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A REVIEW ON CHITOSAN NANOPARTICLES FOR THE TREATMENT OF TUBERCULOSIS

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ABSTRACT

Tuberculosis is a significant public health issue. The current article examines the most recent developments in the use of nanoparticles to treat tuberculosis. Polymers in various forms, such as liposomes, dendrimers, and Nanoemulsions, may be utilized as synthetic and natural carriersfor the treatment's first and second-line medicines. This aids in the reduction of their doses, thereduction of side effects, the rise in medication interactions, and the targeting of drug-resistant bacteria. Because of the difficulties in developing anti-tuberculosis drugs, Nanotherapeutics utilizing chitosan as a carrier, emerged as a silver lining. Because chitosan is a more convenientand cost-effective way to distribute drugs.

KEYWORDS: Tuberculosis**,** *Mycobacterium tuberculosis*, Chitosan.

INTRODUCTION

Tuberculosis is a bacterial infection caused by *Mycobacterium tuberculosis*. It usually affects the lungs, although it may also affect other areas of the body. Tuberculosis is spread from person to person through the air. When people with lung tuberculosis cough, sneeze, or spit, they propel the tuberculosis germs into the air. A person needs to inhale only a few of these germs to become infected. When a person develops active tuberculosis disease, the symptoms(such as cough, fever, night sweats, or weight loss) may be mild for many months. This can lead to delays in seeking care and results in transmission of the bacteria to others. People with active tuberculosis can infect 5–15 other people through close contact over the course of a year. Common symptoms of active lung tuberculosis are cough with sputum and blood at times,chest pains, weakness, weight loss, fever, and night sweats. WHO recommends the use of rapidmolecular diagnostic tests as the initial diagnostic test in all persons with signs and symptoms of tuberculosis as they have high diagnostic accuracy and will lead to major improvements in the early detection of tuberculosis and drug-resistant tuberculosis. Rapid tests recommended by WHO are the Xpert MTUBERCULOSIS/RIF Ultra and Truenat assays. A total of 1.5 million people died from tuberculosis in 2020 (including 214 000 people with HIV). Worldwide, tuberculosis is the 13th leading cause of death and the second leading infectious killer after COVID-19.[1] There are two types of tuberculosis based on their anatomical existence. Latent tuberculosis infection: In this situation, you have a tuberculosis infection, yet the germs stay dormant in your body and produce no symptoms. Inactive tuberculosis, commonly known as latent tuberculosis or tuberculosis infection. They have no symptoms and their chest x-ray may be normal. The only manifestation of this encounter may be the reaction to the tuberculin skin test (TST) or interferon-gamma release assay (IGRA). Active tuberculosis: Active tuberculosis is an illness in which the tuberculosis bacteria are rapidly multiplying and invading different organs of the body. The typical symptoms of active tuberculosis variably include cough, phlegm, chest pain, weakness, weight loss, fever, chills, and sweating at night. A person with active pulmonary tuberculosis disease may spread to others by airborne transmission of infectious particles coughed into the air.[2]

Mycobacterium tuberculosis is transmitted via airborne particles that are 1-5 microns in diameter. When a person inhales Mycobacterium. Tuberculosis-containing droplet nuclei, the droplet nuclei travel via the mouth or nasal passage, upper respiratory tract, and bronchi to reach the lungs' alveoli.[3] Droplet nuclei's tiny size allows them to bypass the bronchial defense system and reach the alveoli. Before an immune response develops, the bacteria may be absorbed by alveolar macrophages, reproduced intracellularly, and infected neighboring cells. Non-phagocytic cells in the alveolar area, such as M cells, epithelial cells, and alveolar endothelial cells, are susceptible to M. tuberculosis infection. In 75–80 percent of patients, the illness

primarily affects the lungs and stays confined. It may also spread to other parts of the body, producing extrapulmonary tuberculosis. The initial infection may develop in to active illness, stay latent infection, or be wiped out by the host's immune system.4 According to the World Health Organization, the standard treatment regimen for new patients with drug-resistant pulmonary tuberculosis includes daily intake of first-line drugs such as isoniazid, rifampicin, pyrazinamide, and ethambutol for two months, followed by isoniazid and rifampicin. Three times a week for four months.[4]

