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AN OVERVIEW OF NANOFIBERS IN DRUG DELIVERY SYSTEM

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ABASTRACT

Nanofibers are a nanomaterial with one dimension less than 100 nm. Wide range of polymers such as polyvinyl alcohol, gelatin, collagen, chitosan and carboxymethylcelulose can be subjected to electro spinning technique, self assembly and phase seperation to produce nanofibers. Their unique porous structures and large surface to volume area make them suitable for a wide variety of applications.these nanofibers are characterised by geometrically, physically and chemically. Electrospinning provides the most versatile process to produce nanofibers with a wide range of properties. The advantages of employing electrospinning technology to prepare DDS are not as yet fully exploited. Nanotechnology is now having an impact in biotechnology, pharmaceutical and medical diagnostics sciences. Furthermore electro-spinning as noted before has gained more attention due in part to a surging interest in nanotechnology, as ultrafine fibers or fibrous structures of various polymers with small diameters. Potential medical applications include efforts to fabricate electrospun polymer nanofiber scaffolds for nerves, tissues, skin and bone. Still several problems must be resolved for further applications such as the drug loading, the initial burst effect, the residual organic solvent, the stability of active agents, and the combined usage of new biocompatible polymers.

KEYWORDS: Nanofibers, Electrospinning, charcterization, application.

INTRODUCTION

Fiber with diameter in nanometer range. Nanofibers are a nanomaterial with one dimension less than 100 nm. Wide range of polymers such as polyvinyl alcohol, gelatin, collagen, chitosan and carboxymethylcelulose can be subjected to electro spinning technique to produce nanofibers. Nanofibers have large specific surface area with small pore size and these unique properties showing opportunités in management of wound care applications.[1] The use of nanofibers proves the importance and convenience of them as drug carriers. Their smaller size plays an important role in delivering the drug to the appropriate site in the body. Delivery of drugs or pharmaceutical agents to patients in a most physiologically acceptable manner has always been an important concern.

The objective of drug delivery systems is to deliver a defined amount of drug efficiently, precisely and for a defined period of time. The new technologies and materials will have a profound impact on drug delivery. Either biodegradable or non-degradable materials can be used to control whether drug release occurs via diffusion alone or diffusion and scaffold degradation. Additionally, due to the flexibility in material selection a number of drugs can be delivered including: antibiotics, anticancer drugs, proteins, and DNA. Using the various electro spinning techniques a number of different drug loading methods can also be utilized: coatings, embedded drug, and encapsulated drug (coaxial and emulsion electro spinning).These techniques can be used to give finer control over drug release kinetics.[2]

Properties of Nanofibers

Nanofibers exhibit special properties mainly due to extremely high surface to weight ratio compared to conventional nonwovens. Low density, large surface area to mass, high pore volume, and tight pore size make the nanofiber nonwoven appropriate for a wide range of filtration applications.[3] Figure: 1 shows how much smaller Nanofibers are compared to a human hair, which is 50-150 µm and Figure: 2 the size of a pollen particle compared to Nanofibers.

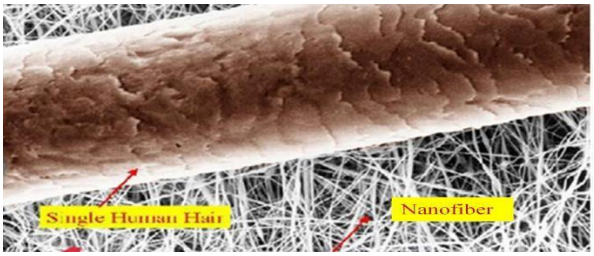


Figure 1: Comparison between human hair and nanofiber web.

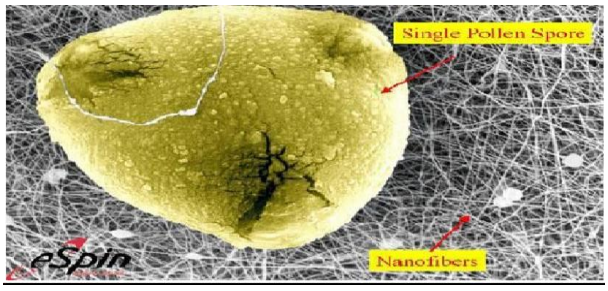


Figure 2: Entrapped pollen spore on nanofiber web 3.

A major upsurge in research on nanofibers has taken place most recently due to its high surface area and nanostructure surface morphologies that enable a myriad of advanced applications. Nanofibers have been reported to have marked differences in their thermal and mechanical properties compared to regular fibers and bulk polymers.[4]

Thermal properties: There are a few published reports on the thermal properties of nanostructured materials. 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 indicated that electrospun PLLA fibers have lower crystallinity, glass transition temperature (T*g*), and melting temperature (T*m*) than semicrystalline PLLA resins. Zong et al. attributed the decrease in the T*g* to the large surface to volume ratio of nanofibers with air as the plasticizer. The high evaporation rate followed by rapid solidification at the final stages of electrospinning is expected to be the reason for the low crystallinity. The T*g* and the peak crystallization temperature (T*c*) of the electrospun polyethylene terephthalate (PET) and poly- ethylene naphthalate (PEN) decreased significantly, while the heat of crystalline melting increased. The decrease in T*g* and Tm, and the increase in the heat of melting were attributed to the increase in the segmental mobility.

