



## DEVELOPMENT OF NITROFURAN DERIVATIVE: COMPOSITION AND TECHNOLOGY OF EFFERVESCENT TABLETS WITH SOLID DISPERSIONS

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Taking into account the current Product specification file, the aim of the work was to develop the composition and technology for obtaining effervescent tablets based on solid dispersions of furazolidone in the form of an aqueous solution for external use.

**Materials and methods.** The used substances were: furazolidone, anhydrous sodium carbonate (chemically pure), polyvinylpyrrolidone-24000±2000 (chemically pure), malic acid (analytically pure), tartaric acid (chemically pure), citric acid (chemically pure), sodium benzoate (chemically pure), ethyl alcohol 96% (chemically pure), purified water. Preparation of granulates is separate wet granulation in a fluidized bed (Mycrolab, BOSCH, Germany). Obtaining tablets is the process of pressing on a manual hydraulic test press ("PRG", VNIR, Russia). The dependence of disintegration, abrasion capacity and crushing resistance on compacting pressure was investigated. Technological parameters of granulates, epy obtained effervescent tablets, shelf life and storage conditions were investigated according to the State Pharmacopoeia of the Russian Federation XIV<sup>th</sup> ed.

**Results.** Two compositions of effervescent tablets containing solid dispersions of furazolidone as an active substance were obtained, which, when dissolved in 100 ml of water at room temperature (20°C), form a solution of furazolidone with a concentration of 0.004% in less than 5 minutes. The method of quantitative determination of the furazolidone content in the effervescent tablets was validated. A complex of physicochemical methods for the analysis of tablets was carried out. Quality standards have been developed. The developed compositions stability of instant tablets during storage during accelerated and long-term tests has been experimentally confirmed. The preliminary shelf life and storage conditions have been determined.

**Conclusion.** The result of technological and chemical-pharmaceutical research is the creation and evaluation of the quality of a new instant furazolidone dosage form as effervescent tablet formulations.

**Keywords:** furazolidone; effervescent tablets; instant tablets; solid dispersions; solubility; dissolution rate; polyvinylpyrrolidone

**Abbreviations:** FZ – furazolidone; SD – solid dispersions; AS – active substance; DF – dosage form; PVP – polyvinylpyrrolidone; SP RF XIV – State Pharmacopoeia of the Russian Federation XIV edition; Es – excipients; PSF – Product Specification File; GL – granulation liquid.

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## РАЗРАБОТКА СОСТАВА И ТЕХНОЛОГИИ ШИПУЧИХ ТАБЛЕТОК С ТВЕРДОЙ ДИСПЕРСИЕЙ ПРОИЗВОДНОГО НИТРОФУРАНА

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**Цель.** С учетом действующей нормативной документации разработать состав и технологию получения шипучих таблеток на основе твердой дисперсии фуразолидона для наружного применения в виде водного раствора.

**Материалы и методы.** Субстанции: фуразолидон, карбонат натрия безводный (х.ч.), поливинилпирролидон-24000±2000 (х.ч.), яблочная кислота (ч.д.а.), винная кислота (х.ч.), лимонная кислота (х.ч.), бензоат натрия (х.ч.), спирт этиловый 96% (х.ч.), вода очищенная. Получение гранулятов: раздельное влажное гранулирование в псевдооживленном слое («Mycrolab», BOSCH, Германия). Получение таблеток: прессование на ручном гидравлическом испытательном прессе («ПРГ», ВНИИР, Россия). Исследовали зависимость распадаемости, истираемости и прочности на раздавливание от давления прессования. Технологические показатели гранулятов, полученные шипучие таблетки, срок годности и условия хранения исследовали согласно Государственной Фармакопее Российской Федерации XIV издания.

**Результаты.** Получены два состава шипучих таблеток, содержащих в качестве действующего вещества твердую дисперсию фуразолидона, образующие при растворении в 100 мл воды комнатной температуры (20°C) раствор фуразолидона с концентрацией 0,004% менее, чем за 5 мин. Осуществлена валидация методики количественного определения содержания фуразолидона в шипучих таблетках. Проведён комплекс физико-химических методов анализа таблеток. Разработаны нормы качества. Экспериментально подтверждена стабильность разработанных составов быстрорастворимых таблеток в процессе хранения в ходе ускоренных и долгосрочных испытаний. Определен предварительный срок годности и условия хранения.

**Заключение.** Результатом технологических и химико-фармацевтических исследований является создание и оценка качества новой быстрорастворимой лекарственной формы фуразолидона в форме шипучих таблеток.

**Ключевые слова:** фуразолидон; шипучие таблетки; быстрорастворимые таблетки; твердые дисперсии; растворимость; скорость растворения; поливинилпирролидон

**Список сокращений:** ФЗ – фуразолидон; ТД – твердая дисперсия; ДВ – действующее вещество; ЛФ – лекарственная форма; ПВП – поливинилпирролидон; ГФ РФ XIV – Государственная Фармакопея Российской Федерации XIV издания; ВВ – вспомогательные вещества; НД – нормативная документация; ГЖ – гранулирующая жидкость.

### INTRODUCTION

Furazolidone (FZ) is a typical representative of the nitrofurans derivatives group, an antimicrobial and antiprotozoal drug that has been successfully used in therapy for more than 80 years to treat protozoal infections (*Iambliosis*, *trichomoniasis*), as well as infectious diseases caused by bacteria (*Streptococcus spp.*, *Staphylococcus spp.*, *Escherichia coli*, *Salmonella spp.*, *Shigella spp.*, *Klebsiella spp.*, *Enterobacter spp.*, *Helicobacter pylori*) [1]. As a drug for the study, FZ is of particular interest

because it is highly effective against a number of bacteria resistant to antibiotics and sulfonamides and, at the same time, it is characterized by a low resistance of microorganisms due to a specific mechanism of its action<sup>1</sup>.

