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Influence of the concentration of oil phase on rheological properties of nonisotonic parenteral emulsions

Wpływ stężenia fazy olejowej na właściwości reologiczne
nieizotonizowanych emulsji parenteralnych

INTRODUCTION

Fat emulsions have been used for many years as energy sources of parenteral nutrition. It has been shown that these preparations, which are made from soybean oil using egg phosphatide as an emulsifier, are well tolerated and effectively utilized as energy sources in intravenous nutrition. Aminoacids, carbohydrates, lipids, electrolytes, microelements, and vitamins are administered by the intravenous route directly into the circulatory system. High energy content of ingredients enables the supply to the body sufficient amounts of energy in a small amount of preparation. Isotonic intravenous fat emulsions are generally well tolerated by the body and introduced nutrients are well metabolized [1, 4, 8, 9].

There has been a renewed interest in emulsions as a vehicle for delivering drugs to human body, especially into the bloodstream through parenteral administration. Extensive research has been published during the last decade and well reviewed by numerous authors [6, 7, 10, 12].

The reasons for using parenteral emulsions as a drug administration vehicle include solubilization of poorly water-soluble drugs, stabilization of hydrolytically susceptible compounds, prevention of drug uptake by infusion sets, reduction of irritation from or toxicity of intravenous administered drugs, potential for sustained release dosage forms and possible directed delivery of drugs to various organs [2].

In the evaluation of parenteral emulsions there are important rheological studies for determining the stability, viscosity and the character of fluidity of these preparations and for examining if thixotropy appears [13].

The aim of this study was determining the kind of flowing and changes in flow properties of nonisotonic emulsions depending on the volume of the external phase.

MATERIALS AND METHODS

EmulsIon preparatIon. Emulsions were prepared aseptically according to the prescriptions given in Table 1. Lecithin was dissolved in absolute ethyl alcohol and this solution was then added to the water. The aqueous phase was stirred and heated to 70°C until most of the alcohol had evaporated. This was estimated by measuring the final volume of the aqueous phase. Oil suspension of albumin at a temperature of 70°C was added in small portions with continuous stirring to the water phase. Further heating was applied, while mixing, until the temperature of 85°C and the total evaporation of alcohol was reached. The emulsion was then cooled rapidly, and after that the weight of the emulsion was supplemented with injection water and everything was mixed for 20 minutes. Then the emulsion was homogenized for 5 minutes with ultrasonics [3.11].

RheologIcal study. „Rheotest-2" Medinger viscometer was used. Measurements were performed after homogenization, at room temperature. Ten minutes after setting up the given rotation speed the values were read. Measurements were made at progressively higher rotation speeds (5 to 243 r/min) to obtain the ascendant curve. The procedure was repeated in reverse order with progressively slower rates (243 to 5 r/min) to obtain the descendant curve. The values on the scale as well as the rotation speed were transformed into the shear stresses (10^{-1} Pa) and shear rates (s^{-1}) by applying the corresponding correlation factors used by Jimenez et al. in their rheological studies of dermopharmaceutical excipients [5].

RESULTS

The values of shear stress at increasing and decreasing shear rates (Dr) have been showed in Fig.1a and Fig.1b.

