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Review on Electrospun Nanofiber for Skin Infection

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ABSTRACT:

Topical/Transdermal drug delivery systems (TDDS) have been designed for drug delivery through the skin. These systems use the permeability property of stratum corneum, the outermost surface layer of the skin. Applying polymeric micro and nanofibers in drug delivery has recently attracted great attention and the electrospinning technique is the preferred method for polymeric micro-nanofibers fabrication with a great potential for drug delivery. More studies in the field of nanofibers containing drug are divided two categories: first, preparation and characterization of nanofibers containing drug and second, investigation of their therapeutic applications. Drugs used in electro spun nanofibers can be categorized into three main groups, including antibiotics and antimicrobial agents, anti-inflammatory agents and vitamins with therapeutic applications. Electrospinning is the method for preparing drug-loaded nanofibers with ultrafine structure, a large surface area to volume ratio, and a high porosity with a small pore size. Among the other nanofiber production methods, electrospinning is the most cost effective one with simple tooling and, it is applicable to produce ultrafine fibers with a simple step-up production for drug delivery applications. The selection of the polymer as carrier for electrospinning and the production procedure design is crucial due to drug-polymer-solvent interactions and the other process parameters which would influence the physicochemical biocompatibility and characteristics. This technique can be applied to produce nanofibers of a wide array of polymer types: natural, synthetic polymers, or their blends. This review focuses on various electrospinning methods to produce drug loaded nanofibers, polymers used, electrospinning process parameters, their advantages and limitations for topical.

KEYWORDS: Drug Delivery, Electrospinning, Nanofiber, Polymeric Scaffold, Topical /transdermal drug delivery applications.

INTRODUCTION

Topical/Transdermal drugs has proven to be one of the most favorable methods among novel drug delivery systems. Since drugs administered by transdermal delivery systems avoid the gastrointestinal tract, and thus avoid conversion by the liver, the likelihood of liver dysfunction and gastrointestinal tract irritation as side effects is low. Drug delivery through the skin has other advantages, such as maintaining an effective rate of drug delivery over time, a steady rate of circulation, and the benefits of a passive delivery system and diffusion. it is achieved using patches that consist of different and specific layers. In the last few decades, many types of patches have been approved worldwide, such as medical plasters, which have been generally applied to the skin for localized diseases. Such patches can be traced back to ancient China (around 2000 BCE) and are the early precursors of today's transdermal patches.

To Providing a programmed rate of continuous intravenous infusion is known to be a superior mode of drug delivery, not only to maintain a stable, therapeutically effective, and prolonged drug level in the body, but also to avoid hepatic "first-pass" exclusion Intravenous infusion delivers the drug directly into the bloodstream and allows control of the concentration of the drug in the bloodstream [2]. However, this method of drug delivery requires some medical regulation of the drug and necessitates hospitalization of the affected person. As an alternative, different types of transdermal drug delivery systems (TDDS) have been developed to deliver systemic medication by application to the skin surface [3].

Historically, the earliest transdermal drug delivery system was a drug-loaded patch [8]. Patches have been manufactured for surface applications, and generally consist of some natural adhesive materials bonded to a backing layer [9]. Their cohesive force helps the drug to come into direct contact with the skin tissue and thus deliver it transdermally. These novel drug-loaded patches contain various additives of organic and natural drugs and are designed to act directly in the tissues below the area of application [10]. Following the invention and success of drug-loaded patches, the idea of Transdermal drug delivery for undamaged skin was pursued.

Skin is typically composed of a heterogeneous membrane but the outermost layer, the stratum corneum with thicknesses of about 20 and 25 µm, plays a major role in absorption and acts as a barrier for foreign materials. [1]

Nevertheless, skin appendages such as hair follicles could be used as alternative routes for the entrance of drugs across the skin due to the presence of blood vessels and dendritic cells surrounding hair follicles [2]. Cosmetics and skin medications use permeability properties to enter the circulatory system. Therefore, this area has great attention for drug delivery and provides the desired media for absorption of medications and entrance into the vascular system [3].

