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PREPARATION OF ANTIMICROBIAL NANO-FIBROUS SCAFFOLD BY ELECTROSPINNING TECHNIQUE FOR SKIN TISSUE REGENERATION IN WOUND

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ABSTRACT
Wounds are generally defined as injury in the epithelial layer of the skin, The treatment of wounds is expensive and challenging. Conventional therapy for wound includes topical antimicrobial agents and wound dressings. Most of the available wound dressings are not effective. The topical formulations like creams and ointments will help to prevent infections only and it requires frequent applications. Moreover the frequent wound dressing delayed the wound healing process by hindering the re-epitheliazation. Electrospinning, as technique, has been heavily used for the preparation of nano- and micro-sized nanofibrous scaffolds. The antimicrobial loaded nanofibrous scaffold potential for treating and preventing wound infections with its multiple benefits compared with traditional treatment approaches. The scaffolds are biodegradable and biocompatible and it promote the cell adhesion, proliferation, and cell differentiation.

KEYWORDS: Wound, Electrospinning, Polymer, Antimicrobials.

INTRODUCTION
Wound is defined as the disruption of the cellular and anatomic continuity of a tissue. Wounds generally termed as physical injuries that result in an opening or breaking of the skin. Wound may be produced by physical, chemical, thermal, microbial or immunological insult to the tissues. The process of wound healing consists of integrated cellular and biochemical events leading to re-establishment of structural and functional integrity with regain of strength in injured tissues. There are different types of wounds which range from mild to potentially fatal.[1] To be distinguished from these are wounds that have their origin in underlying pathologies such as diabetes mellitus, chronic venous/arterial insufficiency, and immunological or dermatological diseases.

Wound healing is the highly coordinated process of restoring damaged tissue that comprises four sequential, yet overlapping, biological stages: hemostasis, inflammation, proliferation, and remodelling. Any perturbation by both external and internal factors in any of the above wound-healing phases may prolong each stage and lead to an unsatisfactory outcome, further resulting in chronic wound status. The most frequently encountered issue concerning complete wound healing is the colonization of contaminating pathogens at the site of skin injury during the natural wound-healing process.

Traditional healing agents assume a central role in wound care due to their clinical efficacy, simplicity, and affordability. These therapies represent a cost-effective alternative for the treatment of diverse difficult-healing wounds (e.g., ulcers, burns, and infected wounds) by providing a wide range of therapeutic effects that stimulate the healing process and improve the quality of the new skin. Traditional therapies can also be combined with modern clinical practices, biomaterials, and drugs, allowing the development of innovative therapeutic treatments that address important medical needs, such as minimize the bacterial resistance and reduce the healing time.[2]

The limitations of conventional therapy (1) need for frequent application over wound, which may cause patient inconvenience (2) frequent dressing changes may hinders the wound healing due to impaired re-epithelialization.

So an effective wound care therapy requires topical treatment to prevent infection and wound dressings that provide temporary non removable coverage for wound, maintain temperature homeostasis, prevent desiccation and promote wound healing. Thus nano-fibrous scaffolds of polymer have been investigated as a biodegradable wound dressing, an antibacterial drug delivery system and also for skin tissue engineering.

Electrospinning technology has been widely utilized for the preparation of tissue-engineering scaffolds. Tissue engineering aims to fabricate functional biomaterials for the repairment and regeneration of defective tissue. In addition to the structural simulation for accelerating the repair process and achieving a high-quality regeneration, the combination of biomaterials and bioactive molecules is required for an ideal tissue-engineering scaffold. Due to the diversity in materials and method selection for electrospinning, a great flexibility in drug delivery systems can be achieved. Various drugs including antibiotic agents, vitamins, peptides, and proteins can be incorporated into electrospun scaffolds using different electrospinning techniques.[3]

Wound

A wound is a break in the epithelial integrity of the skin and may be accompanied by disruption of the structure and function of underlying normal tissue[4]. In humans wound healing is depicted in a discrete timeline of biological phases constituting the post-trauma repairing process. In undamaged skin, the epidermis (surface layer) and dermis (deeper layer) form a protective barrier against the external environment. When the barrier is broken, a regulated sequence of biochemical events is set into motion to repair the damage.

Wound healing is the highly coordinated process of restoring damaged tissue that comprises four sequential, yet overlapping, biological stages: hemostasis, inflammation, proliferation, and remodelling.

