Lipoid

Phospholipid-Based
Delivery Systems

Phospholipids for Pediatric Dosage Forms

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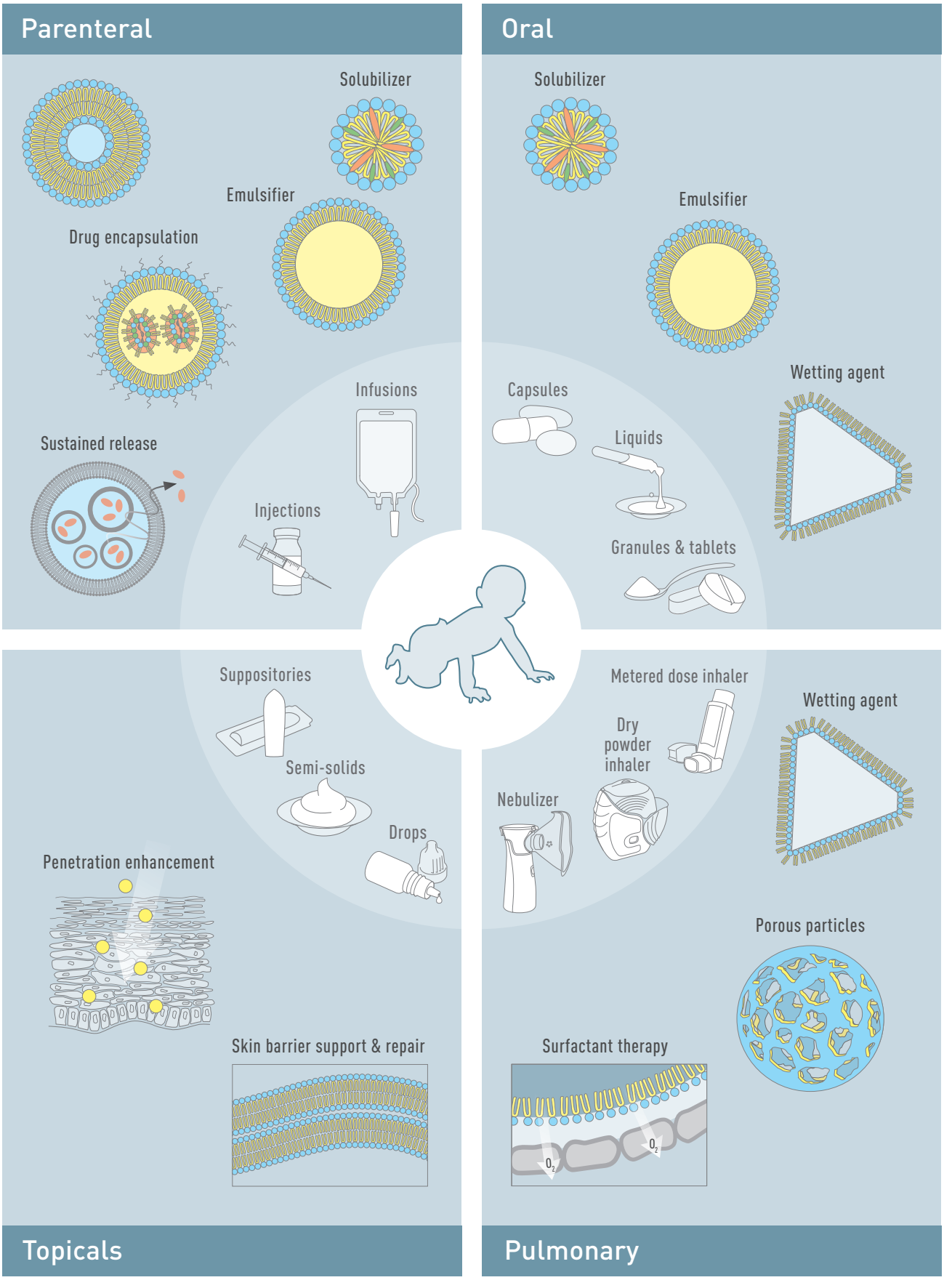

Fig. 1: Schematic presentation of phospholipid-based formulations and their applicability in various age-appropriate dosage forms [6-9].

Phospholipids in Pediatric Formulations

Phospholipids as Safe and Endogenous Compounds

Phospholipids are ubiquitous, endogenous, and nutritional substances. They are among the first nutrients that infants ingest as they are present in breast milk and infant formula [1]. Also for pharmaceutical applications, phospholipids are safe and versatile excipients for any administration route. This is underscored by their long-standing use in several pediatric products and recognition by regulatory authorities.

As endogenous substances, which are also present, e.g., as lung surfactants, phospholipids can serve as actives to treat Respiratory Distress Syndrom (RDS) via the pulmonary route. In addition, phospholipids can form solubilizing colloids such as mixed micelles, liposomes, and emulsions for oral or parenteral administration of lipophilic actives. Moreover, phospholipids are used in topical formulations and vaccines that are suitable for pediatric populations of all age groups.

Excipient Selection for Pediatric Drug Products

Formulating drug products for children poses unique challenges. To address these challenges and prevent insufficient availability of information about pediatric use, the EMA and FDA demand a submission of pediatric drug product strategy in early clinical development stages[2, 3].

Excipients are key components in the formulation of age-appropriate drug products that are suitable for the envisaged administration route, API, and target age group. In addition to functionality and quality, taste and palatability of the dosage form are typical aspects of drug formulation for children [4]. Moreover, particular attention has to be paid to excipient safety when formulating pediatric drug products.[5].

