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Comparison of the physicochemical properties of MCT-containing fat emulsions in total nutrient admixtures

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ABSTRACT

The physical stability of two types of MCT-emulsions made by different technologies – physical mixture vs. structured lipids – was studied as a function of storage time and temperature. Particle size analysis, zeta potential and dynamic surface tension measurements were carried out to evaluate the possible changes in the kinetic stability of the emulsions. Our results indicate that the physical mixture technology of MCT-emulsions resulted in impaired physicochemical stability compared to the ones containing structured triglycerides. In the case of structured lipids, both medium and long chain fatty acids can be found in one triglyceride molecule, leading to a favorable interfacial location of structured triglycerides. Besides the advantageous metabolic effects of structured triglycerides, their application is recommended to improve the physical stability of TPN admixtures.

1. Introduction

Use of fats as part of clinical nutrition started nearly 50 years ago, when Geyer [1], later Carlson and Hallberg [2] published their first studies on soybean-based lipid (long chain triglycerides, LCT) emulsion. Some 20 years later the importance of medium chain triglycerides (MCTs) came into the spotlight [3,4] and the physical mixtures of MCT/LCT was triumphed for several decades. The third big step in this area was the invention of structured lipids, where the glyceride-bone was esterified by different length fatty acids on the place of the three –OH functions. This new technology of "intramolecular mixture" of long chain fatty acids (LCFAs) and medium chain fatty acids (MCFAs) opened new vistas in the therapeutics. By this step the real engineering of fats became possible, and after a while, numerous publications proved that variations of fatty acid substituents play an important role in the nutritional, as well as, in the medical field. Recently authors assessed the effects of a parenteral soybean-oil emulsion (Intralipos®) and citric acid on blood rheology and erythrocyte morphology *in vitro*. Their data demonstrated that citric acid could alleviate the high viscosity induced by Intralipos® intravenous infusion [5].

Researchers proved in the late fifties that enteral use of MCTs pure in small amounts is not harmful but intravenous use started many years later. During the first studies it has been proven that MCTs, due to their very quick metabolism, are not optimal for parenteral nutrition, therefore different mixtures of MCT and LCT have been studied. A few years later 50–50% mixture of MCT and LCT was chosen for further investigations. So by the mid eighties this physical mixture of MCT and LCT as infusion for clinical nutrition has been registered. Since the introduction of Lipofundin MCT®/LCT (B. Braun) hundreds of publications proved its benefits [6].

Structured lipids (SLs) are known for more than one decade. Preliminary investigations were initiated by the food industry. During the early years of the nineties the position of fatty acids on the glycerol backbone has been made possible the production of tailor-made lipids. Nowadays structured lipids can be made in different ways, e.g. via interesterification, by acidolysis, or more recently with the help of lipase enzymes [7,8].

By the late nineties Fresenius–Kabi marketed the first structured lipid emulsion (Structolipid®) for clinical use. This structured lipid is intramolecular random mixture of MCFAs and LCFAs made by transesterification after hydrolysis of genuine MCT- and LCT-containing lipid mixture. Safety has been demonstrated by several studies. This intramolecular random mixture proved further benefits in the parenteral nutrition [9].

From pharmaceutical point of view the stability of lipid-containing mixtures on the globule-size distribution, i.e. ultimately on the concentration and behaviour of lipid-surfactant and the characteristics of lipids are of impact. In case of the above-mentioned pharmaceutical fat emulsions, both of them are made

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Table 1a
Composition of the TPN mixtures F35.

Compounds	Quantity (ml)	
	F35L	F35S
Rindex 10% (TEVA) 500.0 ml Magnesium chloride hexahydrate 0.051 g, calcium chloride 0.09 g, potassium chloride 0.13 g, sodium chloride 1.985 g, glucose monohydrate 55.0 g, water for injection to 500.0 ml	1500	1500
Electrolyte C (University Pharmacy of the Semmelweis University, Hungary) 100.0 ml Sodium chloride 2.337 g, potassium chloride 3.727 g, magnesium sulfate 2.00 g, and water for injection to 100.0 ml	100	100
Aminoven 10% 500 ml inf. (Fresenius Kabi AB Sweden) L-Isoleucine 5.00 g, L-leucine 7.40 g, L-methionine 4.30 g, L-lysine–acetate 9.31 g (=6.6 g L-lysine), L-phenylalanine 5.10 g, L-threonine 4.4 g, L-tryptophane 2.00 g, L-valine 6.20 g, L-arginine 12.0 g, L-histidine 3.00 g, L-alanine 14.0 g, glycine 11.0 g, L-proline 11.2 g, L-serine 6.50 g, L-tyrosine 0.40 g, and taurine 1.00 g/1000 ml solution total amino acid content 100.0 g/l	500	500
Lipofundin MCT® 20% inf. (B. Braun Melsungen AG) Soy oil and MCT oil 50:50% mixture 200 g, purified egg phospholipids 12 g, glycerol (anhydrous) (Ph Eur) 22.0 g, water for injection to 1000 ml	500	–
Structolipid® 20% inf. (Fresenius Kabi, Germany GmbH) Structured triglycerides 200 g, purified egg phospholipids 12 g, glycerol (anhydrous) (Ph Eur) 22.0 g, and water for injection to 1000 ml	–	500

with the same or very similar emulsifier (egg-yolk phospholipids) and is used in a similar proportion. Droplet size and distribution is similar, too. So the only difference is the composition of triacylglyceroles (TAGs) used and the technology of production.

