NANOFIBERS BASED DRUG DELIVERY SYSTEM – A REVIEW

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ABSTRACT
Controlled drug delivery systems have gained much attention in the last few decades. This is due to the many advantages compared with the conventional dosage forms such as improving therapeutic efficacy, reducing toxicity by delivering them at a controlled rate. Recently, nanofibers were explored as new device for drug delivery. Nanofibers are defined as fibres with diameters less than 1000 nanometers (nm). National Science Foundation (NSF) defines nanofibers as having at least one dimension of 100 nanometer (nm) or less. The most often used fibers are prepared using nylon, polystyrene, polyacrylonitrile, polycarbonate, PEO, PET and water-soluble polymers. The main advantages of the fibrous carriers are that they offer site-specific delivery of drugs to the body. Also, more than one drug can be encapsulated directly into the fibers. Due to the high surface area and porous structure of the nanofibers, they find applications in many fields. A variety of bioactive molecules including anti-cancer drugs, enzymes, cytokines, and polysaccharides can be entrapped within the interior or physically immobilized on the surfaces of nanofiber for controlled drug delivery. Surfaces of electrospun nanofibers can also be chemically modified with immobilizing cell specific bioactive ligands to enhance cell adhesion, proliferation, and differentiation by mimicking morphology and biological functions of extracellular matrix. Currently, there are three techniques available for the synthesis of nanofibers: electrospinning, self-assembly, and phase separation. Out of these techniques, electrospinning is the most widely studied technique. A new method for creating nanofibers made of proteins developed and promised to greatly improve drug delivery methods for the treatment of cancers, heart disorders and Alzheimer’s disease, as well as aid in the regeneration of human tissue, bone and cartilage. Due to these applications, this review will

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focus on nanofibers as potential carriers among modern drug delivery systems.

KEYWORDS: Controlled drug delivery, nanofibers, electrospinning, surface modification

INTRODUCTION

Conventional drug delivery is widely used in pharmaceutical field to treat diseases. However, conventional delivery has many drawbacks and major drawback is non-site specificity. Some drugs are absorbed at specific site only. They require release at specific site or a release such that maximum amount of drug reaches to the specific site. Conventional drug delivery system is not suitable for the drug which have the short half life. Also the high dose is required in conventional drug delivery and so there may be chances of toxicity.

Delivery of therapeutic proteins/peptides has received a considerable amount of attention over the last 10 years, but there are number of limitations to oral delivery of proteins. The barriers to peptide bioavailability after oral administration are intestinal membrane permeability, size, intestinal and hepatic metabolism and lastly solubility. Nanofiber approach is site specific delivery approach of the peptides to the most permeable part of the intestine. Metabolism (hepatic and intestinal) of peptides might be controlled by co-administration of competitive enzyme inhibitors, structural modifications and administration of the compound as well as absorbed prodrug into nanofibers that is converted into therapeutically active agent after its absorption.¹

Nanofibers exhibit special properties mainly due to extremely high surface to weight ratio compared to conventional nonwovens. Recently, nano-fibers have been investigated with amazing increased interest due to their many advantages, such as Low density, large surface area to mass, high pore volume, and tight pore size. Among different nano-scaled materials, nanofibers have been widely applied in industry due to the ease in production processes compared to other nano-materials. Nanofibers can be identified as fibers having diameters between tens and hundreds of nanometers. This nanoscaled diameter of fibers can give an enormous surface area per unit mass. Figure 2 shows how much smaller nanofibers are compared to a human hair, which is 50-150 µm. The elastic modulus of polymeric nanofibers of less than 350 nm is found to be 1.0±0.2 Gpa.²

Fig 1. Nanofibers

Fig 2. Nanofiber compare to human hair

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Currently, there are three techniques available for the synthesis of nanofibers: electrospinning, self-assembly, and phase separation, out of these techniques, electrospinning is the most widely studied technique. Electrospinning is a very simple and versatile process by which polymer nanofibers with diameters ranging from a few nanometers to several micrometers can be produced using an electrostatically driven jet of polymer solution or polymer melt.\(^3\,^4\)

**MANUFACTURING OF NANOFIBERS:**

The nanofibers can be manufactured by Electrospinning process. Electrospinning 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 electrospinning has existed for a significant period of time and is relatively easy to execute, the physics of electrospinning nanofibers is only understood to a limited extent.

