Interactions between Parenteral Lipid Emulsions and Container Surfaces

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ABSTRACT: Objective: To evaluate the relationship between changes in emulsion globule size distributions and container uptake of lipid emulsions in total nutrient admixtures.

Methods: A total nutrient admixture was prepared from a commercial lipid emulsion, 20% ClinOleic®, separated into glass (borosilicate) and ethylene vinyl acetate (EVA) plastic containers, and then stored at ambient conditions for approximately 24 h. The large globule size distribution was monitored continuously for both containers, and the quantity of triglycerides associated with both containers was measured by liquid chromatography. The changes in mass of the EVA containers were also measured gravimetrically.

Results: The volume percent of globules greater than 5 microns in diameter (PFAT5) levels for an emulsion admixture in EVA containers showed a 75% reduction compared to a marginal decrease of PFAT5 when in the glass container. Extraction of the containers showed that the quantity of triglycerides associated with the EVA surfaces steadily increased with emulsion exposure time, while the glass showed a significantly lower triglyceride content compared to the EVA. Gravimetric measurements confirmed that the EVA containers gained significant mass during exposure to the emulsion admixture.

Conclusion: A time-dependent decrease in PFAT5 values for an emulsion admixture was associated with container triglyceride absorption where EVA containers had a greater uptake than glass containers. The larger globules appear to absorb preferentially, and the admixture globule size distribution fraction represented by PFAT5 accounts for 15–20% of the total triglyceride adsorption to the container.

KEYWORDS: Lipid emulsion, Total nutrient admixture, Container, Globule size distribution, Liquid chromatography

LAY ABSTRACT: The goal of this work is to evaluate how emulsions in total nutrition admixtures are affected by the containers within which they are stored. Specifically, the study examines how the emulsion globule size distribution in different containers is related to adsorption or absorption of the lipids onto or into the container. The admixtures were prepared from a commercial lipid emulsion, 20% ClinOleic®, and the containers were either glass (borosilicate) or plastic (ethylene vinyl acetate, EVA). The large globule size distribution was monitored continuously for both containers over the course of 24 h, and the quantity of triglycerides taken up by both containers was measured by liquid chromatography. The lipid uptake by the EVA containers was also monitored by gravimetric methods. Briefly, the percent of fat globules greater than 5 micrometers (PFAT5) in EVA containers showed a 75% reduction compared to a marginal decrease of PFAT5 when in the glass container. Extraction of the lipids from the containers showed that the quantity of triglycerides associated with the EVA surfaces steadily increased with admixture exposure time, while the glass showed a significantly lower triglyceride content. Gravimetric measurements confirmed that the EVA containers gained measurable mass during exposure to the emulsion admixture.

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Introduction

Triglyceride emulsions have been meeting the nutritional needs of critically ill patients for more than 50 years with the introduction of soybean oil–based emulsions. Concerns for patient safety stemming from the small fraction of larger globule sizes (>5 microns) present in parenteral emulsions that may produce localized emboli in the narrowed capillaries of the lung have been discussed for decades (1). Based on the combination of safety concerns and manufacturing capability, limits on both the mean globule size and the volume percent of globules greater than 5 microns in diameter (PFAT$_5$) were established. USP mandates that for the parent emulsion, the mean globule size is not to exceed 500 nm and the PFAT$_5$ cannot exceed 0.05%. More recent work has applied the USP limits to evaluate the time-dependent behavior of emulsion globule size distribution (GSD) in total nutrient admixtures (2, 3). This is a natural extension of the existing parent emulsion requirements which probes formulation and admixture storage conditions on emulsion stability (4, 5). The need for safe, effective emulsions for parenteral nutrition and emerging drug delivery applications continue to drive our improved understanding of their physicochemical behavior.

A stable emulsion GSD is one that is unchanging over time for the formulation and storage condition of interest. GSD instability is most often observed as an increase in the large globule fraction of the emulsion (5). However, two previously published works have observed a reproducible decrease in PFAT$_5$ for emulsion admixtures over time (24 h) in a plastic containment system (6, 7). This unique behavior was originally attributed to a decreasing gas bubble concentration, but this hypothesis was subsequently discounted due to identical PFAT$_5$ characteristics observed under pressurized conditions where air bubbles would not be present. Because plastic container surfaces such as ethylene vinyl acetate (EVA) and polyvinylchloride (PVC) have some affinity for lipid emulsions (8–11), a container effect on GSD was another plausible explanation for the observed decrease in PFAT$_5$. Monitoring and understanding transient GSD characteristics is particularly important, as emulsions may be compounded and formulated in a variety of admixtures to meet individual patient needs.

