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Collagen/Gelatin/Chitosan hybrid hydrogel impregnated with Copper Sulphate pentahydrate for slow drug release.

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ABSTRACT

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INTRODUCTION

Hydrogels are three-dimensional polymeric networks capable of retaining large amounts of water while maintaining their structural integrity. Due to their high water content, excellent biocompatibility, tunable mechanical properties, and ability to provide controlled and sustained drug release, hydrogels have emerged as one of the most promising biomaterials in tissue engineering, regenerative medicine, wound healing, and pharmaceutical drug delivery systems. Their porous architecture allows the encapsulation of therapeutic agents and facilitates their gradual release at the target site, thereby improving drug bioavailability, minimizing systemic toxicity, and reducing the frequency of drug administration. These characteristics make hydrogel-based delivery systems particularly suitable for localized therapies, where prolonged drug retention and controlled release are essential for improved clinical outcomes (1,2).

Among the natural polymers used for hydrogel fabrication, collagen and gelatin have gained significant attention because of their excellent biological properties. Collagen is the most abundant structural protein in the extracellular matrix of connective tissues, providing mechanical strength and structural support while promoting cellular adhesion, proliferation, and tissue regeneration. Gelatin, a denatured product obtained through the partial hydrolysis of collagen, retains many of collagen's biological advantages while exhibiting greater solubility, flexibility, and ease of processing. The combination of collagen and gelatin results in a hybrid hydrogel that demonstrates enhanced mechanical stability, improved biodegradability, superior biocompatibility, and increased swelling capacity compared to hydrogels prepared from either polymer alone. Such hybrid systems closely resemble the native extracellular matrix, making them excellent candidates for biomedical applications including wound dressings, tissue scaffolds, and drug delivery platforms (3,4).

Chitosan, another naturally occurring polysaccharide derived from the deacetylation of chitin, further enhances the biological performance of hydrogel systems. Owing to its cationic nature, biodegradability, non-toxicity, antimicrobial activity, and mucoadhesive properties, chitosan contributes to improved mechanical strength, controlled drug diffusion, and enhanced wound healing. The incorporation of chitosan into collagen–gelatin hydrogels creates an interconnected polymeric network capable of maintaining structural integrity while supporting sustained drug release and cellular compatibility (5,6).

Copper sulfate pentahydrate has attracted considerable interest as a bioactive additive because of its antimicrobial, anti-inflammatory, and wound-healing properties. Copper ions play an essential role in several physiological processes, including collagen synthesis, angiogenesis, extracellular matrix remodeling, and enzymatic activity involved in tissue repair. Furthermore, copper exhibits broad-spectrum antimicrobial activity against various pathogenic microorganisms by disrupting microbial cell membranes, generating oxidative stress, and interfering with essential cellular enzymes. Incorporating copper sulfate pentahydrate into a collagen–gelatin–chitosan hydrogel therefore provides dual functionality by combining structural support with therapeutic activity. Such multifunctional hydrogels can simultaneously prevent microbial infection, promote tissue regeneration, and provide sustained release of encapsulated drugs, making them highly suitable for wound management and advanced drug delivery applications (4,7,8)..

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The present study focuses on the development of a collagen–gelatin–chitosan hybrid hydrogel impregnated with copper sulfate pentahydrate as a novel controlled drug delivery system. By integrating the biocompatibility of natural polymers with the therapeutic potential of copper ions, the formulated hydrogel aims to achieve prolonged drug release, enhanced swelling behavior, and improved biomedical performance for future applications in wound healing and regenerative medicine.

MATERIALS AND METHODS

Preparation of Gelatin Solution

A 1% gelatin solution was prepared by dissolving 0.1 g of gelatin in 10 mL of distilled water. The mixture was allowed to stand at room temperature for 30 minutes to ensure complete hydration. It was then stirred continuously using a magnetic stirrer at 40°C for 1 hour until a clear and homogeneous solution was obtained.

Preparation of Chitosan Solution

A 2% chitosan solution was prepared by adding 0.5 mL of acetic acid to 100 mL of distilled water. Subsequently, 2 g of chitosan powder was added gradually to the solution with continuous stirring at 40°C for 1 hour. The mixture was then sonicated at 40°C for 1–3 hours to obtain a uniform and completely dissolved chitosan solution.