A typical electrospinning 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 (electrospraying), 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 nanometer-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.\(^5\)

**Theory of electrospinning**

New applications require fibers with increasingly smaller diameters. Since the surface area is proportional to the fiber diameter and the volume is proportional to the square of the diameter, the specific surface area is inversely proportional to the fiber diameter, leading to high specific surface areas for small fibers. In addition, pore size depends on the fiber diameter; therefore, small fibers produce non-wovens with a small pore size. There are several methods for producing small diameter fibers using high-volume production methods, such as fibrillation, island-in-sea, and the novel melt-blowing system, in addition there are highly accurate methods such as nano-lithography and self-assembly. However, the usefulness of above methods is restricted by combinations of narrow material ranges, high costs and low production rates. In comparison, electrospinning is a simple and low cost process and has an intermediate production rate. Electrospinning is a process for submicron scale polymer-based filament production (usually called nanofibers) by means of an electrostatic field. Due to these forces, the meniscus of a liquid flowing out of a capillary nozzle elongates, forming a fine jet, that is later atomized into fine droplets. The droplets obtained by this method are electrically charged. A basic electrospinning setup consists of 122 Nanofibers three elements: an electrical generator (high voltage supply), a capillary (jet source) and a metal collector (target).
Depending on the flow rate and potential of the capillary, the droplets can be of submicron size, with a narrow size distribution. The solution is usually electrically charged by the generator, and the collector is grounded, but it is also possible to invert the process by electrically charging the collector and grounding the solution. When the electrostatic forces exceed the surface tension force, the pendent droplet at the capillary tip is stretched into a cone (called Taylor cone), and a solution stream is ejected (Dzenis, Y.A., 2004). Whether the jet will form a continuous fiber or disperse into droplets depends on polymer molecular weight, polymer chain entanglement, and the solvent applied to the process (specifically, its evaporation rate). It is known from the literature that smooth fibers are produced when the product of intrinsic viscosity (\( \eta \)) and polymer concentration (\( c \)), known as the Berry’s number, \( \text{Be} = \eta c \), is greater than a certain critical value \( \text{Becr} \), which is characteristic of the polymer. Specific viscosity of a polymer solution is determined as the ratio: 

\[
\eta_{SP} = \frac{\eta_0 - \eta_s}{\eta_s} \quad \text{Eqn 1}
\]

where \( \eta_0 \) is the zero shear rate viscosity of the polymer solution at concentration (\( c \)), and \( \eta_s \) is the solvent viscosity. From this equation, the intrinsic viscosity (\( \eta \)) of the polymer is determined as a linear extrapolation of specific viscosity \( \eta_{SP} \) measured for various concentrations to the concentration at \( c = 0 \). (Eqn 2)

The intrinsic viscosity (\( \eta \)) is also related to the molecular weight (MW) of a linear polymer by the Mark–Houwink equation:

\[
\eta = K MW^\alpha \quad \text{Eqn 3}
\]

where the constants (K) and (\( \alpha \)) depend on the polymer, solvent and temperature. [6]

**Polymer-solvents used in electrospinning [2]**

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. Table 1 gives list of some of polymer solvent systems used in electrospinning.

<table>
<thead>
<tr>
<th>POLYMER</th>
<th>SOLVENTS</th>
</tr>
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<tbody>
<tr>
<td>Nylon 6 and nylon 66</td>
<td>Formic Acid</td>
</tr>
<tr>
<td>Polyacrylonitrile</td>
<td>Dimethyl formaldehyde</td>
</tr>
<tr>
<td>PET</td>
<td>Trifluoroacetic acid/Dimethyl chloride</td>
</tr>
<tr>
<td>PVA</td>
<td>Water</td>
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<tr>
<td>Polystyrene</td>
<td>DMF/Toluene</td>
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<tr>
<td>Nylon-6-co-polyamide</td>
<td>Formic acid</td>
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<tr>
<td>Polybenzimidazole</td>
<td>Dimethyl acetamide</td>
</tr>
<tr>
<td>Polymide</td>
<td>Sulfuric acid</td>
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<tr>
<td>Polymides</td>
<td>Phenol</td>
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Table 1. Polymer solvent systems for electrospinning.
SURFACE MODIFICATION TECHNIQUES OF NANOFIBER MESH

In order to apply electrospun nanofibers in biomedical uses, their surfaces have been chemically and physically modified with bioactive molecules and cell recognizable ligands after the electrospinning method; this subsequently provides bio-modulating or biomimetic microenvironments to contacting cells and tissues. A variety of functionalization strategies of electrospun nanofibers with bioactive molecules including proteins, nucleic acids, and carbohydrates have been employed.

