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Electro spun polymeric membranes for wound healing: A review

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Abstract---Wound dressing materials which are capable of meeting the demands of accelerating wound closure and promoting wound healing process have been highly desired. Electro spun nanofibrous materials show great application potentials for wound healing owing to relatively large surface area, better mimicry of native extracellular matrix, adjustable waterproofness and breathability, and programmable drug delivery process. In this review article, the historical perspective of using electrospun polymeric materials for wound healing is outlined. This review includes, also, the electrospinning parameters, wound measurement methods, phases of wound healing, characteristics of membrane required for wound healing and the required tests. The electrospun extract and the essential oils also included.

Keywords---electro spinning, wound healing, membrane, antibacterial activity, oils.

Introduction

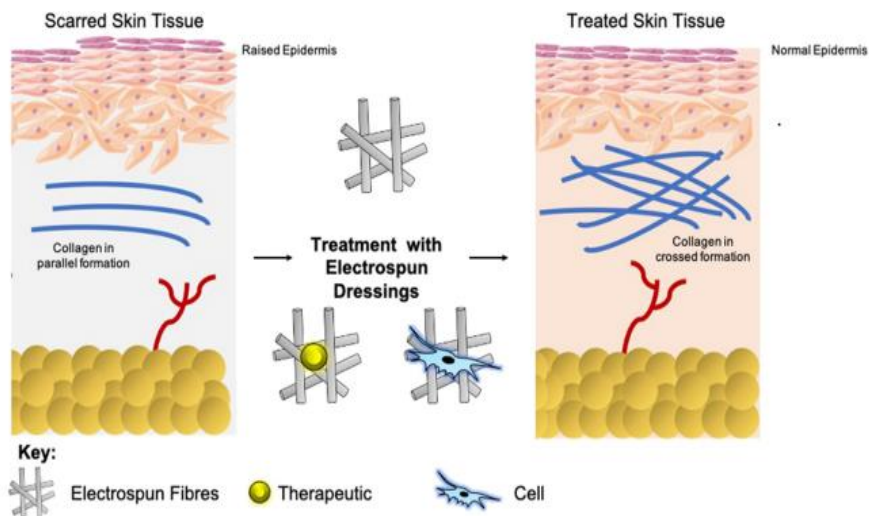
Skin, as the largest and outermost organ of human body, provides the barrier between the internal organism and external environment for protecting body from invasion of pathogens, as well as preventing water loss. It is estimated, that

approximately 312.9 million people throughout the world suffer from the surgically-induced wounds annually, and 76 million people undergo the wounds caused by complications of diabetes, obesity, cardiovascular disease and so on [1]. Over the past decades, wound care has progressively become a major worldwide public health concern. Because, inefficient and defective treatment of skin damages can even be fatal. Hence, intensive research has been performed in this area focusing on the development of efficient therapeutic approaches and design of new dressing materials that can improve the wound healing procedure. For the restoration of the injured tissue, the wound healing process consists of a cascade of events, including hemostasis, inflammation, and proliferation as well as remodeling of the tissue [2].

Wound curing is the net interactions by the whole of cytokines production factors, consanguinity and the extracellular grid [3]. Antimicrobial polymeric materials can be applied in drug delivery, wound healing or dressing, sutures and dental application [4]. Electrospinning (ES) is a simple and effective technique method for preparing nanofibers with diameters ranging from 5 to 500 nm; 10^2 to 10^4 times smaller than those prepared by the traditional methods of solution or melt spinning. Wound dressing from electrospun nanofibrous membranes (NFM), potentially offers many advantages over conventional processes. With its huge surface area and microporous structure, the NFM could quickly start signaling pathway and attract fibroblasts to the derma layer, which can excrete important extracellular matrix components, such as collagen and several cytokines (e.g. growth factors and angiogenic factors), to repair damaged tissue. [5].

Synthetic polymers, especially those with biocompatible and biodegradable characteristics, may offer effective alternatives for the treatment of severe wounds and burn injuries. Ideally, the scaffold material should induce as little pain as possible, enable quick healing, and direct the growth of defect-free epidermal cells. The best material with this multifunctionality, such as self-healing dressings, should be hydrophilic and have uninterrupted and direct contact with the damaged tissue. In addition, the ideal biomaterial should have some antibacterial properties. [6]

The electrospun membrane is also important for cell attachment and proliferation in wound healing. In the electrospinning process, a polymeric solution placed inside a syringe is driven out from a metal capillary that is connected to high voltage power supply. Nanofibers are collected in the form of a nonwoven matrix on a grounded collector after solvent evaporation. By adopting appropriate process parameters, such as solvent, polymer concentration, and flow rate, electrospun nanofibers with various diameters can be obtained [7]



Fig(1):Treatment of Scarred Skin with Electrospun Polymeric Nanofibers.[8]

Wound healing is a complex tissue regeneration process that the body undergoes as a response to wound openings or missing cellular structures as a result of various types of traumatic injury. In adult humans, optimal wound healing involves: (1) rapid hemostasis; (2) appropriate inflammation; (3) mesenchymal cell differentiation, proliferation, and migration to the wound site; (4) suitable angiogenesis; (5) prompt reepithelialization (re-growth of epithelial tissue over the wound surface); and (6) proper synthesis, crosslinking, and alignment of collagen to provide strength to the healing tissue. To facilitate effective wound healing, a wound site is typically covered with a sterile dressing material to avoid infection and to promote the healing process [9].

Historical Perspective

Rachael L. Fischer et al. (2012), used the electrospinning technique to prepare nanofiber meshes from collagen and hyaluronic acid (HA) as a scaffold material for osteoporosis patients who have reduced bone strength. High voltage was applied to the polymer solution to draw out nanofibers that were collected on a ground plate as a uniform mesh. The meshes were then cross-linked to render them insoluble and conjugated with gold nanoparticles to promote biocompatibility. Characterization of the mesh was performed using scanning electron microscope (SEM), electron dispersive spectroscopy (EDS) and Fourier transform infrared spectroscopy (FTIR). A WST-1 assay determined the potential biocompatibility. Results showed that collagen/HA scaffolds were developed that were insoluble in aqueous solutions and promoted cellular attachment that could be used as a tissue engineered scaffold to promote cell growth [10].

Thuy T.T. Nguyen et al. (2013), prepared a nanofiber carrier from Cur and poly(lactic acid) (PLA). PLA nanofibers are biocompatible and have a high-specific surface area and high porosity, which can enhance the functional properties of Cur. Results, showed that an increase from 0.125 to 6.250 wt% Cur in PLA caused a decrease in the diameters of the nanofibers from 971 ± 274 to 562 ± 177

nm. At Cur concentrations of 1.250 wt%, PLA and Cur showed good miscibility in the blended nanofibers. The inclusion of Cur in the blended nanofibers at concentration as low as 0.125 wt% promotes the attachment and proliferation of cells. The in vivo wound healing was assessed in a mouse model; treatment with Cur-loaded PLA nanofibers significantly increased the rate of wound closure (87 %) by day 7 compared with that of PLA nanofibers (58 %).[11]

Bum-Gyu Cha et al.(2014), prepared silk fibroin (SF) nanofiber scaffold containing microalgae *Spirulina* extract by electrospinning method. The viscosity and conductivity of the dope solution of *Spirulina* containing SF were examined for electrospinnability and they found that, the morphological structure of SF nanofiber is affected by the concentration of *Spirulina* extract added. The platelet adhesion and coagulation time test confirmed that, the *Spirulina* containing SF nanofiber scaffold had excellent ability to prevent blood clotting or antithrombogenicity that is comparable to heparin. Low cytotoxicity and excellent cell adhesion and proliferation were also observed for *Spirulina* containing SF nanofiber scaffold by methylthiazolyldiphenyl-tetrazolium bromide assay and confocal fluorescence microscope using fibroblast and human umbilical vein endothelial cells. Based on these results, authors believe SF nanofiber scaffold containing *Spirulina* extract has the potential to be used as tissue engineering scaffold that requires high hemocompatibility. [12]

Mino Sadri et al. (2015), investigated the effect of green tea extract as a natural and ecofriendly antibacterial additive on the healing effect of chitosan/polyethylene oxide wound dressing nanofiber produced by electrospinning method. Results, showed that the optimum conditions were: Voltage; 20 kV, feed rate; 0.5 ml/h, nozzle-collector distance; 10 cm, and chitosan/polyethylene oxide weight ratio; 0.9. The healing ability of the prepared nanofibers was studied on the rat's wound. Chitosan/polyethylene oxide/ green tea showed the best healing effects in comparison with the other prepared wound dressings. These results confirmed that green tea extract helps to keep wound surface moist, reduces inflammation and increases the speed of recovery and healing [13].

Hadi H. et al. (2015), studied the antibacterial and anti-inflammatory activities of sodium alginate-lavender essential oil nanofiber to promote burn healing. Authors demonstrated that nanofibrous dressings of sodium alginate and lavender essential oil not only possessed antibacterial activity against *S. aureus* but they also effectively inhibited the production of pro-inflammatory cytokines both in-vitro and in-vivo. This resulted in a fast recovery of animals exposed to UVB irradiation, without the appearance of erythema on their injured skin. The strong anti-inflammatory action of sodium alginate was evident in all the conducted investigations. On the other hand, lavender oil expressed a high antimicrobial effectiveness and also acted to control the induced inflammation [14].

