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Perspective

Ultrafine Particle Inhale Therapy: Is it Really a Game Changer in the Management of Obstructive Airway Diseases?

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Currently Global research fraternity exploring new horizons to develop novel drug delivery systems such as Nano/Micro particles, modified liposome's, micelles, polymer-drug conjugates, Muco-adhesive and mucus penetrating particles for better clinical control over airway diseases [1].

In the Era of Nano-medicine, delivery of therapeutic agent through inhalation route gain popularity as it provide large surface area in the alveoli with rapid absorption of the delivered drug to the blood. It also reduce first pass metabolism as well as enhance bioavailability in quite lower dose compare to oral administration [2,3]. Currently, several types of therapeutic aerosol delivery systems are in vogue, including pressurized metered-dose inhaler (pMDI), dry powder inhaler (DPI), medical nebulizer, solution mist inhaler and Nasal sprays [4]. Precisely aerodynamics of Inhale devices as well as particle size both play crucial role to achieve optimum clinical outcome by hitting the small airway, which is currently consider as significant site of pathogenesis in chronic airway diseases. However, pathology lying in small airways is not easily diagnosed because of its silent nature; It manifest only when more than 75% of fraction get affected by the diseases, hence impose great challenge for the clinician to clinch the diagnosis in early state [5].

Pulmonary Function Test (PFT), Whole body Plethysmography, Fraction of exhaled nitric oxide (FENO), Hyperpolarised magnetic resonance imaging, Gama Scintigraphy, Single photon emission computerized tomography (SPECT), Positron emission tomography (PET), Inert gas washout, High resolution Computerized tomography (HRCT), and Impulse oscillometry (IOS) are currently used diagnostic modalities for small airway diseases though definitive diagnosis of it is still vacillating due to complex Pathophysiology [6].

William Gairdner first discussed the relationship between Small airway and emphysema in 1850, later Hogg, Macklem and Thurlbeck in 1968 postulate in his research that the small airways (< 2 mm diameter) impose approximately 25% of the total airway resistance in healthy controls, however it increased exponentially; up to 40 fold in emphysema [7] besides this histo-pathological evidence had clearly shown that small airways played crucial role in difficult to treat asthma due to unopposed inflammation hence inhalation strategy need some refinement at molecular level in the form of particle size to enhance benefit by hitting the target site of affected precinct [8].

The therapeutic impact of any inhaled molecule is multi factorial though particle size has their own significance due to its capability to enter in deeper section of tracheobronchial tree. Particle size can be define in various categories in terms of; fine (> 2 µm), ultrafine (< 2 µm - 0.5 µm), sub micron (< 1 µm); or Nano particle (< 0.1 µm), according to their Mass median aerodynamic Diameter (MMAD). *In vitro* study conducted in UK highlighted that Routinely used inhaled particle MMAD > 2 or < 0.5 µm may not effectively deposited in small airway; either exhaled out during expiration or stuck in larger airway during inspiration; In an aerodynamic study of inhaled molecule, it was also revealed that large particle size > 5µm unable to reach in air way and major fraction impacted in upper airway hence not much utilized for therapeutic purpose rather responsible for local complications like irritation of mucosa and oral candidiasis [9].

Therefore, bio scientists are considerably working to explore the magical size of particle with the modification in MMAD of inhaled molecules or using force control carrier agent (Magnesium Stearate) as well as changing in device aerodynamics to optimize flow of inhalation (30 - 60 L/Min) for better deposition in smaller airways by controlling its terminal settling velocity. Recently researchers are exploring the possible beneficial effect of ultrafine particle in obstructive airway diseases by targeting small airway segment of tracheobronchial tree; which may be consider as major site of airflow limitation in diseased lung; though relatively deprived from inhaled medication if notable fraction of particle size is more than 2 µm. *In vitro* study Conducted by Boer., *et al*. affirm that submicron particle MMAD < 1 µm are not suitable for inhalation and largely exhaled again due to poor deposition rate. In an extensive database cohort Study conducted in Netherland by Molen., *et al*. from 1998 to 2012 by including 1339 patients promulgate that extra fine particle inhale therapy improve the outcome in asthma control compare to fine particle therapy [10]. Similarly, Postma and Papi., *et al*. in separate study, illustrated that ultrafine particle (MMAD ≤ 1µm) Ciclesonide HFA (Hydrofloroalkane) inhalers are far better that routine ICS/LABA CFC (Chlorofluorocarbon) (MMAD 2.4 - 3 µm) inhaler in terms of controlling asthma or reduction of air trapping due to small air way obstruction [5]. Contrary to this in a recent Meta analysis lead by Baou., *et al*. by including 23 independent clinical trials divulge the insignificant differences in efficacy or safety of small and standard particle size ICS medications over ultrafine particle used for the treatment of asthma [11].

Perhaps more *in vivo* clinical trials are needed to retrieve decisive inference in favour of ultrafine particle inhale therapy, as impaction of it in small airway or translation of it in positive clinical outcome is versatile; which majorly hinge on particle terminal settling velocity, optimum inspiratory flow as well as holding time of breath after deep inhalation. Therefore, evaluation of the 'Therapeutic index' of different drug delivery devices will be more appropriate and propitious in future research rather overemphasizing on inhaled particle size.

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