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(54) **LIPID PARTICLES, METHODS OF GENERATING SAME, AND METHODS OF USING SAME**

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(52) **U.S. Cl.**

CPC ***A61K 9/1075*** (2013.01); ***A61K 9/0029*** (2013.01); ***A61K 35/20*** (2013.01)

(57) **ABSTRACT**

Lipid particles, methods of generating same, and methods of using same. The lipid particles can be made from milk fat. The methods of generating the lipid particles can include melt fractionating milk fat, combining the melt-fractionated milk fat with a surfactant, obtaining the lipid particles by emulsifying the combined melt-fractionated milk fat and surfactant, and optionally, autoclaving the lipid particles. The methods of using the lipid particles can include parenterally administering the lipid particles to a subject in, for example, parenteral nutrition.

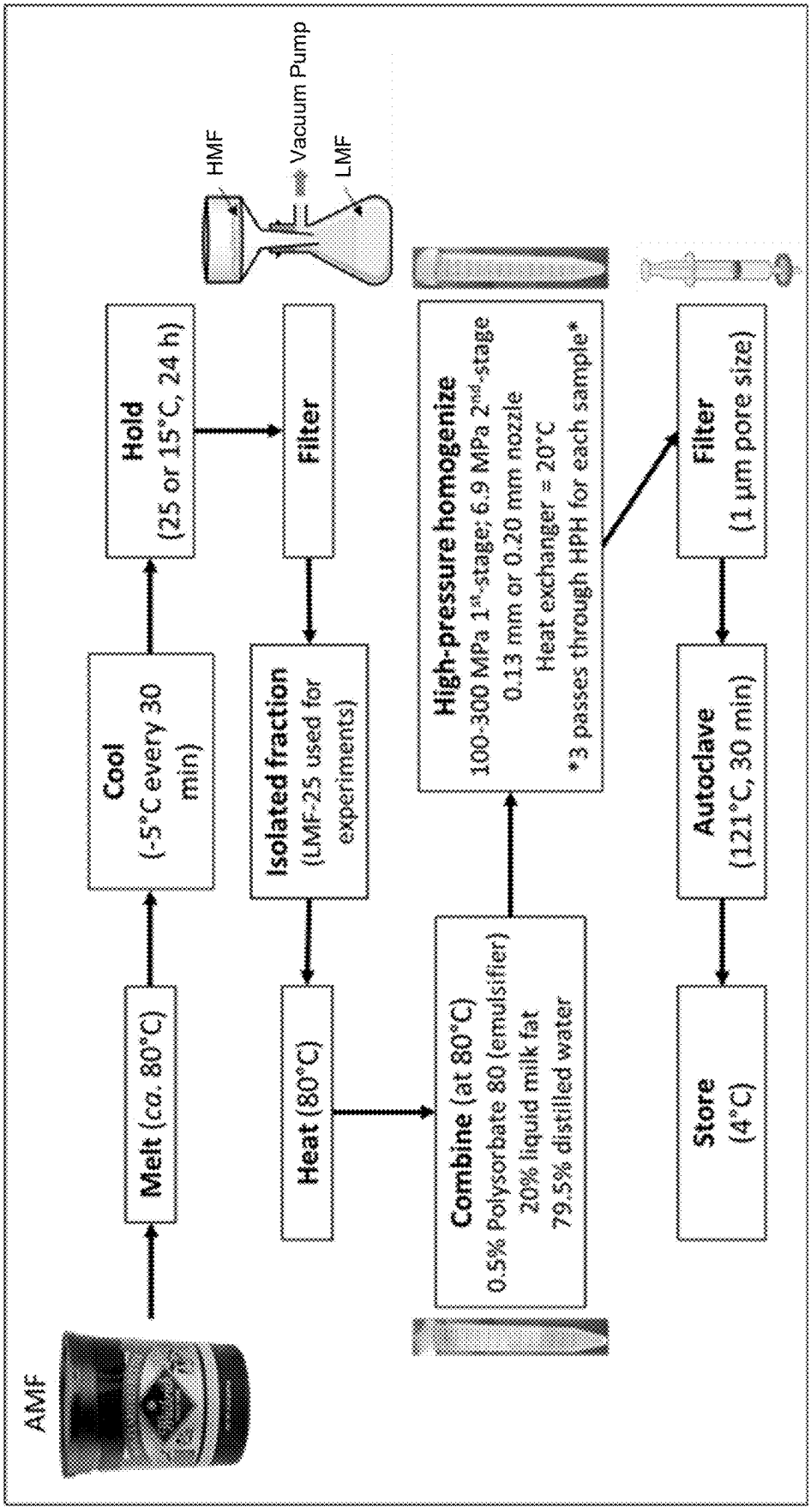
AMF
Melt (ca. 80°C)
Cool
(-5°C every 30 min)
Hold
(25 or 15°C, 24 h)
HMF
Vacuum Pump
LMF
Filter
Isolated fraction
(LMF-25 used for experiments)
Heat (80°C)
Combine (at 80°C)
0.5% Polysorbate 80 (emulsifier)
20% liquid milk fat
79.5% distilled water
High-pressure homogenize
100-300 MPa 1st-stage; 6.9 MPa 2nd-stage
0.13 mm or 0.20 mm nozzle
Heat exchanger = 20°C
3 passes through HPH for each sample
Filter
(1 µm pore size)
Autoclave
(121°C, 30 min)
Store
(4°C)

FIG. 1

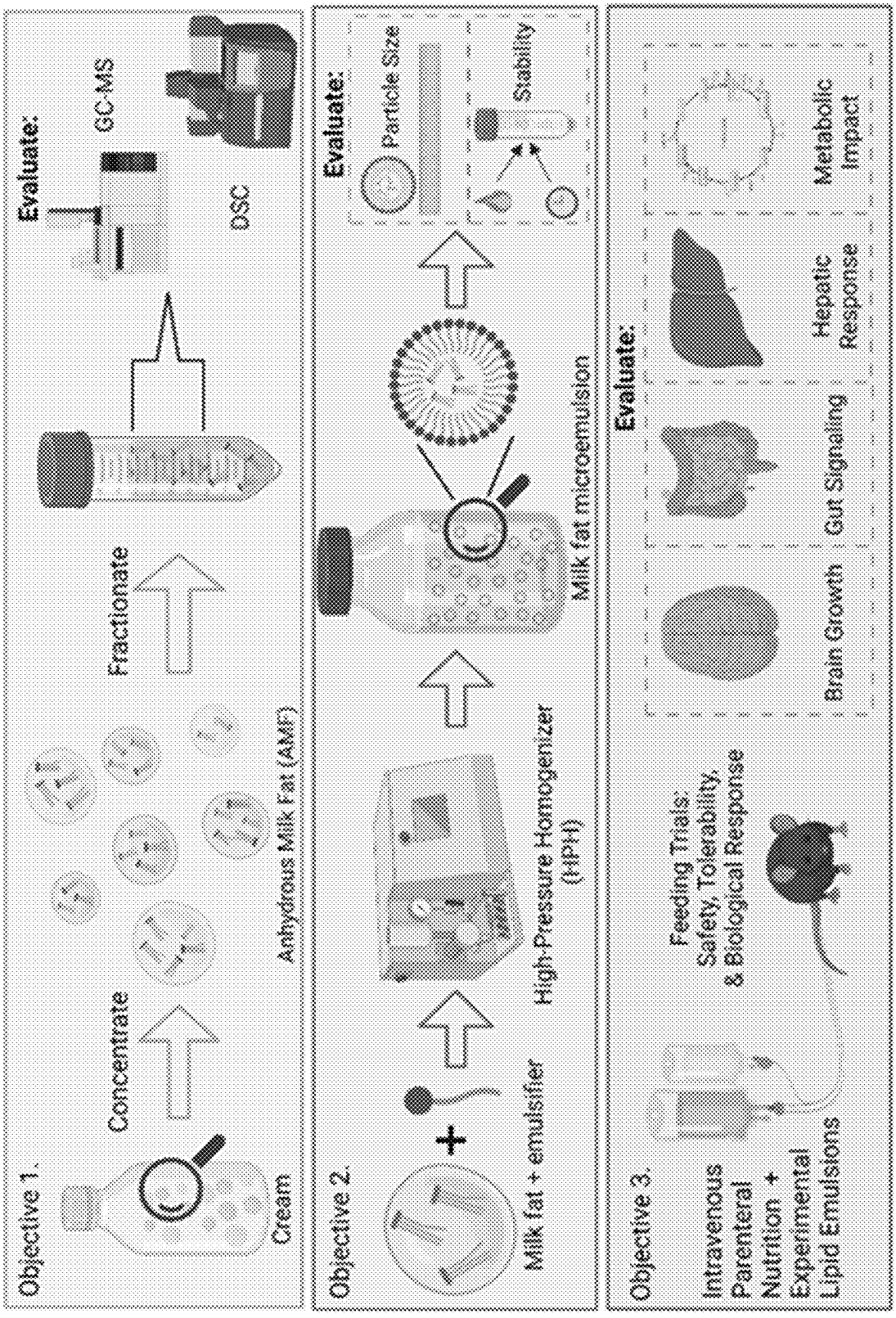
Objective 1.
Cream
Concentrate
Anhydrous Milk Fat (AMF)
Fractionate
Evaluate:
GC-MS
DSC
Objective 2.
Milk fat + emulsifier
High-Pressure Homogenizer (HPH)
Milk fat microemulsion
Evaluate:
Particle Size
Stability
Objective 3.
Intravenous Parenteral Nutrition + Experimental Lipid Emulsions
Feeding Trials: Safety, Tolerability, & Biological Response
Evaluate:
Brain Growth
Gut Signaling
Hepatic Response
Metabolic Impact

FIG. 2

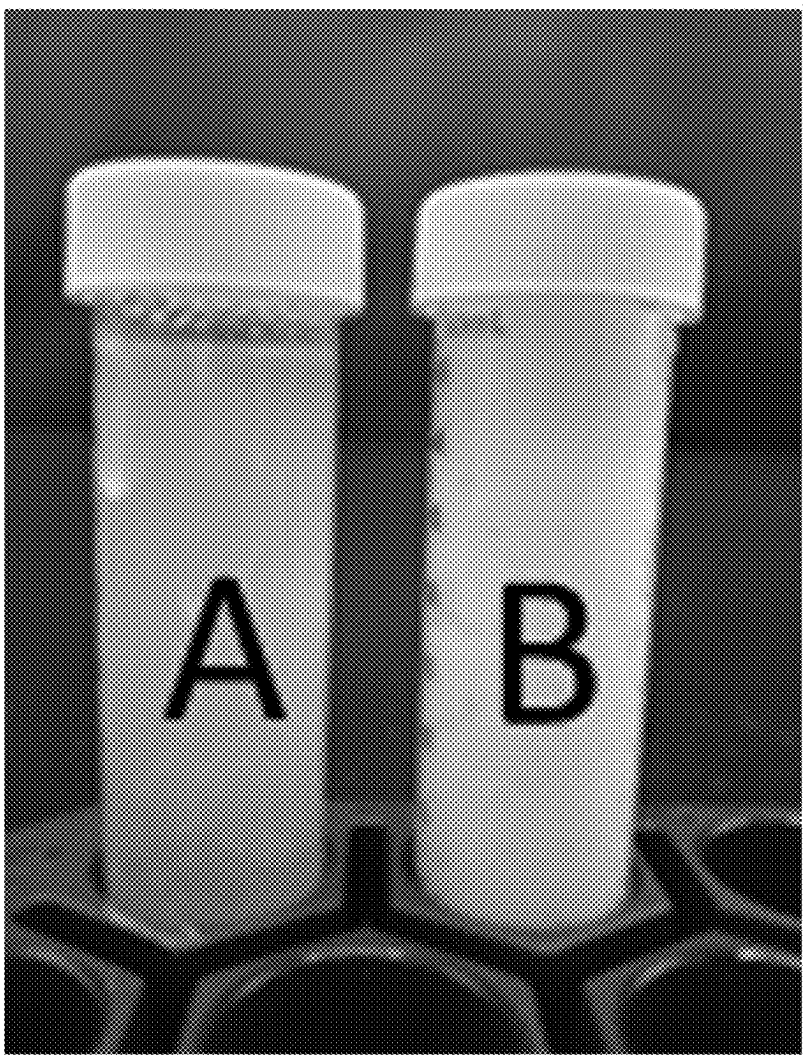

FIG. 3

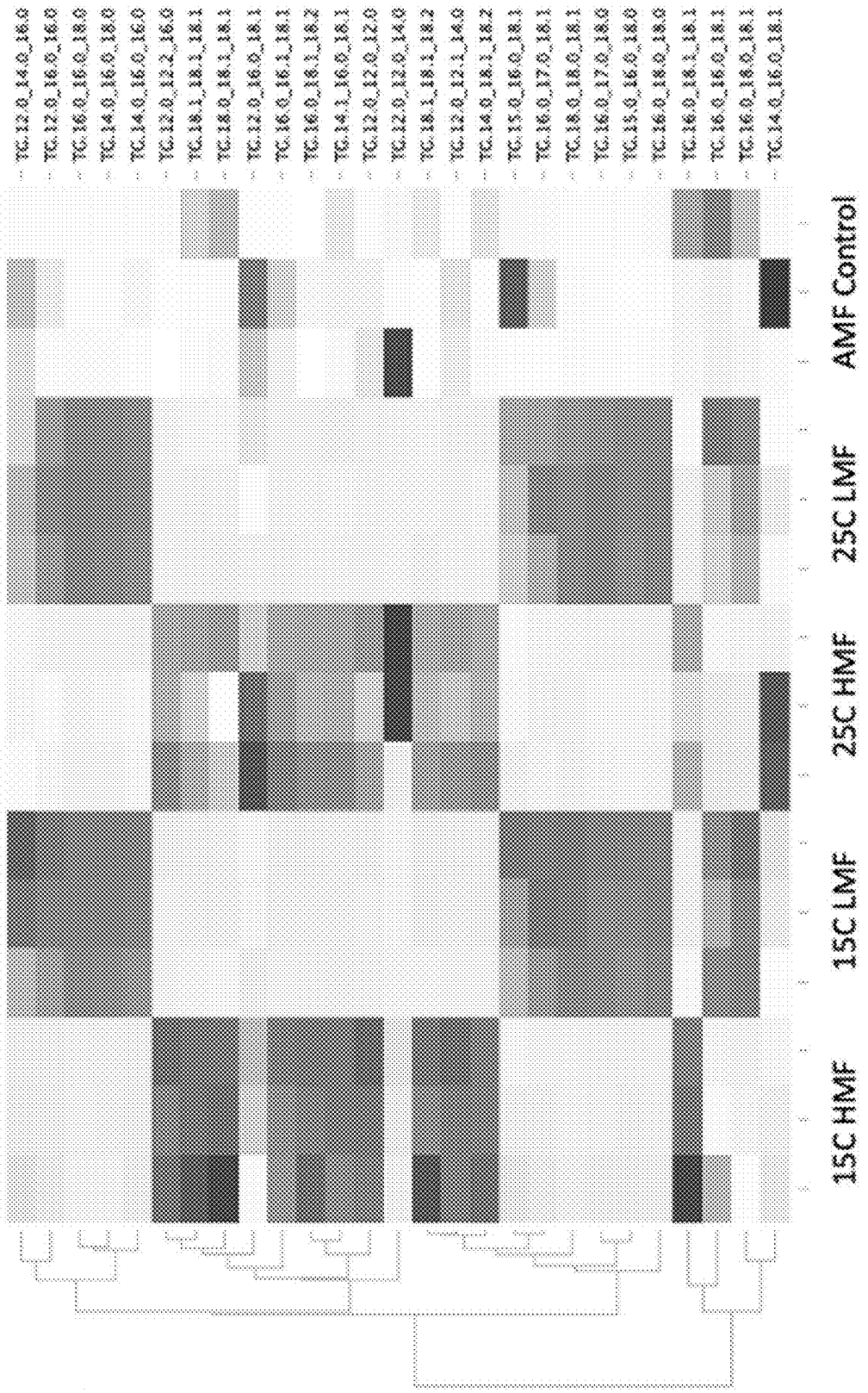
TC.12.0_14.0_16.0
TC.12.0_16.0_16.0
TC.16.0_16.0_18.0
TC.14.0_16.0_18.0
TC.14.0_16.0_16.0
TC.12.0_12.2_16.0
TC.18.1_18.1_18.1
TC.18.0_18.1_18.1
TC.12.0_16.0_18.1
TC.16.0_16.1_18.1
TC.16.0_18.1_18.2
TC.14.1_16.0_16.1
TC.12.0_12.0_12.0
TC.12.0_12.0_14.0
TC.18.1_18.1_18.2
TC.12.0_12.1_14.0
TC.14.0_18.1_18.2
TC.15.0_16.0_18.1
TC.16.0_17.0_18.1
TC.18.0_18.0_18.1
TC.16.0_17.0_18.0
TC.15.0_16.0_18.0
TC.16.0_18.0_18.0
TC.16.0_18.1_18.1
TC.16.0_16.0_18.1
TC.16.0_18.0_18.1
TC.14.0_16.0_18.1
15C HMF
15C LMF
25C HMF
25C LMF
AMF Control

FIG. 4

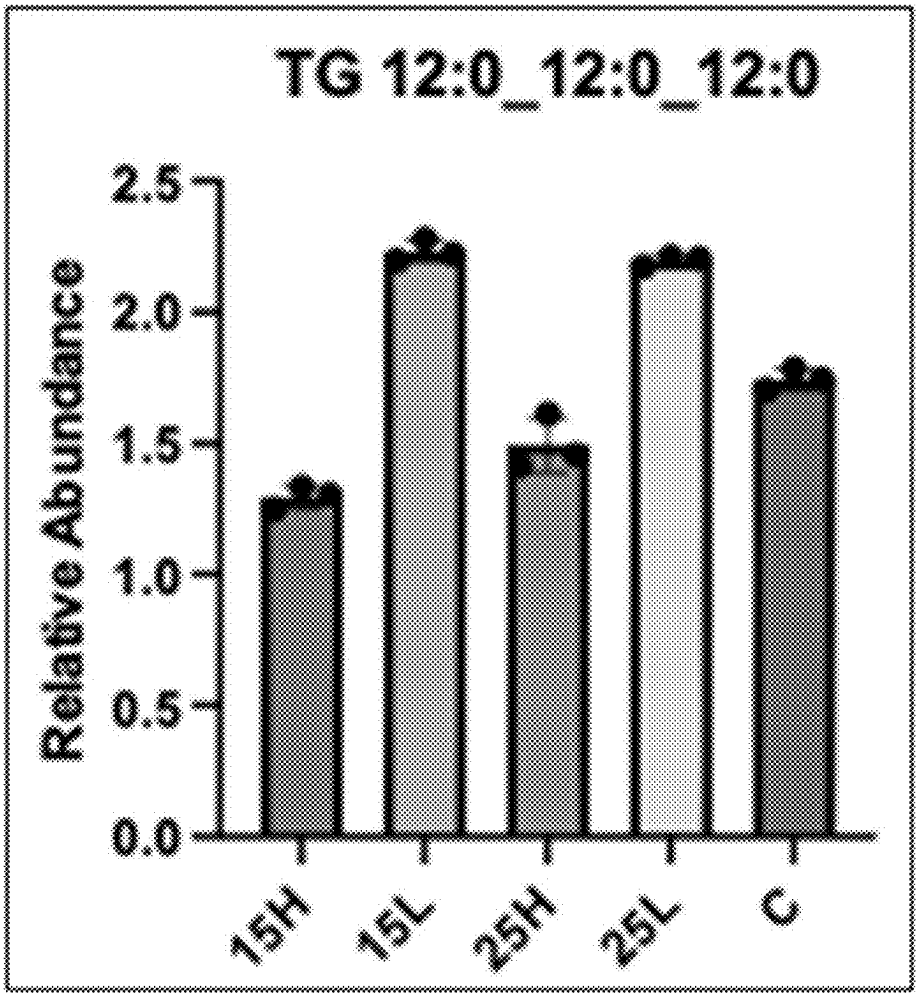
TG 12:0_12:0_12:0
Relative Abundance
2.5
2.0
1.5
1.0
0.5
0.0
15H
15L
25H
25L
C

FIG. 5

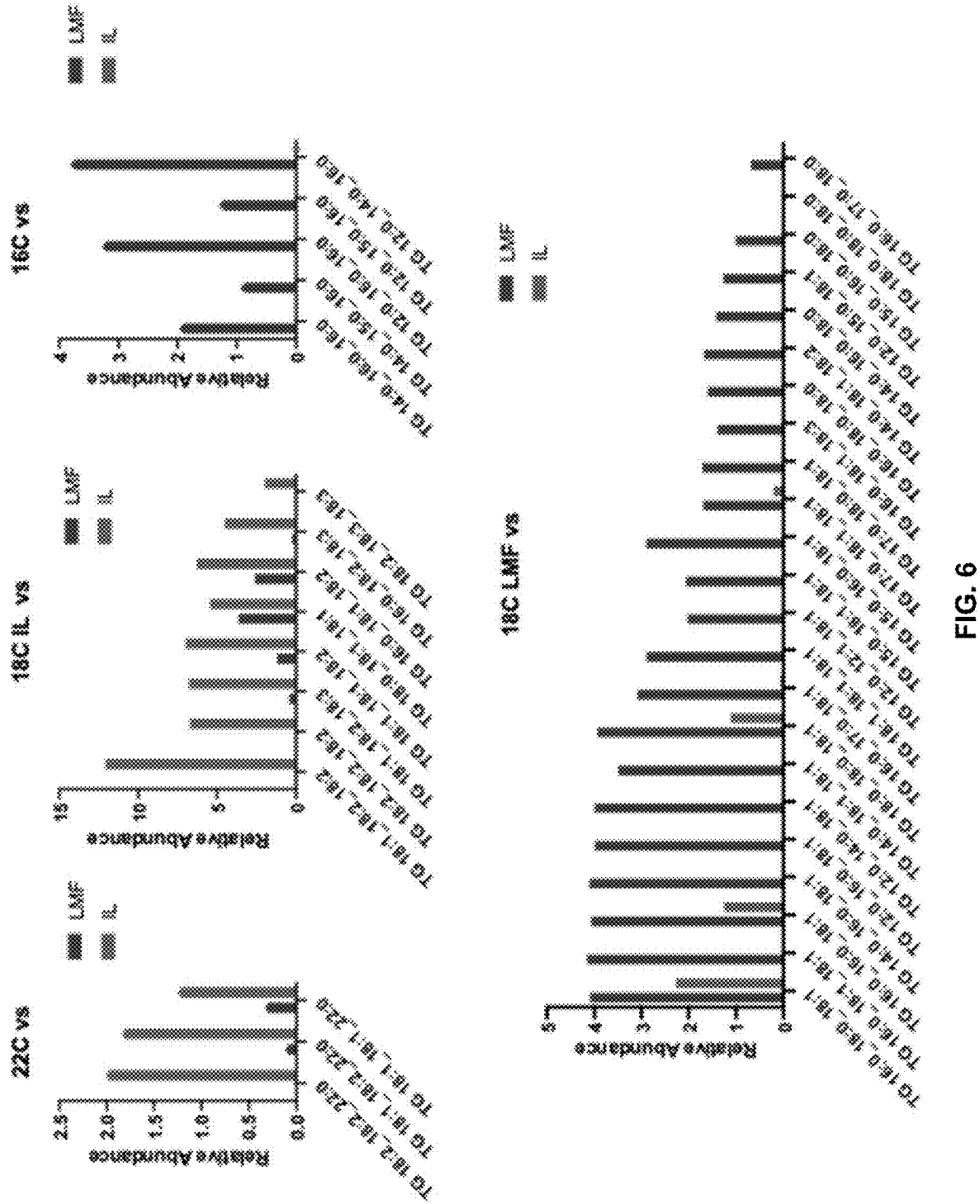
LMF
IL
16C vs
Relative Abundance
TG 14:0_16:0_16:0
TG 12:0_14:0_16:0
TG 12:0_16:0_16:0
TG 14:0_16:0_16:0
18C IL vs
Relative Abundance
TG 18:1_18:2_18:2
TG 18:2_18:2_18:2
TG 18:1_18:1_18:2
TG 18:0_18:1_18:2
TG 16:0_18:1_18:2
TG 18:2_18:2_18:3
22C vs
Relative Abundance
TG 18:1_18:2_22:0
TG 18:2_18:2_22:0
18C LMF vs
Relative Abundance
TG 16:0_18:1_18:1
TG 16:0_16:1_18:1
TG 16:0_18:0_18:1
TG 14:0_16:0_18:1
TG 12:0_16:0_18:1
TG 16:1_18:1_18:1
TG 15:0_16:0_18:1
TG 17:0_18:1_18:1
TG 16:0_18:0_18:0
TG 14:0_16:0_18:0
TG 12:0_15:0_18:1
TG 16:0_18:1_18:2
TG 14:0_16:0_18:2
TG 12:0_16:0_18:2
TG 14:0_16:0_18:1
TG 16:0_16:0_18:1
TG 16:0_17:0_18:1
TG 15:0_16:0_18:1
TG 12:0_16:1_18:1
TG 16:1_17:0_18:1
TG 16:0_17:0_18:0
TG 14:0_16:0_18:0
TG 12:0_16:0_18:1
TG 14:0_16:0_18:1
TG 16:0_16:0_18:1
TG 16:0_18:0_18:1
TG 16:0_18:0_18:0
TG 16:0_17:0_18:0

