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INVESTIGATION OF PHARMACOTECHNOLOGICAL AND PHYSICOCHEMICAL CHARACTERISTICS OF DENSE CARROT EXTRACT AND ITS TABLET MIXTURES WITH AUXILIARY SUBSTANCES

Actuality. *At present, the effectiveness of treatment for cardiovascular diseases remains a major challenge in both pharmacy and medicine. Atherosclerosis can lead to the development of stroke and myocardial infarction. Analysis of literary sources allows us to conclude that the development of cardiovascular diseases involves a uniform shift in biochemical processes, particularly the activation of free radical oxidation due to the disruption of the balance in the "oxidants-antioxidants" system. Under the influence of reactive oxygen species, low-density lipoproteins undergo oxidation, leading to the accumulation of atherosclerotic plaques on the vessel walls and the narrowing of the vessel lumen. Therefore, oxidative stress is considered one of the main factors in the development of atherosclerosis.*

In our time, the use of a complex of biologically active substances derived from plant raw materials plays a significant role in the development of solid dosage forms. Due to the minimal number of side effects, it can be utilized over an extended period. Pharmacological research results indicate the expediency of combined therapy using statins and herbal preparations. This therapeutic approach has the potential to improve patient compliance and reduce the prescribed dose of synthetic drugs.

According to literary sources, the feasibility of using common carrot (Daucus carota L.) as an active pharmaceutical ingredient has been demonstrated. This plant possesses a sufficient raw material base in Ukraine.

Aim. *The study of pharmacotechnological and physico-chemical characteristics of dense extracts of common carrot (Daucus carota L.) and its mixtures with auxiliary substances.*

Materials and methods. *The extract of carrot seed root crops is thick and its mixture with auxiliary substances. In the course of the work, a complex of physicochemical and pharmacotechnological research methods was used.*

Results. *The pharmacotechnological properties of dense carrot seed extract in combination with MCC-102 and Neusilin® US2 have been determined. It has been established that the most effective carrier for improved incorporation of the dense extract into the composition of a solid dosage form is MCC-102. It has been demonstrated that with an increase in the mass fraction of the auxiliary substance, the density index decreases, the mass becomes non-uniform, and the obtained granules are not firm.*

Conclusions. *A mixture of MCC-102 in a 1:1 ratio has been chosen for further research. It has been determined that its use will allow for the production of tablets without the need for additional equipment.*

Key words: *carrot extract, technology, atherosclerosis, MCC-102, Neusilin® US2, physicochemical properties, pharmacotechnological indicators.*

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ДОСЛІДЖЕННЯ ФАРМАКОТЕХНОЛОГІЧНИХ ТА ФІЗИКО-ХІМІЧНИХ ХАРАКТЕРИСТИК ЕКСТРАКТУ МОРКВИ ПОСІВНОЇ ГУСТОГО ТА ЙОГО СУМІШЕЙ ІЗ ДОПОМІЖНИМИ РЕЧОВИНАМИ

Актуальність. *На цей час ефективність лікування захворювань серцево-судинної системи є головною проблемою фармації та медицини. Атеросклероз призводить до розвитку інсульту й інфаркту міокарда. Аналіз літературних джерел дає змогу зробити висновок, що з розвитком серцево-судинних захворювань відбувається однотипний зсув біохімічних процесів, зокрема активація вільнорадикального окислення внаслідок порушення рівноваги системи «оксиданти – антиоксиданти». Під впливом активних форм кисню ліпопротеїни низької щільності переходять у стан окислених, що призводить до накопичення атеросклеротичних бляшок на стінках судин і закриття просвіту судин. Отже, окислювальний стрес є одним з основних факторів розвитку атеросклерозу.*

У наш час для розробки твердих лікарських форм вагомого значення має використання комплексу біологічно активних речовин із рослинної сировини. У зв'язку з мінімальною кількістю побічних ефектів його можна використовувати протягом тривалого періоду. Результати фармакологічних досліджень свідчать про доцільність комплексної терапії статинами та рослинними препаратами. Цей напрям терапії здатний покращити комплаєнс пацієнта, знизити призначену дозу синтетичних лікарських засобів.

За даними джерел літератури показана доцільність використання як активного фармацевтичного інгредієнта моркви посівної (Daucus carota L.), яка має достатню сировинну базу в Україні.