Essential drug (abbreviation)	**Recommended dosage(dose range) in mg/kg Daily times weekly**	
Isoniazid(H)	5 (4-6)	10 (8-12)
Rifampicin(R)	10 (8-12)	10 (8-12)
Pyrazinamide(Z)	25 (20-30)	35 (30-40)
Streptomycin(S)	15 (12-18)	15 (12-18)
Ethambutol(E)	15 (15-20)	30 (25-35)
Thioazetazone(T)	2.5	Not acceptable

According to WHO, Multidrug-resistant tuberculosis (MRD) treatment regiment includes a combination of at least four drugs certain to be effective. In a standard regimen for treating MRD Tuberculosis, it is recommended to choose one drug from each group 1, 2,and 3 and theremaining from group 4.

Group	**Drug**
Group 1	PyrazinamideEthambutol Rifabutin
Group 2	StreptomycinKanamycin Amikacin Capreomycin
Group 3	Levofloxacin MoxifloxacinOfloxacin
Group 4	P- Aminosalicylic acid
	Cycloserin Terizidone Ehionamide Protionamide
Group 5	Clofazine Linezolid Amoxicilline ThioacetazoneImipenem Clarithromycin

Since tuberculosis patients need to take a large number of drugs for long period, adherence canbe an issue leading to increase possibilities of drug resistance.[5] Therefore the WHO recommended fixed - dose combination of multiple drugs.

Drug combination	**Dose**
Etambutol +isoniazid+ pyrazinamide + rifampicin	275mg +75mg+400mg+150mg
Ethambutol + isoniazid + rifampicin	275 + 75mg + 150 mg
Isoniazid + pyrazinamide + rifampicin	75mg + 400mg+ 150 mg
Isoniazid + rifampicin	400mg + 150mg

The duration of treatment is long, and it varies from 6 months for drugs, susceptible tuberculosisto more than 2 years for MDR TUBERCULOSIS. This can lead to poor adherence. The drug concentration at the site of infection in the lungs is very low after oral and parenteral administration requiring the administration of the high dose of drugs. The early termination oftreatment leads to relapse and drug resistance.[6]

NANO PARTICLES

Nanoparticles are particles that are between 1 and 100 nanometers in size and have a interfacial layer around them. The interfacial layer is a fundamentally nanoscale component of matter thataffects all of its characteristics. NPs have a relatively large (functional) surface that is able to bind, adsorb and carry other compounds such as drugs, probes, and proteins.

PULMONARY DRUG CARRIERS

Compared to oral, intramuscular, and intravascular drug administration, pulmonary medicationdelivery has many potential advantages.

- When compared to oral administration, pulmonary delivery requires a lower dosage of medication, and decreased toxicity is linked to the lower quantity of drug in the body andbetter patient compliance.

- The frequency and dosage of administration of drugs can be reduced.
- Reduced toxicity is associated with the reduced amount of drugs in the body.
- Decomposition of drugs by the gastrointestinal environment can be avoided.
- Drugs that are poorly water-soluble and difficult to formulate as the injection can beadministrate.
- Site -directed delivery of drugs to the pulmonary for treatment of respiratory disease canbe obtained.

However, many challenges must be overcome if the application of nanotechnology is to realizethe anticipated improved understanding of the pathophysiological basis of disease, bring more sophisticated diagnostic opportunities, and yield improved therapies. Different types of drug carriers can be used in the formulation of a pulmonary drug delivery systems. The polymer should be adaptable to the body in terms of toxicity and non-antigenicity, and it should also be biocompatible and biodegradable. Polymers derived from biopolymeric materials: Chitosan, gelatin, sodium alginate, xanthan gum, cellulose, liposome, Polymeric micelles, Dendrimers, Inorganic nanoparticles, Polysaccharides and proteins, and albumin are the most frequently utilized polymers in the production of polymeric non-particles.[7]