As endogenous compounds with an established regulatory framework, phospholipids perfectly fulfill existing safety and quality requirements. Moreover, they provide versatile functionalities and are comatible with a wide range of age-appropriate dosage forms (Fig. 1).

Key advantages of phospholipids for pediatric dosage forms:

- **Excellent tolerability and safety profile**
- **Established regulatory framework**
- **Essential component of several approved pediatric drug products**
- **Suitable for all administration routes and a wide variety of different formulations**
- **Available in cGMP quality at industrial scale**
- **Pleasant taste**

Marketed Pediatric Products with Phospholipids

Phospholipids have been used for decades as excipients and actives in several pediatric drug products. They are applied in formulations for all age groups, including newborn and even pre-term infants (Table 1).

The use of phospholipids in high-volume dosage forms and in conjunction with highly potent APIs underlines their excellent tolerability and functionality for a wide range of indications.

Table 1: Representative phospholipid-based drug products with approval for pediatric populations

Age group	Product	API	Administration route	Phospholipid(s)	Indication	Company
Pre-term and older	Konakion® MM	Phytomenadion (Vitamin K)	Oral / Intravenous	Soy PC	Prevention and treatment of vitamin K deficiency haemorrhage	Cheplapharm
Pre-term	Survanta®	Polar lipids	Pulmonary	Polar lipids extracted from bovine lung, DPPC	Respiratory Distress Syndrom (RDS)	AbbVie
Birth and older	Intralipid®	Soybean oil	Intravenous	Egg phospholipids	Parenteral nutrition	Fresenius Kabi
Birth and older	Hametum® wound and healing ointment	Hamamelis distillate	Topical	Phospholipids	Skin lesions and inflammations	Dr. Willmar Schwabe
6 weeks+	Mosquirix®	RTS,S	Intramuscular	DOPC	Vaccination against malaria and hepatitis B	GlaxoSmith Kline
1 month+	AmBisome®	Amphotericin B	Intravenous	DSPG, HSPC	Systemic fungal infections	Gilead
6 months+	Betaisodona® Advanced	Povidone iodine	Topical	HSPC	Wound healing	Mundipharma
1+ year	Vyxeos®	Daunorubicin, cytarabine	Intravenous	DSPC, DSPG	Acute myeloid leukemia	Jazz Pharmaceuticals
2+ years	Mepact®	Mifamurtide	Intravenous	POPC, DOPS	Osteosarcoma	Takeda Pharma
6+ years	Exparel®	Bupivacaine	Subcutaneous	DPPG, DEPC	Postsurgical analgesia	Pacira
6+ years	TOBI® Podhaler®	Tobramycin	Pulmonary	DSPC	Cystic fibrosis patients with *Pseudomonas aeruginosa*	Mylan
12+ years	SpikeVax® / Comirnaty®	mRNA	Intramuscular	DSPC	Vaccination against COVID-19	Moderna / BioNTech

Abbreviations:

DEPC: 1,2-Dierucoylphosphatidylcholine, **DOPC:** 1,2-Dioleoylphosphatidylcholine, **DOPS:** 1,2-Dioleoylphosphatidylserine, **DPPC:** 1,2-Dipalmitoylphosphatidylcholine, **DPPG:** 1,2-Dipalmitoylphosphatidylglycerol, **DSPC:** 1,2-Distearoylphosphatidylcholine, **DSPG:** 1,2-Distearoylphosphatidylglycerol, **HSPC:** Hydrogenated soybean phosphatidylcholine, **PC:** Phosphatidylcholine, **POPC:** 1-Palmitoyl-2-oleoylphosphatidylcholine

Innovative Oral Dosage Forms

The specific challenges of oral administration are tackled by innovative pediatric dosage forms. Phospholipids offer several benefits for these approaches: They can form potent solubilizing formulations, serve as wetting agents, and enhance processability, e.g., of melts during extrusion.

Mixed micelles and self-emulsifying systems can be formulated in liquid and solid dosage forms and provide a viable alternative to unfavorable solvents such as propylene glycol. As wetting agents, phospholipids can be used in the formulation of micronized particles. These particles can be converted into suspensions and minitablets [10]. In addition, phospholipids can be applied as sole or complementary excipients in amorphous solid dispersions, e.g., to formulate easily dosable pellets [11, 12]. Moreover, compatibility with technologies such as extrusion makes phospholipids an attractive choice for 3D printing [13]. Increased wettability and solubilization of drugs provide added value for this approach.

Concluding Remarks

Regulatory authorities require consideration of pediatric dosage forms early in the product development. The unique needs of children in terms of safety and efficacy must therefore be taken into account when selecting excipients. Because of their excellent safety profile, multifunctionality, and compatibility with a wide variety of dosage forms, phospholipids are ideally suited for this purpose. They allow simultaneous development of pediatric and adult formulations. Various organizations have confirmed the safety of lecithin and phospholipids from a regulatory perspective including their suitability for pediatric formulations (Table 2).

Lipoid provides phospholipids in cGMP quality from small to large scale to support your product development from pre-clinical to clinical and commercial stages.

Table 2: Safety of lecithin and phospholipids from a regulatory perspective

Agency/organization	Outcome
WHO / JECFA	Acceptable daily intake (ADI) not limited [14]
EFSA	No need for numerical ADI [15]
FDA	Lecithin is generally recognized as safe (GRAS) for oral uptake [16]
Inactive Ingredient Database	Several entries for lecithin and phospholipids showcase their extensive use in approved drug products
STEP Database (Safety and Toxicity of Excipients for Pediatrics)	Egg yolk lecithin, soybean lecithin, and hydrogenated phospholipids are recognized as safe for pediatric use

Phospholipids are safe and clinically proven compounds for all pediatric age groups.

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