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Optimization of the composition and technology of the solid dosage form "Romethine"

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Abstract

Interferons (IFNs) are immunity mediators (cytokines) with a universally wide spectrum of biological activity, in particular, antiviral and immunomodulatory effects. The drug romethine, which is currently recommended as an antiviral agent for influenza, in particular, an interferon inducer, has the same effect. The aim of this paper is to find the optimal composition and develop a technology for an encapsulated dosage form of romethine. The object of the study was the substance romethine, obtained on the basis of gosiipol by means of synthesis. As a result of the studies, the following excipients were selected to ensure satisfactory encapsulation of the romethine substance: lactose (filler - a1); aerosil (sliding substance - b2); calcium stearate (lubricant - c2). As an oral dosage form, gastro-soluble capsule number 1 was selected, and also, the quality of the developed dosage form was assessed, which meets the regulatory and technical requirements of SP XIII.

Keywords: substance, technological properties, capsules, composition, technology, excipients, quality assessment

Relevance of the topic

According to the World Health Organization, acute viral infections alone annually claim the lives of 10 to 14 million people [1]. The statistics should be supplemented by millions of patients who die due to complications of viruses: from a number of malignant processes, diseases of the central nervous system, heart, liver, genitourinary system, etc. Currently, more than 300 viruses pathogenic for humans are described, which are combined into 30 families and 51 genera. They can cause various epidemic processes: from sporadic diseases and epidemic outbreaks (hepatitis viruses) to epidemics (dengue, yellow, West Nile fever viruses, etc.) and pandemics (influenza, smallpox, polio, HIV viruses). Also, more than 2 million must be added to the above information for the past period due to the COVID-19 pandemic people who died from coronavirus worldwide [2,3]. The latter represent the greatest epidemic danger. Therefore, the government of the Republic of Uzbekistan has taken drastic measures to prevent the spread of coronavirus infection, ensure a safe sanitary and epidemiological situation in our region and protect public health [4].

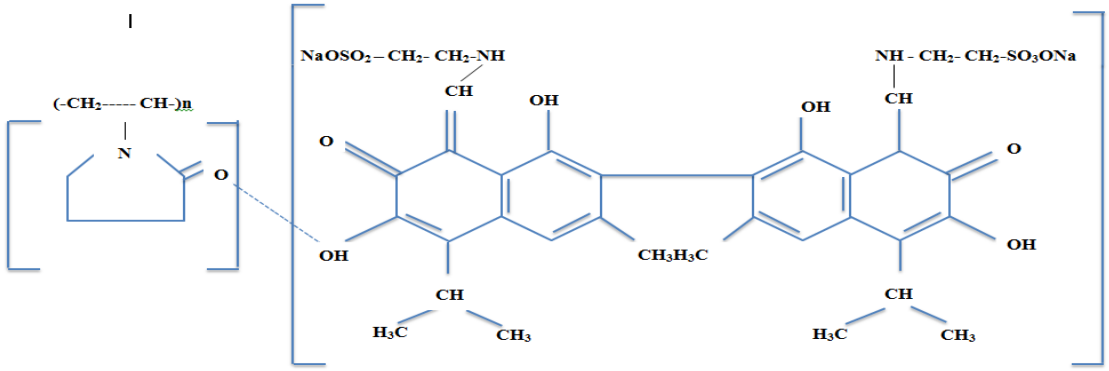
As you know, interferons (IFNs) themselves are immunity mediators (cytokines) with a universally wide spectrum of biological activity, in particular, antiviral and immunomodulatory effects. The formation and action of IFN is the most important mechanism of innate (natural) immunity. The interferon system is present in all cells of the body. When any virus enters the cell, IFNs are produced in it, suppressing viral replication, blocking the synthesis of virus-specific proteins.

The object used was a substance - romethine, synthesized by scientists of the Institute of Bioorganic Chemistry named after Academician A.S. Sadykov of the Academy of Sciences of the Republic of Uzbekistan and recommended as an antiviral agent for influenza, in particular, an interferon inducer [3].

