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Bio Aerogels as Carriers for Pulmonary Drug Delivery - A Review

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ABSTRACT

Pulmonary drug delivery offers unique advantages due to the large alveolar surface area, thin epithelial barrier, and rich vascularization, enabling both local and systemic therapies. Aerogels have ultralight, highly porous materials with low density and large surface area are emerging as promising carriers for inhaled medications. Their physicochemical properties allow the formation of microparticles with optimal aerodynamic diameters for deep lung deposition. Particle deposition in the respiratory tract occurs via inertial impaction, sedimentation, and diffusion, all strongly influenced by aerodynamic diameter rather than geometric size. Bio aerogels derived from polysaccharides such as chitosan and alginate demonstrate biocompatibility, biodegradability, and tunable drug release profiles. Supercritical fluid drying preserves pore structures more effectively than freeze-drying, producing particles with lower tapped density and improved aerosolization. Current studies highlight bio aerogel microparticles with ultralow density, high porosity, and controlled release capacity, suitable for delivering both hydrophilic and hydrophobic drugs. Future trends emphasize the integration of aerogels with supercritical fluid technology to develop dry powder inhalers with enhanced efficacy, reduced systemic exposure, and controlled release. Bio aerogels thus represent a next-generation platform for respiratory drug delivery, with potential applications in treating local diseases such as asthma, COPD, and lung cancer, as well as systemic conditions like diabetes and migraine.

Keywords: Supercritical fluid drying (SCF), Particle deposition, Aerodynamic diameter (dae), Aerosolization performance, Polysaccharide-based carriers.

1. INTRODUCTION

The pulmonary route is being investigated for both the treatment of respiratory conditions and the systemic distribution of medications. Because of the unique characteristics of the alveolar region, such as its vast surface area (about 100 m^2), thin epithelial layer, and strong vascularization, this administration route can improve the absorption of medications for systemic therapy. By directly targeting the intended area and raising the medication concentration in the lungs, inhalation therapy can also deliver local therapies with greater efficacy and fewer adverse effects than systemic administration (1). However, lung deposition is a crucial component of pulmonary administration that determines medication effectiveness because to the intricacy of the lungs, and it is typically linked to with lung capacity, patient clinical state and breathing patterns, inhaled particle physicochemical characteristics, and inhalation device design (1). The primary issue with pulmonary medication delivery is the extremely low required particle size (1–3 μm) combined with the high tapped density (about 1 g/mL) (7). Aerogels are gaining interest in pulmonary drug delivery system due to their ultra-low density which allows producing large porous microparticles with excellent aerodynamic diameters (8). Aerogels are open-cell, extremely porous materials having a very large surface area and a very low tapped density.

They are typically made with sol-gel technique and are mostly amorphous (7). The goal of freeze-drying is to maintain the initial swelling that the hydrogel produced in a suitable aqueous media by quickly freezing the water inside the pores and then sublimating it under low pressure. However, the liquid-solid adhesive forces and liquid-gas surface tension might cause the pores to contract and encourage more solid-solid interactions. The structure may potentially sustain damage from the expansion of water during freezing (9).

A unique drying method, such as supercritical fluid (SCF) technology, removes the solvent to preserve the gel's structure and stop the pore collapse phenomena by shielding the dried product from shrinking and breaking (8). By avoiding the liquid-solid adhesion forces and liquid-gas surface tension, this procedure stops the initial pores from collapsing (9).A wide range of solvents may be used using supercritical drying technology, and it even makes it possible to employ compounds that are not suited as hydrogel components

because they are poorly soluble in water(5). Adsorption of the drug on the surface and drug precipitation following solvent evaporation occur during drug confinement regardless of the solvent utilized.

One or the other mechanism may predominate, depending on the drug-surface interactions and the total concentration of the solution. Because it emphasizes the significance of both components, we encourage the community to adopt the word "adsorptive precipitation." This phrase can be further defined as "adsorptive crystallization" or "adsorptive amorphization" depending on the result (19)(20)(21).

