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Nanoparticles embedded biomaterials in wound treatment: a review

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ABSTRACT

Wound healing still remains a challenging clinical problem for which efficient wound management is necessary. Biomaterials like chitosan, alginate, collagen, fibrin etc play an important role as wound dressing materials. It stimulates wound healing by fibrogenesis and plays a major role in skin development. Biomaterials can embed with many nanoparticles and used as a potential wound dressing materials. Metal nano particle, especially those made of noble metals such as gold and silver show excellent properties such as signaling the regeneration of collagen, low toxicity in vivo, bacteriostatic and bactericidal activities, and inhibiting the targeting of bacteria in wound. This review provides an insight of the applications of various nanoparticles in wound healing.

Keywords: Biomaterials, Nano particles, wound healing.

INTRODUCTION

The most important natural barrier which protects the internal organs and helps in preventing body dehydration is the SKIN . If skin is damaged in any way, it would lose its protective mechanism and pave way for the microorganisms to enter, form colonies, infect the wounded site and delay the healing process, even causing life threatening complications. Skin wound is nothing but a disruption of skin structure and function; encompasses acute burns of the skin as well as chronic ulcers. In spite of so many medical advancements, Wound healing still remains an inefficiently managed area. The process of wound healing involves 4 main stages: Haemostasis, inflammation, proliferation and remodeling ultimately leading to scar formation. The ultimate goal of wound healing is to have a speedy recovery with minimal scaring.

Since the last 30 years, there has been a drastic shift in the design of wound dressing materials from traditional to advanced therapies to optimize the wound healing environment and there is an absolute necessity to maintain optimum conditions for fastening the process. If the wound gets dehydrated, it would disturb the moist wound healing and delay the healing process on the whole. For this purpose, biomaterials must be developed in such a way that they prevent infection and dehydration. Wound care products developed recently aim to replicate ECM (Extra Cellular Matrix) which is the major component in the dermis and provides a structural support for cells, growth factors and receptors that play a major role in wound healing (International consensus, 2011).Because of the fact that the skin provides a route of delivery for local and systemic drugs, it is being efficiently used to deliver therapeutic products like medically important nanoparticles for treating skin diseases, antimicrobial activity in wounds and burns, cancer treatment As days pass with advancement in antibiotics, pathogenic bacteria and virus have become more resistant and due to the outbreak of infectious diseases, the pharmaceutical companies and researchers are searching for new drugs. Nanotechnology is emerging rapidly with the development of nanoscale materials which have potential biomedical applications by fighting against and preventing diseases. Nanomaterials are those of size 10^{-9} m (1nm). The new age drugs include the nanoparticles of polymers, metals, ceramics which can fight against human pathogens like bacteria and even cancer. The importance of nanoparticle study with potent bactericidal activity is because of their effect against resistant strains of pathogens. Nanoparticles increase the chemical activity due to their large surface volume ratio. Metallic nanoparticles are proven to be the best of all other nanoparticles.

NANOPARTICLES

Silver: Since the time of Hippocrates, silver has been used as a potent bactericidal agent because of its strong toxicity to a wide range of microorganisms. Because of its bactericidal property, silver is used to treat burns and a variety of wound infections. But with the advent of antibiotics, the use of silver in medicine decreased. However, it is used in different biomedical fields, especially in wound healing and burn treatment. Silver nitrate is still used for treating chronic wounds. Though it is a well known fact that the silver ions possess antibacterial effect, its mechanism is only partially understood. It has been proposed that the silver ions interact with the thiol groups and vital enzymes, finally inactivating them.

Studies were carried out on antibiotic resistant (ampicillin) and non antibiotic resistant strains of *Escherichia coli* (Gram negative) and non resistant strains of *Staphylococcus aureus* (Gram positive). A multi drug resistant strain, *Salmonella typhus* was also subjected to the analysis. The results showed that there was an enhanced antibacterial effect of nanoparticles in the medium as a colloid, which modulates the phosphotyrosine profile and then finally arrests the bacterial growth. This effect of bactericidal property was more on gram negative bacteria than gram positive bacteria. Commendable efforts were taken to prove the fact that the bactericidal effect was size (<10nm) and dose dependent interaction of silver nanoparticles with bacteria. The shape of the silver nanoparticles also played a major role in the sense that triangular nanoparticles displayed stronger bactericidal effect than spherical or rod shaped due to the existence of different effective surface areas. Dressings also play a major role in wound management. Now a days, different formulations of silver coatings, wound dressings is used for efficient distribution, affinity of dressing to the wound and also provide moisture for efficient killing of microorganisms.

