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STUDY OF PHARMACO-TECHNOLOGICAL
PROPERTIES OF SOLID DISPERSIONS OF
THIOCTIC ACID OBTAINED BY
MICRONIZATION METHOD

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Introduction

Thioctic acid is used in the treatment of diseases characterized by lack of mitochondrial activity, responsible for the formation of free radicals. Widespread use of thioctic acid is due to its chemical structure - it exhibits biological activity in both the hydrophilic (cytoplasm, extracellular matrix) and in the hydrophobic (plasmalemma) environments. Thioctic acid is an enzyme cofactor and a powerful antioxidant, it regulates the transcription of numerous genes, participates in regulating the metabolism of glucose and lipids, increases sensitivity to insulin, forms complexes with heavy metals. Thioctic acid has a high pharmacological potential, which is confirmed by the evidence base of clinical trials. An analysis of literature data on the oral use of thioctic acid indicates that solid dosage forms can be used for long-term therapy. This route of administration is limited by factors such as reduced solubility in the acidic environment and enzymatic degradation. For this reason, the search for various compositions of auxiliary substances and methods for the

obtaining of thioctic acid preparations is an urgent task of pharmaceutical technology [1, 2].

Recently, a promising direction of increasing the bioavailability of an active pharmaceutical ingredient (API) in solid dosage forms is the use of solid dispersions (SD) - multicomponent systems consisting of a highly dispersed solid phase of API in the matrix of a carrier with partial formation of complexes of variable composition. A characteristic feature of solid dispersions obtaining is the ability to modify the properties of the active ingredient and obtain new pharmaceuticals with improved bioavailability on its basis [3].

The aim of the work was to study the physical and chemical properties of solid dispersions of thioctic acid for the development of the composition and technology of solid dosage form with improved bioavailability.

Materials & methods

The study objects were solid dispersions of thioctic acid (SDTA) on the basis of cellulose derivatives: microcrystalline (MCC) - sample 1T, HPMC (hydroxypropyl methylcellulose) - sample 2T and polyvinylpyrrolidone (PVP) - sample 3T compared with thioctic acid (TA). The samples were prepared by solid-phase method using micronization in a laboratory shredder for 15 minutes at a ratio of 1: 1. Pharmacological parameters were determined according to generally accepted methods. Wetting was determined by the cosine of the marginal angle using the drop method, measuring several of its values as a function of time (Fig.1) [4].

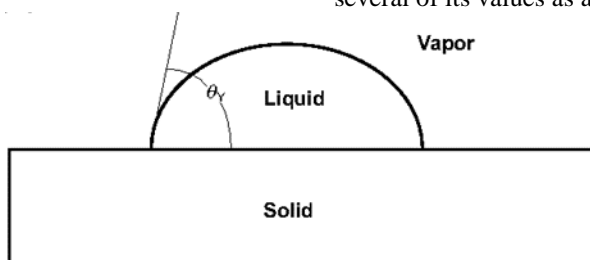


Fig. 1. Determination of the cosine of the wetting angle

The kinetics of moisture absorption was determined by the weight method in extreme conditions, using a desiccator, in which created conditions of 100% relative humidity with purified water.

The degree of dissolution in the aqueous medium was determined by spectrophotometric method at Evolution 60-S spectrophotometer in a cell with a layer thickness of 10 mm [5].

Flowability was determined by the method of SPU-II ed., using a funnel with a diameter of 1.5 cm. The Carr Index and the Hausner ratio were calculated according to formulas 1 and 2, respectively:

$$\text{Carr index} = \frac{\rho_{\max} - \rho_0}{\rho_{\max}} \times 100 \quad (1)$$

$$HR = \frac{\rho_{\max}}{\rho_0} \quad (2)$$

where: ρ_{\max} - tapped density, g / ml;
 ρ_0 - bulk density, g / ml.

Porosity (P, %) was determined based on the values of bulk density and true density by the formula 3:

$$P = \left(1 - \frac{\rho_{\max}}{\rho_0} \right) \quad (3)$$

The coefficient of compression was determined by the ratio of the height of the powder in the matrix to the height of the resulting tablet.

Hardness (HB) was determined by Brinell method. To obtain comparable results, the relative

hardness measurement was carried out at $D_s = 10$ mm, $P = 250$ kgf, duration of exposure 30 s [6, 7].

