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Recent Trends in Treating Wound Healing Using Nano Drugs Delivery Systems

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Abstract

Nanomedicine, a branch of medicine, applies tools and knowledge of nanotechnology towards treatment and prevention of disease it incorporates utilisation of nanoscale materials, for example, nanorobots, and biocompatible nanoparticles regarding delivery, diagnosis, actuation and sensing purposes within a living organism. This assignment has reviewed recent trends within drug delivery systems for treating any particular disease and this assignment has chosen wound healing. It has elaborated the process of wound healing and its different stages, along with it is illustrated possible wound infection by discussing different types of wounds, wound dressing, and delay of wound healing process.

Additionally, it has discussed the nano-drug delivery system for wound healing where different nanoparticles that are significantly used in healing wounds are discussed. The findings have shown the most promising nanoparticle is liposome and hydrogels. This review paper has represented an updated summary of recent trends in NDDS by comprehensive scrutiny of delivery and application of nanoparticles by enhancing the efficacy of current and new drugs. The information has highlighted that nanotechnology has gained remarkable attention in the past few decades and nowadays, these are extremely used in many sectors, especially pharmaceutical industry. Thus, nanomedicine has a great future and research has effectively used them to develop treatment solutions.

Keywords: Wound healing; Nanoparticles; Nano particulate drug delivery systems; Wound dressings; Inflammation due to wounds; Future trends in wound healing.

Introduction

Background

Nanotechnology has been implemented in the pharmaceutical industry for several reasons; however, the purpose of those reasons is to improve bioavailability and drug solubility and deliver various sites of action (Patra *et al*. 2018). In addition, nanotechnology has been employed for developing improved and new therapeutic devices. Farjadian *et al.* (2019) explained that Eric Drexler first introduced nanomedicine in 1986 in a book named "Engines of creation: the coming era of nanotechnology". Currently, nanotechnology applications within the healthcare sector and biomedical sciences have been called nanomedicine as this is considered nanotechnology's growth area. Nowadays, nanotechnology plays an extraordinary role in biomedical science.

In this context, Wang *et al.* (2019) explained that skin damage is a common lesion individuals suffer from, and a few wounds are extremely difficult for eradicating, for example, deep burns and chronic wounds. Present wound therapies have been proved insufficient, whereas nanotechnology offers unprecedented opportunities for revolutionizing and inventing therapies and boosting the effectiveness of present medical treatments. Naskar & Kim (2020) elaborated that nanomaterial-based wound healing processes have huge potential to treat and prevent wound infection with various benefits as compared to traditional approaches. The traditional approach regarding healing wounds is dry in nature, and these are uncomfortable as well as not easy to use or user-friendly. That is why nanotechnology is gaining more attention nowadays in pharmaceutical industries developing new therapeutic approaches for different diseases.

Wound healing process

Healing wounds is a crucial process that contains a collaboration of numerous cell strains as well as their products. The process of wound healing is majorly divided into three stages: inflammatory, proliferative, and remodeling stages (Gonzalez *et al*. 2016). However, after having any injury, the injured area goes through the homeostasis stage, which is about the process of preventing and stopping bleeding.

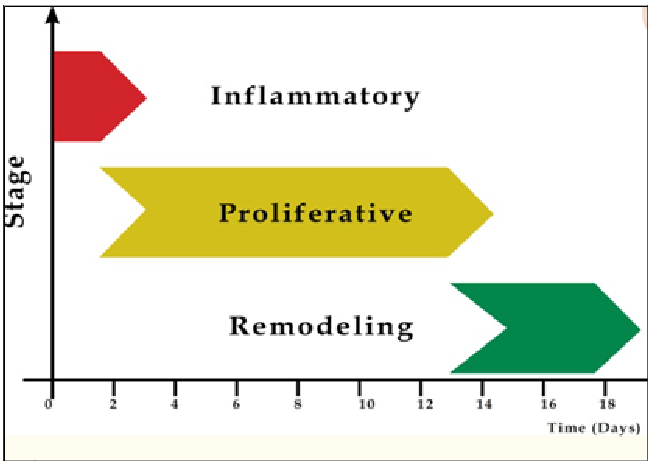

Figure 1: Stages of wound healing procedure.
(Source: Gonzalez *et al*. 2016)

Inflammatory stage

In this stage, lesion blood vessels contract and leak blood coagulate for contributing towards the maintenance of the integrity. This stage starts at the time of injury, and it lasts up to 4-days. Cell responses in this phase are characterized by leukocyte influx in the wound area (Wilkinson & Hardman, 2020). These responses coincide and are quick with key signs with the key signs of inflammation revealed by erythematic and edema at the location of the lesion.

