Invited Editorial: How can the Challenges Faced by Nanoparticle-based Pulmonary Drug Formulations be Overcome

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Pulmonary drug delivery via inhalation has a long history of development and can be stretched back into antiquity when Egyptians inhaled black henbane vapor for treating various diseases. Since then, it has been relatively neglected as a major route of drug administration although it has several advantages such as non-invasive in nature, local drug delivery, rapid onset of action and circumvention of first-pass effect [1]. Thanks to the

recent advances in nanotechnology, a resurgence of research interests toward developing nanoparticle-based pulmonary drug formulations for deep lung delivery has been seen for all three commercially available inhalation devices, i.e., nebulizers, metered dose inhalers (MDI) and dry powder inhalers (DPI) [2-4].

Current Challenges in Nanoparticle-based Pulmonary Drug Formulations

While nanoparticles have been proven to possess unique merits to drug delivery, its applications for pulmonary delivery are not that straightforward and pose significant challenges in formulation development. An obvious hurdle is control of particle size. A widely accepted range of aerodynamic diameter for effective pulmonary delivery is from 1– 5 μm [5]. For DPI formulations, nanoparticles tend to remain airborne in the airways and readily exhaled before reaching the alveoli. Nanoparticles-carriers and nanoparticle agglomeration are two possible formulation strategies to tackle the issue. For the former system, nanoparticles are adhered to the surface of a micron-sized inert carrier (~20–30 μm) and the release of nanoparticles from the carrier is promoted by the high air flowrate in the bronchi. On the other hand, nanoparticle agglomeration is achieved by controlled aggregation of primary nanoparticles to an optimal aerodynamic size. Deagglomeration of nanoparticles can be activated upon contact with alveolar lining fluid. This eliminates the requirement of high airflow velocity for particle dispersion and is desirable to the patient with reduced pulmonary function. For MDIs- and nebulizer-based formulations, as the size of aerosol is mainly governed by the liquid atomization but not the size of nanoparticles, size control here is not a consideration. However, this triggers another key challenge to the formulation development, which is the physical instability of nanoparticles.

Being thermodynamically unstable, nanoparticles tend to aggregate and grow uncontrollably in order to minimize their surface energy, especially when they are formulated as a nanosuspension. There are several approaches to enhance the stability of a nanosuspension, for example, surface modification using hydrophilic or amphiphilic polymers (e.g., polyethylene glycol (PEG) and PEG-based block copolymers) [6], incorporation of pharmaceutical excipients as stabilizers or co-stabilizers (e.g., polyvinyl pyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), and cholesterol) [7, 8] and control of storage temperature [8]. In addition, shear force exerted on the nanoparticles

during liquid atomization is also an important factor that cannot be overlooked as it could disrupt the surface properties and even the particle architecture. Drying of nanosuspension is a visible way to extend the shelf life of nanoparticles, as well as fabricating DPI formulations. Among various available drying techniques, spray drying is probably the most widely used technology for producing nanoparticles in dry powder form due to its relative simplicity for particle engineering of the final product and scale-up capability.

However, sole drying of drug nanosuspension as dispersible nanoparticles is generally not possible as thermal and mechanical stresses could lead to uncontrolled particle aggregation and recrystallization during drying. Sugars (e.g. mannitol, lactose, glucose and trehalose) and polymers [e.g. poly (lactide-co-glycolide) (PLGA), polylactide (PLA), PVA and chitosan] as protectants [9, 10] are highly desirable in the nanosuspension to preserve the particle integrity against the stresses via surface coating or entrapment of nanoparticles. Co-spraying of nanosuspension with a gel forming polymer at an evaluated temperature is also a feasible way to yield redispersible nanoparticle agglomerates [11], but attention should be paid to the gelation temperature and safety profile of the polymer. Although spray drying appears to be a pragmatic method for producing nanoparticle-based pulmonary drug formulations, it should be noted that this technology may not work for processing heat sensitive materials such as biologics (protein, peptides, nucleic acids or combinations of these substances) and compounds with a low melting point. Alternative techniques such as spray freeze drying, which are free from heating stress and amenable of agglomerate size, are worthy of consideration if spray drying fails to produce redispersible nanoparticles formulations [12].

In addition to size and physical instability, potential cytotoxicity and clearance mechanism of inhaled nanoparticles are important topics which deserve more in-depth understanding. In alveoli, particles in the micron size range tend to stay on the epithelia surface while nanoparticles are capable of penetrating the epithelial layer and surrounding interstitium due to the presence of nanosized pores in the epithelium [13]. Interestingly, it has been found that part of the nanoparticles could return to the epithelial surface [14]. Such a repeated penetration and re-entrainment cycle can provide a uniform drug concentration throughout the alveoli and is desirable for pulmonary disease treatment.

Nevertheless, the dose-dependent toxicity of nanoparticles should be carefully examined as the toxicity of the nanoparticle could be significantly different with its coarse counterpart. Regarding the clearance mechanism of particles deposited in alveoli, micron particles are typically cleared from the alveoli within 24 hours via phagocytosis by macrophages on the epithelial surface, whereas nanoparticles tend to be retained in the alveoli [15]. This perhaps is not unexpected as most of the nanoparticles move into the lung tissue and therefore get less exposure to macrophages present at the epithelial surface. Nanoparticles have also been shown to possess the ability to circumvent phagocytosis by macrophages [15]. While the exact clearance mechanism of nanoparticles at alveoli is not understood yet, particles size and surface properties appear to be the most critical factors that affect the translocations of deposited nanoparticles from the alveolar space to the systematic circulation. For example, it has been revealed that titanium dioxide (TiO_2) nanoparticles with a mean particle size of 22 nm could enter the blood capillaries more readily than other types of particles of larger or smaller size after intratracheal administration in rats [16]. The amount of albumin-coated gold nanoparticles translocated was significantly higher than that of the uncoated gold nanoparticles [17, 18].

Conclusion and Future Perspective

In conclusion, the presence of nanotechnology opens up new vistas for developing novel nanoparticle-based drug formulations for superior pulmonary delivery. Particle size control, physical instability, potential cytotoxicity and clearance mechanism of inhaled nanoparticles are the major considerations in formulation development. To our knowledge, currently there is no marketed therapeutics related to nanoparticle-based pulmonary drug formulations. To make full use of the advantages of nanotechnology in pulmonary drug delivery and develop related products for commercialization, extensive research efforts should be dedicated to following research aspects in the future:

- Excipients and critical processing parameters that control agglomeration of nanoparticles to a desired size range using spray drying and spray freeze drying;
- Novel formulation strategy that enhances the physical stability of nanosuspension and dry powder formulation;
- The release rate of nanoparticles from carriers or the rate of deagglomeration in

nanoparticle agglomerates, and their correlation to pulmonary pharmacokinetic;

- The effects of particle size and surface properties on potential cytotoxicity and clearance rate of inhalable nanoparticles that are constituted of organic materials as most of the existing literatures drawn the results based on the inorganic materials such as gold and titanium dioxide;
- Application of nanotechnology to biologic therapeutics for pulmonary delivery

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