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 shown a lower melting temperature and heat of fusion than the PEO powder, which is attributed to the poor crystallinity of the electrospun fibers.[5]

Mechanical properties: Electrospun fibers have nano structured surface morphologies with tiny pores that influence mechanical properties like tensile strength, Youngs modulus, etc.. When compared with cast films, electrospun elastomers have shown a 40% reductionin the peak tensile strength and 60% reduction in elongation at maximum applied stress.. 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-fold greater than the pure Styrene-Butadiene rubber. As is evident, 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 essential for a greater understanding on the contributions of nanofibers to the mechanical and performance related characteristics of nanofiber composites.[6]

Physical properties: The simplest comparison between eletrospun Nanofibers, meltblown fibers and spun bonded fibers size. The differences in basic web properties such as fiber area, basis weights, thicknesses, permeability, and strength. Electrospun Nanofibers have diameters that are 1to 2 orders of magnitude corresponding increase in fiber surface area and decrease in basis weight.

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 nanofiber 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 have been applied on to various substrates. Substrates are selected to provide complementary functionally 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.. The polyester spun bond substrate is chosen to provide mechanical properties, while the nanofiber web Domionates 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. Additionally figure shows a comparison between a light layer of Nanofibers and a heavier layer of Nanofibers.[7]

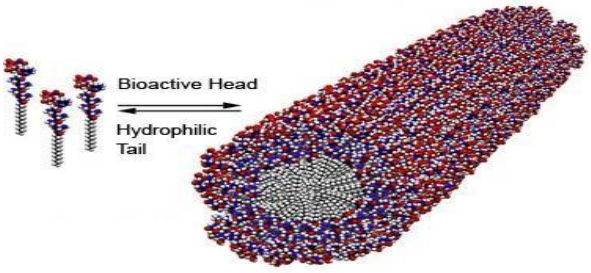
Fabrication of Nanofibres

Principle

Drug delivery with polymer nanofibers is based on the principle that dissolution rate of a drug particulate increases with increased surface area of both the drug and the corresponding carrier if necessary. For controlled drug delivery, in addition to their large surface area to volume ratio, polymer nanofibers also have other additional advantages. For example, unlike common

encapsulation involving, Controlled delivery systems are used to improve the therapeutic efficacy and safety of drugs by delivering them to the site of action at a rate dictated by the need of the physiological environment. A wide variety of polymeric materials have been used as delivery matrices, and the choice of the delivery vehicle polymer is determined by the requirements of the specific application. Polymeric nanofibers have recently been explored for their ability to encapsulate and deliver bioactive molecules for therapeutic applications. Three distinct techniques have proven successful in routinely creating nanofibrous tissue structures: self assembly, phase separation, and electrospinning. The electrospinning method is the most simple and efficient. Electro spinning as a polymer- processing technology has been known for more than 70 years.[8,9]

Self-assembly: Self-assembly involves the spontaneous organization of individual components into an ordered and stable structure with preprogrammed non-covalent bonds Self-assembly, that is, the autonomous organization of molecules into patterns or structures without human intervention, are common throughout nature and technology. Self-assembly of natural or synthetic macromolecules produces nano scaled supramolecular structures, sometimes nanofibers. Compared with electrospinning, self-assembly can produce much thinner nanofibers only several nanometers in diameter, but requires much more complicated procedures and extremely elaborate techniques. The low productivity of the self-assembly method is another limitation.[10]



Phase separation: Phase separation is a method frequently used to prepare 3-D tissue- engineering scaffolds. Phase separation of a polymer solution can produce a polymer-rich domain and a solvent-rich domain, of which the morphology can be fixed by quenching under low temperature. Removal of the solvent through freeze-drying or extraction can produce porous polymer scaffolds. Phase separation can be induced by changing the temperature or by adding non solvent to the polymer solution, thus called thermal induced or non-solvent-induced phase separation, respectively. Polymer scaffolds obtained by the phase separation method usually have a sponge like porous morphology with microscale spherical pores Unlike self-assembly, phase separation is a simple technique that does not require much specialized equipment. It is also easy to achieve batch-to-batch consistency and tailoring of scaffold mechanical properties and architecture is easily achieved by varying polymer/porogen concentrations. However, this method is limited to being effective with only a select number of polymers and is strictly a laboratory scale technique.[11]

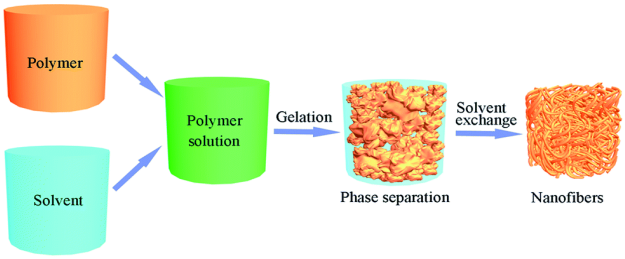


Figure 4: Phase separation process.

