Investigating the Potential of Bacteriophage Hydrogel in Treating Inflammatory Conditions of the Eye

Nikitha Mundlapudi1 , S.Darshan1,a)

1MUNDLAPUDI Dental Solutions, Andhra Pradesh, India

**Corresponding Author**: a)[darshan152501071saveetha@gmail.com](mailto:darshan152501071saveetha@gmail.com)

**Abstract:** As antibiotic resistance becomes more common, bacteriophage therapy is becoming a more effective therapeutic option for bacterial infections than traditional antibiotics. Bacteriophages are a type of selective strategy that accurately targets and eliminates bad bacteria, reducing the development of resistance and retaining helpful germs. In conjunction with hydrogels, which provide extended drug release and maintain visual clarity, this strategy presents a novel and targeted approach to the treatment of inflammatory ocular diseases. Hydrogels have the capacity to deliver bacteriophages exactly to the site of infection due to their biocompatibility and flexibility, which may increase therapeutic precision and enhance patient outcomes. This study looks into the creation of hydrogels loaded with bacteriophages and how well they perform to lower inflammation and oxidative stress in vitro. At greater concentrations, the data demonstrate the phage hydrogel's strong anti-inflammatory and antioxidant properties. The effectiveness of the bacteriophages' incorporation into the hydrogel matrix without altering its amorphous structure is confirmed by FTIR and XRD spectroscopic investigations. These findings imply that bacteriophage hydrogels may revolutionize the treatment of ocular infections by providing a more targeted, durable, and effective therapy; nevertheless, prior to widespread clinical implementation, additional research is necessary to address stability, immune responses, and regulatory issues.

**Keywords:** Bacteriophage Therapy,Antibiotic Resistance ,Targeted Bacterial Treatment ,Microbiome Disruption ,Hydrogel Drug Delivery, Ocular Medicine ,Inflammatory Eye Disorders

