



Topical Applications

Natural Phospholipids

Formulate Dermal Pharmaceutical
Products with Phospholipids



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Phospholipids in Dermal Applications

Phospholipids are the excipients of choice in dermal formulations to modulate the interaction of active pharmaceutical ingredients (APIs) with the skin.

Phospholipids have unique multifunctional properties. They are natural components of every human cell. Therefore they are highly biocompatible and well tolerated – even by sensitive skin. The external application of phospholipids makes it possible to influence the degree of skin interaction: On using natural unsaturated phospholipids fluidization of the stratum corneum allows the penetration of APIs into deeper skin layers, while use of saturated (hydrogenated) phospholipids will restore/improve the barrier function of the skin in order to keep APIs in place longer^[1].

In addition, they can replace missing or attenuated substances in the stressed skin (e.g. linoleic acid) via intrinsic metabolic pathways in the skin.

Besides their use as penetration enhancer or retention time prolonger, phospholipids can also act as emulsifiers, natural moisturizers, texturizers or emollients, highlighting their role as multifunctional excipients contributing multiple benefits to dermal formulations^[2].

Two classes of phospholipids (saturated phospholipids and unsaturated phospholipids) and three classes of phospholipid-based delivery systems (liposomes, emulsions, and lamellar structures) are commonly used in dermal pharmaceutical products.

Saturated (hydrogenated) phospholipids have a phase transition temperature above the skin temperature and therefore form rigid structures that enhance the skin retention time of actives, while natural unsaturated phospholipids have a phase transition temperature

below the skin temperature, enabling the formation of more flexible carrier systems with increased skin interaction, resulting in deeper tissue penetration of active ingredients^[3].

In addition to being used to functionally improve dermal drug products, phospholipids can also be considered to make pharmaceutical form line extensions, by replacing other functional excipients^[4,5,6].

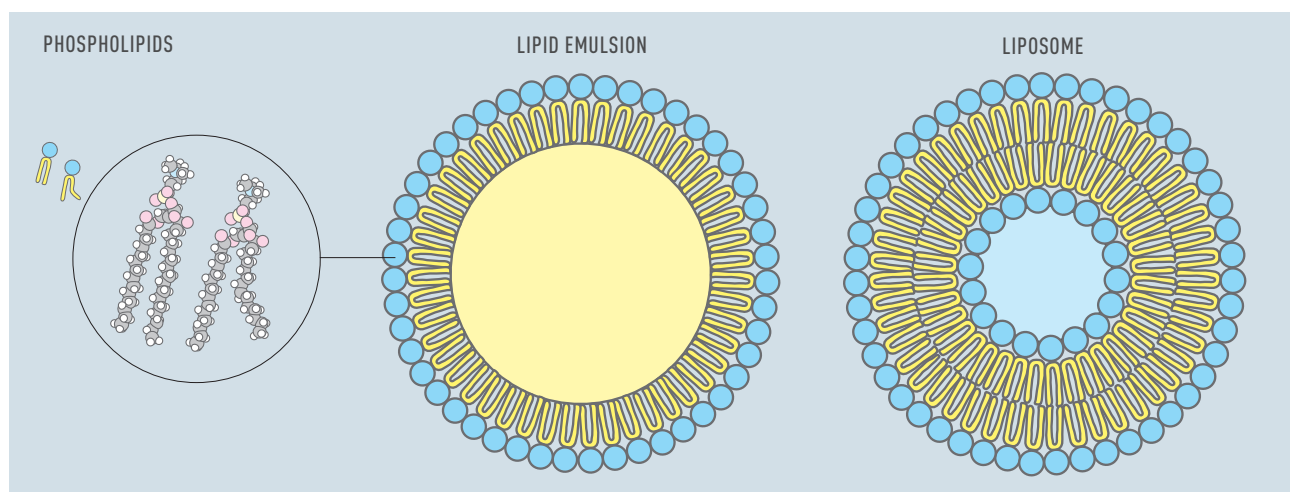
Properties of phospholipids in dermal formulations

- Natural non-toxic emulsifiers
- Formation of liposomes
- Solubilization of lipophilic APIs
- Unsaturated phospholipids:
 - Deeper skin penetration of active ingredients
- Hydrogenated phospholipids:
 - Enhanced skin retention time of actives
 - Improvement of texture and better skin feel

Further positive effects

- Outstanding moisturizers
- Promoting the healing process
- Integration into damaged cell membranes (cell repair)
- Reduction of trans-epidermal water loss

The utilization of phospholipids in preparation of typical dermatological formulations is described in generic flow diagrams on pages 4 and 5.