Conventional transdermal drug delivery systems and transdermal patches, release the medications in this manner. The patch is designed to deliver therapeutic agent across the skin and can be considered as the desired alternative to oral drug delivery [4]. Drug controlled release from transdermal drug delivery systems with reduction of the dose fluctuations in the body can lead to the improvement of efficacy of medications, stabilization of drug diffusion profile and greater bioavailability [5]

A wide range of polymers is used in transdermal drug diffusion vehicles as gelatinization factors in gel systems and stabilizer in emulsions and creams [7]. They could form patches matrix and wound dressings [8] and act as skin adhesives in transdermal systems and provide enhanced permeability for the improvement of treatment efficiency [2].

Modern polymeric drug delivery systems for topical/transdermal therapy are systems which are designed to release drug(s) to diseased sites of the skin in a consistent and sustained release manner. In recent years, electro-spun polymeric nanofibers have been considered as drug delivery systems in wound healing, and skin burn therapy as topical and transdermal drug delivery systems.

Nanofiber mats produced by this technique have considerable properties, including high surface area, nanoscale pores, unique physical and mechanical properties besides surface capability for physical and chemical activation [11-13]

Advantage of nanofiber.

- Inexpensive cost
- Adjustability
- Industrialization possibility

Disadvantage of nanofiber

- Low yield
- High voltages need
- Large scale remain complex

DIFFERENT METHOD FOR NANOFIBER PRODUCTION.

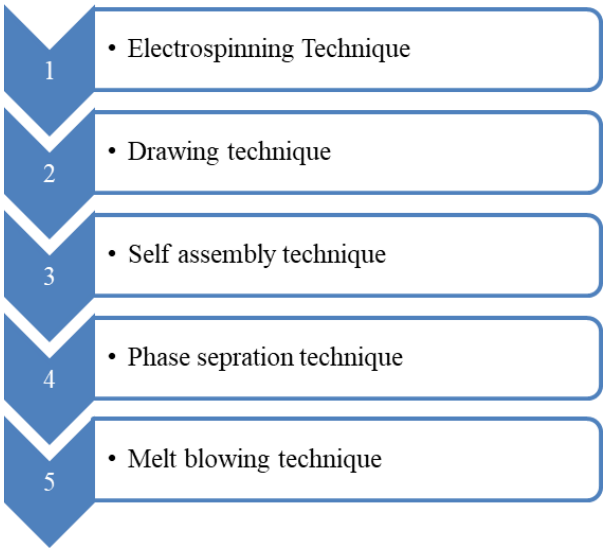

Figure 1 Nanofiber production by different methods

Electrospinning method

Electrospinning is the most frequently chosen because it is a simple, cost-effective, and versatile process to produce large volumes of nanofibers. Nanofiber was discovered in the late 16th century by William Gilbert that an electric field can affect fluid dynamics, electrospinning technique was first observed by Rayleigh in 1897 and investigated in detail by Zeleny in the early 1900s and then patented in 1934 by Formhals.[14]

Electrospinning process has four components:[15]

1. Syringe pump
2. Voltage power supply
3. Metallic needle
4. Collector

Process of electrospinning[16]

One electrode is placed on the syringe needle of a polymer solution and the other electrode is linked to a metal collector.

