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A Review of the Drug Delivery Systems and Materials for Wound Healing Application

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Abstract: *- It is important to note that chronic, nonhealing wounds are the most common and recurring. In affluent nations, around 1-2 percent of the population will have to deal with chronic wounds that never heal. Different cellular actions must be coordinated to ensure that injured cells are repaired as quickly as possible during wound healing. Chronic, non-healing wounds may develop as a result of impaired wound healing brought on by diseases such as diabetes and age. Because of this, it is imperative that wound healing be better understood biologically and clinically. Wound healing materials and drug delivery systems have a significant impact on improving wound care, as well as a significant difficulty in the healing of wounds that are infected. For example, nano-drug delivery systems may minimise the toxicity of drugs, improve skin penetration, adjust the rate at which they are released, and reduce inflammation. Wounds and healing, medication delivery methods, wound dressings, skin regrowth and biomaterials are all covered in this short study.*

Keywords:*Wound and wound healing, medication delivery methods, wound dressing, skin regeneration, and biomaterials*

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INTRODUCTION

Wounds are injuries that cause the skin or other tissues to be torn or broken, often as a result of an accident, surgical procedure, or sutures. The process through which tissues recover from trauma is known as wound healing. Hemostasis, inflammation, proliferation, and remodelling are the four stages of the wound healing process. Drug delivery systems (DDS) for pharmacological reasons, such as controlled release wound dressings, biocompatible nano carriers for biomedical applications, etc. have a substantial impact from nanomedicine. [1] Although the skin is the body's biggest organ, it provides protection by encasing other cells and tissues, yet skin wounds of many kinds need quick healing [2]. There are a variety of wound dressings, ointments, and medical devices available for use in clinical settings, but new ones are constantly being developed. There is a significant amount of time spent on wound repair rather than regeneration throughout the healing process.[3] The fundamental challenge in skin regeneration is how to restore the wounded organ's original structure and function, particularly the blood capillaries. A number of studies have recently emphasised the importance of biomaterial carriers in nanomedicine as a means to increase skin regeneration and the quality of scar reduction[4]. Wound healing and tissue regeneration may be hastened by using nanomedicine in wound dressings and transdermal formulations. It is also used to treat skin cancer. A variety of circumstances may necessitate the healing and care of wounds in individuals[5]. Accurate antimicrobial agent distribution in the treatment of wounds, particularly those that are infected by microorganisms, is the preferred method of wound care therapy for both acute and chronic wounds. Drug delivery techniques for bioactive proteins such as peptides and growth factors, in addition to antibacterial wound dressing processes, were established. Wound treatment may benefit from a new technique based on cell therapy and stem cell strategy[6]. Transferring DNA and RNA to damaged tissues is made possible by the gene delivery system for wound healing. Wound healing delivery system control may be tricky. The biomaterials and scaffolds used have a significant impact on this. [7]

Wound Healing Process:

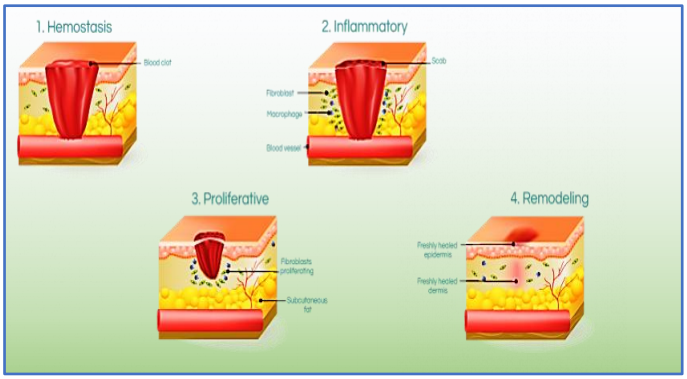
- There are four steps in the process.