Various degradable and non-degradable synthetic nanofibers have been surface-modified with bioactive molecules for advanced biological and therapeutic applications. Synthetic polymers offer easier processability for electrospinning and more controllable nanofibrous morphology than natural polymers. Water soluble natural polymers are often considered to be difficult to directly process into nanofibers due to their unstable nature such as being vulnerable to processing conditions and having a weak mechanical property.\(^7,8\)

For sustained drug delivery applications, the electrospinning process enables a wide variety of hydrophobic therapeutic agents to be directly incorporated within the bulk phase of nanoscale fibers for controlled release. For example, a biodegradable polymer solution containing hydrophobic anti-cancer drugs such as paclitaxel was directly electrospun to produce drug releasing nanofibrous mesh \(^9\). Alternatively, hydrophilic and charged macromolecular drugs such as proteins and nucleic acids were covalently and physically immobilized onto the modified surface of nanofibrous mesh for modulating cellular functions. The electrospun nanofiber mesh possesses highly interconnected open nano-porous structure with a high specific surface area, offering an ideal condition for sustained and local drug delivery.\(^{10}\) Various surface modification techniques for applying synthetic polymer nanofibers to tissue engineering and drug delivery are presented here.

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Plasma treatment

Plasma treatment of polymer substrates has been commonly employed to tailor surface adhesion and wetting properties by changing the surface chemical composition.\(^{11–14}\) Appropriate selection of the plasma source enables the introduction of diverse functional groups on the target surface to improve biocompatibility or to allow subsequent covalent immobilization of various bioactive molecules. For example, typical plasma treatments with oxygen, ammonia, or air can generate carboxyl groups or amine groups on the surface.\(^{15–18}\) A variety of extracellular matrix protein components such as gelatin, collagen, laminin, and fibronectin could be immobilized onto the plasma treated surface to enhance cellular adhesion and proliferation.\(^{19–22}\) Electrospun nanofibers composed of poly(glycolic acid) (PGA), poly(l-lactic acid) (PLLA), or poly(lactic-co-glycolic acid) (PLGA) were modified with carboxylic acid groups through plasma glow discharge with oxygen and gas-phased acrylic acid.\(^{23}\) Such hydrophilized nanofibers were shown to enhance fibroblast adhesion and proliferation without compromising physical and mechanical bulk properties. Air or argon plasma treatment has been widely used as a facile surface modification technique for many biomaterials, since its surface hydrophilicity can be easily increased with concomitant elimination of surface contaminants. For example, various electrospun nanofibers made of poly(ε-caprolactone) (PCL), PCL/ hydroxyapatite, polystyrene, and silk fibroin were surface-modified by air or argon plasma, resulting in an improved cell adhesion and proliferation.\(^{15,24–26}\) When PCL nanofibers were modified with argon plasma, enriched carboxylic acid groups could be produced on the surface.\(^{23}\) When the surface activated nanofibers were soaked in a simulated body fluid solution, the bone-like calcium phosphate mineralization occurred on the surface.\(^{27}\) When the surface activated nanofibers were soaked in a simulated body fluid solution, the bone-like calcium phosphate mineralization occurred on the surface. This mineralized nanofibrous scaffold exhibited improved wettability with a biomimicking bone structure, indicative of potential application for bone grafting.
**Wet chemical method**