A separate direction in the FD application is its use for the *Helicobacter pylori* eradication in duodenal ulcer and / or stomach ulcer. FZ is used as a second-wave drug of choice in case of ineffective treatment of a patient

<sup>1</sup> Mashkovsky MD. Lekarstvennye sredstva [Medicines]. 16<sup>th</sup> ed.; Moscow: New Wave; 2016. – P. 1216. Russian

with metronidazole, antibiotics and sulfonamides or, in case of intolerance, clarithromycin or amoxicillin. FZ is prescribed alone or in triple therapy with drugs based on bismuth, as well as using drugs that block  $H_2$ -receptors and inhibit the proton pump [2].

According to the clinical recommendations of the Ministry of Health dated January 23, 2019 (ICD 10: N30.0/N30.1/N30.2/N30.8), FZ is recommended for the prevention and treatment of diseases of the genitourinary system, such as urethritis and vaginitis, cystitis<sup>2</sup> [3]. FZ is also used topically for gargling in the complex treatment of infectious and inflammatory diseases of the oral cavity and nasopharynx. It is applied externally in the complex treatment of skin lesions, small wounds, scratches and burns prone to infection [1].

The FZ substance (Fig. 1) is a yellow or greenish-yellow fine-crystalline powder; it is odorless, non-hygroscopic<sup>3</sup>. FZ is recommended for an external and topical use in the form of aqueous solutions with a concentration of 0.004%<sup>4</sup>. However, its use is limited by physical properties, i.e.: FZ is practically insoluble in water and 95%<sup>5</sup> ethyl alcohol. On the domestic market, there is only one registered dosage form (DF) of FZ - 50 mg tablets for the administration *per os*<sup>6</sup>.

The compounds characterized by a poor solubility belong to classes II and IV of the biopharmaceutical classification system (BCS) [4]. On the modern pharmaceutical market, about 40% of active ingredients (AI) have a low solubility in water, and at the development stage, the percentage of such compounds characterized by an insufficient solubility, according to various sources, reaches 75–90% [5–8].

As a substance with a poor solubility but a good permeability, FZ belongs to the BCS class II [4]. One of the priority methods to increase the solubility and dissolution rate of BCS class II AS, is the solid dispersions (SD) method. SDs are bi- or multicomponent systems consisting of an active ingredient and a carrier, which are a highly dispersed solid phase of an active agent or molecularly dispersed solid solutions with a partial formation of complexes of variable compositions with the carrier material [9–11].

In SD manufacturing, polymers of various chemical nature are used as the basic excipient (E). The introduction of a polymer supports the AS substance transition from the crystalline to the amorphous state: the polymer molecules intercalate into AS crystals, leading the ordered AS crystal to disintegration. There is a critical difference between the enthalpy of the crystal lattice

and the enthalpy of solvation in favor of the process of crystal dissolution. In already the amorphous state, the bonds between the polymer and AS improve, the surface area of the interaction between the AS and biological fluid or solvent increases, resulting in the increase of the AS solubility and its dissolution rate [8, 12–14].

In the course of previous studies on increasing the solubility and dissolution rate of FZ by the SD method, several compositions with various carriers were developed and manufactured: PVP –10000; –12600; –24000 and PEG-400; –1500; –2000; –3000; –4000; –6000 at ratios with AS from 1:1 to 1:10. As a result of the experiment, PVP-24000 was chosen as the optimal carrier at the ratio of 6:1 to FZ by weight. At this ratio, the solubility of SD FZ increases by 1.56 times, and the dissolution rate – by 3 times at the point of 5 min from the start of dissolution [15]. The SD technology is used to increase the release of the AS from the DF, increase a bioavailability and a pharmacological activity by increasing the solubility and release rate of AS [16–19].

Increasing the solubility and dissolution rate of FZ due to the use of the SD method will allow the creation of the instant effervescent DF FZ, which will expand the convenience and possibilities of using this compound due to the possibility of obtaining a solution of the desired concentration in less than 5 minutes [20]. The acceleration of the AS dissolution process is achieved as a result of an acid-base reaction with the release of carbon dioxide, which acts as a super disintegrant [21, 22]. At the same time, effervescent DFs favorably differ in high stability and convenience in storage and transportation compared to liquid DFs [23]. A high dissolution rate of the AS, the speed and completeness of the manifestation of the pharmacological effect, dosing accuracy, microbiological and physicochemical stability, economic feasibility, and, most importantly, the ease of use, ensure a high adherence of patients to taking effervescent DFs [20, 24–26]. Given the numerous advantages of effervescent DFs, it is advisable to expand their range.

In accordance with Pharmaceutical development ICH Harmonised Tripartite Guideline Q8(R2)<sup>7</sup>, to manage the development process best, it is necessary to identify the critical formulation and manufacturing parameters that affect the key characteristics of the DF. Under these conditions, the information obtained during the development process determines the requirements for quality indicators and, in the future, becomes part of the continuous quality control system for the production of a medicinal product [27].

For effervescent tablets of the developed DF, disintegration is a key characteristic. This indicator may depend on a number of factors: the solubility of AS, the amount and ratio of the acidic and basic components of the effervescent system in the composition, as well as the compacting pressure value. Thus, the critical for-

<sup>2</sup> Clinical recommendations of the Ministry of Health of the Russian Federation. 01/23/2019. (ICD 10: N30.0/N30.1/N30.2/N30.8). Russian

<sup>3</sup> State Pharmacopoeia of the Russian Federation. XIV<sup>th</sup> ed. Vol. 1–4.; M., 2018. – P. 5004. Available from: <https://femb.ru/record/pharmacopea14>.

<sup>4</sup> Mashkovsky MD. Lekarstvennye sredstva [Medicines]. 16<sup>th</sup> ed.

<sup>5</sup> State Pharmacopoeia of the Russian Federation. XIV<sup>th</sup> ed.

<sup>6</sup> Register of medicines of Russia. Furazolidone. Available from: [https://www.rlsnet.ru/mnn\\_index\\_id\\_1371.htm](https://www.rlsnet.ru/mnn_index_id_1371.htm). Russian

<sup>7</sup> Pharmaceutical development Q8(R2). ICH Harmonised Tripartite Guideline. London, 2009;28.

mulation parameters for FZ effervescent tablets are: the presence of SD as a component that increases the solubility and dissolution rate of the AS; the amount and ratio of gas-forming components of the effervescent system. The compacting pressure during the tablet production becomes a critical indicator of the manufacturing process.

