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NANOFIBERS IN DRUG DELIVERY: AN OVERVIEW

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ABSTRACT

Nanofibers are solid fibers with several remarkable nanoscale features, like very large ratio of surface area to mass, porous structure, and a theoretically unlimited length, together with a better mechanical performance and flexibility than any other form of the same material. Compared with other fabrication techniques, such as drawing, template synthesis and phase separation, electrospinning is a simple, elegant, reproducible, continuous and scalable technology with the ability to produce nanofibers from a wide variety of polymers. More recently, nanofibers of protein have been demonstrated to have promising use in tissue engineering. The unique properties of electrospun mats – high specific surface area and small pores are very favorable for the adsorption of liquids and for preventing bacteria penetration and thus provide good conditions for wound healing. 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. Nanofiber drug delivery systems may provide insight into the direct incorporation of bioactive growth factors into scaffolds. Additionally, drug delivery systems can be combined with implantable tissue engineering scaffolds to prevent infection while repair and regeneration occur. The future should see a move towards more *in vivo* testing, since the majority of work is currently done *in vitro*, in

order to evaluate the performance of nanofibers in a biological environment. Consequently, more studies are needed to fully explore the potential of nanofibers for clinical applications.

KEYWORDS: Nanofiber, Drug delivery, Electrospinning, Polymer.

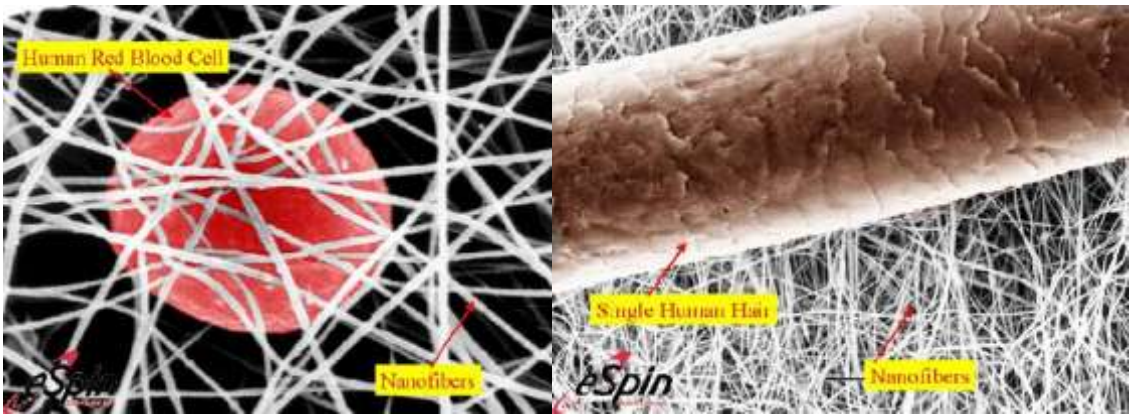
INTRODUCTION[1-5]

In the past decade, nanomedicine has experienced an unprecedented rate of advancement, with nanofibers being particularly active field, due to their enormous potential in biomedicine. A bibliometric analysis of scientific publications in the "Web of Science" database clearly shows the tremendous interest in polymeric nanofibers, with the number of publications rising from just 100 articles in 2000 to more than 2300 in 2011, with drug delivery being the largest research field[1]. Moreover, it is estimated that the global market for nanofiber products will be worth $176 million in 2012. This market is forecast to grow at a compound annual rate of 34 %, and this despite the fact that there are just 50 companies in the world producing nanofibers.

Nanofibers are solid fibers with several remarkable nanoscale features, among them is a very large ratio of surface area to mass, a porous structure, and a theoretically unlimited length, together with a better mechanical performance and flexibility than any other form of the same material. They are a unique class of materials in the biomedical field since they provide a biomimetic environment on the nanometer scale, a three-dimensional architecture with the desired surface properties on the micrometer scale, combined with mechanical strength and physiological acceptability on the macro scale.