• ***Haemostasis***: The initial step is called hemostasis. After two days, it is over. Vasoconstriction is the process that occurs as soon as a wound area becomes constricted in order to limit blood flow. Meanwhile, clotting factors are released into circulation, causing fibrin to congeal with the wound's surrounding blood vessels and form a thrombus. Blood is prevented from leaking out of the ruptured vessels by the clot.

• ***Inflammation***: During the inflammatory phase of wound healing, the body's natural defences are activated. Chronic wounds need phagocytic cells that emit reactive oxygen species for a prolonged period of time. There is a lot of redness and swelling at the injured region, as well as edoema, heat, and discomfort in this phase of the healing process.

• ***Proliferation:*** Wound proliferation is the next step in the healing process. It might last anywhere from four days to three weeks or longer, although it is mostly used to fill and hide the wounds. Because of the presence of inflammatory chemicals, new tissues look red or pink.

• ***Remodeling:***This is the last stage of wound healing before closure. How long it lasts depends on the severity of your wound and how well you've treated it. New tissue becomes stronger and more pliable during this period.



System for administering wound healing medication:

An increasing number of people are suffering from wounds that are either chronic or infectious. The use of drug delivery systems (DDS) in wound healing, which may release antibacterial and anti-inflammatory medications, has the potential to prevent infections or increase the efficacy of commercial treatments. (8)

As a result of this extensive research, a wide range of biocompatible materials such as polymeric microspheres and microsphere nanosphere hydrogel lipid nanoparticle nanofibrous structures and scaffolds have been developed in order to deliver drugs into the wound bed in order to promote wound healing. (9)

Delivery of antibiotics:

Wound healing is aided by the use of antibiotics. DDS of antibiotics is chosen for optimising and improving the use of already existing antibiotics. Antibiotics used in wound-healing delivery systems are dangerous[10].

• Cefazolin
• Gentamicin sulphate
• Ceftazidime pentahydrate
• Ciprofloxacin
• Gentamicin
• Diclofenac (anti-inflammatory action)

Electro spun nanofibers, microspheres, composites, and films of various biodegradable polymeric scaffolds were investigated for antibiotic delivery systems, including PLAGA nanofibers, composites of polyglyconate core and poly(lactic and coglycolic acid core) shells, chitosan (CS) gelatin composite films, a three-dimensional (3D), polycaprolactone tricalcium-phosphate mesh, and bacterial cellulose (BC) mem[11].

Typically, antibiotics used in wound healing are associated with negative outcomes as well as undesirable side effects. (12)

• Vancomycin- Nephrotoxicity
• Ciprofloxacin- Cytotoxicity
• Antimicrobial polymers- Haemolysis

Delivery of silver:

Using methods that inhibit bacteria's capacity to develop into more antibiotic-resistant strains, silver is being utilised to minimise and eradicate wound infections. [13] The development of silver-containing wound

dressings for healing promotion and infection control has presented promising techniques at this time [14,15]. Chemical reduction, microbiological reduction, microwave-assisted photochemical reduction, and laser ablation are among the most common methods for producing silver nanoparticles. When irradiated at a dosage of 25, 35, or 45 kg, wound dressings with AgNP-embedded polyvinylpyrrolidone hydrogel (PVP) hydrogels are created. At 12 and 6 hours, antibacterial testing revealed that the 1 and 5 mm AgNP embedded PVP hydrogels had 99.99% bactericidal activity[16]. For burn treatment applications, another hydrogel was produced that was gamma irradiated PVA/nano silver. Intriguingly, 0.1 percent w/w AgNPs in Pluronic F127 gels significantly improved wound healing activity [17,18]. It was discovered that extremely porous silver micro particles (AgMPs) had a large surface area [19]. Highly porous AgMPs or AgNPs were effectively loaded onto PLA nanofibers. Co-culture of human epidermal keratinocytes and S. aureus bacteria on wound dressings was mimicked using a 3D co-culture system. Compared to nanofibers with AgNPs, PLA nanofibers with extremely porous AgMPs showed a consistent silver ion release at a higher release rate.

