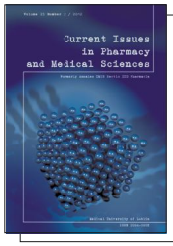

2012 © Curr. Issues Pharm. Med. Sci. Vol. 25, No. 2

Current Issues in Pharmacy and Medical Sciences

Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA
on-line: www.umlub.pl/pharmacy

Influence of the isotonic agents on physical properties of concentrated parenteral emulsions

DOROTA DWORNICKA*, MARIA ZUŃ,
KATARZYNA WOJCIECHOWSKA, SYLWIA WOŚKO, EWA POLESZAK

Chair and Department of Applied Pharmacy, Medical University of Lublin, Poland

ABSTRACT

Four concentrated emulsions were made of soybean oil, human albumin and lecithin, hiperisotonised with: glucose, natrium chloride, Ringer salt or glyceride. The studies of physical properties were carried out directly after homogenization. Additionally an analysis of droplet diameter size of the internal phase was conducted after half-a-year storage at 4 - 5 °C. The results show the smallest increase of droplet size in the presence of glucose. All o/w emulsions have pseudoplastic flow and their fluidity can be described by the general equation $\hat{o} = K D_r^N$, where: K – speed fluidization, D_r – shear stress, N – power exponent. The size of thixotropy, evaluated on the basis of the value of liquefaction coefficient (F), is biggest also in the case of emulsion with glucose. Thus it can be concluded that among four proposed isotonic agents, glucose appears to be the best.

Keywords: fluidity, parenteral emulsions, rheology, thixotropy

INTRODUCTION

Total parenteral nutrition provides the nutrients directly into the circulation in the form in which they are absorbed from the gastrointestinal tract, and thus: aminoacids, carbohydrates, lipids, electrolytes, microelements, vitamins and water [1]. Fat emulsions are considered the most common source of energy. A lot of evidence argues that for application of this dosage form, however, there are many real difficulties with determining the appropriate dosage scheme for the long-term treatment. The main advantage of fat emulsions is concentrating the high content of nutrients in a small volume, which enables the supply of sufficient amounts of energy to the body without necessity of application large volume of the preparation. An additional advantage is their isotonicity, so they can be administrated as the infusion into peripheral veins [2, 9].

The solutions we have today ensure satisfactory levels of nitrogen and vitamins, but do not allow the introduction into the bloodstream of large amounts of the calories, without the risk of overloading the body and the irritation or venous thrombosis.

The caloric level of the blood, plasma, albumins, protein hydrolysates, even with the addition of carbohydrates, is low. The classic, isotonic solutions of 50% glucose supply only 100 calories in 500ml. Thus, to ensure a sufficient supply of the calories, there is a need to use very big quantities of the isotonic solution causing the overload of the organism, or increasing the concentration of the solutions, but it is known, that hipertonic solutions are dangerous [3, 10].

That is why in this study, the attempts were made to prepare and examine the soy bean oil emulsion concentrates with the addition of human albumin and egg lecithin, isotonised with glucose, natrium chloride, Ringer salt or glyceride, in such quantities which ensure obtaining isotonic preparation after supplementing with sterile water to 100 parts.

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 added to the water containing the isotonic agent. The aqueous phase was stirred and heated to 70°C until most of the alcohol had evaporated. Oil suspension of albumin at a temperature of 70°C was added, in small portions with continuous stirring, to the water phase. The rest of the alcohol was evaporated at 85°C. After cooling, the weight of the emulsion was supplemented with injection water containing isotonic agent and everything was mixed for 20 minutes. Small amount of the emulsion was left to research, the rest was homogenized for 5 minutes with ultrasonics [1,4,5]. Homogenized emulsion was divided into 3 portions and placed in 3 sterile test tubes. One of them was put in the fridge at 4-5°C for half a year.

