STUDYING THE INFLUENCE OF FRACTIONAL COMPOSITION AND KINETICS OF MOISTURE SORPTION ON THE QUALITY OF CAPSULATED MASS AND CAPSULES“CELNINCIL”

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Abstract---*This report presents experimental data on the influence of technological factors and humidity on the quality indicators of “Tselnincil” capsules of the selected composition, which was determined using mathematical planning of the experiment using the 3 × 4 Latin square method. The effect of fractional composition, relative humidity, and moisture absorption kinetics on the quality indicators of Tselnincil capsules was studied. The obtained results are used to test capsule technology in a production environment. The method and mode of granulation are selected.*

Keywords---*Capsules, fractional composition, technology, wet granulation, moisture absorption.*

I. INTRODUCTION

Pharmaceutical factors determine the quality, bioavailability of the finished product. One of them is the manufacturing process for the production of dosage forms, which is of particular importance and significance in the development of new drugs and the improvement of compositions and technology. The study of pharmaceutical factors is of practical importance and remains promising [1,3].

The quality of the capsules substantially depends on a number of technological factors - fractional composition, particle shapes, residual moisture, moisture absorption kinetics, which have a significant impact on the technological parameters of granules and the quality indicators of encapsulated dosage forms.
The fractional composition, or particle size distribution of material particles, has a certain effect on the fluidity of powdered materials, and therefore on the rhythmic operation of encapsulated machines, the stability of the mass of capsules obtained, and the dosage accuracy of the drug substance. Studying the moisture-sorption properties of the substance will allow you to choose the type and optimal amount of excipients and to develop the features of the process, conditions and shelf life of the substance, guaranteeing the stability of the tablets. The value of the fractional composition helps the technologist to select the optimal granulation conditions. With the "transfer" of the technology of drugs from laboratory conditions to production, methods and modes of granulation on the appropriate equipment are of no small importance [2,4,5].

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Earlier, using the mathematical method of planning an experiment of the Latin square 3×4, a statistical analysis of the results obtained according to the Fisher criterion, the Duncan criterion and the function of desirability, we revealed the regularity of the influence of excipients on technological properties, quality indicators, the dynamics of capsule dissolution, established the preferred series of excipients and selected the optimal composition of the encapsulated drug “Celnincil” [2].

Based on the foregoing, in order to develop optimal technology, it became necessary to study the influence of pharmaceutical factors (fractional composition, kinetics of moisture absorption and relative humidity) on the quality indicators of recommended capsules.

II. MATERIALS AND RESEARCH METHODS

The object of the study was the granular mass of the capsule “Celnincil” obtained according to our recommendations recommended composition and technology. The studied properties of the properties of materials were determined according to generally accepted methods:

For determination, we used a special set of 5 screens, located one above the other, with a hole diameter of 2, 1, 0.5, 0.25, mm.An exact sample of the substance (100 g) was placed on the upper sieve witha hole diameter of 2 mm. The entire kit was shaken on a vibrator for 5 minutes. Then the sieves were successively removed and their contents were weighed, finding the percentage of each fraction. Moisture-absorbing properties were studied by the method of S.A. Nosovitskaya et al. At various values of relative humidity. To determine the residual moisture in the granulate, a Kett moisture meter was used, and it was also determined by the method of drying to constant weight according to GF XI. The flowability of the mixture and the angle of repose (the angle between the formed cone of bulk material and the horizontal plane was determined using a vibratory funnel of the VP-12A serial device with an opening diameter of 12 mm. The determination of bulk density was carried out on a device of model 545 R-AK-3 of the Mariupol plant of technological equipment on a device for vibrational compaction of powders. Disintegration, - was carried out on devices of the Erweka company (Germany).

Mixing uniformity was found using dosing uniformity techniques; capsule disintegration was calculated according to the methods specified in the State Pharmacopoeia of the 11thedition [6]. Statistical data processing was performed using the computer program Microsoft Excel.

III. RESULTS AND DISCUSSION

The study of obtaining granules of the selected composition in laboratory conditions was carried out by wet granulation followed by sieving through a sieve with a hole diameter of 1.15 mm. The obtained granules were determined by such technological properties as fractional composition, relative humidity, flowability, bulk density, uniformity of mixing, disintegration of the capsules. The obtained data are presented in table. 1.

The data obtained showed that the state of the fractional composition, which affects the technological parameters of the granulate and the quality indicators of the capsules, depends on the granulation mode. It was found that with an increase in the dusty fraction of particles (0.17 mm or less) in the fractional composition of more than 22%, flowability worsens. Based on the studies, the optimal granulation mode was selected.

