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Applications of Nanoparticles Preparations on Wound: A New Approach for Wound Repair and Regeneration

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***Abstract* - Wound healing is an inherent physiological response that aids restore cellular and anatomic continuity of a tissue. It is an intricate process and for a long time has been the subject of intense research. Impaired wound healing has resulted into socio-economical loss and decreased the quality of life of patient. So, there is always need to develop some alternative wound healing agent which can accelerate the healing mechanisms. The recent development of technology has provided a novel therapeutic modality in nanoparticles for use in wounds. Nanoparticles (NPs) are small entities that comprises of a hydroxyapatite core, which can bind ions, proteins, and other organic molecules from the surrounding environment. Nanotechnology has provided a new therapeutic route for wound treatment in clinical practice. This article aims to review the wound healing activities of nanoparticles during the past years.**
Keywords: **Nanoparticles, Therapeutic, Wound Healing**

I. INTRODUCTION

Wound healing is one of the complex and dynamic processes of substituting devitalized and missing cellular structures and tissue layers. The human adult wound healing process can be divided into 4 different phases. These are the hemostasis phase, the inflammatory phase, the proliferative phase, and the remodeling phase [1]. All four phases must occur in the appropriate sequence and time frame for a wound to heal successfully. Delayed wound healing or a non-healing chronic wound can occur as a result of interruptions, aberrancies, or prolongation in the process. Acute wounds heal in an arranged progression, maturing through artificially well-defined phases of coagulation, inflammation, matrix synthesis and deposition, angiogenesis, fibroplasia, epithelialization, contraction, and remodeling [2]. Chronic wounds are the wounds that have futile to evolve through standard stages of healing and hence arrived a state of delayed, incomplete, and uncoordinated restoration [3]. These types of wounds do not progress through an orderly process and have mislaid ideal synchrony of actions that lead to normal healing [4]. The result of improper wound healing and untimely sequence of events is an inability to reestablish normal structural integrity resulting in poor anatomical and functional outcomes [2, 3]. These types of wounds are considered to be chronic and can be a major disability [3]. Over the past two decades, there has been a surge in the development of nanoparticle technologies for therapeutic applications. Nanoparticles (NPs) are defined as particles having one or more dimensions in the order of 100 nm or less. In the area of skin wound healing, silver nanoparticles have been long used as topical antibacterials, but new types of multifunctional nanosystems that can provide more comprehensive therapeutic effects on wounds are being rolled out [5]. The ability to provide a reservoir of bioactive molecules that can be released over time is a feature of many of these systems, which is critically important for non-healing wounds, where there often is a persistent bacterial load and a chronic lack of growth factors necessary for healing. A great advantage of nanosystems is that by virtue of their extremely small size, they can be easily incorporated into a wide variety of topical treatments that are currently available for use in the clinic. For example, nanoparticles can be easily introduced into decellularized skin products as well as other bioengineered skin substitutes. The design options available for the nano carriers are very diverse, including encapsulating the drug in the particle's core or presenting it on the outside of the particle, which can also be decorated with a targeting agent, and the ability to change conformation in response to environmental cues (e.g., pH).

II. TISSUE ENGINEERING

The term tissue engineering originated in 1987 at a bioengineering panel meeting held at the National Science Foundation. In early 1988 the first tissue engineering meeting was held at Lake Tahoe, California in which a working definition was formulated [6]. Tissue engineering is the application of the principles and methods of engineering and the life sciences toward the fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain, or improve functions. Three general strategies can be followed for the creation of new tissue. First, isolated cells or cell substitutes may be used to supply the needed function. A second approach use, tissue inducing substances introduced into target areas. Finally, cells placed on or within matrices may

be implanted and incorporated into the body [7]. A combination of all of these approaches may also be used. Utilizing scaffolds to facilitate wound healing has been attempted as a modality to reestablish normal tissue structure, or engineer the tissue back to normal. As mentioned above, a scaffold based tissue engineering approach can include three elements [8]

1. Biomaterials from which scaffolds are formulated. These materials provide a three dimensional template for tissue reconstitution. These can be either natural or synthetic materials that are designed to help in organization, growth, and cell differentiation. These biomaterial scaffolds should be able to provide both chemical and physical signals to facilitate this process.
2. A suitable cellular population present from an autologous, allogenic, xenogenic, or stem cell source. Isolated cells can be expanded in a cell culture 20 and then seeded onto the scaffold to guide their growth and tissues regeneration in three dimensions [9]. Proliferation and differentiation of these cells is instrumental for success of the process.
3. The incorporation of biomolecules including angiogenic factors, growth factors, differentiation factors and signaling molecules.