Corresponding author
* Chair and Department of Applied Pharmacy,
Medical University of Lublin, 1 Chodzki Str., 20-097 Lublin, Poland
e-mail address: dor.dwor@wp.pl

Table 1. Composition of the emulsions

Emulsions	Components (g)							
	Soybean oil	Human albumin	Lecithin	Glucose	Natrium chloride	Ringer´s salt	Glyceride	Water
A	10	2.5	1.2	4.315	–	–	–	5.125
B	10	2.5	1.2	–	0.777	–	–	8.663
C	10	2.5	1.2	–	–	0.777	–	8.663
D	10	2.5	1.2	–	–	–	2.158	7.283

Evaluation of emulsion properties

The droplet size was measured by the microscope with lens DIL IMM 100/1,301 (160,0,17) and ocular (PZO 10x) with a scale. The measurements were conducted before, after the homogenization and after half-a-year storage.

Emulsion type was examined by dilution with water and coloring method using 0.1% methylene blue as an indicator.

Density of the emulsion was determined after homogenization using aerometer and experimentally using pycnometer [11].

Rheological studies were performed using "Rheotest-2" Medinger viscometer, after homogenization, at room temperature. The values (α) on the scale were read 10 minutes after setting up the given rotation speed, at 50 Hz. Measurements were made at progressively higher rotation speeds (5-243 r/min) to obtain the ascendant curve and repeated in reverse with progressively slower rotation speeds (243-5 r/min) to obtain the descendant curve. The values (α) at given rotation speed were transformed into the shear stress (10^{-1} Pa) [8]. Shear stress (τr) was calculated:

$$\tau r = z \cdot \alpha$$

where:
τr – shear stress (10^{-1} Pa), z – cylinder constant (10^{-1} Pa/ skt), α – the values on the scale (skt).

RESULTS

1. Particle size analysis
   Mean droplet diameter size of the internal phase was calculated with:

$$d = \frac{\sum(fd_i)}{\sum f}$$

   where: d_i – mean droplet diameter size in the class (μm), f – the number of droplets in the class, Σf – the total number.
   The results of measurements are presented in Table 2, 3. All preparations are emulsions o/w.
2. The results of the density measurements are presented in Table 4.
3. Rheological measurements
   The values of shear stress (τr) at increasing and decreasing shear rates (D_r) are showed in Fig. 1.
   Dynamic viscosity was calculated by the following equation:

$$\eta = \frac{\tau r}{Dr} \cdot 100$$

   where: η – the dynamic viscosity (mPa s), τr – shear stress (10^{-1} Pa), D_r – shear rates (s^{-1}) [7].
   The values of fluidity (Φ) were obtained with:

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

Table 2. The droplet size of the internal phase before homogenization

d_i (μm)	Emulsion											
	A			B			C			D		
	f	Σf	d (μm)	f	Σf	d (μm)	f	Σf	d (μm)	f	Σf	d (μm)
6.05	–	–		9	9		65	65		27	27	
12.2	6	6		8	17		14	79		24	51	
18.3	14	20		7	24		7	86		12	63	
24.4	13	33		12	36		2	88		8	71	
30.5	28	61		16	52		4	92		14	85	
36.6	10	71		2	54		4	96		2	87	
42.7	10	81		8	62		1	97		1	88	
48.8	6	87		11	73		1	98		1	89	
54.9	3	90		4	77		–	98		–	89	
61.5	2	92		5	82		–	98		1	90	
68.2	1	93	35.97	2	84	39.01	1	99	12.9	4	94	23.86
74.3	–	93		5	89		–	99		2	96	
80.4	1	94		4	93		–	99		–	96	
86.5	–	94		3	96		–	99		–	96	
92.6	–	94		1	97		–	99		–	96	
98.7	1	95		2	99		–	99		1	97	
104.8	1	96		–	99		–	99		1	98	
110.9	1	97		–	99		–	99		1	99	
117.5	1	98		–	99		1	100		1	100	
124.2	–	98		–	99		–	–		–	–	
130.3	2	100		1	100		–	–		–	–	

Table 3. The droplet size of the internal phase after homogenization and six months storage time