Chitosan based wound healing:

Chitosan is used to prevent infection and speed up wound healing because of its antibacterial, coagulation-improving, and immune-stimulating properties(20). Chitosan dressing is a mixture of gels, microparticles, sponges, and films made from chitosan. silver-containing antimicrobial membranes based on TPP hydrogel and chitosan tripolyphosphate hydrogel have been developed by Sacco and colleagues for wound healing therapies(21,22). The macroscopically chitosan hydrogels, featuring AgNPs stabilised by lactose-modified chitosan, were generated by slow diffusion of TPP(23,24). The biocompatibility experiments on keratinocytes and fibroblast cell lines using the MTT [1-(4,5-dimethylthiazol-2-yl)-3,5-diphenylformazan] technique did not show any adverse effects on the viability of cells(25). The nano silver was incorporated into the chitin scaffolds. S. aureus and E. coli were discovered to be killed by these chitins or nano silver composites with excellent blood-clotting properties. (26)

Bioelectric wound healing:

Silver may also be supplied to the wound bed using a bioelectric wound dressing. Infections caused by Pseudomonas aeruginosa are frequent in patients with chronic wounds. A pathogenic strain of P. aeruginosa, PAO1, was used to assess the anti-biofilm characteristics of a USFDA-approved wireless electroceutical (WED) dressing that generates an electric field (0.3-0.9V) when activated by conductive wound exudates(27). In a context where standard silver dressing was infectious, WED significantly disturbed biofilm integrity. By acting as a natural catalyst for reactive oxygen species, WED reduced biofilm thickness and bacterial cell viability(28).

Bioactive protein delivery systems in wound healing: -

Complex, multicellular wound healing in skin is carried out and controlled by a signalling network that includes several growth factors, and cytokines, as well as other chemokines [29]. When it comes to tissue regeneration, growth factors are soluble proteins that have the ability to alter a wide range of cellular activities. However, owing to a lack of effective delivery mechanisms and carriers, the use of growth factors in clinics is still restricted. Research in this field has recently focused on the use of nanoparticles and nanofibers as carriers and delivery systems for growth factors and peptides linked to wound healing [30].

Pepsin delivery:

Matrix, gels, and synthetic skin tissue are the mainstays of modern wound-healing regimens. As a result, new grafting materials must be developed to allow biotherapeutic spatiotemporal targeting from clinically acceptable matrices[31]. Using peptides in wound care is a great option. For the treatment of persistent wound infections, a medication carrier system was created to deliver an insect metalloproteinase inhibitor (IMPI) Lactate from PLGA, the Polylactic co glycolic acid, aids wound healing by accelerating revascularization. Full-thickness excision wounds were examined for the delivery systems of the peptide, known as LL37 peptide, encapsulated within PLGA nanoparticles[32]. The collagen deposition, epithelial zed, and neovascularized composition were considerably greater in the PLGALL37 NP-treated group. No impact on keratinocyte metabolism or proliferation was seen when PLGALL37 NPs were used in vitro. It has been shown to have antibacterial action against E. coli, which is intriguing [33]. CM11 peptide (WKLFKKILKVLNH2) (128 mg/L), a short cecropin, melittin hybrid peptide, was used as an antibacterial wound dressing in an alginate sulphate-based hydrogel. Skin infections produced by MRSA (200 l, 3 108 CFU/ml) in a mouse model were investigated for its healing effects [34].

