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Proceeding paper

Burgeoning nanotechnology for diabetic wound healing: a novel approach towards future

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Abstract: Diabetes mellitus (DM) is a widespread long-term illness recognised by elevated blood sugar. Infection, inadequate blood flow, neuropathy, and insufficient proliferative and cytokine signalling slow down wound healing in diabetics. Recent research has shown that the majority of wound treatments that are currently on the market are not sufficient enough to meet patients' needs. Advancements in nanotechnology can help researchers to establish new therapeutic methods or improve existing ones. Nanodrug delivery systems, in particular, have emerged as a major player in the area of dermal restoration due to their ability to tether bioactive components to the targeted area, slow drug release, and dramatically improve the effectiveness of medication. Manufactured agents from the field of nanotherapy, such as nanoparticles and nanoscafolds, have recently shown promise for use in the management of diabetic wounds. Nanoparticles used in medicine have a large surface area relative to their size. Because of this, they have a better chance of interacting with living things and entering wounds. They work wonderfully for the slow, localised delivery of drugs that stimulate cell-to-cell communication, proliferation, blood vessel formation, signalling, and biomolecule production during wound healing. One or more therapeutic molecules can be released into the intended site slowly over time by using nanoparticles. The promising results seen with nanoparticulate systems indicate that research into the technology's capabilities will expand in the near future, expanding nanotechnology's substantial medical benefits. Focusing on diabetic wounds, we had evaluated the viability and efficacy of the most recently developed nanotechnology-based medications. In this article, we scrutinise the unmet needs of the wound-healing field as well as the future directions of the current available technologies, while also discussing novel approaches that can advance the field.

Keywords- Diabetes mellitus (DM); wound; nanotechnology; wound healing; nanotherapeutics

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1. Introduction

Diabetes mellitus, more commonly referred to by its medical name, diabetes, is a widespread condition that affects millions of people worldwide. Diabetes mellitus develops when the body either develops a resistance to insulin or is unable to produce enough insulin [1]. The genesis of this phenomenon is mostly attributable to a conjunction of two primary factors. The first cause is a malfunction in the production of insulin by beta cells in the pancreas. The second factor is that insulin-sensitive cells do not respond appropriately to insulin [2]. Prevalence estimates from the International Diabetes Federation (IDF) indicate that there would be 537 million individuals (20-79) with DM in the world in 2021, with that figure rising to 643 million by 2030 & 783 million by 2045. One out of every five people will lose their life to diabetes in 2021. The rise in worldwide health care costs attributable to diabetes has been significant, rising approximately USD 232 billion in 2007 to approximately USD 966 billion in 2021 for people aged 20–79 years. This is a growth of 316% over the course of the previous 15 years [3].

Our skin is an extremely versatile and adaptive organ that has developed over the course of millennia to serve as a barrier against the chemical, mechanical, and ultraviolet radiation hazards that we are exposed to on a daily basis [4],[5]. Our skin's highly evolved compensatory processes allow it to recover fast and effectively from the harsh external environment. Many cellular components of the damage response can become attenuated, preventing the lesion from closing [6].

Diabetes decreases metabolic activity, which increases infection risk and delays wound healing. The main reason for this is disturbed blood glucose management. Type 2 diabetic patients often need to have limbs amputated or otherwise handicapped as a significant secondary consequence due to their poor ability to heal wounds [7]. Tissue repair involves blood coagulation, swelling, proliferation, and reorganisation. Hyperglycaemia disrupts the natural transition between these wound healing stages, keeping the site inflamed and preventing epithelialization. Indeed, having diabetes increases the likelihood that a wound may become chronic (one that takes more than 12 weeks to completely heal)[8].

Nanotechnology is already transforming our lives. The biological sciences are using it creatively, leading to new frameworks, technologies, and systems that potentially change illness treatment and diagnosis. On the other hand, conventional medicines often include treatments that are both expensive and time-consuming, in contrast to those of medication based on nanotechnology [9]. In comparison to traditional methods, nanotechnology-based drug delivery systems hold more promise because of their controlled release and targeted activity [10]. In this review article we focus on the implications of advancements in nanotechnology and nanoformulations in speeding diabetes associated wound healing.

2. Nanotechnology in wound healing

When it comes to skin regeneration, nanotechnology is a promising new area of study. Nano based therapeutics like nanofibers, nanoemulsions etc. have attracted considerable interest for application as key component in skin regeneration because of their structural resemblance to the extracellular matrix [11]. Many different forms of polymeric nanofibers have been developed and tried as scaffolds for tissue restoration; this is after years of intensive study and testing. A number of nanoscale drug delivery scaffolds, including nanomaterials, nanoemulsions, nanocapsules, and liposomes, have been shown to hasten wound healing. Furthermore, nanofibrous materials can be modified in terms of shape, biodegradability, and other qualities to optimise wound healing in a range of contexts [11-13] [Figure 1].

