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REVIEW ARTICLE

pH-Sensitive Polysaccharide Nanocomposites for Management of Wound Healing

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ABSTRACT
Wound healing is a complicated and multi-step biological phenomenon encompassing several stages such as coagulation, inflammation, proliferation, and remodeling. Nevertheless, chronic wounds like diabetic foot ulcers, burns, and those inflicted by bacterial infection pose a considerable problem for medical practice due to delayed healing, susceptibility to infection, and the presence of inappropriate microenvironment in wounds. Existing wound healing treatments are unable to ensure controlled drug delivery and adequate wound environment. Nanomaterials have proved to be a breakthrough in wound therapy in recent years, providing sophisticated technologies for delivering drugs into target wounds. Notably, nanocomposites have become increasingly popular for drug delivery as they increase drug stability, provide high bioavailability, and promote controlled release. Specifically, pH-responsive drug delivery systems have found wide application owing to the variation in wound microenvironment pH. The pH of a wound changes depending on its location, health status, and the presence of infection; accordingly, pH-responsive systems can be used for local release of drugs in response to changes in the microenvironment. Polysaccharides based nanocomposites prepared from biopolymers such as chitosan, alginate, and hyaluronic acid have emerged to be highly promising owing to their biocompatibility, biodegradability, and inherent ability to promote wound healing. Such materials may be developed to form smart and stimuli-responsive systems which not only act as carriers for efficient drug delivery but also offer an ideal platform for tissue regeneration. This paper focuses on the latest developments in the area of pH sensitive polysaccharide nanocomposites for wound healing applications. Besides elaborating on various aspects like design and mode of action, the paper also throws light on existing difficulties and future prospects of this emerging field of study.
Keywords: *Wound healing, pH-sensitive drug delivery, polysaccharides, nanocomposites, smart biomaterials, controlled release.*

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INTRODUCTION

Wound healing is a very complicated and highly coordinated physiological procedure consisting of several sequential processes: hemostasis, inflammation, proliferation, and remodeling. Wound healing is extremely important for repairing the function and structure of damaged tissues. In most cases, acute wounds take place within a reasonable period of time, while chronic wounds, which include diabetic ulcers, pressure sores, burns, etc., are considered clinical problems because of the development of an extended inflammation process, infections, and improper tissue repair [1]. Chronic wounds affect the well-being of patients, as well as impose a great financial burden on health care systems [2].

Traditional wound dressings, which consist of gauze, bandages, cotton, etc., can be defined as protective layers, preventing any external factors from coming into contact with the wound. Although they are used commonly owing to low costs and ease of use, they have many disadvantages compared to modern products because traditional dressings cannot contribute to wound healing in any way [3]. They cannot create a proper wetness of the wound, release drugs, or prevent microorganisms from infecting the wound [4].

In order to resolve the challenges faced by the conventional delivery approaches, there arises a necessity for developing efficient and modern drug delivery systems which are capable of delivering the therapeutic drugs to the wounded site in a targeted, controlled and sustained manner. These delivery systems aim at maximizing the bioavailability of the drugs, avoiding any systemic side effects and providing an ideal environment for the wound healing process [5].

Nanotechnology deals with the engineering and utilization of materials in the nanometer range, usually between 1-100 nm. In the field of wound management, there has been considerable promise shown by nanotechnology-based systems like nanoparticles, nanofibers, and nanocomposites. The benefits offered by these systems include high surface area, higher drug loading capability, deeper tissue penetration, and better-controlled release [6]. Furthermore, nanocomposites, which involve the combination of multiple materials at the nanometer level, provide synergy in terms of enhanced mechanical properties, stability, and biological functions [7].

A notable development in the realm of nanotechnology-based drug delivery systems is the introduction of stimuli-sensitive or "intelligent" systems. Stimuli-responsive systems are designed to respond to specific external stimuli, such as temperature, pH, enzymes, or light, resulting in controlled and targeted drug delivery. In particular, pH-sensitive systems are pertinent in wound management applications because the pH levels vary with the different phases of wound management [8].

The normal state of healthy skin is that it is always characterized by a slight acidic nature with pH ranging between 4.5 to 6.0 [9]. It is worth mentioning that chronic and infected wounds display alkaline nature with pH range of 7.5 to 8.9, which fosters bacteria growth and delays healing. The pH-responsive material responds to the difference in acidity by undergoing some physical and chemical transformation including swelling, dissolution, and ionization to trigger the release of encapsulated drug molecules in the targeted location [10].

Polysaccharides are known to be highly useful and valuable among other materials used in designing pH-responsive drug delivery systems due to their natural composition, biocompatible and biodegradable nature alongside biological functions. Nanocomposite based on polysaccharides, including chitosan, alginate, and hyaluronic acid can deliver drugs to target locations and at the same time accelerate wound healing due to antimicrobial actions, moisture retention, and cell growth stimulation [11].

PHYSIOLOGY OF WOUND HEALING

The healing of wounds is an intricate process that requires proper regulation by biology to restore the disrupted cells within tissues by following certain stages. The process entails the coordination of different cell types and their interactions with other molecules such as growth factors, cytokines, and extracellular matrix proteins. Wounds healing follows four overlapping stages: Hemostasis, Inflammation, Proliferation, and Remodeling. Any interference in these stages may lead to delayed healing or even the development of chronic wounds [12].

