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## Development of composition and technology of metronidazole with silver nanoparticles tablets

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#### Abstract

The composition and technology of metronidazole with silver nanoparticles tablets for the treatment of infectious diseases has been developed. The choice of auxiliary substances for the development of tablets is justified by the mathematical planning of the experiment. For the selection of the optimal composition of the tablets a study of the uniformity of mass of tablets, resistance to crushing, friability of uncoated tablets, disintegration of tablets and evaluation of their appearance was conducted. The dispersion analysis of the obtained results made it possible to choose the optimal composition of auxiliary substances for tablets: magnesium carbonate heavy, microcrystalline cellulose 102, sodium starch glycollate and magnesium stearate.

**Keywords:** tablets, metronidazole, silver nanoparticles, infectious diseases, resistant of microorganisms

#### Introduction

In Ukraine and in the world the growth of microbial resistance to existing antimicrobial drugs and the increase in the number of combined infections requires from specialists changes in traditional approaches to antibiotic therapy and taking into account these phenomena in the development of new antimicrobial preparations <sup>[1, 2]</sup>.

At the time of significant increase of bacterial resistance in clinical practice around the world in recent decades a very limited number of new antibacterial preparations have been introduced. The tendency to reduce research on the development of such preparations is associated with a number of reasons <sup>[1]</sup>:

- High financial costs for the development of a new antibiotic;
- A short course of treatment with antibiotics (while treatment of chronic diseases can last for months or even years), what makes the development of such drugs a non-profit for the pharmaceutical industry;
- Short (for the developer) duration of the patent rights, after the expiration of which the commercial benefit may have been very small;
- Increasing requirements for clinical trials of antibiotics, what increases the costs for conducting I and II phases of clinical trials;
- Influence of rational pharmacotherapy methods, for example, carrying out antibiograms before appointment of an antibiotic, strict adherence to the schemes of antibiotic therapy, etc.

These reasons have contributed to the limitation of innovative approaches and investments in the development of new antimicrobials.

Recently, with the active development of nanotechnology and the creation of new nanomaterials, nanoparticles of metals, in particular silver, copper, and others that have effective antimicrobial, antifungal and immunomodulatory effects, are interesting in the production of antimicrobial drugs <sup>[3]</sup>.

Studies of pharmaceutical development of antimicrobial preparations on the basis of nanomaterials are actively conducted in recent years, their results prove that metal nanoparticles, in particular silver, mainly enhance the action of antibiotics and antifungal agents. Thus, nanoparticles of silver demonstrate synergy when combined with polymyxin B in relation to all gram-negative bacteria <sup>[4]</sup>. In combination with gentamicin, streptomycin, kanamycin and sulfanilamides, silver nanoparticles also demonstrate a stronger antimicrobial effect <sup>[5, 6]</sup>. As for the antagonism of silver nanoparticles and antibiotics, such results were obtained only in combination with chloramphenicol <sup>[5]</sup>.

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Interestingly, studies show that silver nanoparticles intensify the antimicrobial action of antibiotics not only when nanoparticles are introduced into the molecule of these substances, but also at the simultaneous combination of antibiotics and nanoparticles in another dosage form, for example, a solution. Thus, in studies conducted with 19 antibiotics by their combined use with the solution Silver-Water Dispersion, which is a product of nanotechnology, synergy or additive effect of used antibiotics in relation to methicillin-resistant strains of organisms was confirmed [7]. In practical medicine for the treatment of many infectious diseases are widely used preparations of metronidazole, which are administered alone or in combination with other antimicrobial preparations in the treatment of infections caused primarily anaerobic bacteria and protozoa [8]. Therefore, it is important to develop and research the tablets of metronidazole with silver nanoparticles for the treatment of infectious diseases.

**Materials and Methods**

For development of tablets with antimicrobial action as the active pharmaceutical ingredient metronidazole with silver nanoparticles, made by “Laboratory of Electron-Ray Nanotechnology of Inorganic Materials for Medicine” of E.O. Paton Electric Welding Institute NAS of Ukraine, has been used. [9]. Mathematical planning of the experiment, technological and pharmaco-technological methods has been used.