III. WOUND TREATMENT

The earliest information on wound treatment is found in Egyptian medical documents, called the Ebers Papyrus. It is known that ancient Egyptians treated wounds by covering them frog skin and castor oil. The results have been limited and partially misleading, although humans have used many materials of biological origin in wound and burn treatment throughout history and have conducted various experiments on animals. Researchers subsequently sought new materials for use in wound healing, due to the disadvantages of traditional dressings such as gauze, paraffin gauze, biological dressings, etc. The first synthetic material used for wound coverage was methyl cellulose. The common feature of all these materials is the necessity of physical protection from external factors and conditions. Nanoparticles are also found to be widely used in wound healing because of their extremely small size. Rigo *et al.*, applied the silver nanoparticle (Ag NP) - based dressing, Acticoat™ Flex 3, to a 3D fibroblast cell culture in vitro and to a real partial thickness burn patient [10].The in vitro results showed that Ag NPs greatly reduce mitochondrial activity, while cellular staining techniques showed that nuclear integrity is maintained, with no signs of cell death. For the first time, transmission electron microscopy (TEM) and inductively coupled plasma mass spectrometry (ICP-MS) analyses were carried out on skin biopsies taken from a single patient during treatment. The results showed that Ag NPs are released as aggregates and are localized in the cytoplasm of fibroblasts. No signs of cell death were observed, and the nanoparticles had different distributions within the cells of the upper and lower dermis. Depth profiles of the Ag concentrations were determined along the skin biopsies. In the healed sample, most of the silver remained in the surface layers, whereas in the unhealed sample, the silver penetrated more deeply. The Ag concentrations in the cell cultures were also determined using inductively coupled plasma-quadrupole-mass spectrometry (ICP-QMS) using a model 7500cx instrument from Agilent Technologies (Tokyo, Japan). They observed that AgNP-based dressing does not create an obstacle to the recovery of severe partial thickness burns. After application for an extended period (17 days), the organized skin structure (dermis and epidermis) was re-established in a previously unhealed part of the wound. In their pilot study, they have also demonstrated that the application of Ag NP-based dressings, even for a prolonged time, does not seem to negatively affect the proliferation of fibroblasts and keratinocytes, leading to the restoration of normal skin.

Augustine *et al.*, synthesized silver nanoparticles using chemical reduction method. These nanoparticles were coated over an absorbable surgical gut suture, after the immobilization of them in sodium alginate, by slurry dipping technique [11]. The controlled release of the nanoparticles checked in vitro in simulated body fluid. The successful release of silver nanoparticles under physiological PH depicted the applicability of this novel suture in surgery for the prevention of surgical wound infection and to enhance wound healing. The nanoparticles immobilized on surgical gut sutures by the use of alginate as cross linking agent. As a result of the formation of calcium alginate coating over the sutures it can facilitate moist environment that promotes wound healing along with the microbial inhibition contributed by the silver nanoparticles. The in vitro release studies in simulated body fluid showed the potential of the designed suture to deliver nanoparticles, the active principles on the wounds for a required period of time. The disc diffusion assay carried out on nutrient agar plates indicated the ability of the designed suture to inhibit the growth of both gram positive and gram negative bacteria successfully.