FIG. 6

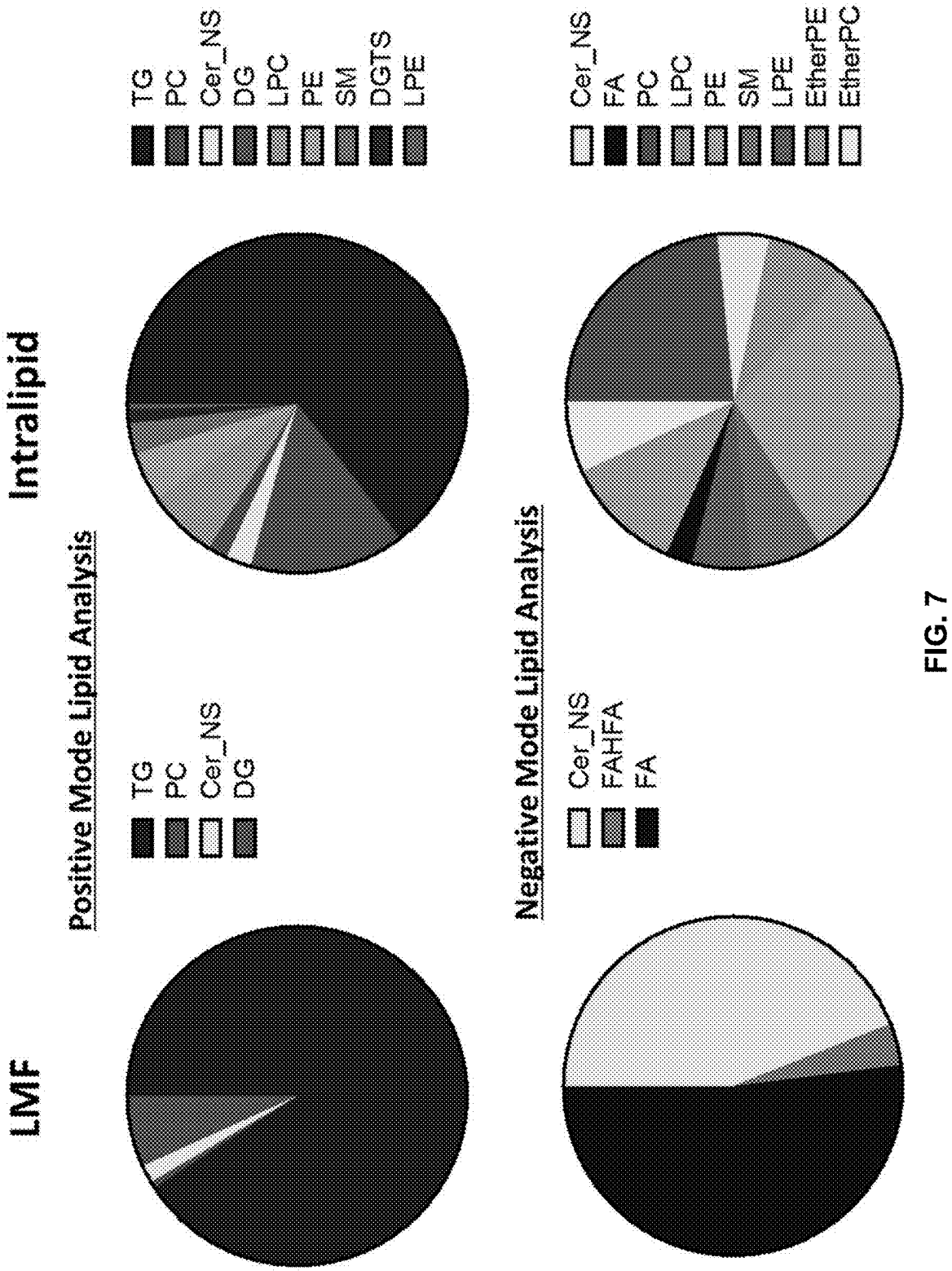
LMF
Intralipid
Positive Mode Lipid Analysis
TG
PC
Cer_NS
DG
LPC
PE
SM
DGTS
LPE
Negative Mode Lipid Analysis
Cer_NS
FAHFA
FA
FA
PC
LPC
PE
SM
LPE
EtherPE
EtherPC

FIG. 7

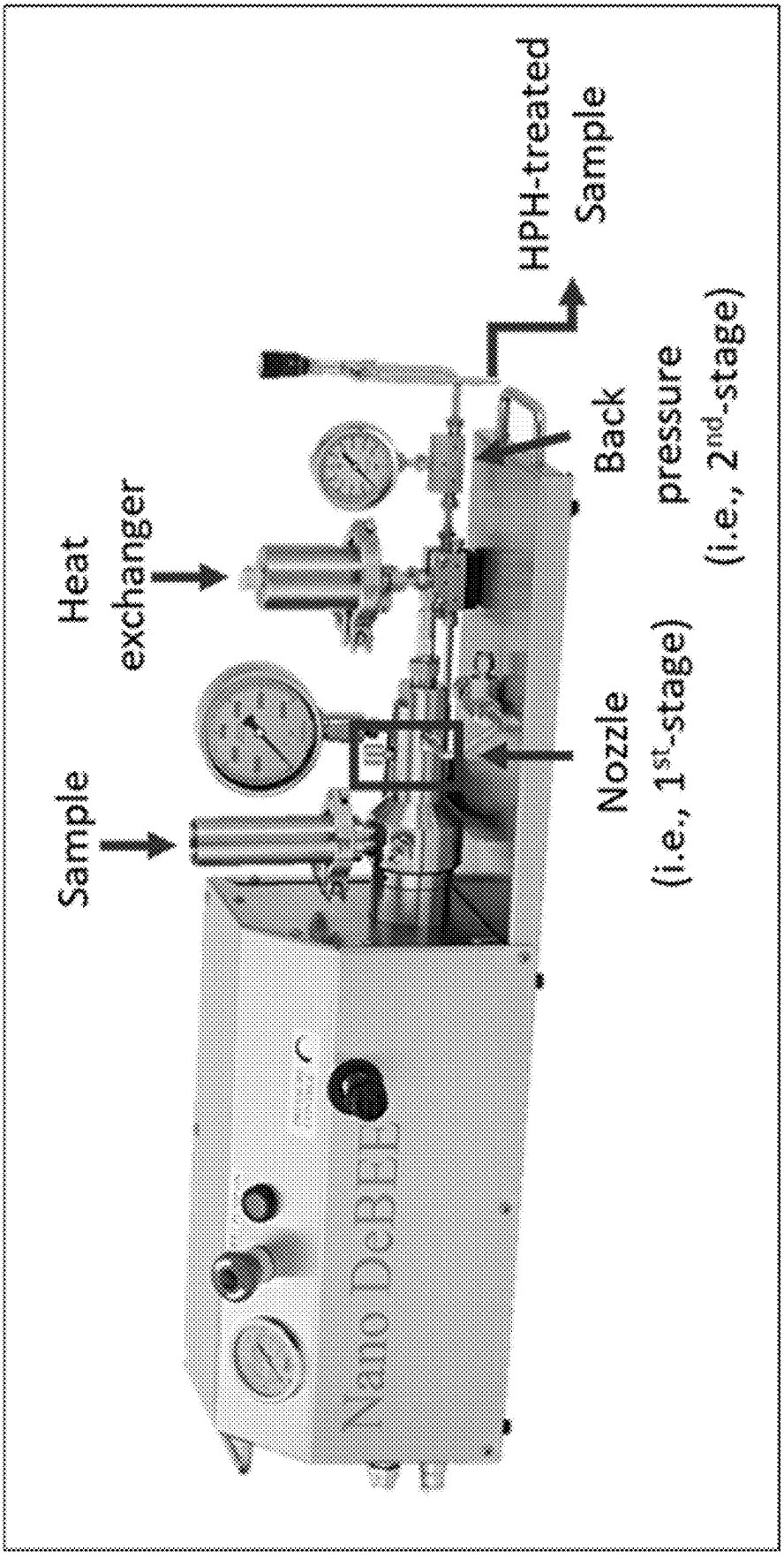
Sample
Heat exchanger
Nozzle (i.e., 1st-stage)
Back pressure (i.e., 2nd-stage)
HPH-treated Sample

FIG. 8

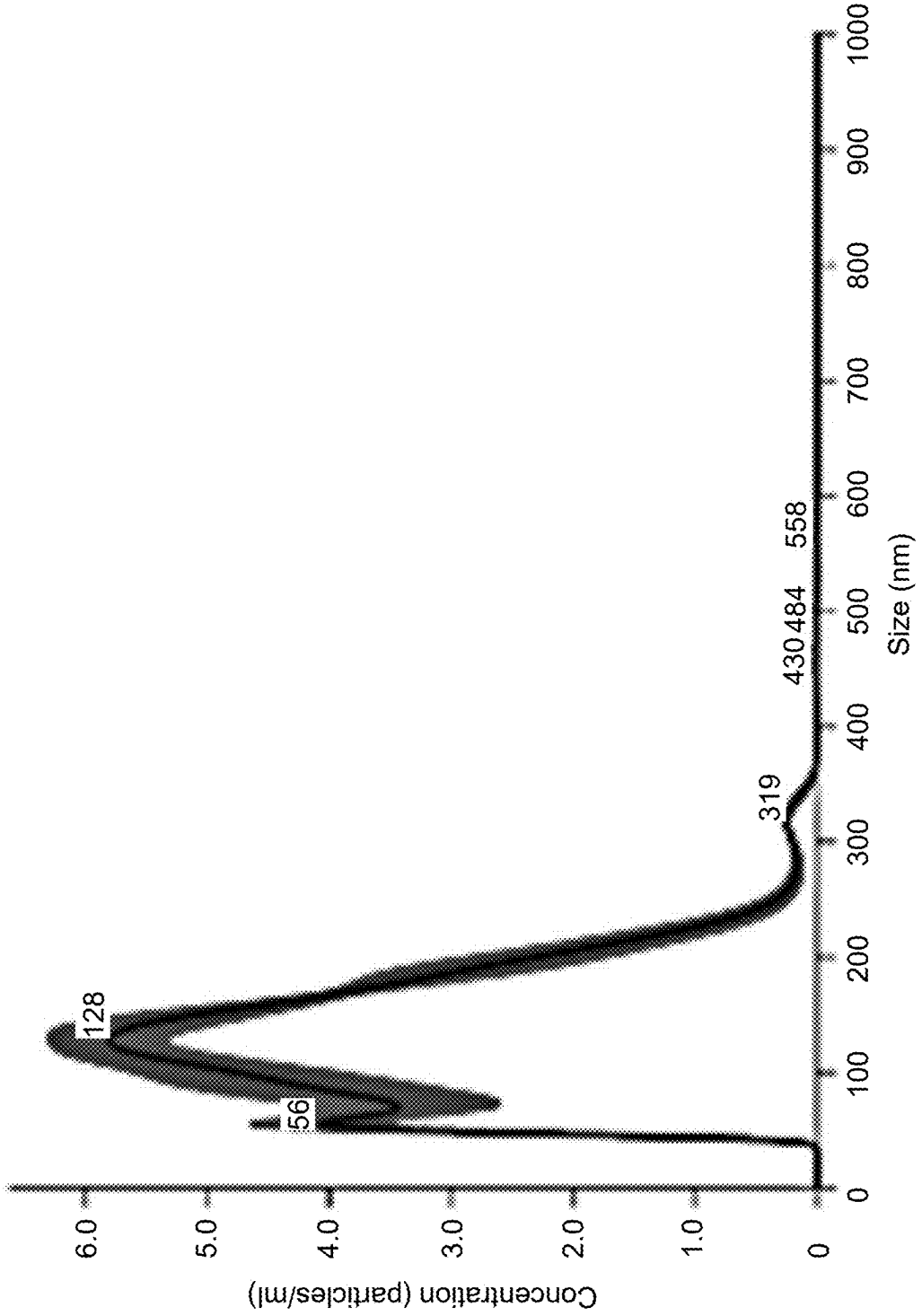
Concentration (particles/ml)
6.0
5.0
4.0
3.0
2.0
1.0
0
0
100
200
300
400
500
600
700
800
900
1000
Size (nm)
128
56
319
430
484
558

FIG. 9A

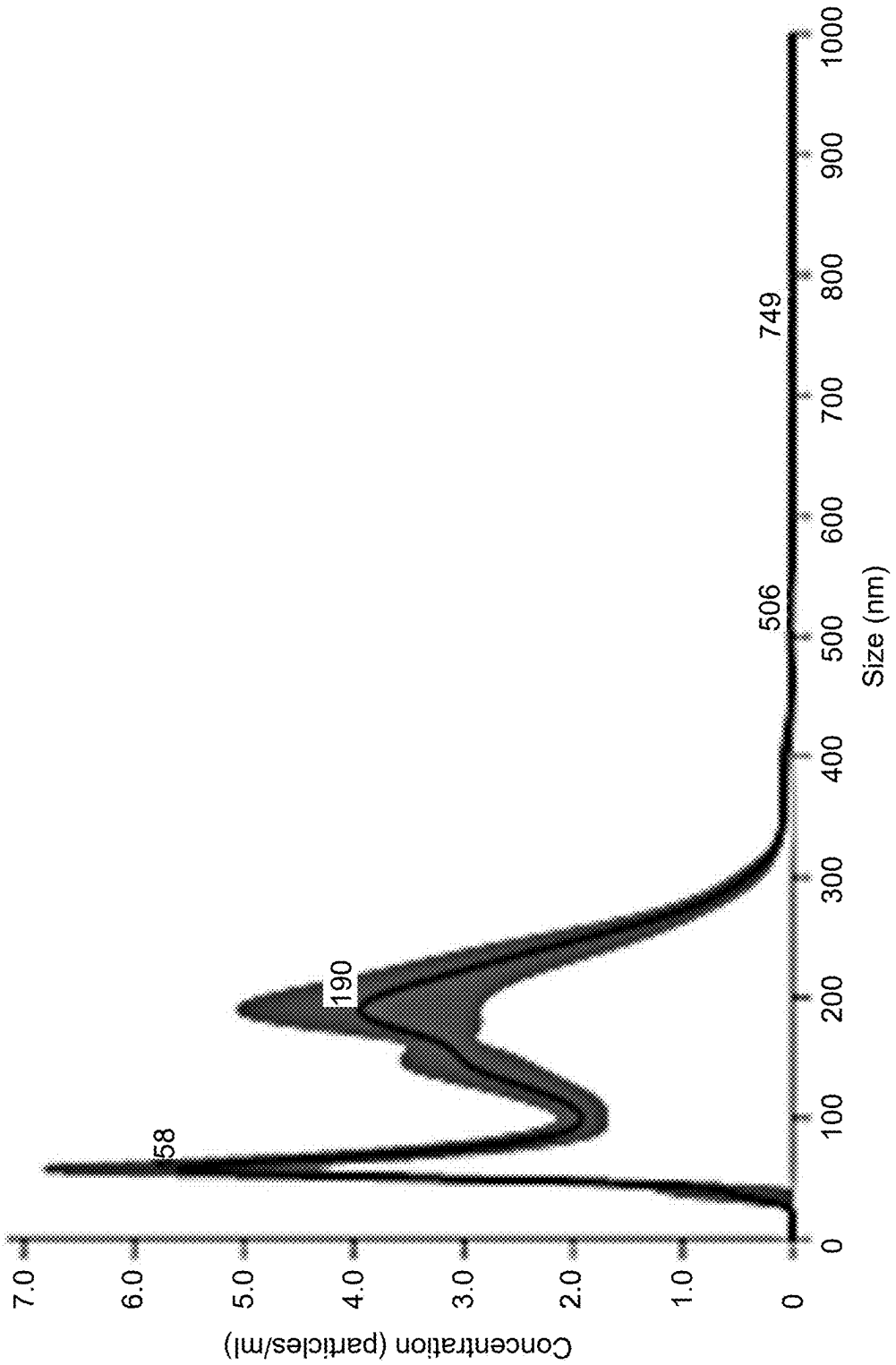
Concentration (particles/ml)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
58
190
506
749
0
100
200
300
400
500
600
700
800
900
1000
Size (nm)

FIG. 9B

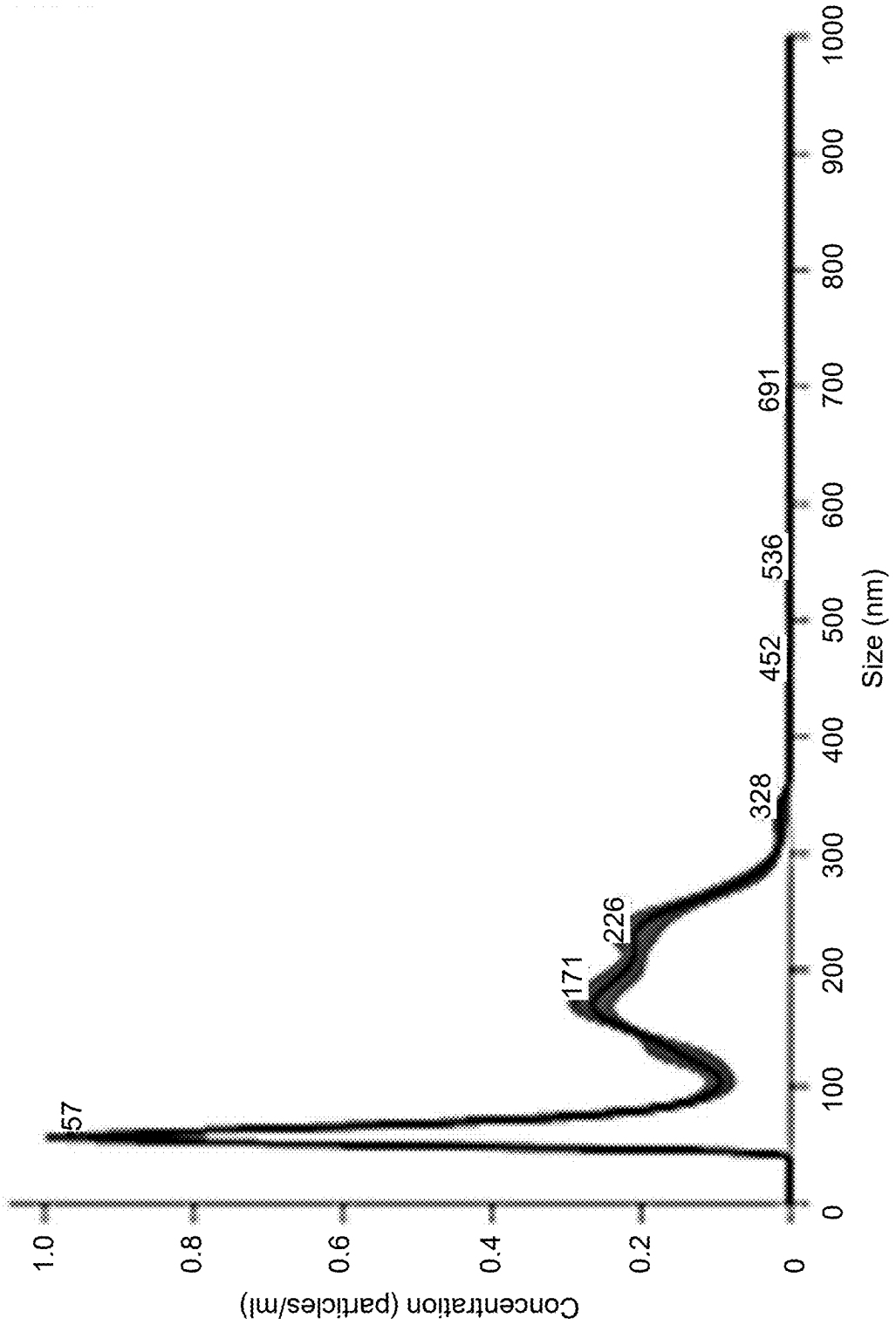
Concentration (particles/ml)
1.0
0.8
0.6
0.4
0.2
0
0
100
200
300
400
500
600
700
800
900
1000
Size (nm)
57
171
226
328
452
536
691

FIG. 9C

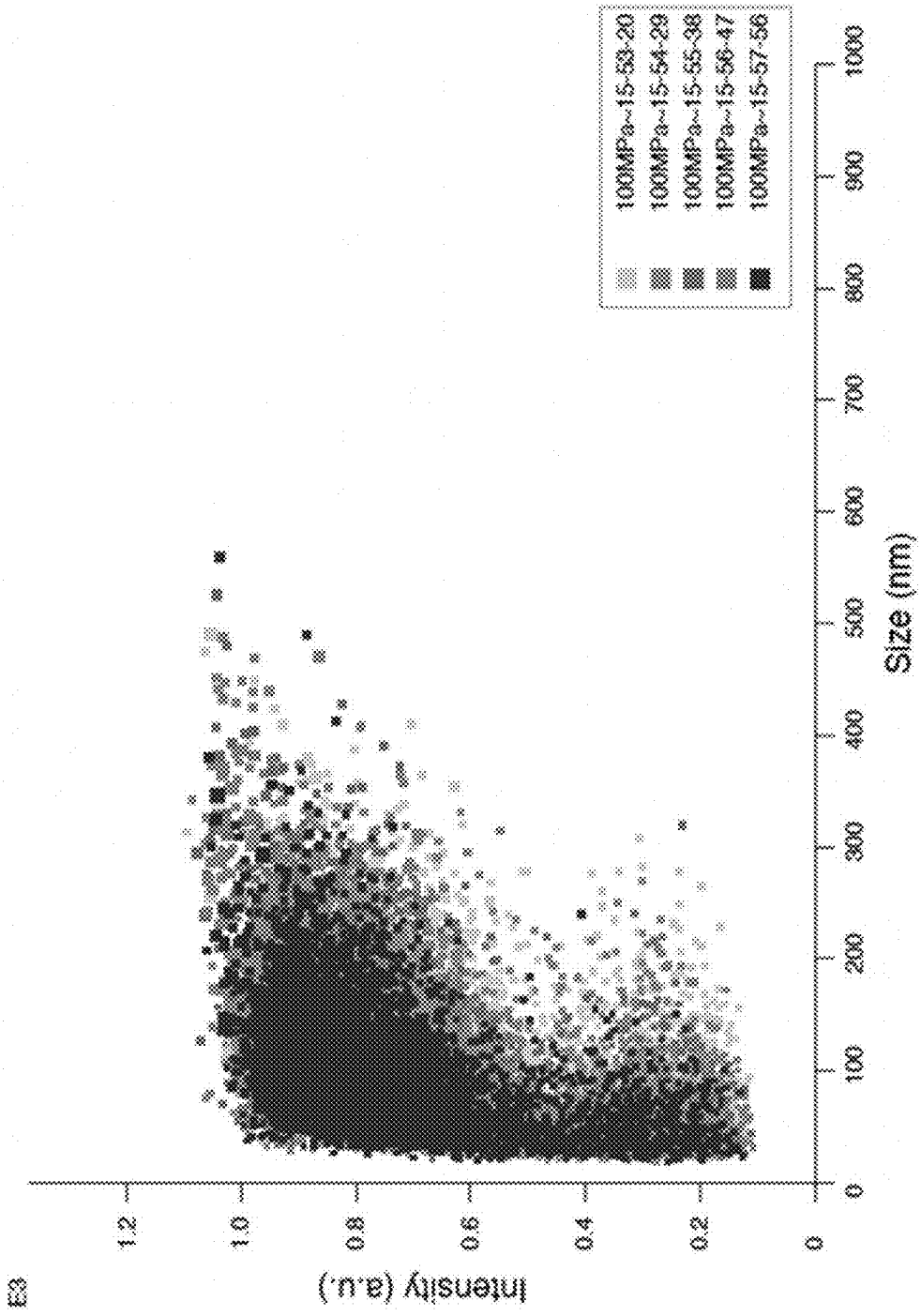
E3
Intensity (a.u.)
1.2
1.0
0.8
0.6
0.4
0.2
0
0
100
200
300
400
500
600
700
800
900
1000
Size (nm)
100MPa--15-53-20
100MPa--15-54-29
100MPa--15-55-38
100MPa--15-56-47
100MPa--15-57-56
Intensity / Size graph for Experiment:
100MPa 2022-09-21 15-52-26

FIG. 10

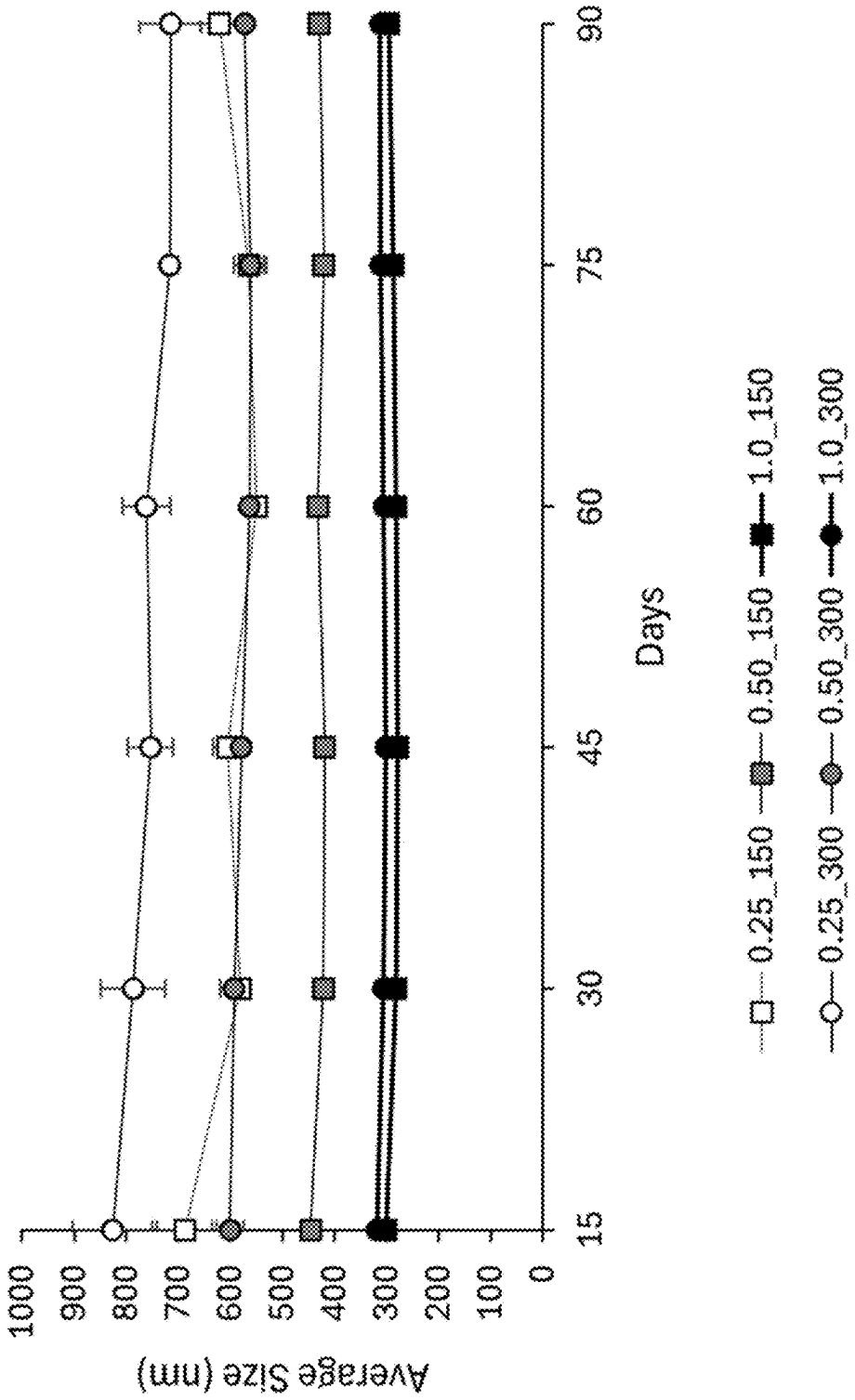
Average Size (nm)
1000
900
800
700
600
500
400
300
200
100
0
15
30
45
60
75
90
Days
0.25_150
0.50_150
1.0_150
0.25_300
0.50_300
1.0_300