Phases of Wound Healing

Hemostasis

The process of hemostasis is the body's reaction to any form of injury to tissues, taking place almost immediately after wounding. Its main goal is to prevent bleeding and to create an initial protection against microbes. In case of injury, blood vessels constrict, minimizing the amount of blood lost due to damage. Platelets form a clot by sticking together and attaching to exposed collagen fibers, creating a platelet plug [13].

Platelets release growth factors, including PDGF, TGF-β, and VEGF. These growth factors activate further processes involved in tissue regeneration and healing. At the same time, the process of coagulation activates the coagulation cascade, where fibrinogen converts to fibrin, creating a stable clot and providing a platform for cells to migrate [14].

Inflammation

The inflammatory phase follows soon after hemostasis and may last for up to several days. Inflammation leads to vasodilation, thereby promoting blood flow, allowing immune cells to move to the injury site. The first cells to appear at the wound site are neutrophils, which engage in phagocytosis to eliminate debris, bacteria, and necrotic tissue [15].

The next cell type to arrive at the injury site is macrophages, which act as key coordinators of the healing process. Macrophages release growth factors and cytokines that stimulate angiogenesis, fibroblast proliferation, and the synthesis of extracellular matrix. While inflammation is vital for wound repair, excess inflammation can result in tissue injury and chronic wounds [16].

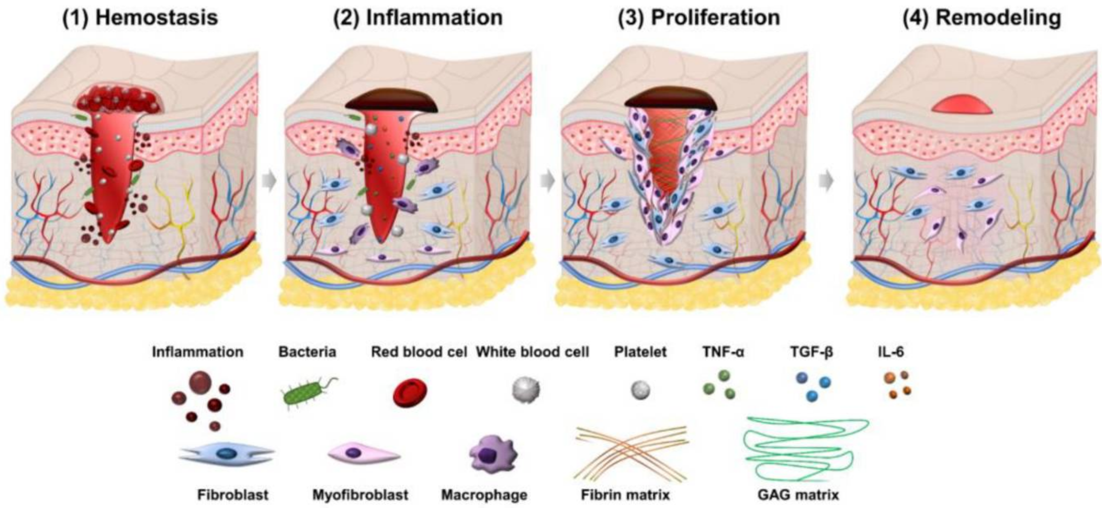

Figure 1: Physiology of Wound Healing

Proliferation

The proliferation stage is marked by the development of new tissues and normally takes place between days 3 and 21 post-injury [17]. In this stage, fibroblasts move into the wounded area and manufacture extracellular matrix products like collagen that act as the building blocks.

Another process that is common in this stage is angiogenesis, the development of new capillaries to ensure there is an ample supply of nutrients and oxygen for the development of new tissues. Epithelial cells grow and migrate over the injured part in a process called re-epithelialization. The wound bed will be filled by granulation tissues that consist of fibroblasts, collagen, and new blood vessels [18].

Remodeling (Maturation)

The remodeling process is the last step in the wound healing process, and it may last for weeks, months, or even years. In the remodeling process, the collagen formed earlier (of type III) is slowly replaced with collagen of type I, which improves the tensile strength of the tissues [19].

Fibroblasts rearrange the extracellular matrix, and the surplus blood vessels, formed as a result of angiogenesis, are reduced. Despite the fact that there will be a significant increase in strength in the tissue being healed, it is unlikely to return to its normal strength.

Factors Affecting Wound Healing

Wound healing is influenced by various local and systemic factors that can either promote or delay the healing process.

Infection

Infections are among the most important causes of problems in the healing process of wounds. The microorganisms in wounds extend the inflammatory phase and cause the production of toxic substances which harm tissues [21]. Moreover, infections hinder the processes of collagen production and angiogenesis and delay wound closure and even lead to chronic wounds.

pH Changes

The pH of the wound microenvironment is vital in determining the success of wound healing. The normal skin surface is mildly acidic and discourages microbial colonization and enzyme action. Chronic wounds, on the other hand, have a high pH, thus allowing bacteria to flourish and preventing hemoglobin from releasing oxygen [22].

