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The influence of medium-chain triglycerides on the stability of all-in-one formulations

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Abstract

When mixed with parenteral nutrients as an all-in-one admixture, previous data have demonstrated that lipid emulsions composed of medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs) yield more stable formulations compared with those compounded with pure LCT lipid emulsions. We investigated the physical stability of various preparations of intravenous lipid emulsions as all-in-one admixtures. Each final lipid emulsion used to compound the all-in-one formulation was a 20% w/v mixture containing MCTs and LCTs as either a single emulsion containing both triglycerides, or an emulsion made extemporaneously from separate starting emulsions of pure MCT and LCT. The first emulsion was composed of a 50:50 (by weight) physical mixture of MCTs and LCTs, and consisted of 50% MCT:40% ω-6 LCT (soybean oil):10% ω-3 LCT (fish oil) that was available as a single 20% w/v lipid emulsion. The second and third emulsions were specially prepared from separate stock dispersions containing pure 20% w/v MCT and pure 20% w/v LCT (soybean oil) lipid emulsions, and were made in volume ratios of 75% MCT:25% ω-6 LCT and 50% MCT:50% ω-6 LCT, respectively. This was done in order to investigate whether the method of emulsion preparation and/or ratio of MCT to LCT influenced all-in-one admixture stability. Each all-in-one admixture was studied at four intervals over 30 h at room temperature conditions by light extinction (or obscuration) using a single-particle optical sensing (LE/SPOS) technique. The data, performed in duplicate at each interval, is expressed as the volume-weighted percent of fat (PFAT) globules >5 μm. The results confirm the stabilizing effects of MCTs when made as a physical oil mixture as a single lipid emulsion. However, stabilization is lost if the MCT and LCT emulsions are mixed from separate starting emulsions and then compounded as an all-in-one formulation. The extemporaneous mixing of commercial lipid emulsions is not recommended.

Keywords: Long-chain triglycerides; Medium-chain triglycerides; Emulsion; Stability

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1. Introduction

Intravenous lipid emulsions (IVLEs) have been used in the clinical setting for over 40 years. By substitution of a portion of the calories derived from carbohydrate, IVLEs have significantly reduced the clinical complications associated with hypertonic glucose infusions as part of TPN therapy (Driscoll, 1990). In particular, hyperglycemia significantly increases the risk of infectious complications (Khaodhiar et al., 1999). Moreover, as long as the rate of lipid infusion from long-chain triglycerides (LCTs) does not exceed 0.11 g/kg/h, major toxicities such as immune dysfunction and pulmonary gas diffusion abnormalities are avoided (Klein and Miles, 1994). Providing IVLEs continuously as an all-in-one admixture fosters a safe administration rate that minimizes infusion-related complications, yet can induce emulsion instability (Driscoll et al., 2000a). Alternative lipid emulsion mixtures containing medium-chain triglycerides (MCTs) may reduce the toxicity associated with pure LCT-based lipid emulsions (Smyrniotis et al., 2001) and may also yield more stable all-in-one admixtures (Driscoll et al., 2000b). Nevertheless, it is the ultimate goal of the pharmacist to assign a beyond-use date to such compounded preparations that ensures the admixture does not progress to a state that produces clinically-evident adverse effects (Driscoll, 1995a).

