# ТЕХНОЛОГІЯ ЛІКАРСЬКИХ ПРЕПАРАТІВ

*Recommended by Doctor of Pharmacy, professor T.G.Yarnykh*

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## DEVELOPMENT OF THE COMPOSITION AND TECHNOLOGY OF THE CAPSULATED DRUG BASED ON BEE BREAD AND HONEY POWDER. REPORT 2. THE STUDY OF PHARMACOTECHNOLOGICAL PROPERTIES OF THE MIXTURES OF ACTIVE PHARMACEUTICAL INGREDIENTS WITH EXCIPIENTS OF "API-IMMUNO-VIT" CAPSULES

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*Key words: bee bread; powdered honey; excipients; physicochemical properties; pharmacotechnological tests; "Api-Immuno-Vit" capsules; immunomodulatory action*

*The physical, physicochemical and pharmacotechnological properties of active pharmaceutical ingredients and their mixtures with the excipients of "Api-Immuno-Vit" capsules with the immunomodulatory action based on bee bread and powdered honey have been studied. The results of the analysis of the resulting masses for encapsulation of the mixtures with active substances indicate the necessity of introduction of antifriction substances and humidity regulators into the composition of the drug being developed and allow determining the rational composition and the quantitative content of excipients. By the pharmacotechnological studies conducted the expediency of obtaining granules by the wet granulation method of the mass for encapsulation using the alcohol-water mixture in the concentration of 80% as a moisturizer has been determined.*

When developing the rational composition of a drug in the form of capsules it is important to substantiate scientifically the choice of active pharmaceutical ingredients (API) and excipients, which presence can affect the therapeutic efficacy. Taking into account the literature data and our own experimental studies the new domestic standardized substances of apiculture products – bee bread and powdered honey (PH) have been selected as active ingredients in the composition of the drug "Api-Immuno-Vit" with the immunomodulatory action. Thanks to the presence of significant amounts of biologically active substances (BAS) in their composition bee bread and PH exhibit a wide range of the pharmacological activity, in particular the immunomodulatory action [3, 5, 6, 7].

The pharmacological studies at the premises of Central Research laboratory of the NPhU under the supervision of Doctor of Medicine, professor S.Yu.Shtrygol' have determined the single therapeutic doses of API included to the composition of "Api-Immuno-Vit" capsules, and they are from 0.1 to 0.5 g for bee bread and from 0.05 to 0.2 g – for powdered honey, respectively.

The previous studies also determined the safety profile of the substances under research in accordance with the requirements of the national and interstate standards, as well as the content of toxic elements, pesticides, radionuclides and antibiotics in the experimental samples was found. The results are given in Report 1 [4].

The aim of this work was to develop the composition and technology of "Api-Immuno-Vit" capsules, to study the physical, physicochemical and pharmacotechnological properties of the mixtures of API with excipients.

**Materials and Methods**

Crystallographic analysis of bee bread and powdered honey was carried out by the method of scanning electron microscopy using a "Sigeta Forward 10-500X 5.0MPX LCD" digital microscope produced by "Sigeta" company (Ukraine) according to the requirements of the State Pharmacopoeia of Ukraine (SPhU) [1]. For studies the fractions of API previously sieved through a 0.25 mm sieve size were chosen (Fig. 1, 2).

The physical, physicochemical and pharmacotechnological properties of bee bread and powdered honey, their mixture (in the ratio of 1:3), as well as of granules of the mixture of API with excipients, were determined according to the methods of the SPhU (Tab. 1-3) [1].

The bulk volume, settling qualities, bulk density and tapped density were determined using a 545P-AK-3 device for powder vibratory compacting manufactured by the Mariupol Plant of Technological Equipment (Ukraine).