This work describes the application of a new, automated sampling tool for exploring dynamic changes in GSD as a function of time and for different container systems. Glass and EVA containers were monitored using an automated, single-particle optical sensing tool under ambient conditions where sampling of emulsion admixtures could be performed continuously over the 24 h time interval of interest. Triglyceride associated with the containers was quantified by a high-performance liquid chromatography (HPLC) method and by gravimetric measurements in order to confirm surface affinity. The results provide a new perspective on the importance of container interactions on PFAT$_5$ measurements. Furthermore, there may be opportunities for mitigating large globule risk beyond customary formulation, processing, and filtration approaches.

Materials and Methods

Parent Lipid Emulsion and Containers

The parent intravenous lipid emulsion used in this study was a 20% ClinOleic® lipid emulsion, which has a 20:80 soybean:olive oil composition. The plastic containers used for the ClinOleic® commercial product (12) consist of a multilayer film with the following material components: polypropylene (PP), styrene-ethylene-butylene-styrene block copolymer (SEBS), poly(ethylene vinyl acetate) (EVA), and poly(cyclohexylenedimethylene cyclohexanediacarboxylate) (PCCE). The PP-SEBS/EVA/PCCE container is phthalate-free, has an oxygen barrier outer packaging, and the PP-SEBS layer is contacting the lipid emulsion dispersion. After preparation of the total nutrient admixture (TNA), the TNA was transferred to either the EVA (Baxter Empty ALL-IN-ONE E.V.A Container for Gravity Transfer, 1000 mL, code 2B8114, Baxter, Deerfield, IL) comprised of EVA or the glass containers (1000 mL glass bottles, catalog 89000-240, VWR, Radnor, PA) comprised of borosilicate glass.

Admixtures

The admixture studied was prepared by mixing 1 part 20% ClinOleic® and 8 parts of Clinimix® E 5/25 and had a final composition as shown in Table I. Clinimix® E 5/25 (13) is a sterile, nonpyrogenic, hypertonic, dual-chamber product that when mixed produces a final amino acid concentration of 5% and a dextrose concentration of 25% with additional electrolytes. Controls consisting of either Clinimix® E 5/25 (2-in-1 Clinimix® control) or empty EVA containers were
also used in this study. Approximately 900 g of the 2-in-1 Clinimix® control or 3-in-1 test admixture was transferred into the separate 1 L EVA or 1 L glass bottles, with all samples prepared in triplicate for each time point tested.

Testing was designed such that three 3-in-1 admixture units in glass containers and three 3-in-1 admixture units in EVA containers were sampled periodically over approximately 24 h for PFAT₅ determination at ambient conditions. The remaining test and control units were consumed for testing and processing at the scheduled interval.

**Gravimetric Analysis**

The added mass to the EVA containers from exposure to the parenteral lipid emulsion was determined gravimetrically using an analytical balance (Sartorius Model- Research RC210 S Range 0.2 g to 210 g ± 0.00015 g). Prior to use, each empty EVA container was placed into a stainless steel cup and weighed in triplicate, wrapped in aluminum foil to protect it from inadvertent contact, and then filled with test solution. After completion of exposure time (0 and 24 h), the solution contents of each EVA container were carefully removed and rinsed with copious amounts of MilliQ water followed by drying with filtered nitrogen gas for 7 days. The final mass measurements were also made in triplicate. Gravimetric analysis was not performed on the glass containers.

**Single-Particle Optical Sensing (SPOS)**

The PFAT₅ was determined using an AccuSizer™ model 780 APS (Particle Sizing Systems, Santa Barbara, CA) utilizing an LE 400 sensor in extinction mode, which was previously calibrated with polystyrene latex spheres. Measurements were performed using the L2W788 software, version 2.19 from Particle Sizing Systems.

