Phospholipid Research Center

Workshop: Recent Advances in the Use of Phospholipid Excipients

Introduction on the use and properties of phospholipid excipients

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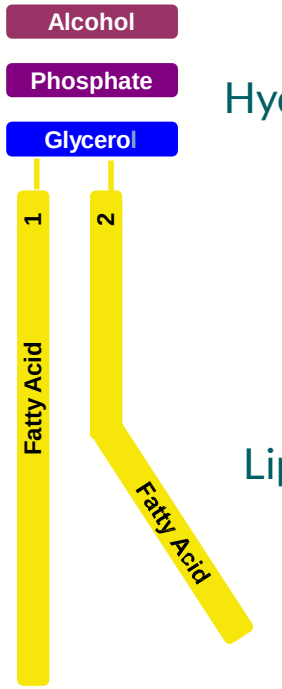
DEFINITION OF PHOSPHOLIPIDS

All lipids that contain phosphorus are called phosphatides or phospholipids (PLs)



Hydrophilic

Lipophilic

Depending on the alcohol component, different phospholipids exist.

The most prevalent naturally occurring phospholipids (*e.g.* Soybean Lecithin) include:

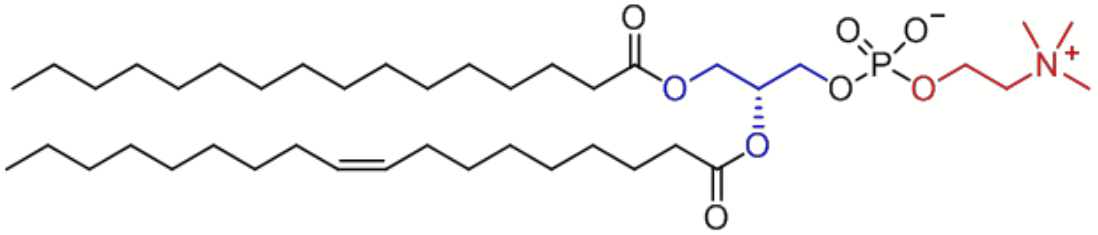
- Phosphatidylcholine (PC)
- Phosphatidylethanolamine (PE)
- Phosphatidylserine (PS)
- Phosphatidylinositol (PI)

PHOSPHOLIPIDS

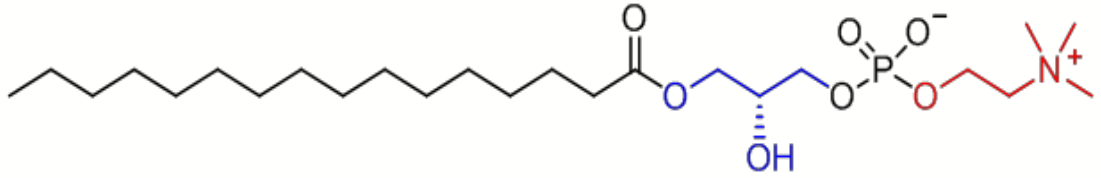
Structure and Properties I

→ Zwitterionic

Phosphatidylcholine (PC)



Monoacyl PC (LPC)

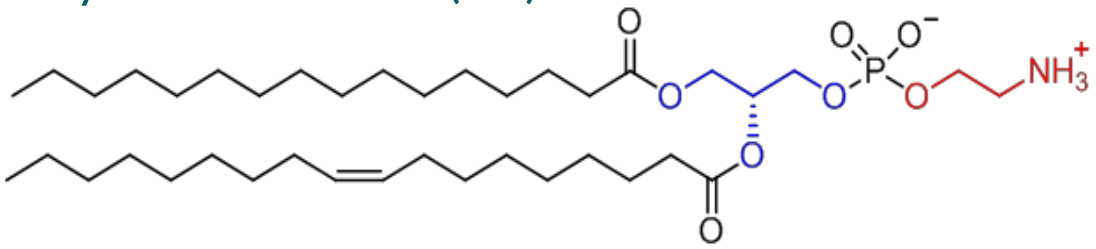


PHOSPHOLIPIDS

Structure and Properties II

→ Zwitterionic at pH 7 and negatively charged at basic pH

Phosphatidylethanolamine (PE)

