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DEVELOPMENT OF TECHNOLOGY FOR OBTAINING TABLETS BY DOUBLE GRANULATION METHOD WITH PIPSISSEWA (*CHIMAPHILA UMBELLATA*) EXTRACT

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The use of the therapeutic potential of medicinal plants is currently considered a physiological method of prevention and treatment, which affects the normalization of metabolic processes and the restoration of the body's functional capabilities. Medicinal products created based on plants can be used for a longer period, including in the treatment of chronic diseases.

***The aim of the work** is to select a technology to produce tablets containing wintergreen umbrella herb liquid extract, considering the pharmaco-technological properties of the resulting dosage form.*

***Materials and methods.** The objects of the study were pipsissewa herb liquid extract and experimental model samples of mixtures of this plant substance with excipients permitted for medical use. The research on the analysis of the liquid extract and pharmaco-technological indicators of test samples of tablet mass and tablets was carried out according to the methods of the State Pharmacopoeia of Ukraine (SPhU).*

Determination of the optimal technology for obtaining and quantitative composition of excipients of tablets from pipsissewa herb liquid extract was carried out using mathematical design of experiments (MDE) by the method of a four-factor experiment based on the Greco-Latin square.

***Results**. The analysis of the liquid extract of pipsissewa showed the presence of 47.0±1.0 % of extractive (dry residue) substances. It was determined that the use of Liquid-Solid technology in the technology of obtaining tablets with plant extract based on the amorphous form of magnesium aluminometasilicate (Neusilin US2) requires the use of a combined approach that will ensure the quality of the finished product. During experimental studies, the use of three interrelated production strategies was proposed. In the process of applying the proposed strategy, it was determined that microcrystalline cellulose effectively performs the function of an adsorbent and filler; the consistency of the mixtures significantly depends on the ratio of MCC 101:extract. It was investigated that the use of double granulation will allow for the increase of the amount of active ingredient in the granulate without changing the volume of MCC 101, which will allow for the achievement of a higher extract content in the finished tablets. The use of double granulation technology can also ensure uniform distribution of the active ingredient and maintain the necessary flowability of the mixture for subsequent tabletting. The use of mathematical, experimental planning in the development of double granulation (drying) technology and the composition of excipients based on studies of the fluidity of the tabletting mass; attrition, disintegration, resistance of tablets to crushing, and organoleptic indicators became the basis for the development of the composition of the medicinal product in the form of tablets containing pipsissewa liquid extract.*

***Conclusions**. The adsorption property and its influence on the tabletting process of the synthetic amorphous form of magnesium aluminometasilicate (Neusilin US2) and microcrystalline cellulose 101 (MCC 101) were determined when using these substances as a carrier for pipsissewa grass liquid extract. The possibility of conducting a double granulation process using microcrystalline cellulose 101 (MCC 101) according to a given amount of liquid extract was proven. Using mathematical planning of the experiment, the drying conditions of the granulate and the quantitative composition of excipients were selected*

***Keywords**: pipsissewa herb liquid extract, tablets, composition, technology, excipients, granulation, mathematical modelling, pharmaco-technological properties*

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1. Introduction

The development of modern pharmacy involves the creation of medicines based on natural biologically active substances, which are characterized by a mild effect and a minimum number of side effects. Liquid extract of pipsissewa is a promising component for the creation of tablet forms due to its anti-inflammatory and immunostimulating properties [1, 2].

When developing a medicine, it is extremely important to choose the right manufacturing technology and qualitative and quantitative composition – the quality, effectiveness and stability of the drug depend on this [3, 4]. The optimal technology ensures a uniform distribution of the active substance, mechanical strength of the tablets, their ability to quickly or prolonged release of the active component in the body [5].

The liquisolid technique is an innovative approach in pharmaceutical development, aimed, for example, at increasing the solubility and dissolution rate of medicines with low water solubility. This method involves the conversion of liquid formulations, such as solutions or suspensions of drugs in non-volatile solvents, into dry, free-flowing, and compressible powders. The process is achieved by mixing the liquid formulation with selected carriers and coating materials, resulting in a liquisolid system [6].

The main advantage of this method is the significant improvement of the bioavailability of hydrophobic drugs, as it increases their wettability and increases the surface area available for dissolution [7]. In addition, the liquisolid system can be used for sustained or controlled release of drugs, making it a versatile tool in the development of various oral dosage forms [8]. Recent studies have also demonstrated the potential of liquisolid technology in improving the stability and efficacy of drugs with low water solubility, which expands its applicability in the pharmaceutical industry [9]. The liquisolid technique is an innovative method for creating tablets with plant extracts that have antioxidant properties. This approach involves the adsorption of liquid extracts onto porous carriers, such as magnesium aluminometasilicate, followed by compression into tablets [10–12]. This technique has been successfully applied to various plant extracts, including Aronia melanocarpa, Crataegus leavigata, Rosa canina, and Curcuma comosa [10, 11].

Liquisolid tablets demonstrate improved dissolution profiles and increased bioavailability of active compounds compared to native extracts [11]. The choice of solvent (water or ethanol) and drying method (microwave or hot air) can affect tablet properties and antioxidant activity [5, 12]. In general, the liquisolid technique allows for tablets with excellent physical characteristics, including short disintegration and dissolution times, making it a promising approach for processing a wide range of liquid plant extracts into solid dosage forms [12]. The composition of the dosage form determines the bioavailability of the active substance and its compatibility with excipients (fillers, disintegrants, binders, disintegrants, etc.), and affects the organoleptic properties and stability of the drug during storage. Irrational selection of the composition or technology can lead to loss of therapeutic activity, impaired pharmacokinetics, or complications during the manufacturing process [3, 4].