FIG. 11

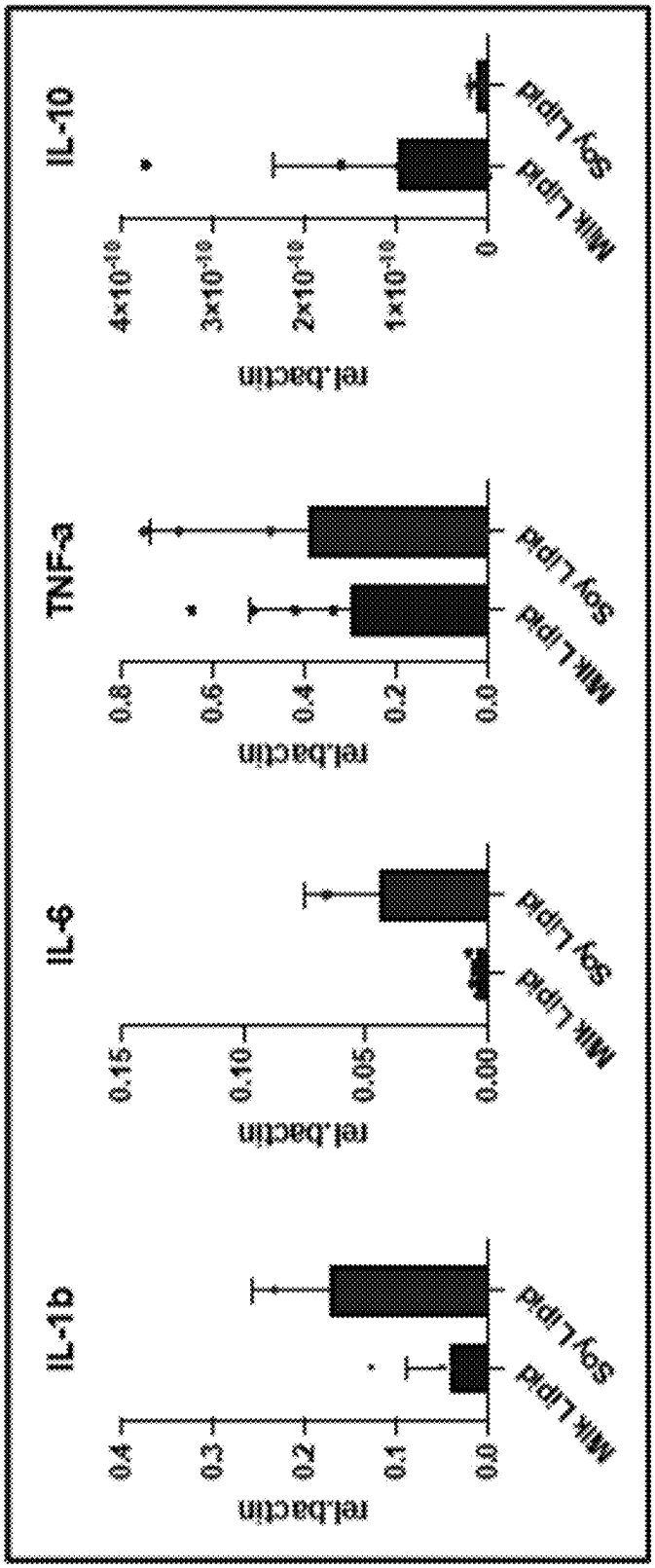
IL-10
TNF-a
IL-6
IL-1b
rel.bactin
MilkLipid
SoyLipid
0
1×10⁻¹⁰
2×10⁻¹⁰
3×10⁻¹⁰
4×10⁻¹⁰
0.0
0.2
0.4
0.6
0.8
0.00
0.05
0.10
0.15
0.0
0.1
0.2
0.3
0.4

FIG. 12

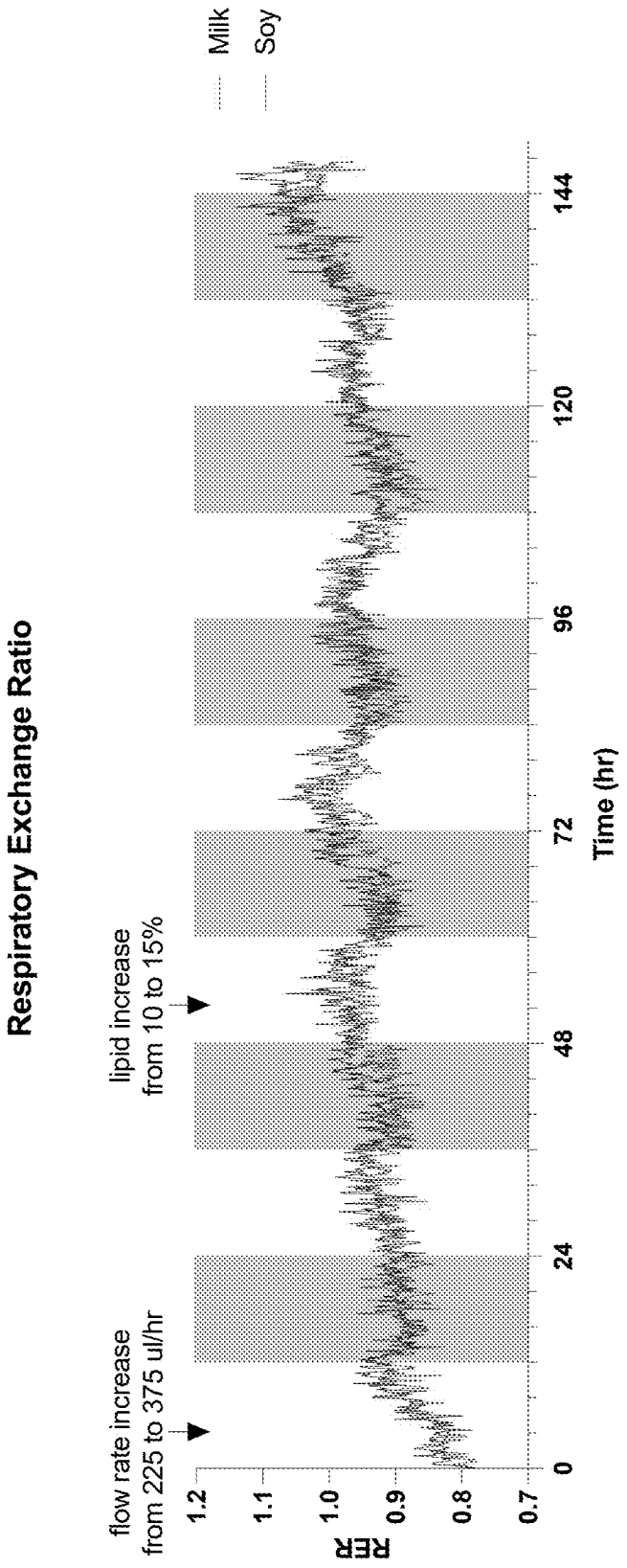
Respiratory Exchange Ratio
Milk
Soy
flow rate increase
from 225 to 375 ul/hr
lipid increase
from 10 to 15%
RER
1.2
1.1
1.0
0.9
0.8
0.7
0
24
48
72
96
120
144
Time (hr)

FIG. 13A

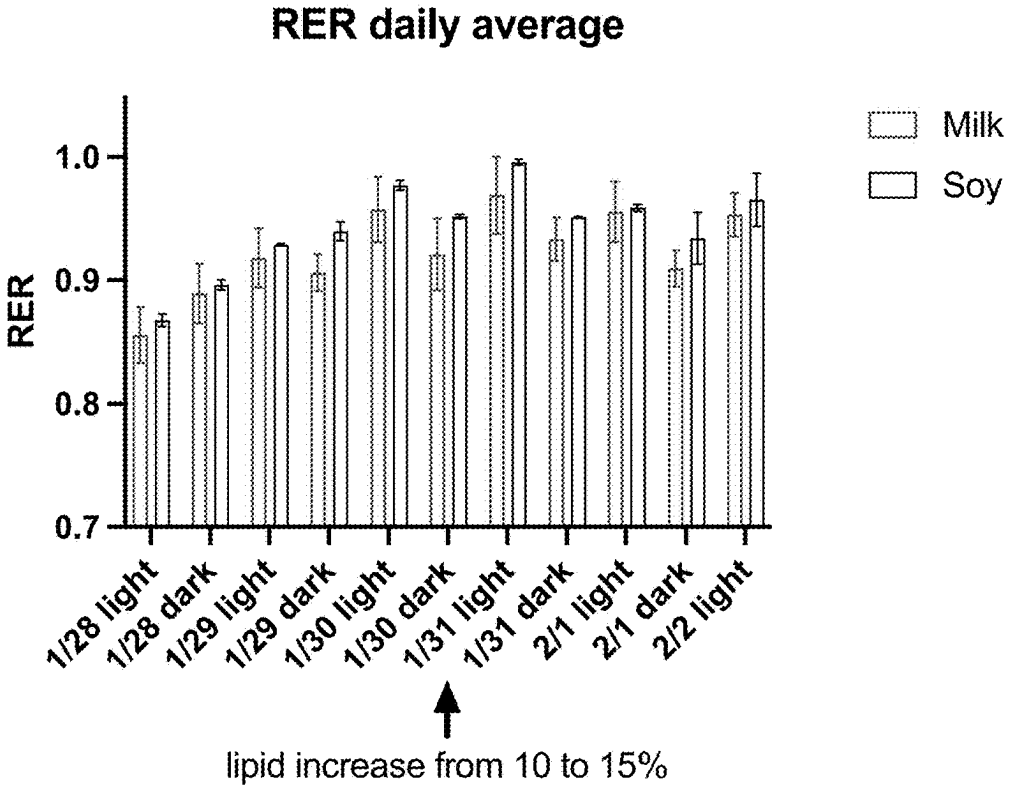

FIG. 13B

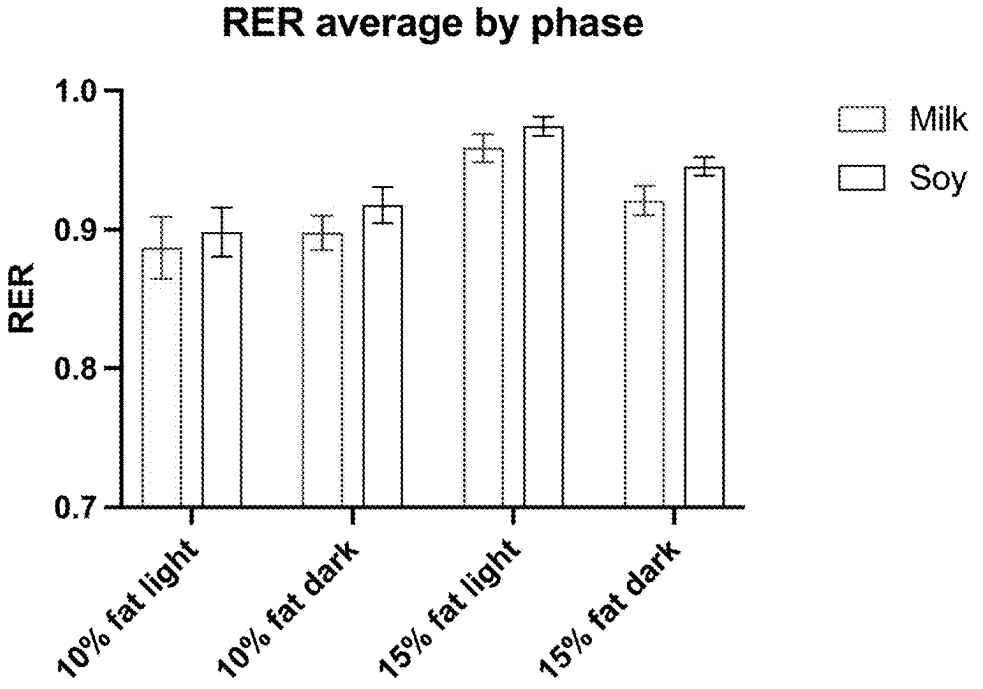

FIG. 13C

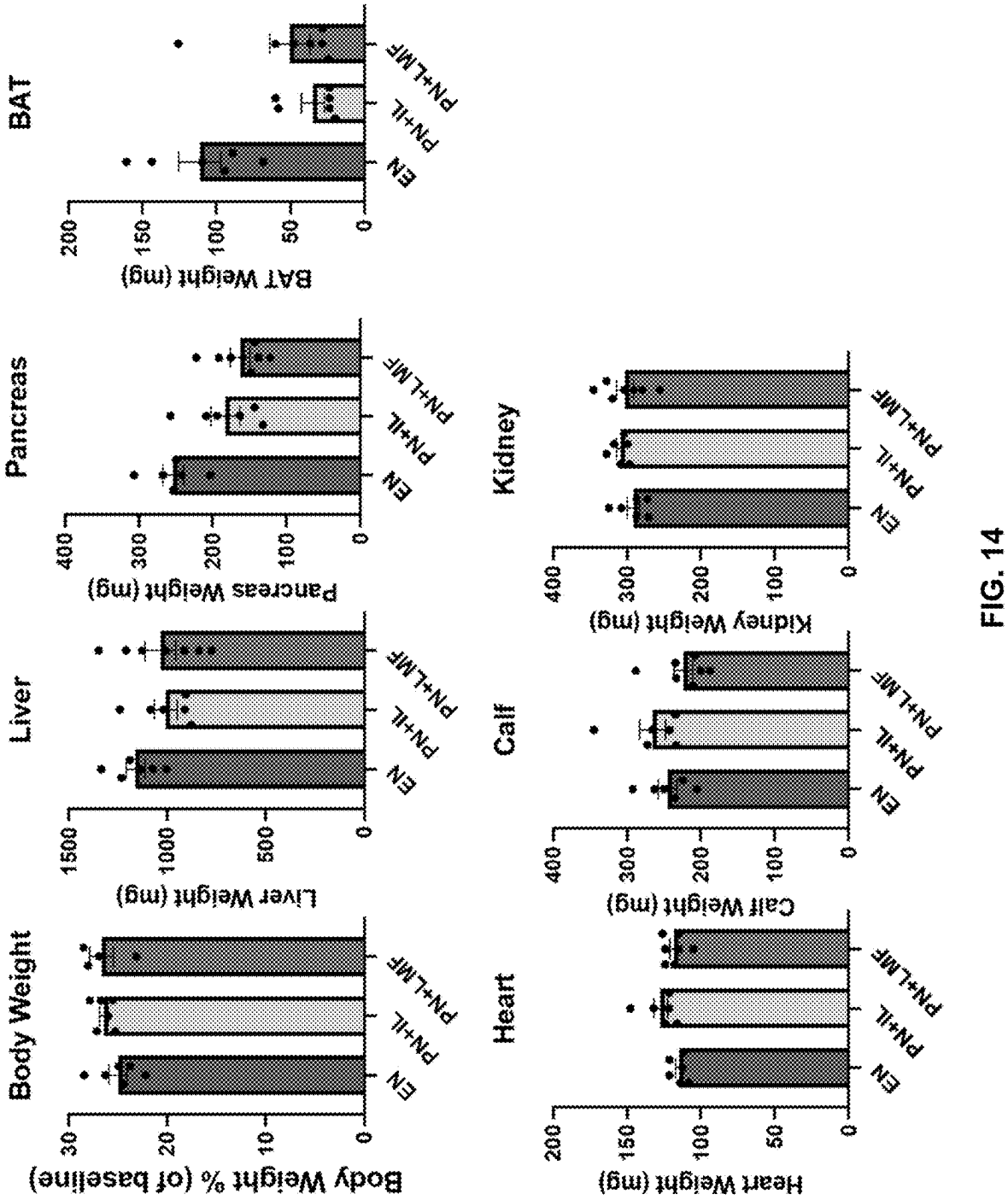
Body Weight
Body Weight % (of baseline)
Liver
Liver Weight (mg)
Pancreas
Pancreas Weight (mg)
BAT
BAT Weight (mg)
Heart
Heart Weight (mg)
Calf
Calf Weight (mg)
Kidney
Kidney Weight (mg)
EN
PN+IL
PN+L.MF

FIG. 14

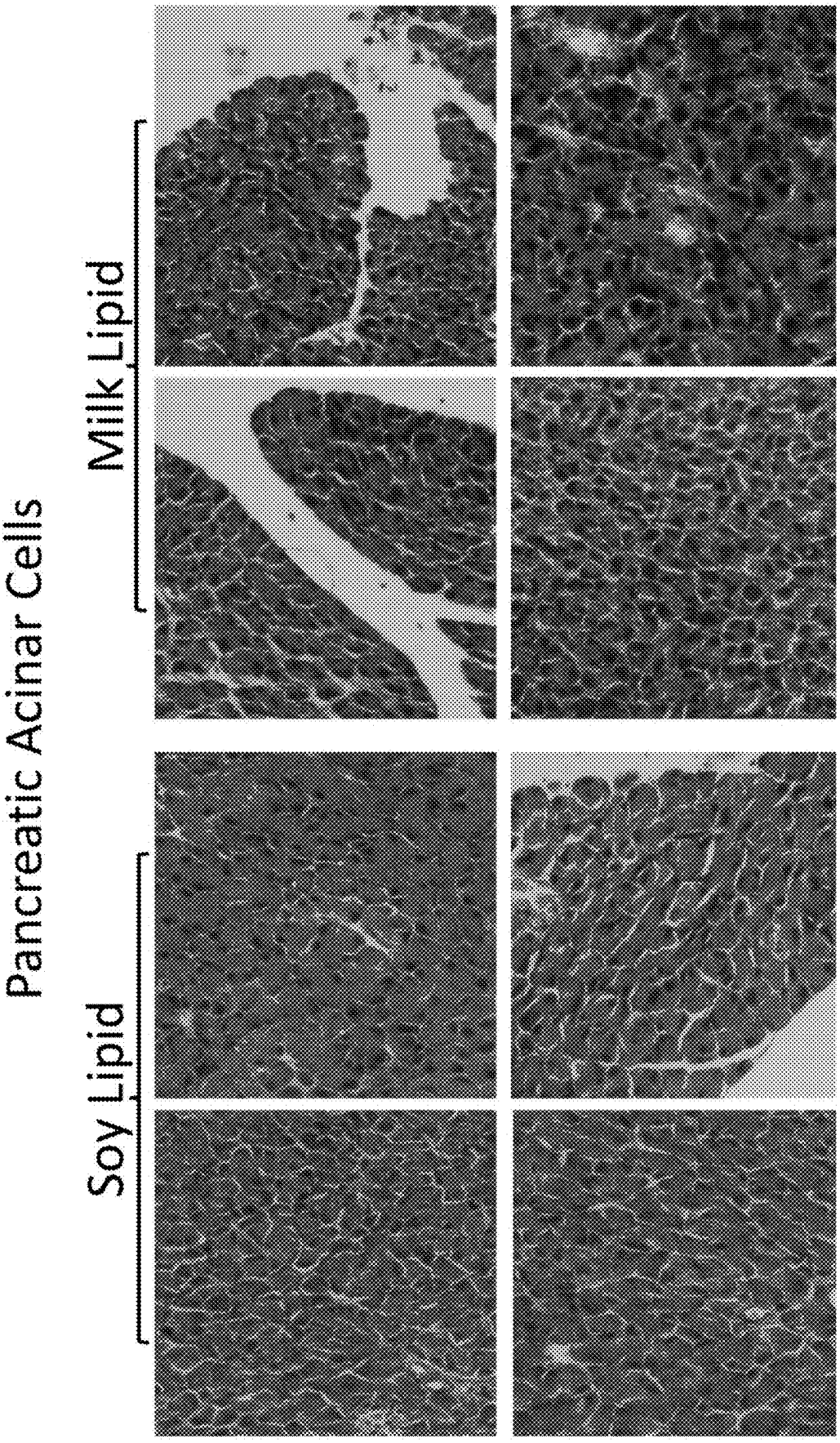

FIG. 15

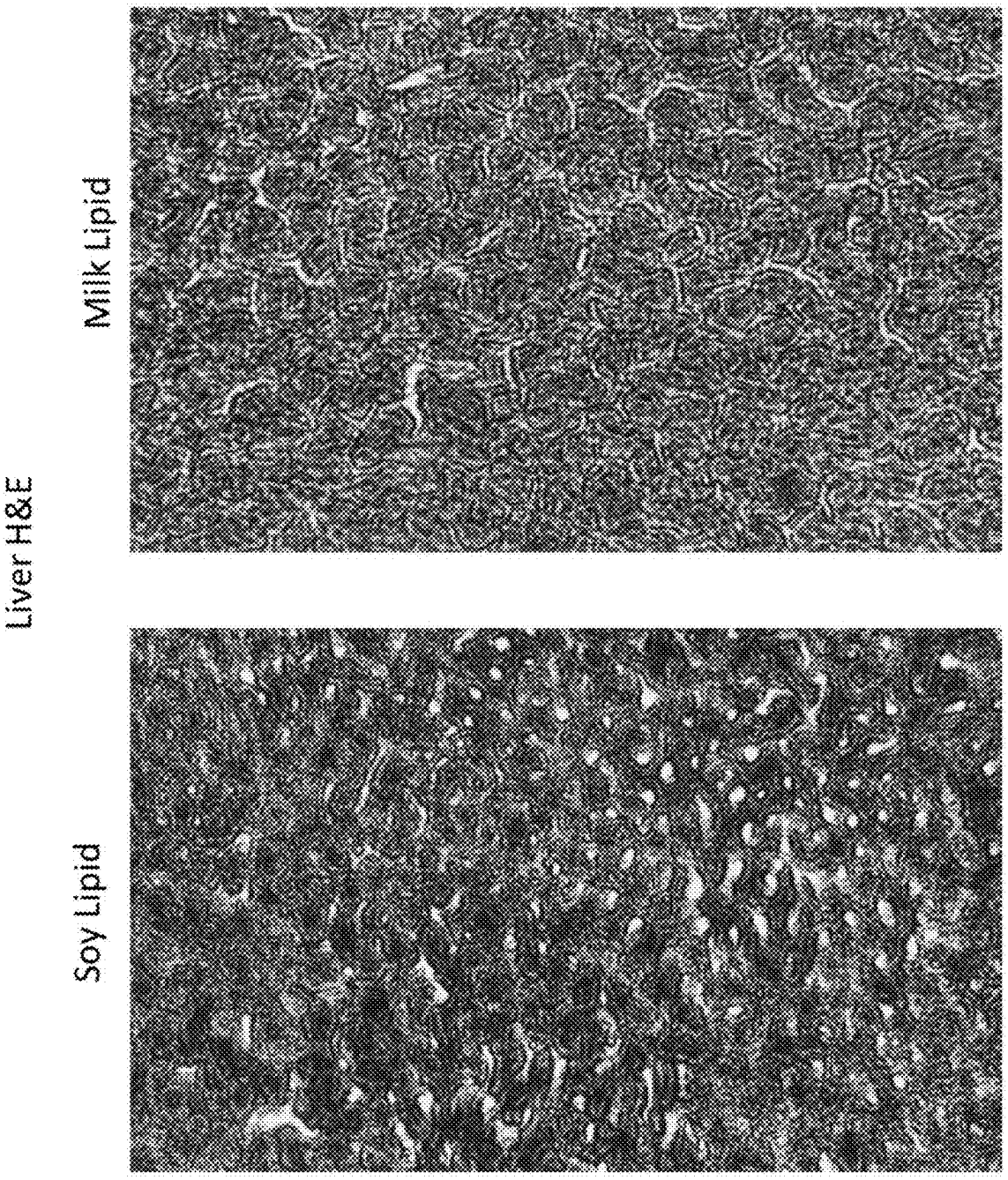

FIG. 16

LIPID PARTICLES, METHODS OF GENERATING SAME, AND METHODS OF USING SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] Priority is hereby claimed to U.S. Provisional Application 63/594,799, filed Oct. 31, 2023, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The invention is directed to lipid particles, methods of generating same, and methods of using same. The invention in some embodiments is specifically directed to lipid particles comprising milk fat and methods of using same for parenteral nutrition.

BACKGROUND

[0003] Parenteral nutrition (PN) is a clinical method of intravenous feeding that provides lifesaving nutrition support in patients who cannot feed via the gastrointestinal tract, due to trauma, surgery, intestinal inflammation or obstruction, or premature birth. PN is composed of dextrose, amino acids, vitamins, minerals, electrolytes, and lipids provided as emulsions. While lifesaving and used in over 300,000 patients a year in the U.S., the lipid emulsion formulations developed over the last 50 years remain problematic and are a major hurdle in optimizing metabolic requirements, growth, and preventing progressive hepatic complications. For instance, plant derived lipid fractions obtained from soybean, safflower, coconut, and olive oil have limited complexity, being dominated by either linoleic acid (soybean, safflower), oleic acid (olive oil), or medium chain triglycerides (coconut), resulting in efforts to mix plant oils together and better optimize formulations (Fell et al., 2015; Sadu Singh et al., 2020). Soybean oil is commonly used in many emulsion formulations despite containing phytosterols that likely induce hepatic toxicity. In European markets, extracted fish oils are included for their essential fatty acids (FAs), but have not been adopted in the U.S. The consensus in the field of surgical nutrition is that current lipids are sufficient but not optimal for patient care (Johnson et al., 2021). Furthermore, supply chain issues and the availability of raw lipid sources create frequent shortages.

[0004] Lipid formulations that overcome the foregoing problems are needed.

SUMMARY OF THE INVENTION

[0005] One aspect of the invention is directed to methods of generating lipid particles.

[0006] In some versions the methods comprise generating a combined composition. In some versions, generating the combined composition comprises combining a milk fat composition comprising a solids portion comprising target milk fat with a surfactant.

[0007] In some versions, the methods further comprise generating a lipid-particle composition comprising lipid particles. In some versions, generating the lipid-particle composition comprises emulsifying the combined composition.

