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Nanomedicine Delivery using Biopolymers for the Treatment of Cancerous Wounds

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Abstract

Biopolymer-based nano drug delivery systems are an emerging and promising strategy for addressing the challenges of cancer treatment and wound healing. These natural nanocarriers are like alginate, chitosan, gelatin, and hyaluronic acid. These nano-systems offer biocompatibility, biodegradability, and reduced toxicity of the therapeutics. The nanoparticles can be loaded with growth factors, which accelerate tissue These provide targeted delivery sites and also modulate the microenvironment of the tissue by sustained drug release and reducing the damage to healthy tissues, thus promoting cancer treatment and wound tissue regeneration in a synergistic manner. Drug delivery system (DDS) technology includes a variety of approaches such as liposomes, nanofibers, and inorganic and lipid nanoparticles. The focus of this chapter is to provide the recent developments in biopolymer-based strategies and their applications for the future prospects for clinical implementation.

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INTRODUCTION

Cancer diseases are among the biggest and most prevalent issues facing modern medicine, with implications for society and the economy. Additionally, they are the primary cause of death in the developed nations. The two most popular methods of treating malignant neoplasms are chemotherapy and radiotherapy. Their side effects are therefore a serious problem and significant obstacle for contemporary oncology. Skin homeostasis issues are among the most significant side effects of chemotherapy and radiation therapy.[1] Chronic wounds may develop as a result of surgery itself or adjuvant therapies like chemotherapy and radiotherapy. Both chemotherapy and radiotherapy are adjuvant treatments that have a number of systemic side effects, such as skin disruptions. Oncological patients experience tissue loss, and continuously search for an effective healing treatment. Biomaterials, growth factors, tissue engineering products derived from in vitro cultured allogeneic or autologous cells, and traditional dressings are some of the intriguing techniques.[2] These days, there is increased interest in the application of nanomaterials in the pharmaceutical industry, particularly in drug delivery systems (DDS).[3] DDS-based nanotechnology is a new multidisciplinary program in the biomedical field that addresses issues like drug side effects, plasma inconsistency, therapeutic potency, and poor intestinal absorption mechanisms through degradation and bioavailability due to reduced solubility.[4] The aim of this chapter is to address the dual challenges of cancer treatment and wound healing by focusing on biopolymer-based Nano drug delivery systems, which can be optimized to enhance the cancer treatment and wound tissue regeneration.

BIOPOLYMER: PROPERTIES AND APPLICATIONS

Biopolymers are a broad and incredibly adaptable class of chemicals that are either manufactured from biological sources or produced by organisms. Biopolymers are made up of identical repeating units named monomers that are linked together.[5] Diverse natural and synthetic biomaterials, biodegradable and non-degradable, are explored potentially as drug delivery for tissue engineering with medical applications. The key features of biopolymers are biocompatibility, biodegradability, and antibacterial activity. There is lots of similarity in the chemical structures and composition of the macromolecules of the natural extracellular environment.[6-8]

TYPES OF BIOPOLYMERS

1. Chitosan

One of the well-known polysaccharides that is natural in origin and a chitin byproduct is chitosan. copolymers Glucosamine and N-acetylglucosamine are linked by β-1,4-glycosidic bonds.[9] The research utilized solid lipid nanoparticles (SLN) loaded with all-trans retinoic acid (ATRA) and wrapped in chitosan film. Under the controlled conditions, the medications are released by chitosan film, and the SLN-ATRA accelerated wound closure by minimizing scarring, collagen deposition was boosted, and leucocyte infiltration in the wound area was lowered. Chitosan-encased SLN-ATRA is a suitable option for the treatment of diabetic wounds and promoting wound tissue recovery.[10] Chitosan is known for the antibacterial and antibiofilm properties that were studied. A chitosan film release nitric oxide (NO) (CS/NO film) was formed. The result depicted that NO was released from simulated wound fluid continuously for 72-hours. Furthermore, CS/NO represented more enhanced antibiofilm activity and substantially increased the antimicrobial action against MRSA and decreased bacterial viability. CS/NO film surged the elimination of biofilms, minimized wound size, and encouraged collagen deposition and epithelialization. Hence, it can be used in the future to cure infected wounds.[11]