Auddy *et al.*, in their study modified guar gum, a polymeric galactomannan, intrinsically to a new cationic biopolymer guar gum alkylamine (GGAA) for wound healing applications [12]. Biologically synthesized silver nanoparticles (Agnp) were further impregnated in GGAA for extended evaluations in punch wound models in rodents. The new GGAA matrix provided stabilization of silver nanoparticles. SEM studies showed silver nanoparticles well dispersed in the new guar matrix with a particle size of ~18 nm. In wound healing experiments, faster healing and improved cosmetic appearance were observed in the new nanobiomaterial treated group compared to commercially available silver alginate cream. The total protein, DNA, and hydroxyproline contents of the wound tissues were also significantly higher in the treated group as compared with the silver alginate cream ($P< 0.05$). Silver nanoparticles exerted positive effects because of their antimicrobial properties. The nanobiomaterial was observed to promote wound closure by inducing proliferation and migration of

the keratinocytes at the wound site. The derivatized guar gummatrix additionally provided a hydrated surface necessary for cell proliferation. The nanobiocomposite was found to promote wound healing by modulation of collagen deposition and regulation of keratinocytes and support the essential re-epithelialization process.

Li *et al.,* synthesized a mixture of polyvinylalcohol (PVA) and chitosan oligosaccharides (COS) was electrospun with silver nanoparticles (AgNPs) to produce fibrous mats for use in wound healing [13]. The AgNPs were reduced by COS prior to electrospinning or Ag^+ was reduced via ultraviolet irradiation in nanofibers. The nanofibers significantly inhibited growth of Escherichia coli and Staphylococcus aureus bacteria. PVA/COS-AgNP nanofibers accelerated the rate of wound healing over that of the control (gauze). The in vitro results and in vivo animal experiments suggested that PVA/COS-AgNP nanofibers should be of greater interest than PVA/COS/AgNO3 nanofibers for clinical use as a bioactive wound dressing.

To assess wound healing, four full-thickness circular wounds were cut into the back of each rat, and the wounds were covered with PVA/COS/AgNO3, PVA/COS-AgNP nanofiber mats, commercially available wound plasts (positive control), or gauze (negative control).According to the histological examination, the PVA/COS-AgNP nanofiber demonstrated superior wound healing compared with gauze and the PVA/COS/AgNO3 nanofiber. Seven days after grafting, the wounds in the PVA/COS/AgNO3 nanofiber and gauze groups displayed ulcerated surfaces, formation of granulation tissue, and infiltration of inflammatory cells. In contrast, the granulated tissue in the PVA/COS-AgNP group disappeared without capillary hyperplasia. Late-stage healing processes in the control group were similar to those in the AgNP-containing nanofiber groups. On day 14, newly synthesized fibrous tissue and sparse inflammatory cells in the dermis and subcutaneous were covered by completely re-epithelialized epidermis in each group.

Mathivanan *et al.,* studied the impact of silver nanoparticles on the wounded skin of freshwater fish, Anabas testudineus [14]. Five fishes were taken and released into to experimental trough with 5 litter of water to which 10 and 20% concentration of the silver nanoparticle solution was taken. The wounded test fish Anabus testudineus was allowed to rear in the experimental trough. It was found that the wounded fish Anabas testudineus showed wound healing after 12 days only when it was kept in 10% solution of silver nanoparticles. Whereas, the wounded test fish kept in 20% solution of silver nanoparticles showed the wound healing within 8 days. Wound healing experiments using this fish model (Anabas testudineus) showed that the application of silver nanoparticles on to an open wound induces significant wound contraction and accelerates the wound closure and healing time.

Tian *et al.,* investigated the wound-healing properties of silver nanoparticles in an animal model and found that rapid healing and improved cosmetic appearance occur in a dose-dependent manner [15]. Furthermore, through quantitative PCR, immunohistochemistry, and proteomic studies, they showed that silver nanoparticles exert positive effects through their antimicrobial properties, reduction in wound inflammation, and modulation of fibrogenic cytokines. In their thermal injury model, the deep partial-thickness wounds normally healed after 35.41.29 days. In animals treated with silver nanoparticles (ND), these healed in 26.50.93 days, whereas wounds treated with silver sulfadiazine (SSD) needed 37.43.43 days. The rate of healing in the three groups was also compared as with healing time, rate of healing was increased in animals treated with ND. These observations indicate that wound healing is accelerated by silver nanoparticles. Appearance of healed wounds were compared and it was found that wounds in the ND group showed the most resemblance to normal skin, with less hypertrophic scarring and nearly normal hair growth on the wound surface. The worst cosmetic appearance was observed in the SSD treatment group. Under histological evaluation, healed wounds from the ND group resembled normal skin, with a thin epidermis and nearly normal hair follicles. In contrast, histological sections from the SSD-treated group showed thickened epidermis and no evidence of hair growth.