Growth factors:

Skin has a wide variety of growth factors, including EGF, pdgf, FGF2, kgf, Tgfb, IGF-like growth factor (IGF), VEGF, gmcsf, and connective tissue growth factor (CTGF), which all play an important role in

wound healing [35]. Due to their short half-lives, growth factors are frequently ineffective when applied to wounds in the body because of their fast deactivation. Some bioactive and biodegradable matrixes, such as extracellular matrixes, have been employed as carriers for growth factor delivery systems [36]. Growth factors like EGF are often used to heal skin wounds. Free human recombinant EGF was delivered through succinoylated dextrin (85,000 g/mol; 19 mole percent succinoylation)—a clinically proven well-tolerated polymer—and released over time at an increasing rate (52.7% after 168 h) [37]. When encapsulating EGF in poly (acrylic acid)-modified polyurethane (PU) films or chitosan and alginate films, researchers used a layer-by-layer construction process. Using a heparin binding epidermal growth factor coacervate delivery system, the scientists Johnson and Wang were able to enhance keratinocyte migration while maintaining their proliferative potential, resulting in a confluent layer that allowed the mice to regain their barrier function within seven days [38]. EGF and egg yolk oil-based chitosan-based gel formulations are superior alternatives to Silverdin (1 percent silver sulfadiazine) for treating wounds in Wild star rats [39]. The FGF2 clearly has clinical efficacy in a variety of wound managements because the healing rate of wounds is an important factor in the outcome of clinical treatments, as well as a crucial step in burn wound treatment, and the quality of wound healing has a direct bearing on the life quality of patients [40]. When it comes to plastic surgery reconstruction, the life of the skin flap is a big concern. A rat animal model's skin flap survival was considerably improved employing a sustained administration strategy of FGF2 using heparin-conjugated fibrin [41]. fibrin hydrogels with bFGF loaded double emulsion are an effective delivery mechanism, as the proliferation of endothelial cells was enhanced in comparison to non-treated controls, showing that the released bFGF was bioactive [42]. When employing two-component polyurethane scaffolds, an injectable PDGF delivery method has been found to provide a long-lasting effect of up to 21 days. The lyophilized powder was able to maintain the PDGF's in vitro bioactivity to an extent. After just three days in the test tube, the presence of PDGF attracted both fibroblasts and mononuclear cells, dramatically speeding up degradative processes and increasing granulation tissue production [43]. For the administration of PDGF, hyaluronan-based porous nanoparticles have also been studied. Alginate gel was used to provide SDF-1, an overexpressed chemokine that occurs spontaneously in response to tissue damage and speeds up wound healing and reduces scar formation [44]. An acute surgical Yorkshire pig model was used to investigate SDF 1 delivery devices. Alginate patches loaded with plasmids (n = 6) and SDF 1 protein (n = 10) healed wounds more quickly than sham (n = 4) or control (n = 4). On day 9, wound healing was substantially faster in the SDF-1-treated groups (55.0 14.3 percent healed) than in the non-treated groups (8.2 6.0 percent, p 0.05).

Wound healing using cell delivery systems:

When a wound heals, numerous kinds of cells come together to help, such as platelets, macrophages and keratinocytes, to aid in the process. There will be a wound closure as a result of these cells migrating infiltration proliferating, and eventually differentiating into new tissue[45]. Due to inadequate delivery mechanisms and failure to shield cells from acute inflammatory conditions, wound healing is hindered by cell-based treatments.

i) Stem cells:

Wound healing may soon be aided by a novel approach based on stem cells. According to the latest research, wound-associated stem cells either perish or move. It also has a negative impact on the treatment's effectiveness. Mesenchymal, endothelial, adipose-derived, umbilical cord perivascular, and circulating angiogenic stem cells are the most often used delivery mechanisms for diverse types of wound healing (CACs). MSCs technology has improved tissue regeneration in preclinical and clinical studies [46]. Wound healing delivery systems have used MSCs from a variety of sources, including bone marrow and adipose tissue [47,48].

