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Structural-Mechanical Studies of Phytogel «Zhivitan»

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Abstract

The object of research was the phytogel «Zhivitan» developed on the basis of extracts of comfrey and chestnut with complex of veno-protective, anticoagulant, anti-inflammatory and reparative properties. Structural and mechanical studies were carried out using the «Rheolab QC» rotary viscometer by Anton Paar (Austria) with coaxial cylinders CCC27/SS. With the aim of the software, graphs of the investigated phytogel were automatically plotted. These rheograms have confirmed the plastic type of flow and the presence of certain thixotropic properties of the gel developed. The area of the hysteresis loop for the gel «Zhivitan» is 1263.05 Pa sec, and the degree of thixotropy indicates that the drug restores its structural and mechanical properties. The data obtained allow to predict processes of homogenization and transportation for preservation of the structured system. It has been established that the gel «Zhivitan» developed is a structured disperse system with a non-Newtonian type of flow.

Keywords: Phytogel, comfrey extract, chestnut extract, structural and mechanical properties.

INTRODUCTION

One of the great challenges in medicine is the treatment of long-term non-healing wounds, namely, trophic ulcers developed on the background of chronic venous insufficiency (CVI). For 50% of patients, trophic ulcers healing may take for 4 months, for 20% of patients trophic ulcers remain open for 2 years, trophic ulcers of 8% of patients do not heal for 5 years of treatment, and the relapse rate remains at 6-15% [8].

The main requirements for modern combined veno-tropic ointments and gels include the influence of venous insufficiency on various pathogenesis links, which causes the preparation to have a veno-protective, anticoagulant, anti-inflammatory and reparative effect.

The modern pharmaceutical market of Ukraine presents a wide range of medicines for local therapy of lesions of the veins of the lower extremities. To the agents with angioprotective action for local application phytopreparations are ranked with an extract of chestnut horse seeds in their composition. The main active substance of the extract – escin – has anti-inflammatory, capillarotropic, veno-protective, antioxidant action, reduces the activity of lysosomal enzymes, increased for chronic venous insufficiency [1].

Taking into account the main pathogenetic aspects of the development of trophic ulcers, a component with reparative activity must be included in the composition of the active components together with the extract of chestnut chestnut seeds. There is only one combined preparation on the pharmaceutical market – the gel «Pantavenol» intended for the local treatment of the chronic venous insufficiency and trophic ulcers, which includes escin and dexpanthenol. All mentioned above indicates the necessity to develop new combined medicines in the form of semisolid drug with a veno-protective, anti-inflammatory and reparative effect [5].

In order to create a new combined veno-tropic preparation, staff of the National University of Pharmacy has suggested applying a combination of two plant extracts from 3% horse chestnut seeds and 5% rhizomes with comfrey roots. The main BAS of the phytoextracts are triterpene saponin β-escin and alkaloid allantoin. Their combination in the new phytogel «Zhivitan» will strengthen anti-inflammatory, angioprotective, antioxidant action and stimulate reparative processes, which is important for local therapy of trophic ulcers. The new preparation is designed as a hydrophilic gel, which provides rapid resorption, deep penetration into tissues and has a protective effect, which is necessary for thinning of the skin in conditions of trophic disorders.

One of the indicators of the quality of semisolid drugs (SSD), according to the State Pharmacopoeia of Ukraine [9], is rheological parameters [3]. It is known that the rheological properties of SSD depend on many factors: the nature and quantitative ratio of components, the degree of its mechanical processing, changes in the manufacturing process, time and temperature of mixing, etc. [6]. Since the structural and mechanical properties affect the consumer and therapeutic properties of SSD, the measures should be applied within development the composition of the drug for external use, which guarantee stability of the rheological parameters [2].

The purpose of the research was to study the structural and mechanical properties of the combined phytogel «Zhivitan» to assess its quality at the stage of pharmaceutical development and serial production.

MATERIALS AND METHODS

Rheological properties

The object of the study was phytogel «Zhivitan» containing in its composition the extracts of chestnut and comfrey and carbopol, PEG-40 hydrogenated castor oil, preservative, stabilizer and purified water as auxiliary substances.

The rheological (structural-mechanical) properties of the samples were determined with the means of «Rheolab QC» rotary viscometer (Anton Paar, Austria) with coaxial cylinders CC27/S-SN29766. The rheological parameters were studied at a temperature of 20,0±0.5° C.

The batch of sample weighed about 17,0 (±0,5) g was placed in the container of an external stationary cylinder, the required temperature of the experiment was set, the time of thermostating was 20 min.

