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

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ლაშა ბაკურიძე [1], მარიანა ლანდინ პერესი [2]

პოტენციური ანტიჰიპერტენზიული მოქმედების მქონე აპიგენინის 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 ვაზოკონსტ-რიქციულ და ვაზოდილატაციურ მექანიზმებში მონაწილე ახალი ენდოგენური ნივთიერებების გამოსავლენად. ამ მიმართულებით განსაკუთრებულ ყურადღებას იპყრობს არაქიდონის მჟავის ეპოქსიგენაზური მეტაბოლიზმის ვაზოდილატაციური პროდუქტები, როგორიცაა ეპოქსი-ეიკოზატრიენოის 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 - პიგენინს 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. ფარმაკოლოგიური კვლევების საფუძველზე შესწავლილ იქნა მცენარეული წარმოშობის ფენოლური ნაერთი sEH-ს ინჰიბიტორი - აპიგენინი EETs-ის ვაზოდილატორული აქტივობის გაძლიერებით, რაც დადებით გავლენას ახდენს ჰემოდინამიკურ პარამეტრებზე და ბარორეფლექსის მგრძნობელობაზე ჰიპერტენზიულ მდგომარეობაში, რომელიც წარმოადგნს პერსპექტიულ აგენტს სხვადასხვა გულ-სისხლძარღვთა დარღვევების გასაუმჯობესებლად.

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

ნაჩვენებია, რომ კეთილხარისხოვნების მაჩვენებლების მიხედვით აპიგენინის ოროდისპერსიული ტაბლეტები აკმაყოფილებს სტანდარტის მოთხოვნებს. გამაჯირჯვებელ აგენტად ნატრიუმის სახამებლის გლიკოლატის გამოყენება უზრუნველყოფს წყლის შეწოვას ტაბლეტებში, რაც ამცირებს ნაწილაკებს შორის შეკავშირების ძალას და იწვევს ტაბლეტების დაშლას.

Arterial hypertension (AH) still remains as a major risk factor for stroke and different cardiovascular complications [9,17]. A new insight for the successful treatment of AH is associated with a new target involving in the regulation of arterial pressure (AP) [3,6]. Studies provide evidence [5,10] that epoxyeicosatrienoic acids (EETs) cause vasodilation by activating [14,22] the smooth muscle large

conductance Ca2+-activated K+ channels. EETs are implicated in the regulation of arterial pressure, including vascular endothelium, heart and kidneys [12,13,20]. They improve vascular endothelium function in hypertensive animals [9] with reduction of inflammation and increased Na+ elimination prevented AH [16].

The vasodilatory action of EETs decreased by an enzyme soluble epoxide hydrolase (sEH) to less active compounds dihydroxyeicosatrienoic acids (DHET), limiting their pharmacological activity [7,11,25]. In last years a great interest is directed to compounds providing sEH inhibitory properties to prolong EETs vasodilatory effectiveness and enhancing their antihypertensive potential, as well as to their new pharmaceutical formulation.

From solid oral dosage forms, orodispersible tablets are convenient to use, as they disperse and dissolve in the oral cavity without taking water. Most often, disintegration of orodispersible tablets (ODT) in saliva does not exceed 10-30 seconds. They can be taken not only by patients with difficulty swallowing, but also travelling people who do not have direct access to water while taking the medicine. Taking fast-dissolving ODT is also proper for the elderly and bedridden patients who have difficulty taking the drug orally due to impaired swallowing. ODT that dissolve quickly in the mouth are especially important for patients with arterial hypertension. 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 [21,23].

Based on literature data and our pharmacological studies, it has been revealed that the plant origin phenolic compound - Apigenin, has the ability to inhibit soluble epoxide hydrolase [18,19].

The purpose of this study was to evaluate the influence of Apigenin on hemodynamic indices in hypertensive animals and development the formulation and technology of Apigenin ODT based on biopharmaceutical studies.

To achieve this goal, we set the following tasks:

- To investigate antihypertensive potential of apigenin in experimental model of arterial hypertension (AH).
- Determination of physico-chemical and technological properties of active pharmaceutical ingredients (APIs);
- Determination of the formulation of apigenin orodispersible tablets based on biopharmaceutical studies;
- Development of apigenin orodispersible tablets technology based on technological studies;
- Evaluation of the prepared orodispersible tablets.

Materials and methods. Pharmacological Experiments were carried out in male unanesthetized Wistar sham-operated (SO) and hypertensive (two-kidney, one clip) rats weighing 200-250g. Both models were created under pentobarbital-40mg/kg i.p. anesthesia. Animals were in the study after 4 weeks of development of AH. Hemodynamic parameters were measured by noninvasive "tail cuff" method using computerized device "Neurobotics" allowing to obtain systolic, diastolic pressure and cardiac rhythm. Apigenin (5mg/kg) solution i.p. was administered in both group of animals during 2 weeks. Statistical analysis employed analysis of variance (ANOVA) and student's test with significant at $P<0.05$. Results are expressed as the mean ± SEM.

The following materials have been used during investigation: Active pharmaceutical ingredient (API)- Apigenin, 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. polyethylene glycol – 6000 was purchased from carl Roth Ltd. (Germany).

Residual moisture content of API was determined by using an automatic humidity detector (MS-70) at 105°C. 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.

