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# Spray-freeze-drying production of thermally sensitive polymeric nanoparticle aggregates for inhaled drug delivery: Effect of freeze-drying adjuvants

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ABSTRACT

Inhalable dry-powder aggregates of drug-loaded thermally sensitive poly(caprolactone) (PCL) nanoparticles are produced using spray-freeze-drying (SFD) as the low melting point of PCL prohibits the use of high-temperature spray-drying. The effects of freeze-drying adjuvant formulation on the particle morphology, aerodynamic diameter, aqueous re-dispersibility, flowability, and production yield are examined using mannitol and poly(vinyl alcohol) (PVA) as the adjuvants. The primary role of the adjuvant is to prevent irreversible nanoparticle coalescences during freeze-drying, thereby the nanoparticle aggregates can readily re-disperse into primary nanoparticles in an aqueous environment hence retaining their therapeutic functions. The nanoparticle aggregates produced using either adjuvant exhibit large, porous, and spherical morphologies suitable for dry-powder-inhaler delivery. The nanoparticle aggregates exhibit good flowability and effective aerosolization off the inhaler. The adjuvant selection governs the resultant nanoparticle–adjuvant structures, where PCL nanoparticles are physically dispersed in porous mannitol matrix, whereas PVA are coated onto the nanoparticle surface. Importantly, nanoparticle aggregates produced by SFD exhibit significantly higher aqueous re-dispersibility than those produced by spray-drying, which signifies the suitability of SFD as the method to produce solid-dosage-form of thermally sensitive nanoparticles. Overall, using PVA as adjuvant leads to more stable morphology, superior aqueous re-dispersibility, and higher production yield compared to the mannitol formulation.



## 1. Introduction

Dry powder inhaler (DPI) represents an effective pulmonary delivery platform for direct dosing of therapeutic agents to the lungs because of its portability, long shelf-life, and high delivery efficiency. These characteristics of DPI are in contrast to the relative inconvenience (e.g. lengthy treatment time, non-portability) and low delivery efficiency associated with the more conventional nebulization delivery platform. The use of nanoparticles as therapeutic carriers in DPI delivery has recently gained significant interest as nano-scale formulations enable the therapeutic agents to evade the lung phagocytic clearance and enhances the dissolution rate of poorly water-soluble drugs (Rogueda and Traini, 2007).

Direct inhalation of dry-powder nanoparticles, however, is not plausible because nanoparticles have a strong tendency to agglomerate resulting in difficult physical handling. Furthermore, nanoparticles, with the exception of particles <50 nm in size, are predominantly exhaled from the lung without depositing due to their low aerodynamic diameters ($d_A$) (Rogueda and Traini, 2007). In this regard, inhaled particles should possess $d_A$ defined in Eq. (1) between 1 and 5 μm to effectively deposit in the lungs.

$$d_A = d_G\sqrt{\frac{\rho_e}{\rho_S}} \quad (1)$$

where $d_G$ is the particle geometric diameter, $\rho_S = 1\ \mathrm{g/cm^3}$, and $\rho_e$ is the particle effective density defined as the mass of particles divided by their total volume including the open and closed pores.

To facilitate their delivery by inhalation, nanoparticles are typically transformed by spray drying into low-density micro-scale nanoparticle aggregates (i.e. nano-aggregates) with large $d_G$ (>5 μm) and low $\rho_e$ ($\ll 1\ \mathrm{g/cm^3}$) using various pharmaceutical excipients as drying adjuvants (Grenha et al., 2005; Hadinoto and Cheow, 2009; Sham et al., 2004; Sung et al., 2009). The large $d_G$ of the nano-aggregates alleviates the problem of particle agglomerations resulting in effective aerosolization off the inhaler, without the need for coarse carrier particle inclusion, and improved physical handling. Their low $\rho_e$, which is owed to either hollow or porous morphologies, ensures their $d_A$ to fall within the range suitable for effective lung depositions despite the large $d_G$. Another advantage of this carrier-free DPI formulation is in eliminating the concern of poor liberations of drug particles from carrier particles observed in the conventional DPI formulation.

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**Nomenclature**

| | |
|---|---|
| $\rho_e$ | effective density |
| $\rho_S$ | unit density |
| $\rho_{tap}$ | tap density |
| $\rho_{bulk}$ | bulk density |
| CI | Carr's index |
| $d_A$ | aerodynamic diameter |
| $d_G$ | geometric diameter |
| ED | emitted dose |
| FPF | fine particle fraction |
| IP | induction port |
| N/M | nanoparticle to mannitol ratio |
| N/P | nanoparticle to PVA ratio |
| NGI | next generation impactor |
| PS | pre-separator |
| $S_f$ | size of particles present in suspension after SFD |
| $S_i$ | initial size of nanoparticles before SFD |
| SPET | standardized powder entrainment tube |
| Yield | production yield |

The spray dryer is typically operated at inlet temperatures ≥100 °C to achieve a fast convective drying rate needed to obtain the low $\rho_e$. Exposure to high temperatures in the spray dryer, where the outlet spray-dryer temperatures vary in the range of 60–70 °C, however, is prohibitive when low melting-point or thermally sensitive biodegradable polymers, such as poly(caprolactone) (PCL) and poly(propylene succinate), are employed as therapeutic carriers. The high temperature can jeopardize the structural integrity of the nanoparticles, even in the presence of drying adjuvants, leading to nanoparticle degradations or coalescences that diminish their therapeutic functions.