The device allows measuring the tangential bias voltage (τ) in the range 0,5-3,0$\cdot 10^4$ Pa, the gradient of the shear rate (γ) from 0,1 to 4000 s^{-1}, the viscosity (η) is from 1 to 10^6 Pa sec.

The device is equipped with RheoPlus software, which provides with capacity to set the necessary conditions for the experiment. Measurements of the rheological flow curve were performed in 3 stages:

1) Linear increase at the rate of shear velocity from 0,1 s^{-1} to 350 s^{-1}1 with 105 measurement points and duration of the measurement point is 1 s;
2) Constant shift at a speed of 350 s^{-1} for 1 s of duration;
3) Linear decrease at the rate of shear velocity from 350 s^{-1} to 0,1 s^{-1} with 105 measurement points and duration of the measurement point for 1 s.

Investigation of the thixotropic properties of the samples was performed under the following experimental conditions:

1) Constant shift at a speed of 1 s^{-1}, 5 measuring points, the duration of the measurement point is 5 s;
2) Constant shift at a speed of 150 s^{-1}, 100 measurement points, the duration of the measurement point is 1 s;
3) Constant shift at a speed of 1 s^{-1}, 500 measuring points, duration of the measurement point is 1 s.

Besides investigations of the rheological curve and the viscosity curve, the yield point was determined using the Casson model. The yield point was calculated in the range from 0,1 s^{-1} to 350 s^{-1}.

Coefficient of dynamic flow

A coefficient of dynamic flow was determined at the speed rates of 3,4 and 10,1 s^{-1}, corresponding to the velocity of the palm while soft dosage form distributing over the surface of the mucous membranes and the viscosity of the system at the velocity rates of 25,6 and 148,0 s^{-1}, which display velocity of the processing procedure while manufacturing. Based on the results obtained, the values of coefficients of the dynamic flow of the system have been calculated by the formulas:

$$K_{d1} = \frac{\eta_{3,4} - \eta_{10,1}}{\eta_{3,4}} \cdot 100\,\%,$$

$$K_{d2} = \frac{\eta_{25,6} - \eta_{148,0}}{\eta_{25,6}} \cdot 100\,\%$$

where K_{d1}, K_{d2} – the dynamic flow coefficients;
η – Apparent viscosity at specified shear rates.

Mechanical stability

For more complete study of gel samples, the parameters of their mechanical stability (MS) have been calculated. It is known that the optimal value of MS is 1 [4].

The MS value is defined as the ratio of the strength of the structure to failure (τ_1) to the strength value after fracture (τ_2) according to the formula:

$$MS = \frac{\tau_1}{\tau_2}$$

Index of destruction et index of thixotropy

The index of destruction (Kd) was calculated by the formula:

$$K_d = \frac{\tau_0 - \tau_2}{\tau_0} \times 100$$

where: τ_0 – breaking strength (shear stress) of undistracted sample, Pa;

τ_2 – breaking strength (shear stress) after the destruction, Pa.

The index of thixotropy recovery (Kt) was calculated by the formula:

$$K_t = \frac{\tau_2 - \tau_1}{\tau_2} \times 100$$

where: τ_2 – breaking strength (shear stress) after the destruction of a sample, Pa;

τ_1 – breaking strength (shear stress) after restoring, Pa.

Results And Discussion

At the first stage of the research, the rheological parameters of phytogel «Zhivitan» have been examined. In order to study the strength of the gel's structure, to determine the type of flow and the presence of thixotropic properties, the complete rheograms of the flow of the gel have been constructed, which characterize the dependence of the shear stress (τ) on the velocity gradient (γ) (Figure 1). These rheoparamars were obtained by the method of continuous fracture of the structure, as a function of the shear stress.

This dependence is typical for systems with a plastic type of flow and characterizes the examined phytogel as a structured dispersive system. The use of such a gel ensures more easier and uniform application of the drug to the damaged skin surface [7].

The results of research of phytogel «Zhivitan» are presented in Figure 1-2 and allow to refer the examined object to the structured systems with a certain fluidity.

The results of studies in Figure 1 allow us to evaluate the following indicators. Phytogel «Zhivitan» has a yield point, which is expressed by a shear stress of 37,714 Pa, which characterizes the insignificant resistance of the structure to an external destructive force (shear rate) until which the system behaves like a solid body. Having such a yield point, this system is characterized by a pseudo-plastic type of flow. This allows to state that the gel has a high extrusion ability, and on the surface of the skin, the gel squeezed from the tube can be evenly distributed.