# Introduction

Bacteriophage therapy has garnered attention in recent biomedical research as a promising alternative to traditional antibiotics for combating bacterial infections [(Harsha & Subramanian, 2022)](https://paperpile.com/c/zB1mbm/MM1Oc)[(Deepika et al., 2022)](https://paperpile.com/c/zB1mbm/YBelp)[(Solanki et al., 2022)](https://paperpile.com/c/zB1mbm/z0EGV). Bacteriophages are viruses that specifically target and infect bacteria, providing a highly selective approach to treatment that minimizes disruption to beneficial bacteria and addresses concerns related to antibiotic resistance, a growing global health challenge [(Furfaro et al., 2018)](https://paperpile.com/c/zB1mbm/piO0).Compared to antibiotics that have a wide range of effects and could disturb the natural balance of the microbiome, bacteriophages offer a more targeted method of eradicating pathogens without compromising beneficial microorganisms [(Chidambaram et al., 2022)](https://paperpile.com/c/zB1mbm/Hzp5H).[(Ajay, Sasikala, et al., 2022)](https://paperpile.com/c/zB1mbm/kzGWo). This accuracy is particularly useful for treating infections that are becoming increasingly resistant to conventional medications.[(Dinan & Dinan, 2022)](https://paperpile.com/c/zB1mbm/8Z1d)The increasing prevalence of antibiotic-resistant bacteria has become a major public health concern, leading to a pressing need for alternative therapeutic approaches [(Ajay, Rakshagan, et al., 2022)](https://paperpile.com/c/zB1mbm/Cf7XH). Traditional antibiotics, while effective in many cases, have contributed to the rise of resistant strains through their broad-spectrum activity and overuse [(Ajay, Suma, et al., 2022)](https://paperpile.com/c/zB1mbm/ThfY0) [(Katyal et al., 2021)](https://paperpile.com/c/zB1mbm/HtGkl). Bacteriophage therapy represents a targeted alternative that could potentially address this issue by specifically targeting and eliminating resistant bacterial strains [(Jabin et al., 2021)](https://paperpile.com/c/zB1mbm/DSXl5)[(Balaji Ganesh S & Sugumar, 2021)](https://paperpile.com/c/zB1mbm/NTxAC) [(Govindaraj & Dinesh, 2021)](https://paperpile.com/c/zB1mbm/kuzGZ) . This approach not only preserves the beneficial bacteria in the body but also reduces the selective pressure that drives the development of resistance, making it a promising strategy for combating persistent and multidrug-resistant infections.[(Pang et al., 2019)](https://paperpile.com/c/zB1mbm/egm5)While hydrogels are very useful in ocular medicine because they may stick to the surface of the eye, delivering drugs over time while preserving clarity and reducing discomfort, they have also become highly adaptable biomaterials due to their adjustable characteristics, biocompatibility, and controlled release of therapeutic ingredients [(Aghamirsalim et al., 2022)](https://paperpile.com/c/zB1mbm/YW9p)Hydrogels have the remarkable ability to retain water and conform to the surface of the eye [(Tiwari & Jain, 2023)](https://paperpile.com/c/zB1mbm/lQRRZ)[(Graf et al., 2023)](https://paperpile.com/c/zB1mbm/90s1s). As a result, they can gradually release therapeutic chemicals, which can enhance the efficacy of treatment. Beyond ocular applications, their adaptability makes them valuable tools in drug delivery systems for a variety of medical specialties.[(Torres-Luna et al., 2020)](https://paperpile.com/c/zB1mbm/jfq1)In addition to their use in ocular medicine, hydrogels have shown promise in other therapeutic areas, including wound care and tissue engineering [(Sabarathinam & Madhulaxmi, 2021)](https://paperpile.com/c/zB1mbm/4wy2U)[(Sushanthi et al., 2021)](https://paperpile.com/c/zB1mbm/iuTuT)[(Harsha et al., 2022)](https://paperpile.com/c/zB1mbm/Hlcxj). Their biocompatibility and ability to deliver drugs or growth factors in a controlled manner make them suitable for a wide range of applications [(Neha et al., 2021)](https://paperpile.com/c/zB1mbm/aWBGM)[(Maliael et al., 2021)](https://paperpile.com/c/zB1mbm/asJfy)[(Lakshmi, 2021)](https://paperpile.com/c/zB1mbm/73G2d). For example, in wound care, hydrogels can provide a moist environment that promotes healing while delivering antimicrobial agents to prevent infection. Similarly, in tissue engineering, hydrogels can serve as scaffolds that support cell growth and tissue regeneration. This versatility highlights the potential of hydrogels as key components in advanced therapeutic strategies.