UDC 615.014.2:615.453.6:615.32:616.13-004.6 https://doi.org/10.24959/nphj.26.203

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The development of a tablet formulation of quercetin with the carrot extract with improved solubility for the atherosclerosis prevention

The primary goal in the development of tablet dosage forms is to ensure their quality, safety, and therapeutic effectiveness. In addition to containing the required amount of the active pharmaceutical ingredient (API), a tablet must meet specific technological parameters that ensure stability, consistent dose uniformity, and ease of use for the patient. The determination of pharmacotechnological mass parameters during tableting is of particular importance as this factor directly affects the accuracy of the active substance dosing, formulation homogeneity and uniform distribution of the API, as well as the mechanical strength and resistance of tablets to fracture. In addition, these parameters significantly influence biopharmaceutical characteristics, including the disintegration time and drug release rate. In the development of tablets intended for the prevention and treatment of atherosclerosis, pharmacotechnological considerations become even more critical.

Aim. To study the pharmacotechnological parameters of tablet formulations, which is a fundamental task in pharmaceutical technology as it determines the success of the drug development and further clinical application of the medicine.

Materials and methods. A tableting blend and tablet samples previously designated as “Carocetin” were used as the study objects. The study employed methods regulated by the State Pharmacopoeia of Ukraine (SPhU). In addition, the coefficients of vibration compaction and heterogeneity, as well as the angle of collapse, were determined. The tablet quality was assessed based on the mechanical strength, friability, disintegration time, and the coefficients of compaction and compressibility.

Results. It has been found that the use of a solid dispersion of quercetin with polyvinylpyrrolidone K-30 improves its technological properties and creates prerequisites for enhanced bioavailability. The role of modifying the thick extract of roots by blending it with microcrystalline cellulose-102 in a ratio of 1:1 has been evaluated; this approach ensures reduced hygroscopicity and improved flowability of the mixture without the loss of the biological activity. The analysis of pharmacotechnological parameters has demonstrated that, according to the Carr classification, the tableting blend corresponds to flowability class I, which allows the use of the direct compression method without prior granulation. The relationships between compression pressure and the physicomechanical quality parameters of tablets have been characterized, and it has been found that optimal characteristics, namely the sufficient mechanical strength, low friability, and acceptable disintegration time are achieved at a compression pressure of 100 ± 1 kN.

Conclusions. It has been demonstrated that the pharmaceutical composition developed on the basis of a solid dispersion of quercetin and a thick extract of carrot roots is technologically justified for producing tablets by the direct compression method. The use of a moderate compression pressure (100 ± 1 kN) has been proven to be optimal, ensuring the proper tablet quality and compliance with the requirements of the SPhU for tablets previously designated as “Carocetin”. The approach proposed is considered to create favorable conditions for increasing the bioavailability of biologically active compounds and can be applied in the further development of combined solid dosage forms with anti-atherogenic properties in the tablet form.

Keywords: *atherosclerosis; quercetin; thick extract of Daucus carota L. roots; tablets; pharmaceutical technology; quality.*

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Розроблення таблетованої форми кверцетину з екстрактом моркви з поліпшеною розчинністю для профілактики атеросклерозу

Головною метою у розробленні таблетованих лікарських форм є забезпечення їхньої якості, безпечності і терапевтичної ефективності. Таблетка має не лише містити необхідну кількість активного фармацевтичного інгредієнта (АФІ), але й відповідати технологічним параметрам, що гарантують стабільність, відтворюваність дозування та зручність застосування для пацієнта. Особливого значення набуває встановлення фармакотехнологічних показників маси під час таблетування, адже саме цей параметр визначає точність дозування активних речовин; однорідність складу та рівномірність розподілу АФІ; механічної міцності та стійкості таблеток до руйнування; біофармацевтичних характеристик, зокрема швидкості розпаду та вивільнення діючої речовини. У створенні таблеток для профілактики та лікування атеросклерозу фармакотехнологічні аспекти набувають ще більшої актуальності.

Мета – дослідження фармакотехнологічних параметрів маси таблеток, що є фундаментальним завданням фармацевтичної технології, яке визначає успішність розробки препарату та його подальше клінічне застосування.

Матеріали та методи. Як об'єкти дослідження використовували суміш для таблетування та зразки таблеток під умовною назвою «Кароцетин». У ході дослідження використано методи, які регламентовані Державною фармакопеєю України (ДФУ). Додатково було визначено коефіцієнти вібраційного ущільнення та неоднорідності й кута обрушення. Якість таблеток оцінювали за показниками міцності, стираності, часу розпадання, коефіцієнтів ущільнення та спресованості.

