Electrospinning Nanotechnology-A Robust Method for Preparation of Nanofibers for Medicinal and Pharmaceutical Application.

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ABSTRACT

Nanotechnology has evolved as a preferred choice in current research arena due to the advantages offered by it. The current research in pharmaceutical development is all about exploring and/or adopting different approaches for preparation of nanostructured drug delivery systems. Electrospinning nanotechnology has made its mark as a technology of choice for preparation of nanofibers for different applications. Electrospinning is a novel, robust and efficient fabrication process that is widely accepted and used to assemble nanofibers with distinct features such as length of several kilometers and diameter less than 300 nm. One of the most striking features of nanofibers is that they provide exceptionally high surface area-to-volume ratio and high porosity, making them a robust and attractive candidate for many advanced applications. Many researchers working on development of medicinal and pharmaceutical product design and development have reported their studies indicating successful implementation of electrospinning method for preparation of nanofibers with respect to theoretical principle, mechanics of electrospinning, critical process parameters, polymers and drug loaded nanofibers incorporated in different drug delivery systems for various pharmaceutical application.

Keywords: Nanofibers; Electrospinning technique; drug loaded nanofibers.

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1. INTRODUCTION

Nanofibers are defined as fibers that have a minimum ratio of length to thickness of 1000:1. According to the definition of American National Science Foundation, “Nanofiber are characterized as nanomaterials that have at least one dimension, that is, 100 nm or less”. Nanofiber formulations can be developed by choosing suitable polymers, convenient additives, and proper production methods based on different critical parameters which has an influence to meet the requirements of their specific application area. Nanofibers are produced by different methods such as electrospinning, self-assembly, drawing, meltblowing, template synthesis, phase separation, melt spinning and centrifugal spinning.

Amongst these methods electrospinning is observed to be a robust method for preparation of nanofibers. Table1 summerizes aforementioned methods used for preparation of nanofibers with respect to different parameters namely principle, technology advances, scalability, repeatability, convenient to process the samples and dimension quality of nanofibers.
Table: 1 Summary of methods for preparation of nanofibers.

| Process                  | Principle                                                                 | Technological advances       | Scalable process | Repeatability                        | Convenient to process the samples | Control on fiber dimension |
|--------------------------|---------------------------------------------------------------------------|-------------------------------|------------------|--------------------------------------|----------------------------------|---------------------------|
| Electrospinning          | Electrospinning uses an electrical charge to draw very fine micro or nanofibers from a polymer in a liquid solution or melt. | Laboratory with industrial potential | Highly scalable | Extremely good reproducibility compared to other methods | Comparatively more convenient | Yes                       |
| Phase Separation         | Polymer rich and polymer poor phases are formed, removal of polymer poor phase leads to formation of nanofibrous structure. | Laboratory                   | Limited scalability | Reproducible but not better than electrospinning method | Yes                              | No                        |
| Template Synthesis       | It is a method in which nanoporous membrane is used as a template by using various materials like carbon, metals, conductive polymers,etc. | Laboratory                   | Difficult to scale up | Yes                                  | Yes                              | Yes                       |
| Drawing                  | In this fibers are formed by pulling followed by solidification which converts dissolved spinning material into a solid material. | Laboratory                   | Very difficult to scale up | Yes                                  | Yes                              | No                        |
| Self Assembly            | It is used to generate peptide nanofibers                                  | Laboratory                   | Highly difficult to scale up | Reproducible but poor then other methods | Not convenient to proceed        | No                        |

Other current techniques for nanofiber fabrications are:

- CO₂ laser suspension drawing: It is done in the absence of solvent. It is used to produce long nanofibers. Generally used polymers for this techniques are Polylactic acid(PLLA), Polyethylene terephthalate (PET), Polyglycolic acid(PGA).
- Solution blow spinning: It consist of air brush, concentrated polymer solution and a compressed gas source. Most widely used in tissue engineering.
- Plasma induced synthesis: Following steps are required for plasma induced synthesis:
  - Rapid and energetic bombardment
  - Atomic vapor deposition
  - Expansion of plasma
  - Condensation of solution medium and in situ reaction of oxygen and growth of nanofibers.

Based on the literature review of reported scientific data for preparation of nanofibers, Electrospinning technology is observed to be a robust and preformed method for preparation of nanofibers.