An analysis of the data on technological indicators allowed us to conclude that for testing capsule technology under industrial conditions, wet granulation of granulate production can be recommended. The relative humidity of the powders

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are important technological factors for encapsulation, the optimization of which allows increasing the productivity of the equipment and improving the quality of the finished product.

Table1. The influence of fractional composition on the technological parameters of the granulate and quality indicators recommended “Celnincil” blown capsules

Index	Fractional composition, particle size, mm - content,%				
	1,0–1,45 0,7–8,20 0,5–15,02 0,315–32,35 0,2–24,08 0,16–10,30 dust – 8,60	1,0–1,08 0,7–8,26 0,5–15,70 0,315–14,4 0,2–15,18 0,16–4,82 dust–40,56	1,0–0,80 0,7–1,42 0,5–18,55 0,315–23,20 0,2–20,90 0,16–17,13 dust – 18,0	1,0–1,11 0,7–5,60 0,5–16,65 0,315–27,7 0,2–34,00 0,16–12,34 dust – 2,60	1,0–9,6 0,7–12,3 0,5–28,4 0,315–22,7 0,2–8,0 0,16–7,0 dust – 12,0
Humidity of granulate,%	0,60 ± 0,93	0,3 ± 0,53	0,98 ± 0,13	1,33 ± 0,43	1,11 ± 0,23
Bulk density g/cm^3: - with seal - without compaction	0,665±0,02 0,505 ± 0,03	0,565 ± 0,04 0,495 ± 0,05	0,606 ± 0,03 0,500 ± 0,05	0,623 ± 0,04 0,509 ± 0,02	0,645 ± 0,01 0,550 ± 0,01
Flowability, g / s: - with vibration - without vibration	6,20 ± 0,29 6,98 ± 0,19	3,5 ± 0,31 0,42 ± 0,49	2,90 ± 0,24 0,64 ± 0,32	6,50 ± 0,12 7,20 ± 0,18	6,06 ± 0,18 7,43 ± 0,15
Strength, - abrasion,% - for compression, N	99,2 ± 0,23 76,00 ± 5,28	97,80 ± 0,75 53,00 ± 5,12	99,98 ± 0,02 44,6 ± 7,23	99,60 ± 0,12 75,00 ± 4,65	99,68 ± 0,23 71,23 ± 6,12
Disintegration of tablets, s	180 ± 25,00	215 ± 5,00	111 ± 21,00	224 ± 41,00	210 ± 35,00

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Disintegration of capsules, s	165±15,00	230±6,00	102±11,00	213±31,00	242±9,00

The aim of our next research was to study the moisture sorption activity of the encapsulated mass ensuring the stability of the drug. Moisture-absorbing properties of the substance were studied by the method of S.A. Nosovitskaya et al. At various values of relative humidity [4].

To study the kinetics of moisture absorption, pre-weighed mass samples (0.5 g each) were placed in open containers with a diameter of 2.0-2.6-3.3 cm, then the containers were placed in desiccators containing saturated sodium bromide solutions (relative humidity 58 %), ammonium chloride (relative humidity 78%), zinc sulfate (relative humidity 90%) and purified water (relative humidity 100%).

Within 7 days, every 24 hours, the boxes were removed, closed with lids and weighed on an analytical balance with an accuracy of + 0.0001 g, the mass of the test substance was determined with the subsequent calculation of the absorbed moisture. Desiccators were thermostated at a temperature of 22 + 10C. The results of the kinetics of moisture absorption of the substance at various indicators of relative humidity of the environment are presented in Figure 1.