Proliferative stage

The proliferative stage diminishes lesioned tissue by fibroplasia and contraction, establishing an epithelial barrier for activating keratinocytes. This stage begins about 3-days after the injury; however, this phase overlaps with the inflammatory stage.

Remodelling stage

Rodrigues *et al*. (2019) stated that the remodeling phase begins two to three weeks after injury, and it can last for six months to one year or more than that. A key aim of this stage is about achieving highest tensile strength by resynthesis, degradation, and reorganisation of the extracellular matrix.

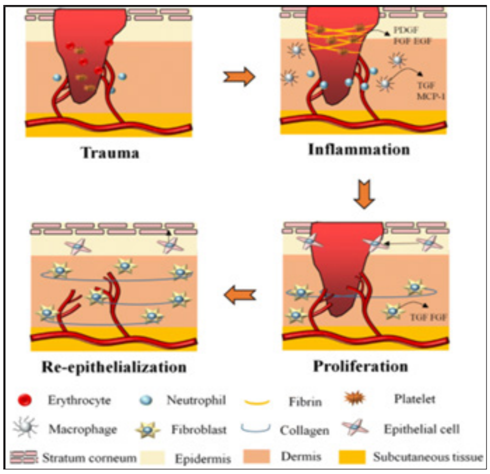

Figure 2: The process of wound healing.
(Source: Wang *et al*. 2019)

The stages, as mentioned above, are regulated through signaling modules created by a huge range of cells available in the extracellular matrix.

Nanotechnology in wound healing

Wound healing processes have been studied for developing absolute techniques that accomplish speedy recovery and reduce scarring to a minimum; therefore, making sure function preservation. Mihai *et al*. (2019) explained that nanotechnology studies the structure, dynamic and synthesis of molecular and atomic nanomeric particles on which nanoproducts are made. Nanoparticles regarding tissue recognition have been developed under several structures such as nanospheres, nanoemulsions, nano-carriers, nanocolloids, nanoparticles and Nano capsules. According to this scholar, two special types of nanomaterials have been used in wound therapy: nanoparticles having intrinsic characteristics, which aid wound closure and nanoparticles used as a delivery vector regarding therapeutic agents.

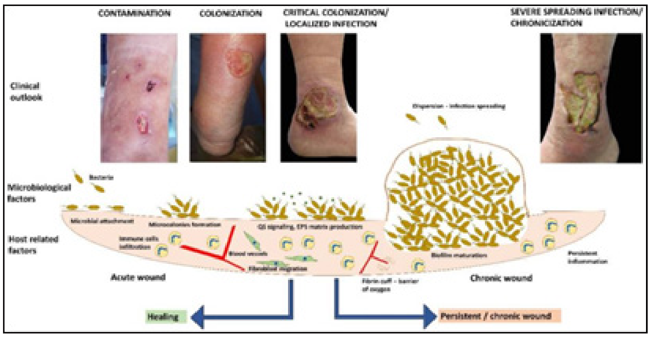

Figure 3: Chronic and acute wounds
(Source: Mihai *et al*. 2019)

Additionally, metallic and non-metallic nanomaterials have also been used in wound therapy. For example, regarding metallic nanomaterials, the most used metals are zinc, silver and gold because they have antibacterial activity, and these can reduce penetration into skin. Hence, nanoparticles in wound healing have gained huge attention due to their antibacterial and low toxicity activity.

Discussion

Wound infection

Wound Types

Wang *et al.* (2019) defined that depending upon methods and duration of wound healing; wounds are divided into two distinct categories as chronic and acute wounds. In addition, Rajendran *et al.* (2018) stated that wound outcomes from radioactivity, abrasive chemicals, heat, electric shock, and mechanical injury are contemplated as acute wounds. These types of wounds are healed by taking appropriate treatment within a short time period. Conversely, chronic wounds are connected to particular diseases, for example, diabetes mellitus. Wounds related to the health issue does not follow an orderly set of phases as well as it requires a foreseeable amount of time, which characterize the normal process of wound healing (Naskar & Kim, 2020). These kinds of wounds remain within the inflammatory phase for a long time, and their duration is connected to different factors, including necrotic tissue, moisture balance, and bacterial load.