Gold: An in vitro wound healing study was conducted by placing gold nanoparticles and nanorods in a decellularized porcine matrix and the impact on wound healing was noted. The results showed favorable properties like ROS (reactive oxygen Species) scavenging, and inducing adhesion and proliferation. The study also showed that the constructs were biocompatible, promoted cell proliferation and ROS could be decreased under some conditions.Since Au nanoparticles are biocompatible and can be functionalized with biomolecules, they can be used in drug delivery or to target specific cells. Since Au nanoparticles are biocompatible and can be functionalized with biomolecules, they can be used in drug delivery or to target specific cells.

Zinc Oxide: Zinc is normally required for various cellular and enzymatic activities besides playing a major role in wound healing, especially burns. It enhances the wound healing process by remaining at the site for an extended period of time. Zinc oxide nanoparticles (nZnO) possess antibacterial properties and are widely used in cosmetics. It is widely used in skin creams because of its excellent anti-inflammatory, drying, and mild astringent and antiseptic properties The size and concentration of nanoparticles also influence the wound healing characteristics. A size of <100nm and an appropriate concentration present a potent antibacterial activity and would show no adverse effects. Zn ions released from ZnO can promote wound healing by enhancing the keratinocyte migration.

Graphene Oxide: Graphene oxide is used in the field of biomedicine because of its antibacterial properties. Graphene related materials have shown promising results in the area of tissue engineering and wound healing. Because of its concentration dependent toxicity, graphene oxide cannot be used as such in biological applications. However, it is functionalized with other biomaterials for its efficient application tissue engineering, wound healing, cell culturing etc. Graphene oxide, in addition to its anti bacterial properties, also helps in the proliferation of cells. The material is in fact toxic to some microorganisms, whereas it is safe for human beings. It showed anti bacterial activity against both Gram positive and Gram negative organisms. A number of studies have shown the antibacterial effect of Graphene oxide against bacteria like Escherichia coli, Staphylococcus aureus. This antibacterial effect can be exploited in wound healing applications or external injuries to prevent infections. It is also evident that size, shape and chemistry of graphene oxide play an important role in determining their interactions with cell membrane, intracellular uptake and fate. Graphene, derived from graphene oxide has excellent mechanical strength, big surface area, good thermal and electrical conductivity and excellent biocompatibility.

Titanium Dioxide: The titanium dioxide nanoparticles (TiO_2NPs) are one of the most important among the metal oxide nanoparticles and used in glass ceramics, electrical ceramics, catalysts, solar cell sensors, electric conductors and chemical intermediates but still a limited evidence only available in biological related aspects. They have good mechanical properties, antibacterial effect against Gram positive and Gram negative bacteria, cell growth and high corrosion resistance.One study on wound healing using green synthesis of Titanium dioxide exhibited significant wound healing activity in an albino rat which was confirmed by measuring wound closure, histopathology and protein expression profiling.

BIOMATERIALS

Fibrin: Fibrin is the first scaffold that a cell encounters in wound healing due to trauma or other damages to normal tissue. Neutrophils, macrophages and fibroblasts first anchor to fibrin as they enter the wound site to dispose the dead tissue, infectious agents that have breached out the epidermal barrier and rebuild the tissue [61-62]. Fibrin gels formed from purified plasma proteins have properties similar to a blood clot and it is biodegradable Fibrin networks also bind to numerous proteins in normal blood and many other factors like fibronectins, growth factors and protease inhibitors, in response to wound healing. The abundance of fibrinogen, ease of purification, mechanical properties, thrombin concentration all have advantageous aspects for wound healing and tissue engineering. Fibrin glue can be used as an effective haemostatic glue to stop bleeding, replace sutures and also in wound healing. Fibrin can also be injected in situ as a drug delivery vehicle because it can degrade naturally and stimulate body's own wound healing response.

Gelatin: Gelatin, a derivative of collagen is used in numerous biomedical applications. The physio-chemical and biological properties render it a candidate for fabricating tissue engineered scaffolds. and it is convenient to use it as a biomaterial. Gelatin biomaterials can also be used for the production of nanoparticles as drug carriers. Gelatin has many merits like biodegradability, biocompatibility, excellent physical, chemical and mechanical properties and commercial availability at low cost. It also has good elongation and deformation properties which provide easier opening of spaces for cell penetration to a deeper level of scaffold. Hence it can be used as a biodegradable scaffold for skin substitutes in case of skin loss.

