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The Mechanism of Forming the Granules on the Basis of Lactose and Microcrystalline Cellulose.

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ABSTRACT

The granulation of powder mixtures is used to improve their technical characteristics and describes with physicochemical and rheological results of the used materials. The main part to choose the quantity of moisturizer belongs to auxiliary substances. Analyzing received results of pharmaco-technological and microscopic researches it is possible to assume that equal liquid distribution, substance particle size and the moisturizer concentration have an influence on the mechanism of granule formation. The end point of granule forming can be identified using pharmaco-technological indicators (particle size distribution, strength and flowability). The investigations permit to claim the reasonability of further assessment of the extend of influence of moistening, solubility of substances included in the granulate and the way of its formation.
Keywords: granulation, powder, pharmaco-technological characteristics, microscopic researches

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INTRODUCTION

The granulation of powder mixtures is used to improve their technical characteristics and describes with physicochemical and rheological results of the used materials. The known ways of granulation provides the getting of the ready product with the setting properties: homogeneity, size, strength. The type of the granulation method depends on the type of the material. In the Pharmaceutical Industry three types of the granulation are mainly used: dry, wet and structured. In most cases the wet granulation is applied. It provides all the necessary functions of the mixtures to get solid drug formulations: flowability, compactness, uniformity of the drug substances distribution based on the properties of medicinal and auxiliary substances. In case of using little doses of active ingredient, modification and prolongation of the action, the wet granulation allows to get intermediate product with stabilizing agents, like modifiers pH, and thereby to achieve the maximum of the product stability. The granulation of low doses of active ingredients lets to fix substances into granules, that helps to avoid segregation problem [1].

The microscopic research was performed considering the existing methods for the determination of powder dispersion. In accordance with the accepted classification all the methods can be divided into the following groups:

- Mechanical separation of particles which includes sieve and filtration analyses.
- Sediment analysis, which includes fractional sedimentation, elutriation, sediment accumulation and the selection of weighted samples.
- Dynamic methods based on the separation of particles in the flow in vertical tanks and centrifugal devices.
- Individual study of particles, including microscopic and ultramicroscopic analyses.
- Determination of specific surface, which includes the adsorption method as well as the rate of solution one and so on.

The most common methods of express analysis of the powders disperse content in the range of measured sizes > 0.5 micron are sieve and microscopic.

The main part to choose the quantity of moisturizer belongs to auxiliary substances. In table 1 there are facts of average quantity of auxiliary substances which are used in wet granulation [3].

As we can see from the table data the main part belongs to diluents. So the aim of our work is to study the mechanism of forming of the granules with lactose, microcrystalline cellulose and the mix of them by the method of wet granulation.

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Table 1: The average quantity of auxiliary substances which are used in wet granulation

Function	Name	Quantity, %
1	2	3
Diluents	Microcrystalline cellulose (MCC)	10–30
	Lactose Monohydrate	up to 90
	Dibasic calcium phosphate	up to 90
	Mannitol	up to 90
Binders	Starch	2–5
	Povidone	1–3
	Hypromellose	1–3
Disintegrants	Starch	5–20
	Sodium starch glycolate	2–6
	Croscarmellose sodium	2–6
Disintegrants	Crospovidone	2–6
Antifriction agents	Magnesium stearate	0,5–1
	Talc	3–5
	Stearic acid	1–2
	Aerosil	0,1–0,3

Objects and Methods of Research

The objects of research are microcrystalline cellulose, lactose and the samples of the granules which were got on their basis. The size of lactose parts is 0,1–0,2 mm, shape factor is 0,1; the size of microcrystalline cellulose parts is 0,1 μm, shape factor – 0,1. The treated water was used as a binder. Adding it to the ready mixtures allows validating the technological process of production solid drug formulations. To get the granules the mixture for the granulation was wetted by the treated water at the certain concentration and forced through the perforated plate with diameter of holes is 1 mm. The final determination of the moisturizer quantity was conducted before the adhesion of the granulator mesh holes.

