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Saturated phosphatidylcholine as matrix former for oral extended release dosage forms

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ABSTRACT

The aim of this study was to evaluate the suitability of saturated phosphatidylcholine (Phospholipon® 90H) as extended release excipient in matrix tablets for three model drugs with different aqueous solubility (theophylline, caffeine and diprophylline). The tablets could be prepared by direct compression because of the favorable phospholipid powder flow properties (Carr's index: 12.64 and angle of repose: 28.85) and good compactibility. Tablets of low porosity were formed already at low pressure of 40 MPa and with drug loadings up to 70% due to high plasticity of the phospholipid. Extended drug release was achieved with the drugs of different solubility and at various drug loadings. For example, the caffeine release time ($t_{80\%}$) from 8 mm tablets ranged from 1.5 h to 18 h at 70% and 10% drug loading, respectively. The drug release was governed by diffusion and could therefore be modelled by Fick's law of diffusion. Drug release profiles were thus a function of drug solubility, drug loading and tablet dimension. Matrix tablets of caffeine (20% drug loading) showed robust dissolution with regard to agitation (50–100 rpm) and ionic strength of the release media (100–600 mOsmol/kg). Caffeine release was pH-dependent with a faster drug release at acidic pH, which was attributed to a protonization of the phosphatidyl group of the matrix-former and thus a higher hydrophilicity.

1. Introduction

Phospholipids are isolated from natural sources like egg, soybean, rapeseed, and sunflower seed. The most common phospholipid is phosphatidylcholine, which is also the most abundant component of lecithin. Normally, lecithin grades containing > 80% phosphatidylcholine are called arbitrarily phosphatidylcholine, whereas grades containing < 80% phosphatidylcholine can be arbitrarily called lecithin (van Hoogevest and Wendel, 2014). Structurally, phospholipids comprise a glycerol backbone, which is esterified in positions 1 and 2 with fatty acids and in position 3 with phosphate and other functional groups. The length and degree of saturation of fatty acids chains as well the variation of functional groups, leads to the existence of a wide variety of phospholipids.

Phospholipids have become attractive candidates as carriers for oral formulations during the last years, due to their favorable biocompatibility, biodegradability and diversity (Chakraborty et al., 2009).

Phospholipids have been used in two major applications in drug delivery. Firstly, their solubility- and bioavailability-enhancing properties for poorly water-soluble drugs have been investigated for several decades. Several lipid-based drug delivery systems have been developed, which make use of their amphiphilic nature and the ability to form vesicular structures in aqueous environments (Fricker et al., 2010). In addition, phospholipids have been studied in extended release drug delivery systems to some extent. Acetaminophen tablets were prepared by direct compression with different hydrogenated phospholipids rich in phosphatidylcholine, phosphatidylethanolamine and phosphatidylinositol fractions in order to determine effect of phospholipid species and pH on drug release (Fujii et al., 1998). Orally disintegrating ibuprofen tablets with controlled release were formulated (Fini et al., 2008). Granules of ibuprofen and hydrogenated phosphatidylcholine at 4:1 weight ratio prepared by wet granulation showed a slower drug release compared to pure drug granules. In another study, unsaturated lecithin (Lipoid S 45) was used as a binder to form soft agglomerates of gastro-resistant pantoprazole microparticles for an oral, delayed release dosage form (Raffin et al., 2009). Likewise, soy phosphatidylcholines have been used for extended release tablets prepared by wet granulation or compression moulding of drug-phospholipid blends (Chime, 2013; Nishihata et al., 1987). Phospholipids have also been studied as potential protectants of the gastric mucosa in combination with non-steroidal anti-inflammatory drugs (Anand et al., 1999; Dial et al., 2008), as well as potential taste masking agents

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(Katsuragi et al., 1997).

Direct compression is usually preferred for tablet manufacture due to its simplicity and cost-effectiveness. This approach has been successfully applied to synthetic or semi-synthetic polymers such as Kollidon® SR (polyvinyl acetate-based), Eudragit® RS (polymethacrylate derivatives) or ethyl cellulose (Boza et al., 1999; Crowley et al., 2004; Grund et al., 2014; Kranz et al., 2005). Potential matrix-formers of natural origin, with regulatory acceptance and the feasibility to control the drug release from a blend matrix are rare (e.g. carnauba wax, bees wax and shellac). In contrast to other natural waxes such as carnauba or bees wax, saturated phosphatidylcholines could be an interesting alternative as tableting excipients due to their natural origin, proven safety (GRAS listed compound) and biocompatibility as well as a reproducible quality, high melting temperature and their availability in fine powder form (van Hoogevest and Wendel, 2014).

In this study, saturated phosphatidylcholine, composed of stearic and palmitic acids and manufactured by hydrogenation of unsaturated phospholipids and chemically identical to the fraction of saturated phosphatidylcholines naturally contained in lecithin, was evaluated as matrix former for extended drug release due to its insoluble nature in aqueous medium (solubility of dipalmitoyl phosphatidylcholine: 0.3 ng/mL; Smith and Tanford, 1972). The drug release from insoluble matrices is predominantly governed by diffusion (Grund et al., 2013; Kreye et al., 2008). Therefore, a number of formulation factors which affect the drug diffusivity (i.e. drug loading, matrix former particle size, tablet porosity, etc.), and hence the drug release rate, were studied. Diprophylline, caffeine and theophylline, with corresponding aqueous solubilities (at 25 °C) of 330, 20 and 8 mg/mL (Remington and Gennaro, 1990), were used as model drugs. Direct compression of binary blends of drug and phospholipid was used in order to establish clear cause-effect relationships and to evaluate the general applicability of this excipient as release retarding matrix-former.