Admixtures were tested periodically for PFAT₅ values for up to 24 h while they were stored at ambient laboratory conditions in both glass and EVA containers. The 24 h periodic Accusizer testing was facilitated by using catheters (Catalog PE200, B&D Development, Inc., Franklin Lakes, NJ) to sample directly from the sealed EVA and glass containers, and a laboratory shaker (Catalog 14-271-9, Thermo Scientific, Asheville, NC) was used to gently mix the samples. A 10 port sample valve with supported software (Catalog C25-6180E, Valco Instruments, Houston TX) was used to select each sample for analysis, and finally, the automation software (Automate 6, Network Automation, Los Angeles CA) was programmed to automatically activate and control the Accusizer instrument and sampling valve to transfer samples to the APS sampler in a specified sequence. The time between runs was not exactly 1 h, and so the time points at which the globule size distribution was measured do not coincide exactly with the times when the HPLC samples were acquired.

**Liquid Chromatography (HPLC)**

After test solution exposure, the containers were rinsed with water and dried with nitrogen. In some cases, the containers were also weighed. Each dried EVA container was filled with 50 mL of isopropyl alcohol (IPA), taking care to ensure that the IPA contacted the entire interior surface of the EVA unit. The IPA-filled EVA containers were left at ambient conditions for 24 h, at which time a portion of the IPA solution was transferred into an HPLC vial. Glass containers followed a similar procedure for preparation of IPA solutions suitable for HPLC.

Using each of the oils (soybean, olive, and 20:80 soybean:olive), three stock standard solutions were prepared where ~50 mg of an oil was measured into a tared 50 mL flask and diluted with IPA to make approximately 1000 µg oil/mL stocks that were further diluted in IPA to make the 100, 50, 25, 10, and 5 µg oil/mL standards. All of these IPA samples and standards were analyzed with an HPLC system equipped with a corona-charged aerosol detector (HPLC-CAD). The sequence was set up so that the

### TABLE I

**Nutrition Profile of Formulas**

<table>
<thead>
<tr>
<th>Component</th>
<th>3-in-1 Test Article Concentration</th>
<th>2-in-1 Control Article Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino Acid</td>
<td>4.4 %</td>
<td>5.0 %</td>
</tr>
<tr>
<td>Dextrose</td>
<td>22.2 %</td>
<td>25.0 %</td>
</tr>
<tr>
<td>ClinOleic®</td>
<td>2.2 %</td>
<td>0 %</td>
</tr>
<tr>
<td>Phosphates</td>
<td>15.4 mmol/L</td>
<td>15 mmol/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>31 mEq/L</td>
<td>35 mEq/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>27 mEq/L</td>
<td>30 mEq/L</td>
</tr>
<tr>
<td>Magnesium</td>
<td>4.4 mEq/L</td>
<td>5 mEq/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>4 mEq/L</td>
<td>4.5 mEq/L</td>
</tr>
</tbody>
</table>

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mixed oil standards were run in increasing concentration followed by the individual olive oil and soybean oil standards, with the entire set bracketed by a blank IPA rinse. This standard set was followed by 10 samples, and this was repeated for all samples, with the final sample set being followed by a standard set. The HPLC-CAD was set up using a Grace Adsorbosphere (Grace Davison Discovery Science, Deerfield, IL) column (C18; 150 × 4.6 mm; 3 micron) at a column temperature of 25 °C. An isocratic mobile phase comprised of 60% IPA and 40% acetonitrile was used at a flow rate of 750 μL/min.

**Results**

Figure 1 shows the time-dependent change in PFAT\(_5\) as a function of container type, EVA or glass. While the differences in initial PFAT\(_5\) values are within experimental error for each container type, there are clearly a smaller percentage of large emulsion particles for the EVA container relative to the glass at 24 h. The observed decrease in PFAT\(_5\) for the admixture in the EVA container from an initial value of 0.022% to about 0.004% in 24 h reproduces the significant decrease previously observed (6, 7). The PFAT\(_5\) for the admixture in glass showed a more modest decrease from about 0.018% to about 0.014%. Given that the PFAT\(_x\) values represent percentages of the oil that is in the form of globules greater than x microns, the PFAT\(_x\) can be converted into a mass of oil. For 900 g of admixture composed of 2.22% oil by mass (19.98 g), the average initial EVA PFAT\(_5\) value of 0.022% corresponds to a mass of 4.44 mg of oil in the form of globules greater than 5 microns. In addition, the automated sampling system employed in this study reveals for the first time a more detailed picture of kinetics of the decrease in PFAT\(_5\).