The physicochemical stability of IVLEs is crucial to their safety, as the coalescence of submicron lipid droplets (< 0.5 μm) forming oversized fat globules (> 5 μm) in the large diameter tail of the particle size distribution may be trapped in the pulmonary microcirculation (Globule Size Distribution in Intravenous Emulsions, 1998). As the internal diameter of the pulmonary capillaries is between 4 and 9 μm, the intravenous infusion of unstable lipid emulsions may produce an embolic syndrome. Thus, any critical assessment of IVLE stability and safety must include this remote population of unstable fat globules for active signs of coalescence manifested by an expanding population of oversized fat globules in the large-diameter tail of the droplet size distribution. The usual volume-weighted percent of fat (PFAT) globules found in the large diameter tail (> 5 μm) of commercially available IVLEs ranging in concentrations of 100–300 g/l (10, 20 and 30% formulations), has been shown to be as low as 0.001% up to 0.05% (Driscoll et al., 2001a). In stable all-in-one admixtures with much lower final lipid concentrations commonly ranging from 20 to 50 g/l (2–5%), these volume-weighted values are similar, i.e. PFAT > 5 μm are $< 0.1\%$ for 24–30 h at room temperature (Driscoll et al., 2000b, 2001b). However, when the growth of fat globules in the large diameter tail progresses to a PFAT > 5 μm of 0.4% or higher, the emulsions exhibit signs of phase separation and has been suggested to be a 'threshold' concentration that defines the pharmaceutical instability of IVLEs (Driscoll et al., 1995b). Clearly, this definition focuses on a quantitatively small fraction of the total population of lipid droplets in the emulsion, as the vast majority of these are < 1 μm (i.e. $> 99\%$ of the total fat present). For example, at the proposed threshold of pharmaceutical instability (PFAT > 5 μm = 0.4%), only 0.08–0.2 g/l of free oil are in the large diameter tail of the globule size distribution based on typical final lipid concentrations in all-in-one admixtures. Although the amounts of free oil present are relatively small at this pre-selected threshold, it is a quantitatively significant population of enlarged fat globules, largely spanning a size range between 5 and 20 μm and containing 10^5–10^6 globules/ml. If inadvertently administered by intravenous infusion, it might produce an embolic syndrome given the typical flow rates of TPN infusions. Generally, all-in-one admixtures are given as 24-h continuous infusions, and in adults often range from 42 to 125 ml/h (1–3 l/day). Thus, the cumulative dose of enlarged fat globules (i.e. PFAT > 5 μm) from unstable all-in-one admixtures is capable of saturating the perfused surface area of the pulmonary microvasculature. The precise toxic parenteral dose of coalesced fat globules > 5 μm is not known, but such globules are likely to be most dangerous in either critically ill patients and/or those with pre-existing pulmonary disease (El-Ebiary et al., 1995; Driscoll, 1997; Moore, 2001). Clearly, large fat globules > 5 μm are likely less toxic than similarly sized precipitates, such as dibasic calcium phosphate crystals, owing to the flexibility of the globules in the former example

compared to the rigidity of the solid particles in the latter case. Nevertheless, because of the potentially adverse clinical consequences and insidious nature of unstable IVLEs, the principal focus of our investigations are on the extent of coalescence by changes in the large diameter tail (PFAT > 5 μm) of the globule size distribution rather than on earlier stages of emulsion instability (i.e. aggregation).

We have previously demonstrated that IVLEs containing physical mixtures of MCTs and LCTs are more stable than pure LCTs in both high (Driscoll et al., 2000a) and low osmolality (Driscoll et al., 2001b) all-in-one admixtures, and more recently in pediatric formulations (Driscoll et al., in press). To further investigate the stabilizing influence of MCTs on emulsion stability, we studied these effects using a low osmolality all-in-one admixture with two types of MCT–LCT physical mixtures; one single emulsion formulation containing these oils versus two extemporaneously compounded formulations containing different ratios of MCT and LCT prepared from two separate starting emulsions. This was performed in order to investigate whether the method of emulsion preparation and/or the ratio of MCT to LCT affected the otherwise stabilizing influence of MCTs on all-in-one admixtures previously demonstrated.

2. Materials and methods

Three different all-in-one admixtures were studied in duplicate. The final concentration of the lipid emulsion in the all-in-one admixtures was constant, but the ratios of MCTs to LCTs differed. The IVLE used in each all-in-one admixture differed in terms of the preparation of the starting emulsion. The low osmolality formulation used throughout appears in Table 1 and was made from sterile ingredients in a 3:1 volume ratio of solution[1] to emulsion.[2,3,4] The first starting emulsion was a 50:50 physical mixture of MCTs and LCTs and consisted of 50% MCT:40% ω-6 LCT:10% ω-3 LCT that was available as a single 20% w/v lipid emulsion[2] and was used in Admixture I. The second and third starting emulsions were prepared in ratios of 75% MCT:25% ω-6 LCT and 50% MCT:50% ω-6 LCT, respectively, to simulate the concentrations of commercial lipid emulsion formulations. However, these were specially prepared from separate stock dispersions containing pure 20% w/v MCT[3] and pure 20% w/v LCT[4] lipid emulsions, and used in Admix-tures II and III, respectively. Thus, the starting emulsions used in compounding the all-in-one admixtures differed in terms of being either a