Biological phases of wound healing

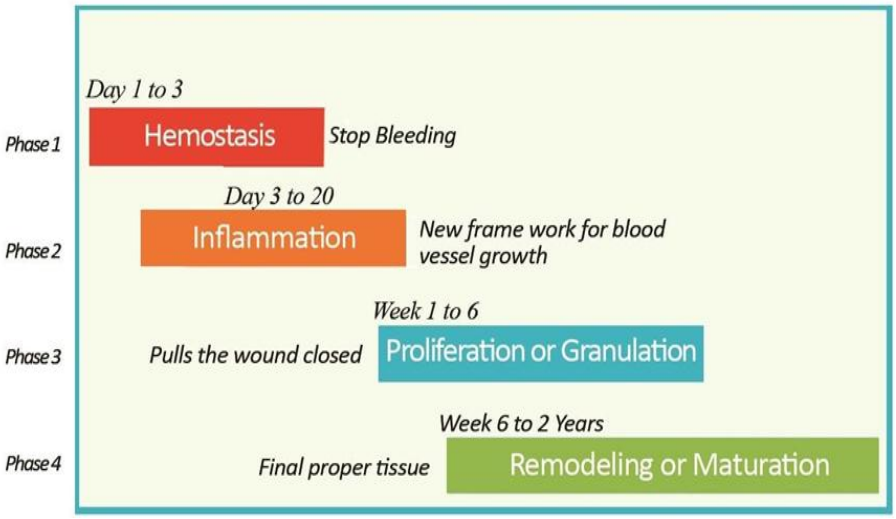

Fig. no. 1: Biological phases of wound healing.

Local treatment for wound

Local treatment of wound includes cleansing and debridement, topical antimicrobial agents, and dressings. Cleaning then applying topical antimicrobial agent, followed by wound dressing is best suitable for wound coverage to prevent or control infection.

Cleaning

Although various solutions have been recommended for cleansing wounds, normal saline is favoured as it is an isotonic solution and Tap water. In hospitals normal saline solution and tap water are commonly used for cleansing wounds.[5] The cleaning time may be the chance of impair the wound re-epithelialization and thus increase the time required for wound healing.

Debridement

Debridement is a procedure for treating a wound in the skin. It involves thoroughly cleaning the wound and removing all hyperkeratotic (thickened skin or callus), infected, and nonviable (necrotic or dead) tissue, foreign debris, and residual material from dressings.

Complications of debridement

- Irritation
- Bleeding
- Damage to healthy tissue (impaired re-epitheliazation)
- Allergic reaction
- Pain
- Bacterial infection

Wound dressing

There are a wide variety of dressing techniques and materials available for management of wound healing. The primary objective in both the cases is to achieve a healed closed wound. An ideal dressing material should not only accelerate wound healing but also reduce loss of protein, electrolytes and fluid from the wound, and help to minimize pain and infection. Dressings are one

important aspect that promotes wound healing apart from treating the underlying cause and other supportive measures like nutrition and systemic antibiotics need to be given equal attention.[6]

General types of wound dressing

Currently more than 3000 types of dressings are available in the market making the physician to address all aspects of wound care. But still there is no superior product that heals chronic wounds like venous leg ulcers, diabetic wound and pressure ulcers which often fail to achieve complete healing.

Table no. 1: Type of wound dressing.

