Powder Technology 256 (2014) 217–223

Contents lists available at ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

Influence of excipients on spray-dried powders for inhalation

En-Yu Xu [a,b], Jing Guo [b], Ying Xu [c], Hao-Ying Li [b], Peter C. Seville [d,*]

[a] College of Basic Medical Science, China Medical University, Shen-Yang 110001, China
[b] Biomanufacturing Research Centre, School of Mechanical and Electrical Engineering, Soochow University, Su-Zhou 215021, China
[c] Testing and Analysis Centre, Soochow University, Su-Zhou 215123, China
[d] School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

ARTICLE INFO

Article history:
Received 7 November 2013
Received in revised form 3 February 2014
Accepted 9 February 2014
Available online 16 February 2014

Keywords:
Saccharides
Pulmonary delivery
Sustained release
Aerosolisation

ABSTRACT

Two areas attracting considerable attention when developing effective pulmonary drug delivery systems include the improvement of aerosolisation efficiency of the inhaled formulation and the controlled release of drug from the formulation following deposition within the lung. In this study, four saccharides were employed as excipients in the preparation of spray-dried powder formulations for the pulmonary drug delivery. Beta-cyclodextrin-, starch-, and sodium carboxymethylcellulose (NaCMC)-based spray-dried powders showed a significant (one-way ANOVA, Duncan's test, $p < 0.05$) increase in lower stage drug deposition in the Next Generation Impactor (NGI) when compared to lactose-based spray-dried powders. Furthermore, NaCMC-based spray-dried powder formulations exhibited a sustained drug release profile in dissolution testing; approximately 80% of salbutamol sulphate was released after an hour, whereas drug from the lactose-based spray-dried powder formulation was released within 5 min. Our results clearly demonstrate that the inclusion of NaCMC in spray-dried powder formulations increases the aerosolisation efficiency of the powder and also offers the potential for sustained drug release, which may be of benefit in the treatment of local and systemic conditions.

1. Introduction

Pulmonary drug delivery systems have been employed for the treatment of lung conditions such as asthma, chronic pulmonary infections and cystic fibrosis [1,2], as inhalation offers direct access to the drug target, rapid onset of treatment, and lower doses (hence lower incidence of adverse drug effects) compared to other routes of administration [3]. In addition, the lungs have been considered as a potential non-invasive route for the administration of therapeutic biomacromolecules such as insulin, calcitonin, human growth hormone and non-viral gene vectors for the treatment of systemic conditions [1,4–6], as this route avoids the first-pass metabolism and high enzymatic activity associated with oral drug administration [7].

Devices used to aerosolise drug particles for inhalation are typically based on one of three platforms: nebulizer, pressurised metered-dose inhaler (pMDI) or dry powder inhaler (DPI). The nebulizer atomises an aqueous solution or suspension by air jet or ultrasonication, and is especially suitable for infants, elderly or seriously ill patients. However, nebulisers are not portable and are associated with unstable and low drug delivery efficiency. Although the pMDI has been the most widely used device for pulmonary drug delivery, the drawbacks of this device include the need for patient coordination between inhalation and actuation and the contribution of propellants employed in the formulation of these devices to the 'greenhouse effect'. In contrast, DPIs, being breath-activated, propellant-free devices, have attracted substantial interest for the development of pulmonary drug delivery systems for local and systemic therapies.

For efficient deposition within the central and alveolar regions of the lung, the optimal aerodynamic diameter of particles for inhalation is approximately 1–5 μm [8]. Spray-drying is a common approach for powder preparation for a wide range of drug powders, and is especially suitable for preparing powders for inhalation because this process allows control over the particle size and shape, generating powders with narrow particle size distributions and low particle surface energy [9]. Furthermore, spray-drying enables the incorporation of excipients to improve the dispersibility of the powder, to improve the stability of the drug or the formulation on storage, to enhance the absorption of the drug across the pulmonary epithelium following delivery, or to generate powders that display a modified drug release profile [10].