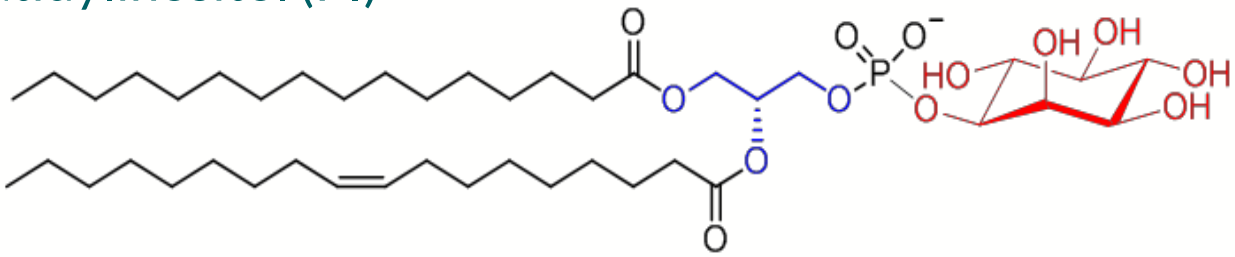


PHOSPHOLIPIDS

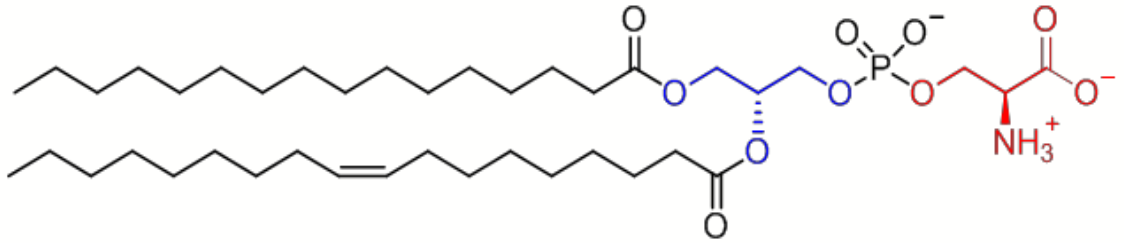
Structure and Properties III

→ Negatively charged at pH 7

Phosphatidylinositol (PI)



Phosphatidylserine (PS)



PHOSPHOLIPIDS

Nomenclature

General: „Fatty acids" – „Phosphatidyl" – „Alcohol"

