Lipoid

Phospholipid-based
Delivery Systems

Advanced Pulmonary Applications Using Phospholipids

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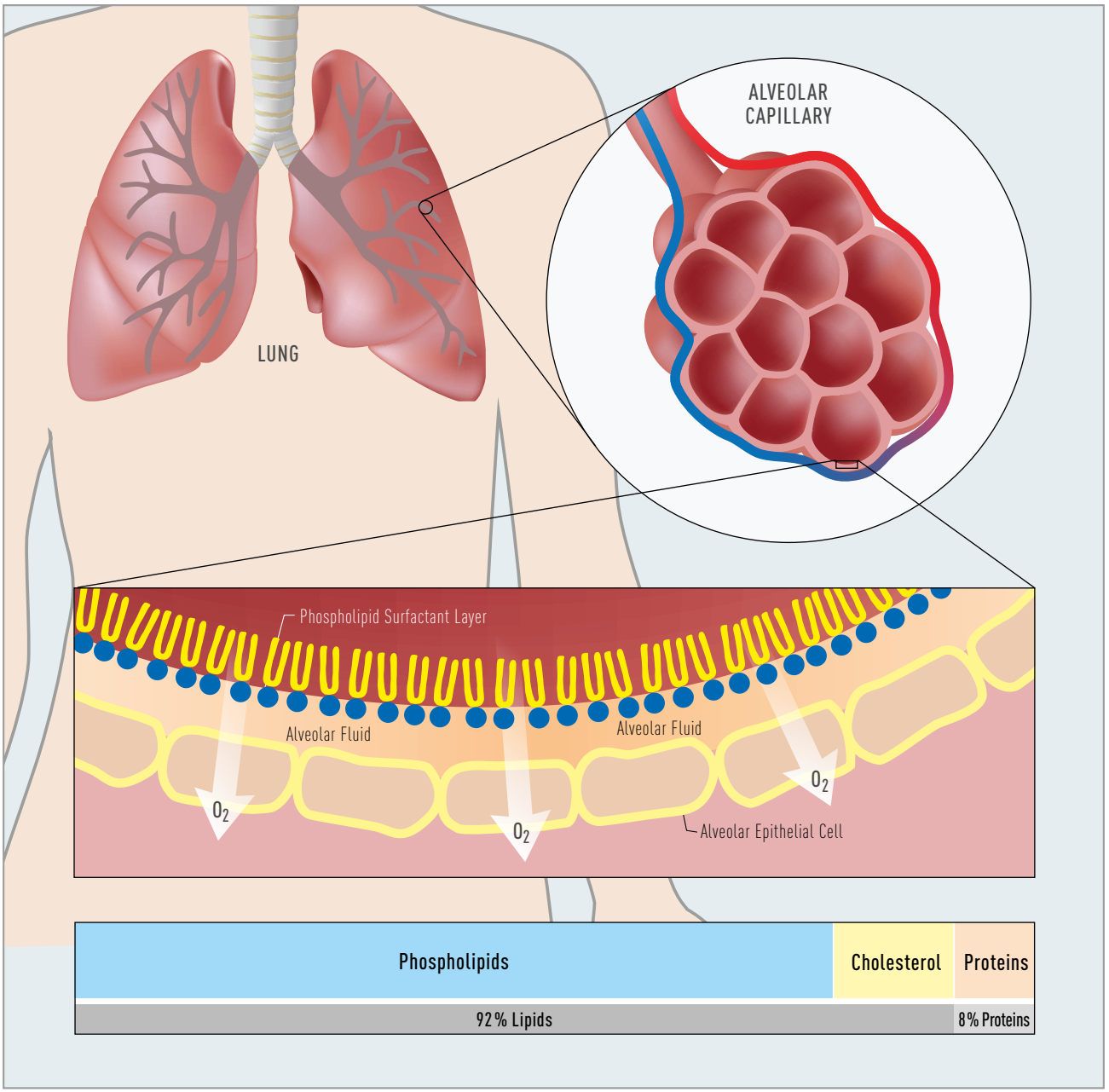


Fig. 1: Schematic diagram of pulmonary tissue and approximate composition of human lung surfactant [1].

