The use of natural phospholipids as pharmaceutical excipients

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Phospholipids are used in many types of formulations, such as fat emulsions, mixed micelles, suspensions, and liposomal preparations for any administration route [1-3]. Phospholipids are surface-active comprising a polar headgroup and a lipophilic tail. They are used as emulsifier, wetting agent, solubilizer, and liposome former. The phospholipid molecule comprises a glycerol backbone esterified in positions 1 and 2 with fatty acids and in position 3 with phosphate, the latter being further esterified with an alcohol. The most common phospholipid is phosphatidylcholine (PC), and PC is the main component of lecithin as described in the United States Pharmacopoeia (USP). Phospholipids play, e.g., a role in cell membranes, have digestion/metabolic functions [4] as lipoprotein component, and as source for acetylcholine (in case of PC) and of (essential) fatty acids and energy [5].

Natural phospholipids are phospholipids isolated from natural sources such as soybean, rape- and sunflower-seed and animal material, like egg yolk, milk, or krill. These raw materials are world-wide produced at very large scale. The phospholipid compositions of the lecithins are dependent on the raw material sources. In all cases, PC is the main phospholipid component. Higher quality pharmaceutical grade phospholipids are obtained, with an excellent inter-batch reproducibility, by validated extraction and chromatography procedures using non-toxic solvent (Fig 1).

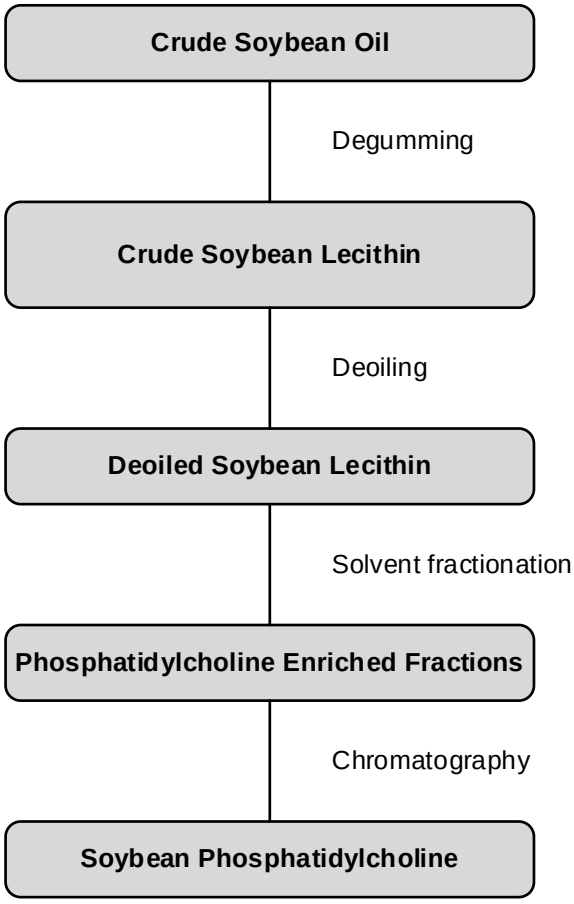

Figure 1. Flow chart of the isolation process steps of soybean phosphatidylcholine from crude soybean oil.

Control on the quality of the raw material and use of validated purification method guarantees the quality of the phospholipid excipients. Egg phospholipids, isolated from hen egg yolk with similar methods as for soybean lecithin, play an important role as excipient as well.

The natural phospholipids can be further modified to saturated phospholipids by hydrogenation [6] and use of enzymes to make from soy PC, e.g., soy phosphatidylethanolamine (PE) and soy phosphatidylglycerol (PG), respectively (Fig. 2). Besides natural phospholipids, synthetic phospholipids are also being used in pharmaceutical products.

