# Saturated Phosphatidylcholine as Matrix Former for Extended Oral Drug Release

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## Introduction

Saturated phosphatidylcholine was evaluated as tablet matrix former for extended oral drug release. Being of natural origin, with regulatory acceptance and the feasibility to control the drug release saturated phosphatidylcholine could be an alternative to polymeric excipients. 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.

## Aims

To evaluate general suitability of saturated phosphatidylcholine for tablet processing by direct compression.
To evaluate the predictability of *in vitro* drug release with an established solution of Fick's second law of diffusion.

## Methods

Powder flow was assessed with Carr's Index and Hausner ratio. Flat-faced tablets (160 ± 2 mg) with 5, 8 and 12 mm diameter were compressed from physical powder mixtures at pressures ranging from 5 to 400 MPa and drug loadings from 10 to 90% (w/w) using a single punch tablet press at 10 rpm (Korsch EK0, Korsch AG, Berlin, Germany). The tablet thickness and the diameter were measured by an electronic micrometer (± 0.01 mm, Digi-Met; Helios Preisser, Gammertingen, Germany) and tablet hardness by tablet hardness tester (Multicheck, Erweka GmbH, Heusenstamm, Germany). The tablet porosity was calculated as the ratio of apparent and true densities. Drug release was performed using an USP paddle apparatus (900 mL, hydrochloric acid solution pH 1.2 and pH 2, phosphate buffer pH 3, 0.05 M phosphate buffer pH 4.5 and 0.05 M phosphate buffer pH 6.8 at 37 °C, 75 rpm, n=3) (VK 7000, Agilent Technologies Deutschland GmbH, Böblingen, Germany). Osmolality of the medium was measured by freezing-point osmometer (Osmomat 3000, Gonotec, Berlin, Germany) and was adjusted with sodium chloride. Samples were taken at predefined time points and analysed UV-spectrophotometrically (λ=273 nm). Fitting into the non-linear regressions was done with MS Excel software, Solver add-in, applying least squares method.

## Results

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. Compacts of the pure excipient were characterized by a relatively low tensile strength and a low friability (~0.1%). The tensile strength was independent of compaction pressure above 40 MPa. Overall, very dense tablets were achieved for diprophylline with loadings up to 50% at 200 MPa compression force. Extended drug release was achieved with drugs of different solubility (330, 20 and 8 mg/mL). Formulations with diprophylline, caffeine and theophylline released 80% drug in 3.5, 6 and 24 h, respectively. Drug release rate increased with increasing drug content; the caffeine release time ($t_{80}$) from 8 mm tablets increased from 1.5 h to 18 h at 70% to 10% drug loading, respectively. The drug release was

governed by diffusion and could therefore be modelled by Fick's law of diffusion. Low porosity of the phosphatidylcholine matrixes at wide range of drug loadings simplified the model for *in vitro* drug release prediction (Grund et al., 2013)**.** Drug release profiles were thus a function of drug solubility, drug loading and tablet dimensions. During dissolution, agitation speed (50-100 rpm) and ionic strength of the release media (100-600 mOsmol/kg) had only a small effect on caffeine release (20% drug loading). An about 3-times faster release of caffeine was observed at pH 1.2 and 2 compared to pH 4.5 and 6.8, with an intermediate behaviour at pH 3. This was attributed to protonization of the phosphatidyl group of the matrix-former and thus a higher hydrophilicity.

## Conclusion

The evaluation of saturated phosphatidylcholine as a direct compression, controlled release excipient was performed. The phospholipid powder had good flow properties and good compactibility. Tablets with very low porosity were formed with up to 70% drug loading. Extended drug release could be achieved with drugs with different solubility, combining different drug loadings and tablets sizes. The drug release was robust to media ionic strength and mechanical forces; however, a pH-dependent release was observed.

## Keywords

Phosphatidylcholine; phospholipids; direct compression; extended release; matrix tablet

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