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Technology development of herbal remedies for androgenic alopecia external application

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Abstract
This work is aimed to substantiate the method of Saw Palmetto extract introduction to emulsion bases in technology development of medicines for androgenic alopecia treatment using physical-chemical and biopharmaceutical analysis. At the first stage it was investigated the solubility of Saw Palmetto extract in different liquids: pumpkin seed oil, water, glycerin, propylene glycol, alcohol-water-glycerol mixture (1:6:3), ethanol 48%. The results showed that it is impossible to achieve complete dissolution of the substance with any liquid, but microscopic analysis showed that the 48 % ethanol provide the dispersion of the extract with particles size 0.005-0.05 mm. The next step was *in vitro* agar plates biopharmaceutical study of the Saw Palmetto extract penetration from emulsion bases, which was inserted by mixing with 48 % ethanol, glycerin, alcohol-water-glycerol mixture (at the end of technology) and pumpkin seed oil (at the beginning of emulation bases preparation). Thus it was found that the optimum method of extract introduction to emulsion bases is adding it at the end of the technological process in the form of a finely dispersed suspension with 48% ethanol.

Keywords: androgenic alopecia, emulsion bases, Saw Palmetto extract, dispersion, biopharmaceutical research.

1. Introduction
The problem of androgenic alopecia (AA) treatment is an issue of cosmetology and dermatology. The range of medicines for AA cutaneous treatment is limited and mainly represented with minoxidil – strong peripheral vasodilator with symptomatic action [2]. Thus new drug developing with plant biologically active substances (BAS) for AA cutaneous application with pathogenetic effect is very prospective. Saw Palmetto (Serenoa repens) extracts from Saw Palmetto berries possess fatty acids and sterols. Sterols act directly on hair follicles, preventing degenerative changes caused by the influence of trigger zone of dihydrotestosterone (DHT). They create a barrier for 5-Alpha-Reductase, and also decrease DHT uptake by hair follicles. Moreover, they lower down the block binding of DHT to androgen receptors. The dermal application of Saw Palmetto extract has delivered significant improvements in anti-androgen activity in various research studies [3, 6].
The rational introduction of active substances in the composition of semi-solid drugs provides their high bioavailability. Particularly important factors in the technology development of medicines for dermal application are the degree of active ingredients dispersion, method of their introduction into the ointment or cream bases. These parameters will affect the consistency, uniformity, rheological properties, storage stability and therapeutic activity of drugs.
The purpose of the research is to substantiate the method of Saw Palmetto extract introduction to emulsion bases in technology development of medicinal cosmetic remedies for AA treatment using physical-chemical and biopharmaceutical analysis.

2. Materials and Methods
At the first stage we investigated the solubility of Saw Palmetto extract in different liquids: pumpkin seed oil, water, glycerin, propylene glycol, alcohol-water-glycerol mixture (1:6:3), ethanol 48%. These liquids were selected taking into account the extract main BAS and ingredient presence in the bases composition (pumpkin seeds oil, water, glycerin etc.). The developing remedies also contain the Sophora japonica tincture made on 48% ethanol, so ethyl alcohol the above-mentioned concentration was used. The research was performed according to the Ukraine State Pharmacopoeia method [1]. The dispersion degree and the particles linear sizes determination were studied with the microscope "Delta Optical Genetic Pro" with built-in camera (lens 40/0,65 160/0.17; eyepiece WF 10×18) and the micrometer ruler.

and thus on its pharmacological action effectiveness. So the next step was *in vitro* agar plates biopharmaceutical study of the Saw Palmetto extract introduction to emulsion bases [4]. Saw Palmetto extract was inserted into emulsion bases by mixing it with the appropriate liquids. In the study we used four samples, where the extract was added differently: in the first sample extract was mixed with 48 % ethanol and added to compounded bases at the end of technology; for the second sample at the beginning of technology the extract was dissolved in the pumpkin seed oil; in the third and fourth samples the extract was inserted to the prepared bases by dispersing it with glycerin and alcohol-water-glycerin mixture respectively.

For carrying out the analysis 2% agar gel was filled in Petri dishes. As analytical reagent Sudan III alcohol-glycerol solution in 25% amount was used (react with fatty acids – the key active ingredients of Saw Palmetto extract). In Petri dishes six holes with 8 mm diameter were made. Agar holes was filled with the investigated samples (0.5 g.) and incubated in thermostat at 37 °C for 24 hours. The extract active substances diffused in agar gel and formed with the reagent bright orange color zones. The zones diameter was measured every hour during 6 hours, and the last measurement was carried out after 24 hours. If necessary (in the ellipse formation) greater and lesser diameter were measured and the average value of the colored areas were determined.

3. Results and Discussion

The results showed that it is impossible to achieve complete dissolution of the substance with any liquid, but dispersion varies depending on the dispersion medium nature (table. 1).