Besides these, Caló & Khutoryanskiy (2015) explained that wounds could again be divided into some other types such as superficial, partial-thickness and full-thickness. In superficial wounds, the injured area loses one part of the epidermis. In the case of partial-thickness, deeper dermal layers and epidermis layers get affected and lastly, in full-thickness wounds, deeper tissues and subcutaneous fat are ruptured.

Wound dressing

Wound dressing has the aim of protecting wounds from any kind of external infection. This retains hydration within the wound for enhancing regeneration as well as preventing exposure of wound origin (Alberti *et al*. 2017). Thus, materials of wound dressing have to be semi-absorbent towards oxygen and water, cost-effective and hypoallergenic. Rezvani Ghomi *et al*. (2019) explained that wound dressing needs technologically new-fangled materials compared to traditional compounds, such as wool and cotton.

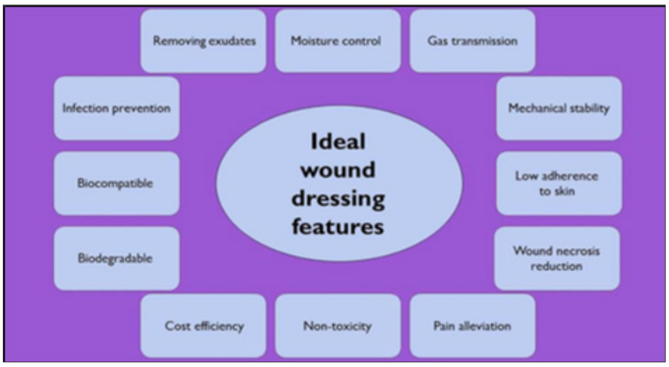

Figure 4: Features of proper wound dressing.
(Source: Rezvani Ghomi *et al.* 2019)

Matica *et al*. (2019) explained that new material is capable of preserving wound environment as well as transferring active compounds for aiding the process of wound healing. In this regard, Wang *et al.* (2019); Mir *et al.* (2018) stated that many wound-dressing products, for example, ointments, antibacterial cream, and hydrogels are available, and currently, many biodegradable materials, including hyaluronic acid, silicon, gelatine, cellulose and chitosan are using wound-dressing products.

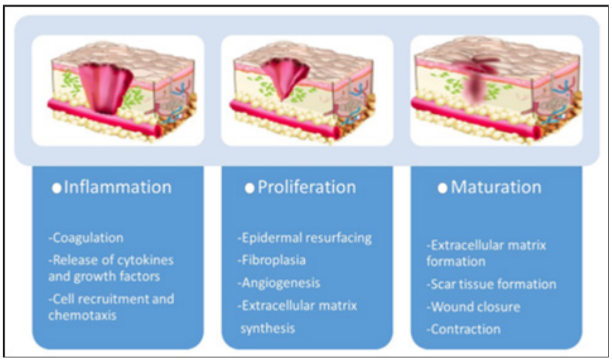

Figure 5: Wound Healing
(Source: Rezvani Ghomi *et al.* 2019)

Mir *et al.* (2018); Srinivasan *et al.* (2018) explained that cephalosporins, neomycin, and tetracyclines are most commonly utilized antibiotics in case of wound dressing as they have the possibility for preventing bacterial proliferation. Although antibiotics have been used for wound dressing; however, inappropriate administration can induce inflammation of antibacterial resistance.

Reason for delayed wound healing

Information has suggested that an acute wound takes approximately 5 to 7 days to enter the proliferative wound healing stage and then enter the remodeling phase, which could be extended for two years. However, if any abnormalities within physiological healing occur and that does not follow a normal healing process, it could halt one of the phases of the healing process. Mori *et al*. (2016) explained that chronic wounds are generally considered non-healing wounds that fail to progress by any systematic process regarding the normal healing process. Wound infection, chronic irritation, inadequate blood supply, and preservation of bacterial proteins can be the potential reasons regarding a delay in wound healing.