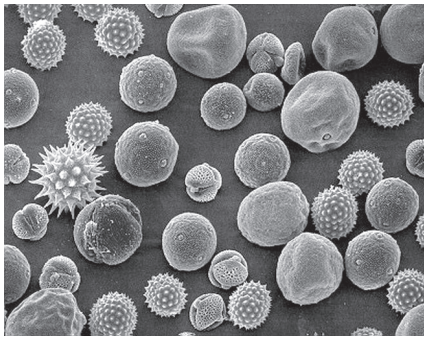

Fig. 1. Crystals of bee bread (500 times magnification).

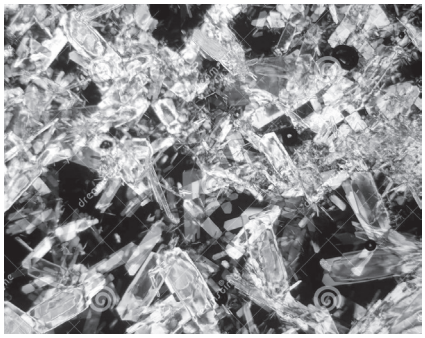

Fig. 2. Crystals of powdered honey (500 times magnification).

Table 1

The physical, physicochemical and pharmacotechnological properties of bee bread and powdered honey and their mixture

| Indicator | Bee bread | Powdered honey | The mixture of bee bread and powdered honey (1:3) |
|---|---|---|---|
| Fluidity, g/s | 1.86±0.33 | 3.49±0.23 | 3.29±0.05 |
| Angle of repose, degrees | 38-39 | 32-33 | 27-28 |
| Bulk volume, ($V_0$), ml | 173.55±1.66 | 122.32±1.12 | 187.62±2.8 |
| Settled volume, ($V_{10}$), ml | 155.29±0.98 | 114.45±0.74 | 181.72±1.42 |
| Settled volume, ($V_{500}$), ml | 142.69±3.31 | 104.70±0.4 | 174.47±0.43 |
| Settled volume, ($V_{1250}$), ml | 130.63±0.95 | 94.40±1.13 | 170.57±0.38 |
| Settling qualities, ($V_{10}$-$V_{500}$), ml | 12.60±1.05 | 9.69±0.78 | 7.25±0.87 |
| Bulk density, ($m/V_0$), g/ml | 0.58±0.04 | 0.81±0.56 | 0.53±0.46 |
| Tapped density, ($m/V_{1250}$), g/ ml | 0.77±0.05 | 1.05±0.69 | 0.58±0.32 |
| Moisture content, % | 12.65±0.84 | 2.07±1.4 | 0.38±0.04 |
| Moisture absorption in 100%, rel. hum., 25°C, % | 5.13±1.37 | 13.34±1.8 | 17.02±2.7 |

Note: n = 5; P = 0.95.

Table 2

The physical, physicochemical and pharmacotechnological properties of mixtures of bee bread and powdered honey with excipients

| Indicator | Composition 1 | Composition 2 | Composition 3 |
|---|---|---|---|
| | The mixture of API with sorbitol and aerosil | The mixture of API with mannitol and aerosil | The mixture of API with starch and magnesium carbonate |
| Fluidity, g/s | 2.69±0.03 | 3.91±0.04 | 3.29±0.04 |
| Angle of repose, degrees | 29-30 | 26-27 | 27-28 |
| Bulk volume, ($V_0$), ml | 184.24±1.9 | 176.46±2.4 | 179.37±2.3 |
| Settled volume, ($V_{10}$), ml | 176.04±1.21 | 171.08±1.11 | 174.87±1.13 |
| Settled volume, ($V_{500}$), ml | 168.14±0.57 | 162.57±0.74 | 165.12±0.34 |
| Settled volume, ($V_{1250}$), ml | 161.45±0.41 | 154.56±0.56 | 159.23±0.32 |
| Settling qualities, ($V_{10}$-$V_{500}$), ml | 7.9±0.63 | 8.51±0.74 | 9.75±0.42 |
| Bulk density, ($m/V_0$), g/ml | 0.54±0.12 | 0.56±0.61 | 0.56±0.41 |
| Tapped density, ($m/V_{1250}$), g/ml | 0.62±0.49 | 0.66±0.46 | 0.55±0.46 |
| Moisture content, % | 0.35±0.05 | 0.29±0.03 | 0.34±0.02 |
| Moisture absorption in 100%, rel. hum., 25°C, % | 14.02±1.7 | 9.02±2.3 | 11.02±1.9 |

Note: n = 5; P = 0.95.

