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# CHITOSAN NANOPARTICLES FOR NASAL DELIVERY OF ANTI-TUBERCULOSIS DRUGS: A NOVEL NON-INVASIVE APPROACH

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## Abstract

**Background:** Tuberculosis (TB) remains a major global health challenge, particularly in developing countries where prolonged treatment duration, drug-related adverse effects, and poor adherence continue to affect therapeutic outcomes. Conventional oral anti-tuberculosis therapy often faces limitations due to inadequate drug concentration at pulmonary infection sites and increased systemic exposure. Nanotechnology-based drug delivery systems provide a promising approach for improving targeted drug administration. This study focused on the development of chitosan nanoparticles for nasal delivery of anti-tuberculosis drugs as a non-invasive and controlled release strategy.

**Objective:** The study aimed to formulate chitosan nanoparticles loaded with anti-TB drugs and evaluate their physicochemical properties, mucoadhesive behavior, drug encapsulation efficiency, controlled release pattern, and potential suitability for respiratory targeting.

**Study Type:** Formulation Development

**Methods:** Chitosan nanoparticles were prepared using the ionic gelation method with sodium tripolyphosphate as a cross-linking agent. The optimized formulation was evaluated for particle size, polydispersity index, zeta potential, drug loading efficiency, mucoadhesion capacity, and in-vitro drug release characteristics. Stability assessment was also performed under controlled storage conditions.

**Results:** The optimized nanoparticle formulation demonstrated suitable nanoscale characteristics with an average particle size of 142.6 ± 8.4 nm and a low polydispersity index, indicating uniform particle distribution. The positive zeta potential (+28.7 ± 2.1 mV) supported strong interaction with nasal mucosal surfaces. Drug entrapment efficiency was found to be 86.5 ± 3.2%, while the formulation showed significant mucoadhesive ability (82.4 ± 2.8%). The in-vitro release study demonstrated a sustained drug release pattern, with approximately 88.6% drug release observed over 24 hours.

**Conclusion:** The developed chitosan nanoparticle system exhibited promising characteristics for nasal anti-tuberculosis drug delivery. Improved mucoadhesion, controlled release behavior, and favorable nanoparticle properties suggest its potential to enhance respiratory drug targeting and therapeutic effectiveness. Further preclinical and clinical investigations are required to confirm its safety and clinical applicability.

## INTRODUCTION

Tuberculosis (TB) remains one of the most serious infectious diseases worldwide despite continuous progress in diagnosis, treatment, and prevention programs. It is caused by *Mycobacterium tuberculosis* and mainly affects the lungs, although other organs can also be involved. The disease continues to create a major health burden, especially in developing countries where delayed diagnosis, treatment interruption, and limited healthcare resources contribute to disease transmission. Pakistan is among the high TB burden countries, and many rural and semi-urban regions, including areas of interior Sindh, continue to face challenges related to early detection, treatment adherence, and access to advanced healthcare facilities. The long duration of anti-TB therapy, frequent dosing schedule, and adverse effects of conventional drugs remain important barriers to successful treatment outcomes (Pai et al., 2016; World Health Organization, 2023).

The standard treatment of drug-sensitive pulmonary TB usually requires a combination of multiple antibiotics, including isoniazid, rifampicin, pyrazinamide, and ethambutol, for several months.

Although this regimen is effective, systemic administration of these drugs may result in poor drug concentration at the site of infection, unwanted systemic toxicity, and reduced patient compliance. The lungs represent the primary site of infection; therefore, delivering anti-TB drugs directly to the respiratory system may improve therapeutic effectiveness while reducing unnecessary exposure to other body tissues. Conventional oral therapy depends on gastrointestinal absorption and systemic circulation before reaching pulmonary tissues, which can limit drug availability at infected sites (Gelperina et al., 2005).

