COMPLETE FORMULAE FOR PARENTERAL NUTRITION IN NEONATAL INTENSIVE CARE UNIT: A STABILITY TRIAL

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Background

Complete neonatal parenteral formulae (All-in-One) have a main role in Neonatal Intensive Care Unit nutrition. They allow to correctly feed newborn children (mainly premature infants) who cannot be fed orally. These formulae are personalized prescriptions often very difficult to prepare. The difficulty lies in the volume (small quantities) and the high concentration of electrolytes that are usually required. Subsequently, compounding these formulae requires a careful feasibility study, aseptic preparation technique and an automatic filling system in a controlled contamination room, according to NBP - Italian Pharmacopoeia (F.U.I.) XII Ed. and Good Manufacturing Practice (GMP) - European Pharmacopoeia VII Ed. Finally, All-in-One admixtures must be stable during the different phases of preparation, storage and infusion to patients, in order to guarantee a high quality, safe and effective product. The European Nutritional Guidelines report a safe infusion to patients when lipid particle diameter ranges between 0.4 - 1.0 micrometer, like chylomicrons.

Purpose

The aim of this study is the evaluation of the stability over time of neonatal All-in-One admixtures compounded with calcium different concentrations and lipid emulsions characterized by different lipid matrix and viscosity. These are the critical parameters which affect the variation of the emulsion Z-potential and hence the stability of the admixtures themselves. Finally, they cause the increase of lipid particle diameter and the consequent phenomena of flocculation, creaming and coalescence.

Materials and Methods

Stability trial was performed with six different neonatal parenteral formulae (F1-F6), three variations for each, using three kinds of lipid emulsions, also combined together:

- 10% long chain triglycerides (LCT) soybean oil + 10% middle chain triglycerides (MCT) coconut oil based emulsion (Lipofundin MCT®10%+10%);
- 20% composite soybean-olive-MCT-fish-oil based emulsion (SMOFlipid® 20%);
- 10% omega-3 (n-3) pure fish oil based emulsion (Omegaven®10%)

(Examples in Table 1).

Analyses were carried out on nutritional admixture samples 1:3 v/v water diluted by means of a "Helium-Neon Laser Particle Sizer" with "Light Scattering - Reverse Fourier Optics Technique" at 632 nm laser beam wavelength. Measurement range was 0.16 μm - 1160 μm. Lipid particle sizes were evaluated with the inverse proportionality between the incident laser beam diffraction angle and the lipid particle maximum diameter of 10% (d10) and 90% (d90) of particles, respectively (Figures 1,2). Analyses were performed at preparation time t=0 and 24, 48, 72 and 96 hours after compounding, in order to reproduce usual storage conditions and clinical use. Each sample was stored in the refrigerator (2°- 8°C) and brought back to room temperature two hours before analysis, then it was tested in triplicate for a total amount of 270 analyses. Statistics was provide by T-test.

Table 1. Quali-quantitative composition of F1 and F2 formulae in three variations.

Components	F1 MCT	F2 MCT	F1 SMOF	F2 SMOF	F1 MCT + n-3	F2 MCT + n-3
Volume (mL)	150.0	150.0	150.0	150.0	150.0	150.0
Glucose (g)	9.8	9.8	9.8	9.8	9.8	9.8
Lipids (g)	3.2 MCT	3.2 MCT	3.2 SMOF	3.2 SMOF	2.2 MCT + 0.8 n-3	2.2 MCT + 0.8 n-3
Pediatric amino acids (g)	1.1	1.1	1.1	1.1	1.1	1.1
Sodium (mmol)	6.2	6.2	6.2	6.2	6.2	6.2
Potassium (mmol)	2.1	2.1	2.1	2.1	2.1	2.1
Chloride (mmol)	6.2	6.2	6.2	6.2	6.2	6.2
Calcium gluconate (mmol)	0.4	1.2	0.4	1.2	0.4	1.2
Magnesium (mmol)	0.05	0.05	0.05	0.05	0.05	0.05
Organic phosphate (mmol)	0.7	0.7	0.7	0.7	0.7	0.7
Pediatric trace elements (mL)	1.5	1.5	1.5	1.5	1.5	1.5
Water-soluble vitamins (mL)	2.0	2.0	2.0	2.0	2.0	2.0
Fat-soluble vitamins (mL)	8.0	8.0	8.0	8.0	8.0	8.0
Water for injections (mL)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Figure 1. Helium - Neon Laser Particle Sizer Analysette 22, Fritsch & Gamble, D with interfaced computer for data processing.

