

Influence of Excipients on the Structural and Mechanical Properties of Semisolid Dosage Forms

Halyna Kukhtenko, Ievgenii Gladukh, Oleksandr Kukhtenko, Dmitrii Soldatov

Department of Industrial Pharmacy, National University of Pharmacy, 4, Valentinovskaya Street, Kharkov, Ukraine

Abstract

Context: In the scientific article presents data are presented on investigation of the influence of nonaqueous solvents such as propylene glycol, polyethylene oxide-400 (PEO-400) and glycerin on the structural, and mechanical properties of the emulsion and gel coagulation systems. The regularity of the structural viscosity changes of the systems studied from concentrations of propylene glycol, PEO-400, glycerol, and combinations thereof have been determined. **Aim:** The aim of the work is to study the effect of propylene glycol, PEO-400, and glycerol on the rheological (structural and mechanical) properties of soft dosage forms. **Materials and Methods:** The objects of research were concentrated (creamy) 1 kind emulsion systems and gel formulations. Three series of samples were prepared. All samples were subjected to rheological studies on rheoviscometer "RheolabQC" of company Anton Paar (Austria). **Results:** It has been found that glycerol in an amount up to 5% increases the viscoplastic properties of emulsion systems, at its concentration above 5% there is a decrease in these properties. Propylene glycol and PEO-400 at a concentration of 5%, on the contrary, lower viscoelastic properties of emulsion systems, at their concentrations from 5% to 15% there is an increase in the structural viscosity of the concentrated emulsion and at a concentration of more than 15% the systems thin. At the introduction of propylene glycol and PEO-400 in the gel coagulation system in concentrations of up to 30%, viscoplastic properties increase slightly. Increasing the amount of these substances to 60% in a different degree affects the structural viscosity of the gel system, so propylene glycol in the concentration of 60% reduces structural viscosity from 34.9 to 19.4 Pa·s at shear rate of 10.4 Pa, and introduction of 60% PEO-400 - 4.8 Pa·s at the same shear rate. Combining these substances in the formulation leads to potentiating each other's action. **Conclusions:** Introduction of propylene glycol, PEO-400 and glycerol to soft medicinal forms allows varying their viscoelastic properties. It should be outlined that the ability to modify the thixotropic properties of both the emulsion and gel systems are more pronounced in the PEO-400.

Key words: Emulsifiers, emulsions, gels, glycerol, polyethylene oxide-400, propylene glycol, rheological, semisolid dosage forms, structural viscosity

INTRODUCTION

Semisolid dosage forms are widely used in various fields of medicine and cosmetology. Considered over a long period of time as formulations for topical application, mainly in the treatment of a number of dermatological disorders, ointments get increasingly used in ophthalmology, otolaryngology, surgery, obstetrics, gynecology, proctology, and other branches of clinical medicine.^[1,2] Due to the development of structural mechanical (rheological) and biopharmaceutical research methods in recent years, have been explained, some individual statements and general trends, indicating dependence of bioavailability of medicinal substances administered in the form

of semisolids, on a number of factors.^[3-5] This is a consequence of changes in the technological instrumentation of laboratory and industrial equipment, as well as the expansion of the range of auxiliaries playing an active role in the manifestation of the pharmacological and pharmacokinetic properties of ointments.^[6-9]

Address for correspondence:

Halina Kukhtenko, Department of Industrial Pharmacy, National University of Pharmacy, 4, Valentinovskaya Street, Kharkov, Ukraine. Phone: +380984004890. E-mail: galinakukh@gmail.com

Received: 11-07-2017

Revised: 22-07-2017

Accepted: 27-07-2017

Rheology as a science has found wide application, and its research methods are widely used in various industries. In the pharmaceutical industry rheological research methods form the basis of scientific developments of composition of soft and hard drugs such as ointments, creams, suppositories, gels, liniments, pastes, suspensions, and emulsions, and also allow a rational choice of optimal process parameters of production and control safety of consumer quality throughout shelf life. Rheological research methods make it possible to evaluate the effect of excipients on such structural and mechanical properties as: Strength, elasticity, plasticity, and viscosity, which together determine the consumer properties of medicines.^[10-17]