[0008] In some versions, the solids portion comprises the target milk fat in amount of at least 50% w/w, at least 55% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 75% w/w, at least 80% w/w, at least 85% w/w, at least 90% w/w, at least 95% w/w, at least 96% w/w, at least 97% w/w, at least 98% w/w, or at least 99% w/w.

[0009] In some versions, the lipid composition comprises the solids portion in an amount of at least 50% w/w, at least 55% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 75% w/w, at least 80% w/w, at least 85% w/w, at least 90% w/w, at least 95% w/w, at least 96% w/w, at least 97% w/w, at least 98% w/w, or at least 99% w/w.

[0010] In some versions, the lipid particles comprise triglycerides in an amount greater than 50% w/w, greater than 52.5% w/w, greater than 55% w/w, greater than 57.5% w/w, greater than 60%, greater than 62.5% w/w, greater than 65% w/w, greater than 67.5% w/w, greater than 70% w/w, greater than 72.5% w/w, greater than 75% w/w, greater than 77.5% w/w, greater than 80% w/w, greater than 82.5% w/w, or greater than 85% w/w of combined total of triglyceride, diglyceride, 1,2-diacylglyceryl-3-O-4'-(N,N,N-trimethyl)-homoserine, phosphatidylcholine, ether-linked phosphatidylcholine, fatty acyl ester of hydroxy fatty acid, free fatty acid, lysophosphatidylcholine, phosphatidylethanolamine, ether-linked phosphatidylethanolamine, lysophosphatidylethanolamine, non-hydroxy-fatty acid sphingosine ceramide, and sphingomyelin detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry.

[0011] In some versions, the lipid particles comprise a relative amount of any 2 or more, any 3 or more, any 4 or more, or each of the following lipids within 5× of each other as detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry: TG 14:0_16:0_16:0, TG 14:0_15:0_16:0, TG 12:0_16:0_16:0, TG 12:0_15:0_16:0, and TG 12:0_14:0_16:0.

[0012] In some versions, the lipid particles comprise a relative amount of any 2 or more, any 3 or more, any 4 or more, any 5 or more, any 6 or more, any 7 or more, any 8 or more, any 9 or more, any 10 or more, any 11 or more, any 12 or more, any 13 or more, any 14 or more, any 15 or more, any 16 or more, any 17 or more, any 18 or more, any 19 or more, any 20 or more, any 21 or more, or each of the following lipids within 5× of each other as detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry: TG 14:0_16:0_16:0, TG 14:0_15:0_16:0, TG 12:0_16:0_16:0, TG 12:0_15:0_16:0, TG 12:0_14:0_16:0, TG 16:0_18:0_18:1, TG 16:0_18:1_18:1, TG 16:0_16:0_18:1, TG 14:0_16:0_18:1, TG 12:0_16:0_18:1, TG 12:0_14:0_18:1, TG 14:0_18:1_18:1, TG 18:0_18:0_18:1, TG 16:0_17:0_18:1, TG 18:1_18:1_18:1, TG 12:0_12:1_18:1, TG 15:0_18:1_18:1, TG 15:0_16:0_18:1, TG 17:0_18:1_18:1, TG 17:0_18:0_18:1, TG 16:0_18:1_18:3, TG 16:0_18:0_18:0, TG 14:0_18:1_18:2, TG 14:0_16:0_18:0, TG 12:0_15:0_18:1, TG 15:0_16:0_18:0, and TG 16:0_17:0_18:0.

[0013] In some versions, the combined composition comprises the solids portion of the milk fat composition in an amount of at least 2.5% w/w, at least 5% w/w, at least 7.5% w/w, at least 10% w/w, at least 12.5% w/w, at least 15% w/w, at least 17.5% w/w, at least 20% w/w, at least 22.5% w/w, at least 25% w/w, at least 27.5% w/w, at least 30% w/w, at least 32.5% w/w, at least 35% w/w, at least 37.5% w/w, at least 40% w/w, at least 42.5% w/w, at least 45% w/w, at least 47.5% w/w, or at least 50% w/w.

[0014] In some versions, the generating the combined composition further comprises combining the milk fat composition with water.

[0015] In some versions, the combined composition comprises water in an amount of at least 50% w/w, at least 55% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 75% w/w, at least 80% w/w, at least 85% w/w, or at least 90% w/w.

[0016] In some versions, the combined composition comprises the surfactant in an amount of at least 0.01% w/w, at least 0.02% w/w, at least 0.03% w/w, at least 0.04% w/w, at least 0.05% w/w, at least 0.06% w/w, at least 0.07% w/w, at least 0.08% w/w, at least 0.09% w/w, at least 0.1% w/w, at least 0.2% w/w, at least 0.3% w/w, at least 0.4% w/w, at least 0.5% w/w and/or up to 0.5% w/w, up to 0.6% w/w, up to 0.7% w/w, up to 0.8% w/w, up to 0.9% w/w, up to 1% w/w, up to 2.5% w/w, up to 5% w/w, up to 7.5% w/w, up to 10% w/w, or more.

[0017] In some versions, greater than 90% by number of the lipid particles in the lipid-particle composition have a diameter of less than 500 nm.

[0018] In some versions, the emulsifying comprises high-pressure homogenization.

[0019] In some versions, the emulsifying generates an emulsified composition and the generating the lipid-particle composition further comprises size-filtering the emulsified composition with a filter comprising a pore size from 0.5 μm to 5.0 μm.

[0020] Some versions further comprise autoclaving the lipid particles.

[0021] Some versions further comprise generating the milk fat composition from a prior milk fat composition comprising the target milk fat and additional milk fat by removing the additional fat from the target milk fat.

[0022] In some versions, the generating the milk fat composition comprises melt fractionating the prior milk fat composition.

[0023] In some versions, the prior milk fat composition comprises at least one of anhydrous milk fat, butter oil, and ghee.

[0024] In some versions, the target milk fat comprises ruminant milk fat.

[0025] Another aspect of the invention is directed lipid particles. The lipid particles can be made according to the methods as described herein.

[0026] Another aspect of the invention is directed to methods of administering parenteral nutrition. In some versions, the methods comprise parenterally administering the lipid particles of the invention to a subject. In some versions, the subject has a condition comprising at least one of pancreatitis and hepatitis. In some versions, the administering results in a reduced pro-inflammatory response relative to administering an equivalent amount of lipid particles generated from vegetable fat.

[0027] The objects and advantages of the invention will appear more fully from the following detailed description of the preferred embodiment of the invention made in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0029] FIG. **1**. Schematic of an exemplary preparation of a milkfat-based intravenous fat emulsion. HMF: High melting fraction. LMF: low melting fraction.

[0030] FIG. **2**. Schematic of the experimental steps carried out in the following examples.

[0031] FIG. **3**. Low melting fraction (A) and high melting fraction (B) following fractionation of anhydrous milk fat (AMF) at 25° C.

[0032] FIG. **4**. The relative abundance of various triglycerides for low melting fractions and high melting fractions at 15 and 25° C. (FIG. **4**). 15C HMF, high melting fraction at 15° C. (HMF-15). 15C LMF, low melting fraction at 15° C. 25C HMF, high melting fraction at 25° C. 25C LMF, low melting fraction at 25° C. AMF Control, anhydrous milk fat. Shown are normalized log fold changes in concentration, wherein yellow is an increase in concentration and blue is a decrease.

[0033] FIG. **5**. Relative abundance of triglyceride with three medium-chain, saturated (12:0) fatty acids (lauric acid) esterified to the glycerol backbone in AMF, a 15° C. high melting fraction (15H), a 15° C. low melting fraction (15 L), a 25° C. high melting fraction (25H), and a 25° C. low melting fraction (25 L).

[0034] FIG. **6**. Fatty acid profile of a low melting fraction (LMF-25) of milk fat (AMF) vs. soy lipid (Intralipid® 20%). The milk fat had a much more diverse fatty acid profile. The bar to the left of the hash mark for each condition is LMF. The bar to the right of the hash mark for each condition is Intralipid® (IL).

[0035] FIG. **7**. LC/MS/MS lipid analysis under positive mode and negative mode of a low melting fraction (LMF-25) of milk fat (AMF) and soy lipid (Intralipid® 20%). TG, triglyceride. DG, diglyceride. DGTS, 1,2-diacylglyceryl-3-O-4'-(N,N,N-trimethyl)-homoserine. PC, phosphatidylcholine. Ether PC, ether-linked phosphatidylcholine. FAHFA, fatty acyl ester of hydroxy fatty acid. FA, free fatty acid. LPC, lysophosphatidylcholine. PE, phosphatidylethanolamine. EtherPE, ether-linked phosphatidylethanolamine. LPE, lysophosphatidylethanolamine. Cer_NS, non-hydroxy-fatty acid sphingosine ceramide. SM, sphingomyelin.

[0036] FIG. **8**. Annotated picture of a Nano DeBEE High-Pressure Homogenizer.

[0037] FIGS. **9**A-**9**C. Size of milkfat IVFEs made according to a method as shown in FIG. **1** using 100 MPa (FIG. **9**A), 200 MPa (FIG. **9**B), and 300 MPa (FIG. **9**C) in the high-pressure homogenization step.

[0038] FIG. **10**. Sizes of milkfat IVFEs made according to a method as shown in FIG. **1** using 100 MPa in the high-pressure homogenization step. Graph indicates the size vs. intensity, where colors indicate the frequency of shown size vs. intensity plotted. Colors at the top of the legend are less frequent and grow more frequent at the lower shown symbols.

[0039] FIG. **11**. Size stability of IVFEs over three months. Particle size over time for emulsions generated from 20% fractionated milkfat in water with 0.25, 0.5, or 1.0% polysorbate 80 emulsifier, and 150 or 300 MPa high-pressure homogenization for three passes. 0.25_150:0.25% polysorbate 80 processed at 150 MPa. 0.50_150:0.25% polysorbate 80 processed at 150 MPa. 1.0_150:0.25% polysorbate 80 processed at 150 MPa. 0.25_300:0.25% polysorbate 80

processed at 300 MPa. 0.50_300:0.25% polysorbate 80 processed at 300 MPa. 1.0_300:0.25% polysorbate 80 processed at 300 MPa.

[0040] FIG. **12**. In vitro macrophage analysis. Milk lipid IVFEs (made according to FIG. **1**) had a less inflammatory response (IL-1b, IL-6, and TNF-a) than soy lipid IVFEs (Intralipid® 20%) in stimulated macrophages (IL-1b, IL-6, and TNF-a), while inducing an anti-inflammatory response with IL-10.

[0041] FIGS. **13**A-**13**C. Respiratory exchange ratio (RER) of mice administered milk lipid IVFEs (made according to FIG. **1**) versus soy lipid IVFEs (Intralipid® 20%). FIG. **13**A. RER time course.

[0042] FIG. **13**B. RER daily average. FIG. **13**C. RER average by phase. In FIGS. **13**B and **13**C, the bar to the left of the hash mark for each condition is milk lipid IVFE, and the bar to the right of the hash mark for each condition is soy lipid IVFE.

[0043] FIG. **14**. Body, organ and tissue weights in mice administered milk lipid IVFEs (made according to FIG. **1**) versus soy lipid IVFEs (Intralipid® 20%).

[0044] FIG. **15**. Hematoxylin and eosin stain of pancreatic acinar tissue from mice administered milk lipid IVFEs (made according to FIG. **1**) versus soy lipid IVFEs (Intralipid®).

[0045] FIG. **16**. Hematoxylin and eosin stain of liver tissue from mice administered milk lipid IVFEs (made according to FIG. **1**) versus soy lipid IVFEs (Intralipid® 20%).

DETAILED DESCRIPTION OF THE INVENTION

[0046] One aspect of the invention is directed to methods of generating lipid particles. "Lipid particle(s)" as used herein refers to particle(s) comprising lipid. The particles of the invention can be in the form of micelles, such as oil-in-water micelles, and can be provided in a compositional form of an oil-in-water emulsion.

[0047] The methods of generating the lipid particles can comprise a step of generating a combined composition. The combined composition can generally comprise lipid in combination with a surfactant and water. The step of generating the combined composition can comprise combining a lipid composition with a surfactant and, optionally, water.

[0048] "Lipid composition" as used herein refers to any composition comprising, consisting of, or consisting essentially of lipid. "Lipid" and "fat" are used synonymously herein to refer to any substance comprising carbon, hydrogen, and, optionally, oxygen that is insoluble in water but soluble in non-polar solvents. The lipid can be in any form, such as triglycerides, diglycerides, monoglycerides, sterols, waxes, and free fatty acids, among others.

[0049] The lipid in the lipid composition preferably comprises milk fat, and more specifically target milk fat. "Milk fat" as used herein refers to fat contained in, isolated from, or derived from milk. "Target milk fat" as used herein refers to fat isolated or derived from milk. "Isolated from milk" refers to the isolation or separation of a given milk component (e.g., lipid or specific lipids) from at least a portion of at least one other component of milk (e.g., water, protein, sugar etc.). "Derived from milk" refers to a component that has been isolated from milk and chemically modified (e.g., esterified, etc.). Unless the context explicitly indicates otherwise, the general term "milk" as used herein refers to mammalian milk, as opposed to liquid extractions derived from plants, such as "almond milk" or "soy milk." In some versions of the invention, the milk fat (e.g., target milk fat) in the lipid composition ruminant milk fat. The ruminant milk fat can be isolated or obtained from any ruminant, such as domesticated and wild bovines, goats, sheep, giraffes, deer, gazelles, and antelopes, among others. The target milk fat can be any type of fat or lipid or any combination of fats or lipids described herein.

[0050] The lipid composition and/or the combined composition can comprise a solids portion that comprises the lipid. "Solids portion" as used herein refers to the total combination of components of a given composition other than water. In addition to the lipid, the solids portion lipid composition and/or the combined composition can include protein such as casein and lactalbumin, carbohydrates such as lactose, minerals such as calcium and phosphorus, and other trace elements. If the lipid in the lipid composition and/or combined composition is a milk fat, the solids portion can include lipid solids (e.g., the milk fat) and non-lipid solids, such as typical non-lipid solids ("solids-not-fat" or "non-fat solids") typically found in milk. Typical non-lipid solids found in milk include protein such as casein and lactalbumin, carbohydrates such as lactose, minerals such as calcium and phosphorus, and other trace elements. If the lipid in the lipid composition and/or combined composition is a target milk fat, the solids portion can have at least a portion of one or more non-lipid solids removed from the lipid solids present in the composition.

[0051] In various versions of the invention, the solids portion of the lipid composition (e.g., target milk fat composition) can comprise total lipid in amount of at least 5% w/w, at least 10% w/w, at least 15% w/w, at least 20% w/w, at least 25% w/w, at least 30% w/w, at least 35% w/w, at least 40% w/w, at least 45% w/w, at least 50% w/w, at least 55% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 75% w/w, at least 80% w/w, at least 85% w/w, at least 90% w/w, at least 91% w/w, at least 92% w/w, at least 93% w/w, at least 94% w/w, at least 95% w/w, at least 96% w/w, at least 97% w/w, at least 98% w/w, or at least 99% w/w. Amounts of 80% w/w or greater are preferred.

[0052] In various versions of the invention, the solids portion of the lipid composition (e.g., target milk fat composition) can comprise total lipid in amount of up to 5% w/w, up to 10% w/w, up to 15% w/w, up to 20% w/w, up to 25% w/w, up to 30% w/w, up to 35% w/w, up to 40% w/w, up to 45% w/w, up to 50% w/w, up to 55% w/w, up to 60% w/w, up to 65% w/w, up to 70% w/w, up to 75% w/w, up to 80% w/w, up to 85% w/w, up to 90% w/w, up to 91% w/w, up to 92% w/w, up to 93% w/w, up to 94% w/w, up to 95% w/w, up to 96% w/w, up to 97% w/w, up to 98% w/w, up to 99% w/w, or up to 99.9% or more.

[0053] In various versions of the invention, the solids portion of the lipid composition (e.g., target milk fat composition) can comprise target milk fat in amount of at least 5% w/w, at least 10% w/w, at least 15% w/w, at least 20% w/w, at least 25% w/w, at least 30% w/w, at least 35% w/w, at least 40% w/w, at least 45% w/w, at least 50% w/w, at least 55% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 75% w/w, at least 80% w/w, at least 85% w/w, at least 90% w/w, at least 91% w/w, at least 92% w/w, at least 93% w/w, at least 94% w/w, at least 95% w/w, at least 96% w/w, at least 97% w/w, at least 98% w/w, or at least 99% w/w. Amounts of 80% w/w or greater are preferred.

[0054] In various versions of the invention, the solids portion of the lipid composition (e.g., target milk fat composition) can comprise target milk fat in amount of up to 5% w/w, up to 10% w/w, up to 15% w/w, up to 20% w/w, up to 25% w/w, up to 30% w/w, up to 35% w/w, up to 40% w/w, up to 45% w/w, up to 50% w/w, up to 55% w/w, up to 60% w/w, up to 65% w/w, up to 70% w/w, up to 75% w/w, up to 80% w/w, up to 85% w/w, up to 90% w/w, up to 91% w/w, up to 92% w/w, up to 93% w/w, up to 94% w/w, up to 95% w/w, up to 96% w/w, up to 97% w/w, up to 98% w/w, up to 99% w/w, or up to 99.9% or more.

[0055] In various versions of the invention, the lipid composition (e.g., target milk fat composition) can comprise a solids portion in amount of at least 5% w/w, at least 10% w/w, at least 15% w/w, at least 20% w/w, at least 25% w/w, at least 30% w/w, at least 35% w/w, at least 40% w/w, at least 45% w/w, at least 50% w/w, at least 55% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 75% w/w, at least 80% w/w, at least 85% w/w, at least 90% w/w, at least 95% w/w, at least 96% w/w, at least 97% w/w, at least 98% w/w, or at least 99% w/w. Amounts 80% w/w or greater are preferred.

[0056] In various versions of the invention, the lipid composition (e.g., target milk fat composition) can comprise a solids portion in amount of up to 5% w/w, up to 10% w/w, up to 15% w/w, up to 20% w/w, up to 25% w/w, up to 30% w/w, up to 35% w/w, up to 40% w/w, up to 45% w/w, up to 50% w/w, up to 55% w/w, up to 60% w/w, up to 65% w/w, up to 70% w/w, up to 75% w/w, up to 80% w/w, up to 85% w/w, up to 90% w/w, up to 95% w/w, up to 96% w/w, up to 97% w/w, up to 98% w/w, up to 99% w/w, or up to 99.9% or more.

[0057] In various versions of the invention, the combined composition can comprise the solids portion of the lipid composition (e.g., milk fat composition) in an amount of at least 2.5% w/w, at least 5% w/w, at least 7.5% w/w, at least 10% w/w, at least 12.5% w/w, at least 15% w/w, at least 17.5% w/w, at least 20% w/w, at least 22.5% w/w, at least 25% w/w, at least 27.5% w/w, at least 30% w/w, at least 32.5% w/w, at least 35% w/w, at least 37.5% w/w, at least 40% w/w, at least 42.5% w/w, at least 45% w/w, at least 47.5% w/w, at least 50% w/w, at least 52.5% w/w, at least 55% w/w, at least 57.5% w/w, or at least 60% w/w. In various versions of the invention, the combined composition can comprise the solids portion of the lipid composition (e.g., milk fat composition) in an amount of up to 25% w/w, up to 27.5% w/w, up to 30% w/w, up to 32.5% w/w, up to 35% w/w, up to 37.5% w/w, up to 40% w/w, up to 42.5% w/w, up to 45% w/w, up to 47.5% w/w, up to 50% w/w, up to 52.5% w/w, up to 55% w/w, up to 57.5% w/w, up to 60% w/w, up to up to 62.5% w/w, up to 65% w/w, up to 67.5% w/w, up to 70% w/w, or more. Amounts from 5% w/w to 40% w/w are preferred.

[0058] In various versions of the invention, the combined composition can comprise water in an amount of at least 40% w/w, at least 45% w/w, at least 50% w/w, at least 55% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 75% w/w, at least 80% w/w, at least 85% w/w, or at least 90% w/w. In various versions of the invention, the combined composition can comprise water in an amount up to up to 60% w/w, up to 65% w/w, up to 70% w/w, up to 75% w/w, up to 80% w/w, up to 85% w/w, up to 90% w/w, up to 95% w/w, up to 99% w/w, or more. Amounts from 60% w/w to 95% are preferred.

[0059] In some versions, the generating the combined composition further comprises combining the lipid composition (e.g., milk fat composition) with water. This step, and the amount of water added in this step, will depend on the amount of water in the lipid composition (e.g., milk fat composition) and the desired amount of water in the combined composition.

[0060] In some versions, the lipid particles comprise triglycerides in an amount greater than 50% w/w, greater than 52.5% w/w, greater than 55% w/w, greater than 57.5% w/w, greater than 60%, greater than 62.5% w/w, greater than 65% w/w, greater than 67.5% w/w, greater than 70% w/w, greater than 72.5% w/w, greater than 75% w/w, greater than 77.5% w/w, greater than 80% w/w, greater than 82.5% w/w, greater than 85% w/w of total lipids detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry. In some versions, the lipid particles comprise triglycerides in an amount up to 75% w/w, up to 77.5% w/w, up to 80% w/w, up to 82.5% w/w, up to 85% w/w, up to 87.5% w/w, up to 90% w/w, or more of total lipids detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry. In some versions, the lipid particles comprise triglycerides in an amount greater than 50% w/w, greater than 52.5% w/w, greater than 55% w/w, greater than 57.5% w/w, greater than 60%, greater than 62.5% w/w, greater than 65% w/w, greater than 67.5% w/w, greater than 70% w/w, greater than 72.5% w/w, greater than 75% w/w, greater than 77.5% w/w, greater than 80% w/w, greater than 82.5% w/w, or greater than 85% w/w of combined total of triglyceride, diglyceride, 1,2-diacylglyceryl-3-O-4'-(N,N,N-trimethyl)-homoserine, phosphatidylcholine, ether-linked phosphatidylcholine, fatty acyl ester of hydroxy fatty acid, free fatty acid, lysophosphatidylcholine, phosphatidylethanolamine, ether-linked phosphatidylethanolamine, lysophosphatidylethanolamine, non-hydroxy-fatty acid sphingosine ceramide, and sphingomyelin detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry. In some versions, the lipid particles comprise triglycerides in an amount up to 75% w/w, up to 77.5% w/w, up to 80% w/w, up to 82.5% w/w, up to 85% w/w, up to 87.5% w/w, up to 90% w/w, or more of combined total of triglyceride, diglyceride, 1,2-diacylglyceryl-3-O-4'-(N,N,N-trimethyl)-homoserine, phosphatidylcholine, ether-linked phosphatidylcholine, fatty acyl ester of hydroxy fatty acid, free fatty acid, lysophosphatidylcholine, phosphatidylethanolamine, ether-linked phosphatidylethanolamine, lysophosphatidylethanolamine, non-hydroxy-fatty acid sphingosine ceramide, and sphingomyelin detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry. The positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry can be performed as described in the following examples.

[0061] In some versions, the lipid particles comprise a greater relative amount of any 1 or more, any 2 or more, any 3 or more, any 4 or more, any 5 or more, any 6 or more, any 7 or more, any 8 or more, any 9 or more, any 10 or more, any 11 or more, any 12 or more, any 13 or more, any 14 or more, any 15 or more, any 16 or more, any 17 or more, any 18 or more, any 19 or more, any 20 or more, any 21 or more, any 22 or more, any 23 or more, any 24 or more, any 25 or more, any 26 or more, or each of the following triglycerides

compared to Intralipid® 20 lipid particles as detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry: TG 14:0_16:0_16:0, TG 14:0_15:0_16:0, TG 12:0_16:0_16:0, TG 12:0_15:0_16:0, TG 12:0_14:0_16:0, TG 16:0_18:0_18:1, TG 16:0_18:1_18:1, TG 16:0_16:0_18:1, TG 14:0_16:0_18:1, TG 12:0_16:0_18:1, TG 12:0_14:0_18:1, TG 14:0_18:1_18:1, TG 18:0_18:0_18:1, TG 16:0_17:0_18:1, TG 18:1_18:1_18:1, TG 12:0_12:1_18:1, TG 15:0_18:1_18:1, TG 15:0_16:0_18:1, TG 17:0_18:1_18:1, TG 17:0_18:0_18:1, TG 16:0_18:1_18:3, TG 16:0_18:0_18:0, TG 14:0_18:1_18:2, TG 14:0_16:0_18:0, TG 12:0_15:0_18:1, TG 15:0_16:0_18:0, and TG 16:0_17:0_18:0. The positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry can be performed as described in the following examples.

[0062] In some versions, the lipid particles comprise a relative amount of any 2 or more, any 3 or more, any 4 or more, or each of the following lipids within 5× of each other as detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry: TG 14:0_16:0_16:0, TG 14:0_15:0_16:0, TG 12:0_16:0_16:0, TG 12:0_15:0_16:0, and TG 12:0_14:0_16:0. The positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry can be performed as described in the following examples.

[0063] In some versions, the lipid particles comprise a relative amount of any 2 or more, any 3 or more, any 4 or more, any 5 or more, any 6 or more, any 7 or more, any 8 or more, any 9 or more, any 10 or more, any 11 or more, any 12 or more, any 13 or more, any 14 or more, any 15 or more, any 16 or more, any 17 or more, any 18 or more, any 19 or more, any 20 or more, any 21 or more, or each of the following lipids within 5× of each other as detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry: TG 14:0_16:0_16:0, TG 14:0_15:0_16:0, TG 12:0_16:0_16:0, TG 12:0_15:0_16:0, TG 12:0_14:0_16:0, TG 16:0_18:0_18:1, TG 16:0_18:1_18:1, TG 16:0_16:0_18:1, TG 14:0_16:0_18:1, TG 12:0_16:0_18:1, TG 12:0_14:0_18:1, TG 14:0_18:1_18:1, TG 18:0_18:0_18:1, TG 16:0_17:0_18:1, TG 18:1_18:1_18:1, TG 12:0_12:1_18:1, TG 15:0_18:1_18:1, TG 15:0_16:0_18:1, TG 17:0_18:1_18:1, TG 17:0_18:0_18:1, TG 16:0_18:1_18:3, TG 16:0_18:0_18:0, TG 14:0_18:1_18:2, TG 14:0_16:0_18:0, TG 12:0_15:0_18:1, TG 15:0_16:0_18:0, and TG 16:0_17:0_18:0. The positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry can be performed as described in the following examples.

