Status: Currently Official on 15-Feb-2025
Official Date: Official as of 01-May-2018
Document Type: USP Monographs
DocId: GUID-9939A9B4-7588-4628-9652-623CEE9D75ED_3_en-US
DOI: https://doi.org/10.31003/USPNF_M32635_03_01
DOI Ref: l612j

Lipid Injectable Emulsion

» Lipid Injectable Emulsion used in total parenteral nutrition is a sterile 10 (0.10 g per mL), 20 (0.20 g per mL), or 30 (0.30 g per mL) percent w/v emulsion in an aqueous vehicle. The aqueous phase contains 0.6 percent to 1.8 percent w/v parenteral Egg Phospholipids in Water for Injection and contains, if necessary, an osmotic agent, such as glycerin in amounts of 1.7 percent to 2.5 percent w/v, or a suitable stabilizer, such as a fatty acid salt. The most frequently used oil present is Soybean Oil, which provides an ample supply of the essential fatty acids: linoleic acid and linolenic acid. Other oils, such as Safflower Oil, Medium-Chain Triglycerides, Olive Oil, Fish Oil, or other suitable oils, can be mixed with Soybean Oil. Hence, Soybean Oil can be the only oil or be part of a mixture of these other oils. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of the total oil(s). It contains no antimicrobial agents. The final products are terminally sterilized.

Packaging and storage—Preserve in an appropriate container (see *Packaging and Storage Requirements ⟨659⟩, Injection Packaging*). Use elastomeric closures that are compatible with both the oil and water phases of the Emulsion. Store at a temperature not below 4° (protect from freezing) or above 30° (protect from excessive heat).

Labeling—The label states the identity and the quantities of the specific oils in the Emulsion. The label states the total osmolar concentration (or osmolarity) in mOsm per L. The labeling provides the following information: do not use if there is evidence of excessive creaming or aggregation, if excessive free oil droplets are visible, or if there are other indications of compromised integrity, such as microbial growth, present in the product.

Fatty acid composition—Transfer a volume of the Emulsion, equivalent to about 200 mg of lipids, to a stoppered extraction vessel, add 10 mL of ether, and mix. Add 5 g of anhydrous sodium sulfate, mix, and allow the mixture to stand until separation of the layers is complete. Wet the packing of a chromatographic silica cartridge with a few mL of ether, transfer about 5 mL of the ether layer from the extraction vessel to the column reservoir, and elute at a rate of between 5 and 10 drops per minute into a suitable vessel. Evaporate the ether from the eluant, and dissolve the residue in 5.0 mL of toluene. Transfer 1.0 mL of the toluene solution to a reaction vial, and add 0.4 mL of (*m*-trifluoromethylphenyl) trimethylammonium hydroxide in methanol. Cover, mix, and allow to stand for 30 minutes. Inject about 1 µL of this solution into a gas chromatograph equipped with a 0.53-mm × 50-m wide-bore, fused-silica capillary column coated with a 2.0-µm thickness of liquid phase G16 and maintained at a temperature of 200°. The column is connected to a flame-ionization detector. Helium is used as the carrier gas at a flow rate of about 10 mL per minute. Measure the main peak areas of the methyl esters of the fatty acids. The relative peak areas expressed as a percentage of the main peaks are in the known ranges for the oil (e.g., Soybean Oil, USP; Safflower Oil, USP) as specified on the label. For oil mixtures, analysis of each oil should be performed to identify known peaks prior to emulsification as specified on the label.

Bacterial Endotoxins Test ⟨85⟩ —It contains not more than 0.5 USP Endotoxin Unit per mL.

pH ⟨791⟩**:** between 6.0 and 9.0.

Globule size limits—The Injectable Emulsion meets the requirements of the limits specified in both *Method I* and *Method II* as directed under *Globule Size Distribution in Lipid Injectable Emulsions* ⟨729⟩.

Limit of oil droplet mean diameters (See *Method I—Light Scattering Method* under *Globule Size Distribution in Lipid Injectable Emulsions* ⟨729⟩)—Using the method of light scattering, determine the mean droplet diameter (MDD): the sample meets the requirements. The intensity-weighted mean droplet diameter (MDD) for the Injectable Emulsion must be ≤500 nm, or 0.5 µm, irrespective of the concentration of the dispersed lipid phase.

