



Technical Guide

Lipid Injectable Emulsions

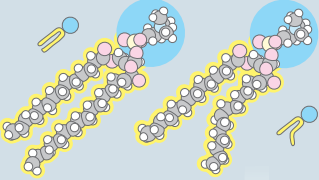
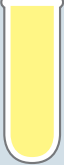



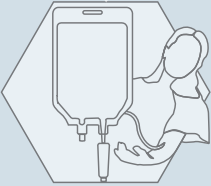


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Production of Lipid Injectable Emulsions

To produce emulsions, phospholipids and co-emulsifiers are dispersed or dissolved in the aqueous or the oil phase. The aqueous and the oil phase are then combined via high shear mixing under heating to form a homogeneous pre-emulsion. The resulting pre-emul-

sion is subjected to high pressure homogenization until the desired droplet size is reached. After filtration and sterilization, the final product is obtained. The whole process is conducted under a nitrogen atmosphere.

GENERAL PROCEDURE	EXAMPLE PROCEDURE: PROPOFOL INJECTABLE EMULSION	REQUIRED EQUIPMENT
<p>Phospholipids</p> <ul style="list-style-type: none">Disperse/dissolve phospholipids in oil phase or aqueous phase 	<ul style="list-style-type: none">Disperse egg phospholipids, sodium oleate and glycerol in water via high shear mixing at 75°C for 60 minpH adjustment	<ul style="list-style-type: none">Rotor-stator homogenizerVessel with temperature control
<p>Oil phase (+ Drug substance)</p>  <p>Aqueous phase (+ Co-emulsifier + Additives)</p>  <ul style="list-style-type: none">High shear mixing at elevated temperature	<ul style="list-style-type: none">Filtration of soybean oil (0.2 µm)Dissolution of propofol in oil phase at 75°CSlowly add oil phase to water phase in a high shear mixer at 75°CMix for > 30 min at 75°C	<ul style="list-style-type: none">FilterRotor-stator homogenizerVessel with temperature control
<p>Coarse emulsion</p>  <ul style="list-style-type: none">High pressure homogenizationCooling between cycles	<ul style="list-style-type: none">4 to 6 cycles of high pressure homogenization (1st stage pressure: 400 – 600 bar, 2nd stage pressure: 40 – 60 bar)Cooling between cycles	<ul style="list-style-type: none">High pressure homogenizer
<p>Fine emulsion</p>  <ul style="list-style-type: none">FiltrationSterilization	<ul style="list-style-type: none">Filtration (5 – 10 µm)FillingSterilization at 121°C and 2 bar for 15 min	<ul style="list-style-type: none">FilterRotating autoclave
<p>Final product</p> 	<p>Critical quality attributes</p> <ul style="list-style-type: none">Intensity weighted mean droplet diameter < 500 nm¹Percentage of fat residing in globules larger than 5 µm (PFAT5) < 0.05 %¹pH: 6.0 – 9.0 (Lipid Injectable Emulsion)²; 4.5-8.5 (Propofol Injectable Emulsion)³	

¹ According to USP <729>, ² According to USP <Lipid Injectable Emulsion> and ³ According to USP <Propofol Injectable Emulsion>

Lipid Injectable Emulsions

Lipid injectable emulsions are used in total parenteral nutrition and for parenteral administration of lipophilic drugs. Phospholipids are key excipients as emulsifiers that stabilize the oil-in-water emulsion. Because of their functionality, tolerability, and availability in pharmaceutical quality at large scale, phospholipids are ideal excipients for this purpose.

Egg phospholipids are the preferred origin in marketed products. In addition, phospholipids from further natural sources such as sunflower are viable emulsifiers for lipid injectable emulsions.

Typical Composition of Lipid Injectable Emulsions

Oil-in-water emulsions are comprised of a dispersed lipid phase and a continuous aqueous phase. The two immiscible phases are stabilized by an emulsifier and a co-emulsifier. The lipid phase of the emulsion can accommodate lipophilic drugs (Fig. 1).

