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Review Article

Nanotechnology and pharmaceutical inhalation aerosols

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Pharmaceutical inhalation aerosols have been playing a crucial role in the health and well being of millions of people throughout the world for many years. The technology's continual advancement, the ease of use and the more desirable pulmonary-rather-than-needle delivery for systemic drugs has increased the attraction for the pharmaceutical aerosol in recent years. But administration of drugs by the pulmonary route is technically challenging because oral deposition can be high, and variations in inhalation technique can affect the quantity of drug delivered to the lungs. Recent advances in nanotechnology, particularly drug delivery field have encouraged formulation scientists to expand their reach in solving tricky problems related to drug delivery. Moreover, application of nanotechnology to aerosol science has opened up a new category of pharmaceutical aerosols (collectively known as nanoenabled-aerosols) with added advantages and effectiveness. In this review, some of the latest approaches of nano-enabled aerosol drug delivery system (including nano-suspension, trojan particles, bioadhesive nanoparticles and smart particle aerosols) that can be employed successfully to overcome problems of conventional aerosol systems have been introduced.

Keywords: Bioadhesive nanoparticles, Inhalation aerosols, Nanosuspension, Smart particle aerosols, Trojan particles

What exactly is a pharmaceutical aerosol? A pharmaceutical aerosol in a general way can be defined as an aerosol product containing therapeutically active ingredients dissolved, suspended or emulsified in a propellant or a mixture of solvent and propellant and intended for oral or topical administration or for administration into body orifices. The adjectives therapeutic and pharmaceutical convey the idea that an active component in the delivery system is present and that this substance is capable of bringing about either a prophylactic response or palliative treatment of disease[1]. Of all the pharmaceutical aerosols, Inhalation aerosols are used extensively in clinical practice, constituting a major therapeutic category. Moreover, the non-invasive nature of delivering systemic drug has increased the attraction for the inhalation aerosol in recent years[2].

Pharmaceutical Inhalation aerosols represent a complex dosage form which allows delivery of a therapeutically active medicament to the respiratory tract. Inhalation aerosols provide high drug concentration in brocho-alveolar fluids and other lung tissues when presented as oral inhalation products[3]. For this reason, pulmonary delivery has become the most useful drug presentation for ameliorating lung disease[4,5]. Oral inhalation aerosols often provide rapid absorption kinetics for poorly absorbed drugs[6,7]. It also provides means to prevent significant liver extraction for compounds with high first pass metabolism (e.g. Leuprolide acetate)[8,9]. Thus, owing to the discussed advantages, inhaled aerosols have become realistic alternative for administering drugs for asthma, respiratory distress syndrome and other lung diseases[10]. Inhaled aerosols are also rapidly changing the mode for treating several systemic conditions with peptides and proteins as these often are not orally active[11]. However, for both systemic and non-systemic aerosol products, there are significant advantages and disadvantages that a drug delivery scientist working in the field ought to be familiar with. (Table1) summarizes a few relevant development issues related to lung drug delivery compared with conventional routes of drug administration. Of the relevant pharmaceutical issues, reliability of the lung as a target for drug delivery, specificity, and control of the mechanism by which the drug is aerosolized to the airways, and biocompatibility of the dosage form with chronic dosing are by far the most significant to the development scientist[12]. Conventional aerosols have

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Table 1—Rationale for using inhalation aerosols

Critical drug delivery issues	Key benefits of lung drug delivery
Dosimetry and dose uniformity	Dose reduction potential compared with injection Often, lung delivery is quantitative based on fractional deposition in the lung.
Ruggedness	Noninvasive, flexible Dosimetry. Most inhalation technologies offer great flexibility and adaptability of dosage form to a wide range of clinical needs
Drug targeting	Site specificity and decreased systemic exposure. Most inhalation products can target only the lung and even when absorbed, systemic drug concentrations are too low to elicit significant risks.
Onset and extent of action	Fast onset of action. The lung has a large, highly permeable, and robust absorptive surface which enables absorption kinetics often comparable to injection.
Patient compliance	Painless, often nonirritating, and useful in ambulatory care.