Aerogels may be effectively loaded with amorphous medications using solvent exchange, the sol–gel method, or diffusion following drying employing SCF technology. An aerogel is generated by the replacement of the liquid inside a gel with a gas (7). Aerogels are created by 3D networks of organic polymers, inorganic materials, or composites constructed colloidal materials, much like the hydrogels commonly utilized in biomedicine (9).

Liposomes, micelles, and polymeric drug particles are examples of pulmonary drug particles. Because of their unique chemical and structural properties, biocompatibility, and biodegradability, polysaccharides and other natural polymers, such as gelatin, chitosan, and alginate, have drawn interest from researchers for their use in the biomedical area (6). In biomedical and pharmaceutical applications, polysaccharide-based aerogels made from natural resources such as cellulose, chitosan, chitin, alginate, starch, pectin, and agar are sustainable materials that effectively replace silica aerogels (10). Lung deposition, which is typically related to the volume of lungs, clinical status and breath patterns of patients, physicochemical properties of inhaled particles, and design of inhalation devices, is a crucial factor in pulmonary administration that determines the drug efficiency due to the complexity of the lungs. Specifically, poor patient handling practices are linked to greater exacerbations, a detrimental effect on everyday activities, and worse lung function (1). Lung deposition is a crucial factor to produce the desired therapeutic outcomes in pulmonary drug delivery system (1).

2. Mechanism of particle deposition

In the respiratory system, particle deposition occurs primarily through three mechanisms inertial impaction, sedimentation, diffusion, interception and electrostatic precipitation. The aerodynamic diameter of the inhaled particles primarily controls these mechanisms. The methods of deposition that are either directly or indirectly correlated with particle size(11)(12)(13).

2.1 Inertial impaction:

When airborne particles have sufficient momentum to maintain their trajectory in the face of changes in the air stream's indirection, they collide with the respiratory tract's walls, a phenomenon known as inertial impaction. Depending on the particle mobility (velocity per unit force) B, mass, m, and velocity, v, the likelihood of deposition by impact increases as the particles are more likely to go farther, S.

$$S = B.m.v$$

Particles will be deposited by inertial impaction more readily the higher the Stokes number.

$$Stk = \rho_{p} . d^{2}. V /18.\mu.R$$

Where,

ρ_p is the particle density, d is the particle diameter, V is the air velocity, μ is the air viscosity, R is the airway Radius. Large particles moving through the airways at high airflow velocity are therefore more likely to affect the proximal segment of the respiratory tract due to bifurcated architecture of the lungs (11).

2.2 Sedimentation

Particles settle as a result of gravity's impact during the time dependent process of sedimentation. Therefore, breathing techniques that give the particles more time to settle (such as breath-holding) may result in increased lung deposition. According to Stoke's Law, there is no relative velocity between the particle's surface and the airstream. The terminal settling velocity, V_{ts} can be predicting using Stoke's law when unit density spheres of 1-40 m are taken into consideration (11).

$$V_{ts} = d^{2}_{p} (\rho_{p} - \rho_{f}). g / 18\mu$$

Vts is the settling velocity, d_p is particle diameter, ρ_p is particle density, ρ_f air density, g is acceleration due to gravity , μ is viscosity of air.

2.3 Diffusion

Diffusion happens when particles are tiny enough to move randomly as a result of molecular bombardment. Brownian motion, another name for this mechanism, is connected with particle size. According to Stokes–Einstein equation,(11)

$$Dif = k \cdot T / 3\pi.\mu.d$$

where Dif is the diffusion coefficient, k is the Boltzmann's constant and T is the absolute temperature. Diffusional deposition, in contrast to impaction and sedimentation processes, is thus inversely proportional to particle size(11).

3. Particle aerodynamic diameter

In addition to geometric particle size and size distribution, inhalation aerosols differ in a variety of other aspects that affect particle deposition, such as physical condition (solid or liquid), density, shape, and velocity. A dynamic system of forces, including gravity, the inspiratory air's resistance force, and inertial force, is also interacting with the airborne particles throughout the airways. What ultimately defines the process of particle deposition in the lungs is the balance between these forces and the aerosol characteristics. (11)(14).

