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FORMULATION AND TECHNOLOGY OF ORODISPERSIBLE TABLETS OF LUTEOLIN WITH POTENTIAL ANTIHYPERTENSIVE ACTION

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პოტენციური ანტიჰიპერტენზიული მოქმედების მქონე ლუტეოლინის ოროდისპერსული ტაბლეტების ფორმულაცია და ტექნოლოგია

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რეზიუმე

არტერიული ჰიპერტენზია ერთ-ერთ ყველაზე გავრცელებულ ქრონიკულ დაავადებად არის მიჩნეული მსოფლიოს ეკონომიკურად განვითარებულ ქვეყნებში, რომელიც ქრონიკული ინვალიდიზაციისა და ლეტალური გამოსავლის ხშირ მიზეზად გვევლინება.

ბოლო წლებში მკვლევართა ყურადღება აქცენტირებულია სისხლძარღვთა ვაზოკონსტრიქციულ და ვაზოდილატაციურ მექანიზმებში მონაწილე ახალი ენდოგენური ნივთიერებების გამოსავლენად. ამ მიმართულებით განსაკუთრებულ ყურადღებას იპყრობს არაქიდონის მჟავის ეპოქსიგენაზური მეტაბოლიზმის ვაზოდილატაციური პროდუქტები, როგორიცაა ეპოქსიეიკოზატრიენოის მჟავები (EETs), რომელთა სწრაფ გარდაქმნას ორგანიზმში ნაკლებად აქტიურ მეტაბოლიტებად, როგორიცაა დიჰიდროქსიეიკოზატრიენოის მჟავები (DHETs), ხელს უწყობს ფერმენტი ხსნადი ეპოქსიდ ჰიდროლაზა (sHE).

ლიტერატურული მონაცემებით, მცენარეული წარმოშობის ბიოლოგიურად აქტიურ ნივთიერებას - ლუტეოლინს გააჩნია ხსნადი ეპოქსიდ ჰიდროლაზას ინჰიბირების და EETs-ის ვაზოდილატაციური მოქმედების პროლონგირების უნარი.

არტერიული ჰიპერტენზიის მკურნალობის დროს განსაკუთრებული ყურადღება ექცევა პაციენტის მიერ წამალთფორმის დამოუკიდებლად გამოყენების შესაძლებლობას, ყოველგვარი დამხმარე საშუალებების (წყალი, შპრიცი და ა.შ.) გარეშე და სწრაფ მოქმედებას.

ხელოვნური ინტელექტისა და ბიოფარმაცევტული კვლევების საფუძველზე შემუშავდა ლუტეოლინის ოროდისპერსიული ტაბლეტების ტექნოლოგია სუბლიმაციური მეთოდით.

ნაჩვენებია, რომ კეთილხარისხოვნების მაჩვენებლების მიხედვით ლუტეოლინის ოროდისპერსიული ტაბლეტები აკმაყოფილებს სტანდარტის მოთხოვნებს. სუბლიმაციურ აგენტად ქაფურის გამოყენება უზრუნველყოფს ფოროვანი სტრუქტურის წარმოქმნას, რაც ხელს უწყობს ტაბლეტებში სითხის შეღწევადობას და მათ სწრაფ დაშლას.

Arterial hypertension still remains one of the main problems of modern cardiology. It is a major risk factor for cardiovascular disease, in economically developed countries leading to chronic disability and lethal outcome [3].

Despite the wide spectrum of medicines for treating arterial hypertension, till today this pathology is characterized by high mortality. The cause of this presumably is the lack of knowledge of pathogenic mechanisms for development of arterial hypertension, which would be able to help for identification of new medical targets for prevention and treatment of this disease based on individualized, personalized medicine. In this regard during the recent years the attention of the researchers was focused on the new

endogenous substances involved in vasoconstriction and vasodilation mechanisms [3]. In this direction special attention is paid to vasodilating products of epoxygenic acid metabolism such as epoxyeicosatrienoic acids (EETs), which rapid conversion in the body into less active metabolites such as dihydroxyeicosatrienoic acids (DHETs) is promoted by enzyme epoxide hydrolase (sEH). It is particularly noteworthy that till today in the literature there is little data on the study of natural compounds with suppression of sEH action which would promote the prolongation of EETs vasodilating activity [8].