Table 1
Final composition of the emulsion admixture studied

Component		Concentration (g/l)
Crystalline amino acids (eight essential and seven non-essential)		22.5
Glycerin USP (glycerol)		22.5
Electrolytes		
Sodium acetate·3H_2O USP		1.5
Magnesium acetate·4H_2O		0.41
Calcium acetate·H_2O		0.19
Sodium chloride USP		0.9
Potassium chloride USP		1.13
Phosphoric acid NF		0.3
Potassium metabisulfite NF		<0.37
Lipid emulsion		50
(1) MCT oil	50%	25
Soybean oil	40%	20
Fish oil	10%	5
(2) MCT oil	75%	37.5
Soybean oil	25%	12.5
(3) MCT oil	50%	25
Soybean oil	50%	25
Egg phosphatides		3
Glycerin		6.2
Water for injection USP		*Quantum satis*

[1] Procalamine solution (3% amino acids and 3% glycerin injection with electrolytes), lot no. J9D028, McGaw Labs, Irvine, CA, USA.

[2] Lipoplus 20% lipid emulsion, lot no. 9235A32, B. Braun, Melsungen AG, Germany.

[3] MCT 20% lipid emulsion, lot no. 0091a31a, B. Braun, Melsungen AG, Germany.

[4] LCT 20% lipid emulsion, lot no. 0091b31b, B. Braun, Melsungen AG, Germany.

Table 2
Volume-weighted percent fat (PFAT) >5 μm

Time (h)	Admixture I[a]	Admixture II[b]	Admixture III[c]
MCT 20%		0.013	0.009
LCT 20%		0.014	0.009
Pre-admixture (*emulsion mixture*)	0.009	0.016	0.009
All-in-one admixture			
0	0.035 ± 0.008	0.034 ± 0.011	0.131 ± 0.019
6	0.026 ± 0.003	0.348 ± 0.041	1.033 ± 0.071
24	0.008 ± 0.003	0.794 ± 0.010	1.731 ± 0.144
30	0.003 ± 0.000	0.673 ± 0.041	1.529 ± 0.153

[a] 50% MCT:40% n-6 LCT:10% n-3 LCT as a single emulsion.
[b] 75% MCT:25% n-6 LCT made from separate starting emulsions of 20% MCT and 20% n-6 LCT.
[c] 50% MCT:50% n-6 LCT made from separate starting emulsions of 20% MCT and 20% n-6 LCT.

physical blend of oils in a single emulsion[2] or those extemporaneously compounded from two separate emulsions.[3,4]

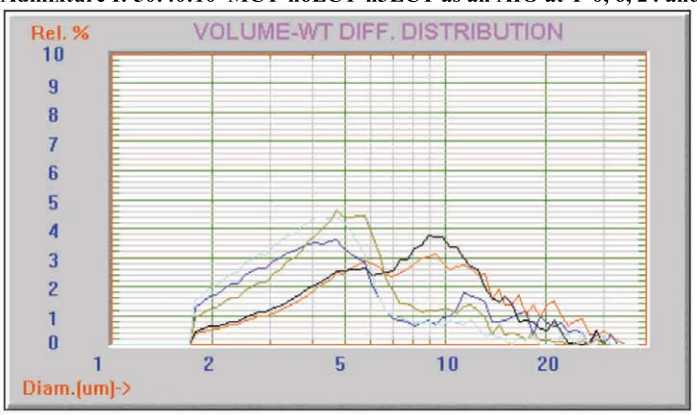
The physicochemical stability of the various emulsion preparations was assessed by light extinction using a single-particle optical sensing (LE/SPOS) instrument[5] to detect growth of submicron lipid droplets into enlarged fat globules over time. In addition, microscopic analyses were also performed to verify adverse changes in fat globule sizes detected by LE/SPOS, as well as by gross physical examination of the all-in-one admixtures for evidence of phase separation at each sample time interval. All starting emulsions were analyzed separately prior to compounding the all-in-one formulations. Each all-in-one admixture prepared for study was made in duplicate and studied at time 0 (immediately after preparation) and at times 6, 24 and 30 h later, at controlled room temperature conditions (22–26 °C). All formulations were aseptically prepared in a laminar airflow environment.

