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Nano Carriers in Augmented Wound Healing Management

Dr. Poonam Kushwaha[1*], Babita Shukla[1]

[1]*Faculty of Pharmacy, Integral University, Luck now, India*

ABSTRACT

Wound healing management has always been an interesting field of research till date due to serious need for new wound treatment. Appropriate wound care is a significant challenge because of the complications associated with wounds as well as low permeability through the skin. The chronic nature and associated complications of nonhealing wounds have led to the emergence of nanotechnology-based therapies that aim at facilitating the healing process and ultimately repairing the injured tissue. They offer several benefits in the healing process such as decrease in drug's cytotoxicity, administration of poorly water-soluble drugs, better skin permeation, controlled release behavior, antimicrobial activity, as well as stimulation of fibroblast proliferation and reduced inflammation. In this outlook, present review highlights the recently developed nanotechnology-based promising strategies that can advance the wound-healing field.

Keywords: Wound Healing; Nanotechnology; Polymeric nanoparticles; Nano emulsion; Liposomes; Hydrogels; Scaffolds

INTRODUCTION

Skin, the largest organ of the body has three different layers, which are self-renewable and have various functions and roles in maintaining tissue integrity and cellular functions [1]. It also provides protection from microbial invasion. Naturally, wound can be healed because of the regenerative property of the skin. However, sometimes, this property does not work perfectly leading to formation of chronic wounds and further brings risk in patient's health [2].

Wound is defined as the disruption of the anatomic and cellular continuity of tissue caused by chemical, physical, thermal, microbial, or immunological injury to the tissue [3]. As recorded, normally wound healing takes two to three weeks in normal healthy persons. Chronic wounds build up because of a disturbance during the healing process. They fail to heal within the normal period sufficient for the healing of acute one, in another meaning fail to close due to a problem in one or more of the wound healing stages. Venous leg ulcers, pressure sores, ischemic ulcers, and diabetic foot ulcers are the main causes of chronic wounds, which may be associated with individual's mortality. Many signs characterize the chronic wounds such as increasing in inflammation, exudates accumulation, swelling, pain and stiffness in the affected area, hyper proliferative, so far non-advancing wound margin. Inflammation associated the wound may delay healing process. In addition, the ulceration, which appears as a result from chronic wound, plays an important role in the pathogenesis of unhealed wounds [4]. It has been noticed that, in recent years the prevalence of people suffering from chronic wounds has raised due to the dramatically

increasing incidence of obesity and chronic diseases such as diabetes, venous and arterial insufficiency.

Chronic wounds and infected wounds currently pose a significant burden worldwide. Drug delivery systems in wound healing that release antimicrobial and anti-inflammatory drugs represent a great opportunity to prevent infections or enhance the effectiveness of current commercial drugs. Recently, many researchers showed that the wound dressing materials have entered a new level of standards and there is a far better understanding based on the pathogenesis of chronic wounds. Wound care management mainly depends on the development of new and effective wound dressing materials. Consequently, an extensive percentage of Nano delivery systems are used in diverse biomedical applications for wound dressings, drug delivery and other medical purposes [2, 4, 5, and 6]. These Nano delivery systems have been proven the most promising approach for faster wound healing among all the other wound healing strategies. The present review briefly discusses the wound healing process, the recent developments of wound healing by nanotechnology, their applicability and advantages and the state of the art in Nano delivery carriers that holds a promising potential for future application, with a special focus on liposomes, polymeric nanoparticles, lipid nanoparticles, Nano fibrous structures and Nano hydrogel [7].

WOUND CATEGORIES AND WOUND HEALING PROCESS

WOUND CATEGORIES

Depending on the duration and methods of the healing process, wounds can be classified into acute and chronic wounds. Wounds resulting from corrosive chemicals, radioactivity, mechanical injury, heat, or electrical shock are considered acute wounds; they usually heal in a predictable manner with no complications. The wound, which takes more than 12 weeks to heal, is considered as a chronic wound. Usually, wounds taking more than 90 days to heal are referred as chronic wounds. Chronic wounds, however, are associated with specific diseases, such as diabetes mellitus, and do not follow the orderly set of stages and predictable amount of time that characterize the normal wound-healing process. Chronic wounds frequently remain in the inflammatory stage for a long time, and their duration is associated with factors such as bacterial load, necrotic tissue, and moisture balance of the wound site. Further, the risks of this reappearance of chronic wounds are exceedingly high, unless the root of the disease is cured.

