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PHLEBOPROTECTORS BASED ON FLAVONOIDS: DOSAGE FORMS, BIOPHARMACEUTICAL CHARACTERISTICS, TECHNOLOGICAL FEATURES

E.F. Stepanova, I.P. Remezova, A.M. Shevchenko, A.V. Morozov, V.K. Maltseva

Pyatigorsk Medical and Pharmaceutical Institute – a branch of Volgograd State Medical University
11, Kalinin Ave., Pyatigorsk, Russia, 357532

E-mail: efstepanova@yandex.ru

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Micronized purified flavonoid fraction (MPFF) is the original phlebotropic drug. Its marketed form (Detralex®) consists of 90% diosmin and 10% of other flavonoids. Calculated as hesperidin, it is the most widely used drug today. Diosmin and hesperidin, which are parts of the majority of venoactive drugs, are sparingly water-soluble compounds, and this feature can effect on their clinical efficacy. One of the ways to increase the solubility of these compounds leading to an increase in bioavailability, is the micronization of the active ingredients.

The aim of the investigation is a comparative determination of the dynamics and dissolution efficiency of the drugs containing bioflavonoid fractions in the dissolution test, as well as the analysis of the micronization degree and its impact on technology and biopharmaceutical parameters.

Materials and methods. A biopharmaceutical release profile was determined using HPLC. Disintegration, characteristics of the shape and size of the tablets' particles were determined according to the methods of the State Pharmacopoeia of the XIV edition.

Results. The objects created with the use of diosmin and hesperidin, have been considered in detail. The role of technological solutions in relation to the corresponding dosage forms is notified. Detailed biopharmaceutical characteristics have been established with a choice of HPLC-based release control methodology. All the drugs in this group have a low water solubility leading to the maximum bioavailability for Detralex® which is about 1.26%; and no more than 0.2% for other analyzed models.

Conclusion. Detralex® dominates among the analyzed objects (tablets) in terms of the release rate. With regard to the overall quantitative indicators of release, the actual numbers are quite low, which is associated with the poor water solubility of the active substances.

Keywords: diosmin; hesperidin; Detralex® tablets; release profile; HPLC

Abbreviations: CVD – chronic venous diseases; GIT – Gastrointestinal tract; SRMR of the RF – State Register of Medicinal Remedies of the Russian Federation; MCC – microcrystalline cellulose

ФЛЕБОПРОТЕКТОРЫ НА БАЗЕ ФЛАВОНОИДОВ: ЛЕКАРСТВЕННЫЕ ФОРМЫ, БИОФАРМАЦЕВТИЧЕСКАЯ ХАРАКТЕРИСТИКА, ТЕХНОЛОГИЧЕСКИЕ ОСОБЕННОСТИ

Э.Ф. Степанова, И.П. Ремезова, А.М. Шевченко, А.В.Морозов, В.К. Мальцева

Пятигорский медико-фармацевтический институт – филиал федерального государственного бюджетного образовательного учреждения высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации
357532, Россия, г. Пятигорск, пр-т Калинина, д. 11

E-mail: efstepanova@yandex.ru.

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RESEARCH ARTICLE

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Микронизированная очищенная флавоноидная фракция (МОФФ) – оригинальный флеботропный препарат, и его выпускаемая на рынок форма (Детралекс®) состоит из 90% диосмина и 10% – другие флавоноиды, в пересчете на гесперидин и является наиболее широко используемым в настоящее время лекарственным препаратом. Диосмин и гесперидин, входящие в состав большинства веноактивных лекарственных средств, являются труднорастворимыми в воде соединениями, что может сказываться на их клинической эффективности. Одним из способов повышения растворимости данных соединений, который приводит к повышению биодоступности, является микронизация действующих веществ.

Цель. Сравнительное определение динамики и результативности растворения лекарственных препаратов, содержащих биофлавоноидные фракции, при проведении теста растворения, а также анализ степени микронизации и ее влияние на технологию и биофармацевтические показатели.

Материалы и методы. Биофармацевтический профиль высвобождения определяли с помощью ВЭЖХ. Распадаемость, характеристика формы и размера частиц таблеток определяли согласно методикам Государственной Фармакопеи XIV издания.

Результаты. Подробно рассмотрены объекты, созданные с использованием диосмина и гесперидина. Отмечена роль технологических решений в отношении соответствующих лекарственных форм. Установлена подробная биофармацевтическая характеристика с выбором методики для контроля высвобождения на основе ВЭЖХ. Все препараты данной группы обладают небольшой растворимостью в воде, что приводит к максимальной биодоступности для Детралекса®, составляющей около 1,26%; для других анализируемых моделей – не более 0,2%.

Заключение. Среди проанализированных объектов (таблетки) по степени высвобождения доминирует Детралекс®. Что касается общих количественных показателей высвобождения, то фактические числа довольно низкие, что связано с плохой растворимостью в воде действующих веществ.

Ключевые слова: диосмин; гесперидин; таблетки Детралекс®; профиль высвобождения; ВЭЖХ

Список сокращений: ХЗВ – хронические заболевания вен; ЖКТ – желудочно-кишечный тракт; ГРЛС – Государственный реестр лекарственных средств РФ; МКЦ – микрокристаллическая целлюлоза

INTRODUCTION

Chronic venous diseases (CVD) take a distinctive place among the diseases with a substantial social impact. They are manifested clinically by variable signs and symptoms that generally worsen the patients' quality of life. These are, first of all, venous outflow disorders, feelings of leg fatigue, heaviness and tightness, leg swelling and pain after prolonged standing or sitting, and, finally, trophic skin disorders including venous ulcers [1–4].

