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Amorphous drug dispersions with mono- and diacyl lecithin: On molecular categorization of their feasibility and UV dissolution imaging

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ABSTRACT

There is a growing interest in drug–phospholipid complexes and similar formulations that are mostly solid dispersions with high drug load. This study aims to explore the feasibility of such phospholipid-based solid dispersions as well as to characterize them. A particular aim was to compare monoacyl phosphatidylcholine (PC) with the diacyl excipient. The solid dispersions were manufactured using a solvent evaporation technique and characterized by means of differential scanning calorimetry and X-ray diffractometry. Density functional theory was used to calculate molecular frontier orbitals of the different compounds. Finally, the dissolution properties were analyzed in a flow-through cell by means of UV imaging. It was found that the ability to form solid dispersions with the phospholipids containing amorphous or solubilized drug (at equimolar ratio with the lipid) was dependent on the drug's frontier orbital energy, the enthalpy of fusion, as well as the log *P* value. In a subsequent dissolution study, UV imaging revealed pronounced surface swelling of the solid dispersions. Only the monoacyl PC was found to substantially enhance *in vitro* dissolution compared to pure drug. The gained understanding will support a future development of solid drug dispersions using phospholipids as matrix components.

1. Introduction

Lipid-based formulations have become an indispensable approach to formulate challenging oral drugs (Porter et al., 2008; Muellertz et al., 2010; O'Driscoll and Griffin, 2008; Kuentz, 2012). Several of these formulations comprise phospholipids and the different formulation approaches can be mixed-micelles, liposomes, emulsions, suspensions, nanodispersions or self-emulsifying formulations (Fricker et al., 2010). A special type of delivery system is given by drug–phospholipid complexes. The phospholipid is here interacting with functional groups of the drug but not in a covalent way, which would otherwise be a conjugate or pro-drug (Dvir et al., 2007; Dahan et al., 2008). The complexation degree of the drug with the phospholipid is expected to be compound and lipid specific. The drug–lipid interaction can span from rather unspecific weak hydrophobic interactions to rather strong hydrophobic interactions in combination with electrostatic (ion-pair or charge–transfer complexes) interactions (Al-Hilal et al., 2013). Since the nature of the molecular drug–phospholipid association is often not clearly described in the literature, the term "drug–phospholipid complexes" has been used (Huesch et al., 2011).

Pioneer work using phospholipid complexes with non-steroidal anti-inflammatory drugs (NSAIDs) dates to the 1990s (Lichtenberger et al., 1995). The focus of this initial work was rather not the characterization of the drug–phospholipid solid state at the molecular level, but to reduce gastro-intestinal side effects of NSAIDs (Lichtenberger et al., 2009; Leyck et al., 1985). However, the possibility to achieve a high drug load (with an equimolar ratio of drug and phospholipid) makes this oral delivery approach very interesting to formulate poorly soluble drugs. Several recent articles focused on such complexes with phyto-pharmaceuticals such as for example berberine (Zhang et al., 2014) bergenin (Guan et al., 2014), chrysophanol (Singh et al., 2013), curcumin (Maiti et al., 2007), emodin (Singh et al., 2012c), etoposide (Wu et al., 2011). mangiferin (Ma et al., 2014), marsupsin (Sikarwar et al., 2008), quercetin (Singh et al., 2012a), or rutin (Singh et al., 2012b). More examples can be inferred from Semalty et al. (2010) and Khan et al. (2013), who excellently reviewed this emerging field of phyto-phospholipid systems.

An important research question is how drugs interact with the phospholipid on a molecular level. Previous mechanistic studies on NSAIDs in liposomes revealed an interaction of sodium diclofenac with the phosphate region of the polar head group (Lopes et al.,

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2014) and in a study of aspirin with 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), the importance of the aromatic drug moiety in the phospholipid interaction has been pointed out (Panicker et al., 1995). Interesting is a recent study of liposomes with several drugs using isothermal titration calorimetry (Osanai et al., 2013), wherein the observed enthalpies were very specific for the tested drugs. Data suggest that in hydrated phospholipids, a strong enthalpy contribution to the molecular interaction was limited to a few drugs. Other compounds exhibited a free energy change that was mostly driven by entropy. Thus, formation of a well-defined drug–phospholipid complex may only exist for a few drugs. Even though such considerations are again different in a condensed phase, the so-called phospholipid complexes may provide a rather heterogeneous group of formulations, also considering the heterogeneity of the fatty acid composition of the phospholipids (Van Hoogevest and Wendel, 2014), when phospholipids from natural sources have been used.

The different drug–phospholipid systems can be viewed as solid dispersions. In case of 1:1 molar drug to carrier load, it is likely that these are amorphous solid dispersions or more specifically amorphous complexes of drug and phospholipid. A differentiation from other solid dispersions such as solid solutions or mixed forms of solid dispersions would be subject to further mechanistic research.. From a biopharmaceutical perspective, however, such discrimination is not as important as for example learning about the release performance of the concentrated drug dispersions.