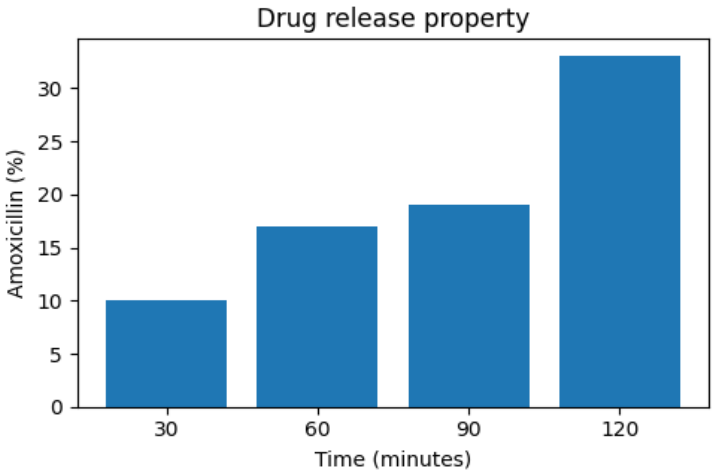
Preparation of Collagen–Gelatin–Chitosan Hybrid Hydrogel

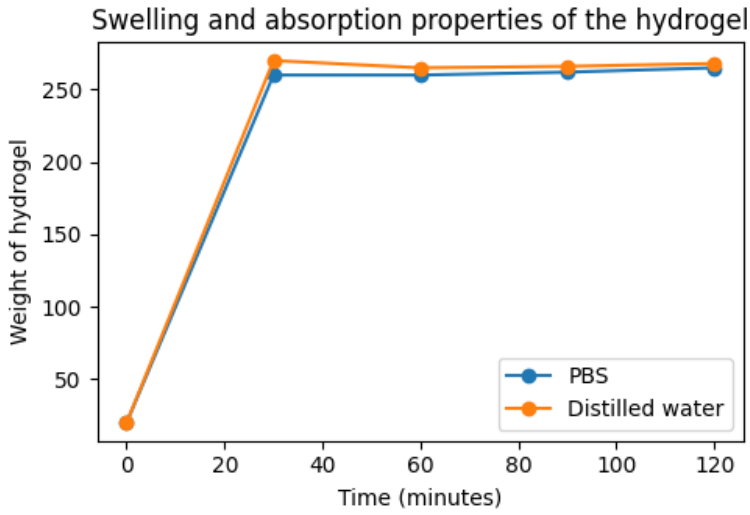
The hybrid hydrogel was prepared by mixing 10 mL of the prepared 1% gelatin solution with 10 mL of 1% copper sulfate pentahydrate solution in a beaker under continuous stirring at 40°C. Following this, 20 mL of the 2% chitosan solution was added slowly and mixed thoroughly to obtain a homogeneous blend. Finally, 2.5% glutaraldehyde solution was added dropwise as a cross-linking agent while the mixture was continuously stirred using a magnetic stirrer until gel formation was observed. The resulting collagen–gelatin–chitosan hybrid hydrogel impregnated with copper sulfate pentahydrate was then used for further evaluation of its swelling, absorption, and drug release properties.

RESULTS

The prepared collagen–gelatin–chitosan hybrid hydrogel impregnated with copper sulfate pentahydrate demonstrated sustained drug release and excellent swelling behavior. Drug release analysis was carried out using amoxicillin as the model drug. The hydrogel exhibited a gradual increase in drug release over time, with approximately 10% release at 30 minutes, 17% at 60 minutes, and 19% at 90 minutes. At 120 minutes, approximately 35% of the drug still remained within the hydrogel matrix, indicating a slow and controlled release pattern. This sustained release profile suggests that the hydrogel is capable of prolonging drug availability, making it a suitable carrier for localized drug delivery applications where extended therapeutic action is required.

The swelling and absorption study showed that the hydrogel rapidly absorbed fluid during the initial 30 minutes, after which the swelling reached a plateau and remained relatively stable throughout the observation period. The hydrogel exhibited slightly higher absorption in distilled water than in phosphate-buffered saline (PBS), indicating that ionic strength influences its swelling behavior. The ability of the hydrogel to retain a large amount of water while maintaining its structural integrity demonstrates its excellent hydrophilic nature. Such swelling characteristics are beneficial for wound dressing and controlled drug delivery applications, as they facilitate the diffusion of therapeutic agents while maintaining a moist environment conducive to tissue healing.