The diameter of a sphere with unit density ($\rho=1$) that has the same terminal settling velocity in still air as the particle under discussion is known as the aerodynamic diameter($dae_)$ (14). This independent variable can thus correlate the influence of geometric diameter and particle density while taking into account the particle properties.(11)

$$dae = d.\sqrt{(\rho/\rho 0)}$$

Where d is the particle diameter, ρ is the spherical particle density, ρ_0 is unit density. A study of large porous particles for pulmonary delivery demonstrates the link between the geometric diameter and the particle density for aerodynamic diameter. Edwards et al. successfully delivered very lightweight big particles ($\rho=0.1 g/cm_3$; d=8.5 m) to the deep lung in this study. Therefore, in order to relate to particle deposition that is predominantly controlled by inertial impaction, aerodynamic diameter rather than geometric diameter must be used as an independent variable. Cascade impactors, such as Andersen Cascade Impactors, Multi-Stage Liquid Impinger, and Next Generation Cascade Impactors, can be used to determine the aerodynamic size of inhalation products in vitro. To assess the particle accumulation in the lungs, this characterisation is crucial. Geometric standard deviation (GSD) and mass median aerodynamic diameter (MMAD) are typically provided. The cutoff particle size known as MMAD occurs when 50% of the aerosol's mass is less than the specified parameter and the other 50% is greater (11).

Pharmaceutical particles are aerosolized when a particular gadget is placed in the patient's mouth during the inhalation process. These particles move through the airways, and their deposition in the respiratory tract—which can be anywhere from the oral cavity to the alveoli—depends on several factors. The literature contains a variety of computational techniques and mathematical models that help forecast the patterns of particle deposition in the lung as a whole and in its individual areas, even taking into account various disease states(11)(15)(16)(17).

4. Particle deposition in the lungs

The oropharyngeal (mouth and throat) deposition for particles larger than 10 m was more than 90% and 50% at 60 and 18 L/min, respectively, when a tube was placed into the mouth. Using scintigraphy techniques, the bigger airways in their study were distinguished from the smaller airways based on the duration of particle removal from the lungs. Because mucociliary clearance in the tracheobronchial region (or bigger airways) is known to occur there, a "fast-cleared" proportion was linked to lung deposition there. On the other hand, a "slow-cleared" fraction was associated with the lack of cilia in the airway's terminal section, suggesting deposition in the lower airways and an anticipated particle removal of around a day. The initial total lung dosage is subtracted from the slow-cleared fraction seen after around 24 hours to determine the regional particle deposition.

Stahlhofen et al. discovered that particles of roughly 6 and 3 m are deposited mostly in the bigger and smaller airways, respectively, based on this experimental design and particle aerodynamic diameter determined at an airflow rate of 30L/min. The specific mechanisms of deposition—sedimentation and inertial impaction—are consistent with these findings. This investigation also revealed an interesting finding: total lung deposition decreased when particle sizes shrank to submicron dimensions. The overall amount of lung deposition returned to levels equal to or higher than micronized particles when the particle size continued to fall