[(Zhang & Zhao, 2020)](https://paperpile.com/c/zB1mbm/0U9H)Combining bacteriophages with hydrogels offers a promising synergistic approach to treating inflammatory eye disorders [(Dharman et al., 2021)](https://paperpile.com/c/zB1mbm/8N3mg). By encasing bacteriophages in hydrogel matrices, researchers aim to achieve several objectives, such as targeted delivery directly to the site of infection, a prolonged therapeutic impact by controlled release, and local inflammation caused by the reduction of bacterial pathogens by combining the advantages of both technologies, this integration may result in better treatments for diseases like bacterial conjunctivitis, which is frequently difficult to cure with conventional medicine.[(Chen et al., 2023)](https://paperpile.com/c/zB1mbm/esMQ)Combining hydrogels and bacteriophages is an idea that fits with the larger personalized medicine movement, which aims to customize therapies for each patient. This strategy can be tailored to the specific type of bacterial illness and the individual patient by employing hydrogels to transport bacteriophages to the infection site. By improving treatment outcomes and lowering the possibility of side effects, this individualized strategy could advance the field of ocular therapies.[(Yu et al., 2024)](https://paperpile.com/c/zB1mbm/EyFF)However, before bacteriophage hydrogels are applied in clinical settings, a few problems need to be fixed. These include navigating the approval processes for ocular therapies, proving clinical trial efficacy in comparison to conventional treatments, and ensuring the stability and safety of bacteriophages in hydrogel formulations[(Nagai & Otake, 2022)](https://paperpile.com/c/zB1mbm/Gz2d)The regulatory landscape for new medical technologies can be complex, and securing approval for novel therapies often involves extensive testing and documentation. Researchers must demonstrate that bacteriophage hydrogels are both safe and effective through rigorous clinical trials, addressing any concerns related to their stability and performance.[(Hu et al., 2023)](https://paperpile.com/c/zB1mbm/HjEf)Additionally, ensuring the long-term safety and efficacy of bacteriophage hydrogels is crucial. This involves monitoring potential side effects, such as immune responses to the bacteriophages or unintended interactions with the eye's natural microbiome. Addressing these concerns through well-designed clinical studies will be essential for gaining regulatory approval and establishing the therapeutic value of this innovative approach.[(Huiting et al., 2023)](https://paperpile.com/c/zB1mbm/mR9Z)But because bacteriophage hydrogels provide ophthalmologists with a more targeted, durable, and potentially even more effective treatment option, they have the potential to fundamentally alter the way inflammatory eye illnesses are treated. Continued research and development could lead to new strategies that improve patient outcomes while addressing antibiotic resistance and lowering treatment-related risks[(Bai et al., 2024)](https://paperpile.com/c/zB1mbm/tEh4)To fully reap the benefits of the technology, it will be imperative to explore new applications and make improvements as the industry expands. This novel approach could completely change the way eye infections are treated and serve as a template for analogous approaches in other medical specialties, opening up access to more accurate and potent treatment options.[(Rosenquist et al., 2023)](https://paperpile.com/c/zB1mbm/qtvL)