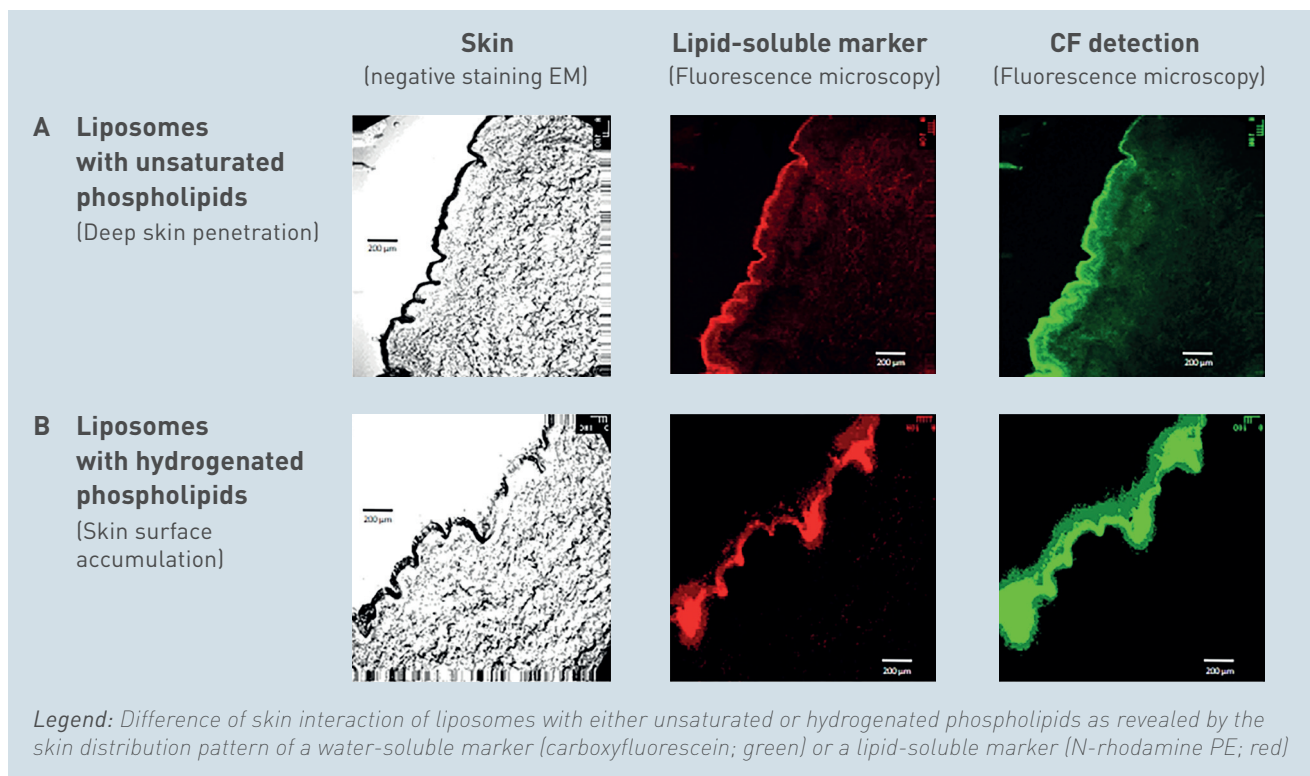


Fig. 1 shows that the liposomes comprising saturated phospholipids were located more at the surface of the stratum corneum, whereas liposomes comprising unsaturated phospholipids resulted in a localization of both markers in deeper layers of the studied skin fragments; This underscores the suitability of saturated phospholipids for maintaining/restoring the skin barrier and the use of unsaturated phospholipids as skin penetration enhancers^[7].

