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RHEOLOGICAL INVESTIGATIONS OF PHARMACEUTICAL EMULSIONS PREPARED WITH MODIFIED LECITHIN

BADANIA REOLOGICZNE EMULSJI FARMACEUTYCZNYCH SPORZĄDZONYCH Z ZASTOSOWANIEM MODYFIKOWANEJ LECYTYNY

Abstract

In this paper the results of rheological investigations of pharmaceutical microemulsions prepared using modern lecithine derived emulsifiers has been prevented out. High stability of obtained systems and wide possibilities of controlling rheological parameters were found.

Keywords: *microemulsion*, *lecithin*, *rheology*

Streszczenie

W artykule przedstawiono wyniki badań reologicznych mikroemulsji farmaceutycznych, sporządzonych z wykorzystaniem nowoczesnych emulgatorów na bazie lecytyny. Stwierdzono wysoką stabilność tych układów oraz duże możliwości regulowania właściwości reologicznych.

Słowa kluczowe: *mikroemulsion*, *lecytyna*, *reologia*

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1. Introduction

Development of modern pharmaceuticals is a complex process, consuming both time and money. In case of topical medications progress made in recent years enabled the elaboration of completely new types of pharmaceutical vehicles which transfer medical substances through the skin or mucosa by means of polymers, gels, emulsions and microemulsions [1]. Those materials exhibit various rheological properties, therefore determination of their flow properties, which are different from those of traditional ointment bases, is necessary when designing new pharmaceutical, as well as cosmetic products. Growing requirements for quality of final products and competition between producers require extended rheologial investigation of raw materials to select optimal process parameters as well as the readymade product, to evaluate its stability and textural characteristics [2].

In this work several medical-type microemulsions, which use modified lecithin as surfactant and rheology modifier, were prepared with the aid of a pharmaceutical mixer – Unguator 2100® by GAKO, and their rheological properties were determined using appropriate measurement procedures. Obtained flow curves confirmed non-Newtonian nature of microemulsions investigated and were interpreted using basic rheological models.

2. Multiphase therapeutic systems

Many of the pharmaceutically active substances have very low solubility in water. In these cases so called vehicle is needed to increase the solubility of active compound [3]. The typical systems which facilitate are:

- solvents which can be mixed with water;
- surfactants forming aggregates;
- complexing agents;
- emulsions.

Unfortunately, these traditional systems have various drawbacks, especially concerning stability. Pharmaceutical products come in form of multiphase systems, usually with high degree of dispersion. The particles can be solid, as in case of suspensions, or liquid as in emulsions. Individual droplet size in typical stable pharmaceutical emulsion is usually below 10 μm. Due to strong interactions of particles, such products usually show features of non-Newtonian fluids. To weaken these phenomena and enhance emulsion stability, various types of surfactants have to be added [4]. When the amount of surfactant is small, the system can be treated as typical oil-water, with lowered interfacial tension. In such systems, there is no direct contact between water and oil phases, because of surfactant molecules being adsorbed at the interphase. When the amount of surfactant in the solution exceeds the critical micellisation concentration, association of surfactant molecules contained in the solvent begins. They combine into larger aggregates, micelles or reverse micelles, depending on the type of solvent. As the amount of surfactant rises further, the system can no longer be treated by this simplified method, and becomes oil-water-Surfactant rather than oil-water. Surplus of surfactants leads to generation of surfactant molecules structures, much more complicated than simple micelles [5]. The interfacial tension in such systems is close to zero, and instead

of typical disperse system consisting of continuous phase and dispersed phase droplets, dispersed structures with periodic order of complex objects are formed. When the amount of surfactant is sufficiently high, the interface becomes disordered and bicontinuous structures emerge. Those systems, known under name of microemulsions, are thermodynamically stable and can be formed with low addition of external energy. They are also transparent, what makes them attractive for pharmaceutical usage.

Winsor classification of such systems takes into account the impact of surfactant with water and oil phases and depending on it, divides microemulsions into four groups:

- Type I, in which the surfactant is soluble both in water and oil in microemulsion O/W. Water phase, which contains a large amount of surfactant coexists with an oil phase containing a small amount of surfactant.
- Type II, in which the surfactant is present mainly in the oil phase in microemulsion W/O. The oil phase coexists with an aqueous phase, in which the surfactant is very low.
- Type III, three-phase arrangement, in which intermediate phase containing large amounts of surfactant exists in parallel with the phases of water and oil.
- Type IV, where there isotropic (single phase) micellar solution occurs.

