ORIGINAL ARTICLE

RESEARCH OF RHEOLOGICAL PROPERTIES OF MEDICINAL SYRUP FOR ORAL USE

DOI: 10.36740/WLek202004113

Lena L. Davtian[1], Galyna P. Kukhtenko[2], Alona S. Voronkina[3], Viktoria V. Kudria[3]

[1]PHARMACEUTICAL TECHNOLOGY AND BIOPHARMACY DEPARTMENT, SHUPYK NATIONAL MEDICAL ACADEMY OF POSTGRADUATE EDUCATION, KYIV, UKRAINE

[2] INDUSTRIAL PHARMACY DEPARTMENT, NATIONAL UNIVERSITY OF PHARMACY, KHARKIV, UKRAINE

[3] PHARMACY DEPARTMENT, NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE

ABSTRACT

The aim of the present research was to investigate the rheological properties of the medicinal syrup for oral administration with glucosamine hydrochloride and levocarnitine.

Matherials and methods: Coefficient of the dynamic flow (at shear rates of 3,49 and 10,3 s^{-1}, as well as at shear rates of 27.2 and 149.0 s^{-1}), mechanical stability, the index of destruction and restoration were studied. The rheological (structural-mechanical) properties of the samples were determined using a Rheolab QC rotary viscometer (AntonPaar, Austria) with coaxial cylinders CC27 / S-SN29766. The rheological parameters were studied at the temperature 20±0,5 °C.

Results: It is established that the syrup has weakly expressed plastic viscous and thixotropic properties (the hysteresis area for the syrupis 1710.19 Pas/s). Such results characterize the system as a reopex.

Conclusions: The results of the study enables classification of the research object as system with a low degree of fluidity. Such dependence is typical for systems of the Newtonian type of flow and characterizes the syrup under investigation as a weakly structured disperse system.

KEY WORDS: medicinal syrup, rheology, effective viscosity, mechanical stability, rheopexy

Wiad Lek. 2020;73(4):696-699

INTRODUCTION

Marketing analysis of levocarnitine and glucosamine preparations defined the market needs for the development of combined drugs for oral use containing both Glucosamine and Levocarnine [1].

Research on the development of a new drug should be conducted in accordance with Guideline 42–3.1: 2004 “Medicines. Guidance on quality. Pharmaceutical development” a compulsory section of the registration dossier (module 3: Quality: Chemical, pharmaceutical, and biological information about the drug containing chemical and/or biological active substances) [2] and “ICH harmonised tripartite guideline pharmaceutical development Q8(R2)”[3].

Information about rheological properties is important for the design of technological processes in the development of a medicinal product and its quality control[4].

Emulsions, suspensions, polymer solutions and gels are the examples of non-Newtonian fluids with non-fixed viscosity that depends on the degree of shear they are subjected to. Nowadays, the most common form of non-Newtonian behavior of liquids is dilution – viscosity decreases with increasing rate of displacement.

Dilution under shear can provide the desired attributes of the product – stability[5][6]. Based on the theory of rheology, we studied the rheological behavior of glucosamine syrup with glucosamine hydrochloride and levocarnitine (L-carnitine) [7]. Rheological parameters of medicinal syrup affect the efficiency of the production processes and processing of sugars-boiling, crystallization, etc. [8].

In our previous research, compatibility of all the ingredients selected for pharmaceutical development of medicinal syrup was confirmed [9]there was a need to check the compatibility of active pharmaceutical ingredients (APIs.

THE AIM

The aim of the present research was to investigate the rheological properties of the medicinal syrup for oral administration with glucosamine hydrochloride and levocarnitine.

MATERIALS AND METHODS

The rheological (structural-mechanical) properties of the samples were determined using a Rheolab QC rotary viscometer (Anton Paar, Austria) with coaxial cylinders CC27/S-SN29766. The rheological parameters were studied at a temperature 20 ± 0.5 °C. Thermostatting of the samples was carried out with a MLM U15c thermostat.