Key applications of lipid injectable emulsions:

- Parenteral nutrition
- Solubilization of lipophilic compounds

Key advantages of phospholipids:

- Safe for intravenous use in humans (non-irritant, non-toxic)
- Reduction of pain and irritation at injection site
- Proven performance in market products
- Available at industrial scale
- Pharmacopoeial compliance

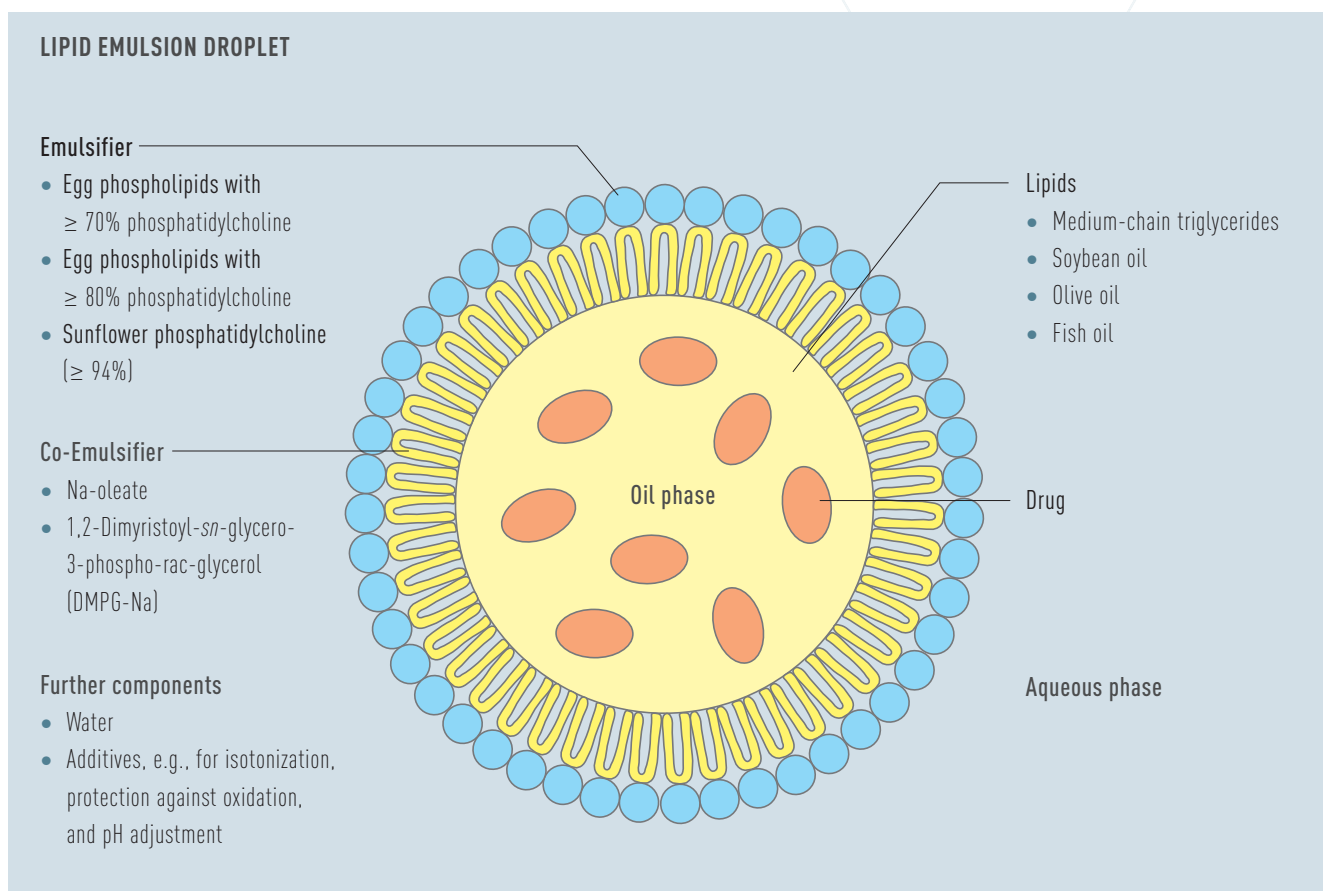


Fig. 1: Typical components of lipid injectable emulsions.