2. ELECTROSPINNING METHOD

In this review author wish to emphasize on Electrospinning technology for preparation of drug loaded nanofibers. This review presents insights of electospinning technology with respect to principle, instrumentation, mechanism, formulation aspects, inprocess parameters, reported studies on pharmaceutical electrospun nanofibers and their characterization. Electrospinning method was patented by Formhals in the year 1934. Since 1980s and especially in recent years, the electrospinning process has regained more attention probably due to the surging interest in nanotechnology, as ultrafine fibers or fibrous structures of various polymers with diameters down to submicrons or nanometers can be easily fabricated with this process. Electrospinning is a method of choice for preparation of longer, highly porous and thin nanofibers, offering extremely high surface area to volume ratio. Figure 1 gives a digramatic representation for preparation of nanofibers.
2.1 Principle of electrospinning
The main principle behind this process is preparing a nanofibrous mats using different polymers and solvents incorporated with drug, proteins, etc. by using a very high voltage source of either positive or negative polarity on polymer solution. When a required amount of charge is accumulated and the repulsive force is equal to the surface tension, the drop surface on the conducting tube forms a cone like shape called as Taylor cone. On further increase in electric field, the repulsive force overcomes the surface tension which leads to formation of liquid jet from the Taylor cone due to sufficient attraction between the molecules in the solution/melt. If there is no sufficient cohesive attraction in the solution, the jet breaks and the resulting particles are sprayed onto a collector plate, and during this process the solvent evaporates to form a solid fiber deposit onto the collector plate. Electrospinning technique uses electric power to produce polymer fibers with diameter ranging from nanometer to several micrometer.

2.2 The electrospinning apparatus
2.2.1 A syringe pump
To deliver solution from syringe to the needle for spraying it on a collector. A syringe pump can hold 10 µl to 10 ml of liquid solution.

2.2.2 A high voltage device
It is used to vary the positive and negative polarity, most commonly supplied output voltage is 50 Kv and output current is 400 microA.

2.2.3 Collectors
A collector is assembled to collect the nano or microfibers after being spun from the spinneret. Example: Rotatory drum, rotating disc and a flat plate collector is used to collect the nanofibers. The above mentioned apparatus can be seen in fig. 2 with its horizontal spinning arrangement.

Figure 1: Schematic of a standard horizontal Electrospinning setup.

Figure 2: Horizontal Spinning arrangement of a Electrospinning instrument.
2.3 Mechanism of Electrospinning technique

The following flowchart explains the mechanism behind electrospinning technique for preparing nanofibers.

The needle of the syringe containing liquid solution is connected to a high voltage (tens of kV).

When a sufficient high voltage is applied to a liquid droplet, the body of the liquid becomes charged and electrostatic repulsion counteracts the surface tension and droplet is stretched to give rise to a Taylor cone.

The charged strand squirts out of the Taylor cone and the strands of polymer solution undergoes instability and lengthening, whereas meanwhile the solvent evaporates.

The fibers are then deposited on collector to produce a non-woven fibrous layer.

1. POLYMERS AND SOLVENTS USED FOR PREPARATION OF NANOFIBERS USING ELECTROSPINNING TECHNIQUE

Polymer consists of long chain of molecules with repeating units called as monomers which are covalently bonded to each other. Eg: Polyethylene, which consists of repeating units of [-CH₂CH₂]ₙ. Various combinations of polymers and solvents can be used for preparing nanofibers amongst which few are listed below in a tabular format.

| Polymers                        | Solvents                        |
|---------------------------------|---------------------------------|
| Polyimides                      | Phenol                          |
| Polyamic acid                   | m-cresol                        |
| Polyetherimide                  | Methylene chloride              |
| Polyaramide                     | Sulphuric acid                  |
| Poly-gamma-benzyl-glutamate     | Dimethylformamide               |
| Poly(p-phenyleneterephthalamide) | Sulphuric acid                  |
| Nylon 6-polyimide               | Fornic acid                     |
| Polycylacronitrile              | Dimethylformamide               |
| Polyethylene-terephthalate Nylon| Trifluoroacetic acid            |
| Polyacrylonitrile               | Dichloromethan                  |
| Polyaniline                     | Sulphuric acid                  |
| DNA                             | Water                           |
| Polyhydroxybutyrate-e           | Chloroform                      |
| PLLA                            | Chloroform or Mixed methylene chloride |
|                                | Dimethylformamide               |
| Poly(D,L-lactic acid)           | Dimethylformamide               |
| PEO                             | Water                           |
| PMMA                            | Toluene                         |
| PU                              | Dimethylformamide               |

Abbreviations: DNA (Deoxyribonucleic acid), PLLA (Poly L-lactic acid), PEO (Polyethylene oxide), PMMA (Poly methyl methacrylate), PU (Polyurethane).