Table 2—Limitations of conventional aerosols

- Hydrophobic drugs with poor water solubility are hard to deal with
- Micro particular nature of the particles results in limited diffusion and dissolution of the hydrophobic drug at the site of action resulting in low bioavailability.
- Low residence time of drug leading to absence of prolonged duration of action.
- Unwanted deposition of the drug particles in the upper airways (e.g. pharynx).
- Because of the devices inherent inefficiency, patients must inhale relatively large quantities of a drug to ensure that an adequate amount reaches the lungs.
- Not suitable for modulated drug release
- In conventional suspension aerosols many droplets are drug free and others are highly loaded with drug leading to uneven distribution of drug in the lung.

their own disadvantages (Table 2). Majority of these problems are dependant on inherent properties of drug molecules and thus formulation scientist are faced with an uphill task of overcoming these limitations.

Rapid advances in the filed of nanotechnology and nanoscience have lead to integration of nanoscience with various fields. Recent studies show that bringing nanotechnology to the pharmaceutical aerosol field can help overcome drawbacks associated with the conventional aerosol drug delivery and aid in obtaining more efficient and efficacious mode of drug presentation to the lung[13,14]. Here, we review various approaches dealing with the application of nanotechnology to the pulmonary drug delivery.

Applications of nanotechnology to aerosol science field

Nano suspension as drug concentrate

Majority of the drug used in clinical practice are known to be poor candidates for aerosol delivery due to their solubility limitations. Moreover, the advent of hydroflurocarbon (HFC) as propellant for pharmaceutical aerosols has aggravated the solvency related problems as HFC is known to have poor solvency as compared to its clorofluorocarbons (CFC) predecessors[15]. Owing to the lower solvency of pharmaceutical HFC fluids, recent attention has turned more and more to suspension inhalers. In suspension inhalers, the drug is relatively insoluble in the propellant and hence drug particles are maintained as slurry inside the can. While the drug substance itself is usually more chemically stable in the solid state than in the dissolved state, there are still stability related challenges in formulating a stable suspension inhalers[16]. Moreover, the micro particular nature of suspension particles further results in limited dissolution and diffusion at the site, resulting in low bioavailability. Using nanosuspension as a drug concentrate can be an efficient way of ruling out the above mentioned problems[17].

Nanosuspensions are different from coarse suspension with respect to the size of suspended particles. In simplest terms a suspension with the particle size of the dispersed phase below 1μm (1000nm) can be considered as nanosusupension[18]. Nanosuspension technology is applied to drugs that are insoluble in both water and oils. The drugs which have high crystal energy i.e. high melting point, reduce the solubility of drug substances; by this technology the drug is maintained in required crystalline state with reduced particle size and this cause increased dissolution rate and therefore improved bioavailability[19]. Nanosuspension technology helps in effective drug dispersion in the

propellant and provides chemically and physically stable product[20].

Nanosuspensions are formed by building particles as in precipitation or breaking as in milling. In both the cases, new surface area is formed which leads to increase in the free energy and the system tends to agglomerate; this agglomeration is prevented by addition of surfactants. Surfactants cause high energy barrier and prevent particles from coming together[21,22]. It is found that the concentration and type of surfactants used in preparation can play a major role in determining the size of final product[23].

Techniques used to formulate a nanosuspension include:

Homogenization: The suspension is forced under pressure through a valve that has nanoaperture. This causes bubbles of water to form which collapse as they come out of valves. This mechanism cracks the particles[24, 25].

Wet milling: Active drug in presence of surfactant is defragmented by milling[26]. The process is carried out with the use of sophisticated mills like High Pressure Media Mill (Fig. 1)[26].

Other technique involves the spraying of a drug solution in a volatile organic solvent into a heated aqueous solution[27]. Rapid solvent evaporation produces drug precipitation in the presence of surfactants[28, 29]. In our lab, we are working on double emulsion ultrasonication technique which involves use of ultrasonic vibration to achieve desired size range[30]. The technique to be used for nanosuspension preparation has to be selected depending upon the desired final product[31].