High pH values also hinder fibroblast functions and collagen production, slowing down the wound-healing process. Thus, it is vital to create the right pH environment, making it imperative to design pH-sensitive delivery mechanisms.

Oxygen Supply

Oxygen plays a crucial role in many physiological processes related to wound healing, such as collagen formation, vascular growth, and antibacterial mechanisms. Sufficient oxygen concentrations promote the generation of reactive oxygen species (ROS) that act as a signal molecule and are capable of eliminating microorganisms [23].

Conditions of hypoxia (oxygen deficiency) can negatively affect wound healing through the inhibition of fibroblast activities, collagen accumulation, and epithelization. Wounds frequently exhibit low oxygen supply because of inadequate blood flow.

Chronic Diseases (Diabetes, etc.)
Systemic factors including diabetes mellitus have an immense influence on the wound healing process. Hyperglycemia in the case of diabetics causes damage to the immune system, poor blood circulation, and inadequate growth factor formation [24].
In addition, diabetic wounds exhibit high levels of inflammatory response, poor collagen formation, and are highly prone to infections. Furthermore, other systemic disorders like vascular disorders and immunological disorders impair the wound healing process, resulting in poorly healed wounds.

ROLE OF pH IN WOUND ENVIRONMENT
Wound pH is one of the most important parameters that play a crucial role in the wound healing process. Wound pH affects several biological processes, such as enzyme activity, bacterial growth, oxygen delivery, and cell multiplication. The ideal wound pH helps in wound healing, whereas deviation from the optimal wound pH causes wound healing to be delayed or become infected [25].

Normal Skin pH vs Wound pH
Healthy skin usually keeps its natural acidity, which has a pH between 4.5 and 6.0, and is known as an "acid mantle." This acidic nature is essential for keeping the skin safe from microbes because it suppresses the proliferation of disease-causing bacteria and activates enzymes that ensure the functioning of the skin barrier [26].
However, when the skin is damaged, the protective shield becomes vulnerable, and the pH balance within the wound moves toward becoming neutral or even alkaline. Wounds just made have a pH value of about 7.0, whereas chronic wounds have an increased tendency to develop alkalinity with a pH range from 7.5 to 8.9 [27].

pH Variation in Acute vs Chronic Wounds
Unlike acute wounds, which tend to have a normal healing process and eventually achieve normal acidic pH levels as healing occurs, chronic wounds like diabetic ulcers, pressure ulcers, and venous ulcers maintain an inflammatory phase with high levels of alkalinity in the wound bed [28].
These chronic wounds have a difficult time progressing through the stages of healing due to their inability to restore their pH to normal acidic levels, as they are usually kept in a highly alkaline environment that hampers cell functioning and provides a good habitat for bacteria and biofilm formation [29].

Impact of Alkaline pH on Infection and Healing Delay
There are many negative impacts of wound exposure to an alkaline environment. First, it stimulates the growth and multiplication of harmful bacteria that can cause an infection. The presence of bacteria results in the formation of toxic enzymes which cause destruction of normal tissues [30].
Second, the alkali pH of wounds impairs the release of oxygen from hemoglobin (Bohr effect). As oxygen plays a critical role in wound healing, any decrease in its concentration will hinder the healing process [31].
Furthermore, an alkaline wound environment has a negative impact on the metabolism of fibroblasts and keratinocytes required for wound repair and reconstruction. Enzyme functions responsible for the remodeling of the extracellular matrix are also affected, thus prolonging the healing process [32].

Rationale for pH-Sensitive Drug Delivery
The difference in pH between healthy wounds and those inflicted with diseases makes it possible to develop delivery systems that take advantage of this condition. pH-sensitive drug delivery systems are designed specifically to recognize changes in pH of the wound site and release therapeutic compounds in response [33].
At either an acidic or alkaline pH, the system will swell, undergo chemical changes, break down, or release charged ions, thus releasing any drugs incorporated into the matrix [34]. It guarantees a site-specific delivery of drugs and helps reduce adverse reactions since the drug is only released at the affected site. Moreover, delivery systems with a pH-responsive behavior can be utilized for the release of antimicrobial agents when dealing with alkaline infected wounds or release regenerative drugs in case of almost normal wound conditions [35].

POLYSACCHARIDES IN WOUND HEALING
Polysaccharides refer to natural polymers made up of monosaccharides, which are joined together by glycosidic bonds. Being very bio-compatible and degradable along with the functional diversity that they offer, polysaccharides have attracted much interest due to their biomedical applications, especially wound healing. They can easily be engineered to produce drug delivery systems, such as hydrogels and films that aid wound healing [36].

Introduction to Polysaccharides

Polysaccharides are mainly obtained from natural resources, which include plant, animal, and microbial sources. These compounds' natural origin makes them biocompatible because they are unlikely to elicit any harmful immune responses when introduced into the biological system. Moreover, they are biodegradable, meaning that they will degrade into harmless compounds inside the body, thus avoiding any buildup of toxicity [37].

The use of polysaccharides in wound healing is highly significant because they mimic ECM constituents and facilitate cellular adhesion, proliferation, and migration. Since polysaccharides are structurally similar to natural biological polymers, they have the ability to interact well with cells and tissues, leading to faster and efficient wound healing [38]. They also have the capacity to form gels and films, making them suitable for wound dressing applications.