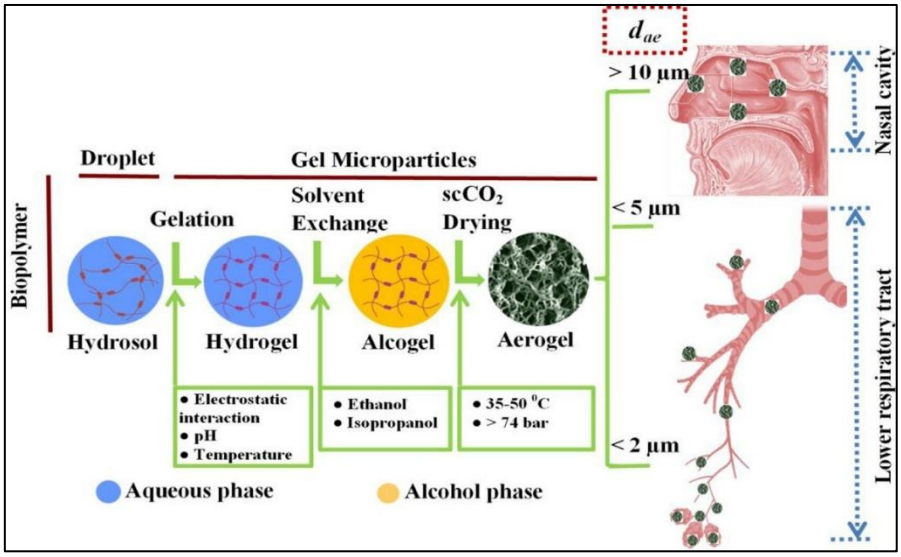
into the nanometric region. Early on, the associated therapeutic response also provided information regarding the accumulation of tiny particles in the smaller airways. The pathophysiology of asthma states that inflammation can happen anywhere in the airway. Early research on this chronic inflammation had focused on the proximal core region, ignoring the prevalence in the distal airways, due to the large airways' easy accessibility.

5. Aerogel in drug delivery system

Aerogels are extremely light porous materials that have not yet been fully investigated for use in biomedicine. Aerogel-based materials may be used in drug delivery system carriers, wound healing, bone tissue engineering, and bioimaging (1)(2)(21). Particularly for therapeutic proteins, cytotoxic pharmaceuticals, or poorly bioavailable medications, the large surface area, accessible pores, good aerodynamic qualities, and physicochemical stability of the aerogels hold promise for achieving adequate drug loadings in a variety of administration routes (1)(2). Both organic and inorganic aerogels can be used to design drug carriers that are insoluble in water. Drug loading efficiency is improved by inorganic aerogels, including silica aerogels, which typically have larger surface areas than organic aerogels (1)(2)(3). Nonetheless, biopolymer or polysaccharide aerogels (gelatine, agar, cellulose, alginate, chitin, and pectin) are favoured in biomedical applications because of their biodegradability and biocompatibility. Aerogels can be produced in a variety of forms, including films, cylinders, microspheres, and three-dimensional scaffolds (1).

There are four primary methods for loading drugs into aerogels that can determine the processes of drug release. Drugs may be added (i) before to gelling, (ii) during solvent exchange, (iii) during drying, or (iv) utilizing supercritical fluid impregnation with aerogels that have already been created. In Generally, the physicochemical characteristics of the drugs specifically, their solubility in organic solvents and supercritical fluid, their hydrophilic and lipophilic qualities, and their stability in the chosen solvent determine the loading method. For instance, drugs that are soluble in organic solvents but weakly soluble in supercritical fluids may be included through solvent exchange. On the other hand, if drugs are soluble in supercritical fluids but not in organic solvents, supercritical fluid impregnation is becoming the best option (1).

The hydration characteristics of both pharmaceuticals and carriers (erosion and swelling), the intermolecular forces between drugs and carriers (hydrogen bond, ionic bonding), and the mass transfer all play a major role in the drug release from the aerogel carriers. For example, hydrophilic medications often dissolve quickly in the hydrophilic aerogel matrix. The release profile of bioactive chemicals in this situation is significantly influenced by the drug's mass transfer to body fluids. In contrast, hydrophobic chemicals often have delayed release characteristics in the aerogel matrix. The hydrophilic or hydrophobic nature of the aerogels has a significant impact on the hydration characteristics of aerogel carriers. The rate of drug release, erosion, and/or swelling of the aerogel structure can all be influenced by the hydration in respiratory fluid in the particular context of pulmonary inhalation (1).



The technical process to prepare drug-loaded Bio aerogel microparticles for respiratory drug delivery (18).

