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A comprehensive overview on nanofiber technology and their advancements in the field of pharmaceuticals

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ABSTRACT

Nanotechnology is a growing technology that has been marked as the most vital scientific and commercial venture across the world with great benefits. Globally many researchers are involved in the development of newer types of nanomaterials through modifications of various fabrication techniques. Nanofibers have been an emerging trend in the field of nanomaterials due to its unique physicochemical characteristics. Properties such as high surface area and high porosity absorbance ratio with the interconnected fibrous networks makes nanofibers unique. The current review explores the present status and upcoming advancements in the field of nanofiber technology. The article is focused on the various preparation techniques and applications in medicine, tissue engineering and regenerative medicine and pharmaceuticals. Despite the advancements, the limitations and future prospects in the area of nanofiber technology have been highlighted.

Keywords: Nanofibers, electrospinning process, phase separation technique, pharmaceuticals, bioengineering.

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INTRODUCTION

The advancements in the field of drug discovery augmented from the middle of 19th century. The world of nanomaterials embraces for their outstanding physicochemical characteristics. Nanomaterials include quantum dots, nanorods, nano tubes, nano wires, nano fibers and one-dimensional nanosheets. Amongst all, nanofibers stand apart due to their impending applications. Nanofibers have been fabricated from various materials such as natural and synthetic polymers; carbon based, semi-conducting and composite nanomaterials[1]. Nanofibers are defined as fibers with diameters less than 50-500 nm. National Science Foundation (NSF) defines nanofibers as having at least one dimension of 100 nm or less. The objective of nanofiber drug delivery system is to deliver a defined amount of drug proficiently, specifically for a defined period of time. Many techniques have been reported till date for the fabrication of nanofibrous scaffolds including electrospinning, self-assembly and phase separation techniques. Out of all, electrospinning is a relatively simple and robust production method. Electrospinning has become a widely used and reliable method since it allows the production of different alignment scaffolds of ultra-fine fibers, in the range of nano to microscale in diameter, from a variety of natural and synthetic polymers.

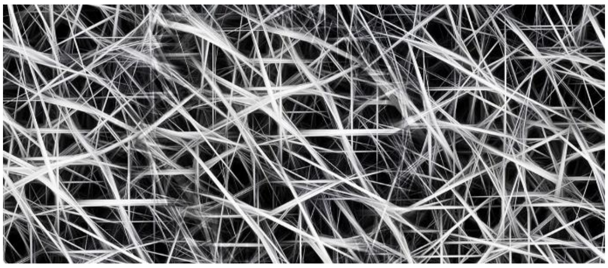

Figure 1: Structure of Nanofibers

Electron microscopic view of a nanofiber Advantages

Now-a-days, nanofibers are emerging as a means for various drug delivery systems for the treatment of diseases in the healthcare systems. The nanofibers demonstrate the significance and suitability of them as drug carriers. The smaller size and surface area to volume ratio of nanofibers is the winsome property in the delivery of drug to the specific-site in the body[2]. Several biodegradable and/or biocompatible polymers are used as fiber matrices in drug delivery, biosensors, tissue engineering, wound healing and numerous other applications. Advances in electrospinning technology have led to foster tubular nanofibrous structures and 3D nanofiber blocks. Electrospinning technique is the most expedient and cost-effective method for the commercial scale fabrication of nanofibers.

Properties

The distinctive feature of nanofibers that highlights them among other conventional fiber preparations is their high surface area to volume ratio. Alignment of channels within nanofibers is mainly differentiated by their mechanical and thermal properties in comparison to bulk polymers and conventional fibers.

Thermal properties

Thermal analysis has been carried out on a number of electrospun polymeric materials to understand the relationship between nanostructure and thermal properties. DSC studies have showed that electrospun PLLA fibers have lower crystallinity, glass transition temperature (Tg), and melting temperature (Tm) than semi crystalline PLLA resins. Lower crystallinity is an unique feature for the nanofibers. The high evaporation rate followed by a rapid solidification is the reason behind that character. The Tg and the peak crystallization temperature (Tc) of the electrospun polyethylene terephthalate (PET) and poly- ethylene naphthalate (PEN) decreased significantly, while the heat of crystalline melting increased. Whereas the melting temperature of the PET and PEN electrospun fibers remained almost constant, without any significant variations compared to that of regular fiber forms. PEO Nanofibers have a lower melting temperature and heat of fusion than the PEO powder, which is attributed to the poor crystallinity of the electrospun fibers.