Common Polysaccharides Used

Chitosan

Chitosan is a positively charged polymer that is produced from chitin, which can be extracted from the hard shells of crustaceans through deacetylation. This compound has been extensively applied in the treatment of wounds because of its biocompatibility, biodegradability, and antimicrobial activity. Chitosan facilitates clotting by promoting platelet adhesion, as well as hastens wound healing by promoting fibroblast proliferation and collagen synthesis [39].

Moreover, the positive charge on chitosan enables the substance to bind to the negatively charged bacterial cell membranes, resulting in damage and preventing bacterial proliferation.

Alginate

Alginate is an anionic polysaccharide isolated from the brown algae. Alginate is made up of mannuronic acid and guluronic acid. This molecule has excellent gelation properties when combined with divalent ions such as calcium ions [40]. Alginate dressings have high absorbency capabilities, allowing them to provide moist healing environment that is necessary for proper healing.

These bandages are especially important in treating exudating wounds because they help to keep the wound moist by absorbing excess fluids. Alginate helps in cell migration, therefore promoting regeneration.

Hyaluronic Acid

The hyaluronic acid is a glycosaminoglycan naturally present in the connective tissue of the body. The substance is very important in maintaining hydration, lubrication, and cell signaling in tissues. Hyaluronic acid helps in cell migration, angiogenesis, and inflammation during wound healing process [41].

Hyaluronic acid also assists in the formation of granulation tissue and promotes re-epithelialization. Due to its ability to retain water, hyaluronic acid ensures that there is enough moisture in the wound, hence aiding efficient wound healing. The substance is applied in dressing wounds through hydrogels and nanocomposites.

Cellulose Derivatives

Cellulose is an example of a natural polysaccharide that can be extracted from the cell walls of plants. It is one of the most common biopolymers found in nature. Derivatives of cellulose like CMC and HPMC have been utilized extensively in wound care treatments owing to their superior film-forming and water-binding capabilities [42].

Cellulose-based biomaterials impart strength, regulate moisture levels, and shield the wound from mechanical stress and microorganism attack. They are frequently used in conjunction with other types of polymers.

Dextran

Dextran is a polymer made up of glucose units arranged in a branched structure, synthesized by specific types of bacteria through the fermentation process involving sucrose. Dextran is considered highly biocompatible and possesses excellent water solubility. Dextran derivatives have been applied in wound healing due to their capacity to induce cell attachment and proliferation [43].

Moreover, dextran may be derivatized to include functional groups, which allow for the controlled delivery of drugs and improved binding with biological tissue.

Properties Relevant to Wound Healing

Biodegradability

Biodegradation represents the key property of polysaccharides, as this process helps to break down the material into biocompatible degradation products in vivo. The removal from the body via surgery is not required and decreases the risk of developing chronic inflammatory reactions and toxicity. It is possible to manage the rate of biodegradation by altering the structure of the material, which allows it to mimic the rate of tissue healing [44].

Antimicrobial Activity
Some polysaccharides, especially chitosan, possess natural antimicrobial characteristics. They have the ability to suppress bacterial and fungal growth by affecting the integrity of the cell membrane and hindering metabolic activities within cells. Such an advantage proves very helpful during the process of wound healing since it prevents infections and speeds up the healing process [45].
Moisture Retention
Wound hydration is an important factor in wound healing because it improves cell migration, prevents dehydration, and decreases scabbing. Polysaccharides have superior water absorption and retention properties, which help them achieve the necessary wound moisture balance. This contributes to faster wound healing [46].
Film-Forming Ability
The polysaccharides exhibit good film-forming capabilities, which enable them to be used as wound protective materials like films, membranes, and hydrogels. Such films serve as a physical barrier to microbial attacks but allow the passage of oxygen and carbon dioxide gases through them. The films also offer structural strength and enhance patient comfort during wound healing [47].

