EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 11
Issue: 11
Year: 2024

CHITOSAN NANOPARTICLE DELIVERY SYSTEMS: A PROMISING STRATEGY FOR IMPROVING THE EFFICACY AND SAFETY OF ANTITUBERCULAR DRUGS

Jaseena P.[1]*, Megha H.[2] and Prof. Dr. N. Tamil Selvan[3]

[1,2,3]Department of Pharmaceutics, Nehru College of Pharmacy, Thrissur.

***Corresponding Author: Jaseena P.**
Department of Pharmaceutics, Nehru College of Pharmacy, Thrissur.

Article Received on 17/09/2024 **Article Revised on 07/10/2024** **Article Accepted on 27/10/2024**

ABSTRACT
Tuberculosis (TB) remains a global health challenge, with significant morbidity and mortality despite existing treatments. Tuberculosis is a common and often deadly infectious disease caused by various strains of mycobacterium, usually Mycobacterium tuberculosis. Tuberculosis usually attacks the lungs but can also affect other parts of the body. It is spread through the air. It becomes deadly disease due to drug resistance, which generally developed in a couple of months, weeks, day or hours. This resistance mainly developed due to non-availability of drug, discontinuation or patient noncompliance. Therefore, the development of intelligent drug release systems is essential. Nanoparticle delivery systems are promising strategies to improve therapeutic efficacy and safety, overcoming challenges. Among these systems, a natural polysaccharide called chitosan, a derivative of chitin, has gained considerable attention as a biocompatible, biodegradable, and mucoadhesive material for creating nanoparticles. Chitosan nanoparticles provide several advantages, including improved stability, cellular uptake, solubility of antitubercular drugs, modulation of release kinetics, and biodistribution. Additionally, chitosan nanoparticles can be modified on their surface with ligands or stimuli-responsive moieties to achieve targeted delivery to specific tubercular cells or tissues. This review explores recent advances in chitosan-based nanoparticle drug delivery and their applications in tubercular therapy. Enhancing the efficacy and safety of antitubercular drugs through innovative delivery systems like chitosan nanoparticles has gained attention in recent research. This journal review aims to critically evaluate the effectiveness of chitosan nanoparticle delivery systems in improving the outcomes of antitubercular therapy.

KEYWORDS: Tuberculosis, Drug resistance, Nanoparticle, Chitosan, Mucoadhesive.

1. INTRODUCTION

Chitosan nanoparticle delivery systems represent a promising strategy to enhance the efficacy and safety of antitubercular drugs. Their ability to deliver drugs directly to infected cells while minimizing systemic toxicity makes them a valuable tool in combating tuberculosis. Studies have demonstrated that encapsulating antitubercular drugs within chitosan nanoparticles can improve their efficacy. This enhancement is primarily attributed to the ability of nanoparticles to penetrate macrophages efficiently, thereby delivering drugs directly to the intracellular pathogens. For instance, rifampicin-loaded chitosan nanoparticles have shown superior bactericidal activity compared to free rifampicin, potentially due to prolonged drug release and improved cellular uptake. Chitosan nanoparticles can mitigate the effects of anti-tubercular drugs on host cells by reducing the required dosage and minimizing systemic exposure while maintaining therapeutic efficacy. This targeted delivery approach minimizes off-target effects and enhances patient compliance.

Drug delivery methods based on nanoparticles can potentially increase the safety and efficacy of antitubercular medications. Using nanotechnology without damaging healthy cells, drug molecules can be delivered to specific locations. Because of their ability to enclose, transport, and discharge drugs at specific sites of action, nanoparticles can improve pharmaceuticals solubility, stability, circulation time, and targeting ability.[1] Furthermore, multidrug resistance mechanisms that restrict the efficacy of conventional antitubercular medications can be overcome by nanoparticles.[2]