Partial surface hydrolysis of biodegradable aliphatic polyester films and scaffolds under acidic or basic condition has been widely used to modify the surface wettability property or to create new functionalities [28–30]. This is based on the random chemical scission of ester linkages on the polymer backbones located on the very surface, resulting in the surface generation of carboxylic and hydroxyl groups from degraded, yet water insoluble polymer fragments. Since the plasma treatment for nanofibrous mesh cannot effectively modify the surface of buried nanofibers deeply located in the mesh due to the limited penetration depth of plasma in the nanopores, wet chemical etching methods can offer the flexibility for surface modification of thick nanofibrous meshes [31]. When biodegradable polymeric nanofibrous meshes are surface-modified using the partial hydrolysis method, a special care must be taken. The duration of the hydrolysis and the concentration of hydrolyzing agents are important to optimally produce surface functional groups only with minimally changing the bulk property [31]. NaOH-treated PLLA nanofibrous mesh was also used for hydroxyapatite mineralization [34]. Since carboxylic acids can chelate calcium ions, surface-induced nucleation and growth of minerals were shown to be enhanced on the surface-modified PLLA electrospun scaffold. PCL electrospun nanofibers were also used to modify the surface of thin PCL membrane for generating nano-topographical surface [33]. When the modified membrane was treated with 5 M NaOH, wettability was dramatically enhanced, showing almost zero water contact angle due to the capillary action on the highly rough surface. When NIH 3T3 cells were cultured on the surface of the modified nano-topographical membrane, favorable cell morphology and adhesion was observed on the modified surface, possibly due to the unique hydrophilic surface topography. A surface aminolysis method using diamine species as an alternative hydrolyzing agent for polyester nanofibers was also employed to ensure positive surface charge as well as to create amine functionalized surface [31,34].

**Surface graft polymerization**

Virtually all types of synthetic biodegradable polymers retain their hydrophobic surface nature, often requiring hydrophilic surface modification for desired cellular responses. Surface graft polymerization has been introduced not only to confer surface hydrophilicity, but also to introduce multi-functional groups on the surface for covalent immobilization of bioactive molecules for the purpose of enhanced cell adhesion, proliferation, and differentiation [37–40]. The surface graft polymerization is often initiated with plasma and UV radiation treatment to generate free radicals for the polymerization. Electrospun polyethylene terephthalate (PET) nanofibers were modified with poly (methacrylic acid) by graft polymerization in a mild condition without any structural damage in the bulk phase [41]. The PET nanofibers were pretreated with formaldehyde to generate hydroxyl groups on the surface. The subsequent oxidization of surface hydroxyl groups by Ce (IV) produced free radicals, thereby initiating the polymerization of methacrylic acid monomers from the surface. The carboxylic acid moieties on the surface were then conjugated to immobilize gelatin on the nanofibers. The surface density of carboxylic acid was shown to increase with reaction time and the monomer concentration. For antibacterial applications, electrospun polyurethane (PU) nanofibers were modified with poly(4-vinyl-N-hexyl pyridinium bromide) on the surface [42]. In this study, the PU fibers were first treated with argon plasma, which produced surface oxide and peroxide groups. When the plasma treated PU fibers were immersed in a 4-vinylpyridine monomer solution with exposure of UV irradiation, poly(4-vinylpyridine) grafted PU fibers were successfully produced. Through quaternization of the grafted pyridine groups with hexylbromide, the surface-modified PU fibers were endowed with antibacterial activities. The viability of
Grampositive Staphylococcus aureus (S. aureus) and Gram-negative Escherichia coli (E. coli) after contact with the PU fibers was measured. The antibacterial efficacy of the modified PU fibers for S. aureus and E. coli were 99.999% and 99.9%, respectively after 4 h contact, indicating highly effective antibacterial activities.

Co-electrospinning of surface active agents and polymers

While the aforementioned surface modification methods are intended to be used for prefabricated electrospun nanofibers, nanoparticles and functional polymer segments can be directly exposed on the surface of nanofibers by co-electrospinning with bulk polymers [43–45]. For example, when PLLA solution blended with hydroxyapatite (HAp) nanocrystals was co-electrospun, HAp was exposed on the surface of the resultant fibers, giving rise to high surface free energy and low water contact angle [46]. These composite fibers exhibited a retarded degradation rate as compared to pure PLLA fibers due to the internal ionic bonding between ester groups in PLLA and calcium ions in HAp. In addition, a novel in-situ peptide bio-functionalization method driven by an electric field was developed [47]. Firstly, an antimicrobial peptide, with three repeating units of three anionic amino acids, serine, glutamic acid, and another glutamic acid (SEE)3, was terminally conjugated to polyethylene oxide (PEO). The addition of (SEE)3-PEO conjugate to PEO solution decreased viscosity, but increased solution conductivity. During co-electrospinning of the PEO/(SEE)3-PEO blend solution, electrically polarizable SEE segment had significant influence on fiber morphology. When the collector was connected as an anode, thick and inter-welded fiber morphology could be observed due to the high flow rate of the blend solution under an electric field. Electric field driven surface orientation of the SEE segment was also confirmed. It was expected that other combinations of electrospinnable polymer and polarizable polymer conjugate could be possible for in-situ fabrication of surface bio-functionalized nanofibers.

