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Original article

Experimental investigation of rheological properties of niosomal dispersions

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ABSTRACT In this work, the rheological properties of niosomal dispersions of various concentrations in the temperature range of 30 – 60 °C is investigated. The viscosity coefficient and the values of the activation energy were determined experimentally. It is found that the flow of niosomal dispersions exhibits the properties of Newtonian fluids in the studied range of temperatures and shear rates. Conditions were determined for obtaining stable homogeneous niosomal dispersions with an average vesicle size of 80 – 150 nm.

KEYWORDS nonionic surfactant vesicles, rheological properties, niosomal dispersion

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1. Introduction

The creation of new pharmaceuticals using nanotechnology seems to be an urgent task. The direction of scientific research in this area is determined by the needs for modern medicine in highly active and safe pharmaceutical preparations.

Vesicular systems have attracted great attention in drug delivery because of their amphiphilic nature, biodegradability, non-toxicity, an increase in the duration of exposure and potential for increasing drug bioavailability. Furthermore, their structure can be manipulated in terms of shape, size, and rheological properties, in order to enhance their performance [1–4].

Modified release dosage forms are a group of drugs characterized by an altered release mechanism and pattern. Such dosage forms really affect the pharmacokinetics of drugs, leading to changes in the parameters of efficacy and tolerability in accordance with clinical needs [5–7]. Drug delivery systems using colloidal particulate carrier such as niosomes, ethosomes or liposomes have distinct advantages over conventional dosage forms.

Niosomes are thought to be better candidate's drug delivery system due to the various factor like cost, stability and less toxic. In contemporary times, niosomes have been extensively studied for their potential to serve as carrier for delivery of drugs, hormone, antigen and other bioactive agents [8–14].

Niosomal vesicles can be used to deliver a wide range of drugs due to the ability to retain hydro- lipo- and amphiphilic substances [15–17]. Further advantages provided by vesicular carriers include protection of the active agents against enzymatic and chemical degradation, and possibility minimization of side effects.

Investigation of the rheological properties of niosomal dispersions is necessary in designing targeted drug delivery systems because it allows one to substantiate and optimize effective technologies for increasing their bioavailability, stability and biodistribution in the body [18–24].

As known, the relation of viscosity with the structure of colloidal systems was revealed long ago and was well described in a literature [25–28]. However, many of the proposed rheological equations for description of the dispersed systems indicate the absence of unified approach. There are some rheological equations that describe disperse systems of different physical and chemical nature, and, conversely, one disperse system can be described by fundamentally different rheological equations.

In general case, the rheological equation can be presented in the form:

$$\tau^m = \tau_0^m + \eta^n \upsilon^n, \tag{1}$$

where τ is the shear stress, τ_0 is the ultimate shear stress, η is the dynamic viscosity coefficient, m and n are exponents, υ is the shear rate. Such equations make it possible to achieve the most accurate calculations of the flow of the dispersed

systems. But they are not informative for fundamental research, since there are no parameters characterizing colloidal systems at the level of intermolecular interactions. Nowadays, the universal equation that allows one to study the viscosity of dispersed systems taking into account intermolecular interactions is the Eyring–Frenkel equation:

$$\eta = A \exp\left(E/RT\right), \tag{2}$$

where A is a constant which has units of viscosity, R is the universal gas constant, T is the temperature, E is the activation energy of a viscous flow, which characterizes intermolecular and interparticle interactions, as well as the microstructural ordering and the stability of the dispersed systems. It can be concluded that the rheological behavior of niosomal dispersions is determined not only by the temperature and the volume concentrations of the dispersed phase, but also by the stress and the shear rate at which the flow occurs.

This study is aimed to the main structural and mechanical (rheological) properties of niosomal dispersions based on PEG-12 Dimethicone and to identification of factors that affect the rheological stability during their storage.

2. Material and methods

Structural and mechanical properties were evaluated for the samples of niosomal dispersions by using of rotational viscometer Rheotest RN 4.1, ("RHEOTEST Messgerate Medingen Gmbh", Germany). To obtain the flow curves of the samples study, the cylindrical system was used, which made it possible to achieve greater accuracy in measuring the viscosity. The temperature system operates in the temperature range (-10 °C; $+180$ °C). It allows one to quickly set and control the temperature of the test sample with an accuracy higher than 0.1 °C.