Determination of the granulate strength was made by way of friability test with the help of friabilator. The angle of repose was calculated from the ratio of the height to the radius of the cone, which was formed by the granulate. The Hausner ratio according to the formula is

$$H = \frac{\rho_{1250}}{\rho_0}.$$

Compression ability (the Carr index)

$$\% = \frac{\rho_{1250} - \rho_0}{\rho_{1250}},$$

Where ρ1250 is the tapped density, ρ0 – pour density.

Disintegration of the granule samples was determined according to the methods of the first edition of State Pharmacopoeia of Ukraine for the solid dosage forms in the neutral environment. The granule shape and size were defined using a laboratory microscope which has a camera by the software ScopePhoto providing the simple process of processing of the

received image. Particle sizes were measured observing individual fields of view which were selected in the studied powder sample by moving it to a value greater than the rectangle diagonal or circle diameter, which limits the field of view. The area in which the measurements were carried out and the number of particles equals the sum of their areas when observing the individual fields of view. The determination of particles in individual fields of view is done using the obtained images by measuring the maximum chord in horizontal or vertical directions.

A particle is considered belonging to the observed field, if it is on one of the limit halves. For example, if working with a rectangle, the particles that are inside it, on the left vertical and top horizontal sides, at the intersection of the sides and at another end of one of them are taken into consideration. Particles that are on the other sides and corners are not considered [2].

RESULTS AND THEIR DISCUSSION

The received granule samples were investigated on indicators of pharmaco-technological characteristics. The properties of the granulate on the basis of different diluents are given in the Tables 2−4.

Table 2: The technological indicators of the granulate consisting of lactose

Moisture, %	Hausner ratio	Carr index	Strength, %	Angle of repose	Disintegration, s
5	1,23	18,8	1,450	29	20
10	1,17	14,8	1,350	27	25
15	1,175	15,1	0,990	26,5	32
20	1,19	15,7	0,950	28	50
25	1,1	8	0,946	25	75
30	1,09	8,01	0,940	25	90

The obtained data suggest that at increasing the humidity of the mass for the granulation a straight-line correlation of rise of mass flowability, strength, disintegration and decrease of angle of repose are observed. The compression index in granule samples has the peak after which press capability of the mass is going down. The granule formation begins when treated water is added in an amount of 10 % as evidenced by the structure of the parts which is shown in Fig. 1. The technical property values of the samples in moisture range of 10 % − 20 % permit to assume that at this stage the capillary and surface forces at the boundary between the liquid and solid phases have involved. Further moisture increasing doesn't lead to significant structuring due to adhesive forces arising in adsorbed layers.

Findings of the granulate study consisting MCC with humidity of 5, 10, 15, 20, 25, 30, 40, 50 % are shown in Table 3.

The granule samples which were obtained from the mixture of lactose and MCC 1:2 give us completely different results (Table 4).

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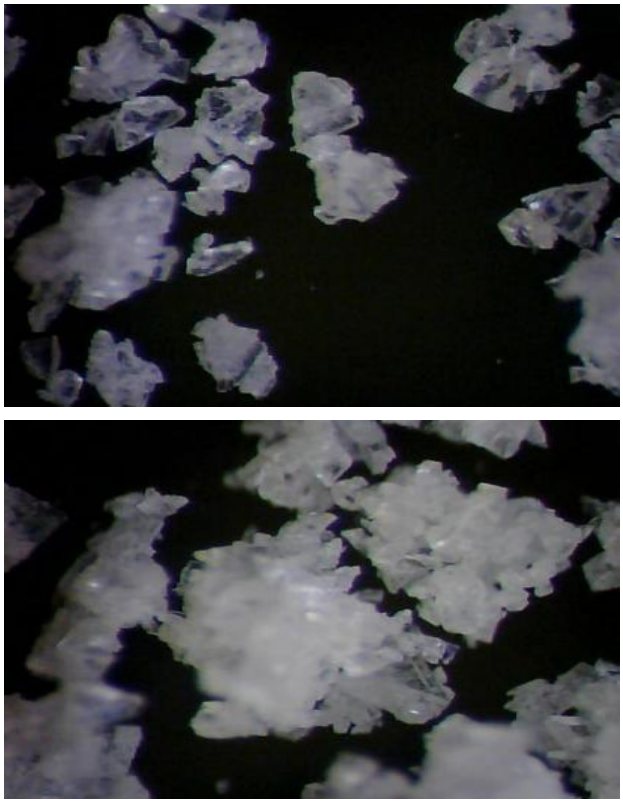
Table 3: The technological indicators of the granulate consisting of MCC