Romethine is a complex compound of N-polyvinylpyrrolidone megosine M.M. 8000 ± 2000: $C_{34}H_{38}N_2O_{14}S_2Na_2 \bullet (C_6H_9NO)_n$, where n = 75; x/y=9; x= 91.00-90.8 wt%; y = 9.0-9.2 mass%.

Romethine is an amorphous powder, from dark yellow to light brown in color, with a specific odor. It is hygroscopic, darkens in the light, therefore romethine should be stored in a well-closed container, protected from light. The drug is soluble in chloroform, slightly soluble in water, insoluble in acetone.

Figure 1. Structural formula of romethine



According to the results of clinical studies in patients with acute respiratory infections, ARI (influenza) (+ rhinitis, pharyngitis, nasopharyngitis), it was found that the drug Romethine 100 mg tablets is comparable in clinical efficacy and tolerability (safety) with the drug Arbidol 100 mg capsules manufactured by OTICIPHARM JCC (Russia) [5].

1. The drug was well tolerated, has sufficient clinical activity, an effective drug in the treatment of patients diagnosed with acute respiratory infections, ARI (influenza) and can be recommended as an antiviral drug.

Objective of the study

The main objective of this study is to find the optimal composition and develop a technology for an encapsulated dosage form of romethine.

The creation of dosage forms with high therapeutic efficacy is possible by studying the entire complex of interdependent factors that ensure high bioavailability of the drug.

With an empirical approach, the search for a scientifically grounded composition and optimization of the technological process require a significant amount of experimental research, spending more time and materials. For the successful solution of the set tasks, we carried out research using the method of mathematical planning of experiments - Latin squares 4x4, where a study was carried out at 4 levels of change. According to the literature, the following factors are usually used as qualitative indicators for the selection of the composition and technology of capsules - the method of obtaining capsules, the type of capsule shell material, the type of plasticizer, preservative, colorant, and to optimize the parameters of the encapsulated material, such groups of excipients are used as fillers that bind, sliding substances and lubricants .

To ensure the quality of filling the capsules and the correct dosing, the qualitative indicators of the substance "Romethine" were studied (Table 1). Determination of the technological parameters of the substance and the test samples (shape and size of particles, fractional particle size distribution, bulk density, angle of repose, flowability, compressibility and residual moisture) was carried out according to the methods described in SP XIII [6,7].

Evaluation of the parameters of the substance was carried out on the following devices: shape and size of particles under an electron microscope Leica Icc 50 from Leica Microsystems with a 40x10/0.65 objective, flowability - an electronic tester for measuring the flowability of granular material ERWEKA GTB (Germany); bulk density - device HY-100C SBN-Impex (PRC); fractional (granulometric) composition of the substance - sieve analysis unit CHITRA apparatus - vibrating sieves CIPL-VS30-GMP (Chitra Impex Pvt. Ltd., India); compressibility - on the device proposed by the staff of the Department of Industrial Technology of

Medicines, moisture content - moisture analyzer SF-1 Fast moisture tester, Tianjin Guoming medicinal equipment (temperature -105 ± 1^0C; measurement accuracy - 0.01%)[8].

Table 1. Results of studying the technological properties of the substance and the encapsulated mass "Romethine"

№	Studied indicators	Measurement unit	Results	
			Substance	Encapsulated mass
1.	Appearance		Powder from dark yellow to light brown	Weight from dark yellow to light brown
2.	Fractional composition:+500 -500 +300 -300 +200 -200 +150 -150 +100 -100	micron, %	- 11.9 24.9 12.4 22.7 19.5	- 0.9 2.4 2.8 71.6 22.3
3.	Bulk density (with seal)	kg/m^3	587	902
4.	Angle of repose	degree	42.8	32.4
5.	Looseness	g/s	0.82	7±0.5
6.	Compressibility	H		
7.	Moistness	%	7.5	

As shown by the results of studying the technological parameters of the substance "Romethine", all indicators - bulk density, angle of repose, flowability and moisture, with the exception of indicators of fractional composition, are not positive, which indicates the need to use auxiliary substances to improve the technological properties of the substance.