Polymers play a critical role in developing nanoparticles for tuberculosis control. Polymeric nanoparticles offer several benefits, including flexibility, ease of modification, stability in biological environments, controlled drug release, biodegradability, and

biocompatibility. Among these, chitosan nanoparticles (CNPs) have garnered significant interest due to their unique properties and versatility. CNPs can effectively carry proteins, oligosaccharides, and antitubercular drugs, making them strong candidates for drug delivery systems. Chitosan, a cationic polymer derived from chitin found in crustaceans and insects, consists of repeating units of d-glucosamine and N-acetyl-d-glucosamine. It features two hydroxyl (OH) groups and one amino (NH2) group in each unit, particularly at C2, C3, and C6, making it reactive and functional for various applications.[3] (Fig. 1).[4]

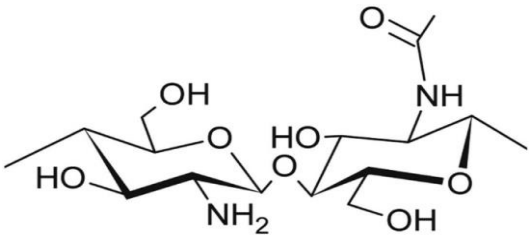

Fig. 1: Chemical structure of chitosan.[5]

Chitosan is commonly utilized in drug delivery systems due to its versatile formulation capabilities. It possesses several important properties, including haemostatic, anti-carcinogenic, anti-cholesterol, fungistatic, and bacteriostatic effects. In drug delivery systems that use chitosan, factors such as particle size, toxicity, thermal and chemical stability, and kinetics are heavily influenced by the preparation methods employed. Among the various techniques, the ionic gelation method has gained significant attention for its controlled, non-toxic, and solvent-free preparation, making it highly practical. This method is notable for its safety and efficiency, involving the interaction between the positively charged amino groups of chitosan and the negatively charged polyanion sodium tripolyphosphate (TPP). The properties of the nanoparticles are closely linked to the ionic cross-linker used, and TPP is particularly appealing due to its reliable performance, ease of process control, and safety. TPP effectively interacts with chitosan's positively charged amino groups (-NH3+), facilitating the synthesis of stable and uniform nanoparticles.[5]

Despite its numerous advantages, chitosan presents certain challenges in drug transport. It is hydrophilic and exhibits a degree of swelling, yet it has limited thermal stability and ductility. The low solubility of chitosan restricts its effectiveness, necessitating the development of chemical derivatives to improve its practical applications. As derivatives of chitosan gain traction among researchers, various modifications have been implemented. The most commonly used pharmaceutical derivatives include acylation, carboxymethylation, quaternization, and thiolation.[5]

2. Characteristics of chitosan nanoparticles

Chitosan nanoparticles are an excellent option for drug delivery due to their numerous advantageous properties, including responsiveness to various stimuli, mucoadhesion, surface modifiability, and biodegradability.[6]

2.1. Biodegradability

Biodegradability is a crucial attribute for biomaterials, especially those used in biomedical contexts. Chitosan is notable for its favourable qualities such as biocompatibility, antibacterial effects, promotion of wound healing, and improved drug delivery. One of its primary benefits is that it is biodegradable, enabling safe elimination from the body after performing its intended function.[7]

Chitosan degradation occurs through two main processes: enzymatic hydrolysis and acidic dissolution. Enzymatic hydrolysis involves the cleavage of glycosidic bonds between chitosan glucosamine units by enzymes like lysozyme, chitinase, and chitosanase, which are present in various biological fluids and tissues, such as saliva, tears, blood, and macrophages [90]. The degradation rate is influenced by factors such as deacetylation, molecular weight, crystallinity, and crosslinking. Higher deacetylation, lower molecular weight, decreased crystallinity, and reduced crosslinking all contribute to faster degradation.[8]

