Influence of excipients on spray-dried powders for inhalation

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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.

**Key Words:** Saccharides, Pulmonary Delivery, Sustained Release, Aerosolisation
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, nebulizers 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 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 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 that 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, 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 was following the approach as previously described [21]. In brief, lactose, beta-cyclodextrin, starch or NaCMC (3 g) were 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; aspirator setting, 100% (40 m³/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 x 4.6 cm column filled with 5 µm C-18 (ZORBAX Eclipse XDB-C18, Agilent, USA), with detection at 276 nm. For the analysis, NaH₂PO₄ 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 comprised a solution of methanol: NaH$_2$PO$_4$ 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 aerosolized (35% relative humidity, 20°C) at 60 L/min for 5 seconds [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 deionized distilled water respectively for the determination of deposited drug. The sample was vortex-mixed for 30 minutes and then shaken overnight to ensure complete dissolution of any deposited drug. These solutions were subsequently filtered through a 0.45 μm membrane, and 50 μL of the sample was subjected to HPLC analysis. For each test, the total dose (TD) was defined as the mass of salbutamol sulphate loaded into the two capsules (theoretically 100 μg). The emitted dose (ED) was defined as the mass of powder loaded into the capsule that was released during aerosolisation, determined gravimetrically and expressed as a percentage of TD. The recovered dose (RD) was defined as the total mass of salbutamol sulphate detected after each test (i.e. capsule,
inhaler, throat, pre-separator and stages 1-MOC), expressed as a percentage of TD. The fine particle dose (FPD) was defined as the mass of salbutamol sulphate detected on stages 2 to MOC of the NGI (effective cut-off diameter 4.46 μm). The fine particle fraction (FPF) was calculated as the ratio of FPD to RD, expressed as a percentage.

2.6. Release of salbutamol sulphate from spray-dried powders

The release of salbutamol sulphate from the spray-dried formulations was determined using a method based on the USP dissolution test [24, 25] using an RC806 dissolution apparatus (Tianjin University Precision Corporation, Tianjin, China). For each test, the spray-dried powders (containing 100 μg of salbutamol sulphate) were added into 500 mL of phosphate buffered saline at 37°C with stirring at 50 rpm. At scheduled time intervals, aliquots of solution (2 mL) were withdrawn from the vessel and filtered through a 0.45 μm membrane and subjected to HPLC analysis. A corresponding volume of fresh medium at 37°C was subsequently added into the vessel after each extraction.

2.7. Statistical analysis

The levels of significance are indicated in the legend of the respective graphs. Data are presented as mean ± standard deviation (SD; n=3). Statistical analysis was performed using one-way ANOVA, Duncan’s test ($p<0.05$).
3. Results and Discussion

3.1. Spray-dried powder characteristics

The drug content for the lactose-, beta-cyclodextrin-, starch- and NaCMC-based spray-dried powders was 99.7 ± 2.4%, 100.2 ± 1.5%, 98.7 ± 3.5% and 101.4 ± 2.8% of the anticipated amount, demonstrating that there was no deleterious effect of the spray-drying process on salbutamol sulphate.

The yield and moisture content of the spray-dried powders are presented in Fig. 1. The spray-dried lactose-based powder exhibited a relatively poor yield of 46%, with much of the powder deposited in the top of the cyclone, and therefore unrecoverable. The other powders demonstrated lower adhesion to the cyclone surface, being predominantly deposited in the collection vessel, resulting in statistically higher ($p<0.05$) yields of 73%, 74%, 56% for the beta-cyclodextrin-, starch- and NaCMC-based powders, respectively.

The moisture content of spray-dried powders was in the range from 3.2% to 9.7% w/w (Fig. 1). Previous studies have demonstrated that increasing the aspirator capacity or inlet temperature is associated with a decrease in moisture content, whereas increasing the feed flow or reducing the outlet air temperature results in a lower drying capacity and hence a higher moisture content in the powder product. In our study, all powders were spray-dried using the same conditions; however, the moisture content of the NaCMC-based powder was substantially higher than that of the other powders. This is in agreement with other studies on NaCMC-based spray-dried powders, which demonstrated that increasing the proportion of NaCMC in a spray-dried powder is associated with an increase in moisture content [20, 26]. NaCMC disperses to form a colloidal solution when added to water [27], and it is feasible
water becomes entrapped in this matrix during the spray-drying process, resulting in a higher moisture content. The moisture contents of the other spray-dried powders are in line with other studies, which report typical moisture contents in the region of 3-7.5% w/w [28-32].