Electro spinning process: The nanofibers can be manufactured by Electro spinning process. Electro spinning is a process that was originally developed in the early 1930s, but did not receive much attention until recent decades. Most likely the increased interest is due to the refocusing of more research groups on nanotechnology. Although electro spinning has existed for a significant period of time and is relatively easy to execute, the physics of electro spinning nanofibers is only understood to a limited extent. A typical electro spinning process involves dissolving the drug of interest and a polymer in an appropriate solvent. The solution is then placed in a syringe, and a high voltage is applied. A small amount of the polymer solution is drawn out of the syringe, forming a Taylor cone. Increasing the applied voltage further results in the initiation of a charged fluid jet, which follows a chaotic trajectory of stretching and bending until it reaches the grounded target.

A stable jet is formed when the charge is increased above a critical voltage, and there is a balance between the surface tension of the fluid and the repulsive nature of the charge distribution on the surface of the fluid. The presence of molecular entanglements in the polymer solution prevents the jet from breaking into droplets (electro spraying), and when combined with the electrical forces results in a whip-like motion of the jet, known as bending instability. This process typically results in the drawing of a virtually endless fiber with a nanometre-sized to micrometer sized diameter. The final product is a three-dimensional nonwoven mat of entangled Nanofibers with a high surface-area-to-volume ratio. A schematic diagram of electro spinning is as shown in Figure 4 The process makes use of electrostatic and mechanical force to spin fibers from the tip of a fine orifice or spinneret. The spinneret is maintained at positive or negative charge by a DC power supply. When the electrostatic repelling force overcomes the surface tension force of the polymer solution, the liquid spills out of the spinneret and forms an extremely fine continuous filament. It has the misleading appearance of forming multiple filaments from one spinneret nozzle, but current theory is that the filaments do not split.[12,13,14]

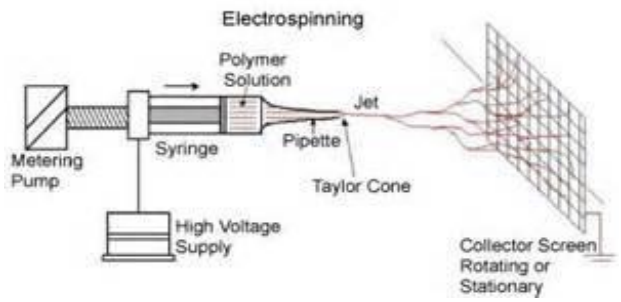


Figure 5: Elecctrospinning.

These filaments are collected onto a rotating or stationary collector with an electrode beneath of the opposite charge to that of the spinneret where they accumulate and bond together to form nanofiber fabric. The distance between the spinneret nozzle and the collector generally varies from 15 –30 cm. The process can be carried out at room temperature unless heat is required to keep the polymer in liquid state. The final fiber properties depend on polymer type and operating conditions. Fiber fineness can be generally regulated from ten to a thousand nanometers in diameter.

Electrospun nanofibers with a high surface area to volume ratio have received much attention because of their potential applications for biomedical devices, tissue engineering scaffolds, and drug delivery carriers. In order to develop electrospun nanofibers as useful nanobiomaterials, surfaces of electrospun nanofibers have been chemically functionalized for achieving sustained delivery through physical adsorption of diverse bioactive molecules. Surface modification of nanofibers includes plasma treatment, wet chemical method, surface graft polymerization, and co-electrospinning of surface active agents and polymers. A variety of bioactive molecules including anti-cancer drugs, enzymes, cytokines, and polysaccharides were entrapped within the interior or physically immobilized on the surface for controlled drug delivery. Surfaces of electrospun nanofibers were also chemically modified with immobilizing cell specific bioactive ligands to enhance cell adhesion, proliferation, and differentiation by mimicking morphology and biological functions of extracellular matrix. This review summarizes surface modification strategies of electrospun polymeric nanofibers for controlled drug delivery and tissue engineering.

Polymer-solvents used in electrospinning: The polymer is usually dissolved in suitable solvent and spun from solution. Nanofibers in the range of 10-to 2000 nm diameter can be achieved by choosing the appropriate polymer solvent system poly (vinyl alcohol) (PVA), poly (ethylene oxide) (PEO) and biodegradable aliphatic polyesters, such as poly (lactic acid) (PLA), poly (lactic-co-glycolic acid) (PLGA), poly(caprolactone) (PCL), while chitosan, alginate, collagen, gelatin, hyaluronic acid and silk are examples of frequently used natural polymers.

Drug Loading: One method to incorporate therapeutic drugs into nanofibers involves solubilising the drug into the polymer solution to be spun. Using this method, a loading efficiency of 90% into PDLA nanofibers was reported for the antibiotic drug Mefoxin. Covalent conjugation to polymers represents another method to modulate drug release. It has also been suggested that the high porosity of nanofibers allows for rapid diffusion of degradation by products. However, the burst release may also be indicative of the drug being attached only on the surface. As the drug and carrier materials can be mixed together for electrospinning of nanofibers, the likely modes of the drug in the resulting nanostructed products are:[15]

1. Drug as particles attached to the surface of the carrier which is in the form of nanofibers,
2. Both drug and carrier are nanofiber-form, hence the end product will be the two kinds of nanofibers interlaced together,
3. The blend of drug and carrier materials integrated into one kind of fibers containing both components, and
4. The carrier material is electrospun into a tubular form in which the drug particles are encapsulated.