Nanofibers are defined as fibers with diameters less than 50-500 nanometers. National Science Foundation (NSF) defines nanofibers as having at least one dimension of 100 nanometer (nm) or less. Recently nanofibers are used in the healthcare systems, as a tool for drug delivery system in various diseases. The use of nanofibers proves the importance and convenience of them as drug carriers. There smaller size plays an important role in delivering the drug to the appropriate site in the body1. 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

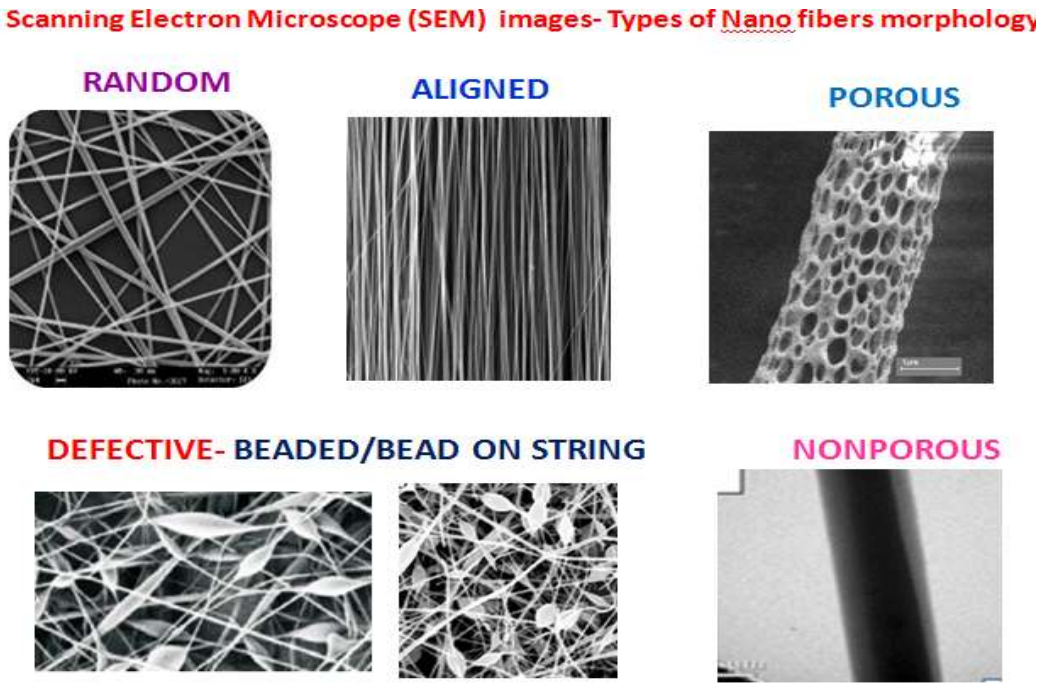
degradation. Additionally, due to the flexibility in material selection a number of drugs can be delivered including: antibiotics, anticancer drugs, proteins, and DNA. Using the various electro spinning techniques a number of different drug loading methods can also be utilized: coatings, embedded drug, and encapsulated drug.



Comparison of Human hair and Red Blood Cell with Nanofibers

Characteristics of nanofibers

- Small size (fibre diameter), Low density and High surface area to mass ratio, Unlimited length?
- High pore volume /porosity and High axial strength combined with extreme flexibility.
- Provide a biomimetic environment on the nanometer scale, Three-dimensional architecture.
- Mechanical strength and physiological acceptability.



TECHNIQUES OF SYNTHESIS OF NANOFIBERS[6-11]

Of the various processing methods available, nanofibers are most often prepared by electrospinning. Compared with other fabrication techniques, such as drawing, template synthesis and phase separation, electrospinning is a simple, elegant, reproducible, continuous and scalable technology with the ability to produce nanofibers from a wide variety of polymers. Three distinct techniques have proven successful in routinely creating nanofibrous tissue structures: self assembly, phase separation, and electrospinning. Electrospinning as a polymer-processing technology has been known for more than 70 years, is the most simple and efficient.