Faegheh P. et al.(2017), prepared a biocompatible and non-toxic herbal wound dressing encapsulation of *Hypericum perforatum* alcoholic extract at different concentrations (10, 30 and 50 % v/v) into poly ϵ -caprolactone electrospun nanofibers. The electrospinning processing parameters such as needle tip to collector distance, applied voltage and flow rate of feed solution were changed

until accumulated nano-scale fibers without bead structures were obtained. The antibacterial activity of the optimized bandages was investigated by the disc diffusion method against strains of *S. aureus* and *E. coli*. The release content of the herbal drug was tested by the total immersion method in phosphate buffer saline and displayed a constant drug liberation with time. Water vapor transmission rate for the wound dressing was evaluated by pseudo-extra cellular fluid for optimal samples. The crystallinity and thermal behavior of the mats with and without *H. perforatum* alcoholic extract were studied by X-ray diffraction and differential scanning calorimetry (DSC). The results of antibacterial activity, cell culture and *In vitro* methyl thiazolyl tetrazolium assays demonstrated these unique structures as being very useful as burn and ulcer dressings. [15]

Jung C. et al. (2017), Prepared polycaprolactone (PCL) nanofibers containing Spirulina extract for dermal wound healing in a rat model. Alginate, with its hydrophilic structures capable of holding large amounts of water, to support the backbone of the nanofibers. The morphological characteristics, hydrophilicity, water absorbance, skin adhesiveness, toxicity to human keratinocyte cells (HaCaT), and Spirulina extract emission over time were assessed. Alginate improved the efficacy of Spirulina PCL nanofibers in moisture maintenance and adhesion ability, which highly affected recovery in the rat skin wound model. [16]

Shababdoust et al. (2017), studied two series of polyurethane (PU), based on polycaprolactone (PCL) as soft segments with two different molecular weights (2000 and 530 Da), and hexamethylene diisocyanate (HDI) and 1,4-butanediol (BDO) as hard segments were synthesized to fabricate curcumin-loaded electrospun nanofibrous PCL-based PU substrate. Chemical structures of the synthesized PUs were characterized by FTIR and NMR spectroscopy techniques. The thermal properties were analyzed by DSC, surface hydrophilicity was studied by static contact angle and bulk hydrophilicity was evaluated by water uptake test. Thereafter, bead-free PU nanofibrous substrate containing curcumin was fabricated by electrospinning and morphology of the mats was observed by SEM. Mechanical properties of the electrospun mats in comparison with polymeric films were assessed by a universal test machine. The *in vitro* release of curcumin was studied by UV-Vis spectroscopy. The optical density of the bacterial solutions was used to evaluate the antibacterial activity of the curcumin-loaded nanofibrous mats against *Escherichia coli*. The results showed that curcumin-loaded PU synthesized by PCL with molecular weight of 2000 Da displayed better mechanical properties as well as better antibacterial properties in wound dressing application. [17]

Rashid A. et al. (2018), prepared novel electrospun chitosan/polyvinyl alcohol/zinc oxide nanofibrous mats by electrospinning technique with antibacterial and antioxidant properties for diabetic wound healing. Non-healing wound is a serious complication of diabetes, associated with extremely slow wound closure, and a high rate of infection, resulting in amputation or losses of limbs, high health care cost and poor quality of patient's life. These nanofiber mats comprises of wound healing activities of chitosan-PVA nanofibers and antibacterial properties of ZnO. The results revealed that chitosan/PVA/ZnO nanofibrous membranes possessed higher antibacterial potential against *E. coli*, *P. aeruginosa*, *B. subtilis* and *S. aureus* compared to chitosan/PVA nanofibrous membranes and higher

antioxidant potential The *in vivo* wound healing studies showed that chitosan/PVA/ZnO nanofibrous membranes resulted in accelerated wound healing [18].

Min S. K. et al. (2018), developed a coaxial Alginate-PCL nanofibrous dressing for controlled release of spirulina extract. The bioactivity release pattern, water absorbance, and mechanical strength must be controllable. Spirulina extract was physically impregnated inside a nanofiber without significant chemical bonding to PCL or Alginate polymers. This led to an initial burst and continual release of bioactive molecules from the nanofiber. By altering the concentration of Spirulina extract, mechanical strength and water absorbance were controllable. In addition, the dressing patch showed no cytotoxicity towards human epithelial cells, not causing skin-irritation.[19]

Qingchang C. et al.(2019),fabricated nanobioglass incorporated chitosan-PVA (polyvinyl alcohol) trilayer nanofibrous membrane (nBG-TFM) via sequential electrospinning. This membrane exhibited excellent biocompatibility, antibacterial activity and regeneration promotion effect. Furthermore, spatially designed structure optimized functions of each component and provided more suitable microenvironment as compared with uniform membrane. Rat full-thickness skin defects model and mice diabetic chronic wound model showed that nBG-TFM could achieve significantly accelerated and enhanced healing, in terms of complete re-epithelialization, improved collagen alignment and formation of skin appendages[20]

Ozlem E. et al.(2019),produced perforatum oil loaded electrospun polymeric wound dressing material in order to be used in wound therapy. Perforatum oil is known to have curative effect on wound-healing process. Wound dressing material was produced in two layers, the upper layer was made of electrospun PCL nanofibres in order to maintain membrane integrity and mechanical strength while the bottom layer that is designed to be in contact with the wound was formed by electro spraying while the electrospinning of PEG/H. perforatum oil and PCL polymer solutions from opposite directions (concurrently). FTIR, optical and electron microscopy, tensile and gas permeability, contact angle, swelling and *in vitro* release tests were utilized for material characterization. Encapsulation of H. perforatum oil in PEG capsules which were held by PEG fibres among PCL fibres was confirmed. H. perforatum oil was released in controlled manner. Antimicrobial activity tests on *S. aureus* and *E. coli* revealed that H. perforatum content exhibited antimicrobial activity on both. Material was found to be biocompatible and suitable for use as wound dressing according to the results of *in vitro* tests, in which L929 mouse fibroblast cell line incubated with materials for investigation of biocompatibility (WST-1) and cell-material interactions (proliferation, apoptosis/necrosis)[21].

Yan G. et al.(2019),fabricated a notable chitosan/poly(ethylene oxide) nanofiber mats containing tea tree oil liposomes (TOLCENS) using electrospinning process. The microstructures and morphology were characterized by scanning electron microscopy. The porosity, fluid absorbability, water vapor permeability and mechanical properties of nanofiber mats were also estimated by ethanol density method, gravimetric method, dish method and tensile test, respectively.

Compared to the chitosan/poly(ethylene oxide) composite freeze-dried sponges containing tea tree oil liposomes, TOL-CENs had greater porosity, water absorption, breathability and better mechanical properties. In addition, the controlled-release properties and long-term bactericidal capability of the material were also assessed. From the analysis of the release kinetics and mechanism, it was found that the significant decreased terpinen-4-ol concentration gradient from liposomal surface to the outside of material was the key to the sustained terpinen-4-ol release in virtue of liposomal encapsulation. TOL-CENs exhibited long-term and more excellent microbicidal effects against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans* than chitosan/poly(ethylene oxide) nanofiber mats. The combination of tea tree oil liposomes and chitosan in nanofiber mats synergistically destroyed cell membrane, prevented cell adhesion and caused the irregular aggregation of cytoplasm, resulting in cell disintegration observed by transmission electron microscope.[22]

Hasham S. Sof et al. (2019), simultaneously loaded lavender oil and silver nanoparticles (Ag NPs) onto polyurethane nanofibers for wound-healing applications. An abundance of Ag NPs in the fibers decreased the diameter of the fibers while increased concentration of the lavender oil increased the diameter. The Ag NPs and lavender oil improved the hydrophobicity of the nanofibers and ensured the proliferation of chicken embryo fibroblasts cultured in-vitro on these fiber dressings. The anti-bacterial efficiency of the nanofiber dressings was investigated using *E. coli* and *S. aureus*, which yielded zones of inhibition of 16.2 ± 0.8 and 5.9 ± 0.5 mm, respectively, indicating excellent bactericidal properties of the dressings.[23]

Irem U. et al. (2019), fabricated and characterized various concentrations of peppermint essential oil (PEP) loaded on poly(ϵ -caprolactone) (PCL) electrospun fiber mats for healing applications, where PEP was intended to impart antibacterial activity to the fibers. SEM images showed that the morphology of mats was smooth, uniform, and bead-free. The average fiber diameter was reduced by the addition of PEP from 1.6 ± 0.1 to 1.0 ± 0.2 μm . Functional groups of the fibers were determined by Raman spectroscopy. Gas chromatography-mass spectroscopy (GC-MS) analysis demonstrated the actual PEP content in the samples. In vitro degradation was determined by measuring weight loss and their morphology change, showing that the electrospun fibers slightly degraded by the addition of PEP. The wettability of PCL and PEP loaded electrospun fiber mats was measured by determining contact angle and it was shown that wettability increased with the incorporation of PEP. The antimicrobial activity results revealed that PEP loaded PCL electrospun fiber mats exhibited inhibition against *S.aureus* (gram-positive) and *E.coli* (gram-negative) bacteria. In addition, an in-vitro cell viability assay using normal human dermal fibroblast (NHDF) cells revealed improved cell viability on PCL/PCL electrospun fiber mats.[24]

Majid S. et al. (2019), prepared porous electrospun poly(ϵ -caprolactone)/gelatin nanofibrous mat containing cinnamon for wound healing application: in vitro and Cinnamon (cin) was loaded into poly(ϵ -caprolactone)/gelatin (PCL/Gel) nanofibrous matrices in order to fabricate an appropriate mat to improve wound healing. Mats were fabricated from PCL/ Gel [1:1 (w/w)] solution with 1, 5 and 25% (w/v) of cinnamon. The fabricated mats with and without cinnamon were

used to treat the full-thickness excisional wounds in Wistar rats. The results indicated that the amount of cinnamon had a direct effect on porosity, mechanical properties, water uptake capacity, water contact angle, water vapor transmission rate and cell proliferation. In addition, the results of in vivo study indicated that after 14 days, the wounds which were treated with PCL/Gel 5%cin had better wound closure (98%) among other groups. These results suggest that the cinnamon can be used as a suitable material for wound healing[25].

