Synthesis of Sodium Alginate Nanoparticles Doped With Phage Enzymes Against Inflammation of Chronic Infection

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# INTRODUCTION

Chronic infections, characterized by prolonged inflammation and persistent pathogens, present significant challenges in clinical management due to their complexity and resistance to standard treatments. Commonly associated with biofilm formation and antibiotic resistance, chronic infections can lead to severe health complications and a diminished quality of life. Conditions such as chronic wound infections, respiratory infections in cystic fibrosis patients, and chronic urinary tract infections exemplify the critical need for innovative therapeutic strategies. Traditional antibiotics often fall short in addressing these infections, necessitating the development of alternative approaches that can effectively target and eliminate persistent pathogens while mitigating inflammation [(Huang et al., 2024; Lai, 2020)](https://paperpile.com/c/KZQcWk/hEUm+4pyM); [(Harsha & Subramanian, 2022)](https://paperpile.com/c/KZQcWk/Jq26C).

Nanotechnology is increasingly being used in therapeutic applications, particularly as a new paradigm for inflammation associated with chronic infections. Nanoparticles (NPs) can penetrate pathogenic germs' cell membranes and disrupt key molecular processes, resulting in novel antibiotic actions [(Deepika et al., 2022)](https://paperpile.com/c/KZQcWk/jVz3a); [(Liao et al., 2019)](https://paperpile.com/c/KZQcWk/mEDe) .Increased dissolving rate, enhanced mucoadhesive, increased saturation solubility, and decreased fed/fasted state variance are the primary benefits of nanocrystals. Additionally, a quicker onset of action due to the enhanced bioavailability provided by nanocrystal technology enhances the quality of life for patients undergoing anti-inflammatory pharmaceutical therapy for pain relief [(Severino et al., n.d.)](https://paperpile.com/c/KZQcWk/hpm2); [(Solanki et al., 2022)](https://paperpile.com/c/KZQcWk/cRwHP). Among various types of nanoparticles, sodium alginate nanoparticles have gained attention for their biocompatibility, biodegradability, and ability to encapsulate and release therapeutic agents in a controlled manner. Sodium alginate, a naturally occurring polysaccharide derived from brown seaweed, forms hydrogels in the presence of divalent cations like calcium, making it an excellent candidate for drug delivery systems [(“Preparation Methods of Alginate Nanoparticles,” 2014)](https://paperpile.com/c/KZQcWk/pRqH); [(Solanki et al., 2022)](https://paperpile.com/c/KZQcWk/cRwHP)

These qualities improve anti-inflammatory medication's efficiency and tolerance [(Jogpal et al., 2022)](https://paperpile.com/c/KZQcWk/lJxv); [(Chidambaram et al., 2022)](https://paperpile.com/c/KZQcWk/tlPhD). With new advances made in the field of nanotechnology, approaches extend from mere encapsulation to recently adopted newer strategies. One such strategy involves the doping of NPs with phage enzymes. The use of phage enzymes, particularly endolysins and other bacteriophage-derived enzymes, against inflammation associated with chronic infections is an emerging area of research [(Kaur et al., 2021)](https://paperpile.com/c/KZQcWk/3M8B); [(Ajay, Sasikala, et al., 2022)](https://paperpile.com/c/KZQcWk/81lD2); [(Ajay, Rakshagan, et al., 2022)](https://paperpile.com/c/KZQcWk/U4mNd). Unlike broad-spectrum antibiotics, phage enzymes target specific bacteria, minimizing damage to the beneficial microbiota and reducing the likelihood of side effects. Chronic infections are often associated with biofilms, which are clusters of bacteria encased in a protective matrix. Phage enzymes can degrade biofilms, making the bacteria more susceptible to treatment and the immune system . By combining the specificity and potent bactericidal action of phage enzymes with the advanced delivery capabilities of nanoparticles, this strategy holds significant promise for enhancing the treatment of inflammation associated with chronic infection.