Taking into account the current Product specification file, **THE AIM** of the work was to develop the composition and technology for obtaining effervescent tablets based on solid dispersions of furazolidone in the form of an aqueous solution for external use.

## MATERIALS AND METHODS

### Preparations and reagents

The used preparations and reagents were: Furazolidone substance (JSC Irbitsky Khimfarmzavod, Russia), anhydrous sodium carbonate (chemically pure) (Kupavnareaktiv, Russia), polyvinylpyrrolidone-24000±2000 (Sigma-Aldrich, USA), malic acid (AlbaKhim, Russia), tartaric acid (AlbaChem, Russia), citric acid (AlbaChem, Russia), sodium benzoate (Tengzhou Tenglong Chemical, China), 96% ethyl alcohol, analytical grade (LLC Constanta-Pharm M, Russia), purified water.

### Devices and equipment

The devices and equipment used were as follows: laboratory balance MWP-150 (CAS, South Korea), analytical balance GH-202 (AND, Japan), UNICO 2800X SpectroQuest spectrophotometer (Unitedproducts & instruments, USA), MSH Basic magnetic stirrer (IKA, Germany), laboratory ionomer "I-160MI" (OOO Izmeritelnaya Tekhnika, Russia), moisture meter MA35M (Sartorius Weighing Technology, Germany), granulation machine Mycrolab (BOSCH, Germany), screening machine AS 200 Control (Retsch, Germany), compaction tester SVM 223 (Erweka, Germany), flowability tester GTL (Erweka, Germany), compression tester TBF 1000 (Copley Scientific, Great Britain), abrasion tester PT F30ERA (Pharma Test, Germany), a protractor, manual hydraulic "Press test" brand PRG (VNIR, Russia), climate chamber KK115 (Pol-EKO, Poland). Filtration was carried out through syringe nozzles (Minisart, Germany) with a pore diameter of 0.45 µm, the filter material was nylon.

### Manufacturing technology of acid granulates

Powders of the two most widely used effervescent tablet technologies, tartaric and malic acids, weighing 1 kg, were separately loaded into the product container of the Mycrolab granulation unit, preliminarily crushed and sequentially sifted through sieves with hole diameters of 250 µ and 45 µ; then the particle fraction was granulated of more than 45 µ and less than 250 µ.

To obtain a granulating liquid (GL), PVP-24000 was dissolved in 96% ethyl alcohol when heated in a water bath (65±5°C). Granulation was carried out in a fluidized bed; the granulation parameters were standard.

### Manufacturing technology of the basic granulate with SD FZ

Manufacturing of the basic granulate with SD FZ was carried out similarly to the preparation of acid granulates, with the difference in the following: the powder of anhydrous sodium carbonate and the GL – a solution of FZ and PVP-24000 in 96% ethyl alcohol – were loaded into the container of the Mycrolab granulation unit, followed by heating in a water bath at the temperature of 65±5°C).

### Manufacturing technology of granulates of compositions No. 1 and No. 2

To obtain granulates of compositions No. 1 and No. 2, the basic and acid granules were mixed at the ratios of 1.0:1.3 and 1.0:1.1, respectively, and a lubricating excipient, sodium benzoate, was introduced in the amount of 2% of the powdered mass.

### Tablet manufacturing technology

In the work, a manual hydraulic "Testing Press" (PRG brand, VNIR, Russia) was used. Model tablets weighing 3.800 and 3.500 g for compositions No. 1 and No. 2, respectively, were produced at different compacting pressure values on flat-cylindrical punches with a diameter of 25.0 mm.

### Determining the authenticity of FZ

When interacting with sodium hydroxide, a FZ qualitative reaction has a brown coloration. One tablet was dissolved in 100 ml of purified water, a 10 ml sample was taken and mixed with 10 ml of a mixture of water and a 30% sodium hydroxide solution (3:2), then heated; herewith, a brown coloration was observed.

### Quantitative determination of FZ

Due to the fact that FZ solutions have a clearly defined maximum in the UV spectrum, a quantitative determination is best carried out using the method of spectrometry in the UV region. In the work, a spectrophotometer and quartz cuvettes (the thickness of the absorbing layer was 10 mm) were used.

One tablet weighing 3.800 g (for composition No. 1) and another weighing 3.500 g (for composition No. 2), respectively, were placed in two 500 ml volumetric flasks, dissolved each in 100 ml of purified water, the solutions were stirred on a magnetic stirrer for 5 minutes (speed 200 rpm). The volumes of the resulting solutions were brought to the marks with purified water, mixed. The selected samples with a volume of 5 ml were filtered. The optical densities of the resulting solutions were measured at the wavelength of 367±2 nm (FZ absorption maximum); in the both cases, the reference solution was purified water. It had been preliminarily established that the excipients do not influence the maxima of the FZ absorption spectra and their intensity. The FZ concentrations were calculated using the calibration plot.



This quantitative determination method was developed more than 20 years ago by the Departments of Analytical, Physical and Colloidal Chemistry and Pharmaceutical Technology of the Institute of Pharmacy ("First Moscow State Medical University n. a. I.M. Sechenov"). It is successfully used for a quantitative determination of poorly soluble active substances from various pharmacological groups introduced into solid dispersions with various polymers to increase bioavailability from a number of solid and soft dosage forms. A detailed description of this technique are disclosed in a number of publications, patents of the Russian Federation for the invention [15, 28–41], and in the applications for inventions deposited with Rospatent They are: No.2021105988 dated March 10, 2021 "Instantly soluble dosage form of furazolidone and its preparation method" (the authors are Krasnyuk II, Krasnyuk II(Jr), Stepanova OI, Belyatskaya AV, Elagina AO; No. 2021129748 dated October 13, 2021 "Instantly soluble dosage form of metronidazole and its preparation method" (the authors are Krasnyuk II(Jr.), Naryshkin SR, Krasnyuk II, Belyatskaya AV, Stepanova OI.