In practice, these values allow characterizing the process of extrusion (extrusion of the SSD from the tube), which is quite complicated for the examined samples at 20 °C, i.e. some effort is needed.

The phytogel «Zhivitan» has not significant indicators of structural viscosity (Figure 2, Table 1). Thus, at a minimum initial shear rate of γ 0.01 s^{-1}, the structural viscosity approaches the viscosity at the state of the rest and is 13,7 Pa sec. The gradual increase in the shear rate to 350 s^{-1} results in partial destruction of the system, reducing the structural viscosity to 0,417 Pa sec. This process displays the ascending curve of the hysteresis loop and the upper curve of the dependence of the structural viscosity on the gradient of the shear rate (Figure 1 and 2, curves 1). While the shear rate is being reduced to the opposite direction (from 350 s^{-1} to 0,1 s^{-1}), a partial restoration of the gel structure is observed up to 99,27% (Figure 1, curve 2), that characterizes this system as pseudo-plastic one with a good reducing structure.

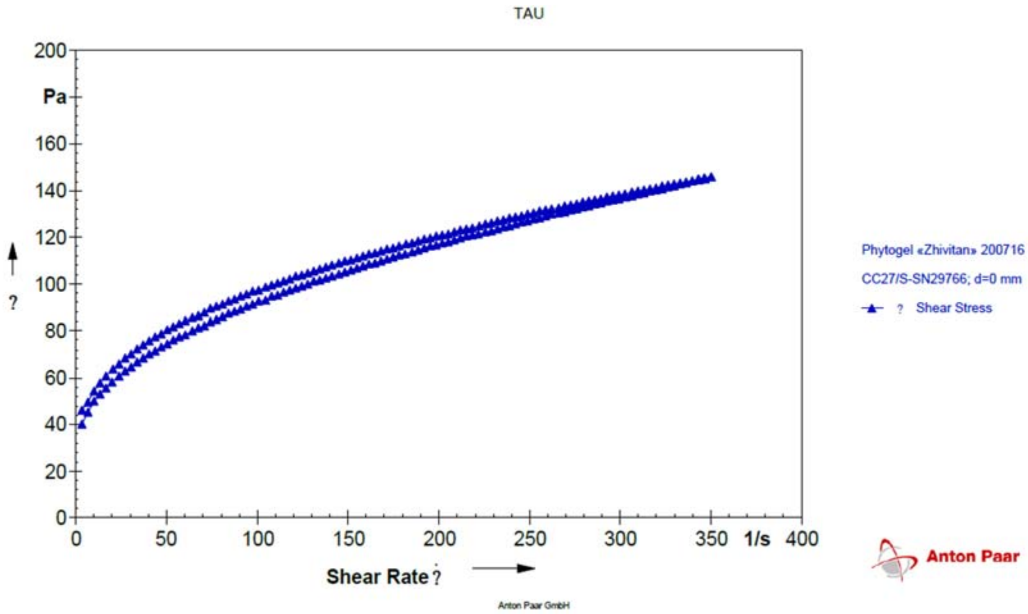

Figure 1 – Dependence of the shear stress (τ, Pa s) from the shear rate (γ, s^{-1}) of the phytogel «Zhivitan»