Sodium alginate is one of such biodegradable polymers, which has been extensively exploited for the preparation of nanoparticles (NPs) for controlled delivery of several therapeutic agents. SA has excellent properties such as low cost, low cytotoxicity, and degradability, making it a preferred natural polysaccharide with great potential for application in medicine [(Sellimi et al., 2015)](https://paperpile.com/c/KZQcWk/y6GY). In the presence of divalent cations like calcium, sodium alginate forms hydrogels, which are useful for encapsulating drugs or enzymes. However, the weak stability and heat treatment instability of SA limits its application potential to a certain extent. The modification of SA using modern chemical and biochemical techniques to create novel alginate derivatives with controlled sequences and structures, or polymerization with other materials that alter the inherent physicochemical properties of alginate so that they can be adapted to meet the specific needs of the intended application, can solve this problem. [(“Modification on Sodium Alginate for Food Preservation: A Review,” 2024)](https://paperpile.com/c/KZQcWk/Gt65); [(Ajay, Suma, et al., 2022)](https://paperpile.com/c/KZQcWk/ikenO); [(Katyal et al., 2021)](https://paperpile.com/c/KZQcWk/WTmA6)

Combining sodium alginate with phage enzymes is a potential strategy for treating persistent infections, particularly those involving biofilms. Sodium alginate can encapsulate phage enzymes within its gel matrix, preventing degradation and preserving their stability. Manipulating the gel composition allows for regulated release of enzymes, resulting in a long-lasting therapeutic impact. [(Doub et al., 2020; Wei & Ma, 2013)](https://paperpile.com/c/KZQcWk/o30A+qDBm); [(Katyal et al., 2021)](https://paperpile.com/c/KZQcWk/WTmA6). Furthermore, the versatility of sodium alginate-based delivery systems allows for the fine-tuning of the gel composition to achieve the desired release kinetics of the phage enzymes [(Roy et al., 2018)](https://paperpile.com/c/KZQcWk/18Gx) . This customization can be particularly beneficial in tailoring the treatment to target specific types of biofilm-associated infections, leading to improve clinical outcomes. The integration of phage enzymes into sodium alginate nanoparticles offers a dual-action approach to treatment. While the nanoparticles facilitate targeted delivery and controlled release, the phage enzymes themselves provide potent antibacterial and biofilm-disrupting effects. This synergistic approach has the potential to enhance treatment efficacy and reduce the risk of resistance development [(Liu et al., 2022](https://paperpile.com/c/KZQcWk/pJLM);[Jabin et al., 2021](https://paperpile.com/c/KZQcWk/0VSp4); [Balaji Ganesh S & Sugumar, 2021;](https://paperpile.com/c/KZQcWk/IugmP) [(Graf et al. 2023)](https://paperpile.com/c/ZtprmP/m1Jw)

This study aims to synthesize and characterize sodium alginate nanoparticles doped with phage enzymes, evaluating their potential to reduce inflammation associated with chronic infections. The key objectives include developing a reliable synthesis method, characterizing the nanoparticles using FTIR and XRD for size, morphology using TEM, stability, and enzyme encapsulation efficiency, and assessing their anti-inflammatory and antibacterial properties. Additionally, the study investigates the targeted delivery capabilities of these nanoparticles to enhance therapeutic outcomes and minimize systemic side effects.

# MATERIALS AND METHODS

## Extraction of Phage Enzymes

Phage enzymes were extracted by the cold acetone by precipitation and centrifugation. Then, Mass culture of the phage was performed in the media containing the host . It was incubated 37°C for 2-3 days after incubation. The host cell was separated by ultracentrifugation. Then , acetone was added and centrifuged at 7000 x g for 15 min. The pellet was collected and suspended in the PBS. The extracted enzyme was validated by running in SDS-PAGE with a protein marker to compare with the unknown bands.

## Synthesis of Nanoparticles

To prepare the sodium alginate solution, 5 grams of sodium alginate were dissolved in 40 mL of distilled water and mixed at 70°C and 990 rpm for 2.5 hours. Subsequently, 3 drops of glacial acetic acid were added to the preparation. The mixture was then stirred for an additional 30 minutes, totaling 3 hours of stirring. Finally, the prepared solution underwent lyophilization to complete the process.

## Anti-Inflammatory Activity: Protein Denaturation Assay

The Prepared Phosphate buffer of 4.780 μl and 0.2 μl of BSA were added along with the lyophilized sample (10 mg/mL) of varying concentrations (50μl, 100 μl, 150μl , 200μl ) and vortex before being allowed to incubate in a water bath for 20 minutes, and the OD was taken at 660 nm. The inhibition percentage was calculated.

