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Designing a multi-component spray-dried formulation platform for pulmonary delivery of biopharmaceuticals: The use of polyol, disaccharide, polysaccharide and synthetic polymer to modify solid-state properties for glassy stabilisation

Tomás Sou [a], Robert T. Forbes [b], Jason Gray [b], Richard J. Prankerd [a], Lisa M. Kaminskas [a], Michelle P. McIntosh [a,*], David A.V. Morton [a,*]

[a] Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC 3052, Australia
[b] PI Research Focus Group, School of Pharmacy, University of Bradford, Bradford BD7 1DP, UK

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ABSTRACT

For a dry powder formulation platform to be suitable for pulmonary delivery of potent biopharmaceuticals, e.g., proteins and peptides, it has to be not only efficiently and reproducibly aerosolisable, but also capable of creating a matrix suitable for stabilising the relevant biomacromolecules at temperatures appropriate for storage and distribution. This study systematically evaluated the use of excipient compounds covering a range of molecular sizes: i.e., from polyol (mannitol) and disaccharide (trehalose), to polysaccharide (inulin) and synthetic polymer (PVP K30), in conjunction with other small molecule excipients. It is recognised that larger molecular weight excipients with higher T_g values are less prone to recrystallisation, however there is limited data around the potential for the inclusion of these compounds in inhalable dry powder delivery systems, where historically the focus has been on employing mono- or disaccharides. The results demonstrated that the polymer/leucine systems retained an appropriately high T_g in spite of the relatively high moisture content after spray-drying. The results also showed that sodium citrate, in contrast to glycine and leucine, was effective in inhibiting crystallisation of spray-dried mannitol. The findings demonstrated the synergistic benefits achieved from the concurrent use of several excipients on spray-dried mannitol which have not been previously reported: leucine as a particle formation agent, sodium citrate as a glass-forming agent, and glycine as a morphological modifier.

1. Introduction

Dry powder inhalation is an attractive delivery method for pulmonary delivery of biomacromolecules due to its many advantages over other delivery systems, including direct targeting for local effect, ease of administration, convenient portability, relatively low product cost and potentially improved stability in the solid state [1–3]. Spray-drying is a favoured method for production of such inhalable dry powder formulations due to its adaptability, cost-effectiveness, scalability and potential for complex particle engineering [4]. Particles can be formulated to contain various ingredients by adjusting the content of the feed solution and excipients can, therefore, be incorporated to engineer properties of the dry powder formulation. According to the glassy dynamics theory, an amorphous glassy solid powder should provide a highly viscous vitreous environment which restricts the molecular mobility of biomacromolecules and thereby stabilises proteins in a dry solid state [5,6]. Hence, excipient combinations should be selected to provide particles of an amorphous matrix with high glass transition temperature (T_g), but otherwise inert.

Carbohydrates such as mannitol are commonly used in the stabilisation of biomacromolecules due to their ability to form hydrogen bonds [7–11]. Mannitol is classified as a non-hygroscopic compound and the use of which as a stabilising excipient in dried protein formulations has been widely reviewed, and hence its use here provides a useful reference material [12–15]. However, mannitol has a relatively low T_g of 11 °C and therefore tends to recrystallise shortly after spray-drying [6,16]. Trehalose, in contrast has a T_g of 117 °C, and tends to form an amorphous glass after spray-drying. It has been used to stabilise proteins upon storage in several studies [11,17,18]. However, high concentrations of trehalose (i.e., >50% w/w) without additional excipients may not be ideal for aerosol applications due to the adhesive nature, hygroscopicity and consequently high degree of particle agglomeration and poor aerosolisation of spray-dried trehalose [11].

Alternative carbohydrates (e.g., trehalose, sucrose and lactose) and other small molecules (e.g., glycine, alanine, leucine, sodium citrate

* Corresponding authors.
E-mail addresses: michelle.mcintosh@monash.edu (M.P. McIntosh), david.morton@monash.edu (D.A.V. Morton).

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and sodium phosphate) have previously been studied to modify solid-state properties of mannitol-based formulations [9–11,16,19–22]. However, most formulations examined in these studies contained relatively high proportions of protein ranging from 50% to 90% w/w [9–11,19,20,23]. These formulations may not be ideal for highly potent proteins, such as vaccine antigens, since the maintenance of amorphous matrix critical for protein stability may differ with low protein concentration (e.g., <1% w/w).

Unlike small molecules, polymeric compounds have, by definition, a distribution of higher molecular weights and as a result there is a lower tendency to crystallise. This makes these polymers appealing excipients to generate an amorphous delivery system, and it is perhaps surprising that their evaluation in the literature has not been more widespread. For example, in one study, spray-dried inulin powder has been shown to be amorphous [24]. However, the resultant particles were relatively large (i.e., >10 μm) due to fusion of the drying droplets, and are therefore not suitable for respiratory delivery [24]. Polyvinylpyrrolidone (PVP K30) has been approved by the Food and Drug Administration (FDA) under specified ranges, and where its use for inhalation has been previously studied in a pressurised metered dose inhaler (pMDI) [25,26]. In addition, it has also been previously co-spray-dried with a range of poorly water soluble drugs in order to maintain these small molecules in an amorphous state [27,28]. As a result, it is the proposed aim of this study to evaluate the potential that similar strategies may be employed to produce discrete powder formulations with an amorphous matrix suitable for the incorporation of potent biopharmaceuticals for inhaled drug delivery.