Результати та їхнє обговорення. Установлено, що застосування твердої дисперсії кверцетину з полівінілпіролідоном К-30 сприяє покращанню його технологічних характеристик та створює передумови для підвищення біодоступності. Оцінено роль модифікації моркви посівної коренеплодів екстракту густого шляхом його змішування з мікрокристалічною целюлозою-102 у співвідношенні 1:1, що забезпечує зниження гігроскопічності та поліпшення сипкості суміші без втрати його біологічної активності. Аналіз фармакотехнологічних показників показав, що, за класифікацією Карра, суміш для таблетування відповідає 1-му класу плинності, що дозволяє застосовувати метод прямого пресування без попередньої грануляції. Охарактеризовано закономірності впливу тиску пресування на фізико-механічні показники якості таблеток і встановлено, що оптимальні характеристики достатньої міцності, низької стираності та задовільним часом розпадання досягаються за умови тиску пресування (100 ± 1) кН.

Висновки. Установлено, що розроблена фармацевтична композиція на основі твердої дисперсії кверцетину та моркви посівної коренеплодів екстракту густого є технологічно обґрунтованою для отримання таблеток методом прямого пресування. Доведено доцільність використання середнього тиску пресування (100 ± 1 кН) як оптимального режиму, що забезпечує належну якість та відповідність вимогам ДФУ таблеток під умовною назвою «Кароцетин». Вважається, що запропонований підхід створює передумови для підвищення біодоступності біологічно активних речовин і може бути використаний у подальшому розробленні комбінованих твердих лікарських форм з антиатерогенними властивостями у вигляді таблеток.

Ключові слова: *атеросклероз; кверцетин; моркви посівної коренеплодів екстракт густий; таблетки; технологія; якість.*

Introduction. Atherosclerosis is one of the most prevalent chronic cardiovascular diseases and a leading cause of mortality worldwide. According to the World Health Organization, in 2022 approximately 19.8 million people died from cardiovascular diseases (CVDs), accounting for nearly one-third of all deaths [1]. The main risk factors include hypercholesterolemia, arterial hypertension, obesity, diabetes mellitus, smoking, and genetic predisposition. The prevalence of atherosclerosis increases with age, with men being more susceptible to earlier disease onset compared to women [2].

Additional risk factors include a sedentary lifestyle, a diet high in saturated fats, stress, and the presence of the metabolic syndrome. Epidemiological studies indicate that atherosclerosis primarily affects the aorta, coronary arteries, cerebral vessels, and peripheral arteries, leading to the development of ischemic heart disease, stroke, and peripheral arterial insufficiency [3].

The pathogenesis of atherosclerosis is multifactorial and involves the endothelial dysfunction, subendothelial lipid accumulation, low-density lipoprotein (LDL) oxidation, chronic inflammation of the vascular wall, and the formation of atherosclerotic plaques [2]. Macrophages and smooth muscle cells play a key role in disease progression by contributing to the formation of foam cells. These cells produce pro-inflammatory cytokines and matrix metalloproteinases, which promote plaque destabilization, thereby increasing the risk of rupture and the thrombus formation [4, 5].

One of the early stages of atherosclerosis is the oxidation of LDL, leading to the formation of biologically active lipid peroxidation products. These products activate receptor-mediated pro-inflammatory signaling pathways and exacerbate vascular inflammation. Oxidative stress, resulting from the excessive generation of reactive oxygen species (ROS), contributes to the endothelial damage and the progression of atherosclerosis.

Pathogenetically, atherosclerosis develops due to an imbalance between pro-oxidant and antioxidant mechanisms in the body. Key processes include the LDL oxidation, macrophage accumulation in the vascular wall, foam cell formation, activation of inflammatory cytokines (IL-1, IL-6, TNF-α), and degradation of the extracellular matrix.

Standard therapeutic approaches include the use of lipid-lowering agents (particularly statins), antihypertensive therapy, and antiplatelet agents. While these treatments effectively reduce LDL cholesterol levels, the cardiovascular risk persists due to insufficient control of inflammatory and oxidative processes. This so-called residual inflammatory risk is associated with the systemic inflammation that is not addressed by standard therapy [6, 7].

According to recent studies, even with the optimal LDL cholesterol control, patients with elevated levels of inflammatory markers remain at increased risk of recurrent cardiovascular events. Consequently, there is a growing need to enhance therapeutic strategies based on the antioxidant therapy [8, 9].