Acidic dissolution refers to the solubilization of chitosan in acidic conditions, such as those found in the stomach or lysosomes. While chitosan is insoluble at neutral or alkaline pH levels, it becomes protonated and soluble in acidic environments. This protonation of chitosan's amino groups decreases its vulnerability to enzymatic breakdown. Consequently, acidic dissolution is the main degradation pathway in such environments. The degradation rate via this method is dependent on the solution's pH and ionic strength, with lower pH and higher ionic strength typically leading to faster degradation. Both degradation processes result in the production of non-toxic oligosaccharides and monosaccharides of glucosamine, which can be metabolized or excreted by the body, making chitosan a biodegradable material that poses no harmful effects or accumulation risk.[9]

2.2. Mucoadhesion

Muco-adhesion refers to the ability of a material to adhere to mucosal surfaces within the body, such as those found in the gastrointestinal, respiratory, ocular, nasal, and vaginal areas. This property is beneficial for drug delivery, as it can prolong the duration a drug remains at its target site and enhance local concentration.[10] Chitosan has garnered significant attention as a mucoadhesive substance due to its ability to form electrostatic interactions with the negatively charged mucins in the mucus layer. Additionally, it can establish hydrogen bonds and hydrophobic interactions with mucosal membranes, further improving its adhesive properties.[11]

Chitosan-based formulations, which include films, gels, tablets, and nanoparticles, have been designed for various routes of administration, such as buccal, ophthalmic, nasal, and vaginal delivery. The use of chitosan enhances the bioavailability, stability, and permeability of drugs across mucosal barriers, which can be particularly advantageous. It also offers protection against enzymatic degradation and pH fluctuations. Moreover, chitosan has the ability to modulate immune responses and exhibits anti-inflammatory, antimicrobial, and antitumor effects. Consequently, chitosan stands out as a versatile biomaterial with promising applications in mucoadhesive drug delivery systems.[12]

2.3. Surface modifiability

The capacity to modify the surface of chitosan nanoparticles positions them as a promising vehicle for tuberculosis therapy. This surface alteration creates biocompatible, positively charged nanocarriers that can easily traverse the negatively charged membranes of cells. Incorporating ligands that specifically bind to antigens or receptors can enhance the selectivity and effectiveness of the drug.[13]

A variety of ligands, such as small molecules, aptamers, peptides, and antibodies, can be attached to chitosan nanoparticles. These ligands are capable of recognizing and interacting with specific targets, including growth factor receptors, cell adhesion molecules etc.[14] By functionalizing chitosan nanoparticles with these ligands, the drug delivery system can be directed more precisely toward bacterial cells, thereby preferentially delivering the drug to infected sites while sparing normal tissues. This targeted approach can minimize systemic toxicity and adverse effects, improving the therapeutic index and efficacy of the drug. Additionally, modifying the surfaces of chitosan nanoparticles can enhance their stability, solubility, bioavailability, and distribution within the body. Thus, surface modifiability is a key characteristic of chitosan nanoparticles, making them well-suited for tuberculosis treatment.[15]

2.4. Stimuli-Responsiveness

Chitosan nanoparticles (CNPs) are capable of releasing encapsulated drugs in a controlled manner in response to various stimuli, such as pH, temperature, light, and magnetic fields. Their unique properties and adaptable nature make CNPs a versatile platform for targeted drug delivery in tuberculosis therapy.[16]

The conventional anti-tubercular drug treatment plan is associated with several problems. These include lack of metabolic stability, low membrane permeability, low solubility, high-loaded dosage forms and hepatotoxicity.[17] Traditional TB treatment also entails precise dosages and frequencies, and lengthy treatment periods that lead to patient noncompliance.