2.1. Nanoparticles-

Nanoparticles (NPs) with a size of 1-100 nm have received a great deal of focus from researchers in the biomedical and tissue-regeneration disciplines. There are two primary types of NPs used for wound healing: those having inherent qualities that promote healing, and those used as medication delivery systems. Main benefits include increased medication half-life, bioavailability, and regulated and sustained release. Polymeric nanoparticles and metallic nanoparticles are the two primary categories that can be used to categorise nanoparticles [14],[15]. Biocompatible polymeric nanoparticles for sustained drug delivery to chronic wounds have been developed in recent years. These nanoparticles include substances such as polylactic glycolic acid (PLGA), alginate, gelatine (GEL), and other polycaprolactones (PCLs), as well as PEG [16]. However, for hundreds of years, metals like silver have been utilised to cure a wide range of disorders. However, modern medicine has primarily relied on silver salts and compounds such as silver nitrate and silver sulphadiazine for their antibacterial properties, particularly in the treatment of wounds [17]. Previous research that was published in the scientific literature reported formulations loaded with showed inhibitory activity and the low bactericidal concentration against drug-resistant multidrug-resistant bacteria and standard reference cultures. Gram-negative bacteria were found to be easier to eradicate using the nano formulation than gram-positive bacteria [18].

Gold nanoparticles (AuNPs) are the focus of extensive investigation for wound healing because to their novel electrical, optoelectronic (subatomic size effect), biochemical, and magnetic capabilities [19]. The antioxidant and antimicrobial properties of AuNPs have been demonstrated, and their roles in wound healing have been found to be critical [20],[21]. Photobiomodulation treatment (PBMT), more often known as Low-Level Laser Therapy (LLLT), has recently brought attention to the role of AuNPs in wound healing. When applied to wounds, AuNPs considerably accelerated repair, decreased pain and inflammation, and promoted angiogenesis more effectively throughout the early stages of wound healing [22].

Zinc nanoparticles are another important nanoparticle with a lot of applications in wound healing. A novel sustained release wound dressing was developed by incorporating zinc dioxide nanoparticles (ZnO NPs) coated with gentamicin into a chitosan gel matrix [23].

2.2. Nanoemulsion

Due to their benefits, nanoemulsions have been explored as tissue repair medication delivery mediums. The advantages include a small droplet size, a large surface area, a greater solubilisation efficiency, a long shelf life, and a simple formulation procedure [24]. Compared to normal Neomycin ointment, eucalyptus oil nanoemulsion speed up the healing process of wounds in Wistar rats [25]. In an in vitro experiment, a bio-active nanoemulsion system was made out of Nigella sativa (NS) oil, Calendula officinalis (CO) extract, and lipoic acid capped AuNPs (AuNP-LA). The augmented NS nanoemulsion demonstrated significantly higher antioxidant and anti - thrombotic activity compared to the unenhanced NS emulsion [26]. Several nanoformulations based on nanoemulsions have demonstrated efficacy in promoting diabetic wound healing [27],[28].Researchers also created and tested a nanoemulsion (NE) of curcumin (Cur) to improve transdermal medication delivery. They discovered Cur-anti-inflammatory NE's and wound-healing properties, showing its promise as a nanoformulation for non-invasive transdermal administration [39].

2.3. Nanohydrogel

When it comes to treating wounds, nanohydrogel is frequently seen to be the best formulation, as its porous three-dimensional structure can help prevent wounds from drying out and foster a wet environment that promotes healing [29]. Nanohydrogel's calming texture provides a pleasant therapeutic experience, and its nonadherent nature safeguards the insertion site while still allowing the oxygen penetration necessary for healing [30]. Nanohydrogel can encapsulate several different drugs for skin regeneration without reducing their efficacy or diminishing their compatibility. Baicalin was combined with a gellan-cholesterol to speed up the recovery process [31]. Xi Loh et al. [40] found that bacterial nanocrystal cellulose/acrylic acid nanogels rapidly attached to fibroblasts, maintained the interaction and morphological characteristics of skin fibroblasts, slowed the metabolism of cells, sped up the proliferation of cells, and modulated the expression of 9 genes involved in wound healing (including IL-6, IL-10, GM-CSF, TGF-β ,MMP-2).