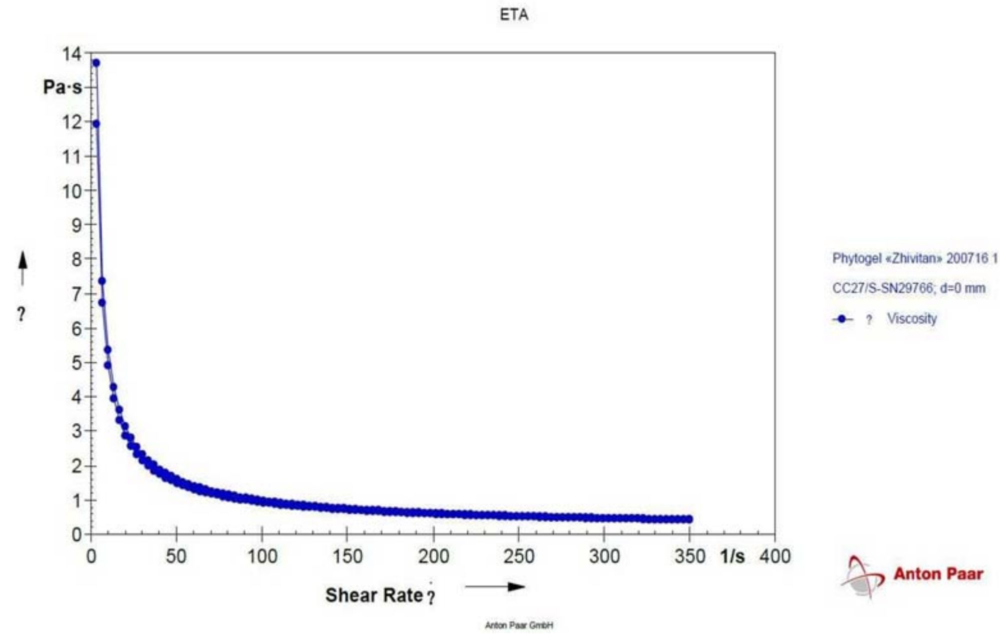

Figure 2 – Dependence of the viscosity (η, Pa) on the shear rate (γ, s-1) of the the phytogel «Zhivitan»

Table 1 – The parameters of the structural viscosity of the gel «Zhivitan» depending on the gradient of the shear rate

№	Gradient of shear rate, (γ, s^{-1})	Shear stress, (τ, Pa sec)		Structural viscosity, (η, Pa sec)	
		ascending	descending	ascending	descending
1	0,1	10,03	16,2	1750	18500
2	3,4	46,2	40,1	13,7	11,9
3	10,1	54,0	49,7	5,35	4,92
4	30,3	70,2	64,5	2,32	2,13
5	148,0	110,0	105,0	0,74	0,709
6	350,0	146,0	146,0	0,417	0,416

While the period of the structured systems' destruction (ascending curve), with the help of the increasing rotation speed of the inner cylinder, the system loses its viscosity (a decrease in their viscosity), which, as a rule, does not reach the end, since some of the bonds can be reversibly restored even at high speeds. The descending curve reflects the ability of the system to recover with a gradual decrease in shear rate. The area between the ascending and descending curves is called the hysteresis loop. According to the square of the hysteresis loop, the mechanical stability of structured systems can be considered, the smaller it is, the more mechanically stable the system is. The hysteresis square (A) for the phytogel «Zhivitan» (1263,05 Pa/sec) testifies to significant plastic-viscous and thixotropic properties of the phytogel developed (Table 2).

A feature of non-Newtonian liquids or pseudoplastic systems is that their viscosity depends on the magnitude of the shear stress, that is, the system exerts a resistance to the applied shear stress until a certain time. The value of the shear stress required for beginning of the system processing is minimal, and then the period of pseudo-plastic type of flow begins. Further, with a gradual increase in the shear stress, a plastic type of flow sets in (a section of the curve that approaches a straight line (Figure 1, 2)). The transition of systems from ones of pseudoplastic flow to plastic one is characterized by a limited shear stress or yield stress (τ_0), which indicates that the structural viscosity in the system is directly proportional to the shear stress. The limited shear stress for the phytogel «Zhivitan» is 37,714 Pa (Table 2). The low value of the limited shear stress of the phytogel, as well as the low value of the structural viscosity at an infinite shear rate (η_∞, Pa sec) indicates the easiness of application and uniform distribution on the surface of the skin.

Table 2 – Rheological parameters of the phytogel «Zhivitan»

№	Indicator	Signs	Value
1	Hysteresis square	A, Pa/sec	1263,05
2	Yield strength	τ_0, Pa	37,714
3	Structural viscosity at the infinite shear rate, at τ_0	η_∞, Pa sec	0,1124
4	Fracture index	K_d, %	38,09
5	Thixotropic reduction factor	K_t at K_{d1}, %	8,12-13,20
6	Thixotropic reduction factor	K_t at K_{d2}, %	4,55-7,96
7	The coefficient of dynamic flow (ascending curve)	K_{d1}, %	60,65
8	The coefficient of dynamic flow (ascending curve)	K_{d2}, %	68,10
9	Mechanical stability (ascending curve)	MS at K_{d1}	1,09-1,15
10	Mechanical stability (ascending curve)	MS at K_{d2}	1,09-1,15
11	The coefficient of dynamic flow (the descending curve)	K_{d1}, %	58,66
12	The coefficient of dynamic flow (the descending curve)	K_{d2}, %	66,71
13	Mechanical stability(downward curve)	MS at K_{d1}	1,04-1,09
14	Mechanical stability(downward curve)	MS at K_{d2}	1,05-1,09