Alginate: Alginate is a naturally occurring anionic and hydrophilic polysaccharide which possesses excellent biocompatibility, biodegradability, mechanical strength, cell affinity, gelling properties, non-antigenicity, chelating ability, immobilization of specific ligands, physical and chemical cross linking and hence has different applications in biomedicine. Because of such properties, alginate based biomaterials can be used in wound healing, drug delivery and also in tissue regeneration applications. They are readily processable in the form of hydrogels, microspheres, sponges, foams and fibers which can be used as wound dressing materials. Alginate dressings can enhance wound healing by stimulating monocytes to produce elevated levels of cytokines. Production of the cytokines at wound sites result in pro-inflammatory factors which are advantageous to wound healing. Alginates also possess high levels of bioactivity due to the presence of endotoxins. Alginate dressings can prevent secondary injury while peeling off. Alginate sponges are specially used to treat large volume exudation. It is well known that a moist wound environment promotes wound healing. Alginate based gel dressings can prevent the wound from drying out and helps in faster wound healing.

Chitin and Chitosan: It is a natural polymer derived from chitin under alkali conditions at high temperature. Chitosan is a nontoxic, biodegradable and biocompatible linear polysachharide. Because of its remarkable biological properties, chitosan is used in pharmaceutical and biomedical fields in drug delivery, scaffold for tissue engineering and in wound dressing. Also its haemostatic properties make chitosan a good applicant for wound dressing. Chitosan has three types of reactive functional groups that allow modifications of itself to produce various useful hydrogels for the aforementioned applications. It also possesses antibacterial property which limits the risk of infection. Due to these properties, it is an excellent candidate for wound dressing and hydrogel scaffolds for tissue engineering. Extensive studies were done for using Chitosan formulations as gels in wound healing application Because of its hydrophilic nature, chitosan can be applied as biocompatible hydrogels.

Collagen: Collagen is the most abundant animal protein and is the major component of leather, glues, gelatin, pharmaceutical applications, etc. Collagen maintains a biological and structural integrity of extra cellular matrix and is a highly organized 3D scaffold. It is non toxic, exogenous, biodegradable and biocompatible than most other biomaterials and only weakly antigenic. It is a dynamic and flexible material that undergoes constant remodeling to refine cellular behavior and tissue functions. Collagen plays a vital role in pre and postoperative surgical procedure. It can form fibers of great tensile strength and stability via cross linking and self aggregation. Collagen based wound dressings are practical and easily remodeled due to simple structure, uniformity and abundance. It is biodegradable, biocompatible, thermally stable, non toxic. They can be used to cover burn wounds and treat ulcers. Extensive studies were done on collagen based wound healing in which one of the study showed that the wounds treated with collagen matrix regranulated and re-epithelialized at a rate greater than control and also that the sequence of cellular response, absorption and remodeling was identical to that of the mechanism of wound healing. Collagen supports the growth of supporting new tissue by adhering to the walls of the wound and absorbing the wound fluids.The reason that the nanoparticles have been embed on biomaterials is because of the promising results of faster wound healing shown by both biomaterials and nanoparticles individually.

NANOPARTICLES EMBEDDED BIOMATERIALS

Silver Nanoparicles embedded Biomaterials: Collagen based silver nanoparticles were synthesized using $NaBH_4$ as a reducing agent. The resulted particles demonstrated favorable properties like spherical shape, diameter between 64.34nm and 81.76 nm, positive zeta potential, antibacterial activity and non toxicity against the tested cells. The presence of positive zeta potential favors the interaction between Gram negative and Gram positive bacteria. The antibacterial activity is due to the electrostatic interaction between negatively charged membranes of bacteria and positive potential of particles [94]. Hence the study reports that silver nanoparticles embedded collagen acts against E.coli and S.aureus. This proves the antibacterial activity of silver which makes it an eligible component for wound dressing material.

A novel β-chitin/nanosilver composite was used prepared using a β-chitin hydrogel with silver nanoparticles and tested for wound dressing applications. It showed bactericidal activity against *E.coli* and *S.aureus* and also good blood clotting ability. The prepared scaffold also showed controlled swelling in water and PBS compared to the control. It also showed inhibitory effects on bacterial growth signifying antibacterial effect.

Cytotoxic studies conducted on the scaffold proved that it was non toxic on the test cells. All the results indicated that the scaffold can be used as a potential wound dressing material. Another study on plumbagin caged silver nanoparticles as a multi-site cross-linking agent of collagen scaffolds demonstrated potent anti-microbial and wound healing activity. Further, cross-linking did not include any structural changes in the collagen molecule and resulted in uniform alignment of collagen fibrils to form orderly aligned porous structural scaffold. The cross linking ability, biochemical and therapeutic properties of plumbagin caged silver nanoparticles were attributed to the cumulative effect of collagen, plumbagin and silver nanoparticles because individual molecules had minimal effect on these parameters.