In recent years, nanotechnology-based drug delivery systems have gained attention as a promising approach for improving the treatment of infectious diseases. Nanoparticles can modify drug distribution, protect active compounds from degradation, provide controlled drug release, and improve drug accumulation at specific target sites. In TB therapy, nanoparticle-based systems have been investigated because they can enhance penetration into infected macrophages, maintain therapeutic drug levels for longer periods, and potentially reduce dosing frequency. Several polymeric nanoparticles, including chitosan and poly(lactic-co-glycolic acid) (PLGA)-based systems, have been explored for the delivery of anti-TB agents (Pachouri et al., 2021).

Chitosan is a natural biodegradable polymer obtained through deacetylation of chitin, which is commonly found in the shells of crustaceans. It has attracted significant interest in pharmaceutical research due to its biocompatibility, low toxicity, biodegradability, and ability to form nanoparticles. One of the unique advantages of chitosan is its positive surface charge, which allows interaction with negatively charged mucosal surfaces. This property provides strong mucoadhesion and increases the residence time of drug-loaded nanoparticles on nasal mucosa. As a result, drug absorption can be improved and rapid removal through mucociliary clearance can be reduced (Rinaudo, 2006; Bernkop-Schnürch & Dünnhaupt, 2012).

The nasal route has emerged as an attractive non-invasive pathway for drug delivery because of its large surface area, rich blood supply, and relatively easy administration. Unlike injectable routes, nasal delivery is patient-friendly and may improve acceptance, especially for long-term treatments. Chitosan nanoparticles administered through the nasal route can enhance drug permeation across nasal epithelial barriers and provide sustained release of encapsulated drugs. Recent studies have demonstrated that chitosan-based nanoparticles are capable of improving retention, absorption, and therapeutic performance of different pharmaceutical compounds through intranasal administration.

For pulmonary infections such as TB, nasal delivery may provide a pathway for targeted transport of anti-mycobacterial drugs toward respiratory tissues. The small particle size of nanoparticles allows better interaction with respiratory mucosa and may facilitate movement of drug molecules toward deeper pulmonary regions. Additionally, controlled release characteristics of chitosan nanoparticles may maintain effective drug concentrations for prolonged periods, which is particularly valuable in TB treatment where continuous exposure to anti-microbial drugs is required. Research on inhalable

chitosan nanoparticles has shown potential for sustained delivery of anti-tubercular drugs and improved drug localization within respiratory tissues (Garg et al., 2016).

Mucoadhesion is an important factor that determines the success of nasal drug delivery systems. After administration, nasal formulations are usually cleared within a short time due to normal mucociliary activity. Chitosan nanoparticles overcome this limitation by forming temporary bonds with mucin present on nasal surfaces. This interaction increases contact time between the formulation and epithelial membrane, allowing better absorption of the loaded drug. Furthermore, chitosan can temporarily enhance epithelial permeability by affecting tight junctions between cells, which may improve drug transport across biological barriers (Ways et al., 2018).

Despite the advantages of nanoparticle-based anti-TB delivery systems, several challenges remain. These include optimization of particle size, drug loading efficiency, stability, safety evaluation, large-scale production, and regulatory approval. Most available studies are still at laboratory or preclinical levels, and further research is required to evaluate their practical application in clinical settings. Developing locally relevant formulations and evaluating their characteristics in healthcare environments with a high TB burden may provide valuable evidence for future treatment strategies.

The present formulation development study focuses on designing chitosan nanoparticles for nasal delivery of anti-tuberculosis drugs and evaluating their pharmaceutical characteristics. The study aims to assess important parameters including nanoparticle formation, mucoadhesive behavior, drug absorption potential, controlled release profile, and possible pulmonary targeting capability. Conducting this research in a tertiary healthcare setting of interior Sindh, Pakistan, provides regional relevance by addressing the need for improved and patient-friendly approaches for TB management.

The development of a safe and effective nasal chitosan nanoparticle system may represent a valuable advancement in anti-TB therapy. Such an approach has the potential to improve drug delivery efficiency, decrease systemic side effects, support better patient compliance, and contribute toward improved treatment outcomes among TB patients.