One of the primary advantages of CNPs is their small size, which typically ranges from 10 to 200 nm. This size allows them to navigate physiological barriers, including interstitial fluid pressure, the blood-brain barrier, and dense extracellular matrices that hinder the effectiveness of traditional drugs. CNPs can achieve higher drug concentrations at the infected site while minimizing exposure to normal tissues, thereby reducing systemic toxicity and side effects associated with antituberculosis treatments.[18]

CNPs are also highly versatile and easily modifiable. Various antituberculosis agents, imaging agents, proteins, peptides, small molecules, and nucleic acids, can be rapidly loaded into these nanoparticles. The loading efficiency and stability of CNPs can be influenced by factors such as the drug's hydrophobicity, charge, and molecular weight[19] This controlled and selective release mechanism of stimuli-responsive CNPs can enhance the efficacy of antitubercular drugs.[20]

3. Targeted Approaches Using Chitosan-Nanoparticles in Tuberculosis Treatment

The effective integration of appropriate carriers with one or more therapeutic agents is fundamental to drug delivery systems. Key requirements for these systems include the accurate targeting of drugs to specific tissues and the provision of effective therapeutic doses at designated intervals. A critical element of drug delivery systems is the regulation of plasma drug levels within the therapeutic range, primarily achieved through the use of drug carriers, often in the form of polymers, which facilitate the development of controlled delivery methods. Additionally, the demand for tailored delivery systems arises from the need to encapsulate active compounds in carriers specifically designed to navigate the complex pathways to their intended destinations. This necessitates careful selection of carriers, routes of administration, and release targets. Chitosan nanoparticles (CS-NPs) can improve TB treatment through several mechanisms:

1. **Targeted delivery:** CS-NPs can be modified with specific ligands that recognize and bind to infected macrophages, enhancing the delivery of anti-TB drugs directly to the site of infection**.**
2. **Controlled release:** Chitosan can be engineered to provide sustained and controlled release of encapsulated drugs, ensuring prolonged therapeutic effects while minimizing side effects.
3. **Enhanced penetration:** The mucoadhesive properties of chitosan facilitate better penetration into biological barriers, potentially improving drug absorption in the lungs.

The effects of antitubercular drugs using chitosan nanoparticles are shown in Table 1.

Table 1: Overview of Antitubercular Drugs Utilizing Chitosan Nanoparticles.

Drug name	Chitosan nanoparticle formulation	Key findings	References
Isoniazid	Chitosan -conjugated nanoparticles	Improved efficacy of drug and reduce drug resistance.	Oana-Maria et al,[21]
Rifampicin	Chitosan-encapsulated Nanoparticles	Provide sustained release of the drug, no toxic effects on cells &organs.	Tejal Rawal et al,[22]
Pyrazinamide	Chitosan-coated Nanoparticles.	Improved drug bioavailability, reduce dosing frequency, improved patient adherence.	Xiaoxin Shi et al,[23]
Streptomycin	Chitosan-conjugated Nanoparticles	Enhanced anti-bacterial activity.	Amin Zhang et al,[24]
Para-amino salicylic acid	Chitosan-conjugated Nanoparticles	Improved pharmacological effect.	Henusha.D. Jhundoo et al,[25]
Ethionamide	Chitosan-loaded Nanoparticles.	Site specific action	Sharif Abdelghany et al,[26]
Prothionamide	Chitosan-coated Nanoparticles.	Reduced dose and increased residence time.	Sujith Kumar Debnath et al,[27]
Kanamycin	Chitosan-conjugated Nanoparticles	More effective antibacterial treatment.	Govindarajan Venkat Kumar,[28]
Rifabutin	Chitosan-encapsulated Nanoparticles	Provide sustained release of drug and enhanced stability.	Lorena Valverde-Fraga et al,[29]
Clofazimine	Chitosan-loaded Nanoparticles.	Improved cellular uptake.	Datta Maroti Pawde et al,[30]
Imipenem	Chitosan-loaded Nanoparticles.	Provide sustained release of the drug.	Isra Umbreen Mufti et al,[31]
Amoxycillin-clavulanate	Chitosan-coated Nanoparticles.	Improved anti-bacterial effect.	Baghat Fayed et al,[32]

Research has demonstrated the efficacy of chitosan nanoparticles in delivering various anti-TB agents, including rifampicin and isoniazid. Studies show that these formulations can enhance drug bioavailability and reduce required dosages, thereby minimizing toxicity.

