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MULTIDISCIPLINARY CONTEXT OF RESEARCH OF A NEW DRUG IN INFECTIOUS AND INFLAMMATORY DISEASES

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Introduction. In emergency situations, in conditions of armed conflict, there are risks that cause the spread of infectious diseases. Among the risks: overcrowding, poor hygienic conditions, stress, weakened immune system, lack of, or limited medical and pharmaceutical care. Infectious diseases create a burden on the health care system in countries around the world. Thus, the spread of the COVID-19 coronavirus in the world caused risks in the organization of pharmacotherapy of covid, post-covid and long-covid disorders [1], depressive disorders [2], hepatitis [3]. An innovative multidisciplinary study of the availability of coronavirus vaccines in the world was conducted [4].

At the beginning of the epidemic, there were no clinical protocols for treatment [5]. In particular, Italy was one of the first Western countries to be seriously affected [6]. To remedy the situation, several volunteer groups of doctors and pharmacists were created. It was possible to promptly cure thousands of patients at home with the help of nonsteroidal anti-inflammatory drugs, vitamins, and antioxidants. Such pharmacotherapy regimens have not been documented in any randomized controlled trials. However, they were based on available evidence. They were aimed at solving unsatisfied basic needs of patients. Led to a significant reduction in the number of hospitalizations, duration of symptoms and full recovery from coronavirus disease. According to research, daily intake of paracetamol and ascorbic acid (vitamin C) or ibuprofen and ascorbic acid may be a simple way to prevent contracting COVID-19 [7].

According to medicine and pharmacy, paracetamol as an analgesic and antipyretic drug is widely used in Italy to reduce fever and pain in viral, cold, and infectious diseases. However, the anti-inflammatory effect of paracetamol is insignificant. Paracetamol is metabolized by glutathione consumption and may worsen oxidative stress. This type of biochemical change can reduce antiviral defenses or worsen the disease course, especially in patients with liver dysfunction [8].

According to pharmacology, proven that ascorbic acid prevents and alleviates viral and bacterial infections. In critically ill patients, the level of ascorbic acid in the plasma is usually very low. Gram doses of vitamin C are necessary to raise the level of ascorbic acid in the plasma of critically ill patients to the level of normal healthy people. Ascorbic acid also reduces the duration of mechanical ventilation in patients in the intensive care unit, reducing mortality in patients with sepsis [9].

While waiting for drugs that solve the problem, the complexity of the dynamic changes of viral diseases requires a multidisciplinary approach. Therefore, the pharmaceutical development of new drugs for pharmacotherapy of infectious and inflammatory diseases based on combinations of evidence-selected pharmacological substances is relevant and necessary.

The goal is to develop a multidisciplinary research context of a new drug for infectious and inflammatory diseases based on a combination of evidence-selected pharmacological substances paracetamol and ascorbic acid.

Materials and methods. The multidisciplinary context of the study included the competencies of the organization of pharmacy, medicine, pharmacology, forensic pharmacy, and pharmaceutical analysis [10]. Research was conducted in the period from 2020 to 2023. The pharmaceutical development of the drug was conducted at the Department of General and Clinical Pharmacy of the Kharkiv Medical Academy of Postgraduate Education (period 2012-2020). Experience in the pharmaceutical development of new drugs based on combinations of evidence-selected pharmacological substances is taken into account [11, 12]. Organizational, documentary, social studies of the drug paracetamol + ascorbic acid were conducted at the Private Scientific Institution "Scientific and Research University of Medical and Pharmaceutical Law". An experimental batch of the drug paracetamol + ascorbic acid was produced on the basis of central district pharmacy in Kharkiv the region and European academy of digital medical technologies in Kyiv. Physical and chemical studies were conducted on the basis of the laboratory of the State Enterprise "Ukrainian Scientific Pharmacopoeia Center for the Quality of Medicinal Products" and the laboratory for the analysis of the quality of medicinal products of the Lik-pharma in the Kharkiv region. Quality control was carried out taking into account the relevant international and national requirements [13-20].

Quality control of paracetamol + ascorbic acid tablets included determination of para-aminophenol admixture in these tablets (Sample 1); release of paracetamol and ascorbic acid from tablets (Sample 2); quantitative determination of paracetamol (Sample 3); quantitative determination of ascorbic acid (Sample 4).

