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Poorly water-soluble drug nanoparticles *via* solvent evaporation in water-soluble porous polymers

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ABSTRACT

A generic method is described to form poorly water-soluble drug nanoparticles within water-soluble porous polymer by solvent evaporation. The simple dissolution of porous polymer with drug nanoparticles results in stable aqueous drug nanoparticle suspension under the optimized conditions. The porous polymers were prepared by freeze-drying aqueous solutions of polyvinyl alcohol, polyethylene glycol, and a surfactant. They were then used as scaffolds for the formation of nanoparticles by initially soaking them in an organic drug solution, followed with removing the solvent *via* evaporation under ambient conditions. This process was optimized for an antifungal drug griseofulvin, before being translated to anticonvulsant carbamazepine and antineoplastic paclitaxel *via* a similar procedure, with an aim to improve the loading of drug nanoparticles. By varying certain process parameters a degree of control over the particle size and surface charge could be attained, as well as the drug to stabilizer ratio (drug payload). Noticeably, aqueous paclitaxel nanoparticles (500 nm) were prepared which used the equivalent of 46% less stabilizer than the formulation Taxol®.

1. Introduction

Overcoming poor aqueous solubility is a significant challenge faced by the pharmaceuticals industry at present, with over 40% of compounds in development pipelines classed as being poorly water soluble (Kasim et al., 2003; Lipinski, 2002). This can lead to issues such as low bioavailability, erratic absorption profiles and reduced patient compliance from having to administer larger or more frequent doses (Rannard and Owen, 2009). The problem is even more acute in the field of oncology due to the high toxicity, cost and the side effects associated with many antineoplastic agents (Shepherd, 2003).

There have been many attempts over the years to overcome this issue through various formulation approaches. These include the application of emulsions (Masahiro, 2000), microemulsions (Lawrence and Rees, 2000), solid dispersions (Vasconcelos et al., 2007) and liposomes (Schwendener and Schott, 1996) as drug delivery systems. Design of polymer architectures (including amphiphilic block copolymers, comb-shaped polymers, dendrimers, and hyperbranched polymers) has been extensively employed for delivery of hydrophobic drugs, by means of encapsulation in micelles, nanoparticles, microspheres or capsules (Qiu and Bae, 2006; Adams et al., 2003; Hoskins et al., 2012; Svenson, 2009). These processes often experience problems such as poor physical stability, difficulty in scale up and inability to achieve high drug loading; issues which have so far prevented them from being widely adopted for wider use (Patravale et al., 2004). Another approach to improving drug solubility is to form a nanosuspension of the desired compound. A nanosuspension can be defined as a colloidal dispersion of pure drug nanoparticles (or nanocrystals) stabilized by appropriate dispersants (Liu et al., 2007, 2012). The principle advantage of employing a nanosuspension over other delivery methods is that the vehicle itself is composed of the pure drug, meaning a relatively high ratio of the active compound to stabilizing excipients can be achieved (Müller et al., 2011).

The standard methods employed to prepare nanosuspensions are typically categorized as either "top-down" or "bottom-up" processes (Liu et al., 2012; Müller et al., 2011; Horn and Rieger, 2001; Shegokar and Müller, 2010). Top-down methods typically form nanocrystals *via* the attrition or ablation of larger drug fragments, whereas bottom-up methods generally produce amorphous nanoparticles *via* controlled precipitation from solutions or emulsions (Horn and Rieger, 2001). Although both categories have led to the development of viable pharmaceutical products, the processes have a number of limitations. For instance, top-down approaches such as wet milling and high pressure homogenization are generally not applicable to soft or temperature-sensitive compounds, and impurities may be introduced into the drug formulations by attrition of milling media or residual solvents.

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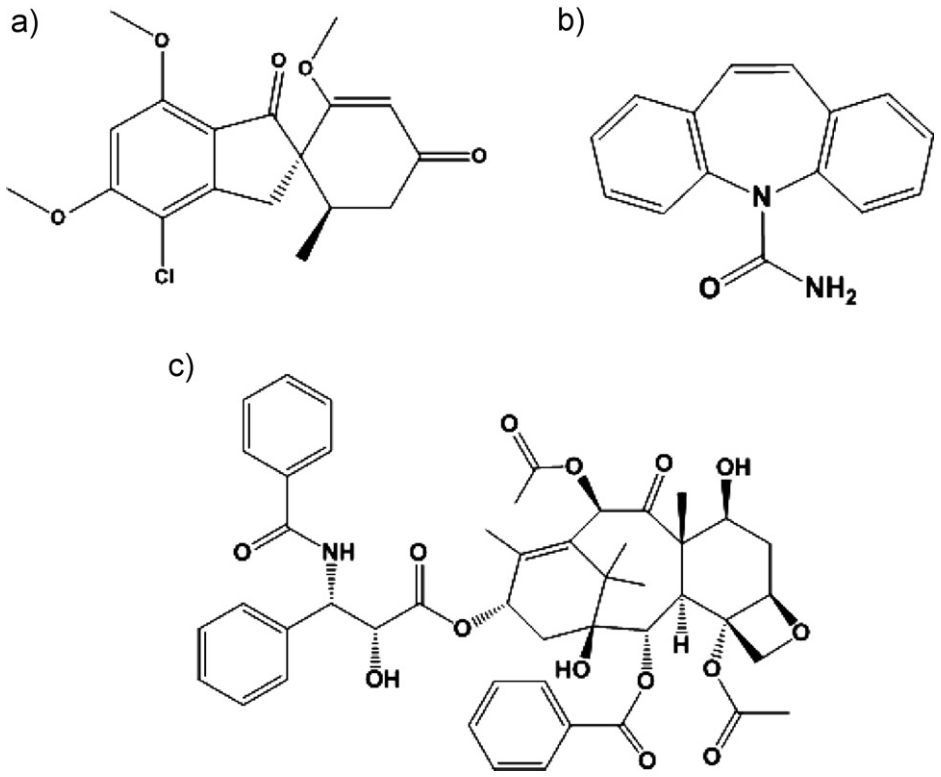