Drug Release

Drug release from nanofibers can be described through three mechanisms: desorption from fiber surface, solid-state diffusion through fibers, and in vivo fiber degradation. Drug release tests from nanofibers are commonly conducted in phosphate buffered saline (PBS) solutions. When the nanofiber drug carrier is subjected to PBS, the fibers will be surrounded by the solution. The solution will also penetrate the space in between individual nanofibers. When the nanofiber drug carrier is swollen by the aqueous phase, drugs or proteins attached to the fiber surfaces can be released. Drug release from nanofiber surface is a two-step mechanism starting from desorption of drugs from the fiber surface, followed by fast diffusion into the aqueous phase. The desorption mechanism is not limited to the outer surface of the nanofibers but also includes drugs on the surfaces of the nanopores inside the nanofibers. Considering the nanometer size scale of the inner pores, and that the nanopores are most likely interconnected to some degree, the surface area would be much larger than the fiber outer surface area.[16,17]

Diffusion-controlled systems: Diffusion-controlled systems are the most widely used systems. They have been formulated in two basic configurations: reservoirs and matrix. In these systems, a core of drug is surrounded by a swollen or non-swollen polymer film, and diffusion of the drug through the polymer is the rate limitingsteps .These systems include membranes, capsules, microcapsules, liposomes, and hollow fibers. While the last four systems have been effectively applied in various areas (e.g. enzyme immobilization, drug targeting), membranes have proven of greatest value in controlled-release applications.

Matrix systems In these systems, the drug is uniformly distributed, throughout a solid polymer as in reservoir systems; drug diffusion through the polymer matrix is the rate limiting step. From the standpoint of fabrication cost, the ease of accomplishing this distribution pattern represents a significant cost decrease compared to reservoir systems. However, because of the different way in which drug is distributed, release characteristics are not generally zero-order. Solution of Fick's equation for transient diffusion.[18]

Case 1: The drug is molecularly dissolved in the polymer matrix and drug diffusion occurs via a solution-diffusion mechanism.

Case 2: The drug is dispersed in the polymer matrix (i.e., it is loaded above its solubility limit) and diffusion occur via a solution-diffusion mechanism.

Case 3: The drug is dissolved in the polymer matrix and diffusion occurs through water-filled pores in the matrix.

Chemically – Controlled Systems In these systems, the drug is distributed, ideally, uniformly, throughout a polymer in the same way as in matrix systems. The difference, however, relates to the fact that while the polymer phase in matrix systems remains unchanged with time and drug is released by diffusion, the polymer phase in bio erodible systems decreases with time. Consequently, as the polymer surrounding the drug is eroded, the drug escapes. This property offers a significant advantage over non-erodible systems in many applications because biodegradable polymers are eventually absorbed by the body, obviating the need for surgical removal. However, this advantage must be weighed against the potential disadvantage that the absorption products may be toxic, immunogenic, or carcinogenic. Mathematical formulations for bio erodible systems may be obtained if the kinetics of the biodegradation reaction of the polymer is known. Hoffenberg' has explored ideal situations where surface erosion is the only factor permitting drug release to occur. He has found that to obtain zero-order release it would be necessary to utilize geometry where the surface area did not change as a function of time. A slab (neglecting edge effects) is such a shape. On the other hand, spheres and cylinders would display decreasing rates with time because their surface areas would diminish.[19]

Pendant chain systems In these systems, a drug is chemically bound to a polymer backbone-chain and is released by hydrolytic or enzymatic cleavage. The use of these therapeutic agents has received considerable attention in drug-related research. The major thrust so far has been the design of polymer-drug complexes for short term use that can reduce toxicity, increase therapeutic efficiency, or be targeted toward specific cells or organs. Many examples exist in the literature. While some studies have explored this type of system for prolonged administration (e.g.; hours), less attention has been paid to the use of these pendant chain systems for controlled long-term drug release. In its simplest form, the pendant chain system consists of drug attached to a polymer backbone. The polymer system can either be soluble or insoluble. Soluble backbone-chains are generally used for transport functions such as cell targeting; insoluble forms are more desirable for long-term controlledrelease implants. The backbone may also be biodegradable or non-biodegradable. For in vivo use, it is important that the polymers do not cause immunological reactions and that the drugs, when coupled to the polymers, do not function as happens and induce allergic reactions. The drug itself can be attached directly to the polymer or it can be attached via a spacer group. The spacer group may be used to affect the rate of release and hydrophobicity of the systemstate.Although diffusion in rubbery systems at equilibrium is generally Fickian, diffusion in a rubbery state which is not at equilibrium (due to the continuous swelling) may be Fickian or non-Fickian.[20]

Magnetically Controlled systems In these systems, drug and small magnetic beads are uniformly dispersed within a polymer matrix (e. g, ethylene vinyl acetate copolymer). Upon exposure to aqueous media, drug is released in a fashion typical of diffusion-controlled matrix systems. However, upon exposure to an oscillating external magnetic field, drug is released at a much higherrate. The mechanism responsible for this magnetic modulation is unclear. It was mentioned previously that the incorporation of powdered drug into solvent-cast ethylene vinyl acetate copolymer caused porous channels to form within the matrix. It is possible that the beads cause alternating compression and expansion of the channels, thus facilitating drug release.