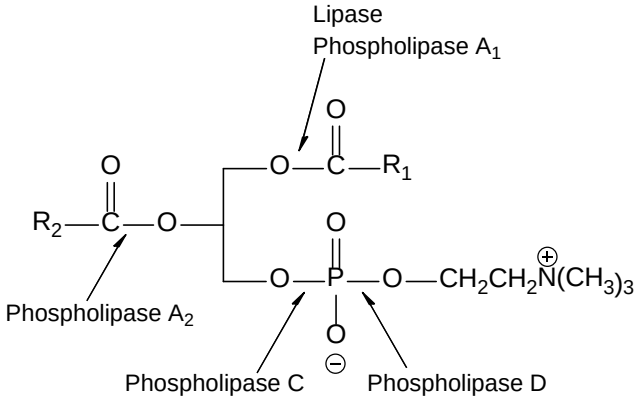

Figure 2. Enzymatic conversion possibilities of phosphatidylcholine [7].

In pharmaceutical products for oral and dermal administration, mainly soybean phospholipids are used. For dermal use also hydrogenated soybean phospholipids are applied. In parenteral products, natural phospholipids are prevalent, besides synthetic phospholipids, as described in the Inactive Ingredient (excipient) list of the US FDA (Table 1) [8].

Table 1. Examples of parenteral liposome products for human use containing natural phospholipids (in bold).

Drug Substance	**Product**	**Main lipid excipients**	**Admin. Route**	**Indication**
Therapeutic products				
Amphotericin B	AmBisome®)[1]	**HSPC**)[3] : DSPG)[4] : Cholesterol	i.v.	Aspergillus, Candida- and/or Cryptococcus species infections, Visceral leishmaniasis
Doxorubicin hydrochloride	Doxil®)[1]/ Caelyx®)[1]	**HSPC** : Cholesterol : MPEG 2000-DSPE)[5]	i.v.	AIDS-related Kaposi's sarcoma, Metastatic ovarian cancer, Multiple myeloma
	Lipodox®)[1]			AIDS-related Kaposi's sarcoma, Metastatic ovarian cancer, Metastatic breast cancer
	Myocet®)[2]	**Egg PC** : Cholesterol	i.v.	Metastatic breast cancer
Vincristine sulphate	Marqibo®)[1]	**SM**)[6]: Cholesterol	i.v.	Philadelphia chromosome-negative, acute lymphoblastic leukemia

)[1] See www.rxlist.com for detailed information;)[2] for details see [9];)[3] Hydrogenated soybean phosphatidylcholine;)[4] 1,2-distearoyl-*sn*-glycero-3-phosphoglycerol;)[5] *N*-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-phosphoethanolamine sodium salt;)[6] sphingomyelin.

Egg phospholipids serve as emulsifier in emulsions for parenteral nutrition (e.g. Intralipid®) [10]. These emulsions can also be used as carrier for oil soluble drug substances such as diazepam (Diazemuls®) and propofol (Diprivan®) [11, 12].

Parenteral mixed micellar formulations, comprising soybean phospholipids and cholate salts, are either suitable as solubilizer for poorly water-soluble compounds such as vitamin K or the

soybean phospholipid is intended as active pharmaceutical ingredient (API) for treatment of liver disorders [13]. These products underscore the safe intravenous use of soybean lecithin [14].

Considering the products comprising phospholipids for pulmonary administration, natural as well as synthetic phospholipids are being applied. The natural phospholipids are from bovine or calf-lung extracts intended for treatment Respiratory Distress Syndrome, a disease in infants characterized by an immature lung epithelium [15]. The inhalation product for systemic treatment with levodopa, Inbrija® comprises 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC).

Natural phospholipids are well known to regulatory authorities and described in many pharmacopoeias [16]. Regarding the toxicity of phospholipids, the World Health Organisation, US FDA, and EU place no limit on the oral intake of lecithin as a food additive [17-19]. The safe intravenous use of soybean and egg phospholipids is well documented [20].

In conclusion, natural phospholipids are derived from renewable sources and produced with ecologically friendly processes and are available in large scale at relatively low costs. They comply with all requirements of the regulatory authorities and are safe for any administration route. For parenteral application, egg-, soybean-, and hydrogenated soybean phospholipids are used, besides synthetic phospholipids. In oral administration soybean phospholipids prevail, whereas for topical administration to the skin, soybean phospholipids and their hydrogenated versions are popular. Inhalation products contain natural phospholipid extracts and synthetic phospholipids. For more information on the pharmaceutical use of natural and synthetic phospholipids reference is made to van Hoogevest, P and Wendel, A: "The use of natural and synthetic phospholipids as pharmaceutical excipients" [16].

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