Sample 1. Determination of para-aminophenol admixture

Paracetamol substance contains free para-aminophenol as an impurity. Determination of para-aminophenol was

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carried out by the spectrophotometric method. It is based on the interaction of para-aminophenol with sodium nitroprusside with the formation of a colored product and measurement of the optical density at 710 nm. About 0.55 g (exact weight) of the powder of crushed tablets was shaken for 10 minutes with 20 ml of a mixture of methyl alcohol and chloroform (1:1). It was filtered into a volumetric flask with a capacity of 25 ml. The precipitate on the filter was washed with 1 ml of this mixture. The volume of the solution was adjusted to the mark with chloroform. Then they stirred; 1 ml of the resulting solution was transferred to a volumetric flask with a capacity of 25 ml. Evaporated to dryness in a water bath. 20 ml of a mixture of methyl alcohol-water (1:1) and 1 ml of sodium nitroprusside solution were added to the dry residue. The volume of the solution was brought up to the mark with water, moved. After 30 min, the optical density of the test solution and the solution of the working standard sample of para-aminophenol (prepared similarly) were measured on a spectrophotometer at a wavelength of 710 nm in a cuvette with a layer thickness of 10 nm. As a solution for comparison, a control solution was used. In the future, quantitative determination of para-aminophenol admixture in tablets was carried out by the standard method. The determined concentration of para-aminophenol was about 1.25 μg/ml. The concentration of para-aminophenol was selected so that the drug under study and the solution of the standard sample contained approximately 0.5% of para-aminophenol (from the content of paracetamol in one tablet). A ratio of optical densities close to unity was achieved. Technical para-aminophenol, which was purified by sublimation, was taken as a standard. For this, the evaporating cup with para-aminophenol in a sand bath was covered with an evaporating cup of a larger diameter, the convex side of which was turned inward relative to the first one. After sublimation, ice was used to obtain para-aminophenol crystals. Crystals were collected in boxes. Stored in a place protected from light. The method of quantitative determination of para-aminophenol in tablets was tested on model mixtures of the drug, both with para-aminophenol additives (from the maximum content to the lowest) and without them.

The content of para-aminophenol in one tablet of the drug under study, in percent (X), was calculated according to the following formula:

$$x = \frac{D1 \times m \times 25 \times 25 \times B \times 100}{D0 \times m1 \times 100 \times 25 \times 25 \times C} = \frac{D1 \times m \times B}{D0 \times m1 \times C},$$

where D1 – optical density of the tested solution of paracetamol + ascorbic acid tablets;

Do – optical density of the solution of the working standard sample of para-aminophenol;

m – weight of the working standard sample of para-aminophenol, g;

m1 – weight of paracetamol + ascorbic acid preparation, g;

B – average weight of 1 tablet of paracetamol + ascorbic acid, g.

C – content of paracetamol in one tablet (must be at least 75% of 0.09-0.11 grams, based on the average weight of one tablet of the tested drug paracetamol + ascorbic acid).

Sample 2. Release of paracetamol and ascorbic acid from tablets

The release of paracetamol and ascorbic acid was carried out in water and hydrochloric acid using different volumes for their dissolution on a rotating basket type device. The solution of paracetamol and ascorbic acid was carried out for 30 minutes. Samples for analysis were taken every 10 minutes.

Sample 3. Quantitative determination of paracetamol

One tablet was placed in a dry basket. Every 30 minutes, a sample of the solution was taken and filtered through a dense paper filter, discarding the first portions of the filtrate of 1 ml of filtrate was placed in a volumetric flask with a capacity of 100 ml. The volume of the solution was brought up to the mark with 0.1 M sodium hydroxide solution. The optical density of the resulting solution and the solution of the working standard sample of paracetamol was measured on a spectrophotometer at a wavelength of 257 nm in a cuvette with a layer thickness of 10 mm. A solution of 0.1 M sodium hydroxide was used as a comparison solution. The amount of paracetamol should be in the range of at least 75% from 0.09 to 0.11 grams, based on the average weight of one tablet.