Among prospective strategies, particular attention is given to the use of biologically active compounds (BACs) with antioxidant and anti-inflammatory properties, which are capable of modulating key pathogenetic mechanisms of the disease. Due to their antioxidant and anti-inflammatory activities, flavonoids represent a promising class of agents in atherosclerosis therapy. Studies have shown that they can reduce oxidative stress by scavenging ROS and enhance the vascular antioxidant defense [10].

One representative of this class is quercetin, a natural flavonoid exhibiting a broad spectrum of biological activities. Quercetin can prevent the oxidation of LDL and support the endothelial function by reducing the inflammatory response associated with atherosclerosis. Additionally, it activates sirtuin-associated signaling pathways, promoting the restoration of the cellular energy homeostasis,

the apoptosis regulation, and the oxidative stress reduction [11, 12]. It regulates the lipid metabolism, reduces the total cholesterol and triglyceride levels, and increases high-density lipoprotein (HDL) concentrations, which exhibit anti-atherogenic effects [13]. However, the main limitation of quercetin use is its low water solubility, which consequently results in poor bioavailability. This restricts its clinical application and highlights the need for the development of new dosage forms, particularly solid dispersions.

Another source of BACs is *Daucus carota* L., which contains carotenoids, polyphenols, and vitamin C. The main carotenoids in carrot roots are β-carotene (75 %), α-carotene (23 %), lutein (1.9 %), as well as β-cryptoxanthin, lycopene, and zeaxanthin. These components exhibit the antioxidant, hypoglycemic, and anti-inflammatory activities [14]. Pharmacological studies have shown that regular consumption of carrot-based preparations reduces the risk of developing CVDs [15]. It helps to normalize blood pressure, improve the redox homeostasis, and reduce the vascular damage, as well as reduce the total cholesterol and triglyceride levels, increase HDL cholesterol, and exhibit anti-atherogenic effects [16, 17].

Therefore, the combination of quercetin with a thick extract of *Daucus carota* L. roots may provide a synergistic effect, enhancing the antioxidant defense, normalizing the lipid metabolism, and exerting the anti-inflammatory activity. This makes such a combination a promising candidate for the development of new therapeutic and preventive agents for atherosclerosis [18].

Materials and methods. The study objects were the tablet blend and tablet samples previously designated as “Carocetin”. Pharmaceutical technology parameters, including bulk density, flowability, moisture content, friability, disintegration, and resistance to crushing, were evaluated according to the methods outlined in the State Pharmacopoeia of Ukraine (SPhU) [19].

The vibration compaction index characterizes the ability of powdered substances to reduce their volume under mechanical vibration. It is used to assess powder flowability and compressibility during tablet manufacturing, and it also provides insight into the material behavior while stored in the hoppers of tablet presses. This parameter was calculated using the following formula:

$$k_v = \frac{p_{max} - p}{p}, \quad (1)$$

where p is the bulk density; p_{max} is the maximum bulk density.

The heterogeneity index reflects the degree of the particle size distribution non-uniformity in a powder system and indicates the extent to which it deviates from a monofractional structure. If the index value approaches 2, the mixture is considered homogeneous. This parameter was determined using the following formula:

$$R_0 = \frac{R_{60}}{R_{10}}, \quad (2)$$

where R_{60} is the sieve size through which 60 % of the mass passed; R_{10} is the sieve size through which 10 % of the material passed.

The angle of repose is a parameter that characterizes the ability of powdered materials to form a stable cone during free pouring. It was measured using a plate with dimensions of 125×20 mm, set at an inclination of 45° to the horizontal. The results were interpreted based on the mean tilt angle and the shape of the powder heap.

The compression ratio is defined as the ratio of the initial powder bed height in the die to the height of the formed tablet. To evaluate it, the die is filled with a powder, followed by compression at a pressure of 120 MPa. After compression, the tablet is ejected using a punch, and its height is measured. The compression ratio was calculated using the following formula:

$$K_C = \frac{H_1}{H_2}, \quad (3)$$

where H_1 is the powder bed height in the die; H_2 is the height of the formed tablet.

The compactibility index determines the strength of the model tablet after compression. The better the powder compacts, the stronger the resulting tablet. In cases of insufficient compactibility, the tablet may be brittle or even break completely during ejection from the die. After compression, the tablet is weighed, its height is measured using a micrometer. The compactibility index (g/mm) was calculated according to the following formula:

$$K_{compac} = \frac{m}{H}, \quad (4)$$

where m is the tablet mass, g; H is the tablet height, mm.