3. Results

The individual profiles of the large-diameter tail of the globule size distribution for the starting emulsions and all-in-one admixtures at each time interval, expressed as the volume-weighted PFAT > 5 μm, are shown in Table 2. The large-diameter tail profiles for the final all-in-one admixtures over the 30 h study period are graphically depicted in Fig. 1A–C as a population analysis of these large fat globules. Table 2 depicts the changes in the number and concentration of lipid droplets constituting the large diameter tail and are particularly evident between the individual starting emulsions and the subsequent extemporaneously made emulsion mixtures of MCTs and LCTs immediately after compounding. This is especially true for Admixture III which exhibits rapid destabilization at time 0 (PFAT > 5 μm = 0.131), compared to the 'pre-admixture' emulsion value (PFAT > 5 μm = 0.009). Subsequently, both Admixtures II and III result in a pharmaceutically unstable all-in-one admixture with levels of PFAT > 5 μm of 0.4% or higher at 24 and 6 h, respectively. Interestingly, the rate and extent of destabilization of Admixture II was substantially less than Admixture III, suggesting higher amounts of MCT produce less unstable all-in-one admixtures. In contrast, the 50:50 MCT–LCT single emulsion product as Admixture I maintained a stable PFAT > 5 μm profile as an all-in-one admixture over the 30-h experimental period.

[5] AccuSizer 780/APS (version 1.59), Particle Sizing Systems, Santa Barbara, CA, USA.

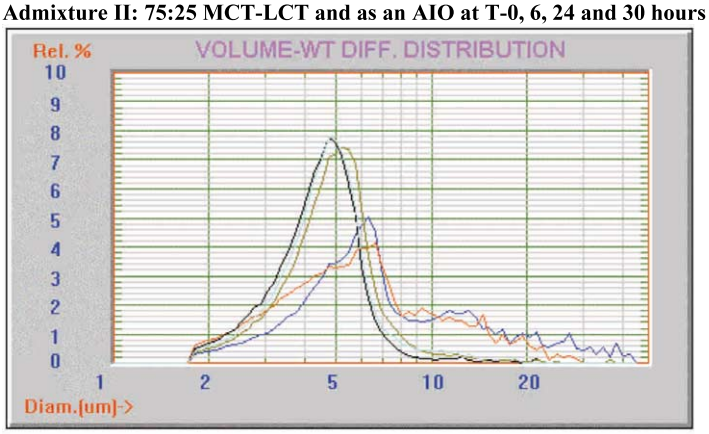
Admixture I: 50:40:10 MCT-n6LCT-n3LCT as an AIO at T-0, 6, 24 and 30 hours



BLUE = 50:40:10 MCT/n-6LCT/n-3LCT 20% Emulsion; RED, BLACK, GOLD, AQUA = All-in-One Admixture at Times 0, 6, 24 and 30 hours, respectively.

(a)

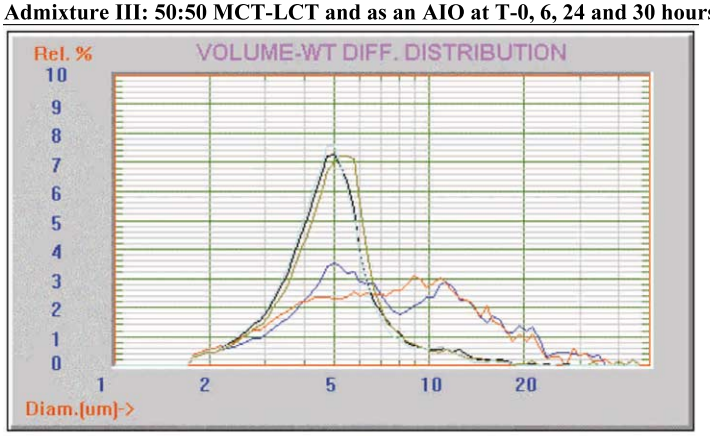
Admixture II: 75:25 MCT-LCT and as an AIO at T-0, 6, 24 and 30 hours



BLUE = 75:25 MCT/LCT 20% Emulsion Mixture; RED, BLACK, GOLD and AQUA = All-in-One Admixture at Times 0, 6, 24 and 30 hours, respectively.