Sample 4. Quantitative determination of ascorbic acid

2 ml of a 2% solution of hydrochloric acid, 0.5 ml of a 1% solution of potassium iodide, 1 ml of a starch solution were added to 100 ml of the obtained filtrate and titrated with a 0.1 solution of potassium iodate until a stable blue color appeared, 1 ml of 0.1 M potassium iodate solution corresponds to 0.008806 g of ascorbic acid. The amount of ascorbic acid should be at least 75% from 0.09 to 0.11 grams, based on the average weight of one tablet of the drug under study.

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and “Pharmaceutical and medical law: integrated approaches to the system of drug circulation from the standpoint of forensic pharmacy and organization of pharmaceutical business” (state registration number 0121U000031, terms 2021-2026); Petro Mohyla Black Sea National University on the topic “Conceptual interdisciplinary approaches to the drug circulation system, taking into account organizational and legal, technological, biopharmaceutical, analytical, pharmacognostic, forensic and pharmaceutical, clinical and pharmacological, pharmacoeconomic, pharmacotherapeutic aspects” (state registration number 0123U100468, implementation period 2023-2028); Luhansk State Medical University “Conceptual interdisciplinary approaches to pharmaceutical provision and availability of drugs, taking into account organizational and legal, technological, analytical, pharmacognostic, forensic and pharmaceutical, clinical and pharmacological, pharmacoeconomic, marketing, social and economic competencies” (state registration number 0123U101632, terms 2023-2027).

Results and discussion

Organizational, documentary, technical and economic study, substantiation of the composition of the drug was carried out taking into account evidence-selected data of clinical pharmacology, medicine, pharmacy on paracetamol and ascorbic acid. Considered that the common cold is a common disease in the Northern Hemisphere between late autumn and early spring. Patients often turn to the pharmacy for pharmaceutical care. Pharmacists in Poland recommended drugs containing paracetamol in four out of five cases. Pharmacists' recommendations were based on patient symptoms, product price, pharmaceutical company promotion, and financial incentive. Pharmaceutical care was not always of high quality [21].

Another study found that paracetamol remains the preferred option for pharmacotherapy of mild to moderate acute pain in healthy adults, elderly patients with health problems, patients with gastrointestinal disorders, renal impairment, and cardiovascular disease. To avoid hepatotoxicity, it is necessary to take into account the individual dosage of paracetamol. Paracetamol can potentiate the analgesic effect of opioids without increasing the risk of side effects [22].

Another study found that combinations of paracetamol, ciprofloxacin and ascorbic acid are often used for pain relief. However, excessive use of drug combinations can lead to serious liver and kidney dysfunction [23].

Proven that an overdose of paracetamol is the main cause of medicinal hepatotoxicity. Antioxidants such as ascorbic acid reduce the hepatotoxicity of paracetamol [24].

Acetaminophen (paracetamol) is a derivative of para-aminophenol. It is metabolized in the liver to glucuronide and sulfate conjugates. Ascorbic acid (Vitamin C) plays an important physiological role in cells as a reductant, antioxidant, and absorber of free radicals. Ascorbic acid restores the functions of hepatocytes. Ascorbic acid in combination with paracetamol is an active hepatoprotector [25].

Currently, in Ukraine, paracetamol-based drugs are practically the only means of symptomatic pharmacotherapy of hyperthermic conditions and fever. According to pharmacy data, the raw material base, production in pharmacies and pharmaceutical enterprises of paracetamol + ascorbic acid tablets is economically expedient, socially oriented in the conditions of a military conflict. According to pharmacology, paracetamol helps lower body temperature, reduces pain and discomfort. Ascorbic acid (Vitamin C) exhibits antioxidant properties, supports the immune system. The combination of paracetamol + ascorbic acid exhibits antipyretic, analgesic, antitoxic and antioxidant properties. It helps to improve the general condition and strengthen the protective functions of the body. According to medical data, the drug is intended for pharmacotherapy of infectious and inflammatory diseases, acute respiratory viral infections. The composition of the new combination of paracetamol + ascorbic acid per 1 tablet: paracetamol – 0.33 grams; acid – 0.2 grams. According to the results of a technological study, the disintegration time of paracetamol + ascorbic acid tablets does not exceed 11 minutes. The average mass of one tablet deviates from the nominal in the range of 0.3375-0.3675, which is ± 5%. The analysis of the experimental series of paracetamol + ascorbic acid tablets showed that the average weight of one tablet is within acceptable limits. Durability to abrasion is at least 97%.