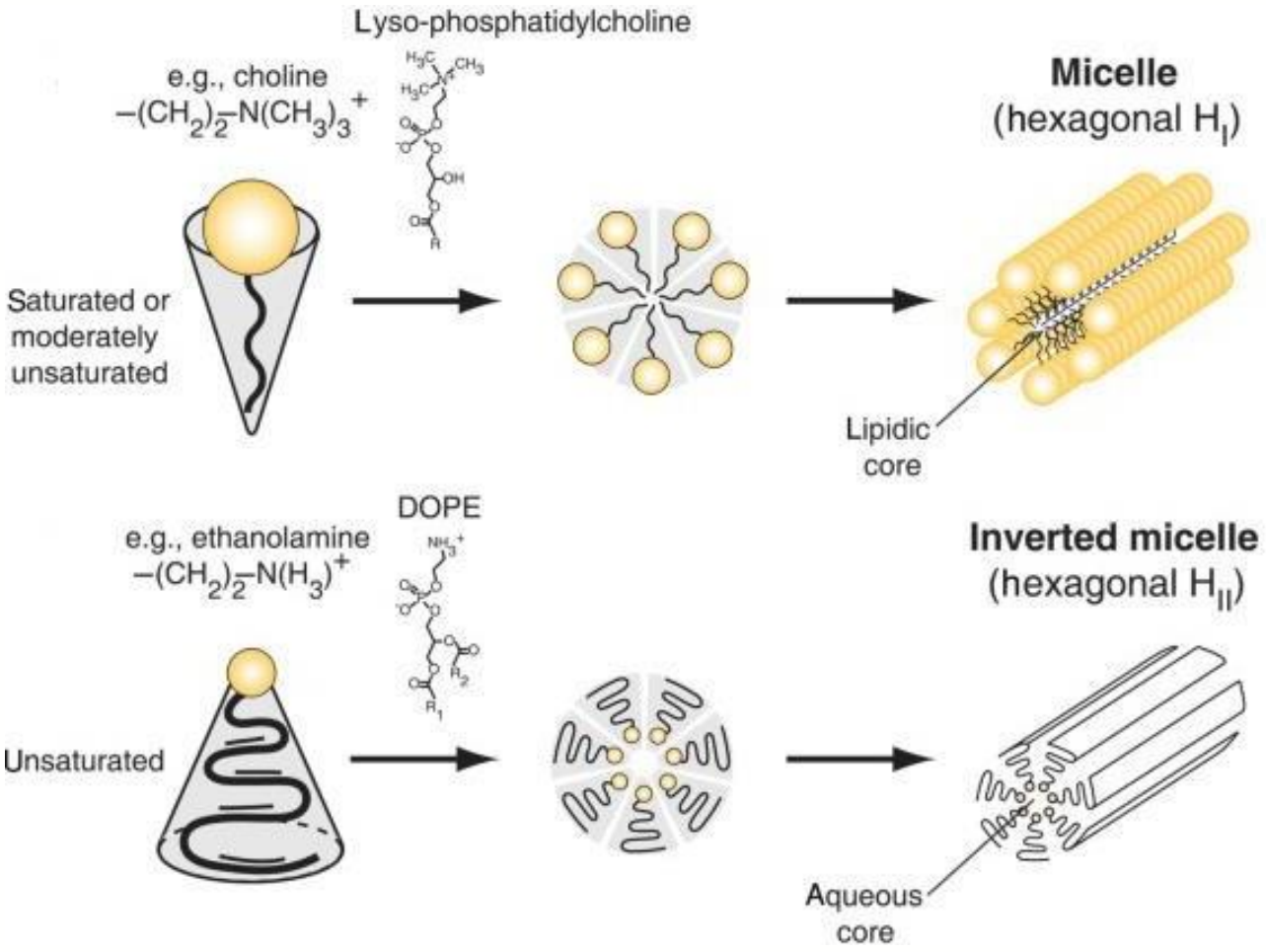
Fatty acids:	Oleic acid	-oleoyl-	„O“
	Stearic acid	-stearoyl-	„S“
	Palmitic acid	-palmitoyl-	„P“
	Myristic acid	-myristoyl-	„M“

Alcohol:	Choline (Lecithin)	„PC“
	Ethanolamine (Cephalin)	„PE“
	Serine	„PS“
	Glycerol	„PG“
	Inositol	„PI“

Examples: 1-**P**almitoyl-2-**o**leoly**p**hosphatidyl**c**holine (POPC)
1,2-**Di**o**l**eoly**p**hosphatidyl**e**thanolamine (DOPE)

