

Original Research Article

Influence of Liquid Paraffin, White Soft Paraffin and Initial Hydration on Viscosity of Corticosteroid Cream

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Abstract

Purpose: To ascertain the influence of paraffin, white soft paraffin and pre-hydrated white soft paraffin on the viscosity of a cream formulated with a corticosteroid.

Methods: The formulations were prepared via homogenization with variable velocity in the range 3300 - 4000 rpm. Individual series of preparations contained the same proportion of macrogol cetostearyl alcohol, cetyl alcohol, stearyl alcohol, sorbitan stearate, propylene glycol, methyl parahydroxybenzoate, propyl parahydroxybenzoate and water. The semi-solid preparations were assessed by viscometric and microscopic methods.

Results: The viscosity of the samples measured ranged from 13050 to 15660 mPas. The particles in dispersed phase sized from 15 to 90 μm . Within the multiple emulsion, the continuous phase included fine particles with diameter < 5 μm . Change of the liquid paraffin used from Ondina 934 to Vara 600P significantly decreased the viscosity of the formulation. Several phases within the formulations were distinguished microscopically. Increased viscosity was observed in formulations with increasing proportion of white soft paraffin.

Conclusion: Both the ratio of liquid paraffin to white soft paraffin, as well as the initial hydration of white soft paraffin influenced the viscosity of the cream as well as the diameter of particles in the dispersed phase.

Keywords: Cream, Ointment, Paraffin, Emulsion, Dispersion, Viscosity, Particle diameter

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INTRODUCTION

Semi-solid pharmaceutical formulations tend to have a high content of inactive additives, which in general should not influence the activity of the active pharmaceutical ingredient (API). The composition of the formulation influences the rheological properties, namely, plastic viscosity (i.e., the ability to spread), and yield point of the finished product [1]. The viscosity of the product is influenced by the temperature, and depends on the shear rate and shear stress [2]. Studies

performed by Sudduth revealed a relationship between the size of the dispersed particles and the viscosity of the entire system [3]. Huang and co-workers examined hydrocolloid gums: carrageenan and arabic gum, and observed changes in surface tension, in viscosity, in the size dispersed particles and in the stability of the system [4].

Water based nano-fluid with aluminium oxide and aqueous nano-fluid containing copper oxide was subjected to viscosity measurements; the

viscosity was correlated with the size of the oxides particles [5]. Tang *et al* studied magnetorheological fluids (MRF), characterized by viscosity changes due to the varied magnetic field. The viscosity of mono-disperse systems increased with decreasing particle size according to the increase of the forces interaction. In the case of polydisperse systems interactions were much more complex [6]. The same conclusions presented Rudyak *et al* examining nano-fluids based on ethylene glycol with silicon oxide [7]. Maranzano and Wagner evaluated the influence of the size of the dispersed particles and the concentration of the particles on the shear stress value in viscosity measurements [8].

Boyl *et al* investigated the effect of particle size in coal-water suspensions the rheological properties [9]. Yongcheng and Park assumed that the average size of the particles in micro-emulsions usually depends on the type of emulsifier and is predictable [10]. The diameter of particles in emulsion of lipid in the film affects the water permeability of the film and its mechanical properties [11]. Stokes equation includes sedimentation rate (U), diameter of the dispersed phase (d), the density of the dispersing phase (ρ_P), the density of the dispersed phase (ρ_L), gravity (g), dynamic viscosity of the dispersion medium (μ) and represents the relationships between the diameter of dispersed particles and the viscosity of the system using Eq 1 [12].

$$U = [d^2_p(\rho_P - \rho_L)g]/18\mu \dots\dots\dots (1)$$

Numerous researchers applied the equation in the studies of semi-solid drug forms. Watanabe *et al* studied the functionally graded materials (FGM), and evaluated the results of the experiment in the terms of Stokes equations [13].

The aim of the study was evaluation of the influence of paraffin, petrolatum and pre-hydrated petrolatum on the viscosity of the cream with the active corticosteroid. The semi-solid formulations were assessed by viscometric and microscopic methods.