NOTE: The above listed polymers can help us to get nanofibers of fiber length in the range of 3 to 1000 nm and fiber diameter in the range of 50 to 300 nm.
3.1 A flow chart of experimental procedure for preparation of drug loaded nanofibers by electrospinning technique

Precursor solution (polymer + drug dissolved in solvent) is delivered to a syringe containing a metal needle.

A part of this needle is connected to a high voltage power supply and positioned vertically on a clamp for electrostatic repulsion.

Aluminium foil is placed on a rotating drum or disc or a stationary plate for collecting the nanofibers sprayed by the syringe pump.

Distance between the collector and the needle tip should be approximately 10cm. Less than 10cm will give microfibers rather than nanofibers. Increase in the voltage supplied to the solution leads to formation of a Taylor cone which is sprayed on a conductive collector.

The solvent gets evaporated to obtain charged fibers onto the collector^8,9.

### 4. CRITICAL PROCESS PARAMETERS OF ELECTROSPINNING TECHNIQUE INFLUENCING THE TEXTURE OF NANOFIBERS

Various critical parameters based on its influence to form nanofibers are listed below in fig 3.

#### 4.1 Solution related parameters of Electrospinning process

**4.1.1 Concentration of Solution**

The spinnability of the solution is dependent on the surface tension and viscosity which can be undertaken to determine the concentration of the solution/melt for electrospinning. At higher concentration, the viscoelastic forces are sufficient to prevent fragmentation to form smooth nanofibers.

**4.1.2 Molecular weight of polymers**

The molecular weight of polymers influence the fiber viscosity which has a direct effect on fiber morphology. Example- Using high molecular weight polymers resulted in the formation of smooth fibers initially followed by ribbon like fibers upon further increase in molecular weight, whereas low molecular weight polymers like poly(vinyl alcohol) resulted in the formation of bead like structure^10.

**4.1.3 Solution viscosity**

The viscosity, molecular weight of the polymer and polymer concentration are interrelated to each other. Yang et al. suggested and used a mixed solvent system of dimethylformamide and ethanol in a ratio of 50:50 for obtaining the best electrospun fibers of polymer PVP Poly(vinyl pyrrolidone).

**4.1.4 Surface tension of the solution**

Surface tension is the measure of cohesive force between the molecules in the solution form which is dependent on the solution composition, polymers and solvent used. Low surface tension with high viscosity formed smooth nanofibers with ethanol as the solvent^11.

**4.1.5 Conductivity and surface charge density**

The diameter of nanofibers formed is inversely proportional to the conductivity and surface charge density^12. Study of PEO solution showed that addition of sodium chloride drastically increased the conductivity and decreased the fiber diameter. Sodium phosphate, potassium phosphate and ammonium chloride can also be used to obtain better fibers by changing the conductivity of solution^13.

**4.1.6 Solvent volatility**

If the fibers are insufficiently dried, it may stick to itself and give a ribbon like structure, therefore volatile solvent like THF (Tetrahydrofuran) is mostly used to produce high
density pores and increase the surface area of fibers up to 40%\textsuperscript{14}.

4.2 Process related parameters of electrospinning process

4.2.1 Applied voltage

The size of the fiber and formation of beads is mainly dependent on the applied DC voltage. During electrospinning, the fibers formed transport the charge to the grounded collector plate to close the circuit. This helps to measure the associated electric current during electrospinning. At first, the current supplied is gradual, whereas it increases sharply later to form a Taylor cone for preventing bead formation\textsuperscript{15}.

4.2.2 Flow rate

The size, shape, and porosity of electrospun are directly dependent on the flow rate of polymers used. Megelski et al. reported in his studies, that the use of polystyrene/tetrahydrofuran solution showed increase in fiber diameter and pore size with increase in flow rate. However, increased in flow rate showed bead-like fibers and flattened ribbon-like structure due to insufficient drying\textsuperscript{14}.

4.2.3 Capillary-collector distance

The distance between a capillary and collector need to be optimized. Typically a distance between the capillary and collector is 10-20 cm. According to Doshi and Reneker, the larger the distance from the Taylor cone, smaller the fiber diameter\textsuperscript{16}.