Current chronic wound treatment

Chronic wounds' current treatment is based on wound aetiology. In every wound case, sufficient wound debridement and cleaning, proper utilization of wound dressing and controlling potential infection. Dickinson & Gerecht (2016) discussed that in the case of non-healing pressure ulcers, dressing that quickens the wound healing procedure and relieves tissue pressure, is important. However, in the case of diabetic foot ulcers (DBU) and venous ulcers (VU), dressing maintains a moist environment favorable towards wound healing. Additionally, Malone *et al*. (2017) stated that leg bandage compression is used in venous ulcers to improve vein circulation and conventional dressings; including gauze dressing can provide protection to wounds from any kind of bacterial contamination and fluid exchange.

Blanco-Fernandez *et al*. (2021) explained that gauze dressings are secondary dressings for covering complex dressings of non-infected wounds. Although these materials are easy to use and cost-effective, it is also associated with several disadvantages, including lack of controlling moisture levels and the need for frequent change. Mangoni *et al*. (2016) mentioned that synthetic dressings could provide a preferred moist environment, and these can be in the type of hydrocolloids, hydrogels, foam, and film. Nanoparticles mainly produce these, for example, polyvinyl chloride, polyethylene glycol, silicone, and polyurethanes. However, these hydrocolloids are considered more promising biomaterials regarding wound dressing because this material can contain high water levels.

This scholar also explained that hydrogels maintain a dumpish environment within wound area, during absorbing extra exudates; it allows gaseous exchange as well as acts as a barrier towards microorganisms. Lastly, it does not adhere towards the wound bed. According to Matica *et al*. (2019), natural polymers, including chitosan, synthetic polymers, and collagen, produce hydrogels for achieving mechanical properties.

In this regard, Hamdan *et al*. (2017) explained that nano-therapeutic approaches that implement materials engineered are pioneered to efficiently control the process of wound healing process and minimize potential complications, which could initiate during the healing process. Additionally, Cheah *et al.* (2021) illustrated that currently, electrical simulation is an attractive sector in clinicians due to wound healing. Skin graft and conventional dressing did not show promise regarding complete wound closure. Several dressing materials are presented in the market related to wounds; however, in case of chronic wounds, the conventional dressings do not respond quickly. This scholar has elaborated that regarding wound healing, endogenous electric field plays a crucial role. When epithelium layers are wounded, trans-epithelial potential (TEP) has been disrupted, and the electric field is short-circled. This scholar has concluded that a successful wound healing process always ensures effective wound closure within a minor with painless procedures. By considering these factors, electrical stimulation has been believed for accelerating the healing process and replaces the skin grafting process.

Han & Ceilley (2017) also explained that in the physiologic wound healing process, this needs to consider that there is oxygen tension an oxygen supply in the wound bed. Over time, several wound dressing techniques have been developed to protect healing wounds from any type of infection, as well as helps in the wound healing procedure. According to this scholar, moist occlusive dressings can help support the inflammatory phase of the wound healing process by making an environment with low oxygen tension. Hydrogels and hydrocolloids take advantage of hydrophilic material as they absorb specific exudates; however, they keep the area moist. By agreeing with other authors, this scholar has explained that hydrocolloids are effective in wound healing; however, this should not be utilized on exudates wounds, as it is impermeable in nature. Alginate is another effective nanoparticle that is utilized in wound healing. These are seaweed-derived non-woven fibres, which are reserved regarding huge exudative wounds because they have the ability for absorbing high amounts of fluids.

Nano drug delivery system

In recent times, significant developments have been noticed in the delivery system for providing therapeutic agents towards tier target locations regarding the treatment of different diseases. Obeid *et al*. (2017) elaborated that drug delivery mentions the use of a delivery tool for carrying therapeutic agents and releasing them at a certain location. DDS can be utilized for facilitating the delivery of small and large molecules, for example, nucleic acids, water-soluble therapeutic components, peptides, and polymers through synthetic and natural sources.