Table 1: The solubility of Saw Palmetto extract in various solvents

Solvents	Liquids solubility
Purified water	Slightly soluble (1:100)
Alcohol-water-glycerol mixture (1:6:3)	Slightly soluble (1:100)
Glycerin	Sparingly soluble (1:30)
Propylene glycol	Sparingly soluble (1:30)
Ethanol 48 %	Soluble (1:20)
Pumpkin seed oil	Soluble (1:20)

It was determined that extract is poorly wetted by water with large particles formation (from 0.2 to 1.5 mm) (Fig. 1-A). In alcohol-water-glycerol mixture extract was poorly dispersed forming a suspension with particles size of 0.2 – 0.8 mm (Fig. 1-B). Glycerin wetted the extract better than alcohol-water-glycerin mixture, but didn't dissolve it, forming a suspension with particles size 0,1 – 0,3 mm (Fig. 1-C). In propylene glycol extract solubility was the same as in glycerol with particles size from 0.1 to 0.5 mm (Fig. 1-D). Saw Palmetto extract, pounded with pumpkin seed oil and 48 % ethanol, approaching a homogeneous system with particles size of 0,005-0,05 mm, which were evenly distributed throughout the area of observation (Fig. 1- E, F). The particle size of the disperse phase depending on the chosen liquid medium are presented in table. 2.

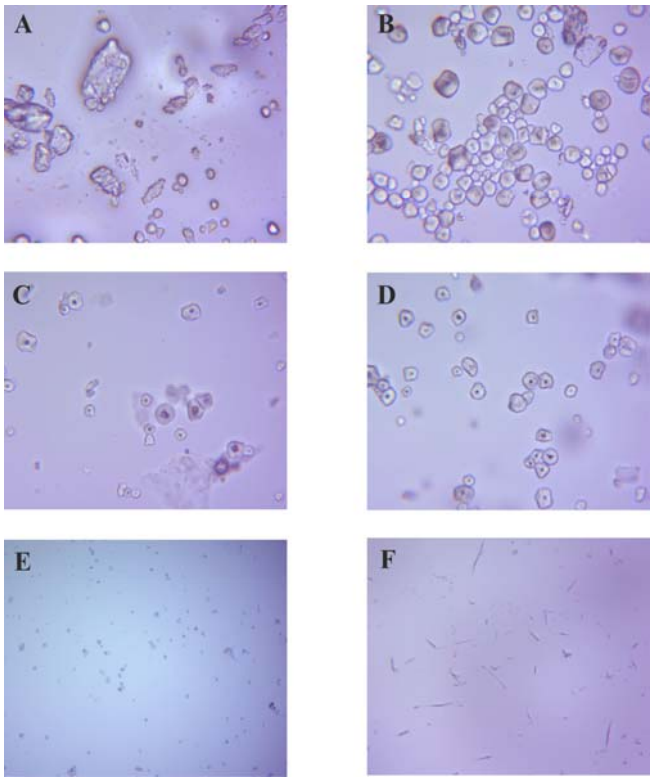

Fig 1: The dispersion of Saw Palmetto extract in different liquids: A – suspension in water; B – suspension in alcohol-water-glycerol mixture; C – suspension in glycerin; D – suspension in propylene glycol; E – suspension in pumpkin seed oil; F – suspension in 48% ethanol

Table 2: The results of disperse analysis of Saw Palmetto extract with different liquids

Solvents	Размер частиц, мм
Purified water	0,2 –1,5
Alcohol-water-glycerol mixture (1:6:3)	0,2 – 0,8
Glycerin	0,1 – 0,5
Propylene glycol	0,1 – 0,3
Ethanol 48 %	0,005-0,07
Pumpkin seed oil	0,005-0,05

The results showed that Saw Palmetto extract is well-dispersed with a partial solubility in pumpkin seed oil and 48% ethanol. For this reason, for biopharmaceutical testing we selected samples in which the extract was mixed with the above liquids; for comparison samples with extract suspensions in glycerol and alcohol-water-glycerol mixture were used.

Biopharmaceutical study proved (Fig. 2) that the best extraction of BAS from emulsion bases in agar gel was in the 1-est sample (extract was dispersed with 48% ethanol). The release of BAS from the 2-nd sample (extract was dissolved in the pumpkin seed oil) was significantly less than in the previous result. The samples (extract was suspended with glycerin and alcohol-water-glycerol mixture) almost did not form colored areas that indicated a low level of BAS releasing from the bases (Fig. 2, 3).

