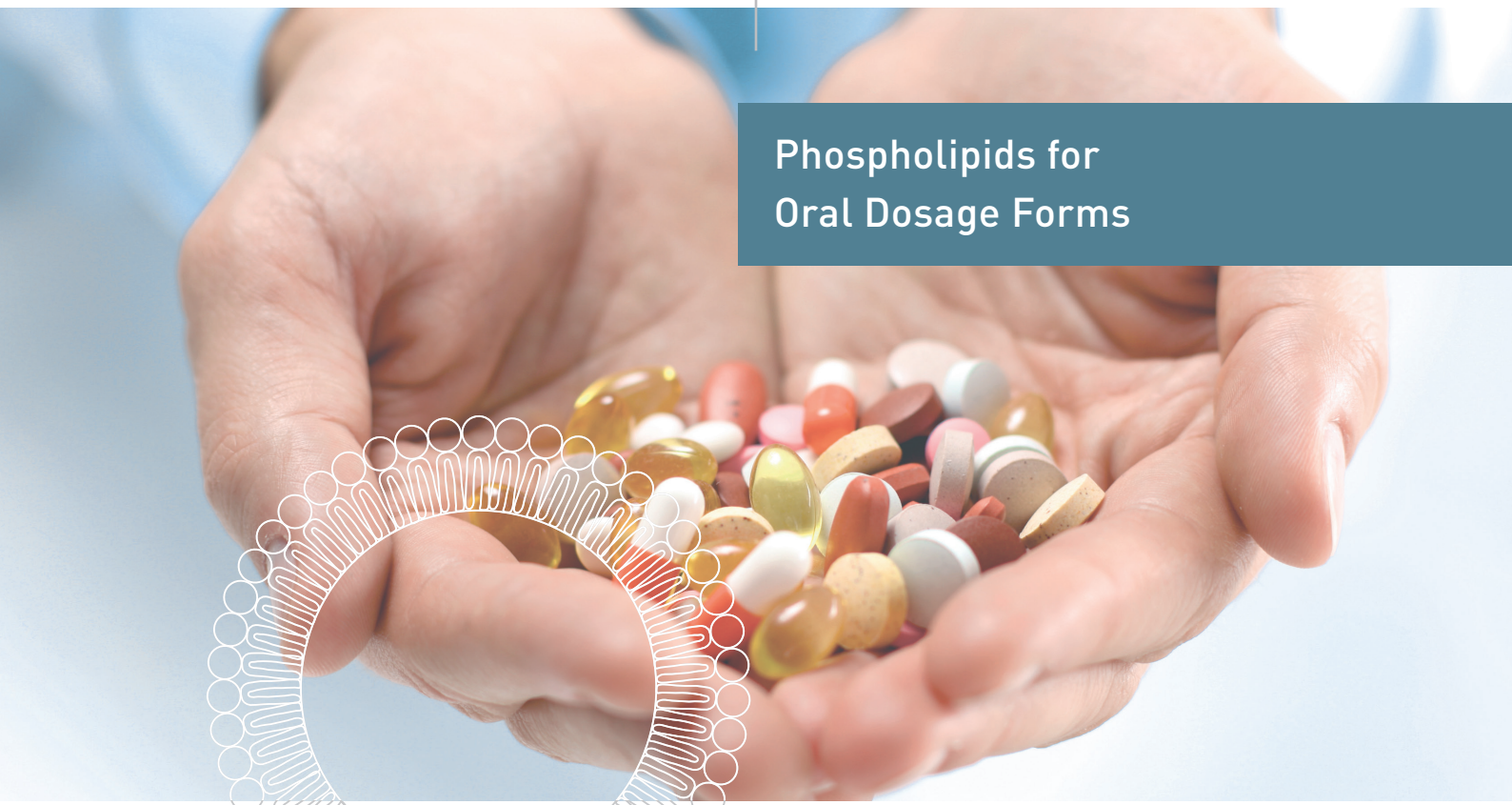
Lipoid

Phospholipid-Based
Delivery Systems



Phospholipids for Oral Dosage Forms

We Invest in Quality.