Conventional suspension aerosols may have smaller drug particles, but they show statistical inhomogeneity in partitioning of drug particles among carrier droplets, leading to uneven distribution of drug in the lung. Nanosuspension provides solution to this by increasing number of particles per droplets and as a result leads to increased onset of action and bioavailability[32].

Trojan particles: Large porous carriers of nanoparticles for drug delivery

Particles of 5 to 7 μm geometric diameter and unit density are considered to be most suitable for lung delivery. This size range minimizes losses from oropharyngeal impaction (large particles) and exhalation (small particles). These particles also show good flow and aerosolization potentials[33]. Unfortunately, particles of this size tend to aggregate and are prone to clearance by alveolar macrophages[34,35].

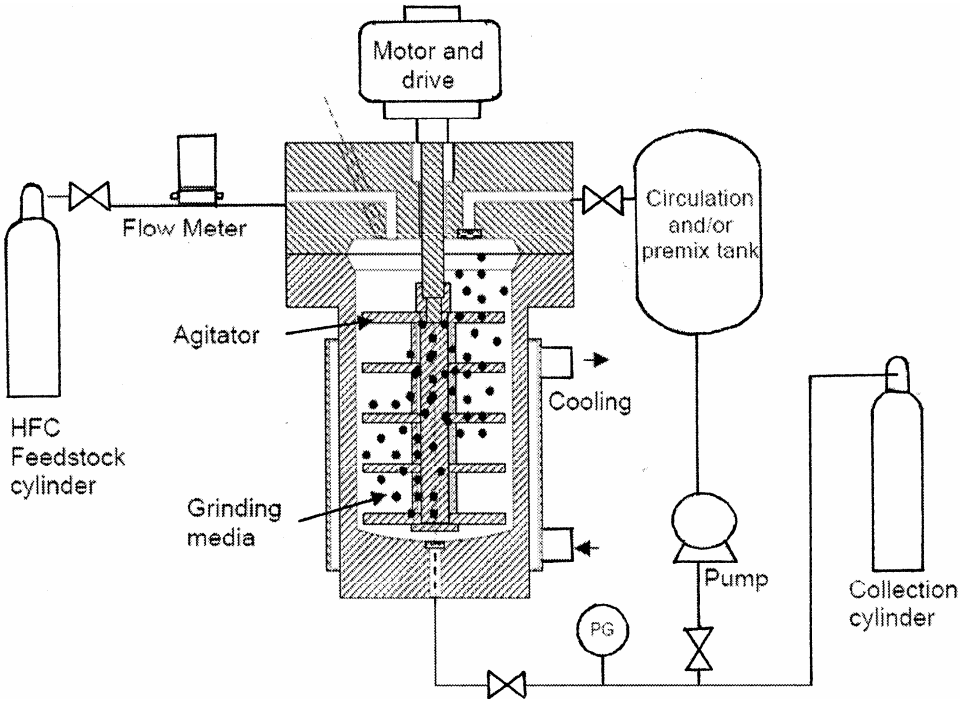

Fig 1—Schematic of the High Pressure Media Mill (HPMM)

On the other hand, particles with geometric diameters less than a few hundred nanometers[36] are found to be tenacious resident of the lungs. Once deposited, nanoparticles (NPs) or "ultrafine" particles often remain in the lung lining fluid until dissolution (assuming they are soluble), escaping both phagocytic and mucociliary clearance mechanisms[37-40]. Thus, deposition of drug-bearing NPs in the lungs may offer the potential for sustained drug action and release throughout the lumen of the lungs and not only in the deep lung or alveolar region, where macrophage clearance occurs[41]. However, the utility of nanoparticles for drug release is severely limited because of their low inertia, which causes them to be predominantly exhaled from the lungs after inspiration[42,43]. Moreover, their small size leads to particle–particle aggregation, making physical handling of nanoparticles difficult in liquid and dry powder forms[44, 45].