Semisolid formulations are coagulation (thixotropic reversible) structures, which rheological properties depend on the quantitative ratio of all components. In the formation of the coagulation grid in contact between the particles there remains very thin layer of a liquid dispersion medium, which prevents further rapprochement of structure particles (the action of van der Waals forces) and ensures the presence of rheological properties. The thicker the layer of the medium, the lower the effect of the molecular forces is, the less solid the structure is and the more liquid-like the system will be. Systems with coagulation structures have a low strength, plasticity, and elasticity which together characterize the spreadable properties of semisolids.^[18-20]

Formulations of soft drugs include auxiliary substances from different groups, one of which are nonaqueous, hydrophilic solvents such as propylene glycol (1,2-propylene glycol), PEO-400, and glycerol having a good solvent activity for a wide range of active pharmaceutical ingredients.^[18,19,21]

The aim of the work is to study the effect of propylene glycol, polyethylene oxide-400 (PEO-400), and glycerol on the rheological (structural and mechanical) properties of soft dosage forms.

MATERIALS AND METHODS

The objects of research were concentrated (creamy) 1 kind emulsion systems and gel formulations. 3 series of samples were prepared. First line – Vaseline oil (10 %) based emulsion, stabilized with emulsifying wax (mixture of potassium salts of phosphoric acid esters with higher fatty alcohols of the same fraction, hydrophilic-lipophilic balance [HLB] 14.9) in an amount of 8% the dispersion medium was water purified. In the first line varied content of propylene glycol (5%, 10%) and glycerol (5%, 10%) and a combination thereof. Line 2 was an emulsion based on Vaseline oil (15%) stabilized with an emulsifier Lanette SX or emulsifier No. 1 (cetearyl alcohol, HLB of 7.5) – 8%, dispersion medium – purified water. In the second line of samples varied content of propylene glycol 5%, 10%, 15%, 20%, 25%, and PEO in the same concentrations. Line 3 – gels based on carbomer

980 (1.5%) neutralized with triethanolamine to pH – 5.5-6.0. In the composition of gels varied concentrations of propylene glycol (30%, 60%), PEO-400 (30%, 60%) and their combination (15% and 30% each).^[2,18,21]

Thixotropic properties of disperse systems depend on the physicochemical (HLB, density, and viscosity) properties of each component. HLB of propylene glycol by Davis is 9.38 density – 1.0363 g/cm³ the dynamic viscosity at 20°C – 0.056 Pa*s; HLB of glycerol – 11.28, density – 1.261 g/cm³, dynamic viscosity at 20°C – 1.261 Pa*s; HLB of PEO-400 – 12.49, and density – 1.1-1.2 g/cm³.^[2,18,21]

The emulsions were prepared by phase inversion, emulsification of samples was performed using a homogenizer Polytron® System PT 3100 and Polytron® System PT 2500 E produced by “Kinematica AG,” Switzerland. All samples were subjected to rheological studies on rheoviscometer “RheolabQC” of company Anton Paar (Austria) with a set of coaxial cylinders C-CC27/SS. Measurements were performed at 25°C.

RESULTS

Results of the first line samples study are shown in Figure 1 and reflect the dependence of structural viscosity at 25°C on the shear rate. As can be seen, the introduction to the concentrated first kind emulsion of glycerin in an amount of 5b% leads to an increase in the yield stress of the system and, respectively, to 25-40b% increase in the structural viscosity in the range of shear rates of 10-80 s⁻¹. At this further increase in the concentration of glycerol to 10% gives opposite effect structural viscosity is reduced by 85-92% at the same shear rates, the system acquires a pseudoplastic type of flow.^[6-9]

A propylene glycol concentration in the test weakens the molecular cohesion of the emulsion particles, the system becomes more flexible, reduces the resistance to the effects of breaking force, the structural viscosity is reduced. By combining propylene glycol with glycerol in the emulsion to 5% of each observed the same phenomena as in the introduction of propylene, but with less severity.

A similar analysis was performed with samples of the second line, which had revealed certain patterns of behavior of disperse systems [Figures 2-4]. Thus, when separately introduced into the 15% emulsion stabilized with Lanette SX propylene glycol and PEO-400 in an amount of 5% there occur lowering of structural and mechanical properties of coagulation structure. Further increasing the concentration of those substances to 15% increases the thixotropic properties of the emulsions, but in excess of 15% concentration behavior of the system changes in the opposite direction, i.e., reduction of viscoelastic properties of the system is observed.