Types	Characteristics	Advantages	Disadvantages
Foam	• Multilayered structure (anti adhesion wound contact layer, infiltration layer,water proof and germresistant layer • They create a moist environment and provide thermal insulation to the wound. • They are nonadherent, easy to apply and remove and are meant for highly exuding wounds	• Don't adhere to the wound • Serve as a cushion to protect the affected area • Provide a barrier against bacteria • Can be used in the case of infection • Are suitable for wounds with hypergranulation • May be used during compression therapy • Are easy to apply and remove	• Wound may dry out if there is no or too little exudate to be absorbed. • These dressings are not suitable for third-degree burns, sinus tracts or wounds with dry eschar. • Dressing removal may damage the new tissue and causes pain.
Alginate	• Alginate is extracted from algae. Woven or nonwoven materials strip and sheet dressings • Alginate dressings are made from calcium salt and sodium alginic acid in the form of foams and flexible fibers.	• Strong exudate absorption capacity, used for infectious wound, with no wound adherence. • Relieve pain, avoid dehydration and promote epithelial regeneration. • Easy to use and remove, no toxicity, no allergy	• Not easy to remove the residual dressing. • High cost. • Need two layers of dressings causing wound bed dry or dehydration • Avoided in light exudate or dry wounds
Hydrogel	• Hydrogel dressings consist of 90 percent water in a gel base Hydrogels are insoluble hydrophilic materials made from synthetic polymers such as poly (methacrylates) and polyvinyl pyrrolidine	• Soft elastic property of hydrogels provides easy application and removal after wound is healed without any damage. • Pain relief protecting germ infection.	• Poor absorptive capacity of exudates • No bacterial barrier. • Easy to cause skin immersion around. • A second layer of dressing is needed low mechanical strength of hydrogels making it difficult to handle
Gauze	• Gauze dressing is made up of woven or non-woven fibres of cotton, rayon, and polyester. • One-time use for operation and wound care in medical units.	• Able to protect wounds and reduce bacterial invasion • Simple to use and suitable for many kinds of wounds. • Widely used in clinic easily available.	• Not for wet wound healing • Gauze dressings should be changed frequently-if it dries out, it may stick to the wound bed and disrupt wound healing. • Dressing removal may damage the new tissue and cause pain. Frequent replacement and wound bed adherence.

Electrospinning

Electrospinning, which is a term derived from a fiber-manufacturing method called electrical spinning, has attracted tremendous interests in the research community simply because it provides a facile and effective means in producing ultrafine fibers with diameters ranging from microns down to a few nano-meters. using a high-voltage power supply.[7] Electrospinning technology has been widely utilized for the various medical fields like drug delivery, sensors, wound dressing and tissue engineering etc. Many advantages are associated with electrospun scaffolds- which mimic the extracellular matrix of almost all the tissues. It provides high surface area to volume ratio with porous structure, which enhances cell adhesion, nutrient and oxygen transport. It is simple, cost effective and versatile technique by which variety polymers can be electrospun to make fibrous matrix [8]. The mechanism of electrospinning nano-fibers is based on a complex electro-physical activity between polymer solution and electrostatic force.

Apparatus

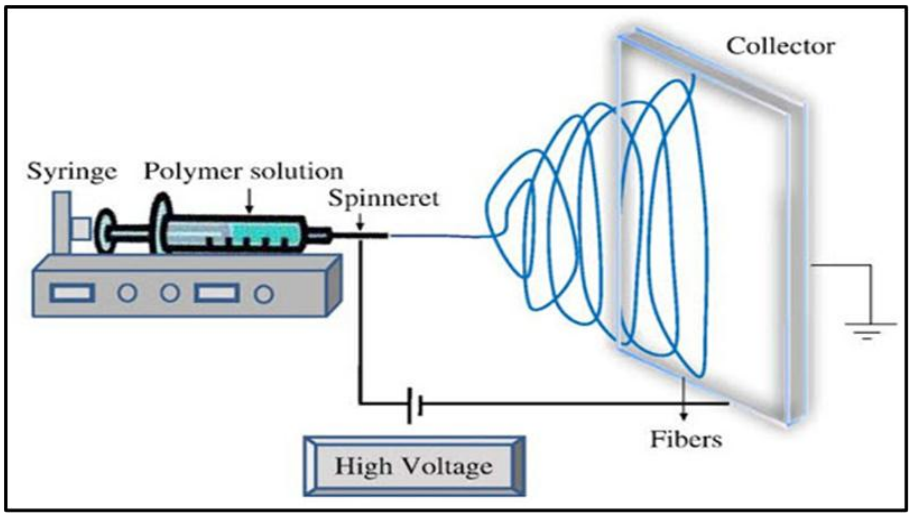

Fig. no. 2: Basic electrospinning experimental setup.

Three basic components as shown in figure 1 are required to setup the electrospinning process: a syringe with a metal spinneret of small diameters, a high voltage supplier and a rotating collector. A high voltage in the range of **10-50 kV** is applied to create an electrically charged jet of polymer solution or melt out of the spinneret in the electrospinning process.[9]

Procedure

The high-voltage electric field is set up between the injection needle and the collecting screen using a power supply and electrodes. A polymer solution, particulate suspension or melt is loaded into the syringe, When the polymer solution is extruded slowly from the syringe, a semi spherical polymer solution droplet is formed at the tip of the needle. With increasing voltage, the charged polymer droplet elongates to form a conical shape known as the **Taylor cone**, and the surface charge on the polymer droplet increases with time (fig no 3).