Heydarnejad *et al.,* found the effects of silver nanoparticles (Ag-NPs) (40 nm) on skin wound healing in mice Mus musculus when innate immune system has been suppressed [16]. The results showed that wound healing is a complex process involving coordinated interactions between diverse immunological and biological systems and that Ag-NPs significantly accelerated wound healing and reduce scar appearance through suppression of immune system as indicated by decreasing levels of all inflammatory factors measured in their study. Transforming growth factor beta (TGF-β), complement component C3, and two other immune system factors involving in inflammation, namely C-reactive protein (CRP) and rheumatoid factor (RF) in sera of both groups were assessed and then confirmed by complement CH_{50} level of the blood. Furthermore, the immune suppression effects of Ag-NPs have been observed with decreased serum levels of TGF- β, C3, RF, CRP following confirmed by CH_{50} in the blood.

Rajendran *et al.,* developed herbal based nanoparticle finishes for wound care textiles. The plant with potent antimicrobial activity was selected for the study [17]. The nanoparticles of the herbal extracts were prepared by ionic gelation using tripolyphosphate anions (TPP). The topographical characterization of the herbal nanoparticles was performed using FESEM and particle size was measured using DLS. Then the herbal nanoparticles were finished onto the wound dressings using pad-dry-cure method. The antimicrobial properties of the herbal nanoparticles treated wound gauze were studied qualitatively by standard AATCC techniques. The

antibacterial assessment of the nanoparticle finished gauze was assessed against the bacterial strains isolated from pus. The bacterial strains isolated from the wound were Escherichia coli, Staphylococcus aureus, Klebsiella sp., Pseudomonas sp., Serratia sp., and Acinetobacter sp. The nanoparticles prepared were roughly spherical and the size of the particles was in the range of 60-90 nm. The herbal nanoparticles treated wound dressing showed excellent antimicrobial property with 100% bacterial reduction almost all the tested bacteria. The results suggested that the use of such antibacterial wound dressing will prevent the microbial infections and reduce the bioburden of the wound thereby enhance the wound healing.

Huang *et al.,* studied that topical gas-injection of aEGCG and gold nanoparticle (AuNP) liquid mixture (AuE) using the GNT GoldMed™ Liquid Drug Delivery System significantly accelerated the wound healing on wild-type and streptozotocin-induced diabetic mouse skin [18]. Immunoblotting of the diabetic wound tissue showed a significant increase of the vascular endothelial cell growth factor on day 7 and the Cu/Zn superoxide dismutase expression from day 3 to day 7. Furthermore, the epidermal growth factor receptor and collagen I & III protein expression both increased significantly in the wound area. After gas-injection of the AuE liquid, hyaluronic acid (HA) expression also significantly increased on day 7 as measured by immunohistochemistry analysis. In conclusion, it was found that gas-injection of AuE significantly increases the rate of wound healing both in wild-type and diabetic mice. Their study provided a new and more effective method for the future clinical delivery of other growth factors or antioxidants as topical treatments for diabetic ulcers. Their study presented gold nanoparticles and a liquid drug delivery system to solve the problem of the low bioavailability of green tea extract. It enhanced the ability of AuNPs to promote the formation of collagen and hyaluronic acid in the deep layers of the skin.