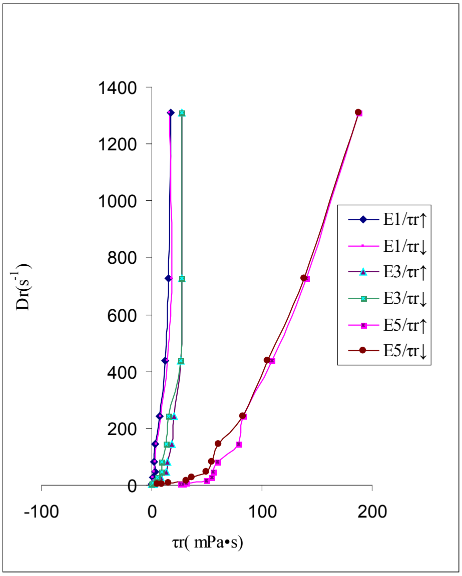

Fig. 1a. Rheograms of emulsions E1, E3, E5 at τr↑ and τr ↓

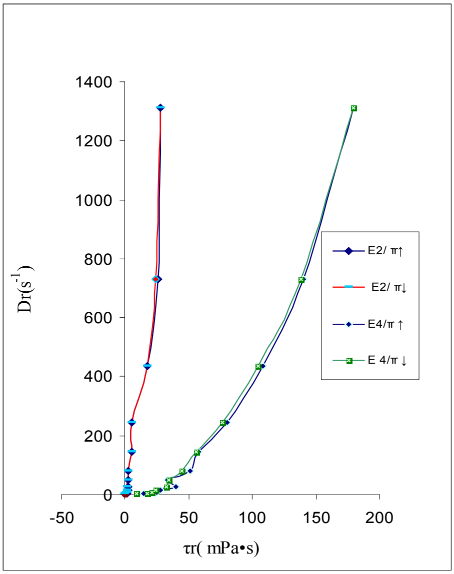

Fig. 1b. Rheograms of emulsions E2, E4 at τr↑ and τr ↓

Dynamic viscosity was calculated by the following equation:

$$\eta = \frac{Tr}{Dr} \bullet 100$$

where: η - the dynamic viscosity (mPa·s), Tr -shear stress(10^{-1}Pa), Dr-shear rates(s^{-1}) [3].

The values of fluidity ϕ were obtained with

$$\phi = \frac{1}{\eta} = \frac{Dr}{100\tau} \bullet (mPa^{-1} \cdot s^{-1})$$

The fluidity of emulsions has been shown in Fig.2a-2e as $\phi = f(Dr^N)$

DISCUSSION

Stability of emulsions is mainly dependent on viscosity. Diluted emulsion systems generally exhibit Newtonian flow, but in more concentrated preparations the character of flow can be changed. Therefore, the rheological studies were conducted to determine the character of flow and the changes of their properties depending on the volume of external phase.

The results show that the emulsions flow is disordered (Fig.1a, 1b).Therefore, interpretation of the results was done by analyzing the changes in fluidity to shear rate, as a function:

$$\phi = f(Dr^N)$$

where: ϕ – fluidity, Dr – shear rate, N – power exponent.

After calculating the fluidity ϕ of the systems, above relationship was solved by changing the value of the power exponent N. The result is a linear function of mileage for each emulsion (Fig.2a-2e). All the lines come out from the origin when $N<1$, which shows pseudoplastic flow. Different angles of slope of lines flow at increasing and decreasing shear rates indicate a change in the speed fluidization of the systems (K), but also to the possibility of thixotropy which can be described with liquefaction coefficient F. Speed fluidization values (K) at both increasing (Dr ↑) and decreasing (Dr↓) shear rates can be calculated by the following equation:

$$K = \frac{\varphi_1 - \varphi_2}{Dr_1^N - Dr_2^N}$$

where: ϕ_1, ϕ_2 – fluidity at shear rates Dr_1 and Dr_2, N – power exponent.