Presently many pharmaceutical and cosmetic systems come in form of microemulsion. The main difference between microemulsion and common emulsion lies not in size of droplets or degree of cloudiness, but in the fact that they form spontaneously when proper composition is attained, and their properties are independent of production method [6]. Microemulsions can be prepared by mixing the components together in no particular order so to allow the mixture to equilibrate for certain time. The biggest difficulty in their production is that since in case of pharmaceutical systems many components are of natural origin and come from a various sources, the concentrations of the final product have to be optimized for each batch.

Under the influence of increasing concentration of the electrolyte (the ionic surfactants), or increasing temperature (for nonionic surfactants), the phases are subject to change.

There are also other forms of the microemulsions, including [7]:

- combined micelles,
- onion structure with diverse internal structure,
- bubble structure.

The primary factors that influence the structure of microemulsions include the shape of surfactant molecules and such properties of the solvent as ionic strength and pH. Interfacial tension between the aqueous and oil phases in microemulsions attain the value of 10^{-2}–10^{-4} [mNm]. The stability of the microemulsion systems are affected by following physical parameters: density, viscosity, interfacial tension, pH, osmotic pressure, refractive index and particle size [5].

Advantages of microemulsions are very large surface area between the phase and the ability to dissolve components of different polarity. To obtain them, a great amount of surfactant is needed. To avoid usage of synthetic emulsifiers, in pharmaceutical, cosmetic and food products natural-based surfactants are used. One of them is lecithin. Lecithin is the common name for a series of related compounds called phosphatidylcholines combined with various other substances, like fatty acids and carbohydrates. Its name originated from the Greek “Lekithos”, referring to egg yolk, but it is also found in many animal and vegetable sources. Lecithins are prepared by extracting and purifying phospholipids from

naturally occurring products such as soybeans, eggs, sunflower and canola seeds. It is an edible and digestible surfactant and emulsifier. Lecithins also have characteristics that help to control the viscosity of liquids and semi-liquids and disperse and suspend powders into liquids. Compared with its synthetic alternatives, lecithin can be totally biodegraded and metabolised. Therefore, it is is regarded as a well tolerated and non-toxic compound, which is used as an emulsifying and stabilizing agent in the food, pharmaceutical, and cosmetic industries. Lecithins are amphiphilic (they have different affinities for oil and water), and their low production costs make them invaluable in a broad range of manufacturing processes. Commercial sources for lecithin may come from soybeans, egg yolk or brain tissue. Although extensive research in this field has been done, there is still disagreement about lecithin based emulsion structure and the influence of the emulsifier. Therefore, it is essential to understand the behaviour of lecithin in order to understand the behaviour of emulsions stabilised with it. The rheological measurements can give some insight in this matter. In the experimental part the pharmaceutic type microemulsions were prepared using three types of commercial lecithin's: deoiled phosphatidyl choline enriched lecithins Epikuron™ 170 and Epikuron™ 200 and hydrogenated phosphatidyl choline enriched lecithin Epikuron™ 200 SH.

3. Experimental

The following basic components were used:

The oil phase:

- oleic acid,
- IPM (isopropyl myristate),
- Epicuron 200 SH,
- Epicuron 200,
- Epicuron 170.

The aqueous phase:

- buffer – PBS (stable solution of 0.85% NaCl, pH = 7.4).

The surfactant:

- Span 80.

Co-surfactants:

- Ethanol,
- Isopropanol (water solutions).

The compositions of systems investigated are given in Table 1.

Microemulsions were prepared at room temperature (20 °C). The first step was preparation of the oil phase (Epicuron, oleic acid, IPM) with co-surfactant (isopropanol, ethanol). These components had been preliminarily mixed using a magnetic stirrer. In the next step aqueous phase (PBS) and surfactant (Span) were added, and mixing was continued for 30 minutes. Prepared premixes were finally processed with UNGUATOR mixer, using "emulsion" program. It is a factory programmed procedure lasting two minutes while the rotational frequency changes within 250–2500 [min^{-1}] range [8].