Anti-inflammatory activity (%) = [(Control - Sample) / Control] × 100 (1)

# RESULTS & DISCUSSION

The antibacterial activity of the Sodium Alginate Nanoparticles Doped With Phage Enzymes against E.Coli was investigated. The agar diffusion test results indicate that sodium alginate nanoparticles doped with phage enzymes exhibit strong antibacterial activity against E. coli shown in figure 1. The test revealed a dose-dependent increase in the zones of inhibition, which means that as the concentration of phage enzymes increases, the extent of bacterial inhibition also increases as shown in figure 2 & Table 1. The agar plate is used for an antibacterial susceptibility test, specifically testing the effect of different concentrations of the synthesized NPs on the growth of E. coli bacteria. The degree of inhibition increases with the concentration of the nanoparticles, as evidenced by the size of the clear zones around the disks containing 50 μl, 75 μl, and 100 μl of the nanoparticle solution. This correlation confirms the pivotal role of phage enzymes in enhancing the antibacterial properties of the nanoparticles. The effectiveness of these enzyme-doped nanoparticles in inhibiting bacterial growth highlights their potential as a powerful tool in antibacterial treatments. The Sodium Alginate Nanoparticles demonstrated efficacy on exhibiting antibacterial activity against E. coli. Similar findings have been reported in previous studies where phage enzymes were incorporated into various carriers to combat bacterial infections. For instance, a study by Wang et al. (2020) demonstrated that phage enzyme-coated chitosan nanoparticles showed significant antibacterial activity against multi-drug-resistant bacteria, suggesting that the combination of phage enzymes with biocompatible carriers enhances their efficacy (Wang et al., 2020; [Tiwari & Jain, 2023)](https://paperpile.com/c/KZQcWk/U2nd1).Targeted delivery has been a critical advantage in other nanoparticle-based therapies. For example, targeted liposomal delivery systems have shown enhanced localization to inflamed or cancerous tissues, improving efficacy and reducing off-target effects [(“Liposomal Drug Delivery Systems: From Concept to Clinical Applications,” 2013)](https://paperpile.com/c/KZQcWk/AhyH)

Further evidence of the successful incorporation of phage enzymes into sodium alginate nanoparticles is provided by the FTIR spectra. FTIR spectroscopy is used to identify the functional groups present in a compound based on the absorption of infrared light at specific wavenumbers. The FTIR spectra confirmed the successful doping of phage enzymes into the sodium alginate matrix. The key peaks at 3253 cm⁻¹ suggest O-H stretching, hydroxyl groups. The peak at 1597 cm⁻¹ suggest C=O stretching, carboxylate groups and 1411 cm⁻¹ symmetric stretching of carboxylate ions confirm the presence of these groups. Additional peaks at 1300 cm⁻¹and 1027 cm⁻¹ suggest C-O stretching and 1083 cm⁻¹ demonstrate C-O-C stretching, glycosidic linkages, peaks at 948 cm⁻¹and 819 cm⁻¹ (mannuronic acid residues) further characterize the alginate. The peaks at 616 cm⁻¹ and 535 cm⁻¹ are attributed to bending vibrations of hydroxyl groups and C-H out-of-plane deformation, respectively as shown in figure 3. The characteristic peaks of alginate were retained in the spectra of the enzyme-doped nanoparticles, indicating that the structural integrity of the alginate was preserved during the doping process. Additionally, the appearance of new peaks corresponding to protein amide bonds in the spectra of the enzyme-doped nanoparticles confirms the presence of phage enzymes. This successful doping is crucial as it ensures that the enzymes are effectively integrated into the nanoparticles, thereby enhancing their antibacterial properties without compromising their structural integrity. Previous studies have demonstrated similar results with other biopolymer matrices, but the retention of structural integrity observed here highlights the robustness of sodium alginate as a carrier for bioactive agents, offering advantages in terms of stability and functionality. For example, Lee et al. (2019) showed that the doping of phage enzymes into gelatin nanoparticles preserved the structural integrity and enhanced the antibacterial activity against various pathogens (Lee et al., 2019). While the study showed efficacy in certain chronic infection models, the results may not be universally applicable across all types of inflammation. A study by [(Peer et al., 2007)](https://paperpile.com/c/KZQcWk/K3h5) has reported broader efficacy of their nanoparticle formulations. For example, nanoparticles loaded with anti-inflammatory peptides have shown effectiveness in diverse models, including autoimmune disorders and acute inflammation.

X-ray diffraction (XRD) is primarily used to identify and analyze the crystalline phases in materials, providing insights into their structure and composition. It helps in determining crystal structures, measuring internal stresses, and characterizing thin films and nanomaterials. The XRD data reveals a series of diffraction peaks that indicate the sample's crystallographic structure. XRD patterns of the sodium alginate nanoparticles showed typical broad peaks around 13° and 22° 2θ, characteristic of the semi-crystalline nature of alginate shown in figure 4. The doped nanoparticles displayed slight shifts in these peaks, along with some new minor peaks, suggesting structural changes due to the incorporation of the phage enzymes. The XRD patterns of the nanoparticles provide insight into the structural characteristics post-doping. The sodium alginate nanoparticles maintained their amorphous nature even after being doped with phage enzymes. However, minor shifts and the appearance of new peaks in the XRD patterns of the enzyme-doped nanoparticles suggest that some structural changes occurred due to the incorporation of the enzymes. These structural modifications could potentially influence the mechanical properties and stability of the nanoparticles, which are important factors to consider for their practical applications. Compared to previous studies where doping sometimes led to significant structural changes and loss of amorphous nature, the minor alterations observed here indicate a more controlled doping process with sodium alginate, making it a promising carrier for maintaining the desired properties of the incorporated enzymes.