2.4. Carbon based nanotherapeutics

Carbon nanomaterials such as fullerenes, carbon nanohorns, and carbon nanotubes, in addition to graphene, have gained attention in the field of biomedicine as a result of the potential applications that they offer in advanced organogenesis and the transport of drugs or genes [32]. Fullerenes and carbon nanotubes both displayed excellent performance in the wound healing process. This was accomplished by changing the immunological and regenerative stages of the wound. Due to the powerful antioxidant characteristics of fullerenes, reactive oxygen species (ROS) and reactive nitrogen species (RNS) can be neutralised and detoxified by fullerenes, hence reducing their harmful effects [33].In order to cure wounds, scientists have developed and introduced CBNs-TES-PAMAM-G3 -collagen scaffolds. Improved mechanical qualities, higher cell viability, and faster wound healing were all observed in the collagen scaffold. According to the findings, the CNT-TES-PAMAM-G3-collagen scaffolds show great promise as a material for use in tissue engineering and wound healing [41].

2.5. Nanocomposite

As previously established, several nanotechnologies can be utilised in the production of a wide variety of wound dressings. It is feasible that by integrating these several nanotechnologies, a brand new way of wound healing that is more efficient will be developed. Chen et al. had produced a konjac glucomannan (KGM)/AgNP composite with powerful antibacterial activity with the intention of facilitating the healing process following an injury [34]. In the treatment of chronic wounds, Giuseppina Sandri and colleagues had created a nanocomposite that was composed of Halloysite Nano Tubes (HNTs) and chitosan oligosaccharides. This nanocomposite was intended to be used as a pour powder to speed up the healing process [35]. Curcumin nanocomposite was produced for use as a wound dressing by G. Devanand Venkatasubbu and his colleagues. The findings of their research showed that the nanocomposite had a high degree of efficacy for the healing of wounds in addition to possessing antibacterial properties [36]. Kokabi et al. prepared a nanocomposite hydrogel wound dressing from a mixture of polyvinyl alcohol hydogel and organoclay. The experimental results demonstrated that the nanocomposite hydrogels have the necessary qualities for a suitable wound dressing, including adequate swelling, an appreciable vapour transmission rate, an effective barrierity against microbial penetration, and satisfactory mechanical properties [42].

2.6. Others

Several different kinds of nanotherapeutics based on nanofiber have been developed [37]. For wound healing perticularly, nanostructured lipid carriers and peptide nanoformulation has been developed [38]. The most exciting development in nanotechnology-based nanoformulation allows the simple production of biocompatible nanomaterials (NMs) and opens the door to a new method of treating wounds [38].

3. Conclusion

Injuries to living tissue, such as wounds, are particularly delicate. Many factors contribute to successful wound healing. Wound healing agents come in a wide range of types and current formulations possess its own set of requirements for application and performance. Wound healing is greatly influenced by elements such as cellular growth, biocompatibility, cell adhesion, and anti-microbial activity. Since many nanotechnologies, such as NPs, hydrogels, and nanocomposites, possess these qualities, they make for great wound healing materials. In this summary, the benefits of utilising nanomaterials in the wound healing process are presented. Because they have antibacterial and anti-inflammatory actions, as well as proangiogenic and proliferative qualities, nanoformulation have the ability to change each phase of the wound healing process. It is possible for nanoformulation to correct the expression level of many essential proteins and signal molecules, which will speed up the healing process. Therefore, nanoformulations may become advantageous enough to overcome the majority of the obstacles that now exist in the management of wound care.

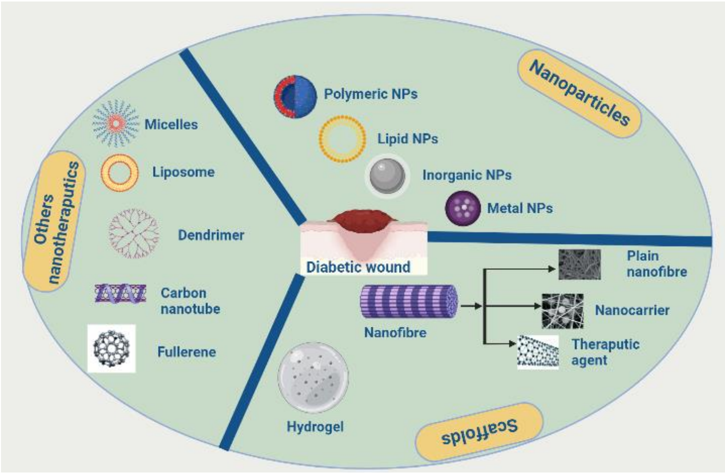

Figure 1. Different types of Nano-based formulation for diabetic wound healing.

Authorship contribution statement

Debojyoti Mandal: Investigation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Jeena Gupta:** Writing – review & editing, Writing – original draft.

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