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Modified release of beclometasone dipropionate from chitosan-based spray-dried respirable powders

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ABSTRACT

Dry powders for inhalation were prepared by spray drying a 30% v/v aqueous ethanol formulation containing beclometasone dipropionate (BDP), lactose, leucine and chitosan (low, medium or high molecular weight (MW), or combinations thereof). Following physical characterisation of the powders, the aerosolisation and dissolution properties of the powders were investigated using Multi-Stage Liquid Impinger and USP II dissolution apparatus, respectively. The powders were highly dispersible, with emitted doses in excess of 90% of loaded powder aerosolised from a Spinhaler dry powder inhaler. The fine particle fraction (FPF) was observed to decrease, whereas the time for 100% drug release increased, with increasing chitosan MW. For example, the low MW formulation exhibited an FPF of 64% and a 100% dissolution time of 2 h, whereas the high MW formulation demonstrated an FPF of 54% and a dissolution time of 12 h. These powders would be anticipated to deposit predominately in the lower regions of the lung following inhalation, and then undergo delayed rather than instantaneous drug release, offering the potential to reduce dosing frequency and improve patient compliance.

1. Introduction

The corticosteroid beclometasone dipropionate (BDP) is a common anti-inflammatory used in the treatment of asthma and chronic obstructive pulmonary disease [1]. Problems associated with its administration surround the frequency of dosing required to avoid any acute exacerbation of respiratory symptoms [2]. These problems involve primarily patient compliance and concordance to a highly detailed regimen often involving dosing several times a day in addition to other required treatments such as short and long acting β2 agonists [3].

Traditional dry powder inhalation (DPI) formulations associate the use of micronised drug, usually 1–3 μm in diameter, with a coarse carrier particle such as lactose, typically 60–90 μm in diameter [4,5]. Such formulations normally deliver around 10–15% of the drug load to the desired target within the lung bronchi [6,7]. The large carrier particles normally impinge in the buccal cavity or in the oropharynx, whereas librated micronised drug particles that overcome the forces of adhesion to the carrier particles deposit further down the respiratory tract. Any micronised drug that remains adhered to the carrier particle will impinge on the buccal cavity and oropharyngeal regions with the coarse carrier [8], which may lead to local side effects; for example, deposition of BDP in the higher regions of the airway is associated with oral candidiasis, hoarseness, throat irritation and persistent cough [9].

Spray drying offers an alternative approach to the generation of dry, potentially respirable powders for local pulmonary drug delivery. This one-step process allows the production of dry powders with control over such variables as particle size and morphology, and can be less destructive than other methods of powder production, such as micronisation [10]. Spray drying has previously been used to deliver agents to the lung, although the powders tend to be cohesive in nature, leading to relatively poor dispersion during aerosolisation [11,12]. The incorporation of leucine into a spray-dried formulation as an aerosolisation enhancer has previously been demonstrated to significantly increase the respirable fraction of particles in a dry powder formulation [10]. The method of action of the amino acid has been attributed to the electrostatic nature of powders produced by spray drying with leucine [13].

The biocompatible polymer chitosan has been extensively explored in nasal delivery as a mucoadhesive and penetration enhancer with a degree of controlled release [14–17]. By incorporating BDP into a spray-dried formulation containing a hydrophobic polymer (chitosan) and an aerosolisation enhancer (leucine), we aim to develop highly respirable modified-release spray-dried powders. This should facilitate improved patient compliance through reduced

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frequency of administration and fewer local side effects through negation of carrier particle use. We explore how the release of BDP from these powders can be tailored through the use of a range of chitosan molecular weights.

2. Materials and methods

2.1. Materials

Beclometasone dipropionate (BDP), low molecular weight (LMW: <190 kDa), medium molecular weight (MMW: 190–310 kDa) and high molecular weight (HMW: >310 kDa) chitosan, phosphate-buffered saline (PBS) tablets, α-lactose monohydrate and L-leucine were purchased from Sigma Aldrich Chemicals (Poole, UK). HPLC grade methanol and ethanol were purchased from Fisher Scientific Ltd (Loughborough, UK).

2.2. Preparation of spray-dried powders

Formulations for spray drying were prepared by the addition of BDP, leucine and lactose (bulking agent) to a chitosan gel, prepared using LMW, MMW, HMW chitosan or combinations thereof.

LMW chitosan gel was prepared by homogenising (Heidolph flat-blade homogeniser: Heidolph-Electro, Kelheim, Germany) 4 g LMW chitosan in 100 mL glacial acetic acid aqueous solution (1.5% v/v) for 2 h at 1600 rpm. MMW chitosan gel was prepared by homogenising 2.5 g MMW chitosan in 100 mL glacial acetic acid aqueous solution (0.5% v/v) for 2 h. HMW chitosan gel was prepared by homogenising 2.7 g HMW chitosan in 100 mL glacial acetic acid aqueous solution (0.55% v/v) for 2 h. All preparations were allowed to stand overnight before use to ensure complete reaction between the chitosan and acetic acid and to allow dissipation of any air bubbles incorporated into the gel during homogenisation.