PHOSPHOLIPIDS

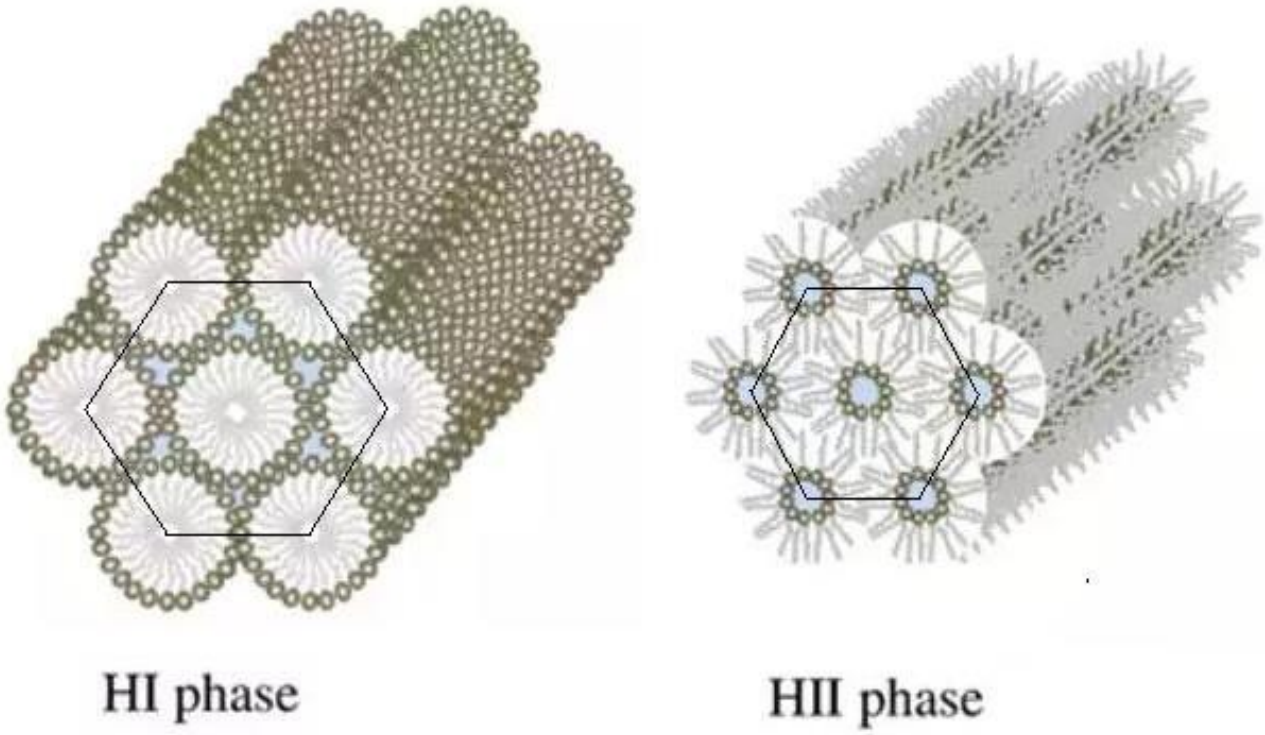
Shape Concept and Hexagonal Phases I



C. Kraft et al., Emerging Research and Clinical Development Trends of Liposome and Lipid Nanoparticle Drug Delivery Systems, *J. Pharm. Sci.* Volume 103, Issue 1, Pages 29–52,