Electrospinning

Generally, polymeric nano fibres are produced by electrospinning, which spins fibers of diameters ranging from 10 nm to several hundred nanometers. This method has been known since 1934, when the first patent on electrospinning was filed. Electrospinning can be carried out from polymer melt or solution. A majority of the published work on electrospinning has been focused on solution-based electro- spinning rather than on melt electrospin- ning due to higher capital investment requirements and the difficulty in producing submicron by melt electrospinning. In electrospinning a high voltage is used to create an electrically charged jet of polymer solution or melt out of the pipette. Before reaching the collecting screen, the solution jet evaporates or solidifies, and is collected as an interconnected web of small fibers. One electrode is placed into the spinning solution/melt and the other attached to the collector. Another interesting aspect of using nanofibers is that it is feasible to modify not only their morphology and their (internal bulk) content but also the surface structure to carry various functionalities.

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 nanoscaled supramolecular structures, sometimes nanofibers. Compared with electrospinning, self-assembly can produce much thinner nanofibers only several nanometers in diameter, but requires much more complicated proce-

dures and extremely elaborate techniques. The low productivity of the self-assembly method is another limitation.

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 nonsolvent 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 spongelike 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.

Nanofiber manufacturing methods – merits and demerits

Process	Lab/ Industrial application	Ease of processing	Advantages	Limitations
Self assembly	Lab	Difficult	Achieves fiber diameter on lowest ECM Scale (5-8 nm).	Only short fibers can be created. Low yield. Matrix directly fabricated. Limited to a few polymers.
Phase separation	Lab	Easy	Tailorable mechanical properties, pore size and interconnectivity. Batch to batch consistency.	Low yield. Matrix directly fabricated. Limited to a few polymers.
Electro spinning	Lab/industrial	Easy	Cost effective. Long continuous nanofiber. Production of aligned nanofiber. Tailorable mechanical properties.	Large nanometer to micron scale fiber. Use of organic solvents. No control over 3D pore structure.

PARAMETERS AFFECTING NANOFIBER MORPHOLOGY[12-14]

The success of the electrospinning process and the morphology of the obtained nanofibers depend on many different, but interrelated, parameter. The parameters affecting the morphology of the obtained nanofibers can be divided into the solution, process and environmental conditions. In terms of the solution parameters, the solution viscosity, surface tension and conductivity are the most determining, while among the process parameters the most decisive are the applied voltage, the feed rate and the distance to the collector.[4,7,8] Although it is well known that the previously mentioned groups of parameters have a predominant influence on the nanofibers formation and morphology, the effect of environmental conditions (temperature and humidity) is not negligible.

Solution parameter	**Effect on nanofiber morphology**
Concentration	Increase in concentration leads to increase in fiber diameter.
Viscosity	Increasing viscosity leads to thicker and beadless nanofibers. Too high viscosity causes generation of beads.
Surface tension	No conclusive correlation has been established between the surface tension and the nanofiber morphology.
Conductivity	Increase in conductivity leads to thinner nanofibers.
Molecular weight of polymer	Increase in polymer molecular weight leads to formation of a nanofiber with fewer beads.
Volatility of solvent	Higher volatility requires higher flow rate and leads to formation of a nanofiber with fewer beads.
Dielectric constant	Sufficient dielectric constant of the solvent is needed for successful electrospinning.
Process parameter	**Effect on nanofiber morphology**
Flow rate	Lower flow rate results in thinner nanofibers. Too high flow rate causes the generation of beads.
Applied voltage	Thinner fiber with higher applied voltage.
Needle tip to collector distance	Minimum distance required to obtain dry nanofibers. Generation of beads when the distance is too small or too large.
Geometry of collector	Metal collectors are preferred. With conductive frame or rotating drum aligned nanofibers are obtained.
Ambient parameter	**Effect on nanofiber morphology**
Humidity	Lower humidity enables higher flow rate and the generation of beads is reduced.
Temperature	A thinner nanofibers are obtained when the temperature is higher.