On the pharmaceutical market, there is a wide variety of drugs available for the treatment of CVD, including phleboprotectors. The drugs based on flavonoids and flavonoid complexes, mainly diosmin and hesperidin, are prevailing among them [1, 5, 6]. The primary mode of action of diosmin is capillary protection. In addition, diosmin has anti-inflammatory, antioxidant and antimutagenic effects, as well as it improves the rheological properties of blood and lymphatic drainage, which substantiate its use in the pharmacotherapy of CVD [1, 7–9]. One of the options for producing diosmin is splitting of another flavonoid, hesperidin, similar in its structure and pharmacological properties. Therefore, their combination in one drug is undoubtedly effective, which has been proven over the years of using this composition in the Detralex® drug [5, 11].

As for the physicochemical properties of the active substances, it is the structure of diosmin and hesperidin molecules that determines their practical insolubility in water. Therefore, to increase solubility and, accordingly, enhance bioavailability, a number of effective technological methods such as changing the particle size of the active substance by micronization, are used [12].

Currently, Detralex® holds a leading position among venotonics on the pharmaceutical market of the Russian Federation due to its proven efficacy associated with the presence of a micronized purified flavonoid fraction in its formula. As a result, in the long term, this drug reduces the severity of CVD symptoms, which makes it appropriate for both the treatment of CVD and the prevention of the disease progression [4].

In terms of many pharmacokinetic parameters, the effectiveness of Detralex® is enhanced due to the manufacturing features of this pharmaceutical form [12]. The active complex of Detralex® is composed of a micronized fraction of flavonoids containing 90% of diosmin and 10% of other active flavonoids equivalent to hesperidin (hesperidin, diosmetin, linarin and isorhoifolin). These components contribute significantly to the activity of the drug [13]. The oral intake of these substances in a finely dispersed state, including the form of micronized complexes, results in the creation of a larger surface of the solid phase and increases the rate and degree/completeness of adsorption in the gastrointestinal tract, which makes it possible to achieve a greater therapeutic effect. There are examples in pharmaceutical practice, such as the micronization of glibenclamide, which significantly increased its pharmacodynamic effects as a hypoglycemic agent used in the treatment of type 2 diabetes mellitus [14].

The drug absorption rate depends on the rate of release of its active substance(s), i.e. its extraction from the solid dosage form. In its turn, the release rate is influenced by a Powder Fineness, and this may require the evaluation of differences in the clinical efficacy between the drugs with the same active substance, as evidenced by the pharmacokinetic parameters [4, 13].

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Therefore, **THE AIM** of these studies was to compare dissolution profiles and effectiveness of the agents containing bioflavonoid fractions, in the dissolution test, as well as to analyze the degree of their micronization and its impact on the manufacturing process and biopharmaceutical parameters. This required using a sufficient number of buffer solutions, study time points and samples for each point.

The following drugs were used as reference objects: Detralex® (tablets 1.0 each)[1] and tablet forms, marked as A, B, C, D, X, Y, and Z (see Materials and Methods), which contain only diosmin or a combination of diosmin and hesperidin as active substances, according to the State Register of Medicines of the Russian Federation [11].

MATERIALS AND METHODS

A biopharmaceutical release profile is a parameter characterizing the rate of release of an active substance (in our case, diosmin and hesperidin) from a dosage form (tablets) in a certain period of time.[2]

The following models were analyzed: Detralex® (tablets 1.0 g) [22], as well as tablet forms of drugs: A (LP-003561), B (LP-005365), C (LP-005215), D (LP-004167), X (LP-003371), Y (LP-002517), Z (P N016081/01), according to the official website of the State Register of Medicines [11].

The release of active substances was studied the following conditions: 0-1 hour (hydrochloric acid solution pH=1.5), 1–4 hours (phosphate buffer solution pH=4.5), and 4–24 hours (phosphate buffer solution pH=7.2). The volume of the medium was 900 ml, the rotation speed was 100 rpm, and the ambient temperature was 37±0.5°C [5].

HPLC studies were carried out using the UltiMate 3000 system (Dionex, USA) with a spectrophotometric detector covering the operating wavelength range from 190 to 900 nm. The data were recorded and processed using the chromatographic data collection and the processing system Chromeleon, version 7 (Dionex, USA).

Centrifugation of the samples before the HPLC analysis was carried out on a laboratory centrifuge with SIGMA 2-16P accessories (SIGMA Laborzentrifugen GmbH, Germany). Before the analysis, the test solutions were filtered using the 25 mm syringe filters with a 0.2 µm nylon membrane (Phenomenex, USA). All sample solutions were centrifuged at 8000 rpm for 3 min. before placing them into the device.

The samples were weighed on a laboratory electronic balance LV 210-A (ZAO Sartogosm, St. Petersburg, Russia).

The pH level of the solutions was measured using a pH-meter pH-150MI (OOO "Izmeritel'naya tekhnika", Moscow, Russia).