(b)

Admixture III: 50:50 MCT-LCT and as an AIO at T-0, 6, 24 and 30 hours



BLUE = 50:50 MCT/LCT 20% Emulsion Mixture; RED, BLACK, GOLD, AQUA = All-in-One Admixture at Times 0, 6, 24 and 30 hours, respectively.

(c)

Fig. 1. (*Continued*)

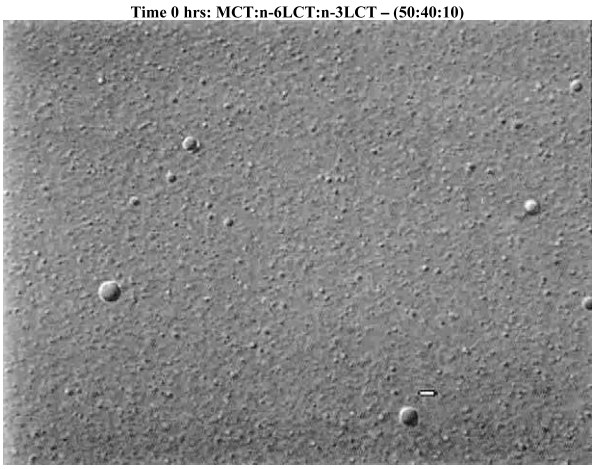
Finally, the findings from the LE/SPOS measurements are supported by microscopy. Fig. 2A–F show the photomicrographs of each emulsion immediately after preparation as an all-in-one admixture, and 30-h later that corroborate the increases in coalesced fat globules in the large diameter tail of unstable all-in-one admixtures measured by the LE/SPOS technique.

4. Discussion

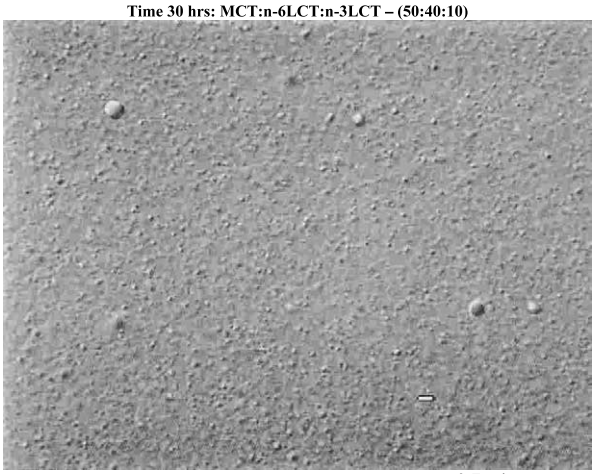
As separate liquids of water and oil, the intermolecular binding forces present in each phase are equal in all directions within the bulk of the liquids; but as a homogenized mixture of lipid droplets dispersed in water, the forces between phases at the interface between liquids are variable and therefore unbalanced. The major competing intermolecular forces responsible at this interface include hydrogen bonding from the water phase and the Van der Waals attractive forces from the oil phase. The greater the difference in the dominant forces of the individual phases within the oil and water, respectively, the less miscible the two liquids are, and interfacial tension is high. An emulsifier is designed to adsorb at the oil droplet–water interface, thus overcoming the cohesive attractive forces present in the individual phases, which lowers the free energy and stabilizes the emulsion system. As the action of the egg yolk phosphatides emulsifier present in commercial IVLEs is to reduce interfacial tension between otherwise immiscible liquids, the physicochemical challenges to the potential energy barriers against coalescence are greatest when the oil phase is least miscible with the aqueous phase. For example, the interfacial tension against water for an 18-carbon fatty acid such as oleic acid, that comprises approximately 25% of the LCT soybean oil is 15.6 dyn/cm, which is nearly double the value for an 8-carbon fatty acid such as caprylic acid, that comprises 70% of the MCT used clinically, which is 8.22 dyn/cm (Martin, 1993). In other words, the longer the hydrocarbon chain length of the dispersed oil phase, the greater the interfacial tension against the continuous aqueous phase. Moreover, MCTs are approximately 100 times more water-soluble than LCTs. For example, at 20 °C the aqueous solubility of caprylic acid (C8:0) is 68 mg/ml compared to palmitic acid (C16:0) which is 0.72 mg/ml (Bach and Babayan, 1982). Whether these differences have significance in terms of the physicochemical stability of phospholipid-stabilized IVLEs as all-in-one admixtures has been, until recently, largely unexplored.

