Lipoid

Technical Guide

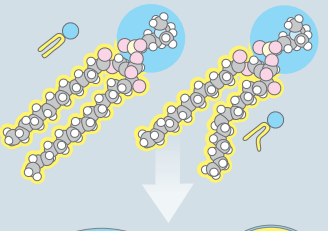
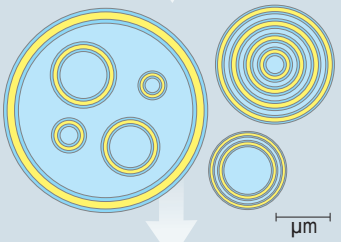
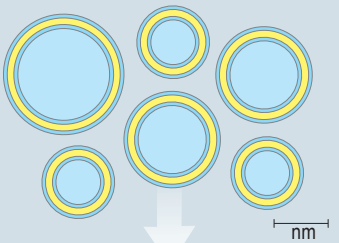
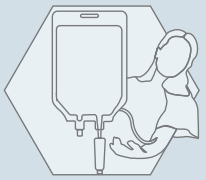
Parenteral Liposomal Formulations

We Invest in Quality.

Production of Liposomal Products

Several methods are available to manufacture liposomes. On an industrial scale, mixing of a lipid solution in an organic solvent or a dry lipid blend with an aqueous phase are most common. Ongoing research efforts may introduce new methods for industrial manufacturing such as microfluidics.[1,2,3]

GENERAL PROCEDURE

PROCESS OPTION 1:		PROCESS OPTION 2:	DRUG LOADING
• Dissolution of lipids in organic solvent (ethanol, acetone)		• Dissolution of lipids in organic solvent • Drying (rotary evaporator, spray dryer, freeze dryer)	• Passive loading of lipophilic and amphiphilic drugs: Dissolution of drug in organic solvent
• Hydration/high shear mixing of lipid solution with aqueous phase (Solvent Injection)		• Hydration/high shear mixing of lipid blend with aqueous phase (Thin Film Hydration)	• Passive loading of hydrophilic drugs: Dissolution of drug in aqueous phase
• Size reduction: Extrusion, high pressure homogenization		• Size reduction: Extrusion, high pressure homogenization	• Active (remote) loading, e.g., via transmembrane gradient
• Solvent removal (e.g., tangential flow filtration) • Filling/sterile filtration • Stabilization		• Filling/Sterile filtration • Stabilization	

QUALITY-RELATED CHARACTERISTICS OF LIPOSOMAL DRUG PRODUCTS[4]

- Chemical composition and impurities
- Particle size and size distribution
- Morphology, and if applicable, lamellarity
- Net charge
- Liposome phase transition temperature
- Parameters of contained drug (e.g., drug encapsulation efficiency, drug loading)
- *In vitro* release characteristics
- Leakage rate of drug during shelf life
- Stability in response to environment

A well-defined submicron diameter and a narrow size distribution are prerequisite for intravenous use. However, liposomal species in the micrometer range such as multilamellar or multivesicular liposomes are also used as parenteral formulations, e.g., as injectable depots. The manufacturing procedures and components employed to produce these formulations can deviate from the protocols described here. More information on other liposomal formulations for parenteral use is available on request.

Manufacturing Parenteral Liposomal Formulations

Liposomes are biocompatible carriers that are composed of one or several phospholipid bilayers. This unique structure allows co-formulation with lipophilic, amphiphilic, and hydrophilic drugs. Advantages such as solubilization of lipophilic and amphiphilic drugs or an increased therapeutic index are realized in several marketed products.

Typical Composition of Liposomes

Phospholipids are the main building blocks for liposomes. The choice of phospholipids governs the characteristics of the resulting liposomes and their fate after injection. The circulation time in the blood can, e.g., be increased by using saturated phospholipids with high phase transition temperature or PEGylated phospholipids that introduce a "stealth" surface.

Co-formulated drugs can be lipophilic, amphiphilic, or hydrophilic. Lipophilic and amphiphilic drugs are typically located in the phospholipid bilayer whereas hydrophilic ones are enclosed in the aqueous compartment.