The chromatographic conditions

The mobile phase – acetonitrile: 0.05 M phosphoric acid (23:77), a stainless steel chromatographic column Luna C18 (2) 250×4.6 mm with a particle size of 5 µm, a flow rate 0.9 mL/min, the temperature of the column 25°C, the detection at 280 nm, the injection volume 20 µl, the analysis time – over 10 minutes.

Disintegration of the tablets was determined according to the methods of the State Pharmacopoeia (14th ed., Vol. 2, Chapter.1.4.2.0015.15) [23].

Characterization of the shape and size of the tablet particles was carried out according to the State Pharmacopoeia, Chapter.1.2.1.0009.15 "Optical microscopy", using the modular brightfield research microscope B-1000BF (Optima spectator 40×400) equipped with a digital camera with a resolution of 16 MP. The microscopy of the tablets matrix of the studied drugs was carried out after a spontaneous disintegration of the tablets in an aqueous solution at pH 6.8. Herewith, the sizes of the particles in the tablet suspension, conisting of the flavonoid fraction and excipients, were measured [5].

The particle shape and size were measured using the MOV-1-16x ocular screw micrometer, an attachment to the Optima spectator 40×400 ocular microscope.

The particle size was determined by the formula [16]:

$$t = \frac{II - I}{\beta},$$

where: t is the particle size, mm; II–I is the difference between two readings on the scales of the ocular microscope, mm; β is the linear magnification of the objective lens 15×40=600.

RESULTS AND DISCUSSION

The biopharmaceutical profiles of the studied tablets are presented in Table 1.

The 24-hour release rates of the active substances were found to be 1.26% for Detralex® tablets, 0.11% for drug A, 0.066% for drug B, 0.103% for drug C, 0.106% for drug D, 0.075% for drug X, 0.033% for drug Y, and 0.202% for drug Z.

The comparisons of the biopharmaceutical profiles of all the studied drugs are presented in Fig. 1.

The presented data indicate that the main constituents of Detralex®, as well as the features of its manufacturing technology (micronization), provide a higher bioavailability of diosmin and hesperidin (1.26%) compared to the analyzed drugs (not more than 0.2%). The results of the analysis allows us to draw conclusions about the differences in the release rate of the active substances from the studied drugs (Fig. 2). If arbitrarily take the release rate of the active substances from Detralex® equal to 1 as the highest value, then the 24-hour release rates for drugs Z, A, C and D, X, B and Y will be 6, 11, 12, 17, 19 and 38 times lower, respectively.

[1] Detralex® tablets indications of use. Tyubik.Net. Available from: https://grls.rosminzdrav.ru/grls.aspx?s=%u0434%u0435%u0442%u0440%u0430%u043b%u0435%u043a%u0441&m=tn (date of access 01 Jan 2020). Russian

[2] State Register of Medicines of the Russian Federation. Available from: http://grls.rosminzdrav.ru/Default.aspx (date of access: 15 March 2020). Russian

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Therefore, to increase the diosmin and hesperidin bioavailability determined *in vitro* and *in vivo,* most of the flavonoid-based drugs require using additional technological approaches. For example, a clinical study of Garner et al. [17] provides evidence of the benefits of micronization in improving the absorption of poorly soluble diosmin. The absorption of micronized forms of diosmin was significantly more effective than the one of non-micronized forms ($P<0.001$), which was confirmed by the data on the accumulated radiation detected in the urine in the period up to 168 hours (with a predominance during the first 24 hours).

Taking into account the reliability of the urine data for studying the minimum absorbed fraction, the obtained results clearly demonstrate that a decrease in the particle size provides a more complete absorption of diosmin [18]. Such an approach improves the efficacy of treating patients with CVD and hemorrhoids, as well as reduces the side effects caused by a high concentration of unabsorbed flavonoids.

When performing the relevant biopharmaceutical tests, the requirements for *in vitro* bioequivalence studies in the frame of the biowaiver procedure were complied [1, 19, 20], which made it possible to use this procedure to assess the bioequivalence of Detralex® tablets and drugs of a similar composition and clinical purpose [16, 21, 22].

To identify the causes of the differences between the studied drugs in the release rate, additional studies were carried out by imaging tablet particles in the solution (using optical microscopy).

Comparative characteristics of the shape and size of the studied tablets' particles

As Fig. 2 shows, after disintegration, the tablet B particles consist mainly of the micronized flavonoid fraction conglomerates with binders gelatin and carboxymethyl starch (additional solvents of hydrophobic compounds) and partially free microcrystals of flavonoids. Their size ranges from 83.4×10^{-3} mm to 0.8×10^{-3} mm in length and from 56.2×10^{-3} mm to 0.42×10^{-3} mm in width, which indicates a marked heterogeneity of the microscopic structure of the drug.

As Fig. 3 shows, after disintegration, the tablet C particles consist mainly of free microcrystals of flavonoids, talc and microcrystalline cellulose and partially of conglomerates of gelatin binder with micronized flavonoid fraction.

All discovered substances, except flavonoids, are excipients and play the role of additional solvents of hydrophobic flavonoids. Particle sizes range from 31.2×10^{-3} mm to 0.8×10^{-3} mm in length and from 21.15×10^{-3} mm to 0.30×10^{-3} mm in width, which indicates the isodiametric nature of crystals and a large spread in particle size.