Key advantages of phospholipids:

- Endogenous excipients with excellent tolerability
- Approved for pulmonary administration
- Compatible with DPIs, MDIs, and nebulizers
- Broad technical use
- Available in cGMP quality at industrial scale

Key applications of phospholipids:

- Carrier-free formulations with increased drug loading
- Homogeneous co-formulation of polar and non-polar drugs
- Formulation of poorly soluble drugs
- Sustained release formulations
- Targeted delivery, e.g., for intracellular infections

Phospholipids in Pulmonary Formulations

The respiratory tract is attractive for local and systemic drug delivery. Local delivery enables higher doses at the site of treatment and lower systemic absorption, preventing off-target effects. Also for systemic delivery the pulmonary route is gaining increasing interest as the respiratory tract has a large surface area with extensive vasculature. Moreover, pulmonary administration circumvents the gastrointestinal tract, resulting in a rapid onset of action [2].

Phospholipids are versatile compounds that are ideally suited for pulmonary administration. As endogenous molecules they provide unique advantages for pharmaceutical formulations. They are biocompatible, biodegradable, and recognized as safe for pulmonary drug delivery [3]. In particular, saturated phospholipids like dipalmitoylphosphatidylcholine (DPPC) are main components of the lung surfactants (Fig 1).

Their endogenous function allows their use in the treatment of respiratory distress syndrome (RDS), which is characterized by a lack of phospholipids [4]. Moreover, they are essential components of a number of pulmonary formulations with versatile benefits.

Formulation and Administration Devices

Phospholipids and phospholipid-based formulations can be used in any type of pulmonary administration device: metered dose inhalers (MDI), dry powder inhalers (DPI), and nebulizers (Fig. 2).

Porous particles and drug suspensions stabilized with phospholipids are established formulations for MDIs. They provide increased drug loadings, homogeneous distribution, even of multiple drugs in one formulation, and are compatible with a broad range of drugs [5]. Moreover, they have been shown to be compatible with low global warming potential propellants, allowing a simple re-formulation of currently approved products [6].

Porous particles can also be formulated for use in DPIs. Moreover, advanced formulations such as liposomes and lipid nanoparticles (LNPs) can be freeze-dried or spray-dried to convert them into dry powders, allowing their application in DPIs [7, 8].

Recent advances in nebulizer technology facilitate the application of nanoparticles in aqueous dispersions, e.g., as targeting formulations, local depots, and solubilizers for poorly soluble drugs without the need for an additional processing step [9].