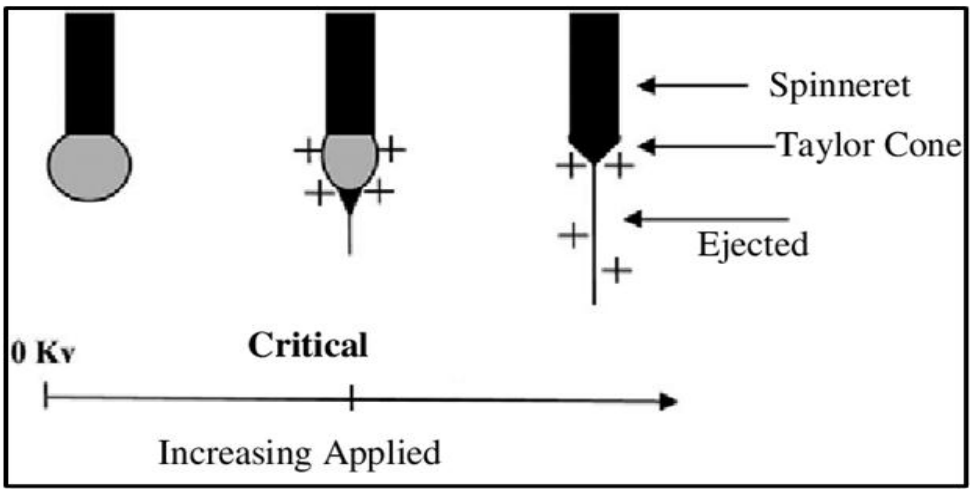

Fig. no. 3: Taylor cone formation with increase in applied voltages.

Once the surface charge overcomes the surface tension of the polymer droplet, a polymer jet is initiated. The solvent in the polymer jet evaporates during its travel to the collecting screen, increasing the surface charge on the jet. This increase in surface charge induces instability in the polymer jet as it passes through the electric field. To compensate for this instability, the polymer jet divides geometrically, first into two jets, and then into many more as the process repeats itself (fig no 4)

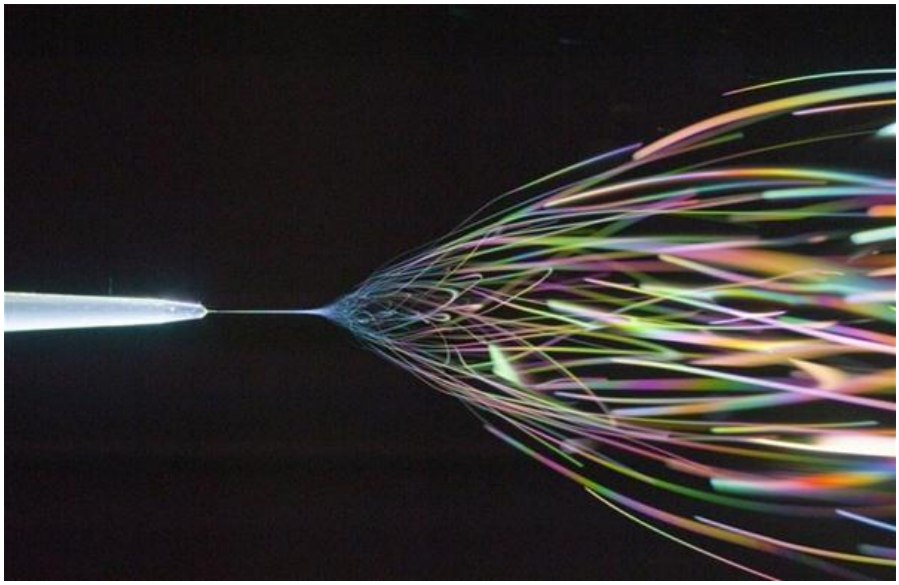

Fig. no. 4: Diagram showing fiber formation by electrospinning.