### Determining shelf life of tablets

In order to study the stability and shelf life, the tablet samples were stored in accordance with GPM.1.10009.15 "Stability and shelf life of medicines"<sup>8</sup> in plastic tubes made of polypropylene, sealed with water absorbers lids. Long-term tests were carried out on 3 series of each composition at the temperature of  $25 \pm 2^\circ\text{C}$  and a relative humidity of  $60 \pm 5\%$ ; accelerated tests were carried out on 3 series of each composition at the temperature of  $40 \pm 2^\circ\text{C}$  and a relative humidity of  $75 \pm 5\%$  using a climatic chamber. The check points for long-term testing were as follows: on the day of manufacturing and during the storage (every 3 months during the first year of storage and every 6 months during 2 years). During accelerated tests, the check points were on the day of manufacturing and during the storage (3 and 6 months). At the check points, the following indicators were investigated: description, mass uniformity, disintegration, abrasion capacity, crushing resistance, weight loss on drying, pH of the solution, quantitative and qualitative determination of AS.

Statistical processing of the results was carried out according to GPM 1.1.0013.15 "Validation of analytical methods"<sup>9</sup> ( $p = 95\%$ ,  $n = 5$ ) using the techniques of variation statistics by means of the Microsoft Office 2010 office software package, as well as the Microsoft Excel spreadsheet processor.

### RESULTS AND DISCUSSION

Preliminarily, the method for quantitative determination of the furazolidone content in effervescent tablets was validated on the drug samples and model mixtures obtained in the laboratory. The following characteristics were studied: specificity, linearity, correctness, precision

(at two levels – convergence, intermediate precision), and an analytical area of the methods.

To determine the specificity of the methods on a spectrophotometer, the spectra of aqueous solutions were sequentially taken: the furazolidone substance, effervescent furazolidone tablets, and excipients. The specificity of the UV spectrophotometry method was proven by the coincidence of the spectra maxima and minima of the FZ effervescent tablet solution and the substance solution, and due to the absence of the excipients effect on the analysis results (Fig. 2).

Next, 5 samples of standard furazolidone solutions were prepared with concentrations of 0.032 mg/ml, 0.036 mg/ml, 0.04 mg/ml, 0.044 mg/ml and 0.048 mg/ml (from 80 to 120%). The optical density the five standard furazolidone solutions obtained after the dilution with concentrations of 0.0064 mg/ml, 0.0072 mg/ml, 0.0080 mg/ml, 0.0088 mg/ml and 0.0096 mg/ml was measured. A linear regression analysis of the data obtained, calculated by the least squares method, made it possible to establish that the dependence of the optical density of furazolidone on its concentration is linear and is described by the equation  $y = 70.000x - 0.002$  (Fig. 3). The correlation coefficient ( $r$ ), equal to 0.99809, meets the necessary condition  $|r| \geq 0.99^{10}$ .

The scope of the experimental data that satisfies the linear model in the concentration range from 80 to 120% can be considered the analytical area of the technique.

The correctness of the technique was confirmed by the analysis of a series of model mixtures prepared from the excipients with the addition of a weighed batch that also corresponded to the range from 80 to 120% of the nominal FZ content in the preparation. The results of the analysis were evaluated by comparing the obtained results with the expected quantity value, e.i., the FZ content in the model mixture, mg (Table 1).

As the data in Table 1 show, the relative errors of the average result ( $\bar{E}$ ) are less than 2.0%; the obtained results lie in the range of the confidence interval of the analysis average result ( $\bar{X} \pm \Delta\bar{X}$ ), which was  $99.66 \pm 1.27$ , and approach the true value. The numerical value of the Student's coefficient ( $t_{\text{calc}}$ ), calculated from the results of the analysis, was 0.62. The tabular value of the Student's coefficient ( $t_{\text{tabular}}$ ) is 2.31, i.e.  $t_{\text{calc}} < t_{\text{tabular}}$ . Therefore, the proposed method is characterized by a satisfactory correctness.

Precision was studied by analyzing the FZ tablets of compositions No. 1 and No. 2 in six replications in the form of parameters "Convergence" and "Intralaboratory (intermediate) precision". To assess the intralaboratory precision, the test samples were analyzed using different analysts and on different days using the same equipment. The results obtained (Tables 2, 3) testify to the satisfactory precision of the proposed method for the quantitative determination of FZ in effervescent tablets at the levels of repeatability and intralaboratory precision.

<sup>8</sup> State Pharmacopoeia of the Russian Federation. XIVth ed.

<sup>9</sup> Ibid.

<sup>10</sup> Ibid.

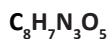
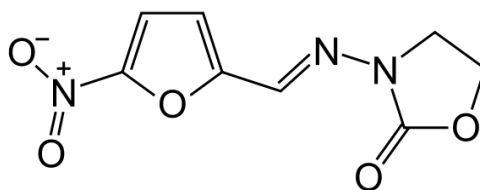


Figure 1 – Furazolidone structural chemical formula

Note: 3-[[[5-Nitrofuran-2-yl)methyliden]amino]-1,3-oxazolidin-2-on

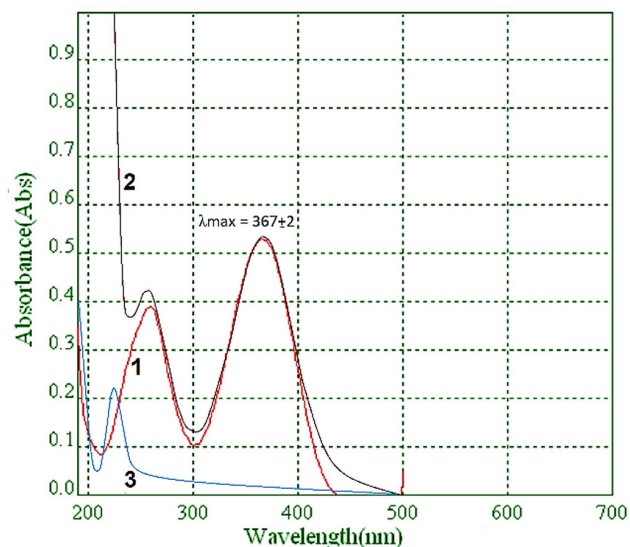


Figure 2 – Ultraviolet absorption spectra of substance furazolidone aqueous solutions (1), effervescent FZ tablets (2) and excipients (3)