PHOSPHOLIPIDS

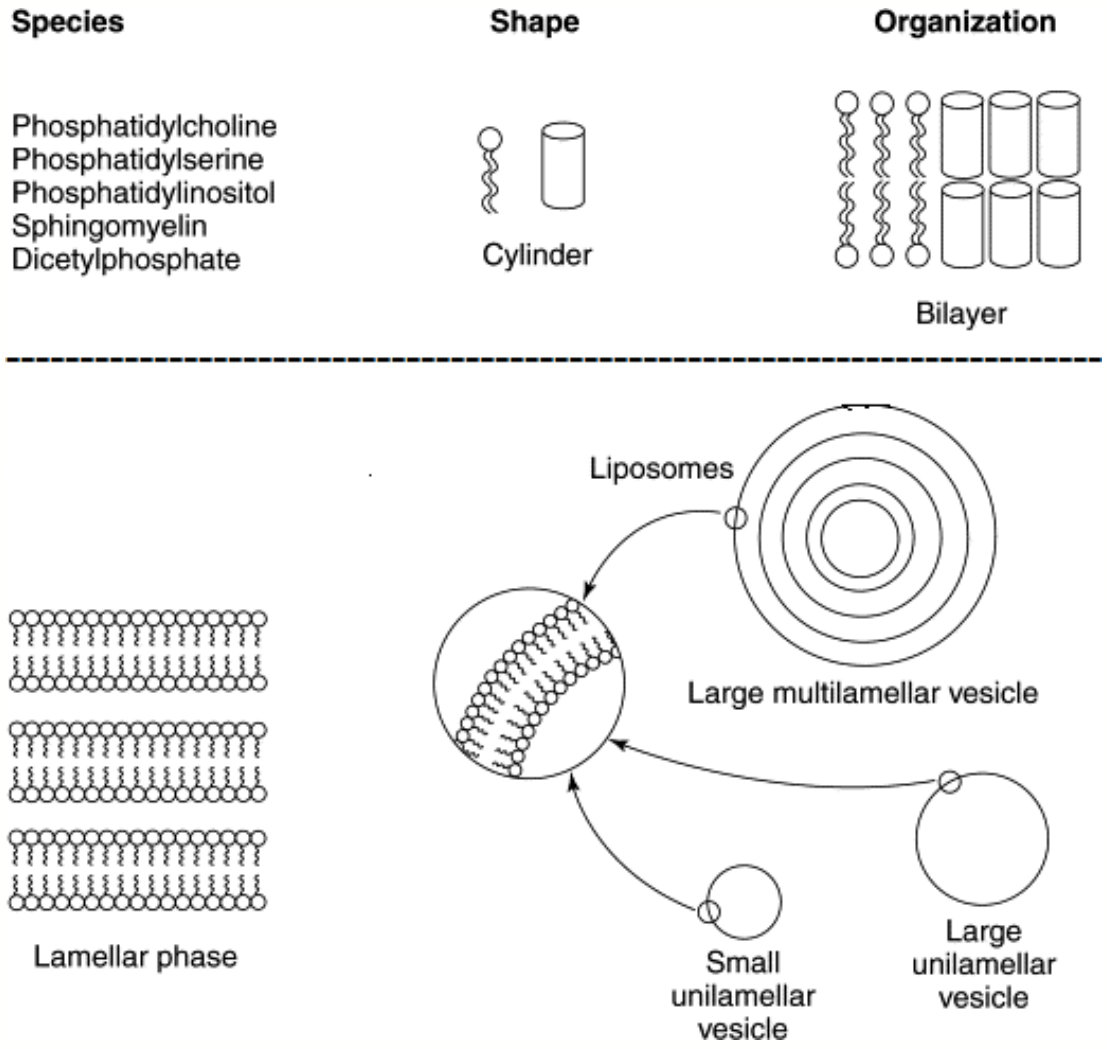
Shape Concept and Hexagonal Phases II



Jouhet J., Importance of the hexagonal lipid phase in biological membrane organization
Front. Plant Sci., 03 December 2013

PHOSPHOLIPIDS

Shape Concept and Lamellar Phases



Lasic, D.D., Novel applications of liposomes, Trend in *Biotechnology* **1998**, 16(7) 307–321,

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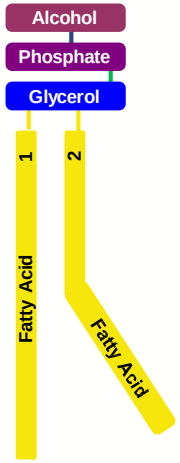
PHOSPHOLIPIDS