Mechanical properties

Electrospun fibers have nano structured surface morphologies with tiny pores that influence mechanical properties like tensile strength, Young's modulus, etc. When these are compared with cast films, electrospun elastomers have shown almost a 40% reduction in the peak tensile strength and 60% reduction in elongation at maximum applied stress. The decrease in the tensile strength has also been reported with SLPF fibers. Nanofiber reinforced polymer composites have shown more highly enhanced mechanical properties than the unfilled or carbon/glass fiber filled composites. Young's modulus of a nanofiber composite has been found to be 10 times greater than the pure Styrene-Butadiene rubber. As it is evident, that there is less information available on the mechanical properties of nanofibers and nanofiber composites. Research on the mechanical properties of nanofibers and their composites from a variety of polymers is important for a greater understanding on the contributions of nanofibers to the mechanical and performance related characteristics of nanofiber composites.

Filtration properties

As the fibers themselves have a small diameter, the thickness of the nanofiber web can likewise be quite small, with a thickness of four diameters approaching only one micron. The thin web has limited mechanical properties that preclude the use of conventional web handling. As a result, nanofiber web has been applied on to various substrates. Substrates are selected to provide complementary functionality to the nanofiber web. In the case of nanofiber filter media, substrates have been selected for pleating, filter fabrication, durability in use, and filter cleaning. is a photomicrograph showing a cross-section of Nanofibers electronspun onto a polyester spun bond substrate. The substrate is chosen to provide mechanical properties, while the nanofiber web dominates filtration performance. Controlling parameters of electrospinning allows the generation of Nanofibers webs with different filtration characteristics. Different fiber sizes can be made, some as small as 40 nm. Fibers can be put on one side or on both sides of a substrate. Nanofibers have been electrospun on to a variety of substrates, including glass polyester, nylon, and cellulose filter media substrates[3-4].

Methods for fabrication of nanofibers

There are many ways to fabricate nanofibers, such as template synthesis, drawing, self-assembly, electrospinning, random, aligned, and core-shell nanofibers, and phase separation. Out of all these techniques template synthesis does not able to produce continuous nanofibers and in the drawing process only the viscoelastic materials to be used which in turn creates a high tensions. That is the reason only three techniques such as phase separation, self assembly and electrospinning are considered as the best methods in the preparation of nanofibers.

Template synthesis

Template synthesis involves the use of membranes or templates to obtain a desired structure. Nanoporous metal oxide membranes (e.g., aluminum oxide membrane) are commonly used, where a polymer solution is allowed to pass with a certain force through to a non solvent bath to produce nanofibers depending on the pore diameter.

Phase separation

One of best method for production of nanofibers which preferentially can be used in many areas is Phase separation, but due to its heavy time consumption during the preparation of the nanofibers this method found to be not an ideal one. In the process of the preparation of nanofibers the selected polymer solution to be gone through its below freezing point and then freeze to produce a set of nanofibers. Various nanofibers can be produced by altering their thermodynamic and kinetic factors. Using phase separation process, preparation of scaffolds occur in five basic steps 1. Suspension of polymer, 2. phase separation and gelation, 3. Extraction of solvent from the gel by means of water, 4. Freezing, and then 5. Freeze-drying under vacuum. The creation of nanoscale fiber complex is caused by low gelation temperature, while as a consequence of crystals nucleation and their development, high gelation temperature produces the creation of platelet like construction and is managed by increasing of cooling rate, which can produce uniform nanofibers[4].

