



Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: [www.elsevier.com/locate/ejps](http://www.elsevier.com/locate/ejps)

## Review – An update on the use of oral phospholipid excipients

Peter van Hoogevest<sup>1</sup>

Phospholipid Research Center, Im Neuenheimer Feld 515, D-69120 Heidelberg, Germany

### ARTICLE INFO

#### Keywords:

Phospholipids  
Oral  
Solid dispersions  
Mixed micelles  
Emulsions  
Absorption  
Conversion to solids

### ABSTRACT

The knowledge and experiences obtained with oral phospholipid excipients is increasing continuously. Nevertheless the present number of oral products using these excipients as essential excipient is very limited. This is remarkable to note, since phospholipids play a significant role in the food uptake mechanisms of the GI tract and these mechanisms could be translated into suitable dosage forms and corresponding drug delivery strategies. In addition, phospholipid excipients are multifunctional biodegradable, non-toxic excipients, which can be used in oral dosage forms as wetting agents, emulsifier, solubilizer and matrix forming excipients. Especially natural phospholipid excipients, made from renewable sources, may be considered as environmentally friendly excipients and as a viable alternative to synthetic phospholipid and non-phospholipid analogues. This review describes 1) essential physico-chemical properties of oral phospholipid excipients 2) the fate of orally administered phospholipids with respect to absorption and metabolism in the GI tract 3) the main dosage forms used for oral administration containing phospholipids. These elements are critically assessed and areas of future research of interest for the use of oral phospholipid excipients are summarized.

### 1. Introduction

This Special Issue of the European Journal of Pharmaceutical Sciences gives an update on the present and future oral use of phospholipid excipients. It was decided to make such an issue to compensate for the relatively low number of publications and pharmaceutical products related to oral phospholipid excipients.

This situation is remarkable to note, since it is well known that phospholipids are multifunctional excipients which can be technologically used as solubilizer, wetting agent, emulsifier and as building component of colloidal particles like liposomes, mixed micelles etc. In addition, phospholipids play an important physiological role in the digestion and food (and drug) absorption process in the gastro intestinal tract as essential component of bile. Also their general role as membrane component of any cell membrane points to an absence of local and systemic toxicity after oral administration. Indeed lecithin as the main representative of oral phospholipid excipients has the GRAS status at the US FDA (U.S. Food and Drug Administration, 2013). The same is true for hydrogenated lecithin (U.S. Food and Drug Administration, 2014) and for enzyme modified lecithin (U.S. Food and Drug

Administration, 2016), which is also called monoacyl-lecithin.

The above mentioned technical use in oral dosage forms requires an understanding of the molecular structure and knowledge of the physicochemical properties of phospholipids and the several classes of phospholipids being used or being considered for oral dosage forms.

This review briefly reviews the pharmaceutically relevant properties of phospholipids and comments the present knowledge of the oral use of phospholipids and their prospects in conjunction with the publications presented in this Special Issue.

In this review, the following nomenclature, in accordance to international pharmacopeias, describing the several commercially available natural lecithins/phospholipid excipient products, differing in phosphatidylcholine content, is being used and recommended. Lecithin is a complex mixture of acetone insoluble phosphatides (i.e. phospholipids), which consist chiefly of phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol and phosphatidic acid, present in conjunction with various amounts of other substances such as triglycerides, fatty acids, and carbohydrates, as separated from the crude vegetable oil source (United States Pharmacopeial Convention, 2014). The term “lecithin” is used when the product contains less than 80% by weight

**Abbreviations:** AUC, Area under the curve; BCS, Biopharmaceutical classification system; BSE, Bovine spongiform encephalopathy; CCK, Cholecystokinin; CFR, Code of Federal Regulations; CVD, Cardiovascular disease; DMSO, Dimethylsulfoxide; DOPE, 1, 2-dioleoyl-sn-glycero-3-phosphoethanolamine; GI, Gastrointestinal; GPC, Glycerophosphocholine; GRAS, Generally recognized as safe; HLB, Hydrophilic-lipophilic-balance; m.t., more than; NDA, New drug application; n.l.t, not less than; NSAID, Non-steroidal anti-inflammatory drug; OTC, Over the counter; PA, Phosphatidic acid; PC, Phosphatidylcholine; PE, Phosphatidylethanolamine; PG, Phosphatidylglycerol; P-gp, P-glycoprotein; PI, Phosphatidylinositol; POPC, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; POV, Peroxide value; SEDDS, Self-emulsifying drug delivery systems; TMA, Trimethylamine; TMAO, Trimethylamine-N-oxide; TSE, Transmissible spongiform encephalopathies

E-mail address: [pvanhoogevest@phospholipid-institute.com](mailto:pvanhoogevest@phospholipid-institute.com).

<sup>1</sup> [www.phospholipid-institute.com](http://www.phospholipid-institute.com)

<http://dx.doi.org/10.1016/j.ejps.2017.07.008>

Received 17 March 2017; Received in revised form 30 June 2017; Accepted 7 July 2017

0928-0987/ © 2017 The Author. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

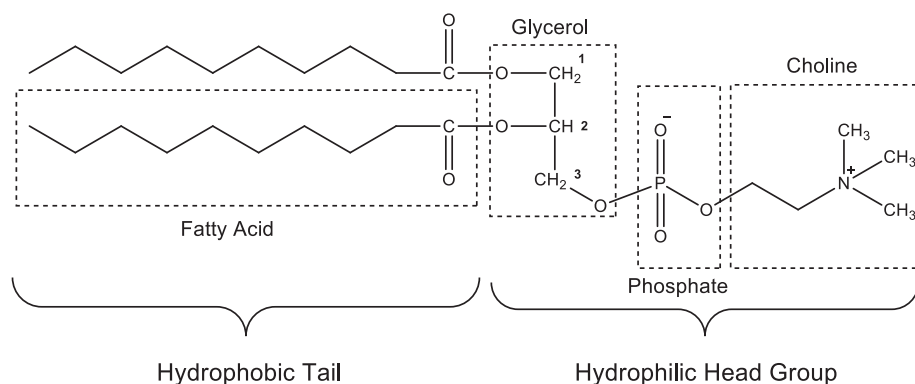


Fig. 1. Molecular structure of a typical phospholipid, phosphatidylcholine.

total phospholipids; the term “phospholipids” is used when the product contains 80–100% by weight phospholipids; the specific phospholipid is mentioned (e.g. phosphatidylcholine) when the product contains more than 90% by weight of the specific phospholipid.

## 2. Properties

The molecular structure of phospholipids comprises a glycerol backbone which is esterified in positions 1 and 2 with fatty acids and in position 3 with phosphate. The systematic designation of e.g. phosphatidic acid (PA) is 1,2-diacyl-sn-glycero-3-phosphate (where sn means stereospecific numbering) (Silvius, 1993). The specific and nonrandom distribution of substituents over the positions 1, 2 and 3 of the glycerol molecule introduces chirality. In typical membrane phospholipids, the phosphate group is further esterified with an additional alcohol, for instance in phosphatidylcholine (PC) with choline (Fig. 1), in phosphatidylethanolamine (PE) with ethanolamine and in phosphatidylglycerol (PG) with glycerol. Depending upon the structure of the polar region and pH of the medium, PE and PC are zwitterionic and have a neutral charge at pH values of about 7.

Dependent on the ratio of the surface areas in the molecule of the polar head group area and fatty acid part area, the phospholipids form upon hydration dispersions with different colloidal structure. When the areas are about the same (example: POPC) they form lamellar structures; when the polar head group is larger than the fatty acid part (example: monoacyl-phosphatidylcholine (i.e. lysolecithin) micelles are formed and when the polar head group is smaller than the fatty acid part (example DOPE or soybean-PE) inverted micelles are formed. Phase diagrams of synthetic phospholipids and water have been published (Marsh, 2013). Although these phase diagrams are of physico-chemical interest to describe the properties of the compounds, the usefulness for pharmaceutical use is limited, since the phases formed are not studied for long term (physical and chemical) stability. Neutral phospholipids have in general an excellent solubility in ethanol and the less preferred solvent methylene chloride, which can be considered when producing formulations requiring a solvent step.

The amphiphilic character of phospholipids or lecithin, respectively, may be described by the HLB value. In the literature values ranging from  $4 \pm 1$  to  $9.7 \pm 1$  can be found (Convergent Cosmetics; Pichot et al., 2013). This broad range of HLB values is explained by the composition of the explored lecithin which comprises beside phosphatidylcholine, other phospholipids like phosphatidylethanolamine, phosphatidylinositol and phosphatidic acid. These phospholipids represent a mixture of co-emulsifiers with a variety of properties, regarding shape of the molecule and presence of a net negative charge, resulting in a broad range of stabilization possibilities of oil-water interfaces both in oil-in-water and in water-in-oil emulsions. Assignment of an accurate specific HLB value of such lecithin are for this reason inappropriate. In the literature the use of lecithin/phospholipids in oil-in-water (Chung et al., 2001; van Hoogevest and Wendel, 2014) as well

as in water-in-oil emulsions has been described (Knoth and Scherze, 2007). The emulsifying properties of monoacyl-phospholipids to prepare oil-in-water emulsions have been compared with polysorbate 20 and cetearyl glucoside. The studied lipids, soybean monoacyl-phosphatidylcholine fractions with 80%, 65%, and 20% monoacyl-phosphatidylcholine, a canola lecithin fraction with 20% monoacyl-phosphatidylcholine and a hydrogenated monoacyl-phosphatidylcholine from soybean (Lipoid GmbH, Ludwigshafen am Rhein, Germany), were found to be suitable to replace these emulsifiers as natural substitutes (Heidecke et al., 2013).

Important for formulation work and the interaction with the physiological milieu is to realize that phospholipids possess a phase transition temperature dictated by the hydration state and by the fatty acid composition and to a lesser extent by the polar head group of the phospholipid molecule. Above this temperature the fatty acids are mobile (liquid crystalline state) and the phospholipids can be easily hydrated. Below this temperature the fatty acids are rigid (gel state). The phospholipids can below the phase transition temperature be hydrated, but not at the same extent and rate as above the phase transition temperature. The rate of hydration is also dependent on the conditions like e.g. the presence of other excipients.

Natural phospholipids possess mono- and polyunsaturated fatty acids and their phase transition temperature is, when fully hydrated, mainly below 0 °C. This means that at processing temperatures above 0 °C the dry form of the lipids can be easily hydrated. At 37 °C the liquid crystalline lipid phase is, compared to the gel state lipid phase, relatively susceptible for lipid exchange and enzymatic degradation.”

In contrast, hydrogenated natural phospholipids contain only saturated fatty acids and possess a phase transition temperature, when fully hydrated, above 50 °C. The pure dry lipids can only be hydrated in excess water at temperatures above this temperature. The hydrated lipid phases are in the gel state at ambient temperatures and 37 °C and form more robust phases. It is important to know for processing of hydrogenated phospholipids at ambient conditions, that in case these lipids are hydrated in the presence of sugars and dried, the resulting powder can be re-hydrated at temperatures below the phase transition temperature (Koynova and Caffrey, 1998).