Polymer Selection in Electrospinning

The selection of a material plays a pivotal role in the design of nanofibers for biomedical applications. The ideal biomaterial should be biocompatible, biodegradable, nontoxic, hydrophilic and with the proper mechanical strength. In theory, the choice of the polymer for electrospinning is not limited, providing the polymer allows the preparation of a solution or a

melt with the proper characteristics. Up to now many different polymers have been electrospun into nanofibers and can be broadly classified as either synthetically or naturally derived. Among the synthetic ones the most commonly used are 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.

Synthetic materials are strong, cheap, reliable, often easily electrospinnable and exert physico- chemical characteristics that can be controlled through the production process. However, they lack cell-recognition sites, causing poor affinity for cell attachment.

On the other hand, natural polymers are preferred due to their similarity with the macro-molecular substances present in the human body. Therefore, the biological environment recognizes and favorably interacts with the natural polymers. The preparation of nanofibers from natural polymers is challenging due to their polyelectrolyte nature and their high viscosity at low concentrations. Thus, natural polymers are often blended with synthetic polymers, which represent a spinnable carrier and enable the formation of nanofibers[12]. Importantly, the nanofibers prepared from polymer blends retain the biological functionability of the natural polymer as well as the mechanical strength and durability of the synthetic component[32]. Using this approach we have successfully prepared nanofibers from chitosan and alginate with the addition of PEO or PVA. However, the research was mainly focused on chitosan, due to its outstanding properties, such as biocompatibility, biodegradability, safety, hydrophilicity, the ability to suppress an inflammation response during healing and antimicrobial activity, and its enormous potential as an effective biomaterial for drug-delivery applications, wound dressings and tissue substitutes. Our results have shown that the morphology of nanofibers obtained from chitosan/PEO solutions depends strongly on the solution composition, since significant changes in the product morphology were observed, when the amount of chitosan in the polymer blend was decreased. Recent results have also indicated that the role of humidity in the electrospinning process was underestimated in previous studies, since the success of the process can be significantly improved only by lowering the humidity.

Solvent selection in Electrospinning

The selection of an optimal solvent for each polymer or polymer blend is fundamental to the success of the electrospinning. Solvent selection is pivotal in determining the critical minimum solution concentration to allow the electrospinning as well as contributing to the solution surface tension and conductivity, thereby affecting the solution's spinnability and the morphology of the electrospun nanofibres. Frequently used solvents for nanofiber preparation are tetrahydrofuran, dimethylforma- mide, chloroform, acetic acid, acetone, ethanol, 2,2,2-trifluoroethanol and distilled water. Distilled water is a favorable solvent when nanofibers are intended for biomedical applications, since solvent residues in the formulated nanofibers do not lead to any safety concerns. Polymers are often not completely soluble in water; therefore, the addition of co-solvents in a relatively small proportion is necessary. For example, chitosan/PEO nanofibers can be successfully prepared from acidic aqueous solu- tions containing 2 % acetic acid. Moreover, a mixture of solvents is not only used for the needs of solubility, but also to accelerate the solvent's evaporation in the electrospinning process. The addition of a volatile, usually organic, solvent increases the solvent evaporation rate and, therefore, decreases the necessary needle-to-collector distance in electro- spinning. Solvent volatility also affects the fiber porosity, being higher when the solvent evaporates quickly. Our results showed that the addition of an organic solvent is only beneficial in the case when the polymer is completely soluble in the solvent mixture.