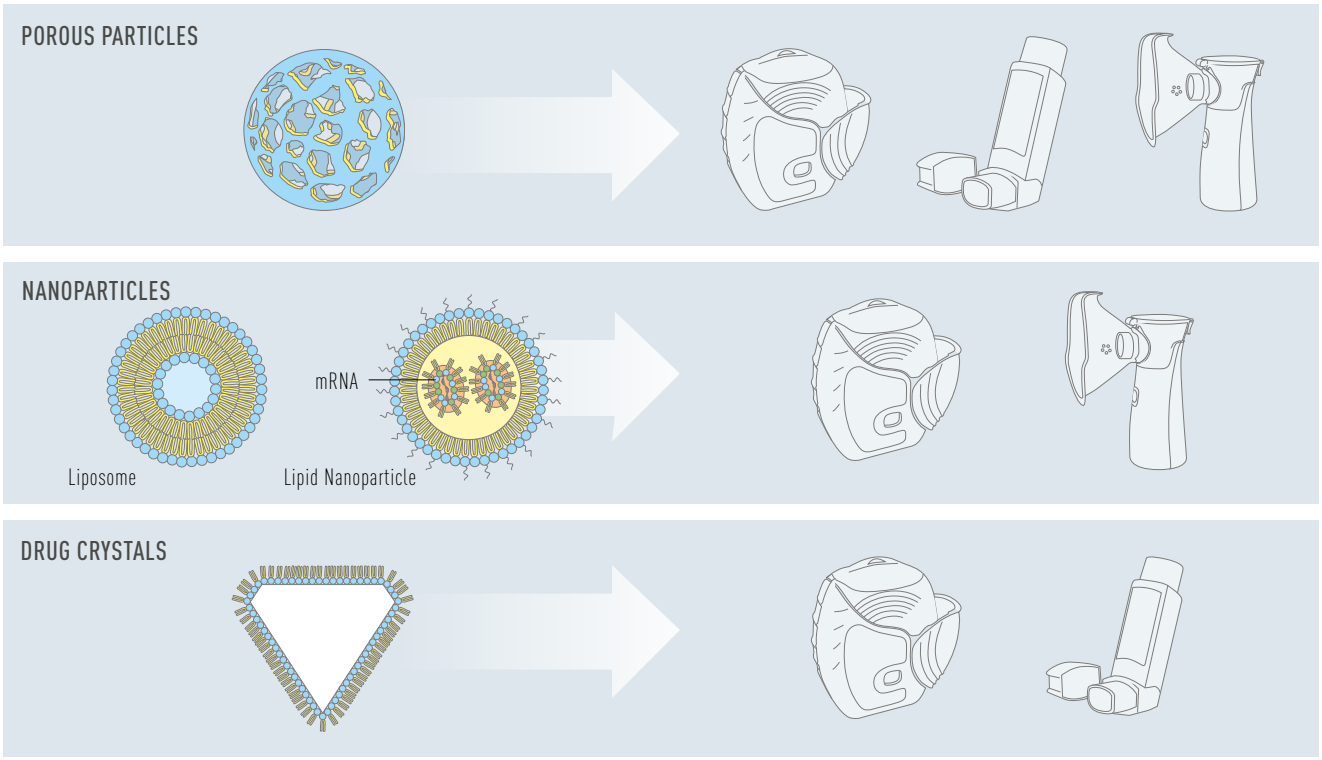


Fig. 2: Schematic illustration of selected phospholipid formulations and their compatibility with pulmonary administration devices.

Marketed Pulmonary Products with Phospholipids

Numerous pulmonary products containing phospholipids are successfully marketed for diverse indications (Tab. 1). The phospholipids in these products fulfill various functions: based on their physicochemical properties they enable stable drug formulations, but they may also alter the pharmacokinetics of a drug substance. Moreover, they endow formulations with advanced functionalities, such as targeting of macrophages or compensating for the loss of phospholipids in lung surfactant [4, 5, 10, 11]. These products highlight the excellent safety profile of phospholipids and their acceptance by regulatory authorities for pulmonary applications.

Table 1: Marketed pulmonary products with phospholipids

Project/Product	Indication	Phospholipid	Dosage Form	Device	Company
Airsupra / Bevespi / Breztri / Trixeo	Asthma / Chronic obstructive pulmonary disease (COPD)	**DSPC**	Co-suspension of crystal and Pulmosphere™/ Aerosphere®	MDI	AstraZeneca
Arikayce®	*Mycobacterium avium* complex lung disease as part of a combination antibacterial drug regimen	**DPPC**	Liposomal Suspension	Nebulizer	Insmed
Curosurf®	Prevention of respiratory distress syndrome in premature infants at high risk for RDS	**Polar lipids from lung extract**	Suspension	Endotracheopulmonary instillation	Chiesi Farmaceutici
Inbrija®	"OFF" episodes in adults with Parkinson's disease	**DPPC**	Powder (ARCUS®)	DPI	Merz Therapeutics
Survanta®	Prevention of respiratory distress syndrome in premature infants at high risk for RDS	**Lung extract, DPPC**	Suspension	Endotracheopulmonary instillation	AbbVie
TOBI® Podhaler®	Lung infections caused by *Pseudomonas aeruginosa*	**DSPC**	Powder (Pulmosphere™)	DPI	Viatris