Table 1 – Results of assessing correctness of methods for furazolidone quantitative determination

Added FZ, mg	Detected FZ, mg	Recovery, %	Metrological characteristics, (p = 95%, n = 9)
3.20	3.14	98.13	$\bar{X} = 99.66\%$
3.40	3.37	99.12	SD = 1.65
3.60	3.64	101.11	RSD = 1.66%
3.80	3.73	98.16	$\Delta\bar{x} = 1.27$
4.00	4.08	102.00	$\Delta x = 3.81$
4.20	4.11	97.86	$\bar{\epsilon} = 1.27\%$
4.40	4.46	101.36	$t_{\text{calc.}} = 0.62$
4.60	4.64	100.87	$t_{\text{tabular.}} = 2.31$
4.80	4.72	98.33	$\bar{X} \pm \Delta\bar{X} = 99.66 \pm 1.27$

Table 2 – The results of determining the convergence of the analytical methods for the quantitative determination of the content of furazolidone in effervescent tablets

No.	Composition No.1		Composition No.2	
	Detected FZ, mg	Metrological characteristics, (n = 6)	Detected FZ, mg	Metrological characteristics, (n = 6)
1	4.06	$\bar{X} = 4.01$	3.93	$\bar{X} = 3.98$
2	4.02	$S^2 = 0.002937$	4.04	$S^2 = 0.003840$
3	3.94	SD = 0.054	4.00	SD = 0.062
4	4.01	RSD = 1.35%	3.97	RSD = 1.56%
5	3.95		4.04	
6	4.07		3.95	

**Table 3 – The results of the intermediate precision study of the method for the quantitative determination of the furazolidone content in effervescent tablets**

No.	Explorer 1		Explorer 2		Metrological characteristics, (n = 6)			
	Composition No.1 Detected	Composition No.2 Detected	Composition No.1 Detected	Composition No.2 Detected	Explorer 1		Explorer 2	
	FZ, mg	FZ, mg	FZ, mg	FZ, mg	Composition No.1	Composition No.2	Composition No.1	Composition No.2
1	3.95	4.04	3.99	4.03	$\bar{X} = 3.98$	$\bar{X} = 4.01$	$\bar{X} = 3.93$	$\bar{X} = 3.98$
2	4.03	4.02	3.93	4.02	$S^2 = 0.0024$	$S^2 = 0.0012$	$S^2 = 0.0016$	$S^2 = 0.0015$
3	3.96	4.06	3.95	3.94	$SD = 0.049$	$SD = 0.035$	$SD = 0.040$	$SD = 0.039$
4	4.06	3.98	4.01	4.01	$RSD = 1.23\%$	$RSD = 0.87\%$	$RSD = 1.01\%$	$RSD = 0.98\%$
5	3.97	4.01	3.98	3.97	$\bar{X} \pm \Delta\bar{X} = 3.98 \pm 0.05$	$\bar{X} \pm \Delta\bar{X} = 4.01 \pm 0.04$	$\bar{X} \pm \Delta\bar{X} = 3.93 \pm 0.04$	$\bar{X} \pm \Delta\bar{X} = 3.98 \pm 0.04$
6	3.95	3.97	4.04	3.95	$t_{(95\%, 5) \text{ calc.}} = 1.00$	$t_{(95\%, 5) \text{ calc.}} = 0.70$	$t_{(95\%, 5) \text{ calc.}} = 1.23$	$t_{(95\%, 5) \text{ calc.}} = 1.26$
					$F_{\text{calc.}} = 1.5$	$F_{\text{calc.}} = 1.27$	$F_{\text{calc.}} = 1.5$	$F_{\text{calc.}} = 1.27$
$t_{(95\%, 5) \text{ tabular.}} = 2.57; F_{(99\%, 5, 5) \text{ tabular.}} = 10.97$								

Note:  $t_{(95\%, 5) \text{ calc.}} < t_{(95\%, 5)}; F_{\text{calc.}} < F_{(99\%, 5, 5) \text{ tabular.}}$  – the differences between the results obtained are random, not burdened by a systematic error.

**Table 4 – Compositions of the developed tablets containing furazolidone solid dispersions as an active substance**

Ingredient	Composition No.1		Composition No.2	
	for 1 dose (tablet)		for 1 dose (tablet)	
	g	%	g	%
Furazolidone	0.004	0.105	0.004	0.114
PVP-24000	0.061/	1.605/	0.061/	1.743/
(in basic and acid granules)	0.006	0.158	0.005	0.143
Sodium carbonate anhydrous	1.558	41.000	1.574	44.971
Tartaric acid	2.095	55.132	–	–
Malic acid	–	–	1.786	51.029
Sodium benzoate	0.076	2.000	0.070	2.000
Total weight:	3.800	100.000	3.500	100.000

**Table 5 – Fractional composition of granulates obtained by separate granulation methods, as well as of compositions prepared for tableting**

Sample name	Size (p) of particles, mm					
	More than 2.0	2.0>p>1.25	1.25>p>710	710>p>315	315>p>0.1	Less than 0.1
Fraction content (%), n=5; $\bar{X}_{av} \pm \Delta\bar{X}$						
Granulate 1	–	0.16±0.03	9.06±0.32	65.91±2.93	24.46±1.15	0.16±0.02
Granulate 2	–	–	26.73±0.93	45.34±1.13	23.38±0.84	4.33±0.17
Granulate 3	–	–	–	25.20±1.74	72.0±1.34	2.45±0.14
Composition No.1	–	–	19.03±1.17	54.73±2.57	22.96±1.31	2.32±0.16
Composition No.2	–	0.08±0.02	4.53±0.31	45.25±2.37	48.20±2.46	1.33±0.07

Note: granulate 1 – basic granulate (FZ + anhydrous sodium carbonate + PVP-24000); granulate 2 – acid granulate (tartaric acid + PVP-24000); granulate 3 – acid granulate (malic acid + PVP-24000).