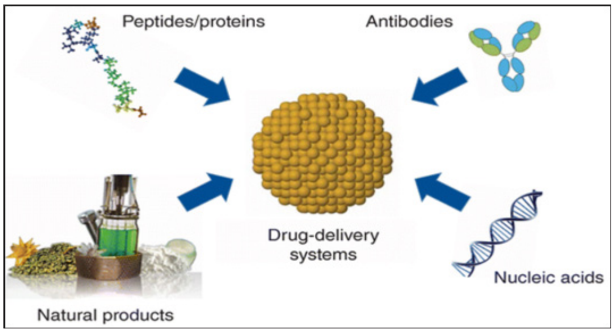

Figure 6: Drug Delivery System (DDS)
(Source: Obeid *et al.* 2017)

In DDS, different kinds of delivery systems have been utilized, such as lipid-based nanoparticles, including niosomes, micelles, solid–lipid particles and liposomes, polymeric nanoparticles including dendrimers, chitosan, and inorganic nanoparticles including metal-based, silica, carbon nanotubes and quantum dots.'

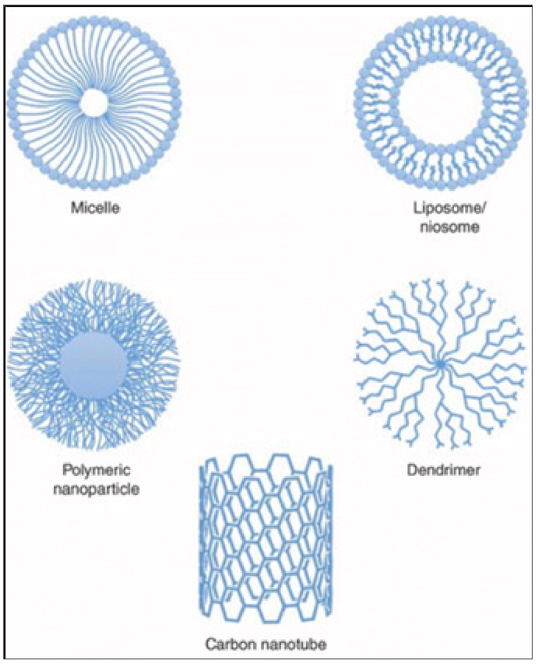

Figure 7: Forms of delivery systems
(Source: Obeid *et al.* 2017)

Nanomedicine is a segment of medicine, which utilizes nanotechnology to cure different diseases, including wound healing. Drugs having low solubility include various pharmaceutical delivery problems, such as restricted bio-accessibility after intaking through the mouth, unwanted after effects, and lower diffusion capacity in outside of the membrane. Wang *et al.* (2019) explained that nano-DDS holds huge potential for enhancement of efficiency of drug therapeutics regarding the ability to prevent and sustain drug releases. Variety of nano-DDS carrying the therapeutic components are leaping up unprecedentedly as well as being adopted for promoting the process of wound healing, including polymeric nanoparticles, lipid nanoparticles, inorganic nanoparticles and nanofibrous structure.

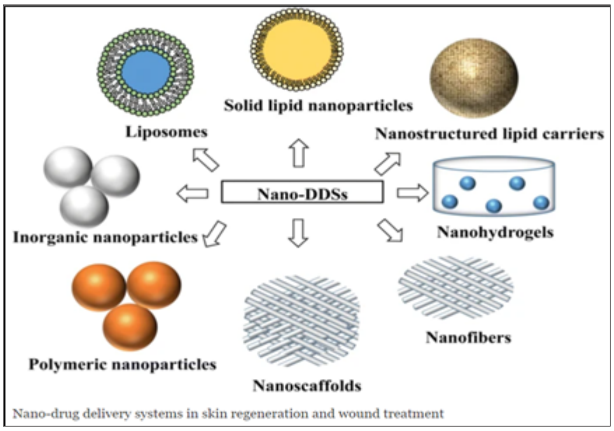

Figure 8: Nano-DDS in wound healing
(Source: Wang *et al.* 2019)

According to Patra *et al.* (2018), two ways are present regarding nanostructure delivery drugs, such as self-delivery and passive delivery. In the earlier, the drug is incorporated within the inner cavity of a structure mainly through a hydrophobic effect.