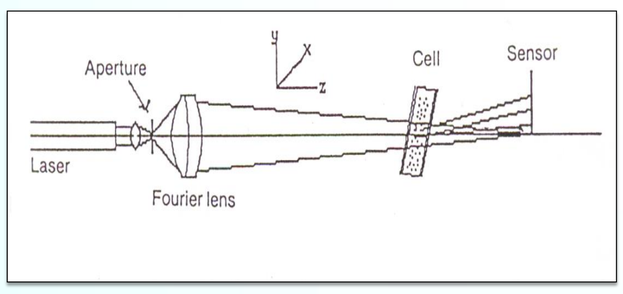

Figure 2. Light Scattering - Reverse Fourier Optics Technique.

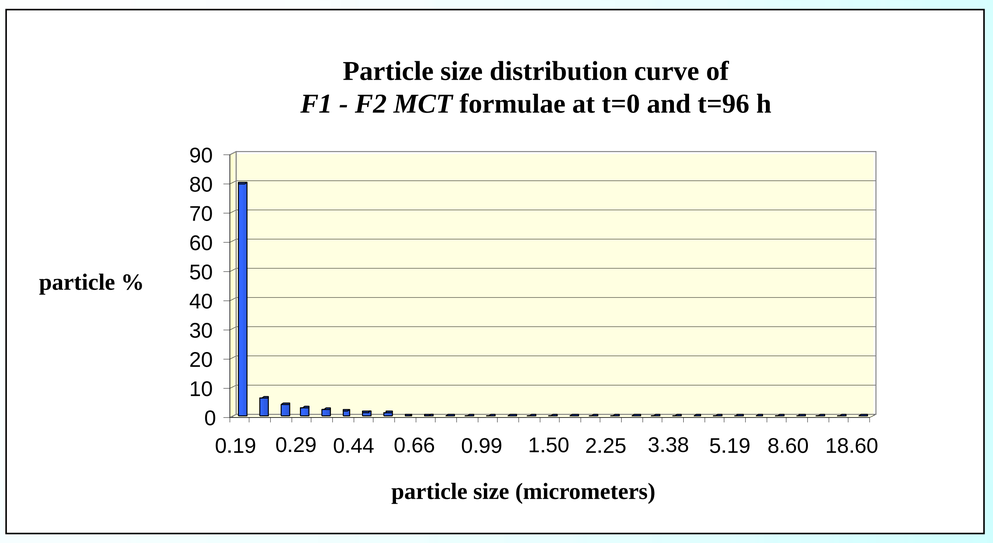

Figure 3. Particle distribution area of MCT formulae.

Results

Analysis results pointed out different stabilities of tested admixtures, according to different kind of lipid emulsion and calcium concentration, in particular:

- parenteral formulae compounded with LCT/MCT proved to be stable 96 hours after compounding independently of calcium concentration. In fact, particle diameters did not change between t=0 and t=96h and remained in the expected range of 0.4-1.0 micrometer (Figure 3);
- parenteral formulae compounded with composite lipids and/or LCT/MCT combined with refined fish oil omega-3 proved to be stable 96 hours after compounding only if calcium concentration was lower than 4.5 mmol/L;
- when calcium concentration exceeded this level, 12% of particle diameters was larger than 1.0 micrometer and 2% exceeded 5.0 micrometers immediately after compounding, causing admixture instability (Figures 4, 5).