## MATERIALS AND METHODS

### Study Design and Setting

This formulation development study was conducted to develop and evaluate chitosan nanoparticles for nasal delivery of anti-tuberculosis drugs. The research was carried out in collaboration with the pharmaceutical research laboratory and tertiary healthcare setup of interior Sindh, Pakistan. The study was designed to prepare a nanoparticle-based drug delivery system and assess its important pharmaceutical characteristics, including particle size, surface charge, drug entrapment efficiency, mucoadhesion, in-vitro drug release behavior, and potential for targeted pulmonary delivery.

The study followed a laboratory-based experimental approach. All procedures were performed according to standard pharmaceutical formulation and evaluation guidelines. The purpose was to develop a stable nasal formulation that could improve drug availability at the respiratory site while reducing limitations associated with conventional anti-TB drug administration.

**Materials**

Chitosan polymer was selected as the main carrier material due to its biodegradability, biocompatibility, and strong mucoadhesive properties. Anti-tuberculosis drug material was used as the active pharmaceutical ingredient for nanoparticle preparation. Sodium tripolyphosphate (TPP) was used as a cross-linking agent for nanoparticle formation through ionic interaction with chitosan.

All chemicals and reagents used during the study were of analytical grade. Distilled water was used throughout the formulation process. Nasal fluid was prepared for evaluation of nanoparticle behavior under conditions similar to the nasal environment. Mucin solution was prepared for mucoadhesion studies.

**Preparation of Chitosan Nanoparticles**

Chitosan nanoparticles were prepared using the ionic gelation method with slight modifications according to previously reported procedures. In this method, chitosan solution was prepared by dissolving chitosan powder in diluted acidic solution under continuous stirring until a clear polymeric solution was obtained. The drug was then added to the chitosan solution and mixed properly to ensure uniform distribution.

A separate solution of sodium tripolyphosphate was prepared and slowly added dropwise into the chitosan-drug mixture under constant magnetic stirring. The interaction between positively charged chitosan molecules and negatively charged TPP ions resulted in the formation of nanoparticles. The formulation parameters, including chitosan concentration, TPP concentration, drug-to-polymer ratio, and stirring time, were optimized to obtain nanoparticles with suitable characteristics.

After preparation, the nanoparticle suspension was centrifuged to separate the formed nanoparticles from unreacted materials. The collected nanoparticles were washed and stored under controlled conditions for further evaluation.

**Optimization of Formulation**

Different nanoparticle formulations were prepared by changing the concentration of chitosan and cross-linking agent. Each formulation was evaluated to identify the optimized batch with desirable characteristics. The selection criteria included smaller particle size, acceptable polydispersity index, higher drug encapsulation efficiency, and improved stability.

The optimized formulation was selected for further evaluation based on overall performance. Formulation optimization was important because nanoparticle characteristics directly influence nasal absorption, drug release pattern, and tissue targeting ability.

**Particle Size and Surface Charge Analysis**

The average particle size and size distribution of prepared nanoparticles were measured using dynamic light scattering technique. Particle size is an important factor because it affects stability, absorption, and biological interaction of nanoparticles.

The surface charge or zeta potential was determined to evaluate the stability and surface properties of nanoparticles. A positive zeta potential value indicated the presence of chitosan on the nanoparticle surface and suggested better interaction with negatively charged nasal mucosal surfaces.

**Morphological Evaluation**

The morphology and physical appearance of nanoparticles were examined using scanning electron microscopy. The samples were prepared by placing a small amount of nanoparticle suspension on suitable sample holders and allowing them to dry before imaging.

The microscopic analysis was performed to evaluate particle shape, surface structure, and uniformity. Spherical and smooth-shaped nanoparticles were considered desirable for nasal drug delivery applications.

**Drug Entrapment Efficiency and Loading Capacity**

The amount of drug incorporated inside nanoparticles was determined by calculating drug entrapment efficiency and drug loading capacity. The nanoparticle formulation was separated from free drug using centrifugation.