Table 1

Composision of systems investigated

Emulsion	Recipe	Ingredient	Amount [g], [ml]
A	1	Epicuron 200SH	5,0 g
		IPM	5,0 ml
		Isopropanol 25 %	5,0 ml
		PBS	5,0 ml
	2	Epicuron 200SH	5,0 g
		IPM	5,0 ml
		Isopropanol 30%	5,0 ml
		PBS	5,0 ml
	3	Epicuron 200SH	5,0 g
		IPM	5,0 ml
		Isopropanol 50%	5,0 ml
		PBS	5,0 ml
B	4	Oleic acid	38,5
		Span 80	7,7
		Ethanol 96%	38,5
		PBS	15,4
C	5	Epicuron 200	5,0 g
		IPM	5,0 ml
		Isopropanol 25 %	5,0 ml
		PBS	5,0 ml
	6	Epicuron 200	5,0 g
		IPM	5,0 ml
		Isopropanol 30%	5,0 ml
		PBS	5,0 ml
	7	Epicuron 200	5,0 g
		IPM	5,0 ml
		Isopropanol 50%	5,0 ml
		PBS	5,0 ml
D	8	Epicuron 170	5,0 g
		IPM	5,0 ml
		Isopropanol 25 %	5,0 ml
		PBS	5,0 ml
	9	Epicuron 170	5,0 g
		IPM	5,0 ml
		Isopropanol 30%	5,0 ml
		PBS	5,0 ml
	10	Epicuron 170	5,0 g
		IPM	5,0 ml
		Isopropanol 50%	5,0 ml
		PBS	5,0 ml

Obtained mixtures were translucent and did not show any heterogeneities under optical microscope, so it was assumed, that they were microemulsions. Additonally they did not show any signs of deterioration during two months.

Rheological investigations were conducted using a rotational rheometer HAAKE RS75. Measurement system uses a cone-plate (titanium cone with a diameter of 20 mm and an angle of 0.3 °). Measurements were taken at three temperatures: 6 °C – typical refrigerator storage temperature, 20 °C – temperature of microemulsions preparation and 32 °C – temperature of formulations application on human skin. The temperature was controlled by HAAKE K15/DC5 circulator. Tests were performed using two measurement modes: flow curve and thixotropy.

4. Results

The results of measurements are presented graphically. All tested microemulsions are non-Newtonian fluids. Figure 1 shows temperature dependence of D-type microemulsion obtained with isopropanol as co-surfactant at concentration of 50%. With increasing temperature noticeable decrease of yield stress can be observed.

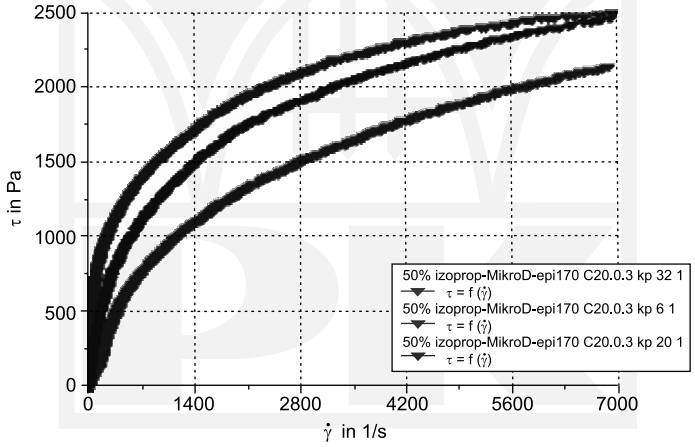

Fig. 1. Flow curves of microemulsion D with 50 % of isopropanol as a temperature function

Rys. 1. Krzywe płynięcia mikroemulsji D z 50% stężeniem izopropanolu w funkcji temperatury

Hysteresis loops shown in Figure 3 have different surfaces depending on the temperature of measurement. At 6 °C microemulsion structure is more compact, thus there is no change in the structure of the preparation.

For the analysis of measurements, two basic rheological models, Ostwald-de Waele and Herschel-Bulkley were used.

The Ostwald-de Waele model is a relatively simple mathematical expression. Although it does not allow for the interpretation of yield stress, it gives satisfactory results for the practical, non zero, range of shear rates (Fig. 3).

Herschel-Bulkley model gives similar results (Fig. 4), but the yield stress value estimate is not always reliable (negative values frequently appear).