EXPERIMENTAL

Materials

Macrogol cetostearyl ether (Croda, UK), cetyl alcohol (Croda, UK), stearyl alcohol (Croda, UK), liquid paraffin (Ondina 934 from Shell, Netherlands or Vara 600P from Sasol, Germany), white soft paraffin (Petrolatum, Merkur 500, Sasol, Germany), sorbitan stearate (Croda, UK), propylene glycol (Sigma-Aldrich, Poland), methyl parahydroxybenzoate (Sigma-Aldrich, Poland), and propyl parahydroxybenzoate (Sigma-Aldrich, Poland) used in the experiments fulfilled the pharmacopoeial standards. Water purified via deionization was used throughout the experimental rules, with conductivity not exceeding 5 mS cm⁻¹ (osmotic column ODOS-20 Preksim, Poland, with Excelon PES filter, Germany).

Preparation of multiphase formulations

The evaluated experimental formulations were prepared in following steps. Mixture A included active ingredient, i.e. corticosteroid dispersed in a mixture of propylene glycol, liquid paraffin, methyl parahydroxybenzoate, and propyl parahydroxybenzoate heated to 75 °C.

Mixture A was homogenized with melted mixture B of cetyl alcohol, stearyl alcohol, macrogol cetostearyl ether, sorbitan stearate, and white soft paraffin in 80 °C. The lipophilic phase A+B was transferred to a beaker with heated to 80 °C water and homogenized with a variable velocity

Table 1: Composition of formulations

Material	A (% w/w)	B (% w/w)	C (% w/w)	D (% w/w)	E (% w/w)	F (% w/w)
API	1.00	1.00	1.00	1.00	1.00	1.00
Macrogol cetostearyl ether	5.00	5.00	5.00	5.00	5.00	5.00
Cetyl alcohol	4.20	4.20	4.20	4.20	4.20	4.20
Stearyl alcohol	4.20	4.20	4.20	4.20	4.20	4.20
Liquid paraffin	6.00 ¹⁾	7.00 ²⁾	6.00 ²⁾	6.00 ¹⁾	6.00 ¹⁾	8.00 ¹⁾
White soft paraffin ³⁾	9.00	9.00	10.00	10.00	10.00	8.00
Sorbitan stearate	3.00	3.00	3.00	3.00	3.00	3.00
Propylene glycol	3.00	3.00	3.00	3.00	3.00	3.00
Methyl parahydroxybenzoate	0.075	0.075	0.075	0.075	0.075	0.075
Propyl parahydroxybenzoate	0.025	0.025	0.025	0.025	0.025	0.025
Purified water	64.50	63.50	63.50	63.50	63.50	63.50

¹⁾Ondina 934, ²⁾Vara 600P, ³⁾Merkur 500

in the range 3300 - 4000 rpm. Individual series of preparations contained the same percentage of macrogol cetostearyl alcohol, cetyl alcohol, stearyl alcohol, sorbitan stearate, propylene glycol, metyl parahydroxybenzoate, propyl parahydroxybenzoate and water. The composition of evaluated preparations is presented in Table 1.

Viscosity measurement

The viscosity measurements were performed using rotational rheometer Brookfield Viscometer RVDV-III Ultra with Brookfield's cone-plate type. The thin, uniform layer of the tested formulation was placed between the cone and the basal plate in standard temperature conditions 32 °C. The rotation was changed in following sequence: 0.5 rpm for 2 min, 2 rpm for 2 min, 5 rpm for 5 min. Results were collected every 10 seconds for 1 min at the maximal shear rate.

Microscopic characterization

Microphotographs were taken using a microscope (Morphologi type G3S Malvern, Great Britain) and 50-fold magnification was applied in all the measurements.

Statistical analysis

Statistical analysis was performed using ANOVA test. Statistica (Statsoft, Poland) application was used for the calculation of the parameters – standard deviation and variation coefficients. The error bars on the graphs represent standard deviation.

RESULTS

The viscosity of prepared formulations ranged from 13.050 to 15.660 mPas, as presented in Fig 1A.

Using the same homogenization rate (4500 rpm) in the preparation process, the lowest viscosity was observed for formulation A, which contained highest percentage of water, comparing to the formulations B - F. The increased contribution of solids with high melting point in the formulation induced high viscosity of assessed semi-solid emulsion system.

The change of liquid paraffin from Ondina 934 to Vara 600P significantly decreased viscosity of the formulation. We distinguished microscopically several phases within the formulation. There was a main phase consisting of fine particles below 5 µm in size, and many particles with higher

diameter. Due to the microphotographs of the formulations A-D in Figure 2A - 2D, we proposed on the attached diagram the hypothetical structure of the assessed formulations Fig. 2E. Moreover, in the formulations there appeared larger particles having a diameter between ca. 20 mcm and 200 mcm. It was observed that the composition formulations A - D affects the particle diameter observed in the microscope.