The microscopic analysis was performed with the help of a laboratory microscope Konus-Akademy of Italian production with an eyepiece- Camera ScopeTek DCM510 (China). ScopePhoto™ software was used to visualize the images, which allows measuring linear dimensions in real-time and in static images. To describe the shape of the particles, the value of the form factor (F) was used, which defines the isodiametricity degree and is calculated by the formula (4),

$$F = \frac{l_{max}}{l_{min}}, \quad (4)$$

where: l_{max} is the maximum linear size of particle projection;
 l_{min} - the minimum linear size of particle projection [8].

Results & discussion

In appearance the resulting mixtures had lemon color, without inclusions and the formation of conglomerates with uniform in size particles.

Results of moisture absorption determination are shown in Fig. 2.

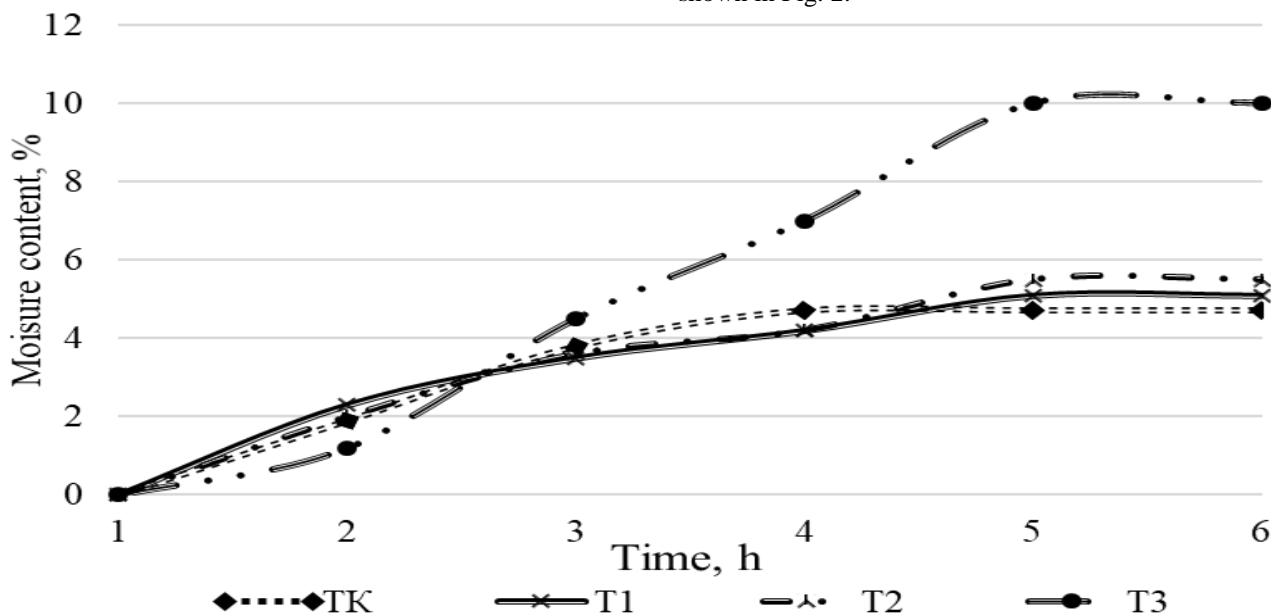


Fig. 2. Kinetics of moisture absorption of solid dispersions at 100% relative humidity

As can be seen from the data shown in Fig. 2 samples reach equilibrium at the fifth hour of the experiment, indicating the presence of physical sorption. The PVP sample, unlike the others has a clear transition from the rectilinear area of air vapor sorption to the nonlinear. This can be explained by the fact that in samples of TA, T1, T2 in the process of mass transfer of water both in the gas and in the condensed phases there are areas with an additional resistance to the process of mass transfer, which reduce the rate of water vapor sorption, and lead to an earlier deviation of sorption dependence on time from the rectilinear. The tangent of the kinetic curves angle for

these samples is 0.17, for T3 - 0.36. The obtained values indicate a higher initial velocity of the moisture absorption process in a sample with PVP. At 100% relative humidity of air for five hours of the experiment, the samples absorbed from 5.1% (TA, T1, T2) to 10.0% (T3) moisture, with a visually determined change in the external state and color: from bright yellow to orange. The kinetic parameters of the sorption process allow suggesting a change in the physical and chemical properties of the thioctic acid in PVP-based sample.