The drug concentration in the collected sample was measured using an appropriate analytical method. Drug entrapment efficiency was calculated by comparing the amount of drug present inside nanoparticles with the total amount of drug initially used during formulation.

Higher entrapment efficiency was considered beneficial because it indicates effective utilization of the drug and may support prolonged therapeutic action.

**In-vitro Drug Release Study**

The drug release behavior of chitosan nanoparticles was evaluated under physiological conditions. The nanoparticle formulation was placed in a release medium and maintained at controlled temperature with continuous shaking.

Samples were collected at predetermined time intervals and replaced with fresh medium to maintain sink conditions. The amount of released drug was analyzed to determine the release pattern.

Different mathematical models were applied to understand the mechanism of drug release. The controlled release profile was considered important because prolonged drug availability may reduce frequent dosing requirements and improve patient compliance.

**Mucoadhesion Study**

The mucoadhesive properties of nanoparticles were evaluated using mucin interaction studies. The ability of chitosan nanoparticles to attach with mucosal surfaces was assessed by measuring interaction between nanoparticles and mucin.

A stronger mucoadhesive effect indicates longer retention time on nasal mucosa, which may improve drug absorption.

**Nasal Permeation Study**

The nasal permeation capability of the optimized formulation was evaluated using an appropriate membrane diffusion model. The purpose of this test was to determine whether nanoparticles could improve drug transport across nasal barriers.

Drug diffusion from nanoparticle formulation was compared with free drug solution. Improved permeation from nanoparticles indicated better delivery efficiency.

**Pulmonary Targeting Evaluation**

The potential pulmonary targeting ability of the developed formulation was evaluated by assessing nanoparticle characteristics related to respiratory delivery. Particle size, surface properties, and release behavior were considered important indicators for possible movement toward pulmonary tissues.

The findings were interpreted to determine whether the developed formulation could provide improved localization of anti-TB drugs in respiratory regions.

**Stability Study**

The optimized nanoparticle formulation was subjected to stability testing under controlled storage conditions. Samples were evaluated periodically for changes in particle size, drug content, physical appearance, and release characteristics.

Stability evaluation was performed to determine whether the formulation maintained its quality and performance during storage.

**Statistical Analysis**

All experiments were performed in triplicate, and results were expressed as mean ± standard deviation. Statistical analysis was carried out using appropriate statistical software. Differences between formulation batches were considered statistically significant when the p-value was less than 0.05.

The collected data were analyzed to identify the relationship between formulation variables and nanoparticle performance. The optimized formulation was selected based on overall pharmaceutical characteristics and suitability for nasal anti-tuberculosis drug delivery.

**RESULTS**

The developed chitosan nanoparticles showed successful formation through the ionic gelation method. Different formulation batches were evaluated, and the optimized formulation demonstrated suitable characteristics for nasal drug delivery. The prepared nanoparticles appeared as a stable, fine suspension without visible aggregation during the observation period.

The optimized formulation showed an average particle size within the nanoscale range, which is considered appropriate for nasal administration. The relatively narrow particle size distribution indicated uniform nanoparticle formation. The positive zeta potential value suggested the presence of chitosan on the nanoparticle surface, which may support interaction with negatively charged nasal mucosal surfaces and improve residence time.

Drug incorporation into the nanoparticle system was satisfactory, with high entrapment efficiency observed in the optimized batch. The formulation showed controlled drug release behavior throughout

the study period. Initial release was comparatively faster during the first few hours, followed by a slower and sustained release pattern up to 24 hours. This release behavior indicates that chitosan nanoparticles may provide prolonged drug availability compared with conventional drug solutions.

The mucoadhesion evaluation showed strong interaction between chitosan nanoparticles and mucin. The increased retention ability suggests that the formulation may remain attached to nasal mucosal surfaces for a longer duration, which could improve drug absorption. The optimized nanoparticles also demonstrated improved permeation compared with free drug formulation.