Key advantages of parenteral liposomal formulations:

- **Delivery system for hydrophilic, lipophilic, and amphiphilic APIs**
- **Solubilization of lipophilic and amphiphilic APIs**
- **Increased therapeutic index**
- **Reduction of side effects and toxicity**
- **Drug targeting**
- **Sustained release**
- **Protection of the API**

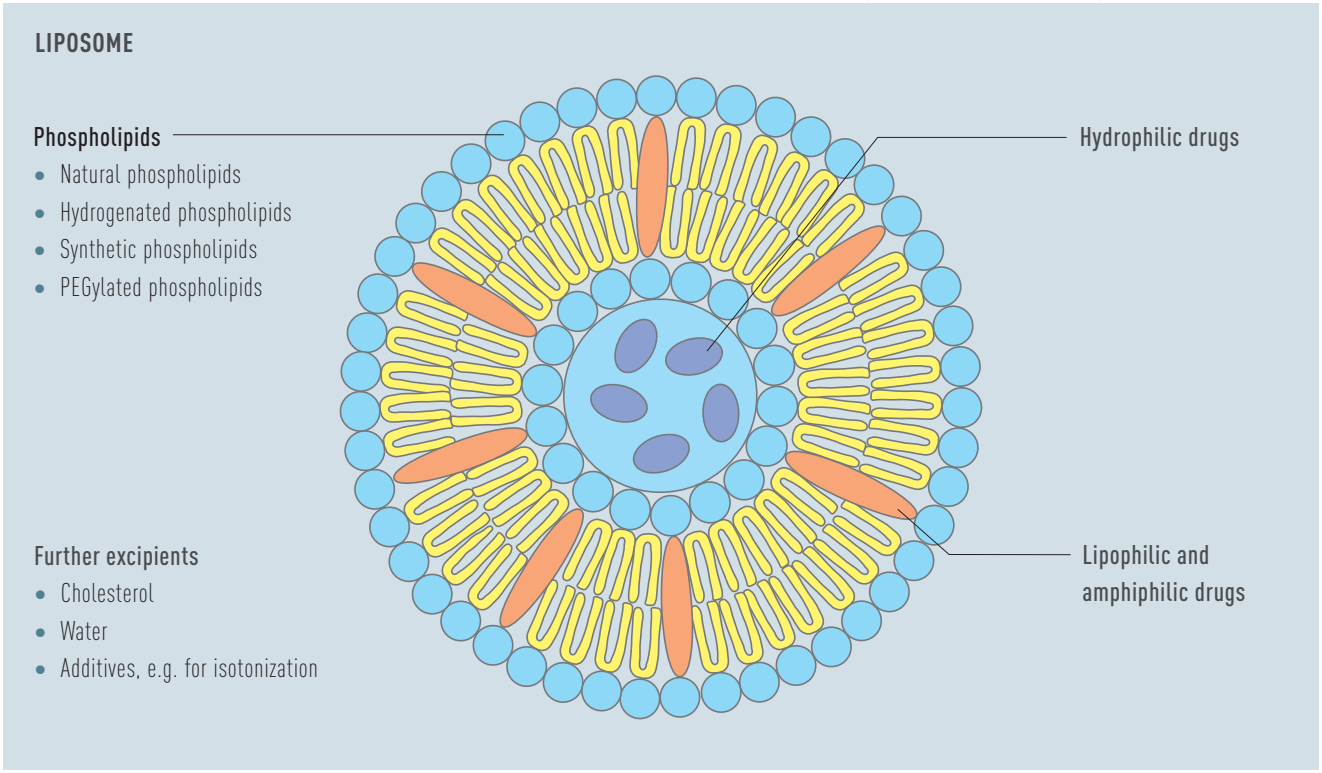


Fig. 1: Typical components of liposomes.

Lipoid's Portfolio for Liposomal Formulations

Lipoid offers a comprehensive product range of natural and synthetic phospholipids. The products are complemented by technical and analytical support, as well as professional advice and documentation to meet the requirements of regulatory authorities. A selection of frequently used phospholipids is listed in Table 1.

Table 1: Selected products for liposomal formulations

Phospholipid type	Phospholipid	Recommended product	Key function
Natural phospholipids	Egg phosphatidylcholine	LIPOID E PC	Main constituent of liposomes with phase transition temperature below body temperature
Hydrogenated phospholipids	Hydrogenated soybean phosphatidylcholine	LIPOID S PC-3	Main constituent of liposomes with phase transition temperature above body temperature
Synthetic phospholipids	1,2-Distearoyl-*sn*-glycero-3-phospho-choline (DSPC)	LIPOID PC 18:0/18:0	Main constituent of liposomes with phase transition temperature above body temperature
	1,2-Dimyristoyl-*sn*-glycero-3-phospho-choline (DMPC)	LIPOID PC 14:0/14:0	Constituent of liposomes with phase transition temperature below body temperature
	1,2-Dioleoyl-*sn*-glycero-3-phospho-choline (DOPC)	LIPOID PC 18:1/18:1	Constituent of liposomes with phase transition temperature below body temperature
	1,2-Dimyristoyl-*sn*-glycero-3-phospho-*rac*-glycerol, sodium salt (DMPG-Na)	LIPOID PG 14:0/14:0	Liposome component conferring negative charge
	1,2-Distearoyl-*sn*-glycero-3-phospho-*rac*-glycerol, sodium salt (DSPG-Na)	LIPOID PG 18:0/18:0	Liposome component conferring negative charge
PEGylated phospholipids	*N*-(Carbonyl-methoxypolyethylene glycol-2000)-1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine, sodium salt (MPEG-2000-DSPE)	LIPOID PE 18:0/18:0-PEG 2000	Liposome component conferring steric stabilization and "stealth" surface

LIPOID E PC

LIPOID S PC-3

LIPOID PG 18:0/18:0

Lipoid provides a wide range of natural and synthetic phospholipids in pharmaceutical quality on an industrial scale to formulate liposomal products.