**Results and Discussion**

Despite the fact that metronidazole has been used for a long time in medical practice, it is still effective in the treatment of acute and chronic trichinosis, giardiasis, amebiasis, purulent anaerobic wound infection, anaerobic infection of the respiratory organs, urinary tract, gastrointestinal tract, and others [10, 11].

The results of microbiological tests conducted in the L.V. Gromashevsky Institute of Epidemiology and Infectious diseases of NAMS of Ukraine showed that silver nanoparticles increase the antimicrobial activity of metronidazole, however there is no direct correlation between the concentration of silver and antimicrobial activity. With an increase in the concentration of silver, the antimicrobial effect does not increase, therefore, the introduction of silver nanoparticles up to 0.01% is sufficient to reduce the dose of

the active pharmaceutical ingredient in 2-3 times. This result was confirmed in studies conducted in cooperation with the Department of Therapeutic Dentistry of Danylo Halytsky Lviv National Medical University on strains isolated from periodontal pockets in patients with periodontitis, for which metronidazole with silver nanoparticles was applied in gel form [12]. Considering that metronidazole tablets are produced by the pharmaceutical industry at a dose of 0.25 g, and the introduction of silver nanoparticles increase the antimicrobial activity in 2-3 times, for developed tablets we used 0.1 g of metronidazole with silver nanoparticles per tablet.

One of the promising methods for obtaining tablets is direct compression. This method is widely used, since it is economically viable and constantly being improved due to the expansion of the market of auxiliary substances and the creation of new equipment [13].

Optimal technology of tablets depends on physicochemical and pharmaco-technological properties of active pharmaceutical ingredients, their amounts in the composition of a tablet, compatibility with excipients, resistance to environmental factors, and others. Therefore, the first stage in the development of the composition and technology of tablets was the study of the technological properties of metronidazole with silver nanoparticles in comparison with the substance of metronidazole used in the pharmaceutical industry. The flow of the metronidazole with silver nanoparticles powder by testing of angle of repose and flow rate through an orifice, the bulk density and tapped density of powder were determined [14]. Determination of these parameters lets predict the method of tablets preparation, tablets sizes and choose the right press tool (diameter of matrix and punches), choose the value of pressure for pressing tablets. The results of these studies have shown that the substance of metronidazole with silver nanoparticles has satisfactory technological properties and be used for the manufacture of tablets by direct compression.

The composition of the tablets, as well as other dosage forms, in addition to the active pharmaceutical ingredient - the main carrier of therapeutic effect, includes a large number of excipients that in combination with active ingredients form efficient and safe preparation.

To select the optimal composition of auxiliary substances for tablets we used the mathematical planning of the experiment using method of the three-factor analysis with the help of the Latin square 3x3 [15]. The list of studied excipients is given in the table 1.

**Table 1:** Auxiliary substances studied during the development of metronidazole with silver nanoparticles tablets

A – fillers	a <sub>1</sub> – lactose
	a <sub>2</sub> – magnesium carbonate heavy
	a <sub>3</sub> - calcium hydrophosphate anhydrous
B –fillers based on microcrystalline cellulose (MCCs)	b <sub>1</sub> – microcrystalline cellulose 102 (MCC 102)
	b <sub>2</sub> – microcrystalline cellulose 12 (MCC 12)
	b <sub>3</sub> – prozolv 90 (silicified microcrystalline cellulose)
C – disintegrants	c <sub>1</sub> – sodium crosscarmellose
	c <sub>2</sub> – sodium starch glycollate
	c <sub>3</sub> - kollidon CL

The mathematical planning of the experiment based on the Latin square 3x3 allows to reduce the number of experiments in 3 times, that is, to reduce the number of studied batches to 9.

The weight of the study tablets was 0.2 g. The content of metronidazole with silver nanoparticles was 0.1 g, what is 50% of the weight of the tablet. The concentration of

excipients was chosen based on literature data, particularly magnesium stearate as anti-friction substance is applied at a concentration of 1%, fillers (factor A) were administered in an amount of 30%, fillers based on MCC (factor B) - 15%, disintegrants - 4%.

