Chapter

Silver Nanoparticles Impregnated Wound Dressings: Recent Progress and Future Challenges

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Abstract

Microbial infection remains all time and unresolved challenge in the management of burns and diabetic wounds. Especially in diabetic wounds infections are prominent reason of amputations. Microbial biofilms pose tough polymeric barrier that is difficult to cross by conventional antibiotics. Therefore, traditional approach of infection control using antibiotics is now failing at some extent that raised a need to shift this paradigm. Presently, silver nanoparticles incorporated scaffolds representing a new concept of nanoparticle dressings which is becoming popular in wound management. Recently developed silver nanoparticles functionalized wound dressings exhibited excellent profile in the management of wound infections and promotion of wound healing. This chapter throw light on the recent strategies used in the development of silver nanoparticles functionalized wound dressings and their outcomes along with potential benefits and future challenges in wound management.

Keywords: Silver nanoparticles, wound infections, biofilms, diabetic wounds, wound dressing

1. Introduction

A wound is any type of injury which can be in the form of a cut, bruise or contusion caused by some external force. Open wounds are susceptible of getting infected by microorganisms like bacteria, virus or fungi if left unattended. Infected wounds pose a major challenge for healthcare system due to its direct relation with mortality and morbidity of the affected patients [1]. When a wound is infected it causes stress (physiological and psychological) and slows down the wound healing process and in some cases worsens the situation [2]. Approximately 2% of all hospitalized patients worldwide have a chronic wound, and older adult patients are at highest risk, because aging impairs the healing process [3, 4]. As many as 70% of these wounds recur, and 34% are accompanied by infection [5]. A survey by Medicare beneficiaries in 2018 stated that approximately 8.2 million individuals were having some kind of wounds, with or without infection and they estimated the treatment cost to be near about 28.1 billion to 96.8 billion dollars making it a big economic challenge as well [6]. Infectious wounds like surgical wounds, diabetic foot and ulcer are more problematic and are reported more frequently than other infectious wounds [7]. Silver since time memorial is used for its good antimicrobial potential due to its interference with the thiol group of the microbial membrane. It also increases production of reactive oxygen species with in the microbe resulting in damage of DNA and bacterial proteins [8]. Due to its broad spectrum antimicrobial activity, silver nanoparticles are getting a great attention especially in the form of dressing for the infected wounds. This chapter will throw light on the various applications and recent trends in the health care system for treatment of infectious wounds using silver nanoparticles.

2. Wound and wound infections

In general, any form of breakage or harm to the surface of skin can be termed as a wound and broadly classified into two types i.e. acute wound and chronic wound. An acute wound is one in which the wound physiology tends to remain normal during the process of healing. Acute wounds are usually bites, minor burns, cuts and surgical wounds. It is seen that such kind of wounds heal within a predictable timespan depending upon the location, depth and type of wound. In case of chronic wounds the physiology of the wound is disturbed due to various endogenous mechanisms which results in damaging the integrity of the tissue. Examples of chronic wounds are ulcers, diabetic foot and pressure sores. These types of wounds aggravate by aging, malnutrition, diseases which results in immunosuppression within the patient like AIDS or in patients on immunosuppressant drugs [9, 10]. Wound is said to be infected when there is entry of a microbe from the breached skin, which slows down the healing process and results in appearance of signs and symptoms like pain, discoloration of the wounded area, edema, puss, abnormal smell, tenderness etc. [11]. Most of the hard to heal infected wounds are observed to possess biofilms in them [12]. Biofilms are surface linked microbial structural communities having sessile cells present in the matrix produced by the microbe itself, made of polysaccharides, deoxyribonucleic acid and other components which are an essential type of adaptation strategy for the survival of bacteria as it protects it from the harsh surroundings and several immune responses by the extracellular polymeric substance (EPS) [13]. Bacteria possessing biofilms has increased chance of gene transfer of antibiotic resistance gene to other bacterial species [14, 15]. Bacteria having biofilms are tough to treat even with higher doses as biofilms prevent antimicrobial agents to reach up to bacteria [16, 17]. Although there are many beliefs regarding the defensive mechanism of biofilms against the antimicrobial agents but till date its nature of defense is unknown [18].