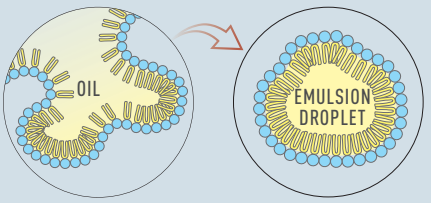
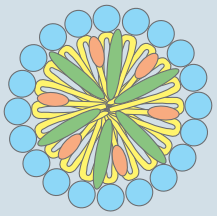
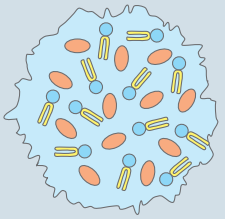
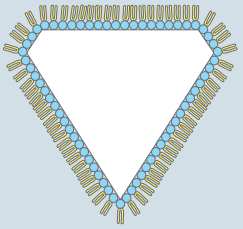
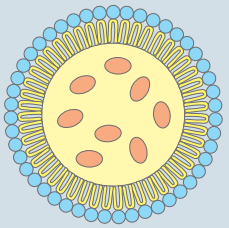
DELIVERY CONCEPT	SUITABLE TECHNOLOGIES/ DOSAGE FORM	RECOMMENDED TYPES OF PHOSPHOLIPIDS			
		Natural	Hydrogenated	Monoacyl	Liquid Formulations
A. SELF-EMULSIFYING SYSTEMS 	• Liquid dosage forms • Soft gel capsules	✓	✓	✓	✓
B. (MIXED) MICELLES 	• Liquid dosage forms • Spray drying • Fluid bed drying	✓	✓	✓	
C. SOLID DISPERSIONS 	• Hot melt extrusion • Spray drying • Fluid bed drying	✓	✓	✓	
D. SUSPENSIONS 	• Micronization and nanosizing	✓	✓	✓	
E. EMULSIONS 	• Liquid dosage forms	✓	✓	✓	✓

Fig. 1: Examples of phospholipid-based oral formulation strategies.

Phospholipids for Oral Dosage Forms

Poor solubility, slow dissolution rate, gastrointestinal degradation, and low permeability are typical factors that limit oral bioavailability of drugs. Fortunately, these limitations can be effectively overcome by use of advanced phospholipid-based formulations.

Phospholipids are diversely used as excipients in such formulations, e.g., as dispersing agents, emulsifiers, or as additional or sole matrix components for solid dispersions (Fig. 1). Although liposomes are not stable in the gastrointestinal tract, they may also be used in solubilising formulations as a source of phospholipids.

Moreover, phospholipids are applied as technical excipients in tablet coatings or as processing aids to produce soft gel capsules.

Role of Phospholipids During Digestion

Phospholipids play a vital role in digestion and absorption of lipophilic food components and drug substances. Upon reaching the gastrointestinal tract, fatty food triggers the release of bile, comprising bile salts and phospholipids, into the small intestine. These endogenous compounds, together with ingested phospholipids and their degradation products, form solubilizing colloids that mediate absorption of lipophilic nutrients and drugs (Fig. 2).

Phospholipid-based formulations enhance drug absorption in a natural way by imitating endogenous solubilizing colloids or stimulating the physiological digestion process [1,2]. Depending on the formulation approach, phospholipids further contribute to oral absorption, e.g., by presenting the drug in a solubilized or rapidly soluble micronized or amorphous form.

Harnessing these endogenous mechanisms with the aid of phospholipids offers an attractive option for effective and safe oral administration for a wide range of active ingredients.