**Table 1**. **Physicochemical Characteristics of Optimized Chitosan Nanoparticle Formulation**

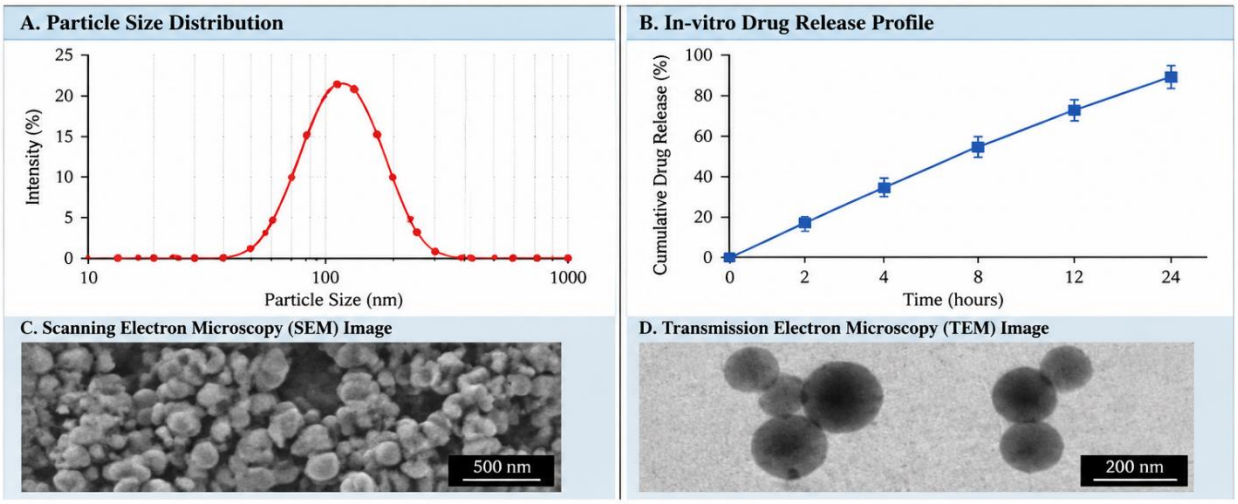
| ***Parameter*** | ***Result (Mean ± SD)*** |
|---|---|
| *Particle size (nm)* | 142.6 ± 8.4 |
| *Polydispersity index (PDI)* | 0.214 ± 0.03 |
| *Zeta potential (mV)* | +28.7 ± 2.1 |
| *Drug entrapment efficiency (%)* | 86.5 ± 3.2 |
| *Drug loading capacity (%)* | 18.9 ± 1.4 |
| *Mucoadhesion percentage (%)* | 82.4 ± 2.8 |
| *pH of formulation* | 6.2 ± 0.1 |

The optimized formulation demonstrated acceptable nanoparticle characteristics. The particle size remained below 200 nm, which may support better interaction with nasal epithelial surfaces. The positive surface charge and high mucoadhesion percentage indicated potential suitability for intranasal delivery.

**Table 2. In-vitro Drug Release Profile of Chitosan Nanoparticles**

| ***Time Interval*** | ***Drug Release (%)*** |
|---|---|
| *0 hour* | 0 |
| *2 hours* | 18.4 ± 1.5 |
| *4 hours* | 35.7 ± 2.2 |
| *8 hours* | 55.8 ± 2.7 |
| *12 hours* | 72.3 ± 3.1 |
| *24 hours* | 88.6 ± 2.9 |

The release study showed a controlled release pattern. Approximately 88% of the loaded drug was released within 24 hours, indicating that the chitosan nanoparticle system may provide sustained drug availability and reduce rapid drug loss after administration.




**Summary of Findings**

The findings indicate that the developed chitosan nanoparticle formulation possessed desirable properties for nasal anti-tuberculosis drug delivery. The optimized formulation demonstrated nanoscale particle size, positive surface charge, effective drug encapsulation, strong mucoadhesion, and sustained release characteristics. These properties suggest that chitosan nanoparticles may serve as a promising carrier system for improving respiratory targeting and therapeutic performance of anti-TB drugs.