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The next important stage of the experiment was the choice of auxiliary substances for the development of the composition and technology of the encapsulated form. In the experiment, such groups of excipients were used as: fillers with moisture-binding properties and antifriction substances (sliding and lubricating). As noted above, the substance of romethine has a pronounced hygroscopicity. It is well known that the presence of moisture reduces the flowability of powders and leads to caking. Therefore, when selecting auxiliary substances, we selected fillers with a moisture-reducing (drying) property - lactose, microcrystalline cellulose (MCC), starch, polydextrose. For example, lactose, which is often used in pharmaceutical technology to reduce the moisture content of hygroscopic substances, differs from other

disaccharides in the absence of hygroscopicity - it does not damp. This property is of great practical importance in pharmacy: if you need to prepare any powder containing an easily hydrolyzed drug with sugar, then take milk sugar; if you take another sugar, it will quickly become damp and the easily hydrolyzed medicinal substance will quickly decompose. According to literature sources, polydextrose is a polysaccharide consisting of glucose residues. A universal ingredient that can be used both as a filler and as a source of soluble dietary fiber with a prebiotic effect, as well as in drug technology, it is used as a moisture regulating agent, stabilizer and thickener [9].

The following sliding substances were added to the encapsulated mass as antifriction substances - aerosil, starch, talc and bentonite ("Navbahor"), as lubricants were used - stearic acid, calcium stearate, magnesium stearate and polyethylene oxide (PEO-4000) (Table 2).

The following indicators Y_1 were investigated as optimization criteria - flowability (10^{-3}kg/s); Y_2 - bulk density (kg/m^3); Y_3 is the rate of release of romethine from capsules (solubility, μg/ml).

In terms of 4x4 Latin squares, each factor studied was examined at 4 levels of change. To check the significance of these factors, according to the experiment plan, 16 experiments were carried out under the conditions provided for by the planning matrix (Table 3).

Table 2. Characteristics of variable factors affecting the filling process of capsules "Romethine"

Levels	Factors		
	Filler with moisture binding property (A)	Sliding substances (B)	Lubricants (C)
1	Lactose (a1)	Starch (в1)	Stearic acid (c1)
2	MCC (a2)	Aerosil (в2)	Calcium stearate (c2)
3	Starch (a3)	Talc (в3)	Magnesium stearate (c3)
4	Polydextrose (a4)	Bentonite (в4)	PEO-4000 (c4)

Table 3. Experiment planning matrix and research results on optimization of “Romethine” capsule technology

Experiment number	Factors			Optimization criteria			D
	A	B	C	flowability Y_1,10^{-3}kg/s	Bulk densityY_2, kg/m^3	Solubility Y_3, μg/ml	
1	a_1	b_1	c_1	4,3	371	26	0,49
2	a_1	b_2	c_2	7,0	902	29	0,75
3	a_1	b_3	c_3	4,8	419	22	0,64
4	a_1	b_4	c_4	3,9	329	31	0,37
5	a_2	b_1	c_2	3,9	330	31	0,37

6	a_2	b_2	c_1	4,1	351	29	0,41
7	a_2	b_3	c_4	4,6	402	24	0,58
8	a_2	b_4	c_3	3,7	310	33	0,30
9	a_3	b_1	c_3	5,3	470	15	0,4
10	a_3	b_2	c_4	4,6	401	24	0,58
11	a_3	b_3	c_1	4,9	432	21	0,65
12	a_3	b_4	c_2	4,5	390	25	0,55
13	a_4	b_1	c_4	4,2	359	28	0,46
14	a_4	b_2	c_3	5,0	441	19	0,67
15	a_4	b_3	c_2	4,3	370	26	0,49
16	a_4	b_4	c_1	4,6	399	24	0,58

The experimental data were subjected to analysis of variance (Table 4).

As can be seen from the results shown in Table 4, the tabular value of the Fisher criterion for degrees of freedom 3 and 6 of the significance level 0.05 is 4.76, while in all factors (A, B and C) the type of the selected auxiliary substances for flowability and bulk the mass of the substance to be encapsulated, as well as the solubility of the Romethine capsules, has no significant effect, i.e. hypothesis H_0 for the above factors is not rejected.