Fig. 4. Surface modification techniques of electrospun nanofibers. (A) Plasma treatment or wet chemical method. (B) Surface graft polymerization. (C) Co-electrospinning.

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PROPERTIES

Physical characteristics
The simplest comparison between electrospun nanofibers, meltblown fibers and spunbonded fibers is fiber size. The difference in fiber size leads to vast differences in basic web properties such as fiber surface area, basis weights, thicknesses, permeability, and strength. Electrospun nanofibers have diameters that are 1 to 2 orders of magnitude smaller than meltblown fibers. This leads to a corresponding increase in fiber surface area and decrease in basis weight.[48]

Mechanical property
Electrospun fibers have nanostructured surface morphologies with tiny pores that influence mechanical properties like tensile strength, Young’s modulus, etc. Gibson et al. have found that there is no significant change in the Young’s modulus of electrospun Pellethane thermoplastic elastomers. When compared with cast films, electrospun elastomers have shown 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 by Buchko et al. 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-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.[5]

Thermal property
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 (Tg), and melting temperature (Tm) than semicrystalline PLLA resins. Zong et al. attributed the decrease in the Tg 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 Tg and the peak crystallization temperature (Tc) of the electrospun polyethylene terephthalate (PET) and polyethylene naphthalate (PEN) decreased significantly, while the heat of crystalline melting increased. The decrease in Tg 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]

Filteration property
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 webs have been applied onto various substrates. Substrates are selected to provide appropriate mechanical properties and 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.

Figure 5 is a photomicrograph showing a cross-section of nanofibers electrospun onto a polyester spunbond substrate. The substrate is chosen to provide mechanical properties, while the nanofiber web dominates filtration performance.
Controlling parameters of electrospinning allows the generation of nanofiber webs with different filtration characteristics. Different fiber sizes can be made, some as small as 40 nanometers. Fibers can be put on one side or on both sides of a substrate. Additionally, Figure 5 shows a comparison between a light layer of nanofibers and a heavier layer of nanofibers. Nanofibers have been electrospun onto a variety of substrates, including glass, polyester, nylon, and cellulose filter media substrates.

The improvement in dirt holding capacity of the nanofibers is due to the small fiber diameter and correspondingly increased surface area of the fibers. These filtration benefits should similarly translate to wipes applications.[48]

APPLICATIONS
Nanofibers have potential medical applications, which include, drug and gene delivery, artificial blood vessels, artificial organs, and medical facemasks. For example, carbon fiber hollow nano tubes, smaller than blood cells, have potential to carry drugs in to blood cells.

Nanofibers are capable of delivering medicines directly to internal tissues. This nanofiber can be used as varieties of medical applications such as bandages or sutures that ultimately dissolve in to body. This nano fiber minimizes infection rate, blood lose and is also absorbed by the body.

Employing electrospun nanofibers as drug delivery vehicles has been based on their unique functionality and inherent nanoscale morphological
characteristics. In addition, due to the flexibility of its material processing option, a variety of structural architectures containing drug molecules could be fabricated from monolithic nanofibers to various multiple composition systems. These important benefits allow finely tuned drug eluting profiles that rely on controlling drug traveling length or modulating the affinity between matrix materials and drugs. Drug release mechanism is associated with polymer degradation and complicated diffusion pathway along nano-void spaces within nanofibermesh. It has been shown that drug release profiles can be tailored by various formulation conditions such as polymer property, combination of different polymers, surface coating, and the state of drug molecules in a solid phase. Hollow nanofibrous tubes by coaxial electrospinning also provided a promising structure for the encapsulation of target drug molecules. This approach succeeded in achieving high drug loading and facilitation of the solubilization of some insoluble and intractable drugs.