Figure 2 shows the chromatograms obtained after 0, 2, 6, and 24 h of contact time with the admixture for both glass and EVA, as well as the controls that correspond to a 24 h contact time Clinimix® controls. A chromatogram of the 20:80 soy:olive mixture is included for reference. The four peaks used for calibration are labeled (*) along with the glyceryl trioleate (**). The IPA extracts from glass (bottom curves) and EVA (middle curves) align well with the oil mixture standard (top curve).
8.7 min and 9.3 min are primarily contributed from the olive oil. The peak at 8.7 min was assigned as glyceryl trioleate based on retention time comparison with a standard, and the retention times for the chromatograms were adjusted by a small scale factor to align the glyceryl trioleate peak. Calibration curves were generated for each of these four peaks with $R^2$ values ranging from 0.980 to 0.993, with the two highest correlation coefficients corresponding to the two peaks mostly contributed from olive oil including the glyceryl trioleate.

Those containers that were filled with only Clinimix® (which contains no triglycerides) and those that were left empty had no detected oil in their IPA extracts, and thus these negative controls confirmed that there were no interfering peaks from the amino acid solution or container extractables. While these negative controls showed no interference with the major triglyceride peaks, they do contain a broad band of peaks starting around 2 min with a maximum around 3 min and a tail extending out to around 5 min. Because this pattern was also observed for the empty EVA container, this pattern is not due to triglycerides, phospholipids, or even the Clinimix components. It seems reasonable to assign this band of peaks to the compounds extracted from the EVA container by the IPA. This band of peaks can be seen to increase in amplitude with the admixture exposure time. One hypothesis for this increase is that the triglyceride intrusion into the EVA film is functioning as a cosolvent to enhance the extraction efficiency of the IPA.

The IPA-extracted triglyceride concentrations for the glass and EVA containers are depicted in Figure 3. Each container type exposed momentarily to the triglyceride-containing admixtures ($t = 0$) showed a low level of detectable triglycerides in their chromatograms. However, at $t = 2$, 6, and 24 h, the EVA containers showed significantly higher peak intensities observed in the chromatograms compared to the glass at similar admixture exposure times. These concentrations, which are expressed in parts per million (ppm) in the IPA solution, can be converted to the total mass of triglyceride extracted from the containers. For the EVA containers exposed to the admixture for 24 h, the IPA extract had an average triglyceride concentration of 68 ppm. As this extraction used 50 mL of IPA, this 68 ppm corresponds to 3.4 mg of triglyceride. The corresponding 24 h glass containers had an average of 0.77 mg of triglyceride, which means that after 24 h there was 4.4 times more triglyceride extracted from the EVA containers compared to the glass containers. This is in addition to the fact that the glass is impermeable to triglycerides, while it is known that the triglycerides can migrate through EVA films.

Finally, simple gravimetric analyses also demonstrated a significant increase in mass for the EVA containers after 24 h contact time to the admixture solution relative to the Clinimix® solution (Table II). Exposure of the EVA containers to the Clinimix® solution alone for 0 and 24 h created an average decrease of 8.5 and 8.6 mg in the container mass, respectively. In this case, the mass loss from the Clinimix® controls may be associated with leachables or extractables of the container system. Using the mass loss from the Clinimix® controls as a baseline, the net gains in container mass due to emulsion absorption would be about 3.5 mg and 20.7 mg for admixture exposure at 0 and 24 h, respectively. While there remains uncertainty in the exact proportions of extractives and absorptions comprising the net gravimetric result, after 24 h there is clearly an increase in EVA container mass. This is consistent with the loss in solution triglycerides (PFAT5 measurements) and the increase in triglyceride extractives (HPLC results) de-
TABLE II
Gravimetric, HPLC, and PFATx Data from Before and After Solution Exposure