As Fig. 4 shows, after disintegration, the tablet Y particles consist mainly of free microcrystals of flavonoids and microcrystalline cellulose. Particle sizes are uniform and relatively equal in diameter, and range from 11.3×10^{-3} mm to 5.2×10^{-3} mm.

As Fig. 5 shows, after disintegration, the tablet D particles consist mainly of conglomerates of hypromellose and sodium carboxymethyl starch binders (the substances that improve the solubility of hydrophobic compounds) with non-micronized flavonoid particles. The mass of the particles includes a small amount of free microcrystals of flavonoids, talc and microcrystalline cellulose. Particle sizes range from 12.1×10^{-3} mm to 1.8×10^{-3} mm. The shape of the particles is generally elongated with a wide variation in size.

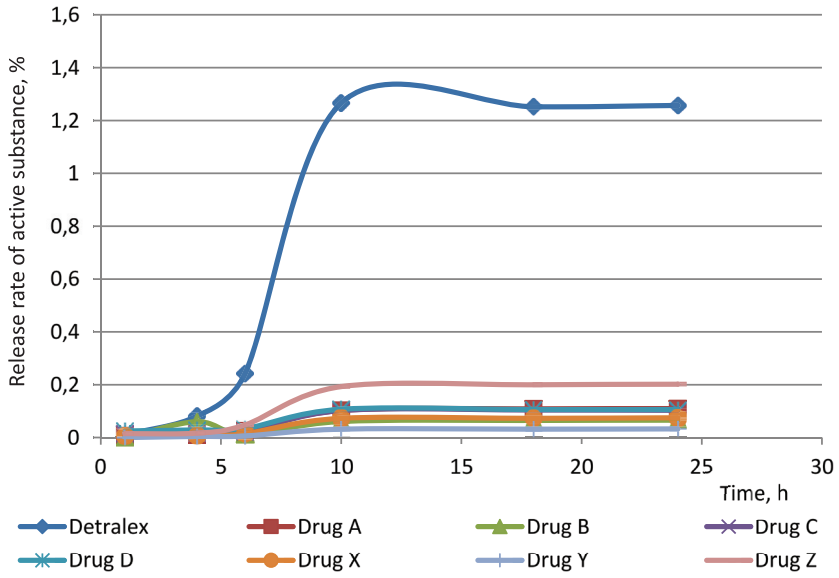

Figure 1 – Comparisons of biopharmaceutical profiles of the studied drugs containing diosmin and hesperidin

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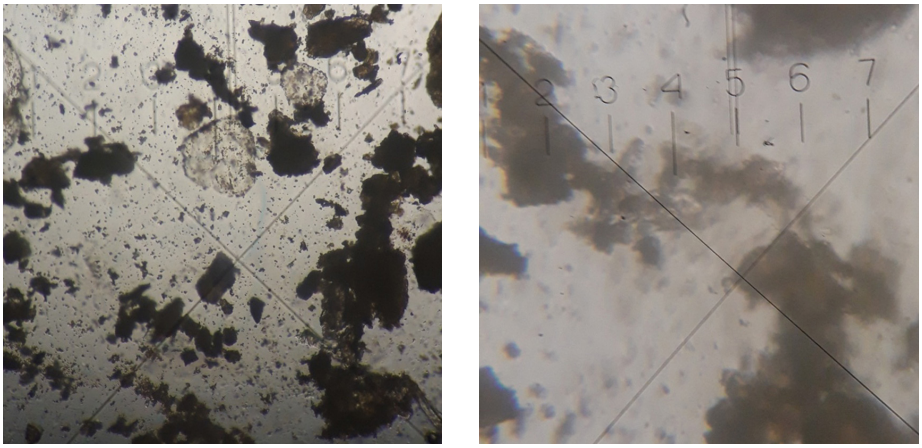
Table 1 – Biopharmaceutical profiles of Detralex® and tablets A, B, C, D, X, Y, and Z