Petr S. et al. (2020), prepared curcumin/usnic acid-loaded electrospun nanofibers based on hyaluronic acid distilled water/DMSO solvent systems at room temperature. The mean nanofibers diameter is 298 nm. The loading of the hydrophobic curcumin and usnic acid into hydrophilic hyaluronic acid matrix was performed without utilizing toxic chemical agents such as DCC and DMAP. It is supposed that, the absence of the above-mentioned catalyst reagents can provide the biocompatibility of materials based on curcumin/usnic acid-loaded hyaluronic acid. The possible presence of DMSO in residual amounts in the fibrous materials is expected to enhance the anti-inflammatory properties and local analgesic and antiseptic activity of the fibers. During the electrospinning process, the effect of the electric voltage was demonstrated. It was found that the prepared solutions are easily electrospun in spite of the molecular ratio of hyaluronic acid and biologically active agents. This technology of curcumin/usnic-acid-loaded hyaluronic acid fibers obtainment significantly broadens the application of the electrospun fibers filled by pharmacological agents in modern biomedical systems, such as wound dressings, ambustial materials and drug delivery scaffolds.[26]

Md. Abdus Shahid et al.(2020),manufactured multicomponent Nano fibrous mat by electro spinning technique from a blended solution of polyvinyl alcohol, honey and Curcumin longa (turmeric) extract as the wound dressing material. Ethyl acetate extraction was followed to obtain a restorative components of turmeric. Nanofibers of fabricated mat show an average diameter of 340 nm with better moisture management properties compared to polyvinyl alcohol nanomat alone. The agar diffusion method has been used to evaluate the antibacterial activity against Staphylococcus[27].

Ismail A. I.etal. (2020), prepared innovative and bioactive wound dressings prepared by electrospinning mimicking the native structure of the extracellular matrix (ECM). Bilayered wound dressing material was produced by sequential electrospinning of quaternized poly(4-vinyl pyridine) (upper layer) on the Centella Asiatica (CA) extract containing electrospun poly(D, L-lactide-co-glycolide) (PLGA)/poly(3- hydroxybutyrate-co-3-hydroxy valerate) (PHBV) blend membrane (lower layer). SEM was utilized to show a uniform and bead-free fiber structure of electrospun membranes. The average diameter of CA extract containing electrospun PLGA/PHBV blend membrane was calculated $0.471\pm 0.11 \mu\text{m}$. Chemical, thermal, mechanical properties, and adsorption capacity of electro spun membranes, as well as the cumulative release of CA from the electro spun PLGA/PHBV membrane, were investigated. Viability, adhesion, and attachment of human fibroblast cells on the electrospun membranes on pre-set days were evaluated by the colorimetric Cell Titer 96 Aqueous One Solution Cell Proliferation Assay (MTS assay) and SEM. Results revealed that CA loaded

bilayeredelectrospun wound dressing showed promoted attachment and proliferation of fibroblasts. Hence, it can be concluded that CA extract containing bilayeredelectrospun wound dressing has a promising potential for wound healing applications[28].

Electrospinning technique

The electrospinning method includes utilizing a high voltage delivered to polymer solution in which charges will induce inside the solution. When critical limit is exceeded by the charge's addition, jet is generated first from drop that is located in the needle tip leading to the construction the "Taylor cone". The jets run to the region of lowest voltage which is the grounded collector. as shown in (Figure 1) [29].

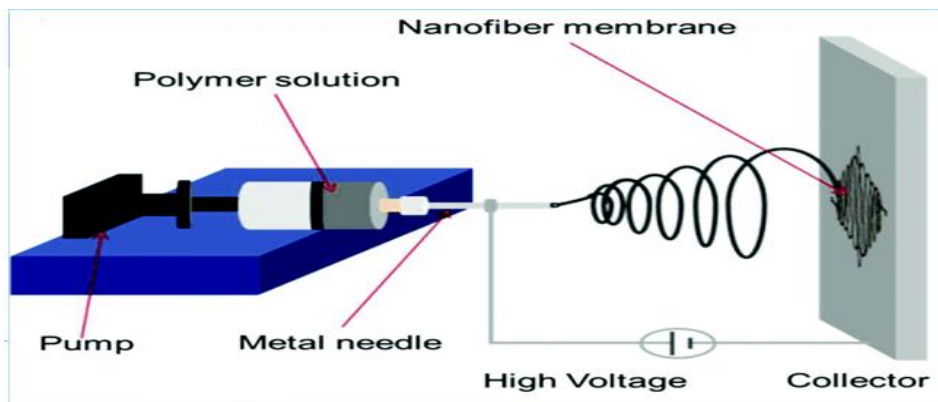


Figure (1) Electrospinning Setup [30]

Factors affecting electrospinning technique

To obtain fibers with high orientation and desirable properties, several parameters must be controlled, some of which belong to the prepared solution, some are specific to the process, and some are specific to ambient conditions

The Polymer Solution parameters

Concentration Effects

Usually, increasing the concentration of solution, the fiber diameter will increase[31].

Molecular weight and viscosity of solution

Basically, polymer solution must have appropriate molecular weight and adequate viscosity. Viscosity makes the polymer solution stretchable and molecular weight plays an important role in entanglement and determines the chain length so that, when increased the chain length, the entanglement chance increases leading to prevent jet solution breakage from occurring [32]. High viscosity is required to form jets without beads but not too high in which difficulties in pumping the solution occur. [33].

Conductivity

The conductivity of solution is necessary property to get smoother fibers with small and high diameters so, charges increased in solution and on the transferred jets if the electrical conductivity of the solution improves. Improving conductivity of solution may be done by adding salts or ions, most of the protein and medicines create ions when dissolved in water. Charges, also play an important role in stretching the solution so that increasing the charges has effect to increase the stretching of solution also tends to form smoother fiber diameter [34].

Surface Tension

The charges that are developed in the polymeric solution should be highly enough in electrospinning to overcome the solution's surface tension. The solution is stretched as the solution jet speeds from the source's tip to the collector, and the solution's surface tension may cause the solution to split up into droplets. Surface tension regarded as a characteristic of a solution's surface that make this phenomenon. A homogeneous attractive force is produced on a liquid molecule immersed inside a solution by the surrounded liquid molecules. molecules which to found near the surface of liquid affected by the two forces one of them is the attractive forces come from the bulk molecules and the other is from the gas molecules and the later stronger than the former. As a result, the surface becomes in tension, causing the surface of the solution contracted, which is counterbalanced by repulsive forces arising the impacts of molecules that exist in the inner of the solution. The total impact of all the surface liquid molecules pushing on each other leads the liquid surface to shrink, decreasing the surface area. As a result, a spherical form has the lowest ratio of surface area to volume for a droplet of water. [35]

Dielectric Constant

Higher dielectric constant gives lesser beads formation and smaller diameter of nanofibers [36]. N, N-Dimethylformamide (DMF) solvent usually added to the solution to enhance fibers morphology due to its higher dielectric constant [37]. With a larger dielectric constant, the electrospinning jet's bending instability improves as well. This may also assist the decrease of the fiber diameter owing to the larger jet path [38].

Volatility

Invariably, it is the evaporation of solvent from the jet that yields a solid polymer nanofiber at the collector plate. Ideally, all traces of solvent must be removed by the time the nanofiber hits the collector. If not, the wet fibers may fuse together to form a melded or reticular mat. Sometimes a flat ribbon-like nanofibers derived from the fluid -filled, incompletely dry nanofiber due to slow subsequent evaporation of solvent and collapse of the tube, are obtained. Using volatile solvents avoids this difficulty. However, when using highly volatile solvents the solution may dry on the capillary or needle, causing blockage to flow [39].

Environment

Humidity

The electrospinning environment's humidity affects the solution of polymer during electrospinning. When electrospinning is done at normal atmosphere, water is likely to condense on the fiber's surface at high humidity. As a result, the fiber morphology, particularly polymer dissolved in volatile solvents, may be affected. The creation of holes on the surface of the nanofibers was discovered to be caused by high humidity [40]. Humidity has a direct effect on nanofiber porosity and in which increasing the humidity will increase the porosity [41].

Atmosphere type

The electrospinning process is influenced by the air composition in the electrospinning environment. Under a high electric field, different gases behave differently. Helium, for example, will decompose in a strong electric field, making electrospinning impossible. When Freon®-12 gas is used instead of air, the fibers produced double the diameter of the nanofibers produced in air [42].