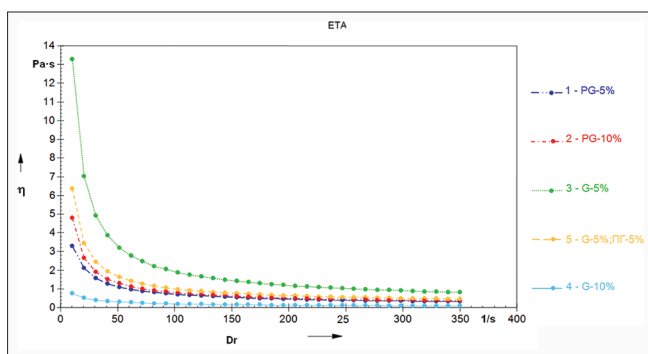


Figure 1: Plots of structural viscosity of samples of the first line against the shear rate

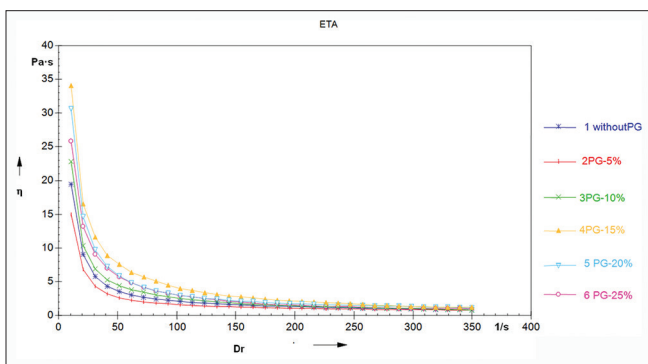


Figure 2: Plots of structural viscosity of samples of the second line against shear rate

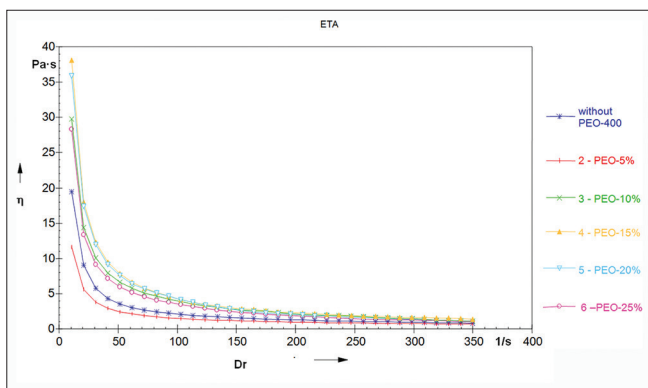


Figure 3: Plots of structural viscosity of samples of the second line against shear rate

DISCUSSION

Analyzing the data obtained in the study of the gels samples (third line) shown in Figure 5, it is seen that for all samples typical is plastic system flow type, since structural viscosity changes against shear rate. As can be seen, propylene glycol and PEO-400 has a different effect on the behavior of the gel system at deformation. Separate introduction of these substances in the gel in an amount of 30%, makes almost no change in its structural viscosity. But combining these substances in the composition of gel of 15% of each leads to an 8-10% increase in viscoplastic properties. The subsequent

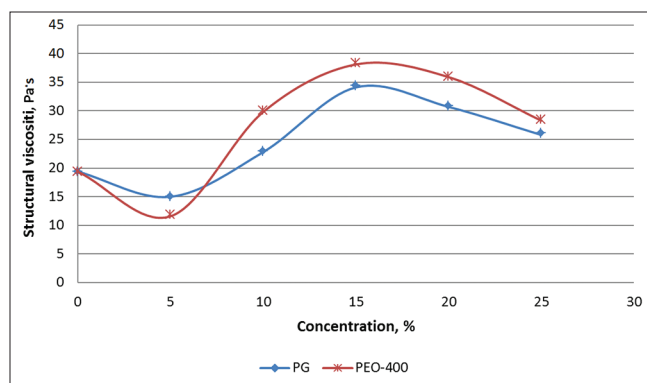


Figure 4: Dependence of second line samples structural viscosity on the concentration of propylene glycol and polyethylene oxide-400 at shear rate of 10.5 s^{-1} and temperature 25°C