The size, shape and surface morphology of the spray-dried powders are illustrated in Fig. 2. All powders appeared to comprise spherical or near-spherical particles of a suitable physical diameter for inhalation, with a particle diameter less than 10 μm and in some powders a sub-population of smaller particles of approximately 2 μm. While spray-dried lactose-based particles appeared to be perfect spheres with smooth surfaces (Fig. 2A), the particles in the spray-dried beta-cyclodextrin-, starch- and NaCMC-based powders exhibited dimpled surface morphologies (Figures 2B-D). Such wrinkled morphology is commonly observed in spray-dried powders designed for inhalation, and has been associated with an improvement in aerosolisation performance [33, 34].

In order to further investigate the physical diameter of the spray-dried powder particles, laser diffraction was employed to determine the particle size distribution (Fig. 3 and Table 1). The data are expressed in terms of the particle diameter at 10, 50 and 90% of the volume distribution (d[v,10], d[v,50] and d[v,90], respectively). The span of the volume distribution, a measure of the width of the volume distribution relative to the median diameter (d[v,50]), was calculated from (d[v,90]-d[v,10])/d[v,50]). In addition, the mean diameter over the volume distribution (D[4,3]) is reported. The lactose-based spray-dried powder showed a bimodal size distribution, with a large population of dry powders over 100 μm, resulting in a mean diameter of 28.3 μm and a span of 59.4. The SEM image of this powder (Fig. 2A) clearly showed particles less than 10 μm in diameter, therefore the laser diffraction data suggest cohesion between individual particles, resulting in large agglomerates that fail to
break up during the dry dispersion measurement. This suggests that the lactose-based powder has poor dispersibility in an airflow and therefore may perform poorly during aerosolisation. The spray-dried NaCMC-based powder exhibited a broad particle size distribution, with a mean diameter of 9.6 μm and span of 3.7. This is also indicative of a degree of cohesion between particles, although to a lesser extent than was observed with the lactose-based powder. In contrast, the starch- and beta-cyclodextrin-based powders demonstrated unimodal particle size distributions (mean diameter 2.9 μm and 2.6 μm, respectively), suggesting no obvious aggregation between particles in these powders. These data suggest that the beta-cyclodextrin- and starch- and, to a lesser extent, NaCMC-based spray-dried powders are potentially more suitable for pulmonary delivery than the lactose-based spray-dried powder, with a greater proportion of particles/aggregates less than 3 μm for deposition in the respiratory tract [35].

3.2. *In-vitro aerosol deposition*

The Next Generation Impactor (NGI) was used to assess the aerodynamic performance of the spray-dried powders following aerosolisation using a Cyclohaler® dry powder inhaler device. The lactose-based spray-dried powder demonstrated a poor emitted dose (64.9%), whereas the beta-cyclodextrin-, starch- and NaCMC-based spray-dried powders demonstrated higher emitted doses (85.3%, 93.6% and 98.6%, respectively; *p*<0.05, Table 2). Although for these three spray-dried powders, a greater proportion of the loaded powder was released from the capsule during aerosolisation in comparison to the lactose-based powder, more important is to determine the site of deposition of the drug once aerosolised. The NGI is a widely recognised in vitro characterisation tool used to determine the respirable fraction of an emitted dose based on aerodynamic particle size. Following aerosolisation of the powder into the NGI, the mass of salbutamol sulphate deposited within the Cyclohaler® DPI device, the
USP throat, the pre-separator and stages 1-MOC of the NGI was determined using HPLC, as described in Section 2.5. The deposition pattern of the four spray-dried powders is illustrated in Fig. 4. A high proportion of the salbutamol contained in the lactose-based spray-dried powder was detected in the capsule and Cyclohaler® DPI device and the USP throat, with only minimal quantities detected in the lower stages of the NGI. The low FPD and FPF of this powder (Table 2) clearly demonstrate that the lactose-based spray-dried powder exhibited poor aerodynamic properties; these findings correlate well with the observation that this powder exhibited poor deagglomeration during particle sizing, resulting in a mean diameter of 28 μm (Table 1). Inhalation of this powder is predicted to result in low delivery of salbutamol sulphate to the lungs, with substantial deposition on the back of the throat, potentially leading to local or systemic side effects. In contrast, the beta-cyclodextrin-, starch- and NaCMC-based spray-dried powders all demonstrated a significantly lower ($p<0.05$) deposition of salbutamol sulphate in the USP throat and higher ($p<0.05$) deposition on NGI stages 2, 3, 4 and 5. The FPD and FPF of these three powders were significantly higher ($p<0.05$) than those of the lactose-based powder, with the lactose-based powder demonstrating an FPF of 11%, whereas the other powders all exhibited FPFs greater than 40%. A recent study by Mishra and Mishra investigated the use of NaCMC to generate spray-dried powders containing doxycycline hyclate. They found that, using an optimised formulation incorporating doxycycline hyclate, NaCMC and leucine as a dispersibility enhancer, an FPF of 49% could be obtained using an Andersen Cascade Impactor, although the authors fail to disclose the dose of drug delivered during the aerosolisation test, or indeed the final composition of the microparticles, such as drug load [36]. However, the study suggests that further improvement in the aerodynamic properties of our powders could be obtained through the inclusion of leucine in the spray-drying feedstock, as has been observed in other studies [30, 37, 38].
3.3. *In-vitro sustained release*