SOME OF THE POLYMERS AND SOLVENTS USED IN ELECTROSPINNING

POLYMER	SOLVENTS
Nylon 6 and nylon 66	Formic Acid
Polyacrylonitrile	Dimethyl formaldehyde
Polyethylene Terephthalate	Trifluoroacetic acid/Dimethyl chloride
Polyvinyl Alcohol	Water
Polystyrene	DMF/Toluene
Nylon-6-co-polyamide	Formic acid
Polybenzimidazole	Dimethyl acetamide
Polyramide	Sulfuric acid
Polyimides	Phenol

The addition of surfactants and salts to the polymer solutions is another well-established practice to achieve spinnability of natural and semi-synthetic polymers, improve the reproducibility of the electrospinning process or transform the product morphology from beads to fibers. For this purpose various salts and surfactants can be ap- plied. In one of our

studies the effects of Tween 80 and NaCl on the electrospinning of a hydroxylethyl cellulose solution were examined. Both supplements were chosen due to their safety and widespread use in several pharmaceutical and cosmetic products. The addition of Tween 80 lowered the surface tension of the solution, which resulted in the elongation of the beads into fibers, an increase in the fiber diameter and an improved process efficacy. The addition of the salt significantly increased the conductivity of the polymer solution, resulting in a reduced bead formation and a larger fiber diameter. It was shown that the addition of a surfactant improved the nanofiber morphology to a much greater extent than the addition of salt.

Polymers, drugs, and solvent types for application in drug delivery

Polymer	Solvent	Drug(s)
		Naproxen, indomethacin, ibuprofen, sulindac
Cellulose acetate	2:1 acetone/DMAc	Curcumin
		Vitamin A and E
PCL	7:3 DCM/methanol	Heparin
	3:1 chloroform/ethanol	Resveratrol, gentamycin
PEO/PCL blend	Chloroform	Lysozyme
PVA	Deionised water	Ketoprofen
		Sodium salicylate, diclofenac, naproxen, indomethacin
Gelatin/PVA blend	Gelatin in formic acid, PVA in deionised water	Raspberry ketone
PLGA	DCM/DMF	Paclitaxel
	DMF	Cefoxitin sodium
Polyurethane	DMF	Itraconazole
	DMAc	Ketanserin
PLLA	2:1 chloroform/acetone	Doxorubicin HCl
		Tetracycline HCl
	Chloroform	Cytochrome C
PEVA	Chloroform	Tetracycline HCl

CHARACTERIZATION OF NANOFIBERS[15-16]

Properties

- Chemical composition.
- Mechanical properties.
- Thermal behavior.
- Hydrophilicity/hydrophobicity.
- Morphology - (fiber diameter, thickness, porosity) important especially in biomedical field.

Imaging methods

- Optical (light) microscopy in the visible range.
- Scanning electron microscopy (SEM) – Most common method.
- Transmission electron microscopy (TEM).
- Atomic force microscopy (AFM).
- Mercury Porosimetry - for measurement of porosity and pore size.
- Capillary flow porometer- for measurement of porosity and pore size.

Geometrical characterization

- Properties: fiber diameter,diameter distribution, fiber orientation and fiber morphology (e.g. cross-section shape and surfaceroughness).
- SEM), Field emission scanning electron microscopy (FESEM), TEM, and AFM.

Chemical Characterization

- Molecular structural characterization of a nanofiber – by techniques like.
- Fourier tranform infra red (FTIR) spectroscopy.
- Nuclear magnetic resonance (NMR).
- Wideangle X-ray diffraction (WAXD).
- Small angle X-ray scattering (SAXC).
- Differential scanning calorimeter (DSC).

APPLICATION OF NANOFIBERS[17-18]

More recently, nanofibers of protein have been demonstrated to have promising use in tissue engineering. The unique properties of electrospun mats - high specific surface area and small pores are very favorable for the adsorption of liquids and for preventing bacteria penetration and thus provide good conditions for wound healing. The simplicity allows for electrospinning to be the only nanofibrous processing technique that can be taken out of a laboratory setting and be utilized successfully in scale-up and mass production. The following table explains the merits and demerits of different nanofiber manufacturing methods. The use of polymer nanofibers for biomedical and biotechnological applications has some intrinsic advantages. From a biological point of view, a great variety of natural biomaterials are deposited in fibrous forms or structures. polymer nanofibers can provide a proper route to emulate or duplicate biosystems—a biomimetic approach. On the other hand, many researches have shown evidences that apart from surface chemistry, the nanometer scale surface features and topography also have important effect on regulating cell behavior

in terms of cell adhesion, activation, proliferation, alignment and orientation. The bio-medical application of nanofiber include tissue engineering, controlled drug release, dressings for wound healing, medical implants, nanocomposites for dental applications, molecular separation, biosensors and preservation of bioactive agents.