2. Alginate

It is also known as alginic acid and is an anionic polymer that is widely distributed in the cell walls of brown algae, particularly in Ascophyllum and Laminaria species. They are produced by copolymerizing d-mannuronic acid and l-guluronic acid.[9] They are unbranched linear polysaccharides that include distinct amounts of (1→4)-linked β-d mannuronic acid and α-l-guluronic acid residues. These are unbranched linear polysaccharides that can be connected to other physiologically active molecules, have tractable porosity, and are biodegradable.[12] Hydrogels dominating role in wound closure was demonstrated by the full healing of the PVA/alginate hydrogel wrapping the new tea polyphenol nanospheres (TPN) after 5-days of injury. The PI3K/AKT pathway is triggered by TPN@H, which reduces inflammation and improves wound healing.[13]

3. Hyaluronic acid

Hyaluronic acid (HA) is a naturally occurring GAG that is highly hydrophilic, non-immunogenic, non-sulfated, and anionic. It is found extensively distributed throughout the connective tissues, neural tissues, synovial fluids, and epithelia. It is comprised of cockscomb, cartilage skin, and vitreous humor. It comprises 2-acetamide-2-deoxy-α-d-glucose and β-d-gluconic acid that are bounded by numerous (1,3) and (1,4) glycoside bonds.[9] HA is widely used in the biomedical field because of its bacteriostatic effect.[14] It is also used in tissue engineering, ocular surgery, wound healing,[15] and along with material for implant preparation in reconstructive plastic surgery.[16] In order to conduct research on hyaluronic acid oligosaccharides, Huang et al. prepared an ointment that contained a blend of hyaluronan fragments. In addition to developing tubes of endothelial cells in the midst of high glucose, o-HA significantly boosted migration and proliferation. Applying O-HA ointment accelerates the wound healing by enhancing angiogenesis in the injured skin region. This suggests that using O-HA topically in a clinical setting may be a useful strategy for treating diabetes patient's wounds.[17]

4. Gelation

Gelatin is primarily made from denatured protein collagen, via. a hydrolysis process that produces significant peptides that initiate signal transduction and cellular adhesion pathways during wound healing. It is biocompatible, biodegradable, and non-immunogenic.[18] Gelatin promotes the homeostasis stage; gelatin absorbs watery waste products from the wound and residues in the tissue regeneration. Because of these features, the creation of scaffolds for wound closure and regeneration of tissues. Furthermore, it is utilized in the development of absorbent-adhesive pads and surgical wound dressings.[19,20]

Nano Drug Delivery Systems

NDDSs are drug delivery systems that can be made from a range of biomaterials and have particle diameters within the nanoscale. They have the ability to improve drug stability, sustained release, and controlled release.[21] In order to promote wound healing and skin regeneration, a variety of nano-DDSs containing therapeutic agents are emerging at an unprecedented rate. These include liposomes, polymeric nanomaterials, inorganic nanoparticles, lipid nanoparticles, nanofibrous structures, and nanohydrogels.[22-24]

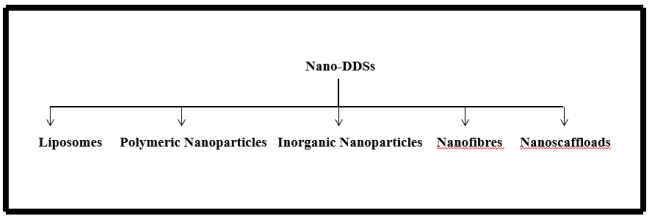

Figure 1: It represents various Nano DDSs.

1. Liposomes

Liposomes are synthetic membranes primarily made up of amphiphilic molecules that assemble into a bilayer structure resembling a skin cell membrane. The hollow portion of the lipid bilayer contains drugs, making liposomes sophisticated drug delivery nanocarriers.[25] They are biocompatible with skin, biodegradable, and nontoxic; they can hold hydrophilic medications (like growth factors) in the inner water cavity and hydrophobic agents in the bilayer.[26,27] Liposomes preserve

the drugs release, while protecting the encapsulating medication. Moreover, after application, liposomes efficiently cover the wound and produce a moist environment on the surface that promotes wound healing.[28]

2. Inorganic Nanoparticles

Inorganic nanoparticles are defined as those that have been stripped from the inorganic sources like metallic nanoparticles, carbon-based ceramics, ceramics nanoparticles etc.[29] Inorganic nanoparticles like silver nanoparticles which is frequently used as antimicrobial agents because of inherent properties as materials. They have strong antibacterial properties and comparable benefits for wound healing. Consequently, in order to achieve a syngisitic promoting effect of both materials and drugs, as it is more desirable in research to combine inorganic nanoparticles.[30]