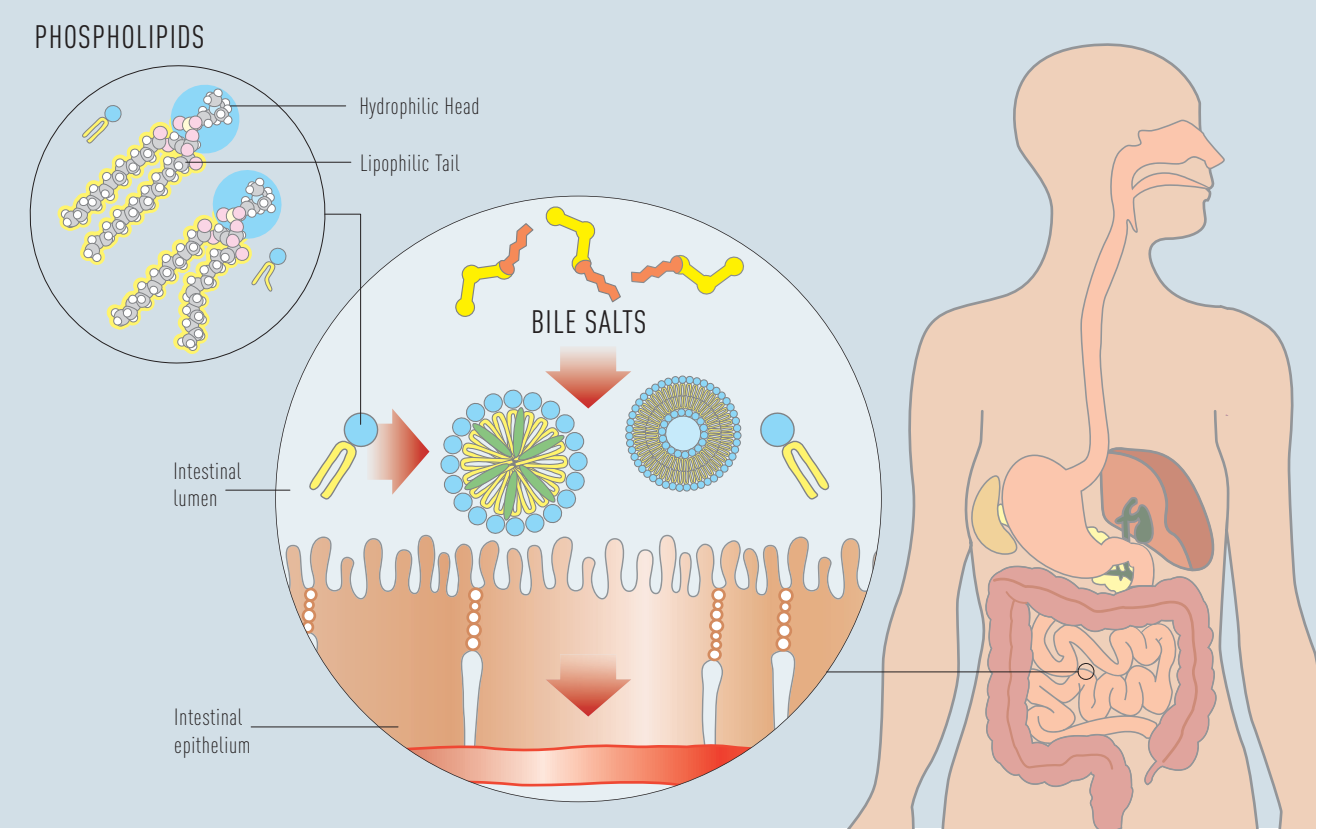


Fig. 2: Endogenous phospholipids are secreted with bile and contribute to solubilization and absorption of drugs and nutrients from the gastrointestinal tract.

Phospholipid-based Oral Formulations

Phospholipids are essential components of formulations used in many marketed products. Moreover, they can be introduced as complementary or alternative excipients to enhance the performance of established formulations. Explorative phospholipid-based technologies are being extensively investigated in industrial and academic research and may open new functionalities. In addition to their versatile use as excipients, phospholipids restore the natural lining of the gastric mucosa. Local disruption of the gastric mucosa by non-steroidal anti-inflammatory drugs can thus be mitigated and mucosal irritation effectively reduced [3,4].

Self-Emulsifying Systems

Self-emulsifying systems (often referred to as SEDDS) are water-free formulations that spontaneously form emulsions in aqueous media, including gastrointestinal fluids. They are used predominantly for solubilization of lipophilic drugs to increase their bioavailability. In formulations for oral ingestion (Rapamune®, Deximune™), self-emulsifying systems are typically applied as oily liquid or in form of a soft gel capsule. The preconcentrate can be administered in its water-free form, but may also be diluted in an appropriate beverage before administration [5].

Lipoid offers several different self-emulsifying systems with its PHOSAL® product line in cGMP quality at industrial scale. These ready-to-use products are ideally suited for a fast track development from preclinical and clinical development stages to a marketed product without a need to change the formulation.

Mixed Micelles

In the gastrointestinal tract, mixed micelles composed of endogenous phospholipids and bile salts solubilize lipophilic nutrients to make them available for absorption. Pharmaceutically applied mixed micellar formulations consist of soybean phosphatidylcholine and therefore offer a natural vehicle for lipophilic drugs such as Vitamin K (Konakion® MM).

In addition, substitution of bile salts with monoacyl phospholipids may enable the manufacture of fully plant-based micelles e.g. from soybean.

Solid Dispersions

Solid dispersions are widely employed to enhance the dissolution of poorly soluble crystalline drugs by amorphization of the drug substance. Phospholipids are investigated as complementary or sole matrix material for this purpose. In addition to amorphization, phospholipids contribute to drug solubilization by enhancing wettability, forming colloidal stuctures upon hydration and stimulating the secretion of bile [6,7,8].

Cochleates

Cochleates consist of phospholipid-cation complexes, typically between phosphatidylserine and calcium. Cochleates can accommodate a wide array of drugs, including water-soluble and water-insoluble ones. The tightly packed bilayers protect the cargo from degradation and increase its absorption [9]. Cochleates are currently being investigated in clinical trials for oral administration of amphotericin B [10].