Intuitively, it would appear for the same (relatively) emulsifier used in most commercial IVLEs, i.e. egg lecithin, that the stability of the emulsion would greatly vary with the composition of the oil phase. Not only may the differing interfacial tension values between oils be a stability factor, but the partitioning of the triglyceride from the oil phase to the emulsifier along the oil–water interface could also be affected. Such changes at the interface have been suggested to underlie the greater rates of hydrolysis seen with MCT–LCT single emulsions, compared with those made solely from LCT (Deckelbaum et al., 1990; Sato et al., 1994; Hamburger et al., 1998). In support of this hypothesis, MCTs have been shown to displace LCT at the lipid droplet surfaces of MCT–LCT single emulsions by ^{13}C NMR spectroscopy (Hamilton et al., 1996). Thus, the favorable interfacial location of MCT in MCT–LCT single emulsions, that allows the interaction with water-soluble proteins such as lipases for more efficient in vivo hydrolysis, may also be operative between oils of varying hydrocarbon chain lengths in the dispersed phase with respect to the aqueous continuous phase that leads to a more stable lipid emulsion. These potential pharmaceutical-stabilizing effects might be manifested under conditions of physicochemical stress. Hence, we decided to investigate if the stabilizing effects of MCTs observed previously for both high and low osmolality all-in-one admixtures were also present when a

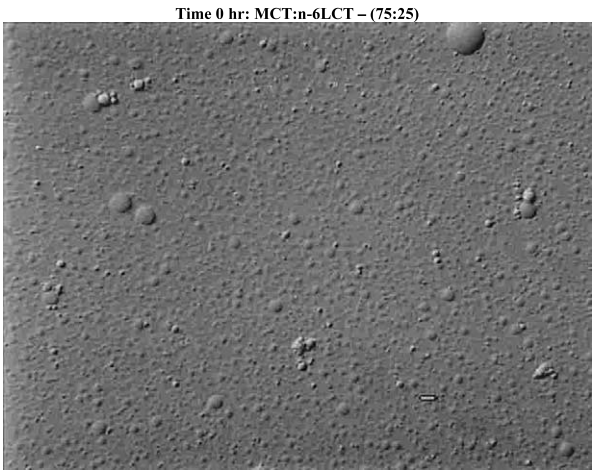
Fig. 1. (a) Admixture I: 50:40:10 MCT n-6 LCT n-3 LCT as an AIO at times 0, 6, 24 and 30 h; (b) Admixture II: 75:25 MCT–LCT and as an AIO at times 0, 6, 24 and 30 h; (c) Admixture III: 50:50 MCT–LCT and as an AIO at times 0, 6, 24 and 30 h.



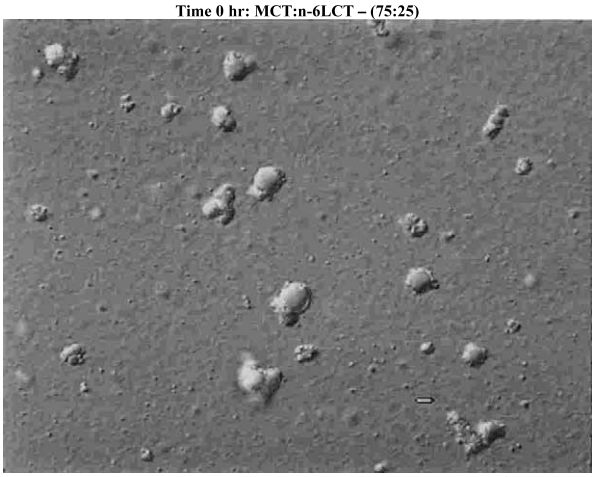
(a)