6. Aerogel Production

The "sol-gel reaction" is a wet chemical synthesis technique that is often used to generate nearly all types of aerogels, including organic, inorganic, and hybrid ones. The process typically consists of the following steps: mixing precursors, hydrolysis,

polycondensation, gelation, aging, and drying. Each step is carried out by relevant parameters, such as the concentration of precursors, pH, temperature, type of solvent, time, etc., to adjust the properties of the prepared aerogel structure (10). The most important process among the ones listed that affects many of the aerogels' characteristics is drying the gels. The 3D network is anticipated to remain intact while the solvent, residues, byproducts, and unreacted compounds are eliminated. The required end-product characterisation determines which drying process is best. The most popular techniques for drying wet gels are freeze-drying, ambient-conditioned evaporation, and supercritical drying (high and low temperatures) (10).

The procedures involved in making polysaccharide-based aerogels are: 1) An aqueous sol is created from a hydrogel by a chemical or physical cross-linker promoter; 2) alcohol replaces the water in the gel's structure to create an alcogel (note: this step can be skipped if the alcohol is used as the solvent to prepare the prime gel); and 3) drying the wet gel using the right techniques is the last step. It should be mentioned that while utilizing the SC drying process, the limited solubility of water in supercritical CO2 is the primary reason for substituting another solvent, such as alcohol or acetone (10).

(i) Polysaccharides gelation:

The dripping method (external gelation) and the emulsification method (internal gelation) are the two major methods used to create biopolymer-based aerogel particles (4)(5). The traditional dripping techniques employ dripping tools that are accessible on a laboratory scale, including pipettes, syringes, vibrating nozzles, and electro valves. Aerogel beads with enormous droplet sizes of a few millimetres that do not satisfy the criteria in inhaled formulations are produced when a droplet of polymer solution falls into the gelation bath due to gravity (1)(4). Recently, a modified dripping technique utilizing thermal inkjet printing has been suggested to produce 10–20 µm aerogel microspheres for DPI formulations (1)(4). To create gel microparticles, the solvent-emulsification method employs internal gelation. The polymer solution (aqueous phase) is distributed throughout the oil phase under continuous stirring, creating an emulsion. To stabilize the two immiscible liquids, an emulsifier with a hydrophilic-lipophilic balance (HLB) in the range of 3–6 is often used. On a small scale, the water-to-oil ratio is often used between 1:2 and 1:10, however in order to form an emulsion, the water-to-oil phase viscosity ratio must be smaller than 1(1).

Using varying sodium tripolyphosphate (TPP) concentrations, which served as a crosslinker. Following an ethanol soak, the chitosan gel was loaded with salbutamol sulphate in an ethanolic solution and either supercritical fluid drying or freeze drying. The drying process was thought to be essential for producing inhaled particles with the right properties.

In comparison to freeze drying (60–68 µm and 0.22–0.25 g/mL, respectively), salbutamol-loaded chitosan aerogel particles generated by supercritical drying exhibited smaller particle sizes (7–12 µm) and lower tapped densities (0.10–0.14 g/mL) and better conserved the shape of the wet gel. Furthermore, freeze drying took 48 hours to process, whereas supercritical drying took only two hours. The molecular weight of chitosan and the TPP concentration influenced the salbutamol release profile. The TPP concentration has the ability to alter the drug release patterns by modifying the aerogels' swelling behaviour (1) Hybrid aerogel-based carriers for pulmonary drug administration were created by taking advantage of the ionic interactions between chitosan, a cationic polysaccharide, and alginate, an anionic polymer. The emulsion-gelation process was used to create these aerogels. The final aerogel characteristics were affected by the sequence in which the two polymers were added. Particles made with Span 80 or a combination of the two surfactants had low zeta potential values and a greater propensity for particle agglomeration, whereas aerogels made with Span 85 had higher zeta potential values, aerodynamic sizes, and improved performances. The ideal working conditions were 4% surfactant concentration, 4,000 rpm mixing rate for the emulsification stage, and 2 hours extraction time in addition to the previously indicated parameters. The final gel particle sizes were not significantly impacted by the emulsion preparation temperature. Subsequent process optimization produced fine particles with 500 ±45m_2/g specific surface areas (1).