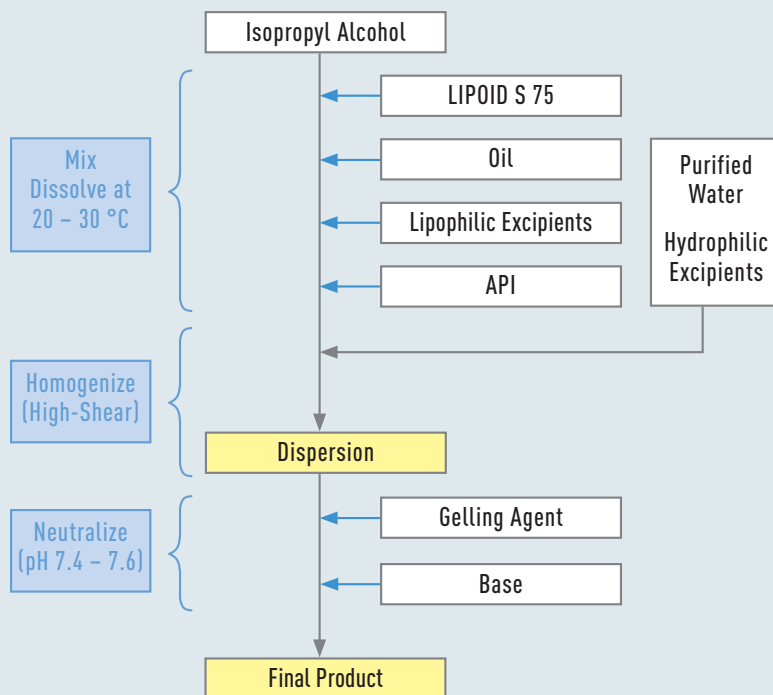
The following Table shows details of representative dermal products with phospholipids as key excipients.

Table 1: Marketed topical applications with phospholipids

Product	API/Active Principle	Excipient	Indication	Company
Bepanthen® Spray	Dexpanthenol	Soybean PC	Sunburn	Bayer AG
Diclo-ratiopharm®	Diclofenac-Na	Soybean PC	Pain, inflammation	Ratiopharm GmbH
Skinoren® / Finacea®	Azelaic acid	Soybean PC	Acne	Bayer AG
Repithel®	PVP iodine	Hydrogenated soybean PC	Wound treatment	Mundipharma GmbH
Elocon®	Mometasone furoate	Hydrogenated soybean PC	Skin inflammation	MSD Sharp & Dohme GmbH
FlexiSeq™	Soybean PC	Soybean PC	Reumatic	Pro Bono Bio Int. Trading Ltd.
Morr-F™	Minoxidil + finasteride	Soybean PC	Hair loss	Intas Pharmaceuticals Ltd.
Physiogel®	Hydrogenated soybean PC	Hydrogenated soybean PC	Dry skin, atopic skin	Klinge Pharma GmbH
Ceramax™	Ceramides, palmitic acid, cholesterol	Hydrogenated soybean PC	Various forms of dermatitis	SONOMA Pharmaceuticals Inc.
LMX 4®/ LMX 5®	Lidocaine	Hydrogenated soy lecithin	Anesthetic (local)	Ferndale Pharma Group, Inc.
Hametum®	Hamamelis extract	Soybean PC	Wound healing	Dr. Willmar Schwabe GmbH & Co. KG
Skin Disinfection Spray	Ethanol	Soybean PC	Disinfection	Aurena Laboratories AB