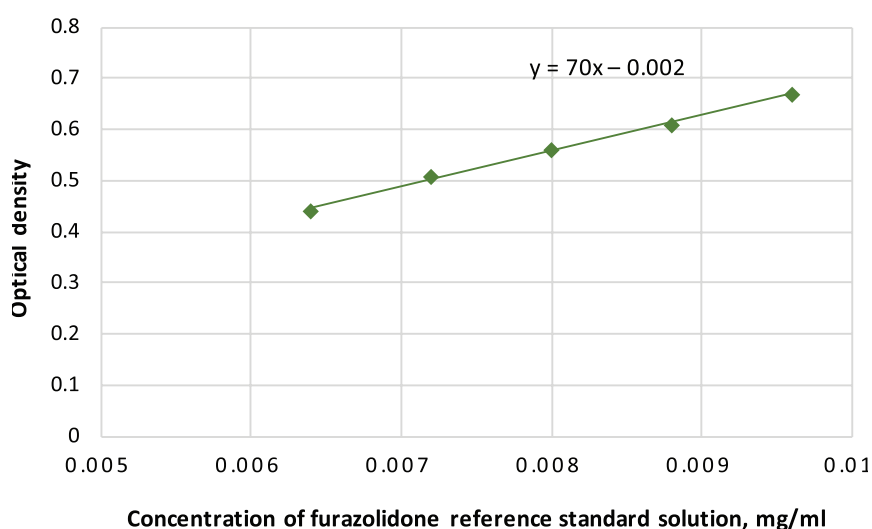
**Table 6 – Quality indicators of the developed granules at the moment of manufacturing**

Indicators	Granulates			Compositions	
	No.1	No.2	No.3	No.1	No.2
Appearance	Yellow granules	White granules		Mixture of white and yellow granules	
Bulk volume, ( $\bar{X}_{av} \pm \Delta\bar{X}$ , n=3), (g/ml) before compaction	0.89±0.03	0.77±0.02	0.78±0.03	0.83±0.02	0.81±0.02
After compaction, (g/cm <sup>3</sup> )	1.01±0.05	0.85±0.03	0.87±0.04	0.93±0.03	0.92±0.03
Flowability ( $\bar{X}_{av} \pm \Delta\bar{X}$ , n=3), (g/s)	14.90±0.11	11.03±0.07	11.06±0.04	13.01±0.09	12.90±0.07
Angle of natural repose ( $\bar{X}_{cp} \pm \Delta\bar{X}$ , n=5), (°)	35±2	25±2	25±2	30±2	32±2
Residual moisture ( $\bar{X}_{cp} \pm \Delta\bar{X}$ , n=5), (%)	1.15±0.12	1.04±0.11	0.61±0.09	1.11±0.10	1.07±0.09

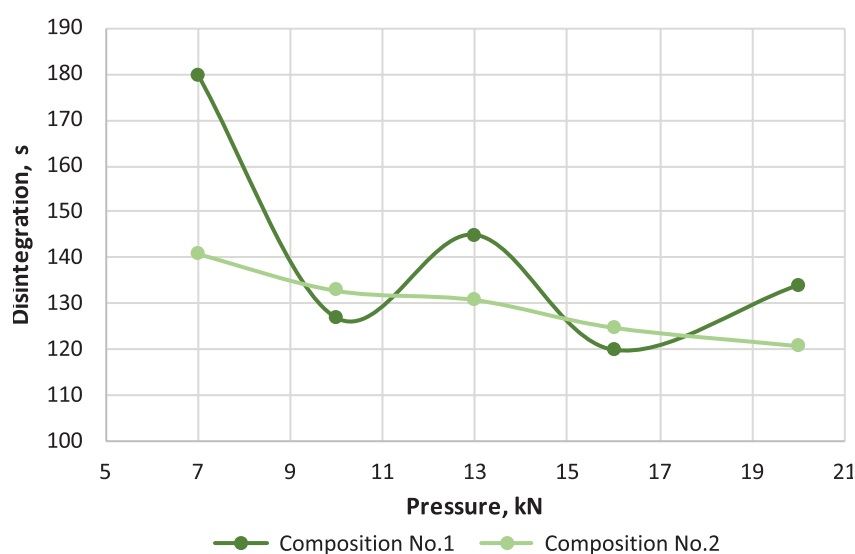
**Table 7 – Quality indicators of instant tablets containing a solid furazolidone dispersion at the moment of manufacturing**

Indicators	Methods (guidelines)	Composition No.1	Composition No.2
Description	SP RF XIV GPM.1.4.1.0015.15 Visual	Effervescent tablets, white, interspersed with pale yellow to bright yellow, cylindrical, flat, with a bevelled edge on both sides; tablets dissolve in water with a release of bubbles, forming a greenish-yellow, transparent, odorless solution. Roughness and marbling are allowed.	
Authenticity	SP RF XIV GPM.1.2.1.1.0003.15 GPM.2.1.0203.18 UV spectrophotometry qualitative reaction	The UV spectra of the aqueous solution from 230 to 400 nm must correspond to the characteristic peaks of the FZ standard. Qualitative reaction with sodium hydroxide, brown color appears.	
Quantification ( $C_{av} \pm \Delta C$ , n=5), (g/l)	SP RF XIV GPM.1.2.1.1.0003.15 UV spectrophotometry	0.040±0.004	0.040±0.004
Crushing resistance ( $X_{av} \pm \Delta X$ , n=10), (H) <sup>1</sup>	SP RF XIV GPM.1.4.2.0011.15 (not less than 50 H)	77.2±3.0	79.6±5.0
Abrasion rate ( $X_{av} \pm \Delta X$ , n=5), (%)	SP RF XIV GPM.1.4.1.0004.15 (not more than 3%)	1.00±0.23	0.50±0.31
Weight loss on drying	SP RF XIV GPM.1.2.1.0010.15 (less than 2%)	1.5±0.5	1.3±0.5
Disintegration ( $t_{av} \pm \Delta t$ , n=5), (s)	SP RF XIV GPM.1.4.1.0015.15 (less than 5 min)	135±15	125±15
pH ( $X_{av} \pm \Delta X$ , n=5)	SP RF XIV GPM.1.2.1.0004.15	6.0±0.5	6.0±0.5
Package	SP RF XIV GPM.1.1.0025.18 10 tablets in a plastic tube made of polypropylene, sealed with a lid with a desiccant		
Marking	SP RF XIV GPM.1.1.0025.18 Warning: "The tablet must be dissolved in ½ cup (100 ml) of water before use".		
Storage	SP RF XIV GPM.1.1.0010.18 In a dry place protected from light at the temperature not exceeding 25°C		
Shelf life	SP RF XIV GPM.1.1.0009.18 2 years		