With a quantitative assessment of the influence of the studied three factors on the chosen optimization criteria, it is obvious that the combination of the interaction of factors A, B and C is significant.

Table 4. ANOVA of Romethine capsule optimization data

Optimization criterion	Source of variance	Sum of squares	Number of freedom degrees	Medium square	$F_{exp.}$	$F_{tab.}$	Hypothesis H_0
Flowability	Factor a	3	1,97	0,6567	0,00000128	4,76	α≠0
	Factor B	3	2,18	0,7267	0,00000142	4,76	β≠0
	Factor C	3	0,7875	0,2625	0,000000512	4,76	γ≠0
	Residue	6	339,48	512573,65	-	-	
	Total amount	15	3075441,93	-	-	-	
Bulk density	Factor a	3	2837807,75	945935,92	1,042	4,76	α≠0
	Factor B	3	2850392,25	950130,75	1,047	4,76	β≠0
	Factor C	3	2822721,25	940907,08	1,036	4,76	γ≠0

	Residue	6	5416598,5	907766,42	-	-	
	Total amount	15	3064522,75	-	-	-	
Solubility	Factor a	3	10471,26	3490,42	0,404	4,76	α≠0
	Factor B	3	10379,31	3459,77	0,400	4,76	β≠0
	Factor C	3	41665,56	13888,52	1,607	4,76	γ≠0
	Residue	6	51848,57	-	-	-	
	Total amount	15	10667,56	-	-	-	

In order to optimize the encapsulation process of romethine, three criteria were studied with different measurement values. In order to reveal the degree of influence of all responses on the encapsulation process, it was necessary to generalize these measurement values into one common indicator - the generalized desirability function (D), defined as the geometric mean of the desirability of individual properties:

$$D = \sqrt[n]{d_1 d_2 d_3 \ldots d_n} \qquad (1)$$

The Harrington desirability function scale was used to convert the natural values having different measurement values into the particular values of the desirability function.

To construct the desirability scale, the method of quantitative assessments was used with an interval of desirability values from zero to one, intermediate desirability values correspond to points reflecting certain quality levels of Romethine capsules (Table 5).

Table 5. Standard scores on a scale of desirability

Empirical system of preferences (desirability)	Numerical system of preferences (system of psychological parameters)
Very good	1.00-0.80
Good	0.80-0.63
Satisfactorily	0.63-0.37
Bad	0.37-0.20
Very bad	0.20-0.00

The numerical preference system shown in Table 5 is the dimensionless desirability scale developed by Harrington. The values of this scale range from 0 to 1 and are denoted by d (from desirable fr. - desirable). The value of the i particular optimization parameter, converted into a dimensionless desirability scale, denoted by di, is called a particular desirability, where i = 1,2,3,…, n is the current parameter number, n is the number of private parameters. The value di = 0 corresponds to an absolutely unacceptable level of the i optimization parameter.

The value $d_i = 1$ - corresponds to the best value of the i parameter.

The desirability function corresponding to the Harrington desirability scale is as follows (for a one-sided constraint):