4. Varied Mechanisms of Antitubercular Efficacy in Chitosan Nanoparticles

Chitosan nanoparticles (NPs) have gained attention for their diverse mechanisms of antitubercular activity. Here are some key mechanisms through which chitosan NPs exert their effects against tuberculosis:

1. **Cell Membrane disruption:** Chitosan NPs can interact with the bacterial cell membrane, leading to structural changes and increased permeability. This can disrupt the integrity of Mycobacterium tuberculosis (M. tuberculosis), promoting cell lysis.
2. **Intracellular delivery:** The nanoparticles can facilitate the delivery of antitubercular agents directly into the cells infected by M. tuberculosis, enhancing the effectiveness of these drugs and improving therapeutic outcomes.
3. **Biofilm disruption:** Chitosan has the ability to disrupt biofilms formed by M. tuberculosis, which can protect the bacteria from antibiotic treatment. By disrupting these biofilms, chitosan NPs enhance the efficacy of existing antibiotics.
4. **Immunomodulation:** Chitosan NPs can stimulate the immune system, promoting a stronger immune response against M. tuberculosis. They may enhance the activity of macrophages, which play a crucial role in controlling tuberculosis infection.
5. **Antioxidant properties:** Chitosan possesses antioxidant properties that can help in reducing oxidative stress in infected cells, potentially aiding in the recovery of immune cells and enhancing their ability to fight the infection.
6. **Sustained drug release:** The controlled release of encapsulated drugs from chitosan NPs can provide a sustained therapeutic effect, improving the pharmacokinetics and bioavailability of antitubercular agents.
7. **Antibacterial activity:** Chitosan itself has intrinsic antibacterial properties, which can directly inhibit the growth of M. tuberculosis.
8. **Synergistic effects:** When used in combination with other antitubercular drugs, chitosan NPs can

enhance the overall effectiveness of treatment through synergistic interactions.

These mechanisms make chitosan nanoparticles a promising platform for developing novel antitubercular therapies and improving the management of tuberculosis. Further research into their formulation, optimization, and clinical application is essential to fully realize their potential.

5. Challenges and Future directions

Despite the promising results, several challenges remain:

- **Toxicity and Biocompatibility:** The safety of nanoparticles needs thorough investigation to prevent adverse effects.
- **Scalability and Manufacturing:** Developing scalable production methods for nanoparticles while maintaining quality and efficacy is crucial for clinical translation.
- **Regulatory hurdles:** Navigating the regulatory landscape for new nanoparticle-based therapies can be complex.

Future research should focus on optimizing formulations, conducting clinical trials, and exploring combination therapies to enhance efficacy against TB.

6. CONCLUSION

Chitosan nanoparticles represent a novel and effective approach for targeted tuberculosis treatment. Their unique properties may improve drug delivery, reduce side effects, and ultimately lead to better treatment outcomes for patients suffering from this disease. Targeted approaches using nanoparticles represent a promising frontier in the fight against tuberculosis. Ongoing research is essential to overcome existing challenges and bring these innovative therapies from the laboratory to clinical practice, ultimately improving TB management and patient outcomes. Future studies should focus on long-term efficacy, safety assessments, and real-world applicability of these nanoparticle systems in diverse populations.

ACKNOWLEDGEMENT

I express my sincere thanks to Prof. Dr. N Tamil Selvan for his guidance and insightful feedback throughout. I am also deeply grateful to Ms. Megha.H. for her unwavering support to our study. This work would not have been possible without their collective support and commitment.

