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Development of a novel dry powder inhalation formulation for the delivery of rivastigmine hydrogen tartrate

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ABSTRACT

The purpose of this study was to prepare engineered particles of rivastigmine hydrogen tartrate (RHT) and to characterize the physicochemical and aerodynamic properties, in comparison to a lactose carrier formulation (LCF). Microparticles were prepared from ethanol/water solutions containing RHT with and without the incorporation of L-leucine (Leu), using a spray dryer. Dry powder inhaler formulations prepared were characterized by scanning electron microscopy, powder X-ray diffraction, laser diffraction particle sizing, ATR-FTIR, differential scanning calorimetry, bulk and tapped density, dynamic vapour sorption and *in vitro* aerosol deposition behaviour using a next generation impactor. The smooth-surfaced spherical morphology of the spray dried microparticles was altered by adding Leu, resulting in particles becoming increasingly wrinkled with increasing Leu. Powders presented low densities. The glass transition temperature was sufficiently high (>90 °C) to suggest good stability at room temperature. As Leu content increased, spray dried powders presented lower residual solvent content, lower particle size, higher fine particle fraction (FPF < 5 μm), and lower mass median aerodynamic diameter (MMAD). The LCF showed a lower FPF and higher MMAD, relative to the spray dried formulations containing more than 10% Leu. Spray dried RHT powders presented better aerodynamic properties, constituting a potential drug delivery system for oral inhalation.

1. Introduction

There is an increasing interest in systemic drug delivery *via* the pulmonary route, mainly because the respiratory system represents an attractive non-invasive administration route for new disease therapeutics (Hickey, 2013; Pilcer and Amighi, 2010; Stank and Steckel, 2013), and, in most cases, using an inhalation device, a lower dose of drug is required to achieve a therapeutic effect relative to oral administration (Price et al., 2002). In addition, the pulmonary route can provide substantially higher bioavailability, as the lungs has a large surface area (70–140 m^2 in adult human lung) (Groneberg et al., 2003) combined with an extremely thin alveolar epithelial barrier (0.1–0.2 μm). The lungs also present a high level of vascularization that allows for rapid drug absorption with relatively low local metabolic activity, and no hepatic first pass effect (Marianecci et al., 2011; Pilcer and Amighi, 2010; Stank and Steckel, 2013).

Devices for pulmonary drug delivery introduce the drug into the airways in the form of an aerosol. Drug delivery to the lungs requires inhalable particles in the dispersed phase of this aerosol to have an aerodynamic diameter between 1 and 5 μm in order to be deposited in the lower respiratory tract (Stank and Steckel, 2013; Zeng et al., 2001). Most dry powder inhaler (DPI) formulations consist of micronized drug particles blended with larger carrier particles, typically α-lactose monohydrate, which enhance powder flowability, dispersion and reduce particle agglomeration (Healy et al., 2014; Pilcer et al., 2012; Young et al., 2009; Zeng et al., 2001).

Abbreviations: API, active pharmaceutical ingredients; ATR-FTIR, attenuated total reflection-FTIR spectroscopy; DPI, dry powder inhaler; DSC, differential scanning calorimetry; DVS, dynamic vapour sorption; ED, emitted recovered dose; FPF, fine particle fraction; GSD, geometric standard deviation; HPLC, high performance liquid chromatography; Inu, inulin; LCF, lactose carrier formulation; Leu, L-leucine; MMAD, mass median aerodynamic diameter; NGI, next generator impactor; PXRD, powder X-ray diffraction; RH, relative humidity; RHT, rivastigmine hydrogen tartrate; RSC, residual solvent content; RSD, relative standard deviation; SD, standard deviation; SEM, scanning electron microscopy; TGA, thermogravimetric analysis.

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Drug particles stick to the carrier particle surface by physical forces of interaction and should detach from the carrier on device actuation and powder inhalation (Pilcer et al., 2012; Young et al., 2009). A number of factors influence these interactions, *e.g.* physicochemical properties such as, particle size, particle shape and morphology, surface area and surface energy, which in turn determine flow, dispersion, and deposition in the respiratory tract (Pilcer et al., 2012; Telko and Hickey, 2005; Zeng et al., 2001).

Nonetheless, the carrier may be omitted and the performance of DPI formulations may be significantly enhanced through particle engineering approaches, by lowering the geometric diameter of the particles and/or particle density (Boraey et al., 2013; Bosquillon et al., 2001; Bosquillon et al., 2004; Nolan et al., 2009; Seville et al., 2007; Steckel and Brandes, 2004), altering particle shape (Bosquillon et al., 2001; Feng et al., 2011; Kaialy et al., 2011; Larhrib et al., 2003; Steckel and Brandes, 2004) and by forming particles with rough surfaces (Seville et al., 2007; Sou et al., 2013; Young et al., 2009). Research in the last decade, has focused on the development of aerodynamically light particles with particle size lower than 5 μm, bulk density less than 0.3 g/cm^3 and mass median aerodynamic diameter (MMAD) between 1 and 5 μm to achieve a higher respirable fraction and, consequently successful drug delivery (Bosquillon et al., 2004; Edwards et al., 2005; Healy et al., 2014; Pilcer et al., 2012; Steckel and Brandes, 2004).

Spray drying has been explored as a promising technique to produce particles with the above mentioned characteristics, often without the need to use coarse carriers, and as a process that can be easily translated to large scale production (Chow et al., 2007; Healy et al., 2014; Pilcer et al., 2012; Vehring, 2008). A number of studies suggest that further improvement in the aerodynamic properties of spray dried particles could be achieved through the inclusion of L-leucine in formulations, since L-leucine is a low-density amino acid with hydrophobic characteristics (Boraey et al., 2013; Chow et al., 2007; Seville et al., 2007; Sou et al., 2013).