CHITOSAN

Chitosan nanoparticles have expanded growing attention for Nano-medicine, development of new therapeutic and biomedical engineering with improved availability, increased specificity, and compact toxicity.[8] Chitin (β-(1–4)-poly-N-acetyl-D-glucosamine) is widely distributed in nature and is the second most abundant polysaccharide. For biomedical applications, chitin is usually converted to its deacetylated derivative, chitosan.[9] Chitosan is a powdered polysaccharide polymer that contains more than 5000 glucosamine and acetyl glucosamine units and has a molecular weight of over one million Daltons. The chitosan molecule is an N acetyl D glucosamine copolymer. The backbone of sucrose is made up of 1,4-linked D glucosamine with a high level of N acetylation. With a pH range of 6.5-7.5.[10] Being polysaccharide, chitosan is mucoadhesive and possesses viscous attribute that is essential in drug encapsulation, drug release, and drug absorption kinetics modulation.[11]

INFECTIOUS DISORDERS OF THE LUNGS AND THE USE OF CHITOSAN-BASED CARRIERS

Bacteria (*Mycobacterium tuberculosis*, *Pseudomonas aeruginosa*, Haemophilus *influenzae*, *Streptococcus pneumoniae*), fungus (*Aspergillus fumigates*, *Histoplasmosis*, *Blastomycosis*), and viruses (*influenza virus A, influenza virus B*, hospital-acquired pneumonia caused by more resistant bacteria (*Staphylococcus aureus, Klebsiella pneumonia, Pseudomonas aeruginosa, and Escherichia coli*.), severe acute respiratory syndrome coronavirus 2 (SRS-CV-2)) cause pulmonary infections.[12,13] In immunocompromised and pulmonarly dysfunctioned individuals,this infection may be deadly. Traditionally, medicines are administered via oral or parenteral methods. Systemic medication delivery may result in low drug concentrations at the infected lung location and microbial resistance. Drug-resistant tuberculosis is one of the most difficult diseases to treat. Multidrug-resistant tuberculosis (MDR-TUBERCULOSIS) and extensively drug-resistant tuberculosis (XDR-TUBERCULOSIS) are the two forms of drug-resistant tuberculosis (XDR-TUBERCULOSIS). In 2018, an estimated 484,000 new cases of MDR- TUBERCULOSIS resistance to RIF were diagnosed. According to WHO, 78 percent of individuals acquired MDR-TUBERCULOSIS, whereas 6.2 percent of MDR- TUBERCULOSIS patients developed XDR-TUBERCULOSIS. The usual therapy for tuberculosis is to adhere to a six-month medication regimen while receiving patient care and monitoring. The continued spread of drug-resistant tuberculosis is due to ineffective tuberculosis management and treatment adherence[7]. Drug-resistant tuberculosis is mostly caused by a mutation in the antibiotic-targeted genes as a result of prior tuberculosis mistreatment. As a consequence, the tuberculosis bacteria mutate to become increasingly resistant to the medicines given.[14] A reduction in the permeability of the tuberculosis bacterium cell wall limits the entrance of antibiotics into the cell, and targeted gene modification over theperiod of time. As a result, the antibiotics that have accumulated are progressively destroyed by enzymes produced by bacterial cells.[15] M. tuberculosis generates an enzyme called - lactamase that may breakdown - lactam drugs, causing the bacterium to become resistant to those medicines. Furthermore, the efflux pump in M. tuberculosis may pump drugs out of bacterial cells, resulting in drug resistance. The effectiveness of presently available medicines is hampered by drug dose restrictions, unpleasant effects, and limited drug penetration into infection sites owing to inadequate vascularization of lesions.[16]To prevent multiple drug resistance administering the medication locally to the lungs may be an efficient way to avoid the drawbacks. The use of chitosan in drug delivery systems is expected to benefit from its antimicrobial properties.[17] Chitosan is a mucoadhesive substance. Chitosan, which is positivelycharged, may inhibit microbial development by preferentially attaching to bacteria's vital nutrients.[18] Antimicrobial activity has been found to be greater in low molecular weight chitosan with higher degrees of deacetylation and charge densities. Gram-negative bacteria have a greater negative charge on their cell surface than gram-positive bacteria. Because the former is more hydrophilic, more chitosan is adsorbed onto cell surfaces, causing them to have a greater growth - inhibitory impact.[19]