Moisture, %	Hausner ratio	Carr index	Strength, %	Angle of repose	Disintegration, s
5	1,46	31,4	1,29	35	50
10	1,41	28,8	1,19	33,8	63
15	1,405	27,7	1,11	33,7	69
20	1,38	28,1	1,01	33,1	78
25	1,36	27,3	0,98	32,6	121
30	1,11	23,1	0,93	26,6	123
40	1,39	27,9	0,88	33,4	123
50	1,05	4,9	0,87	25	124

Table 4:The technological indicators of the granulate consisting of lactose and MCC in a ratio 1:2

Moisture, %	Carr index	Hausner ratio	Angle of repose	Disintegration, s
5	10,0	1,11	26,6	53
10	25,0	1,33	31,9	81
15	16,7	1,20	25,8	88

When adding moisturizer in the amount of 5 % the mixture has good rheological indicators with low compression factor. But findings of the microscopic analysis show that the granule forming is not going, but the aggregation due to increasing of contact surface of moistened powders. With further moisture adding effective decreasing of the distance between the particles is observed, bonding strength increase due to Van der Waals' forces. Adding of 15 % moisturizer let us to get the granulate with good rheological and pharmaco-technological indicators.



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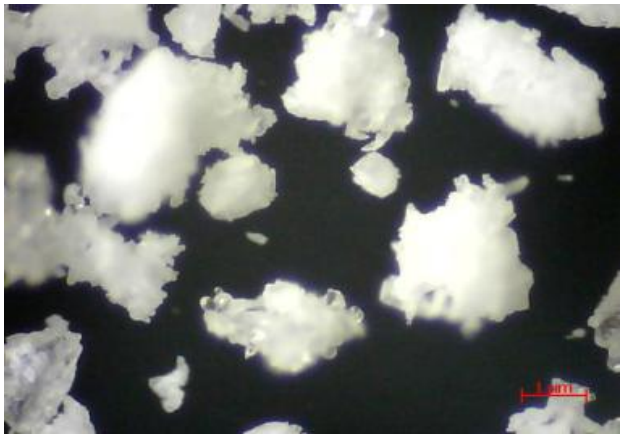
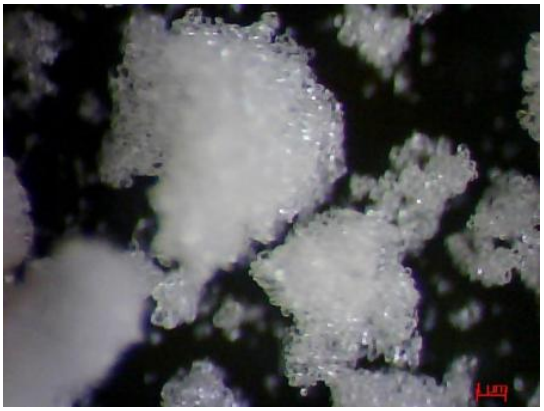


Fig. 1. The structure of granulate consisting lactose in amount of 5 %, 10 %, 25 %