Tableting (pressing) is the crucial operation in the manufacture of tablets. Tableting process depends on the

technological properties of the powder mixture for tableting, so prepared powder mixture for tableting studied on bulk density ( $y_1$ ) and tapped density ( $y_2$ ) and the angle of repose ( $y_3$ ). Made tablets subjected to the following studies: evaluation of appearance of tablets ( $y_4$ ), uniformity mass of tablets ( $y_5$ ), resistance to crushing of tablets ( $y_6$ ), friability of tablets ( $y_7$ ) and disintegration of tablets ( $y_8$ ) [14].

The experimental design and the results of the study of powder mixtures for tableting and tablets of methondynazole with silver nanoparticles are given in Table 2.

All experiments were implemented in two replicates. The results of the studies were subject of a dispersion analysis [15].

Results of dispersion analysis showed that the effect of the studied factors on the bulk density of powder mixtures

metronidazole with silver nanoparticles ( $y_1$  and  $y'_1$ ) can be placed in the following row of advantages:  $A > res > C > B$ . Comparison of average values of factor levels allowed to build next rows of advantages: for the factor A -  $a_3 > a_2 > a_1$ ; for the factor C -  $c_2 > c_3 > c_1$  and for the factor B -  $b_2 > b_3 > b_1$ . The *res* significance indicates that there is a significant interaction between the levels of the studied factors. The studied factors influence on tapped density of powder mixtures of metronidazole with silver nanoparticles ( $y_2$  and  $y'_2$ ) in the following sequence:  $A > B > C > res$ . Ranked rows of advantages for the levels of the studied factors are as follows: for the factor A -  $a_3 > a_2 = a_1$ ; for the factor B -  $b_2 > b_1 > b_3$ ; for the factor C -  $c_3 > c_2 > c_1$ .

**Table 2:** Three-factor experiment and results of studies of powder mixtures for tableting and tablets of metronidazole with silver nanoparticles

Batch N	A	B	C	$y_1$	$y'_1$	$y_2$	$y'_2$	$y_3$	$y'_3$	$y_4$	$y'_4$	$y_5$	$y'_5$	$y_6$	$y'_6$	$y_7$	$y'_7$	$y_8$	$y'_8$	D	D'
1	$a_1$	$b_1$	$c_1$	0,482	0,489	0,700	0,706	22	24	5	5	2,57	3,43	16	20	1,26	1,86	1	1	0,43	0
2	$a_1$	$b_2$	$c_2$	0,583	0,588	0,777	0,783	27	26	3	4	1,20	1,83	15	19	0,26	0,36	1	1	0,66	0,86
3	$a_1$	$b_3$	$c_3$	0,583	0,586	0,736	0,739	25	27	4	5	1,64	2,24	32	35	0,36	0,44	2	2	0,90	0,93
4	$a_2$	$b_1$	$c_2$	0,608	0,612	0,736	0,741	25	27	5	5	1,67	1,34	28	33	0,34	0,44	1	1	0,93	0,94
5	$a_2$	$b_2$	$c_3$	0,538	0,543	0,777	0,781	28	26	4	5	4,27	3,74	39	42	0,07	0,12	1	1	0,81	0,90
6	$a_2$	$b_3$	$c_1$	0,560	0,569	0,700	0,707	24	25	4	5	2,87	3,07	16	18	4,90	5,40	1	1	0	0
7	$a_3$	$b_1$	$c_3$	0,667	0,671	0,875	0,879	23	24	3	3	3,66	2,02	25	30	0,65	0,58	2	2	0,71	0,72
8	$a_3$	$b_2$	$c_1$	0,700	0,708	0,875	0,882	25	24	3	3	3,50	3,85	40	43	0,94	1,15	1	1	0,58	0,37
9	$a_3$	$b_3$	$c_2$	0,636	0,642	0,777	0,784	22	23	3	3	2,10	3,70	24	28	2,11	2,63	1	1	0	0