NANOPARTICLES

The chitosan nanoparticles of varying size, size distribution, zeta potential, crystallinity, shape, and

surface roughness were prepared by spray drying technique as a function of chitosan, surfactant, and processing conditions.[20] Exhalation-prone and highly aggregative solid nanoparticles are known to obstruct their dispersion and inhalation performance. They were either co-spray dried into inhalable microparticles with lactose, mannitol, maltodextrin, and leucine as the bulking and/or dispersion agent, or directly mixed with lactose-polyethylene glycol 3000 microparticles with the nanoparticles adsorbed onto the microparticles' surfaces. The mass median aerodynamic diameter of the co-spray dried microparticles is 3–15 m. They are mainly aggregative in nature and are considered less favorable when it comes to pulmonary inhalation.[21] Nanoparticles and microparticles are both cohesive on their own. By distributing the nanoparticles across the surfaces of the microparticles, blending them in precise weight ratios minimizes nanoparticulate aggregation. The nanoparticles may function as a glidant. Their presence on microparticulate surfaces lowers the microparticles' aggregation propensity, resulting in an inhalable powder with suitable flow properties.

It was discovered that The chitosan nanoparticles, physically mixed with fine lactose- PEG3000 microparticles, exhibit a comparable inhalation performance with the commercially available dry powder inhaler products where the FPF lies between 20% and 30%. Both aerosolization and inhalation performances of chitosan nanoparticles are primarily governed by their zeta potential, circularity, and size. Chitosan nanoparticles characterized by a larger magnitude of zeta potential, higher levels of circularity, and sizes are envisaged to undergo a lower extent of inter-nanoparticulate aggregation and have largely interacted with fine lactose-PEG3000 microparticles that aid their delivery to the lower lung regions.[21] Alexandru-Flaviu Tabaran et al (2020) designed silver nanoparticles for the therapy of tuberculosis. AgNP in conjugation with different biomolecules as peptide and chitosan have a good antimycobacterial effect. The study concludes that the combination of AgNPs with classical anti-TB therapeutics surgically enhance the antimycotic activity both extra and intracellularly.[22]

DIRECT INHALATION

Antibiotics are encapsulated with nanocarriers and delivering them directly to the lower respiratory tract through direct inhalation, which prevents antibiotic degradation. As a result, medication delivered may be more accurate. Using chitosan-based nano and microcarriers, anti- tubercular medicines may be administered to the lungs. The use of chitosan nanocarriers in the form of solid nanoparticles and liquid nanoemulsions for pulmonary anti-tubercular drug delivery has been investigated. Solid nanoparticles are made via solvent evaporation emulsification or ionic gelation or double emulsion method of oppositely charged materials in a liquid form.[23] Spray drying was utilized by Kundawala et al. to make INH-loaded polymeric microspheres for pulmonary administration. INH is a novel therapeutic approach with the potential to boost therapy efficacy. To make efficient INH-loaded polymeric microspheres for pulmonary delivery, a spray drying method was utilized. The drug-loaded microspheres were made using INH, chitosan, tripolyphosphate (TPP), leucine, and lactose. The level of deacetylation has a significant impact on how chitosan interacts with crosslinkers and media. The deacetylation level of the chitosan used was 89 percent, suggesting that it has good water solubility.[24]

For EDH DPI TB therapy, AHEMAD et al. (2017) created a dimple-shaped chitosan carrier. A rough chitosan carrier surface may be used to improve aerosol performance and reduce Van der Waals forces of attraction between the medicine and the carrier system. The formulations used in this study had a constant drug ratio (2.25 mg) but a variable chitosan ratio. The surface area of the chitosan increased from 11.0 to 15.4 m2 /g as the chitosan concentration increased (0.1– 0.4%). However, at 0.5 and 1% chitosan, the surface area started to decline.[25]