The detrimental effects of the high temperature in a spray-drying process have been demonstrated in our earlier study (Kho et al., 2010) in which PCL nanoparticles were spray dried using mannitol, lactose, and leucine as drying adjuvants. PCL, a low melting point polymer (62 °C), has been widely studied as potential therapeutic carriers attributed to its high matrix permeability towards a wide range of therapeutic agents and its high physical stability owed to its highly crystalline structures (Sinha et al., 2004). Even though the nano-aggregates produced exhibited $d_A$ in the range ideal for inhaled delivery, less than half of the nanoparticles were recovered from the nano-aggregates upon re-dispersion. The poor aqueous re-dispersibility of the spray-dried PCL nano-aggregates was caused by irreversible nanoparticle coalescences, where PCL nanoparticles softened and fused together upon exposure to temperature near or above their melting point.

Owing to its non-elevated temperature operation, spray freeze drying (SFD) represents a viable alternative to spray drying to produce dry-powder nano-aggregates. In terms of its applications, SFD has primarily been employed to produce dry-powder proteins as the sub-zero temperature, unlike the high temperature, does not adversely affect protein structures and functions (Costantino et al., 2000; Maa et al., 1999). SFD has also been used to produce solid dosage forms of poorly water-soluble drugs (Hu et al., 2002; Niwa et al., 2009) and to transform aqueous suspensions of drug-loaded liposomes into their dry-powder forms using lactose, sucrose, and mannitol as freeze-drying adjuvants (Bi et al., 2008; Sweeney et al., 2005). To the best of our knowledge, the use of SFD to transform aqueous suspensions of biodegradable polymeric nanoparticles into their inhalable dry-powder form has never been examined.

The two-step SFD process (i.e. atomization into a cryogen followed by lyophilization) to produce nano-aggregates is illustrated in Fig. 1. The first step involves channeling of the nanoparticle suspension through a nozzle to be atomized into tiny droplets. As the nanoparticle suspension is atomized into droplets, the cold temperature provided by the cryogen (i.e. liquid nitrogen) is sufficient to freeze water molecules present within the air-borne droplets. The droplets are completely frozen when they are immersed in the liquid nitrogen. The rapid freezing allows the water molecules to be frozen into ice crystals that are interspersed among the dissolved or suspended materials consisting of nanoparticles and freeze-drying adjuvants. Excess liquid nitrogen is subsequently removed from the slurry containing the frozen droplets by evaporation or decanting. The evaporation of the liquid nitrogen is carried out by holding the slurry at a temperature between the boiling point of the liquid nitrogen and the melting point of ice (i.e. between −196 °C and 0 °C) to ensure the droplets remain frozen while the liquid nitrogen is being evaporated.

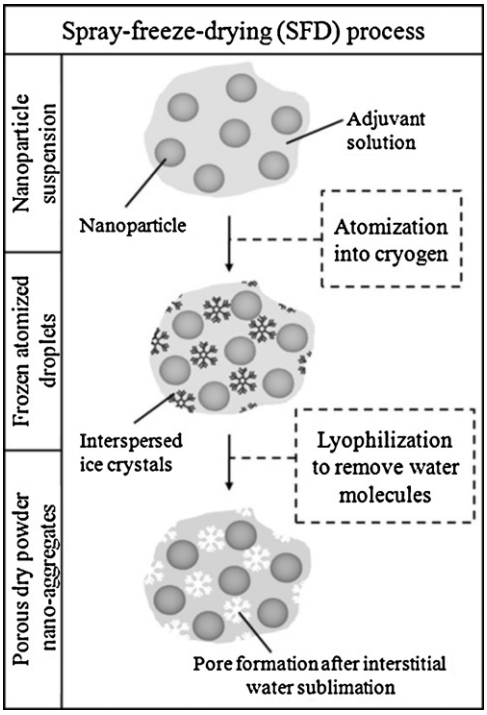


**Fig. 1.** Physical mechanisms of the spray-freeze-drying (SFD) process.

To obtain dry powders, the ice crystals are removed from the frozen droplets via sublimation in the lyophilization stage. The sublimation is carried out below the triple point of water (6 mbar, 0.01 °C) to prevent the melting of ice crystals into liquid water that can destroy the solid structure of the nano-aggregates. As the ice crystals in the frozen droplets are sublimed interstitially, the frozen droplets retain their size and do not shrink upon sublimation. Therefore, for identical atomizing conditions, SFD produces particles having larger $d_G$ compared to spray drying in which the atomized droplets shrink due to convective evaporation of the aqueous medium. Furthermore, due to the interstitial sublimation, particles produced by SFD exhibit highly porous structures attributed to the presence of voids previously occupied by the sublimed ice crystals. As a result, nano-aggregates having large $d_G$ and low $\rho_e$ are straightforwardly produced by SFD.

In SFD of nanoparticle suspension, freeze-drying adjuvants need to be included in the formulation (i) to function as cryoprotective agents protecting the nanoparticles from the sub-zero temperature, and (ii) to facilitate re-dispersions of the nano-aggregates back into primary nanoparticles, so that the nanoparticles can perform their intended therapeutic functions. In inhaled drug deliv-