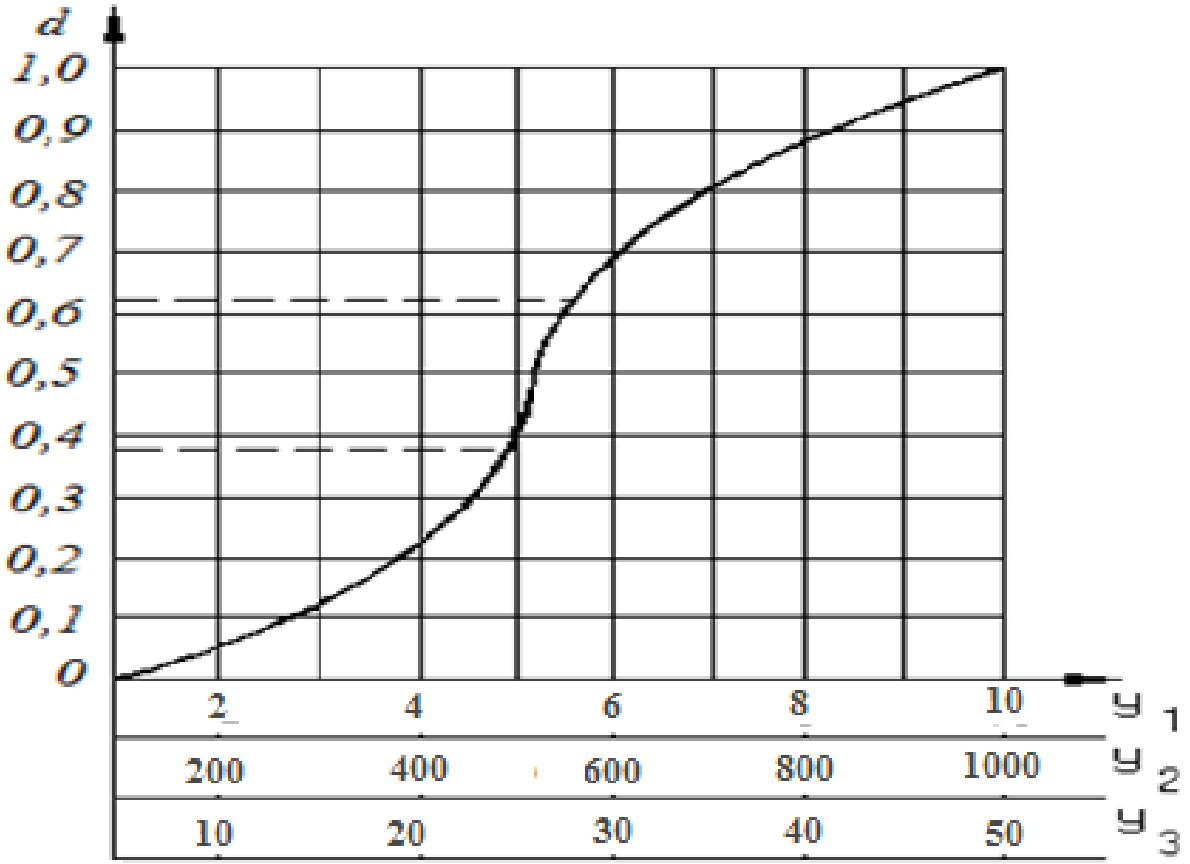
$$d = \exp(-\exp(-y')) \qquad (2)$$

When constructing the desirability scale, which ascertains the ratio of the response values y_1, y_2, y_3 and the corresponding partial desirability criteria d_1, d_2, d_3, we proceeded from the fact that the worst quality (d = 0) corresponds to the rate of release of romethine from capsules 15 µg/ml, flowability - 3.7 kg/s, bulk density - 329 kg/m^3, and the best quality indicator corresponds to the response values: y_1=7.0 kg/s, y_2=902 kg/m^3, y_3=29 µg/ml, respectively intermediate responses were selected. A graphical representation of the desirability function is shown in Figure 1. Using this scale, the values of the responses y_1, y_2, y_3 were converted into particular desirability criteria d_1, d_2, d_3 and found the generalized desirability function (D) presented in Table 3. From Table 3 it can be seen that the quality indicators of romethine capsules have a certain effect type of selected auxiliary substances: filler with moisture-binding property (A), sliding (B) and lubricating (C) substances. For example, under the condition $F_{0,05}$ = 4.8, $F_{exp} < F_{table}$, then this makes it possible to determine that the chosen model is linear and it is possible to check the significance of the main studied factors.

According to the experiment planning matrix, 16 experiments were carried out and, according to the optimization criteria, the values of the selected excipients were determined, arranged in the following order: fillers - $a_1 > a_3 > a_4 > a_2$; sliding substances - $b_2 > b_3 > b_1 > b_4$; lubricants - $c_2 > c_4 > c_1 > c_3$. In this case, the property of the desirability function d(x) from 0 to 1, the indicators change and $d_i \approx 0$.

