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SUBSTANTIATION OF THE SELECTION OF EXCIPIENTS IN THE DEVELOPMENT OF GRANULES BASED ON COUCH GRASS HERB PHYTOSUBSTANCE

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pharmaceutical factors, granules, couch grass herb phytosubstance, mathematical planning, excipients.

ABSTRACT

The aim is to study the influence of pharmaceutical factors, namely excipients, on the technological properties of granules containing couch grass herb phytosubstance and to select the most appropriate ones for further research.

Materials and methods. The object of the study was granules based on couch grass herb phytosubstance and 9 excipients grouped into 3 categories of pharmaceutical factors used in the experiment. The influence of excipients on the pharmacotechnological properties of granules based on couch grass herb phytosubstance was investigated using the method of mathematical experimental design. The granules were prepared by wet granulation.

Results and discussion. The influence of excipients on the pharmacotechnological properties of granules based on a phytosubstance derived from couch grass herb was analyzed. Ranked preference series were constructed to assess the positive effects of nine excipients on the following quality attributes: loss on drying, bulk volume before and after tapping, flowability, disintegration, and friability of the granules, as well as on the integrated response parameter, namely the desirability function.

Conclusions. Following the obtained results, the selection of excipients that exerted the most favorable effect on the pharmaco-technological properties of the granules based on the phytosubstance derived from couch grass herb was scientifically substantiated for further studies. The selected excipients comprised microcrystalline cellulose 200 and lactose (1:1), pregelatinized starch, and Neusilin® US2.

Introduction. The development and implementation of herbal medicinal products in industrial production is a relevant area for the advancement of modern domestic pharmaceutical science. The relevance of this field is confirmed by the results of contemporary scientific studies devoted to improving technologies for the extraction of medicinal plant raw materials and obtaining phytoextracts using innovative equipment that ensures efficient recovery of biologically active substances during extraction [1; 2]. Current studies in phytochemistry highlight

scientifically grounded approaches to the pharmacotechnological aspects of developing solid dosage forms based on phytoextracts.

Alongside traditional oral dosage forms, particularly tablets and capsules, increasing interest has been observed in medicinal products in the form of granules or powders intended for the preparation of oral suspensions [3–5]. These dosage forms have advantages over tablet formulations in terms of solubility and bioavailability [6].

In the technology of granule production, as in the manufacture of other dosage forms, a key stage is the justified selection of excipients that ensure appropriate quality indicators and therapeutic efficacy. The main excipients used in granule production include fillers, disintegrants, binders, glidants, as well as flavoring agents and colorants [7].

In our opinion, couch grass herb is a promising medicinal plant raw material for the development of a solid dosage form, namely granules. According to the scientific literature, the complex of biologically active substances in this plant exhibits a wide range of effects, including immunomodulatory, antioxidant, antibacterial, hepatoprotective, anti-inflammatory, and other activities [8–13]. As is well known, herbal medicinal products have advantages over synthetic drugs due to a lower incidence of adverse effects, a complex mode of action, and the availability of raw materials [14; 15]. Therefore, the development of new herbal medicines remains an important task in pharmacy.

The aim of the study was to investigate the influence of pharmaceutical factors, namely excipients, on the technological properties of granules containing couch grass herb phytosubstance and to select the best candidates for further research.

Materials and Methods. The study used couch grass herb phytosubstance obtained with a 70% ethanol solution according to the technology described in the patent [16], excipients (Table 1), and granules based on couch grass herb phytosubstance. The obtained granules were evaluated for loss on drying, flowability, bulk density before and after tapping, friability, and disintegration. A mathematical experimental design involving 9 series was used. The results were processed and analyzed by analysis of variance [17; 18]. The design matrix and the results are presented in Table 2.

Table 1

Excipients studied in the development of granules based on couch grass herb phytosubstance

Factor	Factor level
A – fillers	a ₁ – MCC 200 + lactose (1:1) a ₂ – MCC 101 + lactose (1:1) a ₃ – lactose
B – disintegrants	b ₁ – sodium carboxymethyl starch b ₂ – sodium starch glycolate b ₃ – pregelatinized starch
C – glidants	c ₁ – Prosolv 90 c ₂ – Neusilin US 2 c ₃ – Aerosil

Results and Discussion. The granules were prepared by wet granulation, the most rational and widespread method; it is regarded as the most justified and appropriate approach in the development of herbal medicinal products based on phytoextracts [19; 20]. A thick couch grass herb phytosubstance was used as the moistening solution. Since the granulated mass was not sufficiently moistened and, consequently, the granules would not have had the required structure and shape, it was decided to additionally add 5% starch paste.