Experiment	d_i (μm)	Emulsion											
		A			B			C			D		
		f	Σf	d (μm)	f	Σf	d (μm)	f	Σf	d (μm)	f	Σf	d (μm)
After homogenization	1.25	39	39		89	89		67	67		82	82	
	1.85	44	83		9	98		32	99		9	91	
	2.45	4	87		2	1		1	100		–	91	
	3.05	8	95	1.85	–	–	1.32	–	–	1.45	1	92	1.55
	3.65	–	95		–	–		–	–		3	95	
	4,25	5	100		–	–		–	–		3	98	
	4.8	–	–		–	–		–	–		2	100	
After 6 months	1.25	27	27		39	39		31	31		22	22	
	1.85	26	53		25	64		35	66		35	57	
	2.45	16	69		18	82		17	83		17	74	
	3.05	14	83	2.33	10	92	2.01	8	91	2.05	12	86	2.26
	3.65	8	91		5	97		6	97		8	94	
	4.25	6	97		3	100		2	99		4	98	
	4.8	3	100		–	–		1	100		2	100	

Table 4. The density of the emulsions

Emulsions	A	B	C	D
Density measured by areometr (g/cm3)	1.020	1.030	1.040	1.000
Density measured by pyknometr (g/cm3)	1.014	1.023	1.031	0.994

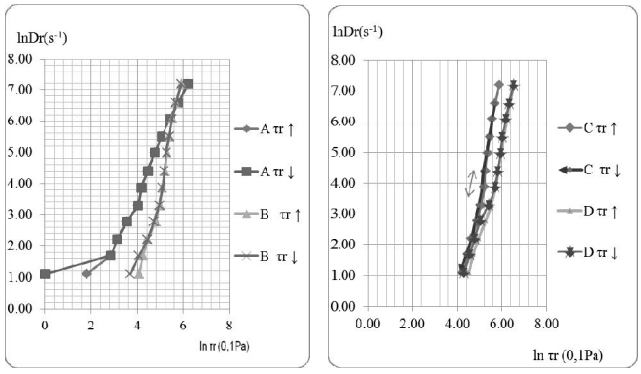

Fig. 1. Rheograms of emulsions A,B,C,D at $\tau r\uparrow$ and $\tau r\downarrow$

The fluidity of analyzed emulsions has been shown in Fig. 2-5, as:

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

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

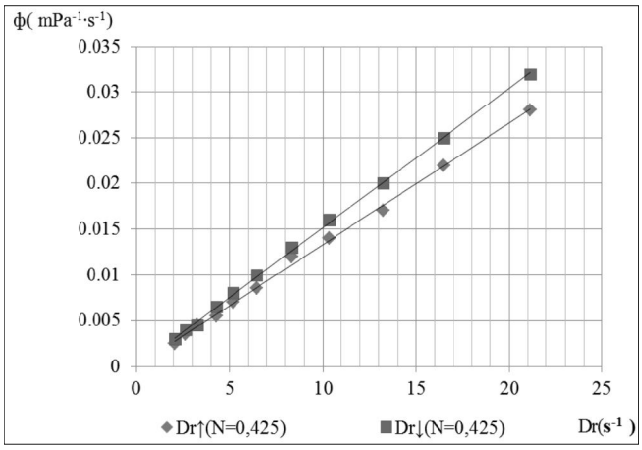

Fig. 2. Fluidity of the emulsion A at Dr↑ and Dr↓

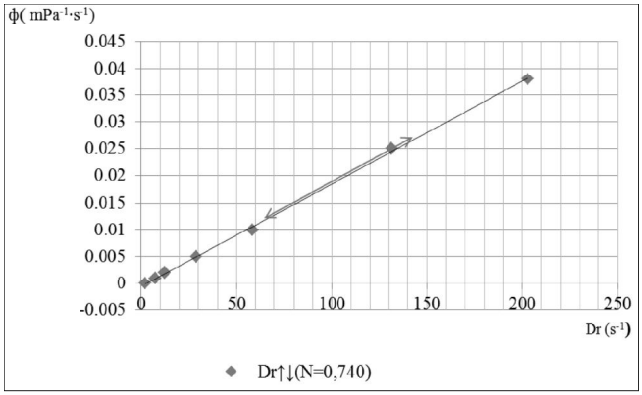

Fig. 3. Fluidity of the emulsion B at Dr↑ and Dr↓

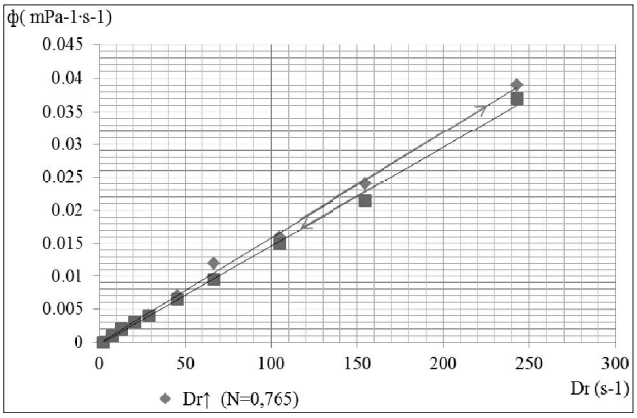

Fig. 4. Fluidity of emulsion C at Dr↑ and Dr↓

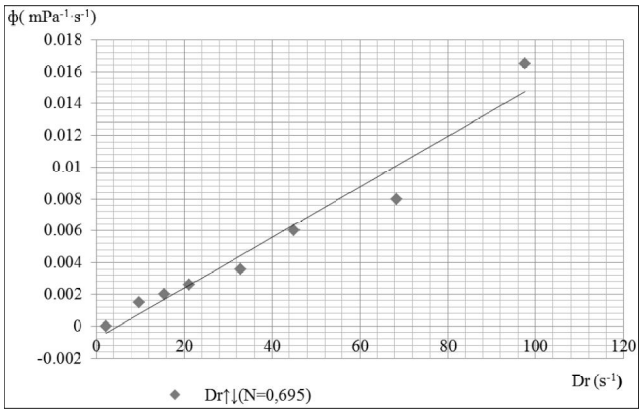

Fig. 5. Fluidity of the emulsion D at Dr↑ and Dr↓

DISCUSSION

Four concentrated emulsions o/w containing about 40% aqueous phase were prepared with such content of isotonic agents that after the dilution of the emulsion with water up to 10% of the oil phase give the isotonic preparations.

Microscopic analysis showed that the droplet diameter size of internal phase before homogenization was 12.90–35.97 μm. After homogenization and 6 months of storage the particle size was 1.45–1.85 μm and increased up to 2.01–2.33 μm at the end of storage time. However, none of the emulsions has been broken in this time, but it can be concluded that glucose is the most effective hyperisotonic agent. The concentrated emulsions with natrium chloride, Ringer's salt, and glyceride are not so stable.

The density of concentrated emulsions isotonised with glucose, Ringer's salt and natrium chloride changed slightly (1.02–1.04 g/cm^3). The lowest density (1.00 g/cm^3) had the emulsions with glyceride.

Rheological studies were aimed at determining the character of the flow and an occurrence, or not of the phenomenon of the thixotropy depending on used isotonic agents. Diluted emulsions always have Newtonian flow, but in more concentrated the character of the flow can change [7,8].

Fig. 2-5 show that examined concentrated emulsions have pseudoplastic character of flow (N<1). Different angles of slope of lines flow at increasing and decreasing shear rates indicate a change in the speed of fluidization of the systems (K), but also the possibility of thixotropy, which can be described with liquefaction coefficient F. Speed fluidization values (K) at both increasing ($D_r\uparrow$) and decreasing ($D_r\downarrow$) 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 D_{r1} and D_{r2}, N – power exponent.