Wounds can also be classified into three types according to wound depth: (1) superficial wounds, which lost a part of epidermis; (2) partial-thickness wounds, where epidermis and deeper dermal layers are affected; (3) full-thickness wounds, where the subcutaneous fat and deeper tissue are ruptured [8, 9].

WOUND HEALING PROCESSES

Wound healing is a natural physiological reaction to tissue injury. However, it is a complex process consists of integrated cellular and biochemical cascades leading to reestablishment of structural and functional integrity of the damaged tissue [3]. The cascade of initial vasoconstriction of blood vessels and platelet aggregation is designed to stop bleeding. This is followed by an influx of a variety of inflammatory cells, starting with the neutrophil. These inflammatory cells, in turn, release a variety of mediators and cytokines to promote angiogenesis, thrombosis, and reepithelialisation. The fibroblasts, in turn, lay down extracellular components, which will serve as scaffolding. The inflammatory phase is characterized by homeostasis, chemo taxis, and increased vascular permeability which limits further damage closes the wound, removes cellular debris and bacteria, and fosters cellular migration. The duration of the inflammatory stage usually lasts several days. The proliferative phase is characterized by the formation of granulation tissue, reepithelialisation, and neovascularization. This phase can last several weeks. The maturation and remodelling phase is where the wound achieves maximum strength as it matures [10, 11].

Various phases occur in wound healing, is represented in Figure 1 involving inflammation, cells proliferation, and tissue remodelling [11].

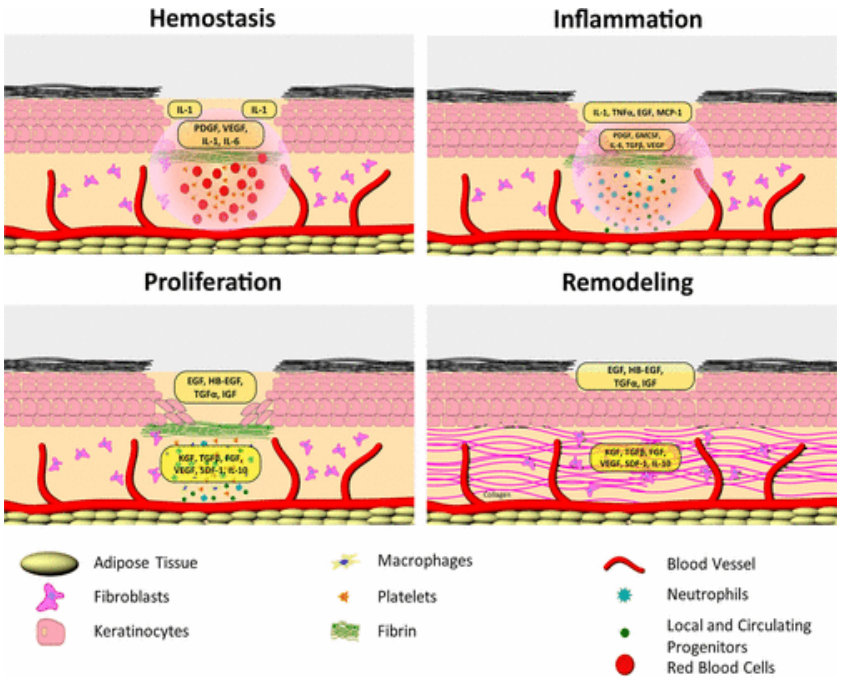

Figure 1. Phases of cutaneous wound healing depicting the cells and molecules responsible for the regaining of a healthy barrier [11].