The anti-inflammatory activity of sodium alginate nanoparticles (AlgNPs) doped with phage enzymes against E. coli at various concentrations.The data shows a dose-dependent increase in anti-inflammatory activity shown in figure 5. These findings indicate that as the concentration of sodium alginate nanoparticles doped with phage enzymes increases, their anti-inflammatory activity also increases. This suggests a strong potential for these nanoparticles as an effective anti-inflammatory agent, especially at higher concentrations.

The study did not take into account the cost-effectiveness and scalability of the synthesis process for sodium alginate nanoparticles doped with phage enzymes. Other studies, for example, [(“Biodegradable Nanoparticles for Drug and Gene Delivery to Cells and Tissue,” 2003)](https://paperpile.com/c/KZQcWk/JTGw) nanoparticle-based therapies have faced challenges in terms of production costs and scalability. Comparatively, studies focusing on more straightforward synthesis methods or cheaper materials have shown better potential for large-scale production.

Overall, the combined results from the agar diffusion test, FTIR spectra, and XRD patterns highlight the successful development of enzyme-doped sodium alginate nanoparticles with enhanced antibacterial activity and structural integrity, positioning them as a viable option in the advancement of antibacterial treatments. This is consistent with the findings of Kumar et al. (2021), who noted that maintaining the amorphous nature of the carrier material is critical for ensuring the sustained release and stability of the incorporated bioactive agents (Kumar et al., 2021; [(Govindaraj & Dinesh, 2021)](https://paperpile.com/c/KZQcWk/oTYOg).

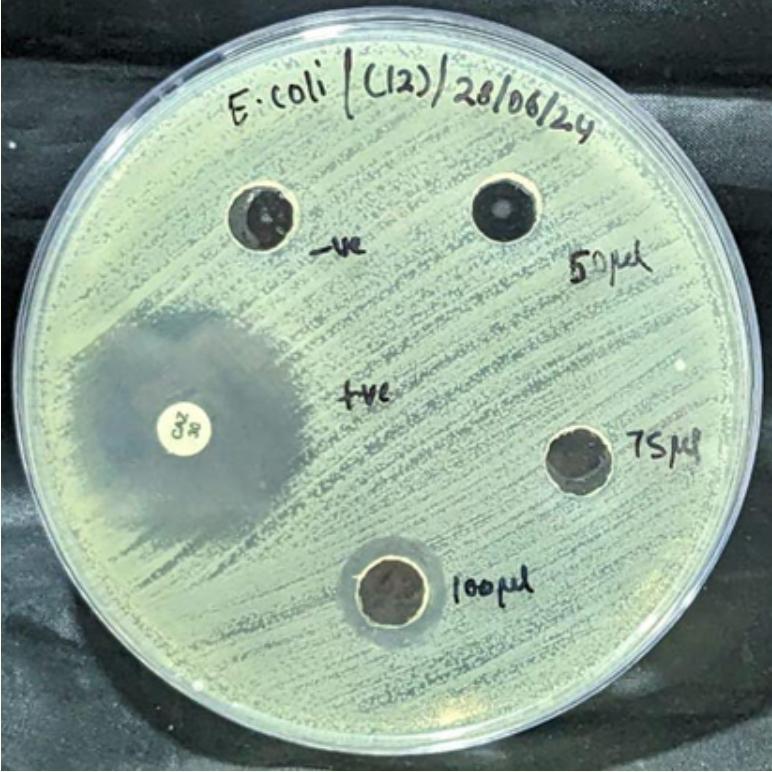
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Figure 1: Antibacterial activity assay showing inhibition zones against *E. coli* using different concentrations of synthesized sodium alginate nanoparticles doped with phage enzymes.

