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A review on the superiority of spray freeze drying over spray drying method in the preparation of nano composite microcarriers (NCMs) for pulmonary drug delivery

Pepakayala Hema[1], Pidaparthy Lakshmi Mounika[2], Battu Gnananjali[1], Aruna Devi Mantena[2], Peddinti Vasu[1], K.T. Sunil Kumar[2], Ashok Thulluru[1*]

Abstract

It is difficult to formulate nanoparticles for deep lung delivery and several techniques struggle in terms of nanoparticle stability. Spray freeze drying (SFD) is proposed here for the manufacture of inhalable nano composite microcarriers (NCM). Including polymeric and lipid nanoparticles, various nanostructures have been prepared and defined. Nanoparticle suspensions were co-sprayed into a cooled, stainless steel spray tower with an appropriate cryoprotectant, followed by freeze-drying to form a dry powder while spray dried (SD) compositions were equivalent as controls. SFD-NCM has greater specific surface areas (67-77 m2/g) and lower densities (0.02 g/cm3) than their respective SD-NCM areas. SFD provided NCM with a mass median aerodynamic diameter (MMAD) of 3.0 ± 0.5 lm and fine particle fraction (FPF 6 5.2 lm) of 45 ± 1.6 % with aerodynamic efficiency comparable to SD-NCM, except for NCM for lipid-based nanocarriers. However, in terms of preserving the particle size of all the polymeric and lipid nanocarriers investigated after reconstitution, SFD was superior to SD (Sf/Si ratio for SFD 1 versus >1.5 for SD). The cooled air SFD has proven to be an effective technique to prepare NCM for pulmonary delivery while preserving the nanoparticles' stability.

Keywords: Dry Powder Inhalation, Nano Composite microcarriers (NCM), Spray Drying, Spray Freeze Drying, Pulmonary Delivery.

Author Affiliation: [1] Department of Pharmaceutical Quality Assurance, Shri Vishnu College of Pharmacy (Autonomous), Vishnupur, Bhimavaram-534 202, W.G. Dist., A. P., India.

[2] Department of Pharmaceutics, Shri Vishnu College of Pharmacy (Autonomous), Vishnupur, Bhimavaram-534 202, W.G. Dist., A. P., India.

Corresponding Author: Ashok Thulluru. Department of Pharmaceutical Quality Assurance, Shri Vishnu College of Pharmacy (Autonomous), Vishnupur, Bhimavaram-534 202, W.G. Dist., A.P., India.

Email: ashokayaanasrith@gmail.com

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1. Introduction

The largest respiratory organ is the lungs [1]. Inhaled drug delivery has been very effective for the treatment of different pulmonary disorders such as tuberculosis, lung cancer, asthma, chronic obstructive pulmonary disease (COPD), and pulmonary infections [2]. Because of its wide surface area, high permeability characteristics, and lower first-pass metabolism stage, the lung provides an ideal way for local and systemic drug delivery [3]. Nanoparticles are a commonly used delivery system for medicines. They primarily increase the solubility of drugs, enhance the half-life, improve the therapeutic index, and decrease the immunogenicity of drugs [4, 5]. The important explanation for these lung-based nanoparticles is that nano-sized particles can easily cross the cellular barrier independently of the supply of energy. Nanoparticles are engineered to be taken up and transmitted directly to the bacteria by macrophages and used to treat diseases such as tuberculosis [6].

These are also used in the treatment of systemic diseases to deliver macromolecular drugs such as protein and peptides through the lungs [6]. These are used to treat local diseases of lung like, asthma, cystic fibrosis, COPD, Mucus-hyper secretion, and extreme inflammatory lung diseases [7]. Due to their ability to reach the intracellular compartments and their bioavailability enhancement potential attributed to the unusual ability of nanoparticles to resist alveolar macrophages and mucociliary clearance mechanisms, the use of nanoparticles as therapeutic carriers for pulmonary delivery has gained considerable interest, resulting in extended drug residence period [9].