In the treatment of arterial hypertension, special attention is paid to the ability of the patient to use the drug independently, without any additional materials (water, syringe, etc.) and their rapid action [8]. Difficulty in swallowing is common among all age groups, occurring in 35% of the population. Indication of difficulty in swallowing occurs especially in cases of sore throat, seasickness, allergies and bronchitis. This time orally taken soluble forms of dispersible drugs are optimal [10,11]. Modern technology gives the opportunity to create drug forms with different speeds of release of substances, absorption and consequently difference bioavailability. This is especially actual for oral solid dosage forms, which account for 50-60% of all forms of administration. In the last years, fast-dissolving solid formulations have become particularly popular, in which the effect of rapid solubility or disintegration is achieved through the use of special excipients or special technological methods. Orodispersible tablets (ODT) dissolve or disperse rapidly, when they come into the contact with saliva in the oral cavity and do not require water while taking the drug. The use of ODT is especially convenient in pediatric and geriatric practice [10,11].

Based on literature data and preliminary pharmacological studies, it has been revealed that biologically active substances of plant origin - phenolic compounds: camphorol, apigen, luteolin, etc. have the ability to inhibit soluble epoxy hydrolase activity and provide vasodilatory action [8].

The purpose of this study was the development of the formulation and technology of luteolin Orodispersible tablets (ODT) based on biopharmaceutical studies.

To achieve this goal, we set the following tasks:

- Determination of physico-chemical and technological properties of active pharmaceutical ingredients (APIs);
- Determination of the formulation of luteolin orodispersible tablets based on biopharmaceutical studies;
- Development of luteolin orodispersible tablets technology based on technological studies;
- Evaluation of the prepared orodispersible tablets.

Materials and methods

The following materials have been used during investigation: Active pharmaceutical ingredient (API)- Luteolin, was purchased from Dalian launcher fine chemical co. (China), Prosolve SMCC HD90 was purchased from JRS Pharma (Germany), Kollidon® 30 was purchased from BASF (Germany), Mannitol was purchased from Dalian launcher fine chemical co.(china), Sodium Stearyl Fumarate was purchased from Jiangxi Alpha Hi-tech Pharmaceutical Co., Ltd.

Residual moisture content of API was determined by using an automatic humidity detector (MS-70) at 1050C. The moisture content in the study sample was determined by achieving a constant weight.

To evaluate the fractional composition and morphological properties of the powder (size, shape, surface relief) we used the method of Direct Optical Microscopy with visible light.

1 mg of the substance was placed in a clean, pre-degreased glass jar and added the immersed liquid (dimethicone, mineral oil). The powder is suspended in the liquid with a spatula until the solid particles are equally distributed in the liquid. Then the micro particle is covered with a glass so that air bubbles do not hit. The samples are examined under a microscope Axio Observer.Z1 Carl Zeiss (Germany) and the lens (A-Plan 10x / 0.25 Ph 1.) is used to measure the particles size of the test substance.

Determination of dispersion was performed through sampling analysis.

The flowability of API was determined by measuring the powder flow rate and the angle of inclination using the device ERWEKA GTB (Germany).

The angle of repose was determined by using protractor, which is the angle between the cone formed from the friable material and the horizontal plane. The bulk density of the API was determined using with ERWEKA SVM 223 (Germany).

Thickness of tablet was measured by using electronic vernier caliper (Mitutoyo, Model CD-6 CS, Japan).

For weight variation, twenty tablets were selected randomly after compression and the mean weight was determined using analytical balance. None of the tablets deviated from the average weight by more than ±7.5% (USPXX).

Crushing strength parameter of ODT was measured using ERWEKA TBH 125 (Germany) testers. Friability was determined using TAR 220 ERWEKA (Germany) following USP Pharmacopoeia (reference of the USP pharmacopoeia), rotational frequency at 20 rpm for 5 minutes.