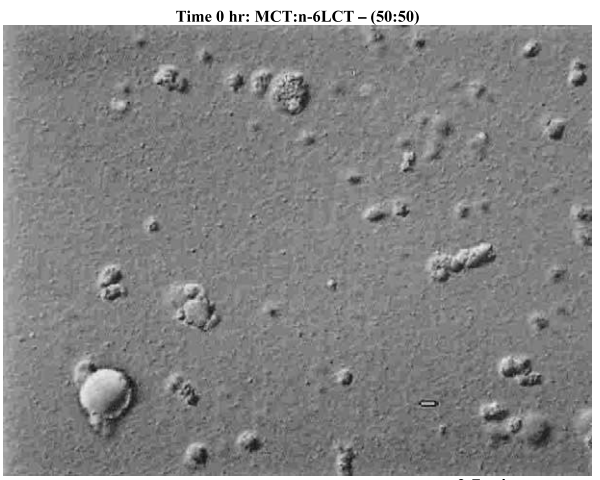
(b)



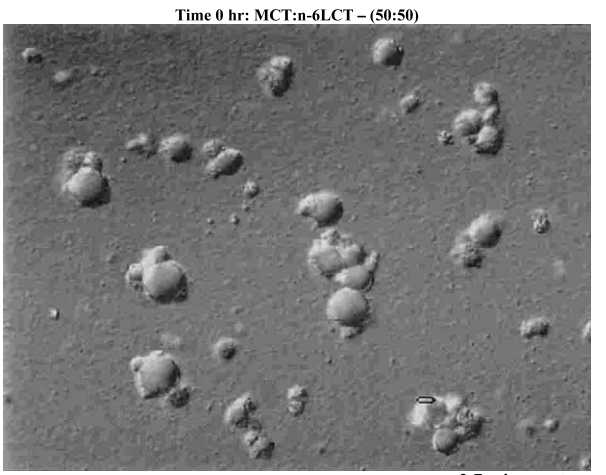
(c)



(d)



(e)



(f)

Fig. 2. Photomicrographs of: (a) Admixture I at time 0 h;(b) Admixture I at time 30 h; (c) Admixture II at time 0 h; (d) Admixture II at time 30 h; (e) Admixture III at time 0 h; (f) Admixture III at time 30 h.

very LCT oil, such as fish oil rich in the ω-3 fatty acids, eicosapentaenoic acid (c:20:5ω-3) and docosahexaenoic acid (c:22:6ω-3) was added. In addition, we wanted to know if the way the starting emulsions were prepared prior to compounding would affect the stability. Finally, the extemporaneous mixing of commercial IVLEs is recommended for certain formulations; thus, the present study is relevant to the clinical setting (Omegaven Fresenius, 1998).

Our current findings confirm previous work that showed the inclusion of MCT in a physical mixture with LCTs as a single emulsion yields stable all-in-one admixtures. The present study shows this to be true even when very long-chain triglycerides, such as fish oil, is present in the physical mixture. However, when MCTs and LCTs are manufactured as separate starting emulsions and then combined to form various ratios of the two, the stabilizing effects of MCTs with LCTs when used to compound an all-in-one admixture, are no longer present. This is presumably the result of pre-formed separate droplets of MCT or LCT in the individual emulsions that are protected by a coating of emulsifier which prevents displacement of LCT by MCT at the lipid droplet surface upon mixing. However, such displacement in these extemporaneously prepared starting emulsions could randomly occur upon coalescence of two different droplets, but would do so at the expense of colloidal stability. In contrast, when the oils are blended together and homogenized as a single emulsion physical mixture, a favorable interfacial location for MCT is achieved, as the individual droplets consist of both MCTs and LCTs which is maintained in the final emulsion.

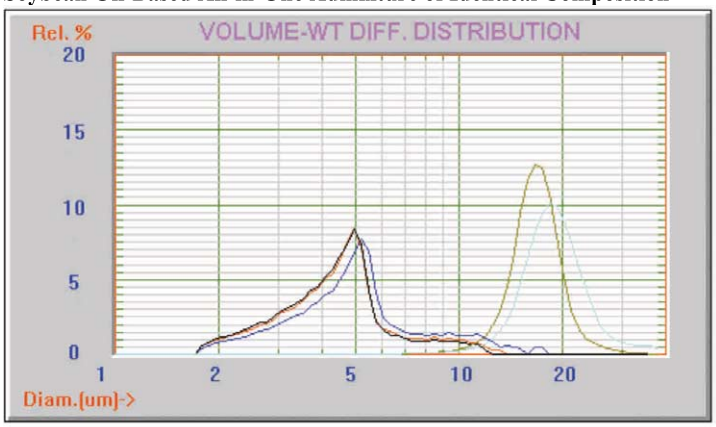
We speculate the apparent decline in PFAT > 5 μm seen in Table 2 for Admixture I is more likely an artifact related to the introduction of small amounts of air bubbles upon agitating the admixture prior to analysis in order to ensure a homogeneous sample. Such artifacts are not seen with Admixtures II and III as the contribution from such a small amount of air (volume-weighted) is overwhelmed by a rapidly expanding globule size distribution from active coalescence. However, there is a decline in PFAT > 5 μm between 24 and 30 h for both Admixtures II and III, and is also likely to be the result of oil adhering to the bag at these later stages of emulsion destabilization that affects the relative homogeneity of the sample.