(ii) Solvent exchange:

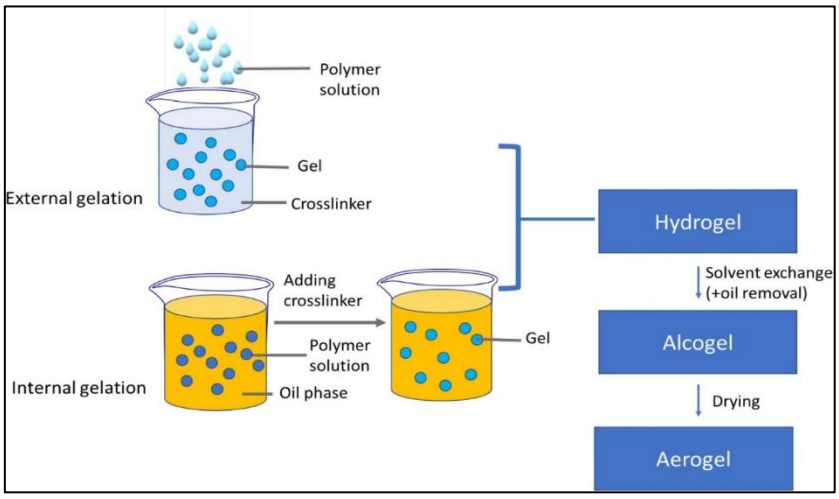
Solvent exchange is the process of completely replacing the water phase in the biopolymer hydrogel with an organic solvent that can be miscible with both the upstream water and downstream scCO2. 10:90, 30:70, 50:50, 70:30, 90:10, and 100:0 v/v are common alcohol/water ratios. The biopolymer hydrogel microparticles are soaked in these co-solvents one after the other for a long enough period of time to completely eliminate water residues, completing the transition from hydrogel to alcogel (18).

(iii) Supercritical fluid drying:

Out of all the supercritical fluids, scCO2 is the best choice because of its low Tc (31.1 ◦C) and Pc (73.8 bar), which indicate that it has a lot of potential for treating thermally sensitive materials and the advantage of being a gas at room temperature that can remove solvent traces with little energy. There are two methods for using scCO2 for desiccation (scCO2-D) when drying alcogels to create aerogels. In order to create completely CO2-filled gels (also known as "carbogels"), the first method (scCO2-D1) is more akin to another form of solvent exchange, in which the alcogel is soaked in liquid CO2 at a low temperature (i.e., 18 °C) over time. This

process is repeated as needed. After that, CO2 is converted into a supercritical fluid by raising the temperature and pressure over the critical point, which is then released from carbogels to create aerogels.

By applying a condition above the binary critical curve of CO2 and alcohol, the second technique (scCO2-D2) will put CO2-alcohol in a supercritical state where they are completely miscible. Aerogels are created when all traces of alcohol are eliminated from alcogels by regulated outflow and inflow of scCO2 fluid. Generally, the CO2 liquid from the buffer tank (5 ◦C, 50 bar) is first pressured to 85 bar (>Pc, CO2) and then heated to 35 ◦C (>Tc, CO2) in order to dry ethyl alcohol alcogels. After that, the scCO2 fluid is sent from the bottom into an extractor to mix with ethyl alcohol inside alcogels. The continuous CO2 supply into the extractor raises the temperature and pressure, converting the CO2-ETHYL ALCOHOL binary into a supercritical fluid and fully miscible. The recovered EA from alcogel is then expelled by releasing the supercritical binary fluid. All ethyl alcohol traces will be eliminated by continuously supplying scCO2 fluid into and discharging binary supercritical fluid from the extractor, which will ultimately produce dry aerogel (18).



Aerogel particle production for pulmonary delivery by external and internal gelation method (1).