2. Materials and Methods

2.1. Materials

Saturated phosphatidylcholine of stearic and palmitic acid (Phospholipon® 90H, Lipoid GmbH, Ludwigshafen, Germany); caffeine anhydrous fine powder, theophylline anhydrous micronized powder, diprophylline (BASF SE, Ludwigshafen, Germany); TLC plates silicagel 60, β-(N-Morpholino)ethanesulfonic acid (MES) monohydrate (Merck KGaA, Darmstadt, Germany), polysorbate 80 (Sigma-Aldrich); PLA_2 (DSM, Heerlen, Netherlands); purified water (Fresenius Kabi Deutschland GmbH, Bad Homburg); magnesium stearate (Baerlocher GmbH, Unterschleissheim, Germany).

2.2. Particle Size Measurements

The particle size of phosphatidylcholine powder was measured in triplicates by powder laser diffraction (Sympatec® Helos Rodos GmbH, Clausthal-Zellerfeld, Germany) after eliminating particles larger than 850 µm by sieving (Fritsch GmbH, Idar-Oberstein, Germany).

2.3. Powder Densities and Flow Properties

The bulk and tapped densities were determined by filling 100 g powder into 250 mL measuring cylinder undergoing 1250 taps (Erweka GmbH, Heusenstamm, Germany) and were calculated as ratio of powder weight to volume occupied before and after tapping, respectively. The Carr's index (Eq. (1)) and Hausner ratio (Eq. (2)) were calculated as follows:

$$CI = \frac{(\rho_{tapped} - \rho_{bulk})}{\rho_{bulk}} \times 100\,(\%) \quad (1)$$

$$HR = \frac{\rho_{tapped}}{\rho_{bulk}} \quad (2)$$

where, ρ_{tapped} is the tapped density and ρ_{bulk} is the bulk density.

The angle of repose was measured with Erweka Powder Flow tester (Erweka GmbH, Heusenstamm, Germany).

2.4. Preparation of Tablets

The phosphatidylcholine powder (sieve fraction 90–180 µm) was blended with the drug for 10 min in a Turbula mixer (Willy A. Bachofen AG, Basel, Switzerland). The drug loadings ranged from 10 to 90% w/w. Then, 1% w/w magnesium stearate was added to the blend and further mixed for 3 min. The powders were compressed into 8 mm diameter, flat-faced tablets (160 ± 2 mg) at pressures ranging from 5 to 400 MPa using a single punch tablet press at 10 rpm (Korsch EK0, Korsch AG, Berlin, Germany). The compression force was recorded (MGCplus, Catman, HBM Inc., USA). Tablets prepared with the powder particle size fractions 0–90 µm and 180–315 µm were used to study the effect of particle size on drug release.

Placebo tablets were prepared by compressing phosphatidylcholine powder into 11 mm flat-faced tablets with a compaction simulator (Huxley Bertram, Cambridge, UK) at pressures ranging from 5 to 210 MPa and dwell time of 23 ms. Data acquisition was recorded with a time interval of 0.02 ms. The plastic work of compaction was calculated as the area under the curve of the force-displacement diagram with MS Excel software, applying the trapezoidal approximation method. The compensated upper punch position was used in calculations.

2.5. Tablets Characterization

The tablet thickness and the diameter were measured by an electronic micrometer (± 0.01 mm, Digi-Met; Helios Preisser, Gammertingen, Germany). The weight was recorded (± 0.1 mg; Mettler AT200) 24 h after compression. The tablet breaking force was measured on a tablet hardness tester (Multicheck, Erweka GmbH, Heusenstamm, Germany), and the tensile strength (3) was calculated as follows:

$$\sigma = \frac{2F}{\pi dh} \quad (3)$$

where σ is radial tensile strength [MPa]; F is breaking force [N]; d is tablet diameter [mm]; h is tablet thickness [mm].

The tablet porosity was calculated as the ratio of apparent and true density. The true density of phosphatidylcholine was determined by the method described by C. Sun, (Sun, 2005), where the compaction pressure and tablet apparent densities are fitted into the non-linear regression of the modified Heckel equation (Kuentz and Leuenberger, 1999) (Eq. A.1). The method was validated with Avicel® 102, and the results were in accordance with published data (Fig. A1).

2.6. Determination of the Degree of Phospholipid Hydrolysis in Incubation Medium with PLA_2

Incubation buffer was prepared as follows: 6.11 g of β-(N-Morpholino)ethanesulfonic acid (MES) monohydrate, 6.19 g of NaCl and 0.15 g of polysorbate 80 were dissolved in purified water. The pH was adjusted to 6.50 with 0.1 M solution of NaOH. Water was added to give a total volume of 1.0 L of buffer solution.

Calcium acetate (1 g) was dissolved in 40 ml of the buffer solution, matrix tablet and PLA_2 (44,372 U) were added and the resulting mixture was stirred at 37 °C. Samples were taken after 2 h, 4 h, 6 h, 8 h and 24 h and analysed by thin layer chromatography (TLC). After 24 h the tablet was removed from the medium by filtration, rinsed with water and lyophilized to determine the dried tablet weight.