[0064] In some versions, the lipid particles comprise a lower relative amount of any 1 or more, any 2 or more, any 3 or more, any 4 or more, any 5 or more, any 6 or more, any 7 or more, any 8 or more, any 9 or more, any 10 or more, or each of the following triglycerides compared to Intralipid® 20 lipid particles as detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry: TG 18:2_18:2_22:0, TG 18:1_18:2_22:0, TG 18:1_18:1_22:0, TG 18:1_18:2_18:2, TG 18:2_18:2_18:2, TG 18:1_18:2_18:3, TG 18:1_18:1_18:2, TG 18:0_18:1_18:1, TG 16:0_18:1_18:2, TG 16:0_18:2_18:3, and TG 18:2_18:3_18:3. The positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry can be performed as described in the following examples.

[0065] In some versions, the lipid particles comprise any 1 or more, any 2 or more, any 3 or more, any 4 or more, any 5 or more, any 6 or more, any 7 or more, any 8 or more, any 9 or more, any 10 or more, any 11 or more, any 12 or more, any 13 or more, any 14 or more, any 15 or more, any 16 or more, any 17 or more, any 18 or more, any 19 or more, any 20 or more, any 21 or more, any 22 or more, any 23 or more, any 24 or more, any 25 or more, any 26 or more, or each of the lipids shown in Tables 6A-6F. The positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry can be performed as described in the following examples.

[0066] In some versions, the lipid particles comprise any 2 or more, any 3 or more, any 4 or more, any 5 or more, any 6 or more, any 7 or more, any 8 or more, any 9 or more, any 10 or more, any 11 or more, any 12 or more, any 13 or more, any 14 or more, any 15 or more, any 16 or more, any 17 or more, any 18 or more, any 19 or more, any 20 or more, any 21 or more, any 22 or more, any 23 or more, any 24 or more, any 25 or more, any 26 or more, or each of the lipids shown in Tables 6A-6F in relative amounts with respect to each other within +/−10-fold, +/−5-fold, +/−2-fold, +/−95%, +/−90%, +/−85%, +/−80%, +/−75%, +/−70%, +/−75%, +/−70%, +/−65%, +/−60%, +/−55%, +/−50%, +/−45%, +/−40%, +/−35%, +/−30%, +/−25%, +/−20%, +/−15%, +/−10%, +/−5%, or +/−1% of the relative amounts between such lipids as shown in Tables 6A-6F, as detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry. The positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry can be performed as described in the following examples.

[0067] The surfactant combined with the lipid composition (e.g., milk fat composition) in generating the combined composition can be any surfactant that can serve as an emulsifier in generating an emulsion from the combined composition.

[0068] The surfactant can be an amphiphilic compound that comprises a hydrophilic head and a hydrophobic tail. The hydrophilic head can comprise a polar, nonionic head group or an ionic head group. The ionic head group can be an anionic head group, a cationic head group, or a zwitterionic head group.

[0069] The nonionic head groups can include hydroxyl groups or other polar groups. Examples of surfactants that comprise a nonionic head group include long chain alcohols, such as cetyl alcohol, stearyl alcohol, cetostearyl alcohol (consisting predominantly of cetyl and stearyl alcohols), and oleyl alcohol; polyoxyethylene glycol alkyl ethers (Brij), such as those having the formula CH_3-$(CH_2)_{10-16}$—$(O—C_2H_4)_{1-25}$—OH, including octaethylene glycol monododecyl ether and pentaethylene glycol monododecyl ether, among others; polyoxypropylene glycol alkyl ethers, such as those having the formula CH_3—$(CH_2)_{10-16}$—$(O—C_3H_6)_{1-25}$—O; glucoside alkyl ethers, such as those having the formula CH_3—$(CH_2)_{10-16}$—(O-Glucoside)$_{1-3}$-OH, including decyl glucoside, lauryl glucoside, and octyl glucoside, among others; polyoxyethylene glycol octylphenol ethers, such as those having the formula C_8H_{17}—(C_6H_4)—$(O—C_2H_4)_{1-25}$—OH, including Triton X-100, among others; polyoxyethylene glycol alkylphenol ethers, such as those having the formula C_9H_{19}—(C_6H_4)—$(O—C_2H_4)_{1-25}$—OH, including nonoxynol-9, among others; glycerol alkyl esters, such as glyceryl laurate, among others; polyoxyethylene

glycol sorbitan alkyl esters, such as polysorbate (e.g., polysorbate 20 (polyoxyethylene (20) sorbitan monolaurate), polysorbate 40 (polyoxyethylene (20) sorbitan monopalmitate), polysorbate 60 (polyoxyethylene (20) sorbitan monostearate), polysorbate 80 (polyoxyethylene (20) sorbitan monooleate)), among others; sorbitan alkyl esters, such as Spans, among others; cocamide MEA; cocamide DEA; codecyldimethylamine oxide; block copolymers of polyethylene glycol and polypropylene glycol, such as poloxamers, among others; and polyethoxylated tallow amine (POEA).

[0070] The anionic head groups can include sulfate, sulfonate, phosphate, and/or carboxylate groups, among others. Examples of surfactants that comprise an anionic head group include alkyl sulfates, such as ammonium lauryl sulfate, sodium lauryl sulfate (SDS, sodium dodecyl sulfate), alkyl-ether sulfates such as sodium laureth sulfate, and sodium myreth sulfate, among others. Examples of surfactants that comprise an anionic head group also include sulfonates, such as dioctyl sodium sulfosuccinate, perfluorooctanesulfonate (PFOS), perfluorobutanesulfonate, linear alkylbenzene sulfonates (LABs), and carboxylates, among others. Carboxylates include alkyl carboxylates, such as fatty acids and salts thereof. Examples of carboxylates include sodium stearate, sodium lauroyl sarcosinate, and carboxylate-based fluorosurfactants, such as perfluorononanoate, and perfluorooctanoate (PFOA or PFO). Other examples of anionic surfactants include cocoyl isethionate, sodium dodecylbenzinesulfonate, and sodium isethionate.

[0071] The cationic head groups can include pH-dependent primary, secondary, or tertiary amines and permanently charged quaternary ammonium cations, among others. Primary amines become positively charged at pH<10, secondary amines become positively charged at pH<4. An example of a pH-dependent amine is octenidine dihydrochloride. Permanently charged quaternary ammonium cations include alkyltrimethylammonium salts, such as cetyl trimethylammonium bromide (CTAB, hexadecyl trimethyl ammonium bromide), cetyl trimethylammonium chloride (CTAC), cetylpyridinium chloride (CPC), benzalkonium chloride (BAC), benzethonium chloride (BZT), 5-Bromo-5-nitro-1, 3-dioxane, dimethyldioctadecylammonium chloride, cetrimonium bromide, and dioctadecyldimethylammonium bromide (DODAB), among others.

[0072] Zwitterionic (amphoteric) surfactants have both cationic and anionic centers attached to the same molecule. The cationic center can be based on primary, secondary, or tertiary amines, quaternary ammonium cations, or others. The anionic part can include sulfonates, as in CHAPS (3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate), or sultaines, as in cocamidopropyl hydroxysultaine. Other examples of zwitterionic head groups include betaines, such as cocamidopropyl betaine, and cholinephosphates, such as those occurring in lecithin, among others.

[0073] For ionic head groups, the counter-ion can be monoatomic/inorganic or polyatomic/organic. Monoatomic/inorganic cationic counter-ions include metals, such as the alkali metals, alkaline earth metals, and transition metals. Monoatomic/inorganic anionic counter-ions include the halides, such as chloride (Cl^-), bromide (Br^-), and iodide (I^-). Polyatomic/organic cationic counter-ions include ammonium, pyridinium, and triethanolamine (TEA), among others. Polyatomic/organic anionic counter-ions include tosyls, trifluoromethanesulfonates, and methylsulfate, among others.

[0074] The hydrophobic tail of the surfactant can include a linear, branched, or aromatic hydrocarbon chain. The hydrocarbon chain can have any number of carbon atoms suitable to render it hydrophobic. The number of carbon atoms can include from 9 to 30 carbon atoms, from 10 to 20 carbon atoms, or from 12 to 18 carbon atoms. Such carbon atoms can be saturated, unsaturated, straight-chained, branched, or cyclic.

[0075] The surfactant can comprise a natural surfactant and/or a synthetic surfactant. As used herein, "natural surfactant" refers to a saponified animal or vegetable fat or purified components thereof. "Synthetic surfactant" refers to a surfactant that is not a natural surfactant. The animal or vegetable fat used to generate the natural surfactant can be a solid fat or a liquid fat (i.e., an oil). Examples of solid fats include lard, tallow, and vegetable shortening, among others. Examples of liquid fats include oils such as coconut oil, peanut oil, almond oil, palm oil, olive oil, and soybean oil, among others. Other suitable fats include apricot kernel, sweet almond, jojoba, evening primrose, wheat germ, avocado, shea butter, and coconut butter, among others. To generate the natural surfactant, the fats are saponified, i.e., hydrolyzed, with a strong base. Lye is a suitable strong base. Caustic soda (sodium hydroxide) and caustic potash (potassium hydroxide) are both examples of lye. Saponification of fat results in a saponified fat composition. The saponified fat composition can comprise fatty acids or salts thereof, glycerol, any cations remaining from the saponification, such as sodium and/or potassium, and/or any non-hydrolyzed fat. The sodium and potassium can be complexed with the fatty acid to form a fatty salt or can be free ions. The glycerol may or may not be removed from the saponified fat.

[0076] In various versions of the invention, the surfactant can be included in the combined composition in an amount of at least 0.01% w/w, at least 0.02% w/w, at least 0.03% w/w, at least 0.04% w/w, at least 0.05% w/w, at least 0.06% w/w, at least 0.07% w/w, at least 0.08% w/w, at least 0.09% w/w, at least 0.1% w/w, at least 0.2% w/w, at least 0.3% w/w, at least 0.4% w/w, at least 0.5% w/w and/or up to 0.5% w/w, up to 0.6% w/w, up to 0.7% w/w, up to 0.8% w/w, up to 0.9% w/w, up to 1% w/w, up to 2.5% w/w, up to 5% w/w, up to 7.5% w/w, up to 10% w/w, or more. In various versions of the invention, the surfactant can be included in the combined composition in an amount up to 0.6% w/w, up to 0.7% w/w, up to 0.8% w/w, up to 0.9% w/w, up to 1% w/w, up to 2.5% w/w, up to 5% w/w, up to 7.5% w/w, up to 10% w/w, up to 12.5% w/w, up to 15% w/w, up to 17.5% w/w, up to 20% w/w or more. Amounts from 0.05% to 2% are preferred.

[0077] The methods of generating the lipid particles of the invention can further comprise a step of emulsifying the combined composition to generate an emulsified composition. "Emulsifying" as used herein refers to any method suitable for emulsifying the lipid of the combined composition in the water of the combined composition, e.g., in the form of micelles in an oil-in-water emulsion. Any emulsifying method can be used. Examples include mixing, stirring, homogenization, microfluidization, sonication, etc.

[0078] Preferred emulsification methods include methods capable of generating lipid particles (e.g., micelles) having a diameter less than 1,000 nm, and more preferably less than, 900, 800, 700, 600, or 500 nm. Exemplary emulsifi-

cation methods capable generating lipid particles of this size include high-pressure homogenization. In the form of micelles, the lipid particles of the invention are typically spherical in shape. Thus, the term "diameter" represents a true diameter of the lipid particles. In cases in which the lipid particles are not spherical in shape, the term "diameter" is defined according to maximum dimension.

[0079] In various versions of the invention, the emulsification is effective to generate a high proportion of lipid particles having a diameter less than 1,000 nm. For example, the lipid particles in various versions of the invention can have a diameter less than 1,000 nm, less than 950 nm, less than 900 nm, less than 850 nm, less than 800 nm, less than 750 nm, less than 700 nm, less than 650 nm, less than 600 nm, less than 550 nm, less than 500 nm, less than 450 nm, or less than 400 nm. The lipid particles in various versions of the invention can have a diameter greater than 1 nm, greater than 5 nm, greater than 25 nm, greater than 50 nm, greater than 75 nm, greater than 100 nm, greater than 150 nm, or greater than 200 nm. In various embodiments, the lipid particles having any of these stated values (e.g., less than 500 nm) or combination of stated values (e.g., less than 500 nm and greater than 200 nm) can constitute at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the total number lipid particles in a given composition, such as the emulsified composition or compositions obtained or derived therefrom. In various embodiments, the lipid particles having any of these stated values (e.g., less than 500 nm) or combination of stated values (e.g., less than 500 nm and greater than 200 nm) can constitute up to 5%, up to 10%, up to 15%, up to 20%, up to 25%, up to 30%, up to 35%, up to 40%, up to 45%, up to 50%, up to 55%, up to 60%, up to 65%, up to 70%, up to 75%, up to 80%, up to 85%, up to 90%, up to 95%, or up to 100% of the total number lipid particles in a given composition, such as the emulsified composition or compositions obtained or derived therefrom. In various versions of the invention at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% of the total number lipid particles in a given composition, such as the emulsified composition or compositions obtained or derived therefrom, have a diameter from 5 nm to 500 nm. In any of the foregoing embodiments, the lipid particles of the invention can have any one of the aforementioned sizes or size ranges for a period of at least 10 days, at least 20, days, at least 30 days, at least 40 days, at least 50 days, at least 60 days, at least 70 days, at least 80 days, at least 90 days, at least 100 days, at least 120, days, at least 130 days, at least 140 days, at least 150 days, at least 160 days, at least 170 days, at least 180 days, at least 190 days, at least 200 days or more. In any of the foregoing embodiments, the lipid particles of the invention can have any one of the aforementioned sizes or size ranges for a period up to 50 days, up to 60 days, up to 70 days, up to 80 days, up to 90 days, up to 100 days, up to 120, days, up to 130 days, up to 140 days, up to 150 days, up to 160 days, up to 170 days, up to 180 days, up to 190 days, up to 200 days or more.

[0080] In addition to the step of emulsifying the combined composition, the methods of generating the lipid particles can further comprise a step of size-filtering the lipid particles. The lipid particles can be size-filtered by size-filtering any composition comprising the lipid particles, for example, the emulsified composition and/or the autoclaved composition (as described below), to thereby generate a size-filtered composition. The lipid particles can be filtered using a filter with a pore size from 0.5 μm to 5.0 μm or more, such as from 0.5 μm to 2 μm, or about 1 μm.

[0081] The method of generating the lipid particles can further comprise a step of autoclaving the lipid particles. The lipid particles can be autoclaved in any composition comprising the lipid particles, including the emulsified composition and/or the size-filtered composition, to thereby generate an autoclaved composition.

[0082] The method of any prior claim, further comprising autoclaving the lipid particles. Methods of autoclaving are well known in the art. Exemplary autoclaving conditions include exposure to pressurized saturated steam at about 121° C. (250° F.) for around 30-60 minutes at a pressure of about 15 psi above atmospheric pressure (205 kPa or 2.02 atm). Variations of these conditions are well known in the art.

[0083] In some versions of the invention, the lipid composition used for generating the combined composition is a milk fat composition comprising target milk fat that is generated from a prior milk fat composition. The prior milk fat composition can comprise the target milk fat and additional milk fat. The milk fat composition in such embodiments can be made by removing the additional fat in the prior milk fat composition from the target milk fat to thereby generate the milk fat composition. The removing the additional fat can be performed by any of a variety of lipid purification methods. In some embodiments, the removing the additional fat can comprise melt fractionation. Melt fractionation is described in further detail herein. Briefly, melt fractionating comprises holding a lipid composition at a specific temperature to generate a liquid phase and a solid phase, separating the liquid phase from the solid phase, and retaining either the removed liquid phase or the solid phase depending on the target lipids that are desired. In various versions of the invention, the target milk fat obtained from melt fractionation can comprise a liquid fraction of the prior milk fat composition from a temperature of 0° C., 5° C., 10° C., 15° C., 20° C., 25° C., 30° C., 35° C., 40° C., 45° C., 50° C., 55° C., 60° C., 65° C., 70° C., 75° C., 80° C., 85° C., or any range between and including any two of the foregoing values. In various versions of the invention, the target milk fat obtained from melt fractionation can comprise a solid fraction of the prior milk fat composition from a temperature of 0° C., 5° C., 10° C., 15° C., 20° C., 25° C., 30° C., 35° C., 40° C., 45° C., 50° C., 55° C., 60° C., 65° C., 70° C., 75° C., 80° C., 85° C., or any range between and including any two of the foregoing values. In preferred embodiments, the target milk fat obtained from melt fractionation can comprise a liquid fraction of the prior milk fat composition from a temperature of from 15° C. to 35° C., such as from 20° C. to 30° C., or about 25° C.

[0084] The prior milk fat composition can comprise milk or any downstream product derived therefrom. The prior milk fat composition preferably comprises a composition generated from milk by removing at least a portion of solids-not-fat and/or water from the milk. In various versions of the invention, the prior milk fat composition can comprise any of the characteristics described above for the lipid composition, including but not limited to any of the above-referenced total lipid amounts, any of the above-

referenced milk fat amounts (e.g., in a solids portion thereof), and any of the above-referenced solids portion amounts. Exemplary prior milk fat compositions comprise anhydrous milk fat, butter oil, and ghee, among others.

[0085] The lipid particles of the invention can be used for parenteral nutrition. Accordingly, some versions of the invention are directed to methods of administering parenteral nutrition. The methods can comprise parenterally administering the lipid particles of the invention to a subject. The subject can be a subject in need of parenteral nutrition. The lipid particles of the invention have reduced deleterious immunological effects than intravenous fat emulsions made from vegetable fats conventionally used in parenteral nutrition. The particles of the invention can therefore be used for parenteral nutrition for subjects with various inflammatory complications or disorders, such as pancreatitis, hepatitis, or other inflammatory complications.

[0086] The lipid particles of the invention can be administered in the form of a parenteral nutrition composition. The parenteral nutrition composition can comprise the particles of the invention in a carrier. Parenteral nutrition carriers are well known in the art.

[0087] The particles of the invention can be administered separately from other parenteral nutrition solutions or in all-in-one parenteral nutrition compositions containing the lipid particles of the invention in combination with other nutrients. Compositions containing all essential nutrients are preferred to reduce the possibility of microbiological contamination, simplify in-home usage, decrease nursing time, and decrease risk of error (Hardy and Puzovic, 2009). Exemplary parenteral nutrition nutrients include amino acids and dextrose, among others. "Intralipid®" is a registered trademark of Riker Laboratories, Inc., Northridge, CA.

[0088] Intralipid® 20% (a 20% intravenous fat emulsion) is a sterile, non-pyrogenic fat emulsion prepared for intravenous administration as a source of calories and essential fatty acids. It is made up of 20% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, and water for injection. In addition, sodium hydroxide has been added to adjust the pH so that the final product pH is 8. pH range is 6 to 8.9. Intralipid® 20% can be obtained by Baxter Healthcare Corporation, Deerfield, IL.

[0089] The elements and method steps described herein can be used in any combination whether explicitly described or not.

[0090] All combinations of method steps as used herein can be performed in any order, unless otherwise specified or clearly implied to the contrary by the context in which the referenced combination is made.

[0091] As used herein, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise.

[0092] Numerical ranges as used herein are intended to include every number and subset of numbers contained within that range, whether specifically disclosed or not. Further, these numerical ranges should be construed as providing support for a claim directed to any number or subset of numbers in that range. For example, a disclosure of from 1 to 10 should be construed as supporting a range of from 2 to 8, from 3 to 7, from 5 to 6, from 1 to 9, from 3.6 to 4.6, from 3.5 to 9.9, and so forth.

[0093] All patents, patent publications, and peer-reviewed publications (i.e., "references") cited herein are expressly incorporated by reference to the same extent as if each individual reference were specifically and individually indicated as being incorporated by reference. In case of conflict between the present disclosure and the incorporated references, the present disclosure controls.

[0094] It is understood that the invention is not confined to the particular construction and arrangement of parts herein illustrated and described, but embraces such modified forms thereof as come within the scope of the claims.

EXAMPLES

Overview

IVFEs and Parenteral Nutrition

[0095] For parenteral nutrition, intravenous fat emulsions (IVFEs) containing suspended fat droplets (200-500 nm in diameter) can be prepared using an emulsifying agent (e.g., egg lecithin). IVFEs can be prepared in a manner to avoid essential FA deficiency and other complications (Anez-Bustillos et al., 2016). Essential FA deficiency occurs when <1-2% of energy consumed comes from essential FA (i.e., α-linolenic acid and linoleic acid). This is far more common in patients who are dependent on IVFEs than the general population. Patients who rely on IVFEs can also experience fat overload syndrome (i.e., elevated plasma triglycerides), hepatic steatosis (i.e., fatty liver disease), and other complications, reflecting the importance of balanced FA compositions when utilizing IVFEs for patients requiring parenteral nutrition. Here, we show that milk lipids will have a broad FA profile that can be manipulated and be prepared as a solution to remedy this important clinical problem.

Milk Fat Composition and Structure

[0096] Milk fat is ca. 95-98% triglycerides with 0.8-1.1% phospholipids and minimal (<0.5%) monoglycerides and free FAs (Kailasapathy, 2015). The FA profile of milk is diverse with more than 400 distinct FAs detected. On average, milk fat contains ca. 62% saturated FAs, 29% monounsaturated FAs, and 4% polyunsaturated FAs with palmitic acid (16:0, ca. 29.5% of the FAs in milk) and oleic acid (18:1, ca. 27.4% of the FAs in milk) being the most abundant FAs (Table 1). Additionally, compared to other fat sources, milk fat is relatively abundant in short chain FAs (C_4-C_8), conjugated linoleic acid, and contains detectable essential FAs depending on the feeds used. With every FA having a characteristic melting temperature, the diverse FA profile of milk is responsible for the uniquely broad melting profile in dairy products (e.g., butter).

TABLE 1

Fatty acid profile (expressed in % composition) of bovine milk fat without fractionation (control) or post-fractionation as well as commercially available lipid emulsions used in parenteral nutrition, including: Intralipid ® 20% and SMOFlipid ®.

Fatty Acid	Common Name	Control	LMF-10	Intralipid ®	SMOFlipid ®
4:0	Butyric acid	3.55 ± 0.06	4.63 ± 0.15	NS	NS
6:0	Caproic acid	2.24 ± 0.04	2.75 ± 0.13	NS	NS
8:0	Caprylic acid	1.27 ± 0.11	1.84 ± 0.06	NS	13-24
10:0	Capric acid	3.14 ± 0.06	4.27 ± 0.09	NS	5-15
12:0	Lauric acid	4.28 ± 0.04	5.09 ± 0.08	NS	NS
14:0	Myristic acid	11.92 ± 0.33	12.51 ± 0.17	NS	NS
16:0	Palmitic acid	30.55 ± 1.55	18.46 ± 0.19	7-14	7-12
18:0	Stearic acid	10.55 ± 0.72	5.19 ± 0.05	1.4-5.5	1.5-4
18:1	Oleic acid	23.19 ± 0.44	31.12 ± 0.71	19-30	23-35
18:2	Linoleic acid	1.88 ± 0.13	3.16 ± 0.09	44-62	14-25
18:3	Linolenic acid	NS	—	4-11	1.5-3.5
20:5	Eicosapentaenoic acid (EPA)	NS/SD	—	—	1-3.5
22:6	Docosahexaenoic acid (DHA)	NS	—	—	1-3.5

LMF-10 = low-melting fractions obtained at 10° C.; Intralipid ® lipids = 100% soybean oil; SMOFlipid ® lipids = 30% soybean oil, 30% coconut oil, 25% olive oil, and 15% fish oil; NS = not specified.
SD = sometimes detected.

[0097] Milk FA profile can be altered by direct manufacturing interventions such as melt fractionation, as outlined herein. Typically, milk fat fractionation takes advantage of the broad melting range of milk fat, allowing for the controlled crystallization and removal of specific groups of FAs. For example, milk fat can be fractionated by incubating cream at a specific temperature, allowing some fat to crystallize, and then separating the liquid fat from the fat crystals via filtration, centrifugation, or any other suitable method, such as methods suitable for phase separation. The present examples employ melt curve to generate favorable FA profiles for parenteral nutrition.

[0098] The fat content and FA profile of milk can also be manipulated during milk production through cow genetics (e.g., breed; Coffey et al., 2016), lactation and milking stages (Rico et al., 2014), diet (Atkins et al., 2020), and environmental factors (e.g., season; Bailey et al., 2005). For example, many studies have found that α-Linolenic acid (18:3) content in milk increases in pasture-fed cows compared to cows fed a total mixed ration ad libitum (Barca et al., 2017, Atkins et al., 2020).

[0099] Concentrated milkfat sources are preferred lipid sources for prepare the exemplary IVFE of the invention. These include anhydrous milkfat and butter oil, among others (Table 2). These lipid sources preferably have at least some of the solids-not-fat constituents of milk removed.

TABLE 2

Composition of concentrated milkfat sources

Constituent	Butter	Butteroil	Anhydrous milkfat
Milkfat	≥80.0%	≥99.6%	≥99.8%
Moisture	ND	≤0.3%	≤0.1%
Other butter constituents	ND	≤0.1%	≤0.1%
Free fatty acids	ND	≤0.5% (calculated as oleic acid)	≤0.3% (calculated as oleic acid)

ND = not defined

Ultra High-Pressure Homogenization for Micelle Formation

[0100] In milk, lipids are primarily contained in globules (1-20 μm in diameter) surrounded by a milk fat globule membrane (MFGM, 5-10 nm thick; Kailasapathy, 2015). The native MFGM, containing proteins, polar lipids, lipoproteins, phospholipids, and other components, helps to protect milk fat from lipoprotein lipase (i.e., reducing the rate of hydrolytic rancidity) and stabilizes milk fat in an emulsion (i.e., reducing the rate of creaming). Conventional homogenization (ca. 10-20 MPa), which involves forcing liquid product through flow restriction(s), effectively splits the milk fat globules into many smaller globules (average size <1 μm) and subsequently disrupts the native MFGM (Chandan, 2015).

[0101] Ultra high-pressure homogenization (UHPH) operates under more extreme pressures (100-400 MPa) than conventional dairy homogenization using abrasion-resistant nozzles, inducing more extreme shear, friction, cavitation, and heat to samples. This processing methodology has been shown to alter protein quaternary structures (Harte et al., 2002), change polysaccharide functionality (Harte and Venegas, 2010), inactivate microorganisms (Diels and Michiels, 2006), and enhance emulsion stability (Galvão et al., 2018). UHPH induces the formation of small, monodisperse droplets, especially when droplet re-coalescence is discouraged by adding surfactants and optimizing processing pressure to reduce UHPH-induced heating and decrease cavitation. UHPH is employed in the present examples to achieve IVFE sizes similar to circulating chylomicrons for use in parenteral nutrition.