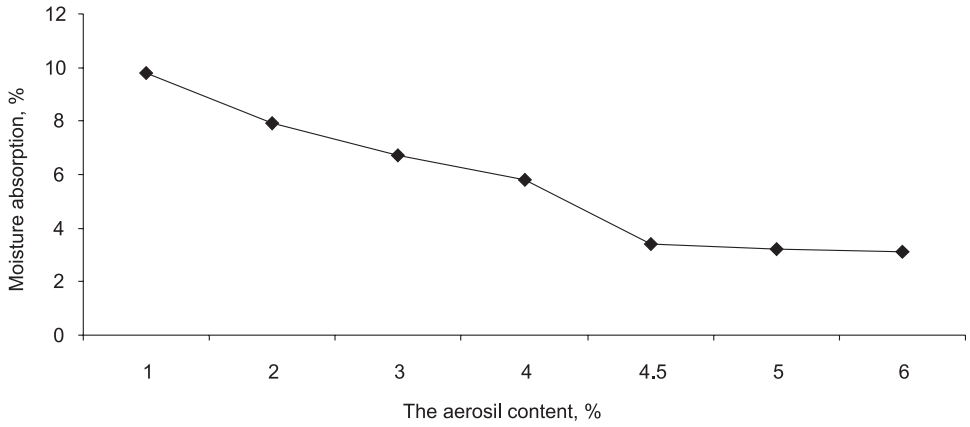


Fig. 3. The dependence of moisture absorption of the mixture for encapsulation on the amount of the aerosil content.

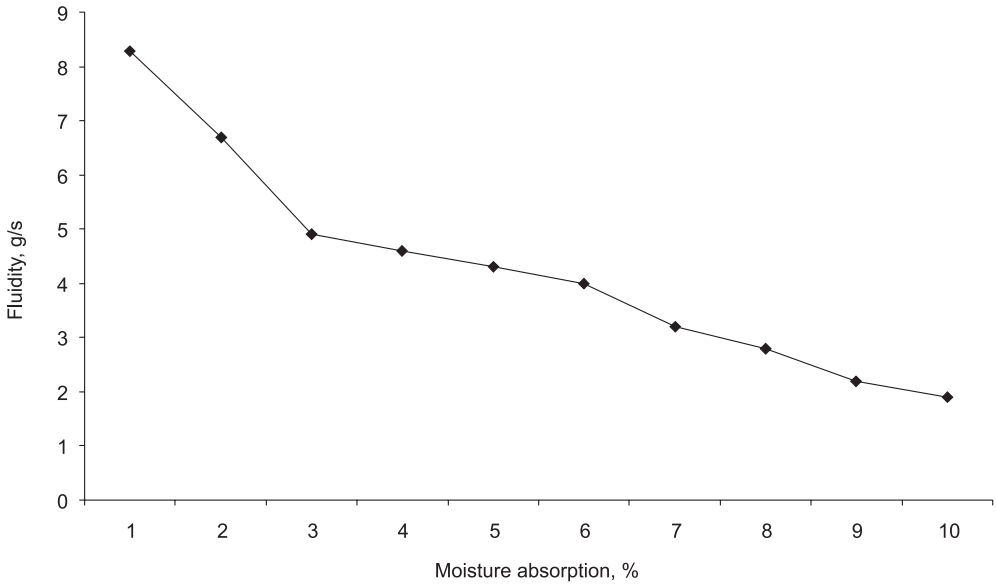


Fig. 4. The dependence of fluidity of the mixture of bee bread and the substance of powdered honey on the moisture content.