NANO DELIVERY CARRIERS IN WOUND HEALING

Nano delivery carriers showed remarkable and significant potential in enhancement of drug solubility, therapeutic efficacy, and augmentation of stability, protection from toxicity, drug and sustaining drug release. In recent years, they are emerging as an excellent strategy to target the complexity of the normal wound-healing process, cell type specificity, and plethora of regulating molecules as well as pathophysiology of chronic wounds. An increasing number of innovative Nano scale strategies were explored for targeting different phases of wound repair including liposomes, polymeric nanoparticles, Nano emulsion, lipid nanoparticles, Nano fibrous structures and Nano hydrogel (Figure 2).

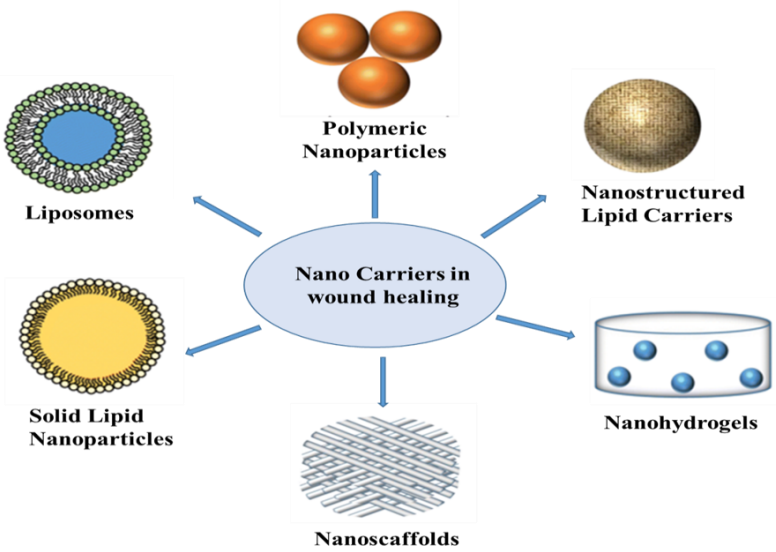

Figure 2: Nano carriers in wound healing applications

POLYMERIC NANOPARTICLES

In the topical area polymeric nanoparticle have been gained an increased attention to overcome the limitations related to other lipid system. The limitations include lower drug loading capacity, higher drug permeation and phase stability issues.

Polymeric nanoparticles are biocompatible colloidal systems drawing increasing attention in both biomedicine and bioengineering fields. When embedded or conjugated with these polymeric devices, drugs are protected from degradation by the proteases presenting in the wound, and released in a controlled manner to reduce administration frequency. The need of effectively delivering biomolecules such as antimicrobial agents, growth factors and genes, will be met with aid of nanoparticles. Currently, polymeric nanoparticles are prepared by poly lactic-co-glycolic acid (PLGA, crowned as the mostly used polymers), alginate, gelatin, chitosan, as well as other polymer combinations [13]. These polymeric carriers show good controlled and sustained release by modifying the composition of polymers [14]. Many researches focus on developing polymeric nanoparticles encapsulating antimicrobial agents. Chereddy et.al, reported a PLGA nanoparticle loaded with antimicrobial peptide LL37 (PLGA-LL37 NPs) could be a biodegradable drug delivery system that accelerated healing process. The drug permeation is higher in case of polymeric nanoparticle due to steady release of drug from nanoparticles on the skin surface. However, it is unable to permeate deeper skin layers [15]. Luengo et.al, reported that, PLGA nanoparticles showed maximum proliferation and reduce the time of healing [16]. In addition, chitosan (CS) acts as prophylactic agent to prevent spreading of infections. It is a polysaccharide with numerous significant biopharmaceutical characteristics and it acts as penetration enhancer in topical formulations. Dai et.al, reported chitosan-based PLGA nanoparticles could advance the topical delivery in several ways, like increased stability of the macromolecules. Two drugs can be incorporated in outer and inner layers of the nanoparticles. The free amino group of chitosan helps to conjugate with other molecule and thus acts as penetration enhancer [17]. In some research studies, it has been found that CS NPs were used in the preparation of films and various bandages to give more mechanical support to wound as well as to treat infected open wounds [18].