Interesting is the seminal work of Huesch et al., 2011, who studied diclofenac sodium, ibuprofen, and piroxicam with DPPC. Not only were the hydrated systems analyzed but also other intermediate products of a possible complex formation. Thus, different nuclear magnetic resonance techniques and molecular dynamics simulations were employed to elucidate the molecular interactions in organic solvents. Moreover, the solid state of the products was studied by means of X-ray powder diffractometry (XRPD) and Fourier transform infrared spectroscopy. It was concluded that existence of an 1:1 molar complex was probable in case of both diclofenac andibuprofen but not for piroxicam. For diclofenac and ibuprofen, their aromatic systems were forming with the quaternary ammonium group of DPPC a cation–π interaction that contributed to the complex formation. In aqueous media, diclofenac was interacting mainly with the polar head group of the phospholipid but some interaction with the hydrophobic core was also observed. In contrast, piroxicam was not showing any pronounced excipient association but precipitated upon hydration of the solid phospholipid product. Like in the organic solvent, the molecular interactions appeared to be highly compound specific. However, an isolated equimolar complex of NSAID with phospholipid was unlikely to form upon hydration of the drug–phospholipid complex.

The study of drug–excipient interactions in the dry as well as hydrated state constitutes a research field on its own (Misic et al., 2014). There are still several research gaps to overcome regarding solid drug–phospholipid systems. Most interesting is to understand which active compounds result in amorphous drug systems with phospholipids, *i.e.* without exhibiting drug crystallinity. Such drug crystallinity can be the consequence of insufficient drug association with phospholipid or occasionally; it can be due to co-crystal formation. Interesting is here for example that a new solid form was observed for diclofenac and DPPC, which was found after evaporation of the organic solvent (Huesch et al., 2011). Finally, drug–excipient interactions should be better understood when a phospholipid product is hydrated because a resulting drug supersaturation and optional precipitation are likely to affect oral drug absorption. Such knowledge is required to finally assess the suitability of the solid dispersions.

The focus of the current work is first to better understand the feasibility of amorphous solid drug dispersions with phospholipids (at an equimolar drug to lipid ratio). There is a need to study more drugs in such solid dispersions and there is currently only limited knowledge on the influence of different phospholipids on the product properties. A most interesting excipient candidate is here monoacyl phosphatidylcholine (PC). This phospholipid is an important species in small intestinal fluids (Vertzoni et al., 2012). Without the double chain, the lipophilic moiety of the single chain phospholipid becomes smaller, which means a more cone-like molecular geometry and a lower packing parameter. Therefore, monoacyl PC forms micelles upon hydration (Leigh and Leigh, 2003), which are promising for drug solubilization. It would be crucial to analyze release data from a series of concentrated drug–phospholipid dispersions but such data appear to be missing in the literature. It is expected that drug release from phospholipid systems is not trivial when thinking of phospholipid hydration. Therefore, an experimental imaging approach may be helpful to elucidate the mechanisms of drug dissolution in such systems.

The outlined research gaps were leading directly to the current study objectives. A broad series of poorly soluble compounds was studied regarding the feasibility to make solid dispersions using monoacyl as well as (unsaturated) diacyl PC as lipids. Solid state analysis included differential scanning calorimetry (DSC) as well as XPRD. It was particularly intended to explore the correlation between the frontier orbital energies of the drugs by quantum mechanical modeling (density functional theory, DFT (Hohenberg and Kohn, 1964)) and the drug's ability to form a solid dispersion with phospholipids in the dry solid state. The obtained drug products were then analyzed by UV imaging to study the drug release process.

2. Materials and methods

2.1. Materials

Monoacyl PC (Lipoid S LCP 80) and diacyl PC (Lipoid E 80) were kindly donated by Lipoid GmbH. (Ludwigshafen, Germany) and used without further purification. Lipoid S LCP 80 is a pharmaceutical grade mixture of ~80% monoacyl (synonymously named lyso PC) and ~20% diacyl lecithin purified form soy beans. Lipoid E80 is a pharmaceutical grade mixture of diacyl PC purified from eggs yolks and contains approx. 80% PC. Albendazole (methyl *N*-(5-(propylsulfanyl)-1H-1,3-benzodiazol-2-yl) carbamate), indomethacin (2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl) acetic acid), mebendazole (methyl *N*-(5-benzoyl-1H-1,3-benzodiazol-2-yl) carbamate), mefenamic acid (2-((2,3-dimethylphenyl) amino) benzoic acid), phenytoin (5,5-diphenylimidazolidine-2,4-dione), and sulfathiazole (4-amino-*N*-(1,3-thiazol-2-yl) benzene-1-sulfonamide) were purchased from Sigma–Aldrich Chemistry Ltd. (Buchs, Switzerland). Ezetimibe ((3R,4S)-1-(4-fluorophenyl)-3-((3S)-3-(4-fluorophenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl) azetidin-2-one), furosemide (4-chloro-2-((furan-2-ylmethyl) amino)-5-sulfamoylbenzoic acid) and glibenclamide (5-chloro-*N*-(2-(4-{((cyclohexylcarbamoyl) amino) sulfonyl}phenyl) ethyl)-2-methoxybenzamide) were obtained from Molekula Ltd. (Munich, Germany), and celecoxib (4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl) benzene-1-sulfonamide) was purchased from Matrix Scientific (Columbus, USA). Probucol (2,6-di-*tert*-butyl-4-({2-((3,5-di-tert-butyl-4-hydroxyphenyl) sulfanyl) propan-2-yl}sulfanyl) phenol) was acquired from Eurasian Chemicals Pvt., Ltd. (Mumbai, India), and sulfasalazine (2-hydroxy-5-((E)-2-{4-((pyridin-2-yl)sulfamoyl) phenyl}diazen-1-yl) benzoic acid) was purchased from LKT Laboratories Inc. (St. Paul, USA). Ethanol and tetrahydrofuran (both HPLC grade) were supplied from Aventor Performance Materials B.V. (Deventer, Netherlands).