3. Wound healing

Replacement of damaged tissue by newly produced tissue is termed as wound healing [19]. Skin (epidermis and dermis) acts as a protective layer against the harsh environment and when this barrier is breached a sequence of biochemical events takes place to repair the damage [19, 20]. The process of wound healing is generally described in four phases i.e. blood clotting, inflammation, tissue growth and tissue remodeling [21]. In the first phase with in some time platelets starts covering the area of the affected site. They release a particular chemical signal which promotes clotting resulting in activation of fibrin which produces a mesh to which platelets bind and forms a clot. This phase is also known as hemostasis [22, 23]. In second phase or inflammation stage clearing of debris and bacterial cells takes place via process of phagocytosis where white blood cells and macrophages engulf and destroys them [24]. In the next phase that is proliferation phase or tissue growth phase angiogenesis, collagen deposition, granulation tissue formation, epithelialization and wound contraction takes place [25]. At last the tissue enters the maturation or the remodeling phase in which collagen is realigned and the cells which are not needed are removed by apoptosis [26].

4. Silver as an antimicrobial agent

Since early times silver appeared in recorded history texts for its excellent antimicrobial action. The ancient Greek historian 'Herodotus' describes that at the times of war Persian kings among with his provisions used to take boiled water from silver jars [27, 28]. Raulin in 1869 was the first person who observed the antimicrobial activity of silver by observing that *Aspergillus niger* (most common type of fungus) was not able to grow in silver vessels [29, 30]. Carl Wilhelm von Nageli, a Swiss botanist came up with a term 'oligodynamics' (oligo means small; dynamics means power) which describes any metal having some antibacterial properties at very small concentration [31, 32]. Silver compounds are being used in the process of wound healing since 1970s, leading to discovery of silver sulphadiazine which has an effective, broad spectrum antibacterial activity [33]. The silver element in nature is inert and ionizes when it comes in contact with environment, producing Ag^+ ions which are believed to show antimicrobial activity [34]. Because of its strong antimicrobial activity, silver is a mostly used as an adjunct therapy in wound care. However, it also has the potential to delay the process of wound healing by producing toxic effects on keratinocytes and fibroblasts [35].

5. Silver nanoparticles

Any small particle which ranges between 1 to 100 nanometers (10^{-9}) in size is known as a nanoparticle. It cannot be detected with naked human eye and it exhibits different chemical and physical properties in comparison to their large material counterparts [36]. Among many inorganic nanoparticles, silver nanoparticles (AgNPs) have got researchers attention around the globe due its novel physical, chemical and biological properties as compared to their bulk form. They have particular chemical and physical properties like high electrical and thermal conductivity [37], surface enhanced Raman scattering effect [38], catalytic activity [39], chemical stability [40] and nonlinear optical behavior [41]. The above stated properties make it the material of choice to be used in electronics, and for medical use. Silver nanoparticles are also known for their antiviral, antibacterial and antifungal activity. Due to smaller size, surface area to volume ratio is increased which results in increase in the amount of atoms on the surface, that other forms. The net effect gives rise to unpredictable properties associated with nanoparticles [42]. Silver nanoparticles has shown proven antimicrobial activity in many in vivo and in vitro studies and have application in soaps, cosmetics, food packaging and wound dressing [43]. Due to epidermal keratin and phospholipids, and protein thiol groups, skin was thought to be impermeable to silver nanoparticles but some studies demonstrated, if any absorption beyond the stratum corneum [44, 45]. Silver wound dressings are in direct contact with damaged skin resulting in systemic absorption also associated with some toxicity [46].