The niosomes were prepared by an original technology [29]. Niosomes vesicles consisted of PEG-12 Dimethicone ("Dow Corning", USA), which possesses amphiphilic properties. Its allow the water-soluble part (polyethylene glycol) to orient itself into water, and the fat-soluble part (dimethicone) into lipids (Fig. 1).

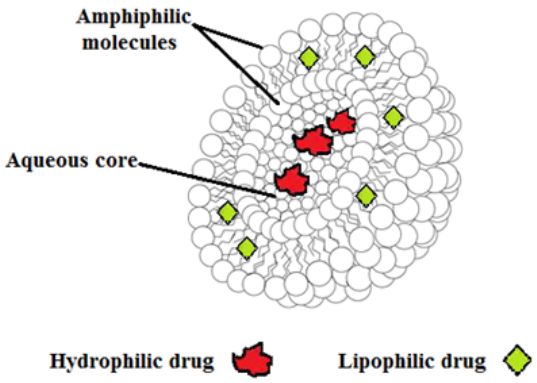


FIG. 1. Structure of a silicone-based niosome

In the hydrophilic part of dimethicone, there are functional groups of silicon oxide. The length of the Si–O bond is 1.6 Å, which is much longer than the C–C bond of 1.4 Å. The Si–O–Si bond angle is 130 degrees, in contrast to the 109 degrees of C–C–C bond. It leads to increase of the elasticity and the stability (Fig. 2). Due to this, the functional groups of the molecules are able to rotate with respect to each other. This gives one niosomes with greater elasticity than liposomes made up of phospholipids.

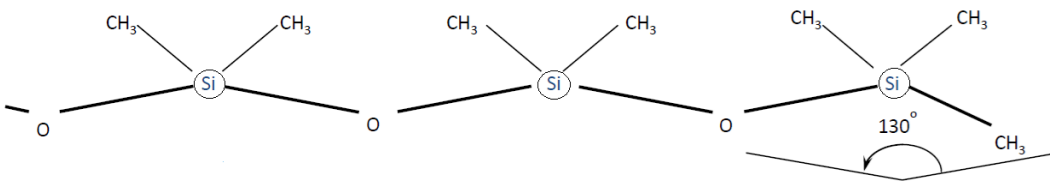


FIG. 2. Chemical structural PEG-12 Dimethicone

Using of PEG-12 Dimethicone led to the formation of vesicles without significant energy efforts. Stage of formation of vesicles occurred with intensive mechanical mixing using an automatic reclosure homogeniser. Dispersion was placed in a vessel for ultrasonic treatment. Ultrasonic sounding was carried out at frequency of 20 kHz, power of 200 W, the exposure time of 10 min. Monolamellar niosomes with 80 – 150 nm in size were formed. Then samples were diluted

with ultrapure water to the required concentrations. All the reagents and chemical used in present study were of the highest purity available and were used as received. For a degree estimation heterogeneous niosomal dispersions used the microphotos received by means of scanning electronic microscopy (Tescan Mira 3 Im). The particle size, determined by Image J, MS Excel statistical package program, was used to perform the analysis [30, 31].

3. Results and discussion

Niosomal dispersions with volumetric concentrations of 1, 5 or 10 % were selected for the research. It is clear that the rheological features of the behavior of niosomal dispersions with a change in temperature may indicate a change in indicators of both sedimentation and aggregative stability. Dependences of the viscosity on the temperature of niosomal vesicles of various concentrations were studied (Fig. 3). The viscosity at different temperatures was determined by changing the shear stress in the direction of increasing the shear rate.