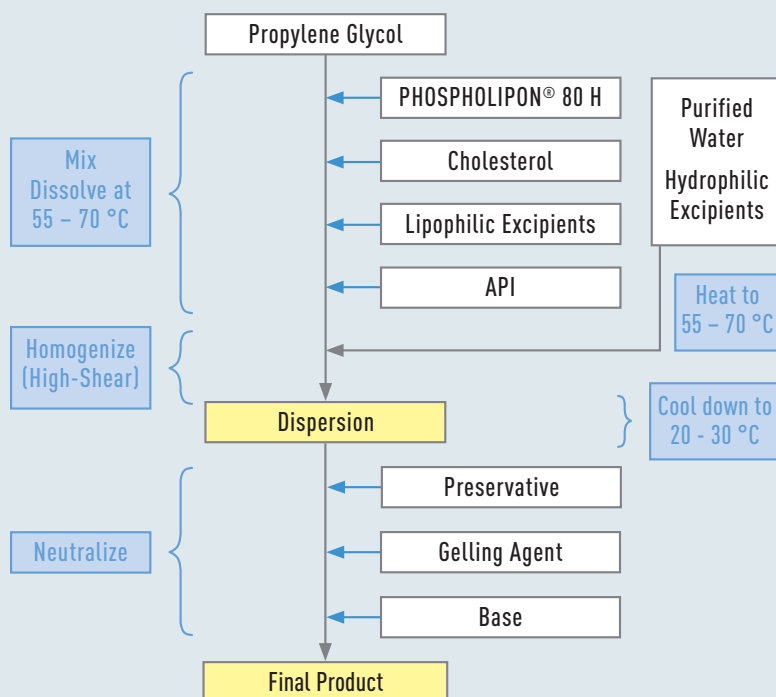
Dermal Formulations – Generic Flow Diagrams

Liposomal Cream with Unsaturated Phospholipids



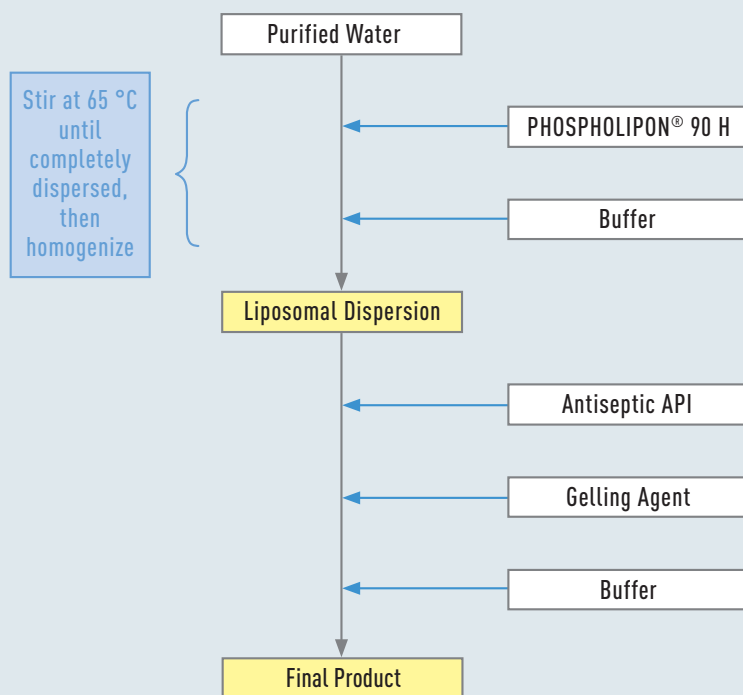
- Light yellow emulsion gel (base formulation)
- Role of phospholipids: the phospholipids act as penetration enhancers and effect a deeper penetration of active ingredients. They also function as co-emulsifiers in the formulation.
- Addition of phospholipids provides a pleasant skin feel and the formulation is rapidly absorbed.
- Typical range of phospholipid concentration: 5 - 10 %
- Phospholipid processing: LIPOID S 75 is an unsaturated phospholipid. Therefore it can be dissolved in alcohols at ambient temperature.
- Suitable actives, e.g.: Diclofenac, Ibuprofen, Ketoprofen