Temperature

The temperature of the solution increases the rate of evaporation, also increasing it will decrease the viscosity of the polymer solution. The fibers formed at a higher temperature when polyurethane is electrospun have a more uniform diameter [43]. This maybe because the solution has a lower viscosity and the polymer is more soluble, permit the solution from being stretched

Processing Parameters

Applied Voltage V

Generally, one can summarize the increasing of applied voltage on the fiber diameter and morphology as following:

- 1- Increasing of voltage leads to greater the stretching of the electro spinning jet due to the increase in columbic force exerted by the charges .
- 2- Increasing the voltage leads to increasing of the jet acceleration and hence decreasing the flight time of the electro spinning jet.
- 3- Increasing the voltage can reduce fiber diameters.
- 4- Crystallinity also increases with proper flight time.[44]

Feed Rate

Feed rate will determine the amount of solution available for the ES process, generally:

- a. Low flow rate suitable to get enough time of polarization of solution
- b. High flow rate lead to increase the beads of fibers with thick diameter.
- c. Short drying time prior to reach the collector and low stretching forces. [45]

Capillary Tip Diameter

The using of smaller diameter lead to :

- 1- Reduce the formation of beads, this is because less volume of solution at the tip is collected which lead to reduce fiber diameter.
- 2- Also smaller needle diameter produces the smaller droplet, this means higher the surface tension, for fixed voltage the time for stretch increases and fiber will elongate before it reaching the collector. [46]

Gap Distance

The distance between the needle tip to collector seems less important in the formation and morphology of resultant Nano fibers. [47]. The using electrospinning distance is between (5-15 cm) , (5-10 cm) range is very effected on nanofibers morphology and diameter, while over (10 cm) there is no there no significantly effect on the nanofibers diameter and morphology . Generally low distance leads to:

- 1- Incomplete evaporation of the solvent and increases the speed of resulting fiber to access to the collector.
- 2- Possible lead to the formation of beads Nano fibers.[48]

Collector Geometry

There are many types of collector discovered for different application such as : wire mesh , pin , grids , parallel or gridded bar , rotating rods or wheel ,liquid bath [49], fig (10) shows the most widely used form of collectors. A non-conducting material collector reducing the amount of fiber being deposited with lower packing density. Porous collector yields fibers with lower packing density as compared to non-porous collector plate. In porous collector plate, the surface area is increased so residual solvent molecules gets evaporated fast as compared to non-porous. Cylinder rotate collector leads to alignment nanofibers while the flat plate collector leads to collect the nanofibers as a random shape [50]

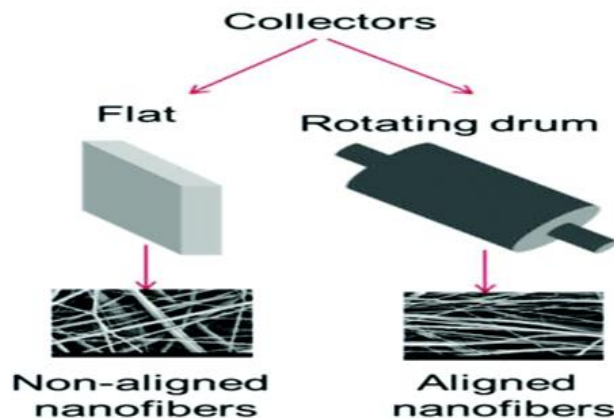


Fig. 10: Types of collectors[51]

Wound measurement methods

1. Ruler method: The simplest and quickest method is to use a disposable paper ruler (Figure 11) to measure the length and width of the wound [52]. Multiplying these together will give an estimated surface area.

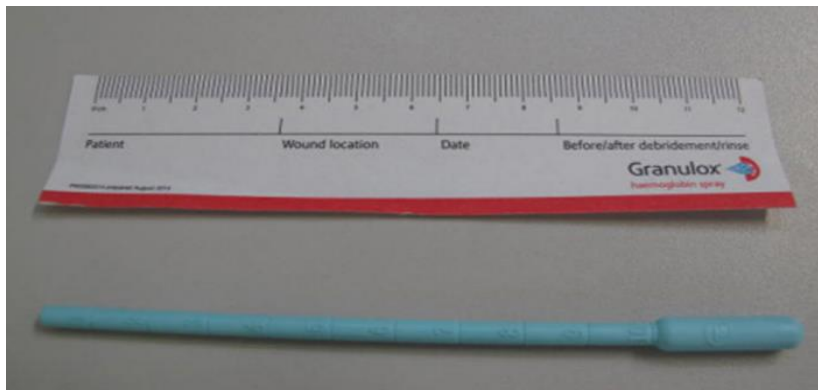


Figure 11. Ruler and probe[53].

2. Tracing
Tracing a wound is an easy and inexpensive method and has advantages over length \times width measurements. It gives more information about the shape of the wound, but still has limitations. In this method, a clear film layer is applied over the wound and an acetate layer is applied on top. A fine-tipped permanent marker is used to draw around the wound outline and then the wound contact layer is disposed of in the clinical waste and the acetate sheet stored in the patient's record after being clearly dated and labeled [54].
3. Depth
It is important to establish the depth of a wound as part of the assessment process, and to determine whether there is any sinus or undermining present. The recommended method for measuring depth is to use a sterile cotton tip swab, gently insert it into the area of undermining, then grasping it at the wound edge measure against a ruler. Plastic probes, are also available that are pre-marked with cm markings[55]
- 4- Photography
Photography is becoming increasingly popular as a method of recording wound assessment and monitoring progress. The advantages of a photograph are that it can provide greater information about the wound, such as tissue type and condition of the surrounding skin. The value of a photograph for monitoring progress is dependent on certain conditions being fulfilled to ensure consistency [56]

Video image analysis

This method employs a video camera to film the wound. The recording of the image is then analyzed by a computer using a special software program, which permits correction of the figures obtained for wound dimensions to compensate for the concave or convex nature of the wound. The technique is more accurate than the analysis of photographs, and is simple, rapid, and inexpensive.[57].

Capable eletrospun polymers

Significant progress in the production of polymers to avoid bacterial attack has been produced over the last decades.[58]

Synthetic polymers

Many synthetic polymers have been used in electrospinning applications. These include:

1. polylactic acid (PLA) is an aliphatic polyester derived from renewable sources, such as cornstarch, sugarcane, and other annually renewable biomass products and wastes, which can be obtained from direct condensation polymerization of lactic acid monomers or the ringopening polymerization of the cyclic lactide dimers. It is highly versatile, biocompatible, biodegradable at a slow rate, and semi-crystalline solid. This polymer is widely used in agriculture, packaging, sutures, scaffolds for tissue engineering, and carriers for drug delivery [59].
2. Polyglycolide (PGA):is one of a group of biodegradable aliphatic polyesters currently exploited in a variety of medical applications. The successful clinical use of PGA sutures has demonstrated that PGA-containing polymers can be used safely in soft tissue applications. PGA has also been found to be useful in the engineering of many types of tissues and is also used in vascular tissue engineering [60].
3. poly(lactide-co-glycolide) (PLGA): is one of the most widely investigated biomedical polymers for scaffolds in tissue engineering. PLGA is biodegradable aliphatic polyester of which degradation rate is controllable according to the molar ratio of lactic acid and glycolic acid.[61].
4. Polycaprolactone (PCL): a biodegradable polyester emerging into biomedical applications because of its biodegradability, biocompatibility, chemical stability, thermal stability and good mechanical properties[62].
5. Polyvinyl alcohol (PVA) is a water-soluble polymer with many hydroxyl groups pendant in the side chains.[63]. It has been studied intensively because it has high hydrophilicity, processability, biocompatibility , good physical and mechanical properties, complete biodegradability , excellent chemical resistance, and a favorable capacity to form a film.pva melts at around $(180-228)^{\circ}\text{C}$ display glass to rubber transition at $(75-85)^{\circ}\text{C}$. [64].
6. Polyethylene Oxide (PEO): is well-known synthetic biocompatible and water soluble polymer, suitable for a range of pharmaceutical uses and it is known for facilitating the electrospinning of biopolymers solutions, that are otherwise not electrospinnable, like lowmolecular weight biopolymers, such as proteins and carbohydrates[65].
7. Poly(vinyl pyrrolidone) PVP: has been used as a film-forming agent and a viscosity-enhancement agent and is considered an essential element in detergents, paints and biological engineering. Due to its low chemical toxicity and biocompatibility, PVP K-30 is widely used in the commercial products and in the cosmetic market, for example, hair-spray reagents, shampoos, eye makeup, lotions, sunscreen and skin care products. Furthermore, PVP can react with iodine to generate a chemical compound with iodophor characteristics that is utilized as an antiseptic material. The

- PVP-iodine complex (PVP-I) works as an iodophor that releases active iodine, an effective antimicrobial agent[66].
8. Polyurethanes (PUs) are block copolymers with rigid urethane hard segments and polyether/polyester soft segments with low glass transition temperature. Thermoplastic PUs are commonly used as implantable materials showing high mechanical strength, toughness, abrasion resistance, and resistance to degradation in watery solution. PU plays a major role in developing implants, such as catheters, stent, pacemaker leads, total artificial heart, and many more [67]. PUs are widely used in wound dressings because of their good barrier properties and oxygen permeability [68]
 9. Carboxymethyl cellulose (CMC), an anionic derivative of the regenerated cellulose forms polyelectrolytic complex under controlled condition leading to difficulties in spinning nanofibers. It is a suitable candidate for preparation of cellulose based electrospun wound dressing material with incorporated plant extracts with initial burst release profile. The chemical properties of CMC make it a promising biomaterial for applications in tissue engineering of skin, cartilage and bone [69].
 10. Polyester urethane (PEU) :has been considered as a biomaterial for some time, due to its favourable physical properties, chemical inertness, and biocompatibility. PEU is a soft and hydrophobic polymer. If it is used alone for a dressing material, these two properties would be drawbacks because the dressing may be too soft for clinical handling and its hydrophobic property may prevent fluid exuding from wound surface.[70]