According to the results of the determination of para-aminophenol admixture in the tested tablets, it was established that paracetamol under the conditions of the reaction does not interfere with the determination of para-aminophenol. Preparation of para-aminophenol from the powder of crushed tablets was carried out with methyl alcohol. Paracetamol and para-aminophenol dissolve easily, ascorbic acid dissolves poorly. Addition of chloroform reduces the solubility of ascorbic acid. The amount of ascorbic acid passed into the solution does not affect the determination of para-aminophenol. The dependence of the optical density of the product of the interaction of para-aminophenol with sodium nitroprusside on the concentration is linear (Fig. 1). When using the method of quantitative determination of para-aminophenol in the studied tablets in comparison with model mixtures of the studied drug, established that when the maximum content of para-aminophenol was introduced into the tablet mass, the spectra of the solution of the working standard sample of para-aminophenol and the solution of the model mixture of paracetamol +

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ascorbic acid tablets coincided (Fig. 2). When determining para-aminophenol in experimental series of tablets, it was found that para-aminophenol admixture is absent both in newly produced series and in tablets that have been stored for two years. The normalized content of para-aminophenol was no more than 0.1

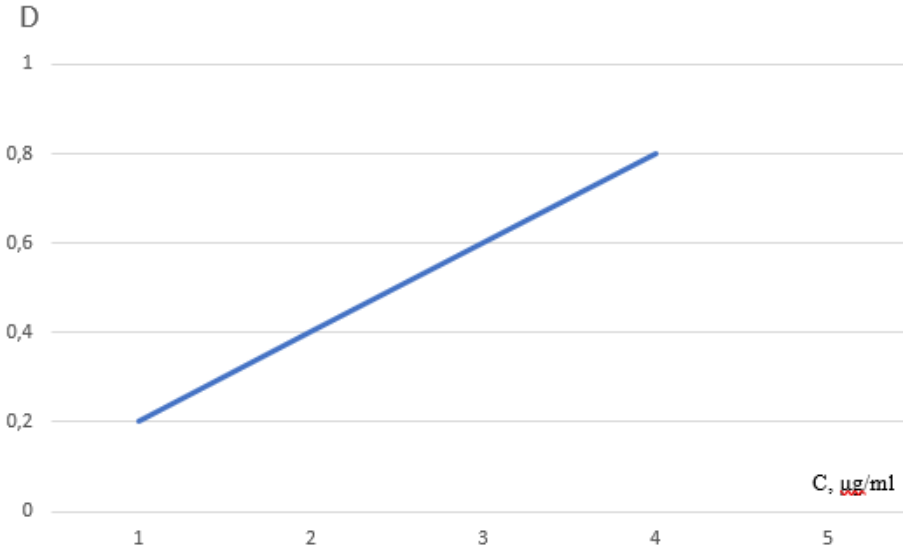

Fig. 1. Dependence of the optical density (D) of the product of the interaction of para-a C, µg/ml **h sodium nitroprusside on the concentration of para-aminophenol (C).**

%, which meets the requirements of quality control.

