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Probing adsorption of DSPE-PEG2000 and DSPE-PEG5000 to the surface of felodipine and griseofulvin nanocrystals

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ABSTRACT

Nanosized formulations of poorly water-soluble drugs show great potential due to improved bioavailability. In order to retain colloidal stability, the nanocrystals need to be stabilized. Here we explore the use of the poly(ethylene glycol) (PEG) conjugated phospholipids DSPE-PEG2000 and DSPE-PEG5000 as stabilizers of felodipine and griseofulvin nanocrystals. Nanocrystal stability and physicochemical properties were examined and the interaction between the PEGylated lipids and the nanocrystal surface as well as a macroscopic model surface was investigated. Using quartz crystal microbalance with dissipation monitoring both mass adsorption and the thickness of the adsorbed layer were estimated. The results indicate that the PEGylated lipids are adsorbed as flat layers of around 1–3 nm, and that DSPE-PEG5000 forms a thicker layer compared with DSPE-PEG2000. In addition, the mass adsorption to the drug crystals and the model surface are seemingly comparable. Furthermore, both DSPE-PEG2000 and DSPE-PEG5000 rendered stable drug nanocrystals, with a somewhat higher surface binding and stability seen for DSPE-PEG2000. These results suggest DSPE-PEG2000 and DSPE-PEG5000 as efficient nanocrystal stabilizers, with DSPE-PEG2000 giving a somewhat higher surface coverage and superior colloidal stability, whereas DSPE-PEG5000 shows a more extended structure that may have advantages for prolongation of circulation time *in vivo* and facilitation for targeting modifications.

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1. Introduction

A large proportion of new drug candidates are poorly water-soluble. One successful approach to increase the bioavailability of these drugs is nanosizing (Kipp, 2004; Möschwitzer, 2013). By manufacture of nanosized drug crystals, using techniques including ultrasonic crystallization and wet milling (Pawar et al., 2014), drug nanoparticles with increased dissolution rate and subsequently improved bioavailability can be made. These nanocrystals have a drug load of almost 100%, which is far superior to other nanodrug delivery approaches. The particles consist of crystals of almost pure drug and, in order to retain particle stability, a small addition of various ionic and/or polymeric stabilizers, such as poly (vinyl pyrrolidone) (PVP), dioctyl sulfosuccinate and pluronics type triblock copolymers (Pawar et al., 2014; Wu et al., 2011). Nanosizing leads to an increase in the total surface area, which increases the free energy of the system. Nanoparticles, therefore, tend to aggregate to minimize the surface energy. In order to retain a thermodynamically stable colloidal system, stabilization by the addition of surface modifiers is needed. There are two main mechanism by which these surface modifiers, or stabilizers, can maintain nanoparticle stability; by electrostatic repulsive forces and by steric hindrance. Stabilization by electrostatic repulsion is described by the Derjaguin, Landau, Verwey, Overbeek (DLVO) theory (Derjaguin and Landau, 1941; Verwey and Overbeek, 1948), in which it is assumed that the total force acting on a colloidal particle is the resultant force of all attractive van der Waals forces and the repulsive electrostatic forces. By addition of charged surfactants, the electrostatic repulsion can be increased. Steric stabilization instead is achieved by the adsorption of polymers that act as mechanical barriers to aggregation.

In addition to causing stable nanoparticles, the stabilizers added may also affect what happens to the drug particles *in vivo* (Farace et al., 2016; Huang et al., 2010). A nanoparticle in a physiological environment will be covered by serum proteins, the so called “protein corona”. The protein corona is suggested to

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influence transport and biodistribution of the nanoparticles (Lynch and Dawson, 2008). Depending on the surface properties of the nanoparticles, the proteins will have different affinities for the surface (Lundqvist et al., 2008; Perry et al., 2012) Some stabilizers, like PVP, pluronics and polyethylene glycol (PEG), inhibit protein binding, a trait that is believed to result in prolonged circulation time *in vivo* (Allen, 1994; Owens and Peppas, 2006; Salmaso and Caliceti, 2013; Torchilin, 2005). PEG is probably the most well-known polymer for this purpose. It is extensively used as surface modifier of various nanosized drug delivery vehicles, in particular lipid based ones, creating sterically stabilized particles with prolonged circulation time (Gref et al., 2000; Kolate et al., 2014). Reports have shown that the type of PEGylation (Lazos et al., 2005), the length of the PEG chain (Gref et al., 2000; Hoarau et al., 2004) and the PEG density on the surface (Gref et al., 2000; Perry et al., 2012) affect the surface properties of the particles and the subsequent biological response.