It is further important to realize that phase transition temperatures of natural and synthetic phospholipids found in the literature are mostly referring to the phospholipids in the fully hydrated state (i.e. mainly in liposomal dispersions). This information is for dry formulations, like e.g. solid dispersions when phospholipids are used as matrix material, irrelevant, since it is known that water-free hydrogenated soybean phospholipid possess a twice higher phase transition temperature compared to the fully hydrated phospholipids. Also, water free unsaturated soybean phosphatidylcholine has a phase transition temperature of about 48 °C, compared to ca –9 °C when fully hydrated. Intermediate phase transition temperatures appear to be observed at intermediate hydration states of the phospholipids (Koch, 1987).

Unsaturated natural phospholipids may have a sticky appearance

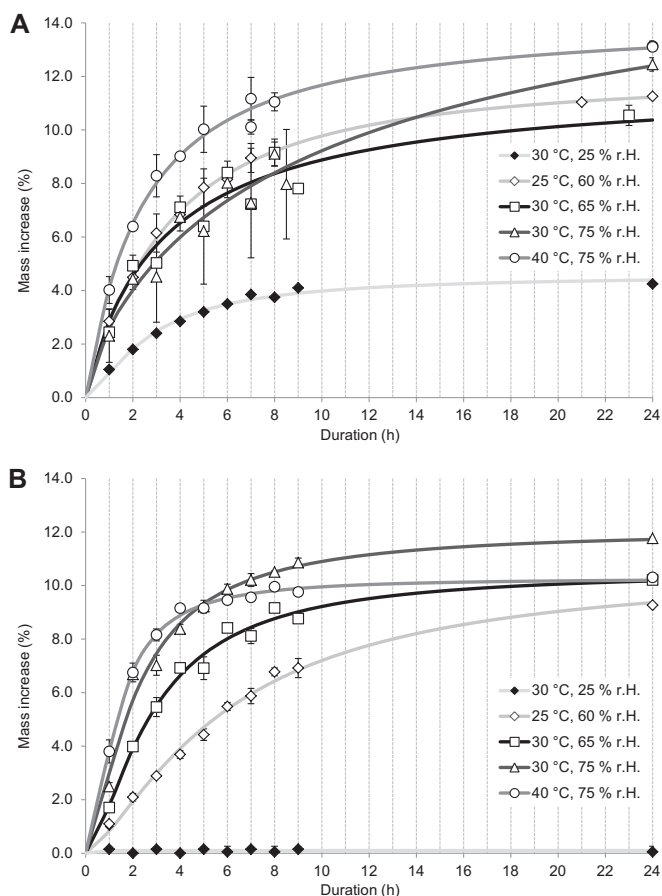


Fig. 2. Hygroscopicity of (A) unsaturated soybean phosphatidylcholine with n.l.t. 94% PC and (B) a saturated soybean phosphatidylcholine with n.l.t. 90% PC, as determined according to (Yee and E Davis, 1944).

and poor flow properties, whereas saturated natural phospholipids, especially grades with at least 90% phosphatidylcholine have acceptable powder flow properties (Carr's Index 12.64, Hausner ratio 1.15, (Kolbina et al., 2015)).

In general, phospholipids have hygroscopic properties. In order to illustrate this in Fig. 2 the hygroscopicity of an unsaturated soybean phosphatidylcholine and a saturated soybean phosphatidylcholine are provided (data kindly provided by Lipoid GmbH, Ludwigshafen am Rhein, Germany).

Fig. 2 shows that unsaturated soybean phosphatidylcholine is more hygroscopic than saturated soybean phosphatidylcholine. At 25% RH and 30 °C, the mass increase of unsaturated soybean phosphatidylcholine is largely suppressed to only 3% after 5 h. The saturated soybean phosphatidylcholine are under these conditions not hygroscopic. When soybean phospholipids are processed in dry form or into dry formulations, the humidity and temperature of the production environment should therefore be controlled and preferably the humidity should be 25% RH at 30 °C or lower.

Unsaturated natural phospholipids are susceptible for oxidation and precautions have to be taken by means of addition of antioxidants, proper processing and packaging conditions (see below). Food quality lecithins are still acceptable for use when the POV is not more than 100 (United States Pharmacopeial Convention, 2009), whereas for pharmaceutical oral use the POV is more stringent and set to be no more than 10 (United States Pharmacopeial Convention, 2014).

In case of processing or storage in aqueous media, it should be realized that phospholipids are ester molecules. Especially the ester-bond at the second position of the glycerol backbone is sensitive for hydrolysis. As any hydrolysis, this is pH dependent. The least hydrolysis

Table 1

Bitter values of soybean monoacyl-phospholipids compared to polysorbates.

Phospholipid	Description	Bitter value
LIPOID R LPC 20	20% monoacyl-phospholipid content, canola origin	69,500
LIPOID S LPC 20–3	20% monoacyl-phospholipid content, but saturated, soybean origin	52,000
LIPOID S LPC 65	65% monoacyl-phospholipid content, soybean origin	103,600
LIPOID S LPC 80	80% monoacyl-phospholipid content, soybean origin	93,200
Polysorbate 20	Reference detergent	204,000
Polysorbate 80	Reference detergent	166,000

of the ester bond at position 2 of phosphatidylcholine is at pH around pH 6.8 (Grit et al., 1993), and under these conditions even aqueous dispersions meeting long term stability requirements of years can be developed and produced (Van Hoogevest et al., 2011b). The pH dependency relevant for oral administration, especially in the stomach, is discussed below. In vivo, chemical hydrolysis plays a minor role. The initial metabolism of phospholipids is mainly the result of enzymatic hydrolysis by means of phospholipases.

Soybean diacylphospholipids possess a nutty like taste. Monoacyl-phospholipids as stronger detergents revealed a less bitter value than polysorbates (pharmacopoeial method EP 2.8.15, data kindly provided by Lipoid GmbH, Ludwigshafen am Rhein, Germany) (Table 1). The results also show that the bitter value of the monoacyl-phospholipids increases upon increasing the monoacyl-phospholipid content.

### 3. Physiological Fate After Oral Ingestion

The digestion of lipids begins in the oral cavity through exposure to lingual lipases, which are secreted in the buccal cavity by the Ebner's glands located on the tongue to begin the process of lipid digesting. Digestion continues in the stomach through the effects of both lingual and gastric enzymes. The stomach is also the major site for the emulsification of dietary fat and fat-soluble vitamins, with peristalsis as a major contributing factor. Crude emulsions of lipids enter the duodenum as fine lipid droplets and then mix with bile and pancreatic juice to undergo marked changes in chemical and physical structure. Emulsification continues in the duodenum along with hydrolysis and micellization in preparation of the absorption across the intestinal wall. (For details about the emulsification, hydrolysis, and micellization of fats, see Refs. 131 and 144. In: (Iqbal and Hussain, 2009)).

In the stomach the formulated diacylphospholipids meet, beside enzymes, gastric fluids with a pH 1.5–3.5 – unless no gastric coating is applied on the dosage form (Marieb and Hoehn, 2010). Being esters the phospholipids may undergo hydrolysis. Recently the hydrolysis rate at relevant pH values in the empty stomach of the following phospholipids LIPOID S LPC 20–3 (saturated soybean monoacyl-phospholipid with ca. 20% monoacyl-phospholipid content), LIPOID R LPC 20 (unsaturated canola monoacyl-phospholipid with n.l.t. 20% monoacyl-phospholipid content), LIPOID S LPC 80 (unsaturated soybean monoacyl-phospholipid with n.l.t. 80% monoacyl-phospholipid content), PHOSPHOLIPON® 80 H (saturated diacyl-phosphatidylcholine with n.l.t. 70% PC content), PHOSPHOLIPON® 90 G (unsaturated diacyl-phosphatidylcholine with 94.0–100.0% PC) was investigated (Table 2).

The table shows, as expected, a decreasing hydrolysis rate of the studied phospholipids at increasing pH of the medium in the pH range of pH 1–3. The hydrogenated saturated phospholipid PHOSPHOLIPON® 80 H and the product with the highest monoacyl content LIPOID S LPC 80 were the least sensitive for hydrolysis. Considering the transition time of ca 30 min of solid dosage forms through the empty stomach (Ewe et al., 1991), for which the studied pH values are relevant, the degree of hydrolysis even at pH 1 will be very minor. Stomach

**Table 2**

Influence of pH of SGF (Simulated Gastric Fluids) at 37 °C on the hydrolysis rate of phospholipids. Aqueous phospholipid dispersions with 1.8 mM phospholipid were adjusted to the desired pH value at a final phospholipid concentration of 1 mM and stored at 37 °C. Samples were drawn at 1 h and 2 h and added to a neutralizing buffer medium and the content of free fatty acids was measured with a NEFA-HR(2) Kit of Wako Diagnostics using an adapted protocol (Weinheimer, 2016). The Table shows average values of  $n = 3$  measurements. The degree of hydrolysis was derived from the concentration of free fatty acids found after the incubation period relative to the expected molecular fatty acid content of the tested phospholipids and corrected for the free fatty acid content at  $T = 0$  (data kindly provided by M. Weinheimer, E. Dengler, F. Schmid, R. Schubert, Albert Ludwig University of Freiburg, Germany).

Phospholipid	Hydrolysis rate (%)							
	Incubation period 1 h at 37 °C				Incubation period 2 h at 37 °C			
	pH 1	pH 1.3	pH 2	pH 3	pH 1	pH 1.3	pH 2	pH 3
LIPOIDS LPC 20–3	5	4	3	2	7	6	4	3.5
LIPOID R LPC 20	5	4	2.5	2.5	9	8	6	4
LIPOID S LPC 80	2.8	2.8	1	0	6	6	2	0
PHOSPHOLIPON® 80H	2	1.75	1.5	1.5	2	1.75	1.5	1.5
PHOSPHOLIPON® 90 G	6	6	2	2	8	8	3	3

emptying time-periods after uptake of food are much longer, but also the pH of the stomach shifts then to higher values. This condition also does not give rise to a significant hydrolysis of the phospholipids.

When aqueous formulations with only monoacyl-phospholipids are administered stomach irritation may occur, due to the micellar/detergent activity. This sort of side effect finding is, however, irrelevant for formulations, wherein the monoacyl-phospholipids are used as emulsifier or solubilizer being bound to a lipophilic component like an oil phase or another lipophilic solubilized component, and thus resulting in an elimination of the detergent related irritation potential. This rationale is underscored by the GRAS status (and therefore lack of toxicity) of enzyme modified lecithin, a product with high monoacyl-phosphatidylcholine content (see assessment of the US FDA (US FDA Federal Register, 1996)) and related literature (Bolin et al., 1986; Davenport, 1970; Johnson and McDermott, 1974; Ritchie, 1987; Salo et al., 1987).