Dairy Solution for Intravenous Lipid Emulsions

[0102] We show herein that extracting and purifying bovine milk lipids is a solution to the supply chain and lipid sourcing space that convers unique metabolic and immunological health benefits in patients requiring intravenous nutrition. We also show that extracting and purifying bovine milk lipids is a solution to the supply chain and lipid sourcing space that confers unique metabolic and immunological health benefits in patients requiring intravenous nutrition. The objectives of the present examples are to: (1) Melt fractionate an initial milk fat composition into a preferrable FA profile; (2) Develop a stable milk fat emulsion suitable for intravenous usage using UHPH; and (3) Evaluate the suitability of emulsified milk fat and identified milk fat fractions suitable for intravenous lipid support (FIG. **2** and Table 3).

TABLE 3

The objectives, hypotheses and, and deliverables with this work.

Objectives	Hypotheses	Deliverables
Objective 1. Develop a desirable fatty acid profile using fractionation by monitoring fatty acid composition using GC-MS.		Improved fatty acid profile for IVFEs.
Objective 2. Evaluate the particle size and stability of milk fat-based IVFEs made using high-pressure homogenization with varied processing parameters.	A UHPH pressure of 150 MPa (0.20 mm orifice) with some back pressure will be sufficient to produce IVFEs suitable for intravenous use (<500 nm). Droplet size will decrease and stability will increase with higher processing pressures if coalescence can be controlled.	Optimized procedure for milk fat-based IVFE preparation.
Objective 3. Determine the suitability of milk fat-based IVFEs for intravenous lipid support using mouse models.	Purified milk fat lipid fraction emulsions will support metabolism and optimize organ growth and function throughout the lifespan.	Milk fat-based IVFEs suitable for parenteral nutrition.

Objective 1. Develop a Desirable Fatty Acid Profile Using Fractionation by Monitoring Fatty Acid Composition Using GC-MS.

[0103] We identify herein suitable milk fat sources (e.g., anhydrous milk fat), fractionate milk fat using controlled crystallization, and evaluate components using GCMS+DSC (crystallization).

Objective 2. Evaluate the Particle Size and Stability of Milk Fat-Based IVFEs Made Using High-Pressure Homogenization with Varied Processing Parameters.

[0104] Beyond selecting a FA profile that is suitable for parenteral nutrition, other issues associated with IVFEs are the desire to (1) generate lipid particles that are very small (200-500 nm), (2) generate lipid particles that are stable to typical handling and storage practices, and (3) avoid inadvertently introducing microorganisms that increase the risk of infection (Hardy and Puzovic, 2009). A UHPH system is used for generating the lipid particles (Nano DeBEE 45-2, BEE International) is used to produce highly stable particles with adequate diameters suitable for IVFEs. Multiple emulsifiers and UHPH processing parameters will be utilized to optimize the particle size, storage stability, and heat stability of IVFEs (Table 4).

TABLE 4

The variables to be tested in IVFE formation, including emulsifier and HPH parameters.

Parameter	Variables
Emulsifier	Type - lecithin, glycerin Concentration - 0.5%, 1%, 1.5% Surfactant-to-lipid ratio - 1:4, 1:3, 1:2
UHPH conditions	Pressure - 150 MPa, 300 MPa Back pressure - 0 psi, 1000 psi, 2000 psi Orifice size - 0.13 mm, 0.20 mm Number of passes - 1, 2, or 3 Other options: Parallel or reverse flow, reactor cell orientation, input/output temperature

[0105] IVFE particle size can be determined using a Malvern MasterSizer 3000 (at UW-Madison), as described in Shi et al. (2009). IVFE storage stability can be determined by monitoring IVFE particle size at 15 day intervals through 12 months of storage at 4° C. and 20° C. Heat stability can be evaluated by holding prepared IVFEs in water baths at 40, 60, 80, and 90° C. and collecting aliquots at 0, 1, 2, 4, 8, 12, 24, and 48 h for particle size determination. IVFE microbiological safety can be determined following sterile filtration methods followed by endotoxin testing, 16S amplification, and aerobic and anerobic culturing techniques to confirm the presence or absence of viable or non-viable microorganisms remain in emulsion solutions. Additional processing steps can be introduced to promote sterility, including (1) a 0.2 μm filtration step or (2) heat sterilization prior.

Objective 3. To Determine the Suitability of Milk Fat-Based IVFEs for Intravenous Lipid Support Using Mouse Models.

[0106] The dairy based IVFEs can be tested in preclinical animal models alongside existing commercial lipid sources, including Intralipid® and SMOFlipid®. Following intravenous catheterization under sterile technique, animals can be fed parenteral nutrition and experimental lipid emulsions at 5-10% volume/volume. Administration rates can be based on animal body weight, tolerability, and calculated to meet caloric, nitrogen, and fat requirements for the animals. Systemic lipid metabolism, including clearance and uptake, can be examined. After a period of time (e.g., 5 days), animals can be humanely sacrificed for additional metabolic and immunological responses. Solutions can first be tested in adult animals (6-8 weeks of age) to establish safety, tolerability, and baseline metabolic impacts between the lipid emulsion formulations. Following this, pediatric animals (8-10 days of age) can be used, since mice at this age are developmentally equivalent to human newborns who often require parenteral nutrition. Animals can be fed for a period of time (e.g., 5 days) prior to assessment of hepatic homeostasis, endocrine signaling, organ development and body weight gain. In both sets of experiments, adult control animals can receive a jugular catheter and be provided saline with ab libitum access to food, or pediatric animals can undergo jugular vein occlusion to control for the presence of a catheter and be returned to the dam to continue maternal milk feeding.

Materials, Methods, and Results

Fat Fractionation

[0107] Milk fat with high purity was obtained in the form of anhydrous milkfat (AMF, Grassland, Greenwood, WI).

[0108] Native AMF was fractionated using dry fractionation at fractionation temperatures of 25 and 15° C. Specifically, the AMF was heated to >65° C. (e.g., 80° C.) to erase any crystal nuclei memory (i.e., melted), then the AMF was slowly cooled to the desired fractionation temperature and held at this temperature for 24 h under constant agitation in a rotary evaporator (Rotavapor R-100, BUCHI Corporation, New Castle, DE). The solid and liquid fractions were separated using vacuum filtration. Centrifugation or other suitable methods, such as methods for phase separation, can be used. Samples of the unfractionated AMF as well as high melting fractions (HMFs, solid portion at each respective temperature) and low melting fractions (LMFs, liquid portion at respective temperature) at each temperature were collected and analyzed (FIG. **3**). The fractionated samples were designated as: HMF-25, LMF-25, HMF-15, LMF-15.

Lipid Analysis

Lipid Sample Preparation

[0109] Milk fat fractions were stored in 1.5 mL centrifuge tubes. Samples were either solid or liquid at room temperature, therefore, in order to render the samples suitable for manipulation, all samples were heated to 37° C. in a water bath. Samples that remained solid at 37° C. were heated further until fully liquid. All samples were diluted 25-fold (25×) in isopropyl alcohol (IPA) by adding 20-μL sample to 480 μL IPA and vortexing. These 25× dilutions were then held at 37° C. to keep solids from forming while the samples underwent further dilution. For positive mode analysis, samples were diluted a further 40× with IPA to a final dilution factor of 1000×. For negative mode analysis, samples were diluted to a final dilution factor of 100× with IPA. These dilution factors were chosen to both yield a sufficient signal level in positive ion mode, while attempting to prevent excessive overloading of the chromatographic system and generating carryover. The negative ion dilution factors were chosen with the knowledge that the material detected in positive ion mode is being loaded onto the chromatographic and mass spectrometric systems, even though the lipids giving rise to those signals are not visible in negative ion mode. After preparing all dilution levels, the diluted samples were placed at 4° C. for approximately 15 minutes to determine if any solids would precipitate, because this is the temperature that the autosampler is maintained at while samples are waiting to be run. No solids were observed.

Lipid Data Acquisition

[0110] Samples were analyzed by ultra-high-performance liquid chromatography/mass spectrometry (UHPLC/MS) and ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry (UHPLC/MS/MS) in positive ion and negative ion modes. The UHPLC conditions were the same for all acquisitions, regardless of ionization polarity, dilution factor, or MS level (MS or MS/MS). The solvents consisted of A: 10 mM ammonium formate, 0.1% (v/v) formic acid, 60% (v/v) acetonitrile in water; and B: 10 mM ammonium formate, 0.1% (v/v) formic acid, 9% (v/v) acetonitrile, 1% (v/v) water in 2-propanol. The column was a Waters Acquity UPLC BEH C18 1.7 μm 2.1 mm×100 mm, with a guard column containing the same stationary phase with dimensions 2.1 mm×5 mm. The gradient is shown in Table 5 below.

TABLE 5

Time	% A	% B	Flow
0.00 min	85.00%	15.00%	0.500 mL/min
2.40 min	70.00%	30.00%	0.500 mL/min
3.00 min	52.00%	48.00%	0.500 mL/min
13.20 min	18.00%	82.00%	0.500 mL/min
13.80 min	1.00%	99.00%	0.500 mL/min
15.40 min	1.00%	99.00%	0.500 mL/min
16.00 min	85.00%	15.00%	0.500 mL/min
20.00 min	85.00%	15.00%	0.500 mL/min

[0111] The column was maintained at 50° C. Samples were placed in an autosampler held at 8° C. until injection. The UHPLC was an Agilent model 1290 Infinity II with individual components consisting of a model G7120A binary pump, model G7167B multisampler, model G7116B column compartment, and model G7110B isocratic pump. The HPLC was connected to the inlet port of an Agilent G6546A QTOF mass spectrometer, incorporating an Agilent JetStream dual ESI source. The column effluent was delivered to the sample nebulizer of the dual ESI source, while the isocratic pump delivered internal calibrant to the reference nebulizer of the dual ESI source. QTOF parameters differed depending on the ionization polarity and MS level of the acquired data. Parameters for individual acquisition methods are shown below.

[0112] Sample injection volumes also varied depending on MS level and polarity. For positive ion MS, injection volumes were 2 μL; for negative ion MS, injection volumes were 5 μL; for positive ion MS/MS, injection volumes were 4 μL; for negative ion MS/MS injection volumes were 7 μL. After sample pickup, the needle was washed for 3s in the autosampler flush port with 1:1 2-propanol:methanol. LC/MS data were collected with one technical replicate injection per sample. LC/MS/MS data were collected in iterative mode as described above with 5 iterative injections made per ionization mode.

Lipid Data Analysis

[0113] Assignment of lipid identities to mass and retention time signal pairs was made using Lipid Annotator software (Agilent) (Koelmel et al, Metabolites. 10 (3); 101. 2020) and the LC/MS/MS data. Lipid Annotator uses the accurate mass of the precursor and product ions observed within the fragmentation spectra to assign a dominant constituent lipid to a molecular feature in the data, or where that is not possible, a sum composition. Dominant compositions have lipid acyl chains and degree of unsaturation explicitly enumerated, whereas sum compositions only indicate the lipid class, total carbon number, and number of unsaturated sites. After assignment of lipid identities by Lipid Annotator, a database is exported containing the lipid, the mass, and the retention time. This database can then be used by Profinder software (Agilent) to align retention times across samples and extract and integrate ion chromatograms for each lipid in each sample LC/MS data file. These integrations are then reviewed for accuracy and a comma-separated value (.csv)

file exported for further analysis. Because lipids are frequently present in different structural isomers, which can be resolved chromatographically, there are often more than a single chromatographic peak assigned to the same lipid identity. This is particularly true in cases where only a sum composition can be reported, and the acyl chains cannot be individually identified. In these cases, the exported.csv file will have multiple entries assigned to the same lipid species, so a suffix "#" is added to the lipid i.d. to distinguish the different chromatographic species.

[0114] Because the goal of the current experiment was to identify the lipids present in the various fractions and evaluate the fatty acid profile, peak integrations were not performed and data were evaluated by comparing the lipid identifications from Lipid Annotator.

Lipid Findings

[0115] The relative abundance of triglycerides are shown in FIG. **4** for AMF, HMF-15 (15° C. high melting fraction), LMF-15 (15° C. low melting fraction), HMF-25 (25° C. high melting fraction), and LMF-25 (25° C. low melting fraction). Raw mass spec data obtained on identified lipid targets obtained by liquid chromatography with tandem mass spectrometry are provided in Tables 6A-6F. The triglycerides with three medium-chain, saturated (12:0) fatty acids (lauric acid) esterified to the glycerol backbone are shown in FIG. **5** for was compared among the AMF ("C" in FIG. **5**), HMF-15 ("15H" in FIG. **5**), LMF-15 ("15L" in FIG. **5**), HMF-25 ("25H" in FIG. **5**), and LMF-25 ("25L" in FIG. **5**). These medium-chain triglycerides were abundant in the LMFs and are associated with numerous health benefits (Jadhav & Annapure, 2023).

[0116] The lipids in LMF-25 and a conventional soy protein intravenous fat emulsion (Intralipid® 20%) were analyzed and compared (FIGS. **6** and **7**). LMF-25 had a much more diverse fatty acid profile compared to Intralipid® 20%. LMF-25 showed some 22-carbon triglyceride acyl groups but was enriched in 12-18-carbon triglyceride acyl groups. By contrast, Intralipid® 20% was dominated by 18- and 22-carbon triglyceride acyl groups.

TABLE 6A

Raw mass spec data obtained on identified lipid targets obtained by liquid chromatography with tandem mass spectrometry: Formula, mass and retention time (rt) of compounds.

Compound Name	Formula	Mass	RT
DG 16:0_16:0	C35 H68 O5	568.5066	9.91
DG 18:0_18:1	C39 H74 O5	622.5536	10.77
PC 18:1_19:1	C45 H86 N O8 P	799.6091	9.01
PC 34:1	C42 H82 N O8 P	759.5778	8.38
PC 36:2	C44 H84 N O8 P	785.5933	8.36
PC 37:2	C45 H86 N O8 P	799.609	8.8
TG 12:0_12:0_12:0	C39 H74 O6	638.5489	10.94
TG 12:0_12:0_12:1	C39 H72 O6	636.5329	10.11
TG 12:0_12:0_13:0	C40 H76 O6	652.5642	11.33
TG 12:0_12:0_14:0	C41 H78 O6	666.5804	11.71
TG 12:0_12:0_15:0	C42 H80 O6	680.5955	11.95
TG 12:0_12:0_17:0	C44 H84 O6	708.6267	12.62
TG 12:0_12:0_17:1	C44 H82 O6	706.6112	11.96
TG 12:0_12:1_14:0	C41 H76 O6	664.5644	10.94
TG 12:0_12:1_14:3	C41 H70 O6	658.5174	8.88
TG 12:0_12:1_20:5	C47 H78 O6	738.5801	10.13
TG 12:0_12:2_15:0	C42 H76 O6	676.5641	10.71
TG 12:0_12:2_16:0	C43 H78 O6	690.5801	11.08
TG 12:0_12:2_18:2	C45 H78 O6	714.5797	10.46

TABLE 6A-continued

Raw mass spec data obtained on identified lipid targets obtained by liquid chromatography with tandem mass spectrometry: Formula, mass and retention time (rt) of compounds.

Compound Name	Formula	Mass	RT
TG 12:0_14:0_16:0	C45 H86 O6	722.643	12.94
TG 12:0_14:0_20:4	C49 H86 O6	770.6417	12.15
TG 12:0_15:0_16:0	C46 H88 O6	736.658	13.24
TG 12:0_15:0_16:0	C46 H88 O6	736.6579	13.12
TG 12:0_16:0_16:0	C47 H90 O6	750.6743	13.53
TG 12:0_16:0_16:0	C47 H90 O6	750.6733	14.45
TG 12:0_16:0_18:1	C49 H92 O6	776.6895	13.51
TG 13:0_18:1_18:2	C52 H94 O6	814.7053	13.27
TG 14:0_14:0_16:0	C47 H90 O6	750.674	13.25
TG 14:0_14:3_16:0	C47 H84 O6	744.6253	12.48
TG 14:0_14:3_18:0	C49 H88 O6	772.655	13.1
TG 14:0_15:0_16:0	C48 H92 O6	764.6893	13.8
TG 14:0_15:0_16:0	C48 H92 O6	764.6892	13.69
TG 14:0_15:0_18:1	C50 H94 O6	790.7049	13.78
TG 14:0_16:0_16:0	C49 H94 O6	778.7057	14.07
TG 14:0_16:0_17:1	C50 H94 O6	790.7049	14.18
TG 14:0_16:0_18:0	C51 H98 O6	806.7371	14.37
TG 14:0_16:0_18:1	C51 H96 O6	804.7209	14.05
TG 14:0_16:0_18:1	C51 H96 O6	804.7197	14.59
TG 14:0_16:0_20:4	C53 H94 O6	826.7043	13.38
TG 14:0_16:0_20:5	C53 H92 O6	824.6887	12.94
TG 14:0_18:1_18:2	C53 H96 O6	828.7207	13.54
TG 14:1_16:0_18:1	C51 H94 O6	802.7054	13.51
TG 15:0_16:0_18:0	C52 H100 O6	820.752	14.43
TG 15:0_16:0_18:1	C52 H98 O6	818.7362	14.23
TG 16:0_16:0_17:1	C52 H98 O6	818.7361	14.42
TG 16:0_16:0_18:0	C53 H102 O6	834.7683	14.53
TG 16:0_16:0_18:1	C53 H100 O6	832.7526	14.36
TG 16:0_16:0_20:4	C55 H98 O6	854.7355	13.92
TG 16:0_16:1_18:1	C53 H98 O6	830.7369	14.04
TG 16:0_17:0_18:0	C54 H104 O6	848.7832	14.57
TG 16:0_17:0_18:1	C54 H102 O6	846.7675	14.44
TG 16:0_17:1_18:0	C54 H102 O6	846.767	14.57
TG 16:0_18:0_18:0	C55 H106 O6	862.7993	14.63
TG 16:0_18:0_18:1	C55 H104 O6	860.7834	14.52
TG 16:0_18:0_21:0	C58 H112 O6	904.8456	14.74
TG 16:0_18:1_18:1	C55 H102 O6	858.7678	14.35
TG 16:0_18:1_18:2	C55 H100 O6	856.7524	14.07
TG 16:0_18:1_18:3	C55 H98 O6	854.7362	13.63
TG 16:0_18:1_20:5	C57 H98 O6	878.7357	13.49
TG 16:0_20:0_22:0	C61 H118 O6	946.8926	14.85
TG 17:0_18:0_18:0	C56 H108 O6	876.8141	14.66
TG 17:0_18:0_18:1	C56 H106 O6	874.7988	14.57
TG 17:0_18:1_18:1	C56 H104 O6	872.7832	14.44
TG 17:1_18:0_18:1	C56 H104 O6	872.7828	14.56
TG 18:0_18:0_18:0	C57 H110 O6	890.8299	14.71
TG 18:0_18:0_18:1	C57 H108 O6	888.815	14.62
TG 18:0_18:1_18:1	C57 H106 O6	886.7999	14.51
TG 18:1_18:1_18:1	C57 H104 O6	884.7843	14.34
TG 18:1_18:1_18:2	C57 H102 O6	882.7678	14.06
TG 18:1_18:2_18:2	C57 H100 O6	880.7519	13.61
TG 18:1_18:2_18:3	C57 H98 O6	878.7361	13.14
TG 18:1_18:3_18:3	C57 H96 O6	876.7208	12.66
TG 18:1_20:0_22:0	C63 H120 O6	972.9082	14.85
TG 38:2	C41 H74 O6	662.5485	10.24
TG 38:3	C41 H72 O6	660.5327	9.57
TG 40:0	C43 H82 O6	694.6116	12.3
TG 40:1	C43 H80 O6	692.5956	11.71
TG 40:3	C43 H76 O6	688.5642	10.4
TG 40:4	C43 H74 O6	686.5485	9.76
TG 42:1	C45 H84 O6	720.6271	12.3
TG 42:4	C45 H78 O6	714.5798	10.7
TG 43:1	C46 H86 O6	734.6424	12.62
TG 44:1	C47 H88 O6	748.6582	12.93
TG 44:2	C47 H86 O6	746.6425	12.33
TG 44:5	C47 H80 O6	740.5957	10.8
TG 45:1	C48 H90 O6	762.6736	13.22
TG 46:2	C49 H90 O6	774.6739	12.93
TG 46:3	C49 H88 O6	772.658	12.36
TG 47:0	C50 H96 O6	792.7206	14.24
TG 47:1	C50 H94 O6	790.7049	13.78

TABLE 6A-continued

Raw mass spec data obtained on identified lipid targets obtained by liquid chromatography with tandem mass spectrometry: Formula, mass and retention time (rt) of compounds.

Compound Name	Formula	Mass	RT
TG 47:2	C50 H92 O6	788.6893	13.22
TG 47:3	C50 H90 O6	786.6739	12.69
TG 48:3	C51 H92 O6	800.6893	12.98
TG 48:4	C51 H90 O6	798.6731	12.79
TG 48:5	C51 H88 O6	796.658	12.12
TG 49:2	C52 H96 O6	816.7206	13.77
TG 51:2	C54 H100 O6	844.7521	14.22
TG 51:4	C54 H96 O6	840.7207	13.37
TG 52:5	C55 H96 O6	852.7166	13.52
TG 52:5	C55 H96 O6	852.7206	13.15
TG 52:6	C55 H94 O6	850.7061	12.76
TG 53:4	C56 H100 O6	868.7519	13.83
TG 54:5	C57 H100 O6	880.7517	13.9
TG 55:1	C58 H110 O6	902.8296	14.67
TG 56:1	C59 H112 O6	916.845	14.71
TG 56:6	C59 H102 O6	906.7677	13.88
TG 57:0	C60 H116 O6	932.8767	14.81
TG 57:2	C60 H112 O6	928.8456	14.66
TG 58:2	C61 H114 O6	942.8612	14.7

TABLE 6B

Raw mass spec data obtained on identified lipid targets obtained by liquid chromatography with tandem mass spectrometry: HMF-15.

Compound Name	HMF-15 Replicate 1	HMF-15 Replicate 2	HMF-15 Replicate 3
DG 16:0_16:0	0.06384539	0.066072921	0.066587608
DG 18:0_18:1	0.021972192	0.013111251	0.022672526
PC 18:1_19:1	0.005104499	0.00676606	0.008570779
PC 34:1	0.006087907	0.007937543	0.007025569
PC 36:2	0.009927778	0.013034357	0.017802487
PC 37:2	0.002975157	0.005052031	0.005730281
TG 12:0_12:0_12:0	1.33417069	1.306083429	1.246018195
TG 12:0_12:0_12:1	0.312769442	0.297152495	0.182381794
TG 12:0_12:0_13:0	0.329301765	0.319973131	0.333147907
TG 12:0_12:0_14:0	2.670568148	2.605408194	2.51474175
TG 12:0_12:0_15:0	0.476373121	0.400537828	0.480262538
TG 12:0_12:0_17:0	0.423855658	0.417172358	0.414357689
TG 12:0_12:0_17:1	0.256587351	0.035868165	0.079433725
TG 12:0_12:1_14:0	0.911250904	0.907551099	0.858786024
TG 12:0_12:1_14:3	0.002741952	0.007897229	0.000599403
TG 12:0_12:1_20:5	0.001155414	0.005413378	0.009955272
TG 12:0_12:2_15:0	0.036884979	0.033884619	0.056074986
TG 12:0_12:2_16:0	2.084669251	2.221848782	2.055488503
TG 12:0_12:2_18:2	0.01689252	0.007657393	0.012079444
TG 12:0_14:0_16:0	3.518542717	3.283197857	3.231421904
TG 12:0_14:0_20:4	0.012547566	0.010680357	0.017636791
TG 12:0_15:0_16:0	0.383644724	0.369414583	0.367295525
TG 12:0_15:0_16:0	0.120714732	0.118094669	0.120905955
TG 12:0_16:0_16:0	4.049204549	3.815514792	3.755474309
TG 12:0_16:0_16:0	0.001832176	0	0.00123848
TG 12:0_16:0_18:1	3.368177698	3.199916559	3.166048058
TG 13:0_18:1_18:2	0.011325462	0.058022314	0.012233362
TG 14:0_14:0_16:0	0	0.004858184	0
TG 14:0_14:3_16:0	0.002335027	0.002701704	0.00223507
TG 14:0_14:3_18:0	0.000961739	0.001664743	0.002170224
TG 14:0_15:0_16:0	0.468200137	0.441498455	0.441065967
TG 14:0_15:0_16:0	0.177544881	0.215428263	0.18447307
TG 14:0_15:0_18:1	0.542451116	0.520667331	0.513094973
TG 14:0_16:0_16:0	4.927713192	4.802666077	4.645969341
TG 14:0_16:0_17:1	0.039935625	0.038427106	0.036142854
TG 14:0_16:0_18:0	4.702783397	5.027203709	5.122366878
TG 14:0_16:0_18:1	5.243126536	5.144237623	5.024723319
TG 14:0_16:0_18:1	0.005146041	0.000700106	0.010557488
TG 14:0_16:0_20:4	0.032083113	0.041413637	0.03934032
TG 14:0_16:0_20:5	0.006713526	0.008268444	0.010752006

TABLE 6B-continued

Raw mass spec data obtained on identified lipid targets obtained by liquid chromatography with tandem mass spectrometry: HMF-15.