Time	1 h	4 h	6 h	10 h	18 h	24 h
1	2	3	4	5	6	7
Detralex®						
Substance release, %	0.01	0.08	0.242	1.262	1.236	1.264
	0.009	0.078	0.236	1.284	1.288	1.293
	0.009	0.076	0.244	1.285	1.267	1.214
	0.011	0.085	0.252	1.298	1.174	1.194
	0.01	0.092	0.238	1.226	1.284	1.302
	0.01	0.076	0.239	1.239	1.263	1.273
Mean	**0.01**	**0.081**	**0.242**	**1.266**	**1.252**	**1.257**
Drug A						
Substance release, %	0.009	0.011	0.022	0.094	0.088	0.095
	0.0075	0.009	0.036	0.105	0.124	0.087
	0.0068	0.009	0.019	0.116	0.126	0.135
	0.0078	0.0085	0.024	0.084	0.115	0.114
	0.0081	0.012	0.035	0.094	0.096	0.124
	0.0065	0.011	0.021	0.123	0.105	0.108
Mean	**0.0076**	**0.01**	**0.026**	**0.103**	**0.109**	**0.110**
Drug B						
Substance release, %	0.0005	0.008	0.012	0.068	0.072	0.074
	0.0008	0.006	0.009	0.074	0.087	0.078
	0.0010	0.008	0.009	0.053	0.056	0.053
	0.0005	0.004	0.014	0.049	0.054	0.058
	0.0004	0.006	0.016	0.058	0.059	0.069
	0.0005	0.006	0.012	0.065	0.062	0.066
Mean	**0.0006**	**0.060**	**0.012**	**0.061**	**0.065**	**0.066**
Drug C						
Substance release, %	0.014	0.018	0.024	0.104	0.117	0.106
	0.017	0.014	0.018	0.114	0.101	0.118
	0.015	0.016	0.019	0.094	0.093	0.112
	0.014	0.014	0.026	0.092	0.098	0.092
	0.012	0.018	0.021	0.111	0.114	0.094
	0.014	0.019	0.018	0.097	0.102	0.097
Mean	0.014	0.016	0.021	0.102	0.104	0.103
Drug D						
Substance release, %	0.024	0.028	0.029	0.098	0.124	0.106
	0.018	0.024	0.033	0.118	0.111	0.124
	0.031	0.036	0.036	0.114	0.102	0.116
	0.026	0.028	0.041	0.096	0.094	0.091
	0.026	0.026	0.028	0.111	0.094	0.103
	0.022	0.031	0.034	0.105	0.110	0.097
Mean	**0.025**	**0.029**	**0.034**	**0.107**	**0.106**	**0.106**
Drug X						
Substance release, %	0.0005	0.009	0.012	0.067	0.077	0.077
	0.0008	0.006	0.016	0.078	0.068	0.078
	0.0006	0.008	0.009	0.079	0.075	0.075
	0.0008	0.008	0.018	0.086	0.076	0.069
	0.0004	0.006	0.018	0.061	0.071	0.081
	0.0005	0.008	0.014	0.065	0.073	0.068
Mean	**0.006**	**0.0075**	**0.015**	**0.073**	**0.073**	**0.075**
Drug Y						
Substance release, %	0	0.0035	0.0062	0.028	0.035	0.034
	0	0.0038	0.0074	0.028	0.038	0.028
	0	0.0048	0.0058	0.029	0.033	0.036
	0	0.0052	0.0064	0.039	0.029	0.031
	0	0.0044	0.0058	0.036	0.026	0.038
	0	0.0048	0.0056	0.031	0.030	0.031
Mean	**0**	**0.0044**	**0.0062**	**0.032**	**0.032**	**0.033**
Drug Z						
Substance release, %	0.014	0.014	0.054	0.188	0.214	0.198
	0.016	0.018	0.050	0.212	0.197	0.206
	0.008	0.015	0.048	0.186	0.203	0.209
	0.018	0.016	0.044	0.189	0.187	0.211
	0.016	0.021	0.048	0.198	0.197	0.193
	0.015	0.018	0.046	0.185	0.201	0.197
Mean	**0.015**	**0.017**	**0.048**	**0.193**	**0.200**	**0.202**

1. Drug B (tablets, MPFF, 500 mg)

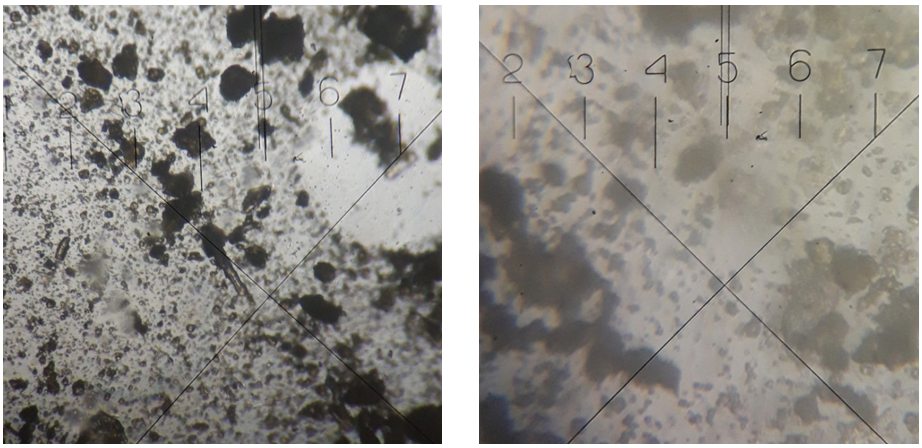


a) b)

Figure 2 – Micrographs of the drug B

Note: a) magnification 15×8; b) magnification 15×40

2. Drug C (tablets, MPFF, 1000 mg)

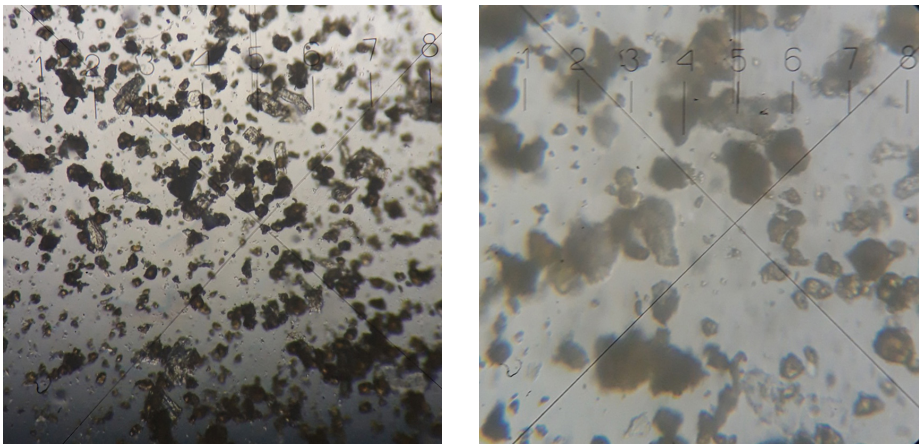


a) b)