3. Polymeric Nanoparticles

Polymeric Nanoparticles are biocompatible colloidal system with precise formulation parameters.[31] It is possible to achieve reduced degradation rates and controlled release of drugs in the wound area by embedding or conjugating with biodegrable polymers. The field of nano-drug delivery systems is paying more attention to polymeric nanoparticles because of these advantages.[32] The core-shell structure of polymeric nanoparticles contains drugs whereas the hydrophilic polymeric outer surface offers stearic stability.[33]

4. Nanofibers

Nanofibres are created from natural and synthetic continuous polymer which can be used in tissue engineering as 3D scaffloads or nanofibrous sheets.[34] Nanofibres typically having diameter of less than 100nm which is important class of nanomaterials.[35] Nanofibres include numerous exceptional characterstics like large surface area, variable porous rate, fantastic material selection flexibility and advanced fabrication technology.[36] These nanofibrous structures are intended to function as a substitute for artificial dermal analogs by simulating the extracellular matrix, promoting cell attachment and improving cell-drug interaction.[37,38]

5. Nanohydrogels

Nanohydrogels is a three dimensional polymeric network that is assumed to be the best formulation for controlling wounds because of its porous three dimensional structure which allows to absorb aqueous fluids,[39] preventing dehydration and fostering a beneficial moist environment for wound healing,[40] additionally it is non-adhesive which can preserve the wound bed and allowing oxygen to penetrate which is essential for wound healing,[41] the soft texture of nanohydrogel makes the treatment process comfortable.[42]

6. Lipid Nanoparticles

lipid nanoparticles are created by glycerophospholipids, cationic lipids, sterol lipids and PEGylated lipids coated

Table 1: Various advantages of Nano-DDSs.

Type of Nano-DDSs	Incorpated material	Observation	References
Liposomes	Hyrogel and liposomes	enhanced bFGF stability in wound fluids and preserved cell proliferation activity in comparison to conventional liposomes, effectively speed up wound healing especially by promoting angiogenesis	[45]
Inorganic Nanoparticles	Silver nanoparticle ZnO_2	Induced elevation of TGF-β, VEGF, and IL-6 may mediate the relatively quick wound healing and improved superficial wound appearance were also noted Histopathological evaluation results confirmed that ZnO_2 nanoparticles could hasten in vivo skin wound healing in animal models	[46] [47]
Polymeric Nanoparticles	PLGA nanoparticle loaded with antimicrobial peptide LL37	Expediated healing procedure, it also demonstrated antimicrobial activity against Escherichia.coli and stimulated cell migration without affecting keratinocyte proliferation, it enhanced angiogenesis and regulated the inflammatory wound response via upregulated vascular endotheial growth factors and interleukin-6(IL-6)	[48]
Nanofibres	Mouse bone marrow stem cells to a porous polyethylene glycol – polyurethane (PEG-PU) scafflod	Invivo observation depicted significant increase in fibroblast, collagen deposition and antioxidant enzyme activity , at initial stage healing stage there was clear decrease in the expression of inflammatory cytokines (LI-1β,TNF-α,IL-8,etc) and increase in (IL-10,IL-13)	[49]
Nanohydrogels	VEGF-loaded nanohydrogel	Improved cell adhesion and spreading, increased in vitro regeneration, decreased blood clotting time	[50]
Lipid Nanoparticles	SLNs and NLCs loading with rh-EGF	Significant improvement in wound closure, inflammation restoration and re-epithelialization, superior ability to promote cell proliferation	[51]

with oligonucleotides.[43] Nanostructured lipid carriers (NLCs), and solid lipid nanoparticle (SLNs) are two types of LNPs which can improve the stability, and solubility of medications that are encapsulated.[44]

Cancer Treatment and Wound Healing Mechanisms

It is demonstrated both malignant process and wound healing overlap certain characteristics.[52-54] Consequently, it makes appropriate to search and discuss regarding procedure. Wound healing is a complicated process with several stages. The main phases are tissue remodeling, proliferation and inflammation. Trama healing is an expression to describe the traits of this process.