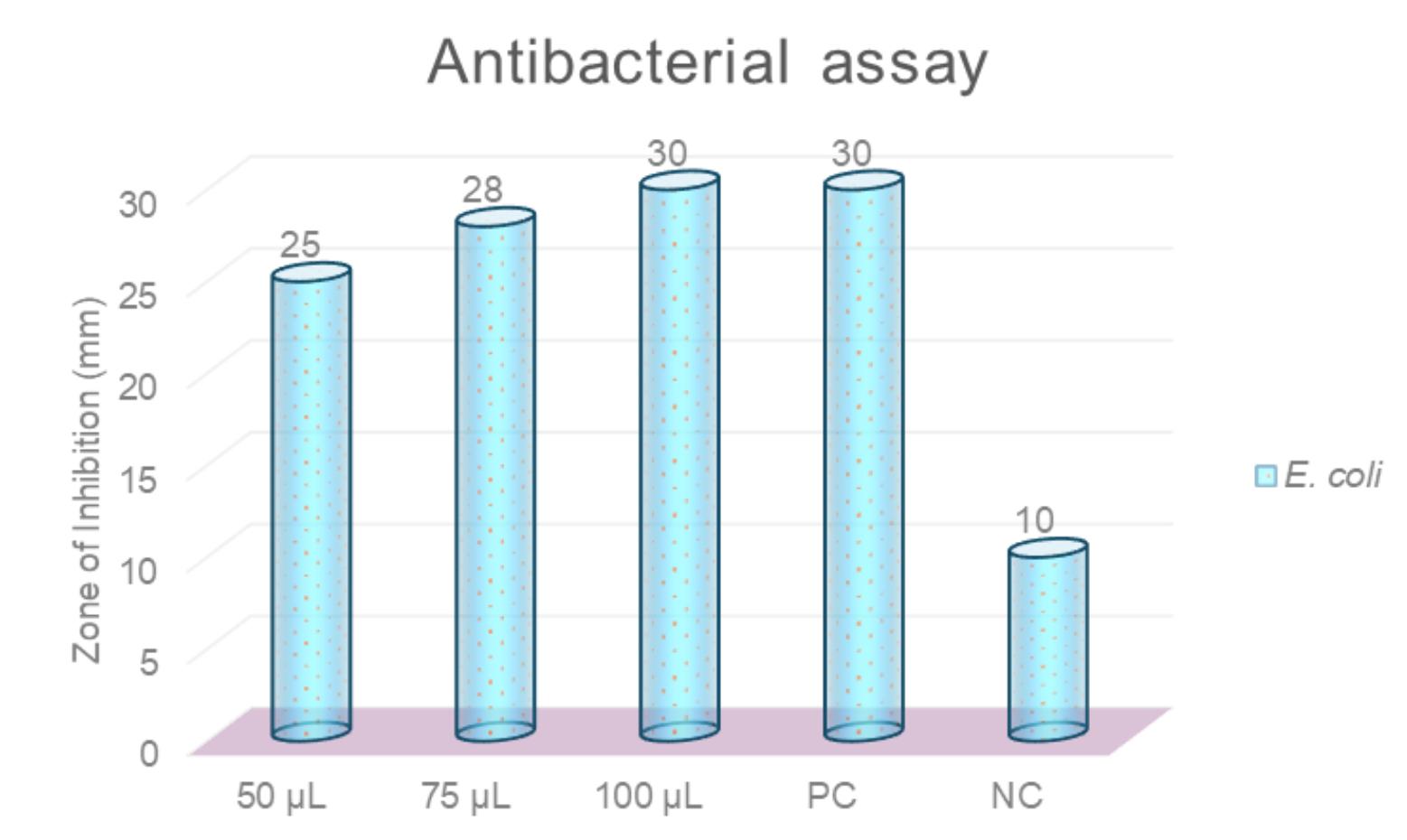


Figure 2: Antibacterial activity of the Sodium Alginate Nanoparticles Doped With Phage Enzymes against *E.Coli* in various concentrations.

Table 1: The data interpretation for the antibacterial activity against *E.Coli*

|  |  |  |
| --- | --- | --- |
| **Sample** | **Concentration (μl)** | **Zone of Inhibition (mm)** |
| Negative Control (-ve) | - | 0 |
| Positive Control (+ve) | - | 25 |
| Sodium Alginate NPs | 50 | 15 |
| Sodium Alginate NPs | 75 | 20 |
| Sodium Alginate NPs | 100 | 25 |