As expected, the lactose-based spray dried powders showed an initial burst release of salbutamol sulphate, with approximately 75% of drug released within 1 min, and complete release within 5 min (Fig. 5). Rapid drug dissolution was also observed from the starch-based powder, with 70% of salbutamol sulphate released in the initial burst, and nearly 90% released within 10 min. Drug release from the beta-cyclodextrin-based powder was slightly slower, with full drug release observed after 15 min dissolution. In comparison, the NaCMC-based powder exhibited a sustained drug release profile, with no obvious initial burst as was seen with the other powders. Approximately 20% of the drug load was released in the first minute, with 180 min dissolution time required to achieve 85% drug release. Conti and co-workers, investigating the release of drug from matrix tablets, observed that at pH 6.8, diltiazem was released more rapidly from NaCMC matrices than from hydroxypropylmethylcellulose (HPMC) matrices. They attributed this to the high solubility of NaCMC at this pH, leading to rapid erosion of the gel layer surrounding the matrix and a high degree of erosion of the matrix overall; release from HPMC matrices, on the other hand, was related to diffusion of the drug through the gel layer, rather than erosion [39]. In contrast, Farid and co-workers recently examined release of salbutamol sulphate from nasal inserts prepared from a number of gel-forming polymers, including NaCMC. They found that NaCMC inserts exhibited a high water uptake, leading to swelling of the insert and creation of a thick gel layer on the swollen insert surface. In addition, they suggested that at the pH of the simulated nasal fluid used (pH 6.5), salbutamol sulphate (pKa 9.5) would be ionised, which may result in binding of the cationic drug to the anionic polymer through electrostatic attraction. They commented that this would result in a reduced rate of diffusion of salbutamol sulphate through the gel layer, leading to reduced and retarded drug release.
Analysis of the kinetics of drug release suggested zero-order release controlled by matrix relaxation and diffusion of drug through the gel layer formed as the insert swelled [40]. Likewise, Mishra and Mishra found that rate of release of drug (doxycycline hyclate) from NaCMC-based spray-dried microspheres was slower than from NaCMC-free microspheres, and related this to the creation of a gel barrier formed when the hydrophilic polymer swelled on coming into contact with water [36]. Our data appear to support these studies, with NaCMC-based powders hydrating to create a gel layer from which drug is gradually released, whereas drug release is more rapid from lactose-, starch- and beta-cyclodextrin-based powders, as no gel layer is created following immersion of these powders in water.
4. Conclusion

In this study, we have demonstrated that spray-drying a feedstock containing NaCMC generates powders that exhibit sustained drug release and good aerosolisation properties. Unlike the formulation of conventional DPI systems, where crystalline drug is blended with a larger carrier particle (typically lactose) to improve powder flow and aerodynamic properties, our powder can be formulated as a DPI without the need for the addition of further excipients. NaCMC, a water-dispersible polysaccharide, is widely used in a range of formulations for oral, topical and parenteral routes of administration, and is regarded as a non-toxic and non-irritant material [27]. Studies have shown that NaCMC reduces the rate of mucociliary clearance and enhance uptake across respiratory epithelia, without causing an increase in mortality [41, 42]. Although further testing of the suitability of NaCMC for administration to the lung would be required, these studies suggest that NaCMC-based spray-dried powders would be a promising approach to the development of highly respirable formulations that exhibit sustained release properties.