The results of the determination of the pharmacotechnological parameters of solid dispersions are given in Table 1.

Table 1 - The pharmaco-technological properties of solid dispersions of thioctic acid obtained by the solid phase method

Indicator	Sample			
	TA	1T	2T	3T
Carr Index, %	28,3±1,12	42,00±1,12	48,39±1,12	33,96±1,12
HR	1,39±0,06	1,72±0,06	1,94±0,06	1,51±0,06
The angle of the natural slope, °	60±1,03	55,7 ± 1,0	70,00 ± 2,0	63,3 ± 1,0
Fluidity, g / s	1,12±0,001	1,31 ± 0,01	1,46 ± ,0,01	1,17 ± 0,01

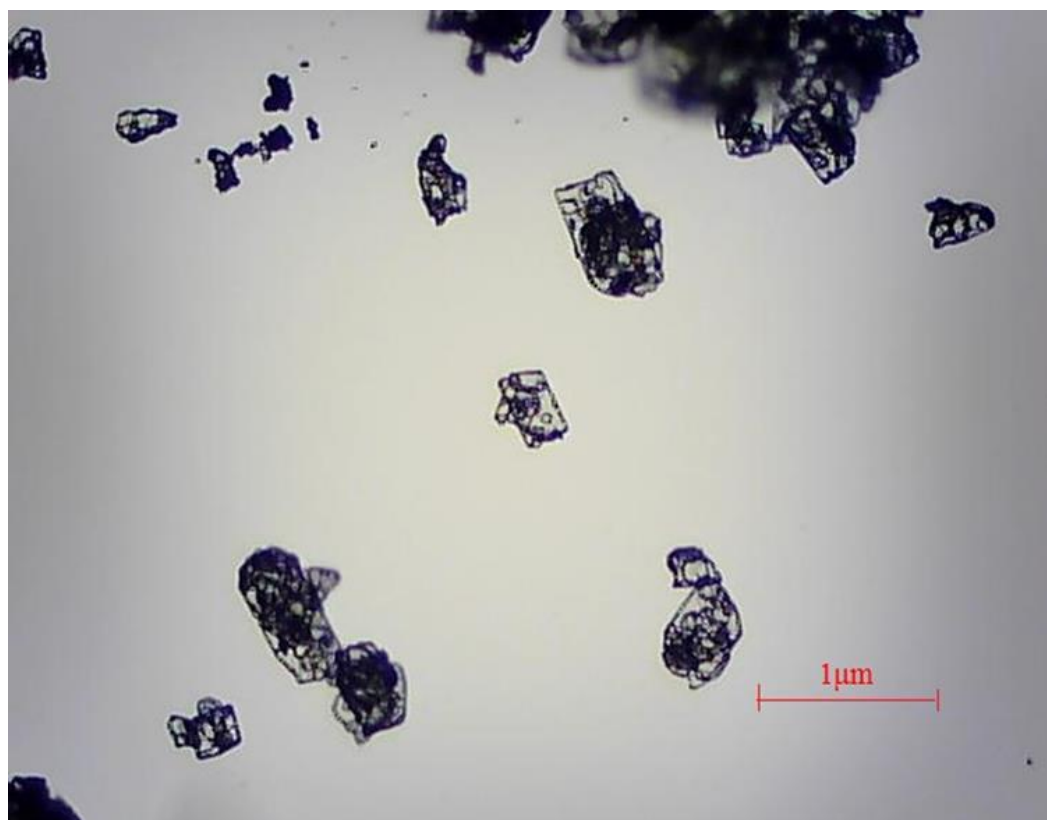
Porosity,%	28,24±0,36	42±0,36	48±0,36	34±0,36
Compaction ratio	0,495±0,0183	0,93±0,0157	0,98±0,0162	0,94±0,0145
Moisture content,%	0,50±0,01	0,75±0,02	0,56±0,01	0,96±0,02
Relative density	0,7176±0,0086	0,586±0,01	0,526±0,006	0,666±0,007
Wettability, cosθ	0,096±0,001	0,976±0,001	0,716±0,002	0,706±0,002