NANOFIBERS FOR CONTROLLED DRUG DELIVERY[19-25]

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. 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 electrospinning). These techniques can be used to give finer control over drug release kinetics.

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.

Active substances can be incorporated inside the nanofibers, physically adsorbed or chemically bound to the surface. However, knowledge of the drug's behavior during its incorporation in the nanofibers and its subsequent release from the nanofibers is much more limited, compared to the knowledge available for drug incorporation and release from, for

example, solid lipid nanoparticles. The loading of many different drugs and their localization in the lipid matrix have been systematically investigated. The results showed that the drug incorporation, localization and release depend on the physicochemical properties of the drug and the carrier matrix. Therefore, it is also expected that for nanofibers the loading mechanism will be governed by the drug solubility in the polymer solution and the drug-polymer interactions in the solid state.

Of the various loading possibilities, physical entrapment is currently the most widespread, since the drug in the nanofibers is protected against unfavorable environmental conditions and it offers good control over the drug's release. A typically observed release profile from such nanofibers exhibits an initial burst effect followed by an almost linear, sustained release. Furthermore, the preparation of core-shell nanofibers provides a drug-reservoir system with a shell barrier protecting the incorporated drug and controlling the drug diffusion rate. The burst effect from such nanofibers is small and the entire release profile is more sustained.

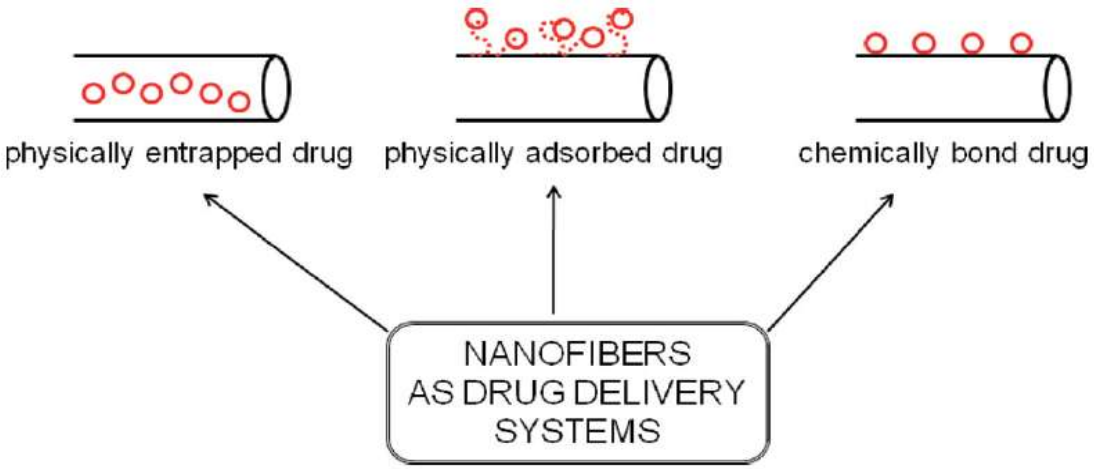
The incorporation of a drug in nanofibers, either in the form of a matrix or as a core-shell system, is relatively easy to perform, since the drug is simply dissolved in the polymer solution prior to electrospinning. The formation of an amorphous drug, which shows a higher solubility with respect to the crystalline form, is favored, due to a very limited time being available for the drug's recrystallization during the electrospinning process. Furthermore, a reasonable question can be raised concerning the preservation of the chemical and biological integrity of the incorporated drug due to the application of a high voltage during the electrospinning. Various studies using H-NMR, DSC, X-ray and IR spectroscopy have proven that the electrospinning process does not affect the structural integrity of the incorporated drug.