The morphology of nanofibers is based on various solution and process parameters, amongst which few critical ones are listed in Table 3 and the reported optimized values of these critical parameters for few drug loaded nanofibers are listed in Table 4.

| Parameters                        | Effect on nanofiber morphology                                      |
|-----------------------------------|---------------------------------------------------------------------|
| Polymer concentration             | Increase in polymer viscosity leads to increase in fiber diameter.  |
| Applied voltage                   | Increase in the applied voltage leads to decrease in the fiber diameter at initial stage. |
| Flow rate                         | Increase in the flow rate leads to increase in the fiber diameter but if the flow rate is too high sometimes it may lead to beaded morphology. |
| Capillary collector distance      | More is the distance between capillary and collector, less will be the fiber diameter. Too short distance may lead to beaded morphology. |

| Drug       | Polymer used | Molecular weight of Polymer (Da) | Applied voltage (kV) | Flow rate (ml h\textsuperscript{-1}) | Capillary collector distance (cm) | References |
|------------|--------------|---------------------------------|----------------------|--------------------------------------|----------------------------------|------------|
| Ciprofloxacin | PVP         | 360,000                         | 12                   | 0.5                                  | 15                               | 17         |
| Acyclovir   | PCL          | 70,000                          | 12                   | 0.5                                  | 15                               | 17         |
| Ibuprofen   | PCL          | 70,000-90,000                   | 17.5                 | 1.63                                 | 15                               | 18         |
| Methylprednisolone | Eudragit\textsuperscript{®} RS100 | 32,000                      | 25                   | 5.0                                  | 10                               | 19         |
| Carvedilol  | PCL          | 70,000-90,000                   | 17.5                 | 1.63                                 | 15                               | 20         |
| Nicorandil  | PVA          | 85,000                          | 10-15                | 0.2                                  | 15-20                            | 20         |
| Curcumin    | PCL          | 65,000                          | 25                   | 2.0                                  | 20                               | 21         |
| Mupirocin   | Polysurethane | 8,000                         | 15                   | 1.0                                  | 20                               | 22         |
| Titanium dioxide | PVP         | 130,000                        | 22                   | 0.4                                  | 15                               | 8          |
| Lidocaine   | Chitosan     | 50,000                          | 15                   | 1.0                                  | 15                               | 23         |

Key: Da (Dalton), kV (kiloVolts), PVP (Polyvinylpyrrolidone), PCL (Poly-\(\varepsilon\)-caprolactone), PVA (Polyvinylalcohol)
5. METHODS OF DRUG LOADING FOR NANOFOBRES

Various methods of drug loading in the polymeric solution used for electrospinning are Blending, Surface modification, Emulsion and Multi layered coating.

5.1. Blending

In this method the drug is dissolved or dispersed in the polymer and is then subsequently electrospun. This method is simple and easy, but the physicochemical properties of the drug need to be precisely considered for better drug distribution in the fiber and for better release kinetics. In order to obtain a sustained release of drug and to enhance the drug loading efficiency, different combinations of mixtures of hydrophilic and hydrophobic polymers are used.

5.2. Surface modification

In this technique the therapeutic agent is bound to the fiber surface and makes it structurally and biochemically similar to tissues. Modulation in drug release can also be achieved by surface modification. Incorporation of various biomolecules like DNA, enzymes and growth factors may conjugate with fibers, which results in preservation of bioactivity and functionality of these biomolecules.

5.3. Emulsion

In this the drug is emulsified within a polymer solution. The success of this process is dependent on the ratio of polymer and aqueous solution used. This governs the distribution of the molecules of the fiber, which in turn determines the release profile, structural stability and bioactivity of the encapsulated molecule.

5.4 Multi layered coating

This process uses hydrogen bonding, electrostatic or acid base pairing in layer by layer adsorption of polymers. Chundar et al. have used two oppositely charged weak polyelectrolyte, polyacrylic acid and poly allylamine hydrochloride to produce nanofibers loaded with methylene blue as a model drug. Also a hydrophobic layer of perfluorosilane and PAA/poly(N-isopropylacrylamide) was coated.

6. CHARACTERIZATION OF NANOFOBRES

Various methods used for characterization of nanofibers is listed below in Table 5 along with the apparatus used and properties to be characterized.

| Methods                  | Instruments/Apparatus used                                                                                     | Properties to be characterized                                    |
|--------------------------|---------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| Chemical characterization | • FTIR (Fourier Transform Infrared Spectroscopy), NMR (Nuclear Magnetic Resonance) <br>• DSC (Differential Scanning Calorimetry), Wide range X-ray diffraction | • Molecular structure of nanofiber <br>• Configuration of macromolecules in a nanofiber |
| Physical characterization | • DPMC (Dynamic Moisture Permeation Cell)                                                                  | • Air and vapor transport of electrospun nanofibrous mats         |
| Mechanical characterization | • Sample was stretched with a computer controlled instron                                                   | • Cantilever deflection is measured under light microscopy.       |
| Geometrical characterization | • SEM (Scanning Electron Microscopy), FESEM (Field Emission Scanning Electron Microscopy), TEM (Transmission Electron Microscopy), AFM (Atomic Force Microscopy) <br>• Capillary flow porometer | • Fiber diameter, orientation and morphology. <br>• Porosity, pore size of nanofiber. |

7. ADVANTAGES OFFERED BY ELECTROSPUN NANOFOBRES

7.1 High surface area to volume ratio

High surface area to volume ratio makes it very attractive and desirable in application.