A sample weight about 17.0 (± 0.5) g was placed in the conteiner of an external stationary cylinder, the required temperature of the experiment was set, the time of thermostating was 20 min.

The device makes it possible to measure the tangential bias voltage (τ) in the range 0,5-3,0·10^4Pa, the gradient of the shear rate (γ) from 0.1 to 4000 s^{-1}, the viscosity (η) is from 1 to 10^6 Pa·s.

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

1) linear increase in the shear rate from 0.1 s^{-1} to 200 s^{-1} with 60 measurement points and the duration of the measurement point is 1 second;

2) constant shift at a speed of 200 s^{-1}, duration of 1 s;

3) linear decrease in the shear rate from 200 s^{-1} to 0.1 s^{-1} with 60 measurement points and the duration of the measurement point is 1 s.

The dynamic flow coefficient was determined at shear rates of 3.49 and 10.3 s^{-1}, as well as at shear rates of 27.2 and 149.0 s^{-1}, reproducing the processing speed in the manufacturing process. Based on the obtained results, we calculated the values of the coefficients of the dynamic flow of the system from formulas 1, 2:

$$K_{d1} = \frac{\eta_{3,49} - \eta_{10,3}}{\eta_{3,49}} \cdot 100\%, \quad (1)$$

$$K_{d2} = \frac{\eta_{27,2} - \eta_{149,0}}{\eta_{27,2}} \cdot 100\% \quad (2)$$

where:
Kd_1, Kd_2– dynamic flow coefficients;
η– is the effective viscosity at certain shear rates.

For the more complete study of the samples, the parameters of their mechanical stability (MS) were calculated. It is known that the optimal value of MS is 1 [10][11].

The value of MS is defined as the ratio of the strength of the structure to failure (τ_1) to the strength value after fracture (τ_2) by the formula 3:

$$MS = \frac{\tau_1}{\tau_2} \quad (3)$$

The fracture index (Kp) was calculated by the formula 4:

$$K_p = \frac{\tau_H - \tau_p}{\tau_H} \cdot 100\% \quad (4)$$

where:
$\tau_н$ – ultimate strength (shear stress) of an undamaged sample, Pa;
τ_p – ultimate strength (shear stress) after failure, Pa.

Table I. Indicators of the structural viscosity of a model sample of syrup depending of the shear rate gradient

№	Gradient of shear rate, (γ, s^{-1})	Shear stress, (τ, Pa s)		Structural viscosity, (η, Pa s)	
		Ascending curve	Downward curve	Ascending curve	Downward curve
1	0,10	0,782	1,27	7,72	12,70
2	3,49	25,0	25,3	7,17	7,24
3	10,30	71,9	71,9	7,00	7,00
4	27,20	189,0	186,0	6,96	6,86
5	149,00	986,0	971,0	6,61	6,51
6	200,00	1290,0	1290,0	6,46	6,45