Wetting time. A piece of circular tissue paper (8cm) folded twice was placed in a Petri dish (Internal Diameter = 9cm) containing 10 ml of buffer solution simulating saliva pH 6.8. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted.

In vitro dispersion time of prepared tablet was done by dropping the tablet in 10 ml measuring cylinder containing 6 ml of simulated salivary fluid (pH 6.8). Time required for complete dispersion of tablet was measured.

On the first stage of the research, the physical and technological characteristics of the active pharmaceutical ingredient were determined. The results are given in Table N1.

Table N1

Results of physical, chemical and technological characteristics study of Luteolin (n = 3)

Physical, chemical and technological characteristics	Results of study
Description	Yellow powder
Particle shape and size	spherical, 232.21-263.14 μm
Flow rate g/s	5.02
Angle of repose ^{0}	25.22±1.14
Aerated bulk density, g/sm^3	0.346±0.05
Tapped density g/cm^3	0.493±0.12
Moisture content %	2.86±0.17

The data in Table (N1) shows that the friable of the luteolin substance is high, represented by small particles and the degree of particle density is optimal. To prepare luteolin orodispersible tablets, we used a model formulation of ODTs selected by artificial intelligence (Table N2), which is a ready-made composition for the preparation of ODT containing various active pharmaceutical ingredients.

Table N2

Optimal formulation of ODT modeling tablets predicted by INForm® Artificial Intelligence

N	Ingredient	Value %
1	Prosolve SMCC HD90	47.5
2	Mannitol	45.0
3	Kollidon 30	6.5
4	Sodium stearyl fumarate	1.0

Luteolin orodispersible tablets were prepared by using sublimation method / 4,7,9 /. The luteolin content in all formulation was 50 mg. For the preparation of ODT tablets by sublimation method, were used easily volatile substances camphor, menthol and thymol. It was prepared 12 formulations for the preparation of luteolin orodispersible tablets. The results are given in Table N3.

Table N3
Composition of Luteolin orally disintegrating tablet formulations

Formulation code	Luteolin (mg)	Ingredients (mg)						
		Camphor	Menthol	Thymol	Prosolve SMCC HD90	Mannitol	Kollidon 30	Sodium stearyl fumarate
F1	50.0	5.0	-	-	47.5	47.5	47.5	47.5
F2	50.0	10.0	-	-	45.0	45.0	45.0	45.0
F3	50.0	15.0	-	-	6.5	6.5	6.5	6.5
F4	50.0	20.0	-	-	1.0	1.0	1.0	1.0
F5	50.0	-	5.0		47.5	47.5	47.5	47.5
F6	50.0	-	10.0	-	45.0	45.0	45.0	45.0
F7	50.0	-	15.0	-	6.5	6.5	6.5	6.5
F8	50.0	-	20.0	-	1.0	1.0	1.0	1.0
F9	50.0	-	-	5.0	47.5	47.5	47.5	47.5
F10	50.0	-	-	10.0	45.0	45.0	45.0	45.0
F11	50.0	-	-	15.0	6.5	6.5	6.5	6.5
F12	50.0	-	-	20.0	1.0	1.0	1.0	1.0

The technological process of preparation of tablets consists of the following stages: preparation of raw materials, preparation of tablet mass, tablet-making, packaging of finished products.

Prosolv SMCC HD90, mannitol, kollidon 30 placed into mortar and add the desintegrated camphor, menthol and thymol using 96% ethyl alcohol with quantities specified in the formulations and mix for 2-3 minutes. The resulting compositions are added to a certain amount of sterile fumarate sodium, mixed well and crush into a perforated plate or sieve with a size of 1.5-2 mm.

The tablets were produced using a single punch tablet eccentric type of press, by pressing - using 8 mm punch, with a compressive strength of 20 kg / cm 2.

Prepared tablets keep in a drying oven at 40 ° C for 2 hours, in order to remove volatile agents from ODT. After evaporation of camphor, menthol and thymol, we evaluated the quality of the tablets according to the physical and technological parameters [1,2,5,6]. The results are given in Table N4.

