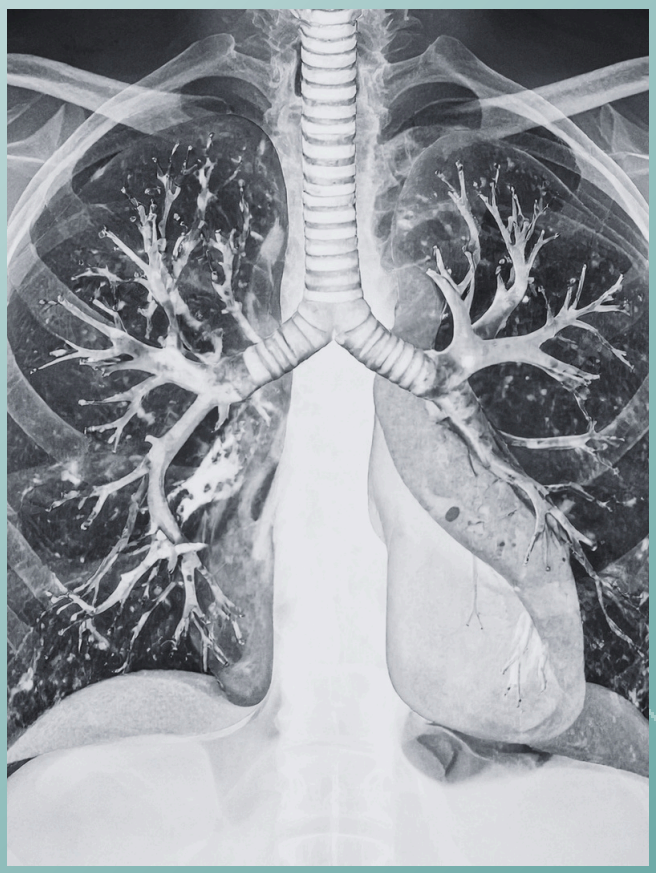
PULMONARY DRUG DELIVERY CHALLENGES FOR ASTHMA/CHRONIC OBSTRUCTIVE PULMONARY DISORDER TREATMENT



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Interest in pulmonary drug delivery has increased over the last decade, prompting the translation of various medications that were traditionally administered only via the oral or parenteral route. The inhaled delivery approach allows precise delivery of drugs to various regions of the respiratory system, making it suitable for both local and systemic treatments. Its enhanced targeting capability, large lung surface area (~70-140 m^2), lower drug dosages required to achieve a rapid pharmacological effect, and minimal systemic side effects make pulmonary delivery an ideal route for asthma and chronic obstructive pulmonary disorder treatment. Despite these merits, pulmonary delivery also presents limitations, such as achieving a pharmacological effect requires overcoming anatomical barriers during inhalation.

Inhaled particles should ideally have an aerodynamic size (D_{ae}) between 1 and 5 µm for deposition in the lower lung. Particles with D_{ae} >10 µm are trapped and removed by mucociliary clearance. Particles with D_{ae} between 5 and 10 µm tend to lodge in multidimensional, narrow-angled passages of the upper airways, including trachea and primary bronchi subdivisions. Particles characterized by D_{ae} between 5 and 1 µm tend to deposit in the middle lung (large non-respiratory bronchioles) to smaller airways (smaller non-respiratory bronchioles), while particles with D_{ae} < 1 µm can efficiently reach the respiratory bronchioles and alveolar region. Particles with D_{ae} ~ 0.5 µm are prone to be directly exhaled after administration, whereas particles < 0.5 µm are deposited in the peripheral lung.

Current strategies for producing inhalable powder face several limitations, including complex formulation designs that are often specific to particular particulate types, thereby reducing versatility.

In addition, drug particles (submicron or nano) exhibit poor flowability and dispersibility due to their cohesive nature. To address these issues, coarse carriers are commonly employed (Fig. 1); however, the strong adhesive forces between drug particles and carrier particles, together with the overall large particulate structure, hinder efficient drug deposition in the deeper regions of the lungs. Most inhalable particulate systems are developed as nano-in-microparticles, agglomerates, or composites of nano/submicron drug particles (Fig. 1), with their evaluation largely confined to *in vitro* cascade impactor studies. These microscale particles, however, are associated with poor particle/drug re-dispersibility, inadequate particle/drug-target interaction, and altered particle nanoscale essential for endocytic and biological actions.