A rich variety of therapeutic agents such as antibiotics, anti-cancer drugs, polysaccharides, proteins, and growth factors have been physically or chemically formulated within the bulk phase of electrospun nanofibers or on their surface for accomplishing controlled topical release within the defined period of time. Such medicated nanofibers could be applied to various purposes including tissue engineering scaffolds, wound healing materials, and abdominal anti-adhesions after surgical procedure. While previous approaches mainly focused on the encapsulation or embedding of drugs within the nanofiber bulk phase, recently introduced surfacemodified designs for drug loading open up the new possibility of constructing more sophisticated drug delivery platforms.

**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 adheresiveness toward biological surfaces allows nanofibers to be an ideal candidate for topical drug delivery devices.

**Vitamins**

Electrospun CA 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 or a-tocopherol and all-trans retinoic acid or vitamin A acid (Retin-A), a vitamin A or retinol derivative, were selected as the model vitamins, due to their benefits in cosmetics. Retin-A, a naturally occurring derivative of vitamin A, is a lipid-soluble substance, known to be used for the treatment of acute promyelocytic leukemia, acne, and other skin disorders, and it is believed to help slow skin aging, remove wrinkles, or reduce hyperpigmentation due to photo-aging. Vit-E, also a lipidsoluble vitamin, is known for its potent antioxidant ability, owing to the presence of a hydroxyl group on its chromanol ring which can readily donate a proton to reduce free radicals (viz. free radicals can cause cell damage that may contribute to the development of cardiovascular disease and cancer).

**Protein delivery**

Chew et al. encapsulate human nerve growth factor (hNGF) along with BSA as a carrier protein into nanofibers composed of a copolymer of poly(ε-caprolactone (PCL) and poly(ethyl ethylene phosphate) (PCLEEP). The protein was uniformly dispersed in the polymer solution as aggregates. The induction of PC12 cells into the neuronal lineage by the released hNGF indicates a partial retention of the bioactivity of the growth factor in the electrospinning process. A sustained release of hNGF through three months is demonstrated, albeit of reduced bioactivity towards the end of release. The same group demonstrates the delivery of human glial cell-derived neurotrophic factor (GDNF) from a similar polymeric nanofibrous platform for peripheral nerve regeneration in a sciatic model in rats. The nanofibers are aligned in the lumen of the nerve conduit to purportedly provide topographical guidance to the regenerating
neurons. Highest functional and morphological recovery is observed in the group treated with longitudinally aligned fibers eluting GDNF, sustained over a period of 2 months [65]. Casper et al. incorporate low molecular weight heparin (LMWH) or its conjugated form with PEG in fibers spun from 10 wt.% poly(ethylene oxide) (PEO) or 45 wt.% poly(lactide-co-glycolide) (PLGA) [66]. Heparin is included to take advantage of its high affinity with a host of growth factors such as fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), heparin-binding epidermal growth factor (HBE GF), and transforming growth factor-β (TGF-β). PEG improves the retention of heparin within the fibers to achieve a sustained release over 14 days.

Li and coworkers fabricate nanofibers from an aqueous solution of silk protein, BMP-2 and nanoparticles of hydroxyapatite. They observe a pro-osteogenic effect on hMSCs seeded onto the fibrous scaffold. The combined presence of BMP-2 and hydroxyapatite lead to maximum in vitro bone formation as confirmed by enhanced mineralization and BMP-2 transcript expression [67]. Liao et al. demonstrate the incorporation of PEG into the shell of PCL nanofibers to regulate the release of the encapsulated proteins in the core [68]: A near zero-order release of 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. The released PDGF-bb maintained its bioactivity throughout the release period, at least partially, as demonstrated by a proliferation assay on NIH 3T3 cells.

**Nucleic acid**

Luu et al. describe the encapsulation of plasmid DNA in a PLA–PEG block copolymer nanofibrous matrix for tissue engineering purposes [69]. Approximately 80% of the β-galactosidase reporter gene is released in 20 days. Transfection experiments performed on the osteoblastic cell 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 transfecting reagent. For improving stability of DNA during the electrospinning process Liang et al. have incorporated solvent-induced compacted DNA in PLA–PEG–PLA triblock copolymer [70]. The non-woven nanofiber mats produce a significant improvement on transfection efficiency when the cells are directly seeded onto the scaffold. In a similar effort, Nie et al. design a composite nanofibrous scaffold with DNA (BMP-2 plasmid DNA)/chitosan nanoparticles dispersed in PLGA/hydroxylapatite (HAp) matrix for bone tissue engineering.