Nano drug delivery system in wound healing

Liposomes

A liposome is a bilayer vesicle that is built with the help of amphiphilic molecules, including phospholipids, which is the most promising nano-carriers regarding topical drug delivery. It is non-toxic, biocompatible, biodegradable, and able to accommodate both hydrophobic and hydrophilic agents. In this manner, liposomes give protection regarding encapsulated drugs as well as sustain the release of drugs. According to Manca *et al.* (2016), liposomes successfully cover wounds and provide a moist environment wound surface after application. By considering all these benefits, liposomes are universally applied within wound treatment. Xu *et al.* (2017) stated that liposomes are engrained formulation strategies for improving drug delivery. This has been proven that liposomes create therapeutic agents steady, improve bio-distribution, and be utilized with hydrophobic and hydrophilic drugs in case of wound healing.

Polymeric nanoparticles

Next polymeric nanoparticle is biocompatible colloidal materials that increase attention in bioengineering and biomedical fields. Information has suggested that, in current time, PLGA (poly lactic-co-glycolic acid), chitosan, gelatine, and alginate as well as various polymer combinations prepare the majority of polymeric nanoparticles. Dave *et al.* (2017) found that a PLGA nanoparticle contained antimicrobial peptide, which could be biodegradable DDS and accelerate the healing process. Chitosan is a polymeric nanoparticle that has mucoadhesive properties as well as it can be utilized for acting in tight epithelial junctions.

Inorganic nanoparticles

These refer to nanomaterials that are deprived of inorganic particles such as carbon-based, metallic nanoparticles, and ceramic nanoparticles. These nanoparticles contain both similar trends within healing wound and robust antibacterial effects. For instance, silver nanoparticle is frequently used as antimicrobial compounds (Cheah *et al*. 2021; Han & Ceilley, 2017; Obeid *et al.* 2017). Thus, research mostly prefers a combination of inorganic nanoparticles for achieving synergistic promoting impacts of drugs and materials. Jahromi *et al.* (2018) mentioned that metallic nanoparticles mainly used copper, silver, and gold compounds in wound healing. In addition, research has also found that thrombin is a widely utilized drug regarding topical wound healing and homeostasis.

Lipid nanoparticles

The representatives of lipid-based nanoparticles are NLCs (nanostructured lipid carriers) and SLNs (Solid lipid nanoparticles) and these are introduced for overcoming liposome limitations. Lipid molecules or physiological lipids prepare these and the preparation procedure needs no involvement of organic potentially toxic solvents. Because of their non-toxic characteristics, they contribute to the drug's controlled release. Sanad & Abdel-Bar (2017) found that if NLC and SLN are used with rh-EGF (Epidermal Growth Factor) it could be a great treatment approach for chronic wounds. This scholar also found that composition of hyaluronic acid and chitosan can be used with Andrographolide-loaded lipid nanoparticles to enhance the process of wound healing. Additionally, Fumakia & Ho (2016) explained that fabricated SLNs along with antimicrobial peptide and elastase-inhibitor serpin are effective for achieving synergistic effects upon wound healing.

Nanofibrous structure

These are fabricated through synthetic and natural polymer chains that can act as the nanofibrous sheets applied within tissue engineering. Adeli-Sardou *et al.* (2019) electrospun lawsuit into PCL/gel (polycaprolactone-gelatin) polymers within key-shell architecture for producing special nanofibres regarding regeneration of skin tissue.

Nanohydrogel

Next nanoparticle that is effectively used in the process of wound healing is nanohydrogel, which is a 3D polymeric network and considered as an appropriate formulation of wound management. Information has suggested that it is non-adhesive and that is why it preserves wound beds while maintaining oxygen penetration because that is crucial to heal wounds. Manconi *et al.* (2018) elaborated that an embedding of gellan-cholesterol nanohydrogel was introduced for speeding up the healing procedure. It is characterized by preferable biocompatibility, enhanced skin retention, and proper viscosity. In addition, Xi Loh *et al.* (2018) found that freshly-produced acrylic acid hydrogel or bacterial-nanocrystal cellulose can rapidly adhere towards fibroblasts as well as maintain morphology and activity of dermal fibroblasts of human, promote quick cell proliferation, limit migration if cells and affect nine gene expression regarding wound healing procedure. Thus, hydrogel plays a crucial role regarding skin regeneration.