Principle of electrospinning technique

"When a sufficiently high voltage, usually between 1 and 30 kV is applied to a liquid droplet, the liquid becomes charged When the applied electric field is strong enough to overcome the surface tension, charged polymer forms a "Taylor cone" at the tip of the needle and tiny jet is ejected from the surface of the droplet. As the polymer solution accelerates, the solvent evaporates in the air and nanofibers are formed on the collector."[17]

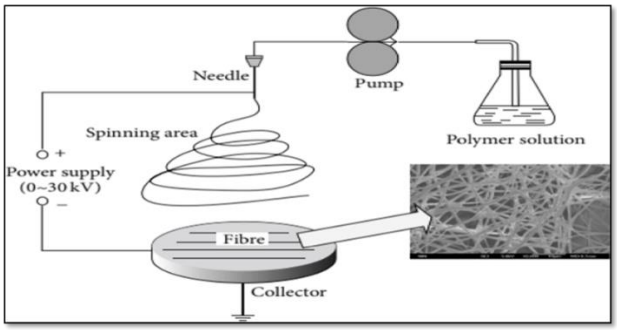

Figure 2 Process of electrospinning technique

Ingredients used for nanofiber production

Polymer selection is important for the production of nanofibers and their interaction with cells. The ideal polymer is not only biocompatible and biodegradable, but also non-toxic, moderately hydrophilic, and has appropriate mechanical strength. Nanofiber can be produced with polymers alone or in blends. Since the use of natural polymers has certain disadvantages like low stability, and toxic degradation products which can be harmful to the cells, the natural polymers are often blended with synthetic polymers. Composite nanofibers composed of natural and synthetic polymers express the ideal biological properties of the natural polymers and the mechanical strength of the synthetic polymers. Polymers used in nanofiber production have variety of mechanical properties, degradation rates, and cell-material interactions.[18-20]

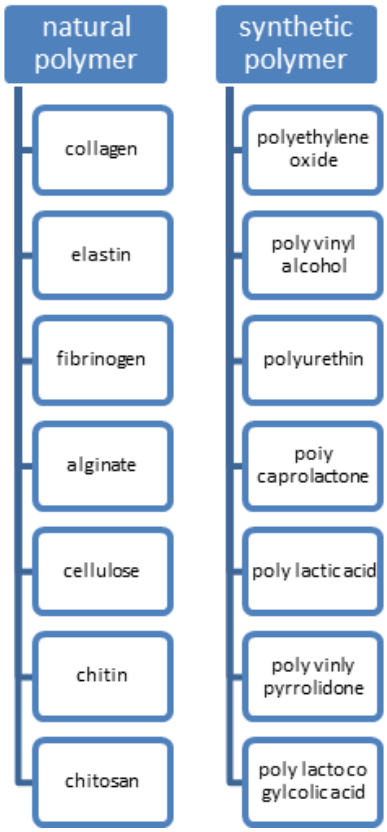

Figure 3 Natural and synthetic cpolymers

a. Solvents used in nanofiber production Water is the most commonly used solvent due to its safety and biocompatibility. However, its use is limited to hydrophilic polymers. In addition to this limitation, the solubility of polymers in water is often low, or water-based solutions have high viscosity at low concentrations, resulting in a small amount of electrospun product per large volume of polymer dispersion (Pelipenko et al., 2015).Most of the natural polymers are soluble in water, as example; alginate and cellulose. The commonly used organic solvents in electrospinning are acetone, dichloromethane, methanol, ethanol, acetic acid, dimethylformamide, ethyl acetate, trifluoroethanol, tetrahydrofuran, and formic acid. The major disadvantages of organic solvents are their toxicity, price, and often too high volatility. To achieve optimal solution viscosity, surface tension, and solvent volatility, a combination of two or more solvents is often used(Pelipenko et al., 2015). As an example, for

electrospinning of polylactic acid chloroform, 1,2-dichlorethane, and ethyl acetate are usually used as solvents (Holan et al., 2011).[21-24]

b. Other excipients used in nanofiber production In order to achieve spinnability of natural and semi-synthetic polymers, improve the production process reproducibility, or change the product morphology from beads on fibers to homogeneous, surfactants and salts are added to the polymer solution. As salts, sodium chloride or tetramethyl ammonium chloride has been used to increase the charge density on the liquid jet and thus prevent the formation of beads and obtain uniform thin fibers. Surfactants are amphiphilic molecules that readily absorb at surfaces and thereby lower the interfacial tension; a key parameter that influences electrospinning. Nonionic Tween 20, Tween 80, Triton X-100, Triton X-15, polyoxyethylene glycol lauryl ether (Brij 35), anionic sodium dodecyl sulfate (SDS), and cationic dodecyl trimethyl ammonium bromide (DTAB) can be used as surfactants.[24-26]