Generally, drugs deposited on the pulmonary epithelium are quickly absorbed, which may give rise to toxicity and the need for repeated dosing for drugs with a short duration of action, particularly in the treatment of chronic diseases (for example salbutamol in the treatment of asthma). However, excessive dosing frequency is a well-documented cause of non-compliance in patients [11]. These problems may be potentially avoided by developing sustained release formulations which release drug steadily to maintain drug concentration and reduce peak

* Corresponding author at: Pharmacy, Pharmacology and Therapeutics Section, School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK. Tel.: +44 121 414 3209.
E-mail address: p.c.seville@bham.ac.uk (P.C. Seville).

http://dx.doi.org/10.1016/j.powtec.2014.02.033
0032-5910/

plasma fluctuations, leading to a reduction in dosing frequency and improved patient compliance, and associated cost savings, thereby providing effective medical treatments for both local and systemic therapies [12]. Many interdependent factors, including the physicochemical characteristics of the drug, the preparation conditions, the ionic strength of the dissolution medium and the type of the dissolution apparatus employed have been shown to influence the overall release of drug from a sustained release formulation in vitro. Sustained release in the lung may be achieved by selecting excipients to retard the dissolution of the drug or by co-precipitating relatively insoluble materials with aqueous soluble drugs, although the organic excipients acceptable for inhalation into the human body are somewhat restricted.

Lactose is traditionally used as excipient in dry powder formulations for inhalation, but spray-dried lactose powders are generally highly hygroscopic and particles are typically extremely cohesive; therefore the powders demonstrate poor aerosolisation performance and low delivery efficiency to the lungs [13]. Beta-cyclodextrin, an oligosaccharide, has been reported to enhance drug solubility, and acts as permeation enhancer by transporting the drug through the lipophilic surface of biological membranes [14]. Beta-cyclodextrin has been used to prepare spray-dried powders for pulmonary drug delivery which exhibit enhanced dispersibility and improved drug permeation [15]. Hooton and co-workers, investigating the use of a cohesive–adhesive force balance technique to compare the forces of attraction between salbutamol sulphate and a range of potential carrier particles, noted that beta-cyclodextrin-based powders demonstrated superior in vitro aerosolisation performance to lactose-based powders [16]. Sodium carboxymethylcellulose (NaCMC) and starch have been widely used in the pharmaceutical formulations for the improvement of mucoadhesion [17,18] and for the sustained release of drugs [19]. The addition of NaCMC when preparing spray-dried enzyme powders maintains the bioactivity of enzymes during the spray-drying process, and is further able to improve the aerosolisation of the powder [20].

In this paper, lactose (disaccharide), beta-cyclodextrin (oligosaccharide), starch and NaCMC (polysaccharides) were employed as excipients in the preparation of spray-dried powders for the pulmonary drug delivery, with the aim of investigating the influence of the physiochemical properties of saccharides on the aerosolisation performance of, and the rate of drug release from, the resultant spray-dried powders, using salbutamol sulphate as a model drug.

2. Materials and methods

2.1. Materials

Lactose was purchased from Fisher (Loughborough, UK). Acetic acid, beta-cyclodextrin, soluble starch, and sodium carboxymethylcellulose (NaCMC, 300–800 mPa s) were obtained from Aladdin Chemistry Co. Ltd (Shanghai, China). Salbutamol sulphate was purchased from Sigma-Aldrich (UK). HPLC-grade methanol was acquired from Spectrum Chemicals & Laboratory Products (California, USA) and sodium dihydrogen phosphate was obtained from Sinopharm Chemical Reagent Co. Ltd (Shanghai, China). All other reagents used in this study were certified analytical reagent grade (Shanghai Chemical Reagent Company, Shanghai, China).