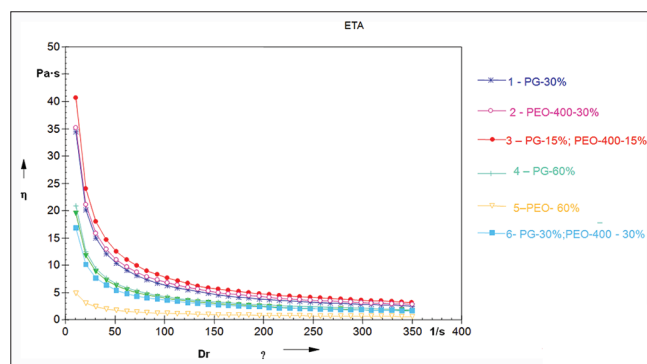


Figure 5: Plots of structural viscosity of third line samples against shear rate

increase in their concentration up to 60% in different degree changes their structural viscosity. Thus, the introduction of 60% propylene glycol in the gel composition leads to a decrease in structural viscosity from 34.9 to 19.4 Pa·s at shear rate of 10.4 Pa, and the introduction of 60% PEO-400 to 4.8 Pa·s at the same shear rate. With their joint jurisdiction to 30% of each the same pattern as in the 15% concentration can be traced, i.e., 16.7% structural viscosity increase at a shear rate of 10.4 Pa.

CONCLUSIONS

Thus, by the introduction of propylene glycol, PEO-400 and glycerol to soft medicinal forms allows varying their viscoelastic properties. It should be outlined that the ability to modify the thixotropic properties of both the emulsion and gel systems are more pronounced in the PEO-400.

REFERENCES

1. Kovalenko VN, Viktorova AP. Kompendium 2016-Lekarstvennyie Preparaty [Compendium 2016-Medicines]. Kyiv: Morion; 2016. p. 2224.

