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Evaluation of the impact of critical quality attributes and critical process parameters on quality and stability of parenteral nutrition nanoemulsions

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ABSTRACT

The aim of this study was to develop, characterize and evaluate concentrated nanoemulsions (20%) for parenteral nutrition. Those systems were developed by the high-pressure homogenization method. Optimal conditions for the nanoemulsion production were identified using 2^{4-1} fractional factorial design. The characterization of physicochemical parameters was carried out immediately after the nanoemulsion production, and after 10 and 30 days. The biological control was conducted 30 days after their preparation as well. The oil phase contained the combination of the soybean (SO) and fish oil (FO) as well as the fish oil and medium-chain triglycerides (MCT), while the aqueous phase was composed of water for injections. The egg yolk phospholipids (EP) were used as surfactants alone, or in combination with Poloxamer 188 (Pl). The obtained results were in accordance with the literature date e.i. quality requirements for parenteral emulsions (the droplet diameter $\leq$ 500 nm, PDI $\leq$ 0.25, absolute value of ζ −potential $\geq$ 25 mV, pH-value in the range of 6–9). It was shown that the combination of two surfactants (the egg yolk phospholipids that provides the electrostatic stabilization and Poloxamer 188−steric stabilizer) used as emulsifiers ensures the optimal quality of the obtained nanoemulsions for parenteral nutrition.

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1. Introduction

Nanoemulsions (also called mini emulsions, ultrafine emulsions or submicron emulsions) that are used for parenteral nutrition are polydispersed, isotropic, kinetically stable, but thermodynamically unstable systems of oil-in-water (O/W) type, which should be sterile and apyrogenic [1]. Due to a very small size of droplets, parenteral nanoemulsions are „resistant" to aggregation processes (flocculation, coagulation, coalescence), what explains their long shelf life. Since they are characterized by a high degree of uniformity of droplet size, nanoemulsions are an almost ideal pharmaceutical form which has found its widespread use in many pharmaceutical areas.

The quality and stability of those colloidal systems may be affected by numerous factors. The factors mostly affecting nanoemulsion properties include a proper choice, the type, quality and concentration of the used substances, the preparation method as well as the process parameters (the number of homogenization cycles and the homogenization pressure) [2].

Nanoemulsions that have so far been used for parenteral nutrition in clinical practice contain either SO or FO only, or the combination of the SO and MCT as well as the combination of the SO, MCT, olive and FO. In this study, two oil combinations were used (the first containing the SO and FO, and the later composed of MCT and the FO.

The utilization of the soybean oil in the emulsion for the parenteral nutrition production has the longest tradition. It is composed of long-chain triglycerides (LCT) which contain polyunsaturated essential fatty acids (linoleic−18:2n-6 and linolenic−18:3n-3). These fatty acids are precursors of arachidonic (ω-6) and eicosapentaenoic acids (ω-3) [3].

The introduction of Medium Chain Triglycerides into the

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parenteral emulsion technology has brought considerable changes. These triglycerides have a greater solubilization effect, a lower accumulation in adipose tissues and the liver, a faster clearance and the resistance to peroxidation [4,5]. They are mostly used in combination with other oil types for they do not contain essential fatty acids [3].

Over the recent years, however, there has been a great deal of interest among numerous researchers in the use of fish oil. Due to the fact that the fish oil provides a rich source of ω-3 polyunsaturated fatty acids (PUFAs), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), it is more and more used in critically ill patients [6]. These essential fatty acids inhibit the production of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) and modulate the production of anti-inflammatory cytokines (IL-10) [7,8]. The application of this oil is also important in post-traumatic and postsurgical patients, early stages of sepsis, patients with inflammatory bowel diseases (Crohn's ulceratic colitis), acute pancreatitis [9], as well as for the retinal and brain development [10,11]. If the combination of soybean and fish oil is used, the proper ratio of ω-6/ω-3 polyunsaturated fatty acids (PUFAs) could be achieved [12].

The proper selection of an emulsifying agent is necessary for the nanoemulsion stabilization. There is a small number of surfactants that are considered safe for the parenteral application. In this study, the egg yolk phospholipids (EP) and Poloxamer 188 (Pl) were used as emulsifying agents [2,3]. EP are ionic emulsifiers of electrostatic effect [13,14], while Pl is a non-ionic emulsifier of amphiphilic character, which, due to its steric effect, serves as an emulsifier. The combination of EP and Pl resulted in the formation of a better close-packed mixed film at the oil-water interface of emulsified droplets. The synergetic effect of these two emulsifiers enhances the stability of prepared nanoemulsions [15,16].