<table>
<thead>
<tr>
<th>Container</th>
<th>Time (hrs)a</th>
<th>Gravimetric (mg)</th>
<th>Triglyceride (mg)</th>
<th>PFAT2 (mg)</th>
<th>PFAT5 (mg)</th>
<th>PFAT10 (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVA</td>
<td>Initial</td>
<td>−8.63 ± 1.3b</td>
<td>0.00 ± 0.0c</td>
<td>10.53 ± 1.0</td>
<td>4.44 ± 0.7</td>
<td>1.31 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>N/A</td>
<td>0.59 ± 0.1</td>
<td>11.57 ± 0.8</td>
<td>4.35 ± 0.6</td>
<td>0.85 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>N/A</td>
<td>1.11 ± 0.3</td>
<td>10.91 ± 0.6</td>
<td>3.50 ± 0.4</td>
<td>0.37 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>12.03 ± 3.5</td>
<td>3.40 ± 0.9</td>
<td>4.06 ± 2.0</td>
<td>0.90 ± 0.4</td>
<td>0.08 ± 0.1</td>
</tr>
<tr>
<td>Differenced</td>
<td>20.66 ± 3.7</td>
<td>3.40 ± 0.9</td>
<td>−6.47 ± 2.2</td>
<td>−3.54 ± 0.9</td>
<td>−1.23 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>%Difference</td>
<td>N/A</td>
<td>N/A</td>
<td>61.4% ↓</td>
<td>79.8% ↓</td>
<td>93.7% ↓</td>
<td></td>
</tr>
<tr>
<td>Glass</td>
<td>Initial</td>
<td>N/A</td>
<td>0.00 ± 0.0c</td>
<td>9.46 ± 0.9</td>
<td>3.67 ± 0.6</td>
<td>0.84 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>N/A</td>
<td>0.09 ± 0.1</td>
<td>10.29 ± 0.4</td>
<td>3.86 ± 0.3</td>
<td>0.74 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>N/A</td>
<td>0.23 ± 0.0</td>
<td>10.71 ± 0.5</td>
<td>3.67 ± 0.3</td>
<td>0.54 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>N/A</td>
<td>0.77 ± 0.2</td>
<td>9.42 ± 1.4</td>
<td>2.89 ± 0.5</td>
<td>0.26 ± 0.1</td>
</tr>
<tr>
<td>Differenced</td>
<td>N/A</td>
<td>0.77 ± 0.2</td>
<td>−0.04 ± 1.7</td>
<td>−0.79 ± 0.7</td>
<td>−0.58 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>%Difference</td>
<td>N/A</td>
<td>N/A</td>
<td>0.4% ↓</td>
<td>21.4% ↓</td>
<td>69.3% ↓</td>
<td></td>
</tr>
</tbody>
</table>

a Time points—The timepoints used for the PFATx data were the closest to the stated 2, 6, and 24 h times.
b Clinimix 24 h control—Gravimetric mass as calculated from control units filled with only Clinimix and stored for 24 h in EVA containers.
 c Clinimix control—Triglyceride mass as calculated from control units filled with only Clinimix and stored for 24 h in either EVA or glass containers.
d Difference—Difference between measured mass at initial interval and 24 h interval for both EVA and glass containers for each test.

scribed above. No gravimetric data was obtained for the glass containers due to limitations of the analytical balance method.

Discussion

Time-dependent triglyceride adsorption onto or absorption within the EVA container was confirmed as a primary mode of solution globule loss by HPLC analysis. The triglyceride levels in the IPA extract solutions were found to increase more significantly for the EVA container relative to the glass container, especially at 24 h. A small but measurable amount of triglycerides were also observed for each container at t = 0 where the containers were simply exposed to the admixture solution. The increase in triglyceride levels from EVA containers is consistent with the greater loss of emulsion globules from solution described by the decrease in PFAT5 and by the increase in mass observed for the EVA containers.