# Materials and methods

## Extraction of Bacteriophage Enzyme

The enzyme was extracted using the cold acetone method. Initially, the bacteriophage was cultured in a medium containing the host bacterium. After an incubation period of 2-3 days, the phage lysate was prepared through ultracentrifugation. The phage enzyme was then precipitated using cold acetone and subjected to centrifugation at 7000 xg for 10 minutes at 4°C. The resulting pellet was collected and suspended in PBS buffer for further use.

## Synthesis of Hydrogel

The hydrogel was prepared using sodium alginate. To begin, a 2% solution of sodium alginate was dissolved in distilled water and heated to 70°C using a magnetic stirrer until fully dissolved. Once the solution cooled, 500 µL of the phage enzyme was added. The hydrogel was then cross-linked by adding 0.1M CaCl₂ and allowed to mix for 10-15 minutes. After mixing, the solution was poured into molds and kept at -20°C for 24 hours. The prepared hydrogel was subsequently used for further studies.

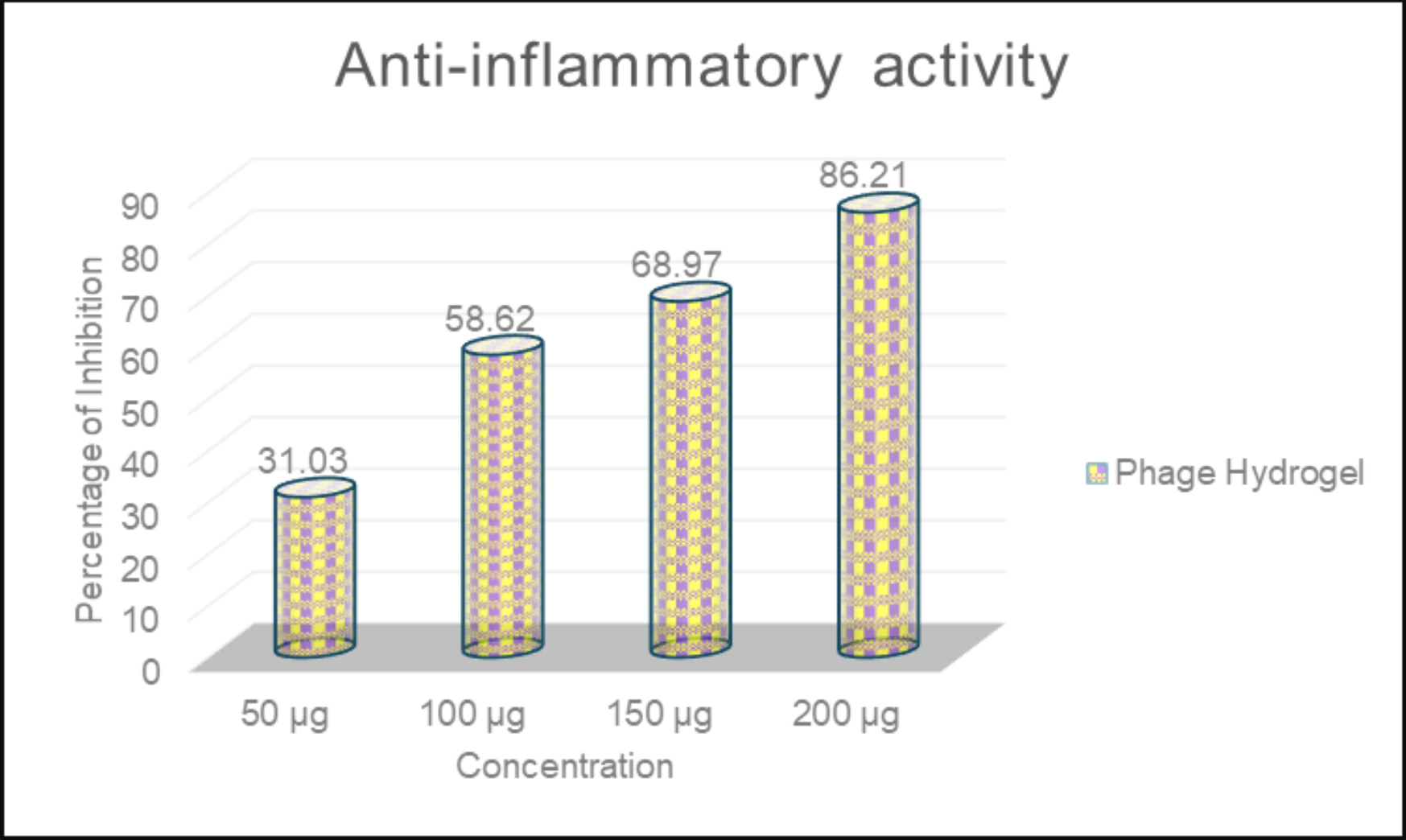
## Protein Denaturation Assay

The anti-inflammatory activity of the hydrogel was assessed using a protein denaturation assay. For this assay, isophosphate buffer was prepared, and 0.3 µL of bovine serum albumin (BSA) was added along with the hydrogel sample at varying concentrations. The mixture was cooled for 1-2 minutes and then incubated in a water bath for 20 minutes. The absorbance was measured at 660 nm, and the inhibition percentage was calculated using the following formula:

Anti inflammatory activity percentage = control-sample divided by control multiplied by 100