The formation of nano-fibers results from the action of the spinning force provided by the electrostatic force on the continuously splitting polymer droplets. Nano-fibers are deposited layer-by-layer on the metal target plate, forming a nonwoven nano-fibrous mat. During the electrospinning process, both extrinsic and intrinsic parameters are known to affect the structural morphology of the nano-fibers (Doshi and Reneker, 1995). Specifically, extrinsic parameters, such as environmental humidity and temperature, and intrinsic parameters, including applied voltage, working distance, and conductivity and viscosity of the polymer solution, need to be optimized to produce uniform nano-fibers.[10]

Fig. no. 5: Electrospinning scaffolds for wound Healing and Skin bioengineering applications (Image source: Blessy Joseph et.al., Recent advances in electrospun polycaprolactone based scaffolds for wound healing and skin bioengineering applications; Materials today communications; Volume 19, June 2019, Pages 319-335.)

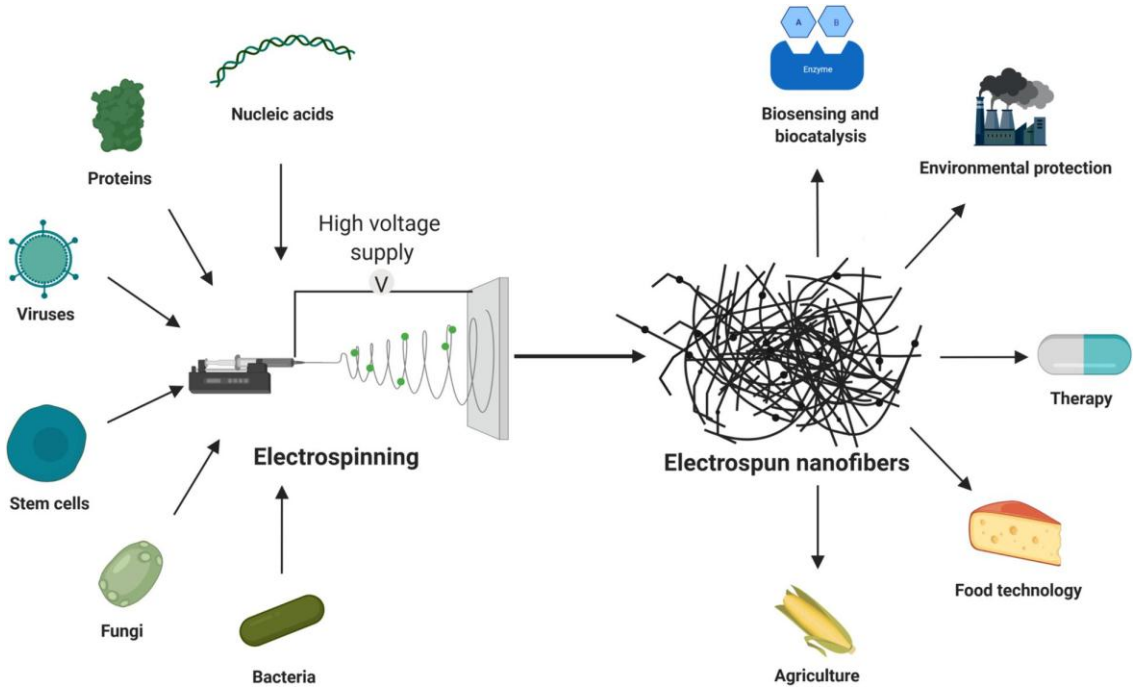

Fig. no. 6: Incorporation of living cells, proteins and nucleic acids into electrospun nanofibers and their applications. (Image source: Spase stojanov et.,al. Electrospun Nanofibers as Carriers of Microorganisms, Stem Cells, Proteins, and Nucleic Acids in Therapeutic and Other Applications. Front. Bioeng. Biotechnol; 2020. Vol.8. Article 130.

Parameters affecting electrospinning process

The electrospinning process is affected by many parameters, classified broadly into polymer solution parameters, process parameters and ambient parameters. Although, many of these electrospinning parameters are interdependent and there are interactions between them.

The parameters of polymer solution may be viscosity, conductivity, molecular weight, surface tension and process parameters include applied electric field, tip to collector distance and flow rate. Each of the parameters significantly affect the fibers morphology obtained as a result of electrospinning and by proper manipulation of these parameters, it is possible to get the nanofibers of desired morphology and diameters (Chong et al., 2007). Finally, ambient parameters encompass the humidity and temperature of the surroundings, which play a significant role in determining the morphology and diameter of electrospun nanofibers (Li and Xia, 2004).