Limit of large globule volume-diameter(See *Method II—Light Obscuration or Extinction Method* under *Globule Size Distribution in Lipid Injectable Emulsions* ⟨729⟩)—Using the method of light obscuration, determine the size distribution of globules in the large-diameter tail of the dispersion (detection threshold ≥2.0 µm). Calculate the volume-weighted mass of lipid in the form of globules with diameters in excess of 5.0 µm per 100 mL of the Injectable Emulsion. The volume-weighted, large-diameter fat globule limits of the dispersed phase, expressed as the percentage of fat residing in globules larger than 5 µm (PFAT5) for a given Injectable Emulsion, is not to exceed 0.05%.

Limit of free fatty acid—

Solvent—Prepare a mixture of heptane, isopropanol, and water (400:400:200) in a separatory funnel. Allow the phases to separate, and discard the lower phase. Filter the upper phase (heptane solution) through 40 g of anhydrous sodium sulfate. Store in a tightly capped glass container, and use within 1 week.

Chromatographic column—Prepare a slurry of heptane and chromatographic silica gel having an average pore size of 6 nm, and activate at a temperature of 110° for not less than 1 hour prior to use. Transfer the slurry to a 2.3-cm chromatographic tube (see *Column Chromatography* under *Chromatography ⟨621⟩*), and pack to a bed height of between 5 cm and 6 cm. Wash the column with about 40 mL of heptane, and drain the heptane through the column to a level of about 0.5 cm above the silica gel bed.

Procedure—Transfer 20.0 mL of the Injectable Emulsion to a flask, freeze, and lyophilize. Dissolve the residue in 30 mL of *Solvent,* and transfer the solution to the column. Rinse the flask with three 30-mL portions of *Solvent,* and transfer the washings to the column, allowing each rinsing to drain to the top of the column bed before applying the next rinse. Collect a total of 120 mL of effluent. Add 10 drops of phenolphthalein TS to the effluent, bubble nitrogen through the solution, and titrate with 0.02 N alcoholic potassium hydroxide VS until the solution remains pale pink after mixing for 10 seconds. Titrate a blank using 120 mL of *Solvent.* Calculate the quantity, in mEq, of free fatty acids per g of oil in the Injectable Emulsion using the formula:

$$(V_U - V_B)N/20C$$

in which V_U is the volume, in mL, of 0.02 N alcoholic potassium hydroxide consumed by the eluant; V_B is the volume, in mL, of 0.02 N alcoholic potassium hydroxide consumed by the blank; N is the normality of the 0.02 N alcoholic potassium hydroxide; and C is the labeled concentration, in g per mL, of the total oil(s) in the Injectable Emulsion: not more than 0.07 mEq of free fatty acids per g of oil is found.

Other requirements—It meets the requirements under *Injections and Implanted Drug Products ⟨1⟩*.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of isopropanol, ethyl acetate, and glacial acetic acid (179:20:1).

Standard preparation—Dissolve an accurately weighed portion of Soybean Oil (or other relevant oils used in the Emulsion) in *Mobile phase* to obtain a solution having a known concentration of about 8 mg per mL.

Assay preparation—Transfer an accurately measured portion of Emulsion, equivalent to about 800 mg of oil, to a 100-mL volumetric flask with the aid of additional portions of *Mobile phase.* Dilute with *Mobile phase* to volume, and mix to obtain a solution containing about 8 mg of oil per mL.

Chromatographic system (see *Chromatography ⟨621⟩*)—The liquid chromatograph is equipped with a refractive index detector and a 4.1-mm × 25-cm column that contains packing L21. The flow rate is about 1 mL per minute, adjusted so that the peak due to oil elutes at about 6.5 minutes. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the capacity factor, *k',* is not less than 1.0; the tailing factor for the oil peak is not more than 2.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of oil in the portion of Emulsion taken by the formula:

$$100C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of Soybean Oil or other relevant oils used in the Emulsion in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
LIPID INJECTABLE EMULSION	Documentary Standards Support	SM52020 Small Molecules 5
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 34(3)

Current DocID: GUID-9939A9B4-7588-4628-9652-623CEE9D75ED_3_en-US
Previous DocID: GUID-9939A9B4-7588-4628-9652-623CEE9D75ED_1_en-US
DOI: https://doi.org/10.31003/USPNF_M32635_03_01
DOI ref: l612j