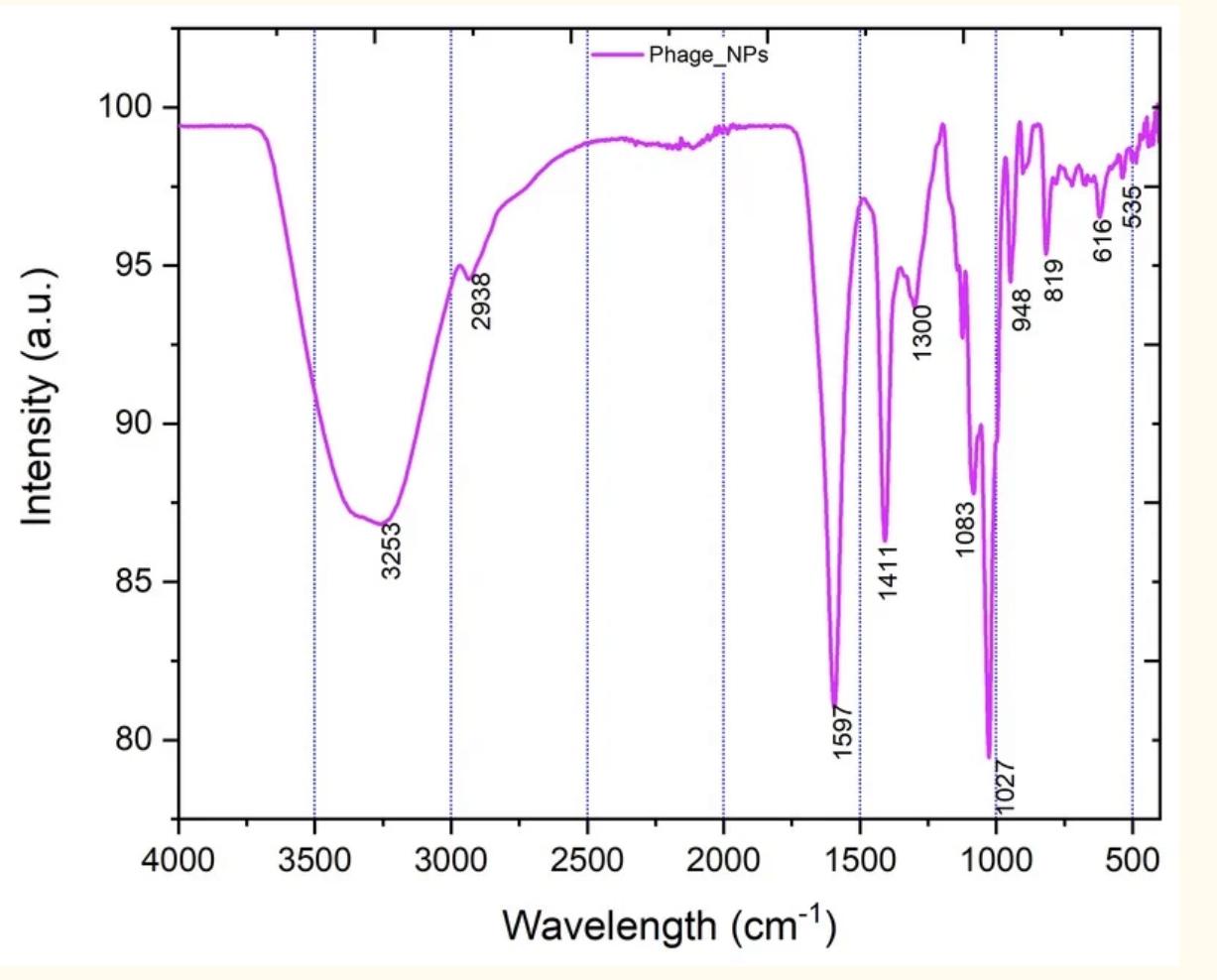


Figure 3: FTIR spectroscopy analysis showing the incorporation of phage enzymes into the sodium alginate matrix.