Figure 3 – Micrographs of the drug C

Note: a) magnification 15×8; b) magnification 15×40

3. Drug Y (tablets, diosmin, 600 mg)



a) b)

Figure 4 – Micrographs of the drug Y

Note: a) magnification 15×8; b) magnification 15×40

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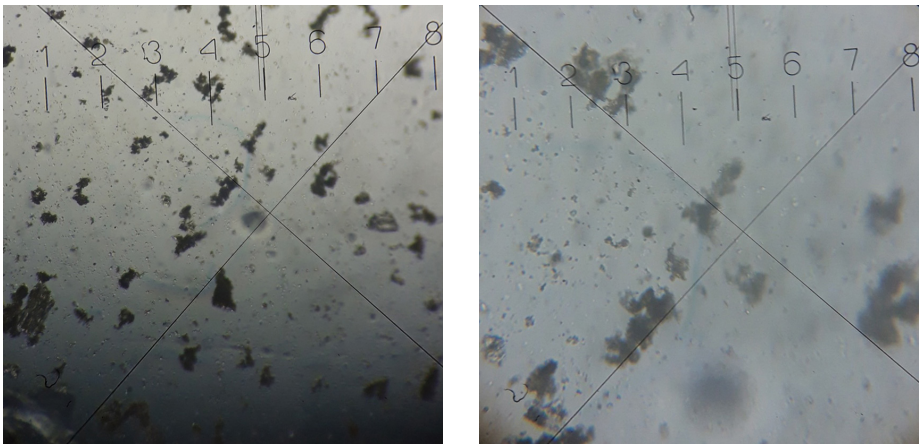
4. Drug D (tablets, diosmin 450 mg + hesperidin 50 mg)

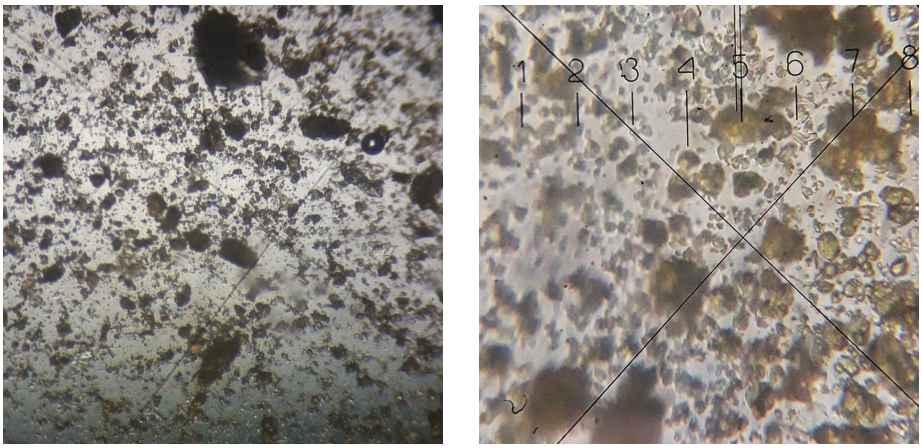


a) b)

Figure 5 – Micrographs of the drug D

Note: a) magnification 15×8; b) magnification 15×40

5. Drug Z (tablets, diosmin, 600 mg)

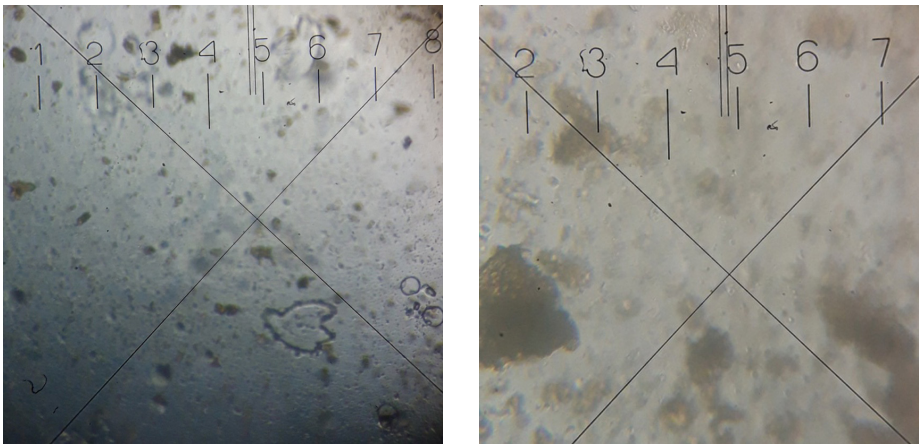


a) b)