REFERENCES

1. Rahman MM, Islam MR, Akash S, Harun-Or Rashid M, Ray TK, Rahaman MS, Islam M, Anika F, Hosain MK, Aovi FI. Recent advancements of nanoparticles application in cancer and neurodegenerative disorders: at a glance. Biomed Pharmacother, 2022; 153: 113305.
2. Nigro A, Pellegrino M, Greco M, Comande A, Sisci D, Pasqua L, Leggio A, Morelli C. Dealing with skin and blood-brain barriers: the unconventional challenges of mesoporous silica nanoparticles. Pharmaceutics, 2018; 10(4): 250.
3. Bigaj-Jozefowska MJ, Grzeskowiak BF. Polymeric nanoparticles wrapped in biological membranes for targeted anticancer treatment. Eur Polym J, 2022; 176: 111427.
4. Alemu D, Getachew E, Mondal AK. Study on the physicochemical properties of chitosan and their applications in the biomedical sector. Int J Polym Sci, 2023; 2023: 025341.
5. Grewal AK, Salar RK. Chitosan nanoparticle delivery systems: An effective approach to enhancing efficacy and safety of anticancer drugs. Mater Adv, 2024; 3: 100040.
6. Nguyen DD, Lai JY. Advancing the stimuli response of polymer-based drug delivery systems for ocular disease treatment. Polym Chem, 2020; 11(44): 6988-7008.
7. Tamilarasi GP, Sabarees G, Manikandan K, Gouthaman S, Alagarsamy V, Solomon VR. Advances in electro spun chitosan nanofiber biomaterials for biomedical applications. Mater Adv, 2023; 4(15): 3114-3139.
8. Tajvar S, Hadjizadeh A, Samandari SS. Scaffold degradation in bone tissue engineering: an overview. Int Biodeterior Biodegrad, 2023; 180: 105599.
9. Wang L, Xu Z, Zhang H, Yao C. A review on chitosan-based biomaterial as carrier in tissue engineering and medical applications. Eur Polym J, 2023; 191: 112059.
10. Jawadi Z, Yang C, Haidar ZS, Santa Maria PL, Massa S. Bio-Inspired Muco-adhesive polymers for drug delivery applications. Polymers, 2022; 14(24): 5459.
11. Hamedi H, Moradi S, Hudson SM, Tonelli AE, King MW. Chitosan based bio adhesives for biomedical applications: a review. Carbohydr Polym, 2022; 282: 119100.
12. Fin bloom JA, Huynh C, Huang X, Desai TA. Bioinspired nano topographical design of drug delivery systems, 2023; 1(2): 139-152.
13. Bayat F, Pourmadadi M, Eshaghi MM, Yazdian F, Rashedi H. Improving release profile and anticancer activity of 5-fluorouracil for breast cancer therapy using a double drug delivery system, 2023; 34: 2565-2577.
14. Anderluh M, Berti F, Bzducha-Wróbel A, Chiodo F, Colombo C, Compostella F, Durlik K, Ferhati X, Holmdahl R, Jovanovic D. Emerging glyco-based strategies to steer immune responses. FEBS J, 2021; 288(16): 4746-4772.
15. Kurl S, Kumar A, Mittal N, Singh D, Bassi P, Kaur G. Challenges, opportunities, and future prospects of polysaccharide-based nanoparticles for colon targeting: a comprehensive review, 2023; 6: 100361.
16. Sabourian P, Tavakolian M, Yazdani H, Frounchi M, van de Ven TG, Maysinger D, Kakkar A. Stimuli-responsive chitosan as an advantageous platform for