Thus, the choice of manufacturing technology and composition is a critically important stage in the creation of high-quality and safe tableted medicines.

The aim of the study is to select a technology to produce tablets from pipsissewa herb with liquid extract, taking into account the pharmaco-technological properties of the resulting dosage form.

2. Research planning (methodology)

For the study, the liquid extract of pipsissewa was chosen as the main active ingredient, given the high content of biologically active substances, such as flavonoids and polyphenols, which have significant pharmacological potential, including anti-inflammatory and antioxidant activity. In addition, pipsissewa is an affordable plant raw material, which allows it to be used on an industrial scale. The excipients selected were microcrystalline cellulose, which ensures the formation of a stable granulate, Vivasol to improve the dispersion of tablets, magnesium stearate as an antifriction agent, ethanol as a solvent, purified water for diluting the liquid extract, Neusilin US2 to improve the flowability of the granules and silicon dioxide to ensure the fluidity of the mixture and prevent the granules from sticking. The selection of these components was based on their technological properties and ability to ensure a uniform distribution of active substances in the finished tablets.

Pharmaceutical drug development in Ukraine is based on the following main recommendation documents: ICH Q8 Guidelines “Pharmaceutical Development”, ICH Q9 “Risk Management for Quality” and ICH Q10 “Pharmaceutical Quality System”. In combination with the use of process analytical technology (PAT), they explain the “Quality by Design” (QbD) approach [3, 13]. The use of QbD in the development of drugs contributes to ensuring their quality, risk management and is an integral part of the development process. Based on the requirements and recommendations of the ICH Q8 Guidelines “Pharmaceutical Development”, our work proposed a systematic approach to determining the pharmaco-technological indicators (quality) of a drug based on the selected composition and manufacturing technology.

3. Materials and methods

The study was conducted in the period 2023–2024 at the Department of Industrial Technology of Drugs of the National Pharmaceutical University, Kharkiv, Ukraine.

The object of the study is pipsissewa herb liquid extract, which was obtained with 50 % ethyl alcohol according to the technology [2]. The conducted pharmacological studies showed [14] that the therapeutic dose of this extract is 0.72 ml/kg (daily dose per person). The amount of active ingredients of the extract (phenolic compounds) was standardized [15].

Excipients included in the list of excipients permitted for use in medicinal products and approved by the Order of the Ministry of Health of Ukraine No. 339 dated 19.06.2007 [16] were used as excipients.

The evaluation of the quality parameters of the developed tablets and granulate (determination of average weight, dry matter content, fluidity, abrasion, and organoleptic indicators) was determined according to the relevant methods of the State Pharmacopoeia of Ukraine (SPhU) [17].

Determination of the content of extractive (dry residue) substances in the composition of the liquid extract of pipsissewa herb was carried out according to the following method. A sample weighing 10 g was selected and placed in a pre-dried and weighed cup. The sample was dried in a drying oven at a temperature of 105°C for 3 hours to constant weight. The temperature regime was chosen to prevent the loss of active components that may be thermolabile. After drying, the sample was cooled in a desiccator and reweighed. The difference in mass before and after drying determined the amount of water that evaporated, and the residual mass corresponded to the amount of dry matter.

The content of dry substances in the extract was calculated by the formula:

$$\text{Dry substances content, \%} = M_2/M_1 \cdot 100\ \%,$$

where M_2 – mass after drying, g; M_1 – initial mass of the sample, g

4. Results and discussion

The primary stage of determining the technology for obtaining tablets was the study of the content of extractives (dry residue) substances in the composition of the liquid extract of pipsissewa grass.

The stage of determining the content of dry substances is key in the standardization of pipsissewa extract since it determines the number of active components that will be used in the composition of tablets.

According to the conducted research and the data obtained, the content of extractives in the pipsissewa extract is 47.0±1.0 %. This indicator was used for further stages of development, including determining the proportions of components in the composition of tablets. The results obtained allowed the standardization of the extract to ensure the repeatability of the technological process.

Research into the possibility of using liquid-solid technology (LSS).

The introduction of plant extract into tablets requires the use of a significant amount of excipients or preliminary granulation in the tablet technology process. The presence of a liquid phase of the extract requires studying the possibility of using liquid-solid technology, which will ensure uniform distribution of active components in the solid matrix and increase bioavailability [18, 19].

To conduct a study on the use of liquid-solid technology (LSS), pipsissewa extract with a mass fraction of extractive substances of 47.0 % was dissolved in a water-ethanol solution (extract:solvent ratio as 1:1). This technological method ensured uniform distribution of active components in the liquid phase.

As a solid phase (matrix), a synthetic amorphous form of magnesium aluminometasilicate (Neusilin US2) was used. In a mortar, a liquid phase with pipsissewa extract was gradually added to the solid matrix, constantly stirring with a plastic spatula until a homogeneous mixture was obtained. The mixture of the solid matrix with the liquid phase was passed through a sieve with a mesh size of 1.0 mm. To the sieved mixture with the extract, which was absorbed on the Neusilin US2 particles, a filler microcrystalline cellulose (Avicel PH101), a disintegrant croscarmellose sodium (Vivasol) and antifriction agents' silicon dioxide (Aerosil 200) and Magnesium Stearate were added. The ratio of the components was selected according to the classical requirements to produce solid dosage forms [5, 10]. The components of the mixture were mixed in a mortar with a plastic spatula until a homogeneous mixture was obtained.