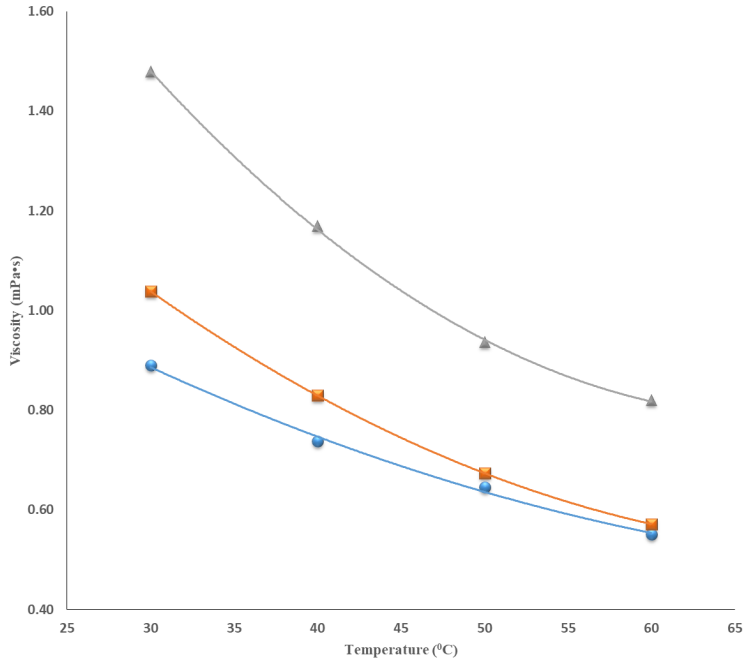


FIG. 3. Change in viscosity with rise in temperature for 1 % (circles), 5 % (squares) and 10 % (triangles) concentration

These curves illustrate a typical decrease in viscosity with increasing temperature for various concentrations, but with different degrees of intensity. This can be explained by a decrease in the forces of interaction between the niosomes vesicles with increasing temperature. As the volume concentration increases, a more pronounced dependence of the viscosity on temperature was observed. It can be assumed that further increase concentration of the dispersed phase will lead to the interaction of its particles, similar to the association of molecules and ions in true solutions up to the onset of coagulation.

To characterize the intensity of intervesicular interaction, it is necessary to estimate the value of the activation energy. In this connection, for the investigation of the behavior of niosomal dispersions of various concentrations, graphical dependences of the effective viscosity on the absolute temperature were plotted in coordinates $\ln \eta - 1/T$ (Fig. 4).

The energy of activation of the viscous flow was calculated based on the Arrhenius law. It can be presented of the form:

$$\Delta E = R \cdot \frac{d\left(\ln \eta\right)}{d\left(1/T\right)}, \tag{3}$$

where T is temperature, K; $R = 8.3144$, J/(mole·K) is the universal gas constant; E is the energy of activation of the viscous flow (J/mole) required for the transition of particle (flow unit) from one equilibrium position to another.

A typical electron micrograph of niosomes vesicles with an average size of 100 nm is shown in Fig. 5. The microphotograph shows that niosomes, for the most part, are spherical particles. Niosomal dispersion is heterogenous in volume [26, 27], but may be considered as a system consisting of separate particles each of which can move on free volume not occupied by other vesicles, but influencing it. In this case, we can consider the niosomal dispersion like a pseudohomogeneous system.

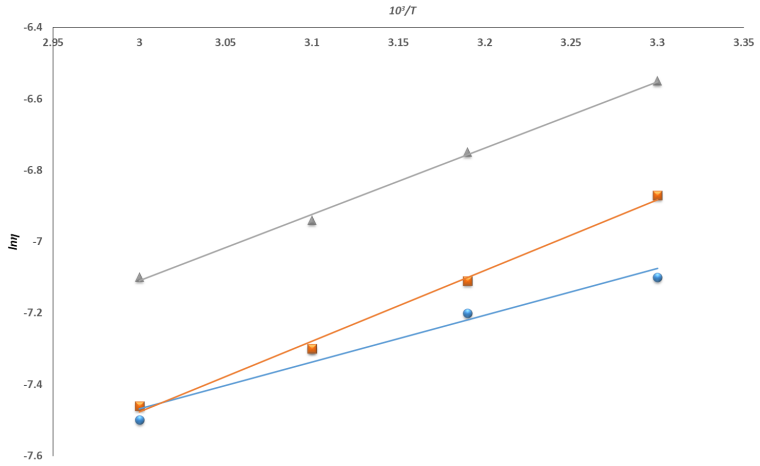


FIG. 4. Dependences of the logarithm of viscosity of niosomal dispersion on the inverse absolute temperature for different concentration: 1 % (circles), 5 % (squares) and 10 % (triangles)