6. Mechanistic insight of silver nanoparticles

In an average human concentration of silver in plasma is less than 2 μg/mL which is derived from inhalation of particulate matter and diet [44]. Silver can enter human body by inhalation, oral ingestion and dermal absorption [34]. Pinocytosis and endocytosis are believed to be two processes by which the silver nanoparticles may enter the body. It is seen that the particles that are of nanoscale penetrate much deeper than those of regular size leading to a novel delivery therapy [47, 48]. Till now exact mechanism of action of silver nanoparticles is not clear but several actions have been proposed by the scientists for its antimicrobial activity. Continual release of silver ion is considered to be the main reason for its antimicrobial activity [49]. Due to sulfur protein affinity and electrostatic attraction silver ions adhere to the wall of cells and cytoplasmic membrane which increases its permeability and penetrability into the cytoplasmic membrane leading to disruption of the bacterial cell wall [50]. When the silver ion enters the cell it can deactivate the respiratory enzymes and can generate reactive oxygen species [51]. Reactive oxygen species acts as a key component and a major reason for cell membrane disruption and DNA damage (by interacting with sulfur and phosphorus of DNA) causing problem in DNA replication, reproduction results in death of the microbes. Silver ions also inhibit the synthesis of proteins by denaturation of ribosomes and cause interruption the production of ATP [52]. After anchoring the surface of the cell silver nanoparticles gets accumulated in the pits of the cellular wall of microbe resulting in cell membrane denaturation [53]. Due to nanosize they easily penetrate cell membrane, leading to rupture of cell organelles and even lysis. They also affect the bacterial transduction process by interfering with the phosphorylation of protein substrates which can result in cell apoptosis and cell multiplication [53, 54]. Gram-negative bacterial strains are more sensitive towards the effect of silver nanoparticles because the cellular walls of these bacteria are narrower than the gram positive bacteria [55]. One drawback of silver nanoparticles is that they are not much effective in the case of bacteria having biofilms. Biofilms protects the membrane from both nanoparticles and silver ions by altering their transport due to its complicated structure [56]. The pathway of the nanoparticles penetration is highly obstructed if the size is grater that 50 nm [57]. It is also observed that adsorption and accumulation of the silver nanoparticles on the biofilm results in reduced diffusion of nanoparticles in bacteria [58].

7. Silver nanoparticles wound dressings

A dressing is a sterile material applied to a wound to promote healing and protect the wound from further harm [59, 60]. It has been designed in such a way that it is in direct contact with the wound, as distinguished from a bandage, which is most often used to hold a dressing in place. Silver dressings are used for both types of wounds (acute and chronic) and when there is risk of high level of bio burden or local infection for example in the case of burns [61]. Silver dressings helps in reducing the bioburden in infected or colonized wounds and also acts as a barrier to reduce any further chance of infection [62].

8. Synthesis of silver nanoparticles for wound dressing

There are four types of silver nanoparticles synthesis, namely chemical, irradiation, green and thermal. In chemical synthesis, two types of synthesis methods are used which are Brust-Schiffrin synthesis which is mainly used for golden nanoparticles and Turkevich method which is based on reduction of the boiling solution of silver salt with citrate salt solution [63, 64]. Irradiation synthesis is connected with radiation of precursors or intermediate products of reaction with electromagnetic radiation with different wavelengths [65–67]. In green synthesis plant, fungus or bacterial extract is mixed with silver ion usually silver nitrate, the bioactive molecules of extracts reduce silver ion to elementary silver and then it is precipitated in alcohol. Advantages of this synthesis are that cost involved in synthesis is low, environment friendly and plant extracts contain medicinal compounds which are used in conventional medicine [68–77]. Thermal synthesis is based on the principle of thermal reduction of silver salt. After the synthesis of the silver nanoparticles, they are incorporated in membrane or composite material, nanofibers, hydrogels, etc. and are used as a wound dressing.

8.1 Silver nanoparticles incorporated into membrane and composite material

Membrane and composite material-immobilized nanoparticles can have many functions including antimicrobial activity. Silver nanoparticles incorporated in membranes like polyethersulfone, acetate cellulose, polydopamine-coated poly(ether imide) etc. showed significant antimicrobial activity against diverse

Polymer used	Method of preparation of nanoparticles	Size (nm)	Result
Bacterial cellulose	Thermal method (thermal reduction at 80° C	10–30	Reduction seen in *Staphylococcus aureus*; 99%. Growth of cells observed with no cytotoxicity [79]
Chitin	Irradiation method, (gamma rays, ^{60}Co)	3–13	Significant bactericidal effect ($p < 0.01$) [80]
Bacterial cellulose	Green method (cellulose from *Acetobacter xylinum)*	50–150	Strong activity against *Escherichia coli* and *Staphylococcus aureus* [81]
Chitosan, Polyvinyl alcohol, Curcumine	Green method (chitosan)	16	Significant effects against *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa and Candida albicans* [82]
Chitosan and Chitin	Green method (*Camelia sinensis*)	60–150	Good healing activity [83]
Konjac Glucomannan	Green method (egg white)	8–32	Accelerates wound healing and fibroblast growth promotion [84]
Bacterial cellulose	Chemical method ($NaBH_4$)	3–17	Inhibiton of growth of *Escherichia coli and Staphylococcus aureus* [85]
Chitin	Chemical method (sodium citrate)	5	Inhibiton of growth of *Escherichia coli and Staphylococcus aureus* [86]
Poly vinyl pyrrolidine chitosan	Chemical method (sodium citrate)	10–30	Reduces growth of *Escherichia coli and Staphylococcus aureus* [87]
Chitosan	Chemical method ($NaBH_4$)	15	Facilitates cell proliferation and mitigate bacterial infection [88]
Bacterial cellulose	Chemical method ($NaBH_4$)	5–14	Inhibition of growth of *Escherichia coli and Staphylococcus aureus* [89]