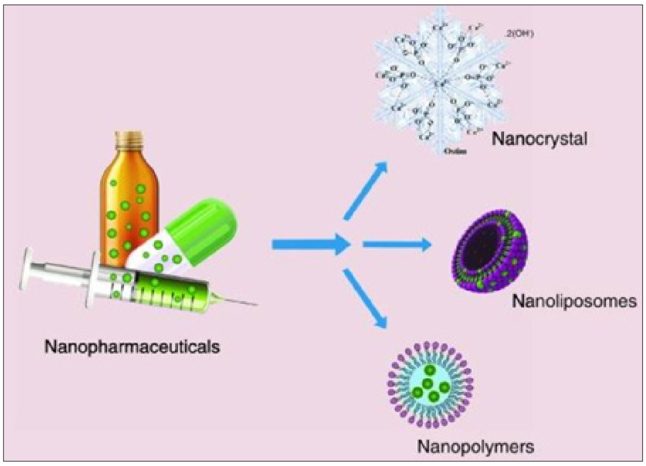

Figure 9: Types of nanoparticles available in market.
(Source: Farjadian *et al*. 2019)

Alginate

This is a biopolymeric material and it has been utilized as drug delivery. Aderibigbe & Buyana (2018) stated that alginate-based healing compounds are present in the form of films, hydrogels, nanofibers, sponges, and foams. These dressings absorb the wound fluid and results in gel, which maintains a moist environment as well as minimizes bacterial infection at wound area. Alginate-based hydrogels are used in wound healing areas; they have biocompatibility characteristics, additionally, they have the ability to release and load bioactive agents (Wilkinson & Hardman, 2020; Caló & Khutoryanskiy, 2015; Dickinson & Gerecht, 2016). Moreover, Kamoun *et al.* (2017) explained that hydrogels have poor mechanical stability and that is why if they are prepared with a specific composition of natural and synthetic polymers then it can result in good mechanical properties.

Dendrimers

These are mono-disperse, bifurcated and 3D structures and these are globular in shape and its surface is nationalized easily within controlled ways that make the structure effective candidates as the drug delivery agents (Chis *et al.* 2020). Treatment of healing wounds is expensive and difficult and that requires appropriate treatment strategies to reduce costs and ease burden. In case of wound healing treatment, dendrimers have shown extraordinary results as it reduces inflammation within burn wounds and relieves oxidative stress from wounds (Tetteh-Quarshie *et al.* 2021). Since the number of diabetes cases increases, simultaneously it increases the number of chronic wounds, thus treatment with dendrimers nanoparticles can be helpful in this case (Gomes *et al.* 2017; Anselmo & Mitragotri, 2016).

Xanthan gum

XG is the heteropolysaccharide that has high-molecular weight and it is made by Xanthomonas campestris (Laffleur & Michalek, 2017). Alves *et al.* (2020) elaborated that XG hydrogel is hydrophilic and can provide most of the environment during absorbing excessive exudate. XG polysaccharide degradation can encourage the cell migration. Additionally, XG can enhance wound healing. Thus, XG hydrogels can improve healing of wound through promoting proliferation, adhesion, and fibroblast migration. When fibroblasts present in wound site, produce collagen type-3, as well as secrete growth factors, which are incorporated in reestablishment of damaged skin.

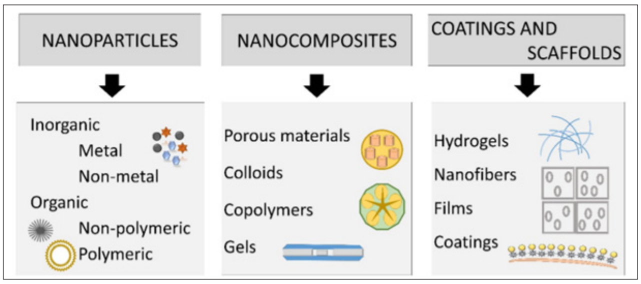

Figure 10: Nanoparticles used in wound treatment.
(Source: Mihai *et al*. 2019)

Chitin and cellulose

Cellulose is highly utilized in DDS regarding modification of solubility as well as drugs gelation, which resulted within control of release profile (Sun *et al*. 2019). Abazari *et al.* (2021) explained that cellulose-based nanoparticles are promising because of their tunable biological, chemical, physical, and mechanical properties as well as it has biocompatibility characters and at the time, it is cost-effective. Bacterial and plant cellulose can act as a scaffolding layer regarding recovery of huge range of tissue and cells and it has been identified that if bacterial cellulose processed effectively, then it can become an important biomaterial substitute regarding current wound dressing materials (Pei *et al.* 2015)