7. Loading of drugs

The pre-dried aerogels are hung in the vessel after being covered with filter paper to prevent direct contact with BA. A little container at the bottom of the tank is filled with a predetermined amount of BA. In order to accomplish loading by adsorption, the vessel's temperature and pressure are kept constant for the required amount of time during which BA dissolves in scCO2, the mixture diffuses into the aerogel's pores, and BA adsorbs on the aerogel's surface. Then, using a gas flow meter with a capacity of three Liters per revolution, the vessel is flushed with three times the volume of scCO2 at the same pressure and temperature (200 bar and 328 K) at a steady flow rate of five to ten standard Liters per minute. This flushing guarantees that there is no chance of BA precipitation during pressure release and eliminates up to 99% of the BA found in the bulk scCO2 phase. The vessel is depressurized from 200 to 1 bar in about 600 seconds after flushing. To eliminate any remaining adsorbed moisture and CO2, the aerogel is taken out of the vessel and baked at 323 K for 24 hours (22)(23).

8. Current state of respiratory medication delivery using bio aerogels

In 2019, the use of Inject Printing technology to create alginate Bio Aerogel Microparticles for pulmonary drug administration was investigated. These microparticles showed open pores throughout the body, with pore sizes ranging from 9.0 to 17.8 nm, pore volumes ranging from 0.65 to 1.48 cm_3/g, and specific surface area ranging from 180 to 430 m_2/g. These ultralight microparticles can be efficiently absorbed into the lower respiratory tract while having a high dv of 24 µm. They demonstrated a significantly reduced dae of 4.0 µm. In addition, alginate-HA Bio aerogel microparticles were made using external gelation technology, which showed porosity of >97% v/v, ultralow density of ~0.03–0.06 g/cm_3, dv of 22.5–51.4 µm, and d_{ae} of 3 µm , indicating the ability to deliver medications to central pulmonary areas. Alginate-chitosan Bio Aerogel Microparticles with pore size of ~13 nm, pore volume of 0.09–0.29 cm3/g, SSA of 29.36–86.2 m2/g, ρb of 0.048–0.19 g/cm3, ρt of 0.08–1.2 g/cm3, dv of <4.17 µm, and dae of <2.29 µm. These BAMs had adjustable ZP (from 5.98 to +45.3 mV) and may have additional uses in drug delivery (18).

9. Future Trends of bio aerogel carriers for pulmonary drug delivery:

Aerogels are cutting-edge materials with great promise for innovative inhalation compositions. A novel class of biocarriers for pulmonary medication administration may result from the combination of aerogels with SCF technology .The distinctive qualities of bio aerogels produced by supercritical drying pave the door for new DPIs with improved efficacy, cost, and environmental friendliness(1). From the standpoint of therapeutic impact, the main objective of novel inhaled drugs that use aerogel carriers is to address the present demands in the local treatment of respiratory disorders. Aerogels' huge surface area makes it possible to increase the pace at which poorly water-soluble medications dissolve, which is particularly useful for innovative inhalation chemotherapy. Aerogels are also excellent options for inhaled systemic distribution because to their large surface area and high porosity. (1).

In addition to the potential to lower the overall drug dose with less frequent inhaled delivery in a controlled-release system, bio aerogels have high porosity and can transport medications to the bronchi decreasing systemic exposure (1).

Aerogel-based novel inhaled formulations can perform better because they rely less on the respiratory flow rate of patients, which is advantageous because patients with respiratory diseases typically struggle to supply a sufficient flowrate when using DPIs (1). It may be beneficial for the aerogel design to validate existing mathematical models or create new ones that forecast the deposition of aerogel particles in the lungs. Furthermore, the prediction of drug loading capacities and drug release behaviour in respiratory fluid medium would benefit from a deeper understanding of the drug-aerogel interaction at the molecular level. Drugs can also be loaded onto the aerogels' surface or impregnated into their accessible pores because to their porous nature. Another element that significantly affects the pace of drug breakdown in pulmonary administration is the solid state of the medication. Because it has a larger free energy than other forms, the amorphous form is frequently better for solubility and dissolution rate than the crystalline state. Bio aerogel microparticles have special physiochemical characteristics, such as extreme porosity, ultralow density, and therefore much lower dae. These Bio aerogel microparticles can be adequately loaded with both polar and non-polar medications, have predictable physical dimensions, and should exhibit remarkable aerosolization capabilities for effective drug delivery to the designated respiratory tracts. In order to treat both local (such as asthma, COPD, lung cancer, etc.) and systemic (such as migraine, diabetes, etc.) disorders Bio aerogel microparticles hold great promise as a platform for delivering a variety of hydrophilic and lipophilic chemical medicines and biotherapeutics to the targeted locations in the airway.