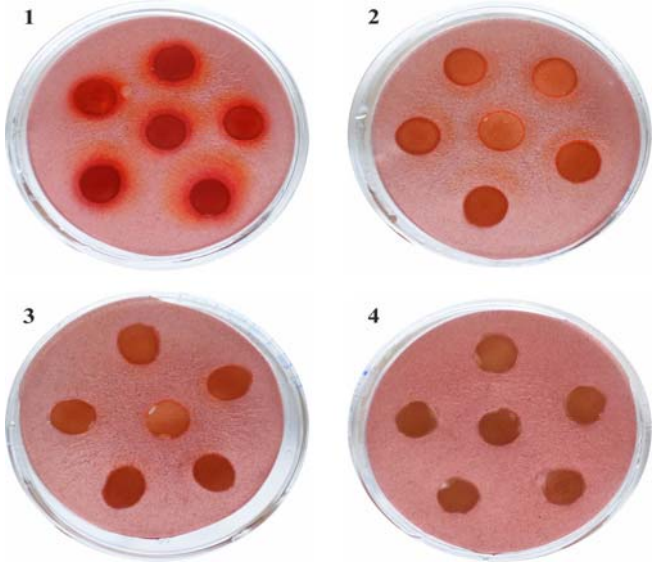

Fig 2: The degree of biologically active substances penetration from researched samples in agar gel: 1 – sample with 48% ethanol; 2 – sample with pumpkin seed oil; 3 – sample with glycerin; 4 – sample with alcohol-water-glycerin mixture

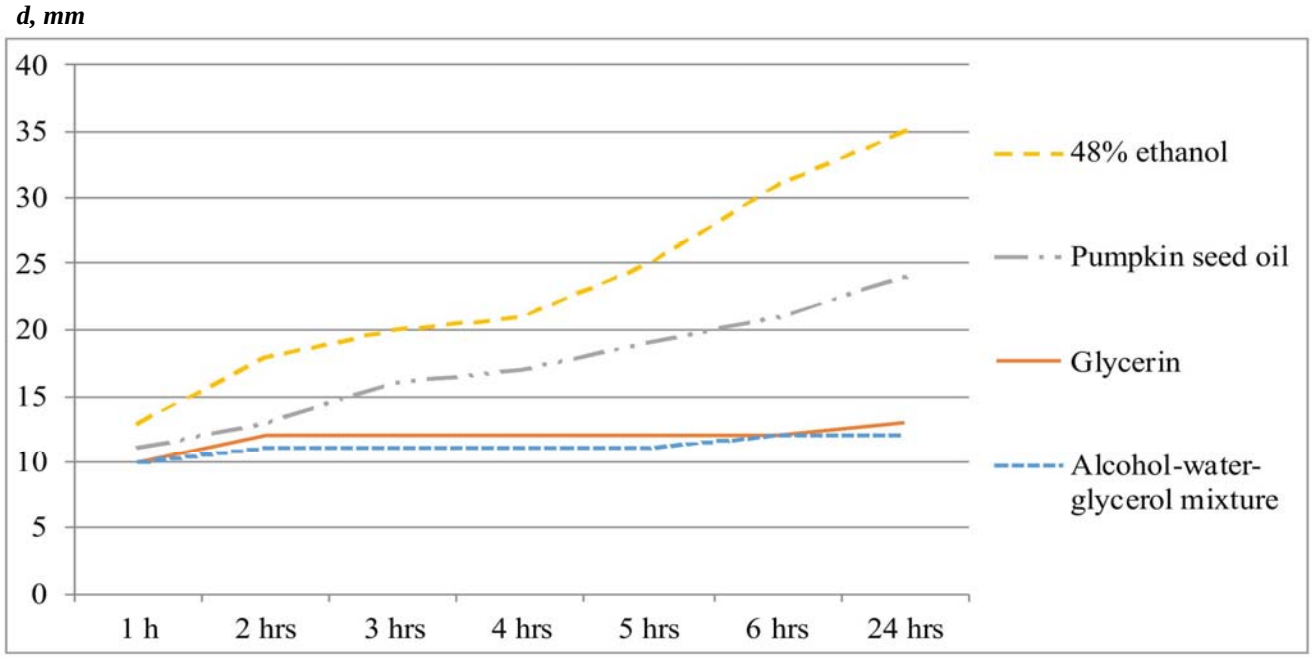

Fig 3: Diagram of penetration speed of Saw Palmetto extract BAS from emulsion bases in agar gel depending on the dispersing liquids and technology.

Thus, the results of physical-chemical and biopharmaceutical investigations showed that the best technological method of Saw Palmetto extract introduction to emulsion bases was in the form of finely dispersed suspension with 48 % ethanol at the end of preparation process.

4. Conclusions

1. It was determined that Saw Palmetto extract is introduced into the emulsion bases as fine-dispersed suspension. Microscopic analysis showed that the 48 % ethanol provide the dispersion of the extract with particles size 0.005-0.05 mm.
2. It was found according with biopharmaceutical study that the optimum method of extract introduction to emulsion bases is adding it at the end of the technological process in the form of a finely dispersed suspension with 48 % ethanol. The results showed that the developed technology provides the maximum penetration of biologically active substances with the medicines cutaneous application.

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