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Development of solid dispersions of artemisinin for transdermal delivery

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ABSTRACT

Solid dispersions of the poorly soluble drug artemisinin were developed using polymer blends of polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) with the aim of enhancing solubility and in vitro permeation of artemisinin through skin. Formulations were characterised using a combination of molecular dynamics (MD) simulations, differential scanning calorimetry (DSC), X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FT-IR). Solubility of artemisinin was determined in two solvents: de-ionised water and phosphate buffered saline (PBS; pH 7.4), while in vitro drug permeation studies were carried out using rabbit skin as a model membrane. MD simulations revealed miscibility between the drug and polymers. DSC confirmed the molecular dispersion of the drug in the polymer blend. Decrease in crystallinity of artemisinin with respect to polymer content and the absence of specific drug–polymer interactions were confirmed using XRD and FT-IR, respectively. The solubility of artemisinin was dramatically enhanced for the solid dispersions, as was the permeation of artemisinin from saturated solid-dispersion vehicles relative to that from saturated solutions of the pure drug. The study suggests that high energy solid forms of artemisinin could possibly enable transdermal delivery of artemisinin.

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1. Introduction

Malaria is the major and the most prevalent public health problem in many parts of the world (Chamchod and Beier, 2013). According to WHO, about half of the world's population is exposed to the risk of malaria (World Health Organization, 2010a) and it is the foremost cause of morbidity and mortality in the world with a million of deaths every year (World Health Organization, 2010a; Eastman and Fidock, 2009). Resistance to conventional antimalarial drugs has led to changes in malaria control policies globally in favour of artemisinin. Currently, the treatment of choice for uncomplicated and severe malaria is based on administration of artemisinin and its derivatives (Shahzad et al., 2011), either used alone or in combination with other drugs (Eastman and Fidock, 2009; World Health Organization, 2010b). Average plasma concentration of artemisinin after single oral dose of 500 mg tablet formulation range between 400 and 700 ng/mL (Gordi et al., 2000).

Artemisinin (Fig. 1) is a parent compound of a novel family of antimalarials extracted from the Chinese traditional plant, *Artemisia annua*, L. Asteraceae. It is effective against malaria parasites, including the multidrug-resistant falciparum species due to its high potency and rapid onset of action (Klayman, 1985; Svensson et al., 1999; Thaithong and Beale, 1985). Structurally, it is a sesquiterpene lactone with an inner peroxide bridge which is responsible for its antimalarial activity. It is characterised as a poorly water-soluble drug with an octanol–water partition coefficient greater than 2 and a short half-life of 2–3 h, and is extensively metabolised by the liver. Thus, oral bioavailability can be as low as 32% (Sahoo et al., 2011; Svensson et al., 1999; Wong and Yuen, 2001). Although artemisinin has shown excellent permeability across the intestinal mucosa, it has low bioavailability because of its poor aqueous solubility, which can adversely affect its efficacy (Titulaer et al., 1991). This makes artemisinin a suitable candidate for transdermal drug delivery, which circumvents the first pass metabolism by the liver.

Solid dispersion of an insoluble drug in hydrophilic polymers is an attractive technique for enhancing drug solubility and the dissolution rate, which for rapidly absorbing molecules such as artemisinin could enhance their drug bioavailability (Lima et al., 2011); (Craig, 2002). Most solid dispersions are prepared using highly water-soluble polymers as the carrier, where the polymer can be amorphous (for example polyvinylpyrrolidone; PVP) or partially crystalline (for example polyethylene glycol; PEG) (Zhu et al., 2012). Solid dispersions are generally prepared by either a solvent

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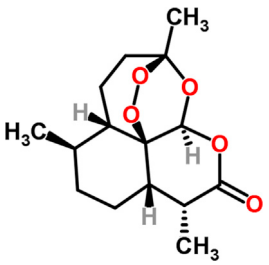

Fig. 1. Structure of artemisinin.

method, whereby the drug and carrier are dissolved in a mutual solvent followed by the removal of solvent by evaporation, or by a melting method, whereby drug–carrier mixtures are prepared by co-melting/cooling (Bley et al., 2010). Upon dissolution of the solid dispersion in an aqueous medium the carrier will dissolve rapidly, releasing very fine colloidal drug particles of very high surface area resulting in dissolution rate enhancement (Serajuddln, 1999). The primary issue with solid dispersions is re-crystallisation of the drug on storage and also immediately on dissolution, which can be addressed by judicious choice of stabilising polymer(s) taking into account the drug–polymer intermolecular interactions, the viscosity of the polymer, and the glass transition temperature of the solid dispersion (Andrews et al., 2010).