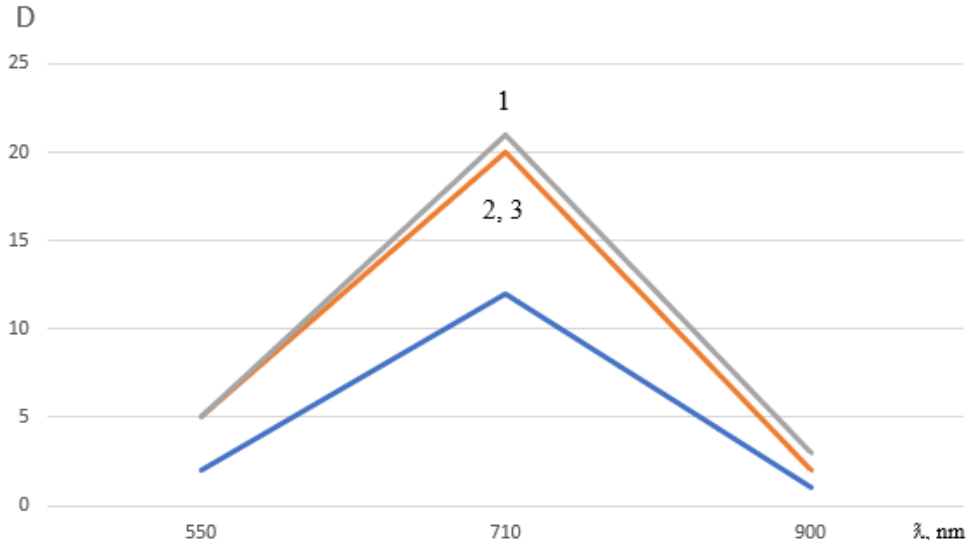

Fig. 2. Absorption spectra of the product of the interaction of para-aminophenol with sodium nitroprusside:
1 – a solution of a standard sample of para-aminophenol (C=1.25 µg/ml);
2 – a solution of paracetamol, which contains 1.25 µg/ml of para-aminophenol; λ, nm
3 – a solution of a model mixture of paracetamol + ascorbic acid tablets, which contains 1.25 µg/ml of para-aminophenol;
4 – a solution of the studied paracetamol + ascorbic acid tablets, artificially decomposed.

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On the basis of the obtained data on the control of the release of the studied active substances, proved that the optimal solvent is water in a volume of 200 ml. The results of the study shown in Fig. 3. It can be seen that the amount of paracetamol and ascorbic acid that passed from the tablet into the water in 30 minutes at a speed of rotation of the basket of 100 rpm were at least 75% of the nominal amount of each of the components.

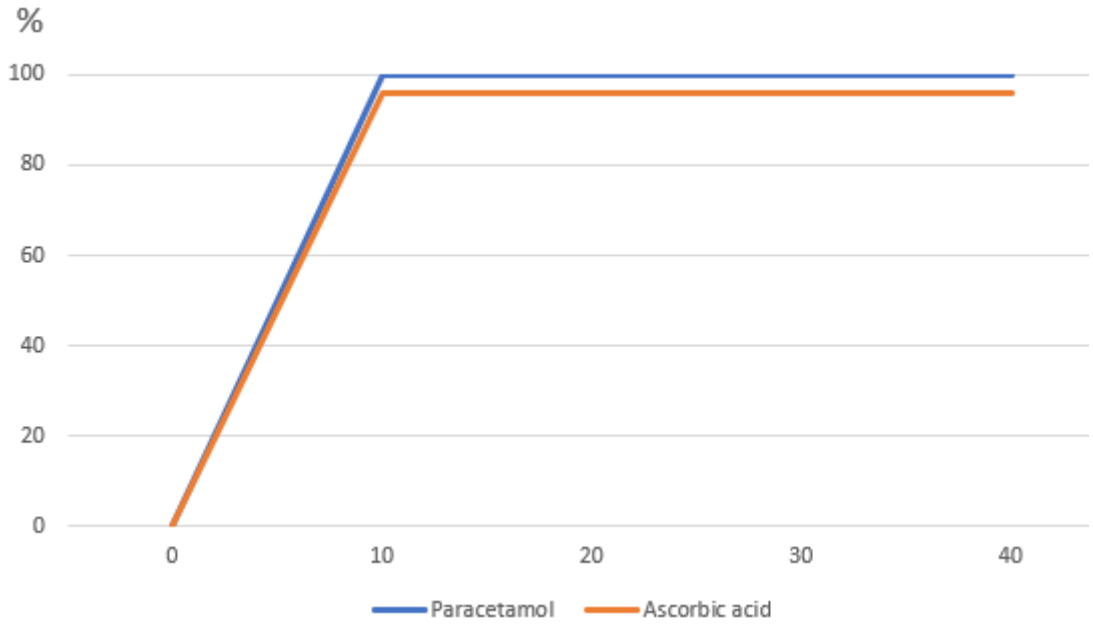

Fig. 3. Release of paracetamol and ascorbic acid from the studied tablets.

The quantitative determination of paracetamol, in percentage (X), was calculated according to the following formula:

$$x = \frac{D1 \times mst \times 100 \times 200 \times 100}{D0 \times 200 \times 100 \times C} = \frac{D1 \times mst \times 100}{D0 \times C},$$

where D1 – optical density of the tested solution of paracetamol + ascorbic acid tablets;

Do – optical density of the solution of the working standard sample of paracetamol;

mst – weight of the working standard sample of paracetamol, g;

C – nominal content of paracetamol in 1 tablet of the tested drug paracetamol + ascorbic acid.