Another study conducted by Bilgi et.al, demonstrated that the application of gelatin-based scaffolds to rat wounds resulted in faster wound closure and enhanced overall wound healing [19]. Lee et al. observed the same result, after application of fibrin scaffolds. Fibrin can reduce inflammation, increases immunological response and cell adhesion properties. It has been widely used for tissue engineering and wound healing [20].

NANO EMULSIONS

Nano emulsions (NE) are the mixture of two immiscible liquids, which are stabilized by addition of surfactant. The nanoparticles formed are of size range of 20–200 nm [21]. The antimicrobial oil-in-water Nano emulsions is efficient against bacterial pathogens and show broad-spectrum activity due to the less droplet diameter [22]. As reported by Song et.al, chlorhexidine acetate formulated in a Nano emulsion was used against a Methicillin-Resistant S. Aurerus (MRSA) infection in a skin burn wound model. The nanoemulsion revealed successful and fast action against MRSA in-vitro and in-vivo. In addition, the formula allows delayed formation of biofilm, and disrupted MRSA cell walls, led to increased leakage of DNA, protein, Mg^{2+}, K^{+} and alkaline phosphates out of the cells [23].

In another study, Shanmugapriya et.al, developed a nanoemulsion formulation loaded with alpha tocopherol in combination with astaxanthin, which revealed a good antibacterial effect against S. aureus. Nanoemulsion formulation showed a significant damage to the bacterial cell membrane, facilitating its uses as an efficient antibacterial agent in addition to preventing them from developing resistance [24]. Recently, Morsy et.al, prepared topical nanoemulgel of ATR

and evaluated for the wound healing efficacy. Wound healing efficacy of nanoemulgel was compared with other gel and emulgel preparation. In vitro study showed significant skin permeation potential of ATR nanoemulgel. In vivo wound healing studies revealed remarkable wound contraction with ATR nanoemulgel exhibited the highest percent wound contraction. Histopathological assessment showed marked improvement in the skin histological architecture after 21 days of ATR nanoemulgel treatment. In conclusion, nanoemulgel could serve as an innovative therapeutic approach in wound healing [25].

LIPOSOMES

Liposomes are bilayer vesicles built by amphiphilic molecules such as phospholipids, emerging as one of promising Nano-carriers for topical drug delivery [26]. They are nontoxic, biodegradable, biocompatible with skin, and capable of accommodating both hydrophilic drugs (e.g., growth factors) in inner water cavity and hydrophobic agent in bilayer [27, 28]. In this way, liposomes provide protection for encapsulated drug and sustain the drug release. Furthermore, liposomes effectively cover wound and create moist environment on wound surface after application, which is very conducive to wound healing [29]. Taking advantage of all these merits, liposomes have been universally applied in wound treatment and skin regeneration. Xu et.al, prepared a novel liposome with hydrogel core of silk fibroin, which effectively encapsulated bFGF. The vehicles remarkably improved the stability of bFGF in wound fluids and maintained cell proliferation activity with respect to traditional liposomes. Furthermore, the liposomes with hydrogel core efficiently accelerated wound healing, particularly in inducing angiogenesis [30]. Nunes et.al, evaluated the promoting effect of a gelatin-based membrane containing usnic acid-loaded liposome on wound healing. The experiments on a porcine model indicated that the liposomal membrane conspicuously controlled the secondary infection. In addition, more exuberant and cellularized granulation tissue with better collagen deposition was observed in the liposomal membrane treated group, therefore the special membrane boasted a comparable capacity to commercial product DuoDerme with regard to enhance maturation of granulation tissue and scar repair [31].