The mixture was immediately subjected to tabletting after preparation. The average weight of the obtained tablets was 0.29 g. It was experimentally established [17] that the obtained tablets had sufficient strength and uniformity. The optimal composition was determined for the manufacture of tablets (Table 1).

Table 1

Tablet composition (model sample F1)

Component	Ratio (%)
Plant Extract	12.5
Ethanol (Water)	12.5
Neusilin US2	25.0
Aerosil 200	0.5
Avicel PH101	46.5
Magnesium Stearate	1.0
Vivasol	2.0
Total mass	100.0

Despite the successful use of Liquid-Solid technology to create tablets with pipsissewa extract, significant shortcomings were identified during the study that affect the quality of the finished product:

1. Neusilin US2, which was used as an adsorbent for the integration of the liquid phase, has high porosity, therefore it occupies a significant volume in the tablet composition. Because of this, the volume of the solid matrix increases significantly, which limits the possibility of including other components, particularly the active ingredient. The finished tablet has unsatisfactory geometric parameters (thin) and low density, which may affect its mechanical stability and ease of consumption.

2. Low dosage of the extract. Due to the significant volume occupied by excipients, the content of the active ingredient (pipsissewa extract) in the tablet remains low. In a formed tablet weighing 0.29 g, the extract content is only 12.5 % (~0.036 g). Such a low dosage requires an increase in the number of tablets needed to achieve a therapeutic effect. This not only reduces the convenience of use for the patient but can also lead to increased treatment costs due to a larger volume of drug intake.

3. The use of bulk Neusilin US2 results in an uneven tablet surface, which may negatively affect consumer acceptance of the product. Thin tablets are more difficult to tablet because of the risk of delamination or microcracking under mechanical stress.

4. A significant amount of adsorbent may make it difficult to control the reproducibility of the tablet composition between batches. A high volume of excipients increases the risk of degradation of the active ingredient due to possible contact with residual moisture or adsorbed solvent.

To minimize the impact of the identified shortcomings, it is advisable to implement a combined approach that combines three interrelated strategies (Fig. 1):

The change in technology, shown in the figure (Fig. 1), consists in replacing Neusilin US2 with microcrystalline cellulose (MCC 101), which has a smaller volume and better binding properties, which allows to reduce the size of the tablet and increase the proportion of the active ingredient. Optimization of the ratio of components and the use of MCC 101 as the main adsorbent ensure uniform distribution of pipsissewa extract, improve the mechanical strength and stability of the tablets.

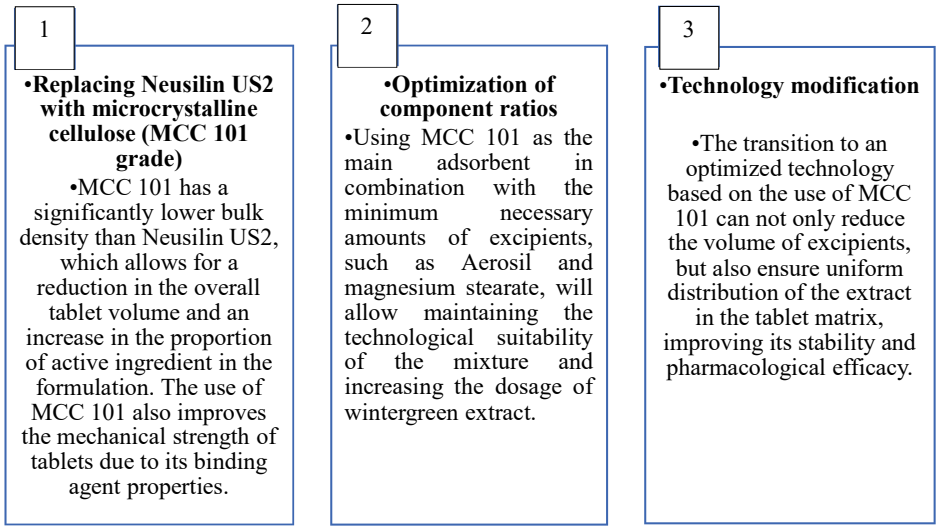

Fig. 1. Strategies to improve the tableting process

Despite the advantages of Liquid-Solid (LSS) technology, such as uniform distribution of the liquid phase and the absence of a drying stage, the disadvantages of low dosage of the extract and a large volume of excipients significantly limit its application. Therefore, further research was aimed at optimizing the tablet composition and improving the technological process.

The next stage of the work was to determine the ability of microcrystalline cellulose 101 (MCC 101) to absorb pipsissewa extract and perform the function of a filler to ensure the stability and technological suitability of the mixture.

For the experiment, pipsissewa herb liquid extract with an extractives content of 47.0 % and MCC 101 were used as an adsorbent and filler.

For the batch (model mixtures) F2, the ratio of MCC 101:extract was 4:5.2. For the batch (model mixtures) F3, the ratio of MCC 101:extract was 2.5:5.