Table 1.
Silver nanoparticles based membrane composites for wound management.

Material used for preparation of clothing and dressings	Method of preparation of nanoparticles	Size (nm)	Result
Cotton fabrics	Chemical method (alkali solution of starch)	22–24	Inhibition of growth of *Escherichia coli and Staphylococcus aureus* [90]
Dressing material	Chemical method ($NaBH_4$)	4–24	Reduction in wound inflammation and fibrogenic cytokines modulation [91]
Cotton fabrics	Green method (*Fusarium oxysporum*)	2	Reduction of growth on *Staphylococcus aureus* [92]
Silver nanoparticles incorporated wound dressing	Green method (*Aspergillus niger*)	200–800	Effective wound healing activity [93]

Table 2.
Silver nanoparticles incorporated clothing and dressings for wound management.

Polymer used for preparation of nanofibers	Method of preparation of nanoparticles	Size (nm)	Result
Collagen	Chemical method (sodium citrate)	25–55	Accelerated wound healing [96]
Poly vinyl pyrrolidine	Chemical method (N,N- DMF)	3–5	Effective antibacterial action [97]
Poly methyl methacrylate-co-dopamine	Chemical method (Silver ion dipped in PMMDM)	<20	Effective antibacterial and wound healing action [98]
Plumbagine	Chemical method (PBG reduction)	60	High antibacterial activity [99]
Gelatine	Chemical method (Silver nitrate reduced with gelatin powder)	11–20	High anti antibacterial activity against Gram positive bacteria [100]
Poly ethylene oxide poly caprolactone	Chemical method (Silver nitrate reduced with PEO and DMF)	13–17	Good antibacterial potential [101]
Alginate	Chemical method ($NaBH_4$)	5–17	Reduces the inflammatory phase and increased epidermal thickness [102]
Chitosan, glucose, Poly vinyl alcohol	Green method (chitosan, glucose)	10–30	Good antibacterial activity against gram negative bacteria [103]
Poly galacturonic acid	Green method (PGA, HA)	5–13	Maximum wound epithelization and collagen deposition [104]
Poly caprolactone	Green method (*P. nigrum*)	5–20	Excellent antibacterial activity against *Escherichia coli and Staphylococcus aureus* [105]
Poly vinyl alcohol	Irreadiation method	23–24	Significant antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* [106]

Table 3.
Silver nanoparticles incorporated nanofibers for wound management.

range of microbes thus have capability to sterile wound environment and promote healing process [78], representative examples are summarized in **Table 1**.

8.2 Powdered silver nanoparticle and topical application

Powdered silver nanoparticles are used for incorporation into different types of clothing and dressings. Representative examples are summarized in **Table 2**.

8.3 Nanofibers

Nanofibers are emerged as an important structures with wide range of biological as well as physical applications like air filtration, immunoanalysis and as pseudo-enzymes etc. [81–84, 94, 95]. Apart from that active research is also ongoing for utilization of silver nanoparticles incorporated nanofibers for wound management. Examples of nanofibers are given in **Table 3**.

8.4 AgNPs-hydrogels

Hydrogels have excellent capacity to absorb wound exudates and at the same time maintain the moisture in wound environment to ensure proper healing. Hydrogels form impermeable physical barrier on wound surface and prevent bacterial invasion (**Figure 1**) and apart from that hydrogels also showcased its tendency to absorb wide range of metals [59, 96, 107, 108]. Some silver nanoparticles incorporated hydrogels showed excellent wound healing activity as shown in **Table 4**.