Characterization

Geometrical characterization: Geometric properties of nanofibers such as fiber diameter, diameter distribution, fiber orientation and fiber morphology (e.g. cross-section shape and surface roughness) can be characterized using scanning electron microscopy (SEM), field emission scanning electron microscopy (FESEM), transmission electron microscopy (TEM) and atomic force microscopy (AFM). The use of TEM does not require the sample in a dry state as that of SEM. Hence, nanofibers electrospun from a polymer solution can be directly observed under TEM. An accurate measurement of the nanofiber diameter with AFM requires a rather precise procedure. The fibers appear larger than their actual diameters because of the AFM tip geometry. For a precise measurement, two fibers crossing to each other on the surface are generally chosen. The upper horizontal tangent of the lower fiber is taken as a reference, and the vertical distance above this reference is considered to be the exact diameter of the upper nanofiber .The roughness value is the arithmetic average of the deviations of height from the central horizontal plane given in terms of millivolts of measured current .Another geometric

parameter is porosity. The porosity and pore size of nanofiber membranes are important for applications of filtration, tissue template, protective clothing, etc. The pore size measurement can be conducted by, for example, a capillary flow porometer They found that Nylon 6,6 could be electrospun into a very fine membrane with extremely small pore throat sizes (with a mean flow pore diameter of 0.12 mm) which were much smaller than the average fiber diameters. FBI also exhibited pore sizes (0.20 mm) smaller than the electrospun fiber sizes. However, the Estane1 and Pellethane1 exhibited mean pore sizes which were significantly higher, with average flow pore diameters of 0.76 and 2.6mm, respectively.[21]

Chemical Characterization: Molecular structure of a nanofiber can be characterized by Fourier transform infra red (FTIR) and nuclear magnetic resonance (NMR) techniques. If two polymers were blended together for the fabrication of nanofibers, not only the structure of the two materials can be detected but also the inter-molecular interaction can be determined. In the case of a collagen and PEO blend used for electrospinning of nanofibers, the NMR spectrum showed a new phase structure which was caused by the hydrogen bond formation between the ether oxygen of PEO and the protons of the amino and hydroxyl groups in collagen. Supermolecular structure describes the configuration of the macromolecules in a nanofiber, and can be characterized by optical birefringence, wide angle X-ray diffraction (WAXD), small angle X-ray scattering (SAXC) and differential scanning calorimeter (DSC).[22] Fong & Reneker studied the birefringence of the styrene–butadiene–styrene (SBS) triblockco polymer nanofibers with diameters around 100 nm under an optical microscope noticed that the electrospun PLLA fibers quenched below 0 c resulted in amorphous fiber structure. After drying the electrospun nanofibers at room temperature, they found that melting point transitions appeared at two peaks by DSC. It was explained that during electro spinning of this polymer molecule had no time to crystallize and hence it could only have an amorphous super molecular structure. It should be noted that polymer crystallization does occur during electro spinning when the polymer is in a molten form, see a subsequent discussion. Since the supermolecular structure changed during the electro spinning the transition points of the polymers also changed. One of them was lower than the normal melting point due to defects existing in crystallization while drying.

Surface chemical properties can be determined by XPS, water contact angle measurement, and FTIR– ATR analysesmeasured the atomic percentage of fluorine in PMMA-TAN blend. It was shown that the atomic percentage of fluorine in the near surface region of the electrospun fibers was about double the atomic percentage in a bulk polymer. Surface chemical properties of nanofiber can also be evaluated by its hydrophilicity, which can be measured by the water contact angle analysis of the nanofiber membrane surface.[23]

Physical characterization: Air and vapor transport properties of electrospun nanofibrous mats have been measured using an apparatus called dynamic moisture vapor permeation cell (DMPC). This device has been designed to measure both the moisture vapor transport and the air permeability (convective gas flow) of continuous films, fabrics, coated textiles and open foams and battings. Average pore size of the electrospun nonwovens was 4– 100 times smaller than that of the meltblown nonwovens, resulting in an increase in air flow resistance by as much as 156 times. Crosslinking the fibers of the electrospun membrane significantly decreases liquid transport through the membrane. Electrical transport properties of electrospun nanofibers were investigated by Norris et al. measured the conductivity of the electrospun nonwoven ultra-fine fiber mat of polyaniline doped with camphorsulfonic acid blended with PEO (polyethylene oxide). As the non-woven mat was highly porous and the fill factor of the fibers was less than that of a cast film, the measured conductivity seemed to be lower than that of the bulk measured the conductivities of PAN (polyacrylonitrile) nanofibers before and after carbonized using a digital electrometer with two neighboring contacts of 4 mm distance. The electrospinning was conducted carefully and briefly so that there was only one continuous fiber deposited across the two neighboring contacts. The PAN fiber (before carbonized) exhibited a resistance which was beyond the upper limit of the electrometer, whereas the graphitization of the PAN nanofiber led to a sharp increase in conductivity to around 490 S/m 39 the thermal properties of nanofibers of pure PET [poly (ethylene terephthalate)] and PEN [poly (ethylene naphthalate)] polymers and PET/PEN blends obtained in melt form. They found that the electrospinning of polymers resulted in increase of crystallinity and decrease of Tg (glass transition temperature) and Tc (crystallization peak temperature) of PET and PEN. The crystalline melting peaktempe ratures (Tm) of PET and PEN were almost the same before and after electrsopinnning. On the other hand, not only Tg and Tc but also Tm of the electrospun PET/PEN nanofibers were lower than those of the bulk. The change in thermal properties of electrospun neat polyesters was primarily resulted from decrease of molecular weight after the electrospinning by thermal as well as mechanical degradation. However, the change in those of PET/PEN blends was attributed to exchange reactions of PET and PEN in melt blends.[24]