When determining the indicator of moisture absorption the mixture of active substances was transferred into the weighing bottles with the diameter of 29±0.5 mm and the height of 35 mm previously weighed, the moisturizer was added to it; then the mixture was placed in a desiccator with the diameter of 140 mm. The test was carried out under the following conditions: the ambient temperature – 18-20°C, the air humidity – 100% (created using purified water). The moisture content in the samples of the drug being developed was determined using BT-500 torsion scales according to the method of the SPhU (art. 2.9.36) [1] (Fig. 3).

Due to the fact that with increase of moisture absorption the fluidity of the mixture of bee bread and powdered honey decreased, and its encapsulation became impossible (Fig. 4) the pharmaceutically accepted excipients in different combinations were introduced to the mixture of API, as well as their ability to moisture absorption was studied (Fig. 5).

Since introduction of excipients almost had no effect on improvement of the fluidity indicators of the samples under study and made impossible their further

Table 3

The physical, physicochemical and pharmacotechnological properties of granules in the mixture bee bread and powdered honey with mannitol (4.5%) and aerosil (4.5%)

| The name of the indicator | Value |
|---|---|
| Fluidity, g/s (s/100 g) | 8.32±0.13 |
| Angle of repose, degrees | 28.2±0.8 |
| Bulk volume, ($V_0$), ml | 190.54±1.9 |
| Settled volume, ($V_{10}$), ml | 176.27±1.44 |
| Settled volume, ($V_{500}$), ml | 169.58±0.71 |
| Settled volume, ($V_{1250}$), ml | 167.43±0.74 |
| Settling qualities, ($V_{10}$-$V_{500}$), ml | 6.69±0.47 |
| Bulk density, ($m/V_0$), g/ml | 0.52±0.21 |
| Tapped density, ($m/V_{1250}$), g/ml | 0.60±0.33 |
| Moisture content, % | 0.69±0.09 |
| Moisture absorption in 100%, rel. hum., 25°C, % | 0.87±1.7 |

Note: n = 5; P = 0.95.

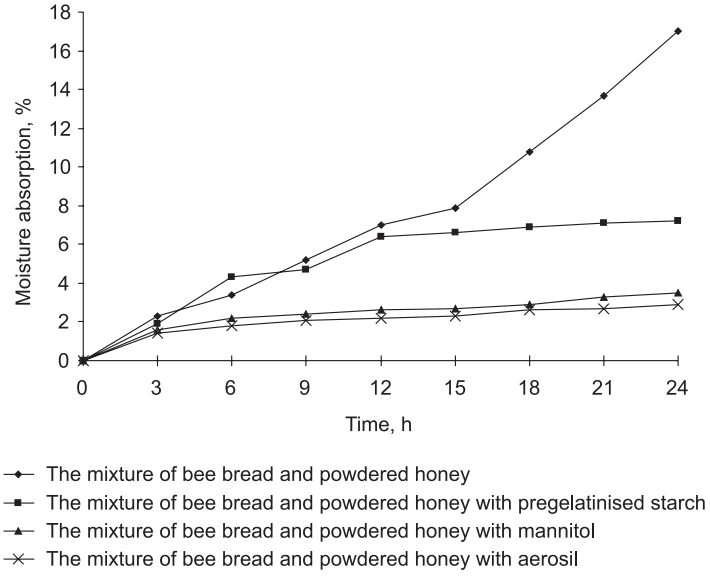


Fig. 5. The dependence of moisture absorption of the mixture for encapsulation on the content of different variants of the mixture of API with the excipients.