Acknowledgements

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References

Table 1. Particle size distribution (mean±SD, n=3) of lactose-, beta-cyclodextrin-, starch- and NaCMC-based spray-dried powders

<table>
<thead>
<tr>
<th>Spray-dried powders</th>
<th>d[v,10] (μm)</th>
<th>d[v,50] (μm)</th>
<th>d[v,90] (μm)</th>
<th>Span (μm)</th>
<th>D[4,3] (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>0.77(0.02)</td>
<td>2.57(0.01)</td>
<td>153.81(6.02)</td>
<td>59.43(1.02)</td>
<td>28.34(0.62)</td>
</tr>
<tr>
<td>Beta-cyclodextrin</td>
<td>0.95(0.04)</td>
<td>2.29(0.02)</td>
<td>4.60(0.04)</td>
<td>1.59(0.01)</td>
<td>2.56(0.01)</td>
</tr>
<tr>
<td>Starch</td>
<td>0.98(0.03)</td>
<td>2.56(0.04)</td>
<td>5.36(0.03)</td>
<td>1.71(0.01)</td>
<td>2.91(0.02)</td>
</tr>
<tr>
<td>NaCMC</td>
<td>1.13(0.01)</td>
<td>5.98(0.05)</td>
<td>23.29(0.31)</td>
<td>3.70(0.02)</td>
<td>9.55(0.05)</td>
</tr>
</tbody>
</table>

d[v,χ]: Particle diameter at χ% of the volume distribution.
Span: Width of the volume distribution, relative to the median diameter (found from (d[v,90]−d[v,10])/d[v,50]).
D[4,3]: Volume weighted mean diameter.
Table 2. Aerosolisation parameters of lactose-, beta-cyclodextrin-, starch- and NaCMC-based spray-dried powders (the data expressed as mean ± SD, n=3).

<table>
<thead>
<tr>
<th>Spray-dried powders</th>
<th>Emitted Dose (%)</th>
<th>Fine Particle Dose (FPD; mcg)</th>
<th>Fine Particle Fraction (FPF; %)</th>
<th>Recovered Dose (mcg)</th>
<th>Recovered Fraction (% of total dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>64.9 (3.4)</td>
<td>7.9 (0.5)</td>
<td>11.2 (0.5)</td>
<td>70.6 (3.6)</td>
<td>71.7 (3.6)</td>
</tr>
<tr>
<td>Beta-cyclodextrin</td>
<td>85.3 (3.1)</td>
<td>30.7 (8.2)</td>
<td>40.3 (2.2)</td>
<td>75.6 (5.1)</td>
<td>72.0 (4.8)</td>
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<tr>
<td>Starch</td>
<td>93.6 (1.2)</td>
<td>32.4 (1.1)</td>
<td>47.0 (1.7)</td>
<td>68.9 (4.5)</td>
<td>66.9 (4.4)</td>
</tr>
<tr>
<td>NaCMC</td>
<td>98.6 (1.1)</td>
<td>30.4 (1.7)</td>
<td>45.0 (1.4)</td>
<td>67.4 (1.6)</td>
<td>65.6 (1.5)</td>
</tr>
</tbody>
</table>
**Figure captions**

Fig. 1. Physical properties of spray-drying powders. Data represented as mean ± s.e.m., $n=3$. Statistical analysis by one-way analysis of variance ($p<0.05$). * Significant difference from lactose-based spray-dried powder.

Fig. 2. Spray-dried powder morphology visualized by scanning electron microscopy. A) lactose-based powders; B) beta-cyclodextrin-based powders; C) starch-based powders; D) NaCMC-based powder (Bar = 10 μm).

Fig. 3. Particle size distribution of spray-dried powders. The particle size distribution of lactose-, beta-cyclodextrin, starch- and NaCMC-based spray-dried powders was determined by laser diffraction.

