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Design, Optimization and Evaluation of Copper Nanoparticle-loaded Hydrogel for Drug Delivery and Wound Healing Applications

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Abstract

This study presents the design, optimization, and evaluation of a novel copper nanoparticle-loaded hydrogel aimed at enhancing drug delivery and wound healing applications. Copper nanoparticles (CuNPs) are recognized for their potent antimicrobial, anti-inflammatory, and angiogenic properties, making them ideal candidates for accelerating wound healing processes and improving drug delivery efficiency. The hydrogel matrix, composed of biocompatible and biodegradable polymers, acts as a controlled release system, ensuring sustained delivery of copper nanoparticles and therapeutic agents to the wound site.

Keywords: Nanoparticles, Hydrogel, Antimicrobial

Introduction

A major worldwide problem in the treatment of illnesses caused by microorganisms is the limited antimicrobial efficiency of traditional antibiotics, the rise of antibiotic resistance, and poor patient compliance. The treatment of these disorders has been very difficult because of these variables. As an example, antibiotic-resistant bacteria causing chronic skin wound infections have recently emerged as a major global public health concern, leading to high mortality rates and a heavy financial strain on healthcare systems. In addition, healthcare-associated infections (HAIs) slowed the healing process, which posed big problems for clinicians, even though biomaterials and medical devices were developing quickly. The World Health Organization (WHO) reported in 2019 that drug-resistant germs cause at least 700,000 deaths worldwide annually. In the absence of intervention, the projected annual death toll is expected to reach 10 million by 2050. Inappropriate or overuse of conventional antibiotics and a shrinking pipeline for the creation of new antibiotics that work against resistant bacteria are the main causes of the rise of antibiotic resistance in many different types of infections. This highlights the critical need for research into new methods of medication distribution for antimicrobials.

Nanoparticle–Hydrogel System

A novel family of biomaterials called nanoparticle-hydrogel systems combines the benefits of hydrogels with nanoparticles to make up for the drawbacks of either component used alone. These systems have many potential uses in biomedical fields, including drug delivery and tissue engineering. 36 Injectability, release kinetics, chemistry, manufacturing methods, and categorization of nanoparticle-hydrogel complexes for medication delivery are all covered in this section.

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Material and Methods

Materials

In the previous essay, we covered the topic of creating copper nanoparticles. A central drug house in New Delhi, India, was also consulted for the acquisition of HPMC, PVP K30, and polyethylene glycol 400 (PEG-400). The analytical value was used to grade all of the other substances.

Preparation of Hydrogel

To make the hydrogel, dissolve PVP K30 and HPMC in distilled water. Stir constantly for one hour. Refrigerate the hydrogel overnight in 25 milliliters of distilled water. Blending followed with the addition of PEG 400. The next step was to add fifty milliliters of distilled water to the gel mixture after dispersing the copper nanoparticles in the rest of the water.

Visual Evaluation of Nanogel

A reddish brown tint, uniform distribution, and a silky smooth texture characterized the nanogel formulation. These were the distinguishing features of its physical form.

Factor Screening Studies

Using a five-factor ten-run fractional factorial design, factor screening tests were conducted to determine which variables significantly affected the nanogels' properties. The design matrix that details the examined components is shown in Table 2.1. Factor screening research relies on the "factor sparsity" hypothesis. This approach entails selecting certain variables from a vast set of possible elements in order to ascertain the preponderant experimental variation in the medicinal product. The "factors" that caused the variables that mattered were called the active or influencing variables, while the ones that didn't have less of an impact were called the noise variables. The active or influencing variable goes by many names than just that. In order to determine which factors significantly affect the response variables, factor screening experiments were conducted before the formulation creation process began. The components used to make nanogel and the quantitative effect it had on critical quality attributes (CQA). According to Taguchi's design, the data in Table 1 indicate the individual high and low levels of variables in the formulation and design matrix. In analyzing essential formulation factors, the most significant quality features were determined to be the MRT, viscosity, wound healing days, and swelling index. Nanogel was created by dispersing nanoparticles throughout the gel. After putting the polymer in phosphate buffer saline and chilling it for a whole night, thirteen distinct formulations were created. Following that, what really set these formulations apart was their absence of key quality attributes. The coefficient of each component connected to the response variable was determined by using the interaction effect between the elements after getting the polynomial equation. This was done with the intention of ascertaining the nature of the connection that exists between the variables. The half-normal plot and Pareto charts were used to quantitatively examine the influence of various non-dependent factors on the formulation.