Note: P≥95, n = 5

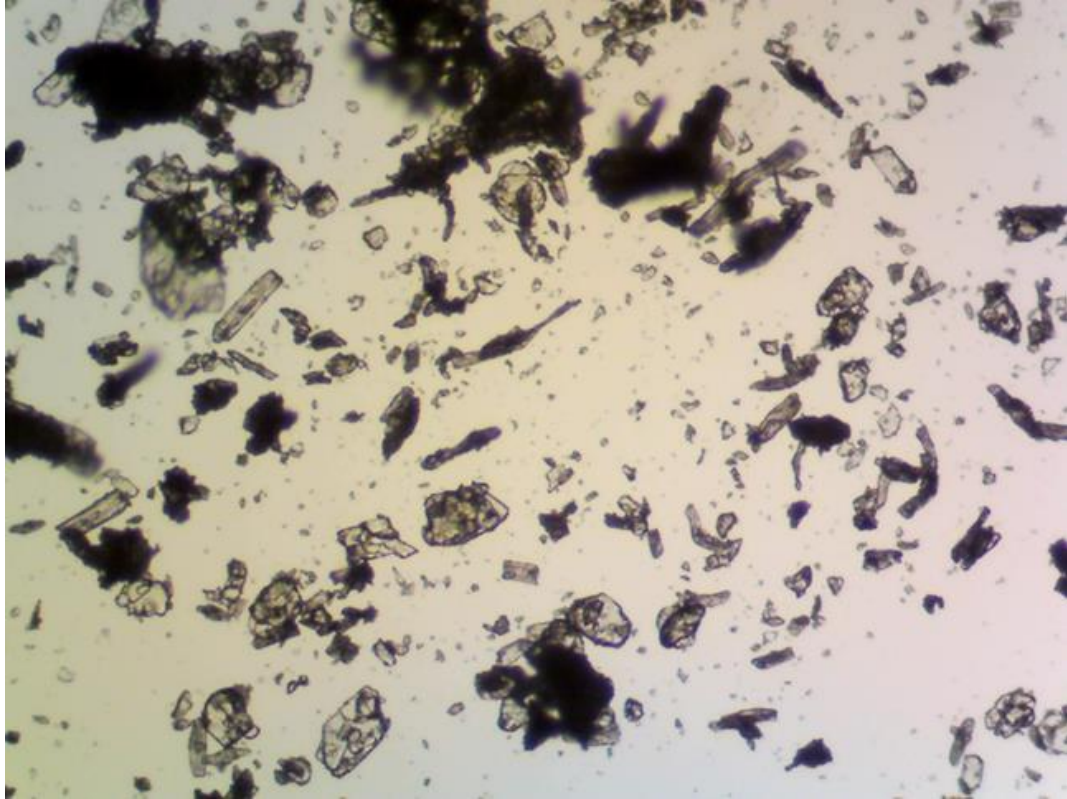
As can be seen from the data in the table, all samples have no satisfactory fluidity. The values of the Carr index (> 25) and the Hausner ratio (> 1.4) make it possible to conclude that there is a large force of cohesion between particles and a significant aeration of the material. The micronization of the substance in a mixture with MCC, PVP and HPMC has led to a change in the stacking density, which is characteristic of powders with an anisodiametric form of particles, but the strength of the internal friction coefficient has practically not changed, as evidenced by the indicators of the angle of natural slope. Porosity indicators suggest a significant degree in the action of the Van der Waals forces between the SD particles. All samples of solid dispersions can be attributed to fragile materials: HB was 5.57 kgf / mm². When stored at rest there was a partial

agglomeration observed. The results show that all samples of SD are well wetted with purified water (T1: cosθ = 0,97, T2: cosθ = 0,71, T3: cosθ = 0,7) in contrast to the sample of thioctic acid (cosθ = 0.09). Analysis of the marginal wetting angle indicates that the addition of high molecular substances increases the degree of interaction with the aqueous environment. The speed of setting the equilibrium marginal angle is in the following dependence: 1T > 3T = 2T, this is due to the degree of the sample surface roughness, the fractional void volume and the properties of the auxiliary substances.