DISCUSSION

The present study successfully developed a collagen–gelatin–chitosan hybrid hydrogel impregnated with copper sulfate pentahydrate for controlled drug delivery. The hydrogel demonstrated desirable swelling behavior together with sustained drug release, indicating its potential as a multifunctional biomaterial for biomedical applications. Natural polymer-based hydrogels have gained considerable attention because of their excellent biocompatibility, biodegradability, and ability to mimic the extracellular matrix, making them suitable for wound healing, tissue engineering, and localized drug delivery systems (2,3).

Chitosan plays a crucial role in the performance of the developed hydrogel. As a naturally occurring marine-derived cationic polysaccharide, chitosan has been extensively investigated for biomedical applications because of its non-toxic nature, biodegradability, bioadhesive properties, and inherent antimicrobial activity. It has received regulatory approval for several biomedical applications, including wound dressings and cartilage repair formulations. The positive surface charge of chitosan enables interaction with negatively charged cell membranes and biological tissues, thereby improving cell adhesion, accelerating wound healing, and enhancing drug retention at the target site (5,6,9). Furthermore, its excellent film-forming ability and compatibility with other natural polymers contribute to the formation of stable hydrogel matrices suitable for sustained drug release.

The combination of collagen and gelatin further enhanced the biological performance of the hydrogel. Collagen provides structural integrity and serves as a natural scaffold for cell attachment and tissue regeneration, whereas gelatin improves flexibility, swelling capacity, and ease of processing. Together, these polymers form an interconnected three-dimensional network capable of retaining large amounts of water while maintaining sufficient mechanical strength. Such characteristics closely resemble the extracellular matrix and facilitate nutrient diffusion, cell proliferation, and prolonged release of therapeutic agents (3,4). The swelling behavior observed in the present study supports these findings, as the hydrogel exhibited rapid water uptake followed by structural stability throughout the experimental period.

The sustained drug release observed in this study can be attributed to the cross-linked polymeric network formed by gelatin, collagen, chitosan, and glutaraldehyde. The gradual diffusion of amoxicillin from the hydrogel indicates that the matrix effectively regulates drug release rather than allowing rapid burst release. Controlled drug delivery systems are advantageous because they maintain therapeutic drug concentrations for extended periods, reduce dosing frequency, minimize systemic side effects, and improve patient compliance. Similar sustained release behavior has been reported in chitosan-based hydrogels developed for nano-insulin delivery, where the hydrogel components demonstrated excellent compatibility and formed a porous honeycomb-like structure with favorable mechanical and thermal properties. These characteristics contribute to efficient drug encapsulation and prolonged release kinetics (4,10).

Copper sulfate pentahydrate was incorporated into the hydrogel to provide additional therapeutic functionality. Copper ions are well known for their broad-spectrum antimicrobial activity against Gram-positive and Gram-negative bacteria, fungi, and certain viruses. Their antimicrobial mechanism involves disruption of microbial cell membranes, generation of reactive oxygen species, interference with essential enzymes, and damage to nucleic acids, ultimately leading to bacteriostatic or bactericidal effects depending on copper concentration (7,8,11). Besides antimicrobial activity, copper also plays an important physiological role in collagen synthesis, angiogenesis, extracellular matrix remodeling, and tissue regeneration,

making it particularly beneficial for wound healing applications.

The higher swelling observed in distilled water compared with phosphate-buffered saline is consistent with the ionic sensitivity of chitosan-based hydrogels. Electrolytes present in PBS reduce osmotic pressure within the hydrogel network, resulting in slightly lower water uptake compared with distilled water. Nevertheless, the hydrogel maintained its structural integrity in both media, indicating sufficient cross-linking and stability for biomedical use. This balance between swelling and structural stability is important because excessive swelling may weaken the hydrogel, whereas insufficient swelling may limit drug diffusion and tissue hydration (1,2).

Overall, the findings of the present study demonstrate that the collagen–gelatin–chitosan hybrid hydrogel impregnated with copper sulfate pentahydrate possesses favorable physicochemical and biological characteristics, including sustained drug release, high swelling capacity, structural stability, and potential antimicrobial activity. The synergistic combination of natural polymers with copper ions provides a promising platform for controlled drug delivery and wound management, supporting its potential application as an advanced biomaterial in regenerative medicine.

CONCLUSION

The collagen–gelatin–chitosan hybrid hydrogel impregnated with copper sulfate pentahydrate showed successful gel formation, sustained drug release, and good swelling properties. Its biocompatible nature and controlled drug release capability make it a promising material for drug delivery and wound healing applications. Overall, the developed hydrogel demonstrated good potential as an effective and reliable biomedical drug delivery system..

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