Saturated *versus* Unsaturated I



Unsaturated Phospholipids

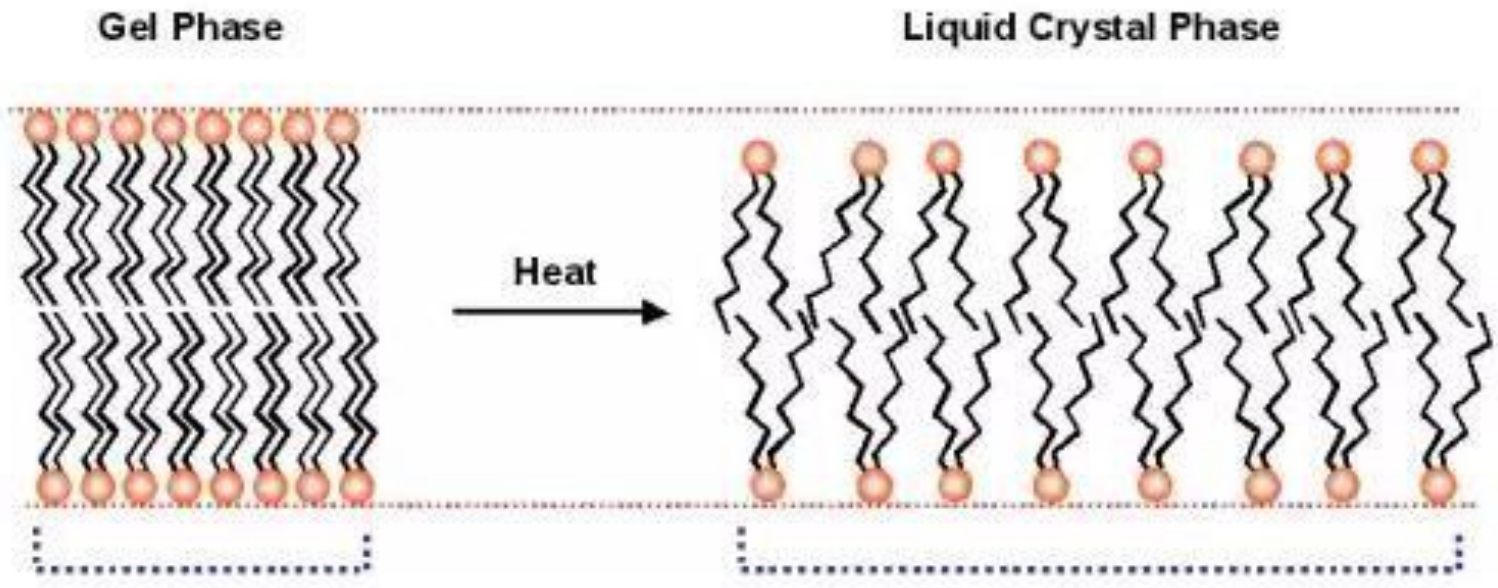
- Soybean PL: rich in Ω-6 essential fatty acids
- Phosphatidylcholine soluble in alcohols
- Phase transition temperature (T_m) < 0°C
- Water-dispersible at RT
- Flexible, fluid-state aggregates in water
- High membrane fluidization capacity

Saturated Phospholipids

- Fully saturated fatty acids (*e.g.* palmitic/stearic acid)
- Soluble in warm ethanol or isopropanol
- Phase transition temperature (40-55°C)
- Water-dispersible at temperature above T_m
- Low membrane fluidization capacity

PHOSPHOLIPIDS

Saturated *versus* Unsaturated II



Above T_m in liquid crystalline state; below T_m in gel state

PHOSPHOLIPID EXCIPIENTS

Sources

Vegetable	Animal	Synthetic
• **Soybean**	• **Egg Yolk**	• DSPC
• Rapeseed	• Milk	• DOPC
• Sunflower	• Bovine Brain (mainly PS)	• DSPG
• Wheat Germ	• Krill	• PEGylated PL
• Flaxseed		• Etc.

LECITHIN

Monograph

Definition according to the USP

Lecithin is a complex mixture of acetone-insoluble phosphatides, which consist chiefly of phosphatidylcholine, phosphatidyl-ethanolamine, phosphatidylserine and phosphatidylinositol, combined with various amounts of other substances such as triglycerides, fatty acids and carbohydrates, as separated from the crude vegetable oil source.

It contains not less than 50% of “Acetone-Insoluble Matter“.