Drug loading procedures in Electro spun nanofibers

In order to construct the electro-spun micro and nanofibers used in drug delivery, a variety of methods have been used. They can be divided into several categories:-

1. Blending

In this mode, the drug is dissolved or dispersed in a polymer solution to be encapsulated by fibers. This method is simpler than the other techniques, but to achieve desired results needs some supplies. For example, the drug release profile is strongly affected by the distribution of drug molecules and the morphology of nanofibers. In addition, it is also important for drug and polymer to be hydrophilic and or hydrophobic. For this reason, in order to achieve an optimal mode of drug encapsulation in the fiber, lipophilic drugs such as Rifampicin and Paclitaxel should be electrospun with hydrophobic polymers, and hydrophilic drugs such as Doxorubicin Hydrochloride, electrospinning process should be done in blend with hydrophilic polymers [27-29].

2. Core-shell electrospinning (Coaxial)

This method is a modified technique for the production of Core-Shell electrospun fibers. The solution containing a drug or biological molecule formed by the inner jet and Polymer solution would be Electrospun from the outer jet which is concentric with the inner jet simultaneously [7,37,38]. Shell polymer not only causes a slow and delayed release of the drug but also plays a vital role in the protection of the drug from the surrounding environment [39]. This technique is used in Transdermal drug delivery (e.g. Antibiotics) and Tissue Engineering [30-31].

3. Surface modification

It is another form of loading a drug in electro-spun nanofibers is their chemical or physical surface modification. In this technique, drug agent is immobilized chemically on the nanofibers surface, resulting in drug release reduction and its stability on electro spun nanofibers surface due to strong bonding. This method is appropriate for delivery of genes, growth factors, and enzymes.

4. Emulsion electrospinning

In this technique, a hydrophilic drug with polymer solution (As the oil phase) makes an emulsion. After electrospinning process, a drug with low molecular weight is distributed into nanofibers prevent their accumulation on the nanofibers surface [41]. If macromolecules with high weights are applied, fibers are shaped into the core-shell structure, and the drug is placed in the aqueous phase of the core [42,43]. However, there is a risk of damage or destruction in some macromolecules such as DNA, which can be due to shear or tension force between the aqueous phase and the organic emulsion. This problem is resolved with modifications such as DNA condensing.

Drug Release from Electro spun Nanofibers Mechanism A wide range of polymers has been used to fabricate Electrospun scaffolds. Natural polymers are collagen, chitosan, gelatin, hyaluronic acid, and famous synthetic polymers like polylactic acid (PLA), polycaprolactone (PCL), polyethylene oxide (PEO), and other similar copolymers[45].

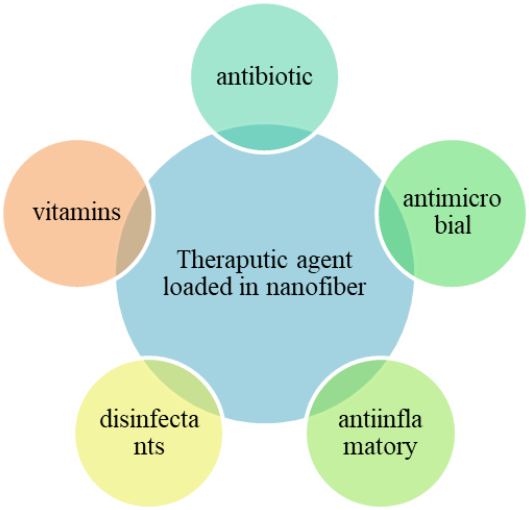

Figure 4 Different materials to be loaded in the nanofiber encapsulation as therapeutic agents

The selection of materials for drug delivery and polymer fibers, the drug release rate, and the degradation rate of the polymer should be optimized simultaneously[45]. Both hydrophilic drugs (such as tetracycline hydrochloride and doxorubicin hydrochloride) and hydrophobic ones (such as Rifampin and Paclitaxel), and biomacromolecules (such as proteins and DNAs) can be encapsulated in electrospun nanofibers. For drug delivery using electrospun nanofibers.