Compound Name	HMF-15 Replicate 1	HMF-15 Replicate 2	HMF-15 Replicate 3
TG 14:0_18:1_18:2	0.885368604	0.921190391	0.919250885
TG 14:1_16:0_18:1	1.856904788	1.808117593	1.803530634
TG 15:0_16:0_18:0	1.107622831	1.030161857	0.98355993
TG 15:0_16:0_18:1	1.103979884	1.064487315	1.038645807
TG 16:0_16:0_17:1	0.072147722	0.078385597	0.073013093
TG 16:0_16:0_18:0	4.223134372	4.419063367	4.469922927
TG 16:0_16:0_18:1	6.318967829	7.151852623	7.452668293
TG 16:0_16:0_20:4	0.05105581	0.059963642	0.067975775
TG 16:0_16:1_18:1	3.419483616	3.386333032	3.293894393
TG 16:0_17:0_18:0	0.673964192	0.597613677	0.60290225
TG 16:0_17:0_18:1	1.202498288	1.173595773	1.150660013
TG 16:0_17:1_18:0	0.059943375	0.058316783	0.058823723
TG 16:0_18:0_18:0	2.412389029	2.170649034	2.142139779
TG 16:0_18:0_18:1	4.971203591	5.466532959	5.627424868
TG 16:0_18:0_21:0	0.06837693	0.067588731	0.062903836
TG 16:0_18:1_18:1	4.949506114	5.340677746	5.430724443
TG 16:0_18:1_18:2	1.733365518	1.841590261	1.798389909
TG 16:0_18:1_18:3	0.368497208	0.430714134	0.448733832
TG 16:0_18:1_20:5	0.015518079	0.020093178	0.036183
TG 16:0_20:0_22:0	0.034853719	0.031240561	0.026458123
TG 17:0_18:0_18:0	0.225595279	0.210402363	0.19410848
TG 17:0_18:0_18:1	0.551210725	0.550632443	0.549894835
TG 17:0_18:1_18:1	0.530718117	0.539385164	0.578422937
TG 17:1_18:0_18:1	0.041902162	0.044152897	0.036444981
TG 18:0_18:0_18:0	0.473121751	0.397319818	0.386044427
TG 18:0_18:0_18:1	1.84101425	1.756113699	1.778889427
TG 18:0_18:1_18:1	2.302990722	2.439033233	2.479657578
TG 18:1_18:1_18:1	2.117680537	2.31568233	2.308131795
TG 18:1_18:1_18:2	0.818718182	0.973811903	0.919892332
TG 18:1_18:2_18:2	0.243702626	0.307888565	0.316370234
TG 18:1_18:2_18:3	0.054860196	0.082899693	0.090366794
TG 18:1_18:3_18:3	0.015267589	0.028201654	0.024253245
TG 18:1_20:0_22:0	0.031709376	0.031229894	0.031402986
TG 38:2	0.108725449	0.058747701	0.187177827
TG 38:3	0.04544691	0.026451452	0.045675324
TG 40:0	2.870659039	2.763887264	2.65860393
TG 40:1	2.398322585	2.305424621	2.244146286
TG 40:3	0.480872884	0.56860464	0.533636788
TG 40:4	0.090699903	0.117915076	0.038072125
TG 42:1	2.446894958	2.327003335	2.294915533
TG 42:4	0.000571206	0.003481376	0.001456867
TG 43:1	0.312286628	0.231204359	0.292152915
TG 44:1	2.802819513	2.662554167	2.614313933
TG 44:2	1.120297139	1.098224411	1.061818763
TG 44:5	0.007426814	0.018946165	0.016167275
TG 45:1	0.354688144	0.351208538	0.288792189
TG 46:2	1.350473716	1.265179232	1.322314286
TG 46:3	0.396845552	0.178683059	0.411866384
TG 47:0	0.979202719	0.923655938	0.886474424
TG 47:1	0.542455836	0.520917892	0.513064705
TG 47:2	0.085921831	0.151701258	0.137611858
TG 47:3	0.007374666	0.002980978	0.005332527
TG 48:3	0.475807326	0.101614256	0.504344566
TG 48:4	0.012662018	0.010196948	0.023256173
TG 48:5	0.006820213	0.011931967	0.018737204
TG 49:2	0.311213266	0.297401183	0.29508272
TG 51:2	0.633500786	0.651473936	0.625176906
TG 51:4	0.013259808	0.014503466	0.018064455
TG 52:5	0.01309407	0.003905443	0.002693132
TG 52:5	0.025707729	0.019476045	0.018262662
TG 52:6	0.002289746	0.002816504	0.010392927
TG 53:4	0.03949827	0.008024283	0.002306938
TG 54:5	0.072666811	0.079317816	0.079353056
TG 55:1	0.157708009	0.15707103	0.142561128
TG 56:1	0.268555333	0.257001144	0.258640079
TG 56:6	0.03357517	0.060659362	0.026456135
TG 57:0	0.031034124	0.028323797	0.030049486
TG 57:2	0.061162947	0.0602707	0.06027486
TG 58:2	0.080067796	0.081319971	0.07220569

TABLE 6C

Raw mass spec data obtained on identified lipid targets obtained by liquid chromatography with tandem mass spectrometry: LMF-15.

Compound Name	LMF-15 Replicate 1	LMF-15 Replicate 2	LMF-15 Replicate 3
DG 16:0_16:0	0.074675398	0.07922151	0.075302076
DG 18:0_18:1	0.03191818	0.033234211	0.034417446
PC 18:1_19:1	0.0080174	0.007644015	0.007627554
PC 34:1	0.00821994	0.009226828	0.007905224
PC 36:2	0.012280589	0.015915574	0.013749068
PC 37:2	0.005063075	0.004306771	0.006525816
TG 12:0_12:0_12:0	2.2216066	2.197261839	2.278178719
TG 12:0_12:0_12:1	0.563587539	0.566356279	0.583090841
TG 12:0_12:0_13:0	0.54497782	0.520716769	0.533020605
TG 12:0_12:0_14:0	4.075841287	3.976198393	3.980393432
TG 12:0_12:0_15:0	0.356552409	0.427514068	0.690872957
TG 12:0_12:0_17:0	0.346275137	0.33429942	0.335247146
TG 12:0_12:0_17:1	0.50809555	0.325866657	0.159581232
TG 12:0_12:1_14:0	1.588419094	1.630846299	1.651334745
TG 12:0_12:1_14:3	0.004514583	0.011225696	0.003994158
TG 12:0_12:1_20:5	0.007269731	0.014904753	0.003995342
TG 12:0_12:2_15:0	0.021238001	0.049851387	0.147600652
TG 12:0_12:2_16:0	3.844642675	3.830155446	4.053622896
TG 12:0_12:2_18:2	0.016141232	0.029607832	0.051019113
TG 12:0_14:0_16:0	2.561902136	2.361372544	2.286279123
TG 12:0_14:0_20:4	0.029404428	0.016898517	0.014015289
TG 12:0_15:0_16:0	0.209732673	0.184729827	0.171669971
TG 12:0_15:0_16:0	0.118967834	0.121863275	0.130997759
TG 12:0_16:0_16:0	1.573876759	1.328297566	1.219300168
TG 12:0_16:0_16:0	0.002157695	0	0
TG 12:0_16:0_18:1	3.557776769	3.463465226	3.442622684
TG 13:0_18:1_18:2	0.067664798	0.073934801	0.038258874
TG 14:0_14:0_16:0	0.002686039	0.002783857	0
TG 14:0_14:3_16:0	0.004237777	0	0.003475414
TG 14:0_14:3_18:0	0.002123662	0.001207409	0.002654303
TG 14:0_15:0_16:0	0.106009051	0.086398468	0.074999977
TG 14:0_15:0_16:0	0.133236721	0.122648917	0.128801529
TG 14:0_15:0_18:1	0.529013026	0.521432643	0.471613407
TG 14:0_16:0_16:0	0.956418583	0.740419691	0.685833772
TG 14:0_16:0_17:1	0.015666723	0.01264211	0.013171862
TG 14:0_16:0_18:0	0.640647803	0.470329392	0.437474956
TG 14:0_16:0_18:1	4.907613337	4.836941944	4.822955167
TG 14:0_16:0_18:1	0.004514518	0.004007577	0.005752608
TG 14:0_16:0_20:4	0.071447624	0.058334882	0.0731716
TG 14:0_16:0_20:5	0.010006008	0.01076081	0.010743847
TG 14:0_18:1_18:2	1.479820826	1.530648655	1.53363575
TG 14:1_16:0_18:1	2.727553647	2.718098289	2.72613516
TG 15:0_16:0_18:0	0.174437707	0.14943788	0.134741784
TG 15:0_16:0_18:1	0.962778494	0.949348517	0.93035524
TG 16:0_16:0_17:1	0.011120541	0.022575792	0.018844523
TG 16:0_16:0_18:0	0.355966114	0.253512841	0.220400502
TG 16:0_16:0_18:1	6.014358526	6.265154099	6.042817427
TG 16:0_16:0_20:4	0.087517331	0.108407512	0.093052396
TG 16:0_16:1_18:1	4.627522175	4.688321366	4.715726417
TG 16:0_17:0_18:0	0.074071572	0.079508092	0.061996223
TG 16:0_17:0_18:1	0.932486527	0.902554275	0.908512201
TG 16:0_17:1_18:0	0.018851313	0.019494957	0.021192158
TG 16:0_18:0_18:0	0.11895725	0.094750166	0.096023548
TG 16:0_18:0_18:1	4.113344061	4.132119807	4.000560502
TG 16:0_18:0_21:0	0.012045472	0.016209989	0.01745061
TG 16:0_18:1_18:1	6.888264377	7.442501349	7.360639326
TG 16:0_18:1_18:2	3.040718668	3.055398657	3.129942085
TG 16:0_18:1_18:3	0.727009406	0.762610454	0.769636818
TG 16:0_18:1_20:5	0.058456272	0.044165372	0.05726769
TG 16:0_20:0_22:0	0.012941721	0.009265732	0.003732027
TG 17:0_18:0_18:0	0.032425397	0.0269943	0.02795409
TG 17:0_18:0_18:1	0.365719228	0.377864745	0.37058453
TG 17:0_18:1_18:1	0.731939393	0.782372112	0.774501584
TG 17:1_18:0_18:1	0.036092697	0.058191197	0.057857812
TG 18:0_18:0_18:0	0.019071597	0.041272316	0.047733835
TG 18:0_18:0_18:1	0.979973334	0.95105258	0.93953443
TG 18:0_18:1_18:1	3.2358535	3.39084842	3.391725899
TG 18:1_18:1_18:1	3.816954714	4.078317571	4.12626876
TG 18:1_18:1_18:2	1.5982653	1.714025231	1.735507677
TG 18:1_18:2_18:2	0.54481299	0.55750938	0.561702003
TG 18:1_18:2_18:3	0.144727971	0.143232607	0.160105452

TABLE 6C-continued

Raw mass spec data obtained on identified lipid targets obtained by liquid chromatography with tandem mass spectrometry: LMF-15.

Compound Name	LMF-15 Replicate 1	LMF-15 Replicate 2	LMF-15 Replicate 3
TG 18:1_18:3_18:3	0.042263845	0.041651721	0.045379025
TG 18:1_20:0_22:0	0.015690302	0.013331848	0.0166694
TG 38:2	0.737097008	0.771857834	0.727719856
TG 38:3	0.046684284	0.01509347	0.08515105
TG 40:0	3.480822027	3.316096674	3.23924327
TG 40:1	4.007929503	4.066200157	4.120617847
TG 40:3	1.013469639	1.034044553	1.052031232
TG 40:4	0.199384959	0.219567412	0.180358909
TG 42:1	3.755297497	3.705863509	3.711244376
TG 42:4	0.04741849	0.048175758	0.005604033
TG 43:1	0.434393355	0.362236021	0.363999809
TG 44:1	3.58543397	3.498326356	3.570622928
TG 44:2	1.916025705	1.885409485	1.951737988
TG 44:5	0.036105552	0.025123214	0.027577723
TG 45:1	0.424261482	0.434300065	0.441540744
TG 46:2	2.129073036	2.142250451	2.198801709
TG 46:3	0.731867937	0.738169013	0.72360007
TG 47:0	0.223326688	0.204729837	0.173695339
TG 47:1	0.529454737	0.521432643	0.53762306
TG 47:2	0.183384513	0.045174321	0.226137791
TG 47:3	0.018250663	0.03556461	0.021338069
TG 48:3	0.819667354	0.888021422	0.865493908
TG 48:4	0.035741503	0.04065518	0.037729155
TG 48:5	0.022506586	0.030236397	0.020108608
TG 49:2	0.379299395	0.441194358	0.398921122
TG 51:2	0.847290608	0.8958577	0.884816236
TG 51:4	0.007833551	0.044850753	0.028845182
TG 52:5	0.021848511	0.024440459	0.009100726
TG 52:5	0.116979676	0.084597009	0.019270755
TG 52:6	0	0	0.016028531
TG 53:4	0.012254491	0.011874362	0.055852225
TG 54:5	0.126277231	0.152031521	0.15821621
TG 55:1	0.076002384	0.063032108	0.076231533
TG 56:1	0.094791592	0.097402135	0.092501337
TG 56:6	0.050823156	0.104656478	0.061082813
TG 57:0	0.012941371	0.015509625	0.013036341
TG 57:2	0.053459001	0.054617458	0.067106733
TG 58:2	0.076150068	0.077836619	0.087554572

TABLE 6D

Raw mass spec data obtained on identified lipid targets obtained by liquid chromatography with tandem mass spectrometry: HMF-25.

Compound Name	HMF-25 Replicate 1	HMF-25 Replicate 2	HMF-25 Replicate 3
DG 16:0_16:0	0.087727818	0.104432559	0.066839214
DG 18:0_18:1	0.035127201	0	0.024467584
PC 18:1_19:1	0.032489836	0.037240708	0.008945855
PC 34:1	0.027652112	0.034427593	0.010174949
PC 36:2	0.056013603	0.057424478	0.014987827
PC 37:2	0.024357393	0.025373629	0.006249598
TG 12:0_12:0_12:0	1.457260816	1.613623329	1.415710284
TG 12:0_12:0_12:1	0.184199755	0.315033234	0.379584003
TG 12:0_12:0_13:0	0.365856022	0.419025551	0.332139899
TG 12:0_12:0_14:0	2.666889137	0.658536647	0.583708689
TG 12:0_12:0_15:0	0.258681103	0.283540939	0.487672261
TG 12:0_12:0_17:0	0.346195953	0.400050044	0.3985408
TG 12:0_12:0_17:1	0.294251897	0.338755443	0.298535259
TG 12:0_12:1_14:0	0.974067963	1.11016049	1.011936717
TG 12:0_12:1_14:3	0.007038194	0.005957586	0.001400746
TG 12:0_12:1_20:5	0.016856589	0.022596532	0.003928555
TG 12:0_12:2_15:0	0.097107687	0.048994478	0.021169274
TG 12:0_12:2_16:0	2.25158608	2.521351484	2.470207862
TG 12:0_12:2_18:2	0.007351485	0.00980989	0.012206841
TG 12:0_14:0_16:0	2.878166195	2.758210105	2.995731598
TG 12:0_14:0_20:4	0.012157854	0.008250944	0.018421401

TABLE 6D-continued

Raw mass spec data obtained on identified lipid targets obtained by liquid chromatography with tandem mass spectrometry: HMF-25.

Compound Name	HMF-25 Replicate 1	HMF-25 Replicate 2	HMF-25 Replicate 3
TG 12:0_15:0_16:0	0.364875689	0.351516518	0.345243907
TG 12:0_15:0_16:0	0.120282346	0.139486906	0.101967859
TG 12:0_16:0_16:0	3.109853811	2.880967909	3.445502269
TG 12:0_16:0_16:0	0.003448947	0	0.001272034
TG 12:0_16:0_18:1	2.966038307	3.019331815	3.198704563
TG 13:0_18:1_18:2	0.025826516	0.038050163	0.017336499
TG 14:0_14:0_16:0	0	0	0
TG 14:0_14:3_16:0	0.001803052	0.009445463	0.002916457
TG 14:0_14:3_18:0	0.001702331	0	0.003482451
TG 14:0_15:0_16:0	0.440169334	0.3908777	0.396860609
TG 14:0_15:0_16:0	0.192415978	0.163255408	0.156874329
TG 14:0_15:0_18:1	0.434823546	0.516111917	0.521297039
TG 14:0_16:0_16:0	3.733514982	3.421197627	4.377989225
TG 14:0_16:0_17:1	0.024428547	0.029472633	0.026448939
TG 14:0_16:0_18:0	4.792858952	4.335650299	4.883374486
TG 14:0_16:0_18:1	4.559370872	4.541002348	5.089030968
TG 14:0_16:0_18:1	0.041140564	0	0.005818421
TG 14:0_16:0_20:4	0.03577889	0.033197284	0.0468509
TG 14:0_16:0_20:5	0.006199487	0.018053109	0.008216891
TG 14:0_18:1_18:2	0.951583131	1.035695462	1.024287833
TG 14:1_16:0_18:1	1.865051056	1.988902518	1.952331716
TG 15:0_16:0_18:0	0.839849585	0.844191494	0.939296916
TG 15:0_16:0_18:1	1.06063105	0.992852346	1.016588094
TG 16:0_16:0_17:1	0.056404157	0.056670784	0.067595166
TG 16:0_16:0_18:0	4.341812078	4.01905728	4.344466879
TG 16:0_16:0_18:1	8.056803396	7.966426397	7.285140067
TG 16:0_16:0_20:4	0.040055396	0.061454989	0.063287522
TG 16:0_16:1_18:1	3.30165775	3.457107735	3.524050758
TG 16:0_17:0_18:0	0.537923747	0.511729878	0.581889576
TG 16:0_17:0_18:1	1.128993248	1.146362602	1.124605525
TG 16:0_17:1_18:0	0.076744905	0.080265914	0.049335323
TG 16:0_18:0_18:0	1.956195409	1.880356516	2.151500539
TG 16:0_18:0_18:1	5.921143989	5.80223199	5.445275758
TG 16:0_18:0_21:0	0.056996544	0.070619162	0.058138408
TG 16:0_18:1_18:1	5.837965358	6.161905048	5.780668993
TG 16:0_18:1_18:2	1.895223022	2.092141686	2.021797033
TG 16:0_18:1_18:3	0.467247813	0.55134271	0.496194022
TG 16:0_18:1_20:5	0.058786961	0.056992424	0.035336521
TG 16:0_20:0_22:0	0.045981497	0.037049257	0.027821051
TG 17:0_18:0_18:0	0.212494652	0.18640198	0.200169168
TG 17:0_18:0_18:1	0.589737673	0.58892708	0.502851095
TG 17:0_18:1_18:1	0.633025992	0.664864915	0.594028307
TG 17:1_18:0_18:1	0.037124933	0.044603662	0.046345841
TG 18:0_18:0_18:0	0.402276088	0.440653021	0.405045525
TG 18:0_18:0_18:1	1.814694521	1.803086323	1.729685255
TG 18:0_18:1_18:1	2.762592567	2.976312965	2.597483391
TG 18:1_18:1_18:1	2.662306792	2.914281199	2.608223462
TG 18:1_18:1_18:2	1.038808351	1.117198885	1.067371586
TG 18:1_18:2_18:2	0.284033409	0.365870836	0.322598635
TG 18:1_18:2_18:3	0.077872361	0.088767523	0.068946668
TG 18:1_18:3_18:3	0.036862212	0.042288624	0.032305014
TG 18:1_20:0_22:0	0.045668043	0.050158099	0.030809044
TG 38:2	0.28682814	0.005186608	0.061989455
TG 38:3	0.01360915	0.005486962	0.011384744
TG 40:0	2.668473619	2.782392366	2.562027024
TG 40:1	2.388034965	2.631254546	2.535127681
TG 40:3	0.58319691	0.690850112	0.641054425
TG 40:4	0.131067329	0.033915579	0.127248442
TG 42:1	2.361551381	2.617889762	2.44583078
TG 42:4	0.008395798	0.008816469	0.005285355
TG 43:1	0.296677226	0.299116341	0.296978304
TG 44:1	2.583291792	2.655469396	2.718090486
TG 44:2	1.03877974	1.170330889	1.194301319
TG 44:5	0.013310868	0.027354828	0.017979466
TG 45:1	0.369401165	0.336722902	0.293136724
TG 46:2	1.343895493	1.448408838	1.442621271
TG 46:3	0.121165654	0.462755694	0.451592337
TG 47:0	0.82306192	0.757783218	0.826081699
TG 47:1	0.434823546	0.500135799	0.521297039
TG 47:2	0.117183008	0.178191806	0.141244892
TG 47:3	0.017664253	0.022675384	0.007209064

TABLE 6D-continued

Raw mass spec data obtained on identified lipid targets obtained by liquid chromatography with tandem mass spectrometry: HMF-25.

Compound Name	HMF-25 Replicate 1	HMF-25 Replicate 2	HMF-25 Replicate 3
TG 48:3	0.492901954	0.526914918	0.553869353
TG 48:4	0.019808914	0.027515184	0.021453207
TG 48:5	0.027509725	0.012481726	0.014473965
TG 49:2	0.28285282	0.322120078	0.323962452
TG 51:2	0.590752329	0.752078275	0.665237192
TG 51:4	0.02577173	0.037571919	0.017824198
TG 52:5	0.024328682	0.023363647	0.006426323
TG 52:5	0.076919154	0.054522596	0.049390615
TG 52:6	0.002414795	0.002978884	0.000722302
TG 53:4	0.013946097	0.030430875	0.021857609
TG 54:5	0.088195755	0.105718325	0.054739242
TG 55:1	0.195656348	0.209161452	0.153565835
TG 56:1	0.291502206	0.309405014	0.242264511
TG 56:6	0.051853913	0.050693531	0.034158989
TG 57:0	0.047832286	0.057687992	0.028687215
TG 57:2	0.053563658	0.009190336	0.050084634
TG 58:2	0.083663145	0.07624368	0.073584094

TABLE 6E

Raw mass spec data obtained on identified lipid targets obtained by liquid chromatography with tandem mass spectrometry: LMF-25.

Compound Name	LMF-25 Replicate 1	LMF-25 Replicate 2	LMF-25 Replicate 3
DG 16:0_16:0	0.08292381	0.08364686	0.0751917
DG 18:0_18:1	0.034430447	0.017755208	0.033088665
PC 18:1_19:1	0.011345862	0.009925091	0.007841279
PC 34:1	0.010614635	0.008985988	0.007603842
PC 36:2	0.015200947	0.015045792	0.01191412
PC 37:2	0.006783427	0.007677061	0.005612863
TG 12:0_12:0_12:0	2.204436357	2.173639384	2.21203347
TG 12:0_12:0_12:1	0.462821029	0.549883604	0.550475219
TG 12:0_12:0_13:0	0.503819582	0.527873295	0.516117856
TG 12:0_12:0_14:0	4.038189099	4.048530609	4.200425428
TG 12:0_12:0_15:0	0.364930937	0.71662007	0.650737351
TG 12:0_12:0_17:0	0.361660898	0.360714423	0.362930604
TG 12:0_12:0_17:1	0.499270195	0.525010088	0.145537251
TG 12:0_12:1_14:0	1.58576213	1.593405814	1.61338973
TG 12:0_12:1_14:3	0.003797322	0.003767055	0.013693908
TG 12:0_12:1_20:5	0.015994904	0.014516028	0.002678762
TG 12:0_12:2_15:0	0.068666297	0.108983066	0.040743674
TG 12:0_12:2_16:0	3.818240598	3.855492461	3.793736786
TG 12:0_12:2_18:2	0.00365199	0.024494362	0.083117011
TG 12:0_14:0_16:0	2.584092794	2.562422912	2.668976522
TG 12:0_14:0_20:4	0.015014347	0.028003274	0.03027237
TG 12:0_15:0_16:0	0.206418756	0.164839118	0.200418939
TG 12:0_15:0_16:0	0.132524672	0.12635806	0.130342989
TG 12:0_16:0_16:0	1.51757335	1.391180864	1.546099825
TG 12:0_16:0_16:0	0.001980627	0.001444779	0
TG 12:0_16:0_18:1	3.499436892	3.332064637	3.648631345
TG 13:0_18:1_18:2	0.065710379	0.062557989	0.016311654
TG 14:0_14:0_16:0	0	0	0
TG 14:0_14:3_16:0	0.001053505	0.002286334	0
TG 14:0_14:3_18:0	0.002636853	0.005098055	0.002848979
TG 14:0_15:0_16:0	0.099124195	0.08967871	0.087536323
TG 14:0_15:0_16:0	0.147882624	0.138342979	0.150398661
TG 14:0_15:0_18:1	0.545975365	0.512814946	0.538501046
TG 14:0_16:0_16:0	0.855955626	0.791250273	0.847856191
TG 14:0_16:0_17:1	0.015678953	0.014926271	0.015420499
TG 14:0_16:0_18:0	0.552027367	0.505546546	0.560937015
TG 14:0_16:0_18:1	4.975120485	4.841218014	4.905665897
TG 14:0_16:0_18:1	0.010650424	0.008428861	0.005525004
TG 14:0_16:0_20:4	0.039232711	0.068130734	0.068383492
TG 14:0_16:0_20:5	0.020809154	0.015091999	0.013062347
TG 14:0_18:1_18:2	1.45846712	1.424506602	1.485917391
TG 14:1_16:0_18:1	2.656361373	2.587040123	2.740150717

TABLE 6E-continued

Raw mass spec data obtained on identified lipid targets obtained by liquid chromatography with tandem mass spectrometry: LMF-25.