Results and discussion. Considering the low bioavailability of quercetin, the primary objective at the initial stage was to enhance it by creating solid dispersions with polyvinylpyrrolidone K-30, forming a physical eutectic mixture. Due to intermolecular interactions, this approach promotes the quercetin amorphization, increasing its solubility and, consequently, its bioavailability. This strategy significantly improves the pharmaceutical technology properties of the substance and positions it as a promising basis for the development of solid dosage forms.

The second stage of the technological process involved determination of the method of incorporating a thick extract of *Daucus carota* L. roots characterized by high viscosity and hygroscopicity into the tablet formulation. These properties significantly complicate the tablet production based on the extract. To ensure the required technological characteristics, a mixture of the extract with microcrystalline cellulose-102 in a mass ratio of 1:1 was prepared. This approach is expected to improve the flowability, stability, and compactibility of the tablet blend, allowing an effective integration of the extract into a solid dosage form without compromising its biological activity [20].

Based on this approach, tablet blend samples with the following composition were prepared (Table 1).

The tablet blend was prepared in several stages. First, a solid dispersion of quercetin with polyvinylpyrrolidone K-30 was obtained, dried to a residual moisture

Table 1

The optimal composition of tablets previously designated as "Carocetin"

Quercetin	6.25
Polyvinylpyrrolidone K-30	6.25
Thick extract of carrot roots	37.50
Microcrystalline cellulose-102	43.75
Sodium croscarmellose	5.00
Colloidal silicon dioxide	0.75
Magnesium stearate	0.50
Total mass	**100.00 %**

Table 2

Pharmaceutical technology parameters of the tablet blend

Parameters	Values of the parameters
Bulk density (ρ_b), g/ml	0.48 ± 0.01
Bulk density after compaction (ρ_com), g/ml	0.53 ± 0.01
Hausner ratio	1.11 ± 0.01
Carr index	10.00 ± 1.12
Flow rate, g/s	4.27 ± 0.01
Moisture content, %	6.49 ± 0.02

content of 19 ± 0.01 %, and then mixed with microcrystalline cellulose-102. The second stage involved preparation of a mixture of a thick extract of carrot roots with microcrystalline cellulose-102 with a residual moisture content of 3.93 ± 0.02 %. The blends were then combined and mixed in a paddle mixer at 350 rpm for 10 minutes. After this initial mixing, colloidal silicon dioxide and magnesium stearate were added, and the mixture was blended for additional 10 minutes.

At the next stage of the study, the pharmaceutical technology properties of the tablet blend were assessed (Table 2).

The pharmaceutical technology parameters of the tablet blend obtained indicate satisfactory properties, suggesting the feasibility of using direct compression. The bulk density before tamping (0.48 g/ml) and after tamping (0.53 g/ml) indicates a moderate powder weight, meeting the criteria for materials suitable for tableting without prior granulation. The increase in density after light compaction reflects moderate compressibility, which facilitates the production of tablets with an adequate mechanical strength.

The Hausner ratio (1.11) and the Carr index (10.00) fall within ranges indicative of the excellent powder flowability. Values of <1.25 for the Hausner ratio and <15 % for the compression index reflect a low degree of particle cohesion, reducing the risk of the agglomerate formation and ensuring uniform die filling in the tablet press.

Additionally. the heterogeneity and vibration compaction coefficients, as well as the angle of repose and the angle of collapse, were determined. These parameters are part of the Carr scoring system commonly used for classifying the powder flow and selecting the optimal equipment (Table 3).

The analysis of the results obtained indicated that the tablet mass scored 98 points, classifying the tablet blend as satisfactorily free-flowing. This ensures uniform die filling, reduces the risk of segregation, and prevents powder bridging in the hoppers of tablet presses. According to the Carr R.L. (1965) classification, the blend belongs to flowability class I, indicating a high powder flowability and eliminating the need for additional equipment to facilitate feed into the tablet press hopper.

At the next stage, tablets were compressed at varying pressures, and their compliance with the SPhU was evaluated. Hardness, friability, and disintegration time tests were performed, and the compression ratio and compactibility index were also determined (Table 4).