9. Future challenges

Silver nanoparticles functionalized wound dressings have significant antimicrobial activity and provide faster and effective tissue repair thus they are widely

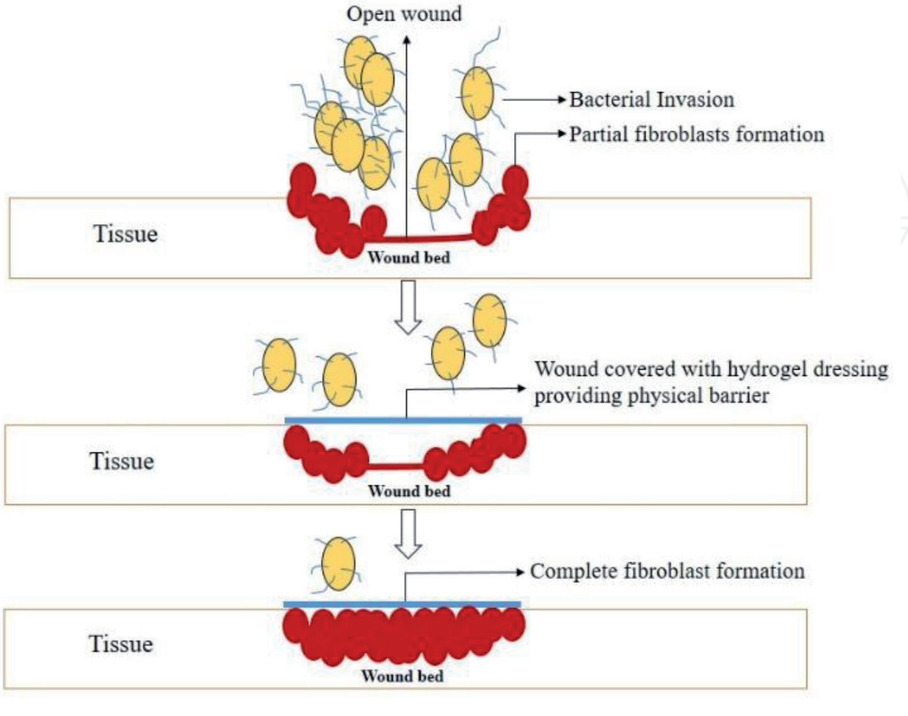

Figure 1.
Schematic layout of hydrogel membrane reducing bacterial invasion and accelerating wound healing process.

Polymer used for preparation of hydrogels	Method of preparation of nanoparticles	Size (nm)	Result
Poly acrylic acid and poly vinyl alcohol	Chemical method ($NaBH_4$)	2–3	Significant antibacterial activity against *Escherichia coli* [109]
Beta- chitin	Chemical method (sodium citrate)	4–8	It showed inhibitory effects on the bacteria growth [110]
Chitosan	Green method (sericin and chitosan)	240–970	Bactericidal action [111]
2-acrylamide-2-methylpropane sulphonic acid sodium salt	Irradiation method (UV radiation)	—	Used as a burn wound dressing due to its good antibacterial activity [112]
Poly vinyl alcohol	Irradiation method (UV radiation, gamma rays ^{60}Co)	90	Antimicrobial activity against *Escherichia coli, Staphylococcus aureus and Candida albicans* [113]
Collagen	Thermal method (reduction at 40°C	5–14	Antimicrobial activity against *Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa* [114]
Carboxymethylcellulose	Thermal method (reduction at 70–100°C	7–21	Removes the exudates and prevents wound maceration [115]

Table 4.
Silver nanoparticles incorporated hydrogels for wound management.

explored for wound healing activity. Beside this they are far away from clinical practice as well as commercialization. More rigorous preclinical investigations are still required to validate their capability for tissue regeneration. Apart from that work is also needed to be done on industrial scale up techniques for commercialization.

10. Conclusion

Nanomaterial's now a days representing potential ways for combating microbial related diseases and disorders. Wounds especially chronic ones burdened with resistant microbes are posing serious challenge to healthcare system. For that purpose silver nanoparticles impregnated wound dressing due to their excellent antimicrobial potential are not less than a boon. Along with sterilization they are proven to fasten tissue repair in wounds. Presently more rigorous efforts are needed in their preclinical investigations to evaluate their efficacy verses safety ratio. They have capability to become potential wound dressing of future.

Acknowledgements

The authors are also thankful to Guru Nanak Dev University, Amritsar for providing various facilities to carry out the work.

Conflict of interest

The authors declare no conflict of interest.

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