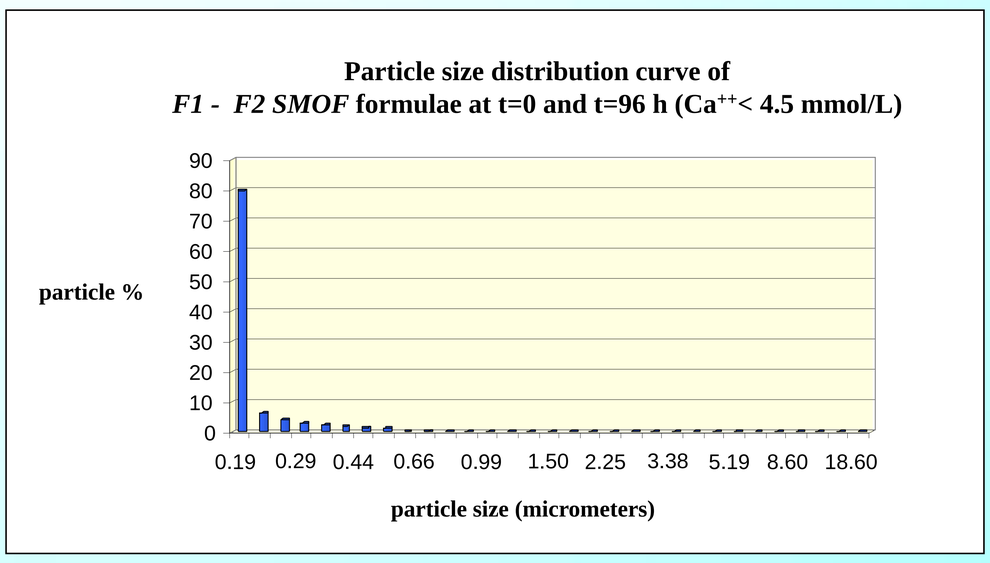

Figure 4. Particle distribution area of SMOF and MCT+n-3 formulae with $Ca^{++} < 4.5$ mmol/L.

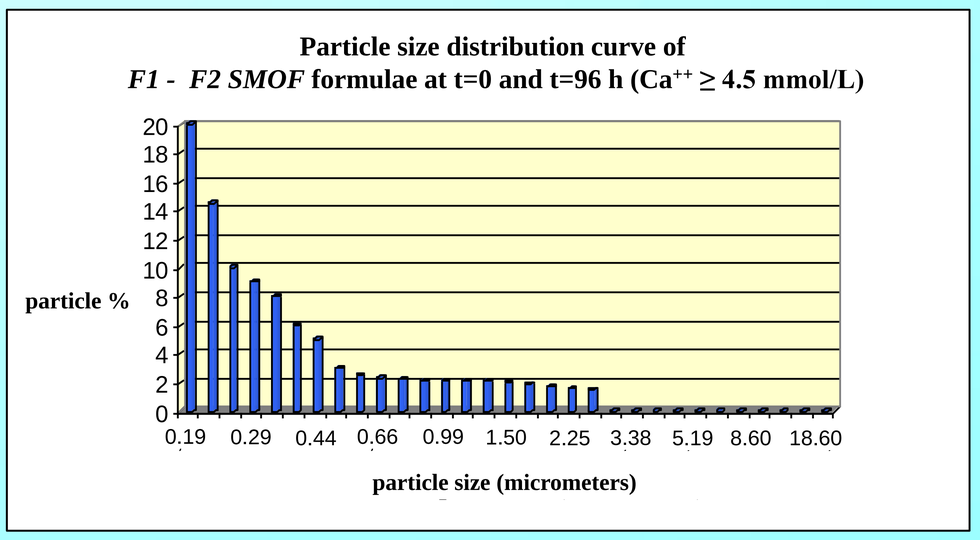

Figure 5. Particle distribution area of SMOF and MCT+n-3 formulae with $Ca^{++} \geq 4.5$ mmol/L.

Conclusions

The results suggest a validity of 96 hours for nutritional admixtures prepared with LCT/MCT. Conversely, nutritional admixtures compounded with composite lipids or LCT/MCT in combination with fish oil remain stable 96 hours only if calcium concentration is lower than 4.5 mmol/L. When this limit is exceeded, parenteral admixtures become unstable and cannot be safely infused to patients, therefore it is required to prepare nutritional formulae with a lower calcium concentration and administrate the remaining calcium by injection. Otherwise, it is advisable to compound the admixtures with LCT/MCT and infuse fish oil based emulsion alone through a second intravenous line.

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