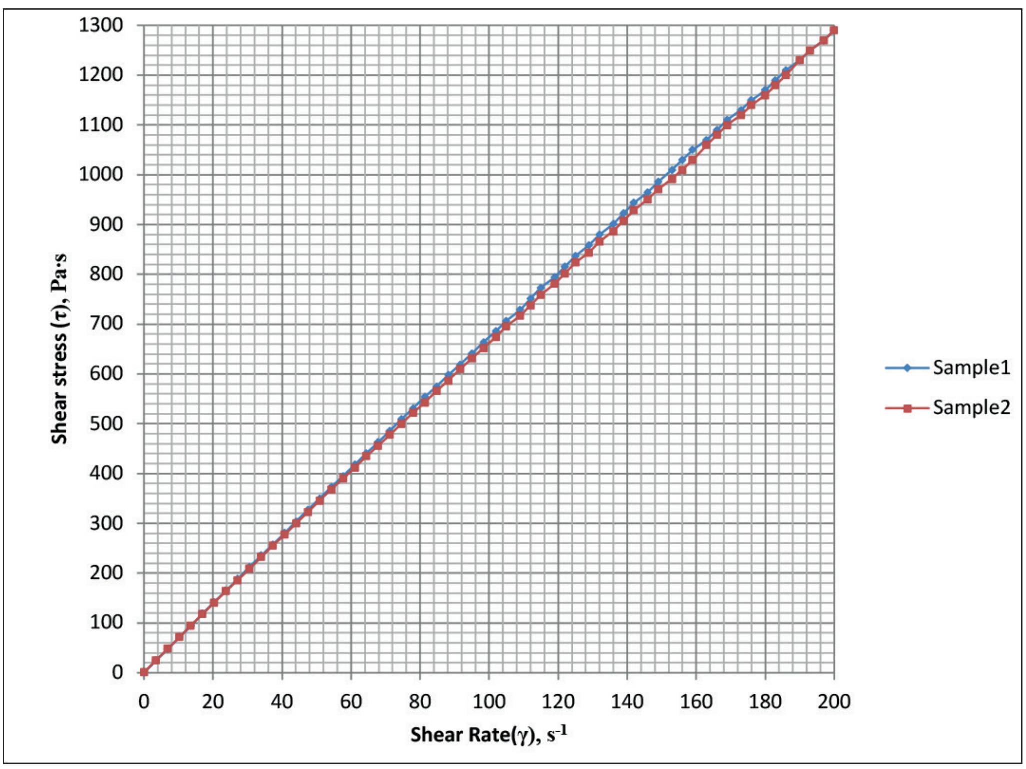

Figure 1. Dependence of the Shear Stress (τ, Pas) on the Shear Rate (γ, s^{-1}) of the syrup samples