As a final point of further comparison, Fig. 3A and B depict the volume-weighted profiles over 30 h for all-in-one admixtures of identical nutrient composition used in this study, except they were composed of pure LCT-based emulsions (Driscoll et al., 2001b). In particular, they show distinctly different peaks of instability (with respect to PFAT > 5 μm) at 24 and 30 h compared to Admixtures II and III in the present study. Finally, even though the emulsion mixtures used to make Admixtures II and III were unstable according to our PFAT > 5 μm criterion (> 0.4%), the coarseness of the dispersion is substantially less than with all-in-one admixtures made from pure LCTs under the same conditions. Thus, it can be inferred from the available data that pure LCT-based all-in-one admixtures degrade to a much greater extent than those containing MCTs and LCTs, and hence, are potentially more dangerous formulations in the clinical setting if they become unstable.

5. Conclusions

This study further corroborates previous findings that single emulsion physical mixtures of MCTs and LCTs produce stable all-in-one admixtures. This is even true when very long-chain triglycerides are included and thus the interfacial behavior of the egg lecithin emulsifier is favorably affected by the 'surface-bound' MCTs in these mixed emulsions. However, the stabilizing influence of MCTs on all-in-one admixtures is lost when physical mixtures of MCT and LCT are made extemporaneously from two separate starting emulsions. Thus, maximum all-in-one stability appears to be achieved when they are formulated from a physical blend of MCT and LCT oils as a single emulsion and therefore, the extemporaneous mixing of commercial IVLEs is not recommended.

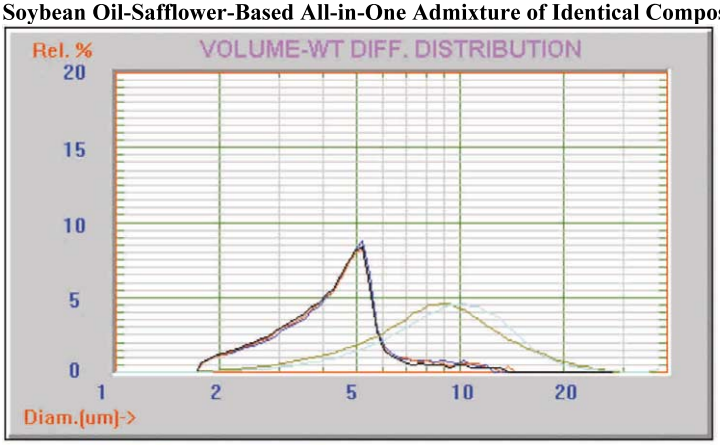
Admixture IV. Historical Comparison of Volume-Weighted Profile of a 100% Soybean Oil-Based All-in-One Admixture of Identical Composition



BLUE, RED, BLACK, GOLD, AQUA = All-in-One Admixture at Times 0, 4,8, 24 and 30 hours, respectively.

(a)

Admixture IV. Historical Comparison of Volume-Weighted Profile of a 50:50 Soybean Oil-Safflower-Based All-in-One Admixture of Identical Composition



BLUE, RED, BLACK, GOLD, AQUA = All-in-One Admixture at Times 0, 4,8, 24 and 30 hours, respectively.

(b)

Fig. 3. Admixture IV. Historical comparison of volume-weighted profile of: (a) a 100% soybean oil-based; (b) a 50:50 soybean oil-safflower-based all-in-one admixture of identical composition (Driscoll et al., 2001b).

Acknowledgements

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