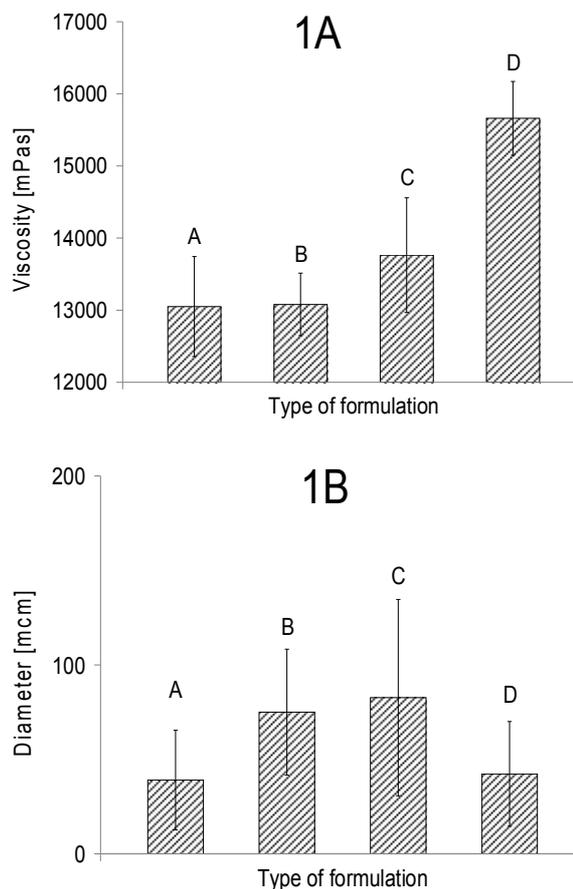


Figure 1: The influence of the homogenization rate on the viscosity of the formulations (1A - significant difference was observed between samples C and D, $p > 0.05$), and on the mean diameter of particles in selected formulations (1B)

The effect of the composition on the viscosity of the formulation was additionally evaluated in two semi-solid formulations E and F (Table 1) according to the diagram on Fig. 3A, where the influence of white soft paraffin and liquid paraffin on the viscosity was observed.

The increased viscosity was observed for formulations with higher proportions of white soft paraffin. The effect of homogenization speed on the viscosity of the formulations was also evaluated. As shown in Fig 3B, among formulations with approximately similar composi-

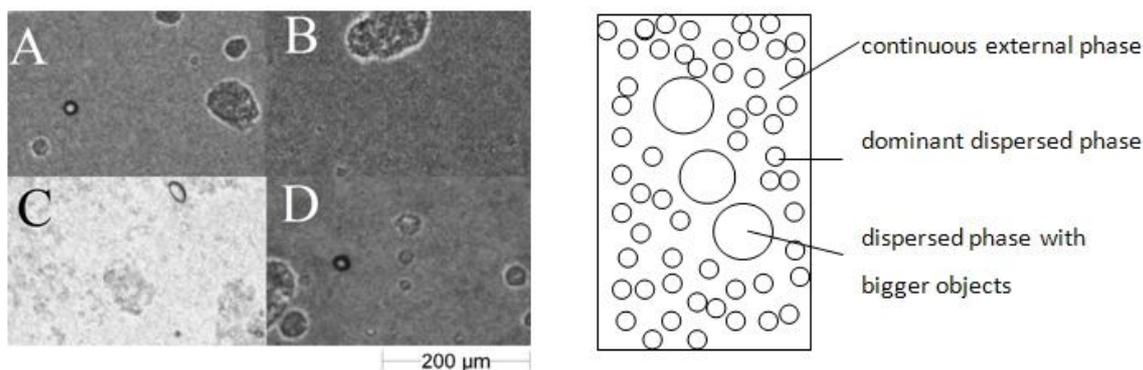


Figure 2: Microphotographs of formulations A – D (left), and the scheme of the phases distribution in the formulation (E – right)