The pipsissewa extract was mixed with MCC 101 in the indicated proportions. The gradual addition of MCC 101 to the extract ensured uniform adsorption of the liquid phase. After mixing, the consistency of the resulting mixture was assessed, and it was visually checked whether lumps were formed. The results of the organoleptic study of the resulting model mixtures F2 and F3 are given in Table 2.

Table 2

Results of the organoleptic analysis of the use of MCC 101 as an adsorbent

Parameter	Model sample F2	Model sample F3
Proportion MCC101:extract	4:5.2	2.5:5
Consistency of the mixture	Not free-flowing, powdery, and did not stick together	Viscose, sticks together into (one) lump

At a ratio of 4:5.2 (batch F2), MCC 101 provides the formation of a powder mixture that is not free-flowing but has sufficient stability for further use. At a ratio of 2.5:5 (batch F3), the mixture provides a higher concentration of the active extract, but is more viscous, which complicates its homogeneity and further use in tablet technology.

The different consistencies of the resulting mixtures demonstrate a significant influence of the MCC 101:extract ratio on the physicochemical properties of the final product. Microcrystalline cellulose effectively performs the function of an adsorbent and filler, however, the consistency of the mixtures significantly depends on the MCC 101:extract ratio. For batches with a high MCC 101 content (F2), stable powder mixtures were obtained, while with a lower MCC 101 content (F3), the mixtures had a viscous consistency. The optimal ratio of components requires further research to achieve the necessary technological suitability.

To determine the possibility of using the granulate obtained by mixing MCC 101 with pipsissewa extract, for the formation of tablets with specified technological characteristics, the granulate containing MCC 101 and pipsissewa extract was tableted.

MCC 101 was mixed in a laboratory mixer with pipsissewa extract in a ratio of 4:5.2 (MCC 101:pipsissewa extract). The mixture was dried to obtain a free-flowing granulate. The Vivasol disintegrant was added to the granulate in an amount of 2 % of the calculated mass of the tablet mass, calibrated through a 2 mm sieve and powdered with magnesium stearate (1.0 %). The resulting mixture was tableted on a single-punch tablet press; the matrix diameter was 10 mm. The average tablet weight was 0.436 g, and according to calculations regarding the content of extractive substances (pipsissewa extract) – 158 mg per tablet (Table 3).

Table 3

Composition of model tablets containing MCC 101 (model sample F4)

Component	Ratio (%)	Weight per 1 tablet (g)
Microcrystalline cellulose 101 (MCC 101)	60.625	0.265
Pipsissewa extract	36.375	0.158
Vivasol	2.000	0.009
Magnesium stearate	1.000	0.004

The results obtained showed that the use of MCC 101 granulate with pipsissewa extract allows to obtain tablets with uniform distribution of components and satisfactory physicochemical characteristics. However, the content of the active substance (158 mg of extractive substances per tablet) is insufficient to achieve therapeutic efficacy. This indicates the need for further optimization of the composition and technological process.

A promising direction for further research is the implementation of double granulation technology, which involves:

– initial formation of MCC granulate with liquid pipsissewa extract;

– repeated granulation with addition of extract to the already formed granulate.

This approach will allow to increase the amount of active ingredient in the granulate without changing the volume of MCC 101, which will allow to achieve a higher extract content in the finished tablets. The use of double granulation technology can also ensure uniform distribution of the active ingredient and maintain the necessary fluidity of the mixture for subsequent tabletting. Thus, the study of double granulation opens prospects for creating tablets that meet both technological and pharmacological requirements.

To conduct research on the possibility of using double granulation, we prepared the following model samples (Table 4).

Table 4

Composition of model samples of tablets manufactured using double granulation technology (model sample F5-F8)

No.	Components	Ratio, %	Granulation approaches
Model sample F5			
1	MCC 101	56,30	1. MCC 101:extract 4:4. 2. MCC 101:extract 4:2
2	Pipsissewa extract on a dry basis	39,70	
3	Vivasol	3,00	
4	Magnesium stearate	1,00	
Model sample F6			
1	MCC 101	65,31	1. MCC 101:mixture extract - purified water (2:1) 4:4. 2. MCC 101:mixture extract - purified water (2:1) 4:2
2	Pipsissewa extract on a dry basis	30,69	
3	Vivasol	3,00	
4	Magnesium stearate	1,00	
Model sample F7			
1	MCC 101	65,31	1. MCC 101:mixture extract - purified water (2:1) 4:3. 2. MCC 101:mixture extract - purified water (2:1) 4:3
2	Pipsissewa extract on a dry basis	30,69	
3	Vivasol	3,00	
4	Magnesium stearate	1,00	
Model sample F8			
1	MCC 101	65,31	1. MCC:extract-ethanol mixture 50 % (2:1) 4:3. 2. MCC:extract-ethanol mixture 50 % (2:1) 4:3
2	Pipsissewa extract on a dry basis	30,69	
3	Vivasol	3,00	
4	Magnesium stearate	1,00	

According to the compositions given in Table 4, when using double granulation, the following technology was applied (drying of granules was carried out to a residual moisture of 4.0 % after each of the granulation stages):

Model sample F5.

For the sample F5, a mixture of microcrystalline cellulose 101 (MCC 101) and undiluted pipsissewa herb liquid extract was used. The components were introduced in two stages. In the first stage, 4 parts of the extract were added to 4 parts of MCC 101. In the second stage, 2 more parts of the extract were added to the resulting granulate, and then Vivasol and magnesium stearate were added to the resulting mixture. The resulting mixture had sufficient flowability, ensuring uniformity of the composition. However, at the second stage of the introduction of the extract, slight clumping of the granulate was observed, which required additional mixing.