efficient delivery of bioactive agents. J Control Release, 2020; 317: 216-231.
17. Nabi et al. Chitosan: a versatile bio-platform for breast cancer theranostics. J Control Release, 2022; 341: 733-752.
18. El-Naggar NE-A, Shiha AM, Mahrous H, Mohammed AA. Green synthesis of chitosan nanoparticles, optimization, characterization and antibacterial efficacy against multi drug resistant biofilm-forming Acinetobacter baumannii. Sci Rep, 2022; 12(1): 19869.
19. Madamsetty VS, Tavakol S, Moghassemi S, Dadashzadeh A, Schneible JD, Fatemi I, Shirvani A, Zarrabi A, Azedi F, Dehshahri A. Chitosan: a versatile bio-platform for breast cancer theranostics. J Control Release, 2022; 341: 733-752.
20. Bhaladhare S, Bhattacharjee S. Chemical, physical, and biological stimuli-responsive nanogels for biomedical applications (mechanisms, concepts, and advancements): a review. Int J Biol Macromol, 2022; 226: 535-553.
21. Dragostin I, Dragostin O-M, Iacob A-T, Dragan M, Chitescu C-L, Confederat L, et al. Chitosan microparticles loaded with new non-cytotoxic isoniazid derivatives for the treatment of tuberculosis: in vitro and in vivo studies, 2022; 7, 14(12): 2310.
22. Rawal A, Parmar R, Tyagi RK, Butani S. Rifampicin loaded chitosan nanoparticle dry powder presents an improved therapeutic approach for alveolar tuberculosis, 2017; 1, 154: 321-330.
23. Shi X, Praphakar RA, Suganya K, Murugan M, Sasidharan P, Rajan M. In vivo approach of simply constructed pyrazinamide conjugated chitosan-g-polycaprolactone micelles for methicillin resistant Staphylococcus aureus. Int J Biol Macromol, 2020; 158: 636-647.
24. Chung KT, Lee H. Chitosan coupling makes microbial biofilms susceptible to antibiotics. *Sci Rep*, 2013; 3(1): 3364.
25. Jhundoo HD, Siefen T, Liang A, Schmidt C, Lokhnauth J, Béduneau A, Pellequer Y, Larsen CC, Lamprecht A. Anti-inflammatory activity of chitosan and 5-amino salicylic acid combinations in experimental colitis. Pharmaceutics, 2020; 29, 12(11): 1038.
26. Abdelghany S, Alkhawaldeh M, AlKhatib HS. Carrageenan-stabilized chitosan alginate nanoparticles loaded with ethionamide for the treatment of tuberculosis. J Drug Deliv Sci Technol, 2017; 39: 442-9.
27. Debnath SK, Saisivam S, Debanth M, Omri A. Development and evaluation of chitosan nanoparticles based dry powder inhalation formulations of prothionamide. PLoS One, 2018; 25: 13(1).
28. Kumar GV, Chia-Hung S, Velusamy P. Preparation and characterization of kanamycin-chitosan nanoparticles to improve the efficacy of antibacterial activity against nosocomial pathogens. J Taiwan Inst Chem Eng, 2016; 65: 574-83.
29. Valverde-Fraga L, Haddad R, Alrabadi N, Sanchez S, Remunann-Lopez C, Csaba N. Design and in vitro assessment of chitosan nano capsules for the pulmonary delivery of rifabutin. Eur J Pharm Sci, 2023; 187: 106484.
30. Pawde DM, Viswanadh MK, Mehata AK, Sonkar R, Narendra, Poddar S, et al. Mannose receptor targeted bioadhesive chitosan nanoparticles of clofazimine for effective therapy of tuberculosis. Saudi Pharm J, 2020; 28(12): 1616-25.
31. Mufti IU, Gondal A, Kiyani KM, Mufti SM, Shahid R, Ihsan A, Imran M. Microstructural, physico-chemical, antibacterial and antibiofilm efficacy of imipenem loaded chitosan nano-carrier systems to eradicate multidrug resistant Acinetobacter baumannii. Mater Today Commun, 2023; 35: 105874.
32. Fayed B, Jagal J, Cagliani R, Kedia RA, Elsherbeny A, Bayraktutan H, Khoder G, Haider M. Co-administration of amoxicillin-loaded chitosan nanoparticles and inulin: A novel strategy for mitigating antibiotic resistance and preserving microbiota balance in Helicobacter pylori treatment. Int J Biol Macromol, 2023; 253(2): 126706.