NANOCOMPOSITES IN DRUG DELIVERY
Nano composites have become an innovative form of material science in the domain of drug delivery because of their novel physical and chemical properties as well as biological characteristics. Nano composite materials can be designed by incorporating nano particles within polymers or inorganic substances, resulting in the formation of new materials that possess improved functionalities. In wound repair, nanocomposites provide many benefits, including precise drug delivery [48].
Definition and Classification
A multiphase material containing components that possess a size scale of 1-100 nm is called a nanocomposite. Nanocomposites have been developed to exploit the strengths of various materials in a single product. Examples of desirable features include mechanical robustness, biocompatibility, and drug delivery capabilities [49]. Depending on the composition and structural aspects of the nanocomposites, there are several types that can be used for drug delivery purposes, including the following:
Polymer-Based Nanocomposites
Nanocomposites made from polymers refer to natural or artificial polymers combined with nanoscale particles, fibers, or clays. For use in wound healing, polymers such as chitosan, alginate, and cellulose, which are natural and biodegradable, are often used [50].
The composite system allows for the development of a matrix that can enclose drugs and release them in a controlled manner. Moreover, the matrix can be engineered to be responsive to stimuli such as pH, temperature, and enzymes. Furthermore, polymer-based nanocomposites can be produced in diverse formats, including hydrogels, films, and nanofiber scaffolds [51].
Hybrid Nanocomposites
Hybrid nanocomposites are formed by the inclusion of both organic and inorganic compounds to leverage the best of both worlds. An illustration of this would be the use of polymers in combination with inorganic nanoparticles like silver, zinc oxide, or silica, which help in achieving antimicrobial efficacy, mechanical properties, and stability [52].
For wound healing applications, hybrid nanocomposites offer a lot of promise because they can confer more than one property to the dressing, such as antimicrobial activity, drug delivery, and tissue regeneration. In addition to these biological functions, the inclusion of an inorganic component offers possibilities of additional physical properties like optical or electrical conductivity [53].
Advantages in Wound Healing
Nanocomposites offer several advantages over conventional drug delivery systems, making them highly suitable for wound healing applications.
Controlled Drug Release
One of the key advantages of nanocomposites is their ability to provide controlled and sustained drug release. The drug can be encapsulated within the nanocomposite matrix and released gradually over time, maintaining therapeutic concentrations at the wound site [54].This controlled release reduces the need for frequent dressing changes and minimizes fluctuations in drug levels, thereby improving patient compliance and treatment effectiveness.
Targeted Delivery
With nanocomposites, the drugs can be delivered locally to the point where they are needed. As the drug-loaded nanocomposites have been made responsive to various stimuli such as change in pH levels, the

local administration of drugs can be achieved through stimuli responsiveness of the composite systems [55]. This will lead to higher efficiency of the drugs.

Enhanced Stability

The drugs contained in the nanocomposites are shielded against any deterioration brought about by environmental elements like sunlight, heat, and enzyme reactions. This increases their stability and longevity [56].

In addition, the physical structure of the nanocomposites guarantees that the drugs stay intact up to the point of delivery to the target area.

Improved Bioavailability

Nanocomposites improve the bioavailability of drugs due to increased solubility and penetration of drugs into tissues. Nanocomposite materials have higher surface area at the nanoscale level, and thus, there is improved penetration of drugs into tissues [57]. This is especially critical when dealing with wound healing.

The effectiveness of drugs in wound healing depends on their ability to penetrate wounds.

pH-SENSITIVE POLYSACCHARIDE NANOCOMPOSITES

Polysaccharide-based nanocomposites that respond to changes in the environmental pH levels form an advanced category of smart biomaterials. They combine the biodegradable and biocompatible properties of polysaccharides with the properties of nanocomposites to deliver drugs in a controlled manner at specific sites. This is advantageous in wound healing, where changes in pH between healthy and infected wounds can be exploited for drug delivery [58].

Concept and Mechanism

It is important to note that the basic principle underlying pH-responsive nanocomposites is the fact that the material can experience alterations in terms of its physicochemical properties as a result of fluctuations in pH within the environment.

Swelling/Deswelling Behavior

One of the main reasons for pH responsiveness in nanoparticles is the swelling and deswelling process of polymeric networks. Nanocomposites based on polysaccharides may have hydrophilic groups that absorb water, causing the particles to swell at certain pH values. In one study, it was observed that when there were high levels of osmotic pressure in the alkaline wound environment due to ionizable groups in the polymeric network, it resulted in swelling and faster drug release [59].

However, depending on the pH values, the polymeric network can deswell, limiting drug release.

Ionization of Functional Groups

The other mechanism is related to the ionization of the functional groups found in the polysaccharide, which include the amino group (-NH_2), the carboxyl group (-COOH), and the hydroxyl group (-OH). The functional groups are capable of accepting and donating protons based on the pH of the medium.

For instance, when the medium is acidic, the amino groups of chitosan will be protonated, making the compound soluble and swollen; conversely, when the medium is basic, the carboxyl group of alginate will be ionized, causing electrostatic repulsion and swelling of the polymer matrix [60].

Drug Release Triggered by pH

The combined action of swelling and ionization is such that eventually the delivery of drugs is induced by pH. In the case of infected wounds, where there is normally an alkaline pH, the matrix of the nanocomposites experiences physical alterations that aid in the delivery of antibiotics or growth factors only where the damage occurs [61].

By doing so, wastage of the drugs is avoided, and hence there are minimal adverse reactions. It is possible through pH-dependent systems to design the rate of drug release based on the intensity of the infection or wound healing process.

Types of pH-Sensitive Systems

pH-sensitive polysaccharide nanocomposites can be fabricated into various forms depending on the intended application and desired drug delivery profile.

Hydrogels

Hydrogels are formed by cross-linking of polymer chains that form a three-dimensional structure which absorbs plenty of water. A hydrogel that is pH sensitive will expand or contract depending on environmental changes in pH level for releasing drugs in a controlled manner. Hydrogels mimic natural tissue structure, creating a moist environment suitable for wound healing [62].