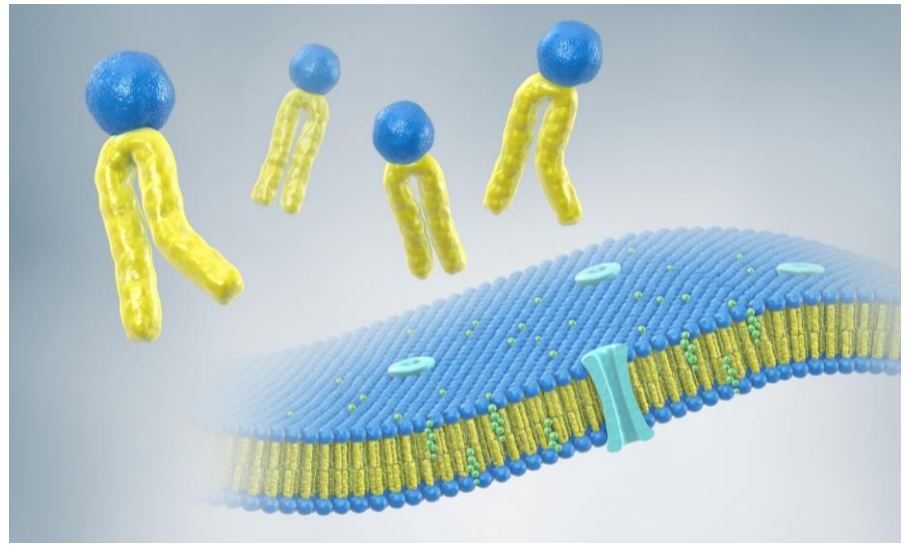
USP
U.S. Pharmacopeial Convention ™

PHOSPHOLIPIDS

Biological Function

Typical lipid membrane composition of an average mammalian cell membrane

45 – 55%	PC
15 – 25%	PE
10 – 15%	PI
5 – 10%	PS
1 – 2%	phosphatidic acid
10 – 20%	cholesterol
5 – 10%	sphingomyelin
2 – 5%	cardiolipin



Functions in the human body

- Building block (membranes and organelles)
- Blood transport (component of lipoproteins)
- Digestion (formation of micelles in bile)
- Surfaces (alveoli, tear film)
- Choline & fatty acid source

LECITHIN

Safety Aspects

Lecithin is considered non-toxic for humans and animals

WHO

- No ADI (Acceptable Daily Intake) limit for Lecithin

FDA

- GRAS status (generally recognized as safe)
- Inactive Ingredient Guide (IIG):
  Many approved drugs containing phospholipids listed

European Commission

- Lecithin is a food additive (E322) *„generally permitted for use in foodstuffs ...“*
- No ADI value has been fixed for lecithin in Europe;
  the material may be used *„quantum satis“*

EUROPEAN COMMISSION

PHOSPHOLIPID
EXCIPIENTS

Production and Quality Aspects I

Suitability for Pharmaceutical Administration

- ✓ Reproducible quality
- ✓ Composition
- ✓ Low content of Lyso-PL and FFA
- ✓ Low peroxide value (POV)
- ✓ Residual raw material
- ✓ Residual intermediates
- ✓ Possible synthetic by-products
- ✓ Residual solvent
- ✓ Low microbial burden
- ✓ Low endotoxin content

PHOSPHOLIPID
EXCIPIENTS

Production and Quality Aspects II

Requirements for the manufacturer of phospholipids

- ✓ cGMP
- ✓ Certified according ICH Q7
- ✓ ISO 9001
- ✓ Drug Master Files
- ✓ Registration Documents

PHOSPHOLIPID EXCIPIENTS

Regulatory Aspects I

	Monograph	US DMF
Soy Lecithin	USP / Ph. Eur / JPE / CHP etc.	DMF available for many phospholipids
Hydrogenated Phospholipids	-	DMF available for many phospholipids
Egg Phospholipids	USP / JP / CP / EP (Draft)	DMF available for many phospholipids
Synthetic Phospholipids	-	DMF available for many phospholipids

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PHOSPHOLIPID EXCIPIENTS

Regulatory Aspects II

	Inactive Ingredient IIST	Other
Soy Lecithin	Lecithin	-
Hydrogenated Phospholipids	Hydrogenated Soybean Lecithin	Draft Guidance for Industry: Liposome Drug Products (FDA, Oct. 2015)
Egg Phospholipids	Egg Phospholipids	Draft Guidance on Verteporfin (FDA, Apr. 2014)
Synthetic Phospholipids	Various entries	Draft Guidance on Doxorubicin Hydrochloride, Amphotericin B, etc. (FDA, 2014)

PHOSPHOLIPIDS IN PHARMACEUTICAL PRODUCTS

Administration Route	Technical Use	Formulation / Drug Delivery System
Oral	Solubilizer	Emulsion (O/W, W/O, etc.)
Parenteral	Emulsifier	Liposomes/LNPs
Topical / skin	Surfactant	(Mixed) Micelles
Pulmonary	Wetting agent	Dispersion (aqueous, solid)