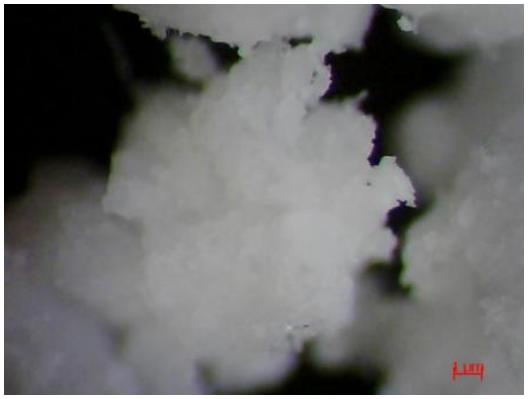


Fig. 2. The structure of granulate consisting MCC in amount of 25 %, 40 %, 50 %

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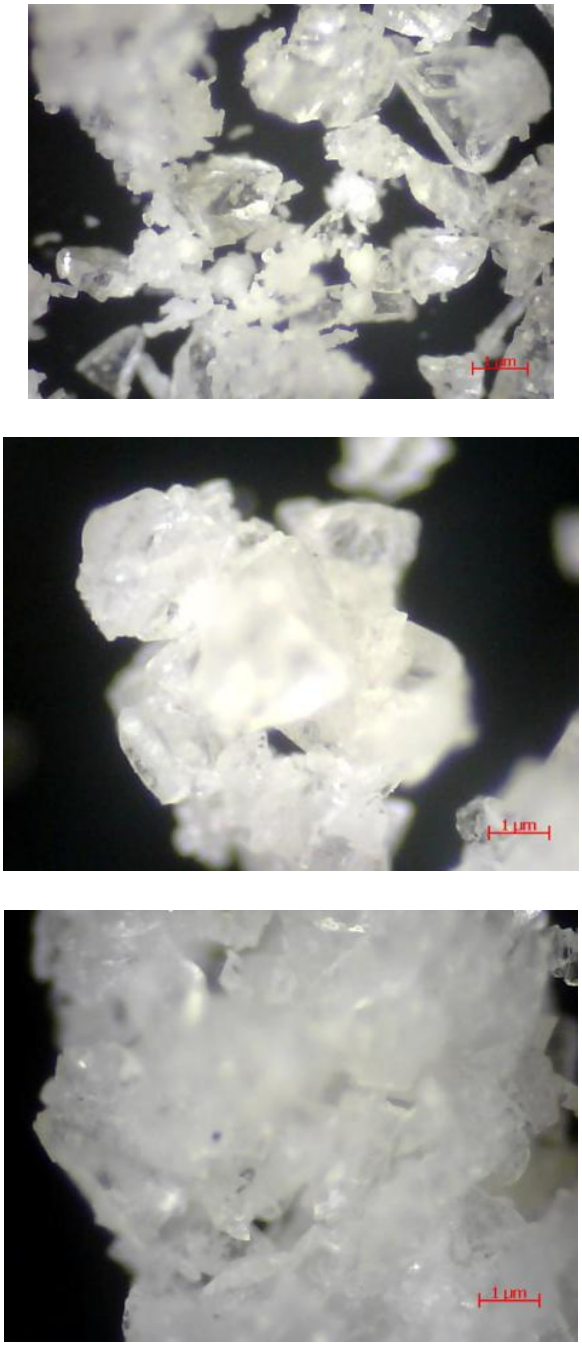

Fig. 3. The structure of granulate consisting lactose and MCC in amount of 5 %, 10 %, 15 %

Analyzing received results of pharmaco-technological and microscopic researches it is possible to assume that equal liquid distribution, substance particle size and the moisturizer concentration have an influence on the mechanism of granule formation. The end point of granule forming can be identified using pharmaco-technological indicators (particle size distribution, strength and flowability). The investigations permit to claim the reasonability of further assessment of the extend of influence of moistening, solubility of substances included in the granulate and the way of its formation.

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REFERENCES

[1] Heinrich S, Peglov M, Ihlow M, Henneberg M, Morl L. Chem Eng Sci 2002;57(20):4369 – 4390

[2] Morl L. Fluidized Bed Spray Granulation. Handbook of powder technology / Morl L., Heinrich S. and Peglow M. Granulation. – 2007. – V. 11. – P. 21–189.

[3] Hapgood KP, Iveson SM, Litster JD, Liu LX. Granulation Rate Processes: Chapter 20. – 2007. – P. 898–962.

[4] Kasatkin A.g. core processes and devices of chemical technology/Kasatkin a.g.-m., 2005. -753.

[5] Klassen Pv Basics techniques of granulation/Klassen PV Grishaev I.g.-m., 1982. – with 272.