Table 4.1: Hydrogel screening design matrix with five factors and two levels.

HPMC%	PVP K30%	PEG (%)	CNPs (µg/ml)	CNPs Size (µm)
1	1	0.2	50	2.5
3	5	0.1	2.5	0.05
150	4	6	0.2	1
2.5	150	0.05	50	8
5	0.1	0.2	150	9
1	0.1	0.2	150	10
5	0.1	0.05	50	

Classification and chemistry

Previous discussion established that the cross-linking of polymers results in the formation of three-dimensional hydrogel networks. The biomedical field has a variety of potential uses for these networks, which can expand in liquids like water, including medication delivery, tissue engineering, diagnosis, and more. Hydrogels can be divided into several categories based on their composition, manufacturing process, network structure, characteristics, stimuli-responsiveness, and applications. For example, hydrogels may be categorized into several groups according to their unique properties and areas of use. Different types of hydrogels may be classified according to their polymer source: (i) natural, synthetic, or hybrid hydrogels; (ii) homo polymeric, co-polymeric, or interpenetrating networks (IPNs) hydrogels; (iii) chemical (covalent contact) or

physical (ionic, hydrogen bonding, hydro) interactions pho Nanoparticles are a huge category of materials that deal with particles between tens of nanometers to one thousand nanometers in size. Furthermore, nanoparticles are useful in many different areas of pharmacological and biological research due to their diverse features. Several distinct groups may be established for nanoparticles according to their chemistry, size, characteristics, and applications. positions 40 and 41 However, most nanoparticles fall into one of two categories: inorganic (made of metals, oxides, ceramics, etc.) or organic (containing polymers, lipids, DNA, or proteins). The authors have employed a diverse vocabulary when describing nanoparticle hydrogel systems. What sets these systems apart is the hydrogel's ability to incorporate nanoparticles. Most often used terminology are nanocomposite/composite hydrogels, hybrid hydrogels, and nanoparticle-hydrogel superstructures. The hydrogel systems that include nano particles into their three-dimensional network structure are the main entities represented by all of these other terms, regardless of whether they are crosslinked or not. For that reason, while talking about nanoparticle hydrogel systems, the terms "hybrid/ hybrid systems" and "hybridhydrogel" are not interchangeable. Hydrogels that include both natural and synthetic polymers are known as hybridhydrogels. Furthermore, these hydrogel systems that combine nanocomposites are called such. Because they include two different kinds of materials—hydrogels and nanoparticles—each with its own unique properties, this is the case. These materials are mixed in a manner that allows them to keep their own identities while also displaying unique properties that help to compensate for the materials' shortcomings when used alone. On the basis of the polymer source (natural or synthetic), the chemistry of synthesis (physical or chemical), the method of preparation, the responsiveness of the system to stimuli (pH, ionic strength, enzymes, thermal, etc.), the type of nanoparticle incorporated (metal, polymeric, liposome, micelle, and metal oxide nanoparticles incorporate), and the biomedical or pharmaceutical application, the nanoparticles-hydrogel systems can also be divided into different classes.

Preparation methods

It is difficult to design a homogeneous nanoparticle-hydrogel system because it requires selecting the appropriate approach based on the characteristics of the nanoparticles and hydrogels as well as the system's intended function. Thorough deliberation is required for the current undertaking. Using five major methodologies, the literature has discussed the creation of nanoparticle-hydrogel systems. The following steps are involved in making hydrogels: (i) adding nanoparticles to a suspension; (ii) trapping the nanoparticles in pre-formed hydrogel networks; (iii) making the nanoparticle in situ inside the pre-formed networks; (iv) making hydrogels using nanoparticles for crosslinking; and (v) making hydrogel coated nanoparticles. The review articles that came before this one provide a thorough explanation of these ideas and processes for making the hydrogel. In contrast, Table 1.1 gives a brief summary of the several ways that nanoparticle-hydrogel systems may be made. There are samples of each approach and their respective pros and cons shown in the table.