However, following pulmonary administration, these nanoparticles have the drawback of being exhaled from the lungs. To allow the drugs to be accumulated in the deep lungs, inhaled particles

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should have an aerodynamic diameter (Dae) of between 1 and 5 µm. Particles with a (Dae) > 5 µm are affected by the broad airway, whereas particles with a (Dae) < 0.5µm are exhaled [8]. Nanomaterials, including nanoparticles, nanofibers and nanotubes, composite materials, and nanostructured surfaces, range from 1 to 100 nm. As a subset of nanomaterials, nanoparticles are presently classified as single particles less than 100 nm in diameter. Nanoparticle agglomerates can be larger than 100 nm in diameter but can be de-agglomerated or distributed in a solvent with poor mechanical forces [8]. There was formulation instability due to higher surface energy, leading to aggregation / particle-particle interactions [8]. Except for nanoparticles of < 50 nm duration, exhaled from the lungs [9]. Nanoparticles are prepared in the form of nano-suspensions and delivered to the lungs to overcome these types of problems. Incase nanosuspensions the size of droplets produced by the nebulizer varies due to the application of some stress in the nebulization process, leading to instability in formulation [10]. By preparing nanoparticles as a dry powder, the instability problems such as aggregation and drug leakage can be solved [11].

2. Applications of NCMs:

Imaging and Diagnostic Applications:

By applying nanotechnology, the creation of imaging potential that will support basic & clinical pulmonary research & disease diagnosis can be visualized. Advances such as nanoparticle imaging agents are administered to cells/tissues. The nanoprobes are created for molecular imaging of disease pathways and better contrast is available for production. Quantum dots are used for imaging & diagnostic purposes. The tiny semiconductor particles are these quantum points and have wide absorption spectra and narrow emission spectra. Multiple quantum dots are simultaneously observed here because their fluorescence is chemically dependent. The attachment of peptides (or) antibodies to target cells/tissues for imaging due to their larger surface area (quantum dots), thus increasing specificity and decreasing background here [12]. Quantum dots coated with a peptide-binding on pulmonary endothelial cells to membrane dipeptidase were found in the lung, but not in the brain or kidney, 5 min after intravenous administration in BALB / c mice. In addition, fast and precise in a study using quantum dots conjugated to monoclonal antibodies [13].

3.Therapeutic Applications:

In respiratory & systemic disorders, nanoparticles have various therapeutic applications. Recent research has focused significantly on determining the suitability of nanoparticles of different types to act as vectors for the pulmonary delivery of drugs or genes via inhalation or systemic administration, although other attempts have been made to create and deliver nano-sized drug particles to the lung. Most of the studies published to date have focal points [13]. As an example, when provided prophylactically or therapeutically, gene transfer using intranasal administration of chitosan-DNA nanospheres was shown to prophylactically inhibit respiratory syncytial virus infection and to reduce allergic airway inflammation in mice [13]. Also, short interfering RNA (siRNA) targeted against a viral gene, NS1, has also been shown to inhibit respiratory syncytial virus infection in mice and rats via nanoparticle-mediated intranasal delivery [13].

4. Potential Applications:

Learning from environmental toxicology studies, nano-sized air contaminants, especially spherical solid materials, enter the lungs easily and reach the alveoli, and are subsequently cleared by various clearance mechanisms from the lungs. Nano-sized particles, however, because of their small size, are not likely to be observed along the lung epithelial barriers. However, nano-sized particles are not likely to be observed along the lung epithelial barriers owing to their small scale. They will translocate and invade other organs in systemic circulation. As the concept of the cut-off size of airborne nanoparticles is the same as that of engineered nanoparticles (100 nm), the same biokinetics should be shared with inhouse nanoparticles [8]. To deliver water-insoluble drugs, nanoparticles are useful. Despite high potency, the efficacy of water-insoluble drugs can be significantly restricted because the solubility is too poor to achieve therapeutic systemic concentrations. However, the increased particle surface-to - volume ratio helps to improve solubility and dissolution rate in an aqueous setting when their size is reduced to nano-level. Nanoparticulate forms of medication could have an immense advantage by dramatically enhancing systemically [14]. Nano-based drug delivery methods focus on crossing a specific physical barrier, such as the gastrointestinal epithelium to absorb macromolecules, the blood-brain barrier, or seeking alternate and suitable routes to deliver drugs that are costly and vulnerable to the gastrointestinal setting. Nano-level pulmonary drug delivery is a non-invasive, promising means of delivering not only local lung effects, but likely high systemic bioavailability [8].