To assess the size-dependent changes in globule size distribution more directly, it is instructive to examine the differential GSDs where the changes occurring for each size bin are easily delineated. Figure 4 shows that the differential GSDs (converted to mass) of the EVA test samples experienced significant loss of mass during the 24 h container exposure. The ratios of the 24 h data to the 2 h data show that as the globule size increases, the percent solution mass loss increases as well. There is an approximately linear increase in globule mass loss from 75% to almost 100% as the size increases from 2 to 10 microns. This means that the larger globules make a larger contribution to absorbed triglycerides on a mass basis. Because the experimental “noise” increases at large sizes (>10 microns) due to the lack of globule counts, those globules were not included in this part of the analysis. Elaborating further by example, the mass of oil for the globules in the 4.5–5 micron bin decreased 84% from ~1.7 mg to 0.27 mg. If this 84% decrease in mass at the 5 micron bin occurred over all globule sizes, we would expect the initial 20 g of oil to decrease by 16.8 g, leaving only 3.2 g of oil in the container. Gravimetric analysis shows that the actual change is on the order of 20 mg, which is only ~0.1% of total oil. Thus, we conclude that the contribution of mass absorbed is weighted more heavily to contributions from the larger sized glob-
ules. In fact, the mass increase from globules >2 microns accounts for almost 31% of the 21 mg total mass gain observed by the container. Table II provides a detailed summary of the mass of oil determined gravimetrically, by HPLC, and as calculated with cumulative PFATx (x=2,5, and 10). The size-dependent trends observed in cumulative PFATx mass loss presented in Table II are simply another way of demonstrating the trends revealed by differential distribution results highlighted in Figure 4.

There are many possible mechanisms for globule-container interactions, ranging from adsorption of intact globules to the container surface and absorption of the triglyceride molecules into the polymeric matrix of the container, and a detailed analysis is beyond the scope of this paper. Nonetheless, a simple closest-packed spheres model calculation showed that 5 micron sized globules adsorbed as a closest packed monolayer would amount to 191 mg, and a monolayer of 200 nm sized globules corresponds to almost 8 mg. Thus, this simple calculation suggests that the gravimetrically measured 21 mg of triglyceride could be explained by less than a full monolayer coverage of large globules or a combination monolayer composed of larger and smaller globules. With the size-dependent adsorption described above, there appears to be sufficient container surface area to account for the mass change without necessarily invoking triglyceride diffusion through the container film. However, the lack of full mass recovery from IPA extraction of the EVA container suggests that significant triglyceride penetration into the EVA does indeed occur.

In addition to triglyceride components, phospholipids were also considered for potential adsorption owing to their functional presence at each globule surface as well as a significant concentration present as micelles. HPLC analyses of phospholipid controls were compared with the chromatograms of IPA-extracted EVA films. There were no significant contributions to the chromatogram peaks that could be attributed to phospholipids. Therefore, the more water-soluble phospholipids and associated micelles do not appear to contribute any significant absorbed mass to the EVA films.

The results highlight the influence that container interactions can have on the physicochemical properties of emulsions. The lipophilic porosity of the EVA container creates a more complex time-dependent response in the admixture GSD profile. While not a significant mass loss from a therapeutic dose point of view, the admixture behavior does challenge traditional interpretations of emulsion instability. For example, in some instances the rate of large globule growth might be offset by a large globule adsorption process by the container, yielding an overall unchanged GSD. While no significant therapeutic impact would be expected from this scenario, clear definitions of admixture stability become more challenging. The impact of formulation and storage conditions on admixture stability is often inferred in large part from GSD behavior. However, there is an opportunity to enhance that understanding by considering container adsorption phenomena.

Conclusions

These experiments show that as a ClinOleic® admixture is incubated with EVA and glass containers, there is a greater association of the triglycerides with the EVA compared to the glass. The uptake of triglycerides was monitored gravimetrically and by HPLC. As the triglyceride uptake by the container increased, the solution PFAT5 value decreased. These results support the hypothesis that the EVA container can function as a sink for the emulsion globule triglycerides. The

Figure 4

Representative differential mass distribution by globule size of ClinOleic®/Clinimix® admixture calculated from SPOS data at the initial time point (solid line) and t ~ 24 h (dashed line) in an EVA container. The relative percent of solution mass loss by globule size at 24 h is also shown (solid circles).
larger globule sizes have been shown to have a greater relative affinity for adsorption compared to the smaller sizes. While the mechanistic details of the phenomena remain to be elucidated, there are implications for container and process technologies that look to control and tailor the size distribution of emulsions. Furthermore, interpreting physiochemical stability data of admixtures by monitoring changes in PFAT5 should consider container interactions. Consequently, time-dependent trends in GSD observed for parent emulsions may not translate directly to admixtures due to dependencies on formulation, storage conditions, and container type.

Conflict of Interest Declaration

At the time that this work was performed, all of the authors were working at Baxter Healthcare, and this research was financially supported by Baxter Healthcare. The research does not provide Baxter with a competitive advantage, and so the authors declare that no apparent conflict of interest exists.

References


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