Figure 11: Properties of Cellulose
(Source: Naomi *et al.* 2020)

Polysaccharides and protein nanoparticles

Polysaccharides and protein are the natural biopolymers and these are highly used in the wound healing process. Aduba & Yang (2017) elaborated that natural polysaccharides have a huge positive role in wound healing because they have the capability promoting any non-specific activation about the immune system through activating macrophages, which clean-up wound sites after any injury. Regarding this, Cherng (2018) explained that chitosan; alginate and hyaluronic acid are contemplated as natural polysaccharides and considered as efficient candidates regarding managing wounds. Their biocompatible, antimicrobial, and non-immunogenic properties lead them to use in wound healing. However, it has some limitations, for example, in dry wounds; polysaccharides can lead to inefficiency and can cause dehydration to dry wounds (Ribeiro *et al.* 2020).

Growth factors based on Nanomaterial

Growth factors are described as the polypeptides that are biologically active and these play a crucial role in coordinating and modulating cellular procedures, for example, differentiation, cell growth, as well as migration in the time of every stage of wound healing (Hamdan *et al.* 2017). In case of wound healing, it needs to consider that recombinant human platelets derived growth factors (rhPDGFs) are present growth factors, which is approved by FDA (Food and Drug Administration). However, there are two growth factors, for example, rh-EGF and rh-VEFG (vascular endothelial growth). There is another issue related to growth factors, which is that growth factors fail in protecting themselves from any type of enzymatic degradation within an environment of proteolytic wound. In order to solve this issue solid-lipid nanoparticles as well as chitosan can be utilized.

Du & Wong (2019) explained that chitosan and solid-lipid nanoparticles are utilized as carriers in the preparation of rh-EGF. Simultaneously, this growth factor is incorporated into the chitosan nanoparticles in fibrin gel regarding sustained and stable release of growth factors. In this context, Negut *et al.* (2018) explained that regarding effective growth factors for wound healing procedure some nanoparticles have considered; however, still some proteolytic enzymatic degradation issues present that need to solve by busting nanomaterials before it is used clinically.

Conclusion

The key purpose of the review paper was to discuss the information provided by the scholars about recent trends in nano DDS for wound healing. While discussion it has provided the information of procedure of wound healing, types of wounds, wounds infection and different nanoparticles that are specifically used to heal any type of wounds. The provided information has concluded that nanotechnology-based wound healing has proven more effective as compared to the conventional therapy that was fundamentally based upon dressings. Additionally, it can be concluded that nanomaterials are able to alter a few stages of wound healing because they have anti-proliferative, anti-inflammatory and antibacterial properties. Additionally, this review has discussed that there are some issues related to growth factors, for example, growth factors failed enzymatic degradation, and that is why more research is required to solve this issue by considering the nanomaterials so that it can successfully contribute to the wound healing process.

Since it has discussed some specific nanomaterials for wound healing, thus, it can be concluded that liposomes are considered as the most useful and beneficial nanoparticles for wound healing because they are biocompatible with skin, and they are biodegradable and non-toxic. Thus, in the wound healing process liposomes can be significantly used. Besides liposomes, polysaccharides nanoparticle dendrimers are also useful for healing wounds and these are most effective polymeric nanoparticles. Thus, from this entire discussion it can be concluded that because of nanotechnology and nano drug delivery systems, the treatment of wound healing has been developed highly.

Future nanotechnology in wound healing

In recent times, nanotechnology, or nanomedicine are the most interesting areas of the pharmaceutical industry. Pharmaceutical industry is developing new and extraordinary medicines and therapeutic agents with the help of nanomaterials. The popularity of nanomedicine indicates that the NDDS trend will remain in the future, especially in the research and development area. Since it also has some issues, researchers need to pay more attention towards the growth factors of nanoparticles so that they can do enzymatic degradation. Additionally, nanomedicine application will develop with people's increasing knowledge about different diseases at the molecular level, which will help them in developing new therapies or therapeutic agents with the help of nanoparticles. Lastly, nanomedicine regulation will continue evolving alongside advances within nanomedicine applications.

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