Model sample F6.

For the composition F6, the extract diluted with purified water (in a ratio of 2:1) was used. The process was also carried out in two stages. In the first stage, 4 parts of the diluted extract mixture were added to 4 parts of MCC 101; in the second stage, another 2 parts of the diluted mixture were added to the granulate. After two granulation operations, Vivasol and magnesium stearate were added to the mixture.

In the first stage, the adsorption of liquid on MCC 101 was satisfactory. However, in the second stage, the adsorption deteriorated due to the oversaturation of MCC 101 with moisture, which made it difficult to introduce the diluted mixture further.

Model sample F7.

For the composition F7, a diluted extract with water (2:1) was used, introduced in two equal stages: in the first stage, 3 parts of the diluted mixture were added to 4 parts of MCC 101. In the second stage, another 3 parts of the diluted mixture were added to the granulate. After two granulation operations, Vivasol and magnesium stearate were added to the mixture.

During the second stage of the process, clumping of the mass was observed, which caused the granulation to stick to the walls of the cup and made mixing difficult. This indicates a limited possibility of introducing a large amount of liquid without deteriorating the flowability of the granulate.

Model sample F8.

For sample F8, a diluted extract with 50 % ethanol (2:1) was used. The process was also carried out in two stages. In the first stage, 3 parts of the mixture were added to 4 parts of MCC. In the second stage, another 3 parts of the mixture were added to the granulate. After two granulation operations, Vivasol and magnesium stearate were added to the mixture.

At the first stage, a homogeneous powder was obtained that had satisfactory flowability and did not clump. However, during the second stage, noticeable clumping of the granulate was observed, which required intensive mixing. Despite this, the use of ethanol improved the distribution of the extract in the mixture compared to water.

Based on the results obtained, the most effective and technologically feasible technology is composition F5. This composition provides:

– the high content of extractive substances in the extract, which is necessary to achieve a therapeutic effect;

– simplicity of the process, minimization of technological stages and preservation of the stability of the mixture;

– minor clumping of the granulate does not affect the quality of the final product.

Therefore, for industrial applications, it is recommended to choose the composition F5 as the optimal one for obtaining tablets from pipsissewa herb with liquid extract.

The selection of components and conditions for preparing the granulate for forming tablets containing the plant substance pipsissewa was carried out using the mathematical planning of the experiment (MPE) method [20]. The study used several groups of excipients and the humidity to which the granules were dried after each of the granulation stages. Their characteristics, factor levels and percentage ratio are presented in Table 5. The variation of the concentration of the disintegrant Vivasol and the antifriction substance (magnesium stearate) occurred due to the correlation of the amount of MCC 101.

Table 5

Factors and their levels investigated in the process of substantiating tablet technology

Factors	Factors' levels
Granulate moisture after the 1st stage of granulation and drying (A)	a_1 – 2.0 %; a_2 – 3.0 %; a_3 – 4.0 %; a_4 – 5.0 %
Granulate moisture after the 2nd stage of granulation and drying (B)	b_1 – 2.0 %; b_2 – 3.0 %; b_3 – 4.0 %; b_4 – 5.0 %
Vivasol disintegrant (C)	c_1 – 1.0 %; c_2 – 2.0 %; c_3 – 3.0 %; c_4 – 4.0 %
Antifriction agent Magnesium stearate (D)	d_1 – 0.3 %; d_2 – 0.5 %; d_3 – 0.7 %; d_4 – 1.0 %

The above variables were divided into factor levels, which were studied by the method of a four-factor experiment based on the Greco-Latin square. The following indicators of the granulate and the resulting tablets containing biologically active compounds pipsissewa were used as responses:

– y_1 and y_1' – fluidity of the tabletting mass after powdering, s/100 g (SPhU 2.9.16);

– y_2 and y_2' – tablet abrasion (SPhU 2.9.7), %

– y_3 and y_3' – tablet disintegration (SPhU 2.9.1), min;

– y_4 and y_4' – tablet crushing resistance (SPhU 2.9.8), H;

– y_5 and y_5' – organoleptic characteristics of tablets, points.

Pharmaco-technological indicators of the obtained granulates were determined according to the methods described in SPhU [17]. Organoleptic indicators of tablets were determined by a score characteristic, where the highest score (5) was given to tablets that had optimal indicators (absence of chips, cracks, uniformity of tablet colour, stable mass). The results of studies of pharmaco-technological indicators of granulate and tablet quality are presented in Table 6.

Based on the results of the studies, diagrams of the influence of factors and their levels on pharmaco-technological and organoleptic properties were constructed. Fig. 2 shows the influence of factors on the fluidity of the tableting mass depending on the amount of the powdering component – magnesium stearate.

According to the data obtained, the effective concentration in the composition of the tablet mass is the presence of 1.0 % magnesium stearate. At this concentration, the mixture meets the recommended fluidity indicators. Increasing the concentration above 1.0 % is not advisable and is not recommended when using antifriction substances in tablet production.