Tablets compressed at low pressure (50 ± 1 kN) exhibited marginal hardness (51.38 ± 0.03 N), which only

Table 3

Technological characteristics of the tablet mass

Parameters	Acceptable limits / score	Values of tablet mass parameters / score
Vibration compaction coefficient	<1.10-1.20 / 25-23	0.10 ± 0.01 / 25
Heterogeneity coefficient	<1.5-2.0 / 23-25	2.00 ± 0.07 / 23
Angle of repose, °	<30-35 / 25-23	30.01 ± 1.03 / 25
Angle of collapse, °	<35-40 / 25-23	35.02 ± 1.01 / 25

Table 4

The quality control of tablets previously designated as "Carocetin"

Parameters	Results depending on the compression pressure, kN		
	50 ± 1	100 ± 1	150 ± 1
Hardness, N	51.38 ± 0.03	97.42 ± 0.01	242.06 ± 0.01
Disintegration time, min	5.00 ± 0.12	12.00 ± 0.06	20.00 ± 2.04
Friability, %	0.82 ± 0.05	0.20 ± 0.03	0.00 ± 0.01
Compression ratio	2.00 ± 0.01	2.40 ± 0.01	2.40 ± 0.01
Compactibility index	1.02 ± 0.01	1.19 ± 0.01	1.22 ± 0.02

formally met the minimum requirements. However, the analysis of the friability test revealed chipping and cracking, indicating brittleness and instability. The compression ratio (2.00 ± 0.01) and compactibility index (1.02 ± 0.01) reflect an insufficient particle consolidation and a low structural stability. Such tablets cannot ensure integrity during handling and administration, and therefore, do not comply with pharmaceutical technology standards.

Tablets compressed at medium pressure (100 ± 1 kN) exhibited the optimal characteristics: an adequate hardness (97.42 ± 0.01 N), a low friability (0.20 ± 0.03 %), and a satisfactory disintegration time (12.00 ± 0.06 min). The compression ratio (2.4 ± 0.01) and compactibility index (1.19 ± 0.01) indicate the effective tablet formation with a proper structural stability. These parameters meet the requirements for oral solid dosage forms, ensure mechanical integrity, and, due to disintegration, predict the appropriate active ingredient release. This compression regime can therefore be considered optimal for ensuring the pharmacological efficacy of the formulation.

In contrast, tablets formed at high pressure (150 ± 1 kN) exhibited the excessive hardness (242.06 ± 0.01 N) and the zero friability, along with a prolonged disintegration time (2.00 ± 2.04 min). The compression ratio (2.4 ± 0.01) and compactibility index (1.22 ± 0.02) approach the threshold beyond which the tablet may become overly dense. This suggests that the tablet could dissolve slowly in the gastrointestinal tract, hindering the release of active ingredients and their pharmacological activity. Thus, tablets obtained under high pressure do not meet the requirements for all key quality parameters.

Therefore, the study results confirm the appropriateness of using medium compression pressure to ensure the proper quality of "Carocetin" tablets and their pharmacological efficacy.

Conclusions and prospects for further research. It has been demonstrated that atherosclerosis is one of the leading chronic cardiovascular diseases requiring novel therapeutic approaches, including the use of natural bioactive compounds. The use of flavonoids, particularly quercetin and concentrated extract from *Daucus carota* L. roots, is considered appropriate as they exhibit antioxidant, anti-inflammatory, and anti-atherogenic activities. It has been substantiated that the combination of quercetin with the concentrated carrot root extract can provide a synergistic effect aimed at reducing oxidative stress, normalizing the lipid metabolism, and stabilizing the endothelial function.

The pharmaceutical and technological properties of the tablet blend containing a solid dispersion of quercetin with polyvinylpyrrolidone K-30 and a modified carrot root extract with microcrystalline cellulose-102 in a ratio of 1:1 have been evaluated. It has been found that this composition provides a good flowability, fluidity, and compactibility, eliminating the need for additional granulation. Based on the bulk density, Hausner ratio, Carr index, and angle of repose, the blend corresponds to flowability class I according to the Carr R. L. classification, indicating predictable uniform dosing and the absence of segregation.

The optimal compression pressure for tablets has been determined. It has been found that tablets produced under medium pressure exhibit the optimal hardness, low friability, and appropriate disintegration time, as well as the satisfactory compression ratio and compactibility index, ensuring the effective pharmacological activity in the human body. Tablets formed under low pressure are brittle and unstable, whereas those compressed at high pressure are excessively dense with a risk of the insufficient dissolution in the gastrointestinal tract.

Conflict of interests: authors have no conflict of interests to declare.

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Дата першого надходження: 19.01.2026 р.
Дата прийняття до друку: 16.02.2626 р.
Дата публікації: 31.03.2026 р.