Upon passage into the small intestines, the diacyl-phospholipid based dosage forms are in the duodenum confronted with bile, excreted by the liver and bile bladder, and pancreatic juice containing phospholipases. Bile contains besides bile salts also phospholipids. Due to the action of phospholipases, especially phospholipase A<sub>2</sub>, the phospholipids in the bile and the formulation phospholipids are hydrolyzed to monoacyl-phospholipids, which form together with the bile salts strong micellar solubilizing vehicles. The excretion of bile into the duodenum is regulated by the hormone cholecystokinin (CCK) which release is triggered by fatty acids being the enzymatic hydrolysis products of phospholipids. This action mechanism (Fig. 3) is supported by the findings of Kossena (Kossena et al., 2007) which showed that excipients comprising long chain fatty acid (in this case oleic acid) may generate a positive food effect. The effect of release of poly-unsaturated fatty acids from phospholipids has not been studied so far.

The fate of diacyl-phospholipid-based dosage forms and the role of

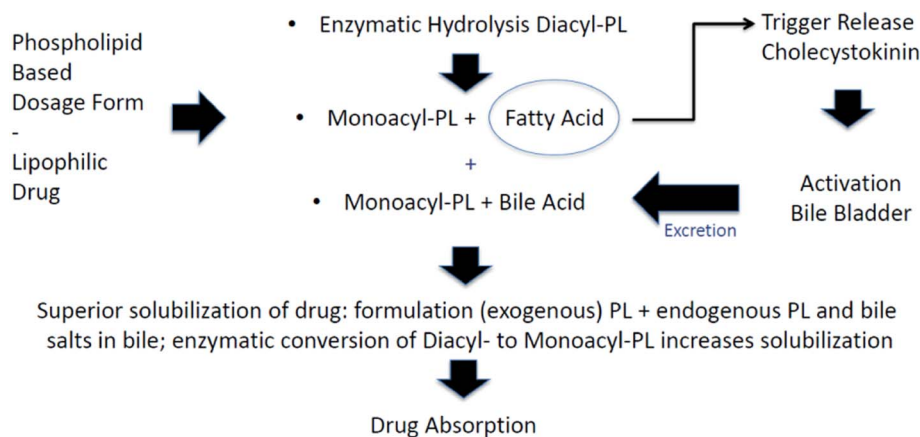
phospholipids may be described as follows. The greatest stimulator of CCK release is the presence of fatty acids and/or certain amino acids in the chyme entering the duodenum (Chaudhri et al., 2006). The minor degree of hydrolysis of phospholipids (present in a dosage form) in the stomach (Table 2) will therefore trigger the release of cholecystokinin, which on its turn triggers the release of bile that contains endogenous phospholipids. The dosage form phospholipids and the endogenous phospholipids are both hydrolysed to monoacyl-phospholipids (and fatty acids, which may trigger the release of cholecystokinin). Together with the bile acid they form a powerful solubilizing vehicle, which stimulates the absorption process of lipophilic compounds.

After enzymatic hydrolysis of diacylphospholipids, the fatty acids are taken up by enterocytes involving protein-mediated as well as protein-independent processes (Iqbal and Hussain, 2009).

Monoacyl-phospholipids are taken up by enterocytes by means of passive diffusion. The monoacyl-phospholipids are intracellularly acylated to diacyl-phospholipids by means of acyl-CoA. A considerable amount of monoacyl-lecithin is further hydrolyzed intracellularly by lysolecithinase to GPC (glycerophosphocholine) and analogues and fatty acids (Fox et al., 1982; Scow et al., 1967; Tso, 1985; Zierenberg and Grundy, 1982).

This metabolic fate of orally absorbed monoacyl-phospholipids to the non-hemolytic diacyl-phospholipids and GPC and its analogues means that oral administration of monoacyl-lecithin does not pose a potential risk for hemolytic problems caused by systemic absorption of intact monoacyl-lecithin.

Upon further passage through the small intestine the fraction of phospholipids/lecithin still not adsorbed will reach the colon. Recently, it was suggested that upon oral administration of (egg) lecithin, the lecithin is partially metabolized by the microbial flora in the colon to TMA (trimethylamine), which upon systemic absorption is metabolized by the liver to trimethylamine-N-oxide (TMAO). It is further claimed



**Fig. 3.** The interplay of exogenous and endogenous phospholipids in the absorption mechanism of lipophilic drugs in the duodenum.

that TMAO could give rise to a higher risk for cardiovascular diseases (CVD), since higher plasma levels of TMAO could be detected in CVD patients (Tang et al., 2013; Wang et al., 2011). This hypothesis is very unlikely, since it is unclear whether the observed higher levels of TMAO could have been caused by the disease, instead of causing the disease. In sharp contrast to the hypothesis, fish consumption, known to give rise to higher TMAO level, results in an actually lower risk for CVD diseases (He et al., 2004; Kris-Etherton et al., 2002; Morris et al., 1995).

In addition, it would be an evolutionary inborn error that endogenous phospholipids entering the GI tract, by means of excretion of bile phospholipids (6 g/day; (Boyer, 2013)), would be the cause of a serious disease. Finally, extensive toxicological testing as basis to grant the GRAS status and the continuous extensive worldwide use of food containing lecithin do not point at all to lecithin as a risk factor for causing CVD. On the contrary, lecithin is considered as highly valuable food component as source of choline and essential fatty acids (Canty et al., 1996).

#### 4. Industrial Perspective

For industrial pharmaceutical development availability and price of excipients play a role. The industrial pharmacist has the choice between natural phospholipids (isolated from e.g. soybean or egg-yolk) and synthetic phospholipids (van Hoogevest and Wendel, 2014). Natural phospholipids possess a fatty acid profile with originates from the raw starting material. Most well-known phospholipid product, from vegetable sources as defined in the USP, is lecithin. When derived from soybeans, dependent on the purity degree, high grade lecithin comprises mainly phosphatidylcholine, whereas lower grade purity lecithin contains other phospholipids like phosphatidylethanolamine, phosphatidylinositol and phosphatidic acid. Synthetic phospholipids have a predetermined well defined fatty acid composition and comprise only one phospholipid species. They are preferably prepared from high purity natural phospholipids (e.g. m.t. 96% soybean phosphatidylcholine) by enzymatic conversion (van Hoogevest and Wendel, 2014). Since oral pharmaceutical products have mostly large production volumes the supply of the corresponding volume of the used excipients should be guaranteed. For these reasons natural phospholipids derived from abundantly available raw material sources are preferred compared to synthetic phospholipids, requiring specific investments in corresponding synthesis capacity. In addition, natural phospholipids are produced by means of extraction and chromatography procedures, without organic chemical synthesis steps, which results in lower costs and more sustainable products. Since there is an increasing awareness in pharmaceutical companies to use product components, which are produced by more environmental-friendly production procedures, natural phospholipids will be, compared to synthetic phospholipids, for future products the preferred obvious choice. The used argumentation that natural phospholipids have a less reproducible quality, compared to synthetic phospholipids, is unjustified. In that respect the heterogeneity of the composition is confused with lack of reproducibility. The use of standardized and quality controlled raw materials and validated extraction and chromatography procedures guarantees a reproducible quality and functionality of the natural phospholipids. The acceptability of natural phospholipid excipients by regulatory authorities is underscored by pharmacopeial monographs, presence in the Inactive Ingredient list of the FDA (i.e. use in commercially available drug products approved by the FDA), and presence in (draft) guidelines for development of parenteral liposomal dosage forms, respectively (van Hoogevest and Wendel, 2014).

Considering marketed oral products soybean phospholipids are exclusively being used (van Hoogevest and Wendel, 2014). In many oral products (soybean) lecithin is mentioned as component. In these products lecithin is mostly used as dispersant and present in only minor amounts. Only in products using soybean lipids as source of polyunsaturated essential fatty acids for treatment of liver cirrhosis large

amounts of soybean phospholipids per dose unit are being used. Also in the case of the Rapamune® (sirolimus) product, soybean phospholipids are present in larger amounts per dose unit (Van Hoogevest et al., 2011b). Hydrogenated phospholipids and monoacyl-phospholipids are so far not abundantly present in oral pharmaceutical products. Although the soybean phospholipids are virtually free of soy-proteins, package leaflets of products containing soy derived excipients still have to mention warnings for patients having an allergy for soy products (European Medicines Agency, 2006). The alternative use of phospholipids derived from non-allergenic sunflower seed may be a viable alternative.

The use of unsaturated natural phospholipids in production processes of oral dosage forms requires the control of humidity/temperature and precautions to prevent oxidation. Also, during storage the dosage form needs to be protected for humidity and oxidation by applying, e.g. of appropriate blister packaging (see below).

Since phospholipids are not routinely considered for industrial product development and generation of corresponding intellectual properties, they may be perfectly suitable to circumvent existing patents or pending patent applications, which do not mention phospholipids or specific phospholipid grades in their claims. Since phospholipids can virtually replace any synthetic, non-phospholipid analogue, phospholipids may be considered to generate line extensions of existing products.

Argumentations that natural phospholipid excipients compared to synthetic excipients are (too) expensive ignore the gain in sustainability of the formulated products. In addition, is not sufficiently realized that phospholipids, as endogenous physiological compounds, have an intrinsic biocompatibility and biodegradability. Further the general (clinical) development and production costs of new products and other product components are immense compared to the small fraction of price increase caused by the alternative use of possibly more expensive natural excipients. In addition, when patented line extensions, by applying phospholipids, can be generated, the period of exclusive sales of patented products more than compensates a possible increase of cost of goods.

#### 5. Main Areas of Application

Phospholipids are multifunctional excipients. By selection of phospholipids having a different number of fatty acids (monoacyl- or diacyl-phospholipids) and fatty acid composition (saturated or unsaturated) or the fraction of lecithin with a specific phosphatidylcholine content and phospholipid profile result in phospholipid excipients, which comprise beside the zwitterionic neutral phosphatidylcholine, charged phospholipid components (e.g. phosphatidylinositol) and wedge shaped phosphatidylethanolamine. This variety makes an enormous arsenal of excipients differing in physicochemical properties available for the formulator. In principle, phospholipids can replace any synthetic detergent and even polymers as matrix materials in solid dispersions and slow release tablets.

Due to their amphiphilic nature they can be technically used in oral dosage forms as emulsifier, wetting agent, solubilizer and liposome former. In addition, they can be used as matrix material for solid dispersions when solubilization and fast release of the API are required, whereas saturated phospholipids may be perfectly suitable for slow release matrix tablet formulations.

For patient compliance of oral intake of uncoated or chewable formulations the taste of excipients is of paramount importance. In case dispersing and/or solubilizing excipients are needed for chewable or buccal formulation, diacylphospholipids or monoacylphospholipids provide a viable alternative compared to synthetic detergents, which mostly have a (very) bitter taste. An example of chewable formulations containing phospholipids can be found in (Kuentz and Roethlisberger, 2004).