**Note:**  $y_1$  i  $y'_1$  – bulk density of powder mixtures of the first and second batch respectively,  $g/cm^3$ ;  
 $y_2$  i  $y'_2$  – tapped density of powder mixtures of the first and second batch, respectively,  $g/cm^3$ ;  
 $y_3$  i  $y'_3$  – angle of repose of powder mixtures of the first and second batch, respectively, degrees;  
 $y_4$  i  $y'_4$  – appearance of the surface of the tablets of the first and second batch, respectively, points;  
 $y_5$  i  $y'_5$  – uniformity of mass of the tablets of the first and second batch, respectively,  $\pm\%$ ;  
 $y_6$  i  $y'_6$  – resistance of the tablets to crushing the first and second batch, respectively, N;  
 $y_7$  i  $y'_7$  – friability of uncoated tablets of the first and second batch respectively,  $\%$ ;  
 $y_8$  i  $y'_8$  – time of disintegration of tablets of the first and second batch, respectively, min.;  
D i D' – desirability function of the first and second batch respectively.

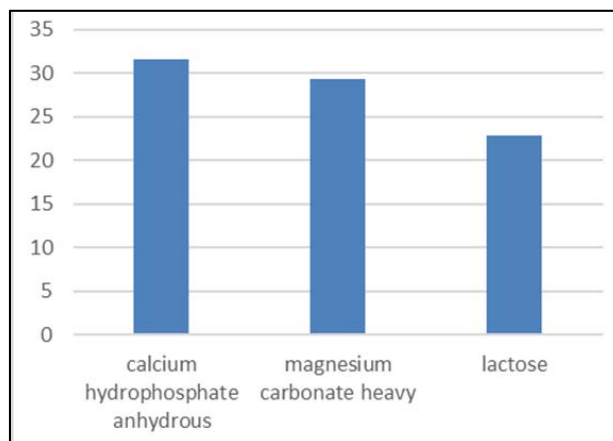
At the study of the angle of repose ( $y_3$  and  $y'_3$ ) of metronidazole with silver nanoparticles powder mixtures statistical significance of factors A and B was set. Ranked rows of advantages for significant factors are as follows: for factor A -  $a_3 > a_1 > a_2$  and for factor B -  $b_1 > b_3 > b_2$ . Angle of repose of metronidazole with silver nanoparticles powder mixtures in all 9 batches of experiments was less than 30 degrees, indicating the possibility of tableting by direct compression.

At pressing of metronidazole with silver nanoparticles tablets in a laboratory tablet machine was set that in all 9 batches of experiments matrix filling was conducted evenly, but quality of obtained tablets surface was different. The dispersion analysis of experimental data on the appearance of the surface of the tablets ( $y_4$  and  $y'_4$ ) showed the statistical significance of factor A:  $a_2 > a_1 > a_3$ . The statistical insignificance of factors B and C indicates that the use of any filler based on the MCC and disintegrant let to obtain similar results in appearance of tablets.

The received tablets of metronidazole with silver nanoparticles were tested on uniformity of mass ( $y_5$  and  $y'_5$ ). It is established that the factor C is statistically significant on this indicator:  $c_2 > c_3 > c_1$ . The uniformity of mass of metronidazole with silver nanoparticles tablets was good and in the primary batches of experiments did not exceed  $\pm 4,00\%$ .

On resistance to crushing of metronidazole with silver nanoparticles tablets affect studied linear factors and the

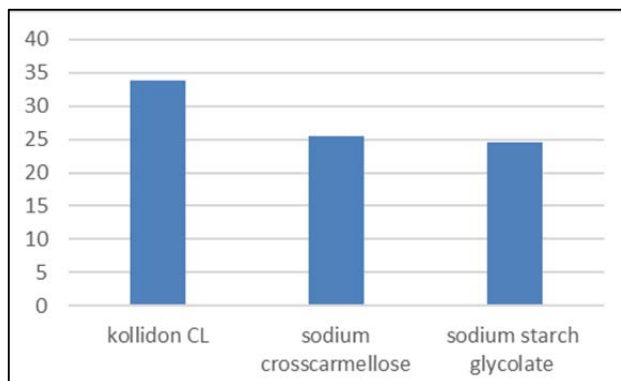
interaction between them:  $A > C > B > res$ . Since this indicator was one of the main ones, which characterizes the possibility of tableting by direct compression, we will consider it with the help of column diagrams. Influence of fillers (factor A) on the resistance to crushing of metronidazole with silver nanoparticles tablets is shown on Fig. 1.