Table 6

Matrix of planning an experiment to obtain granules and tablets with pipsissewa extract

Factors				Responses									
A	B	C	D	y_1	y_1'	y_2	y_2'	y_3	y_3'	y_4	y_4'	y_5	y_5'
a_1	b_1	c_1	d_2	34	32	0.31	0.28	16	19	42	44	3	2
a_2	b_1	c_4	d_4	25	25	0.34	0.32	11	9	45	44	5	5
a_3	b_1	c_3	d_3	42	46	0.81	0.86	13	12	31	33	3	3
a_4	b_1	c_2	d_1	33	30	0.71	0.62	8	9	33	35	4	4
a_1	b_2	c_2	d_2	33	36	0.42	0.37	7	8	49	47	5	5
a_2	b_2	c_3	d_4	15	17	0.60	0.70	15	17	39	35	5	5
a_3	b_2	c_4	d_3	25	27	0.55	0.52	11	13	33	24	4	5
a_4	b_2	c_1	d_1	27	29	0.71	0.75	19	17	41	41	4	4
a_1	b_3	c_3	d_4	26	24	0.35	0.42	9	7	36	35	4	5
a_2	b_3	c_2	d_3	20	18	0.95	0.96	5	6	41	38	5	4
a_3	b_3	c_1	d_2	45	43	1.21	1.23	27	26	27	24	3	4
a_4	b_3	c_4	d_1	48	45	1.3	1.25	18	19	27	27	3	3
a_1	b_4	c_4	d_1	47	49	0.89	0.95	11	11	42	43	2	2
a_2	b_4	c_1	d_2	29	28	0.69	0.75	15	14	39	42	4	4
a_3	b_4	c_2	d_3	24	22	1.23	1.10	9	11	28	33	4	5
a_4	b_4	c_3	d_4	25	23	0.74	0.69	14	13	26	22	4	5

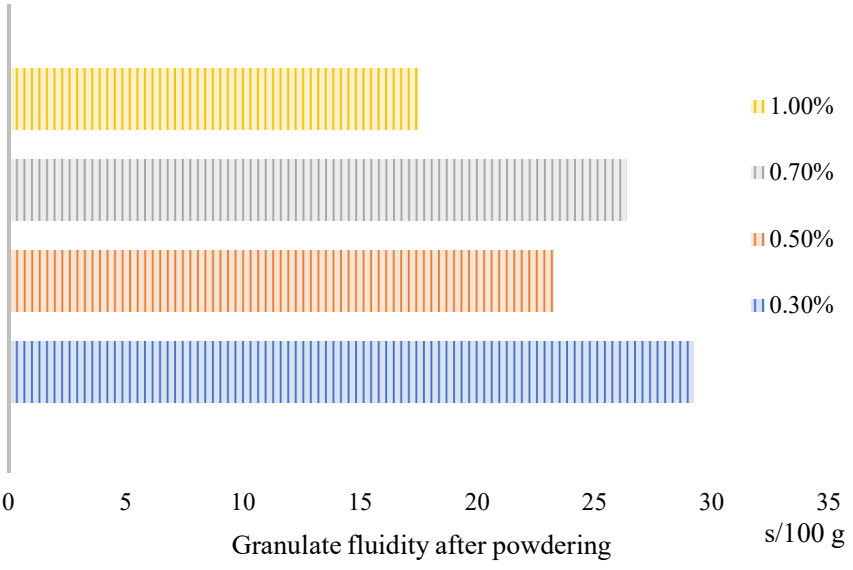

Fig. 2. Effect of magnesium stearate on the fluidity of the tabletting mass

The effect of granulate moisture on the flowability of the tableting mass is given in Table 7. According to the results of the conducted studies, the granulate with a moisture content of 2.0 % - 3.0 % after the first and second stages of granulation has the best fluidity over time. The effect of the amount of disintegrant does not affect the fluidity of the tablet mass (Table 7).

According to the results of the study conducted to determine the influence of granulate moisture content after granulation stages, the presence of disintegrant and the amount of magnesium stearate, it was determined that:

– tablet friability depends to a greater extent on the moisture content of the granulate and the amount of disintegrant. The optimum moisture content of the granulate after each granulation stage is 3.0 %;

– disintegration and resistance of tablets to crushing depends on the amount of disintegrant and the moisture content of the granulate. The presence of 2.0 % disintegrant in the composition of the medicinal product allows you to obtain tablets with optimal indicators of disintegration and resistance.

The organoleptic indicators are influenced by all the factors involved in the research. The presence of 1.0 % magnesium stearate, 2.0 % Vivasol and the drying process at each stage to a moisture content of 3.0 % allows you to obtain tablets with the highest score in terms of organoleptic indicators (Table 8).

Analysis of the levels of factors affecting the pharmaco-technological and organoleptic indicators of tablets and tablet mass shows that to obtain the optimal composition of a solid dosage form in the form of a tablet containing pipsissewa herb liquid extract, the use of the disintegrant Vivasol 2.0 % (c_2) and the antifriction agent magnesium stearate 1.0 % (d_4) is effective. The drying process of the granulate after the first and repeated granulation must be carried out to a final moisture content of 3.0 % (a_2, b_2, respectively). The use of the proposed concentration of excipients and drying technology will allow the obtaining of tablets that will meet the SPhU indicators for pharmaco-technological properties.

According to the results of the conducted studies, the composition of tablets containing pipsissewa extract was proposed.

The composition of tablets, %:

– Microcrystalline cellulose101 – 56.89;

– Pipsissewa extract with dry matter content – 47.0 %;

– in terms of extractive substances – 40.11;

– Vivasol – 2.00;

– Magnesium stearate – 1.00;

– Total – 100.00.