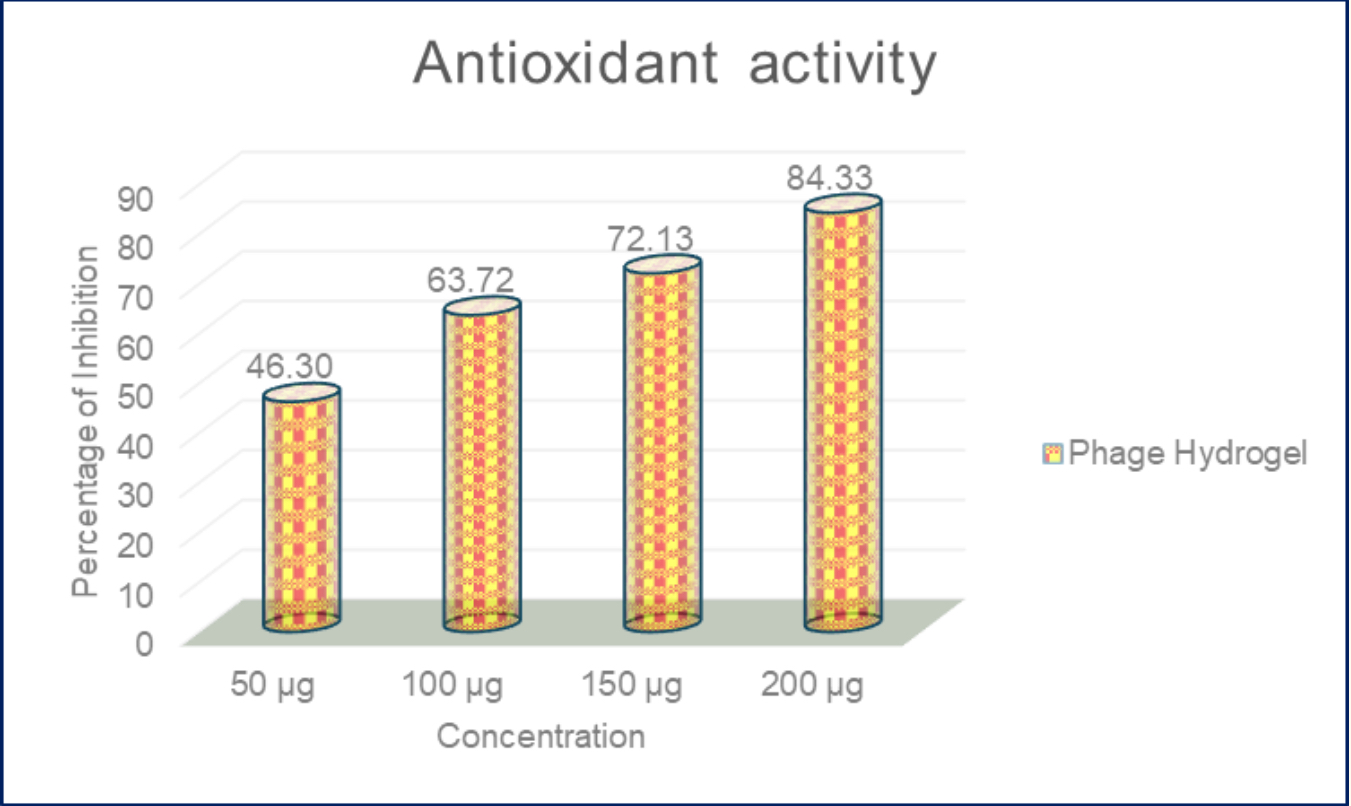
This formula was used to determine the percentage inhibition, reflecting the anti-inflammatory potential of the hydrogel.