10. Evaluation of aerosolization performance:

The inhalable microparticles with dae >10 micrometre, <5 micrometre, and < 2 micrometre are mostly deposited in the upper, lower respiratory tract, and alveolar areas, respectively. The in-vitro impaction data may be used to forecast the in-vivo deposition locations. Lopez-Iglesias et al. used the NGI to roughly examine the aerosolization behaviour of inkjet-printed alginate BAMs loaded with salbutamol sulphate. They reported an emitted dose of 97.5% w/w, fine particle fraction (< 5 µm) of 49.7% w/w, and MMAD of 4.0 µm, indicating a primary deposition of bio aerogel powders in the lower respiratory tract. It was unable to properly compare inhalable bio aerogels with marketed goods since no further significant aerosolization data were provided (18).

The NGI had a micro-orifice collector (MOC) with seven stages. In order to prevent inhaled particles from bouncing back and preserve particle stability inside the impactor, the stages of the impactor were treated with a 1% (w/v) solution of glycerine in methanol before to the examination. Low resistance was exhibited by the employed inhaler device (e.g., Aerolizer or Breezhaler, where the pressure drop across the device is less than 5 Mbar0.5L/min). According to the European Pharmacopeia, the vacuum pump was run at a flow rate of 100 L/min for 2.4 seconds in response to a 4 kPa pressure decrease behind the impactor and 4 L of air volume. Stage 1 (6.12 µm), Stage 2 (3.42 µm), Stage 3 (2.18 µm), Stage 4 (1.31 µm), Stage 5 (0.72 µm), Stage 6 (0.40 µm), and Stage 7 (0.24 µm) were the Da50 aerodynamic cut-off distances for each NGI stage, according to the manufacturer's calibration. Stage 2 (3.42 µm) was the NGI cut-off point that was closest to 5 µm.

An ACN: H_2O (65:35% v/v) solution was used to extract the collected particles from each impactor stage, and HPLC was then used to measure the quantity of BDP in each stage. The fine particle fraction (FPF), emission fraction (EF), and mass median aerodynamic diameter (MMAD) were used to describe in vitro aerodynamic parameters. The particle diameter at which 50% of its total weight is undersized is specified by MMAD. The percentage of drug recovered in the NGI is represented by EF, while the fraction of emitted dosage with an aerodynamic size of less than 5 µm is represented by FPF (8).

11. Conclusion:

Numerous techniques have been investigated to create Bio aerogel microparticles whose physical dimensions may be adjusted by using various preparation techniques and modifying operation settings. The bio aerogel particles have drastically reduced dae due to their exceptional porosity and ultralow densities. They also offer a great capacity to accommodate polar and non-polar drugs at sufficient amounts to satisfy clinical needs, facilitate the formation of drug amorphous states, and can build a system for controlled

drug release**.** These remarkable characteristics clearly suggested that the bio aerogel particles might serve as a platform for the effective delivery of chemical medications, biologics, and therapeutically active nanoparticles to the intended respiratory areas. The bio aerogel powders that are deposited have the ability to increase the therapeutic benefits for the treatment of both systemic and local disorders, prolong the duration of medication residence, and regulate drug release for ongoing healing activity. It is quite encouraging that these special bio aerogel particles will develop into the next generation of carriers for effective medication delivery to the targeted respiratory tract areas, with significantly better overall therapeutic benefits that may be predicted.

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