i) Following the trauma, platelet accumulation and blood vessel constriction occur to halt the bleeding. Then other cells linked to inflammation are drawn to the site: neutrophiles are drawn in the early stages, whereas monocytes and macrophages show up later. Inflammatory response may initiate by numerous cytokines, chemokines, DAMP, and PAMP. The hallmark of the inflammatory phase is hemostasis which seals the wound and stops further harm. Chemotaxis and increased vascular permeability are the features of phases that aid in cell movement to get rid of germs and cellular debris.
ii) The proliferation phase begins when granulation tissue fills the wound defect. In order to help stabilize wounds, fibroblasts multiply and create new collagens and glycosaminoglycans. As a result, new blood vessels form and eventually an immature scar seals the edges of the wound.
iii) The maturation phase begins after the damaged site is repaired, the site reaches its maximum strength and the scar formed. When the skin wound occurs, the edges of wound are drawn together and epithelization occurs.[55,56]

Applications of Biopolymer Based Nanocarriers in Cancer Wound Healing

Nanotechnology is the new therapeutic approach that uses nanoparticles to diagnose, and cure cancer.[57,58] NPs are used in cancer treatment because of their distinct size, which is typically between, 1 and 1000 nanometers, but ideally between, 5 and 200 nm for drug delivery applications. NPs drug delivery system provides clear benefits for cancer treatment compared to free medication administration: -

1) Enhance the therapeutic index of the pharmaceutical agents that are loaded as opposed to those that are administered via traditional dose forms.
2) Enhance medication effectiveness by maintaining stable therapeutic drug levels over time.
3) Decrease the drug toxicity via controlled drug release and increase the medication solubility along this stability to enhance pharmacokinetics.[59] Additionally, anticancer can be incorporated into nanoparticles to reduce chemoresistance to drug activity, which improves therapeutic selectivity for cancer cells and decreases drug toxicity against normal cells.[60] Furthermore, functionalizing the surface of the nanocarriers with certain antibodies, or Ab fragments that identify specific epitopes of tumor-associated antigens (TAA) and tumor-specific antigens (TSA) improves their selectivity for cancer cells.[61] Since, their lymphatic clearance at the tumor site is hampered, nanocarriers are maintained in the tumor interstitium, and gradually accumulate in the tumor tissues.[62] The release of drugs into the tumoral interstitium can be regulated by modifying the nanoparticle structure, such as the polymer utilized and the thickness of the polymer wall covering.[59]

Engineering techniques based on nanotechnology have accelerated the development of these biopolymers into a fresh group of wound care solutions.[63] Studies are conducted to investigate these compounds potential to aid the healing process.[64] Fucoidan promotes angiogenesis and wound healing by stimulating heparin-binding cytokines such as FGF-1 and FGF-2 in the wound exudates.[65] Fucoidan has the ability to modify TGF-β1's impact on wound healing.[66] The polysaccharide EP22, which was isolated from Pseudomonas *stutzeri* AS22, demonstrated effective wound healing in rats, as evidenced by neatly arranged dermal and epidermal layers.[67] The teams research has demonstrated that EPSs isolated from *Nitratireductor* sp. PRIM-31 and *Rhizobium* sp. PRIM-18 exhibit in vitro wound healing properties that are mediated by fibroblast migration and proliferation.[68,69] Likewise, it has been claimed that several polysaccharides generated from fungi have the ability to heal wounds. He Y, *et.al.*, extracted polysaccharide from *Lachnum* sp. and validated its ability to heal tissue.[70]

CHALLENGES AND FUTURE PROSPECTS

The challenges faced by these systems are the stability and biocompatibility of the biomaterials, as these can degrade under varying physiological conditions like pH and temperature. This may trigger the inflammatory response and lead to difficulty in targeting specific tissue sites due to the poor penetration, and specificity can limit the binding. Lastly, preparation of the nanodrugs on a large scale can be costly and may raise sustainability issues due to the complexity of biopolymer synthesis, which can be a major hurdle in the future. The term clinical trials should be conducted to avoid toxicity and immunogenicity. The future prospects of the nanodrugs are the development of the multifunctional nanodrugs that accelerate the cancer wound healing and personalized targeted therapies, but the high reproducibility and cost-effectiveness too.

CONCLUSION

Biopolymer-based nano drug delivery systems hold immense potential for cancer wound healing by offering synergistic solutions to conventional therapies. Additionally, its

biocompatibility and biodegradability allow it to incorporate bioactive molecules that deliver therapeutic agents in a controlled and targeted manner. It is offering targeted drug delivery, promoting tissue regeneration, and reducing the side effects in wound healing. Apart from this, the drug delivery system is a boon for therapeutic solutions, as it is providing personalized medicine and regenerative therapies and significantly improving the clinical management for cancer treatment and wound treatment.

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