Leu *et al.,* studied the effects of Gold nanoparticles (AuNPs), epigallocatechingallate (EGCG), and α-lipoic acid (ALA) in Hs68 and HaCaT cell proliferation and in mouse cutaneous wound healing [19]. They were shown to have antioxidative effects and could be helpful in wound healing. Both the mixture of EGCG+ALA (EA) and AuNPs +EGCG+ALA (AuEA) significantly increased Hs68 and HaCaT proliferation and migration. Topical AuEA application accelerated wound healing on mouse skin. Immunoblotting of wound tissue showed significant increase of vascular endothelial cell growth factor and angiopoietin-1 protein expression, but no change of angiopoietin-2 or CD31 after 7 days. After AuEA treatment, CD68 protein expression decreased and Cu/Zn superoxide dismutase increased significantly in the wound area. The decreased CD68 expression and increased SOD1 expression around the wound area suggested that anti-inflammatory and antioxidative effects of AuEA may have a role in mouse cutaneous wound healing. In conclusion, AuEA significantly accelerated mouse cutaneous wound healing through anti-inflammatory and antioxidation effects. Their study may support future studies using other antioxidant agents in the treatment of cutaneous wounds.

Rakhmetova *et al.,* reported the wound healing potential and physicochemical characteristics of copper nanoparticles prepared by high temperature condensation and modified with a variety of agents (including oxygen, water vapors, and air) [20]. Modified copper nanoparticles in the form of an ointment showed wound healing behavior that differs in effectiveness depending on their physicochemical parameters. Nanoparticles of copper oxide (sample 7) (modified with air), with a particle size of 119 nm and crystalline copper content of ~0.5%, and copper nanoparticles (sample 2) (modified with oxygen), with a particle size of 103 nm and crystalline copper content of 96%, demonstrated the maximum specific rate of wound adhesion. Copper nanoparticles exhibit wound healing activity and the progress of healing depends on the copper nanoparticle's properties. Copper nanoparticle samples 7, 2, and 5, (modified with air), with a particle size of 86.8 nm and crystalline copper content of 94% were the most active, accelerating the process of wound healing by 51.7, 44.8, and 37.9%, respectively, if compared to the control (untreated mice) and by 2–2.3 times when compared to control animals treated with nanoparticle free ointment. A weak wound healing effect was exhibited by copper nanoparticle sample 1 (modified with water vapors), with a particle size of 86 nm and crystalline copper content of 84%, sample 3, (modified with oxygen), with a particle size of 77.3 nm and crystalline copper content of 3.3 %, and sample 4, (modified with oxygen), with a particle size of 47 nm and crystalline copper content of 84%.

Tiwari *et al.,* reported the synthesis of copper nanoparticles by Pseudomonas aeruginosa and tested their efficacy in enhancing the pace of wound healing [21]. Culture supernatant was used to synthesize copper nanoparticles. Optimum conditions were selected to maximize the biosynthesis of nanoparticles. Biosynthesised copper nanoparticles (BNCPs) were characterized by Malvern zeta sizer and scanning electron microscopy. Average particle size, polydispersivity index and zeta potential of BNCPs were found to be 110.9 nm, 0.312 and (−) 18.3 mV, respectively. BNCPs were evaluated for its wound healing activity by excision wound model in rat. The pace of wound healing was enhanced by BNCPs compared with copperin native form. BNCPs showed significant role in wound healing process in the earlier stage. On the second day of drug application, percentage healing in the BNCPs gel-treated animals was found to be twice than in the control group of animals and significantly better than in the control gel- and the copper native gel-treated animals. As the days progressed, the pace of wound healing with control gel was similar to control animal and lesser in native copper gel-treated group of animals. After tenth day of excision, BNCPs treatment reduced the wound size by 92%. After 15^{th} day of excision, no significant difference was observed. Wounds created in both normal control and gel control

healed at the same pace. The pace of wound healing in BNCPs-treated animals was faster compared with the control group. In case of native copper-treated animals, wound healing was slow. During the course of the study it was found that the native copper had actually delayed the wound healing even though BNCPs had remarkably enhanced wound healing compared with the control. This could be because of the toxicity of native copper at the dose used.