Dalia Kamal Eldein et al (2021) formulated and characterized inhalation of chitosan nanoparticles for tuberculosis. The prepared nanoparticle was evaluated and studied. The effect of chitosan nanoparticles against *Mycobacterium tuberculosis* was studied using the paper method. The ionic gelation method followed by spry drying was used for chitosan nanoparticles, the result showed that the obtained particle had a spherical smooth shape with an average size of 255±3.5 nm. The present study concludes that chitosan nanoparticles may be exploited as a prospective tool for the lung tissues for the treatment of tuberculosis.[26] Using a spray-drying technique, Pourshahab et al developed an inhalable powder of INH containing chitosan polymeric nanoparticles. Nanoparticles were prepared by ionic gelation method and spray dried using excipients such as lactose, mannitol and maltodextrin alone or with leucine. The ratio of chitosan: TPP was shown to be significant to the EE, particle size, and drug release profile in research. It was observed that by adding leucine, the particle size of microparticles decreased, and the process yield and fine particle fraction increased significantly. The in-vitro deposition data indicated that spray drying of isoniazid-loaded nanoparticles with lactose in the presence of leucine resulted in the production of inhalable powders with the highest FPF (45%).[27]

When the proportion of chitosan rises, this may be owing to the high chitosan carrier size. Furthermore, during spray drying, the input temperature, chitosan solution concentration, and feeding rate influence the dimples on the chitosan surface. According to the study, when a higher intake temperature (150 C) was used, the particles shrunk on the surface. However, when a lower temperature (80°C) was used, spherical shape particles were formed. Dimple-shaped particles may have formed

from the evaporation of water at a high input temperature.The findings showed that chitosan has no change in molecular weight following spray-drying to produce dimple-shaped carrier particles (3.2 kDa).[28] To enhance the treatment strategy for alveolar TB, Rawal et al. developed RIF-loaded chitosan DPI in 2017. The RIF, chitosan, and TTP formulations were made using a freeze-drying technique. The excipients and the medicine were determined to be compatible. The particles in the formulations were spherical, with sizesranging from 124.1 0.2 nm to 402.3 2.8 nm. TPP concentrations were shown to have a positively effect on formulation particle size, with higher TPP concentrations resulting in bigger formulation particles. In addition, the particle size distribution of the formulation has a PDI of 0.195 to 0.594.[29] Animals administered RIF-loaded chitosan-TPP formulation showed a 1.5- fold and 2.1-fold increase in lung drug concentration compared to conventional DPI (produced by mixing micronized RIF with coarse and fine lactose) and orally given RIF *in-vivo* experiments on male Wistar rats. Aside from that, the RIF-loaded chitosan-TPP formulation's enhanced drug elimination half-life indicated that it possessed sustained drug release properties. Finally, the RIF-loaded chitosan-TPP formulation may enhance aerosolization properties and raise targeted site concentration, resulting in improved therapeutic efficacy.[30]

Pai et al. used the spray drying method to formulate and evaluate chitosan microparticle-based DPI formulations for RFB. The compositions included RFB, chitosan, TPP, and lactose. The microparticles were shown on corrugated and wrinkled surfaces. The yield of the formulation varied from 14.37 to 20.17 percent. The moisture level of the formulation was less than 2%, which would have increased particle size and decreased aerodynamic performance. Regardless of the TPP: chitosan ratio, RFB-loaded microparticles had particle diameters of 1.146 0.832 m to 1.769 0.588 m. All formulations exhibited positive zeta potentials ranging from 18.1–23.2 mV. As the viscosity of the spray dried solution increased, the TPP content was increased, resulting in the formation of larger droplet sizes during the spray drying process. In vitro uptake studies in the U937 human macrophage cell line suggested that microparticles were internalized within the macrophages.[31]

Sujith Kumar Debnath et al (2018) designed and evaluated chitosan nanoparticle based dry powder inhalation formulations of prothionamide by ionic gelation technique. Chitosan, a biodegradable polymer was used to coat PTH and further freeze dried to prepare a dry powderinhaler (DPI) with an aerodynamic particle size of 1.76µm.prepared DPI maintained prothionamide concentration above MIC for more than 12h after single dose administration and also can improve the effectiveness of the treatment by increasing PTH concentration in the lungs tissues with reduce dose.[32]