Compound Name	LMF-25 Replicate 1	LMF-25 Replicate 2	LMF-25 Replicate 3
TG 15:0_16:0_18:0	0.165790647	0.149636711	0.152319438
TG 15:0_16:0_18:1	0.972379748	0.966044089	0.953064143
TG 16:0_16:0_17:1	0.024384227	0.024189454	0.02065462
TG 16:0_16:0_18:0	0.288031214	0.248848739	0.312061514
TG 16:0_16:0_18:1	6.540049801	6.470812704	5.927080071
TG 16:0_16:0_20:4	0.080476933	0.087738497	0.096540132
TG 16:0_16:1_18:1	4.649822193	4.580333075	4.614018464
TG 16:0_17:0_18:0	0.062556639	0.060497149	0.089995876
TG 16:0_17:0_18:1	0.955504895	0.914933075	0.944163958
TG 16:0_17:1_18:0	0.022218583	0.021837776	0.020540039
TG 16:0_18:0_18:0	0.104139289	0.102212484	0.119031911
TG 16:0_18:0_18:1	4.418054282	4.299510899	4.134858421
TG 16:0_18:0_21:0	0.021864064	0.014227246	0.019139847
TG 16:0_18:1_18:1	7.446816485	7.423683112	6.784393004
TG 16:0_18:1_18:2	2.964566518	2.939399194	3.001155877
TG 16:0_18:1_18:3	0.716688127	0.713557003	0.725143257
TG 16:0_18:1_20:5	0.025905709	0.052331145	0.043053941
TG 16:0_20:0_22:0	0.014197831	0.007708108	0.001945485
TG 17:0_18:0_18:0	0.028239511	0.026872132	0.026309833
TG 17:0_18:0_18:1	0.318181584	0.360435198	0.372261311
TG 17:0_18:1_18:1	0.743220838	0.766158692	0.731289523
TG 17:1_18:0_18:1	0.040013169	0.050653774	0.036069921
TG 18:0_18:0_18:0	0.047051312	0.051836583	0.045922254
TG 18:0_18:0_18:1	0.994373485	0.996120785	1.035749422
TG 18:0_18:1_18:1	3.387460636	3.331995486	3.198478477
TG 18:1_18:1_18:1	3.975576655	3.986027872	3.736814711
TG 18:1_18:1_18:2	1.677926388	1.584350466	1.576250004
TG 18:1_18:2_18:2	0.536597144	0.516698082	0.539900348
TG 18:1_18:2_18:3	0.113369187	0.108998421	0.137407565
TG 18:1_18:3_18:3	0.045556605	0.047348512	0.044322988
TG 18:1_20:0_22:0	0.020518142	0.017573543	0.018962337
TG 38:2	0.135317136	0.402337397	0.749729188
TG 38:3	0.030501698	0.083874232	0.015902545
TG 40:0	3.440609944	3.489666749	3.564404095
TG 40:1	3.876127764	4.04882468	4.048566918
TG 40:3	1.012744283	0.928938693	0.986743678
TG 40:4	0.087383672	0.206647031	0.120213784
TG 42:1	3.653080013	3.722658751	3.752693846
TG 42:4	0.000712981	0.014297507	0.046091215
TG 43:1	0.437735343	0.453045843	0.437347052
TG 44:1	3.513861119	3.523726657	3.62626776
TG 44:2	1.829455372	1.899155117	1.88264567
TG 44:5	0.032072401	0.018458276	0.030919598
TG 45:1	0.444729224	0.399964207	0.437003944
TG 46:2	2.104339946	2.128012696	2.136142458
TG 46:3	0.719193935	0.723226258	0.710777845
TG 47:0	0.212444508	0.198379123	0.213195006
TG 47:1	0.543858824	0.512814946	0.538071008
TG 47:2	0.238823526	0.230185989	0.246049969
TG 47:3	0	0.047866822	0.040388519
TG 48:3	0.819711353	0.857471904	0.851110947
TG 48:4	0.032737985	0.031313247	0.022081598
TG 48:5	0.020560995	0.01823703	0.016557939
TG 49:2	0.423314674	0.332530743	0.437366438
TG 51:2	0.887130339	0.887080189	0.863854711
TG 51:4	0.010127386	0.018543484	0.048334575
TG 52:5	0.010057832	0.005448588	0.028206814
TG 52:5	0.02099002	0.005448872	0.085928046
TG 52:6	0.00251482	0.000600462	0.001057459
TG 53:4	0.038545257	0.043945246	0.05994749
TG 54:5	0.151068037	0.125866931	0.144552072
TG 55:1	0.06813333	0.062495827	0.071452062
TG 56:1	0.091173559	0.087162409	0.082773554
TG 56:6	0.037285173	0.072356834	0.10026958
TG 57:0	0.014875853	0.0118588	0.0095572
TG 57:2	0.06837249	0.074702117	0.055553354
TG 58:2	0.092609326	0.091087994	0.089216641

TABLE 6F

Raw mass spec data obtained on identified lipid targets obtained by liquid chromatography with tandem mass spectrometry: AMF.

Compound Name	AMF Replicate 1	AMF Replicate 2	AMF Replicate 3
DG 16:0_16:0	0.07700043	0.087151802	0.06501985
DG 18:0_18:1	0.031994028	0.027749506	0.02659497
PC 18:1_19:1	0.013072543	0.020343013	0.006917932
PC 34:1	0.011844406	0.023632621	0.006977138
PC 36:2	0.022141559	0.034193101	0.011122267
PC 37:2	0.009204478	0.014122682	0.004218691
TG 12:0_12:0_12:0	1.703884233	1.744121638	1.783664753
TG 12:0_12:0_12:1	0.448657482	0.28524621	0.454448714
TG 12:0_12:0_13:0	0.443449086	0.442614242	0.42700045
TG 12:0_12:0_14:0	0.704973301	3.17210206	3.559465903
TG 12:0_12:0_15:0	0.570008313	0.574220671	0.59066953
TG 12:0_12:0_17:0	0.3339353	0.426999274	0.43469695
TG 12:0_12:0_17:1	0.380925289	0.34316863	0.395406841
TG 12:0_12:1_14:0	1.221198428	1.197532099	1.270279634
TG 12:0_12:1_14:3	0.007453902	0.003912377	0.003153121
TG 12:0_12:1_20:5	0.000930108	0.010678576	0.008039605
TG 12:0_12:2_15:0	0.024567781	0.041508742	0.083895992
TG 12:0_12:2_16:0	3.065281404	3.079603275	3.042157607
TG 12:0_12:2_18:2	0.006071273	0.055109594	0.03329877
TG 12:0_14:0_16:0	2.683991887	2.591169703	2.862935544
TG 12:0_14:0_20:4	0.01554744	0.007729466	0.011866544
TG 12:0_15:0_16:0	0.277055897	0.272358445	0.267079583
TG 12:0_15:0_16:0	0.109248198	0.120132205	0.111688604
TG 12:0_16:0_16:0	2.433572383	2.282961847	2.633239659
TG 12:0_16:0_16:0	0.002016797	0.002000073	0.005528301
TG 12:0_16:0_18:1	3.191621084	3.052874989	3.296613893
TG 13:0_18:1_18:2	0.031776931	0.01770822	0.023224005
TG 14:0_14:0_16:0	0	0	0.002801452
TG 14:0_14:3_16:0	0.002433665	0.005655754	0.001105378
TG 14:0_14:3_18:0	0.001806048	0	0.002169407
TG 14:0_15:0_16:0	0.26822491	0.273769493	0.262658333
TG 14:0_15:0_16:0	0.106196524	0.146472158	0.145207738
TG 14:0_15:0_18:1	0.53245595	0.541786064	0.51290625
TG 14:0_16:0_16:0	2.758783588	2.458971759	2.945778785
TG 14:0_16:0_17:1	0.026899227	0.021649458	0.024416837
TG 14:0_16:0_18:0	3.274469524	3.031654388	3.022270685
TG 14:0_16:0_18:1	4.938295972	4.476280912	4.930448928
TG 14:0_16:0_18:1	0.010324584	0.002293542	0.001384243
TG 14:0_16:0_20:4	0.057424412	0.065669376	0.043679979
TG 14:0_16:0_20:5	0.001783588	0.020339288	0.012994572
TG 14:0_18:1_18:2	1.206299908	1.216885863	1.154109325
TG 14:1_16:0_18:1	2.257750535	2.225973697	2.196140094
TG 15:0_16:0_18:0	0.608328494	0.575336216	0.614174128
TG 15:0_16:0_18:1	1.002443739	0.915747956	1.021576796
TG 16:0_16:0_17:1	0.049081236	0.038646246	0.051256663
TG 16:0_16:0_18:0	2.936599912	2.686197192	2.796421572
TG 16:0_16:0_18:1	7.550734206	7.560841924	5.966090395
TG 16:0_16:0_20:4	0.066566817	0.075841349	0.072694702
TG 16:0_16:1_18:1	3.914625885	3.753856543	3.997968681
TG 16:0_17:0_18:0	0.384161354	0.368277725	0.384683056
TG 16:0_17:0_18:1	1.048111711	0.992622169	1.032309876
TG 16:0_17:1_18:0	0.03803704	0.028827318	0.032880481
TG 16:0_18:0_18:0	1.372353411	1.247117451	1.448368673
TG 16:0_18:0_18:1	5.33334875	5.255992985	4.500238994
TG 16:0_18:0_21:0	0.051731053	0.059653532	0.03891537
TG 16:0_18:1_18:1	6.96284474	6.959175354	5.731748617
TG 16:0_18:1_18:2	2.45546346	2.412293796	2.454741141
TG 16:0_18:1_18:3	0.610782645	0.607411885	0.559319191
TG 16:0_18:1_20:5	0.022431136	0.055252565	0.036090463
TG 16:0_20:0_22:0	0.024689791	0.040635883	0.022604719
TG 17:0_18:0_18:0	0.110378793	0.144445276	0.128391169
TG 17:0_18:0_18:1	0.448883568	0.395344778	0.472701028
TG 17:0_18:1_18:1	0.693920932	0.694691255	0.626585189
TG 17:1_18:0_18:1	0.044505135	0.03283075	0.037680749
TG 18:0_18:0_18:0	0.273416243	0.286366982	0.273976153
TG 18:0_18:0_18:1	1.467910039	1.466851314	1.448330034
TG 18:0_18:1_18:1	3.073262941	3.019481761	2.712504612
TG 18:1_18:1_18:1	3.346366762	3.274684792	2.937591013
TG 18:1_18:1_18:2	1.334641317	1.325197216	1.258529094
TG 18:1_18:2_18:2	0.362267619	0.406723852	0.356565368
TG 18:1_18:2_18:3	0.12488557	0.140051459	0.104246905

TABLE 6F-continued

Raw mass spec data obtained on identified lipid targets obtained by liquid chromatography with tandem mass spectrometry: AMF.

Compound Name	AMF Replicate 1	AMF Replicate 2	AMF Replicate 3
TG 18:1_18:3_18:3	0.038921455	0.05485791	0.033849949
TG 18:1_20:0_22:0	0.015741103	0.024492197	0.024108278
TG 38:2	0.189922048	0.114382987	0.07921702
TG 38:3	0.030944225	0.007739121	0.018912327
TG 40:0	2.832381655	2.882605922	3.218468364
TG 40:1	3.018264302	3.066146053	3.239348387
TG 40:3	0.80460911	0.730168482	0.829403125
TG 40:4	0.139885756	0.068867867	0.151157017
TG 42:1	2.868275788	2.910571674	3.172164383
TG 42:4	0.016123624	0	0.03361355
TG 43:1	0.363557285	0.343526966	0.372582617
TG 44:1	2.92915913	2.913836006	3.043457768
TG 44:2	1.430989032	1.413936857	1.530657236
TG 44:5	0.030116748	0.012400428	0.01870016
TG 45:1	0.389288781	0.36664725	0.375458092
TG 46:2	1.700217844	1.724878311	1.674131546
TG 46:3	0.533013454	0.507475762	0.589671534
TG 47:0	0.565650696	0.555891669	0.581152684
TG 47:1	0.53253289	0.54442454	0.51373563
TG 47:2	0.082983299	0.141936854	0.162318417
TG 47:3	0.034298012	0.018948184	0.020749858
TG 48:3	0.653480974	0.485503415	0.65829987
TG 48:4	0.027266051	0.019077109	0.031409068
TG 48:5	0.023400908	0.0186315	0.016401492
TG 49:2	0.368531648	0.240981708	0.353462816
TG 51:2	0.752772534	0.761634904	0.749308587
TG 51:4	0.009869616	0.023202892	0.011268376
TG 52:5	0.003073694	0.015865027	0.024267221
TG 52:5	0.039657437	0.075739577	0.092455793
TG 52:6	0.003961679	0.001022241	0.009053573
TG 53:4	0.006860987	0.006853525	0.036227879
TG 54:5	0.055759621	0.067596308	0.040495262
TG 55:1	0.081275717	0.1495564	0.125534446
TG 56:1	0.224792689	0.21970348	0.187184989
TG 56:6	0.056141959	0.04847447	0.029618946
TG 57:0	0.02714897	0.045656037	0.020491599
TG 57:2	0.065521307	0.081586644	0.054682896
TG 58:2	0.076261277	0.096435389	0.080517554

Milkfat-Based Intravenous Fat Emulsion (IVFE) Preparation

[0117] Distilled water with 0.50% (w/w) polysorbate 80 was heated to 80° C. Selected AMF fraction(s) (80° C.) were added to the solution at 20% (w/w) under constant agitation. Samples were then processed using ultra high-pressure homogenization (UHPH, Nano DeBEE 45-2, BEE International, South Easton, MA, FIG. **8**). Samples were UHPH-treated with three passes at 100, 200, or 300 MPa first-stage pressure and 6.9 MPa second-stage pressure (Table 7). Samples were immediately cooled in the in-line heat exchanger with a co-current flow of water (20° C.). After processing, samples were filtered (1.0 μm pore size, Catalog #76479-036, VWR International, 10 Radnor, PA) and autoclaved (121° C., 30 min) to ensure adequate particle size and sterility prior to analysis and intravenous application. The entire process is depicted in the schematic of FIG. **1**.

TABLE 7

Ultra high-pressure homogenization conditions

First-stage Pressure (MPa)	Second-stage Pressure (MPa)	Orifice size (mm)	# of passes	Heat exchanger temperature (° C.)
100	6.9	0.20	3	20
200	6.9	0.13	3	20
300	6.9	0.13	3	20

Nanoparticle Size Stability

[0118] Particle size and concentration were quantified using a Malvern Panalytical NS300 Nanoparticle Tracking Analyzer (Malvern, UK). Samples were diluted in phosphate buffered saline and vortexed to mix immediately prior to the experiment. Five, 60-second measurements were collected at a flow rate of 70 μl/min for each sample. Examples of particle sizes are shown for homogenization conditions under 100, 200, and 300 MPa, as shown in FIGS. **9A-9C**. Particles made under 100 MPa were stored under 4° C. and retested at 30 days, which confirmed no particles larger than 400 nm in size, as shown in FIG. **10**.

Further Size Stability Testing

[0119] We measured the size stability of our emulsions for several months by monitoring particle size. Emulsions were generated from 20% fractionated milkfat in water with 0.25, 0.5, or 1.0% polysorbate 80 emulsifier, and 150 or 300 MPa high-pressure homogenization (both pressures establish a suitable particle size) for three passes (i.e., sent through the homogenizer three times). The emulsions were stable (particle size ~300 nm) for over three months (FIG. **11**, Tables 8A and 8B).

TABLE 8A

Samples		Days		
Emulsifier Conc. (% w/w)	Homogenization pressure (mPa)	15	30	45
0.25	150	688.13 ± 52.69	580.67 ± 13.80	605.03 ± 29.13
0.50	150	445.93 ± 4.55	421.70 ± 7.39	419.20 ± 4.09
1.0	150	301.50 ± 16.74	282.23 ± 15.56	279.10 ± 11.47
0.25	300	826.17 ± 76.17	786.70 ± 61.91	753.23 ± 44.03
0.50	300	600.50 ± 26.15	593.17 ± 26.81	578.93 ± 10.64
1.0	300	319.30 ± 6.25	306.13 ± 7.09	300.63 ± 5.55

Values shown as mean size (nm) ± StDev (n = 3)

TABLE 8B

Samples		Days		
Emulsifier Conc. (% w/w)	Homogenization pressure (mPa)	60	75	90
0.25	150	549.47 ± 14.10	564.60 ± 29.40	621.27 ± 36.99
0.50	150	431.87 ± 2.32	420.37 ± 5.78	429.40 ± 6.24
1.0	150	282.50 ± 19.50	287.97 ± 17.98	296.30 ± 14.60
0.25	300	761.73 ± 46.01	716.13 ± 14.10	714.47 ± 59.12
0.50	300	563.27 ± 14.93	561.93 ± 31.86	572.43 ± 10.31
1.0	300	305.50 ± 5.38	311.20 ± 3.82	312.47 ± 8.86

Values shown as mean size (nm) ± StDev (n = 3)

[0120] These emulsions are also stable to autoclaving, which is excellent for sterility. We tested emulsifier concentrations of 0.25 and 0.50% (w/w). The particles were much larger (>400 nm) with these concentrations.

In Vitro Inflammatory Response

[0121] The IVFEs prepared from LMF-25 and processed at 300 MPa first-stage pressure were compared with soy-lipid Intralipid® 20% for inflammatory effects on bone

marrow derived macrophages in vitro. The milk lipid IVFEs had less of an inflammatory response (IL-1b, IL-6, and TNF-α) than the soy lipid IVFEs and induced an anti-inflammatory response with IL-10 (FIG. **12**).

Intravenous Administration and Metabolic Response In Vivo

[0122] Following intravenous catheterization under sterile technique, animals were administered parenteral nutrition (PN) and experimental lipid emulsions at 10-15% (v/v). The IVFEs prepared from LMF-25 and processed at 300 MPa first-stage pressure were selected as they achieved the minimum emulsion droplet size and were abundant in medium-chain triglycerides. Administration rates were based on animal body weight, tolerability, and calculated to meet caloric, nitrogen, and fat requirements for the animals.

[0123] All animal experiments were approved by IACUC at the University of Wisconsin-Madison. Male wild-type C57Bl/6 mice housed under standard 12:12 light/dark conditions. Mice were 8-10 weeks of age and maintained in microisolator cages for microbiome containment and fidelity. Animals were weighed, provided buprenorphine ER analgesics (0.6/mg/kg), anesthetized by isoflurane, and underwent placement of silicon rubber catheter (0.012-inch I.D./0.025-inch O.D.; Helix Medical, Inc., Carpinteria, CA) in the vena cava through the right external jugular vein. Intravenous catheters were tunneled subcutaneously and dorsally at the midpoint between the scapulae. Animals were harnessed and tethered in individually housed metabolic cages with continuous gas exchange monitoring.

[0124] Intravenous formulation: Cannulated mice were connected to infusion pumps and intravenous solution was provided at 18, 25 and 32% volume/body weight per day over the first 3 days, with 32% volume/body weight maintained for the final 3 days. At 48 hours, 2% weight/volume fat was increased to 3% weight/volume for all animals. The PN solution contained 1170 kcal/L consisting of 5.0% amino acids, 25% dextrose, 2-3% fat by volume. A standard control IVFE was provided with 20% v/v Intralipid-20 (emulsion, Baxter Healthcare Corporation, Deerfield, IL) and compared with IVFEs prepared from LMF-25 and processed at 300 MPa first-stage pressure. These IVFEs were selected as they achieved the minimum emulsion droplet size and were abundant in medium-chain triglycerides. Intravenous solutions were replaced daily to prevent lipid micelle precipitation. After 6 days, animals were humanely euthanized for collection of serum, tissues, and microbiome samples were collected for analysis.

[0125] FIGS. **13**A-**13**C show respiratory exchange ratio (RER) of the mice, where LMF decreased RER levels compared with Intralipid, supporting enhanced lipid utilization in metabolism. FIG. **14** shows body, organ and tissue weights. FIG. **15** shows hematoxylin and eosin staining of pancreatic acinar tissue, demonstrating smaller acinar cell size in response to LMF emulsions compared with Intralipid. FIG. **16** shows hematoxylin and eosin staining of liver tissue.

CONCLUSIONS

[0126] The approach outlined herein involves fractionation and high-pressure homogenization methodologies to achieve stable milkfat microemulsions for intravenous applications. When provided in preclinical models, milk fat microemulsions lead to comparable or superior survival and potential improvements in digestive organ function homeostasis without evidence of systemic inflammation. Hence, the milkfat microemulsions provided herein provide a satisfactory source of intravenous lipids for patients requiring parenteral nutrition and will contribute to new pharmaceutical applications for dairy lipids markets.

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1. A method of generating lipid particles, the method comprising:

generating a combined composition, comprising combining a milk fat composition comprising a solids portion comprising target milk fat with a surfactant; and

generating a lipid-particle composition comprising lipid particles, comprising emulsifying the combined composition.

2. The method of claim **1**, wherein the solids portion comprises the target milk fat in amount of at least 50% w/w.

3. The method of claim **1**, wherein the lipid composition comprises the solids portion in an amount of at least 50% w/w.

4. The method of claim **1**, wherein the lipid particles comprise triglycerides in an amount greater than 50% w/w of combined total of triglyceride, diglyceride, 1,2-diacylglyceryl-3-O-4'-(N,N,N-trimethyl)-homoserine, phosphatidylcholine, ether-linked phosphatidylcholine, fatty acyl ester of hydroxy fatty acid, free fatty acid, lysophosphatidylcholine, phosphatidylethanolamine, ether-linked phosphatidylethanolamine, lysophosphatidylethanolamine, non-hydroxy-fatty acid sphingosine ceramide, and sphingomyelin detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry.

5. The method of claim **1**, wherein the lipid particles comprise a relative amount of any 3 or more of the following lipids within 5× of each other as detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry: TG 14:0_16:0_16:0, TG 14:0_15:0_16:0, TG 12:0_16:0_16:0, TG 12:0_15:0_16:0, and TG 12:0_14:0_16:0.

6. The method of claim **1**, wherein the lipid particles comprise a relative amount of any 10 or more of the following lipids within 5× of each other as detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry: TG 14:0_16:0_16:0, TG 14:0_15:0_16:0, TG 12:0_16:0_16:0, TG 12:0_15:0_16:0, TG 12:0_14:0_16:0, TG 16:0_18:0_18:1, TG 16:0_18:1_18:1, TG 16:0_16:0_18:1, TG 14:0_16:0_18:1, TG 12:0_16:0_18:1, TG 12:0_14:0_18:1, TG 14:0_18:1_18:1, TG 18:0_18:0_18:1, TG 16:0_17:0_18:1, TG 18:1_18:1_18:1, TG 12:0_12:1_18:1, TG 15:0_18:1_18:1, TG 15:0_16:0_18:1, TG 17:0_18:1_18:1, TG 17:0_18:0_18:1, TG 16:0_18:1_18:3, TG 16:0_18:0_18:0, TG 14:0_18:1_18:2, TG 14:0_16:0_18:0, TG 12:0_15:0_18:1, TG 15:0_16:0_18:0, and TG 16:0_17:0_18:0.

7. The method of claim **1**, wherein the combined composition comprises the solids portion of the milk fat composition in an amount of at least 2.5% w/w.

8. The method of claim **1**, wherein the generating the combined composition further comprises combining the milk fat composition with water.

9. The method of claim **1**, wherein the combined composition comprises water in an amount of at least 50% w/w.

10. The method of claim **1**, wherein the combined composition comprises the surfactant in an amount of at least 0.1% w/w and/or up to 10% w/w.

11. The method of claim **1**, wherein greater than 90% by number of the lipid particles in the lipid-particle composition have a diameter of less than 500 nm.

12. The method of claim **1**, wherein the emulsifying comprises high-pressure homogenization.

13. The method of claim **1**, wherein the emulsifying generates an emulsified composition and the generating the lipid-particle composition further comprises size-filtering the emulsified composition with a filter comprising a pore size from 0.5 μm to 5.0 μm.

14. The method of claim **1**, further comprising autoclaving the lipid particles.

15. The method of claim **1**, further comprising generating the milk fat composition from a prior milk fat composition comprising the target milk fat and additional milk fat by removing the additional fat from the target milk fat.

16. The method of claim **15**, wherein the generating the milk fat composition comprises melt fractionating the prior milk fat composition.

17. The method of claim **15**, wherein the prior milk fat composition comprises at least one of anhydrous milk fat, butter oil, and ghee.

18. The method of claim **1**, wherein the target milk fat comprises ruminant milk fat.

19. The method of claim **1**, wherein:

the solids portion comprises the target milk fat in amount of at least 50% w/w;

the lipid composition comprises the solids portion in an amount of at least 50% w/w;

the lipid particles comprise triglycerides in an amount greater than 50% w/w of combined total of triglyceride, diglyceride, 1,2-diacylglyceryl-3-O-4'-(N,N,N-trimethyl)-homoserine, phosphatidylcholine, ether-linked phosphatidylcholine, fatty acyl ester of hydroxy fatty acid, free fatty acid, lysophosphatidylcholine, phosphatidylethanolamine, ether-linked phosphatidylethanolamine, lysophosphatidylethanolamine, non-hydroxy-fatty acid sphingosine ceramide, and

sphingomyelin detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry;

the lipid particles comprise a relative amount of any 3 or more of the following lipids within 5× of each other as detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry: TG 14:0_16:0_16:0, TG 14:0_15:0_16:0, TG 12:0_16:0_16:0, TG 12:0_15:0_16:0, and TG 12:0_14:0_16:0;

the lipid particles comprise a relative amount of any 10 or more of the following lipids within 5× of each other as detected in positive ion mode of ultra-high-performance liquid chromatography/mass spectrometry/mass spectrometry: TG 14:0_16:0_16:0, TG 14:0_15:0_16:0, TG 12:0_16:0_16:0, TG 12:0_15:0_16:0, TG 12:0_14:0_16:0, TG 16:0_18:0_18:1, TG 16:0_18:1_18:1, TG 16:0_16:0_18:1, TG 14:0_16:0_18:1, TG 12:0_16:0_18:1, TG 12:0_14:0_18:1, TG 14:0_18:1_18:1, TG 18:0_18:0_18:1, TG 1_16:0_17:0_18:1, TG 18:1_18:1_18:1, TG 12:0_12:1_18:1, TG 15:0_18:1_18:1, TG 15:0_16:0_18:1, TG 17:0_18:1_18:1, TG 17:0_18:0_18:1, TG 16:0_18:1_18:3, TG 16:0_18:0_18:0, TG 14:0_18:1_18:2, TG 14:0_16:0_18:0, TG 12:0_15:0_18:1, TG 15:0_16:0_18:0, and TG 16:0_17:0_18:0;

the combined composition comprises the solids portion of the milk fat composition in an amount of at least 7.5% w/w;

the generating the combined composition further comprises combining the milk fat composition with water;

the combined composition comprises water in an amount of at least 60% w/w;

the combined composition comprises the surfactant in an amount of at least 0.1% w/w and up to 10% w/w;

greater than 90% by number of the lipid particles in the lipid-particle composition have a diameter of less than 500 nm;

the emulsifying comprises high-pressure homogenization;

the emulsifying generates an emulsified composition and the generating the lipid-particle composition further comprises size-filtering the emulsified composition with a filter comprising a pore size from 0.5 μm to 5.0 μm;

the method further comprises autoclaving the lipid particles;

the method further comprises generating the milk fat composition from a prior milk fat composition comprising the target milk fat and additional milk fat by removing the additional fat from the target milk fat;

the generating the milk fat composition comprises melt fractionating the prior milk fat composition;

the prior milk fat composition comprises at least one of anhydrous milk fat, butter oil, and ghee; and

the target milk fat comprises ruminant milk fat.

20. Lipid particles made from the method of claim **1**.

21. A method of administering parenteral nutrition, the method comprising parenterally administering the lipid particles of claim **20** to a subject, optionally, wherein the subject has a condition comprising at least one of pancreatitis and hepatitis, optionally, wherein the administering results in a reduced pro-inflammatory response relative to administering an equivalent amount of lipid particles generated from vegetable fat.

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