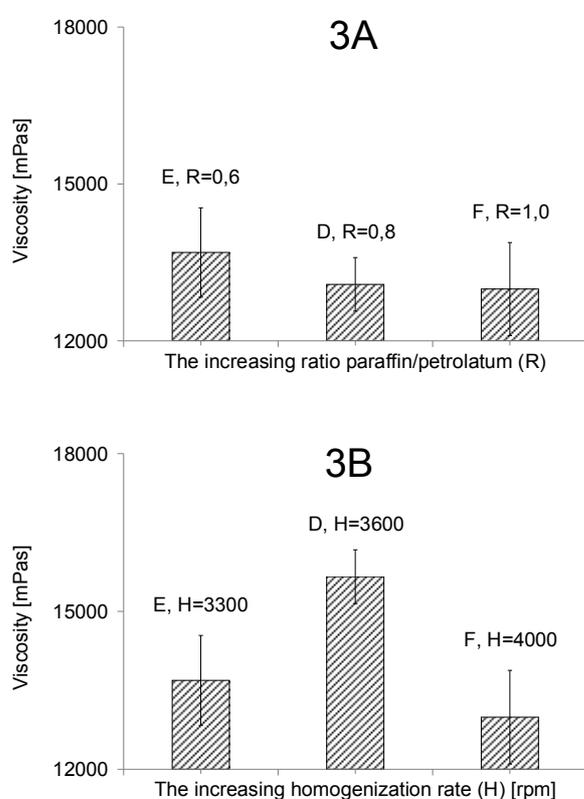


Figure 3: The influence of the contribution of liquid paraffin on the viscosity of the assessed formulations (3A), and the influence of the homogenization rate on the viscosity of selected formulations (3B –the viscosity of formulation D was significantly higher, comparing to E and F, $p > 0,05$)

tion (D, E and F), the highest viscosity was found for formulation D. In the case of formulations with different ratios of white soft paraffin to liquid paraffin we observed that at the homogenization speed of 3600 rpm, viscosity was highest. Both speed reduction and homogenization resulted in a large increase in the loss of the viscosity of formulations.

As shown in Fig 4, intermediate homogenizing rate resulted in the highest values of particles diameters – formulation D.

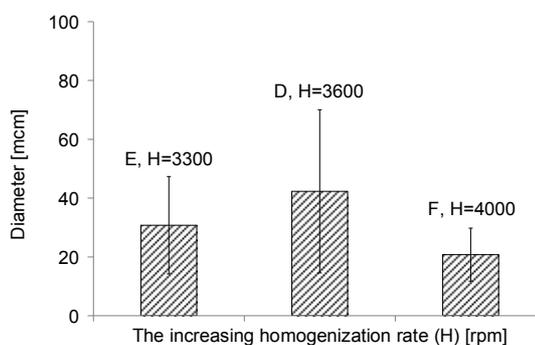


Figure 4: The influence of the homogenization rate on the particle size

DISCUSSION

Numerous authors associated viscosity of the formulations with the diameter of the particles dispersed in the emulsion, therefore, we performed assessment of the effect of the homogenization speed on the particle diameter dispersed in semisolid emulsion formulations. According to the observations, it was found that the homogenization rate of ca. 3600 rpm induces highest viscosity, and the highest mean particle diameter within the formulation. Addition of liquid paraffin of type Vara 600P instead of Ondina 934 resulted in a reduction of viscosity of the system. Dehmoune *et al* demonstrated that with decreasing length of the hydrocarbon chains in petrolatum derivatives, decreases the viscosity, which may affect the viscosity of the formulation [14]. Also Shiao *et al* in his experiments presented similar relationships [15]. In our experiments the increase in amount of white soft paraffin comparing to the liquid paraffin,

enhanced an average particle size of the dispersed phase of the emulsion in semi-solid formulations. The increase of the viscosity and of the size of particles obtained is affected by the preparation process of the formulation. In some formulations addition of the water to the hydrocarbon vehicle influences dramatically the viscosity of the sample, as it is in the case of hydrous and anhydrous lanolin [16]. The unsuspected increase or decrease of viscosity is ascribed to the interaction between the branched hydrocarbon chain and water molecules, classified as solubilization of hydrocarbons particles [17,18], including the formation of hydrogen bonds [19], and van der Waals interactions [20]. Preliminary hydration of white soft paraffin should favor the dispersion of small particles which results in increased viscosity, and is observed in microscopic visualisation.

CONCLUSION

The highest viscosity in the test formulations is obtainable using ratio 6:10 liquid paraffin to white soft paraffin. Increase or decrease in this ratio over a range of compositions decreases the viscosity of the formulations. This study demonstrates that the viscosity of the formulations is influenced by various types of liquid paraffin with the same pharmacopoeial monograph specification. The viscosity is influenced by pre-hydration of lipophilic gel – soft paraffin, and this procedure may affect the size of the dispersed phase.

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