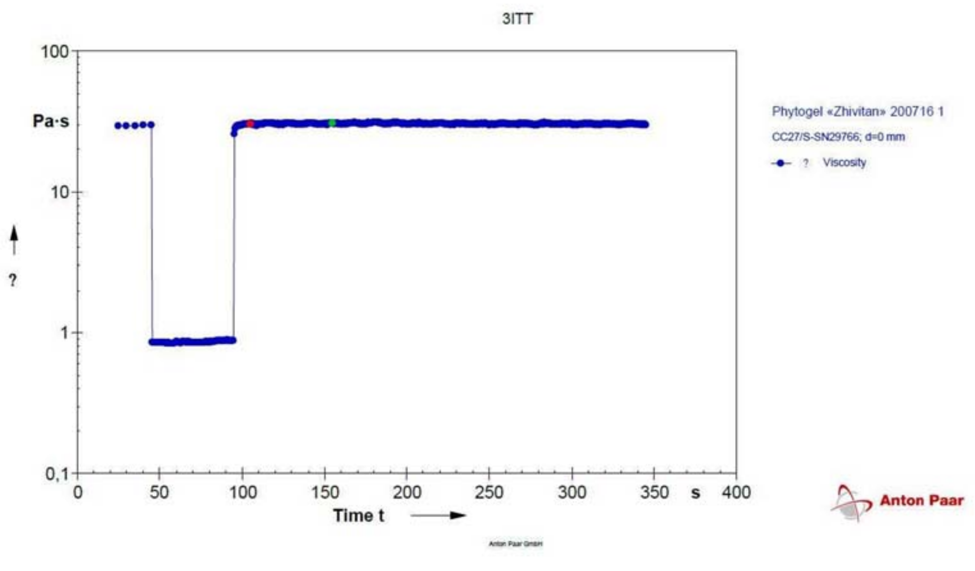

Figure 3 – Graphs of the structural viscosity of the phytogel «Zhivitan» at 20 °C, depending on the gradient of the shear rate under conditions of «destruction-restoration».

Table 3 – Number values of the tick-stitched phytogel «Zhivitan»

Restoration of the structure of the phytogel after 10 sec of destruction	Restoration of the structure of phytogel after 60 sec of destruction	Restoration of the phytogel's structure after 500 sec of destruction
101,83 %	102,58 %	99,27 %

The calculated values of mechanical stability (MS) of the phytogel do not exceed 1.15. This indicates that in its structure coagulation bonds only are provided that ensure full reversibility of deformations after stress relief and the preservation of their rheological properties during long-term storage.

The calculated values of the dynamic flow coefficients of the phytogel (Kd_1 = 58.66-60.65%, Kd_2 = 66.71-68.10%) confirm quantitively the satisfactory degree of distribution of the system during application to the skin or during manufacturing operations.

The presence of thixotropic properties ensures the restoration of the structure after mechanical processing while manufacturing. The study of the thixotropic properties was carried out under conditions of shear at a constant rate for 50 sec and further reduction (a detailed description of the procedure is given above). The results of the experiment are shown in Figure 3 and Table 3.

As can be seen from the data given, phytogel refers to structured dispersive systems, which rheological properties do not depend on the time of destruction. After fracture, the samples restore the original viscosity.

As can be seen from Figure 3 and Table 3, the phytogel «Zhivitan» having an initial viscosity of 29.2 Pa·sec is destroying to a viscosity rate of 0.89 Pa sec (at the 100th sec of experiment) and, until the end of the experiment (at the 500th sec), restoring is almost completely (by 99.27%). These data confirm the previously calculated values of mechanical stability (MS) of the phytogel «Zhivitan». This indicates that the base represented by the gelling agent with the auxiliary substances is restored immediately after the removal of the destructive force, however at the same time the system is easily destroyed. This structured system and systems with similar thixotropic properties are the most technologically advanced.

CONCLUSIONS

The structural and mechanical activity of the developed phytogel «Zhivitan» was studied with help of the rotary viscometer «Rheolab QC» by Anton Paar (Austria) with coaxial cylinders C-CC27/SS. It is established that the developed phytogel is a structured disperse system with a non-Newtonian type of flow, which provides uniform and gradual application of the gel to the skin surface. Data obtained on the backgrounds of the rheological studies have confirmed the plastic type of flow and the presence of certain thixotropic properties of the gel developed. The area of hysteresis loop for the phytogel «Zhivitan» is 1263,05 Pa sec, and the degree of thixotropy indicates that the medicine restores its structural and mechanical properties.

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