Lipoid's Portfolio for Lipid Injectable Emulsions

Lipoid offers a comprehensive product range for lipid injectable emulsions including emulsifiers, co-emulsifiers, and highly purified oils. The products

are complemented by technical and analytical support, as well as professional advice and documentation to meet the requirements of regulatory authorities.

Table 1: Products for lipid injectable emulsions

Compound	Function	Recommended product(s)	Frequently used concentrations ^[1,2,3]
Phospholipids	Emulsifier	LIPOID E 80	1.2 % (m/v)
		LIPOID E 80 SN	
		LIPOID H 100	
Na-oleate	Co-emulsifier	LIPOID Sodium Oleate	0.03 % (m/v)
		LIPOID Purified Oleic Acid	
DMPG-Na		LIPOID PG 14:0/14:0	0.03 – 0.08 % (m/v)
Medium-chain triglycerides	Lipid phase	LIPOID MCT	10 – 30 % (m/v)
Soybean oil		LIPOID Purified Soybean Oil	
Fish oil		LIPOID Purified Fish Oil	

cGMP ✓

SAFE ✓

INDUSTRIAL SCALE ✓



LIPOID E 80



LIPOID Sodium Oleate



LIPOID Purified Soybean Oil

Lipoid provides a wide range of phospholipids and further excipients for lipid injectable emulsions, including lipids and co-emulsifiers.

Marketed Products

Lipid injectable emulsions have been established since decades in clinical practice. They are administered in large quantities in total parenteral nutrition

and allow injection of lipophilic drugs. Their abundant use underlines the excellent tolerability of lipid emulsions and phospholipids.

Table 2: Lipid injectable emulsions for parenteral nutrition

Product	Lipids	Phospholipid(s)	Indication	Company
Lipofundin®	Soybean oil Medium-chain triglycerides	Egg phospholipids	Parenteral nutrition	B.Braun
ClinOleic®	Soybean oil Olive oil	Egg phospholipids	Parenteral nutrition	Baxter
SMOFlipid®	Soybean oil Medium-chain triglycerides Olive oil Fish oil	Egg phospholipids	Parenteral nutrition	Fresenius Kabi

Table 3: Lipid injectable emulsions with drug substance

Product	Drug	Phospholipid(s)	Indication	Company
Amphomul™	Amphotericin B	Egg phospholipids	Fungal infections	Bharat Serums
Cinvanti™	Aprepitant	Egg phospholipids	Chemotherapy-induced nausea and vomiting	Heron Therapeutics
Cleviprex®	Clevidipine butyrate	Egg phospholipids	Calcium channel blocker	Chiesi
Etomidat-Lipuro®	Etomidate	Egg phospholipids	Anesthesia	B.Braun
Propofol-Lipuro® Disoprivan®	Propofol	Egg phospholipids	Anesthesia	B.Braun Aspen
Vitalipid®	Retinol, Ergocalciferol, Phytomenadion, all-rac- α -Tocopherol	Egg phospholipids	Nutrition	Fresenius Kabi
Kaishi®	Alprostadil	Egg phosphatidylcholine	Vasodilatation	Beijing Tide

References *(Additional references upon request)*

- [1] Driscoll, D. F., Pharmaceutical and clinical aspects of lipid injectable emulsions. *Journal of Parenteral and Enteral Nutrition*, 41(1), 125 – 134 (2017).
- [2] Mirtallo, J. M., Ayers, P., *et al.*, ASPEN lipid injectable emulsion safety recommendations, part 1: background and adult considerations. *Nutrition in Clinical Practice*, 35(5), 769 – 782 (2020).
- [3] Raman, M., Almutairdi, A., *et al.*, Parenteral nutrition and lipids. *Nutrients*, 9, 388 (2017).



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