It is known, that the LCT content is decreasing and MCT content is increasing in the aforementioned emulsions: pure LCT contain ca. 100% of glycerol esterified with LCFA longer than C18, in Structolipid® the LCFA content is ca. 64% and in case of Lipofundin MCT®/LCT the LCFA content just 50%. This fact can influence the surface behaviour of droplets in the emulsion, especially under diluted conditions, like in all-in-one (AIO) mixtures because functional groups on the surface of ca. 300 nm globules can interact with other functions. The negatively charged surface of droplets ensures the electrostatic repulsion and all parameters that reduce this force, e.g. ion-containing surroundings (solvent phase), pH-deviation or temperature can support instability of the system.

The physicochemical behaviour of fat droplets in AIO mixtures is essential from safety point of view. Instable emulsion, i.e. formation of globules over 5 μm (coalescence), is potentially dangerous because of the emboli formation [10]. There are different factors that influence droplet stability in the mixtures therefore pharmaceutical evaluation of certain compositions is an important point. Several authors demonstrated emulsion stability in different solvents with different methods. The working group of Semmelweis University, Budapest recently published some differences in behaviour of classical LCT emulsion and structured-MCT/LCT emulsion [11,12] in the AIOs. As the MCT-containing emulsion was compared to LCT, a certain difference could be suspected on basis of former publications. The difference of the behaviour between MCT-emulsions made by different technologies, i.e. physical mixture vs. structured lipids remained an open question. We hypothesized that there are some differences because of the different contents of MCFA and LCFA ligands that express various physicochemical activity. In this study we evaluated the kinetic stability of two total parenteral admixtures made by Lipofundin MCT®/LCT (B. Braun Melsungen AG) and Structolipid® (Fresenius Kabi AG), simultaneously. A further aim was to collect more evidence for the stabilizing effect of structured triglycerides, with special concern to the ionic concentration of the mixtures.

2. Materials and methods

Two type (F37 and F35) of all-in-one mixtures were prepared according to a prescription regularly used at the Semmelweis University, Budapest. Each type of AIO mixtures were prepared with Lipofundin MCT®/LCT or Structolipid® (F37L and F37S or F35L and S35S) and bottles were signed accordingly. Compositions of the experimental mixtures are shown in Tables 1a and 1b. Main differences were higher glucose-content in F37 (9.5% vs. 6.3% in final mixture) and higher electrolyte-concentration including presence of Ca^{2+} in F35 (Table 2).

2.1. Preparation and storage of AIO mixtures

The compounding was made according to the rules of aseptic procedures in the Central Pharmacy of the University under laminar airflow box. Mixtures were prepared in a vacuum-chamber under computer-assisted volume regulated process in a closed filling system. Components were mixed as follows: amino acid was added to 50% of the calculated glucose 40%, in remaining glu-

Table 1b
Composition of the TPN mixtures F37.

Compounds	Quantity (ml)	
	F37L	F37S
Infusio glucosi 20% (University Pharmacy of the Semmelweis University, Budapest) Glucose anhydrate 200 g, hydrochloric acid 0.1N 1.000 ml per 1000 ml solution	500	500
Electrolyte A (University Pharmacy of the Semmelweis University, Budapest) Sodium chloride 4.675 g, potassium chloride 3.727 g, magnesium sulfate cryst. 2.00 g, and aqua destillata pro inj. ad 100.0 ml	100	100
Aminoven 10% 500ml inf. (Fresenius Kabi AB Sweden) L-Isoleucine 5.00 g, L-leucine 7.40 g, L-methionine 4.30 g, L-lysine–acetate 9.31 g (=6.6 g L-lysine), L-phenylalanine 5.10 g, L-threonine 4.4 g, L-tryptophane 2.00 g, L-valine 6.20 g, L-arginine 12.0 g, L-hystidine 3.00 g, L-alanine 14.0 g, glycine 11.0 g, L-proline 11.2 g, L-serine 6.50 g, L-tyrosine 0.40 g, taurine 1.00 g/1000 ml solution total amino acid content 100.0 g/l	1000	1000
Lipofundin MCT® 20% inf. (B. Braun Melsungen AG) Soy oil and MCT oil 50:50% mixture 200 g, purified egg phospholipids 12 g, glycerol (anhydrous) (Ph Eur): 22.0 g, and water for injection to 1000 ml	500	–
Structolipid® 20% inf. (Fresenius Kabi, Germany GmbH) Structured triglycerides 200 g, purified egg phospholipids 12 g, glycerol (anhydrous) (Ph Eur) 22.0 g, water for injection to 1000 ml	–	500