrological characteristics of the analytical method used were evaluated. The main purpose of this evaluation is to scientifically justify the accuracy, repeatability, and reliability of the method.

At this stage, the accuracy of the method was assessed, as well as the reproducibility and sensitivity of the tablets of clarithromycin 250 mg and 500 mg, and the stability of the results obtained was thoroughly analyzed. At the same time, the compliance of the method with the validation requirements and criteria established in accordance with current international standards was also determined.

The results are presented in Table 2.

According to the analysis results, the quantitative analysis of clarithromycin in 250 mg and 500 mg tablets was performed by high-performance liquid chromatography (HPLC). The results obtained were evaluated based on 5 parallel determinations (n = 5).

Table 2.

Quantitative analysis results of 250 mg and 500 mg film-coated tablets of "Clarin" (n = 5)

250 mg film-coated tablets "Clarin"		
Drawer, mg	**The determined amount of clarithromycin is % (250 mg).**	**Metrological description**
495,2	101,12	X_{sr}= 101,1200 f=4, T (95%, 4) =2,7800
497,8	98,200	

498,0	102,27	S^2=3,1715, S=1,7809 S_x=0,7964, R=4,5200 ΔX=4,9508, ΔX_{med} =2,2141 Eps=4,9 Eps_{med}=2,20
496,9	100,05	
503,1	103,34	
500 mg film-coated tablets «Clarin»		
Drawer, mg	**The determined amount of clarithromycin is % (500 mg).**	**Metrological description**
745,0	101,9	X_{sr}=104,45 f=4, T (95%, 4) =2,09 S^2=3,5325, S=1,8795 Sx=0,8405 R=4,500, ΔX=5,2250, ΔX_{med} =2,3367 Eps=5,0 Eps_{med} =2,24
758,1	104,6	
745,7	103,4	
748,5	106,4	
752,6	106,10	

The results showed that the deviation in the 250 mg and 500 mg film-coated tablets of Clarin was 2.2% and 2.24%, respectively. These indicators indicate that the amount of clarithromycin is within the established standards, confirming the satisfactory quality of the proposed drug.

Analyses showed that this indicator was at least 2.0% higher than the established standard for clarithromycin, and the results obtained fully met current requirements [8].

Conclusion: The results of quality control conducted in accordance with the requirements of the State Pharmacopoeia of the Republic of Uzbekistan confirm the safety, efficacy and stability of 250 mg and 500 mg film-coated tablets of "Clarin". The results obtained showed that the main quality indicators of the drug fully comply with the requirements of current regulatory documents, which in turn ensures its therapeutic effectiveness.

Based on the results of the study, a pharmacopoeial article for 250 mg and 500 mg film-coated tablets of "Clarin" was developed and approved.

At the same time, scientifically based and accurate assessment of quality indicators is important in guaranteeing product quality during the pharmaceutical manufacturing process.

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