Table 1.1 a rundown of the pros and cons of several approaches of hydrogel-nanoparticle system preparation

S. No.	Category	Details
1	**Hydrogel Fabrication Techniques**	- Using nanoparticle suspension - Trapping nanoparticles in pre-existing hydrogel networks - Nanoparticle synthesis within hydrogel networks - Nanoparticle crosslinking for hydrogel fabrication - Covering nanoparticles with hydrogel
2	**Preparation Methods**	-Using a mixture of monomers, crosslinkers, and initiators to dissolve nanoparticles - The introduction of nanoparticles via physical means, such as repeated centrifugation, heating, or re-dispersion - How premade hydrogels

		react in nanoparticle solutions: swelling and deswelling
3	**In Situ Nanoparticle Production**	- Introduction of reducing agents or light to hydrogel networks containing metal ions - Using nanoparticles as crosslinkers
4	**Benefits**	- Simple and widely used methods - Reduced nanoparticle aggregation - Improved mechanical stability and flexibility due to multivalency - Broad range of drug loading with protection - Easy scaling for production
5	**Negative Aspects**	- Nanoparticle aggregation - Chemical interactions with hydrogel and gelators - Leakage due to weak crosslinking - Toxic crosslinkers requiring extensive purification - Time-consuming preparation and purification processes
6	**Examples**	- Acrylamide-based hydrogels with repeated swelling/deswelling in different media (gold nanoparticles) - Chitosan-based hydrogel trapping silver nanoparticles - Zinc oxide nanoparticles in carboxymethyl chitosan hydrogels - Silica nanoparticles in hydrogels using double emulsion technique
7	**Constraints**	- Co-dependency of nanoparticles and hydrogels limiting stability - Inefficient nanoparticle trapping - Hydrogel leakage from poor physical contact - Use of organic solvents in deswelling
8	**Materials Used**	- Metal oxide nanoparticles - Silver and gold nanoparticles - Zinc oxide nanoparticles - Silica nanoparticles

Release mechanism

Integrating nanoparticles into hydrogel systems has two primary objectives: one is to improve the stability of the system and the other is to make it easier to control the release of pharmaceuticals or nanoparticles. There are mainly three ways in which hydrogel networks might release their bound medicines or other substances. There are three kinds of these processes: the entrapped molecule's diffusion, the swelling of the hydrogel network, and chemically regulated mechanisms, the most common of which include the erosion or destruction of the hydrogel network. The hydrogel release process is heavily influenced by the loading method, component polymer composition, network structure, and physiochemical properties. Hydrogels may therefore have controlled release by altering these characteristics. Estimating the hydrogel release kinetics has been the subject of many mathematical models published in the literature. When compared to other approaches, hydrogels function better in transporting water-soluble compounds because the network is hydrophilic. Another disadvantage of hydrogel delivery methods is the possibility of burst payload release due to the rapid diffusion from some hydrogel networks. But there are two main ways that therapeutic drug release from nanoparticles may be controlled. Agents attached by covalent bonds may be subjected to linker cleavage, whereas agents loaded via non-covalent interaction or physical entrapment can be subjected to carrier control. Prior reviews have provided detailed descriptions of both of these methods. 1.2.4 Injectability

There are many advantages to injectable hydrogels in clinical settings, such as their ability to be less invasive, to not require open surgery for implantation, to have fewer post-implantation complications, to have less pain, to have a short

recovery time, to be stimuli-responsive, to be inexpensive, and to improve patient compliance. To categorize these hydrogels according to their injectability mechanism, two main groups may be considered: in situ gels and shear-thinning injectable gels. The first kind of gelling, called in situ gelling, involves injecting a solution of the hydrogel gel precursor that has a low viscosity. After the injection (implementation) step, the gel transforms into a gel via in situ crosslinking, which can be physical or chemical. The second kind of injectable hydrogels is called shear-thinning hydrogels, and they are characterized by an initial gel formation outside of the body. The result is that the gel's viscosity decreases when shear force is applied. After being injected into the target area, the gel undergoes a second gel transformation when the shear force is removed. Gel self-healing is another name for this procedure. Nevertheless, injectable hydrogels alone cannot achieve the necessary mechanical and other physiochemical characteristics for biomedical applications, despite their many advantages.