Mechanical characterization: Mechanical tests of nanofibrous nonwoven membrane can be performed using conventional testing techniques. When the membranes are collected on a static collector screen, no anisotropy in the in-plane tensile behavior seems to have been reported. Figure 6 shows typical stress–strain

curves of a PLLA nanofibrous mat obtained by 21 for tissue engineering applications. It has been found the tensile strength of nanofibrous mat was similar to that of a natural skin. However, when the membranes were obtained from a rotating drum the electrospun nonwoven mats had different properties in different directions The fiber orientation depended on the linear velocity of the drum surface and other electrospinning parameters. Due to very small dimension, the mechanical characterization of an individual nanofiber is a challenge for the existing test techniques.

The established methods and standards for determining the mechanical behavior of conventional fibers are inadequate in the case of manipulation or testing of nanofibers. This is probably one of the main reasons why articles addressing the mechanical tests of single nanofibers are rare in the literature. 45 described a cantilever technique to measure the tenacity of a single electrospun PAN (polyacrylonitrile) ultrafine fiber. A cantilever consisting of a 30 mm glass fiber was glued at one end onto a microscope slide and a 15 mm nylon fiber was attached at the free end of the glass fiber. The electrospun test fiber was glued with epoxy resin to the free end of the nylon fiber. A part of the same fiber was cut and deposited on a SEM specimen holder for diameter measurement using SEM. As the sample fiber was stretched with a computer controlled Instron model 5569, the deflection of the cantilever was measured under light microscopy using a calibrated eyepiece. A chart was used to convert the deflections into actual values of fiber tenacity. The elongation-to-breakof electrospun PAN fibers was estimated using a caliper. It was reported that the electrospun PAN fibers with a diameter of 1.25 mm and length of 10 mm exhibited failure at 0.4 mm deflection at 41 mg of force and the resulting tenacity was 2.9 g/day. The mean elongation at breakof the same fiber was 190% with a standard deviation of 16%.. On the other hand, significant efforts have been made to characterize the mechanical specifically tensile properties of single carbon nanotubes.

The methods used wherein can also be applicable for the measurement of tensile properties of single electrospun polymer nanofibers. Due to nanometer specimens, the mechanical measurements for carbon nanotubes reported so far were conducted in terms of AFM, SEM, or TEM. Obtained the bending strength and Young‟s modulus of a carbon nanotube by deflecting one end of the tube with an AFM tip while keeping the other end fixed.. They designed a nanomanipulator so that the carbon nanotube could be manipulated in three dimensions inside the SEM, and was attached to the tips of the AFM. Very recently, Demczyket al. 49 directly measured the tensile strength and elastic modulus of multiwalled carbon nanotubes under TEM by using a tensile testing device fabricated through a microfabrication technique. It is expected that the similar techniques can be applied to understand themechanical properties of single nanofibers.[25,26]

Applications[27,28,29]

Energy Storage Materials

Nanofibers have been applied as a storage media for alternative energy sources such as hydrogen and natural gases. Porous carbon nanofibers have especially been investigated widely due to their large specific surface area and high pore volume. Hydrogen and natural gases can be stored by physical adsorption, indicating that the use of these gases is easy. The superior storage capacity of porous carbon nanofibers was presented through comparison with other porous carbon materials such as graphite, carbon nanotubes, and activated carbon.

Composite application

One of the most important applications of traditional (micro-size) fibers, especially engineering fibers such as carbon, glass, and Kevlar fibers, is to be used as reinforcements in composite developments.With these reinforcements, the composite materials can provide superior structural properties such as high modulus and strength to weight ratios, which generally cannot be achieved by other engineered monolithic materials alone. Needless to say, nanofibers will also eventually find important applications in making Nano composites. This is because nanofibers can have even better mechanical properties than micro fibers of the same materials, and hence the superior structural properties of nanocomposites can be anticipated. Moreover, nanofiber reinforced composites may possess some additional merits which cannot be shared by traditional (microfiber) composites. For instance, if there is a difference in refractive indices between fiber and matrix, the resulting composite becomes opaque or nontransparent due to light scattering. This limitation, however, can be circumvented when the fiber diameters become significantly smaller than the wavelength of visible light.

Filtration Application

Filtration is necessary in many engineering fields. It was estimated that future filtration market would be up to US $700b by the year 2020Fibrous materials used for filter media provide advantages of high filtration efficiency and low air resistance Filtration efficiency, which is closely associated with the fiber fineness, is one of the most important concerns for the filter performance. In the industry, coalescing filter media are studied to produce clean compressed air. These media are required to capture oil droplets as small as 0.3 micron. It is realized that electro spinning is rising to the challenge of providing solutions for the removal of unfriendly particles in such submicron range. Since the channels and structural elements of a filter must be matched to the scale of the particles or droplets that are to be captured in the filter, one direct way of developing high efficient and effective filter media is by using nanometer sized fibers in the filter structure.

Table 1: Fiber surface area per mass of fiber for different fiber size.