NANOEMULSION

Nanoemulsion is a liquid dose form with a high degree of dispersion and inhalation to peripheral lungs. Their size varies from 10 to 1,000 nm. In the instance of nanoemulsion, nebulization is used to transport drugs to the lungs.[33] The cell surface leptin receptor with mannose specificity distinguishes alveolar macrophages. Alveolar macrophages have been shown to detect chitosan. To target the macrophages harboring T. bacilli, the medicated nanoemulsion droplets can be incorporated with chitosan.[34] The folate receptors are found on the cell surfaces of activated alveolar macrophages as well. The use of chitosan and folate in the form of a covalent conjugate to decorate nanoemulsion droplets has been shown to improve particle endocytosis and lung drug retention. Dual receptor targeting is more successful than single receptor targeting and is anticipated to eradicate bacteria from macrophages and diseased lungs to a greater extent.[35] Poly-γ-glutamic acid has been used in the preparation of Polyelectrolyte complex chitosan nanoparticles, which reduced the transepithelial electrical resistance of Caco- 2 cell monolayers. The nanocarrier of anti-tubercular medicines has been prepared using chitosan derivatives such as carboxymethyl chitosan and octanoyl chitosan. Mono-N- carboxymethyl chitosan has been shown to reduce the transepithelial electrical resistance of Caco-2 cell monolayers, suggesting that it may serve as a membrane permeation enhancer.[36]

Petkar, KC, Chavhan et.al (2017) studied and found that Chitosan is acylated with acyl chlorides and anhydrides to give it organic solubility and enhance its hydrophobicity without causing cytotoxicity. The hydrophobic octanoyl chitosan was utilized to produce crosslinker- free nanoparticles for pulmonary administration of Rifampicin using a double emulsion solvent evaporation method. The positively charged nanoparticles had greater mucoadhesive and membrane permeability enhancing capabilities, as well as resistance to enzymatic degradation, than ordinary chitosan. The negatively charged sialic acid found on the surfaces of lung alveolar macrophages attracts the chitosan-based nanoparticles electrostatically. Increased binding affinity between nanoparticles and macrophages leads to increased drug and nanoparticle absorption by T. bacilli-infected alveolar macrophages. The mucoadhesive/ bioadhesive property of chitosan would potentially increase the residence time of the formulations in the lungs, which might enhance the efficiency of antibiotic for the treatment of infections. The use of particulate carriers with positive surface charges promotes both passive membrane adherence and active receptor binding of nanoparticles.In order to avoid medicationresistance in TB, chitosan micro particles may be included utilizing a bioadhesive mannose receptor.[37]

MICROPARTICLES

Chitosan biocompatibility and mucoadhesiveness make it an ideal polymer for antituberculotic drugs

microencapsulation for pulmonary delivery.[38] Oliveira et al. went on to explain the preparation and characterization of microparticles containing isoniazid (INH) and chitosan (50-190kDa) as a non-toxic carrier. Using a spray-drying technique, they created mucoadhesive microparticles from 3.2µm to 3.9µm, entrapping more than 89% of the drug and preserving their chemical stability. Drug release behavior could be controlled by the use of cross-linked or uncross-linked chitosan, the latter leading to a rapid drug release. Mucoadhesive potential of the microparticles was characterized following in vitro and ex vivo assays. Finally, a significant reduction in toxicity against peritoneal macrophages and no toxic effect on alveolar macrophages with the use of such microparticles were observed.[39] The microparticles' mean particle size varied from 3.2–3.9 m, making them appropriate for pulmonary administration. Smooth, spherical forms are typical of INH-loaded chitosan microparticles. The chitosan microparticles that were not treated with INH, on the other hand, had an uneven, rough look.[40]