Large porous particles (LPPs), characterized by geometric sizes larger than 5 μm and mass densities around 0.1 g/cm^3 or less, have achieved recent popularity as carriers of drugs to the lungs for local and systemic applications[46,47]. LPP or Trojan particles as they are popularly known, combine the drug release and delivery potential of nanoparticle systems with the ease of flow, processing, and aerosolization potential of large porous particle (LPP) systems. Once aerosolized, large porous particles (LPPs) deposit homogeneously and reproducibly on the cell surface and appear relatively nontoxic to airway cells from microscopy studies performed in culture[48].

LPP are prepared by spray drying solutions of polymeric and nonpolymeric NPs into extremely thin-walled macroscale structures. These hybrid LPPs exhibit much better flow and aerosolization properties than the NPs; yet, unlike the LPPs, which dissolve in physiological conditions to produce molecular constituents, the hybrid LPPs dissolve to produce NPs (Figs. 2, 3)[49], with the drug release and delivery advantages associated with NP delivery systems[49]. Another principal advantage of LPPs relative to conventional inhaled therapeutic aerosol particles is their aerosolization efficiency[50,51]; in addition, LPPs

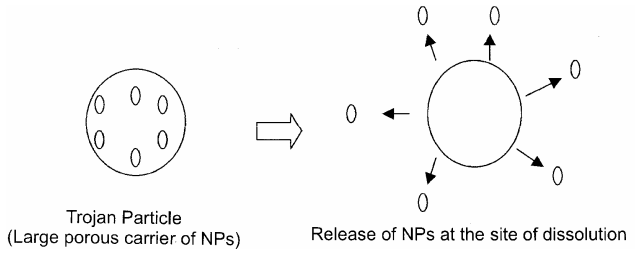

Fig. 2—Schematic presentation of large porous particles / Trojan particles

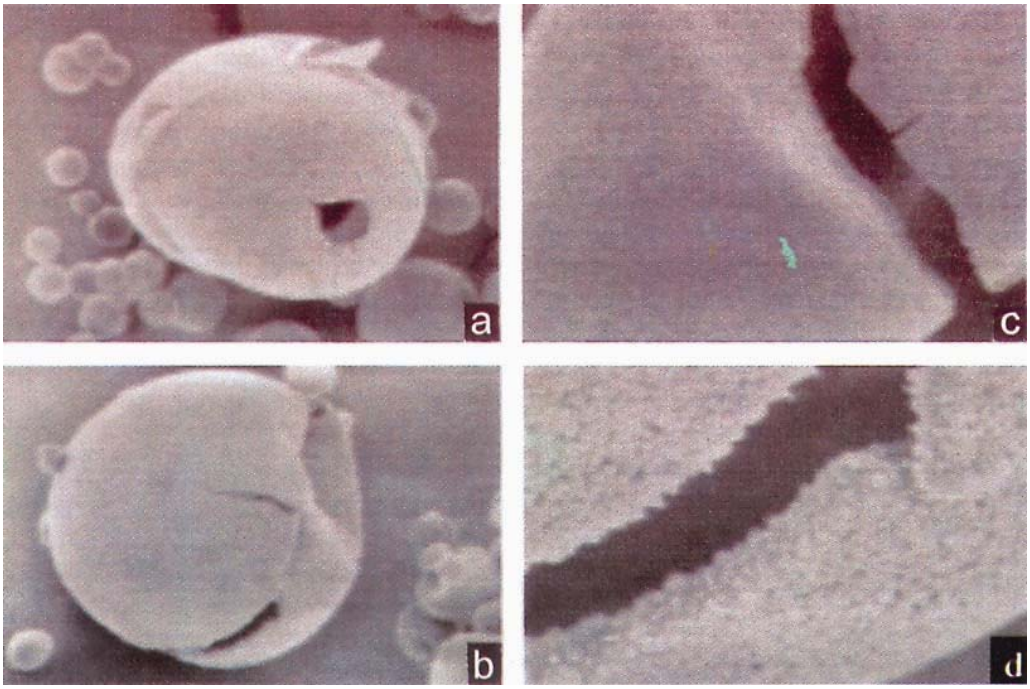

Fig. 3—Scanning electron microscopy surface images of spherical porous Trojan particle. [Scale bars: 10 μm a, b and 2 μm c,d]