The development of a hydrogel loaded with copper nanoparticles:

To develop and manufacture hydrogels containing copper nanoparticles for use in drug delivery and wound healing.

Optimizing the Production of Hydrogels:

To investigate and improve the parameters that influence the synthesis of copper nanoparticles and their incorporation into the hydrogel matrix, ensuring their biocompatibility and stability.

Examining the Loading and Release of Drugs:

To evaluate the hydrogel's controlled and sustained drug release behavior and the hydrogel's drug-loading efficiency.

Examining the Potential for Wound Healing:

To investigate the wound-healing-accelerating tissue regeneration and antimicrobial, anti-inflammatory, and therapeutic properties of copper nanoparticle-loaded hydrogels.

Analysis of Performance and Characterization:

- To evaluate the hydrogel's performance for biomedical applications in vitro and in vivo and its physicochemical, mechanical, and biological characteristics.

Drug Delivery

The most effective drug delivery systems are biocompatible, inert, mechanically robust, and have a large capacity for drug loading. Without triggering an immunogenic response, the medication's concentration should remain constant over time and minimize side effects and discomfort. It ought to maintain the drug's solubility, stability, and half-life. Additionally, it must be simple to make, use, and sterilize. It must specifically target and be stable on the host. Nanoparticles are used in drug delivery because their high surface area to volume ratio makes it easier to encapsulate drugs. They are also able to control medication release, which increases the therapeutic index and reduces toxicity and side effects. Dendrimers, micelles, and liposomes are examples of nanostructures that can be metallic, organic, inorganic, or polymeric (Figure 2.4).

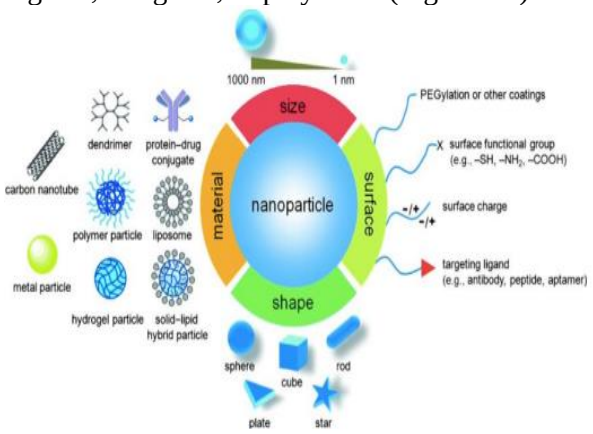

Figure 2.4. Drug-delivery nanoparticle characteristics. Reprinted with permission from (Sun et al., 2014).

The success of nanoparticle delivery is influenced by size, shape, and other biophysical and chemical properties (Patra et al., 2018). According to Yoo et al. (2011), size and shape have an impact on circulation, biodistribution, cellular uptake and accumulation, vascular adhesion, and renal clearance. Their efficiency is also influenced by their surface characteristics. Particles with a positive charge are more likely to attach to cells and be absorbed than those with a negative charge. According to Moghimi et al. (2001), hydrophilic polymers like polyethylene glycol prevent protein adsorption on particles, which impedes circulation and immune clearance. To limit or prevent drug-induced harm to healthy tissues, an effective drug delivery system should

reach pathologic tissue, be identified by the cells it targets, attach to it, and distribute the medication. Small compounds, peptides, antibodies, designer proteins, and nucleic acid aptamers are coated on the surfaces of nanoparticles to target them (Rizvi and Saleh, 2018).