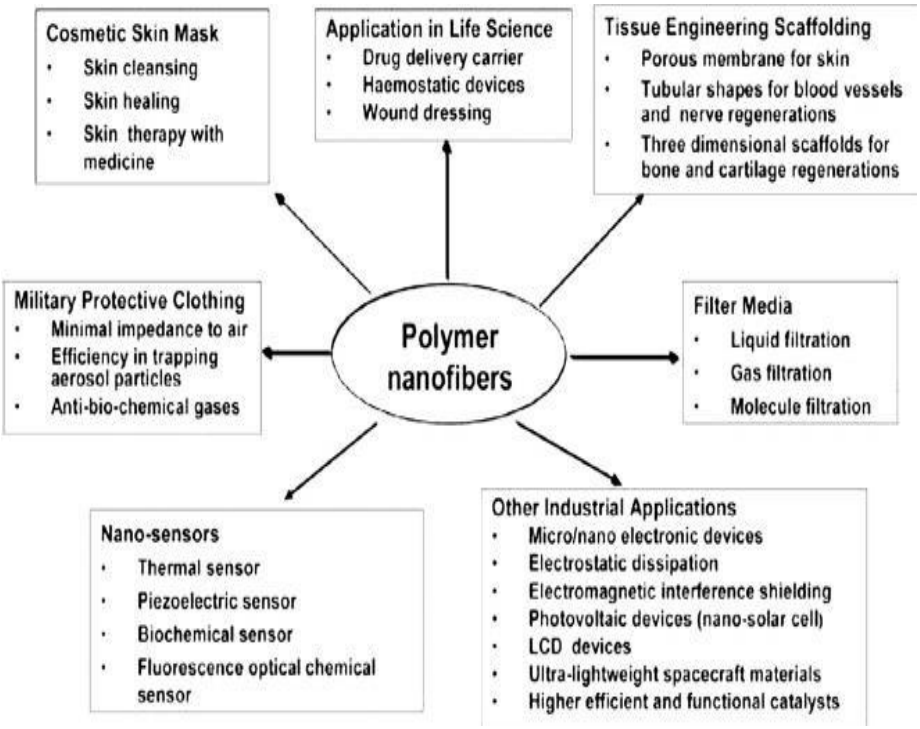
Fiber type	Fiber size in micrometer	Fiber surface area per mass of fiber material in m^2/g
Nanofiber	0.05	80
Spunbound fiber	20	0.2
Meltblown filter	2.0	2

Cosmetics

The current skin care masks applied as topical creams, lotions or ointments may include dusts or liquids prays which may be more likely than fibrous materials to migrate into sensitive areas of the body such as the nose and eyes where the skin mask is being applied to the face. Electro spun polymer nanofibers have been attempted as a cosmetic skin care mask for the treatment of skin healing, skin cleansing, or other therapeuticalor medical properties with or without various additives This nanofibrous skin mask with very small interstices and high surface area can facilitate far greater utilization and speed up the rate of transfer of the additives to the skin for the fullest potential of the additive. The cosmetic skin mask from the electro spun nanofibers can be applied gently and painlessly as well as directly to the three-dimensional topography of the skin to provide healing or care treatment to the skin.

Other Applications

In addition to composite reinforcement, other application fields based on electro spun polymer nanofibers have been steadily extended especially in recent years. One of the best representatives in this regard is shown by relevant US patents, in which most applications are in the field of filtration systems and medical prosthesis mainly grafts and vessels. Other applications which have been targeted include tissue template, electromagnetic shielding, composite delamination resistance, and liquid crystal device. More extended or perspective application areas are summarized in Fig. **7**. It should be realized that most of these applications have not reached their industry level, but just at a laboratory research and development stage. However, their promising potential is believed to be attracting attentions and investments from academia, governments, and industry all over the world.



Nanofibers In Advanced Wound Care[30,31]

In contrast to traditional wound care, advanced wound care dressings operate in moist environments, require less frequent changing and help reduce the pain of dressing changes and lessen scarring.

Nanofibers may help in the improved care of

- Acute wounds, including those caused by burns, surgical or traumatic wounds
- Chronic wounds, such as ulcers, not proceeding through the normal stages of healing.

- ➢ Permeability of gases and liquids.
- ➢ High absorption capacity of liquids (exudate).
- ➢ High filtration efficiency for bacteria resulting in decreased infections.
- ➢ Possibility to add drugs – haemostatic or antimicrobial dressing.

- Swelling and gel forming capability to keep moist environs
- Anti adhesive effect to the derma - painless removal of the dressing without destroying newly formed tissue.

Applications of Nanofibers as Drug Delivery System: Desired properties of Nanofibers for application as drug delivery Protect the drugs in the case of systemic application from decomposition, e. g., in the blood circuit. They should allow controlled release of the drug at a release rate as constant as possible over a longer period of time, adjusted depending on the field of application. Permeate certain membranes or barriers, e.g. BBB. They are supposed to concentrate the drug release only on the targeted body. Nanofibers have potential medical applications, which include, drug and gene delivery, artificial blood vessels, artificial organs, and medical facemasks. For examples carbon nanofiber, hallow Nanofibers are smaller than blood cells, have potential to carry drugs in to blood cells72. Nanofibers are capable of delivering medicines directly to internal tissues. This nanofiber can be used as varies of medical applications such as bandages or sutures that ultimately dissolve in to body. This Nanofiber minimizes infection rate, blood lose and is also adsorbed by the body. Employing electrospun Nanofibers as drug delivery vehicles has been based on their unique functionally and inherent nanoscale morphological characteristics.