Nine series were obtained, and the fractional composition of each was studied. It was established that, in all nine series, the predominant fractions were granules of 1 mm and those smaller than 0.5 mm. Thus, in series 1, 2, 3, 4, 5, and 6, the predominant fraction consisted of granules measuring 1.0 mm (on average 36.97%) and the fraction >0.5 mm (26,27%). In series 7, 8, and 9, the quantitative content of the fraction >0.5 mm was slightly higher and averaged 41.11%, whereas the fraction of 1.0 mm granules accounted for 27.30%.

In studying the dependence of loss on drying on the influence of excipients, it was found that only fillers (factor A) affected this parameter. The lowest loss on drying was obtained when lactose was used. The ranked order of factor levels for this parameter was as follows: a₃ > a₁ > a₂.

When studying the effect of excipients on the flowability (y₂) of granules based on couch grass herb phytosubstance, it was established that all factors influenced this parameter. Among the levels of factor A, lactose had the most positive effect on flowability, whereas the mixture of MCC 200 and lactose (1:1) had the least favorable effect.

According to the results of studying the influence of factor B levels on this property, the fastest outflow was observed for granules containing pregelatinized starch, which showed an advantage over sodium starch glycolate and sodium carboxymethyl starch.

With regard to the influence of factor C levels on granule flowability, the best result was achieved with Prosolv 90, which had an advantage over the other levels of this factor. This can be represented by the following ranked order of preference: c₁ > c₂ > c₃.

When studying the influence of the investigated factors on bulk density (y₃), it was found that this parameter depended most strongly on the introduction of disintegrants (factor B), whereas the other factors had no significant effect.

Following the results of studying the influence of factor B levels on this property, the highest bulk density before tapping was obtained when pregelatinized starch was used (0.48 g/mL). When sodium carboxymethyl starch and sodium starch glycolate were used, the bulk density decreased to 0.34 g/mL and 0.36 g/mL, respectively.

The results of analysis of variance showed that tapped bulk density was also influenced only by factor B.

The highest tapped bulk density was obtained after the introduction of pregelatinized starch (0.522 g/mL). The lowest value of this parameter was recorded when sodium carboxymethyl starch was used (0.37 g/mL).

An important quality indicator of granules is friability. According to the obtained results of analysis of variance, this indicator was most strongly affected by factor A, the group of fillers. The most resistant granules were obtained when the mixture MCC 200 + lactose (1:1) was used, with only 1.47% loss. The most friable granules based on couch grass herb phytosubstance were those containing pure lactose (7.64%).

Table 2

Experimental design matrix and results of the study of granules based on couch grass herb phytosubstance

Series No.	A	B	C	y_1	y_2	y_3	y_4	y_5	y_6	D
1	a_1	b_1	c_1	2.105	24.80	0.361	0.379	0.978	102.00	0.66
2	a_1	b_2	c_2	2.558	26.24	0.368	0.384	1.955	20.53	0.79
3	a_1	b_3	c_3	2.331	23.95	0.424	0.451	1.484	90.00	0.75
4	a_2	b_1	c_2	3.451	27.90	0.324	0.343	1.426	16.07	0.45
5	a_2	b_2	c_3	2.746	29.30	0.332	0.361	1.924	20.62	0.44
6	a_2	b_3	c_1	1.853	15.87	0.577	0.639	1.362	120.00	0.33
7	a_3	b_1	c_3	1.614	26.70	0.350	0.388	7.4455	10.00	0.44
8	a_3	b_2	c_1	1.475	22.66	0.387	0.423	12.535	10.41	0.00
9	a_3	b_3	c_2	1.203	19.44	0.441	0.476	2.949	15.30	0.89

Notes: y_1 – loss on drying, %; y_2 – granule flowability, 100 g/s; y_3 – bulk density, g/cm³; y_4 – tapped bulk density, g/cm³; y_5 – granule friability, %; y_6 – granule disintegration, s; D – desirability function.

The results of analysis of variance in the study of granule disintegration time (y_6) showed that all three factors were statistically significant and substantially affected this parameter in the following order: C > A > B.

The influence of factor C on granule disintegration can be illustrated by the following ranked order: $c_2 > c_3 > c_1$. Thus, the fastest disintegration was observed for granules containing Neusilin US 2.

Among the fillers, the best disintegration time was ensured by lactose, reducing disintegration time to 11.9 s. When mixtures of lactose with different grades of MCC were used, granule disintegration slowed down: with MCC 101 + lactose (1:1), the granules disintegrated in 52 s, whereas with MCC 200 + lactose (1:1), the disintegration time was 71 s.

According to the obtained experimental data, sodium starch glycolate provided the best result among the disintegrants (17 s). The slowest disintegration was observed for granules containing pregelatinized starch.

