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Review – An update on the use of oral phospholipid excipients

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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

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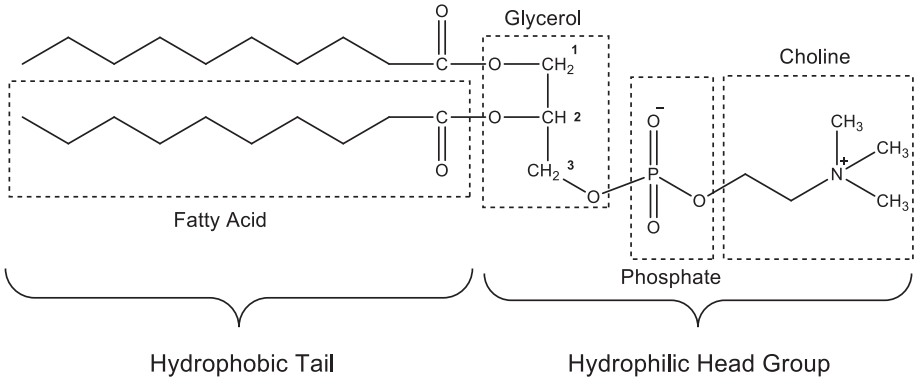

Fig. 1. Molecular structure of a typical phospholipid, phosphatidylcholine.

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 physicochemical 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 ± 1 to 9.7 ± 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

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