# Results



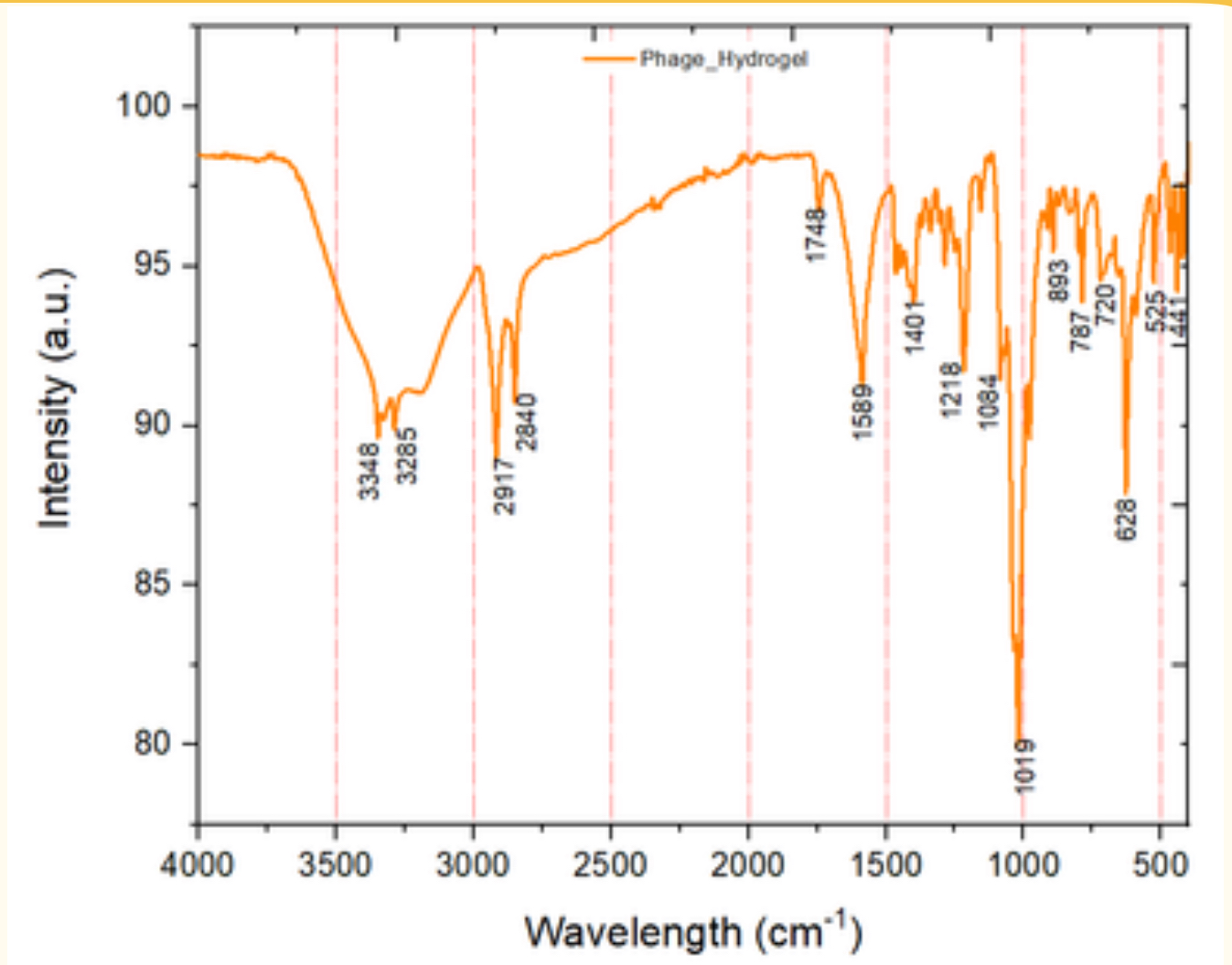
**Figure 1: anti inflammatory activity**

The bar graph illustrates the anti-inflammatory activity of a phage hydrogel across four different concentrations: 50 µg, 100 µg, 150 µg, and 200 µg. The y-axis represents the percentage of inhibition, demonstrating how effectively the hydrogel reduces inflammation. At the lowest concentration of 50 µg, the hydrogel exhibits 31.03% inhibition. As the concentration increases to 100 µg, 150 µg, and 200 µg, the percentage of inhibition also rises to 58.62%, 68.97%, and 86.21%, respectively. These results indicate a clear dose-dependent relationship, where higher concentrations of the phage hydrogel correlate with increased anti-inflammatory activity.