possess the potential for avoidance of alveolar macrophage clearance enabling sustained drug release in the lungs .Thus, Trojan particles offer a method of producing a DPI with good flow and dispersibility properties, which, once delivered to the peripheral airways, will liberate nanoparticles that should avoid clearance mechanisms and provide sustained drug release[52-55].

Bioadhesive nanoparticles

One of the major disadvantages of conventional aerosol is the absence of prolonged duration of action which is due to the low residence time of drug in the respiratory tract. Nanoparticles prepared using bioadhesive agents (Table 3) show a unique property of adhering to the mucosal surface[56,57]. Drug incorporation in bioadhesive particles can help in prolonging the residence time of drug in the respiratory tract by increasing lung deposition and decreasing the nasal mucociliary clearance of the drug[58,59]. Bioadhesive particles also help in increasing the absorption of the drug through mucosal membranes by keeping the drug in close proximity of the absorption surface and increasing the local concentration gradient[60,61]. By prolonging the stay of the drug and increasing its absorption, bioadhesive nanoparticles result in enhancement of bioavailability of the drug[62,63]. Bioadhesive nanoparticles can also be prepared by coating preformed nanoparticles with agents like lectin /wheat germ agglutinin (WGA) or polyethylene glycol which tends to impart bioadhesive characteristics to the nanoparticles[64,65].

Smart particle aerosol

Today's progress in cell biology and biotechnology has enabled scientists to synthesize highly active molecules to target specific intra-cellular receptors. The clinical use of such molecules is often very limited because of their peptide or oligonucleotide nature. They are highly active *in vitro* in isolated cell systems, but a short half-life or limited cell uptake *in vivo* prevents their clinical use[66]. To overcome the limitations in cellular uptake of highly active molecules, the use of nano-sized carriers is the focus of modern drug delivery strategies. The utilization of such particles as drug targeting vectors is an emerging field of pharmaceutical sciences[67].

Smart particle aerosols represent a new field, where the goal is the development of fluid borne particles that exhibit "smart" capabilities in terms of targeting where they deposit, how they release their payload (e.g. drug), and how they interact with their environment[68]. Smart particle aerosol (Fig. 4)[69] makes use of active targeting strategies; the concept involves attachment of targeting moieties (Table 4) to the surface of carrier particles which leads to preferable deposition and release of the drug to the desired site[69,70].

Miscellaneous

Table 5 includes other approaches of application of nanotechnology to aerosol field or pulmonary drug delivery[71-78].

Conclusion

Pulmonary route has always been looked upon as a convenient and painless alternative to the invasive parenteral route. However, it is yet to hold a substantial ground in field of drug delivery, owing to the various drawbacks associated with conventional inhalation delivery.

Table 3—Bioadhesive agents

Polymers	*Gums*
Polyvinyl Pyrollidone (PVP)	Xanthan gum
Sodium alginate	Locust bean gum
Chitosan	Gellan gum
Polyvinyl Alcohol (PVA)	Tragacanth
Hydroxypropyl methylcellulose (HPMC)	

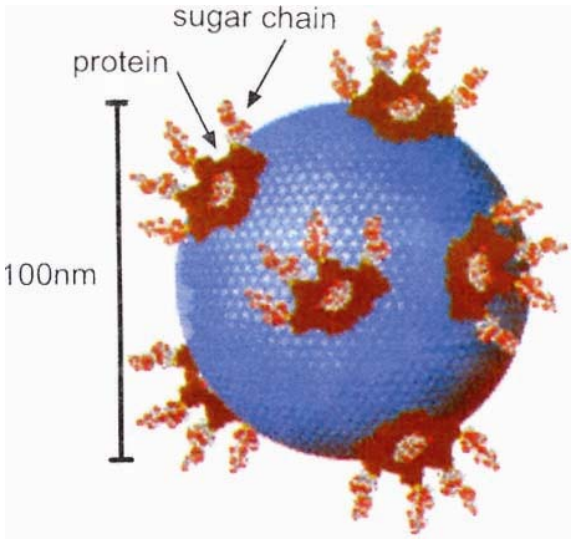

Fig 4—Schematic presentation of Smart Particle (nanoparticles with targeting moieties attached on the surface)