Table N4
Physical properties pre-sublimation and post-sublimation of orally disintegrating luteolin tablets

Formulation code	Average Weight (mg)		Thickness (mm)		Mechanical strength				Disintegration time (s)		Wetting Time (s)	
					Friability (%)		Crushing strength					
	pre-sublimation	post-sublimation	pre-sublimation	post-sublimation	pre-sublimation	post-sublimation	pre-sublimation	post-sublimation	pre-sublimation	post-sublimation	pre-sublimation	post-sublimation
F1	155.2 ±0.4	150.5 ±0.7	3.3	3.1	99.89 ±0.02	99.86 ±0.06	6.0 ±0.15	5.8 ±0.43	38.60 ±0.01	30.73 ±0.02	3.6	2.6
F2	159.8 ±0.5	155.6 ±0.4	3.3	3.2	99.63 ±0.07	99.43 ±0.10	5.5 ±0.08	5.2 ±0.36	34.37 ±0.03	28.37 ±0.01	3.3	2.3
F3	165.3 ±0.5	160.9 ±0.6	3.4	3.3	99.40 ±0.12	99.23 ±0.16	5.1 ±0.34	4.9 ±0.44	29.14 ±0.04	22.58 ±0.05	3.1	2.0

F4	169.9 ±0.3	171.2 ±0.7	3.4	3.2	99.15 ±0.08	99.05 ±0.05	4.6 ±0.62	4.3 ±0.54	25.88 ±0.02	19.36 ±0.04	2.9	1.2
F5	155.1 ±0.4	150.6 ±0.6	3.2	3.1	99.77 ±0.09	99.65 ±0.06	6.5 ±0.54	6.4 ±0.61	46.25 ±0.05	38.49 ±0.06	2.8	1.9
F6	160.1 ±0.5	155.8 ±0.8	3.3	3.2	99.57 ±0.13	99.44 ±0.12	6.1 ±0.54	5.9 ±0.23	41.25 ±0.05	32.31 ±0.04	2.5	1.6
F7	165.2 ±0.4	161.0 ±0.7	3.4	3.1	99.42 ±0.12	99.30 ±0.14	5.4 ±0.43	5.3 ±0.56	36.12 ±0.04	28.74 ±0.05	2.3	1.4
F8	169.8 ±0.6	171.1 ±0.4	3.4	3.1	99.25 ±0.07	99.13 ±0.04	4.8 ±0.32	4.5 ±0.57	31.25 ±0.03	23.25 ±0.05	1.9	1.2
F9	155.3 ±0.6	150.3 ±0.5	3.2	3.1	99.85 ±0.06	99.80 ±0.09	5.8 ±0.56	5.7 ±0.26	52.33 ±0.01	40.45 ±0.02	4.4	3.5
F10	159.9 ±0.5	155.7 ±0.4	3.3	3.1	99.73 ±0.11	99.60 ±0.09	5.1 ±0.23	4.9 ±0.58	45.24 ±0.03	31.56 ±0.02	4.1	2.9
F11	165.4 ±0.5	160.9 ±0.6	3.4	3.2	99.50 ±0.08	99.38 ±0.12	4.7 ±0.51	4.4 ±0.65	35.18 ±0.03	28.62 ±0.02	3.8	1.9
F12	170.1 ±0.4	171.2 ±0.5	3.4	3.1	99.20 ±0.15	99.03 ±0.14	4.1 ±0.45	4.0 ±0.12	32.37 ±0.03	26.44 ±0.01	3.6	1.8

The results of the study (Table N4) show that the strength of luteolin orodispersible tablets decreased after sublimation, but remained within the acceptable limits, not less than 3.6 kg / cm 2. One of the most important factors of using ODT is the rapid action, which is related to the disintegration of the tablets. In this respect, camphor as a sublimating agent is better than menthol and thymol. In addition, a correlation was found between the concentration of the sublimation agent and the dissolution of the orodispersible tablets, 15 mg camphor is optimal amount per tablet. The higher content of sublimating agent, the faster the tablet disintegrates is, this is probably due to the formation of pores during the sublimation process, which promotes fluid penetration into the tablet. Disintegration time of tablets before sublimation ranged from 25.88 to 52.33 sec. After sublimation it decreased to 19.36 - 40.45 sec. It should be noted that the disintegration of tablets is directly correlated with their strength (Tab.3. F1, F2, F3, F4), the stronger the tablet is, the more time it takes to disintegrate.