7.2 Wide variety of polymers and materials can be used

Electrospinning can not only be used to prepare polymeric nanofibers, but also is used to synthesize ceramic and metal nanofibers.

7.3 Ease of fiber functionilization

It can be achieved by simple blending of polymer solution prior to spinning, post spinning surface functionilization or using core shell electrosprining setup.
7.4 Ease of material combination
Different materials can be easily mixed for spinning into fibers.

7.5 Relatively low startup cost
For use in the laboratory environment, this setup can be self assembled and the cost is few thousand dollars.

8. APPLICATION OF NANOFIBERS

8.1 Tissue engineering
In this natural and synthetic biodegradable polymers have been used to synthesize nanofibers which can be used to support and guide cell growth and tissues. Electrospinning can be used to produced nano and submicron scale polystyrene and polycarbonate fibrous mats intended for use as in vitro cell substrates. This early use of electrospun fibrous lattices for cell culture and tissue engineering showed that Human Foreskin Fibroblasts (HFF), transformed Human Carcinoma (HEp-2), and Mink Lung Epithelium (MLE) would adhere to and proliferate upon the fibers. Nanofibers produced via tissue engineering helps to mimic the natural extracellular matrix of the bones.\(^{28,29}\)

8.2 Drug delivery
Drug loaded nanofibers can offer many advantages in drug delivery for topical and internal use. Nanofibers exhibit distinct characteristics such as biocompatibility, biodegradability, high absorbency and loading capacity which enables enhancement in solubility of poorly soluble drugs. Nanofibers have given new direction to pharmaceutical formulation and development research. Natural polymers such as gelatin and alginate can be used as a drug carrier due to its better biocompatibility and biodegradability which results in no harm to the tissues. The high surface to area ratio enables the nanofibers to possess high drug loading capacity and may release therapeutic molecules over a large surface area. Also the dissolution rate of the polymer nanofibers is increased due to small size of the particulate drug having increased surface area.\(^{30}\) Pharmaceutical Researchers have developed and reported nanofibers for different purposes of wound healing and drug delivery.

| Drugs                      | Application                          | Reference |
|----------------------------|--------------------------------------|-----------|
| Ciprofloxacin, Acyclovir, Cyanocobalamin | Ocular drug delivery | 17        |
| Ibufrofen                  | Oromucosal drug delivery             | 18        |
| Methylprednisolone         | For improving the bioavailability of glucocorticoid | 19        |
| Carvedilol, Nicorandil     | Sublingual delivery for angina pectoris | 20        |
| Curcumin                  | Diabetic wound dressing with anti-diabetic and anti-inflammatory activity | 21        |
| Mupirocin                 | Anti infection burn wound dressing   | 22        |
| Titanium dioxide          | Photo catalytic activity of porous TiO\(_2\) nanofibers | 8         |
| Lidocaine                 | Wound dressing                       | 23        |
| Captopril, Ramipril        | Gastroretantive drug delivery- Floating drug delivery | 31,32     |

8.3 Cosmetics
Most of the commercial skin products such as creams, lotions, gels, dusts or liquid spray easily migrate into the sensitive organs such as eyes or nose, but nanofibers will not migrate. Nanofibrinous masks for facial use can be fabricated for more ease of application.\(^{33}\)

8.4 Miscellaneous-
Electrospun nanofibers can be used to remove the volatile organic compounds from the atmosphere. Recent work with the mining equipment manufacturers and MSHA (Mine safety and health administration) has proved that nanofiber filter media can reduce cabin dust concentration to a greater extent compared to standard cellulose filter media.\(^{34,35}\)

- Batteries and fuel cells: Due to large surface area and high porosity of nanofibers, it can be utilized for storing electrolytes and supporting rapid and long term electron/ion transport. Eg: Chamber-confined Si/C composite nanofibers have been synthesized for improving the cycling life and coulombic efficiency of lithium ion batteries.
- Supercapacitors: They are more promising to be utilized compared to the normal batteries. It has better life cycle and high power density with safety. Hence their is increase in fabrication and utilization of the lightweight, knittable and wearable fiber-shaped supercapacitors.\(^{36}\)

9. CONCLUSION
The electrospinning method for preparation of nanofibers is comprehensively reviewed, graphically presented and discussed in detail with respect to theoretical principle, mechanics of electrospinning, critical process parameters, polymers and drug loaded nanofibers incorporated in different drug delivery systems for various pharmaceutical applications.
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