Self assembly

In this method the atoms and molecules make themselves to be attached with each other. Self-assembly method can be used to make different structures, for example unilamellar and multilamellar vesicles, bilayer, nanoparticles, membranes, fibers, films, micelles, tubes and capsules. Based on the self-assembly system, an ampiphilic peptide that allows creation of thermally stable protein was designed. The obtained nanofibers through the self assembly process is morphologically thinner from the fibers produced by the electrospinning process. Complication in the range of productivity of nanofibers is the major problem associated with the self assembly process[4].

Electrospinning

As nanofibers are becoming increasingly important, the high through put preparation of high quality nanofibers has drawn remarkable attentions. Currently, electrospinning is the most widely used method for the preparation of nanofibers. Other methods including Bubbfil spinning, centrifugal spinning have also been reported for their potential applications in the biological field. Many theoretical researches on electrospinning process have been done by many teams and groups. Sir William Gilbert explained the behavior of electrostatic and magnetic emanation. He found that by affecting the water droplet by electrostatic field, the water gets cone and hopper shape, and a droplet extrudes from the head of the hopper. Electrospinning can be viewed as a kind of electro-spraying. As with electro-spraying, the raw material of electrospinning is linked to a high-voltage power supply to enhance the liquid electrostatic potential. High molecular degree of polymers is always used as raw materials based on their inter-molecular interaction.

The surface charge of liquid and electrostatic potential have direct relationship so by increasing or decreasing one of them, the identical action will happen for another one. Usually by surface tension, the volume shape of fluid is deducted. By charging the fluid, the surface charge acts in the reverse manner to surface tension, resulting in the fluid changing shape, forming the structure known as the Taylor cone[5-10].The size of the nanofibers produced through the electrospinning process is in the range of 3nm whereas the nanofibers produced through the other processes is in the range about 300nm this states the fame for the electrospinning process and keeps on the top in the preparation of the nanofibers. Because of these extremely appreciable properties electrospinning is the most popular technique for the preparation of nanofibers.

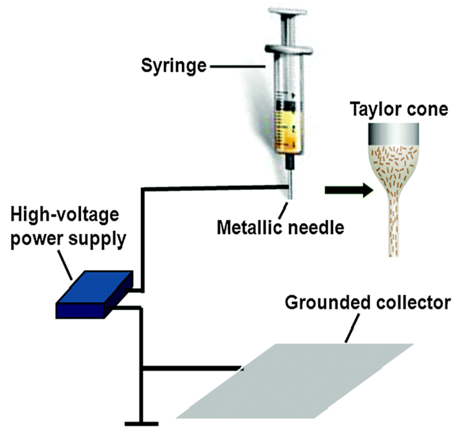

Figure 2: Electrospinning technique

Synthesis of Nanofibers using Electrospinning process

The elctrospun nanofibers are synthesized by making the polymer solution(melt) to pass through high electrostatic potential. Fig. 1 shows the typical schematic preparation procedure of electrospinning. This setup contains a spinneret (needle), high-voltage power supply with the good range of voltage, a glass syringe with a small needle and a metal collector at the base. The spinneret is filled with the melted polymer solution a needle is attached and driven by a syringe pump in order to regulate the flow rate through the spinneret. A strong electrostatic force is applied in between the spinneret and the collector. After the loading of polymer solution, the solution gets charged through the electrostatic force and forms a charged droplet at the tip of the spinneret. Due to the repulsive forces between the electrically conductive liquid and electric field, the polymer solution changes its form and deforms the droplet into a conical-shaped structure known as Taylor cone, [Taylor-who has already made some studies on the jet formation-1969][11-14]. The jet is accelerated and stretched through the atmosphere with the evaporation of the solvent, and is used for preparing interconnected mats of nanofibers on the oppositely charged grounded collector. The collector or electrode plate is coated with acrylic acid. The electrode is usually flatted and is used for the collection of both random and uniformly aligned nanofibers. Many nanofibers with special properties can be obtained by modifying the design of the spinneret and collector, such as the coaxial spinneret, gas jet spinneret, the bi component spinneret, ring electrodes, and the rotating disc collector.