As shown by the results of analysis of variance in the preparation of romethine capsules, the most significant optimization criterion is the solubility of capsules, which mainly predetermined the composition and technology of romethine capsules.

Figure 1. Desirability function scale



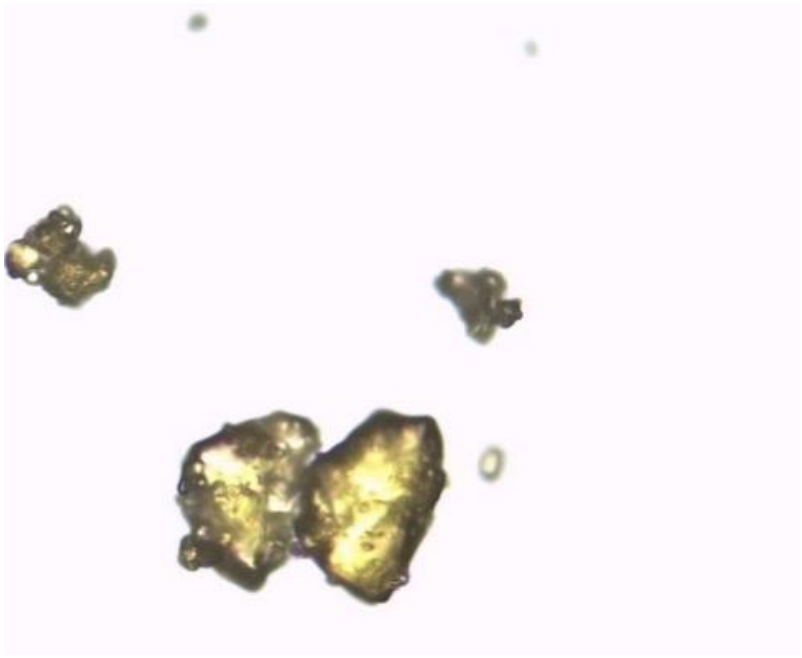
As a result of the studies, the following excipients were selected to ensure satisfactory encapsulation of the romethine substance: lactose (filler - a_1); aerosil (glidant - b_2); calcium stearate (lubricant – c_2) [10].

Technology: the substance of romethine was ground and sieved through a sieve with a hole diameter of 200 µm, then lactose, calcium stearate and aerosil were added to the substance of romethine, pre-crushed and sieved through a sieve with a hole diameter of 150 µm. The mass in the mixer was mixed until uniform for 30 minutes.

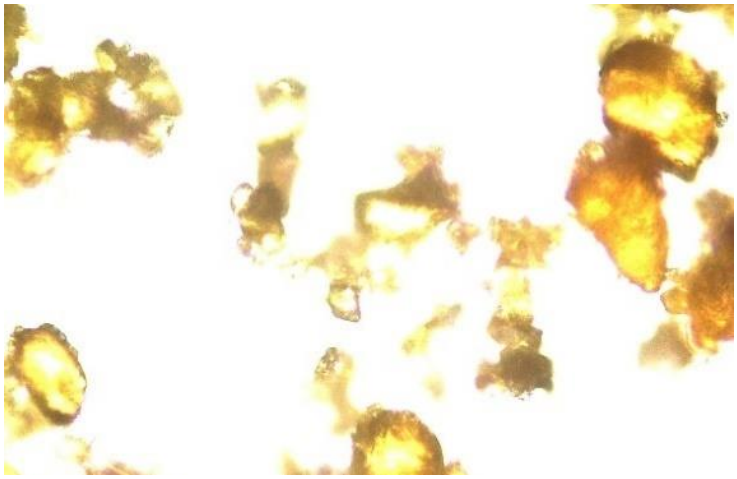
Taking into account the fact that the shape and size of the substance particles can also have an effect on the technological properties of powders, we studied the shape of the substance particles. During the research, it was found that the particles of the investigated substance had an isodiametric shape, i.e. rounded or polyhedral cubic shape (Figure 2).