2.2. Preparation of spray-dried powders

The procedure for the preparation of spray-dried powders follows the approach as previously described [21]. In brief, lactose, beta-cyclodextrin, starch or NaCMC (3 g) was dissolved/dispersed in 200 mL of deionised distilled water to prepare the excipient formulation (1.5% w/v), into which salbutamol sulphate (6 mg) was subsequently dissolved to prepare the spray-drying feedstocks. These feedstocks were then spray-dried (Büchi B-290 mini spray dryer, Büchi Labortechnik AG, Switzerland), operated at the following standard operating conditions: inlet temperature, 150 °C; pump setting, 450 mL/h; spray flow rate, 600 L/h; and aspirator setting, 100% (40 m^3/h). The outlet temperature was approximately 85 °C. The spray-dried powders were collected from the lower part of the cyclone and the collection vessel, and stored in a desiccator under partial vacuum. For each formulation, the spray drying process was carried out in triplicate.

2.3. Characterisation of spray-dried powders

The drug content of each powder was determined by HPLC, and expressed as the percentage of the anticipated amount. Each powder was measured in triplicate. The moisture content of the spray-dried powders was determined using thermogravimetric analysis (Q500, TA Instruments, New Castle, DE, USA). The samples (10 mg) were placed into platinum pans and analysed under a nitrogen purge (20 mL min^{-1}) over the temperature range 40–140 °C at a heating rate of 10 °C per minute. Measurements were performed in triplicate.

The morphology of the spray-dried particles was investigated using a scanning electron microscope (SEM, S-4700, Hitachi Co., Tokyo, Japan) operated at 15 kV under high vacuum. Samples were sputter-coated with a thin layer of gold under partial vacuum (HITACHI E-1010, Tokyo, Japan), and representative micrographs of spray-dried particles were captured.

Laser diffraction (Mastersizer 2000, Malvern Instruments, Malvern, UK) was used to determine the particle size of the spray-dried powders using a dry dispersion technique in air. The air pressure used was 4 bar, and was the same for each powder sample. For each sample, approximately 200 mg of powder was used to achieve the required obscuration of 0.5–5%, and the size and size distribution were subsequently determined. The measurements for each sample were performed in triplicate.

2.4. HPLC analysis of salbutamol sulphate

High performance liquid chromatography (HPLC) was employed to analyse salbutamol sulphate, using an Agilent 1260 infinity HPLC system, pump (1260, G1312B), autosampler (1260 ALS, G1329B), UV detector (1260 VWD, G1314F) and a 25 × 4.6 cm column filled with 5 μm C-18 (ZORBAX Eclipse XDB-C18, Agilent, USA), with detection at 276 nm. For the analysis, NaH_2PO_4 buffer (80 mmol/L) was prepared, filtered using a 0.2 μm membrane, and adjusted to pH 3.1 with phosphoric acid. The mobile phase was composed of a solution of methanol:NaH_2PO_4 buffer (20:80 v/v) at a flow rate of 1 mL/min. The retention time for salbutamol sulphate under these conditions was 5.3 min.

2.5. In vitro powder aerosolisation

The aerosolisation performance of the spray-dried powders from a dry powder inhaler (DPI) device was determined using a Next Generation Impactor (NGI, Copley Scientific, Nottingham, UK) equipped with a USP throat and pre-separator. The NGI is an eight-stage inertial impactor that separates an aerosol cloud into discrete size ranges based on aerodynamic diameter. For the test, powders (25 mg) were accurately weighed and loaded into size 3 gelatin capsules, and subsequently placed into a Cyclohaler® (Pharmachemie BV, Netherlands) DPI device, connected via a mouthpiece adapter to the USP throat. The powders were subsequently aerosolised (35% relative humidity, 20 °C) at 60 L/min for 5 s [22,23]. Two capsules (equivalent to 100 μg salbutamol sulphate) were used for each test, and each powder was tested in triplicate. After aerosolisation, the capsules and inhaler device, the NGI throat, pre-separator, and stage 1 to the micro-orifice collector (MOC) were rinsed with 10 mL of deionised distilled water respectively for the determination of deposited drug. The sample was vortex-mixed for 30 min and then shaken overnight to ensure complete dissolution of any deposited drug. These solutions were subsequently filtered through a 0.45 μm