Nanoparticles
Nanoparticles are nanoparticles used to carry drugs and prevent their breakdown. pH-sensitive nanoparticles are engineered to deliver the drug based on the pH level. They will be released to target only the affected sites.
The small particles enable them to penetrate deep into the tissue and interact well with the cells [63].
Nanofibers
The nanofibers consist of fibers that have dimensions at the nanometer level. They are made through methods like electrospinning. The materials offer a high ratio of surface area to volume, facilitating effective drug delivery and release.
The pH-sensitive nanofibers can detect changes in wound pH levels, allowing them to release drugs and act as scaffolding for cells [64].
Films and Membranes
Films and membranes are thin polymeric layers that form a protective layer over wounds. Films sensitive to pH are capable of regulating drug release depending on the state of the wound site, as well as ensuring gas diffusion and protection from bacteria [65].
Such films are especially effective in treating superficial wounds and burns.

METHODS OF PREPARATION
The synthesis process of pH-sensitive polysaccharide-based nano-composites is an important factor that influences the properties, loading capacity, and drug release profile of the material. Different methods have been adopted for the preparation of these complexes, based on the kind of polymer involved and its intended application.
Ionic Gelation
Ionic gelation represents one of the common ways to synthesize nanocomposites using polysaccharides, including those composed of chitosan and alginate. It is based on electrostatic interactions between ions that have opposite charges. In particular, positively charged chitosan binds with negatively charged cross-linkers, such as sodium tripolyphosphate, which results in forming a gel matrix [66].
This procedure is quite simple, safe, and non-invasive because no aggressive chemical substances or elevated temperatures are involved, and thus it can be employed for encapsulation of sensitive substances, e.g., proteins and growth factors.
Emulsion Cross-Linking
Emulsion crosslinking includes the preparation of the emulsion system, mainly of the W/O or O/W type, where the polymer dispersion exists as a continuous phase. The next step is the addition of the crosslinking agent that will solidify the polymer droplets to form solid nanocomposites [67].
This technique can control the size and morphology of particles effectively. It is ideal for making microspheres or nanoparticles with a highly efficient entrapment rate. On the other hand, the organic solvent and surfactant used may demand some extra steps in the purification process.
Solvent Evaporation
Polymeric nanoparticles can be synthesized using the solvent evaporation method. This involves dissolving the polymer and the drug in an organic solvent that can be evaporated, resulting in particles that are suspended in an aqueous solution [68].
The method has its strengths and weaknesses; it works well for loading hydrophobic drugs and enables precise control over the size and release kinetics of particles. On the downside, traces of solvent have to be carefully eliminated to prevent toxicity.
Electrospinning
Electrospinning is an emerging method that is employed to develop nanofiber scaffolds having higher surface area and porosity. During electrospinning, the polymeric solution is exposed to an electrical voltage, which helps draw the fibers from the solution and collect them on a collector surface [69].
The electrospun nanofibers resemble the structure of extracellular matrix and thus serve well for wound healing processes. Drugs can be loaded into the nanofibers while developing them.
Self-Assembly Techniques
Self-assembly refers to the phenomenon where molecules arrange themselves into definite structures due to non-covalent bonds including hydrogen bonding, hydrophobic bonding, and electrostatic forces. The ability of polysaccharides to produce nanocomposites by means of self-assembly exists under specific environmental conditions [70].
The benefit of using this method is that it enables researchers to obtain highly regular nanostructures without any additional cross-linking agents. It is especially applicable in the development of stimulus-responsive materials such as pH-responsive drug delivery systems.

DRUG LOADING AND RELEASE MECHANISM

The effectiveness of nanocomposite-based drug delivery systems depends largely on their ability to efficiently encapsulate therapeutic agents and release them in a controlled manner at the target site.

Drug Encapsulation Techniques

The encapsulation of drugs relates to their inclusion within the nanocomposite matrix. It can be carried out by means of various techniques, such as physical entrapping, adsorption, or chemical conjugation.

Physical entrapping consists in the inclusion of the drug within the polymeric matrix during the production of nanoparticles or hydrogels. The technique is relatively simple and common but can cause an immediate burst release. Adsorption implies the binding of the drug to the nanocomposite surface via the use of weak interactions, such as van der Waals' forces or electrostatic interactions [71].

Chemical conjugation assumes that the covalent bonds are formed between the drug and polymer molecules.

Release Kinetics Models

It is important to understand drug release kinetics in order to determine and improve the properties of the drug delivery systems. Various mathematical models can be applied for description of the drug release behavior.

Zero-order kinetic model represents constant release rate. Such model is perfect for maintaining constant concentrations of the drugs.

First-order kinetic model implies that the release rate depends on concentration of the released drug in the system [72].

The Higuchi model represents drug release due to the diffusion process from the polymer matrix. Korsmeyer-Peppas model is applied frequently for describing various mechanisms of drug release (Fickian diffusion, non-Fickian and case-II transport) [73].

FACTORS AFFECTING DRUG RELEASE

pH

The pH level is an important parameter which influences the drug release from nanocomposites sensitive to changes in the pH level. It leads to changes in the ionization of the functional group in the polymer which causes either swelling or degradation of the matrix that influences the release kinetics [74].

Type of Polymer

The influence on the drug release depends on the properties of the polymer like its nature, molecular weight, and structure. The more hydrophilic the polymer, the more easily it swells, releasing the drug faster, whereas hydrophobic polymers have the opposite effect on drug release [75].

Cross-Linking Density

It depends on the porosity and mechanical stability of the polymer matrix. High cross-linking density means low porosity and low diffusion of the drug molecules, leading to slower release. On the other hand, low cross-linking density allows faster release of the drug [76].