**Fig. 1:** Influence of fillers (factor A) on resistance to crushing of metronidazole with silver nanoparticles tablets

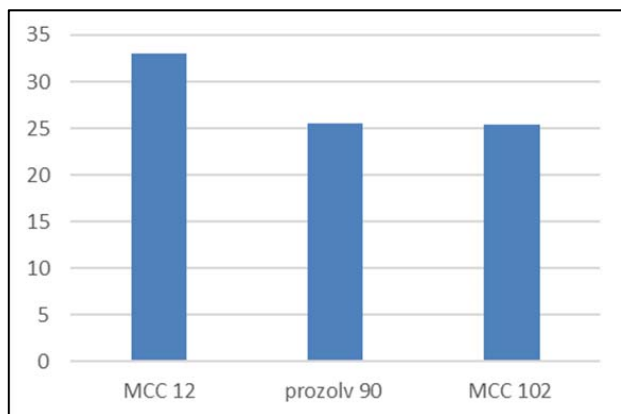
As can be seen on the figure, the most resistant to crushing of metronidazole with silver nanoparticles tablets was obtained

using calcium hydrophosphate anhydrous filler (average 31.67 N), which has an advantage over magnesium carbonate heavy (29.33 N) and lactose (22, 83 N). The effect of disintegrants on resistance to crushing of metronidazole with silver nanoparticles tablets is depicted on Fig. 2.



**Fig 2:** Influence of disintegrants on resistance to crushing of metronidazole with silver nanoparticles tablets

The most resistance to crushing of metronidazole with silver nanoparticles tablets were obtained using kollidon CL (33.83 N), which has an advantage over sodium crosscarmellose (25.50 N) and sodium starch glycolate (24.5 N). Influence of fillers based on MCC on resistance to crushing of metronidazole with silver nanoparticles tablets is depicted on Fig. 3.



**Fig 3:** Influence of fillers based on MCC on resistance to crushing of metronidazole with silver nanoparticles tablets

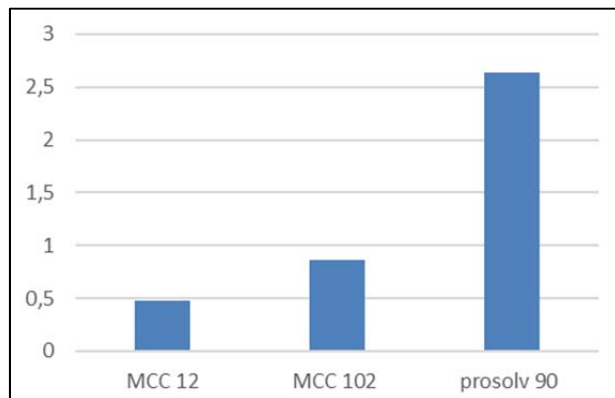
When MCC 12 is used, the most resistance to crushing of metronidazole with silver nanoparticles tablets (33.00 N) were obtained. This auxiliary substance has advantages over prozolv 90 (25.50 N) and MCC 102 (25.33 N).

The obtained metronidazole with silver nanoparticles tablets had different friability. On this indicator studied factors influence in following sequence: B > C > res > A.

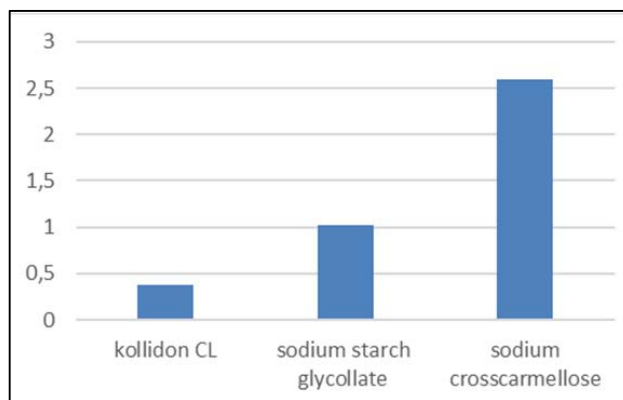
The effect of fillers based on MCC on friability of metronidazole with silver nanoparticles tablets is shown in Fig. 4.