The physical adsorption of a drug on the surface of the preformed nanofibers is achieved by dipping the nanofibers into a solution of the drug, which associates with the nanofibrillar surface via electrostatic interactions. However, this technique is seldom used due to poor control over the drug's release and an undesirable competitive displacement of the drug with the components of biological fluids.

The third approach to drug loading is the covalent immobilization of the drug on the nanofibrillar surface via the formation of chemical bonds. The latter is predominately used for the modification of the surface properties of nanofibers, since the technique is technically

complex. However, there are some reports dealing with this approach for the delivery of active substances. The drug is released after the enzymatic or environmental degradation of the chemical bond.

Nanofiber drug delivery systems may provide insight into the direct incorporation of bioactive growth factors into scaffolds. Additionally, drug delivery systems can be combined with implantable tissue engineering scaffolds to prevent infection while repair and regeneration occur. Biodegradable polymers release drug in one of two ways: erosion and diffusion. Release from biodegradable polymers in vivo is governed by a combination of both mechanisms, which depends on the relative rates of erosion and diffusion. Most biodegradable polymers used for drug delivery are degraded by hydrolysis. Hydrolysis is a reaction between water molecules and bonds in the polymer backbone, typically ester bonds, which repeatedly cuts the polymer chain until it is returned to monomers. Other biodegradable polymers are enzymatically degradable, which is also a type of chain scission. As water molecules break chemical bonds along the polymer chain, the physical integrity of the polymer degrades and allows drug to be released.



Nanofibers in Oral Drug Delivery

- Enhance the delivery of drugs with limited absorption due to poor solubility/dissolution, by improving the dissolution rates and solubility of drug molecules.
- Approaches include.
  - Identification of water-soluble salts of parent drugs.
  - Preparation of stable amorphous drug formulations.
  - Inclusion of solubility-enhancing agents , Particle size reduction.

Nanofibers in Topical Drug Delivery

- Drug and gene delivery application for tissue engineering to improve therapeutic efficacy.
- The superior adhesiveness of fibrous structure to biological surfaces -an ideal candidate for topical drug delivery devices.

Nanofibers for Vitamins delivery

- Carriers for delivery of some vitamins to the skin.
- Vitamin –A in 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

Nanofibers in advanced wound care

- An excellent candidate for wound healing, haemostatic devices, and burn treatments., Possibility to add drugs – haemostatic or antimicrobial dressing
- Similarity between nanofibers and the natural extracellular matrix allows it to support new healthy tissue growth in an injured area, which can reduce the formation of scar tissue and decrease the healing time required.
- Nano-pore sizes also help to protect injured tissue from bacteria that could otherwise infect a vulnerable wounded tissue.
- High porosity and surface area encourage fluid absorption which also encourages wound healing.[1]
- Ciprofloxacin and fusidic acid PLGA fibers have been studied

Nanofibers for delivery of chemotherapeutic agents

- Fibers Loaded with anticancer drugs inserted to cover the solid tumor site-
- provides high local dosage with incorporation of small amounts of the drug , reduces the need for frequent administrations, resulting in patient convenience.
- The majority of nanofiber anti-neoplastic agent delivery systems - treatment of malignant gliomas.
- Examples: Doxorubicin HCl and palcitaxel

Nanofibers for Protein delivery

- Platelet derived growth factor-bb (PDGF-bb) can be produced with no associated burst release.