Table no. 2: Electrospinning parameters and their effects on fiber morphology.

Parameters	Effect of fiber morphology
polymer solution parameters	
Solution concentration	Increase concentration with increase in fiber diameter
Molecular weight	Increase in molecular weight give smooth nano fiber
Viscosity	Increase in viscosity with increase in fiber diameter
Process parameters	
Flow rate	Increase in flow rate with generation of beads Decrease in flow rate with decrease in fiber diameters
Applied high voltage	Increase in voltage with decrease in fiber diameters
Tip to collector distance	Minimum distance required for uniform fiber
Ambient parameters	
Temperature	Increase in temperature with decrease fiber diameters
Humidity	Higher humidity result in circular pores on the fiber

Designing of antibacterial drug loaded nanofibers by electrospinning

For the purpose of fabricating nanofibrous scaffold by electrospinning technique, we had prepared a polymeric solution and the drug is incorporated with the above polymeric solution. The natural bio-compactible and synthetic bio-compactible are used in electrospinning process and mostly the polymers are dissolved in common solvent system or the polymers are dissolved in different solvents. For example, Charu Dwivedi et al used Poly Lactic-co-Glycolic Acid (PLGA) and gelatin in electrospinning technique for wound healing the

gentamycin is used as drug, the 2,2,2- trifluroethanol are used as common solvent [13]. Stanislaw Blazewicz et al used poly(lacticacid)(PLA) and gelatin in electrospinning technique for cartilage tissue engineering PLA was prepared in mixed solvents DCM and DMF 3:1(wt:wt) and GEL solution in the concentration of 20% (wt/v) was prepared in concentrated acetic acid.[11]

The polymer solution was taken in a 10ml plastic syringe with a needle and the mass flow rate was adjusted ml/hr using a syringe pump. Then high voltage of 10-50 kV was applied to the tip of needle attached to syringe. Above the critical voltage, a polymer jet was ejected from the needle tip towards a grounded collector, which was a rotating drum set and it covered with a thin aluminium foil. The distance between the tip of needle and grounded collector was adjusted. After few hours to obtain the nanofibrous mat.[12,13] For example, Reshmi CR et al Uniformly dispersed PCL/NC solution was placed in 10 mL syringe with a needle of internal diameter of 0.2 mm. The syringe was fixed on automated syringe pump connected with high voltage apparatus. The electrospinning parameters were fixed as; flow rate of 1 ml/hr, applied voltage of 18 KV, tip-collector distance of 12 cm and a drum collector of rotation speed of 500 rpm.[14]

Polymers used in electrospinning technique

Natural polymer scaffold

Most of the research on electrospinning of natural polymers is focused on biopolymers, because these naturally occurring polymers normally exhibit better biocompatibility and low toxicity than other polymers.[9] Naturally occurring polymers normally exhibit better biocompatibility and low immunogenicity, compared to synthetic polymers, when used in biomedical applications. A strong reason for using natural polymers for electrospinning is their inherent capacity for binding cells since they carry specific protein sequences, such as RGD (arginine/glycine/aspartic acid).[15]

- **Gelatin[15]** kokate

Gelatin is a natural polymer that is derived from partial hydrolysis of Aq. extract of collagenous tissue like skin tendons, ligaments and bones of various domestic animals with boiling water and is commonly used for pharmaceutical and medical applications because of its biodegradability and biocompatibility in physiological environments. Generally, gelatin is of two types: Type A and Type B depending on the hydrolysis condition of isolation from collagen. Practical microfibers of gelatin produced via the conventional wet/dry spinning were not common because of the polyelectrolytic nature of gelatin, coupled with its strong hydrogen bonding, hinders its fiber forming capacity. Gelatin practically insoluble in water but swells and soften when immersed in it, gradually absorbing from 5 to 10 times its own weight and in most organic solvents. Gelatine is soluble in glycerol and acetic acid and more soluble in hot than in cold water. In hot water gelatin forming gel on cooling to 35 - 40˚C. At temperature greater than 40˚C, the system exists as a solution. Electrospinning of gelatin and mechanical characterizations have been done by blending with other polymers in the preparation of tissue engineering scaffolds.