Natural polymers

- 1- Collagen: Collagen is a good candidate to be used in electrospinning for several reasons. First, collagen is the most abundant protein in the body where it acts as a structural building block of the ECM found in most native tissues. Second, collagen possesses natural binding sites for the adhesion of osteoblasts, which aid in bone formation. Third, it has known chemical, mechanical, and biocompatible properties. Fourth, there are many processing methods that can be used to isolate collagen in large quantities. Lastly, it has the ability to increase cell adhesion and the differentiation of many cells. Unfortunately, collagen alone does not have the mechanical and structural support to perform well after implantation.[71]
- 2- Hyaluronic acid (HA) can be found in the ECM of connective tissues and has unique viscoelastic properties as well as good biocompatibility and biodegradability that make it a good candidate for tissue engineering. Electrospinning using HA can be difficult because of its high viscosity and surface tension, even in low concentrations, and its hydrophilic nature that may not be favorable for some applications. Because of these complications, electrospinning nanofibers containing both collagen and HA has not been seen in research until recently[72].
- 3- Keratin is a major fibrous protein, which forms outer coverings of the body such as hair, wool, nail and so forth. Li's group has evaluated human hair keratin scaffolds for skin wound repair and regeneration.[73]

- 4- Lysozyme: lysozyme nanofibers (LNFs) obtained from an inexpensive globular protein, were used to prepare non-cytotoxic hydrogels that can promote cell spreading at high surface coverage and remain viable for up to 7 days . Furthermore, LNFs, apart from the promotion of cell adhesion and proliferation, also present other relevant properties, namely remarkable mechanical performance and antimicrobial activity , which can be a major asset for designing dressings for cutaneous wound healing. Nevertheless, the LNFs inability to form solid films hampers their application as nanofibrous patches[74].
- 5- Lactoferrin (LF), an 80 kDa iron-binding glycoprotein of the transferrin family, is a major component of milk and can be found in the secondary granules of neutrophils, in mucosal surfaces, and in biological fluids of different mammals, playing an important role in the innate immune response. Among its physiological roles, including iron homeostasis, immune response, antioxidant, anticancer, and anti-inflammatory properties, the antimicrobial activity is the most studied. LF is active against a broad spectrum of Gram-positive and Gram-negative bacteria, fungi, viruses, and protozoa. This activity is based on the ability to sequester iron, an essential nutrient for pathogens, or by direct interaction with the microorganisms; thus, structural integrity under processing is essential for keeping its bioactivity[75].
- 6- Lactoglobulins : β -Lactoglobulin is a self-assembling protein, which potentially bears antimicrobial properties due to its iron-binding ability. It has been electrospun into nanofibers using PEO, but antimicrobial properties have not been investigated. α -Lactoglobulin is also a self-assembling protein and has been electrospun after addition of PEO. α -Lactoglobulin fibers alone did not demonstrate antimicrobial properties, but an incorporation of ampicillin showed time- and concentration-dependent inhibition of *E. coli*[76].
- 7- Cellulose acetate (CA): is the most valuable cellulose derivative that is a constituent of green plant cell walls. The biomedical applications of electrospun CA nanofibers are tissue engineering, antibacterial applications, drug delivery systems, and wound dressings . The application of CA in the drug delivery system is related to a wide range of their properties. In this regard, CA has an excellent electrical conductivity that can be quickly ejected from the needle of syringe under high electrostatic force and deposited randomly on a collector as nanofibers. The electrospun CA nanofibers could be successfully used to deliver the antioxidants, non-steroidal anti-inflammatory drugs (NSAIDs) , and vitamin.[77]
- 8- Gelatin (GT): is an inexpensive natural polymer, which is derived from collagen and exhibits good biological properties similar to collagen. It is a biocompatible, biosoluble, non-immunogenic, and hydrophilic natural protein. This protein also has arginine-glycine-aspartate (RGD) sequences, which provide cell attachment sites. Due to its superior properties, GT also has been extensively employed as a biomaterial for both tissue engineering and drug delivery systems[78].
- 9- Silk is a typical fibrous protein produced by a variety of insects including silkworm. Silk consists of two types of proteins, fibroin and sericin. Fibroin is the protein that forms the filaments of silkworm silk and can be regenerated in various forms, such as gels, powders, fibers, or membranes,

depending on application . Recently, many researchers have investigated silk proteins, mainly silk fibroin (SF), as one of the candidate materials for biomedical applications, because it has several distinctive biological properties including good biocompatibility, good oxygen and water vapor permeability, biodegradability, and minimal inflammatory reaction . In practice, SF has been used in various fields, such as cosmetics, medical materials for human health, and food additives[79].

- 10- Chitosan is a modified natural amino-polysaccharide derived from chitin, known as one of the most abundant organic materials in nature. Chitosan has an apparent pKa of 6.5 and is generally soluble at PHs below 6. This is related to the protonation of the free amino groups on its backbone. The amino groups on the chitosan molecule (Fig 16) are identified as the main source of the unique properties of chitosan, after being protonated in acidic solvents resulting in a polyelectrolyte solution. Hence, beside molecular weight, the degree of deacetylation DDA and the distribution of the amino groups along the polymer chain are the key factors affecting the final properties of chitosan[80].

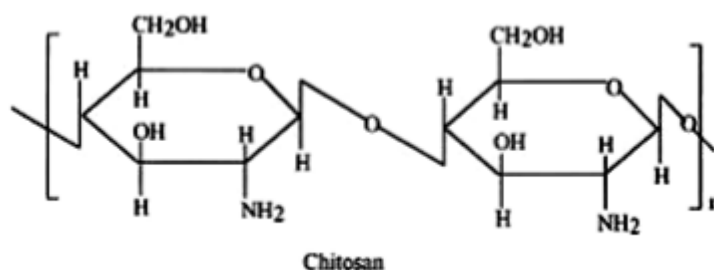


Figure16: Chemical structure of chitosan .[80].

The mechanical and permeable properties of chitosan film can be controlled by selecting the suitable molecular weight, solvent, plasticizer agent, dispersant and compatibilizer[81] .

Chitosan has been widely used in several applications due to its natural origin and exceptional properties such as biodegradability, biocompatibility, non-toxicity [82]and chelation of metal ions. Among them, scaffolds for tissue-engineering, wound healing dressings, water and waste water filtration and antibacterial films were among the interesting ones[83].

Electrospinning of extracts and Essential Oils For wound healing

1. Cinnamon extract and Essential Oil: Antibacterial nanofiber membrane made by cinnamon-loaded electrospun chitosan/gelatin (Chi/Gel) nanofibers. Chi/Gel nanofibers were produced with different Cinnamon extract (CE) amounts, followed by a crosslinking via glutaraldehyde vapor. Morphological studies showed that Chi/Gel nanofibers had an average diameter of around 140–170 nm. After crosslinking, the average diameter increased, and nanofibers fused at some spots, although these changes were less pronounced in the samples containing the extract. The presence of

the CE was confirmed using FTIR and TGA characterization techniques. The water contact angle measurement did not show any significant change in hydrophilic properties in extract loaded samples. However, the CE had substantial effects on the biological properties of scaffolds. For example, nanofibers became more resistant to degradation, which is essential for natural biopolymers whose application is limited by rapid biodegradability. Besides, the antibacterial activity and biocompatibility were improved in the Chi/Gel sample containing 4% of CE. Cell morphology studies indicated better cell attachment and growth in this sample. The extract release profile showed a rapid release in the first 6 h, followed by a zero-order release over the next 138 h. Consequently, this drug delivery nanofiber membrane can be suggested in various biomedical applications, especially in dentistry, wound healing patches, guided bone regeneration (GBR) membrane, and orthopedic healing construct[84].

2. Peppermint Essential Oil: Diabetic ulcer is regarded as one of the most prevalent chronic diseases. Healing of these ulcers enhances with the use of herbal extracts containing wound dressings with high antibacterial property and creating a nano-sized controlled release system. Peppermint extract was used as an herbal antimicrobial and anti-inflammatory agent. The absorption ability of the wound dressing was enhanced by addition of F127 pluronic into the polymer matrix. The release of the extract was optimized by crosslinking the extract with gelatin nanoparticles (CGN) and their eventual incorporation into the nanofibers. The release of the extract was also controlled through direct addition of the extract into the PU matrix. The results showed that the release of extract from nanofibers was continued during 144 hours. The prepared wound dressing had a maximum absorption of 410.65% and an antibacterial property of 99.9% against *Staphylococcus aureus* and *Escherichia coli* bacteria [85].
3. Clove Essential Oil: To produce antibacterial poly(ϵ -caprolactone) (PCL)-gelatin (GEL) electrospun nanofiber mats containing clove essential oil (CLV) using glacial acetic acid (GAA) as a “benign” (non-toxic) solvent. The addition of CLV increased the fiber diameter from 241 ± 96 to 305 ± 82 nm. Aside from this, the wettability of PCL-GEL nanofiber mats was increased by the addition of CLV[86].
4. Thyme Essential Oil:
 - a. Wound dressings are an important element in promoting the healing of wounds. Electrospun fibrous materials have a highly porous structure and controllable antibacterial activity and are therefore popular as potential wound dressings. However, electrospun fibrous wound dressings are usually conveniently packaged for immediate use but cannot accommodate irregularly shaped wounds, and their misuse runs the risk of causing a secondary injury to the wound. To overcome these issues, in situ electrospun zein/ thyme essential oil (TEO) nanofibrous membranes are proposed as a potential type of wound dressing and applied for wound management through an in situ electrospinning process, which uses a portable electrospinning device. The asspun zein/TEO membranes show high gas permeability up to 154 ± 20.9 m² /sand superhydrophilicity with a 0° contact angle. With the addition of TEO, good antibacterial effects are also imparted onto the membrane to prevent infection. Moreover, the in situ electrospinning can directly

deposit the zein/TEO membranes onto the site of the wound to accommodate the shape of the wound with increased convenience and perceived comfort [87].