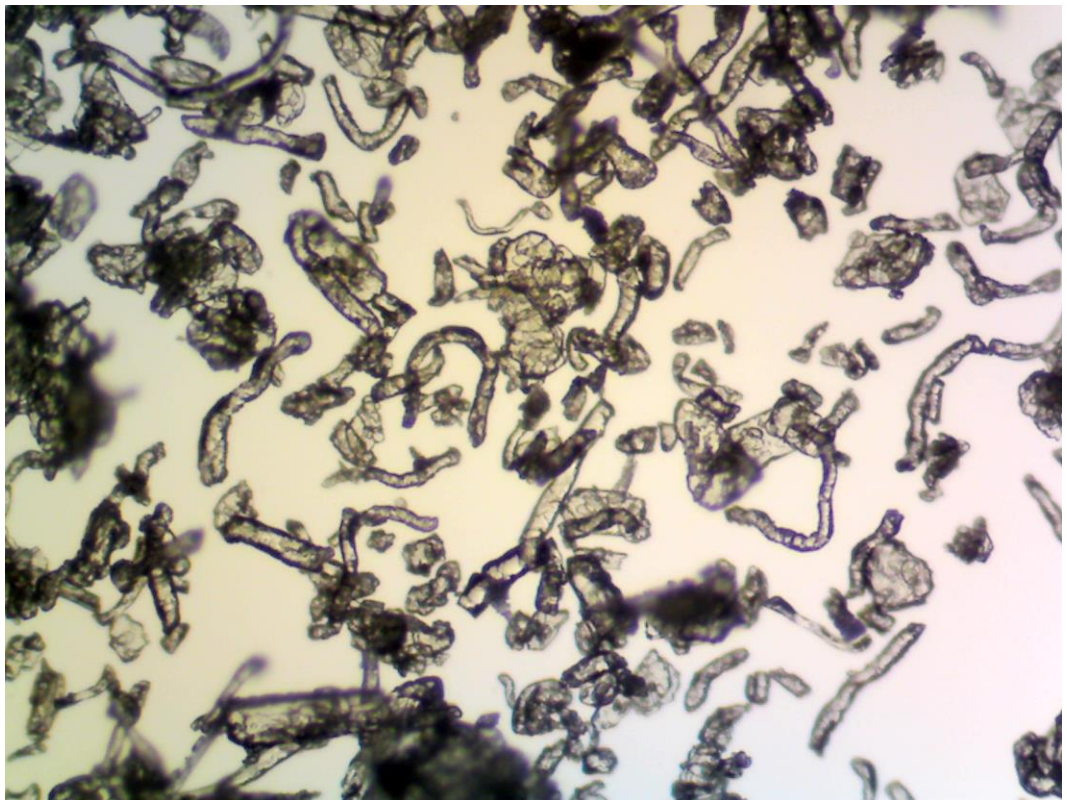
Shape and size of particles is an indispensable characteristic of the pharmaco-technological properties of powders (Fig. 3).