Based on the study results, a generalized indicator, namely the desirability function, was used since it was impossible to select the optimal excipients for the next stage of research.

The obtained desirability function results were subjected to analysis of variance. Based on the values obtained for the levels of the studied factors, the optimal excipients from each group were selected using the desirability function. Thus, among the fillers, the best desirability function value was provided by MCC 200 + lactose (1:1).

The effect of factor B on the desirability function can be represented by the following sequence: pregelatinized starch (0.66) > sodium carboxymethyl starch (0.52) > sodium starch glycolate (0.41).

Among the glidants (factor C), the best desirability function values were provided by Neusilin US 2, which showed advantages over Aerosil and Prosolv 90.

Therefore, after analyzing the obtained results for factor A according to the generalized indicator and its influence on the pharmacotechnological quality indicators of granules based on couch grass herb phytosubstance, the following substance was selected for further studies: the mixture MCC 200 + lactose in a 1:1 ratio,

as it improved granule flowability and reduced friability. From the group of disintegrants (factor B), pregelatinized starch was selected for further study because it improved granule flowability and bulk density and reduced friability and loss on drying.

Among the glidants, Neusilin US 2 was selected for the next stage of research because it ensured granule strength and also had a positive effect on flowability.

Conclusions. The influence of excipients on the pharmacotechnological properties of granules based on couch grass herb phytosubstance was studied. Ranked preference series were constructed regarding the positive effect of excipients on six indicators taken together and on the desirability function. Based on the obtained results, the selection of excipients that most positively influenced the pharmacotechnological properties of the resulting granules for further research was substantiated, namely: MCC 200 + lactose (1:1), pregelatinized starch, and Neusilin US 2.

Limitations of the study. The study was conducted at the laboratory stage of granule development and involved the evaluation of pharmacotechnological parameters within the framework of the selected experimental design. The study did not include an assessment of the stability of the finished granules or biopharmaceutical parameters, specifically the release of the API from the dosage form.

Future research perspectives. Future research should focus on studying the influence of quantitative factors on the pharmacotechnological properties of granules based on *Elymus repens* (couch grass) herb phytosubstance, optimizing their composition using the selected excipients, and further investigating their pharmacotechnological and physicochemical properties.

Compliance with ethical standards. Since the study was conducted using a phytosubstance and model granules and did not involve human or animal subjects, specific ethical approval was not required.

Conflict of interest. None declared.

Author contributions according to the CRediT taxonomy:

M. M. Vasenda – conceptualization, methodology, investigation, formal analysis, project administration, writing – review & editing.

Yu. Yu. Plaskonis – methodology, investigation, formal analysis, writing – original draft.

M. B. Chubka – conceptualization, methodology, formal analysis.

Use of artificial intelligence. No artificial intelligence tools were used in the preparation of this manuscript.

Primary data and materials. The primary data and materials obtained during the study are available from M. M. Vasenda upon reasonable request.

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ОБҐРУНТУВАННЯ ВИБОРУ ДОПОМІЖНИХ РЕЧОВИН У РОЗРОБЦІ ГРАНУЛ НА ОСНОВІ ФІТОСУБСТАНЦІЇ ПИРІЮ ПОВЗУЧОГО ТРАВИ

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Мета роботи – вивчити вплив фармацевтичних факторів, а саме допоміжних речовин на технологічні властивості гранул, що містять фітосубстанцію трави пирію повзучого, та вибрати кращі для подальших досліджень.

Матеріали та методи. Об'єкт дослідження – гранули на основі фітосубстанції трави пирію повзучого, 9 допоміжних речовин, об'єднаних у 3 групи фармацевтичних факторів, які було використано в дослідженні. Для вивчення впливу допоміжних речовин на фармакотехнологічні властивості гранул на основі фітосубстанції трави пирію повзучого використовували метод математичного планування експерименту. Гранули отримували методом вологої грануляції.

Результати й обговорення. Вивчали вплив допоміжних речовин на фармакотехнологічні властивості гранул на основі фітосубстанції трави пирію повзучого. Було побудовано ранжовані ряди переваг щодо позитивного впливу 9 допоміжних речовин на такі показники, як: втрата маси під час висушування, насипний об'єм до і після усадки, текучість, розпадання та крихкість гранул, а також на узагальнюючий показник – функцію бажаності.

Висновки. На основі отриманих результатів обґрунтовано вибір допоміжних речовин, які найбільш позитивно впливали на фармако-технологічні властивості отриманих гранул на основі фітосубстанції трави пирію повзучого для подальших досліджень: МКЦ 200+ лактоза (1:1), крохмаль прежелатинізований, неуселін US 2.

Ключові слова: фармацевтичні фактори, гранули, фітосубстанція пирію повзучого трави, математичне планування, допоміжні речовини.

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