Research Advances

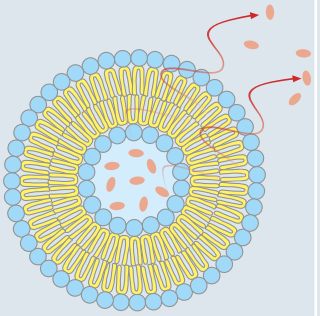
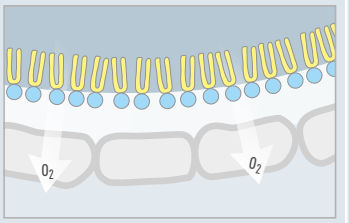
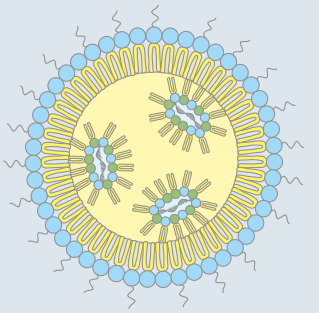
In addition to the already marketed products, a variety of developments are in progress. Examples are provided in Tab. 2.

These efforts range from the replacement of phospholipid extracts from animal sources by more defined structures, to new approaches for local or systemic drug applications. This includes, but is not limited to, antivirals, antibiotics, and cytostatic drug substances [12].

Moreover, respiratory delivery of therapeutic mRNA- and siRNA holds great promise for transmucosal vaccination and the treatment of diseases such as cystic fibrosis [7, 13]. Furthermore, chemically modified phospholipids (e.g. pegylated, MPEG-2000-DSPE) expand the toolbox of phospholipids to achieve more specific functions in pulmonary administration [14].

Latest findings also highlight a direct impact of phospholipids on the suppression of viral airway infections [15].

Table 2: Phospholipid-based technologies for pulmonary administration that are currently* investigated in clinical trials

	Inhalable depots	Synthetic lung surfactant	Gene therapy
Technology			
Advantages	• Reduced dosing frequency • Stable local and/or systemic drug concentration	• Increased availability • Decreased costs • Formulation as dry powder possible	• Causal treatment of diseases without currently approved curative therapy
Exemplary indications	• Pulmonary arterial hypertension	• Respiratory Distress Syndrome	• Cystic fibrosis • Primary ciliary dyskinesia

(*12/2024)

Summary

Phospholipids are endogenous components of the lung tissue. Therefore, they are biodegradable and biocompatible and exhibit an excellent safety profile. Due to their physicochemical properties, they serve as versatile excipients that enable numerous formulation strategies for drugs with diverse properties in different technical application forms.

Phospholipids are compatible with all types of pulmonary administration devices (nebulizer, DPI, MDI). Lipoid provides natural and synthetic phospholipids in cGMP quality at an industrial scale. Because of their unique characteristics, phospholipids are ideal excipients for pulmonary formulations – enabling the formulated drug substance to unfurl its full potential.

Phospholipids are versatile excipients for state-of-the-art pulmonary formulations.

Abbreviations:
COPD: Chronic Obstructive Pulmonary Disease; **DPI:** Dry Powder Inhalter; **DPPC:** 1,2-Dipalmitoyl-*sn*-glycero-3-phosphocholine; **DSPC:** 1,2-Distearoyl-*sn*-glycero-3-phosphocholine; **LNP:** Lipid Nanoparticle; **MDI:** Metered Dose Inhaler; **MPEG-2000-DSPE:** *N*-(Carbonylmethoxypolyethyleneglycol-2000)-1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine; **RDS:** Respiratory Distress Syndrome

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Lipoid GmbH
Frigenstr. 4
67065 Ludwigshafen
GERMANY
Phone: +49 621 5 38 19-0
info@lipoid.com
www.Lipoid.com

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