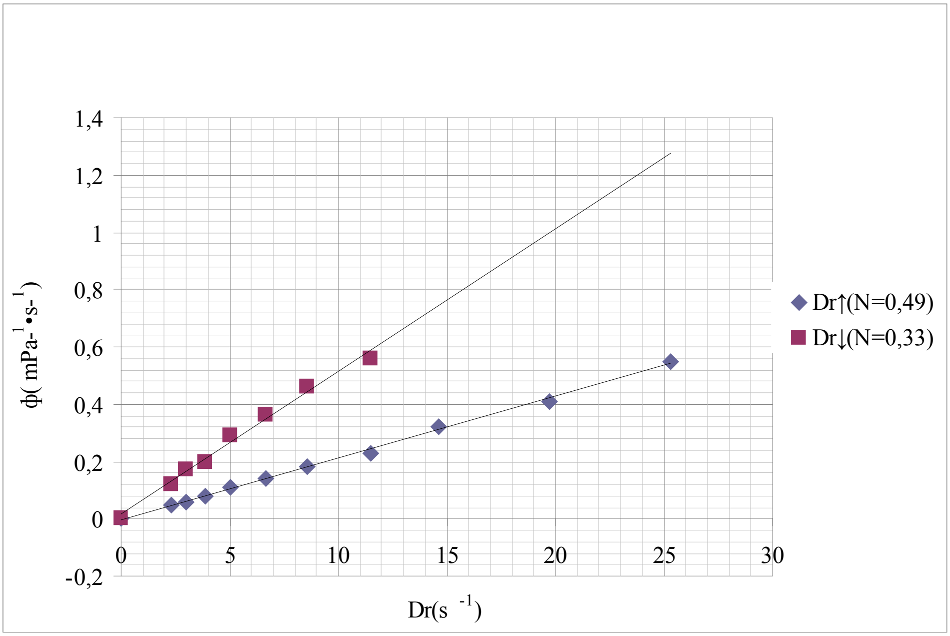

Fig. 2. Fluidity of the emulsions 1 at Dr ↑ and Dr↓

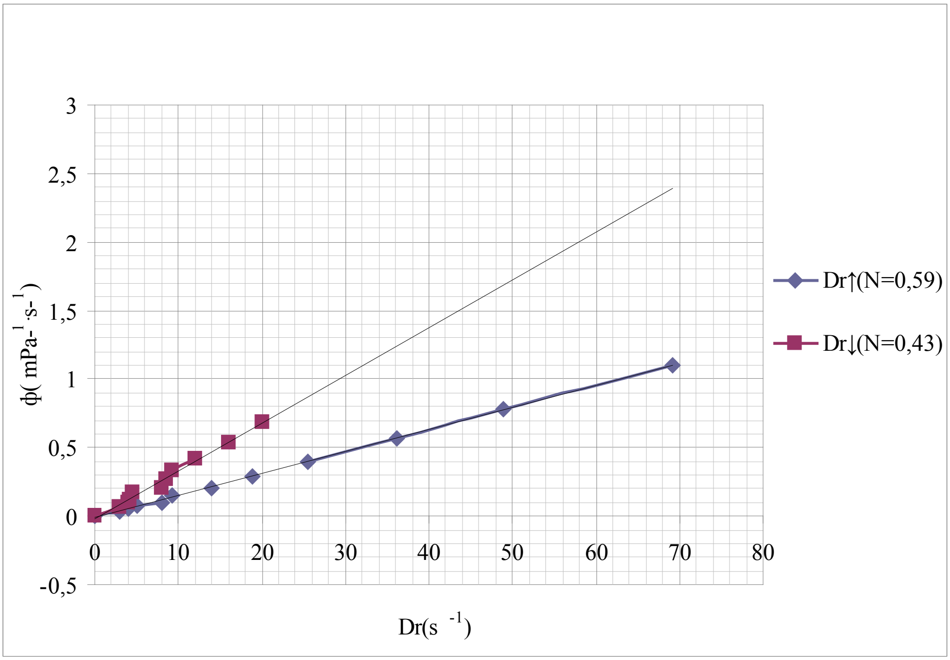

Fig. 3. Fluidity of the emulsions 2 at Dr ↑ and Dr↓

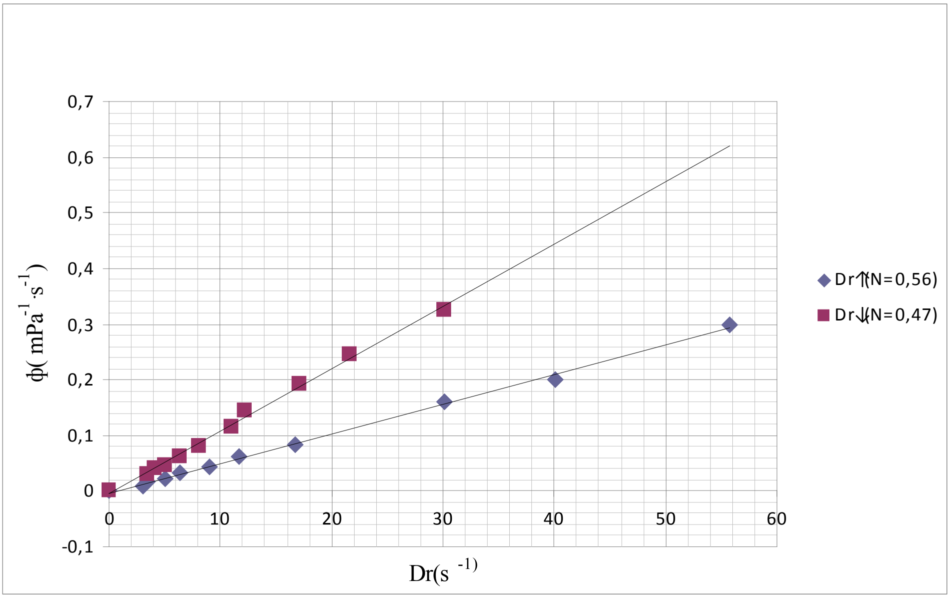

Fig. 4. Fluidity of the emulsions 3 at Dr ↑ and Dr↓

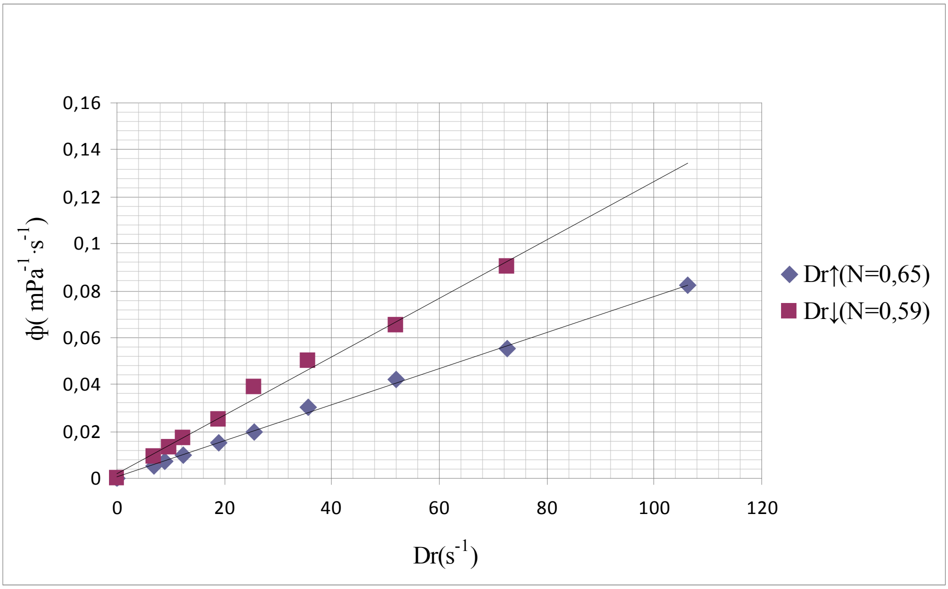

Fig. 5. Fluidity of the emulsions 4 at Dr ↑ and Dr↓

Different slope of the lines in figures indicates the possibility of the thixotropy of systems which can be assessed by comparing field hysteresis loop (P):

$$P=S\downarrow -S\uparrow$$

where: S↓ -field hysteresis loop at decreasing shear rates, S↑ -field hysteresis loop at increasing shear rates.

For these purposes you can also use the ratio:

$$F=K\downarrow /K\uparrow$$

where: K↓ -speed fluidization at Dr↓ ,K ↑-speed fluidization at Dr↑ ,which reflects the degree of destruction of gel structure.

Calculation results are shown in Table 2.