Мета. *Дослідження фармакотехнологічних і фізико-хімічних характеристик екстракту моркви посівної густого та його сумішей с допоміжними речовинами.*

Матеріали та методи. *Екстракт коренеплодів моркви посівної густий та його суміші з допоміжними речовинами. Під час роботи було використано комплекс фізико-хімічних і фармакотехнологічних методів дослідження.*

Результати. *Визначено фармакотехнологічні властивості моркви посівної екстракту густого у сумішах з МКЦ-102 та Neusilin® US2. Встановлено, що найкращим носієм для введення екстракту густого до складу твердої лікарської форми є МКЦ-102. Доведено, що із збільшенням масової частки допоміжної речовини зменшується показник густини, маса є неоднорідною, отримані гранули неміцні.*

Висновки. *Для проведення подальших досліджень вибрана суміш з МКЦ-102 у співвідношенні 1 : 1. Встановлено, що її використання дасть змогу отримати таблетки без застосування додаткового обладнання.*

Ключові слова: *екстракт моркви, технологія, атеросклероз, МКЦ-102, Neusilin® US2, фізико- хімічні властивості, фармакотехнологічні показники.*

Introduction. Atherosclerosis is a condition characterized by the deposition of cholesterol plaques on the walls of blood vessels, which over time can lead to partial or complete blockage of the vessel lumen (Kong, Cui, Huang, Zhang, Guo, Han, 2022). These pathological changes represent the main cause of vascular diseases worldwide. According to the study «Progression of Early Subclinical Atherosclerosis», men and women suffer from atherosclerosis in 71 % and 43 % of cases, respectively. The overall mortality from cardiovascular diseases (CVDs) accounts for 32 % of all deaths globally. Of these, 85 % of cases were attributed to a heart attack or stroke following a previous atherosclerotic vascular event (Wojtasińska, Frąk, Lisińska, Sapeda, Młynarska, Rysz, Franczyk, 2023).

From a pathogenetic perspective, atherosclerosis is an inflammatory disease associated with local and systemic changes in homeostasis, particularly involving the state of the endothelium, the immune system, and lipid metabolism (Gusev, Sarapultsev, 2023). It is known that under normal physiological conditions, oxidative-reductive homeostasis is maintained, playing a crucial role in signal transmission. Any imbalance in this system can trigger a chain of reactions that generate reactive oxygen species (ROS). Disrupted redox balance or an imbalance between reactive substances and the antioxidant system

leads to oxidative stress, which damages proteins, nucleic acids, and lipids. Under normal conditions, the outer layer of low-density lipoproteins (LDL) in the plasma consists of triglycerides and cholesterol esters, which contain phospholipids, free cholesterol, and apolipoprotein B (ApoB). In pathological conditions, apoB-containing lipoproteins in the plasma penetrate through damaged endothelium into the subendothelial space of vessels, where they oxidize due to reactive oxygen species (ROS). Under these conditions, LDL transforms into oxidized LDL (Ox-LDL). The retention of Ox-LDL in the subendothelium promotes the recruitment of monocytes to the intima, where they differentiate into macrophages that engulf Ox-LDL through their scavenger receptors. This leads to the accumulation of atherosclerotic plaques, restricting blood flow to the heart muscle. Therefore, it can be concluded that Ox-LDL, endothelial dysfunction, and oxidative stress are among the key risk factors for the development of atherosclerosis (Khatana, Saini NK, Chakrabarti, Saini V, Sharma, Saini RV, Saini AK, 2020).

It is known that the use of a complex of bioactive substances (BAS) derived from plant sources, particularly polyphenolic compounds, reduces fat deposition and lowers the risk of developing atherosclerosis (Barnard, Goldman, Loomis, Kahleova, Levin, Neabore, Batts, 2019). It has been proven that these substances enhance the protective action of blood vessels and reduce the development of heart diseases. They can also be used in combination therapy with statins to reduce overall cholesterol and LDL cholesterol, aiming to decrease the prescribed dosage, minimize side effects, and improve patient compliance. According to the literature, it is known that the necessary BAS are contained in vegetable crops, which have a large raw material base in Ukraine, namely cultivated carrots (*Daucus carota* L.). Carrot roots contain carotenoids, vitamins, polyphenols, fiber, and minerals capable of absorbing active oxygen forms and enhancing endogenous protective systems, resulting in a reduction of oxidative stress and an overall decrease in the risk of cardiovascular diseases.

As of today, on the pharmaceutical market in Ukraine, carrot-based medications are represented by liquid extracts and complex preparations for treating kidney diseases. Therefore, based on the aforementioned information, it can be concluded that creating a medication with garden carrot extract for the treatment and prevention of atherosclerosis is justified.

Methods and materials. The objects of the study were the concentrated extract from the roots of garden carrots (GCE) and its mixtures with microcrystalline cellulose (MCC) samples № 1 – № 5, and Neusilin® US2 (№ 6 – № 10). The dense extract from the roots of garden carrots was obtained at the Department of Natural Compounds Chemistry of the National University of Pharmacy under the guidance of prof. Kyslychenko V.S. and prof. Zhuravel I.O. (Horiacha, Kyslychenko, Paziuk, Zhuravel, 2017). Samples were prepared by mixing the extract with MCC-102 and Neusilin® US2 in ratios of 1 : 1, 1 : 2, 1 : 3, 1 : 4 and 1 : 5.