- **Chitosan**

Chitosan is a pseudo-natural polymer, is that it becomes water soluble in acidic conditions due to –NH2 protonation as soon as its degree of acetylation is lower than 0.5. Then, chitosan solution processing is relatively easy in order to obtain fibers, nanofibers, films, capsules, beads, sponges, gels, powder, or tablets, as chitosan turns insoluble in neutral medium (i.e., when chitosan is in the –NH2 form). Chitosan is an interesting biodegradable and biocompatible polymer with hemostatic properties, anti-inflammatory response, antibacterial and antifungal properties often described in the literature, and is well adapted for biological applications. Chitosan has already been electrospun using different acid-based solvents. For instance, acetic acid used at concentration from 90% down to 1% gives good fibers but pure chitosan fibers have rarely been obtained in acetic acid at 90% and 70% but mainly with trifluoroacetic acid (TFA) or mixture of TFA and dichloromethane.[17]

- **Collagen[18,19]**

Collagen is present in the extracellular matrix in the form of fibers composed of triple helical molecules organized to accommodate covalent cross-link formation which gives strength and stability to the fibers. The nature of the specific covalent bonds present in a collagen depends on the source material and collagen type.skin predominantly consists of collagen type I and III, whereas collagen type II is the major constituent of cartilage. Abnormality in collagen has been linked to a number of human diseases. so the collagen have number of biomedical applications. It has been used in the form of sheets, tubes, foams, sponges, nanofibers, fleeces, powders, injectable viscous solutions and dispersions. Hence collagen-derived nanofibrous scaffolds have been investigated intensively for tissue engineering applications.

- **Keratin**

Keratins, one of a family of fibrous structural proteins, are ubiquitous in natural polymers including human hair, wool, feather, horns, hooves and nails. Given the unique characteristics of bioactivity, biocompatibility, biodegradability, and natural abundance, keratins have been fabricated into powders, hydrogels, films, sponges, dressings or some other forms for the biomedical applications, which involved hemostasis, wound healing, nerve repair, tissue regeneration and other objects.[20] However, the main disadvantage of keratin-based materials is its poor mechanical stability, so that, it has to be combined with synthetic polymers, that is, PCL, to improve the in vitro stability and biocompatibility.[21]

Synthetic polymers

Synthetic degradable polymers have been used as scaffolds for skin tissue engineering, but also as wound dressing releasing various bioactive molecules by a controllable manner. Degradable polymers typically used in these applications are aliphatic polyesters.

- **PCL [22,23,24]**

Polycaprolactone (PCL) is among the most attractive and commonly used biodegradable polyesters. It can be used in different biomedical applications, such as in scaffolds in tissue engineering, and for controlled release of drugs. PCL has been used for the reconstruction of various tissues such as bone, skin, nerve, retina and has several advantages including its biocompatibility, low cost and easy processability. However, being a synthetic biomaterial, PCL has a hydrophobic surface, lacks functional groups and hence it is not a good substrate for cell adhesion. To improve the hydrophilicity and biological properties of PCL nanofibrous scaffolds various techniques have been applied. PCL (mw 80000) has been electrospun by using different solvents, such as: chloroform, dichloromethane, dimethylformamide and methanol or a combination of the above solvents. Amongst the above-mentioned solvents, chloroform is often employed as a solvent for electrospinning PCL, even though it has often, produced microfibers rather than nanofibers.

- **Poly(lactic-co-glycolic) acid[25]**

PLGA is a combination of the polyester polymers PLLA and PGA and is among the most commonly used biodegradable synthetic polymers for tissue engineering applications. PLGA has been popularized for a variety of reasons, such as biodegradability, adaptability and customization for different types of formulations, and surface modification for targeted drug delivery. Its degradation by products are highly acidic and, in large quantities, can be very difficult for the human body to metabolize rapidly. PLGA has been used to fabricate nanoparticles, microparticles, 3D scaffolds for drug delivery and tissue engineering applications.