We know from the literature that cubic particles have low compressibility and porosity.

Figure 2. The shape of the crystals of the substance of romethine with a magnification of 10x10



A



B

Further, the physical and technological properties of the encapsulated mass were studied (Table 1). The study of physical and mechanical parameters of the encapsulated mass of romethine showed satisfactory results.

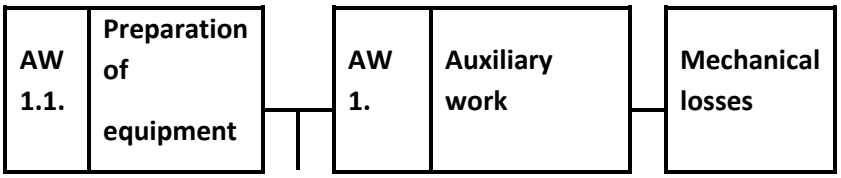
Next, the encapsulated mass was placed in an HD-100 capsule-filling machine (China) and the filling of gelatin capsules was carried out in № 1[11,12,13].

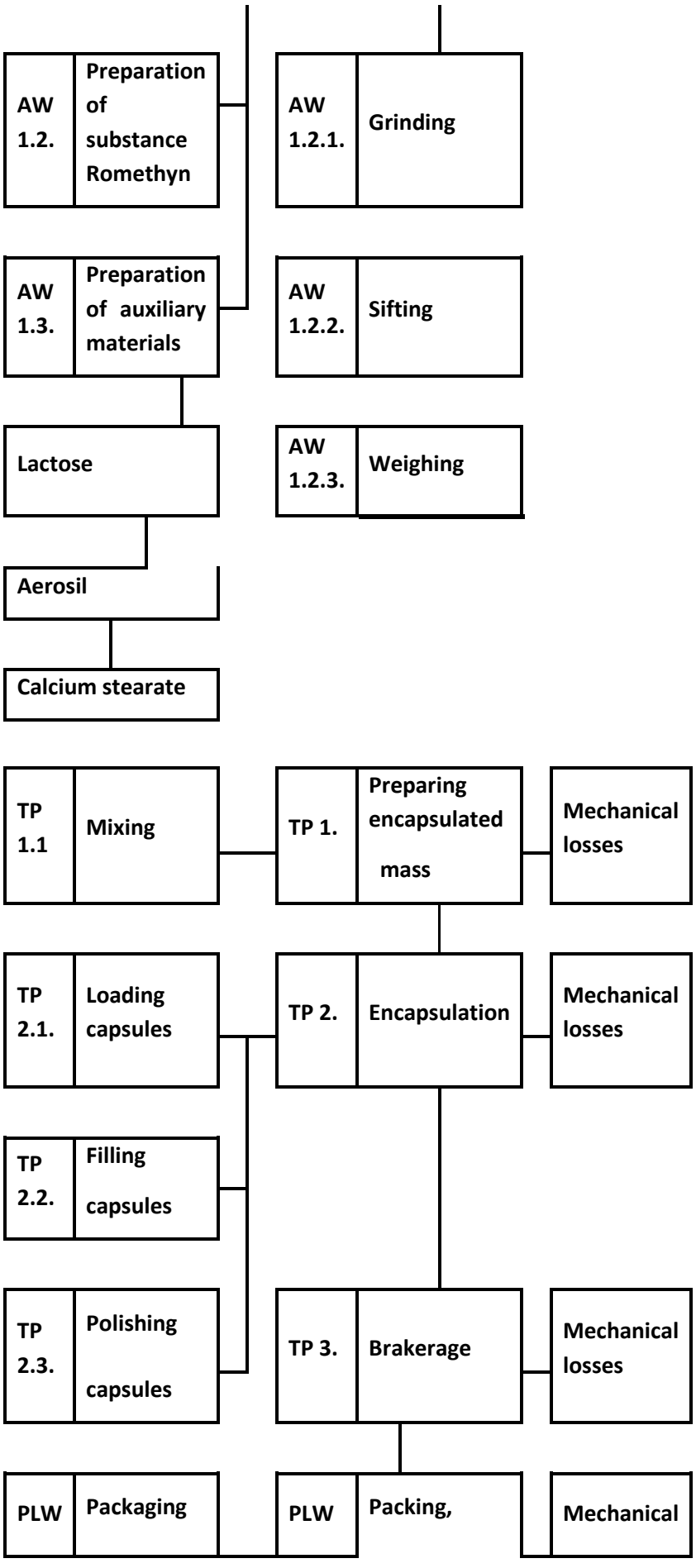
Table 6. Study of physical and mechanical parameters of the encapsulated mass and capsules Romethine