Results. Apigenin in hypertensive (HR) animals after i.p. administration during 2 weeks (5 mg/kg) revealed hypotensive effect by decreasing systolic (-22.4±5.2mmHg) and diastolic (28.0±6.4mmHg) AP vs SO rats (-10.6±2.2 mmHg, $P<0.05$) and (14.5±2.8mmHg, $P<0.05$) respectively, associated with reduction in cardiac rhythm in HR from (430±10.8 to 402±8.2 beats/min) and SO animals from (405±6.5 to 393±5.8 beats/min), respectively ($P<0.05$)

On the first stage of technological 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 Apigenin (n = 3)

Physical, chemical and technological characteristics	Results of study
Description	Yellow powder
Particle shape and size	spherical, 230.24-261.34 μm
Flow rate g/s	5.02
Angle of repose ^{0}	25.22±1.14
Aerated bulk density, g/sm^3	0.342±0.05
Tapped density g/cm^3	0.492±0.12
Moisture content %	2.78±0.17

The data in Table (N1) shows that the friable of the apigenin substance is high, represented by small particles and the degree of particle density is optimal. To prepare apigenin 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

Apigenin orodispersible tablets were prepared by using melting method [2,24]. The apigenin content in all formulation was 50 mg. For the preparation of ODT tablets by melting method, Sodium starch glycolate was used as superdisintegrant. It was prepared 5 formulations for the preparation of apigenin orodispersible tablets. The results are given in Table N3.

Table N3. Composition of Apigenin orally disintegrating tablet formulations

Formulation code	Apigenin (mg)	Ingredients (mg)					
		Sodium starch glycolate	Polyethilen glycol-6000	Prosolve SMCC HD90	Mannitol	Kollidon 30	Sodium stearyl fumarate
F1	50	8	92	47.5	45	6.5	1
F2	50	10	90	47.5	45	6.5	1
F3	50	12	88	47.5	45	6.5	1
F4	50	15	85	47.5	45	6.5	1
F5	50	17	83	47.5	45	6.5	1

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.

All ingredients according to the formula were accurately weighed and passed through 60 and 100 mesh sieve and mixed geometrically for 2-3 minutes. This physical mixture was placed into high shear mixer for about 45 minutes at a temperature of 55ºC.

For preparation of tablet mass, high shear mixers are utilized, where the product temperature is raised above the melting point of the binder by a heating jacket or by the heat of friction generated by impeller blades. 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.

We evaluated the quality of the tablets according to the physical and technological parameters [1,4,8,15]. The results are given in Table N4.

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

Formulation code	Average Weight (mg)	Thickness (mm)	Mechanical strength		Disintegration time (s)	Wetting Time (min)
			Friability (%)	Crushing strength (kg)		
F1	248.5±0.7	99.89±0.02	0.3 ±0.15	9.8±0.01	201.73±0.02	2.6
F2	245.6±0.4	99.63±0.07	0.4 ±0.08	9.1±0.03	172.37±0.01	2.3
F3	246.9±0.6	99.40±0.12	0.5 ±0.34	8.5±0.04	129.58±0.05	2
F4	247.2±0.7	99.15±0.08	0.7 ±0.32	7.4±0.02	70.36±0.04	1.6
F5	249.2±0.7	99.10±0.08	0.8 ±0.20	6.7±0.02	21.36±0.04	0.8

The results of the study (Table N4) show that the strength of apigenin orodispersible tablets decreased in parallel with the increase in the amount of Sodium starch glycolate, 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, Sodium starch glycolate as a disintegrating agent 17 mg is better than another amount. In addition, a correlation was found between the concentration of the disintegrating agent and the dissolution of the orodispersible tablets, 17 mg Sodium starch glycolate is optimal amount per tablet. The higher content of disintegrating agent, the faster the tablet disintegrates is, disintegrants pull water into the pore and reduces the physical bonding force between particles. Disintegration time of tablets ranged from 201.73 to 21.36 sec. It should be noted that the disintegration of tablets is directly correlated with their strength (Tab.4), the stronger the tablet is, the more time it takes to disintegrate.

Conclusion: Our results suggest, that plant origin phenolic compound Apigenin with potential soluble epoxide hydrolase inhibitory activity may provide vasodilatory effect revealing significant antihypertensive potential being promising agent for the treatment of different hypertensive states.

Developed formulation of apigenin orodispersible tablet based on melting method of technology is characterized with rapid disintegration especially in sodium starch glycolate containing formulation – F5, allowing predictable its rapid absorption into systemic circulation for providing desirable hypotensive action.

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СОСТАВ И ТЕХНОЛОГИЯ ОРОДИСПЕРСИРУЕМЫХ ТАБЛЕТОК АПИГЕНИНА 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 (рЕГ).

В 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 фармакологических исследований фенольное соединение растительного происхождения рЭГ ингибитор -апигенин, усиливая сосудорасширяющую активность ЭЭТ, оказывает благотворное влияние на показатели гемодинамики и чувствительность барорефлекса при гипертонической болезни, являясь перспективным средством для улучшения состояния при различных сердечно-сосудистых заболеваниях.

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

Показано, что таблетки апигенина, диспергируемые во рту, по качеству соответствуют стандартным требованиям. Использование натрия крахмал гликолят в качестве разрыхлителя обеспечивает ускоренное всасывание воды в таблетки, что снижает силу связи между частицами и вызывает распад таблеток.

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FORMULATION AND TECHNOLOGY OF ORODISPERSIBLE TABLETS OF APIGENIN 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 sources biologically active substance of plant origin – apigenin 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 pharmacological studies plant origin phenolic compound sEH inhibitor-Apigenin by enhancing EETs vasodilatory activity provide beneficial effect on hemodynamic parameters and baroreflex sensitivity in hypertensive state being promising agent for improvement of different cardiovascular disorders.

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

As it was shown ODT of apigenin meet standard requirements in terms of quality. The use of sodium starch glycolate as disintegrant ensures the accelerated absorption of water into the tablets, which reduces the binding force between the particles and causes the tablets disintegration.

Keywords: Arterial hypertension, Apigenin, Orodispersible tablets.