Figure 6 – Micrographs of the drug Z

Note: a) magnification 15×8; b) magnification 15×40

6. Drug X (tablets, MPFF, 500 mg)

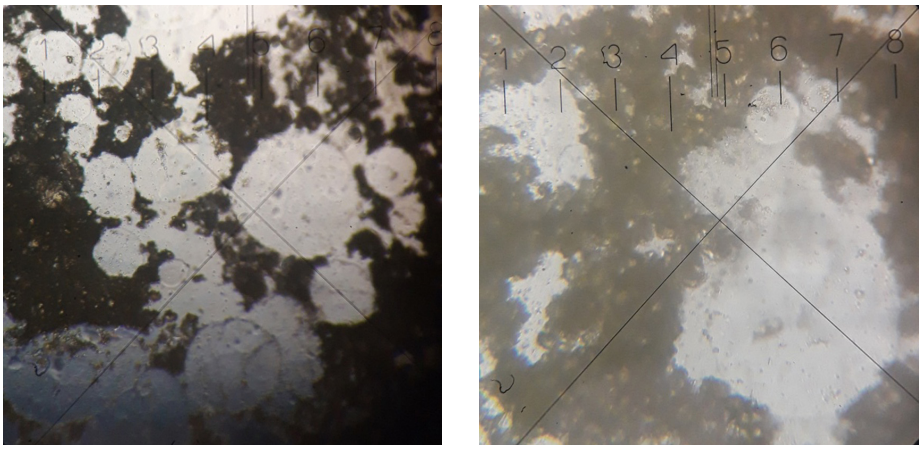


a) b)

Figure 7 – Micrographs of the drug X

Note: a) magnification 15×8; b) magnification 15×40

7. Drug A (tablets, 1000 mg: diosmin 900 mg + hesperidin 100 mg)

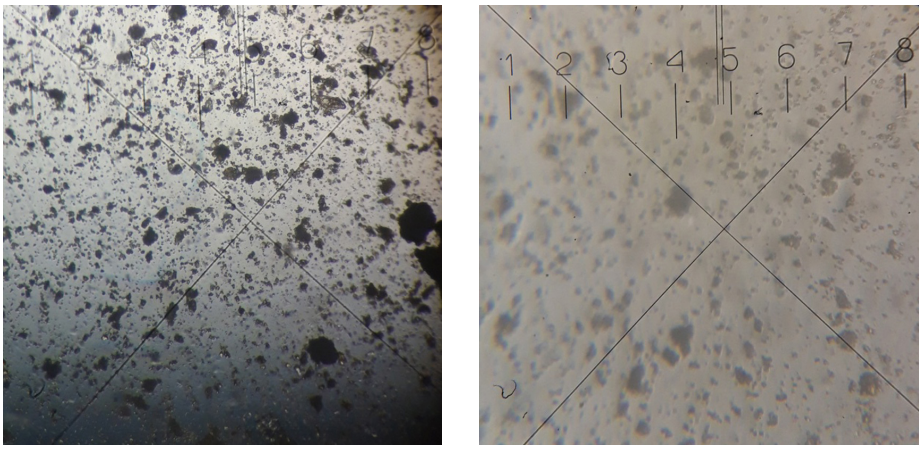


a) b)

Figure 8 – Micrographs of the drug A

Note: a) magnification 15×8; b) magnification 15×40

8. Detralex® (tablets, 1000 mg)



a) b)

Figure 9 – Micrographs of the Detralex® tablets

Note: a) magnification 15×8; b) magnification 15×40

Table 2 – Comparison of the optical microscopy gained results

Drug	Active substance(s)	Dose(s), mg	Particle size, mm	Micronization
A	Diosmin, hesperidin	900/100	$50,1–12,0\times10^{-3}$	No
B	MPFF	500	$83,4–0,8\times10^{-3}$ $56,2–0,42\times10^{-3}$	Yes
C	MPFF	1000	$31,2–0,8\times10^{-3}$ $21,15–0,3\times10^{-3}$	Yes
Y	Diosmin	600	$11,3–5,2\times10^{-3}$	No
D	Diosmin, hesperidin	450/50	$12,1–1,8\times1^{0-}3$	No
Z	Diosmin	600	$18,2–1,2\times10^{-3}$	No
X	MPFF	500	$21,1–1,0\times10^{-3}$	Yes
Detralex®	MPFF	1000	$3,3–0,8\times1^{0-}3$	Yes

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As Fig. 6 shows, after disintegration, the tablet Z particles consist mainly of free microcrystals of flavonoids, as well as inclusions of excipients microcrystalline cellulose, talc and aerosil, which improve the solubility of active flavonoids. The particles are heterogeneous in size, but have a similar diameter ranging from 18.2×10^{-3} mm to 1.2×10^{-3} mm.

As Fig. 7 shows, after disintegration, the tablet X particles consist mainly of conglomerates of micronized flavonoid fraction with binding agents carboxymethyl starch and povidone K 30, as well as inclusions of an excipient microcrystalline cellulose, which act as additional solvents of free microcrystals of flavonoids also visible in the micrograph. The particles' sizes are sharply inhomogeneous, isodiametric (relatively equal in diameter) and range from 21.1×10^{-3} mm to 1.0×10^{-3} mm.

As Fig. 8 shows, after disintegration, the tablet A particles consist mainly of conglomerates of non-micronized flavonoids with binders sodium carboxymethyl starch and gelatin, with small inclusions of excipients (microcrystalline cellulose and talc), apparently, to improve the solubility of active hydrophobic substances. The particles are represented by hardly disintegrating granules sized from 50.1×10^{-3} mm to 12.0×10^{-3} mm, which confirms the lack of micronization in the manufacturing process and, as a result, affects absorption and reduces the therapeutic efficacy of this drug.