- ✓ Non-toxic
- ✓ Multipurpose excipient
- ✓ Physiologically occurring

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PHOSPHOLIPIDS IN PHARMACEUTICAL PRODUCTS

Examples: Liposomes, Lipid Nanoparticles (LNPs)

DOXIL (doxorubicin)	HSPC
AMBISOME (amphotericin B)	HSPC, DSPG
EXPAREL (bupivacaine)	DEPC, DPPG
SHINGRIX (shingles vaccine)	DOPC
COMIRNATY (mRNA vaccine)	DSPC
VISUDYNE (benzoporphyrin)	Egg-PG, DMPC
MEPACT (MTP-PE)	POPC, DOPS
VYXEOS (daunorubicin/cytarabin)	DSPC, DSPG
MYOCET (doxorubicin)	Egg-PC
ONIVYDE (irinotecan)	DSPC
ABELCET (amphotericin B)	DMPC, DMPG
ONPATTRO (siRNA LNPs)	DSPC

COMIRNATY (mRNA vaccine)	DSPC
SPIKEVAX (mRNA vaccine)	DSPC
SHINGRIX (rec. vaccine)	DOPC
NOVAXOVID (rec. vaccine)	Egg PC

Crommelin DJA *et al.* The role of liposomes in clinical nanomedicine development. What now? Now what? *J. Controlled Release* **2020**, 318, 256.

PHOSPHOLIPIDS IN PHARMACEUTICAL PRODUCTS

Examples: O/w Emulsions, Parenteral Nutrition

Egg PC as Emulsifier

Intralipid	Soybean oil
Liposyn II	Soybean oil/safflower oil
Omegaven	Fish oil
ClinOleic	Soybean oil/olive oil
Lipofundin	Soybean oil/MCT
Structolipid	Interesterified mixture of equimolar amounts of long chain triglycerides (LCT) and medium chain triglycerides (MCT)
SMOFlipid	Soybean oil/MCT/olive oil/fish oil

van Hoogevest P, Wendel A. The use of natural and synthetic phospholipids as pharmaceutical excipients. *Eur. J. Lipid Sci. Technol.* 2014 Sep;116(9):1088-1107.

PHOSPHOLIPIDS IN PHARMACEUTICAL PRODUCTS

Examples: Drug-containing O/w Emulsions

Egg PC as Emulsifier

Product	Drug substance	Indication
Diazemuls	Diazepam	Sedative and muscle relaxant
Limethason	Dexamethasone palmitate	Rheumatoid arthritis
Liple	Alprostadil (prostaglandin E1)	Vasodilator, platelet inhibitor
Diprivan/disoprivan	Propofol	Anesthetic
Etomidat®-Lipuro	Etomidate	Anesthetic
Vitalipid	Vitamin A, D2, E, K1	Parenteral nutrition
Cleviprex	Clevidipine butyrate	Antihypertensive

van Hoogevest P, Wendel A. The use of natural and synthetic phospholipids as pharmaceutical excipients. *Eur. J. Lipid Sci. Technol.* 2014 Sep;116(9):1088-1107.

PHOSPHOLIPIDS IN DRUG PRODUCTS

Natural *versus* Synthetic Phospholipids

Application	Natural Phospholipids			Synthetic Phospholipids
	Egg	Soy	Hydrogenated	
Parenteral				
Emulsions	✓			
Liposomes	✓		✓	✓
LNPs				✓
Mixed Micelles		✓		
Suspensions		✓		✓
Pulmonary		✓		✓
Oral		✓		
Topical/Dermal		✓	✓	

CONCLUSION

- Phospholipids are used in a broad range of pharmaceutical formulations for decades
- Phospholipids are considered as excipients by the authorities
- All kind of phospholipids (natural, hydrogenated and synthetic) are used and accepted by authorities worldwide
- In the overall phospholipid market, regarding salles volume synthetic phospholipids play compared to natural phospholipids a minor role
- Phospholipids provide promising solutions in the development of new pharmaceutical formulations not only as they are body- own and biodegradable

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