The liquefaction coefficient (F), which reflects the degree of destruction of gel structure, can be calculated:

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

where: K↓ – speed fluidization at $D_r\downarrow$, K↑ – speed fluidization at $D_r\uparrow$.

Calculation results are shown in Tab. 5.

Table 5. The parameters and constants of equations

Emulsion	Parameters of equations and constants calculated at rates						F K↓/K↑
	increasing			decreasing			
	K↑	N↑	SD	K↓	N↓	SD	
A	$1.372 \cdot 10^{-3}$	0.425	0.91	$1.67 \cdot 10^{-3}$	0.425	0.228	1.2173
B	$1.917 \cdot 10^{-4}$	0.74	0.059	$1.917 \cdot 10^{-4}$	0.74	0.183	1.0000
C	$1.626 \cdot 10^{-4}$	0.765	0.036	$1.481 \cdot 10^{-4}$	0.765	0.116	0.8672
D	$1.222 \cdot 10^{-4}$	0.695	0.141	$1.222 \cdot 10^{-4}$	0.695	0.164	1.0000

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

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

where: K – speed fluidization, N – power exponent.

The correlation function and solutions of this equation show that the prepared emulsions have pseudoplastic flow (N<1).

The liquefaction coefficient values (F) indicate the occurrence of the positive thixotropy when F>1. There is no thixotropy in the systems with F = 1 and negative thixotropy in the systems with F<1.

Formulated emulsions are concentrates containing one of the hyperisotonised agents as: glucose (A), natrium chloride (B), Ringer salt (C), glyceride (D). They have the same amount of the external phase – 40.80%. By comparing the values of liquefaction coefficient (F) it can be concluded that emulsion A has the most thixotropy (the strongest gel structure), but there is no or minimum thixotropy in emulsions B and D.

CONCLUSIONS

1. Using the method of emulsification allows to obtain o/w emulsions, with the droplet diameter size to 2 μm.
2. During half-a-year storage, the increase of droplet diameter size of the external phase depended on the isotonic agent and it is smallest in the presence of glucose.
3. All the concentrates have pseudoplastic flow.
4. Emulsion with glucose has the most thixotropy.

The proposed compositions can be used to obtain concentrated emulsion systems, but using glucose as the isotonic agent is the most favorable.

REFERENCES

1. Alonso Perez L. et al.: Intravenous lipid emulsions in pediatric parenteral nutrition. *Acta Pediatrica Espanola*, 67, 387, 2009.
2. Bour H.: Biul. Inf. Inst. Przem. Farm. 9,974, 1974. (przedruk z J. . Med. Ass., 224,1526,1973.
3. Czarnecki W., Wiktorowicz M.: Porównanie właściwości reologicznych podłoży polietylenowych. *Farm. Pol.*, 49,1,1993.
4. Driscoll D. F.: Lipid injectable emulsions. *Parenteral and Enteral Nutrition*, 21, 381, 2006.
5. Emulsan. Laires, 1989.
6. Grzegorzewska J., Czarnecki A.: Czynniki wpływające na trwałość emulsji tłuszczowych stosowanych w żywieniu pozajelitowym. *Farm. Pol.*, 6, 239, 1995.
7. Jimenez M.M. et al.: Stability and rheology of dermopharmaceutical excipient formulated with honey. *S.T.P. Pharma Sci.*, 5, 216, 1995.
8. Koycha M. et al.: Stabilite des malangesternaires pour nutrition parenterale. *S.T.P. Pharma Sci*., 4, 169, 1994.
9. Muchtar S. et al.: Stability assessment of a fat emulsion prepared with an original mixture of purified phospholipids. *S.T.P. Pharma Sci.*, 1, 130, 1991.
10. Silvander M. et al.: Rheological properties of phospholipid stabilized parenteral oil- in-water emulsions. Effect of electrolyte concentration and presence of heparin. *Int. J. Pharm.*, 252, 123, 2003.
11. *Polish Pharmacopoeia edition VIII*. P.T.Farm. Warsaw, 2008.