As Fig. 9 shows, after disintegration, the Detralex® tablet particles consist mainly of free microcrystals of flavonoids and partially of microcrystalline cellulose. The particle size is uniform, isodiametric and ranges from 3.3×10^{-3} mm to 0.8×10^{-3} mm. It should be notified that microcrystalline cellulose (MCC) is used as a special carrier that promotes a more complete dispersion of hydrophobic compounds. This excipient is indifferent to the body, however, in combination with sodium carboxymethyl starch, a gel-like structure is formed, which makes it possible to significantly increase the dispersed phase of the drug and, therefore, the absorption area. MCC accepts a large amount of parietal water in the intestine, creating optimal conditions for the dissolution of drug microcrystals [12, 23–25].

For the convenient comparison of the optical microscopy data, the summarized results have been presented in Table 2. Out of the four drugs with micronized flavonoid fraction, the drug C and Detralex® have a dose of 1000 mg, while drugs B and X have a dose of 500 mg. Among all the four drugs, Detralex® is predominant with the smallest particle size and uniformity (3.3×10^{-3} to 0.8×10^{-3}), while the other three drugs have large heterogeneous particles.

Therefore, among the four drugs with non-micronized flavonoid fraction, two (A and D) contain two active substances (diosmin and hesperidin) at practically similar maximum doses (900/100 and 450/50 mg, respectively), and the other two drugs (Y and Z) contain only diosmin at the dose of 600 mg. The smallest particle size was found out in two drugs (Y and D), with relatively homogeneous particles in drug Y containing diosmin ($11.3–5.2\times10^{-3}$) and heterogeneous particles of an elongated shape with a wide scatter in size in drug D containing diosmin and hesperidin ($12.1–1.8\times10^{-3}$).

CONCLUSION

The release rates of the active substances of all the studied drugs confirm their poor water-solubility.

The studied biopharmaceutical profiles and, accordingly, revealed differences in the release rates suggest that the Detralex® formula, as well as the features of its manufacturing process (micronization) provide, in a comparative aspect, a higher bioavailability of diosmin and hesperidin. After 24 hours, it is at least 6 times larger than that of the other studied drugs (in general, no more than 0.2%), in particular of the drug Z, and, as a maximum, 38 times larger than that of the drug Y.

The optical microscopy data showed a key advantage of Detralex® over the other studied drugs due to the smallest and most uniform particle size, which indicates a high quality of this drug micronization ~~of~~ and its undoubted compliance with the GMP requirements and a beneficial effect on the drug release.

The release rates measured in this study, confirm a poor water-solubility of flavonoid compounds of all the analyzed tablet preparations and show that Detralex® is predominant among all the other studied drugs due to a more than 6 times better release rate after 24 hours. Its optimal release is also confirmed by microscopic studies and is determined by a high-quality micronization of active hydrophobic substances.

Despite the presence of excipients which can form complexes promoting better solubility, in the all the studied tablet preparations, the micronization technology used in the production of Detralex® determine its superior dissolution characteristics. Therefore, the use of micronization currently seems to be the optimal solution in terms of cost effectiveness and suggests certain advantages of this drug over the other studied preparations as far as biopharmaceutical characteristics are concerned.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

E.F. Stepanova – selection of the optimal variant of biopharmaceutical researches; introduction, conclusion and annotation writing;
I.P. Remezova – performing biopharmaceutical researches, review writing;
A.M. Shevchenko – production of dosage forms, comparative evaluation;
A.V. Morozov – performing biopharmaceutical researches;
V.K. Maltseva – selection of the optimal variant of biopharmaceutical researches, results and discussion writing.

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AUTHORS

Eleonora F. Stepanova – Doctor of Sciences (Pharmacy), Professor of the Department of pharmaceutical technology with a course in medical biotechnology of the Pyatigorsk Medical and Pharmaceutical Institute, a branch of the Volgograd State Medical University. ORCID ID: 0000-0002-4082-3330. E-mail: efstepanova@yandex.ru

Irina P. Remezova – Doctor of Sciences (Pharmacy), Associate Professor of the Department of toxicological and analytical chemistry of the Pyatigorsk Medical and Pharmaceutical Institute, a branch of the Volgograd State Medical University. ORCID ID: 0000-0003-3456-8553. E-mail: i.p.remezova@pmedpharm.ru

Alexander M. Shevchenko – Doctor of Sciences (Pharmacy), Associate Professor, Professor of the Department of pharmaceutical technology with a course in medical biotechnology of the Pyatigorsk Medical and Pharmaceutical Institute, a branch of the Volgograd State Medical University. ORCID ID: 0000-0001-8373-5907. E-mail: nplfarmak-50@yandex.ua

Andrey V. Morozov – Doctor of Sciences (Pharmacy), Associate Professor of the Department of pharmaceutical chemistry of the Pyatigorsk Medical and Pharmaceutical Institute, a branch of Volgograd State Medical University. ORCID ID: 0000-0002-8553-4073. E-mail: andrewmorozov@mail.ru

Victoria K. Maltseva – postgraduate student of the 4th year of study at the Department of pharmaceutical technology with a course in medical biotechnology of the Pyatigorsk Medical and Pharmaceutical Institute, a branch of the Volgograd State Medical University. ORCID ID: 0000-0001-5886-6219. E-mail: maltsev.tom@mail.ru