**Figure 2: Anti oxidant activity**

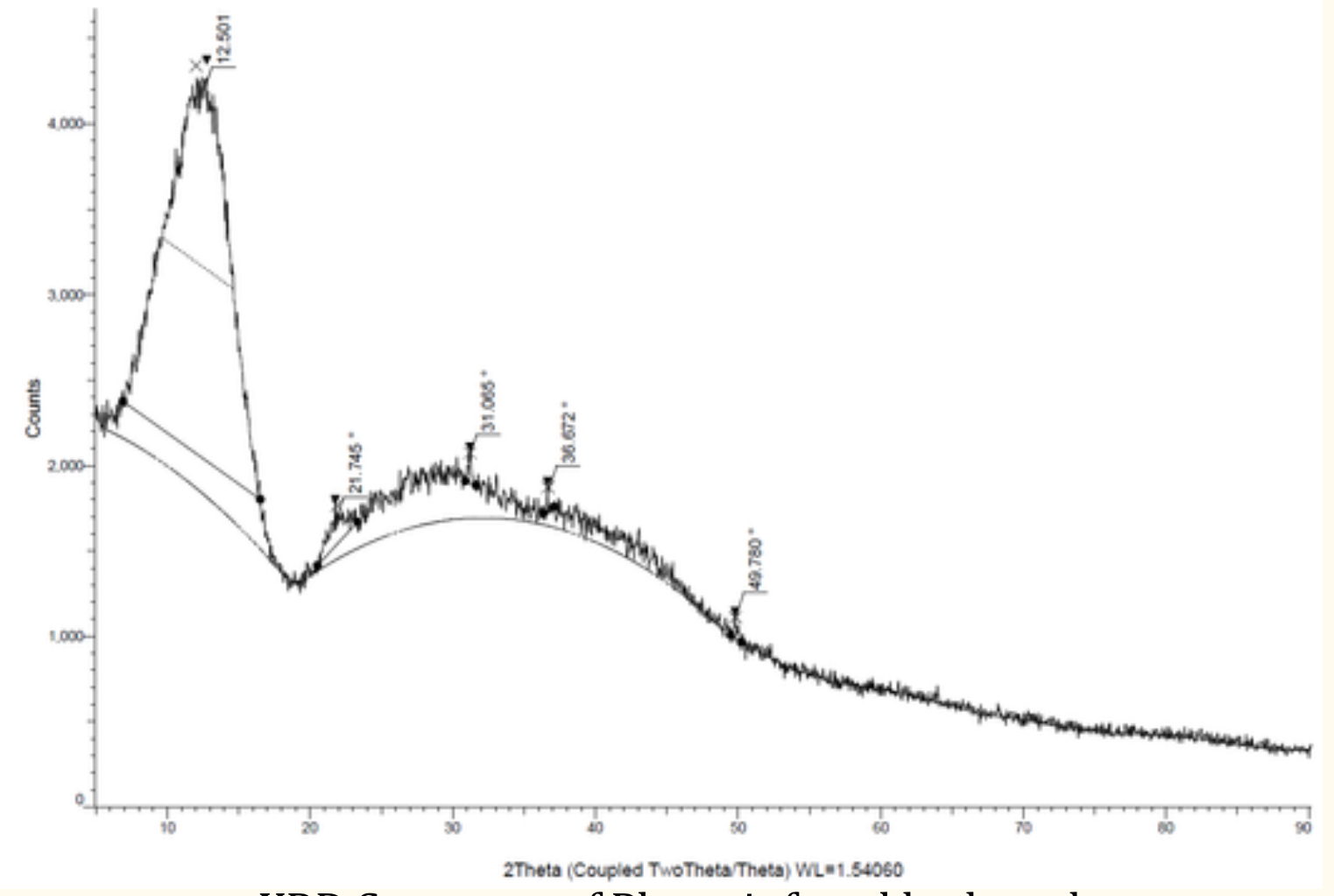
The bar graph illustrates the antioxidant activity of a phage hydrogel across various concentrations: 50 µg, 100 µg, 150 µg, and 200 µg. At 50 µg, the hydrogel shows an inhibition of 46.30%. This inhibition increases to 63.72% at 100 µg, 72.13% at 150 µg, and peaks at 84.33% at 200 µg. These results highlight a dose-dependent relationship, where higher concentrations of the phage hydrogel correspond to increased antioxidant activity, demonstrating that the hydrogel's efficacy improves with greater concentration.



**figure 3: intensity vs wavelength**

## FTIR Spectrum of Phage-infused hydrogel

The IR spectrum of the phage hydrogel exhibits several characteristic peaks indicative of various functional groups. The broad peaks around 3348 cm⁻¹ and 3285 cm⁻¹ are likely due to O-H or N-H stretching vibrations, which suggest the presence of hydroxyl or amine groups within the hydrogel matrix. The peaks at 2917 cm⁻¹ and 2840 cm⁻¹ correspond to C-H stretching vibrations, indicating aliphatic hydrocarbon chains. The peak at 1748 cm⁻¹ is typically associated with C=O stretching vibrations, indicative of ester or carbonyl groups. The peaks at 1569 cm⁻¹ and 1401 cm⁻¹ can be attributed to N-H bending and C-N stretching, respectively, suggesting the presence of amide groups. Further, the peaks at 1218 cm⁻¹ and 1084 cm⁻¹ correspond to C-O stretching vibrations, which may indicate the presence of ether or ester groups. Lastly, the peaks below 1000 cm⁻¹, such as at 1019 cm⁻¹, 893 cm⁻¹, and 787 cm⁻¹, likely represent various bending vibrations and out-of-plane deformations characteristic of the hydrogel's polymeric backbone. This spectrum highlights the complex chemical structure of the phage hydrogel, revealing the presence of multiple functional groups that contribute to its unique properties.