Stem cells of various sorts are also used in conjunction with the 3D scaffolding method. HUCPVC, amniotic fluid-derived stem cells (AFSs), EPCs, and circulating angiogenic cells may all benefit from this method (CACs). Known as early EPCs, CACs are derived from peripheral blood's mononuclear cell component. Diabetic foot ulcers may benefit from a new topical therapy option. A diabetic rabbit ear wound may be treated using the scaffolding approach (it is also induced ulcer). In addition, the rate of angiogenesis and the degree to which wounds close have also risen. With the treatment of collagen and collagen seeded with CSCs [49,50], it has also been seen.

ii) Other cells:

Wound healing and enhanced skin tissue regeneration may be improved not only by studying the stem cells, but also by studying other cells including Endothelial cells (ECs), keratinocytes, and fibroblasts. It has been hypothesised by several researchers that the paracrine processes involved in wound healing may be used by endothelial cells and endothelial progenitor cells to govern vascular repair [51]. Dried reagent patches containing dextran (DEX) and bulk aqueous phases are also being used. Cell detachment may be achieved by

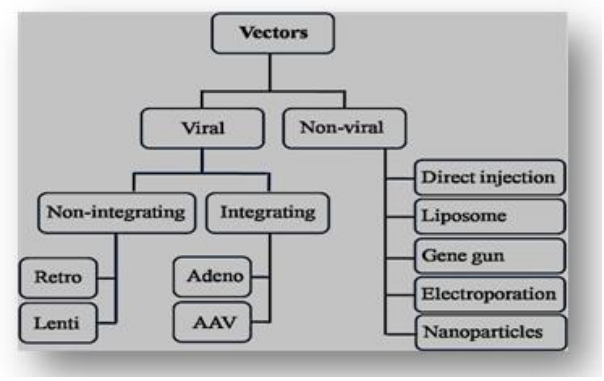
using a cell culture media that contains poly (ethylene) glycol (PEG), which is used by Bethany et al. [52]. Cell adhesive peptides coupled to chitosan-based membranes were used to transfer keratinocytes to wounds in mice [53]. To stimulate robust cell attachment in wound healing, two peptides of 12 or 13 amino acids each (A5G27 and A5G33) have been identified to bind to the cell surface of heparin-like receptors. There was no activity in A99, which is capable of binding to integrins The delivery medium for cultivated autologous skin cells was the rhCol III gel, which contains recombinant human collagen III.

Gene delivery systems in wound healing:

In the realm of tissue repair and medical research, the gene delivery system is an emerging technique that also promotes wound healing or dressing. When delivering genes, the goal is to minimise any adverse consequences while yet achieving sustained release, so that gene silence may be controlled both spatially and temporally. Stabilization and reduction of nonspecific effects of siRNA molecules during successful drug administration, for example, are achieved by chemical modifications of siRNA molecules [54]

i) The use of viral vectors for gene transfer:

An important regulatory function for TGF- family is played in viral vectors to heal and remodel skin wounds. Antithetical to wound closure, TGF3 promoted dermal remodelling in the project. TGF-3 (mutTGF-3) was created by its binding site to the TGF- binding protein (LTBP1) [55]. Transduction of mutTGF3 into the skin of a wounded mouse resulted in a reduction in both fibroblast Trans and epithelialization density in that region of the wound, as indicated by this study. In both cases, the production of scar tissue was minimised. A non-invasive imaging equipment was used to study the kinetics of luciferin gene expression after an adenoviral vector was delivered to the patient. 7 days after birth, gene expression reaches its highest level [56]. Ecrg4, a gene associated with esophageal cancer, delivers a virally mediated gene. When it comes to wound healing, it was also tested on the skin [57]. Skin samples from healthy mice revealed Ecrg4 mRNA and its protein product to be concentrated in the epidermis, dermis, and hair follicles.



ii) Gene Transfer Using Non-Viral Vectors:

The nanofibrous matrix was constructed to regulate the release of DNA in reaction to high concentrations of MMPs, which stands for matrix metalloproteinase and is integrated into electro spun DNA.