Based on the experience of a great number of researchers, it has been shown that the nanoemulsion stability can be increased considerably by adding smaller amounts of co-emulsifiers to the formula. In this experiment, Sodium Oleate (SOl) was used and remained in constant concentration (0,03%, w/w). Used as a co-emulsifying and a pH-adjusting agent, it enables the achievement of better stability and enhances the ζ-potential value [2]. Its localization in the interfacial layer ensures the strengthening of the integral film formed with emulsifiers by strengthening molecular bonds (actions) between EP and Pl, what, thus improves mechanical properties of the film [4,14].

It is well-known that nanoemulsions for parenteral nutrition should be isotonic. In preparing nanoemulsions glycerol (G), the most suitable isotonizing agent was used.

To prevent unwanted peroxidation reactions, antioxidants – α-tocopherol (Toc) and thioglycolic acid (TA) were used [3,14,17].

The known fact is that nanoemulsions for parenteral nutrition are the most stable at the pH value range of 6–9 [18]. During the sterilization process and the shelf life as well, the pH value decreases due to the hydrolysis of triglycerides to their constituents, i.e. free fatty acids. To ensure the upper pH limit, 0,1 mol/l aqueous solution of Sodium Hydroxide is added to nanoemulsions prior to their sterilization.

In addition, the proper of the preparation methodology, as well as the optimally adjusted manufacturing parameters are considered also important. There are various high- and low-energy methods used for the nanoemulsion preparation [2,19,20]. The high-pressure homogenization method that is mostly used for the nanoemulsion preparation is also used for these study. Synergetic effects of several forces such as cavitation, hydraulic shear and intense turbulence are used for carrying out this process.

The aim of the study was to prepare the nanoemulsions for parenteral nutrition and investigate the impact of independent variables (Critical Material Attributes – the types of oil and surfactant phases as well as the Critical Process Parameters – the number of homogenization cycles and the homogenization pressure) on the Critical Quality Attributes (the mean size of droplets, the droplet size distribution i.e. polydispersity index – PDI and ζ–potential).

2. Materials and methods

2.1. Materials

Soybean oil (Lipoid Purified Soybean Oil 700) was purchased from Lipoid GmbH, Germany, the Fish oil – Oleum Jecoris (Ph. Eur. 7.5), Miglyol 812® contains MCT – Medium-Chain Triglycerides, α-tocopherol were obtained from Caelo, GmbH, Hilden, Germany, egg phospholipids with 80% phosphatidylcholine (Lipoid® E80) and Lipoid Sodium Oleate B were kindly supplied by the Lipoid GmbH, Germany, Kolliphor® P 188–Poloxamer 188 (Ph. Eur.) was also a kind gift from BASF (Ludwigshafen, Germany). Glycerol (Ph. Eur.) and Sodium hydroxide (Ph. Eur.) were purchased from Merck, Germany, Thioglycolic acid was purchased from Sigma–Aldrich Chemie GmbH (Steinheim, Germany). Water used in the experiment was double distilled and obtained from the Milli Q-water purification system (Millipore, MA).

2.2. Methods

2.2.1. Experimental design

In order to evaluate the influence of formulation and process variables on the performance of O/W nanoemulsions for parenteral nutrition, 2^{4-1} fractional factorial design was applied. The type of oil phase, the surfactant (egg yolk phospholipids) with or without the use of the second surfactant (Poloxamer 188), the number of homogenization cycles and the pressure were recognized as the critical quality attributes for formulations and processes (input parameters).

These variables were varied according to the 2^{4-1} fractional factorial design, as presented in Table 1.

In order to identify and define the influence of independent variables on a dependent variable, obtained values were fitted into the following model:

$$y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{14}X_1X_4$$

where

y–the dependent variable;
X_1-X_4–independent variables;

Table 1
Experimental matrix according to the 2^{4-1} fractional factorial design.

Formulation	X_1	X_2	X_3	X_4
1	A_1	1	4	300
2	A_2	1	4	700
3	A_1	2	4	700
4	A_2	2	4	300
5	A_1	1	10	700
6	A_2	1	10	300
7	A_1	2	10	300
8	A_2	2	10	700

X_1 - oil phase (A_1 – mixture of FO and SO, A_2 – mixture of FO and MCT); X_2 - surfactant (1–EP, 2–mixture of EP and Pl); X_3 – number of cycles; X_4 – pressure (bar).

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