Gold Nanoparticles embedded Biomaterials: One report showed the cross linking of collagen with gold nanoparticles which allowed the easy incorporation of biomolecules like growth factors, peptides, cell adhesion molecules by their immobilization at the Gold surface without additional altering of collagen structure. Collagen used here is mostly a gel which could be used for drug delivery and tissue engineering applications. The properties of both collagen and gold nanoparticles like biocompatibility, antibacterial, biodegradability gives us a good idea for using this combination for wound healing. A gelatin chitosan combination with gold nanoparticles was found to be safe, haemostatic and also did a good work in wound healing. Polyelectrolyte multilayer coated gold nanorods in combination with collagen have numerous biomedical applications. They alter the polymerization and mechanical properties of the ECM component by elucidating differences in collagen remodeling and cellular phenotype. The collagen gel constructs served as model tissues in which cells can interact with ECM and the nanoparticles in 3 dimensions.

Zinc Oxide Nanoparticles embedded Biomaterials: Zinc oxide nanoparticles were incorporated into chitosan hydrogel and evaluated in vitro as well as in vivo to find out if the composite can be used as a wound dressing material or not. The results demonstrated some disadvantages such as less flexibility, poor mechanical strength, lack of porosity, and a tendency for dressings to adhere onto the wound surface; in addition, a majority of the dressings did not possess antibacterial activity. But the dressing had advantages aswell. Since it is a hydrogel based dressing, it was helpful in providing a cooling sensation and moisture environment as well as acting as a barrier for microbes. It also showed enhanced swelling, blood clotting, and antibacterial activity. All the obtained data stongly encouraged the use of the composite bandages for burns, chronic wounds, and diabetic foot ulcers.

In another study, β-chitin hydrogel/zinc oxide nanoparticles composite bandage was fabricated and evaluated as an alternative to existing bandages. The resultant bandage exhibited controlled swelling and degradation. It also showed blood clotting ability as well as platelet activity which was higher than the control. It also had antibacterial activity against both Gram positive and Gram negative bacteria. In vivo evaluation showed that the composite had faster wound healing and higher collagen deposition when compared to control. Hence, the prepared composite could be used on various types of wounds with large volume of exudates.

Graphene Oxide Nanoparticles embedded Biomaterials: Sodium alginate/graphene oxide (NaAlg/GO) fibers were prepared using a wet spinning method through a Cacl2 coagulating bath. Sodium alginate and GO nanosheets contain large number of hydrophilic groups such as –COO, so they have good compatibility which ensures that GO is well dispersed in sodium alginate matrix. The incorporation of GO into sodium alginate significantly improved the strength of the NaAlg/GO fibers owing to the uniform distribution of the GO nanosheets in the NaAlg matrix. In aqueous solution, the GO/NaAlg fibers swelled to form hydrogel fibers that are nontoxic to cells which demonstrated the potential applications of the as-spun fibers in wound dressing materials. The resultant composite is also non toxic, low cost, good cell affinity, beneficial for cell attachment and growth and hence, it demonstrated potential applications as a wound dressing materials. Graphene oxide incorporated collagen-fibrin biofilm was tested for its properties to be used as a wound dressing material. Histopathological, biochemical and hematology studies were conducted and all of them showed that the combination of collagen, fibrin and graphene oxide treated wounds faster than collagen and fibrin composite. Based on those results, the collagen-fibrin and graphene oxide composite proved that it could be used as a wound dressing material in small and large animals.

Titanium Oxide Nanoparticles embedded Biomaterials: A new dressing consisting of biopolymer chitosan, synthetic polymer poly(N-vinylpyrrolidone) (PVP) and nanoparticle titanium dioxide was developed. It showed powerful antibacterial efficacy against four pathogenic bacteria and found nontoxic toward NIH3T3 and L929 fibroblast cells. The scaffold was also tested against albino rats, the wound closure rate is effective in nanocomposite treated wounds compared with that treated with chitosan, positive control and negative control groups. From the outcome of the in vivo evaluation, it was concluded that the nanocomposite film could be used as an effective dressing for wound care. In another similar study, Titanium dioxide nanoparticles were incorporated into chitosan-pectin because of its properties like biocompatibility, antimicrobial activity, water swellable nature, good healing efficiency and tensile strength. The morphological studies showed well distribution of nanoparticles in the matrix. Chitosan–pectin–TiO2 dressing material controlled evaporative water loss from wound beds at an optimal level and absorbed more exudates and kept the wound beds moist without risking dehydration or exudates accumulation. The blend showed a significant wound closure rate when applied on open wounds in a rat model when compared to a conventional gauze and chitosan.

CONCLUSION

The main aim of the review is to highlight the wound healing properties of biopolymers and nanoparticles. Since both of these biologically important products are capable of healing wounds individually, a combination of nanoparticles and biopolymers would have a high chance of faster wound healing. Different combinations of biopolymers and nanoparticles would achieve excellent results.

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