Diacyl-phospholipids form upon hydration liposomes and drug

substances, depending on their physicochemical properties, are either encapsulated inside the liposomes to a certain extent or/and they can be bound electrostatically or associated with the lipophilic domain of the liposomal membrane. Since the diacyl-phospholipids have on their own an acceptable taste, they may be considered for taste masking (Mizna et al., 2012). Also specific phospholipids like PA and PI and their mixtures with PC may have a more pronounced taste correcting effect (Katsuragi et al., 1997).

The main purpose of the technical use of phospholipids in dosage forms is to enhance the oral absorption of lipophilic, poorly water soluble compounds belonging to the BCS class II, being highly permeable but with low solubility (Yu et al., 2002), by means of increasing their degree of dispersion and solubilization via the type of dosage forms described below.

For a specific drug class, the non-steroidal anti-inflammatory drugs (NSAIDs), there is a need to suppress the stomach irritation typical for this type of drugs. NSAIDs can cause damage to the gastroduodenal mucosa via several mechanisms including the topical irritant effect of these drugs on the epithelium, impairment of the barrier properties of the mucosa, suppression of gastric prostaglandin synthesis, reduction of gastric mucosal blood flow and interference with the repair of superficial injury (Wallace, 2000).

The company PLx Pharma explores the possibility to reduce stomach irritation by interfering with the binding of NSAIDs to mucosal phosphatidylcholine. Their PLxGuard™ delivery system uses phospholipids and free fatty acids to modify the physicochemical properties of various drugs and to selectively release these drugs to targeted portions of the GI tract. Unlike tablet or capsule polymer coating technologies (e.g., enteric coating), which rely solely on drug release based on pH differences in the GI tract, the PLxGuard™ system uses the differential in pH and bile acid contents between the stomach and duodenum to target the release of the NSAID. This approach is intended to more reliably release active pharmaceutical ingredients in the duodenum and decrease their exposure to the stomach, which is more susceptible to NSAID-induced bleeding and ulceration. The product Aspertec 325 mg, based on the PLxGuard™ technology, has been NDA-approved by the FDA for OTC distribution (Cryer et al., 2011; Lanza et al., 2008; PLx Pharma Inc., 2017).

Although it seems that liposomes as oral administration (Schmidt and Michaelis, 1990a, b) vehicle do not make sense, because the liposomal structure is converted to mixed micelles due to the concerted action of phospholipases and bile in the duodenum, the administration of drug substances profiting from the liposomal delivery to specific cells, in regions of the GI tract where liposomes could stay intact, would be useful. An example of this approach, explored by the University of Heidelberg, Heidelberg, Germany (G. Fricker and F. Helm), is the use of liposomal photosensitizers like hypericin for the treatment and diagnosis of stomach cancer by means of photodynamic therapy and diagnosis.

A further interesting oral use of phospholipids is in form of matrix slow release tablets with hydrogenated soybean phosphatidylcholine. This concept is explored by the FU Berlin, Germany (M Kolbina, M Körber, R Bodmeier, College of Pharmacy, Freie Universität Berlin, Berlin, Germany) and published in this Special Issue.

The efflux transporter P-glycoprotein (P-gp) significantly modulates drug transport across the intestinal mucosa, strongly reducing the systemic absorption of various active pharmaceutical ingredients. Some synthetic phospholipids, 1,2-dioctanoyl-*sn*-glycero-3-phosphocholine (di C-8:0 PC) and 1,2-didecanoyl-*sn*-glycero-3-phosphocholine (di C-10:0 PC), have been found to strongly reduce P-gp's activity. These phospholipids were tested for effects on the oral bioavailability of the P-gp substrate drug ritonavir. Both phospholipids significantly increased the area under the ritonavir plasma level curve (AUC) by more than tenfold. These P-gp inhibiting phospholipids may offer a new tool to increase the oral absorption of drugs (Weinheimer et al.).

The enhancement of the oral absorption of BCS III class drug

substance, with low permeability and high water solubility, is still very problematic. Main strategies being explored are the use of muco-adhesive dosage forms, dosage forms/excipients opening tight junctions and the use of small stable particles able to pass or interact with the epithelial membrane. The particles should be stable in presence of bile and pancreatic enzymes. A further advantage of this approach is that an encapsulated peptide or protein drug is also protected for enzymatic degradation by proteases.

In the past attempts were made to stabilize liposomes against solubilization by the bile and enzymes by using polymerized liposomes prepared from 1,2-di (2,4-octadecadienoyl) phosphatidylcholine (Okada et al., 1995). Although detergent resistant liposomes could be prepared and some targeting to M-cells could be achieved (Chen and Langer, 2000) this approach was abandoned, probably because of the presence of reactive residual monomers.

A similar approach is more recently followed by using liposome particle containing archaeal tetraetherlipids, isolated from organisms from extreme environments (Hanford and Peebles, 2002). Although they are not truly phospholipids, they resemble the typical bilayer membrane structure, due to their bipolar structure and covalently bound lipophilic tails which in normal phospholipid bilayers are directed to each other. Due to this structure, bile juice and phospholipase resistant liposomes could be prepared, without polymerization, showing indeed an significant increase (but still around maximally 5%) of oral absorption of BCS III compounds (Jacobsen et al., 2017; Parmentier et al., 2011a; Parmentier et al., 2014; Parmentier et al., 2011b; Uhl et al., 2016).

Because of the need for GI tract stable particles for oral vaccination purposes (Ann Clark et al., 2001; Chen et al., 1996) and targeting to M-cells/Peyer's patches, such liposomes stabilized with tetraether lipids may also be considered.

## 6. Type of Formulations

Phospholipid based formulations belong to the general group of lipid based formulations, which is one of the options to enhance the oral absorption of poorly water soluble compounds (Fricker et al., 2010; van Hoogevest et al., 2011a; Van Hoogevest et al., 2011b).

The main types of special formulations, which can be considered for optimization of the oral bioavailability of poorly water soluble compounds, wherein the drug substance is in the solubilized (and/or amorphous state; solid dispersions) state (van Hoogevest et al., 2011a), are briefly discussed. Classical formulations using the crystalline drug state and phospholipids as dispersant are not discussed.

As starting remark related to the use of phospholipids: when diacyl-phospholipids are being used in formulations and the formulation forms upon hydration liposomes, it should be realized that in the small intestines liposomes are not stable. The liposomal phospholipids are enzymatically digested and mainly integrated in the endogenous mixed micelles of phospholipids and bile salts. Emphasis on the formation of liposomes as the necessary delivery entity for such dosage forms may be confusing and may give rise to questions by regulatory authorities on the particle size distribution etc. of the liposomes, which are relevant for the parenteral use of liposomes, but irrelevant for oral use.

### 6.1. Solid Dispersions

In a recent review on the use and exploration of phospholipids in solid dispersions, mainly prepared by solvent evaporation methods, to enhance the oral absorption of poorly water soluble drugs (Fong et al., 2015a), most cited studies did not mention why a certain phospholipid and a certain drug to lipid weight ratio were selected. As pointed out above, the selection of synthetic phospholipids for oral products in a few cited studies make, from the industrial perspective, not much sense. Also the reason for the inclusion of cholesterol in some formulations is totally unclear. The cited studies were mostly not intended to

demonstrate which phospholipid class and drug to phospholipid ratio was optimal for the studied drug substance, but merely gave an example for demonstration of the use of the phospholipids for a certain drug substance. Also with respect to preparation methods the influence of the solvent removal rate on the degree of solubilized or amorphous drug on the lipid matrix was not systematically investigated (Fong et al., 2015b).

Without an optimization of the drug to lipid ratio and the selection of phospholipids in the formulation of the used drug substance, no final conclusion on the usefulness of phospholipids to enhance the oral absorption of the studied drug substance can be given. The presented studies and observed average increase of oral absorption degree may be an underestimation compared to dosage forms with optimal phospholipid, drug to lipid ratios and manufacturing method. In principle, as part of the design of the phospholipid based formulation, saturated and unsaturated mono- and diacyl-phospholipids should be compared with each other to find the best phospholipid for a solid dispersion formulation. So far no such systematic research has been published to study the use of multifunctional phospholipids as dispersant, matrix former and solubilizer (either alone or in combination with polymers) in solid dispersions with poorly water soluble drugs.

When using the solvent evaporation method to prepare the solid dispersions, the way the organic solvent solution of the drug substance is prepared is important with respect to minimizing the required volume of process solvent. First the phospholipid should be dissolved in the organic phase and then the drug in the phospholipid solution. The drug solubility in the solvent may be significantly increased due to the co-solubilizing effect of the phospholipids. When ethanol is used as process solvent it should be realized that unsaturated diacyl-phospholipids are soluble up to 70% w/w in ethanol at room temperature. Taking this into consideration it is clear that knowledge on the solubility of the drug in a pure solvent is of limited value in the design of a phospholipid based solvent evaporation method to manufacture solid dispersions.

Regarding the industrial development of such formulations, the same methods and strategies to assess whether the solid dispersions are robust regarding the risk for crystallization of the drugs can be followed as for polymer based solid dispersions (see: (Newman, 2015)).

When the purpose of the phospholipid based solid dispersion is to completely solubilize the drug in the phospholipid matrix and to keep the drug upon hydration of the formulation in solution (or to generate a supersaturated solution), several screening methods exist to select the optimal drug to lipid ratio and lipid class to obtain the solubilized state of the drug. In contrast to polymer based formulation, the assessment of degree of solubilization of the drug after hydration of the formulation is slightly more complicated because the drug is not dissolved in the bulk phase but in the colloidal structure formed upon hydration of the phospholipids. The presence/absence of crystalline drug in the (dry) lipid matrix can be performed controlled as for polymer based solid dispersions using e.g. DSC, X-RPD, Raman-spectroscopy.

The degree of solubilization of a poorly water soluble drug in a lipid matrix upon hydration can be assessed by first preparing a drug/lipid matrix film or powder at several drug to lipid ratios by means of (mini) spray drying or rotary-evaporation to remove residual solvent under high vacuum, then followed by hydration and observation under the microscope for the qualitative presence of drug crystals. The amount of solubilized drug substance in the colloidal liposomal/phospholipid fraction can be quantified by filtration of the diluted suspension of the crystallized drug through an e.g. 0.45  $\mu\text{m}$  pore size filter and assessment of the (solubilized) drug content in the filtrate by means of e.g. HPLC. Theoretically, in this filtrate the maximum drug to lipid ratio can be directly determined as well by HPLC methods of drug and lipids. Instead of filtration centrifugation may be used to separate drug crystals and solubilized drug (di Cagno et al., 2011).

An interesting method for fast screening of the maximum drug to lipid ratio can be found in (Leigh et al., 2011). This method uses clear

liposomal or micellar aqueous dispersions of lipid to which a highly concentrated solution of the test drug in DMSO in portions is added till an increase of turbidity is observed in comparison with controls without lipid and the control with lipids but no drug in the DMSO solution, indicating the maximal degree of solubilization of the drug in hydrated lipids. This method can be easily performed in well plates and simultaneously be compared in the same way with other solubilizers.