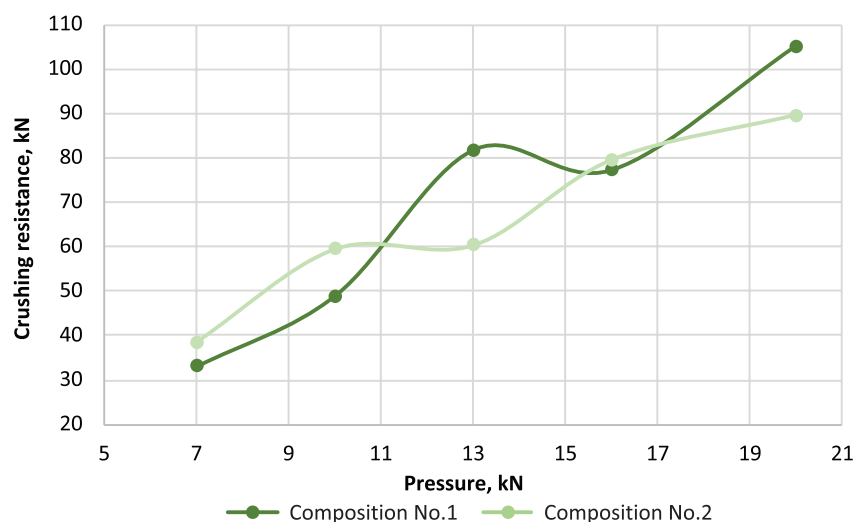
Note: <sup>1</sup> – load on the side face, destroying the tablet.

**Figure 3 – Regression line for quantitative determination of furazolidone content by spectrophotometry**

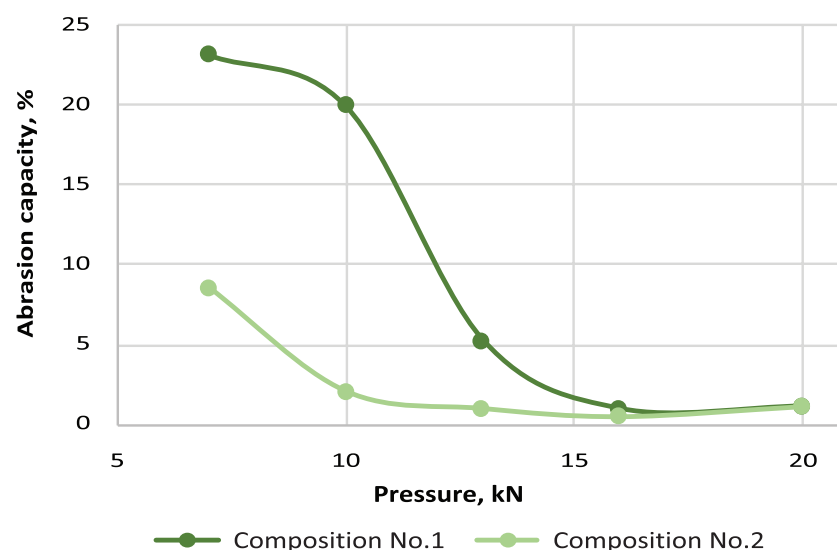




**Figure 4 – Dependence of the effect of compacting pressure values on the disintegration of furazolidone effervescent tablets**



**Figure 5 – Dependence of the effect of compacting pressure value on crushing resistance of furazolidone effervescent tablets**



**Figure 6 – Dependence of the effect of compacting pressure on the abrasion capacity of furazolidone effervescent tablets**



**Figure 7 – Effervescent tablets containing a solid furazolidone dispersion as an active substance**

Thus, with the help of the validation assessment, the correctness, precision, specificity and linearity in the analytical area of the developed method for the quantitative determination of FZ in effervescent tablets, have been established.

When developing the compositions of instant tablets, thermostable anhydrous components of the effervescent system were used – sodium carbonate and organic acids, which increase the stability and shelf life of the developed compositions. Bicarbonates were not used as the basic components of the effervescent system due to their instability when heated (starting from 60°C), and the presence of bound (crystallization) water, reducing the stability and shelf life of the instant DF.

In the course of choosing a gas-forming system, various combinations and mass ratios of organic acids (tartaric, malic, and citric) with sodium carbonate were studied. The basic criteria for screening were such quality indicators of DFs as disintegration, *pH* of the aqueous solution and compressibility. Compositions containing citric acid were characterized by low compressibility and disintegration, and therefore were excluded from further studies. Since the formulation of the compositions, in addition to the effervescent system, contains AS and excipients (PVP-24000 and sodium benzoate), which can also influence the *pH* index, the ratio of basic and acid granulates was determined experimentally.

When developing effervescent tablets, special attention was paid to the risk of a premature neutralization reaction between the basic and acid components of the gas-forming system, which could lead to such undesirable consequences as a reduced quality of finished tablets (change in color, transparency of aqueous solutions of tablets), a reduction of shelf life, an increase in the percentage of rejects, an increase in the duration of the technological process. In this regard, the granulates were obtained by separate wet granulation, using 96% ethyl alcohol as a GL solvent. The use of SD components as a GL ethanol solution is more promising, since it

makes it possible to obtain SD by the “solvent removal” method<sup>11,12</sup> [42].

The basic and acid components of compositions No. 1 and No. 2 (Table 4) were separately granulated with an FZ alcohol solution and PVP-24000 heated to  $65 \pm 5^\circ\text{C}$  in case of the basic granulate and with a 1% alcohol solution of PVP-24000 in case of acid granulates. Thus, the stage of obtaining SD FZ is combined into one technological stage with the stage of granulation, which greatly simplifies the technological process: it reduces the number of technological operations (the technological stage for obtaining SD, which requires a quality assessment and standardization of the intermediate product, is excluded), and reduces the load on the equipment and material costs. This solution also simplified the development process, making the empirical *pH* adjustment easy dosing. In the proposed technology, the stages of obtaining SD, mixing components, granulation and drying are carried out in one apparatus, which contributes to the creation of continuous production with high productivity [43, 44].