Marketed Products

Liposomes are established formulations for a variety of indications, including fungal infections, different kinds of tumors and vaccination.

In addition, formulations like immunostimulating complexes (ISCOMs) and microbubbles are applied in marketed products. Despite similarities to liposomes in essential features, differences in composition and morphology allow their use in specific applications such as medical imaging. The versatile use of phospholipids underscores their safety and functionality.

Table 2: Marketed products with injectable liposomal formulations

Product	Drug	Phospholipid(s)	Indication	Company
Abelcet®	Amphothericin B	DMPC, DMPG	Fungal infection	Leadiant (USA, Canada), Teva
AmBisome®	Amphotericin B	HSPC, DSPG	Fungal infection	Gilead
Doxil®/ Caelyx®	Doxorubicin-HCl	HSPC, MPEG-2000-DSPE	Metastatic cancer	Baxter
Myocet®	Doxorubicin-HCl	Egg PC	Cancer	Sopherion Teva
Visudyne®	Verteporfin	DMPC, Egg PG	Photodynamic therapy	Bausch + Lomb
Lipusu®	Paclitaxel	Egg Phospholipids	Non-small cell lung cancer, breast cancer, ovarian cancer	Luye Pharma
Mepact®	Mifamurtide (MTP-PE)	POPC, DOPS	Osteosarcoma	Takeda
Onivyde®	Irinotecan	DSPC, MPEG-2000-DSPE	Pancreatic cancer	Ipsen
Vyxeos®	Cytarabine, Daunorubicin	DSPC, DSPG	Acute myeloid leukemia	Jazz Pharmaceuticals
DEFINITY®	Perflutren	DPPA, DPPC, MPEG-5000-DPPE	Echocardiography	Lantheus

Table 3: Marketed vaccine formulations with liposomal adjuvants

Product	Adjuvant System	Phospholipid(s)	Indication	Company
Nuvaxovid®	Matrix-M™ (Immunostimulating complex, ISCOM)	PC	Vaccination against COVID-19	Novavax
Shingrix®/ Arexvy®	AS01B / AS01E (Liposomes)	DOPC	Vaccination against herpes zoster virus/ Respiratory syncytial virus	GlaxoSmithKline

Abbreviations:
DMPC: 1,2-Dimyristoyl-*sn*-glycero-3-phosphocholine, **DMPG:** 1,2-Dimyristoyl-*sn*-glycero-3-phospho-*rac*-glycerol, **DOPC:** 1,2-Dioleoyl-*sn*-glycero-3-phosphocholine, **DOPS:** 1,2-Dioleoyl-*sn*-glycero-3-phospho-L-serine, **DPPA:** 1,2-Dipalmitoyl-*sn*-glycero-3-phosphate, **DPPC:** 1,2-Dipalmitoyl-*sn*-glycero-3-phosphocholine, **DSPC:** 1,2-Distearoyl-*sn*-glycero-3-phosphocholine, **DSPG:** 1,2-Distearoyl-*sn*-glycero-3-phospho-*rac*-glycerol, **HSPC:** Hydrogenated soybean phosphatidylcholine, **MPEG-2000-DSPE:** *N*-(carbonyl-methoxypolyethylene glycol-2000)-1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine, **MPEG-5000-DPPE:** *N*-(Carbonyl-methoxypolyethylene glycol-5000)-1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine, **PC:** Phosphatidylcholine, **PG:** Phosphatidylglycerol, **POPC:** 1-Palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine

References *(Additional references upon request)*

[1] Andra, V. V. S. N. L., Pammi, S. V. N., *et. al.*, A comprehensive review on novel liposomal methodologies, commercial formulations, clinical trials and patents. *BioNanoScience*, 12(1), 274 – 291 (2022).
[2] Shah, S., Dhawan, V., *et. al.*, Liposomes: Advancements and innovation in the manufacturing process. *Advanced drug delivery reviews*, 154, 102 – 122 (2020).
[3] Kapoor, M., Lee, S. L., *et. al.*, Liposomal drug product development and quality: current US experience and perspective. *The AAPS Journal*, 19, 632 – 641 (2017).
[4] US Food and Drug Administration, Liposome drug products: chemistry, manufacturing, and controls; human pharmacokinetics and bioavailability; and labeling documentation – guidance for industry. (2018).

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