We are currently exploring the use of PEGylated lipids as nanocrystal stabilizers for intravenous administration. Our aim is to better understand how the PEGylated lipids DSPE-PEG2000 and DSPE-PEG5000 (Fig. 1) affect the properties of the nanocrystal surface. Therefore, we have investigated the stabilization efficiency as well as the binding and interaction of these amphiphiles with nanocrystals of the poorly soluble drugs felodipine and griseofulvin (Fig. 1), as well as to a macroscopic polystyrene coated model surface. Polystyrene coated macroscopic surfaces were chosen as model based on their, in comparison with the drug crystals, similar hydrophobic surface character. The macroscopic polystyrene surface is, in addition, chemically stable, has low surface roughness and is in no need of any additional stabilizing surface modification. To begin with, the stability of the drug nanoparticles was determined by means of light scattering and Z-potential measurements. The binding of the PEGylated lipids to the surface of the nanocrystals was quantified through UPLC analysis. To monitor the interaction of the PEGylated lipids with macroscopic surfaces we used quartz crystal microbalance with dissipation monitoring (QCM-D). QCM-D is a technology based on changes in vibration frequency of a quartz crystal sensor in response to interactions on the sensor surface. With QCM-D, the frequency, which is related to the mass deposition, and the dissipation, which is related to the rigidity of the adsorbed layer, are monitored simultaneously (Rodahl et al., 1995), making it possible to follow the adsorption of the PEGylated lipids to the surface in real-time. The adsorption of the lipids to the model surface was then compared with that to the nanocrystals, and information regarding mass adsorption, the thickness of the adsorbed layer as well as implications for formulation and *in vivo* administration of the drug nanocrystals could be discussed.

2. Materials and methods

2.1. Materials

Felodipine was from AstraZeneca R&D Gothenburg, griseofulvin was from Sigma-Aldrich, phosphate buffered saline (PBS) (tablet) was from Sigma-Aldrich and the PEGylated lipids 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-*N*-[methoxy(polyethylene glycol)-2000] (DSPE-PEG2000) and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-*N*-[methoxy(polyethylene glycol)-5000] (DSPE-PEG5000) were from Corden Pharma. The molecular weights of 2805 g/mol for DSPE-PEG2000 and 5801 g/mol for DSPE-PEG5000 were used in all calculations. All other chemicals used were of at least analytical grade.

2.2. Manufacture of drug nanoparticles

The felodipine and griseofulvin nanocrystals were manufactured by wet milling. In short, a crude suspension of 100 mg/mL felodipine or griseofulvin with 5 mg/mL, 10 mg/mL or 20 mg/mL DSPE-PEG2000 or DSPE-PEG5000 in milliQ water was made by sonication in an ultrasonication bath. The suspension was then stirred over night at room temperature and sonicated again before milling. Wet milling of the suspension was performed using a Fritsch Planetary Micromill P7 equipped with 1.2 mL milling bowls and 0.6–0.8 mm milling beads of zirconium oxide, at 700 rpm, for 4 times 30 min, with 15 min pauses in between. All suspensions were continuously kept in the dark. The crystallinity was verified using X-ray powder diffraction.

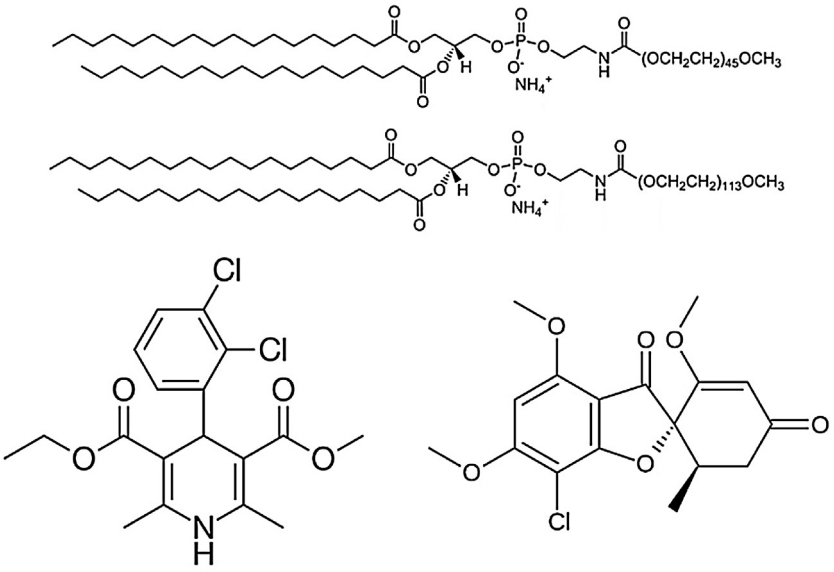

Fig. 1. Chemical structure of the drug nanoparticle stabilizers investigated; 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy(polyethylene glycol)-2000] (DSPE-PEG2000) and 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy(polyethylene glycol)-5000] (DSPE-PEG5000), as well as the active drug substances felodipine (left lower) and griseofulvin (right lower) used as drug nanocrystal model substances.

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