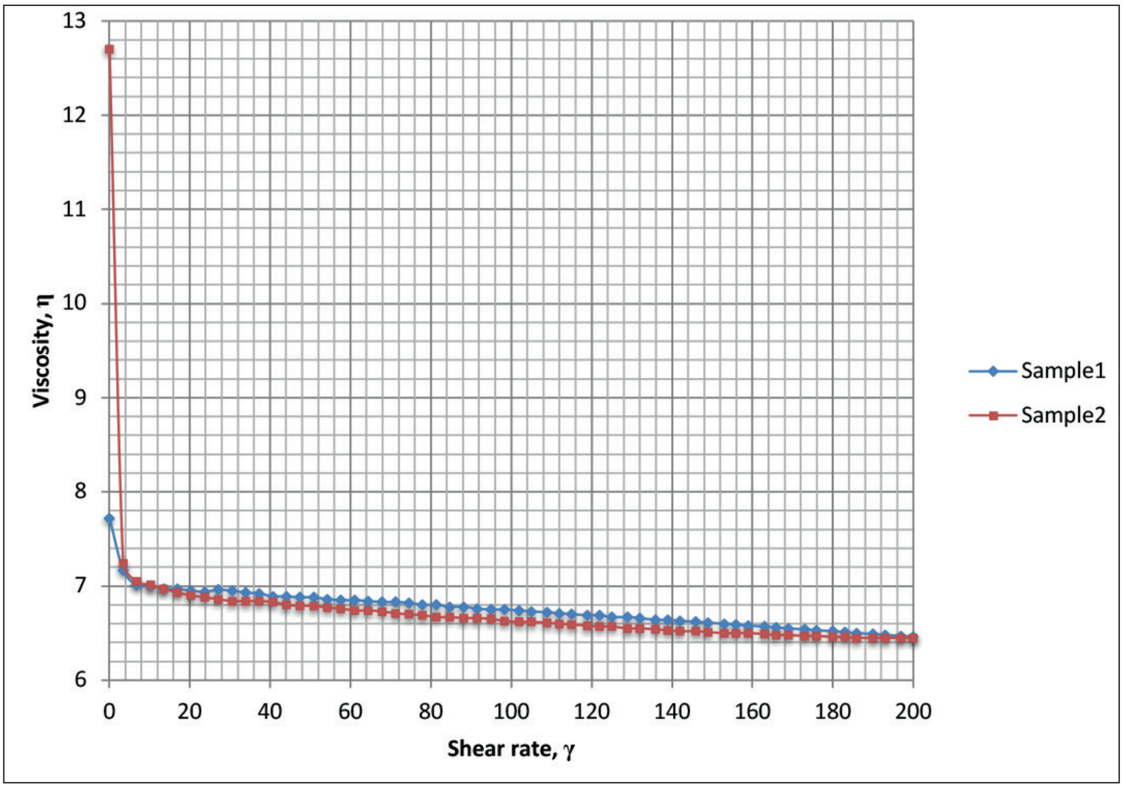

Figure 2. Dependence of the viscosity (η, Pa) on the shear rate (γ, s^{-1}) of the experimental syrup samples

The thixotropic reduction index (K_B) was calculated from the formula 5:

$$K_B = \frac{\tau_2 - \tau_1}{\tau_2} \cdot 100 \quad (5)$$

where:
τ_1–ultimate strength (shear stress) after recovery, Pa;
τ_2–ultimate strength (shear stress) after sample failure, Pa.

RESULTS AND DISCUSSION

The results of studies of the rheological properties of the syrup are shown in the Table I, Fig. 1 and Fig. 2.

The results of the studies (Fig. 1) allow us to estimate that the syrup has a limit of strength, which is expressed by a shear stress of 0.03 Pa. That characterizes the insignificant structural resistance of the external destructive force (shear rate) to which the system behaves as a solid. Having such a yield point, this system is characterized by the Newtonian type of flow. This fact allows us to state that the syrup has low fluidity.

At a minimal initial shear rate (γ 0.10 s^{-1}), the structural viscosity of the syrup is 7.72 Pa·s. The gradual increase in the shear rate to 200 s^{-1} resulted in partial destruction of the system, reducing the structural viscosity to 6.46 Pa·s. 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 (Figures 1 and 2). During the reduction of the shear rate in the opposite direction (from 200 s^{-1} to 0.1 s^{-1}), the structure of the syrup

Table II. Rheological parameters of the model syrup sample

№	Index	Meaning
1	*Area of hysteresis A, Pa/s*	1710,19
2	*yield(limit) of strength τ_0, Pa*	0,03
3	Structural of viscosity at infinite shear rate, at τ0 η∞,, Pa s	6,58
4	The destruction index K_p, %	62,4
5	The coefficient of thixotropic reduction of $K_в$ at K_{d1}, %	1,2
6	Thixotropic reduction factor $K_в$ at K_{d2}, %	1,5
7	Dynamic flow coefficient K_{d1}, %	184,2
8	Dynamic flow coefficient K_{d2}, %	422,0
9	Mechanical stability of MS at K_{d1}	1,012
10	Mechanical stability of MS at K_{d2}	1,015

is completely restored, the viscosity did not only restored but also exceeded the original by 64.5% (12.7 Pa·s). This characterizes the system as a system with a rheopexy.

Rheopexy is a rare property of some non-Newtonian liquids: viscosity increases with increasing shear stresses in a fluid over time. Rheopexation liquids thicken and even solidify when they are mixed. The opposite property is the thixotropy, that makes the liquids become less viscous when they begin to mix. More substances have thixotropy property than rheopexy.

The area enclosed between the ascending and descending curves (Fig. 1, 2) is called the hysteresis loop. By the area of the hysteresis loop, we can judge about the mechanical stability of structured systems. The smaller loop means that the system has greater mechanical stability. The hysteresis area for the syrup (1710.19 Pa / s) indicates weakly pronounced plastic-viscous and thixotropic properties (Table II).