In spite of all these considerations and available methods, the industrial applicability of phospholipid based solid dispersions has so far not been completely assessed. Indications on the initially possible drug to lipid ratios for several drugs, exploring monoacyl-phospholipids for cyclosporine (Leigh et al., 2001), diacyl- as well as monoacyl-phospholipids (Gautschi et al., 2015) and diacyl phospholipids (Fong et al., 2015a; Fong et al., 2015b; Fong et al., 2016) have been investigated. However, information on the maximal degree of increase of bioavailability using the optimal lipid and lipid class for a specific drug and the long term stability of the formulations, with respect to a critical parameter like powder properties and drug crystallization, have not been reported so far.

In addition, it is unclear whether for obtaining optimal oral bioavailability results a completely solubilized or amorphous state of the drug or in the lipid matrix is necessary, or possibly the drug should be present in mini crystallites in the matrix. The assessment of such differences in formulations requires time consuming stability testing and the use of analytical methods operating at their detection limits. A feasible lipid to drug ratio is important because it determines the final dose unit size. When classical oral dosage forms are envisaged and e.g. a 50:1 lipid to drug w/w ratio or more is required and additional tablet excipients have to be added, an unacceptable large dose unit size may result. Capsule filling, omitting the tablet formulation related excipients, may not be helpful because the final specific density of the powder may be too low, still requiring unacceptable large capsule sizes. For such products requiring high lipid to drug ratios, the use of sachets, which contents up to gram amounts, can be dispersed in water for oral intake may be considered.

## 6.2. Phytosomes

Phytosomes are complexes of natural phospholipids with herbal extracts or herbal components proposed in 1989 (Bombardelli et al., 1989). These products are mainly sold as dietary supplements in the US and Asia. Although they are dietary supplements, research papers are increasingly entering pharmaceutical technology oriented journals, suggesting that this technology may be of pharmaceutical interest. These complexes are characterized by weight ratios of the herbal medicine and phospholipid around 1:1 (Kidd, 2009). It is claimed that this 1:1 weight ratio is adequate to give rise to an increase of oral absorption compared to a comparator formulation. This finding is clearly contradicting the work done with pharmaceutical solid dispersion requiring always a significant excess of lipid to drug.

In order to understand this discrepancy, the following should be realized. The herbal extracts are sometimes poorly characterized with respect to their composition. When natural phospholipids are being used as complexing agent, which comprise different lipid species, it is unclear which herbal component is complexing with which lipid component. Also neither the selection of the ratio of lipid to herbal components nor the selection of lipid class has been rationally performed. The selection of the ratio of both components on a weight basis, without mentioning the molecular weight of the components cannot be considered as a step to make a well-defined complex on a molar basis.

The complexes are prepared by refluxing the organic solvent solution of the extract and phospholipids at the boiling point of the solvent. Possibly this may make sense when the herbal components are extracted from a solid herbal extract using a phospholipid containing extraction solvent. When both components clearly dissolve in an organic solvent, the reason for the refluxing is unclear. The higher

temperatures during refluxing may give rise to decomposition of the lipid and herbal components, and the quality of the product after the refluxing procedure has then to be checked. After drying procedures to produce the complex, most papers show by means of spectrophotometric methods that there is an interaction between the components. A further prerequisite that upon hydration of the formulation the drug is solubilized and to which extent it is solubilized is, however, mostly not clear. Also the used dissolution media are mostly not bio-relevant (i.e. containing at least phospholipid/bile salts mixed micelles).

The performance of the phytosome formulation is mostly compared with the extract without any excipients. The higher bioavailability seen in this phytosome group may be caused by the action of the phospholipids as dispersant, dispersing the lipophilic extract component in a better way compared to the extract without excipient. Therefore a control group comprising a physical mixture of herbal components and phospholipids or an aqueous suspension of the herbal components with phospholipids as dispersant should be explored. In addition, as pointed out above, also other phospholipid classes and compound to lipid ratios over a much broader range should be explored as justification for selection of a certain weight ratio of the components without considering the MW of the components. Finally long term stability of these so-called complexes should be performed as for solid dispersions, before it can be judged whether this type of formulation meets industrial pharmaceutical requirements.

In this Special Issue an interesting contribution in the field has been made, which represents a typical example of a phytosome formulation study (Telange et al., 2016). The comments made above are meant as general comments and do not necessarily refer to this specific publication.

Nevertheless these question marks, it is still intriguing to see that using this low lipid content (and therefore a much smaller dose unit site, in comparison to solid dispersions with a large excess of lipid to drug ratio) throughout all publications at least a tendency for improvement of oral bioavailability of the studied herbal compounds can be observed. Therefore, it could be that phospholipids at low content may act as crystal poisoning agents, so stabilizing the amorphous state. In 2013, it was observed that amino acids at 1:1 molar ratio may have such an amorphous state stabilizing effect of poorly water soluble compounds (Löbmann et al., 2013a; Löbmann et al., 2013b). Phospholipids may be even more attractive candidates than amino acids to act as amorphous state stabilizers because the numbers of phospholipid molecules, which can be explored, are innumerable compared to amino acids. Since only relatively small amounts are required even synthetic phospholipids may be considered, at least for a proof of concept study.

### 6.3. Mixed Micelles

It is remarkable to note that the natural solubilization mechanism of lipophilic components in the GI tract by means of mixed micelles comprising phospholipids and bile salts is hardly being considered by pharmaceutical technology. This type of formulation was for the first mentioned in the literature in 1909 (Moore et al., 1909). In 1924, H. Wieland mentioned the use of mixed micelles to solubilize poorly water soluble drugs (Wieland, 1924). In 1976 Hoffmann La Roche patented a mixed micellar formulation for diazepam (Steffen and Schmidt, 1978). Since then mixed micelles formulations have been used in a few injectable and oral products (Konakion MM) to solubilize poorly water soluble drug substances or vitamins for intravenous administration (Cernevit). However, although some formulation research has been performed (Yu et al., 2010) since decades this technology has not been used anymore in new products and not even mentioned in classical review papers on available formulations strategies for poorly water soluble compounds (Strickley, 2004). That is remarkable, considering the many advantages of this technology:

- the excipients are used in marketed products in the EU and USA,

- indicating adequate stability and acceptance by regulatory authorities,
- the excipients are biocompatible and are natural components present e.g. in blood,
- the excipients are available in parenteral quality,
- they can be produced using relatively simple technologies,
- they have no risk for anaphylactic reactions compared to synthetic solubilizers like e.g. Tween®, Cremophor® and Solutol®;
- toxicity testing of mixed micelles has been published (Ballinger et al., 1996; Teilmann et al., 1983).
- they are suitable for oral as well as parenteral formulation and accepted for pediatric use, suggesting that only one formulation for many uses may be suitable.

Possible issues related to the mad-cow disease (BSE/TSE) and the use of bile salts which are of bovine origin are at present becoming less critical considering the decrease of occurrence of the disease in an increasing number of countries (World Organisation for Animal Health, 2017). An interesting option to eliminate any BSE related issue once and for all is to explore the use of mixed micelles comprising a combination of mono- and diacyl-phospholipids. As a matter of fact such a product, comprising mono- and diacylphospholipid 8:2 w/w in an Enzyme Modified Lecithin, which has the GRAS status at the US FDA (U.S. Food and Drug Administration, 2016) exists already.

The mixed micelles can be prepared by dissolving the drug and the mixed micelle components in a suitable solvent, followed by drying and hydration of the dry residue. Solvents can, however, be avoided by first dissolving the drug in the aqueous micellar solution. This seems to be very simple, but some details in the sequence of addition of the formulation components have to be addressed to obtain optimal results. The mixed micelles are not hemolytic because the diacylphospholipid eliminates the hemolytic action of the bile salt. Therefore, mixed micelles are very mild solubilizers. As demonstrated with the compound vitamin K, used in the oral mixed micellar product Konakion (von Kries et al., 2003), it is therefore not surprising that the aqueous mixed micelles, at the commonly used concentrations of 5–10%, poorly water soluble compounds only dissolved very slowly. These compounds can be faster dissolved, when first the bile salt is dissolved at high concentrations in water and the drug is dissolved in the bile salt solution, and then the phospholipid is added in portions and dissolved until a concentration. Alternatively, poorly water soluble compounds can be dissolved in highly concentrated mixed micelle solution at 100% w/w (weight of phospholipid and sodium-glycocholate) followed by dilution to the desired mixed micelle concentration (data kindly provided by Lipoid GmbH, Ludwigshafen am Rhein Germany). Using these methods, the chance that reasonable concentrations of poorly water soluble can be achieved is increased.

### 6.4. PHOSAL®

PHOSAL®s are liquid concentrates of phospholipids for oral use. They are commercially available in several versions which can be explored to accommodate the specific solubility characteristics of the drug substance (Hoepfner and Fiedler, 2007). As easy-to-use and liquid vehicle they are popular for screening purposes at the pre-clinical research stage of the degree of oral absorption of experimental poorly water soluble drugs. Based on this approach oral immunosuppressant Sirolimus/Rapamune® of Wyeth-Ayerst for oral immunosuppression was developed. The oral liquid vehicle used for solubilizing the rapamycin is PHOSAL® 50 PG in 1% Tween® 80. PHOSAL® 50 PG is a mixture comprising a high concentration of n.l.t. 50% phosphatidylcholine, propylene glycol, mono- and diglycerides, 1.5–2.5% ethanol, soy fatty acids and ascorbylpalmitate. PHOSAL® showed increased blood levels of rapamycin compared to a suspension formulation of rapamycin (Carlson et al., 1998). The oral bioavailability of this formulation in man is 14% (Medical Economics Company et al., 2003).



Rapamune® is also available in tablet form comprising a nanosuspension of rapamycin with an oral bioavailability in man of 27% ([Medical Economics Company et al., 2003](#)).

Although this development scenario is highly attractive, also because the PHOSAL® formulation could be perfectly suitable for e.g. preclinical as well as Phase I and II studies allowing a fast track development from the pre-clinical to clinical development stage without a need to change a formulation, it is remarkable to note that so far only one product (Rapamune®), using phospholipids as essential excipient in the oral formulation, reached the market. One of the possible reasons for that may be that the experience of the conversion of a liquid comprising to a solid dosage form is relatively limited (see below for suggestions). A more important reason may be that the efficacious dose of the experimental drug for human use may be much lower than originally expected and a classical solid dosage form using (a lower dose of) the crystalline drug (instead of the solubilized drug) which possibly needs to be micronized in combination with common excipients may be preferred. Also the crystalline drug may have better long term stability in the formulation than the solubilized drug. Originators following this strategy should, however, realize that at this way there is only a low technical hurdle for generic companies to easily copy these formulations as soon the drug substance is off patent protection. A conversion of the liquid PHOSAL® formulation into a solid dosage form with phospholipids may present a more difficult to copy benchmark.