5. Lavender Essential Oil: Lavender's use in medicine can be traced back to the first century ad when Dioscorides, a Greek botanist and physician, praised its effectiveness in relieving indigestion and headaches in *De Materia Medica*, a five-volume collection describing the medicinal plants used in practice at the time. The Ancient Romans used lavender as an antiseptic after bathing, and it was believed to be an aphrodisiac in the Middle Ages. It has also been used for its antioxidant, antibacterial, antifungal, carminative, and analgesic properties. Furthermore, lavender essential oil has long been utilized as an anxiolytic in Eastern medicine. Studies conducted in recent years to investigate the validity of these documented historical uses found lavender essential oil to have measurable antioxidant, antibacterial, anxiolytic, analgesic, and anti-inflammatory properties due to its biologically active terpenoid components, linalool and linalyl acetate.[88]
6. Green tea: is characterized by the high content of polyphenols, which is produced from the tea plant *Camellia sinensis*. (-)-Epigallocatechin gallate (EGCG) is regarded as the most abundant compound in tea leaves with excellent bioactivities, such as antioxidant/free radical scavenging, anti-inflammatory and antimicrobial properties. However, the clinical application of EGCG is restricted by its low bioavailability, since EGCG is unstable under the alkalescent condition of the intestinal track and circulatory system [89].
7. Spirulina: alginate (Alg)/PCL complex nanofibers impregnated with Spirulina extract were fabricated and examined for their potential in the regeneration of full-thickness skin following injury. The nanofibers were structurally stable and non-cytotoxic to human epithelial cells[90].
8. Sorghum: represents a genetically diverse family of C4 grass varieties, varying greatly with respect to their plant height, leaf size, leaf angle, and propensity to tiller. Sorghum morphology is that of a cane-like grass, comprising a slender to stocky stem ranging from 0.5 to 6 meters in height. The stem is either dry or contains sweet or insipid juice, with broad and coarse leaves distributed along the stem and connected via a leaf sheath that encircles the stem [91].
9. *Coptis chinensis*: (CC) is a medicinal plant generally found in western China; for example, in the Sichuan and Shanxi provinces. The root of this plant has been widely used as a traditional Chinese drug for treating diarrhea, fever, and eczema .It comprises a range of alkaloids, including berberine, palmatine, jateorrhizine, epiberberine, and coptisine, which are regarded as its active components[92].
10. *Hypericum perforatum*: is a medicinal herb with a long history of wound healing due to the antimicrobial activity of crude extracts. Hypericum oil is used conventionally for rapid recovery of ulcers and burns because of its wound healing activity.The encapsulation of purified *Hypericum perforatum* extract in PCL by electrospinning. The extract was very rich in flavonoids, mainly quercetin, glucosides and catechins, and exhibited significant antibacterial capacity. The technical parameters for electrospinning PCL, and PCL filled with alcoholic extract at different concentrations of

DCM:DMF were defined and set up. A trial-and-error approach has been employed by varying the solution properties and spinning parameters until uniform defect-free fibers were obtained [93].

11. Alkannin and shikonin (A/S) are optical antipodes of plant origin. They are found in the outer surface of the roots of at least 150 species that belong to the genera *Alkanna*, *Lithospermum*, *Echium*, *Onosma*, and *Anchusa* of the *Boraginaceae* family. Active ingredient Biological investigations over the last 30 years have shown that alkannin, shikonin and their derivatives possess strong wound healing, antimicrobial, anti-inflammatory, tissue regenerative, antioxidant and antitumor properties[94].
12. Thymol oil as an essential oil has many components with different characteristics. Among them, its antimicrobial properties are related to thymol and carvacrol (phenolic components) ingredients, which are conveniently used in mouthwash, soaps, and creams, and their performance has been evaluated by in vitro and in vivo experiments. Thymol is the most abundant component in thyme oil. So far, a few research works have investigated the role of thymol-loaded polymer carriers for wound healing. The use of thymol in some polymer processes, such as encapsulation [18] and film casting, have been reported. There have been no reports on the addition of thymol as an antibacterial and proliferative agent into electrospun polymer nanofibrous mats as wound-dressing materials[95].
13. *Tecomella undulate* : which is locally known as Rohida, found in Thar Desert regions of northwest and western India and it possess excellent antibacterial properties. The bark obtained from the stem contains tecomin which is used as a remedy for wound healing[96].
14. Chamomile (*Matricaria chamomilla*): As the European Medicines Agency (EMA) confirmed a few years ago, chamomile is highly effective in improving benefits and treating eczema and all forms of inflammation when used topically. One of the best properties of chamomile is that it is anti-allergic.[97]
15. Ginger: Raw ginger contains over 400 different compounds and major constituents were 50–70% of carbohydrate, 3–8% of lipids, and remaining are terpenes and phenolic compounds. Terpene components present in the ginger are zingiberene, β -bisabolene, α -farnesene, β -sesquiphellandrene, and α -curcumene, while gingerol, paradols, and shogaol are the phenolic compounds of the ginger. Besides these components, the ginger also reported having amino acids, raw fiber, ash, protein, phytosterols, vitamins, and minerals. Further, active compounds found in the ginger are reported to have antibacterial, antiviral, and antifungal activities. Bhagavathula et al. reported the combination of curcumin and ginger extract has wound-healing potential and they showed improved healing of abrasion wound [98].
16. Grape seed extract (GSE) was successfully loaded into SF/ polyethylene oxide (PEO) by Si lin and co-workers (2016) through electrospinning process. The fabricated material was undergone through SEM characterization, drug release profile, cell viability, anti-oxidation activity etc. Their result revealed no significant morphological change in fiber structure after loading GSE in various concentrations. The fiber diameter remained around 420nm for various concentrations. Cytocompatibility of the nanofibrous mat was assessed in vitro through SEM and MTT assay.

The result indicated a healthy proliferation of the cells on mat which improves more with the increasing concentration of the GSE. However, 3% GSE loaded mat was found to be optimum in this regard. The mechanism through which grape seed extract acts as potential wound healer is its antioxidant activity. The result revealed the significant survival rate of the cells treated with t-BHP and this rate was also concentration dependent and the optimum concentration of GSE remained in between 3 to 5% in this context[99].

17. *Melilotus officinalis* (MO) is a herbal extract that can be added to wound dressing systems as a drug. It is taken into consideration to treat acute and chronic ulcers, especially burn wounds and diabetic lesions. Based on this extract, topical ointments and oral pills have been developed so far. This drug has been found to have strong antioxidant components such as 7-hydroxycoumarin, flavonoids, and oleanane glucuronide. Due to these components, MO can be beneficial in reducing inflammation, regulating the immune system and improvement in vascularization.[100]
18. *Grewia mollis* : *G. mollis* belongs to the flowering plant genus, *Grewia*. It was formerly placed in the family Tiliaceae or Sparrmanniaceae. Today most authors place the genus in the mallow family Malvaceae[101].
19. *Garcinia mangostana* (GM) is a tropical fruit found in Southeast Asia. People in Southeast Asia have used the pericarp (peel, rind, hull or ripe) of GM as a traditional medicine for the treatment of abdominal pain, diarrhea, dysentery, infected wound, suppuration, and chronic ulcer. The pericarp of GM was report to be a good source of xanthone, α -, β -, and γ -mangostins, garcinone E, 8-deoxygartanin, and gartanin. Several studies have revealed that GM extracts exhibit antimicrobial, antiproliferative , anti-inflammatory and analgesic. Because of these useful activities of GM extracts, it can be used for wound healing application[102].
20. *Centella asiatica*: is a small herbaceous annual plant (Apiaceae family) which distributes in many parts of Asia and South Africa. The extract from *C. asiatica* was used for the treatment of wounds in many years past. It is known that the extract contains three active triterpenes, namely, asiatic acid, madecassic acid, and asiaticoside, which have healing properties such as treating skin problems, healing wounds, as well as being an antibacterial and antiviral agent[103].
21. *Nigella sativa*: *Nigella sativa*, commonly known as “black seed”, is an essential oil source that is promising for its therapeutic effects. Since ancient times, *Nigella sativa* and its extracts have been used in traditional medicine to treat diseases such as diabetes, asthma, flatulence, polio, kidney stones, and abdominal pain. *Nigella sativa* contains mainly fixed and essential oils, carbohydrates, proteins, alkaloids, vitamins, and minerals. One of the most prominent constituents of its essential oils is thymoquinone (30% to 48%), which is known for its pharmacological and therapeutic attributes. The analgesic and anti-inflammatory effects, anti-cancer properties, antibacterial activity, anti-fungal effects, anti-oxidant capacity, and wound healing potential of *Nigella sativa* have been proven in the literature[104].
22. lemongrass oil (LgEo): exhibits excellent antioxidant and antibacterial properties. However, low aqueous solubility and instability of its major

constituents reduced the retention of these properties for the longer time[105].