Parameters that influence nanofiber formation and the electrospinning process Although the electrospinning process is simple, several processing variables need to be regulated to generate nanofibers instead of droplets or beaded morphologies. The major challenge of the electrospinning process lies in the optimization of these parameters to achieve desirable nanofiber morphology and properties.

1. Polymer solution parameters-

Polymer type selection has an important effect on nanofiber production. Polymers with high molecular weights (higher degrees of polymerization) are preferable for electrospinning in order to enable a sufficient number of intermolecular entanglements. Polymers with low molecular weight, nonlinear and polyelectrolyte nature are very difficult to electrospinning.

At lower polymeric concentrations, due to the effect of the applied voltage and surface tension of the polymeric solution, droplets occur before reaching the collector (Pillay et al., 2013).At an increased polymeric concentration, solution viscosity increases, and more uniform nanofibers in higher fiber diameters are formed.

The surface tension of the solution depends on the characteristics of the solvent and solute. Usually, low surface tension values result in the formation of fibers without beads and low voltages can be applied in electrospinning. Surface tension can be changed by the addition of surface active substances.

Viscosity and viscoelastic properties of a polymer solution greatly affect jet formation and its stability, and therefore nanofiber morphology (Rošic et al., 2012). There is a need for a balance between the elastic and plastic
moduli of the polymer solution. When elasticity is higher than plasticity droplet formation occurs.

Polymer solutions with low conductivity cannot be electrospun due to the absence of a surface charge on the fluid droplet, which is needed for Taylor cone formation. Generally higher solution conductivities result in thinner nanofibers. In case of uncharged polymers, the problem of low conductivity can be solved by adding salts.

2. Process parameters-

Generally, voltages between 1 and 30 kV are used. Solutions with low conductivity, high surface tension, and high viscosity require higher voltages, and therefore thinner fibers occur(Cremariuc et al., 2013; Heunis et al., 2010).

The nozzle tip-to-collector distance influences the size and morphology of the nanofibers formed. If the distance between the capillary and collector is not optimized properly, bead formation and electrospraying may be observed. Generally, when the distance increases, thinner fibers occur (Bhardwaj &Kundu et al., 2010).

When the flow rate of the solution increases thicker nanofibers form due to thicker jet formulation but also may result in the generation of beads (Bhardwaj & Kundu, 2010; Cramariuc et al., 2013). Another factor affecting nanofiber morphology is nozzle design. A single-channel nozzle allows the formation of uniform nanofibers, whereas a coaxial nozzle enables the formation of core-shell or even multilayered nanofibers (Maleki et al., 2013).

Collector type affects the orientation and morphology of the electrospun nanofibers. Randomly oriented nanofiber mats can be produced when a conductive flat collector is used, but aligned nanofibers can be obtained if the collector is a rotating cylinder or a wheel-like disk(Bhardwaj & Kundu et al., 2010)

3. Ambient parameters-

Environmental temperature and relative humidity are the ambient parameters affecting nanofiber formation. When environmental temperature is high, solvent evaporation rate increases, and thicker nanofibers occur. The effect of temperature on the solution viscosity is the opposite i.e. higher temperatures result in lower viscosity and the formation of thinner nanofibers When hydrophobic polymers dissolved in organic solvents, water acts as a non-solvent and higher relative humidity values lead to the formation of porous nanofibers (Medeiros et al., 2008). In the case of aqueous polymer solutions, at low relative humidity values, rapid solvent evaporation causes thicker nanofiber formation.

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