In the preparation of nanofibers through the electrospinning process there are two main key points that play a vital role in the alignment of fibers such as the choosing of the polymer and the collector. The alignment of the fibers can be affected by the arrangement of collector that sets the morphology of and the properties of synthesized nanofibers. There are different types of collectors such as the plate collector, rotatory collector, grid-type collector, edge-type collector, the collector with blade auxillary ,the water bath collector, and the continuous collector. There are many biodegradable polymers can be used to produce nanofibers such as natural, synthetic, and the combination of both. Bio degradable polymers are also used in the preparation of nanofibers mainly for the surgical purposes and also for the cell carriers, and short-time scaffolds[15-17]. The reason behind using the bio degradable is that they will be degraded in the body upon the time extent, thus they are acting as a replacement for the traditional sutures during the surgeries.

Coaxial electrospinning

Fabrication of the shell nanofibers can be made through the coaxial electrospinning process. This is like an extension to the traditional method of electrospinning technique. Comparing the both the normal electrospinning and the coaxial electrospinning, the coaxial consists of usual complex spinneret(needle) with a multiple polymer solution feed system with a couple of interconnected channels. These interconnected channels shelled by an outer tube required for the injection of one material into the other. Thus nanofibers are collected on a core-sheath structured composite fiber in generating a nanofiber with core-shell structures.

In the recent times the coaxial electrospinning has achieved greater popularity than before in the preparation of protein delivery field. Because the fabricated core-shell fibers have the greatest ability to keep the proteins in the same location for a longer period and providing a uniform distribution throughout the fibers, therefore the proteins have the potential to be delivered in an organized manner because of the shell barricade[18-20].

Types of polymers used

Different types of polymers are used in the preparation of nanofibers such as the natural, synthetic and the combination of the both. The list of the polymers along with their respective solvents were given as a summary in the Table No.1

Applications of Nanofibers

Nanofibers have a very wide range of applications in the textile, biomedical and protective clothing fields. These are also useful in the energy generation and storage in batteries and fuel cells, super capacitors and also in the water treatment and ultrafiltration, photocatalysis, tissue engineering and regenerative medicine, biological sensing and finally in the drug and therapeutic agent delivery[21-23]. The fruits of the nanofibers in the field of biomedical has been known in the recent times. It's an established fact that the nanofibers can deliver enormous changes in the medical practice and also in the wound healing. For example, in treating any wound the nanoparticles enter the wound very easily because of their design and size and start the drug release very effectively therefore treating the wound and also create a barrier in not entering the contaminants into the body without causing pain to the patient.

Wound dressing

Nanofibers produced through electrospinning technique could generate a simple platform to protect wounds. The different studies show that using electric field the ultra fine nanofibers can be directly spun on to the injured place of skin to form a fibrous mat dressing. These nanofibers having the pore size between 500 and 100 μm are suitable for protecting the wounds from bacteria. Most of the synthetic kind of polymers such as carboxyethyl chitosan/PVA, collagen/chitosan, Silk fibroin, and ABA type poly(dioxanone-co-L-lactide)-block-poly ethylene glycol) (PPDO/PLLA-b-PEG) block copolymer have been electrospun and have been suggested for wound dressing usages[24-27]. For example, the multi component chitosan/PVA/AgNPS nanofibers had shown a good effect against the *E.Coli* and also a nanofiber consisting of a continuous uniform polyurethane dextran nanofibrous mats loaded with ciprofloxacin HCl drug have been electrospum and are used as a wound dressing material against both Gram positive and Gram negative bacteria. These are the best examples for the synthetic polymers. Apart from the synthetic polymer usage some naturally biodegradable polymers such as the chitosan/sericin and the silk fibers also showed a good anti microbial effect[28-31]. These are prepared as a non-woven composite nanofibers as they were biocompatible and non-toxic. This outcome clearly explains us that the electrospun nanofibers have a great deal of potency of having anti-microbial properties.