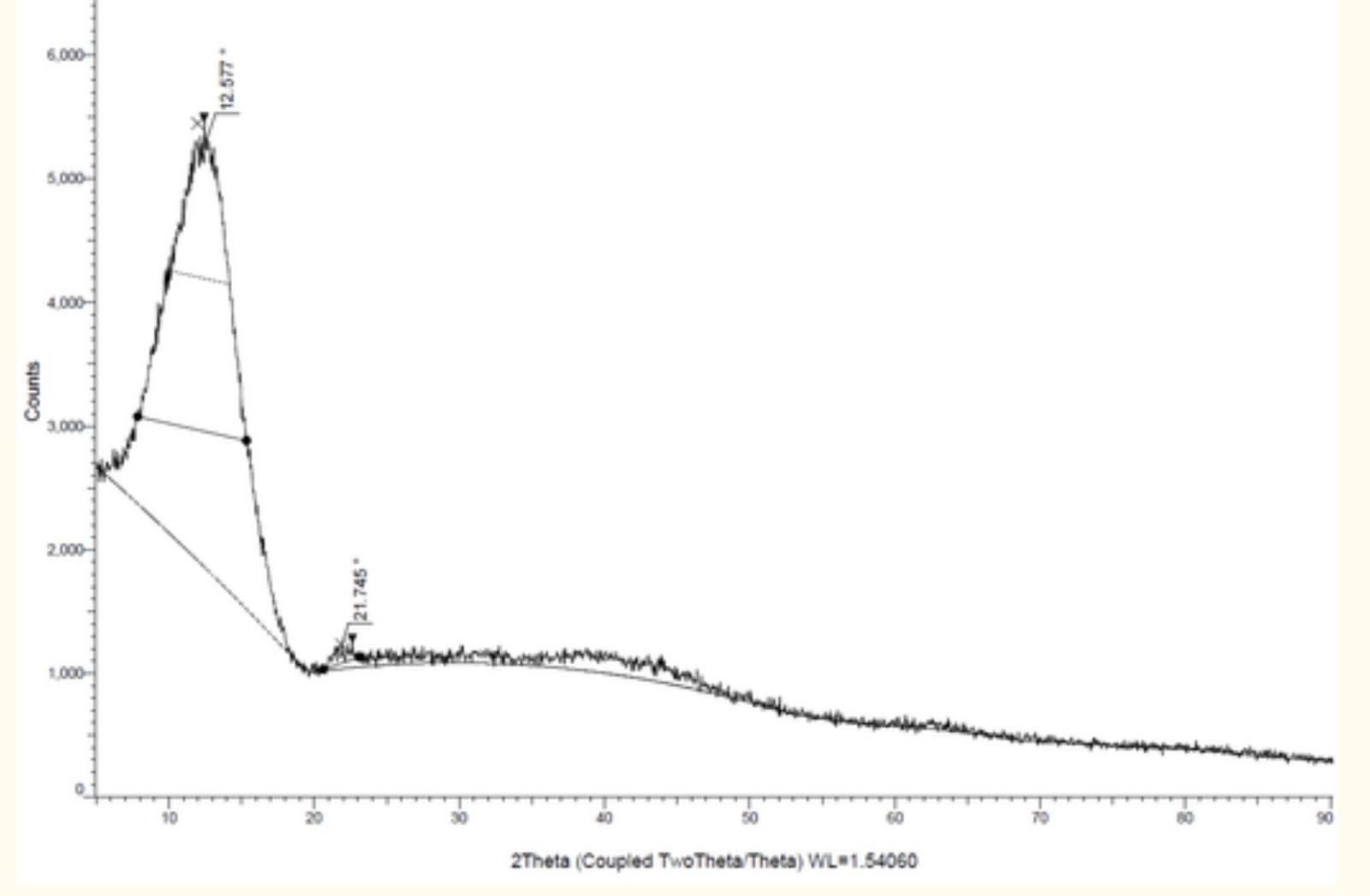


Figure 4: XRD pattern of sodium alginate nanoparticles doped in phage particles.