Table 7

The effect of factors and their levels on the fluidity of the tabletting mass after powdering

Factor	Numerical indicator, s/100 g	Priorities of factor levels (by minimum time s^{-1})
Granulate moisture after the 1st stage of granulation and drying (A)	32.625=28.500>18.125=17.125	$a_3=a_4>a_1=a_2$
Granulate moisture after the 2nd stage of granulation and drying (B)	28.625=26.250=24.000>17.500	$b_3=b_1=b_4>b_2$
Disintegrant Vivasol (C)	26.125=25.250=22.750=22.250	$c_4=c_1=c_2=c_3$
Antifriction agent magnesium stearate (D)	29.250=26.375=23.250>17.500	$d_1=d_3=d_2>d_4$

Table 8

Ranking of factor levels by model sample indicators

Factor	Pharmaco-technological indicators	Dimensionality	Ranking of factor levels	Optimal factor level
Granulate moisture after the 1st stage of granulation and drying (A)	fluidity of tabletting mass after powdering	s/100 g	$a_3=a_4>a_1=a_2$	$\underline{\boldsymbol{a_2}}$, a_1
	tablet abrasion	%	$a_3=a_4>a_2>a_1$	a_1, $\underline{\boldsymbol{a_2}}$
	tablet disintegration	min	$a_3=a_4>a_2=a_1$	a_1, $\underline{\boldsymbol{a_2}}$
	tablet crushing resistance	H	$a_1=a_2>a_4=a_3$	a_1, $\underline{\boldsymbol{a_2}}$
	tablet organoleptic characteristics	points	$a_2>a_3=a_4=a_1$	$\underline{\boldsymbol{a_2}}$, a_3
Granulate moisture after the 2nd stage of granulation and drying (B)	fluidity of tabletting mass after powdering	s/100 g	$b_3=b_1=b_4>b_2$	$\underline{\boldsymbol{b_2}}$, b_4
	tablet abrasion	%	$b_3=b_4>b_2=b_1$	b_1, $\underline{\boldsymbol{b_2}}$
	tablet disintegration	min	$b_3=b_2=b_4=b_1$	b_1, b_4
	tablet crushing resistance	H	$b_2=b_1>b_4=b_3$	$\underline{\boldsymbol{b_2}}$, b_1
	tablet organoleptic characteristics	points	$b_2>b_3=b_4=b_1$	$\underline{\boldsymbol{b_2}}$, b_3
Disintegrant Vivasol (C)	fluidity of tabletting mass after powdering	s/100 g	$c_4=c_1=c_2=c_3$	$\underline{\boldsymbol{c_2}}$, c_3
	tablet abrasion	%	$c_2=c_4=c_1>c_3$	c_3, c_1
	tablet disintegration	min	$c_1>c_4=c_3>c_2$	$\underline{\boldsymbol{c_2}}$, c_3
	tablet crushing resistance	H	$c_2=c_1=c_4>c_3$	$\underline{\boldsymbol{c_2}}$, c_1
	tablet organoleptic characteristics	points	$c_2=c_3>c_4=c_1$	$\underline{\boldsymbol{c_2}}$, c_3
Antifriction agent magnesium stearate (D)	fluidity of tabletting mass after powdering	s/100 g	$d_1=d_3=d_2>d_4$	$\underline{\boldsymbol{d_4}}$
	tablet abrasion	%	$d_1=d_3>d_2>d_4$	d_2, $\underline{\boldsymbol{d_4}}$
	tablet disintegration	min	$d_2>d_1>d_4=d_3$	$\underline{\boldsymbol{d_4}}$, d_3
	tablet crushing resistance	H	$d_2>d_1=d_4>d_3$	d_2, d_1, $\underline{\boldsymbol{d_4}}$
	tablet organoleptic characteristics	points	$d_4>d_3>d_2>d_3$	$\underline{\boldsymbol{d_4}}$, d_3

5 Discussion

The results of the research confirmed that the double granulation technology is the most effective method for ensuring uniform distribution of the active ingredient (liquid extract of pipsissewa) in the composition of the tablets. This method allowed to increase the content of the active substance in the granulate and obtain tablets with the necessary pharmaco-technological properties. Optimal drying conditions (granulate moisture 3.0 %) ensured the stability and fluidity of the granulates.

The use of microcrystalline cellulose (MCC 101) as the main adsorbent showed that the ratio of MCC 101:extract affects the consistency of the mixture and its technological suitability. The ratio of 4:5.2 ensured the receipt of stable powder granulate with sufficient flowability.

The use of Neusilin US2 as an adsorbent for the liquid phase of the extract allowed the creation of tablets with a uniform distribution of active substances. However, due to the significant number of excipients, there were limitations in the content of the active ingredient, which required further optimization.

Tablets manufactured using the developed technology demonstrated satisfactory indicators of fluidity, disintegration, abrasion and resistance to crushing. The best results were obtained in the F5 composition, which confirms the feasibility of using double granulation.

Tablets had a uniform color, stable mass and smooth surface. The use of magnesium stearate (1.0 %) contributed to the improvement of organoleptic characteristics without a negative impact on pharmaco-technological properties.