Tissue engineering and regenerative medicine

Tissue engineering and the regenerative medicine are the advancements in the field of medicine. Several tissues in the body are replaced by an identical structure which is made by different particles and they are made exactly like the same as the simple tissue in both the functions and the metabolism. Nanofibers are the best alternatives in this arena because of their high surface to volume ratio and their versatility in function. Here, nanofibers are just used in the preparation of those new structures which are exactly like the original and to mimic the

Table 1: List of the polymers used in Nanofibers

Name of the polymer	Category	Solvent
Polycaprolactone	Synthetic	Acetone, Chloroform
Polyurethane	Synthetic	DMF
PET	Synthetic	Trifluoroacetic acid/Dimethyl chloride
Nylon-6-co-polyamide	Synthetic	Formic Acid
Polyamide	Synthetic	Dimethylacetamide
PVA	Synthetic	Water
Polystyrene	Synthetic	DMF/Toluene
Collagen	Synthetic	Hexafluoro-2-propanol
Nylon 6 and nylon 66	Synthetic	Formic Acid
Polyvinyl phenol (PVP)	Synthetic	THF
Polyvinylcarbazole	Synthetic	Dichloromethane
PLDLA	Synthetic	Chloroform
Polyramide	Synthetic	Sulfuric acid
Polyvinyl chloride	Synthetic	THF, DMF
Poly-L-Lactide	Synthetic	Dichloromethane
Polyurethane	Synthetic	THF, DMF
Polycarbonate	Synthetic	DMF, THF
Polyethylene oxide	Synthetic	Isopropyl alcohol
Cellulose acetate	Synthetic	Acetone
Polybenzimidazole	Synthetic	Dimethyl acetamide
Polyimides	Synthetic	Phenol
Polyacrylonitrile	Synthetic	Dimethyl formaldehyde
PCL	Synthetic	Chloroform, Dichloromethane, Toluene, Carbon tetrachloride
PLLA	Synthetic	Water
PLGA	Synthetic	Acetone
PCL-PEG, PCL-PLLA	Synthetic (copolymer)	Chloroform, Dichloromethane, Toluene, Carbon tetrachloride
PLGA-PEG, PLLA-PEG	Synthetic (copolymer)	Water, Acetone
Chitosan (CS)	Natural (copolymer)	Trifluoroacetic acid (TFA)
Cellulose	Natural	Organic solvents
Alginate	Natural (copolymer)	Water
Gelatin	Natural (renewable)	Acetic acid, Hot water
Hyaluronic acid	Natural	Water
Collagen	Natural	Soluble in amino acid constituents
Silk fibroin	Natural	Both aqueous and organic solvents

function. Several biomaterials, entities of cells, biomolecules are used in this preparation.

During this preparation scaffolds have been developed and are used in the replacement of the damaged blood vessels and tissues. These are also having a greater impact when they are topographically compared to the *in vivo* test. Nanofiber scaffolds have a greater attention and the similarity with the cell normal activities such as the cellular growth, proliferation and differentiation. The selection of polymer for the preparation of these nanofibers and the scaffolds have been selected depending on their usage and the site of application. The usage of scaffolds in the field of tissue regeneration have been reported very lately, some their examples are discussed as follows:

In the initial preparations natural polymers such as chitin is used in the fabrication of nanofibers micro patterned through replica molding for engineering cell sheets as they are biodegradable and non-toxic these structures are very much smooth and can be aligned along the primary axis of the micro patterned features leading to the formation of ultrathin and free- standing ordered cell sheets which are very flexible and can be used as for the preparation of the complex tissue characters. Secondly, the electrospum PLGA nanofibers were functionalized with the adhesive peptides for cardiac tissue engineering applications, specifically for improving the adhesion and the contraction of the cardiomyocytes. In the third, Biodegradable PCL nanofibers are made to enhance the proliferation and the adhesion of the mesenchymal stem cells (MSCs). In the fourth, multifunctional osteo inductive nanofibers are made by using the natural polymer chitosan basing on the process self-assembly by using three bio active peptide molecules and then used as an implant coating to promote bone-like mineralization on medical grade titanium surface.