APPLICATIONS IN WOUND HEALING

The application of pH-sensitive polysaccharide nanocomposites has exhibited great promise for treating wounds because of their ability to release active agents in a sustained and selective way. They can even be customized for tackling various wound-related issues such as infections, inflammation, and regeneration of tissues.

Antimicrobial Delivery

Antibiotics

It is vital for infected wounds to receive appropriate antimicrobial treatment to prevent further propagation of infection and to facilitate healing. The application of pH-sensitive nanocomposites allows encapsulation of antibiotics, which can be released selectively into infected wounds having an alkaline environment, thus increasing their effectiveness without posing any harm to other parts of the body [77].

Silver Nanoparticles

There is significant use of silver nanoparticles due to their wide-ranging antibacterial properties. When combined with polysaccharide nanocomposites, the nanoparticles exhibit antibacterial properties that not only inhibit but also kill bacteria, fungi, and other forms of resistance against these agents. The nanoparticles cause release of silver ions that act on the microbial cells [78].

Another application of the silver nanoparticles is in enhancing wound healing through reduction of inflammation.

Anti-inflammatory Agents

Inflammation is an important stage in the healing process; however, if it becomes too much or persists for too long, the healing process can be slowed down. The use of pH-responsive nanocomposites is capable of delivering anti-inflammatory agents such as non-steroidal anti-inflammatory drugs (NSAIDs) or even natural components in a controlled way [79].

Through the control of the delivery of these anti-inflammatory agents, the healing process is facilitated through decreasing inflammation and relieving pain.

Growth Factors and Bioactive Molecules

Growth factors like EGF, PDGF, and VEGF have been identified as vital components in tissue regrowth and angiogenesis. But their use directly has been restricted by the problems related to fast breakdown and short lifespan.

The nanocomposite-based approach creates a favorable environment that helps in the delivery of these growth factors over an extended period of time. It stimulates the multiplication of cells, collagen formation, and creation of blood vessels.

Chronic Wound Management (e.g., Diabetic Ulcers)

Chronic wounds like diabetic ulcers are associated with sustained inflammation, infection, and poor tissue regeneration. The presence of pH-responsive nanocomposite formulations is advantageous for the treatment of chronic wounds because they will react to the basic environment of these wounds and provide the corresponding drug delivery [81].

They will provide the simultaneous delivery of antimicrobial, anti-inflammatory, and growth factors.

EVALUATION PARAMETERS

Performance and efficacy of pH-responsive polysaccharides-based nanocomposites are characterized through various physical and chemical properties as well as in vitro and in vivo experiments.

10.1 Physicochemical Properties

Size of Particles

Size is an important property that significantly impacts drug loading capacity, release profile, and internalization. Smaller particle sizes have a greater surface area, which facilitates efficient drug delivery and tissue penetration [82].

Zeta Potential

The zeta potential determines the surface charge and affects the stability of the nanoparticle. High zeta potential guarantees stable dispersion and prevents particle aggregation [83].

Morphology (SEM/TEM)

Application of techniques like SEM and TEM for morphology evaluation aids in studying the structural and surface characteristics of the nanocomposite which have an influence on its drug delivery capabilities and biocompatibility [84].

10.2 In Vitro Studies

Drug Release Studies

The drug release studies are performed in vitro to study the release profile of the drug from the nanocomposites. In addition to helping in optimizing the formulation, these tests provide information on the mechanism of release [85].

Swelling Studies

Swelling tests study the property of the matrix of absorbing fluids, which allows expansion of the polymer matrix. Swelling is a crucial phenomenon to be studied in pH-sensitive systems, as the rate of drug release depends on the swelling capacity of the polymer [86].

Antimicrobial Studies

The antimicrobial efficacy of the formulations is determined by testing their ability to stop microbial growth through zone of inhibition or MIC assays [87].

In vivo Studies

Wound Contraction

Wound contraction studies measure the reduction in wound size over time. Faster wound contraction indicates improved healing efficiency of the formulation [88].

Histopathology

Histopathological analysis involves microscopic examination of tissue samples to assess cellular organization, collagen deposition, and tissue regeneration. It provides detailed insights into the healing process [89].

Healing Rate

The overall healing rate is evaluated by monitoring parameters such as epithelialization time, granulation tissue formation, and complete wound closure. These studies confirm the therapeutic effectiveness of the nanocomposite system [90].

ADVANTAGES AND LIMITATIONS

Advantages

Drug Release Targeted

The drug release is targeted because the nanocomposites respond to the acidity of the wound area, allowing them to release the drugs only at the site [91].

Fewer Side Effects

Through the reduction of systemic drug exposure, there is an improvement in safety since controlled release does not lead to any side effects or toxicities [92].

Improved Wound Healing

Due to the combination of drug release, anti-bacterial properties, and moisture retention, wound healing is greatly improved through such systems.

Limitations

Nanocomposite Stability Problems

There is a chance that some nanocomposites could face stability issues like aggregation or degradation when in storage mode. The conditions under which they were kept, such as temperature and humidity, could also pose a problem [93].