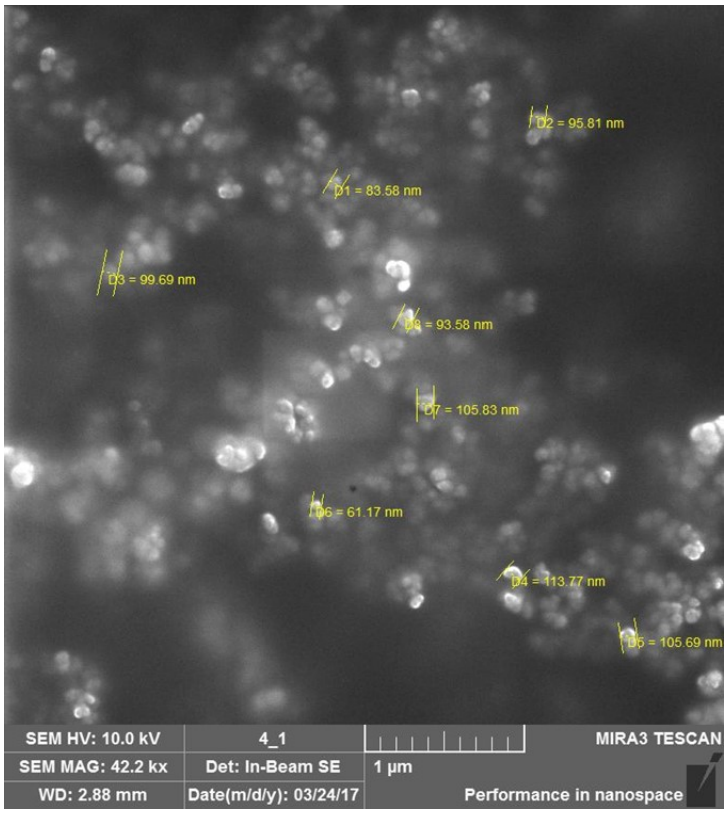


FIG. 5. Micrograph of niosomes obtained by Scanning Electron Microscopy (SEM)

The obtained dependencies are linear. In this case, the activation energy of the viscous flow of niosomal dispersions can be calculated from the slope of the plot of the logarithm of viscosity against the reciprocal temperature:

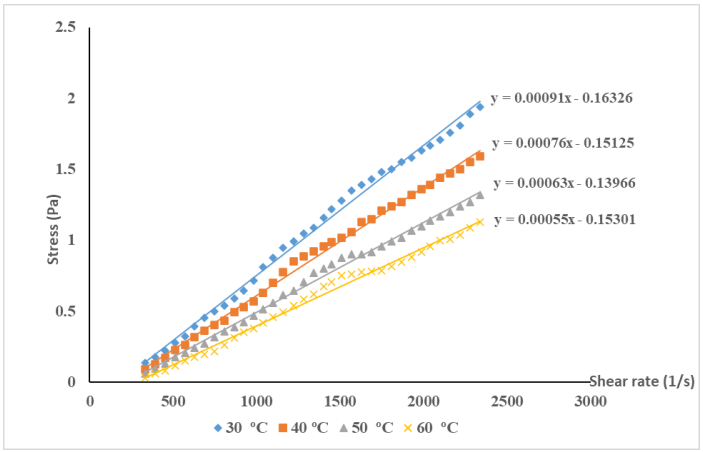
$$a = \tan\alpha = \frac{\left(\ln\eta^0\right)_1 - \left(\ln\eta^0\right)_2}{\left(\frac{10^3}{T}\right)_1 - \left(\frac{10^3}{T}\right)_2}. \tag{4}$$

Increase in the energy of activation of the viscous flow of niosomal dispersions in the concentration range of 1 – 10 % (Table 1) may indicate a decrease in the adsorption interaction and the transition of the system to a more structured (ordered) state. The obtained values of the energy of activation of the viscous flow can be used as a comparative characteristic of their stability during the long-term storage: the higher this indicator, the higher the stability.