Table 2. List of parameters and constants of equations

Reci-pe	Parameters of equations and constants calculated at rates						F K□/K	P S□/ S
	increasing			decreasing				
	K	N	SD	K□	N□	SD		
E1	0.0514	0.49	0.591	0.0562	0.33	0.434	1.0934	-53
E2	0.0168	0.59	0.234	0.0313	0.43	0.428	1.8631	788
E3	$5.185\cdot10^{-3}$	0.56	0.312	0.0108	0.47	0.243	2.0829	1492
E4	$8.533\cdot10^{-4}$	0.65	0.137	$1.328\cdot10^{-3}$	0.59	0.149	1.5563	2600
E5	$5.531\cdot10^{-4}$	0.70	0.108	$8.101\cdot10^{-4}$	0.65	0.289	1.4647	4537

Fluidity of these emulsion systems can be described by the equation of general:

$$\phi=K(Dr^{N})$$

The correlation function and solutions of this equation show that the prepared emulsions are pseudoplastic flow ($N<1$).The size of thixotropy of these emulsions can be evaluated by comparing the values F and P. Coefficient liquefaction values F do not show a direct relationship with the water content in the external phase.

To assess the magnitude of the hysteresis loop P (successive increase from -53 to +4537), it is apparent that the thixotropy of these systems increases with the reduction of the external phase. Thus a direct relationship between the composition of the recipe and thixotropy of the systems can be assessed by considering the P values, but the F values indicate the existence of the phenomenon, however, they do not accurately describe it.

CONCLUSIONS

Direct shear stress (Tr) measurements at increasing and decreasing shear rates (Dr) carried out in the rotational viscometer indicate the disordered character of the flow of the tested emulsions.

Functional analysis of the fluidity of these systems can linearise the curves and describe the general equation:

$$\phi = K(Dr^N)$$

where: K-liquefaction coefficient, Dr-shear stress, N- power exponent.

Test emulsions are characterized by pseudoplastic flow because the power exponent $N<1$, and straight lines come out of the original function $\phi = f(Dr^N)$.

Different angles of slope of the lines flow at increasing and decreasing shear rates indicate the occurrence of gel structures and phenomenon of thixotropy in all emulsions.

The size of thixotropy can be evaluated using the coefficient liquefaction (F) or field hysteresis loop (P).

P values indicate that the size of thixotropy increases with decreasing volume of aqueous phase.

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SUMMARY

Five emulsions were made of soybean oil, human albumin and lecithin-in fixed amounts and water - in decreasing amounts. They were prepared aseptically. After homogenization the rheological measurements were carried out using a rotational viscometer „Rheotest 2”. Knowing the shear stress values (Tr) at the corresponding values of shear rates (Dr), the dynamic viscosity was calculated (η), and then the fluidity (ф) of analyzed preparations which are presented in figures as a function of $ф = f(Dr^N)$. Studies indicate that these systems are characterized by pseudoplastic flow andthey show thixotropy, which increases with decreasing water phase. Their fluidity can be described by the general equation $ф = K(Dr^N)$, where: K-speed fluidization, Dr-shear stress, N- power exponent.

Keywords: fluidity, parenteral emulsions, rheology, thixotropy

STRESZCZENIE

Sporządzono 5 emulsji oleju sojowego, albuminy ludzkiej i lecytyny-w stałych ilościach oraz wody-w zmniejszających się ilościach. Emulsje przygotowano w warunkach aseptycznych. Po homogenizacji przeprowadzono pomiary reologiczne za pomocą wiskozymetru rotacyjnego “Rheotest 2”. Znając wartości naprężenia ścinającego (Tr) przy odpowiednich wartościach szybkości ścinania (Dr) obliczono lepkość dynamiczną (η), a następnie płynność (ф) analizowanych preparatów, którą przedstawiono na wykresach jako funkcję $ф = f(Dr^N)$.

Badania wskazują, że omawiane układy charakteryzuje płynięcie pseudoplastyczne, wykazują tiksotropię, która narasta w miarę zmniejszania się fazy wodnej, a ich płynność można opisać ogólnym równaniem $ф = K(Dr^N)$: gdzie: K-szybkość upłynniania, Dr-szybkość ścinania, N-wykładnik potęgi.

Słowa kluczowe: płynność, emulsje parenteralne, reologia,tiksotropia