**Figure 4:** FTIR Spectrum

## XRD Spectrum of Phage infused hydrogel

* The hydrogel exhibited broad peaks at approximately 20° and 35° 2θ, characteristic of an amorphous structure.
* No significant change in the overall amorphous nature of the hydrogel was observed upon incorporation of bacteriophages.

# Discussion

The potential of bacteriophage hydrogels in treating inflammatory eye conditions presents a novel and promising approach. Bacteriophages, which are viruses that specifically target and destroy pathogenic bacteria, offer a highly targeted method for managing bacterial infections. When combined with hydrogels—water-absorbing polymeric materials that can provide controlled and sustained release of their contents—this technology could address some of the limitations of traditional treatments.[(Liu et al., 2021)](https://paperpile.com/c/zB1mbm/YeNM)One significant advantage of using bacteriophage hydrogels is their ability to deliver bacteriophages directly to the site of infection in the eye, which could improve the precision of the therapy(Rafi et al., 2024). This targeted action minimizes collateral damage to beneficial bacteria and reduces the risk of developing antibiotic resistance. Furthermore, the controlled release of bacteriophages from the hydrogel could provide prolonged therapeutic effects, reducing the need for frequent dosing and potentially improving patient compliance.[(Huemer et al., 2020)](https://paperpile.com/c/zB1mbm/UK4J)However, a few problems must be fixed before bacteriophage hydrogels are widely employed as a therapeutic substitute (Tuluwengjiang et al., 2024). The stability of bacteriophages within the hydrogel must be maintained, as their ability to endure over time is critical to their efficacy. Furthermore, it is crucial to investigate the potential for an immune response against the bacteriophages or hydrogel components in order to avoid unfavorable outcomes. Bacterial biofilms, which can protect bacteria from bacteriophages and antibiotics, are another problem. The hydrogel composition needs to be able to break these biofilms in order for it to work.[(Chameettachal et al., 2023)](https://paperpile.com/c/zB1mbm/H20o)The main goal of future research should be to improve hydrogel compositions in order to improve bacteriophage stability and release kinetics. Additionally, in order to assess the safety and effectiveness of this therapeutic method for treating eye infections, preclinical and clinical trials are required. Bacteriophage hydrogels may work in concert with other antibacterial or anti-inflammatory drugs to overcome present treatment constraints. Overall, even though bacteriophage hydrogels exhibit great promise, more research is necessary to completely grasp their therapeutic potential for inflammatory ocular conditions.[(Bacchi et al., 2012)](https://paperpile.com/c/zB1mbm/U4Wz)

# Conclusion

The unique combination of bacteriophages and hydrogels offers a possible cure for inflammatory eye diseases. A biocompatible medium for controlled and extended drug release is offered by hydrogels, while bacteriophages specifically target bacterial diseases. This treatment strategy may reduce inflammation and oxidative stress caused by eye infections. Studies demonstrate a dose-dependent connection where higher concentrations of phage hydrogel lead to more beneficial benefits. FTIR and XRD tests verify that the bacteriophages were successfully integrated into the hydrogel while preserving its structure and functional groups.Despite the promise, challenges such preserving bacteriophage stability, controlling immune responses, and combating bacterial biofilms must be overcome prior to clinical application. Future research should primarily concentrate on optimizing hydrogel formulation, with large-scale preclinical and clinical trials necessary to verify safety and efficacy. Bacteriophage hydrogels have the potential to revolutionize the management of inflammatory ocular disorders and provide a model for analogous strategies in other medical fields, ultimately addressing the growing problem of antibiotic resistance.

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