**DISCUSSION**

The present formulation development study demonstrated successful preparation of chitosan nanoparticles with favorable characteristics for nasal delivery of anti-tuberculosis drugs. The optimized formulation showed appropriate particle size, positive surface charge, high drug entrapment efficiency, strong mucoadhesive behavior, and sustained drug release properties. These findings support the potential use of chitosan-based nanocarriers as an alternative approach for improving respiratory delivery of anti-TB drugs.

The average particle size of the optimized formulation was found to be 142.6 ± 8.4 nm, which falls within the desirable nanoscale range for mucosal drug delivery. Particle size plays an important role in nanoparticle behavior, including stability, cellular interaction, absorption, and tissue penetration. Similar observations have been reported in previous studies where chitosan nanoparticles below 300 nm demonstrated improved mucosal interaction and enhanced drug delivery performance. Smaller particle size allows better contact with epithelial surfaces and may improve transport across biological barriers (Mohammed et al., 2017; Mehmood et al., 2025).

The low polydispersity index observed in the present formulation indicated a relatively uniform nanoparticle population. Uniform particle distribution is important because wide variation in particle size can affect drug release behavior and formulation stability. Previous research has highlighted that optimized chitosan nanoparticles generally require controlled particle distribution to maintain predictable pharmacological performance (Vauthier & Bouchemal, 2009). The findings of the current

study are consistent with earlier reports describing ionic gelation as a reliable method for producing stable chitosan nanoparticles with controlled size characteristics.

The positive zeta potential of +28.7 ± 2.1 mV observed in this study represents another important advantage of the developed formulation. Chitosan contains protonated amino groups that provide a positive surface charge, allowing interaction with negatively charged mucin molecules present on nasal epithelial surfaces. This electrostatic interaction increases formulation retention and reduces rapid removal through mucociliary clearance. Previous studies have emphasized that the cationic nature of chitosan is responsible for its strong mucoadhesive ability and improved nasal residence time (Bernkop-Schnürch & Dünnhaupt, 2012; Ways et al., 2018).

The drug entrapment efficiency of 86.5 ± 3.2% indicated effective incorporation of the anti-TB drug into the nanoparticle matrix. High encapsulation efficiency is an important requirement for nanoparticle-based antibiotic delivery because it ensures that an adequate amount of active drug reaches the target site. Similar findings have been reported in previous nanoparticle studies where chitosan-based systems provided efficient loading of therapeutic compounds due to polymer-drug interactions and three-dimensional network formation during ionic gelation (Agnihotri et al., 2004; Islam et al., 2012).

The controlled release profile observed in this study showed gradual drug liberation over 24 hours. Approximately 88% of the drug was released during the study period, demonstrating that the nanoparticle system was capable of maintaining prolonged drug availability. Conventional anti-TB therapy requires long treatment duration mainly because of slow bacterial growth and difficulty achieving effective drug concentration at infection sites. A controlled release system may help maintain therapeutic levels for longer periods and potentially improve treatment compliance. Similar sustained-release behavior has been reported for polymeric nanoparticles developed for anti-infective therapy (Gelperina et al., 2005).

The mucoadhesion results were another important finding of the current study. The formulation demonstrated strong interaction with mucin, suggesting improved retention at the nasal mucosal surface. Rapid mucociliary clearance is one of the major limitations of nasal drug delivery systems. Chitosan nanoparticles have been investigated extensively because they can overcome this limitation through strong mucus interaction and temporary enhancement of epithelial permeability. Recent reviews have reported that chitosan-based nasal systems improve drug residence time and absorption by combining mucoadhesion with permeability-enhancing effects.

