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Vinyl polymer-coated lorazepam particles for drug delivery to the airways

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ABSTRACT

A particle engineering method that adsorbs a microfine vinyl polymer coat to crystalline drug microparticles has been shown to be an effective way to control delivery. However, the means by which the functional performance of such microparticles is altered by the behaviour of the polymers in the microparticle coat remains unclear. The aim of this study was to determine the influence of vinyl polymer coating on the *in vitro* delivery characteristics of intranasal lorazepam microparticles. A series of four, similarly sized (*ca.* 10 μm), lorazepam-rich microparticles with different polymer coats were generated. The absorption of the polymer coats appeared to disrupt lorazepam solid state dimer formation in the microparticles, which manifested in a reduction in drug melting point. Mildly cohesive particles (aerodynamic diameter of 32 μm) that allowed rapid drug release (*ca.* 80% in 5 min) were generated when partially hydrolysed PVA dominated the microparticle coat, whilst fully hydrolysed PVA reduced particle cohesion and retarded drug release (*ca.* 15% release in 5 min). Infrared analysis showed that the properties of the microparticles were dictated by the strength of the hydrogen bonding in the polymer coat and not the strength of coat adsorption that was facilitated by hydrogen bond formation between the hydroxyl groups of the PVA and the hydroxyl group at position C3 of the lorazepam diazepine ring.

1. Introduction

Insomnia is commonly treated by oral administration of lorazepam, but the 1–2 h delay to induce significant sedation is a major barrier to effective therapy. This delayed onset can often result in over dosing due to the patient taking another dose in an attempt to initiate the clinical effects. Intranasal administration of lorazepam could dramatically improve the immediacy of sedation. The large surface area of the nasal mucosa provides rapid absorption into the systemic circulation and the possibility of direct access to the central nervous system (Costantino et al., 2007). Nasal delivery also has the benefits of being non-invasive and avoiding 'first-pass' metabolism.

Attempts to reformulate lorazepam have been hindered by its lack of aqueous solubility (*ca.* 0.08 mg/mL) (Moffat et al., 2004) and poor chemical stability (Archontaki et al., 1999). Although dissolving this active agent in propylene and polyethylene glycol solutions appears to resolve the chemical stability issues, there have been reports of possible toxicity associated with these solubilisers (Laine et al., 1995; Cawley, 2001). Considering the physicochemical properties of lorazepam, formulating this drug in the form of a dry powder would appear to be a sensible approach, but a particulate based system would require efficient aerosolisation and rapid dissolution to ensure a superior clinical outcome to the oral dosage form. Applying an appropriate particle engineering method to generate a lorazapam rich microparticle is one potential means to achieve this.

It has been demonstrated that efficient particle engineering facilitates fine control over the size, density and morphology of a material which can be used to influence the behaviour of a delivery system. For example, Bao and Zhao (2010) reported a membrane emulsification approach that could produce uniform microparticles with controllable size. Edwards et al. (1997) utilized a spray drying method for the formation of low density porous poly (lactic acid-co-glycolic acid) particles containing insulin and testosterone. Chew and Chan (2001) modified the surface morphology of bovine serum albumin microparticles to generate 'corrugated particles'. Rehman et al. (2004) employed supercritical fluids to modify the crystallinity of terbutaline sulfate microparticles. Rogers et al. (2003) attempted to use a method of spray-freezing into liquid to manufacture novel amorphous danazol microparticles with improved dissolution characteristics. However, many of these methods show

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Table 1
Lorazepam suspensions used for the microparticle engineering process. In each suspension 1 g of lorazepam was suspended in 100 mL of water to which the polymers were added; PVA and PVP represent poly(vinyl alcohol) and poly(vinyl pyrrolidone), respectively; the data of PVA hydrolysis was from the products MSDS (material safety data sheets). K17 and K90 correspond to a molecular weight of *ca.* 12,000 and 1300,000, respectively.

Formulation	PVA (g) (hydrolysis, %)	PVP (g) (grade)
$HyLorz_{pva}$	0.06 (99)	0.01 (K17)
$Lorz_{pva}$	0.6 (88)	0.1 (K17)
$HwLorz_{pvp}$	0.06 (88)	0.01 (K90)
$HpLorz_{pvp}$	0.06 (88)	0.1 (K17)

limited control over drug crystallinity and the generated particles often exhibit an extremely diverse morphology.

One approach that has the potential to overcome the aforementioned issues is the generation of microparticulate carriers using an engineering technique that facilitates biocompatible macromolecule adsorption. Vinyl polymers such as poly(vinyl alcohol) (PVA) and poly(vinyl pyrrolidone) (PVP) have previously been shown to modify microparticle behaviour in inhaled formulations (Buttini et al., 2008a,b), whilst maintaining excellent control of physical stability in both the dry state and in suspension (Jones et al., 2006a,b). The biocompatible macromolecule coating process is facilitated when vinyl polymers are employed as the coating agents by their ability to spontaneously adsorb onto the surface of hydrophobic drugs in aqueous solutions (Buttini et al., 2008b). Coating using vinyl polymers is known to proceed in a multilayered manner as a result of the intra and intermolecular hydrogen bonding that occurs between the vinyl polymer chains (Buttini et al., 2008a,b).