**Delivery of chemotherapeutic agents**

Nanofibers have been used sparingly as an anti-neoplastic drug delivery device. 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 (a type of brain tumor). 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 implanting a nanofiber delivery system over a wafer-based system. In one study 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU, an anti-neoplastic agent extensively used to treat malignant glioma) is encapsulated by Xu et al. in PEG–PLLA diblock copolymer fibers [71]. The BCNU released from the fibers retains its efficacy for prolonged periods as compared with pristine BCNU. This is reflected in the decreasing viability of rat glioma C6 cells over prolonged periods in an in vitro viability assay. Proposing an alternative drug delivery device for post-surgery glioma management, Xie et al. have also used the platform of PLGA nanofibers to deliver paclitaxel, an anti-neoplastic drug [72]. A sustained release of paclitaxel over 2 months is demonstrated. This represents a distinct advantage when compared to the release
of BCNU from wafers which lasts only a period of days. In another strategy, doxorubicin hydrochloride (Dox), a hydrophilic anti-neoplastic agent is electrospun as an aqueous emulsion in a solution of PEG–PLLA copolymer.[73] This method affords uniform distribution of the drug within the fiber and a diminished burst release.

LIMITATIONS
The process of making nanofibers is quite expensive compared to conventional fibers due to low production rate and high cost of technology. In addition the vapors emitting from electrospinning solution during the process need to be recovered or disposed of in an environmental friendly manner. This involves additional equipment and cost. The fineness of fiber and evaporated vapor also raises much concern over possible health hazard due to inhalation of fibers. Thus the challenges faced can be summarized as:

- Economics
- Health hazards
- Solvent vapor
- Packaging shipping handling

CONCLUSION
Nanofibres as drug delivery system is becoming the hot issue in medical field. Electrospin nanofibers show great promise for developing many types of novel drug delivery systems (DDS) due to their special characteristics and the simple but useful and effective top-down fabricating process. In order to obtain high functionalities of electrospun nanofibers, the surface of electrospun nanofibers was modified in various ways. Surfaces of nanofibrous meshes can be modified by plasma treatment, wet chemical method, surface graft polymerization, and co-electrospinning. Though nanofibers have some limitations, they are expected to have high potentials for drug and gene delivery and tissue engineering applications.

REFERENCES
1. Malik DK, Baboota S, Ahuja A, Hasan S, Ali J. Recent advances in protein and peptide drug delivery systems. Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, Hamdard Nagar, New Delhi 110 062, India.
2. Raghavendra R Hegde, Atul Dahiya, M. G. Kamath . "NANOFIBER NONWOVENS Updated: June 13, 2005
4. Deng-Guang Yu1, Li-Min Zhu1*, Kenneth White2, Chris Branford-White2. Electrospun nanofiber-based drug delivery systems. Received 15 May 2009; revised 8 June 2009; accepted 11 June 2009.
6. Young-Seak Lee and Ji Sun Im, Chungnam Preparation of Functionalized Nanofibers and Their Applications. National University, Republic of Korea
11. Ladizesky N.H., Ward M., A review of plasma treatment and the clinical application of polyethylene fibers to reinforcement of acrylic
17. Ma Z.W., He W., Yong T., Ramakrishna S., Grafting of gelatin on electrospun poly (caprolactone) nanofibers to improve endothelial cell spreading and proliferation and to control cell orientation, Tissue Eng. 11 (2005) 1149–1158.
18. He W., Ma Z.W., Yong T., Teo W.E., Ramakrishna S., Fabrication of collagen-coated biodegradable polymer nanofiber mesh and its potential for endothelial cells growth, Biomaterials 26 (2005) 7606–7615.


41. Ma Z.W., Kotaki M., Yong T., He W., Ramakrishna S., Surface engineering of electrospun polyethylene terephthalate (PET) nanofibers towards development of a new material for blood vessel engineering, Biomaterials 26 (2005) 2527–2536.


44. He W., Yong T., Teo W.E., Ma Z.W., Ramakrishna S., Fabrication and endothelialization of collagen-blended biodegradable polymer nanofibers: potential vascular graft for blood vessel tissue engineering, Tissue Eng. 11 (2005) 1574–1588.


69. Luu Y.K., Kim K., Hsiao B.S., Chu B., Hadjiargyrou M., Development of a nanostructured DNA


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