Diabetic ulcers may also benefit from this treatment [58]. Nanoneedles have been shown to transfer nucleic acids intracellularly with high efficacy and minimum toxicity in vitro [59]. The silicon-based metal aided chemical etching method was used to create biodegradable nanoneedles. VEGF165, an angiogenic gene, is delivered in situ by nanoneedles. New blood vessels began to grow as a result of their influence. The nanoneedles were intended to deliver just a few surface layers of cells to a specific location. The cytosol may be reached by this gene delivery, which has a 90% effectiveness rate for co-delivering DNA and siRNA. Researchers found that the nanoneedles promoted wound healing and scar tissue remodelling by transfecting the VEGF165 gene. A six-fold increase in blood perfusion in the targeted muscle is achieved by inducing long-term neovascularization. Using this limited intracellular delivery, it is possible to target particular tissue locations. They may also lessen the injection's invasiveness and its overall influence on the tissue's structure.

Regulatory Consideration:

The difficult process of commercialising wound healing or dressings that transport drugs, proteins, cells, or genes is a serious problem. Regulatory approval and clinical trial protocol consideration are also part of this. The kind and origin of diverse human and animal-derived materials, as well as the administration of wound dressing, are among the many aspects that must be taken into consideration throughout the regulatory approval process. Drug/device, biologic/device, drug/biologic, or drug/device/biologic are all examples of combination

products that are regulated components that are physically, chemically, or otherwise combined or blended and created as a single entity [60]. The major mode of action of a combination product is the fundamental factor in determining the USFDA's regulation of the product. For wound healing delivery systems that need premarket approval, clinical studies must demonstrate both safety and effectiveness in order to justify the use of the wound healing delivery systems. In the case of ulcer healing and angiogenesis, autologous stem cells are being tested in clinical trials and have shown to be quite beneficial. There is still a long way to go before stem cell transfer to animal models can aid human clinical trials, despite the progress made in the last several years. Using cell delivery devices to treat nonhealing wounds is an effective and safe therapeutic method, according to preliminary investigations. Targeted wound necessitates more clinical studies on human subjects with better data management of the patient's long-term condition. Patients with diabetic foot ulcers may benefit from improved stem cell delivery vehicles in large-scale human clinical trials. It has no serious side effects or complications, but further research is needed to understand its therapeutic mechanisms, effects, and standardisation [61] When it comes to addressing complicated wounds, delivery system-based treatments have the advantages, but they also come with the danger of infectious agent transmission and immunological rejection. Delivery methods for wound healing have significant production, transportation, and storage costs since their present clinical utilisation is restricted [62]

Safety is a major concern in many current clinical studies using stem cell treatments, including the use of stem cells to treat wounds [63]. Stem cell therapy may have major side effects on the immune system and the potential to cause cancer. Cell treatment uses a variety of delivery methods, including systemic administration, injection, topical application, and local administration. Wound healing requires localised cell distribution, which is ideal for wound therapy [64]

I. Conclusion:

Wound dressings and skin replacements have been created during the last several years to address skin loss and wounds that need to be dressed or healed. There is a lot of evidence that delivery methods have enhanced wound healing and skin tissue regeneration. Engineers have come up with new ways to deliver pharmaceuticals to hard-to-treat bacterial diseases, such as the development of nanoparticles and nanofibrous structures, hydrogels, and scaffolds made of polymers. Nanotechnology and biomaterial scaffolds are also attracting attention, as are medication delivery devices that can be managed. Skin wound healing uses growth factor and peptide delivery methods to promote tissue regeneration, reduce scarring, and rebuild blood capillaries. There is considerable hope for the treatment of chronic wounds and diabetic ulcers using the stem cells produced from adipose tissue, endothelial progenitor cells, mesenchymal stem cells, and endothelial keratinocytes examined in delivery systems. Biodegradable polymers, fibrin meshes, and human collagen have been found as promising delivery systems for gene treatments now in clinical studies. It might soon be used in clinical studies for wound treatment. Peripheral nerve regeneration, on the other hand, is a rare occurrence. In the future, these wound healing materials may be able to replace and regenerate more natural skin wounds, as well as obtain targeted distribution to the wound area. Controlling the release of medications requires the healing of burns, chronic, and complicated wounds. Additionally, the role of growth factors and cells, as well as the ability to silence genes, is critical in wound healing and wound dressing.

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