Sufficient chitosan gel to provide 1 g chitosan was measured and subsequently diluted with 30 mL ethanol to prepare LMW, LMW/MMW, MMW, MMW/HMW or HMW chitosan formulations. For example, to prepare the HMW chitosan formulation, 37 mL HMW chitosan gel (containing 1 g HMW chitosan) was mixed with 30 mL ethanol. An aqueous solution of 80 mg BDP, 720 mg leucine and 200 mg lactose was then combined with the chitosan ethanol mixture under homogenisation at 1600 rpm for 10 min to produce 100 mL of a 30% v/v aqueous ethanol solution [10] containing a total solids mass of 2% w/v (50% of which was chitosan). The LMW/MMW and MMW/HMW formulations contained equal proportions of the two components. A control formulation (no chitosan) was prepared using 80 mg BDP, 720 mg leucine and 1.2 g lactose in 100 mL 30% v/v aqueous ethanol solution.

The prepared formulations were subsequently spray dried using a Büchi B-290 mini spray dryer equipped with a high performance cyclone (Büchi Labortechnik AG, Switzerland) with a 0.7 mm two-fluid nozzle, using the following standard operating conditions: inlet temperature, 180 °C; spray flow rate, 600 L/h; pump setting, 10% (3.2 mL/min); aspirator setting, 85% (34 m^3/h). These conditions resulted in an outlet temperature of 87–91 °C. The resultant chitosan powders theoretically contained 4% w/w BDP, 36% w/w leucine, 50% w/w chitosan (LMW, LMW/MMW, MMW, MMW/HMW or HMW) and 10% w/w lactose. The control powder theoretically contained 4% w/w BDP, 36% w/w leucine and 60% w/w lactose.

2.3. Powder characterisation

2.3.1. Spray-drying yield and drug content

The yields of spray-dried powders were quantified as the percentage of anticipated yields. The BDP content of the powders was measured in triplicate, with analysis by HPLC (Section 2.6), and expressed as the percentage of nominal load.

2.3.2. Amorphous nature and water content

Determination of the degree of amorphous material and the water content in the spray-dried powders was performed using differential scanning calorimetery (DSC) and thermogravimetric analysis (TGA), respectively. DSC (Pyris Diamond DSC and Intracooler 2P: Perkin Elmer, Wellessey, USA) was performed on 2 mg samples in aluminium pans using a nitrogen purge at 20 mL min^{-1} (range: ambient −300 °C, heating rate 20 °C/min). TGA analysis (Pyris 1 TGA: Perkin Elmer) was performed on 10 mg samples in platinum pans using a nitrogen purge at 20 mL min^{-1} (range: ambient −360 °C, heating rate 50 °C/min). Measurements were performed in triplicate.

2.3.3. Particle size and powder density

The particle size of the spray-dried powders was measured by laser diffraction (HELOS particle size analyser incorporating VIBRO/RODOS dry dispersion system: Sympatec GmbH System-Partikel-Technik, Clausthal-Zellerfeld, Germany). Approximately 100 mg of each powder was used to achieve the required obscuration of 5%, and each sample was measured in triplicate. The data obtained were expressed as the volume weighted mean particle size.

The poured density of the spray-dried powder was determined by pouring a known mass of powder under gravity into a calibrated measuring cylinder and recording the volume occupied by the powder. The tapped density of the spray-dried powders was determined by tapped density measurements on the same samples using a tamping volumeter (Tapped Density Assessor: Copley Scientific Ltd., Nottingham, UK) until no further change in the powder volume was observed. Measurements were performed in triplicate.

2.3.4. Scanning electron microscopy

Spray-dried powders were mounted onto separate, adhesive-coated, 12.5 mm diameter aluminium pin stubs. Excess powder was removed by tapping the stubs sharply and then gently blowing a jet of particle-free compressed gas across each. The specimen stubs were sputter coated with a thin (approximately 10 nm) layer of gold in a Polaron SC500 coating unit at 10 mA for 2 min using an argon gas purge.

The specimens were examined using a Topcon SM-300 scanning electron microscope (SEM). The SEM was operated at high vacuum with an accelerating voltage of 5 kV and a specimen working distance of 12 mm. Secondary electron images were recorded digitally at a magnification of 5000X.

2.4. In vitro dissolution testing

Dissolution testing was performed on 200 mg spray-dried powder using the Modified USP II dissolution apparatus (Hanson research SR6 Dissolution Test Station: Hanson Ltd California, USA; Caleva SG6 and 65G Dissolution apparatus: Caleva Ltd Dorset, UK; or Sotax A7 Dissolution Apparatus: Sotax: London, UK) with 2 cm diameter stainless steel wire baskets (Copley Scientific Ltd., Nottingham, UK), rotating at 50 rpm in 1000 mL PBS (37 °C, pH 6.8). Samples (3 mL)

Table 1
Physical characterisation of spray-dried powders (values are mean ± SD, $n=3$)

Powder	SD yield	Water content	Volume weighted mean particle size	Tapped density	MMAD
	(%)	(%)	(μm)	(g cm^{-3})	(μm)
Control	64	0.61 ± 0.02	3.80 ± 0.85	0.20 ± 0.02	2.19 ± 0.06
LMW	65	3.57 ± 0.23‡	6.00 ± 3.46	0.13 ± 0.02	2.10 ± 0.16
LMW/MMW	73	3.34 ± 0.14‡	4.94 ± 0.05	0.15 ± 0.01	2.46 ± 0.23
MMW	66	8.30 ± 0.05‡	4.02 ± 0.03	0.27 ± 0.22	2.78 ± 1.86
MMW/HMW	36	4.73 ± 0.74‡	9.25 ± 2.19‡	0.13 ± 0.01	2.71 ± 0.56
HMW	66	2.32 ± 1.98	5.28 ± 0.39	0.14 ± 0.01	3.17 ± 0.52

Statistical difference (one-way ANOVA/Dunnett) from control powder: ‡$p<0.01$.