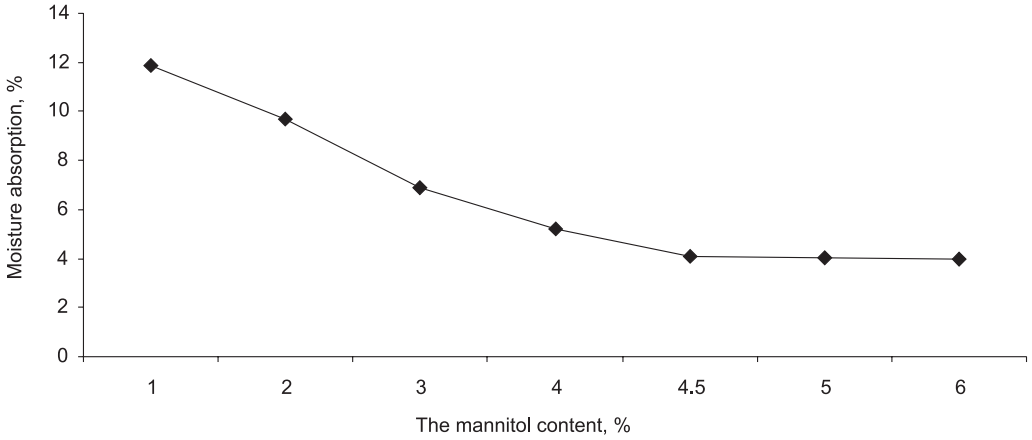


Fig. 6. The dependence of moisture absorption of the mixture for encapsulation on the amount of the mannitol content.

encapsulation, it was proposed to perform wet granulation of the mixtures of the experimental samples to obtain granules. The alcohol-water mixture in the concentration of 80% was used as a moisturizer.

To improve the fluidity of active substances the studies of granulated masses of the mixtures of API for the drug under research were carried out with the subsequent addition of antifriction excipients – aerosil and magnesium carbonate, as well as fillers – mannitol, pregelatinised starch and sorbitol (Tab. 2, Compositions 1-3) [2]. The angle of repose was also measured using the protractor in the samples studied.

Further the optimal concentration of mannitol was determined experimentally in order to introduce it into the composition of the mixture API depending on its ability to moisture absorption (Fig. 6).

To improve the fluidity of the mixture of bee bread and powdered honey the samples of API were prepared with addition of such excipients as pregelatinised starch, lactose monohydrate, aerosil (Fig. 7).

At the last stage of our research the studies of physical, physicochemical and pharmacotechnological properties of the granules obtained with bee bread, powdered honey and the mixture of excipients, in particular with aerosil and mannitol, were carried out (Tab. 3).

**Results and Discussion**

The data of crystallographic analysis of bee bread and powdered honey (Fig. 1, 2) indicate that the experimental samples are polydisperse powders with particles of an isodiametric shape as formless lumps and their fragments with a smooth and stiff-haired surface and the size of the dominant fraction up to 300 μm.

In this regard, it can be concluded that the fractions of powders under study must have the optimum value of fluidity due to the isodiametric shape of their particles.

The results of studying physical, physicochemical and pharmacotechnological properties of bee bread and powdered honey (Tab. 1) indicate that the substance of PH has better fluidity in relation to bee bread, and it is confirmed by the difference in the values of the angles of repose of the experimental samples of API. It should be also noted the presence of high moisture sorption properties for both of the substances studied, moreover, PH has a higher ability to absorb moisture, i.e. it is referred to hygroscopic substances. The difference between the bulk volume and settled volume indicates the ability of the powder to adhesion of particles and lump formation, and it may have a negative effect on the manufacturing process of granules for their further en-