A rich variety of therapeutic agents such as antibiotics, anticancer drugs and growth factors have been physically or chemically formulated within the bulkPhase of electrospun Nanofibers or on their surface for accomplishing controlled topical within the defined period of time. Such medicated Nanofibers could be could be applied to various purposes including tissue engineering scaffolds. Recently introduced surface modified designs for drug loading open up the new possibility of constructing more sophisticated drug delivery platforms.

Table 2: Shows Marketed Nanofibers products available.

Product	Description	Manufacture
Integra	Nano fiberoys bovine type1 collagen/glycosaminoglycons /synthetic polysiolxane based dermal analogue	Integra life sciences
Nanocell	Nanofibrous microbial cellulose masks	Thaionano cellulose
Apligral	Bovine collagen nanofibrous sponge with neonatal foreskin fibroblasts and keratinocytes	Novartis
Kerlix AMD	Nanofibrous PHMB gauge	Kendall
Dermafuse	Bioactive borate glass nanofibrous dressing	Mo-sci corporation U.S.A
Trans type	Eletrospun nylon Mesh/Collagen/Silicone dermal substitute embedded with allogenic fibroblasts	Advanced Tissue Sciences
Tegaderm	Eletrosun poly (caprolactone) (PCL)/gelatin/polyurethane/s caffold	3M company
Chito flex	Fabricated chitosan nanofiberous dressing	Hemcon Med Tech.Inc.
Permacol	Dermal matrix of procine Nanofibers	Covidien
Allo Derm	Condaners a cellular matrix Nanofibers autograft	Life cell corporation

Topical drug delivery Electrospun Nanofibers for drug and gene delivery application have been used for tissue engineering to improve therapeutic efficacy in addition, the fibrous surface structure shows strong adhesiveness to mucous layers because their nano-porous structures instantly absorb moisture at mucous layers through nano-void volumes. The superior adhesiveness to word biological surfaces allows Nanofibers to be an ideal candidate for topical drug delivery devices.

Vitamins Electrospun Nanofibers can be used as carriers for delivery of some vitamins to the skin. Usually, vitamins are applied to the skin in the form of topical creams, lotions, or ointments. Here vitamin – E and vitamin-A, were selected as the model vitamins, due to their benefits in cosmetics. Vitamin –A is naturally occurring, and lipid soluble substances, known to be used for the treatment of leukemia, acne, and other skin disorders. Vitamin-E is also lipid soluble vitamin, it shows potent antioxidant ability, owing to the presences of a hydroxyl group on its chromanol ring which can readily donates a proton to reduce free radicals.

Protein delivery
Nanofiber to regulate the release of the encapsulated proteins in core. A near Zero order releaseof platelet derived growth factor-bb (PDGF-bb) can be produced with no associated burst release. In addition, aligned PDGF-bb loaded Nanofibers are fabricated. These aligned drug loaded fibers may simultaneously provide biochemical and topographical cues to the seeded cells, provisions that should prove beneficial for many tissue engineering applications.

Nucleic acid the encapsulation of plasmid DNA in a PLA-PEG block co-polymer nanofibrous natrix for tissue engineering purposes81. Approximately 80% of the β-galactocidase receptor gene is released in 20 days. Transfection experiments performed on the osteoblastic cells line MC3T3-E1 demonstrate increased transfection efficiency of the fiber-encapsulated DNA over naked plasmid added to the medium, but lower than that with a

commercial transecting reagent. For improving stability of DNA during the electrospinning processes.

Delivery of chemotherapeutic agents Nanfibers have been used sparingly as an anti- neoplastic drug delivery. This has to do with the nature of fibrous scaffolds, which permit delivery only after tumor-resection and surgical implantation of the device. The majority of nanofiber anti-neoplastic agent delivery systems have been envisioned for the treatment of malignant gliomas. The current DDS of choice is post tumor-resection implantation of a drug-eluting wafer. Thus, all these studies have tried to elucidate the benefits of implantation of a drug-eluting wafer. Doxorubicin Hcl , a hydrophilic anti-neoplastic agent is electonspun as an aqueous emulsion in a solution of PEG-PLLA copolymer This method affords uniform distribution of the drug within the fiber and a administered burst release.

CONCLUSION

Today Nanofibers are at the forefront of nanotechnology. Their unique porous structures and large surface to volume area make them suitable for a wide variety of applications. Nanofiber controlled drug delivery system is becoming the flash news in pharma field. Nano structure delivery architecture are promising candidates that will enable efficient in Targeted and Novel drug delivery. Electrospinning provides the most versatile process to produce nanofibers with a wide range of properties. The advantages of employing electrospinning technology to prepare DDS are not as yet fully exploited. Nanotechnology is now having an impact in biotechnology, pharmaceutical and medical diagnostics sciences. Furthermore electro-spinning as noted before has gained more attention due in part to a surging interest in nanotechnology, as ultrafine fibers or fibrous structures of various polymers with small diameters. Potential medical applications include efforts to fabricate electrospun polymer nanofiber scaffolds for nerves, tissues, skin and bone. Still several problems must be resolved for further applications such as the drug loading, the initial burst effect, the residual organic solvent, the stability of active agents, and the combined usage of new biocompatible polymers.

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