2. Dergavna Farmakopeya Ukraini. State Pharmacopoeia of Ukraine. 1st ed., Vol. 1. Kharkiv: State Enterprise, Ukrainian Scientific Center of Quality Pharmacopoeia of Medicines; 2015. p. 1128.
3. Gladukh IeV, Grubnik IM, Kukhtenko GP, Stepanenko SV. Rheological studies of water-ethanol solutions of gel-formers. *J Chem Pharm Res* 2015;7:729-6.
4. Grubnyk I, Kuhtenko A, Omelchenko P, Iudina I, Kuhtenko G, Chueshov V, *et al.* Pharmaceutical development of drugs on the department of industrial pharmacy of national university of pharmacy. In: Novikov V, editor. *Modern Trends in Chemistry, Biology, Pharmacy and Biotechnology*. Lviv: Lviv Polytechnic; 2015. p. 65-8.
5. Karaubayeva AA, Sakipova ZB, Ibragimova LN, Omarova RA, Gladukh EV, Kuhtenko GP. Farmatsevticheskayarazrobotkavulvosorbtseonogogelyanaosnovekaolina [Pharmaceutical development of vulvosorbition gel based on kaolin]. *J Almaty Technol Univ* 2017;114:74-5.
6. Goodwin JW, Hughes RW. *Rheology for Chemists: An Introduction*. Cambridge: Royal Society for Chemistry; 2000. p. 290.
7. Mezger TG. *Rheology Handbook*. 2nd ed. Vincent: Hannover; 2006. p. 299.
8. Shramm H. *Osnovyiprakticheskoyreologiiireometrii* [Foundation of Practicalrheologyandrheometry]. Moscow: Koloss; 2003. p. 312.
9. Malkina Y, Isaev AI. *Reologiya: Kontseptsii, Metodyi, Prilozheniya* [Rheology: Conceptions, Methods, Applications]. St. Petersburg: Profession; 2007. p. 560.
10. Kukhtenko GP, Kukhtenko AS, Kapsalyamova EN, Ayupova RB, Sakipova ZB. Reologicheskieissledovaniyamyagkihlekarsvennyih form [Rheological studies of soft drugs]. *Medicine* 2014;1:6-4.
11. Kukhtenko HP, Liapunova OO, Lysokobylka OA. Vplyvliinoifazytaskladuemulhatorivnareolohichnivlastyovostiviazko-plastychnykhemulsiipershohorodu [The influence of oil phase and composition of emulsifiers on rheological properties of visco-elastic emulsions of the 1st kind]. *J. Pharm* 2012;5:48-6.
12. Kukhtenko HP, Liapunova OO, Lysokobylka OA. Rozrobkatekhnolohiivyrobnystvakremu Sterokort [Development of technology for production of cream "Sterokort"]. *Probl Ecol Med Genet Clin Immunol* 2012;112:302-7.
13. Kukhtenko HP, Liapunova OO, Lysokobylka OA. Vyvchenniiastrukturno-mekhanichnykhvlastyvostei kremunaosnoviemulsii 1 rodu [The study of structural and mechanical properties of the cream emulsion based on one kind]. *Curr Issues Pharm Med* 2012;3:83-5.
14. Savchenko LP, Vraikin VO, Kukhtenko HP, Heorhiants VA. Vyvchenniastupeniazminyareolohichnykhparametrivekstemporalnoimazizhidrokortyzonubutyratom u protsesizberihannia [Study of the extemporal ointment with hydrocortisone butyrate rheological parameters changes degree during the process of storage]. *Pharm Rev* 2014;139:6-5.
15. Savchenko LP, Vraikin VO, Kukhtenko HP, Heorhiants VA. Doslidzhenniareolohichnykhvlastyvostei kombinovanoelekstem poralnoimazi z hidrokortyzonubutyratom [Investigation of the rheological properties of the combined extemporal ointment with hydrocortisone butyrate]. *Farmatsevtichnyizhurnal* 2014;1:44-5.
16. Korotkov VA, Kukhtenko HP, Kukhtenko AS, Gladukh IeV. Strukturno-mekhanicheskiesvoystvasuppozitoriev s ekstraktom maklyurioranzhevoy [Structural-mechanical properties of suppositories with extract of *Maclurapomifera*]. *Vestnik KAZNMU* 2014;2:311-4.
17. Kukhtenko HP. Issledovaniereologicheskiesvoystvemulsionnyih sistemvzavisimostiotsostavaemulgiroyuscheysmesiitehnologiiizgotovleniya [Investigation of rheological properties of emulsion systems depending on the composition of the emulsifying mixture and manufacturing technology]. *J Recipe* 2015;103:85-5.
18. Pertsev IM, Dmytrievskyi ID, Rybachuk VD, Khomenko VM, Gudzenko OP, Kotenko OM, *et al.* Dopomizhnirechovyny v tekhnolohiilikiv: Vplyvnatekhnolohichni, spozhyvchi, ekonomichni kharakterystykitерапевтичнихнаук. [Excipients in drugs technology: Influence on technological, consumer, economic characteristics and therapeutic activity]. Kharkiv: Kharkiv Gold Pages; 2010. p. 600.
19. Chueshov VI, Gladukh IeV, Sayko IV, Liapunova OO, Sichkar AA, Krutskiyh TV, *et al.* *Tekhnologiyalekarstvopromyshlennogoproizvodstva* [Technology of drugs for industrial production]. 2nd ed. Vinnytsia: Newbook; 2014. p. 664.
20. Bashura AG, Tykhonov AI, Rossihin VV, Baranova II., Petrovska LS, Martyniuk TV, *et al.* *Tekhnologiyakosmeticheskikh sredstv*. [Technology of Cosmetics]. Kharkiv: NFaU Originl; 2016. p. 575.
21. Derzhavna Farmakopeya Ukraini. [State Pharmacopoeia of Ukraine]. *Derzha vnepid priemstvoUkrayinskiynaukoviyfarmakopeyniytsentryako stilikarskihasobiv*. Vol. 2. Ch 2. Kharkiv: DerzhavneFarmakopeyapidpriemstvoUkrayinskiynaukoviyfarmakopeyniytsentryakostilikarskihasobiv; 2014. p. 724.

Source of Support: Nil. **Conflict of Interest:** None declared.