Samia M. Omar et.al (2019) formulated INH-loaded chitosan microparticles (Cs-Mps-1-3) as an inhalable carrier for the prepared INH-loaded polyvinylpyrrolidone/polyitaconic acid nanoparticles (NPs) using spray-drying technique. Here, Cs-Mps-1-3 are composed of Cs: INH- loaded NPs: Free INH at w/w ratios (1:1:0), (1: 0:1), and (1:1:1), respectively. Subsequently, the prepared Cs-Mps-1-3 characterizations were studied. Cs-Mps-1-3 showed a spherical, smooth, positively charged surface and a size range 1.52–3.12 µm. The in vitro INH released showed good correlation with first-order pattern, with predominance of the diffusion-controlled mechanism. In vitro aerodynamic deposition of Cs-MPs-3 possessed 56.81% effective fine particle fraction with lower impaction loss and device retention. The minimum inhibitory concentration of Cs-Mps-3 displayed 63-fold more inhibition effects on Mycobacterium tuberculosis than INH solution, owing to the combined effect of positively charged Cs-Mps with their facilitating bacterial cell surface binding and cellular penetration activity of NPs.[41] These findings revealed that drug-polymer interactions have an effect on particle shape. In the drug release research, non-cross-linked chitosan microparticles released loaded INH at a faster rate than free INH dissolution, with non-cross-linked chitosan microparticles dissolving 82 percent of INH and 45 percent of free INH in the first 90 minutes. This research also looked at the mucoadhesiveness of chitosan microparticles to the mucus in the respiratory system. When incubated in mucin dispersion, all chitosan microparticles exhibited a positive zeta potential between 17.7 mV and 29.8 mV at first, then declined (zeta potential remained positive). These findings demonstrated the existence of an ionic connection between chitosan and mucin, indicating that chitosan microparticles were mucoadhesive.[27]

Expert Opinion on Tuberculosis Treatment Drug Delivery

Nanotechnology provides an excellent platform for delivery of anti-TB and anti-HIV drugs via the pulmonary route thereby serving as a viable and effective means of managing the mycobacterial and HIV reservoirs in the lungs.[42]

Furthermore, powder handling throughout the production process may be enhanced, and medication deposition into the lungs can be regulated. Furthermore, nano/micro technologies are often integrated into DPI formulations to improve the drug's solubility, thus increasing bioavailability and therapeutic effectiveness. Numerous excipients, such as Xanthan gum, mannitol, chitosan, lactose, and others, have been studied as carriers to be utilized in DPI formulations. Polymeric carriers, including as chitosan, PVA, and PLGA, are also ideal for use in DPI formulations because of their long-term drug release properties. The use of a chitosan- based pulmonary drug delivery carrier has been demonstrated to decrease anti-TB medication systemic toxicity, enhance drug bioavailability in the lungs, and improve effectiveness.[43] The majority of research are performed in vitro and/or ex vivo. To determine their real potential therapeutic efficacy, aerodynamic characterization and in vivo evaluation of the functioning of these particles through natural breathing are needed.

CONCLUSION

Chitosan and its derivatives are mucoadhesive, biodegradable, biocompactable, less poisonous, simple to manufacture, and permiation promoting. It has the potential to be utilized as a carrier in nanoparticles for the treatment of tuberculosis medicines. The use of chitosan and derivatives is new, and it requires extensive research, including in vitro aerodynamic characterization and in vivo study of the pharmacokinetics and functionality of these particles through natural breathing in order to correlate to real therapeutic performance. SARS-CoV-2 infection causes coronavirus illness, which causes acute respiratory distress syndrome (ARDS), Middle East respiratory syndrome (MERS CoV), and individuals with tuberculosis (TB) seem to be more likely to be diagnosed with COVID-19. Chitosan's discoveries have led to the discovery of medicinal applications for this biopolymer in the treatment of coronavirus-related illnesses and tuberculosis. The recent discovery of chitosan and derivatives as therapeutic compounds to treat tuberculosis (TB) is expected to spark a surge in research combining the drug delivery and drug discovery properties of these biomaterials. From a therapeutic and drug delivery performance standpoint at the molecular level, their structural-activity connections in relation to lung cancer therapy are of considerable interest. Based on this opinion, drug carriers made from natural polymers like alginate and chitosan suggest a smart outlook but still they require more explorations. Chitosan was explored in the context of alveolar macrophage targeting and increasing pulmonary retention time, among other

applications. Nevertheless, pulmonary accumulation, and consequently toxicity, remains a major concern when using polymers. Appropriate clinical studies should be done in order to find out whether or not nanoparticle- based drug delivery system might be much anticipated solution for improving the patient compliance in TB and its efficiency.

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