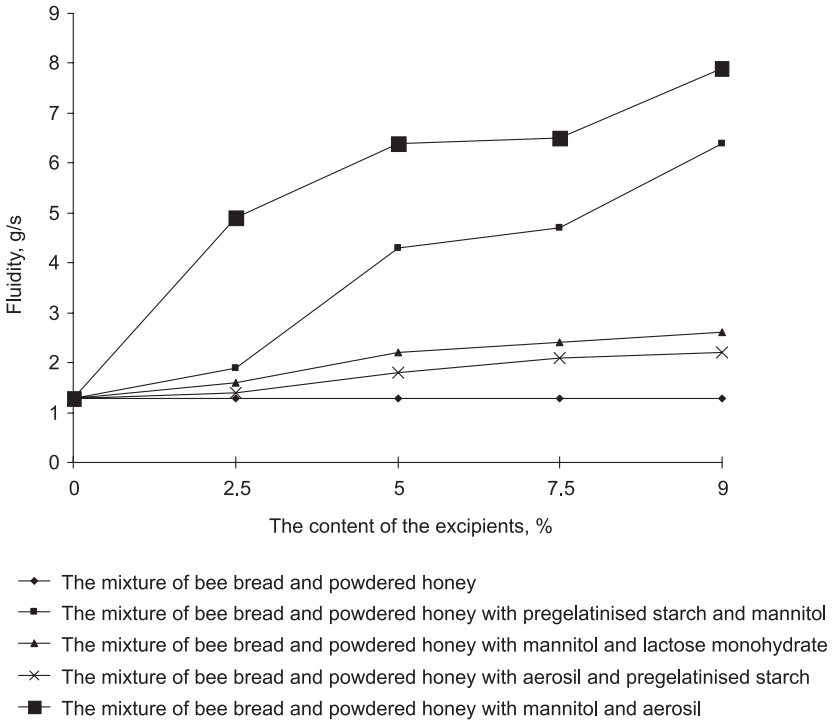


Fig. 7. The dependence of fluidity of the mixture of bee bread and powdered honey on the type and content of the excipients.

capsulation, in particular on homogeneity of mixing and uniformity of dosing. It was considered in our further studies.

The values of these indicators of the mixture of bee bread and powdered honey differ significantly from the results obtained in the study of the active ingredients separately as monocomponents. The unsatisfactory values of fluidity of the mixture of API for further encapsulation on industrial equipment were found since this indicator, as known, should be not more than 25 s/100 g [1, 2, 8].

When mixing API their ability to moisture absorption also increases, and it is an undesirable factor in the manufacture of capsules since the increase in moisture absorption leads to a significant decrease in the indicator of fluidity of the mixture for encapsulation. As a consequence, it reduces the accuracy of dosing, uniformity of distribution of active substances and may adversely affect the stability of the medicinal product during its storage (Fig. 4, 5).

The results of studying the granulated mixtures of API with antifriction substances and fillers (Tab. 2) indicate that the sample of Composition 2, which includes aerosil, differs from Compositions 1 and 3 by the value of fluidity and settling qualities, as well as reveals a higher ability to moisture absorption and reduces the moisture content, which should positively affect the shelf life and the storage conditions the drug being developed.

The study of the dependence of moisture absorption of the mixture for encapsulation on the quantitative content of aerosil (Fig. 3) and mannitol (Fig. 6) has shown that these excipients greatly reduce moisture absorption of the mixture in the process of granulation already in the amount of 2%, and further increase of their concentration up to 4.5% leads to a more efficient moisture content and decrease of moisture absorption. This allows making a conclusion that the combined introduction of aerosil and mannitol greatly improves the fluidity of the mixture of API in the process of granulation with its further encapsulation.

The results of determination of the fluidity of masses for encapsulation with the content of different excipients (Fig. 7) indicate that addition of the mixture of aerosil and mannitol in the concentrations of 4.5% each to the composition of granules is the most rational. A further increase in the quantity of excipients is inexpedient since the pharmacotechnological characteristics of masses for encapsulation of the drug under study are not improved.

Analysis of the test results (Tab. 3) suggests that introduction of excipients, in particular aerosil and mannitol, in the concentrations of 4.5% improves fluidity and reduces the moisture content of the granulated masses. The data obtained allowed to choose rationally their composition and concentration, and, as a result, to prepare the mixture for encapsulation with acceptable moisture-absorbing properties. Therefore, it has been found that adding these excipients is expedient for obtaining high quality granules and allows conducting their encapsulation while preparing and manufacturing capsules both in pharmacy and industrial conditions.