5. Methods for preparation NCMs by Spray drying (SD) and spray freeze drying (SFD):

Spray Drying (SD) Method:

With 5 % w/v of either maltodextrin (for polymeric nanoparticles) or trehalose (for lipid nanocarriers) and 5 % w/v PVP as stabilizer's, nanoparticle dispersions (1 % w/v) were combined. Then, using a Büchi B-191 mini–Spray Dryer fitted with a two-fluid nozzle (0.7 mm), the dispersions were spray-dried. The following settings were used for spray drying feed rate 3% (1 mL/min), inlet temperature 110 °C, airflow rate 189 750 NL/h and aspiration 85%. The outlet temperature of 80 °C was the product of these settings. Until spraying, florescent microcarriers were prepared by adding 0.05 % sodium fluorescein into

the aqueous suspension. The powder obtained was processed until used in a vacuum desiccator over silica gel [16].

Spray Freeze Drying (SFD) Method:

With some changes, SFD was carried out [17]. In short, there were three phases in the process: droplet forming, freezing, and freeze-drying. At the top of a spray tower, a two-fluid nozzle (0.7 mm) was mounted for droplet formation. Inside a cooled, stainless steel spray tower encased by a cooling jacket of liquid nitrogen, the freezing process was performed, where direct spraying into liquid nitrogen was prevented by design. Nanoparticle dispersions (1% w/v) were co-sprayed with either maltodextrin (for polymeric nanoparticles) or trehalose (for lipid nanocarriers) at 5% w/v PVP at a rate of 2 mL/min using a 750 NL/h atomized air flow into a column of cold air at 130 ° C. The droplets in the cooled air are frozen and the frozen spherules are stored for further freeze-drying after sedimentation in a cooled container. Until spraying, fluorescent microcarriers were prepared by using 0.05 % w/v sodium fluorescein in the aqueous suspension. The frozen samples were lyophilized using a STERIS Lyovac GT2 freeze dryer where they were dried for at least 36 h following a normal protocol [15]. Maltodextrin was selected as a suitable cryoprotectant for the polymeric nanoparticle samples based on preliminary studies, while trehalose was selected for the lipid nanocarrier samples. NCM preparation was possible by either SD or SFD for the polymeric nanoparticles. The yields were 91.2 ± 7.9 % w/w for SFD samples, and 68.6 ± 8.4 % w/w for SD samples, as determined from the ratio of the NCM mass recovered after SD or SFD to the initial mass added to the feed [15].

Evaluation and characterization of NCMs prepared by SD vs SFD:

Bulk density and flowability:

Measurement of the SD- and SFD-NCM bulk density showed that the SFD-NCM was 10 times lower than the corresponding SD-NCM density. Also, the SFD-NCM bulk densities were about 0.02 g/cm^3, while the corresponding SD-NCM had bulk densities of about 0.2 g/cm^3 Also, SD-NCMs Carr's Index (CI) values were passable to bad flowability (CI = 22-28), while SFD-NCM values were excellent to good flowability (CI = 6-14). Accordingly, more SFD powder than the SD powder is required to empty from the capsules and inhaler [15].

Scanning electron microscope (SEM) analysis:

On the double-sided adhesive tape, SD- and SFD-NCM samples were mounted, set on aluminum stubs, and sputter-coated by using Polaron SC7640 Sputter Cotter with gold for 4-6 min and imaged with SEM [15]. By this analysis SFD-NCM were smaller with a slightly wrinkled smooth surface, while SFD particles were larger with a slightly rough surface are formed.

Particle size distribution (PSD):

Using a Sympatec Helos LF instrument, laser diffraction spectrometry measured the geometric particle size distributions of the SD- and SFD NCM. The SD dispersing module of the Sympatec Rodo was used to disperse the samples at 0.5 bar pressure into the measurement chamber. Using Window 3.4 software's Fraunhofer theory choice to measure the volume median particle size (d50), diffraction spectra were evaluated. Then, the interval was measured as:

Span = d90-d10/d50 Eq. No. 1

Here, d90 and d10 reflect the diameters with a smaller particle size of 90% and 10% of the distribution, respectively. The lipid nanostructures SFD-NCM showed elevated d50 values that are not appropriate for pulmonary deposition [15].

Specific surface area:

The particle size distributions of SD- and SFD-NCM determined by laser diffraction analysis. The particle size observed for the prepared NCM under the SEM was corroborated by the corresponding data for laser diffraction. Laser diffraction measurements showed that polymeric nanoparticles' d50 of SD-NCM is smaller than that of the respective SFD-NCM. They were both declining in the same order (EC > EDRL > PLGA), however. The lipid nanostructures' SFD-NCM showed elevated d50 values that are not appropriate for pulmonary deposition. The SFD-real NCM's surface areas (60-77 m2/g) were much larger than those of the SD-NCM (1.8-2.4 m2/g), as predicted [15].