In recent years, a new generation of deformable liposomes, called transfersomes, consist of phospholipids and an edge activator (such as sodium cholate, sodium deoxycholate and Tween-80), presented a new insight into topical drug delivery [32]. These novel carriers not only integrate the benefits of traditional liposomes, but also show more merits in topical application. The presence of edge activator renders high flexibility of deformable liposomes and enables them to across the stratum corneum and reach the viable epidermis [33]. Uk Choi et.al, conjugated low-molecular-weight protamine (LMWP) to the N-termini of EGF, PDGF-A and IGF-1, these molecules were subsequently complexed with hyaluronic acid and eventually incorporated into cationic deformable liposomes. The results showed that the cationic elastic liposomes containing the growth factor complex significantly accelerated the wound closure rate in the diabetic mouse model, with the maximal shrink of wound size by 58% compared with the native growth factor complex. It was fully confirmed that the elastic liposomes cooperated with growth factor complex, synergistically exerting both rapid and prolonged effects on promoting chronic wound healing [34]. A new self-assembling core–shell gellan-transfersome loading baicalin was designed by Manconi et.al. They found out that novel transfersomes showed a relatively high skin drug deposition; about 11% of baicalin was retained in the whole skin, 8% of which was in the dermis, considered quite efficient. Daily application of baicalin transfersomes in mice model brought about complete skin restoration and inhibition of inflammatory markers such as oedema, TNF-α and IL-1β [35]. Kianvash et.al, also noticed that their newly prepared propylene glycol nanoliposomes containing curcumin not only featured by preferential physiochemical properties (small size, sustained drug release, good stability and biocompatibility), but promoted second degree burns in rat model in terms of avoiding infections and elevating wound contraction [36].

NANO HYDROGELS

Nano hydrogel is the three-dimensional polymeric networks considered as ideal formulation for wound management. The porous three-dimensional structure of hydrogels endows the ability of aqueous fluid absorption [37], thereby preventing wound dehydration and creating a beneficial moist environment for wound healing [38]. The non-adhesive nature of hydrogels allows it to preserve the wound bed while maintaining the penetration of oxygen, which is necessary for wound healing [39]. Soft texture of nanohydrogel provides comfortable experience in the course of treatment [40]. Furthermore, nanohydrogel is able to encapsulate many related drugs with perfect compatibility and efficacy, exerting an impressive effect on skin regeneration.

A gellan-cholesterol nanohydrogel embedding baicalin was introduced by Manconi et.al, to speed up wound healing process [41]. Characterized by proper viscosity, improved skin retention and preferable biocompatibility, it was further applied to a cutaneous inflammation mice model induced by a phorbol ester. The baicalin-loaded nanohydrogel exhibited optimal performance for a complete skin restoration and inhibition of specific inflammatory markers (i.e., myeloperoxidase, tumor necrosis factor-α and oedema) were realized in vivo. Xi Loh et. al, found that a newly-produced bacterial nanocrystal cellulose/acrylic acid hydrogel could rapidly adhere to fibroblasts, maintain the activity and morphology of human dermal fibroblasts, limit cell migration, promote rapid cell proliferation, and affect 9 gene expression related to wound healing like IL-6, IL-10, GM-CSF, TGF-β and matrix metalloproteinase-2 (MMP-2). Thus, this hydrogel was regarded as playing a pivotal role in skin regeneration [42].

Besides, the versatile administration of nanohydrogel has received considerable interest, with the special focus on injectable nanohydrogel. Giriraj et.al, reported a nanocomposite hydrogel consisted of natural polysaccharide, κ-carrageenan and nanosilicates. This specially designed nanohydrogel was confirmed to feature with high mechanical stiffness and good porosity with an interconnected network. With the addition of VEGF, VEGF-loaded nanohydrogel significantly enhanced cell adhesion and spreading, reduced blood clotting time and facilitated in vitro tissue regeneration. However, the further in vivo investigation is required to fully reveal the therapeutic efficacy of this novel formulation on wound healing [43].