Found that the amount of paracetamol that went into the solution after 30 minutes was in the range of at least 75% from 0.09 to 0.11 grams, based on the average weight of 1 tablet of the tested drug paracetamol + ascorbic acid.

According to the results of the quantitative determination of ascorbic acid, which passed into the solution after 30 minutes, it was at least 75% of 0.09-0.11 grams, based on the average weight of 1 tablet of the tested drug paracetamol + ascorbic acid.

The complex of developed methods and standardization of quality control indicators of paracetamol + ascorbic acid tablets meet the requirements of the latest pharmacopoeias.

According to social studies, in emergency situations, in the conditions of a military conflict, the use of the antipyretic, pain-relieving and anti-inflammatory combination of paracetamol + ascorbic acid can reduce the suffering of the victims, lower the temperature, relieve pain, and improve the quality of life. The combination of paracetamol + ascorbic acid can be prescribed for use by children of all age groups and adults for infectious and inflammatory diseases accompanied by an increase in temperature and for pain syndromes of mild and moderate intensity of various genesis. The main indications for the use of the new drug paracetamol + ascorbic acid include infectious and inflammatory diseases with an increase in temperature; acute respiratory diseases; other infectious diseases that may be accompanied by an increase in body temperature. Pain syndromes of weak and medium intensity of various genesis: headache, neuralgia, myalgia, arthralgia, algodysmenorrhea.

Conclusion. The multidisciplinary context of the study of a new drug for infectious-inflammatory diseases based on the combination of evidence-selected pharmacological substances paracetamol and ascorbic acid was developed. Competences of the organization of pharmacy, medicine, pharmacology, forensic pharmacy, pharmaceutical analysis, and social medicine were used. Quality control methods have been developed: determination of para-aminophenol, paracetamol, and

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ascorbic acid. The results of organizational, documentary, pharmacological, medical, pharmaceutical, physicochemical, and social studies were used. The main areas of application of paracetamol + ascorbic acid tablets are indicated. Research is important for the further development and production of a new drug, as it provides important data on its characteristics, quality, and application areas.

Conflict of interests. The authors confirm that they are the authors of this work and have approved it for publication. The authors also certify that the obtained data and research were conducted in compliance with the requirements of moral and ethical principles based on medical and pharmaceutical law, and in the absence of any commercial or financial relationships that could be interpreted as a conflict or potential conflict of interest.

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Multidisciplinary context of research of a new drug in infectious and inflammatory diseases

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Introduction. The multidisciplinary context of the study of a new drug for infectious-inflammatory diseases based on the combination of evidence-selected pharmacological substances paracetamol and ascorbic acid was developed. Competences of the organization of pharmacy, medicine, pharmacology, forensic pharmacy, pharmaceutical analysis, and social medicine were used. **The aim:** Noted that the raw material base, production in the conditions of pharmacies and pharmaceutical enterprises of paracetamol + ascorbic acid tablets is economically expedient, socially oriented in the conditions of a military conflict. **Materials and methods.** Quality control methods have been developed: determination of para-aminophenol, paracetamol, and ascorbic acid. The results of organizational, documentary, pharmacological, medical, pharmaceutical, physicochemical, and social studies were used. According to physical and chemical studies, the determination of para-aminophenol by spectrophotometric method is proposed. It was determined that experimental samples of the drug do not contain impurities of free para-aminophenol. The maximum permissible content of para-aminophenol in tablets of the drug under study is no more than 0.1%. **Results.** The complex of developed methods and standardization of quality control indicators of paracetamol + ascorbic acid tablets meet the requirements of the latest pharmacopoeias. The methods of quantitative determination of the active substances of the drug used in the development of analytical and control documentation, the system of quality control of the drug in further production in the conditions of pharmacies or pharmaceutical enterprises. **Conclusions.** The main areas of application of paracetamol + ascorbic acid tablets are indicated: infectious diseases with an increase in temperature; pain syndromes of weak and medium intensity of various genesis. Appeared promising to include the new drug in the pharmacotherapy schemes of health care institutions. The social context of the study is relevant in emergency situations, in the conditions of a military conflict, to reduce the suffering of victims of pain, inflammation, fever, and improve the quality of life of patients.

Key words: paracetamol, ascorbic acid, analysis, application.

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