Scheme 1. Chemical structures of (a) GF (M_W 352.8 g mol^{-1}), (b) CBZ (M_W 236.3 g mol^{-1}) and (c) PTX (M_W 853.9 g mol^{-1}).

An emulsion freeze-drying approach was developed to form organic or drug nanoparticles *in situ* within porous polymers; the addition of water to such materials causes them to rapidly dissolve and release the nanoparticle payload to produce aqueous nanoparticle dispersions (Zhang et al., 2008a; Grant and Zhang, 2011). This is an approach that may be applied without the above mentioned limitations. For example, nanoparticle aggregation can be avoided because they are supported within the porous scaffold. In this approach, oil-in-water (O/W) emulsions were formed first with the drugs dissolved in the oil phase. However, many poorly water-soluble drugs are only soluble in polar organic solvents (*e.g.*, ethanol, acetone) particularly when the toxicity of the organic solvents is taken into consideration. It is extremely difficult to form O/W emulsions from these polar organic solvents, thus seriously limiting the application of the emulsion freeze-drying approach. Furthermore, these organic solvents normally have very low melting points (<−100 °C) and it is not economically effective to remove the solvents by freeze drying.

Recently, a 2-step procedure '*Solvent Evaporation within Porous Polymer*' (SEPP) was proposed to address the emulsion and organic solvent freeze-drying issue. Porous polymers were firstly prepared by freeze-drying. These materials were then soaked in organic drug solutions. After filtration, the organic solvent could be removed by evaporation rather than freeze drying (Qian et al., 2011). This procedure can be used for all types of organic solvents including ethanol and acetone. The materials can be composed of various biocompatible polymers and surfactants, giving them the dual role of acting as templates for the initial formation of nanoparticles as well as stabilizers upon dissolution. The materials may also be administered directly as a solid dose platform, which may be more convenient than an aqueous nanosuspension under certain situations from a pharmacological perspective (Lee, 2003).

In this study, the SEPP approach is applied to prepare poorly water-soluble drug nanoparticles. The procedures are investigated to produce porous polymers which are used to generate high ratio of drug nanoparticles to stabilizer in the formulations. The formulation and process parameters were initially optimized using griseofulvin (GF) as a model compound, before the process was translated to carbamazepine (CBZ) and paclitaxel (PTX); drugs which differ in molecular weight and have little structural resemblance (Scheme 1). No additional optimization was performed for the preparation of CBZ and PTX nanosuspensions, suggesting that the formulation developed could be applicable to a wide range of other hydrophobic drug compounds.

2. Materials and methods

2.1. Chemicals and reagents

Polyvinyl alcohol (PVA, 80% hydrolysed, M_W 9000–10,000), polyethylene glycol (PEG, M_W 20,000), sodium dodecyl sulfate (SDS), cetyltrimethylammonium bromide (CTAB), sodium deoxycholate (SDC) and dioctyl sodium sulfosuccinate (AOT) were purchased from Sigma Aldrich and used as received. The drugs griseofulvin (GF, >97% from *Penecillium griseofulvum*), carbamazepine (CBZ) and paclitaxel (PTX, >95% from *Taxus brevifolia*) were also purchased from Sigma. Analytical grade acetone and methanol were purchased from Fischer Scientific. Deionised water was used for the preparation of aqueous solutions.

2.2. Procedure to make porous polymer and drug nanoparticles

A freeze and freeze-drying approach was used to prepare a variety of porous materials. Both O/W emulsions and aqueous solutions were investigated, with the same freeze-drying procedure. It was found that the simpler preparation procedure with aqueous solutions could produce porous materials for the formation of similar quality of drug particles. The optimized procedure for freeze-drying aqueous solutions is described here. Typically, an aqueous solution of PVA (1.5 wt%), PEG (0.5 wt%) and SDS (1 wt%) was firstly