It can be seen from the figure that the minimal friability of metronidazole with silver nanoparticles tablets (0.48%) is observed when MCC 12 is used, what is superior to MCC 102 (0.86%) and prosolv 90 (2.64%).

The effect of disintegrants on friability of metronidazole with silver nanoparticles tablets is shown on Fig. 5.



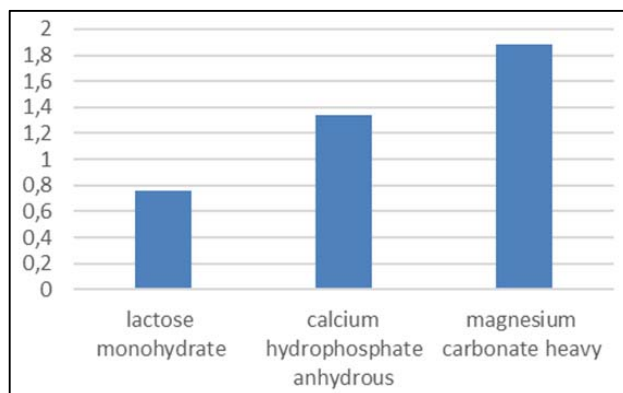
**Fig 4:** Influence of fillers based on MCC on friability of metronidazole with silver nanoparticles tablets



**Fig 5:** Influence of disintegrants on friability of metronidazole with silver nanoparticles tablets

The analysis of the figure showed that the minimal friability of metronidazole with silver nanoparticles tablets (0.37%) was observed when as a disintegrant kollidon CL was used, which has an advantage over sodium starch glycolate (1.02%) and sodium crosscarmellose (2.59%).

The effect of fillers (factor A) on friability of metronidazole with silver nanoparticles tablets is shown on Fig. 6.



**Fig 6:** Influence of fillers (factor A) on friability of metronidazole with silver nanoparticles tablets

The minimal friability of metronidazole with silver nanoparticles tablets was obtained by using lactose monohydrate (0.76%) as a filler, what has an advantage over calcium hydrophosphate anhydrous (1.34%) and magnesium carbonate heavy (1.88%).

The time of disintegration of metronidazole with silver nanoparticles tablets in all studied batches did not exceed 2 min. The studied excipients do not significantly affect the indicated index.

Studies have shown that auxiliary substances have different effect on the basic pharmaco-technological properties of powder masses for tableting and ready-made tablets of metronidazole with silver nanoparticles. To select the best combinations of levels of the studied factors, a generalized indicator, a desirability function was used (Fig. 7). To do this, the primary results for the main indicators - the appearance of the tablets ( $y_4$ ), the uniformity of mass of tablets ( $y_5$ ), the resistance to crushing of tablets ( $y_6$ ) and the friability of tablets ( $y_7$ ) with the help of the figure were translated into dimensionless values in accordance with the procedure described in work [15]. The results of the translation of the primary results into dimensionless values are given in Table 2 (column D and D').