High Cost of Production

The process of creating nanocomposites requires advanced techniques, which might make them expensive to produce in large quantities for use in the clinic [94].

Scale-up Process

It is difficult to scale up nanocomposites from laboratory level production. Some challenges faced by researchers include reproducibility and quality control [95].

RECENT ADVANCES

The field of pH-sensitive polysaccharide nanocomposites has witnessed significant advancements in recent years, driven by innovations in nanotechnology, biomaterials, and drug delivery systems. These developments have enhanced the effectiveness of wound healing strategies and opened new avenues for advanced therapeutic interventions.

Smart Wound Dressings

The development of smart wound dressings is one of the most innovative advances in wound management technologies. Smart dressings have the ability to sense changes in their surrounding wound environments, including pH levels, temperature, and moisture. Nanocomposite polysaccharides with sensitivity to pH are especially helpful for detecting the alkalinity level of infected wounds and releasing medicinal compounds in response to that condition [96].

Today's advanced smart dressing technologies allow the monitoring of wound status, providing information on the current wound conditions.

Stimuli-Responsive Multifunctional Systems

In recent times, there have been developments in nanocomposites that can be used to address different stimuli like pH, temperature, enzymes, and oxidation. Such nanocomposites are intended to achieve more than one function at a time like delivery of drugs, antimicrobial effects, and regeneration of tissues [98].

This means that a nanocomposite can release antibacterial medication when stimulated by pH changes and, at the same time, provide growth factors for regenerating tissues.

Combination Therapies (Drug + Growth Factors)

The use of combination therapy for wound healing is a relatively new concept whereby more than one medication is administered simultaneously to produce synergistic results.

Nanocomposite materials that respond to changes in pH levels may be used to incorporate drugs like antibiotics, growth factors, and anti-inflammatory medications [97]. Combination therapies offer numerous advantages, especially in the treatment of complex wounds.

Use of Nanotechnology with Bioactive Natural Compounds

The combination of nanotechnology with natural bioactive agents has attracted significant interest. Natural agents like curcumin, aloe vera, chitosan-based derivatives, and botanical extracts have antimicrobial, anti-inflammatory, and antioxidant effects.

Their clinical usage, however, is hindered by issues related to solubility and stability. Their incorporation within pH-responsive nanocomposites enhances bioavailability, stability, and sustained release, increasing their clinical efficacy for wound repair [98].

FUTURE PERSPECTIVES

The potential for pH-responsive polysaccharide-based nanocomposites in wound repair is immense, with current work concentrating on enhancing their performance capabilities and ease of application.

Personalized Wound Management

Personalized medicine will likely feature prominently in the treatment of wounds. Nanoengineered composite materials can be designed to suit specific patient requirements by taking into account wound characteristics, severity, and medical history [99].

Such a customized approach can enhance drug delivery mechanisms and maximize wound healing outcomes, particularly among patients with pre-existing medical conditions like diabetes.

Integration with AI and Biosensors

The use of artificial intelligence (AI) and biosensors in wound dressings is becoming popular. The use of biosensors in wound dressings ensures continuous monitoring of various parameters such as pH levels, temperature, and infection. Artificial intelligence, through analysis of the data provided by biosensors, helps make necessary decisions on how to change the method of treatment.

This helps avoid complications in treatment and improve treatment outcomes [100].

Commercialization Potential

Commercialization of these new products for wound management is quite promising due to the high level of research and development going on. The new technologies have many advantages compared to conventional dressing techniques such as better drug delivery and lower risk of infections [101].

Regulatory Challenges

Although nanocomposites hold great promise, there are certain regulatory hurdles that need to be overcome in the translational process. Issues associated with safety, toxicity, quality control, and standardization need to be dealt with comprehensively prior to clinical applications [102].

There is a need for detailed preclinical and clinical testing to confirm the safety and efficiency of such advanced materials. The development of guidelines for nanomedicines is still one of the key priorities.

CONCLUSION

Polymer nanocomposites with pH-dependent properties offer an extremely exciting and innovative technology in the domain of wound healing. These novel nanocomposites incorporate the exceptional characteristics of polymers and the ability to respond to pH levels to achieve the precise targeting and controlled release of active compounds. Due to the changes in pH that occur at wounded sites, especially those that are infected or chronically unhealed, these polymer-based nanocomposites can effectively release the medicines directly at the targeted location.

From a practical standpoint, there are numerous benefits offered by these systems over traditional wound healing techniques. The simultaneous release of antiseptics, anti-inflammatories, and growth factors in one formulation is highly effective for treating complicated wounds like diabetic ulcers, burn injuries, and other non-healing conditions. Furthermore, they help in maintaining a moist wound environment, stimulate tissue repair, and prevent infections.

The significance of pH-sensitive polysaccharide nanocomposites in health care is enormous. Such systems can contribute to reducing the problem of chronic wounds, reducing hospital stay periods, and minimizing expenses for treatment altogether. Moreover, taking into account the development of smart technologies and biosensor applications, one should expect their significant impact on future wound care within the framework of personalized medicine approaches.

In summary, the prospects associated with pH-sensitive polysaccharide nanocomposites are truly exciting for modern wound care, and they will inevitably contribute to improving health care quality in general.

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