23. *Calendula officinalis*: (*C. officinalis*) or pot marigold is an aromatic plant with orange or yellow flowers that can be used for wound healing applications namely burns, cuts, rashes, bruise, and foot ulcer treatments. Its chemical compositions include phenolic compounds (e.g., flavonoids and coumarin), triterpenoids, steroids, terpenoids, phenolic acids, carbohydrates, fatty acids, carotenes, essential oils, minerals, quinones, and tocopherols. This herb has some pharmacological properties including antioxidant, anti-inflammatory, antifungal, antiviral, antibacterial, antiseptic, free radicals inhibitors, and blood coagulation activity . It also supports cell proliferation and fibroblastic migration and increases the metabolism of collagen and glycoprotein at the wound site. Hence, it has a lot of potential for use in medical applications such as wound dressing , scaffold for tissue engineering and drug delivery systems [106].
24. *Matricaria chamomilla* (chamomile): Chamomile contains antimicrobial, anti-inflammatory, and antioxidant effects which directly has been used for a variety of healing applications especially cancer therapy, diabetic wound healing and periodontal injury repair. The interest in using soft nanofibrous patches with high surface to volume ratios as carriers for plant extract delivery has been increasing. These biocompatible nanofibrous mats may be considered as promising carriers with controlled and sustained release of chamomile for above applications[107].
25. *Achillea millefolium* (yarrow) The genus *Achillea* comprises of ~85 species, most of which are endemic to Europe and the Middle East. Turkish flora possesses 42 *Achillea* species and 23 of them are endemic. In literature data, various *Achillea* species have demonstrated several biological activities such as antioxidant, antibacterial, antispasmodic and anti-inflammatory[108]

Characteristics of nanofibres required for wound healing

The Extracellular matrix (ECM) is a ubiquitous non-cellular component of tissues and organs comprised by a heterogeneous fibrillar meshwork of mainly glycoproteins, proteoglycans and other small molecules that provide a support for cells. However, the role of the ECM is not merely structural but also functional . It generates a specific microenvironment in constant communication with cells, interacting with surface receptors and supplying assistance in an array of diverse fundamental processes such as cell adhesion, migration, differentiation, growth, apoptosis, etc. and is thus involved in wound healing [109].

Nanofibres usually show stochastic alignment, which makes them resemble the natural nanofibrous mesh of the ECM [110]. Moreover, the high surface area of nanofibres allows for chemical functionalisation of the surface, efficient fluid absorption and drug delivery of encapsulated pharmaceuticals such as antimicrobials or growth factors, which can enhance wound healing [111]. Small interstices, together with the high effective surface area, can make nanofibres promote haemostasis. Furthermore, the high surface porosity of nanofibres permits gaseous exchange across the wound, preventing desiccation and dehydration [112].

In addition, materials composed of ultrafine fibres can better adapt to the contour of the wound than sophisticated 3D materials, which is paramount in the design of medical dressings. In healthy skin, collagen fibrils form a basket-weaved structure, and thus the special arrangement of electrospun nanofibres can affect the wound healing process. For instance, Ottosson et al. [113] showed that aligned nanofibres can provide faster wound closure than randomly-oriented nanofibres, and Sun et al. [114] demonstrated that crossed nanofibres improved the healing outcome of wounds when compared to randomly-oriented and aligned nanofibres. Fig17 shows a schematic of the potential role of a nanofibrous scaffold in wound healing

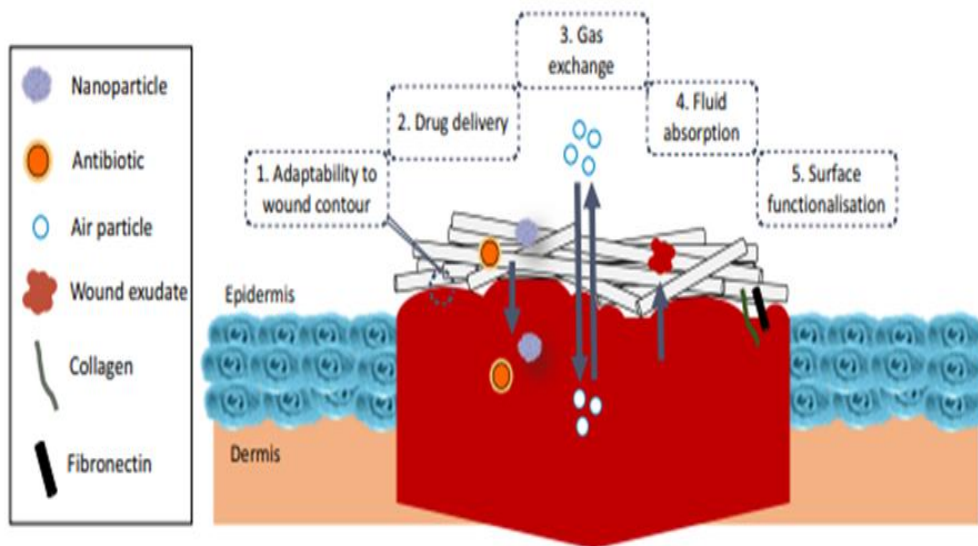


Figure 17: Nanofibres as dressing materials for wound healing.

Owing to dimensions in the nanometre range, porosity, and high surface area, nanofibrous scaffolds can display properties relevant for wound healing, such as: (1) adaptability to the irregular contour of the wound, thus enhancing suppleness and resilience of the scaffold; (2) encapsulation and delivery of different cargos such as antimicrobials and nanoparticles; (3) gas exchange to avoid dehydration; (4) fluid absorption, eliminating the excess of wound exudate typical of chronic wounds and preventing growth of microorganisms and (5) surface functionalisation with molecules such as collagen or fibronectin, which increases biocompatibility and further promotes wound healing. [115]

Phases of Wound Healing

Wound passes by different phases, as shown in figure(18):

- (A) Wound occurring: distribution of the healthy tissues in the site.
- (B) Hemostasis stage: the creation of a clot to prevent any further bleeding.
- (C) Inflammation stage: penetration of neutrophils to the injured site.
- (D) Proliferation stage: infiltration of fibroblasts to the injured site and keratinocytes, and granulation tissue appears.

(E) Maturation, the final phase which may last for years. During the final stage, fibroblasts disappear and the ECM matures[116].

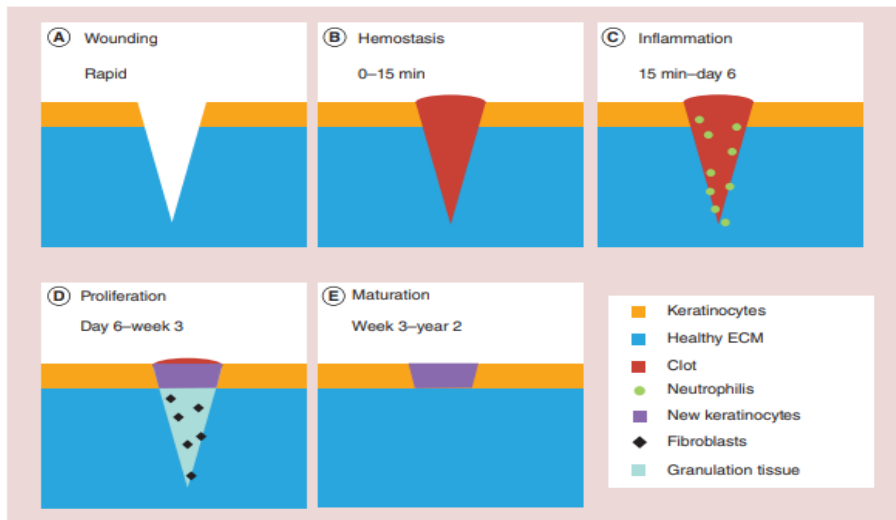


Figure18 . Schematic representation of the different phases of wound healing.

The Effect of PH on Wound

Healthy, intact skin has a slightly acidic pH ranging from 4.0 to 6.0. This is an important aspect of the skin's barrier function, since it regulates bacterial flora and prevents infection. When a wound occurs, the skin's acidic milieu and pH is disrupted, exposing the more neutral pH (7.4) of the underlying tissue. With successful healing and re-epithelialization, the skin returns to being acidic. Acute wounds have a more neutral pH and, during acute wound healing, there is a drop in pH caused by various factors, including hypoxia¹ and increased production of lactic acid. An acidic pH environment is considered to be beneficial, by increasing fibroblast proliferation and migration and also regulating bacterial colonization. If however wound healing is delayed, then the pH will oscillate and become increasingly alkaline over time (Fig. 19). At this stage the wound is described as chronic and the synthesis of ECM molecules becomes impaired, thus arresting the healing process. Recordings of the chronic wound environment have been in the range of pH 7.15 to 8.9 [117].

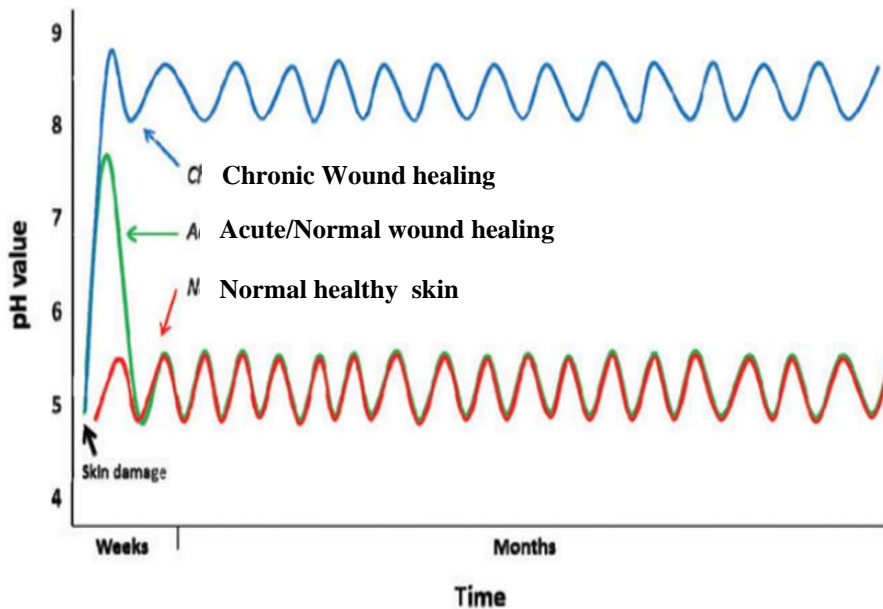


Figure 19 . Time course of pH of healthy skin, acute wounds, and chronic wounds showing the main differences with time.