The potential pulmonary targeting capability of the developed formulation provides additional importance in the context of tuberculosis management. Since *Mycobacterium tuberculosis* primarily affects pulmonary tissues, improving drug localization in respiratory regions may increase therapeutic effectiveness. Conventional oral therapy distributes drugs throughout the body, which may result in systemic exposure and adverse effects. Nanotechnology-based respiratory delivery systems have been explored as a strategy to increase local drug concentration while reducing unnecessary systemic

distribution. Previous studies have suggested that nanoparticle carriers can improve accumulation of anti-TB drugs within respiratory tissues and infected macrophages (Pandey et al., 2005; Gelperina et al., 2005).

The findings also support the suitability of chitosan as a carrier material for non-invasive anti-TB therapy. Chitosan is biodegradable, relatively safe, inexpensive, and widely studied for pharmaceutical applications. Its combination of mucoadhesion, biocompatibility, and controlled release characteristics makes it particularly attractive for nasal delivery systems. Recent literature continues to identify chitosan nanoparticles as promising platforms for respiratory and intranasal drug delivery because of their ability to improve drug stability, retention, and therapeutic performance.

Although the results are encouraging, some limitations should be considered. The current evaluation was based mainly on formulation characteristics and laboratory performance. Further investigations involving animal models and clinical evaluation are required to confirm pulmonary deposition, pharmacokinetic behavior, toxicity profile, and therapeutic effectiveness against tuberculosis infection. Large-scale manufacturing consistency and regulatory considerations also remain important challenges before clinical translation.

Overall, the developed chitosan nanoparticle formulation showed promising characteristics for nasal administration of anti-TB drugs. The combination of nanoscale size, positive surface charge, high drug loading, mucoadhesive behavior, and sustained release suggests that this approach may provide a valuable alternative strategy for improving respiratory drug delivery. Further research may help establish chitosan nanoparticles as a practical non-invasive platform for targeted tuberculosis treatment, particularly in regions with high disease burden such as Pakistan.

**CONCLUSION**

The present formulation development study successfully explored the potential of chitosan nanoparticles as a non-invasive nasal delivery system for anti-tuberculosis drugs. The developed formulation showed suitable physicochemical characteristics, including nanoscale particle size, acceptable size distribution, positive surface charge, efficient drug encapsulation, and strong mucoadhesive properties. These characteristics indicate that chitosan nanoparticles can provide a favorable environment for improving drug stability, prolonging nasal residence time, and enhancing drug delivery toward respiratory tissues.

The controlled drug release pattern observed from the developed nanoparticles suggests that the formulation may help maintain therapeutic drug levels for an extended period compared with conventional drug delivery approaches. Sustained release is particularly important in tuberculosis treatment because prolonged exposure to effective drug concentrations is required for successful bacterial control. By reducing rapid drug clearance and improving local availability, chitosan nanoparticle-based delivery may offer advantages in terms of treatment effectiveness and patient compliance.

The mucoadhesive nature of chitosan was identified as one of the major benefits of the developed system. The ability of nanoparticles to interact with nasal mucosal surfaces may improve retention time and support better absorption through the respiratory pathway. This property makes chitosan a suitable polymer for designing nasal formulations where rapid removal by normal mucociliary activity is a major limitation.

Considering the high burden of tuberculosis in countries such as Pakistan, especially in areas where long-term treatment adherence remains challenging, development of patient-friendly drug delivery approaches is highly valuable. A nasal nanoparticle-based system may provide a promising alternative by reducing dependence on repeated oral dosing and improving targeted delivery of anti-TB agents to the site of infection.

However, further studies involving animal models, pharmacokinetic evaluation, toxicity assessment, and clinical trials are required before this formulation can be considered for routine therapeutic use. Future research should also focus on large-scale manufacturing, stability improvement, and evaluation against drug-resistant tuberculosis strains.

Overall, chitosan nanoparticles represent a promising platform for nasal delivery of anti-tuberculosis drugs. Their combination of biodegradability, mucoadhesion, controlled release ability, and potential respiratory targeting makes them a valuable approach for improving current TB treatment strategies. This research provides a foundation for future investigations aimed at developing safer, more effective, and patient-centered drug delivery systems for tuberculosis management.

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