### 6.5. Emulsions

According to a classical review paper on commercially available formulation and formulation strategies for poorly water soluble drug substances which are oil soluble, solutions of these drugs in oil may be considered ([Strickley, 2004](#)). Oil-in-water macro emulsions are, in general, not a popular option. In pharmaceutical technology there is more interest in self emulsifying drug delivery systems (SEDDS). SEDDS are composed of lipids and hydrophilic surfactant, but often co-solvents are added to enhance the dispersion rate and lipophilic co-surfactants are added to increase the colloidal stability of the SEDDS nano-emulsion. Actual applications of self-micro or nano-emulsifying drug delivery systems in products remain rare. The first drug marketed as a SEDDS was cyclosporin, and it had significantly improved bioavailability compared with the conventional solution. The SEDDS formulation of ritonavir (soft capsules) has been withdrawn in some countries ([Gibaud and Attivi, 2012](#)). Phospholipids may play a role in this type of formulations when using monoacyl phospholipids as surfactant. The published research of the group of Prof. Müllertz (University Copenhagen, Denmark) showed that monoacyl phospholipids alone are not sufficiently strong emulsifier to reduce the oil droplet particle size to the desired small size but that a co-emulsifier is needed ([Tran et al., 2016](#)).

## 7. Conversion to solid oral dosage forms

When considering capsules (hard or soft gelatin) as solid dosage forms, liquid formulations containing high concentrations of phospholipids can be converted to solid dosage forms by a capsule fill. Examples of such liquid formulations are PHOSAL® 25 MCT, PHOSAL® 50 PG, PHOSAL® 53 MCT, PHOSAL® 40 IP, LIPOID PPL 600 and LIPOID PPL, which are compatible with soft gelatin capsules (LIPOID GmbH, Ludwigshafen, Germany, product catalogue). When using higher melting fats, such formulations (LIPOID PPL-400) can also be made suitable for hard gelatin capsule fills ([Duerr et al., 1983](#)).

As pointed out above hydrogenated diacylphospholipids with n.l.t. 90% PC content have suitable powder-flow properties. Unsaturated diacyl-phospholipids have, however, a more sticky appearance and formulations containing relative large amounts of this type of phospholipid may be in need for a conversion to a powder form to enable a production of a solid dosage form. The need for such conversion is

higher when the phospholipid is used as separate component of a physical mixture with a (mostly) crystalline drug substance compared to when the phospholipid is complexed (solid dispersion or phytosome) with a drug substance. It can be assumed that the presence of the drug in the complex will give rise to more powder-like properties. Monoacyl-phospholipids have not been studied in detail with respect to the need and procedures for conversion to powders.

Conversion of unsaturated diacyl-phospholipids into powder form was explored in 1986 ([Payne et al., 1986](#)). An organic solvent solution of lipids and drug was sprayed in a rotary evaporator on a sorbitol powder, followed by drying and sieving the resulting powder to generate a free flowing powder. Nowadays instead of a rotary evaporator, an e.g. high shear powder mixer or a fluidized bed dryer is used to perform the same procedure to prepare on a large scale such phospholipid powder which forms, upon hydration liposomes. Tan et al. review solid carriers which can be used to convert semi-solid or liquid based lipid dosage forms ([Tan et al., 2013](#)).

In order to convert unsaturated diacyl-phospholipids into powders organic (ethanolic) solvent solutions of phospholipid can be mixed with non-absorbing or absorbing (porous) carriers. The non-absorbing material can be used to make granule with up to 30% w/w phospholipid in tablets with up to ca. 15% w/w of unsaturated diacylphospholipid ([Kolbina et al., 2015](#)), whereas absorbing porous materials, like e.g. SiO<sub>2</sub>, magnesium aluminium-metasilicate can be used too for capsule fills and to make tablets with up to 60% w/w unsaturated diacylphospholipid ([Kolbina et al., 2015](#)). Polymers like e.g. Eudragit, povidone, ethylcellulose, polyvinyl alcohol, polyvinyl acetate phthalate can also be used to prepare powder compositions containing high concentrations of phospholipids by dissolving polymer and lipid in solvent followed by removal of the solvent ([Leigh, 2000](#)). Dong et al. provide an example of converting mixed micelles containing fenofibrate in powder form using an organic solvent solution of drug, mixed micellar components and PEG which is sprayed on nonpareil pellets in a fluidized bed dryer ([Dong et al., 2013](#)).

Disadvantage of these processes is the necessary use of organic solvents. The possibility to use alternative solvent-free melt extrusion procedures with phospholipid based have not been explored so far. An alternative solvent-free method to make solid forms with phospholipids is to embed liposomal dispersions in a solid gelatin matrix ([Pantze et al., 2014](#)). This method was developed to preserve intact liposomes, for the oral delivery of encapsulated drugs, which degree of oral absorption could be increased by using intact liposomal structures. The method could, however, also be considered for solidification of phospholipid formulation without the need for preserving liposomes.

As suggested in the original publication on the preparation of liposomes ([Payne et al., 1986](#)) and the recent review publication on solid phospholipid based formulations ([Fong et al., 2015a](#)) conversion of liquid to solid formulations should result in more stable products. Considering the use of e.g. unsaturated soybean phospholipids in such solid formulations this issue is, however, more complicated in regard that solid oral dosage forms should have in pharmaceutical industry a shelf life of at least two years at room temperature and that unsaturated phospholipids are quite sensitive towards oxidation. The stability of saturated monoacyl- and diacyl-soybean phospholipids in solid dosage forms is unproblematic due to the elimination of oxidation risks, but still such dosage forms have to be protected for humidity.

When using solid dosage forms containing unsaturated soybean lecithin/phospholipids as essential formulation excipients, precautions to protect the dosage form and phospholipids from higher temperatures, light, oxygen and humidity should be taken by means of e.g. using (additional) anti-oxidants in the formulation and humidity and oxygen absorbing pouches in the container ([Feng et al., 2013](#)) and/or alu-alu blister packaging.

A practical stability study on a powder comprising a complex of sodium taurocholate and soybean lecithin used to prepare biorelevant dissolution media, showed the usefulness of humidity absorbing pouches;

the powder was at least stable for one year at 2–8 °C, with respect to powder flow, oxidation and hydrolysis of the used phospholipid (Kloefler et al., 2010). Even when for stability reasons, storage at 2–8 °C of an oral solid dosage form is a prerequisite to obtain an adequate shelf life, it should be realized that this prerequisite is not prohibitive to introduce such a product on the market. Products like Kaletra™ capsules/solution, containing lopinavir/ritonavir, Lactinex tablets containing *Lactobacillus acidophilus/Bulgarius*, Leukeran® tablets, containing chlorambucil, Mycostatin® pastilles, containing nystatin, Thyrolar®, tablets, containing liotrix, VePesid® capsules, containing etoposide, are commercially available oral products requiring storage at refrigerated conditions (PharmacyTechnicianToday.com, 2017). Therefore, solid oral dosage forms containing unsaturated phospholipids will still be acceptable for practical use, considering the many packaging options available to protect the product and to use storage temperatures of 2–8 °C, when required.

The careful handling of especially unsaturated phospholipid excipients is by no way a drawback specific for phospholipids. It is well documented in the literatures that more traditional excipients may also be hygroscopic (Callahan et al., 1982; Hancock and Shamblyn, 1998) and may also be sensitive for oxidation and may have compatibility issues with active pharmaceutical ingredient because of specific impurities (Bharate et al., 2010; Wu et al., 2011).

## 8. Conclusions

The knowledge and experiences obtained with oral phospholipid excipients is increasing continuously. Nevertheless, the present number of oral products using these excipients as essential excipient is very limited. This is remarkable to note, since phospholipids play a significant role in the food uptake mechanisms of the GI tract and these mechanisms could be translated into suitable dosage forms and corresponding drug delivery strategies. In principle, due to their diversity in physicochemical properties and lack of toxicity (natural) phospholipids can replace many alternative synthetic excipients. For the pharmaceutical industry this means that the use of natural phospholipids will increase the over-all sustainability balance of their products. In addition, phospholipid excipients offer excellent opportunities to circumvent existing formulation patents or generate formulation patents and generate resulting exclusive line extension products.

In this Special Issue many interesting studies are presented highlighting the potential use of these excipients. In addition, they invite to intensify the pharmaceutical technological research with these fascinating excipients.

The review also shows that certain areas of interest need to be elaborated in order to increase or complete the understanding of the underlying beneficial mechanisms related with the use of phospholipids. Need for further research can e.g. be found in area like taste masking, use of phospholipids in buccal/chewable formulations, improvement of the degree of oral absorption of poorly water soluble drugs by systematically comparing the available phospholipid classes (saturated or unsaturated di- and monoacyl phospholipids), bridging solid dispersion with excess of drug to lipid and phytosome formulations with drug to lipid weight ratios of about 1:1, triggering the excretion of bile by means of cholecystokinin release, which release is triggered by hydrolyzed fatty acids from diacyl or monoacyl-phospholipids, and the use of higher melting phospholipid as matrix material for controlled release solid dosage forms.

The Phospholipid Research Center in Heidelberg, Germany will continue to support research in these directions.

## References

Ann Clark, M., Blair, H., Liang, L., Brey, R.N., Brayden, D., Hirst, B.H., 2001. Targeting polymerised liposome vaccine carriers to intestinal M cells. *Vaccine* 20, 208–217.  
Ballinger, A.B., Forget, D., Brun, A.L., Farthing, M.J.G., 1996. An evaluation of the safety