Kawai *et al.,* synthesized pH-sensitive calcium-based nanoparticles and investigated their ability to enhance cutaneous wound repair [22]. Different populations of nanoparticles were synthesized on collagen-coated plates under various growth conditions. Bilateral dorsal cutaneous wounds were made on 8-week-old female Balb/c mice. Nanoparticles were then either administered intravenously or applied topically to the wound bed. The rate of wound closure was quantified. Intravenously injected nanoparticles were tracked using a FLAG detection system. The effect of nanoparticles on fibroblast contraction and proliferation was assessed. A population of pH-sensitive calcium-based nanoparticles was identified. When intravenously administered, these nanoparticles acutely increased the rate of wound healing. Intravenously administered nanoparticles were localized to the wound site, as evidenced by FLAG staining. Nanoparticles increased fibroblast calcium uptake in vitro and caused contracture of a fibroblast populated collagen lattice in a dose-dependent manner. Nanoparticles also increased the rate of fibroblast proliferation. Intravenously administered, calcium-based nanoparticles can acutely decrease open wound size via contracture. The contraction effect is mediated by the release of ionized calcium into the wound bed, which occurs when the pH-sensitive nanoparticles disintegrate in the acidic wound microenvironment.

Copper nanoparticles also promote the wound healing via acceleration of skin cell migration, proliferation, and neovascularization [23]. In this study, the 1 μM concentration of 80 nm copper nanoparticles accelerated wound healing and decreased the duration of healing via formation of good quality granulation tissue and increased blood vessels. Additionally, serum biochemical analysis did not show any accumulation in the liver during wound healing. Farghaly *et al.,* formulated a hydrogel loaded with polymeric nanoparticles (PoNPs) of simvastatin (SIM) for topical wound healing evaluation [24]. This study revealed that the hydrogel loaded with SIM PoNPs possessed the potential for the acceleration of the wound healing in rat with complete epithelialization and least inflammatory cell infiltration. Mahmoud *et al.,* loaded gold nanoparticles into polymeric hydrogel and studied their potential for wound healing in rats [25]. They showed that hydrogel having gold nanoparticles accelerate the healing process and have promising nano-platform for wound healing.

Now days, synthesizing nanoparticles by greener way has emerged as an alternative method due to its ecological and cost benefits. Li *et al.,* synthesized Ag2O NPs by using Lippia citriodora plant powder. These Ag2O NPs showed excellent antibacterial as well as antifungal activities and Ag2O NPs incorporated hydrogels showed the improved cutaneous wound healing activity in rats [26]. Zangeneh *et al.,* studied the green synthesis of copper nanoparticles from aqueous extract of Falcaria vulgaris leaf (CuNPs) and assessment of their cytotoxicity, antioxidant, antifungal, antibacterial, and cutaneous wound healing properties [27]. The ointment of these nanoparticles increased the wound contracture, blood vessels, hexosamine, hydroxyl proline content, fibroblast proliferation rate. Naraginti *et al.,* showed that topical application of green synthesized, formulated silver and gold nanoparticles ameliorated of excision wounds in albino Wistar rats [28].

The delivery of drugs in combinations with the involvement has also gained interest for the wound healing. Jee *et al.,* prepared and evaluated a topical hydrogel system by incorporating growth factors, quercetin, and oxygen carriers for enhanced diabetic wound-healing therapy [29]. This study revealed that the combination therapy synergistically accelerated the healing of chronic wounds and showed rapid as well as prolonged effects. Kurowska *et al.,* prepared a non-propellant based foam system by the incorporation of antibiotics, pectin capped green nano-silver and sulfadiazine for evaluating its efficacy for burn wounds on topical applications [30]. This study showed that the foam improved the healing of burn wounds and it could be considered as an alternative topical formulation for superficial burn wounds.

IV. CONCLUSION

Different healing drugs in nanoparticles form or their loading in some nanoparticles are considered more effective as wound healing accelerator than artificial polymers. The wound treated with nanoparticles revealed enhanced healing. Consequently, the nanoparticles/ nanoformulations are considered to be one of ideal materials with wound healing property as well as easy application.

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