Table 1: Marketed products with phospholipid-based formulations for oral administration

API	Product	Indication	Phospholipids	Formulation Strategy	Dosage Form	Company
Sirolimus	Rapamune®	Immunosuppressant	PHOSAL® 50 PG	Emulsion	Liquid	Pfizer
Phytomenadion (Vitamin K1)	Konakion® MM	Hemostatic agent, prevention of vitamin K deficiency bleeding	Soy phosphatidylcholine	Mixed micelle	Liquid	Cheplapharm
Ciclosporin	Deximune™	Immunosuppressant	Soy phospholipids	Self-emulsifying system	Soft gel capsules	Dexcel Pharma

Further Applications

Industrial and academic research continuously leads to new phospholipid-based formulations for oral administration.

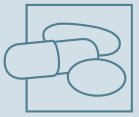
Application as wetting agents in suspensions and for micronized drug crystals [11] and as former of sustained release matrices for hydrophilic drugs [12] are further formulation options with phospholipids.

Concluding Remarks

Phospholipids are multifunctional excipients with versatile applications in oral formulations. Their physiological role in digestion and absorption processes underscores their biocompatibility, functionality, and safety. Lipoid offers phospholipids and phospholipid-based formulations in cGMP quality at industrial scale. The broad range of phospholipids covered by Lipoid's product portfolio enables the formulation of various oral dosage forms for lipophilic, amphiphilic, and hydrophilic drugs.

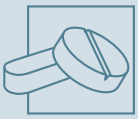
Solid dosage forms

Several options are available to produce phospholipid-based formulations as solid dosage forms:



- Liquid formulations are suitable as filling materials for hard and soft gelatin capsules.

- Unsaturated phospholipids, as well as formulations such as mixed micelles, can be converted into free-flowing powders.



- Hydrogenated phospholipids and phospholipid blends with powder-flow properties can be processed into tablets.

SAFE ✓ **VERSATILE ✓** **cGMP ✓**

Key advantages of phospholipids in oral formulations:

- Diverse formulation strategies (e.g., solubilizing formulations, amorphization)
- Suitable for liquid and solid dosage forms
- Suitable for lipophilic, amphiphilic, and hydrophilic drugs
- GRAS status
- Well-tolerated, endogenously present compounds
- Pleasant taste in comparison to other surfactants
- Available at industrial scale

Lipoid offers a wide range of phospholipids and phospholipid-based formulations with strong technical and regulatory support.

References *(Additional references upon request)*

[1] van Hoogevest, P., Review–an update on the use of oral phospholipid excipients. *European Journal of Pharmaceutical Sciences* 108, 1 – 12 (2017).
[2] Iqbal, J., Hussain, M. M., Intestinal lipid absorption. *American Journal of Physiology-Endocrinology and Metabolism* 296, E1183 – E1194 (2009).
[3] Lichtenberger, L. M., Development of the PC-NSAID technology: from contact angle to Vazalore®. *Drug Discovery Today* 103411 (2022).
[4] Leyck, S., Dereu, N., *et al.,* Improvement of the gastric tolerance of non-steroidal anti-inflammatory drugs by polyene phosphatidylcholine (Phospholipon® 100). *European Journal of Pharmacology* 117, 35 – 42 (1985).
[5] van Hoogevest, P., Non-aqueous phospholipid concentrates for increasing the bioavailability of poorly soluble compounds. *European Journal of Lipid Science and Technology* 122, 1900411 (2020).
[6] Fong, S. Y. K., Brandl, M., *et al.,* Phospholipid-based solid drug formulations for oral bioavailability enhancement: A meta-analysis. *European Journal of Pharmaceutical Sciences* 80, 89 – 110 (2015).
[7] Gautschi, N., Van Hoogevest, P., *et al.*, Molecular insights into the formation of drug-monoacyl phosphatidylcholine solid dispersions for oral delivery. *European Journal of Pharmaceutical Sciences* 108, 93 – 100 (2017).
[8] Czajkowski M., Jacobsen AC., *et al*., Hydrogenated phospholipid, a promising excipient in amorphous solid dispersions of fenofibrate for oral delivery: Preparation and in-vitro biopharmaceutical characterization. *International Journal of Pharmaceutics* (2023).
[9] Syed, U. M., Woo, A. F., *et al.*, Cochleates bridged by drug molecules. *International Journal of Pharmaceutics* 363, 118 – 125 (2008).
[10] Atukunda, M., Kagimu, E., *et al.*, Oral encochleated amphotericin B for cryptococcal meningitis: a phase II randomized trial, *Open Forum Infectious Diseases* 9 (2022).
[11] Mishra, A. K., Vachon, M. G., *et al.* IDD Technology: Oral Delivery of Water-Insoluble Drugs Using Phospholipid Stabilized Microparticulate IDD Formulations. *Modified Release Drug Delivery Technology*, 151-175 (2002).
[12] Kolbina, M., Bodmeier, R., et al. Saturated phosphatidylcholine as matrix former for oral extended release dosage forms. *European Journal of Pharmaceutical Sciences* 108, 86-92 (2017).

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