of mixed micelles in healthy subjects. *J. Parenter. Enter. Nutr.* 20, 110–112.  
Bharate, S.S., Bharate, S.B., Bajaj, A.N., 2010. Incompatibilities of pharmaceutical excipients with active pharmaceutical ingredients: a comprehensive review. *J. Excip. Food Chem.* 21, 3–26.  
Bolin, T., Franzén, L., Sjö Dahl, R., Tagesson, C., 1986. Passage of molecules through the wall of the gastrointestinal tract. *Scand. J. Gastroenterol.* 21, 441–448.  
Bombardelli, E., Curri, S., Della, R.L., Del, N., Tubaro, A., Gariboldi, P., 1989. Complexes between phospholipids and vegetal derivatives of biological interest. *Fitoterapia* 60, 1–9.  
Boyer, J.L., 2013. Bile formation and secretion. *Compr. Physiol.* 3, 1035–1078.  
Callahan, J.C., Cleary, G.W., Elefant, M., Kaplan, G., Kensler, T., Nash, R.A., 1982. Equilibrium moisture content of pharmaceutical excipients. *Drug Dev. Ind. Pharm.* 8, 355–369.  
Canty, D.J., Zeisel, S.H., Jolitz, A.J., 1996. Lecithin and Choline: Research Update on Health and Nutrition. Central Soya Company, Inc., Ft. Wayne, IN.  
Carlson, R.P., Hartman, D.A., Ochalski, S.J., Zimmerman, J.L., Glaser, K.B., 1998. Sirolimus (rapamycin, Rapamune®) and combination therapy with cyclosporin A in the rat developing adjuvant arthritis model: correlation with blood levels and the effects of different oral formulations. *Inflamm. Res.* 47, 339–344.  
Chaudhri, O., Small, C., Bloom, S., 2006. Gastrointestinal hormones regulating appetite. *Philos. Trans. R. Soc., B* 361, 1187–1209.  
Chen, H., Langer, R.S., 2000. US 6060082 - Polymerized Liposomes Targeted to M Cells and Useful for Oral or Mucosal Drug Delivery. Massachusetts Institute of Technology.  
Chen, H., Torchilin, V., Langer, R., 1996. Lectin-bearing polymerized liposomes as potential oral vaccine carriers. *Pharm. Res.* 13, 1378–1383.  
Chung, H., Kim, T.W., Kwon, I.C., Jeong, S.Y., 2001. Stability of the oil-in-water type triacylglycerol emulsions. *Biotechnol. Bioprocess Eng.* 6, 284–288.  
Convergent Cosmetics, Emulsions and the HLB System [http://www.scientificspectator.com/documents/personal%20care%20spectator/HLB\\_Basics.pdf](http://www.scientificspectator.com/documents/personal%20care%20spectator/HLB_Basics.pdf).  
Cryer, B., Bhatt, D.L., Lanza, F.L., Dong, J.-F., Lichtenberger, L.M., Marathi, U.K., 2011. Low-dose aspirin-induced ulceration is attenuated by aspirin-phosphatidylcholine: a randomized clinical trial. *Am. J. Gastroenterol.* 106, 272–277.  
Davenport, H.W., 1970. Effect of lysolecithin, digitonin, and phospholipase A upon the dog's gastric mucosal barrier. *Gastroenterology* 59, 505–509.  
di Cagno, M., Styskala, J., Hlaváč, J., Brandl, M., Bauer-Brandl, A., Skalko-Basnet, N., 2011. Liposomal solubilization of new 3-hydroxy-quinolinone derivatives with promising anticancer activity: a screening method to identify maximum incorporation capacity. *J. Liposome Res.* 21, 272–278.  
Dong, F., Xie, Y., Qi, J., Hu, F., Lu, Y., Li, S., Wu, W., 2013. Bile salt/phospholipid mixed micelle precursor pellets prepared by fluid-bed coating. *Int. J. Nanomedicine* 8, 1653–1663.  
Duerr, M., Fridolin, H.U., Gneuss, K.D., 1983. Entwicklung von Rezepturen und Verfahren zur Abfüllung von flüssigen Massen in Hartgelatinekapseln unter Produktionsbedingungen. *Acta Pharm. Technol.* 29, 245–251.  
European Medicines Agency, 2006. Public Statement on the allergenic potency of herbal medicinal products containing soya or peanut protein - Final.  
Ewe, K., Press, A.G., Bollen, S., Schuhn, I., 1991. Gastric emptying of indigestible tablets in relation to composition and time of ingestion of meals studied by metal detector. *Dig. Dis. Sci.* 36, 146–152.  
Feng, S., Luo, Z., Shao, S., Wu, B., Ying, T., 2013. Effect of relative humidity and temperature on absorption kinetics of two types of oxygen scavengers for packaged food. *Int. J. Food Sci. Technol.* 48, 1390–1395.  
Fong, S.Y.K., Brandl, M., Bauer-Brandl, A., 2015a. Phospholipid-based solid drug formulations for oral bioavailability enhancement: a meta-analysis. *Eur. J. Pharm. Sci.* 80, 89–110.  
Fong, S.Y.K., Ibisogly, A., Bauer-Brandl, A., 2015b. Solubility enhancement of BCS class II drug by solid phospholipid dispersions: spray drying versus freeze-drying. *Int. J. Pharm.* 496, 382–391.  
Fong, S.Y.K., Martins, S.M., Brandl, M., Bauer-Brandl, A., 2016. Solid phospholipid dispersions for oral delivery of poorly soluble drugs: investigation into celecoxib incorporation and solubility-in vitro permeability enhancement. *J. Pharm. Sci.* 105, 1113–1123.  
Fox, J.M., Fontaine, R., Friehe, H., 1982. Kinetics and absorption, toxicity, and safety pharmacology of oral polyenyl phosphatidylcholine. In: Ricci, G. (Ed.), *Therapeutic Selectivity and Risk/benefit Assessment of Hypolipidemic Drugs*. Raven Press, pp. 251–256.  
Fricker, G., Kromp, T., Wendel, A., Blume, A., Zirkel, J., Rebmann, H., Setzer, C., Quinkert, R.O., Martin, F., Muller-Goymann, C., 2010. Phospholipids and lipid-based formulations in oral drug delivery. *Pharm. Res.* 27, 1469–1486.  
Gautschi, N., Van Hoogevest, P., Kuentz, M., 2015. Amorphous drug dispersions with mono- and diacyl lecithin: on molecular categorization of their feasibility and UV dissolution imaging. *Int. J. Pharm.* 491, 218–230.  
Gibaud, S., Attivi, D., 2012. Microemulsions for oral administration and their therapeutic applications. *Expert Opin. Drug Deliv.* 9, 937–951.  
Grit, M., Underberg, W.J.M., Crommelin, D.J.A., 1993. Hydrolysis of saturated soybean phosphatidylcholine in aqueous liposome dispersions. *J. Pharm. Sci.* 82, 362–366.  
Hancock, B.C., Shamblyn, S.L., 1998. Water vapour sorption by pharmaceutical sugars. *Pharm. Sci. Technol. Today* 1, 345–351.  
Hanford, M.J., Peebles, T.L., 2002. Archaical tetraether lipids. *Appl. Biochem. Biotechnol.* 97, 45–62.  
He, K., Song, Y., Daviglius, M.L., Liu, K., Van Horn, L., Dyer, A.R., Greenland, P., 2004. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. *Circulation* 109, 2705–2711.  
Heidecke, C.D., van Hoogevest, P., Mueller, A., 2013. Comparison of the emulsification characteristics of a series of monoacyl phosphatidylcholine products. In: 3rd International Symposium on Phospholipids in Pharmaceutical Research, Heidelberg.