Conclusion:

It is suggested, that developed formulation of luteolin orodispersible tablet based on sublimation method of technology is characterized with rapid disintegration especially in camphor containing formulation - F1, F2, F3, F4.

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СОСТАВ И ТЕХНОЛОГИЯ ОРОДИСПЕРСИРУЕМЫХ ТАБЛЕТОК ЛЮТЕОЛИНА С ПОТЕНЦИАЛЬНЫМ АНТИГИПЕРТЕНЗИВНЫМ ДЕЙСТВИЕМ

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РЕЗЮМЕ

Артериальная гипертензия является наиболее распространенным хроническим заболеванием, в экономически развитых странах, ведущим к хронической инвалидности и летальному исходу.

В последние годы внимание исследователей было сосредоточено на выявлении новых эндогенных веществ, участвующих в механизмах вазоконстрикции и вазодилятации. В этом направлении особое внимание уделяется сосудорасширяющим продуктам эпоксигеназного метаболизма, таким как эпоксиэйкозатриеновые кислоты (ЭЭТК), которые быстро превращаются в организме в менее активные метаболиты - дигидроксиэйкозатриеновые кислоты (ДГЭТК), под влиянием фермента растворимой эпоксид гидролазы.

В согласно литературных данных биологически активное вещество растительного происхождения – лютеолин обладает способностью ингибировать активность растворимой эпоксигидролазы, что способствуем пролонгированию сосудорасширяющей активности ЭЭТК. При лечении артериальной гипертензии особое внимание уделяется возможности больного использовать препарат самостоятельно, без каких-либо дополнительных материалов (воды, шприца и т. д.) и быстрому действию.

На основании искусственного интеллекта и биофармацевтических исследований разработана технология таблеток лютеолина, диспергируемых во рту, сублимационным методом.

Показано, что таблетки лютеолина, диспергируемые во рту, по качеству соответствуют стандартным требованиям. Использование камфоры в качестве сублимационного агента обеспечивает формирование пористой структуры, что способствует проникновению жидкости внутрь таблеток и их быстрой дезинтеграции.

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FORMULATION AND TECHNOLOGY OF ORODISPERSIBLE TABLETS OF LUTEOLIN WITH POTENTIAL ANTIHYPERTENSIVE ACTION

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SUMMARY

Arterial hypertension is the most common chronic disorder in economically developed countries leading to chronic disability and lethal outcome.

During the recent years the attention of the researchers was focused on identifying new endogenous substances involved in vasoconstriction and vasodilation mechanisms. In this direction special attention is paid to vasodilating products of epoxygenic metabolism such as epoxyeicosatrienoic acids (EETs), whose rapid conversion in the body into less active metabolites such as dihydroxyeicosatrienoic acids (DHETs) is promoted by enzymatic epoxide hydrolase (sHE).

According literature sounces biologically active substance of plant origin – luteolin has the ability to inhibit sEH action, promoting the prolongation of EETs vasodilating activity. In the treatment of arterial hypertension, special attention is paid to the ability of the patient to use the drug independently, without any additional materials (water, syringe, etc.) and rapid action.

Based on artificial intelligence and biopharmaceutical studies, the formulation of luteolin orodispersible tablets and its technology was developed by sublimation method.

As it was shown ODT of luteolin meet standard requirements in terms of quality. The use of camphor as a sublimation agent ensures the formation of a porous structure, which promotes the penetration of fluid into the tablets and their fast disintegration.

Keywords: luteolin, formulation, technology, antihypertensive, tablets