Mechanism of Drug Release

The medication is released by diffusion, surface erosion, or bulk breakdown by the polymer nanoparticles (Figure 2.6). Burst release, or the rapid release of drugs from polymer nanoparticles, is typically the result of surface-bound/adsorbed drug desorption (Lu et al., 2011). The release rate decreases over time as a result of the concentration gradient created by drug diffusion from pores to surfaces. Drugs are released when polymers are destroyed by natural hydrolysis based on their molecular weight and chemical properties. It enters the Krebs cycle after being broken down into its biocomponents. Surface-only or matrix-wide deterioration are possible. If drug diffusion is quicker than polymer breakdown, drug release occurs mostly through diffusion. Diffusion or erosion may also be the method. Particle size has an impact on drug release as well. The majority of the medication is at or close to the surface, allowing for faster drug release because of the increased surface area to volume ratio of tiny particles. According to Aguilar (2013), larger particles contain more medication and release it more slowly. Drug release kinetics are also affected by temperature, pH, and solubility (Rizvi and Saleh, 2018).

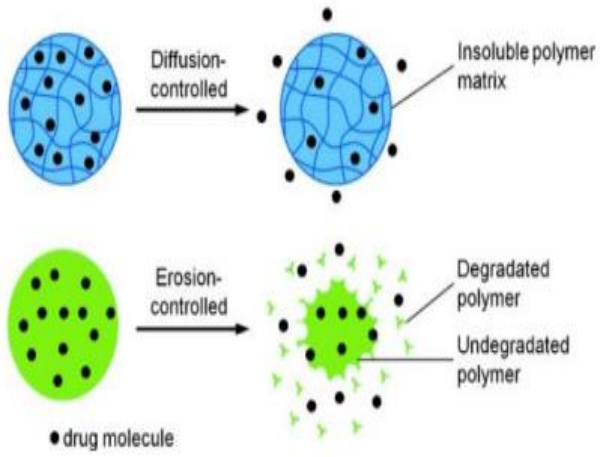

Figure 2.6. Showing medication release mechanisms

Hydrogel Film-Based Drug Delivery For Wound Healing

Rezvanian et al (2021), used an alginate pectin hydrogel film containing simvastatin to test diabetic rats induced by streptozotocin. Wound healing rate, hematology, histology, hydroxyproline, vascular endothelial growth factor, etc. were assessed. Wound healing was improved by pro angiogenic factor, faster reepithelialization, and improved collagen deposition.

Khan et al (2020), a burn wound healing model was used to develop, characterize, and test a Gelatin PVA film containing 12% ginger extract. Silver sulphadiazine cream-like wound healing activity was observed in the optimized film. It helped to organize the tissue and deposit more collagen.

Khasraghi and Thomas (2019), investigated the antirheumatic effects of Lornoxicam film-forming gel through patient-friendly medication administration. Various concentrations of ethanol, polymer, plasticizer, and drug were tested on the film. Formulation F5 was created with a long-lasting and effective effect in mind.

Wathoni et al (2019), used mangostin hydrogel film-based chitosan alginate in an experiment to treat recurrent aphthous stomatitis (RAS). The solvent-cast film underwent SEM, XRD, and DSC testing. Mucus adhesion, swelling ratio, elongation break, and tensile strength are all excellent properties of the film.

Drug Delivery

The goal of drug delivery is to achieve the desired therapeutic effects by introducing a pharmacological substance into the patient's bloodstream. A lot of work has gone into developing hydrogel and nanoparticle-based systems for drug delivery within the last 20 years. The therapeutic efficacy of medicinal compounds may be enhanced by the use of nanoparticles since their administration alters the pharmacokinetic and biodistribution patterns. Evidence suggests that certain nano-formulations have potential as medicinal products. Hydrogels, on the other hand, have found value in drug delivery systems due to their unique properties, such as their sensitivity to stimuli, ability to absorb water, and porous structure. To better administer therapeutic medications, nanoparticle-hydrogel

systems have been developed and are presently in use. These systems were made possible by new technology and developments in material design in the last several years. A versa tile hierarchical delivery system including several components (nanoparticles, hydrogels, and medicinal chemicals) is the central tenet of a hybrid material-based delivery platform. It was impossible for hydrogels or nanoparticles to achieve this result independently. Additionally, the nanoparticle-hydrogel platforms' unique properties make them a promising drug delivery strategy. These characteristics make it possible to target certain tissues or cells with pharmaceuticals and to release them over an extended period of time. Nanoparticles, which are tiny particles ranging in size from one to one hundred nanometers, have been developed by scientists to prevent drugs from being destroyed or removed before they reach their intended target. Indefinitely maintaining a large quantity of water, hydrogels are three-dimensional networks of cross-linked polymer chains**.**