- Hoepfner, E.-M., Fiedler, H.P., 2007. Fiedler Encyclopedia of Excipients : For Pharmaceuticals, Cosmetics and Related Areas, 6th ed. Vol. 2 ECV Editio Cantor Verl, Aulendorf, Württ [L–Z].
- Iqbal, J., Hussain, M.M., 2009. Intestinal lipid absorption. *Am. J. Physiol. Endocrinol. Metab.* 296, E1183–E1194.
- Jacobsen, A.-C., Jensen, S.M., Fricker, G., Brandl, M., Treusch, A.H., 2017. Archaeal lipids in oral delivery of therapeutic peptides. *Eur. J. Pharm. Sci.*
- Johnson, A.G., McDermott, S.J., 1974. Lysolecithin: a factor in the pathogenesis of gastric ulceration? *Gut* 15, 710–713.
- Katsuragi, Y., Mitsui, Y., Umeda, T., Otsuji, K., Yamasawa, S., Kurihara, K., 1997. Basic studies for the practical use of bitterness inhibitors: selective inhibition of bitterness by phospholipids. *Pharm. Res.* 14, 720–724.
- Kidd, P.M., 2009. Bioavailability and activity of phytosome complexes from botanical polyphenols: the silymarin, curcumin, green tea, and grape seed extracts. *Altern. Med. Rev.* 14, 226–246.
- Kloefer, B., van Hoogevest, P., Moloney, R., Kuentz, M., Leigh, M.L., Dressman, J., 2010. Study of a standardized taurocholate-lecithin powder for preparing the bioequivalent media FeSSIF and FaSSIF. *Dissolut. Technol.* 17, 6–13.
- Knöth, A., Scherze, I., Anita, F., 2007. Emulgatoren zur Bildung von multiplen Emulsionen, 3.1.4 Lecithin. In: Muschiolik, P.D.G., Bunjes, P.D.H. (Eds.), *Multiple Emulsionen: Herstellung und Eigenschaften*. Behr's Verlag DE.
- Koch, M., 1987. *Physikalische Eigenschaften von Phosphatidylcholinen*, Fachbereich Chemie. Fachhochschule Niederrhein, Krefeld.
- Kolbina, A., Koerber, M., Bodmeier, R., 2015. Preparation of tablets loaded with telmisartan-phospholipid complexes as potential solubilization approach for poorly soluble drugs. In: 4th international Symposium on Phospholipids in Pharmaceutical Research, Heidelberg.
- Kossena, G.A., Charman, W.N., Wilson, C.G., O'Mahony, B., Lindsay, B., Hempenstall, J.M., Davison, C.L., Crowley, P.J., Porter, C.J.H., 2007. Low dose lipid formulations: effects on gastric emptying and biliary secretion. *Pharm. Res.* 24, 2084–2096.
- Koynova, R., Caffrey, M., 1998. Phases and phase transitions of the phosphatidylcholines. *Biochim. Biophys. Acta* 1376, 91–145.
- Kris-Etherton, P.M., Harris, W.S., Appel, L.J., American Heart Association. Nutrition, C, 2002. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 106, 2747–2757.
- Kuentz, M., Roethlisberger, D., 2004. US 6719996 - Galenic composition for low bioavailability medicaments. Hoffmann-La Roche INC.
- Lanza, F.L., Marathi, U.K., Anand, B.S., Lichtenberger, L.M., 2008. Clinical trial: comparison of ibuprofen-phosphatidylcholine and ibuprofen on the gastrointestinal safety and analgesic efficacy in osteoarthritic patients. *Aliment. Pharmacol. Ther.* 28, 431–442.
- Leigh, M., van Hoogevest, P., Tiemessen, H., 2001. Optimising the oral bioavailability of the poorly water soluble drug cyclosporine a using membrane lipid technology. *Drug Deliv. Syst. Sci.* 1, 73–77.
- Leigh, S., 2000. GB 2344520 - Pharmaceutical Carriers Comprising Lipids and Polymers. Phares Pharmaceutical Research N.V.
- Leigh, S., Leigh, M.L.S., Van, H.P., Tiemessen, H., 2011. EP 1410020 - Test System and Method Suitable for Selecting Test Materials and Formulations. Phares Pharmaceutical Research N.V.
- Löbmann, K., Grohgan, H., Laitinen, R., Strachan, C., Rades, T., 2013a. Amino acids as co-amorphous stabilizers for poorly water soluble drugs – part 1: preparation, stability and dissolution enhancement. *Eur. J. Pharm. Biopharm.* 85, 873–881.
- Löbmann, K., Laitinen, R., Strachan, C., Rades, T., Grohgan, H., 2013b. Amino acids as co-amorphous stabilizers for poorly water-soluble drugs – part 2: molecular interactions. *Eur. J. Pharm. Biopharm.* 85, 882–888.
- Marieb, E.N., Hoehn, K., 2010. *Human Anatomy & Physiology*, 8th ed. Benjamin Cummings, San Francisco.
- Marsh, D., 2013. *Handbook of Lipid Bilayers*. Taylor & Francis, Second Edition. Medical Economics Company, PDR Staff, Physicians, 2003. *Physicians' Desk Reference 2003*. PDR Network, LLC.
- Mizna, N., Vandana, A., Savita, B., 2012. Taste masking of bitter drugs using different techniques for better patient compliance: an overview. *J. Pharm. Sci. Innov.* 1, 7–10.
- Moore, B., Wilson, F.P., Hutchinson, L., 1909. A contribution to the bio-chemistry of Haemolysis:—(a) changes in solubility of the Lipoids in presence of one another, and of certain unsaturated organic substances. (b) the balancing action of certain pairs of Haemolysers in preventing Haemolysis. (c) the protective action of serum proteins against Haemolysers. (d) the effects of Oxidising and reducing agents upon Haemolysis. *Biochem. J.* 4, 346–368.
- Morris, M.C., Manson, J.E., Rosner, B., Buring, J.E., Willett, W.C., Hennekens, C.H., 1995. Fish consumption and cardiovascular disease in the physicians' health study: a prospective study. *Am. J. Epidemiol.* 142, 166–175.
- Newman, A., 2015. *Pharmaceutical Amorphous Solid Dispersions*. Wiley, Hoboken, New Jersey.
- Okada, J.i., Cohen, S., Langer, R., 1995. In vitro evaluation of polymerized liposomes as an oral drug delivery system. *Pharm. Res.* 12, 576–582.
- Pantze, S.F., Parmentier, J., Hofhaus, G., Fricker, G., 2014. Matrix liposomes: a solid liposomal formulation for oral administration. *Eur. J. Lipid Sci. Technol.* 116, 1145–1154.
- Parmentier, J., Becker, M.M.M., Heintz, U., Fricker, G., 2011a. Stability of liposomes containing bio-enhancers and tetraether lipids in simulated gastro-intestinal fluids. *Int. J. Pharm.* 405, 210–217.
- Parmentier, J., Hofhaus, G., Thomas, S., Cuesta, L.C., Gropp, F., Schröder, R., Hartmann, K., Fricker, G., 2014. Improved oral bioavailability of human growth hormone by a combination of liposomes containing bio-enhancers and Tetraether lipids and omeprazole. *J. Pharm. Sci.* 103, 3985–3993.
- Parmentier, J., Thewes, B., Gropp, F., Fricker, G., 2011b. Oral peptide delivery by tetraether lipid liposomes. *Int. J. Pharm.* 415, 150–157.
- Payne, N.I., Timmins, P., Ambrose, C.V., Ward, M.D., Ridgway, F., 1986. Proliposomes: a novel solution to an old problem. *J. Pharm. Sci.* 75, 325–329.
- PharmacyTechnicianToday.com, 2017. Commonly Refrigerated Drugs, Medications & Prescriptions.
- Pichot, R., Watson, R.L., Norton, I.T., 2013. Phospholipids at the interface: current trends and challenges. *Int. J. Mol. Sci.* 14, 11767–11794.
- PLx Pharma Inc., 2017. [www.plxpharma.com](http://www.plxpharma.com).
- Ritchie Jr., W.P., 1987. Other causes of GI mucosal injury: upper intestinal content. *Clin. Invest. Med.* 10, 264–269.
- Salo, J.A., Myllärniemi, H., Kivilaakso, E., 1987. Morphology of lysolecithin-induced damage on esophageal mucosa. An experimental light and scanning electron microscopical study. *J. Surg. Res.* 42, 290–297.
- Schmidt, P.C., Michaelis, J., 1990a. Liposomen zur oralen Anwendung, 1. Mitteilung: Literaturüberblick zu Stabilität und Resorption von Liposomen in vitro/in vivo und zu Ergebnissen mit in vivo getesteten Arzneistoffen. *Pharm. Ztg. Wiss.* 135, 125–134.
- Schmidt, P.C., Michaelis, J., 1990b. Liposomen zur oralen Anwendung, 2. Mitteilung: Herstellung und Charakterisierung von streptokinasehaltigen Liposomen für die orale Applikation. *Pharm. Ztg. Wiss.* 135, 233–242.
- Scow, R.O., Stein, Y., Stein, O., 1967. Incorporation of dietary lecithin and Lysolecithin into lymph chylomicrons in the rat. *J. Biol. Chem.* 242, 4919–4924.
- Silvius, J.R., 1993. Structure and nomenclature. In: Cevc, G. (Ed.), *Phospholipids Handbook*. Dekker, New York, pp. 1–22 [u.a.].
- Steffen, H.D., Schmidt, D.D., 1978. DE 2730570 - Injektionslösungen. Hoffmann La Roche.
- Strickley, R.G., 2004. Solubilizing excipients in oral and injectable formulations. *Pharm. Res.* 21, 201–230.
- Tan, A., Rao, S., Prestidge, C.A., 2013. Transforming lipid-based oral drug delivery systems into solid dosage forms: an overview of solid carriers, physicochemical properties, and biopharmaceutical performance. *Pharm. Res.* 30, 2993–3017.
- Tang, W.H., Wang, Z., Levison, B.S., Koeth, R.A., Britt, E.B., Fu, X., Wu, Y., Hazen, S.L., 2013. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N. Engl. J. Med.* 368, 1575–1584.
- Teelmann, K., Schläppi, B., Schüpbach, M., Kistler, A., 1983. Preclinical safety evaluation of intravenously administered mixed micelles. *Arzneimittelforschung* 34, 1517–1523.
- Telange, D.R., Patil, A.T., Pethé, A.M., Fegade, H., Anand, S., Dave, V.S., 2016. Formulation and characterization of an apigenin-phospholipid phytosome (APLC) for improved solubility, in vivo bioavailability, and antioxidant potential. *Eur. J. Pharm. Sci.*
- Tran, T., Xi, X., Rades, T., Müllertz, A., 2016. Formulation and characterization of self-nanoemulsifying drug delivery systems containing monoacyl phosphatidylcholine. *Int. J. Pharm.* 502, 151–160.
- Tso, P., 1985. In: Rodolfo, P., David, K. (Eds.), *Gastrointestinal Digestion and Absorption of Lipid*. Elsevier, *Advances in Lipid Research*, pp. 143–186.
- US FDA Federal Register, August 30, 1996. Direct Food Substances Affirmed as Generally Recognized As Safe; Enzyme Modified Lecithin. 61 (170), 45886–45889 (21 CFR Part 184, Docket No.85G-0335).
- U.S. Food and Drug Administration, 2013. 21CFR184.1400 revised as of April 1, 2013.
- U.S. Food and Drug Administration, 2014. Hydrogenated lecithin from soy. For general use in foods with no limitations other than current good manufacturing practices. GRAS Notices GRN No. 534.
- U.S. Food and Drug Administration, 2016. 21CFR184.1063 revised as of April 1, 2016.
- Uhl, P., Helm, F., Hofhaus, G., Brings, S., Kaufman, C., Leotta, K., Urban, S., Haberkorn, U., Mier, W., Fricker, G., 2016. A liposomal formulation for the oral application of the investigational hepatitis B drug Myrcyludex B. *Eur. J. Pharm. Biopharm.* 103, 159–166.
- United States Pharmacopeial Convention, 2009. *Lecithin Monograph*, Food Chemicals Codex; (FCC 6).
- United States Pharmacopeial Convention, 2014. *Lecithin monograph, first supplement to USP 37–NF 32 pp. 6564-6567*.
- van Hoogevest, P., Liu, X., Fahr, A., 2011a. Drug delivery strategies for poorly water-soluble drugs: the industrial perspective. *Expert Opin. Drug Deliv.* 8, 1481–1500.
- van Hoogevest, P., Liu, X., Fahr, A., Leigh, M.L.S., 2011b. Role of phospholipids in the oral and parenteral delivery of poorly water soluble drugs. *J. Drug Delivery Sci. Technol.* 21, 5–16.
- van Hoogevest, P., Wendel, A., 2014. The use of natural and synthetic phospholipids as pharmaceutical excipients. *Eur. J. Lipid Sci. Technol.* 116, 1088–1107.
- von Kries, R., Hachmeister, A., Göbel, U., 2003. Oral mixed micellar vitamin K for prevention of late vitamin K deficiency bleeding. *Arch. Dis. Child Fetal Neonatal Ed.* 88, F109–F112.
- Wallace, J.L., 2000. How do NSAIDs cause ulcer disease? *Best Pract. Res. Clin. Gastroenterol.* 14, 147–159.
- Wang, Z., Klipfell, E., Bennett, B.J., Koeth, R., Levison, B.S., Dugar, B., Feldstein, A.E., Britt, E.B., Fu, X., Chung, Y.M., Wu, Y., Schauer, P., Smith, J.D., Allayee, H., Tang, W.H., DiDonato, J.A., Lusis, A.J., Hazen, S.L., 2011. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature* 472, 57–63.
- Weinheimer, M., 2016. Untersuchung von P-Glykoprotein-hemmenden Phospholipiden als bioverfügbarkeitssteigernde Hilfsstoffe. Fakultät für Chemie und Pharmazie Albert-Ludwigs-Universität Freiburg.
- Weinheimer, M., Fricker, G., Burhenne, J., Mylius, P., Schubert, R., The application of P-gp inhibiting phospholipids as novel oral bioavailability enhancers — an in vitro and in vivo comparison. *Eur. J. Pharm. Sci.* 10.1016/j.ejps.2016.08.055.
- Wieland, H., 1924. DE 388321 - Verfahren zum Lösen von in Wasser unloeslichen oder schwerloeslichen Substanzen. Wieland, Heinrich.
- World Organisation for Animal Health, 2017. List of Bovine Spongiform Encephalopathy Risk Status of Member Countries. <http://www.oie.int/animal-health-in-the-world/>

- official-disease-status/bse/list-of-bse-risk-status/.
- Wu, Y., Levons, J., Narang, A.S., Raghavan, K., Rao, V.M., 2011. Reactive impurities in excipients: profiling, identification and mitigation of drug–excipient incompatibility. *AAPS PharmSciTech* 12, 1248–1263.
- Yee, J.Y., E Davis, R.O., 1944. Accelerated method for determining moisture absorption. *Ind. Eng. Chem. Anal. Ed.* 16, 487–490.
- Yu, J.-N., Zhu, Y., Wang, L., Peng, M., Tong, S.-S., Cao, X., Qiu, H., Xu, X.-M., 2010. Enhancement of oral bioavailability of the poorly water-soluble drug silybin by sodium cholate/phospholipid-mixed micelles. *Acta Pharmacol. Sin.* 31, 759–764.
- Yu, L.X., Amidon, G.L., Polli, J.E., Zhao, H., Mehta, M.U., Conner, D.P., Shah, V.P., Lesko, L.J., Chen, M.L., Lee, V.H., Hussain, A.S., 2002. Biopharmaceutics classification system: the scientific basis for biowaiver extensions. *Pharm. Res.* 19, 921–925.
- Zierenberg, O., Grundy, S.M., 1982. Intestinal absorption of polyenephosphatidylcholine in man. *J. Lipid Res.* 23, 1136–1142.