- Aligned PDGF-bb loaded Nanofibers provide biochemical and topographical cues to the seeded cells, in tissue engineering applications

Nanospider Technology for the production of nanofibers

Nanospider is a modified electrospinning method which requires the use of a high-voltage electrostatic field to create an electrically charged stream of polymer solution or melt. Generally, polymer-based drug delivery systems are used to optimize the therapeutic properties of drugs and to render them safer, effective, and reliable . In addition, the use of antimicrobial polymers offers promise for enhancing the efficacy of some existing antimicrobial agents and minimizing the environmental problems accompanying conventional antimicrobial agents by reducing the antibiotic resistance, residual toxicity of the agents, increasing their efficiency and selectivity, and prolonging the lifetime of the antimicrobial agentS. A new way of delivering existing antibiotics involves putting common antibiotics inside nanofibers made of polyvinyl alcohol and polyethylene oxide – wisps of plastic-like material so small that peach hair or a strand of spider silk are gigantic by comparison.

Nanospider is a variant of the electrospinning method, where Taylor cone does not arise from the edge of the syringe, but is pulled out of the level of the solution. On the level of the solution there may occur many of Taylor cones, therefore much higher rate of production of nanofibres is reached (about 100x) compared to the basic method of electrospinning. mpany. Compared to the electrospinning method, Nanospider represents especially acceleration of production, higher process stability, long term production (up to 10hours per batch) and the layer of nanofibers is in uniform, transverse direction. Nanofibers are not applied onto the static collector, but they are produced onto the moving background. It can be called a band production. This technology originated at the beginning of the 21st century at the Technical University, Liberec, Czech republic and is further developed commercially by Elmarco company.

The effects of nanofibers with multiple antibiotics encapsulated directly into fiber, using laboratory cultures of various microbes showed that antibiotics wrapped inside nanofibers were highly effective in killing a variety of disease causing bacteria and fungi, including *Escherichia coli* , *Pseudomonas aeruginosa*, two increasingly drug-resistant microbes and *Aspergillus niger* and *Aspergillus flavus* . Abnormal cell division was observed at high frequencies among cells that tried to divide in the presence of the polymer. This malformation in bacterial and fungal cells may be due to inhibition of cell wall

synthesis, inhibition of protein synthesis, inhibition of nucleic acid synthesis, inhibition of metabolic pathways, and interference with cell membrane integrity. Encapsulating the antibiotic (metronidazole) within the nanofibres will slowly release it and keep its concentration stable within the body over a longer period of time so the bacteria don't have a chance to genetically mutate and become resistant.

ADVANTAGES OF NANOFIBERS IN DRUG DELIVERY[26-28]

- Explored for their ability to encapsulate and deliver bioactive molecules for therapeutic applications
- Increased surface area- Dissolution rate of a drug increases
- Enhanced solubility
- Increased oral bioavailability
- More rapid onset of therapeutic action,
- Less amount of dose required,
- Site-specific delivery of any number of drugs from the scaffold into the body
- Decreased fed/fasted variability,
- Decreased patient-to-patient variability
- Reduced toxicity , which has to be substantiated by further toxicity studies

Limitations

- Economics (processing and production costs)
- Health hazards (processing)- Fibers and Vapors emitting from electrospinning solution
- Solvent hazards
- Packaging/shipping and handling cost
- Minimal Tests and regulations to ensure an adequate characterization and an analytical evaluation
- Limited toxicological and pharmacological assessment

CONCLUSION

Despite the intensive research in the field of nanofibers a number of unanswered questions still remain to act as a driving force for further studies. The largest challenge is a complete understanding of the electrospinning mechanism. In order to control the properties, orientation and mass production of the nanofibers, it is necessary to understand quantitatively

how electrospinning transforms the fluid solution through a millimeter-sized needle into solid fibers having diameters that are four-to-five orders smaller. The next bottleneck in the electro- spinning is the process efficiency and repeatability. Furthermore, the construction of a proper, three-dimensional scaffold remains a technological challenge, while from the point of view of drug delivery the drug loading has to be increased and the initial burst release has to be reduced in many cases. Last but not the least, the future should see a move towards more *in vivo* testing, since the majority of work is currently done *in vitro*, in order to evaluate the performance of nanofibers in a biological environment. Consequently, more animal studies are needed to fully explore the potential of nanofibers for clinical applications. A close cooperation between laboratories and clinics may help to confirm the therapeutic benefit of nanofibers in the near future.

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