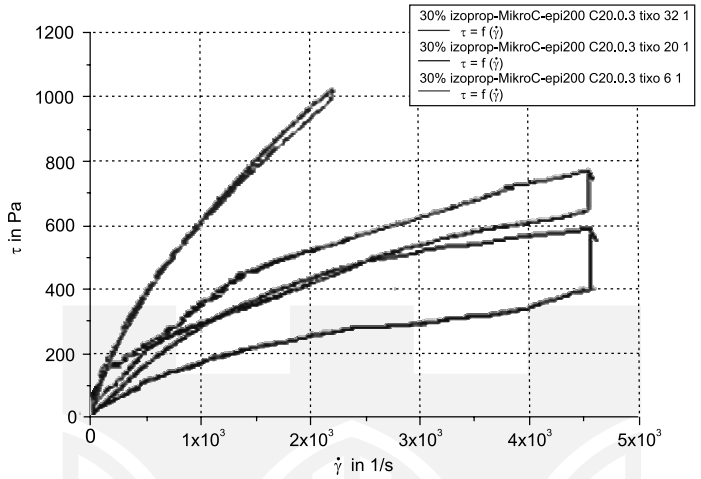

Fig. 2. Thixotropy of microemulsion C with 30% of isopropanol as a temperature function
Rys. 2. Tiksotropia mikroemulsji C z 30% stężeniem izopropanolu w funkcji temperatury

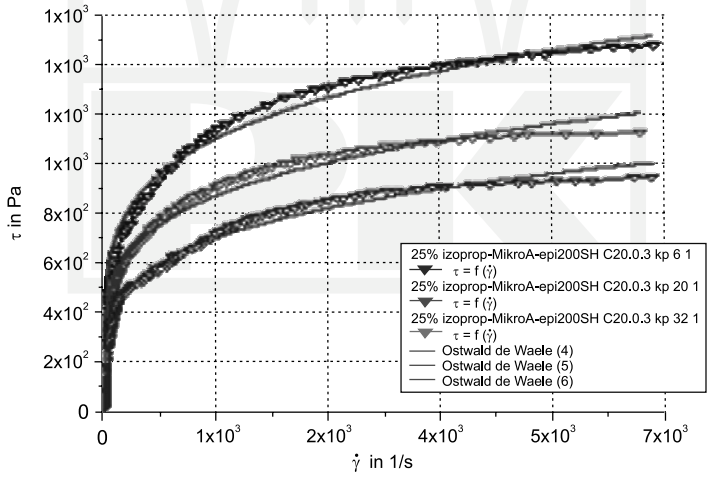

Fig. 3. Approximation of flow curves microemulsion A (25% of isopropanol) by using Ostwald de Waele rheological model
Rys. 3. Aproksymacja krzywych płynięcia mikroemulsji A (25% stężenie izopropanolu) modelem reologicznym Ostwald de Waele

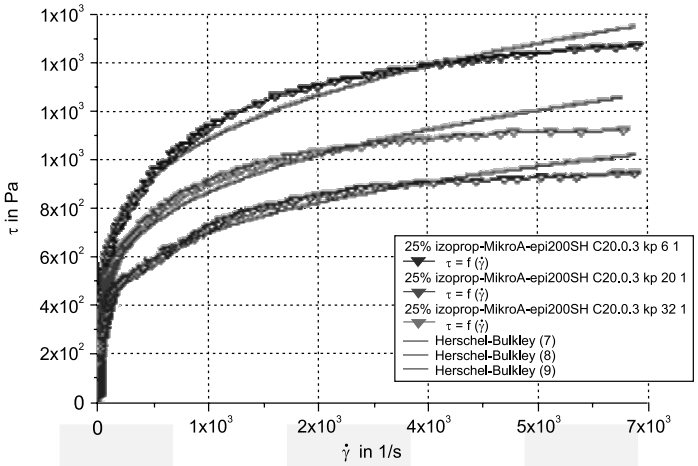

Fig. 4. Approximation of flow curves microemulsion A (25% of isopropanol) by using Herschel-Bulkley rheological model

Rys. 4. Aproksymacja krzywych płynięcia mikroemulsji A (25% stężenie izopropanolu) modelem reologicznym Herschel-Bulkley

5. Conclusions

Microemulsions are peculiar dispersions that in recent years gained great importance in many industries, especially in pharmacy, as a substrate and drug carriers, helping to increase the bioavailability of therapeutic agents and the effectiveness of drugs. Their rheological investigations are important to get complete physical tests.

Investigated microemulsions were found to be non-Newtonian fluids with yield point. With increase of temperature the measured values of yield stress and viscosity decreased, it can therefore be concluded that at 32 °C, the temperature of human skin, the pharmaceutical microemulsions exhibit improved properties, which makes their application easier.

For the analysis of experimental results of the flow curves, approximations using rheological model of Ostwald-de Waele and Herschel-Bulkley'a models were performed. Fitting with these models delivered good results- within the practical shear rate range, the regression line practically coincides with the experimental flow curves.

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