Liposomal Gel with Hydrogenated Phospholipids



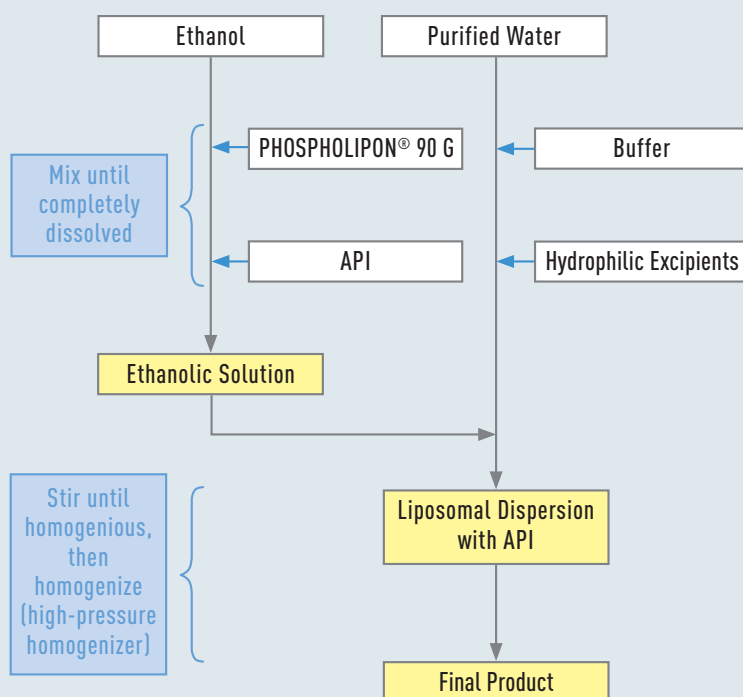
- Whitish to yellowish gel
- Role of phospholipids: hydrogenated phospholipids form liposomes in the formulation. Phospholipids strengthen the skin barrier, and the liposomes support the accumulation of active ingredients in the upper skin layers.
- Addition of phospholipids also provides a pleasant skin feel and the formulation is rapidly absorbed.
- As hydrogenated phospholipids PHOSPHOLIPON® 80 H or PHOSPHOLIPON® 90 H can be used. Typical range of phospholipid concentration: 2.5 - 15 %
- Phospholipid processing: hydrogenated phospholipids need elevated temperatures to dissolve in alcohols or glycols.
- Dissolving the hydrogenated phospholipids together with cholesterol helps the formation of homogeneous liposomes after mixing with the water phase.
- Suitable actives, e.g.: Lidocaine, Tetracaine

Solvent-free Gel Formulation with Hydrogenated Phospholipids



- Whitish gel
- Role of phospholipids: Phospholipids are known to strengthen the skin barrier. Liposomes, formed by the phospholipids, can support and prolong the effects of antiseptics by optimizing their interaction with the affected skin. Liposomes also provide moisture to the skin, thereby supporting wound healing.
- As hydrogenated phospholipids PHOSPHOLIPON® 80 H or PHOSPHOLIPON® 90 H can be used.
- Typical range of phospholipid concentration: 1 - 5 %
- Phospholipid processing: hydrogenated phospholipids are dispersed in water at elevated temperatures above their phase transition temperature of about 55 °C.
- Suitable actives, e.g.: PVP-iodine, Polyhexanide, Octenidine

Spray Formulation with Unsaturated Phospholipids



- Yellow, transparent liquid
- Role of phospholipids: phospholipids effect a good adhesion of the actives to the skin and a penetration enhancement of the active ingredients.
- Typical range of phospholipid concentration: 2.5 - 10 %
- Phospholipid processing: LIPOID S 75 is an unsaturated phospholipid. Therefore it can be dissolved in alcohols at ambient temperature.
- Other alcohols (2-propanol, propylene glycol) or mixtures thereof can be used instead of ethanol.
- Suitable actives, e.g.: Diclofenac, Ketoprofen

References *(Additional references upon request)*

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- [7] Fig. 1 A: A. Fahr *et al.*, Skin penetration enhancement of substances by a novel type of liposomes, *SOFW Journal* 126, 48 – 53 [2000].



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