Aerodynamic Properties:

Using a Next Generation Impactor (NGI) (Copley Scientific, Nottingham, UK), the aerodynamic properties of the prepared powders have been determined. Based on the well-characterized aerodynamic size cut-offs, particles dispersed in an airstream were transmitted through the instrument and impacted on the eight consecutive points. Via a mouthpiece adaptor, the HandiHaler DPI system (Boehringer Ingelheim, Germany) was connected to the NGI. To avoid bouncing and re-entraining of particles between stages, all stages were coated with 1 % w/v silicon oil in n-hexane before each run. Five capsules (size 3), each manually filled with 5-7 mg of powder, were released into the NGI from the DPI. The airflow rate is set to 45 L/min for 5.3 s using the vital flow controller (Copley Science, UK) to simulate 4 l of air drawn by human inhalation. At 45 L/min, the effective aerodynamic cut-off diameters for each stage are 9.1, 5.2, 3.3, 1.9, 1.1, 0.6, and 0.4 lm for stages, respectively. The contents of the capsules, DPI, mouthpiece adaptor, induction port, pre-separator, stages 1-7 and the micro-orifice contactor (MOC) were washed into volumetric flasks with deionized water after actuation. Spectrofluorometry measured the fluorescence intensities of the solutions using a 485 nm excitation filter and emission at 535 nm. Triplicate

testing was conducted on each powder. The recovered dose, the emitted fraction, and the fine particle fraction were analyzed to quantify the data. The determination of the mass median aerodynamic diameter (MMAD, diameter at 50% of the cumulative weight undersize) and the geometric standard deviation (GSD) was made possible by a plot of cumulative% undersize versus effective cut-off diameter [15].

GSD = (d84% / d16%)2 Eq. No. 2

Where size dn is the diameter at the percentile n of the cumulative distribution.

The proximity between d50 and MMAD was found for SD-NMCs, while a clear difference between their large physical diameters and their smaller aerodynamic diameters was found for SFD-NMCs [15].

Reconstitution of NCMs:

In 1 mL of deionized water with gentle shaking, 10 mg of the dried powder is reconstituted to form a colloidal dispersion with subsequent particle size measurements after re-dispersion. The ability to reconstitute was calculated by the change in the size of the nanoparticle before and after reconstitution. After reconstitution, Sf is the mean particle size, while Si is the average particle size before drying. Sf/Si ratio 1 denotes complete reconstitution, while Sf/Si ratio > 1.5 denotes poor reconstitution. As reflected by the Sf/Si ratio, all SFD-NCMs showed full reconstitution of the nanoparticles, except for LNC, which was slightly higher but still within the good reconstitution range. SD-NCMs, on the other hand, only permitted weak nanoparticle reconstitution as reflected by high Sf/Si values, with the sole exception of SD-NCMs of EDRL nanoparticles, which showed full spray-drying reconstitution [17, 18].

Conclusion:

Spray freeze drying (SFD) is a promising solution to the preparation of inhalable Nano composite microcarriers (NCMs). Regarding the viability of the formulation, both polymeric and lipid nanocarriers can be successfully formulated as NCMs using the SFD technique. In addition, SFD produces low-density porous NCMs, with low aerodynamic diameters and ideal for pulmonary deposition. In comparison to spray drying (SD), spray freeze drying (SFD) is the method of choice when the key concern is the reconstitution of the encapsulated nanocarriers.

LIST OF ABBREVIATIONS:

SD- Spray drying, SFD- Spray freeze drying, NCMs- Nano composite microcarriers, NP- nanoparticles; PLGA- poly (DL-lactide-co-glycolide), EDRL- poly(meth) acrylate (Eudragit RL PO), PVP- polyvinylpyrrolidone (kollidon12PF), LNC- lipid nanocapsules, SLN- solid lipid Nanoparticles, PDI- polydispersity index, SEM- scanning electron microscope, d50- volume median particle size, CI- Carr's Index; NGI- next generation impactor, DPI- dry powder inhaler, MOC- micro-orifice contactor, FPF- fine particle fraction, MMAD- mass median aerodynamic diameter, and GSD-geometric standard deviation.

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