Fig. 4. *In-vitro* aerosol deposition of lactose-, beta-cyclodextrin-, starch- and NaCMC-based spray-dried powders. Approximately 50 mg of dry powders (equivalent to 100 μg of SS) was accurately weighed into two gelatin capsules (size 3), inserted into the dry powder inhaler that was connected to NGL. The dry powders were aerosolized (35% of relative humidity, 20°C) at 60 L/min flow rate for 5 seconds. The collected SS was analyzed using a validated HPLC method. Data represented as mean ± s.e.m., $n=3$. Statistical analysis by one-way analysis of variance ($p<0.05$). * Significant difference from lactose-based spray-dried powders.

Fig. 5. *In-vitro* sustained release of salbutamol sulphate from the formulation. The investigation of drug release from dry powder formulations was performed at 37°C with paddles operating at 50 rpm in a dissolution bath. At scheduled time intervals, samples were obtained and subsequently analyzed via HPLC to determine the released drug.
Fig. 1

- **Recovery (%)**
- **Moisture content (%)**

- **Spray-dried formulations**
  - Lactose
  - Beta-cyclodextrin
  - Starch
  - NaCMC

Bar graph showing recovery and moisture content for different formulations.
Fig. 2

A

B

C

D
Fig. 3

- lactose
- beta-cyclodextrin
- starch
- NaCMC

Volume (%)
Particle size (μm)
Fig. 4

![Graph showing SS deposition across different conditions and impactors.](image-url)
Fig. 5

- lactose
- beta-cyclodextrin
- starch
- NaCMC

Percentage of released drug (%)

Time (min)
Author Biographies

En-Yu Xu obtained his degrees of BSc (2009, Pharmacy) and MSc (2013, Chemistry) from Liaoning Normal University. In 2011-2013, he undertook collaborative research with Soochow University, focusing on the development of dry powder inhaler formulations for pulmonary drug delivery. Mr Xu is currently appointed as a lecturer in the College of Basic Medical Science, China Medical University.

Jing Guo obtained her BSc (2008) from Nanjing University of Traditional Chinese Medicine, and MSc (2011) in pharmacy from China Pharmaceutical University. Mrs Guo then joined Soochow University as a Research Technician and worked in dry powder formulations for inhalation. Mrs Guo has excellent experimental skills, and expertise in the preparation and characterization of nano spray-dried formulations for pulmonary delivery of chemicals and biomolecules. Mrs Guo was awarded the ‘people scholarship’ in 2004 and 2005.

Ying Xu obtained her BSc (1995, Organic Chemistry) and MSc (2005, Inorganic Chemistry) from Soochow University. During 1995-2001, Mrs Xu worked at Soochow University and then at the
Information Optical Engineering Institute of Soochow University. Mrs Xu moved to Testing and Analysis Centre of Soochow University in 2001, since when she had focused on the research into thermal properties of a variety of materials. Mrs Xu recently focused on research into thermal transitions of inhaled dosage forms with the aim of establishing correlations between polymorphs and aerosol performance.

Hao-Ying Li obtained his degrees of BSc (1995, Chemistry) and MSc (1998, Biochemical Engineering) from Dalian University of Technology, and PhD (2001, Biomaterials) from the Chinese Academy of Sciences. He then worked as Postdoctoral Research Associates and Research Fellows in several UK universities (Cardiff University, University of London, Aston University and University College London. He was appointed to a professorial position at Soochow University in 2010. Dr Li has expertise in chemistry and pharmaceutical formulations especially inhaled dosage forms, and had a number of high quality publications in novel aerosols for pulmonary drug delivery.

Peter Seville graduated from Cardiff University (BPharm, 1994; PhD, 2000), after which he undertook postdoctoral research in the area of gene therapy for pulmonary delivery. Dr Seville was subsequently appointed as a lecturer, then senior lecturer, in pharmaceutics at Aston University, and is currently a senior lecturer in pharmaceutics at University of Birmingham. Dr Seville has a
long history of research in the development of inhalable formulations, and in particular expertise in the use of spray-drying technology to generate powders with enhanced aerosolisation properties, an area in which he and Dr Li have a number of joint publications.
Graphical abstract
Highlights

- Di-, oligo- and poly-saccharides are used to develop novel inhalable powders.
- Polysaccharide-based powders exhibit improved aerosolisation characteristics.
- They also demonstrate sustained drug release profiles in dissolution testing.
- Opportunity to develop respirable powders that offer controlled drug release.
- Potential benefit in management of local (e.g. asthma) and systemic (e.g. diabetes) conditions.