The calculated values of the mechanical stability (MS) of the syrup are close to the optimum value – 1.012 and 1.015 (Table II). This indicates that in its structure only coagulation bonds [12] are present, which ensure full reversibility of deformations after stress relief and the preservation of their rheological properties during long-term storage.

CONCLUSIONS

Thus, the results of the study allow classifying the research object as system with a low degree of fluidity. This dependence is typical for the systems of the Newtonian type of flow and characterizes the investigated syrupas a weakly structured disperse system. However, the system has shown unexpected rare rheological property, called rheopexy.

REFERENCES

1. Davtian L., Voronkina A., Khomych O., et al. Marketing analysis of levocarnitine and glucosamine preparations. Int J Green Pharm. 2019;12(04):S808-S814. doi:10.22377/ijgp.v12i04.2259
2. Abbès F., Masmoudi M., Kchaou W., et al. Effect of enzymatic treatment on rheological properties, glass temperature transition and microstructure of date syrup. LWT – Food Sci Technol. 2015;60(1):339–45.
3. Gladukh I., Grubnik I., Kukhtenko G. Rheological studies of water-ethanol solutions of gel-formers. J Chem Pharm Res. 2015;7(4):729–734.
4. Davtian L., Vashchuk V., Polishchuk Y. Rheological research process as the basis for creating a new drug. Farmatsevtychnyi Zhurnal. 2013;(4):54–58.
5. Davtian L., Khomich O. Obhruntuvannya skladu osnovy dlya syropu. In: Suchasni dosyahnennya farmatsevtychnoyi tekhnolohiyi ta biotekhnolohiyi: zbirnyk naukovykh prats', Kharkiv. 2016:189–191.
6. Gabsi K., Trigui M., Barrington S., et al. Evaluation of rheological properties of date syrup. J Food Eng. 2013;117(1):165–72.
7. Davtian L., Khomych O., Voronkina A., et al. Study of Compatibility of the Ingredients at Pharmaceutical Development of Medicine Syrup. Asian J Pharm. 2019;12(4):272-80. doi: 10.22377/ajp.v12i04.2835
8. Gladyshev V., Kuchyna H., Burlaka B., et al. Research of rheological properties softnasal medicinal form of diltiazem. Curr issues Pharm Med Sci Pract. 2013;1(11):69–72.
9. Rogachev I., Gladyshev V., Burlaka B., et al. Sravnitel'nyye issledovaniya strukturno-mekhanicheskikh kharakteristik intranazal'nykh myagkikh lekarstvennykh form nimodipina. Zaporozhye medical journal. 2011;3(13):92–4.
10. Malkin A.Y., Isayev A. Reologiya: kontseptsii, metody, prilozheniya: [avtoriz. per. s angl.]. SPb.: Professiya; 2007. 557 p.

The article belongs to researchworks of the department of Pharmaceutical technology and biopharmacy "Scientific and practical substantiation of the composition and technology of drugs and cosmetics" (State registration № 0117U002461) and "Design of composition and technology of drug in the form of syrup containing glucosamine hydrochloride and levocarnitine" (State registration №0117U006430).

ORCID and contributionship:
Lena L. Davtian – 0000-0001-7827-2418 [A,C,D,E,F]
Galyna P. Kukhtenko – 0000-0002-7914-8053 [B,C,E]
Alona S. Voronkina 0000-0003-2750-0884 [A,D,E,F]
Viktoria V. Kudria 0000-0001-6613-8035 [B,C,D]

Conflict of interest:
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Alona S. Voronkina
Pharmacy department, National Pirogov Memorial Medical University
Pirogov street 56, 21018, Vinnytsia, Ukraine
tel: +38050-461-42-61
e-mail: voronkina@vnmu.edu.ua

Received: 12.08.2019
Accepted: 18.02.2020

A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article