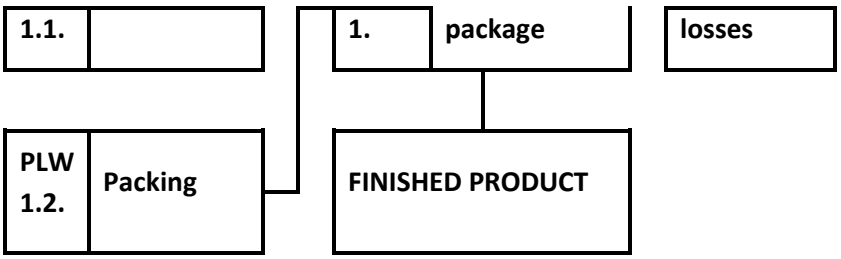
№	Studied indicators	measurement	Results

		unit	Romethine substance	Encapsulated mass
1.	Appearance		amorphous powder from dark yellow to light brown	powder from dark yellow to light brown
2.	Fractional composition: +500 -500+300 -300 +200 - 200+ 150 - 150+ 100 - 100	µm, %	 - 11.9 24.9 12.4 22.7 19.5	 - 10.9 25.9 19.8 17.0 16.5
3.	Bulk density (loosely poured)	kg/m^3	450.0±1.75	732±2.63
4.	Bulk density (with compaction)	kg/m^3	587.0±2.07	902.0±2.07
5.	Flowability	10^{-3}kg/s	0.82±0.83	7.0±0.5
6.	Angle of repose	degree	42.8±1.2	32.4±0.1
7.	Residual moisture	%, no more 7.0%	7.0±0,5	6.0±0.5
8.	Appearance of capsules			Gelatin capsules with pink and white cap
9.	Average capsule mass and deviation from it	g, no more ±10%		0.169 up to 0.227
10.	Disintegration	minutes, not less than 20 minutes		8±0.15
11.	Solubility	minutes, not less than 20 minutes		89±5.0

Figure 3. Scheme of the technological process of romethine capsules




AW 1.2.
Preparation of substance Romethyn
AW 1.2.1.
Grinding
AW 1.3.
Preparation of auxiliary materials
AW 1.2.2.
Sifting
Lactose
AW 1.2.3.
Weighing
Aerosil
Calcium stearate
TP 1.1
Mixing
TP 1.
Preparing encapsulated mass
Mechanical losses
TP 2.1.
Loading capsules
TP 2.
Encapsulation
Mechanical losses
TP 2.2.
Filling capsules
TP 2.3.
Polishing capsules
TP 3.
Brakerage
Mechanical losses
PLW
Packaging
PLW
Packing,
Mechanical



Conclusions

Were studied the physical and technological properties of the substance "Romethine", on the basis of these results, the calculation of mathematical modeling of the composition of the capsule mass was carried out. The optimal ratio of excipients in certain ratios was found. Lactose, MCC, starch, polydextrose were used as fillers; for sliding starch, aerosil, talc and bentonite, as well as lubricants, stearic acid, calcium stearate, magnesium stearate, and PEO-4000. As a result of the experiment, the optimal composition of the encapsulated mass was selected, the composition of which includes lactose, aerosil and calcium sterate. As an oral dosage form, gastro-soluble capsule number 1 was selected, and the quality of the developed dosage form was assessed, which meets the regulatory and technical requirements of SP XIII.

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