Table 5—List of other applications of nanotechnology to drug delivery by aerosols

Approaches	Examples
Nanospheres nanospheres	Pranlukast hydrate dry powder aerosols using
Liposomes	Nebulized interleukin 2 liposomes
Trigger release nanoparticles	Mechanochemically activated doxorubicin nanoparticles
Solid lipid nanoparticles	Radiolabelled cytotoxic drug incorporated Solid Lipid Nanoparticles
Dendrimers	Ibuprofen complexed and incorporated dendrimeric delivery
Agglomerated vesicle	Multimicron sized chemically linked agglomerates of core nanoparticles

Table 4—Targeting moieties

Antibodies and their fragments	Neo glyoconjugates
Glycoproteins	Carbohydrate primers
Lipoproteins and other proteins	Hormones
Low-molecular-weight ligands, such as folate	Charged molecules
Mono-, oligo- and polysaccharides	Lectins

The current nanotechnology boom has assured a future with application of nanotechnology in every field under the sun. Merging nanotechnology with aerosol science can lead to an emergence of a new and improved class of delivery system addressing many problems associated with conventional aerosol drug delivery.

The most promising application of nanoparticles to aerosols involves Trojan particles, which combines the drug release and delivery potential of nanoparticle systems with the ease of flow, processing, and aerosolization potential of large porous particle (LPP) systems. Another potential application includes smart particle aerosols (SPA), which includes particles with intelligent features, the concept of smart particles aerosol is still in the preliminary stages, but it definitely has a brighter potentials.

Current progress in biotechnology and advances in drug discovery process have set a challenging task for the drug delivery formulators to come up with newer delivery systems. Overcoming the obstacles faced by conventional delivery systems through advances in nanotechnology represents a tremendous advance toward development of better therapeutics.

Future vision: Indian scenario

During the past decade, India has really emerged as a quality player in pharmaceutical world, penetrating global market with basket of products. The capacity building exercise over the past 20 years has given India an excellent base of trained and trainable human resource. Additionally, the last decade has seen introduction of "smart drug concept" which includes application of new emerging technologies (e.g nanotechnology) to existing delivery system. In, India, researchers at the Indian institute of Technology (IIT), Mumbai, the Central Drug Research Institute (CDRI), Lucknow, and the National Chemical Laboratory (NCL), Pune, have long been on the path of smart drug delivery systems. Now, even the leading pharmaceutical companies are investing in this area encouraged by the fact that it's a low cost research area compared to developing new drugs and it pays off in a shorter time. Among the known firms, Ranbaxy, Wockhardt, Lupen, Valois India have commissioned research dealing with smart drug delivery systems. Additionally, Global players have also started investing on Indian expertise as a cheaper and efficient source, testified by number of CROs (Contract Research Organisation) mushrooming all over India[79].

With the availability of skilled human resources and investment by leading firms and government agencies the future of nanotechnology based drug delivery holds brighter prospects.

Guidance to readers

Authors wish to advice the readers to understand the know how of nanotechnology (precisely organic nanoparticular systems) before plunging into this area of work. Knowledge of basic aerosol delivery is also an essential pre-requisite. For basic knowledge about the manufacturing of nanoparticles readers are directed to read an excellent review by Dieter horn and Jen Reiger[80]. As nanotechnology based aerosol delivery is relatively a new field, not much has been explored about this field. Thus, there's an open opportunity for researchers involved in the field of aerosol drug delivery.

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