Some compounds are intrinsically difficult to spray-dry into aerosolisable dry powders. For instance, viscous solutions of polymers can produce unacceptably low yield (e.g., 0.5% to 10%), due to high retention of starting material on the wall of the spray-dryer. Some hygroscopic compounds can produce particles with unacceptably large particle size, due to fusion of primary structures during or after the drying process [16,29]. The inclusion of L-leucine in feed solutions has been shown to assist production of inhalable spray-dried powders containing multiple components, while improving aerosolisation properties of the powders. These multi-component formulations were otherwise poorly aerosolisable in the absence of leucine [16,30–33]. Similar strategies may be used in the production of other spray-dried powders with materials that would otherwise be too hygroscopic for efficient spray-drying. For this to be effective, these past studies have reported that the leucine should be capable of migrating to the droplet surface during drying, to create an enriched surface composition.

The present study aims to explore the use of multi-component spray-dried formulations, using leucine as a particle formation agent, for the production of a universal particulate platform with an amorphous matrix and an appropriate T_g suitable for the incorporation of various potent biopharmaceuticals. The model compounds were selected to investigate the influence of molecular size, using excipients with potentially appealing properties for the stabilisation of biopharmaceuticals, as discussed above, across the range of polyol (mannitol), disaccharide (trehalose), polysaccharide (inulin) and synthetic polymer (PVP K30). The influence of change in molecular size on the resultant solid-state properties of spray-dried formulations has not previously been reported in this context, and it is not clear that, for example, what the effects of competition between components to form an enriched surface would be. In addition, the inhibition of crystallisation of spray-dried mannitol using small molecule excipients previously reported in spray-dried protein formulations (i.e., glycine and sodium citrate), and the properties of these multi-component systems in the absence of proteins, were also investigated for comparison. The present study specifically focuses on the influence of these excipients on processing yields, solid-state properties and morphology of these spray-dried formulations to complement our earlier work in this area.

2. Materials and methods

2.1. Materials

D-Mannitol, D-(+)-trehalose dihydrate, inulin (approximate molecular weight = 5000 Da), povidone K30 (PVP K30, approximate molecular weight = 40,000 Da), L-leucine and glycine were obtained from Sigma-Aldrich Chemicals (Castle Hill, NSW, Australia). Tri-sodium citrate was obtained from Ajax Finechem (Seven Hills, NSW, Australia).

2.2. Preparation of spray-dried powders

The formulations in various compositions were made into aqueous solutions containing 5% w/v solid-loading using Milli-Q water. The prepared formulations were subsequently spray-dried using a Buchi 190 mini spray-dryer with a 0.5 mm two-fluid nozzle, using the following standard operating conditions: airflow, 800 L/h; pump setting, 5 (6.67 mL/min); aspirator setting, 20 (−84 mbar) [34]; inlet temperature in the range of 110–120 °C to achieve an outlet temperature of approximately 70 (±2) °C. The compositions of the formulations are shown in Table 1. The processing yields were defined as the percentage of mass of spray-dried powder recovered ($M_{recovered}$) to the mass of total solid loading (M_{total}) in the initial feed solution as shown in Eq. (1).

$$\text{Yield}\% = \frac{M_{recovered}}{M_{total}} \times 100. \quad (1)$$

2.3. Particle size analysis

The particle size distribution of the powders was determined by laser-light scattering using the Malvern Mastersizer 2000 (Malvern Instruments Ltd, Worcestershire, UK) equipped with a Hydro 2000S sample dispersion unit. The powders were suspended in 2,2,4-trimethylpentane with lecithin 0.01% w/v. The average particle size was measured in triplicates for each sample. The volume median diameter (D_{50}) was derived from the diffraction data using the in-built software for each sample.

2.4. X-ray powder diffraction (XRPD)

Samples were analysed approximately two weeks after storage at room temperature in sealed containers. Sample powders were manually compacted at room temperature in silicon sample holders to obtain a level surface for analysis. The samples were then analysed by X-ray powder diffractometry (Bruker D8 Diffractometer, Bruker, Germany) for scanning from $2\theta = 2$ to 60°; step-wise scanning mode with step size $2\theta = 0.02°$; and step time = 1 s. The amorphous nature of the powders was assessed qualitatively from the powder diffraction patterns.

2.5. Differential scanning calorimetry (DSC)

DSC was performed using a TA DSC Q2000 (TA Instruments, UK). Samples (2 to 5 mg) were sealed in Tzero aluminium DSC pans for measurements. Samples were heated from −50 to 250 °C at 200 °C/min. The glass transition temperature (T_g) was defined as the mid-point of the glass transition event where applicable.

2.6. Modulated differential scanning calorimetry (MDSC)

MDSC was performed using the TA DSC Q2000 (TA Instruments, UK). Samples (1.9 to 4.1 mg) were sealed in Tzero aluminium DSC pans. Measurements were recorded with a modulation amplitude of ±1 °C, a modulation period of 60 s, and a heating rate of 4 °C/min from −5 to 200 °C. Samples without detectable glass transition from the standard DSC method were tested with the MDSC method.