Conclusion

In order to explore its possible uses in drug delivery and wound healing, the research effectively designed, improved, and tested a hydrogel that contains copper nanoparticles (CNP). A multifunctional therapeutic platform was developed via this work, which aimed to incorporate the wound healing and antibacterial capabilities of copper nanoparticles into a hydrogel matrix. The hydrogels were created using biocompatible polymers such as polyvinylpyrrolidone (PVP K30) and hydroxypropyl methylcellulose (HPMC). Important characteristics such as viscosity, swelling index, drug release profile, and wound healing effectiveness were used to alter the hydrogels. The optimization procedure was guided by statistical techniques, which guaranteed that the formulation parameters were properly managed to achieve the desired therapeutic benefits.

Excellent mechanical strength, controlled drug release, and wound healing capabilities were observed in the CNP-loaded hydrogel. Copper nanoparticles significantly aided both antibacterial activity and angiogenesis and cell proliferation, two processes that are crucial for efficient wound healing. Furthermore, the hydrogel exhibited a rather significant swelling capacity, enabling the medication to be delivered continuously throughout time and to stay anchored at the wound site for an extended duration. The hydrogel was able to hasten wound healing, decrease infection risk, and increase tissue regeneration in both in vitro and in vivo studies. Furthermore, the hydrogel's safety and biocompatibility were shown beyond a reasonable doubt, making it a promising candidate for clinical use.

Through its demonstration that copper nanoparticles may solve wound healing and targeted medicine delivery concerns, this work adds to the developing area of nanotechnology-based therapeutics. Additional bioactive compounds might be explored for combination therapy, the manufacturing technology could be scaled up, and clinical trials could be conducted to further demonstrate the efficacy and safety of the CNP-loaded hydrogel.

New biomedical applications are being explored via the use of copper nanoparticle-loaded hydrogel, which has shown to be an effective and novel wound therapy method. Finally, this hydrogel formulation is a huge step forward in the field of biomedicine. It is a valuable addition to the field of nanotechnology-based treatments and regenerative medicine because it combines biocompatibility, controlled drug release, and antibacterial activity.

Discussion

1. **Role of Copper Nanoparticles in Drug Delivery and Wound Healing:** Copper nanoparticles, also known as CuNPs, have sparked a lot of interest in biomedical applications due to their antibacterial, anti-inflammatory, and anti-angiogenic properties. They are very effective at facilitating wound healing while also preventing infections because of these characteristics. Copper nanoparticles (CuNPs) can be added to hydrogels to increase the bioavailability, regional distribution, and prolonged release of medicinal compounds. The construction of these hydrogels ensures that the nanoparticles will maintain their bioactivity and stability within the hydrogel matrix. Additionally, the nanoparticles' capacity to produce controlled quantities of reactive oxygen species (ROS) may

further elicit cellular responses necessary for wound healing.

Hydrogel Matrix Selection and Optimization: The hydrogel matrix that is chosen is of the utmost importance if copper nanoparticles (CuNPs) are to be encapsulated and released successfully. Polymers like chitosan, gelatin, alginate, and polyethylene glycol (PEG) are increasingly being used in a variety of applications due to their biocompatibility and biodegradability. The hydrogel's physical characteristics, such as its swelling behavior, porosity, and mechanical strength, need to be customized to ensure effective distribution and adequate adhesion to the wound site. The ideal concentrations of copper nanoparticles (CuNPs) and polymer components can be determined with the assistance of some optimization techniques, such as response surface methodology (RSM) or machine learning approaches, in order to obtain the required attributes. A comprehensive investigation of parameters like the hydrogel's rheological behavior, release kinetics, and loading efficiency of nanoparticles is required.

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