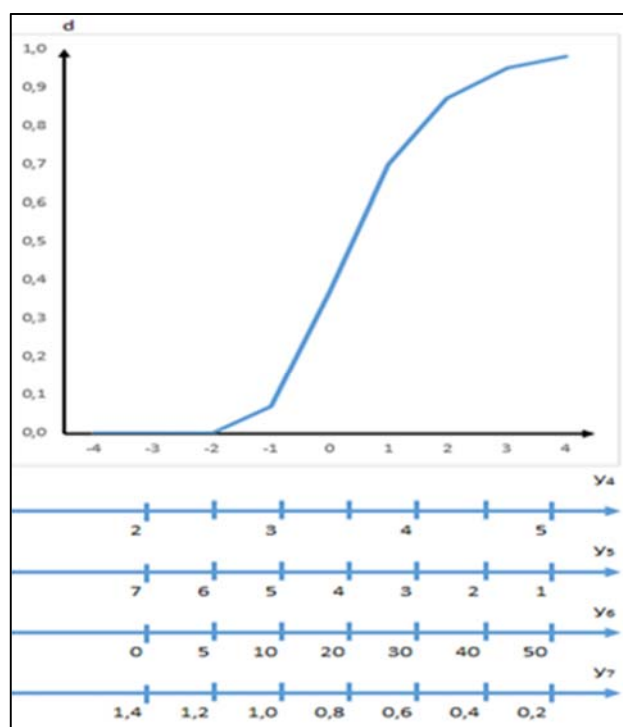


Fig 7: The desirability function for the translation of the original results of the experiment into dimensionless values

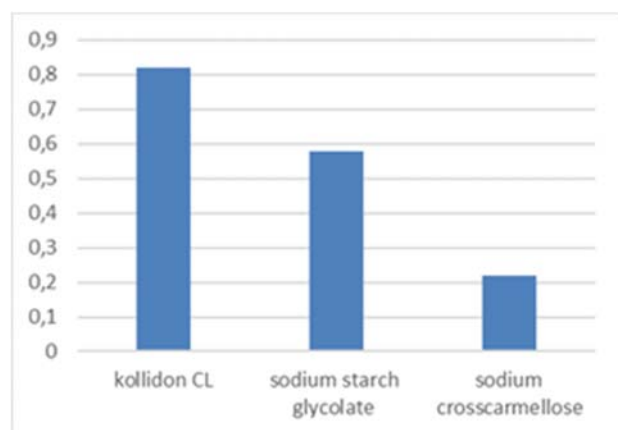


Fig 8: Influence of disintegrants on the generalized indicator of quality of metronidazole with silver nanoparticles tablets

The dispersion analysis of the obtained results by the desirability function showed the statistical significance of the factors C and B.

The effect of disintegrants on the generalized indicator of quality of metronidazole with silver nanoparticles tablets is shown in Fig. 8.

Influence of fillers based on MCC on the generalized indicator of quality of metronidazole with silver nanoparticles tablets is shown in Fig. 9

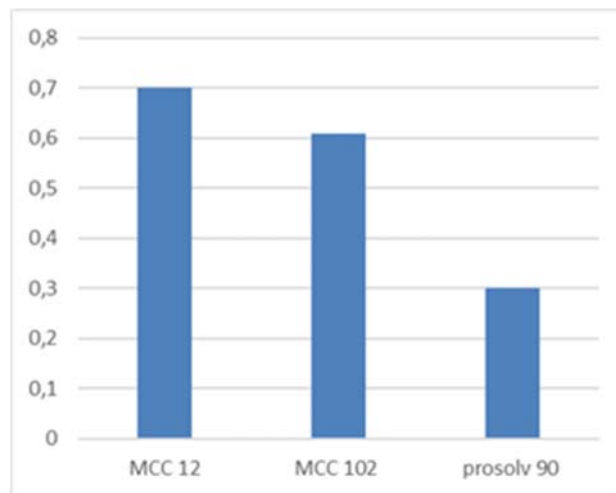


Fig 9: Influence of fillers based on MCC on the generalized indicator of quality of metronidazole with silver nanoparticles tablets

According to the requirements of the state pharmacopoeia of Ukraine (SPU), uncoated tablets should disintegrate until 15 minutes, the deviation of the average mass of the tablet from the indicated mass in the composition should not exceed  $\pm 5\%$  [14].

The dispersion analysis of the results of prepared tablets made possible to choose the optimal composition of the tablets. For further studies, we selected tablets containing the following excipients: magnesium carbonate heavy; MCC 102; sodium starch glycolate and magnesium stearate. They require the SPU by the all pharmaco- technological parameters.

## Conclusions

1. The composition and technology of metronidazole with silver nanoparticles tablets for the treatment of infectious diseases have been developed. The choice of auxiliary substances for tablets and the method of tableting were justified.
2. Studies on pharmaceutical development of tablets demonstrate the promising use of metronidazole with silver nanoparticles as an active pharmaceutical ingredient in tablets and the feasibility of further research to creating a high-quality, effective and safe medicinal preparation.

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