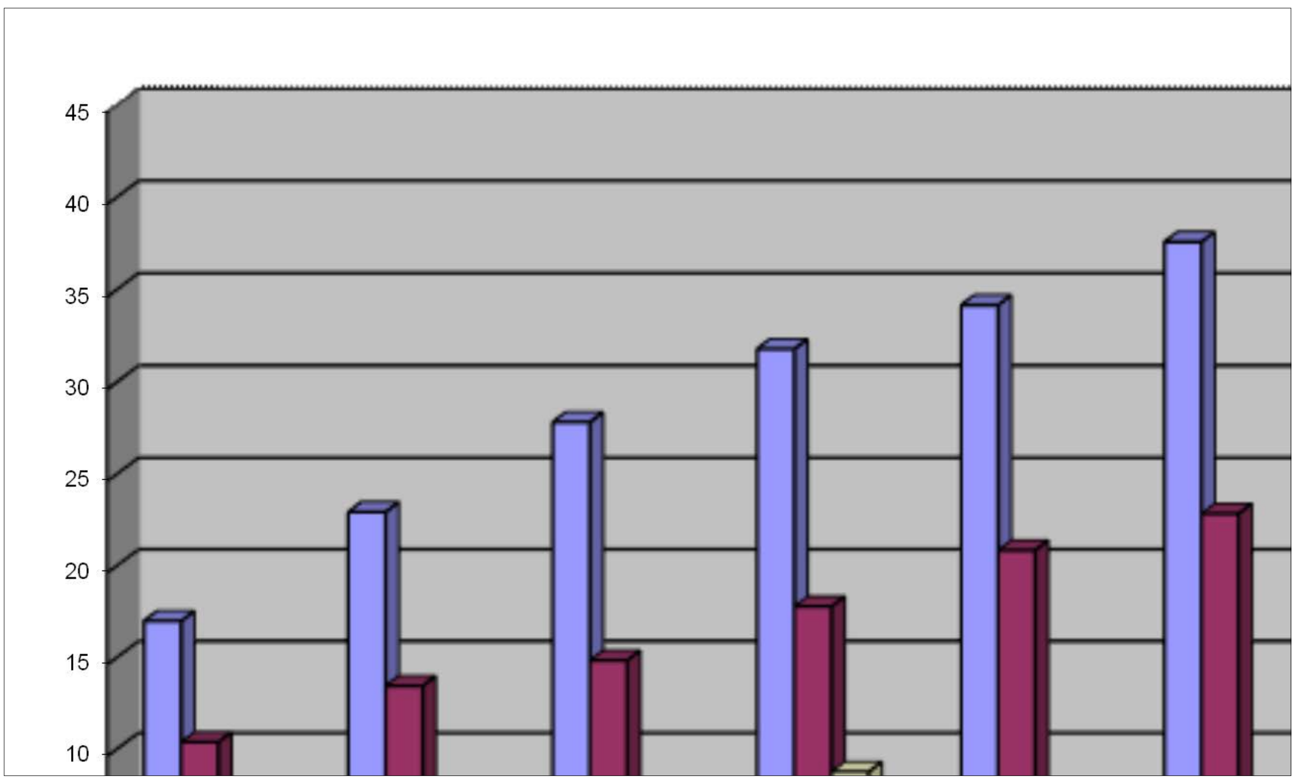

Fig. 1. The results of the kinetics of moisture absorption of the encapsulated mass “Celnincil” at various relativehumidity indicators

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From the above results, it should be noted that at a relative humidity of 58% for 7 days, the amount of adsorbed moisture increased in increasing order. The amount of adsorbed moisture after 1,3,5,7 days is in the range of 17.09-21.05%; 42.32-45.0%; 57.98-67.97%; 75.15-78.02%, respectively. In the relative humidity of the environment up to 79, 90 and 100% increases the moisture sorption properties of the studied samples of mass for encapsulation. Moreover, over the period of the experiment, the amount of adsorbed moisture is 90.94; 112.23 and 120.11, respectively.

The next stage of the experiment was the study of the influence of the moisture sorption properties of the encapsulated mass of the factor — the size of the surface area of the sample.

The studies were also carried out by the gravimetric method at 58% relative humidity, which was created due to a saturated solution of sodium bromide.

For this, a pre-weighed amount of dry extract was placed in boxes of various diameters. In this case, desiccators containing boxes were thermostated at a temperature of 22±10°C.

The specific surface moisture absorption S (g/m^2), which characterizes the amount of moisture sorbed through a surface unit, was calculated by the following formula:

$$У = (m – m_0) / S,$$

Where,

m-is the mass of the sample at certain intervals, g;

m 0-is the initial mass of the sample, g;

S - specific surface moisture absorption, g / m2

The research results are shown in Fig. 2.

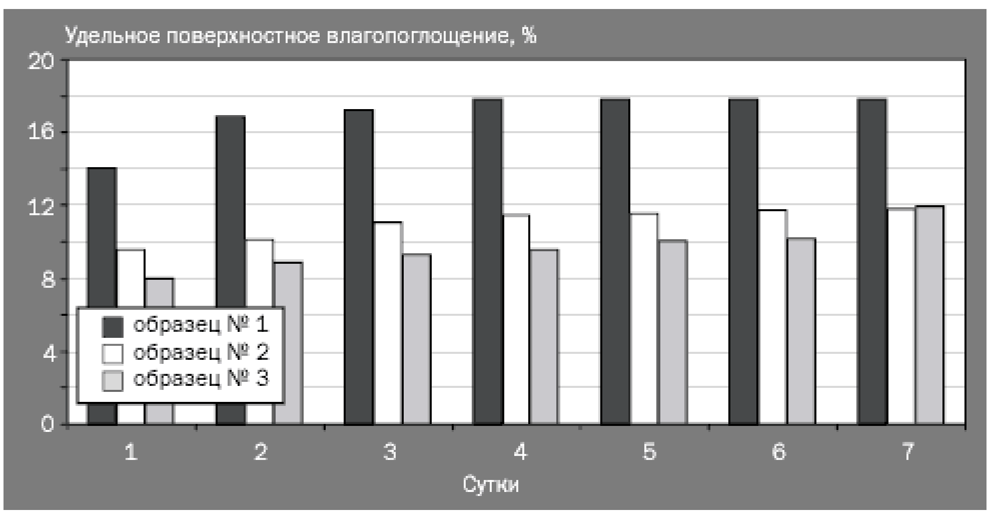

Fig. 2. Specific surface moisture absorption of theencapsulated mass“Celnincil”at various sizes samplesurface