The determination of bulk density, flowability, Carr's index, and Hausner ratio was carried out according to the well-established methods of the State Pharmacopoeia of Ukraine 2nd edition, Volume 2 (SPU). Microscopic examinations were conducted using a laboratory microscope «Konus-Academy» with a camera at a magnification of 120X. For visualization of photographs, DLT Cam Viewer™ software was used to determine linear dimensions in real-time mode.

The determination of moisture was conducted using the pharmacopoeial method (Hryzodub, 2015, p. 96) and with the help of a moisture analyzer. When employing the pharmacopoeial method, the following equipment was utilized: electronic scales SJP620CE by «Shinko Denshi» Japan, electronic scales ME 204 by «Mettler Toledo» Switzerland, and a vacuum drying cabinet SV-50 by LLC «RIVA-STAL» Ukraine. The percentage moisture content was calculated using the following formulas:

$$\frac{(m_{0i} - m_x)}{(m_{0i} - m_0)} * 100 ,$$

where m_{0i} – the mass of the crucible with the substance;

m_x – the mass of the crucible with the substance after the experiment;

m_0 – the mass of the crucible.

Another method of determination was carried out using the moisture analyzer MA 50/C/R by «RADWAG» Poland, under the following conditions: sample weight 1.0 g, experiment temperature 30 °C.

The coefficient of vibration compaction was calculated using the formula:

$$k_v = \frac{p_{max} - p}{p} ,$$

where p – bulk density;

$p_{\max -}$ maximum bulk density.

The coefficient of uniformity was determined using the formula:

$$\Re_0 = \frac{\Re_{60}}{\Re_{10}} ,$$

where $\Re_{60}$ – The size of the sieve opening through which 60 % of the mass passed;

$\Re_{10}$ – The size of the sieve opening through which 10 % of the material passed.

The angle of repose was determined using a plate with dimensions of 125 × 20 mm. The interpretation of the results was conducted by determining the average angle of inclination to the horizontal and by observing the shape of the heap.

Research results. The first step involved microscopic examination of the concentrated extract from the roots of garden carrots (Fig. 1).

Based on the results (Fig. 1), it can be observed that the extract has a heterogeneous structure with mechanical inclusions of various shapes, having a smooth surface. The linear particle size varies from 0.01 to 0.07 μm. The form factor is 1.16.

At the next stage, the moisture content of the extract, samples of the GCE and its mixtures with auxiliary substances were investigated. The moisture content of GCE is 17.9 %. The amount of extractive substances is 82.1 %. Organoleptically, it appears as a mass of dark-brown color, dense, viscous, and has a specific odor.

Fig. 1. Microphotograph of concentrated extract from the roots of garden carrots

Further research aimed to study the bulk density before and after compaction, fluidity, Carr's index, Hausner's ratio, angle of repose, compression ratio, and moisture content for the obtained mixtures in various proportions. The research results are presented in the table 1–2.

Table 1

Pharmacotechnological indicators GCE with MCC-102

Parameters	Sample number and its ratio				
	№ 1 1 : 1	№ 2 1 : 2	№ 3 1 : 3	№ 4 1 : 4	№ 5 1 : 5
Bulk density (ρ_b), g/ml	0,49 ± 0,01	0,31 ± 0,01	0,25 ± 0,01	0,30 ± 0,01	0,30 ± 0,01
Bulk density after compaction (ρ_com), g/ml	0,52 ± 0,01	0,42 ± 0,01	0,35 ± 0,01	0,38 ± 0,01	0,38 ± 0,01
Hausner ratio	1,06 ± 0,01	1,35 ± 0,01	1,40 ± 0,01	1,26 ± 0,01	1,26 ± 0,01
Carr's index	5,77 ± 1,12	26,19 ± 1,12	28,57 ± 1,12	21,05 ± 1,12	21,05 ± 1,12
Angle of repose, °	25 ± 1,03	43 ± 1,03	55 ± 1,03	35 ± 1,03	32 ± 1,03
Compressibility index	1,23 ± 0,02	1,28 ± 0,02	1,28 ± 0,02	1,28 ± 0,02	1,28 ± 0,02
Moisture content, %	0,93 ± 0,02	3,17 ± 0,02	3,16 ± 0,02	2,37 ± 0,02	2,22 ± 0,02
Vibration compaction coefficient	0,06	0,35	0,40	0,27	0,27
Coefficient of uniformity	2,01	5,12	5,35	5,23	5,26
Natural slope angle, °	25	35	55	43	65
Angle of repose, °	30	40	60	45	70

