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Research paper

Chitosan-based spray-dried respirable powders for sustained delivery of terbutaline sulfate

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Abstract

In this study, we describe the preparation of highly dispersible dry powders for pulmonary drug delivery that display sustained drug release characteristics. Powders were prepared by spray-drying 30% v/v aqueous ethanol formulations containing terbutaline sulfate as a model drug, chitosan as a drug release modifier and leucine as an aerosolisation enhancer. The influence of chitosan molecular weight on the drug release profile was investigated by using low, medium and high molecular weight chitosan or combinations thereof. Following spray-drying, resultant powders were characterised using scanning electron microscopy, laser diffraction, tapped density analysis, differential scanning calorimetry and thermogravitational analysis. The in vitro aerosolisation performance and drug release profile were investigated using Multi-Stage Liquid Impinger analysis and modified USP II dissolution apparatus, respectively. The powders generated were of a suitable aerodynamic size for inhalation, had low moisture content and were amorphous in nature. The powders were highly dispersible, with emitted doses of over 90% and fine particle fractions of up to 82% of the total loaded dose, and mass median aerodynamic diameters of less than 2.5 μm. A sustained drug release profile was observed during dissolution testing; increasing the molecular weight of the chitosan in the formulation increased the duration of drug release.

Keywords: Spray-drying; Leucine; Modified release; Inhalation; Aerosolisation; Chitosan

1. Introduction

Inhalation therapy is widely employed to deliver drugs to the respiratory epithelium, predominately for the treatment of local disorders such as asthma and COPD, although there is increasing interest in using pulmonary delivery for the administration of systemically-acting macromolecules, exemplified most notably by the recent launch of the inhaled insulin product, Exubera [1].

When formulating a dry powder for inhalation, micronisation is usually employed to reduce the particle size of the drug powder to less than 5 μm. However, powders in this size range exhibit strong interparticulate cohesion, leading to poor powder flow properties [2,3]. Furthermore, factors known to influence the aerosolisation properties of dry powders (e.g. particle morphology, density and surface composition [4]) cannot be controlled effectively during the micronisation process. Researchers in the field have investigated a number of approaches to improve powder aerosolisation, such as mixing the micronised drug with inert carrier particles [5–8] or modification of particle morphology [9,10], particle surface roughness [11], particle porosity [12] or powder density [2,13]. An alternative approach to the generation of dry powders for pulmonary drug delivery is offered by spray-drying technology. Whereas micronisation is a destructive technique, spray-drying is a one-step constructive process that provides greater control over particle size, particle morphology and powder density. Indeed, dry powders generated by

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spray-drying have been investigated by a number of researchers for suitability as dry powder inhaler (DPI) formulations (e.g. [12,14–19]).

Spray-drying technology also offers the potential to incorporate a range of excipients into the formulation to be spray-dried, including dispersibility enhancers (e.g. leucine [20–22]) to modify the aerosolisation characteristics of the resultant powder. In addition, spray-dried powders that exhibit sustained drug release properties may be generated through the inclusion of drug release modifiers such as hydroxypropyl cellulose [23], glyceryl behenate [24] and polylactic acid [25]. Chitosan, a polysaccharide derived from deacetylation of the naturally occurring polymer chitin, is a promising excipient that can be employed in a wide range of applications, including sustained release preparations [26]. Indeed, this compound has received considerable attention for the formulation of spray-dried powders for nasal drug delivery (e.g. [27–33]).

There are many advantages to developing sustained release formulations for pulmonary drug delivery, including reduced dosing frequency, improved patient compliance and reduction in side effects [34]. Given that chitosan not only acts as a drug release modifier but also has mucoadhesive properties [32,33], it would appear to be a useful excipient when preparing sustained release formulations for pulmonary drug delivery. Although substantial research has been aimed at developing such formulations, only a handful of researchers have investigated the viability of chitosan-modified spray-dried powders for pulmonary drug delivery [35–38], with none apparently having considered the incorporation of dispersibility enhancers such as leucine to improve powder aerosolisation characteristics. This may be due to concerns surrounding the degradation of chitosan in the lung following administration and the potential for chitosan to elicit mild inflammatory responses [39]. Nevertheless, the observation that chitosan is less toxic than other polymers [40] suggests that it may be an interesting compound to investigate.

In this study, we demonstrate that spray-drying formulations of chitosan as a drug release modifier and leucine as a dispersibility enhancer generates highly dispersible powders that exhibit sustained drug release properties. We find that higher molecular weight chitosan powders exhibit somewhat poorer aerosolisation characteristics but substantially longer dissolution profiles compared to lower molecular weight chitosan formulations. We show that drug release from the chitosan powders follows square-root-time kinetics, and is dependent on the molecular weight of the chitosan. We demonstrate that by selecting an appropriate molecular weight of chitosan, it is possible to tailor the rate of drug release, thereby offering the opportunity for reduced frequency of dosing and improving patient compliance, whilst at the same time delivering a high respirable fraction.

2. Materials and methods

2.1. Materials

Terbutaline sulfate, 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 an aqueous solution of terbutaline sulfate (model drug), leucine (aerosolisation enhancer [22]) and lactose (bulking agent) to a chitosan gel, prepared using LMW, MMW, HMW chitosan or combinations thereof.

LMW chitosan gel was prepared by mixing 4 g LMW chitosan in 100 mL glacial acetic acid aqueous solution (1.5% v/v) for 2 h. MMW chitosan gel was prepared by mixing 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 mixing 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.

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 LMW chitosan formulation, 25 mL LMW chitosan gel (containing 1 g LMW chitosan) was mixed with 30 mL ethanol. An aqueous solution of 80 mg terbutaline sulfate, 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 [22] containing a total solid mass of 2% w/v (50% of which was chitosan). A control formulation (no chitosan) was prepared using 80 mg terbutaline sulfate, 720 mg leucine and 1.2 g lactose in 100 mL of 30% v/v aqueous ethanol solution.

The prepared formulations were subsequently spray-dried using a mini spray-dryer equipped with a high performance cyclone (Büchi B-290: 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 84–92 °C. The resultant chitosan powders contained 4% w/w terbutaline, 36% w/w leucine, 50% w/w chitosan (LMW, LMW/MMW, MMW, MMW/HMW or HMW) and 10% w/w lactose. The control powder contained 4% w/w terbutaline, 36% w/w leucine and 60% w/w lactose.