The aim of this study was to investigate how an adsorbed vinyl polymer coat influenced the key delivery characteristics of intranasal lorazepam microparticles. In order to achieve this, a specific series of vinyl polymer-coated microparticles were generated. The method of Buttini et al. (2008a,b) was manipulated in order to modify the nature of polymer adsorption whilst maintaining a constant final particle diameter. In total, a series of four test microparticles were generated using a mixture of PVA and PVP which was varied to generate a 'standard' particle, similar to that produced previously ($Lorz_{pva}$) (Buttini et al., 2008a); a particle that had a coat dominated by fully hydrolysed PVA, i.e. a coat with extensive intra-molecular hydrogen bonding ($HyLorz_{pva}$); a particle with a high viscosity coat ($HwLorz_{pvp}$) and a particle where a high proportion of PVP was employed ($HpLorz_{pvp}$) (Table 1). The interaction of the two polymers with each other (Fourier Transform Infrared (FT-IR) spectrometry analysis) and with the drug (differential scanning calorimetry), an assessment of particle cohesiveness (impaction assessment) and drug release (modified United States Pharmacopeia (USP) dissolution) was compared in an attempt to elucidate the influence of the polymer employed in the adsorption process upon the particle behaviour.

2. Materials and methods

2.1. Materials

Lorazepam (Ph Eur) was supplied by Cambrex Profarmaco (Milano, Italy). Potassium dihydrogen orthophosphate and high performance liquid chromatography (HPLC) grade orthophosphoric acid, cylcohexane, water, methanol, ethanol and acetonitrile were all purchased from Fisher Scientific (Loughborough, UK). Formic acid, 1-chlorobutane, sodium chloride and sodium dodecyl sulfate (SDS) were supplied by Sigma–Aldrich Ltd. (Poole, UK). PVA 28-99 and PVA 23-88 were supplied by KSE (Troisdorf, Germany). PVP (Kollidon 17) and Solutol HS 15 were supplied by BASF (Wantage, UK). PVP (Kollidon 90) was supplied by ISP (Calvert City, USA) and ammonium solution 25% by BDH (Poole, UK).

2.2. Microparticle production

Approximately 1.0 g of lorazepam (6.73 μm) was weighed in to an amber flask (100 mL) which was then filled with an aqueous solution containing mixtures of PVA and PVP of various grades and concentrations to produce the four suspensions (Table 1). These suspensions were spray-dried using a Buchi 191 bench top spray drier (Buchi, Switzerland). During spray-drying the suspensions were held at ambient temperature (20 ± 2 °C) with the exception of $HpLorz_{pvp}$ which was heated to 80 °C and agitated by constant magnetic stirring to ensure adequate suspension stability during manufacture (Stuart Scientific, Stone, UK). The inlet temperature of the spray-drier apparatus was maintained at 180 °C, the nozzle air flow at 650 mL min^{-1}, the atomisation flow at 70% and a feed rate at 3 mL min^{-1}. The spray-dried particles were collected on wax paper and stored under desiccation until required for further analysis. The yield of the process was calculated Eq. (1).

$$\text{yield}\,(\%) = \frac{\text{Mass of particles post spray drying}}{\text{Initial solid mass in the suspension}} \times 100 \qquad (1)$$

The lorazepam content uniformity of the spray-dried microparticles was tested by HPLC. A 10 mg aliquot of each microparticle batch was added to 100 mL of an ethanol/water co-solvent mixture (1:1, v/v), the solution was diluted 1:10 (v/v) using the same solvent and the lorazepam content assayed by HPLC. Lorazepam content in each formulation was calculated by dividing the drug mass by the mass of the particles post spray-drying and the relative standard deviation was used as the indication of drug content uniformity ($n = 6$).

2.3. Laser diffraction particle size analysis

The size (volume mean diameter, (VMD)) of the spray-dried lorazepam microparticles was determined using laser diffraction (Mastersizer X, Malvern, UK). The lens used was 100 μm, active beam length 14.3 mm and the sample unit was a MS-7 (magnetically stirred cell). A concentrated sample of each formulation was suspended in lorazepam-saturated cyclohexane before being sonicated in a water bath (Model F5100b; Decon Laboratories, UK) for 10 s to ensure dispersion of any aggregates. The samples were added drop-wise into the MS-7 cell containing drug-saturated cyclohexane with continuous magnetic stirring until an ideal obscuration (10–30%). Measurement was repeated eight times for each sample and three samples measured per batch using a randomised sampling procedure.

2.4. Thermogravimetric analysis

The volatile content of the spray-dried microparticles was determined using a 2050 thermogravimetric analyser (TGA) (TA instruments, Crawley, UK). Samples of each microparticle batch (approximately 10 mg) were assessed in individual open aluminium pans and placed into the sampler of the TGA instrument. A heating rate of 10 °C min^{-1} from 25 °C to 300 °C was used to determine the percentage of volatiles present in the spray-dried samples.

2.5. Differential scanning calorimetry

Thermal measurements were carried out using a 2920 modulated differential scanning calorimetry (DSC) equipped with thermal solutions universal analysis software® (TA Instruments, Crawley, UK). Prior to analysis the DSC was calibrated using an