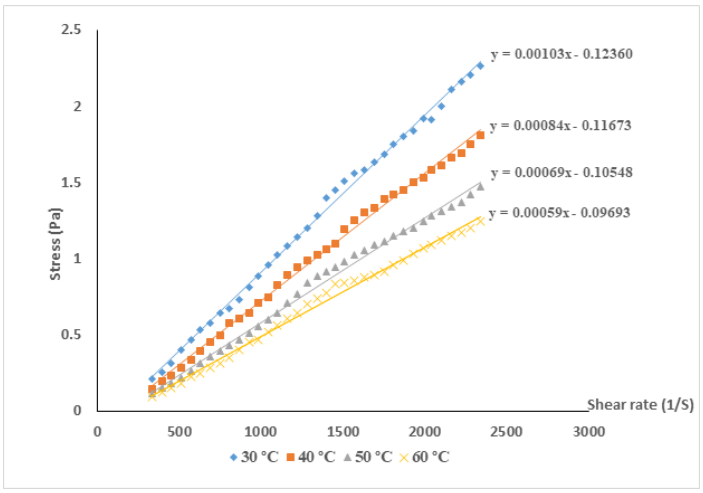
To investigate the rheological behavior of niosomal dispersions in terms of stress and shear rate, the flow curves were studied (Fig. 6(a, b, c)).

TABLE 1. The energy of activation of the viscous flow of the niosomal dispersions for various volumetric concentrations

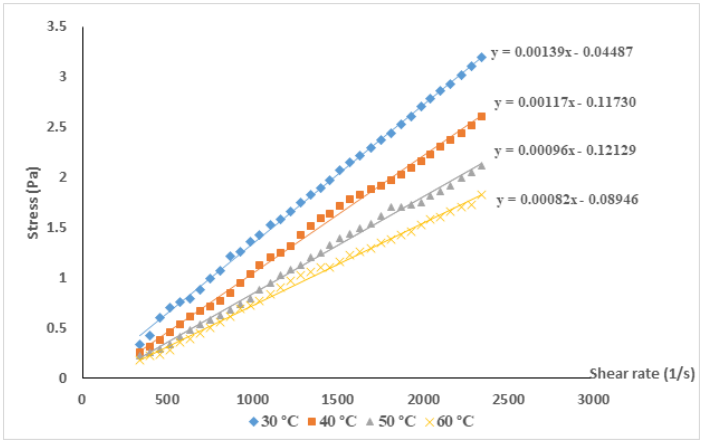
No.	φ, %	a	$E, kJ/(\text{mole} \cdot K)$
1	1.0	1.33	11.05
2	5.0	1.97	16.37
3	10.0	2.00	16.62



(a)



(b)



(c)

FIG. 6. Flow curves of the niosomal dispersions for different values of volumetric concentration: $\varphi = 1$ % (a), $\varphi = 5$ % (b), $\varphi = 10$ % (c)

As can be seen from the graphs, in the studied range of temperatures and shear rates, niosomal dispersions exhibit the properties of Newtonian fluids. It means that we can assume that in the studied colloidal system, there are no large aggregates of particles. The existing aggregates are smaller than the critical size in the given interval of velocities and they are not destroyed in the shear flow. Furthermore, with an increase in the shear rate, the viscosity does not change, which also indicates the constancy of the size of niosomal vesicles. However, the process of formation of some aggregates during interaction of individual vesicles and their subsequent rapid destruction cannot be excluding.

In order to study the stability of niosomal dispersions during their storage, experiments were repeated after 72 hours and the values of viscosity were determined at the same shear rates. Results obtained showed the absence of significant changes in the rheological parameters of the niosomal dispersions of the considered concentrations.

4. Conclusions

The use of niosomes based on PEG-12 Dimethicone as a targeted Drug Delivery System is expected to increase in foreseeable future. Silicon-based niosomes are promising drug carriers for the future with greater physical and chemical stability. Study of the rheological properties of niosomal dispersions based on PEG-12 Dimethicone and the ability to control the processes occurring in them are important for achieving optimal conditions for the development and storage of these nanocontainers.

The primary conclusions of this investigation are as follows:

(1) The niosomal dispersion of various concentrations shows a waiting decrease in viscosity with increasing temperature. This dependence was more significant if the volume concentration increases.
(2) The increases of the energy of activation of the viscous flow of niosomal dispersions with the growth of concentration indicates the pass into a more structured state.
(3) The flow of niosomal dispersions in the investigated temperature range obeys Newton's law.
(4) There are no significant changes in the rheological parameters of the niosomal dispersions with time in range up to 72 hours.

The results can give a better understanding of the mechanism of viscous flow of the niosomal dispersions.

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