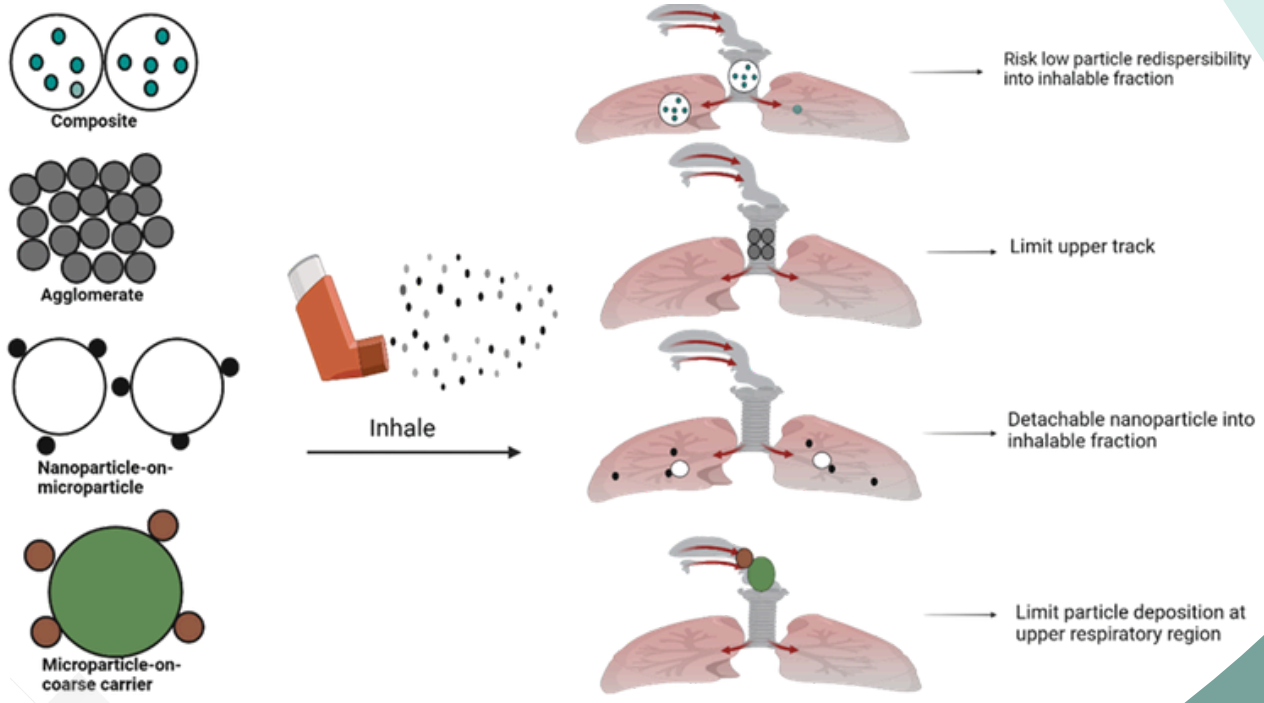

Fig. 1. Different variants of inhalable nano-microparticles for asthma treatment.

In an attempt to achieve efficient pulmonary drug deposition in the lower lung, small lactose microparticles (~ 5 µm) have been developed as the drug carriers. The dry powder formulation is produced via simple physical blending of small lactose microparticles with near-submicron drug particles to generate a free-flowing and inhalable powder mass. The cohesive drug particles, when deposited onto the lactose carrier, become less sticky. The surface-deposited drug particles can act as a glidant, reducing the aggregative behaviour of small lactose microparticles. The overall outcome is reduced powder agglomeration and clump formation. Dispersible solid particles are thus produced, with improved ease of inhalation and enhanced drug delivery to the lower lung regions due to the overall small carrier-drug particulate structure.

REFERENCES :

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