According to the data obtained, it has increased hygroscopicity, which increases with increasing relative humidity of the environment, as evidenced by the appearance of the samples and the amount of absorbed moisture.

In further studies, we studied the effect of relative humidity on the technological indicators of the quality of granules of Tselnincil capsules. We have prepared model mixtures (more than 20) with different relative humidity. The results of the experimental data showed that with an increase in the residual moisture content in the granulate up to 4.00% for compression, it remains high and tends to increase.

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However, granulate with a residual moisture content of 5.15% or more loses its flowability property. It was found that the residual moisture content of the granules of the encapsulation mixture should be no more than 3.50%.

Rational modes of storage of medicines allow a long time to maintain their quality, reasonably approach the selection of packages for them. The process of long-term storage of goods is due to the constant interaction of internal and external factors. Internal factors that make up the qualitative characteristics of the goods - properties and quality of the material, chemical composition, humidity, amount of active substances, etc. External factors include climate, season, type of storage and its condition, relative and absolute humidity and temperature of storage facilities, light, etc.The study of hygroscopic properties helps to create storage conditions appropriate for the physicochemical properties of substances, as well as to select packaging that ensures consistent quality both during storage and during transportation [5,6].

Considering this, the moisture-sorption properties of the capsules were studied by the method of S. A. Nosovitskaya. At various values of relative humidity of the environment according to the above conditions.

Comparative indicators of the kinetics of moisture absorption are given in table.2.

Table2. Thekinetics of moisture absorption of granules and capsules “Celnincil” at various relative valuesenvironmental humidity

Compositions	The amount of absorbed moisture, with relative humidity,%				
	The duration of the study, day	58%		100%	
		granules	capsules	granules	capsules
1	1	3,54	2,82	11,0	13,76
	2	2,11	2,63	10,57	16,69
	3	1,00	1,13	8,4	18,53
2	1	4,36	2,02	29,80	20,10
	2	3,32	1,88	38,80	27,58
	3	2,32	0,75	41,45	29,18
3	1	4,22	2,74	49,80	31,90
	2	3,44	2,24	58,80	85,18
	3	2,11	0,86	11,45	87,50
4	1	5,09	4,05	79,80	42,8
	2	3,10	3,45	12,83	65,0
	3	2,27	2,87	11,52	87,2
5	1	8,12	2,75	49,80	30,34
	2	4,13	1,98	33,80	32,84
	3	3,54	1,94	42,21	44,02

The results of studies of granules and capsules with various fillers in terms of their moisture absorption capacity allowed us to conclude that MCC and Aerosil can be used as promising fillers for capsules.

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The size selection of hard gelatin capsules in order to fill them with a mixture for encapsulation of the selected composition was carried out based on the average capsule capacity according to table GF 11^{th},No.2 edition of the general pharmacopoeial article “Capsules” [6], using the mass of the encapsulated mass of 0.5 g, as well as the bulk density of the mass for encapsulation with compaction (0.638+0.009 g/cm^3).

The results on the selection of the number of hard gelatin capsules for encapsulation of the selected composition are presented in table. 2.

Table 3. Hard gelatin capsule number selection.

Number of capsules	Average capsule capacity, cm3	The volume of the selected composition,%	Free ml% capsule volume,%
000	1,37	-	87,1
00	0,95	-	82,5
0	0,68		75,4
1	0,5	39,5	58,8
2	0,37	-	55,9
3	0,30	-	45,8
4	0,21	-	25,4
5	0,13	-	—

Based on the analysis of the data obtained, it was found that the most optimal size for filling the capsules with the capsule mixture “Tselnincil” are hard gelatin capsules No. 1. The composition and technology of Celnincil capsules developed in the laboratory were tested with a positive result under production conditions at SAMO LLC.

IV. CONCLUSIONS

The method and mode of granulation of encapsulated masses for capsules “Celnincil” was selected, the influence of fractional composition, relative humidity on the quality indicators of capsules “Celnincil” was studied.

It was found that the fractional composition of the granulate should contain a dust fraction of at least 0.16 mm, the residual moisture of the granulate of the mixture for encapsulation should be no more than 3.50%. The positive capsule technology has been tested under production conditions.

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