In the present study we investigate the development of solid dispersions of artemisinin using polyvinylpyrrolidone (PVP) grade PVP-K30 and polyethylene glycol (PEG) 4000 aimed at enhancing in vitro permeation of artemisinin across skin. Both PVP and PEG are polymers of choice for solid dispersions. PVP is an amorphous water-soluble polymer with a glass transition temperature between 110 and 180 °C, while PEG is semicrystalline with a low melting point and is also water-soluble. We show that the permeability of artemisinin from the solid dispersions in enhanced in excess of 10 fold relative to that of a saturated solution of the original drug. The physical state of the drug in the solid dispersions was characterised through X-ray diffraction, Fourier-transform infra-red spectroscopy, and differential scanning calorimetry. The stability of the solid dispersions is linked with the drug–polymer and polymer–polymer (for mixed polymer systems) miscibility, which can be characterised by the solubility parameter. The solubility parameters are typically estimated by a group contribution method (Van Krevelen and Hoftyzer, 1976), but such an approach is challenged by directional hydrogen bonding and long-range electrostatic interactions (Langer et al., 2003). Here we employ the more rigorous approach of molecular dynamics (MD) simulation, which accounts for the individual atomic interactions, to estimate the solubility parameters, following the work of (Gupta et al., 2011). The results reveal that artemisinin and the polymers PVP and PEG are relatively miscible with each other encouraging the formation of a molecular dispersion of the drug in the polymer matrix and its stability, which indeed rationalises the enhanced solubility and permeation observed from the dispersions.

2. Materials and methods

2.1. Materials

The following chemicals were used as purchased: artemisinin 99.9% purity (Alchem, New Delhi, India); PVP-K30 and PEG-4000 (Beijing chemical company, Beijing, China); methanol HPLC grade 99%+ (Merck, Darmstadt, Germany); potassium dihydrogen phosphate (VWR, Lutterworth, Leicestershire UK); sodium chloride and potassium chloride (Sigma–Aldrich, Poole, Dorset, UK); di-sodium hydrogen phosphate (Fischer Scientific Chemicals, Loughborough, Leicestershire, UK); vacuum grease (Dow Corning, Midland, Michigan, USA). De-ionised water was used throughout to make up all solutions.

2.2. Quantitative analysis of artemisinin

Artemisinin was quantified using HPLC method with UV-detection as described previously (Sahoo et al., 2009; Zhao and Zeng, 1985), in which artemisinin is transformed into a UV-absorbing compound through an alkali reaction, i.e. by heating the solution with 0.2% NaOH solution. The alkali reaction was carried out by adding 5 mL of 0.2% NaOH solution to each sample, then heated at 50 ± 1 °C for 30 min and allowed to cool down in a refrigerator. Finally, 1 mL glacial acetic acid was added to each sample before injecting into the HPLC system.

Briefly, the HPLC system comprised of a Severn Analytical solvent delivery system (SA 6410B), a Waters 2487 UV-detector (Waters, Hertfordshire, UK), a Rheodyne injector (Perkin Elmer 7725) fitted with a 20 μL sample loop. The column used was Novapack C18 (4.6 cm × 15 cm, 4 μm) (Waters, Hertfordshire, UK). The composition of mobile phase was 0.01 M di-sodium hydrogen phosphate (75%) and acetonitrile (25%) and the final pH was adjusted to 6.5 using glacial acetic acid. The mobile phase was pumped through the system with a flow rate of 0.8 mL/min. The UV-detector was set at a wavelength of 290 nm.

2.3. Formulation of solid dispersions

Solid dispersions of artemisinin in two hydrophilic polymers, namely PVP and PEG were prepared by conventional solvent evaporation and lyophilisation methods as described previously (Shahzad et al., 2012). Solid dispersion were prepared with different drug to polymer ratios, i.e. 6:4, 5:5, 3:7, 2:8, and 1:9. It should be noted that the quantities of PVP and PEG were kept equal (i.e. 50:50 wt%) with respect to each other in all the formulations. For conventional dispersions (CD), accurately weighed quantities of PVP and PEG were dissolved in 100 mL of methanol in a pre-cleaned vessel. This was followed by the addition of accurately weighed quantities of artemisinin and allowed to dissolve completely by continuous stirring at ambient temperature. Methanol was evaporated on a rotary evaporator at reduced pressure. The resulting residue was dried under vacuum in a desiccator for 24 h at ambient temperature and the dried mass obtained was finally pulverised in a pre-cleaned pestle and mortar for about 5 min until a homogeneous mixture was obtained and then refrigerated in a closed vial at 5 °C until further investigations.

For lyophilised dispersions (LD), each of the drug–polymer mixture of respective ratio was dissolved in methanol until a clear solution was obtained. This solution was quickly solidified by immersing the flask in liquid nitrogen. Upon cooling, the flask was attached to the vacuum adapter of the lyophiliser for sublimation. After the solvent was completely removed, a porous and fluffy powder residue appeared that was kept in a refrigerator at 5 °C until further investigations.

The prepared formulations were subjected to drug content analysis. Three random samples of 10 mg drug equivalent from each formulation were dissolved in methanol and appropriately diluted and the drug content was determined by HPLC analysis after alkali reaction. The drug content in the solid dispersions prepared from both methods was found to be in the range of 88–91%.

2.4. Characterisation of dispersions

2.4.1. Drug–polymer miscibility determination

A key consideration for developing a physically stable dispersion is the miscibility of drug in the polymer matrix. The cohesive

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