The results of the study are similar to the conclusions obtained in [10], which investigated the use of liquisolid technology for the conversion of liquid extracts into solid dosage forms. Both studies showed the effectiveness of using excipients, such as Neusilin® US2, to adsorb liquid extracts and obtain granulates with good pharmaco-technological properties. Although Neusilin® US2 is an effective carrier for liquid extracts, we decided not to use it for the following reasons. Neusilin® US2 is a relatively expensive material, which makes it difficult to widely use in commercial conditions, especially for local manufacturers. The use of Neusilin® requires specific equipment and strict control of drying parameters, which may limit its application in medium and small-scale production. In our study, it was found that microcrystalline cellulose (MCC 101) provides sufficient adsorption capacity, good flowability and uniform distribution of active ingredients, which makes it more affordable and suitable for scaling up.

Double granulation was used, which allows for a uniform distribution of the active ingredients in the granulate mass, while in the study [10] the liquisolid technology with drying by microwave or convection dryer was used.

In the study [10], the effectiveness of Neusilin® US2 for creating stable tablet forms was demonstrated in the Czech Republic. In the USA, the liquisolid technology is also widely used to increase the bioavailability of poorly soluble active substances.

We chose an alternative approach using more affordable microcrystalline cellulose, which ensures the competitiveness of our technology for local and international manufacturers. This approach can be used in the pharmaceutical industry of the EU countries due to compliance with modern GMP standards.

To improve and deepen the obtained results, a number of additional studies are proposed that can contribute to increasing the efficiency and practical value of the developed technologies. First, it is advisable to conduct testing of the long-term stability of tableted forms under standard storage conditions, as well as accelerated methods to assess the influence of time and storage conditions on pharmaco-technological indicators and stability of active substances. In addition, it is important to investigate the bioavailability of active components in the developed tablets, using modern in vitro models or in vivo studies to confirm the effectiveness of the release and absorption of active substances.

A promising direction is the optimization of granulation processes, including the study of the influence of alternative methods, such as extrusion-spheronization granulation or sublimation, on the homogeneity of active substances and physicochemical properties of granulates. Expanding the spectrum of studied extracts, in particular, other plants with anti-inflammatory, antioxidant or antimicrobial activity, will allow assessing the versatility of the developed technology for different pharmacological groups.

The proposed research directions create prospects for further development of the obtained results, their adaptation to international standards and implementation in production conditions.

The obtained research results have significant potential for practical implementation in the pharmaceutical industry. The developed technology of double granulation using microcrystalline cellulose (MCC 101) as the main filler allows the creation of tablet forms with liquid extracts of medicinal plants, characterized by high stability, satisfactory pharmaco-technological indicators and preservation of biological activity. This approach can be adapted to industrial conditions with minimal changes to existing production equipment since the granulation and drying method does not require the use of specific devices or solvents.

Practical significance. The results of the study can be implemented in pharmaceutical practice through the creation of tablet forms based on liquid extracts of medicinal plants using the developed double granulation technology. This technology ensures uniform distribution of active components in the granulate, improves their stability, and also guarantees high quality of the final product. The main direction of implementation is the production of herbal medicines with anti-inflammatory and immunostimulating activity, which can be used for the treatment and prevention of inflammatory and immunological disorders.

The double granulation technology is especially useful for the manufacture of tablets containing liquid extracts, which is important for preserving the biological

activity of unstable components. The use of microcrystalline cellulose brand as an adsorbent and filler makes the process economically profitable and adaptable to large-scale production, which is especially important for small and medium-sized pharmaceutical enterprises.

Study limitations. The study has several objective limitations that affected the results obtained and determined the possibilities of their further application. First, the use of model samples limited the possibility of a full assessment of the stability of the developed forms during long-term storage. The need to comply with optimal granulation and drying conditions to ensure the stability of active substances required limiting the temperature regimes and drying duration, which may affect the scaling of the process in production conditions.

Another limitation is the lack of clinical studies that could confirm the therapeutic efficacy of the developed tablet forms. The results obtained are based mainly on pharmaco-technological studies that ensure the quality and stability of the drug but do not allow for the assessment of its effectiveness in real conditions of use.

In addition, the study focused on the liquid extract of pipsissewa, and although the results confirmed the effectiveness of the developed technology, its adaptation to other types of raw materials requires further experiments. The choice of excipients, in particular microcrystalline cellulose brand, is due to its availability and functional properties, but the study of alternative fillers and adsorbents could ensure a more universal application of the technology.

Prospects for further research lie in conducting studies to determine the biological, pharmaco-technological and consumer properties of the developed tablets during storage.

6. Conclusions

The adsorption property and its influence on the tabletting process of synthetic amorphous form of magnesium aluminometasilicate (Neusilin US2) and microcrystalline cellulose 101 (MCC 101) when using these substances as a carrier for pipsissewa grass liquid extract were determined. The possibility of carrying out a double granulation process when using microcrystalline cellulose 101 (MCC 101) according to a given amount of liquid extract was proven. Using mathematical planning of the experiment, the conditions for drying the granulate and the quantitative composition of excipients were selected. The technology for obtaining tablets includes a two-stage granulation process of the mass using pipsissewa grass liquid extract as a moisturizing solution. When drying, after each of the stages, the granulate should be dried to a moisture content of no more than 3.0 %.

Conflict of interests

The authors declare that they have no conflict of interest regarding this study, including financial, personal, authorship or other, that could influence the study and its results presented in this article.

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Use of artificial intelligence tools

The authors confirm that they did not use artificial intelligence technologies when creating the presented work.

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