Past research has shown that the morphology of spray dried microparticles changed from solid spheres to wrinkled surfaces (Boraey et al., 2013; Feng et al., 2011; Sou et al., 2013) or imparted additional porosity to the particle (Chow et al., 2007) when the L-leucine mass fraction was increased. This change in the particle properties is thought to be due to L-leucine precipitation on the surface of drying droplets, forming a hydrophobic outer shell layer with wrinkled texture (Boraey et al., 2013; Feng et al., 2011; Healy et al., 2014; Sou et al., 2013; Vehring, 2008). The non-displacement of L-leucine into the droplet centre can be considered characteristic of a system where the ratio of time for solute diffusion from the droplet surface to its centre to time for droplet drying is greater than 1 (*i.e.* Peclet number >1) (Feng et al., 2011; Healy et al., 2014; Vehring, 2008). Consequently, the wrinkled or raisin-like morphology that results causes improved dispersion of particles, resulting in efficient drug delivery into the lower regions of the lungs (Boraey et al., 2013; Feng et al., 2011; Healy et al., 2014; Sou et al., 2013; Vehring, 2008). Moreover, spray dried particles containing L-leucine have also demonstrated a low density (Boraey et al., 2013) and an anti-hygroscopic effect, which has been attributed to the enrichment of the excipient on the particle surface (Chang et al., 2014). Improvements in dispersibility, flowability and *in vitro* particle deposition (as demonstrated by increased fine particle fraction (FPF) and decreased MMAD), have all been reported (Boraey et al., 2013; Chow et al., 2007; Feng et al., 2011; Najafabadia et al., 2004; Seville et al., 2007; Sou et al., 2013; Xu et al., 2014).

Rivastigmine is currently a commonly used drug for the symptomatic treatment of mild to moderately severe dementia in Alzheimer's disease. Rivastigmine hydrogen tartrate (RHT) is a carbamate derivative ((*s*)-*N*-ethyl-*N*-methyl-3-[1-1(dimethylamino)ethyl]-phenylcarbamatehydrogen-(2R,3R)-tartrate) that reversibly and non-competitively inhibits the metabolism of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), preferentially in the central nervous system (Williams et al., 2003). RHT, as a 3 mg oral dose, presents a pharmacokinetic half-life of 1.5 h and a bioavailability of 36%, suggesting a high first pass metabolism, however its pharmacodynamic half-life is approximately 10 h due to binding to the esteratic site of the AChE enzyme, from which dissociation is slower than acetylcholine (Agid et al., 1998; Polinsky, 1998; Williams et al., 2003).

Research has previously been conducted in order to develop delivery systems for RHT in the form of controlled release tablets (Ogorka and Kalb, 2005), nanoparticles (Craparo et al., 2008; Fazil et al., 2012; Ismail et al., 2013; Joshi et al., 2010; Nagpal et al., 2013; Wilson et al., 2008), buccoadhesive films (Kapil et al., 2013) and liposomes (Mutlu et al., 2011; Scialabba et al., 2012; Yang et al., 2013); however no commercial product of any of the above-listed formulations is, as yet, available. RHT is commercially available as capsules and a solution for oral administration and as transdermal patches (Exelon® and Exelon®Patch, respectively) produced by Novartis. Dry powder inhalation represents an administration route that has not been previously explored for RHT. Given the increasing interest in DPIs for inhalation therapy to treat diseases other than lung conditions, there is potential to develop a DPI formulation of RHT with potential for improved bioavailability and consequently increased drug therapeutic effectiveness for the treatment of Alzheimer's disease.

The purpose of the present study was to develop a novel DPI formulation of RHT by particle engineering *via* spray drying. A lactose carrier based formulation was also developed for comparison purposes. The physicochemical properties of the lactose carrier-free and lactose carrier-containing formulations were investigated and the *in vitro* deposition characteristics of the engineered particles of RHT prepared by spray drying compared to the formulation containing lactose carrier.

2. Material and methods

2.1. Materials

S-Rivastigmine hydrogen tartrate (RHT) was purchased from Zhejiang Jiuzhou Pharmaceutical (China). L-Leucine (Leu) was purchased from Sigma–Aldrich (Ireland). Inulin DP23 (Inu) was a gift from Sensus (Netherlands). α-Lactose Monohydrate NF Inhalation 40 M was kindly supplied by Kerry (Ireland). Acetonitrile and methanol HPLC grade were acquired from Fisher Scientific (Ireland). Ammonium hydroxide (NH_4OH), ammonium phosphate monobasic ($NH_4H_2PO_4$), and fluorescein sodium salt were purchased from Sigma-Aldrich (Ireland).

2.2. Methods

2.2.1. Lactose carrier-free spray dried formulations preparation

Lactose carrier-free formulations were spray dried as 1% (w/v) solutions of RHT, Inu and Leu in ethanol:water comprising 30% (v/v) ethanol. The spray dried solutions were maintained at 40 °C during the spray drying process in order to solubilize the Inu. Formulation composition is presented in Table 1. In order to allow quantification of the powder deposited in the Next Generator Impactor (NGI) (Section 2.2.12) a fluorescent marker, fluorescein sodium salt, was incorporated at a low loading (0.2%, w/w) in all the spray dried formulations. Ní Ógáin et al. (2011) have previously shown that the incorporation of a fluorescent marker at this level has no impact on the morphology of spray dried powders.

All prepared solutions were spray dried, as previously described (Amaro et al., 2011, 2014; Ní Ógáin et al., 2011), using a Büchi B-290 Mini spray dryer, with a standard 2-fluid nozzle with a 0.7 mm