Various environmental factors affect the growth of bacteria, including temperature, pH (Fig.19), dissolved gases, osmotic pressure, and water availability. Most bacterial organisms grow best around pH values of 6.5–7.0; however, some thrive in very acidic (e.g., *Acetobacter*) or very alkaline conditions (e.g., *Candida*). Organisms grow at a range of pH defined as three cardinal points: (1) the minimum pH, below which the organism cannot grow; (2) the maximum pH, above which the organism cannot grow; and (3) the optimum pH, at which the organism grows best. Each microbial species has its own pH range in which it grows best (Table 1) [117].

Table1 . The optimum growth pH for the most prevalent microorganisms isolated from wounds

Wound-associated microorganisms	Optimum PH for growth
<i>Staphococcus aureus</i>	7.0-7.5
<i>Enterococcus faecelis</i>	7.0-9.0
<i>Pseudomonas aeruuginosa</i>	6.6-7.0
Coagulase-negative staphylococci	7.0-7.5
Anaerobic bacteria	6.0-7.0
<i>Escherichia coli</i>	6.0-7.0
<i>Klebsiella spp.</i>	5.5-7.0
<i>Candida spp.</i>	7.0-8.0

Tests For Polymeric Membranes For Wound Healing Physicochemical characterizations of Nano fiber

a- In vitro drug release:

In order to determine whether the *Angelica keiskei* fractions have toxic effects on the middle back skin of male 9-week-old NZW rabbits (2.1-2.4 kg), several toxicity parameters were evaluated. NZW rabbits are widely used for safety testing. Since a large amount of data for NZW rabbits has been accumulated over a long period of time, it is relatively simple to interpret data from experiments using these animals. The aqueous and ethanol fractions were solubilized in propylene glycol at a concentration of 10 mg/ml. Approximately 24 h prior to the administration of the test samples, the rabbit fur was carefully removed with an electric haircutter. The skin of the shaved back area was divided into four compartments (2.5x2.5 cm); two compartments served as the control areas and two were the test areas. Each compartment was diagonally located from its matching group member in the wound or non-wound group. In the wound group, each site was scratched with an 18-G needle so that only the epithelial tissues were damaged without drawing blood and a # symbol was scratched into the skin. The test sample was applied to each compartment of the skin on the back (90.5 ml/site) using 3-fold gauze (2.5x2.5 cm), then covered with squares of gauze (10x10 cm) and fixed with tape in order to prevent leakage and evaporation. The test substance was removed by carefully removing the gauze squares after 24 h. Draize skin reactions (20) were evaluated and scored by observing skin erythema, crust formation and edema following the administration of the test samples (24, 48 or 72 h). The average score was calculated by adding the scores for edema formation according to the primary skin irritation index (PII) as shown in Table 2[118].

Table 2. Total scores from the phototoxicity test evaluating the effects of aqueous and ethanol fractions obtained from *Angelica keiskei* leaves

Criteria	Total scores	Aqueous	50% Ethanol	100% Ethanol	0.1% 8-MOP
Non-irritating	0.0-0.5	Yes	Yes	Yes	-
Minimally irritating	0.6-1.2	-	-	-	-
Severely irritating	1.3-2.5	-	-	-	Yes
Extremely irritating	2.6-5.0	-	-	-	-

8-MOP, 8-methoxypsoralen.

b- Blood coagulation test

The hemostatic property of TXA mainly relates to its ability for inhibiting conversion of plasminogen to plasmin. Thus, it prevents excessive blood loss in hyperfibrinolytic conditions. Plasmin breaks down fibrinogen and a series of proteins which are involved in coagulation . A general review of blood coagulation was carried out to analyze the potential of scaffoldnanofibrous coagulation. After adding the blood, the nanofibrous coating was completely covered with blood. After 10 min of incubation, the dressings indicated

complete blood coagulation. The red blood cells trapped in the clot were hemolyzed with water. The absorbance of the hemoglobin solution was obtained at 540 nm. The amount of absorption above the hemoglobin solution shows a slower rate of blood coagulation[119].

- c- Cytotoxicity: L-929 mouse fibroblasts were used to determine the cytotoxicity of the membranes. Cells were seeded at a density of 104 cells/well and incubated with CA extract in the range of 78–2500 µg/ml for 2 days. A 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) solution was added to the existing medium in each well to reach a final concentration of 0.5 mg/ml. After 4 h of incubation, the medium was removed, and 100 µl of acidic isopropyl alcohol (0.04 M HCl in isopropyl alcohol) was added to each well. After shaking for 3 min, the optical density was measured using an enzyme-linked immune-sorbent assay (ELISA) reader at a wavelength of 570 nm and a reference wavelength of 650 nm[120].
- d- Antibacterial activity assay: Wound infections are a major global concern and designing antibacterial products for wound healing applications is a prominent field of research. In order to prevent deleterious effects caused by infections in the injury area, it is necessary to use a wound dressing capable of both barricading bacterial penetration and microbial colonization into the wound site and supporting skin regeneration. The developed electrospun scaffolds with antibacterial activity can prevent wound infection. The antibacterial nanofibers are commonly fabricated by incorporating antibacterial agents during electrospinning. Diverse antimicrobial agents (e.g., antibiotics, metallic nanoparticles, and natural extracts derived products) have been embedded into electrospun nanofibers to improve their antibacterial properties. Metallic nanomaterials such as silver nanoparticles (AgNPs) are known as efficient agents for the treatment of wound infections. Nanoscale particles with high surface to volume ratio, afford a significant improvement in antibacterial activity of electrospun wound dressings. Recent strategies rely on using polymers with intrinsic antibacterial activity, due to physical, chemical or morphological cues which cause an obstacle for bacterial colonization and biofilm formation[121]
- e- Hydrophilicity evaluation
Generally, contact angle measurement used to evaluate the hydrophobicity behavior, but Because the hydrophilicity of PVA/glucan films was too high to be distinguished by contact angle measurements, other methods were employed to evaluate the hydrophilicity. In the water diffusion area test, an aliquot of water of 20µl was dropped on the film. The wetting area (i.e. the water diffusion area) expanded with the time and was monitored. The wetting ratio can then be calculated as follows:

$$\text{Wetting ratio} = \frac{\text{water diffusion area at } t}{\text{initial water diffusion area}}$$

To measure the swelling behavior of the films, samples of 1 cm × 1 cm were dried in an oven for 2 h at 105 °C. Afterwards, the samples were placed in a humidifying chamber of 90% relative humidity at 37 °C, and weighed at specific time points. The swelling ratios of the samples were calculated as follows:

$$\text{Swelling ratio} = \frac{W_{wet}}{W_{dry}}$$

where W_{wet} and W_{dry} represent the weights of the film in the wet and dry states, respectively [122].

g- Water vapor transmission

The water vapor transmission tests were conducted according to JIS 1099A standard method. A circular piece of the specimen was fastened over the top of a cup of 7 cm in diameter containing 50 g of CaCl₂. The cup was then placed in an incubator of $90 \pm 5\%$ RH at 40 ± 2 °C. The water vapor transmission rate (WVTR) was calculated as follows: $\text{WVTR} = \frac{W_2 - W_1}{S} \times 24$ (g/m²-day) where W_1 and W_2 are the weights of the whole cup at the first and second hours, respectively, and S is the transmitting area of the specimen. Skin irritation test [122].

f- Wound healing test

Male Wistar rats, aged 3 months and weighing 450–550 g, were used. Prior to the test, the rats were anaesthetized with pentobarbital. After removing the dorsal hair of the rats with an electric razor, 10% aqueous betadine and 70% alcohol were employed to sterilize the dorsal area of the animals. Then four full thickness wounds with a surface area of 2 cm × 2 cm were created from the back. Each wound was covered with an equal size of the specimen, or cotton gauze, or the commercial product (Nexcare™, 3M, USA) for comparison. On top of the wound dressings, a piece of Tegaderm™ (3M, USA) was applied. Treated rats were placed in individual cages and the healing wounds were observed on the 1st, 4th, 7th, 11th, 14th and 21st days using a digital camera. The degree of healing was expressed as the wound contraction ratio (WCR):

$$\text{WCR} = \frac{A_0 - A_t}{A_0} \times 100\%$$

where A_0 and A_t are respectively the initial area and the wound area at time t. Wound tissue was dissected, fixed with 10% phosphate-buffered formalin, and stained with hematoxylin and eosin (HE) reagents for histological observations [122].

g- Skin Adhesive:

To evaluate cell adhesion and spreading of electrospun NFs; the prepared NFs were collected on glass cover slips. The sterilized NFs were located into 24-well plate prior to cell seeding, while plain cover slips without any treatment were served as control. HFB-4 cells (1.0×10^5) were seeded into 24-well plate containing DMEM media supplemented with (10%, w/v FBS at 37 °C) and kept for 2 and 4 h. After incubation, wells were rinsed softly with PBS to eliminate non-adherent cells. The attached cells were calculated by adding 100 µl/well of 0.1 (w/v, %) crystal violet solution and incubated for 1 h at ambient conditions. Subsequently, cells were rinsed twice with 1.0 M PBS and the absorbance was detected spectrophotometrically using a micro-plate-reader at 570 nm.[123]

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