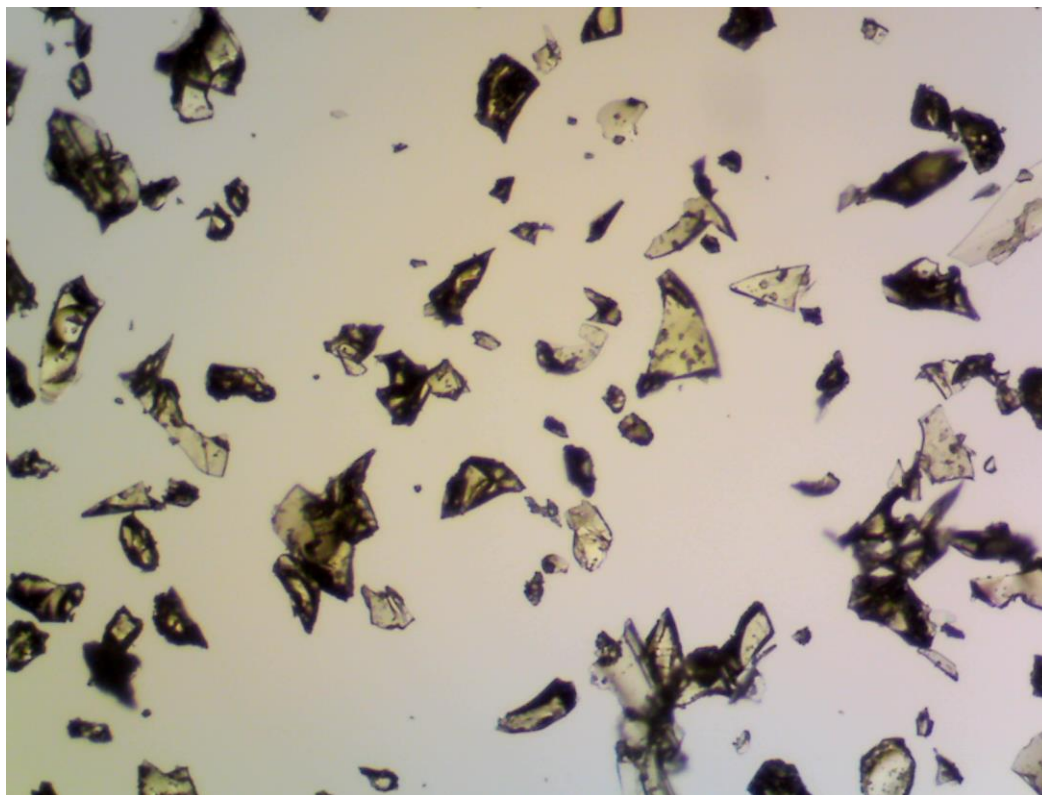
a) Thioctic acid



b) 1T



c) 2T



c) 3T

Fig. 3. Crystallographic characteristics of thioctic acid powder and its solid dispersions

As can be seen from Figure 3, the influence of external forces has changed the shape of thioctic acid: from the lamellar with form factor of 0.85 to an indefinite shape with a low coefficient of proportionality in the sample 3T

(Fig. 3c). In samples 1T and 2T (Figures 3a, 3b) there is a mixture of crushed crystals of thioctic acid and carrier. The form factor has dropped to 0.45.

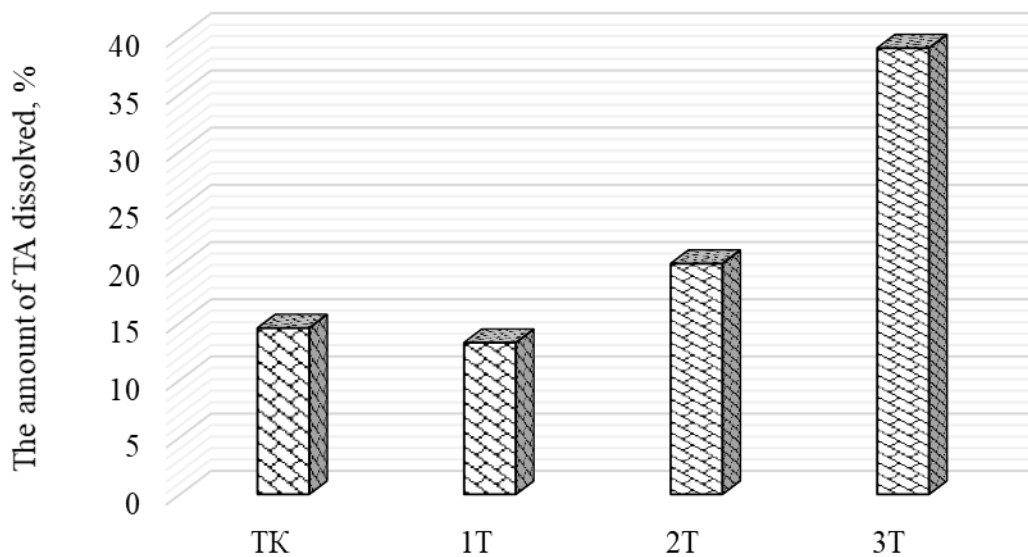


Fig. 4. Thioctic acid and its solid dispersions solubility

Investigation of the degree of solubility of the obtained solid dispersions (Figure 4) has shown that the addition of MCC to thioctic acid even reduces the amount of matter passing into the solution, in contrast to solid dispersions with PVP and HPMC (24% and 37% respectively). The difference in the values of the solubility can be related both to the nature of chemical bonds, and to the nature of electrostatic interaction, which is due to the polarity and the occurrence of hydrogen bridges.

Conclusion

1. It has been established that micronization leads to changes in the pharmaco-technological properties of the thioctic acid. The obtained results allow assuming an increase in the degree of Van der Waals forces action between SD particles compared with thioctic acid. Determination of the hardness of the samples obtained allows attributing them to fragile materials with the ability to agglomeration.