Table 2

Pharmacotechnological indicators GCE with Neusilin® US2

Parameters	Sample number and its ratio				
	№ 6 1 : 1	№ 7 1 : 2	№ 8 1 : 3	№ 9 1 : 4	№ 10 1 : 5
Bulk density (ρ_b), g/ml	0,28 ± 0,01	0,19 ± 0,01	0,17 ± 0,01	0,15 ± 0,01	0,14 ± 0,01
Bulk density after compaction (ρ_com), g/ml	0,41 ± 0,01	0,26 ± 0,01	0,25 ± 0,01	0,22 ± 0,01	0,21 ± 0,01
Hausner ratio	1,46 ± 0,01	1,37 ± 0,01	1,47 ± 0,01	1,47 ± 0,01	1,50 ± 0,01
Carr's index	31,71 ± 1,12	26,92 ± 1,12	32,00 ± 1,12	31,82 ± 1,12	33,33 ± 1,12
Angle of repose, °	55 ± 1,03	60 ± 1,03	55 ± 1,03	50 ± 1,03	65 ± 1,03
Compressibility index	1,29 ± 0,02	1,28 ± 0,02	1,28 ± 0,02	1,25 ± 0,02	1,25 ± 0,02
Moisture content, %	6,41 ± 0,02	7,10 ± 0,02	5,39 ± 0,02	3,94 ± 0,02	3,71 ± 0,02
Vibration compaction coefficient	0,46	0,37	0,47	0,47	0,50
Coefficient of uniformity	5,63	5,72	5,82	5,75	5,81
Natural slope angle, °	55	60	55	50	65
Angle of repose,	60	78	65	60	65

The obtained results of bulk density before and after compaction allow us to conclude that sample № 1 belongs to powders close to heavy powders. Sample № 2, 4–6 can be classified as powders of medium heaviness, while sample № 3, 7–10 belong to light powders. In all samples, with an increase in the mass fraction of the auxiliary substance, the density index decreases, and the mass is heterogeneous, resulting in weakly formed granules. According to the coefficients of Hausner, Carr's index, and the angle of natural repose, sample № 1 has satisfactory pharmacotechnical indicators, while samples № 2–10 suggest insufficient flowability and layering of the tablet mass. The obtained results can also be explained by the formation of a polydisperse structure in the mixture of the extract with the carrier.

The coefficients of non-uniformity and vibrational compaction, as well as the angles of natural repose and collapse, were also determined. These parameters are part of the recognized system for assessing powder flowability and equipment selection.

The analysis of the coefficient of vibrational compaction shows that sample № 1 has a value less than 0.21, which is the limit for well-flowing powders. Samples № 2–10 exceed this value on average by 2 times, indicating a high degree of particle cohesion in these samples. Therefore, samples № 2–10 are agglomerated powders with high cohesive properties.

The analysis of the coefficient of non-uniformity reveals a high degree of cohesion between particles in samples № 2–3, while sample № 1 exhibits a minimal value, predicting a low level of electrostatic interaction between particles, the impossibility of particle agglomeration, and satisfactory flowability.

The obtained results indicate that samples № 2–10 have high values of the angle of repose, indicating unsatisfactory material flowability. Sample № 1 exhibits satisfactory flowability because its angle of repose is less than 40°. In samples № 2–10, the difference in this parameter exceeds the maximum value, indicating a low dispersity and flowability in these samples.

The specified indicators allow classification according to the generally accepted flowability classification. Sample 1 belongs to the 1st class, which does not require additional equipment during pressing, while samples № 2–10 belong to the 7th class of flowability and may undergo technological processing or the addition of anti-caking agents or additional granulation (Carr R L, 1965, pp. 163–168). Based on the above, it can be predicted that samples № 2–10 may hang in the hoppers of tablet machines.

Conclusion. It has been demonstrated that atherosclerosis is the most common cardiovascular disease, requiring advanced pharmaceutical interventions for its treatment. In the therapy of atherosclerosis, it is advisable to use substances of natural origin that can be used both in monotherapy and in combination with synthetic agents. The use of extracts from the roots of cultivated carrots is proposed for the therapy of atherosclerosis, as they possess antioxidant and anti-inflammatory properties.

The pharmacotechnological properties of dense extract from cultivated carrots in mixtures with MCC-102 and Neusilin® US2 were determined. It was found that the optimal carrier for the enhanced incorporation of the dense extract into the composition of a solid dosage form is MCC-102. It has been proven that with an increase in the mass fraction of the auxiliary substance, the density index decreases, the mass becomes heterogeneous, and the obtained granules are not strong. Therefore, for further research, a mixture in a ratio of 1 : 1 was chosen. It was established that the use of sample № 1 in the tablet composition allows obtaining tablets without the use of additional equipment.

The obtained results provide a basis for further development of a solid dosage form with dense extract from cultivated carrot roots.

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