Therefore, based on the physical, physicochemical and pharmacotechnological studies conducted the quantitative content of the mixtures of API and excipients has been determined, and the rational composition of "Api-Immuno-Vit" capsules with the immunomodulatory action has been substantiated. The expediency of obtaining masses for encapsulation with pre-granulation and the use of the alcohol-water mixture in the concentration of 80% as a moisturizer to produce granules

with their subsequent powdering with aerosil has been determined.

CONCLUSIONS

1. The physical, physicochemical and pharmacotechnological properties of active pharmaceutical ingredients (bee bread and powdered honey) and their mixtures with the excipients of "Api-Immuno-Vit" capsules have been studied.

2. The expediency of obtaining granules by the wet granulation method of the mass for encapsulation using the alcohol-water mixture in the concentration of 80% as a moisturizer has been determined.

3. The results of the analysis of the resulting masses for encapsulation of the mixtures with active substances indicate the necessity of introduction of antifriction substances and humidity regulators, in particular aerosil and mannitol, into the composition of the drug being developed, and allow determining the rational composition and the quantitative content of API and excipients.

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**РОЗРОБКА СКЛАДУ ТА ТЕХНОЛОГІЇ КАПСУЛЬОВАНОГО ЛІКАРСЬКОГО ПРЕПАРАТУ НА ОСНОВІ ПЕРГИ ТА МЕДУ ПОРОШКОПОДІБНОГО. Повідомлення 2. Дослідження фармакотехнологічних властивостей сумішей активних фармацевтичних інгредієнтів з допоміжними речовинами капсул «Апі-Імуно-Віт»**

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***Ключові слова:*** *перга; мед порошкоподібний; допоміжні речовини; фармакотехнологічні випробування; капсули «Апі-Імуно-Віт»; імуномодулююча дія*

*Проведено вивчення фізичних, фізико-хімічних та фармакотехнологічних властивостей активних фармацевтичних інгредієнтів та їх сумішей з допоміжними речовинами капсул «Апі-Імуно-Віт» імуномодулюючої дії на основі перги та меду порошкоподібного. Результати аналізу одержаних мас для капсулювання сумішей діючих субстанцій свідчать про необхідність введення до складу розроблюваного лікарського засобу антифрикційних речовин і вологорегуляторів та дозволяють встановити раціональний склад і кількісний вміст допоміжних речовин. За допомогою проведених фармакотехнологічних досліджень встановлена доцільність одержання вологих гранул методом вологого гранулювання маси для інкапсулювання з використанням як зволожувача спирто-водної суміші у концентрації 80%.*

**РАЗРАБОТКА СОСТАВА И ТЕХНОЛОГИИ КАПСУЛИРОВАННОГО ЛЕКАРСТВЕННОГО ПРЕПАРАТА НА ОСНОВЕ ПЕРГИ И МЕДА ПОРОШКООБРАЗНОГО. Сообщение 2. Исследование фармакотехнологических свойств смесей активных фармацевтических ингредиентов с вспомогательными веществами капсул «Апи-Иммуно-Вит»**

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***Ключевые слова:*** *перга; мед порошкообразный; вспомогательные вещества; фармакотехнологические испытания; капсулы «Апи-Иммуно-Вит»; иммуномодулирующее действие*

*Проведено изучение физических, физико-химических и фармакотехнологических свойств активных фармацевтических ингредиентов и их смесей со вспомогательными веществами капсул «Апи-Иммуно-Вит» иммуномодулирующего действия на основе перги и меда порошкообразного. Результаты анализа полученных масс для капсулирования смесей действующих субстанций свидетельствуют о необходимости введения в состав разрабатываемого лекарственного средства антифрикционных веществ и влагорегуляторов и позволяют установить рациональный состав и количественное содержание вспомогательных веществ. С помощью проведенных фармакотехнологических исследований установлена целесообразность получения влажных гранул методом влажного гранулирования массы для инкапсулирования с использованием в качестве увлажнителя спирто-водной смеси в концентрации 80%.*