To obtain a tablet mass, the basic and acid granulates were mixed in ratios (by weight) of 1.0:1.3 for composition No. 1 and 1.0:1.1 for composition No. 2, respectively. These compositions make it possible to obtain an FZ solution for external use with a minimum disintegration index and a *pH* value that is comfortable for external use  $\approx 6.0 \pm 0.5$ .

In the amount of 2% of the powdered mass, sodium benzoate was used as a lubricating excipient, since its good solubility in water makes it possible to obtain transparent solutions when the developed compositions are dissolved.

The fractional composition of granulates of compositions No. 1 and No. 2, as well as basic and acid granules, are presented in table 5.

<sup>11</sup> Tentsova AI. Biofarmaceuticheskie aspekty primeneniya tvordykh dispersii [Biopharmaceutical aspects of the use of solid dispersions]. Epoch in Pharmacy. M.: Pero, 2014: 62–66. Russian

<sup>12</sup> Ruban EA. Sovremennye napravleniya v tekhnologii tverdykh lekarstvennykh sredstv [Modern trends in the technology of solid drugs]. Kharkov: NFAU, 2016: 88 p. Russian

The data in Table 5 indicate that the granulates are homogeneous, they are characterized by uniform flowability and appropriate compressibility.

As Table 6 shows, analyzed granulates No. 1 and No. 2, as well as basic and acid granules, have good technological characteristics. All the samples are characterized by a high bulk density, flowability, at least twice as required values (at least 4–5 g/s), which will provide good indicators of the volumetric flow rate of the tablet mass in pressing in the future. Residual moisture is a critical indicator for the stability of instant tablets, which determines the possibility of a premature start of the neutralization reaction of the effervescent system – less than 1.5%, which is optimal for effervescent tablets [45]. The angle of natural repose also characterizes the studied compositions as well flowing, since its values for all samples are in the range of 20–35°. Such technological indicators of granulates of No. 1 and No. 2 compositions, such as flowability, a moisture content, a bulk density, meet the requirements of Product specification file, providing satisfactory compressibility.

To identify the optimal tableting mode, the dependence of disintegration, abrasion capacity and crushing resistance of tablets on compacting pressure values was investigated. In the compacting pressure range of 5–20 kN, the disintegration of the developed compositions meets the requirements of the State Pharmacopoeia of the Russian Federation, XIVth edition (Fig. 4).

A compacting pressure of more than 16 kN makes it possible to obtain tablets with a crushing resistance of more than 70 N (77.2 N and 79.6 N, respectively) (Fig. 5).

Weight loss during the test for the abrasion capacity does not exceed 3% at the compacting pressure of more than 14 and 10 kN for compositions No. 1 and No. 2, respectively (Fig. 6).

Thus, at the compacting pressure, the developed compositions of FZ effervescent tablets have satisfactory quality indicators of more than 16 kN. Therefore, tablets of compositions No. 1 and No. 2 were obtained at the optimal compacting pressure (Fig. 7).

On the basis of the conducted studies, it can be concluded that the obtained instant effervescent tablets FZ of the proposed compositions No. 1 and No. 2 at the time of manufacturing, according to the main qualita-

tive, quantitative and technological quality indicators, meet the requirements of Product specification file (Table 7).

With the help of long-term and accelerated tests, it has been revealed that the tablets are characterized by the constancy of the main technological characteristics: description, mass uniformity, disintegration, abrasion rate, crushing resistance, weight loss on drying, *pH*, authenticity, quantitative AS content throughout the shelf life. The data obtained make it possible to recommend the shelf life of the tablets of compositions No. 1 and No. 2, packaged in polymer tubes, in a dry, light-protected place at the temperature of 25°C for 2 years.

The results obtained in the course of this study can be used for the implementation in production this highly effective antimicrobial drug for external use – fast-dissolving effervescent FZ tablets.

### CONCLUSION

Two compositions of effervescent tablets including SD FZ, a gas-forming system – acidic and basic components, as well as lubricating excipients, have been developed. They make it possible to obtain an aqueous FZ solution with an AS concentration of 0.004% and *pH* 6.0 ± 0.5 in less than 5 minutes without heating and applying mechanical efforts. The method for quantitative determination of the FZ content in effervescent tablets, has been validated. In accordance with the requirements of SP RF XIV, the quality of the developed effervescent tablets containing SD FZ has been assessed. It has been found out that the technological characteristics of the obtained compositions (description, mass uniformity, disintegration, abrasion rate, crushing resistance, weight loss on drying, *pH* of the solution, authenticity and quantitative determination of the AS) are within the standard values and meet all quality requirements. Experimentally, by methods of long-term and accelerated tests, the preliminary shelf life of effervescent FZ tablets was determined to be 2 years in a dry place protected from light at the temperature not exceeding 25°C.

Based on the results of the work, application No. 2021105988 dated 03/10/2021 “Instant dosage FZ form and method for its preparation” was deposited with Rospatent.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHORS' CONTRIBUTION

Anastasia O. Elagina – text writing, production and quality assessment of effervescent tablets, analysis, processing and preparation of graphic material; Anastasiya V. Belyatskaya – general management and experiment planning, granulates production; Ivan I. (Jr) Krasnyuk – tablet pressing, tablet quality evaluation; Ivan I. Krasnyuk – general management and experiment planning; Olga I. Stepanova – literature data collecting and processing; Tatyana V. Fateeva – quality of tablets evaluation; Elena A. Smolyarchuk – graphic material analysis, processing and preparation; Sergey V. Kozin – graphic material analysis, processing and preparation; Olga N. Plakhotnaya – evaluation of tablets quality; Olga V. Rastopchina – evaluation of tablets quality; Julietta V. Rau – evaluation of tablets quality. All the authors participated in the discussion of the results and writing the article.

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