2. The positive influence of HPMC and PVP as opposed to MCC on the increase of thioctic acid dissolution has been established. The presence of HPMC and PVP in the compositions of solid dispersion contributed to the formation of a water-soluble complex of API-auxiliary substance. The mixed nature of the interaction between the molecules of the SD components causes its new physico-chemical properties. Thus, the obtained results indicate an increase in the dissolution of thioctic acid in the solid dispersion with PVP in 2.6 times, with HPMC in 1.3 times and can serve as the basis for research on the development of solid dosage forms of thioctic acid.

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INVESTIGATION OF THE PHARMACO-TECHNOLOGICAL PROPERTIES OF SOLID DISPERSIONS OF THIOCTIC ACID, OBTAINED BY MICRONIZATION

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Introduction. Thioctic acid is used in the treatment of diseases that are characterized by lack of mitochondrial activity, which is responsible for the formation of free radicals. Widespread use of thioctic acid is due to the chemical structure. The thioctic acid exhibits biological activity in both hydrophilic and hydrophobic environments. Thioctic acid is an enzyme cofactor and a powerful antioxidant, it regulates the transcription of numerous genes, participates in regulation of glucose and lipid metabolism, increases insulin sensitivity, and forms complexes with heavy metals. Thioctic acid has a high pharmacological potential, which is confirmed by the evidence base of clinical trials. An analysis of the literature on the oral use of thioctic acid indicates that solid dosage forms can be used for long-term therapy. This route of administration is limited by factors such as reduced solubility in acidic environments and enzymatic degradation. For this reason, the search for various compositions of auxiliary substances and methods of obtaining drugs is an urgent task of pharmaceutical technology. **Material & methods.** Objects of study were solid dispersions of thioctic acid (SDTA) on the basis of cellulose derivatives: microcrystalline (MCC), HPMC (hydroxypropyl methylcellulose) and polyvinylpyrrolidone (PVP) as compared to thioctic acid (TA). The samples were made by solid phase method using micronization in a laboratory shredder at a ratio of 1: 1. Pharmacological and technological parameters were determined according to generally accepted methods. **Results & discussion.** In appearance the resulting mixtures had lemon color, without inclusions and the formation of conglomerates, with homogeneous sized particles According to the pharmaco-technological studies, the samples do not have a satisfactory flowability. The values of the Carr index and the ratio of Hausner make it possible to conclude that there is a large force of cohesion between the particles, a significant aeration of the material. As can be seen from the data presented in the

table, micronization in the medium of MCC, PVP and HPMC has led to a change in the density of stacking, which is characteristic of powders with an anisodiametric form of particles, but the strength of the internal friction coefficient has practically not changed, as evidenced by the indicators of the natural slope. The value of porosity suggests a significant degree of the Van der Waals forces action between the particles of the SD. All samples of solid dispersions can be attributed to fragile materials: BW was 5.57 kgf / mm². When stored in a static state, there was a partial agglomeration. The results show that all samples of solid dispersions are well moistened with purified water, as opposed to a sample of thioctic acid. An analysis of the marginal wetting angle indicates that the surfaces of samples of solid dispersions are hydrophilic. According to the microscopic analysis it was established that the influence of external forces has changed the form of the thioctic acid: from the plate with the factor of the form 0,85 to the uncertain form. In samples with microcrystalline cellulose and hydroxypropyl methylcellulose there is a mixture of crushed thioctic acid crystals and carrier. The form factor has dropped to 0.45. The investigation of the dissolution of the obtained solid dispersions showed that the addition of MCC to thioctic acid even reduces the amount of matter passing into the solution, as opposed to solid dispersions with PVP and HPMC (24% and 37% respectively). The difference in the values of dissolution can be due to both the nature of chemical bonds, and the nature of electrostatic attraction, due to the polarity and the emergence of hydrogen bridges. The investigation of the dissolution of the obtained solid dispersions showed that the addition of microcrystalline cellulose to thioctic acid even reduces the amount of matter passing into the solution, as opposed to solid dispersions with PVP and HPMC. The difference in the values of dissolution can be due to both the nature of chemical bonds, and the nature of electrostatic attraction, due to the polarity and the emergence of hydrogen bridges. **Conclusion.** Thus, the results indicate an increase in the dissolution of thioctic acid in the solid dispersion with PVP in 2.6 times, with HPMC in 1.3 times, which may be the basis for research on the development of solid dosage forms of thioctic acid.

Keywords: Thioctic acid, solid dispersions, pharmaceutical technology, micronization