LIPID NANOPARTICLE

Lipid nanoparticles are of two types -Solid lipid nanoparticles (SLNs) and nanostructured lipid nanoparticles (NLCs). These are the topical drug delivery vehicles, which can be delivered oral, inhalational and parenteral routes. The lipid nanoparticles consider as an outstanding tool to deliver drugs in dermatological fields [44]. SLNs consist spherical solid lipids with hydrophilic moieties such as PEG derivatives, stabilized by different surfactants. NLCs are the improved generation of SLNs, which consists of both solid and liquid lipid components. On addition, they are having better drug loading capacity as well as better stability [45]. NLCs can overcomes the limitations associated with SLNs such as limited drug loading, drug leakage during storing, and risk of gelation. The lipid core has more biocompatibility and biodegradability. Additionally, the nano size is closely connected to layers of skin and helps in better drug permeation. Hence, these carriers act as a key tool to deliver the drug over an extended period with reduced side effects [46]. Many studies have been performed regarding the efficacy of these nanoparticles on dermal delivery. The types of the lipid used for the preparation influence the penetration profile of the drug, and correlates with drug solubility and lipid polarity. Mendes et al, reported a poorly water-soluble antifungal drug named Miconazole encapsulated in NLCs, which showed better antifungal action against candidiasis [47]. In another recent study, Gainza et.al, found that the NLCs loaded with emulsified recombinant human (rh) EGF-loaded stimulated fibroblast expansion and production of collagen and thus induced wound healing [48].

NANO FIBROUS SCAFFOLDS

The primary aim of tissue engineering is the creation of a biocompatible and biodegradable scaffold combining with living cells and bioactive moieties. A Scaffold is a network like structure, which supports the living tissue and replace, regenerates and repairs affected tissues. The ideal activity of scaffold is to mimic the biological as well as structural properties of extracellular matrices (ECMs) [49]. In case of chronic wounds, tissues are unable to regenerate by themselves thus concept of scaffold is needed which will promote the natural healing. Simple electrospinning technique has been used to produce morphologically similar nanofibrous scaffold to ECM. The electrospun nanofibers have large surface area and porosity, which helps in better permeability for oxygen and water. Additionally, it is capable to adsorb extrudes and protects the affected area from bacterial invasion. In a reported study, Waghmare et. al, fabricated starch-based nanofibrous scaffolds by electrospinning for wound healing applications. Cellular assays with L929 mouse fibroblast cells indicated the ability of the scaffolds to promote cellular proliferation, without exhibiting any toxic effect to the cells [50].

In another study, Örgül et.al, developed tissue scaffolds comprised of mesenchymal stem cells and simvastatin loaded nanostructured lipid carriers (NLCs) dispersed in a polymeric matrix and investigated for healing efficacy in diabetic wound. Study revealed, incorporation of NLCs into tissue scaffolds decreased the initial simvastatin burst release ratio and provided controlled release profile. Tissue scaffolds containing simvastatin lipid nanoparticles increased wound closure rate, promoted vascularization of injured tissue and enhanced viability and proliferation of stem cells. Thereupon, tissue scaffold formulation containing simvastatin lipid nanoparticles and stem cells together provided effective wound healing with increased epithelialization, proliferation and vascularization [51]. In a recent study, Sharifi et.al, manufactured novel hybrid scaffolds from poly (ε-caprolactone [PCL])/ Poly (lactic acid [PLA]) with Nigella sativa [NS] extract by double-nozzle electrospinning for wound healing application. Study indicated, incorporation of NS extract into the scaffolds enhances biological properties, cell viability and cell proliferation without toxicity. Thus, the nanofibrous scaffolds demonstrated potential for wound healing applications [52].

CONCLUSIONS

The treatment of chronic wounds or ulcers remains a thorny and daunting challenge because current therapies mostly failed to provide favorable outcomes of wound healing. Nevertheless, the progressive expansion of Nano carriers in recent years has brought new insight for skin regeneration of wounds. These Nano carriers have successfully overcome the limitation and the barriers associated with the available conventional treatments for wounds. Nanoparticles based delivery system can be more valuable to enhance the therapeutic power of biological molecules. Different types of elements like growth factors, anti-bacterial agents and anti-inflammatory agents can be incorporated to formulate a more potent wound dressing. Nanoparticle based wound materials show site-specific action, as well as drug-loading capacity is more. The reported studies justified that Nano delivery carriers could serves as a promising therapeutic strategy to accelerate wound healing.

CONFLICTS OF INTEREST

There is no conflict of interest.

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