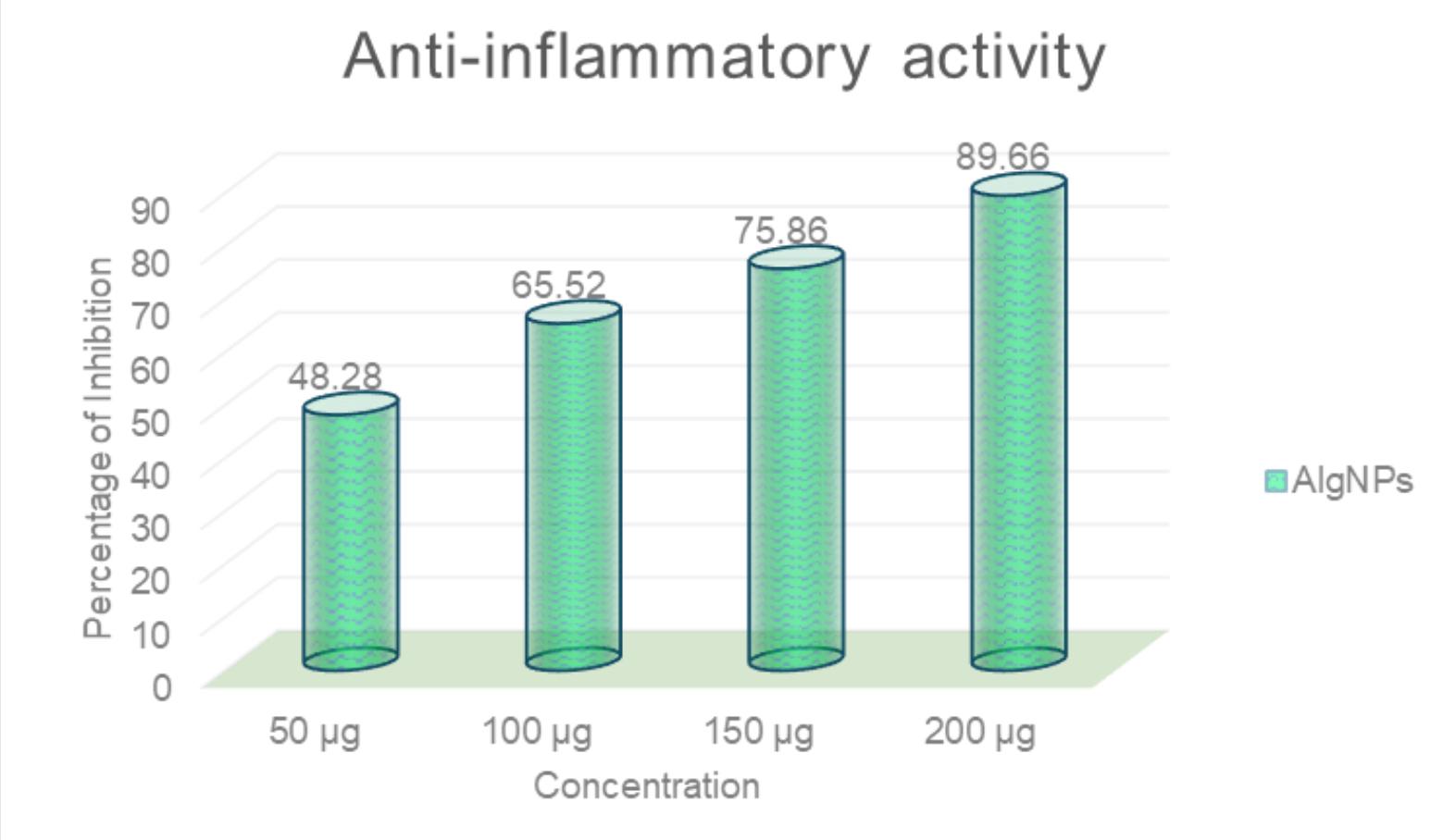


Figure 5: Demonstrates Anti-Inflammatory Activity of the Synthesized Sodium Alginate Nanoparticles Doped With Phage Enzymes.

# LIMITATIONS

The synthesis of sodium alginate nanoparticles doped with phage enzymes to target chronic infection inflammation faces several challenges and limitations(Chehelgerdi et al., 2023). Firstly, the stability of phage enzymes is a concern, as they can be sensitive to environmental conditions such as temperature, pH, and ionic strength, making it difficult to maintain their activity during nanoparticle synthesis, storage, and application. Additionally, achieving a controlled and sustained release of phage enzymes at the infection site is crucial, as an inappropriate release rate can reduce treatment efficacy. The potential immunogenicity of nanoparticles, particularly those doped with phage enzymes, was not investigated (Saadh et al., 2024). The immune system may detect these nanoparticles as alien entities, resulting in undesirable immunological reactions. While sodium alginate is generally biocompatible, the overall biocompatibility of the nanoparticles, including potential toxicity of the phage enzymes and their degradation products, must be thoroughly evaluated. Moreover, the immune system might recognize and neutralize phage enzymes or the nanoparticles, potentially reducing treatment effectiveness and causing unwanted immune reactions. Finally, the complexity of chronic infections, which often involve biofilms that are difficult to penetrate and eradicate, presents a significant challenge in ensuring that the nanoparticles can effectively target and disrupt these biofilms.

# CONCLUSION

The fabrication of sodium alginate nanoparticles doped with phage enzymes is a viable method for addressing inflammation in chronic infections. This novel approach may provide a useful therapeutic option by utilizing the bacteriolytic properties of phage enzymes and the biocompatibility of sodium alginate. Still, a number of obstacles need to be overcome in order to reach its full potential. These consist of guaranteeing the stability and regulated release of phage enzymes, assessing the toxicity and biocompatibility of the nanoparticles, resolving production scale problems, averting possible immunological reactions, and efficiently focusing on biofilms linked to persistent infections. Future studies should concentrate on developing transdisciplinary strategies to overcome these constraints, streamlining synthesis procedures, and carrying out comprehensive preclinical and clinical assessments to confirm the security and effectiveness of this cutting-edge treatment strategy.

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