Drug and therapeutic agent delivery

Individual nanofibers and the scaffolds serves as best vehicles for the localized and therapeutic agents. The larger surface area and the microporous structures of nanofibers helps for an efficient drug delivery along

Table 2: Antimicrobial agent loaded nanofiber applications[36-51]

Antibacterial agent	Polymer	Applications
Ciprofloxacin HCl	Dextran/PU	Wound dressing
Tetracycline hydro-chloride	Halloysite nanotubes/PLGA PLA/PCL	Tissue engineering, Wound dressing and drug delivery applications
Doxycycline hyclate	PAA, PLLA	Wound dressing, Tissue engineering
Ampicillin	PAN/agar	Wound dressing
Vancomycin	PLGA	Implant
Neomycin	PSSA-MA/PVA	Wound dressing
Amoxicillin	Laponite (LAP) doped PLGA	Biomedical applications, Tissue engi-neering
Metronidazole	PCL/gelatin	Bone tissue engineering
Rifampicin	PLGA	Bone tissue engineering
Fusicid acid	PLGA	Implant
Silver nanoparticles	Silk fibroin, PEA, Poly[2-(tert- butylaminoethyl) meth-acrylate], chitosan, Bacterial cellulose, PAN, PVDF	Wound dressing, Tissue engineering, Water filters, Antiadhesion mem-branes
Photocatalytic tita-nia nanoparticles	Nylon 6 and soy protein, PVA	Water purification technology and in biotech- nology, Wound healing
Anthraquinone-2, 6-disulfonic acid	Gelatin	Wound dressing
Biteral	PCL	Prevention of post-surgical adhesion
Polyethyleneimine (PEI)	Silk fibroin	Wound dressing, Bionanotextile
Chitosan	PAN, PCL	Filter applications, wound dressing

with the encapsulation and direct incorporation of the active molecules including drugs and the other substances.

The latest groundbreaking example is the development of Blood brain barrier (BBB) drug delivery by the nanofiber based platform for the delivery of therapeutic peptides across the BBB for a biological response. These were synthesized by the self assembly process in which the active amphiphilic peptide moiety completely surrounds the nanofiber core part. Surprisingly the nanofibrous configuration part helps in the controlled the degradation of the peptide release across the membrane whereas the amphiphilic part helps in the transport of peptide molecules between the blood and the brain.

The localized delivery of antibiotic ciprofloxacin can also be achieved by the hydrophilic and biodegradable PVA- sodium alginate composite nanofiber-based transdermal patch by the functionalization of the antibiotic.

In another work, it showed that the anticancer drug Doxorubicin can also be incorporated into the polymeric core shell nanofibers for an emerging application in the tumor therapy against the ovary cancer. These fibers can be prepared by the co-axial electrospinning process using two water soluble polymers PVA and chitosan. Doxorubicin (DOX) was incorporated into the nanofiber core for targeting SKOV3 human ovary cancer cells. The *in vitro* release studies of these preparations showed that the DOX loaded fibers can be delivered into the nucleus of the cell and the drug release ratio can be controlled by altering the PVA and chitosan ratio. The DOX loaded PVA chitosan core shell nanofibers therefore inhibited the proliferation of the cancer cells, underlining the potential application of the core shell nanofibers for ovarian cancer therapy[32-35].

Challenges for nanofibers:

During the past decade, there has been a notable expansion in the number of cost-effective natural materials in the field of nanotechnology, owing to the advent of electrospinning, and developments in the processing of natural polymers. Interest has continuously been paid to animal-based natural materials, such as chitosan, hyaluronic acid, collagen, gelatin, and silk fibroin, for electrospun nanofibers and pharmaceutical applications. However, plant-based natural materials will be valuable for future research because of cost, availability, and commercial factors, as well as for cultural and geo-political reasons.

CONCLUSION

Nanofibers have a wide range of applications in the field of cosmetics, clothing, environmental safety, tissue engineering and in the preparation of scaffolds and the wound healing. The current situation regarding the delivery of antibacterial drugs is constantly drawing a very great attention. The local delivery of these drugs is achieved by nanofiber based formulations that are capable of localizing the drugs at the site of action. Due to this effect, present investigations are still improving for further delivery opportunities combinely results in the technology transfer from laboratory to industrial scale up processes, which will make these formulations more precious and irreplaceable.

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