- **Poly (L-lactic acid)**

Poly (L-lactic acid) is a synthetic biodegradable polyester formed from the polymerization of l-lactide, obtained from renewable sources such as starch, and has a wide variety of applications such as sutures, drug delivery vehicles, prosthetics, vascular grafts, bone screws, skin regeneration scaffolds, and pins for fixation.[25] PLA-based materials can be fabricated by a number of commercially technologies including solvent casting, particulate leaching, membrane lamination, and melt molding, as well as electrospinning and precise extrusion. Among these techniques, consecutive electrospinning to manufacture PLA-based micro- or nano-fibers attracts considerable attention due to its simplicity, high efficiency, and desirable microstructure. However, electrospun pure PLA fibers normally have the drawbacks of showing weak mechanical properties and low thermal stability, narrowing their industrial applications.[26]

- **Poly-vinylpyrrolidone (PVP)[27]**

Poly-vinylpyrrolidone has excellent biocompatibility and can be used easily electrospinning procedure. It has been used as the main component of wound dressings

- **Polyurethane (polyurethane)[28]**

Polyurethane is a soft and hydrophobic polymer commonly used for wound dressing, sensors, drug delivery and sustained drug delivery applications. It is also frequently used in wound dressing studies because of its good barrier properties and oxygen permeability. The PU have high chemical stability good mechanical properties, and also excellent nanofiber forming characteristic. So the Electrospun PU nanofiber mats exhibiting good mechanical properties, then It has reported that semipermeable dressings, many of which are PU, enhance wound healing.

Antibacterial drugs loaded nanofibrous scaffold for skin tissue regeneration

Nanofibers are one of the most recent applications for the purpose of drug delivery. From the perspective of controlled drug delivery, nanofibers have major advantage of providing high surface area to volume ratio with a porous structure, thus providing an initial burst effect followed by a sustained release of the APIs. As well known, most of the drugs are classified as Class II, according to the Biopharmaceutics Classification System, depending on their low solubility and high permeability. Therefore, this high surface area property might also provide enhancement of drug delivery as well as high loading capacity and high loading efficiency, simple operation techniques and cost effectiveness.[29]

The drug delivery is Depends up on the types of polymers, con of the polymer, solvents used in preparation of feeding solutions. For Example, Seeram Ramakrishna et al prepare a biocomposite PCL/gelatin nanofibrous scaffolds with weight ratios of 50:50 and 70:30, hexafluoro-2-propanol (HFP) was used as common solvent. PCL/gelatin 70:30 nanofibers were selected for cell culture study as it provided better mechanical and biodegradation properties than PCL/gelatin 50:50. So PCL/gelatin 70:30 enhanced the nerve differentiation and proliferation compared to PCL nanofibrous scaffolds.[30]

Table no. 3: Antimicrobial agent loaded nanofiber applications.

Drug	Polymer	Solvents	Application	Reference
Gentamycin	PLGA/ Gelatin	2,2,2trifluoroethanol	Wound dressing	[13]
Metronidazole	PCL /gelatin	2,2,2trifluoroethanol	Tissue regeneration	[31]
Silver nanoparticle	PVDF	N,N-dimethylacetamide	Wound dressing	[32]
Neomycin	PSSA-MA /PVA	Con Hcl / water	Wound dressing	[33]
Amoxicillin	PLGA/LAP	THF**:** DMF	Tissue engineering	[34]
Ciprofloxacin	Dextran/ Polyurethane	DMF**:** THF	Wound dressing	[35]

CONCLUSION

This review article thus makes an attempt to have a basic idea about the process antimicrobial loaded nanofibrous scaffolds in wound healing. The electrospinning technique is able to produce micro to nano-meter sized nanofibrous scaffolds is used for tissue engineering, delivery of regenerative medicines and wound healing applications. Scaffolds give support for cells, growth factors, and other biomolecules that eventually will enhance the formation of new tissue in the human body. The parameters of the spinning process have high impact on the resulting nano fibers. Nanofibrous scaffolds made of nature-derived polymers and synthetic polymers, they hold a great promise for skin tissue engineering and wound healing. Therefore, natural polymers can increase the bioactivity, cell adhesion, proliferation, and differentiation of synthetic polymers, when combined with them in nanofibrous scaffolds. Similarly, synthetic polymers can improve the electrospinnability and mechanical properties of the natural polymers. So the nanofibrous scaffolds can be more or less biodegradable in human body. The drugs (mostly class II drugs) loaded nanofibrous scaffolds have release the drug in controlled manner and also the solvent systems that can also significantly influence the fiber formation during polymer electrospinning process.

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