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"THE POTENTIAL OF NANOFIBERS": REVIEW ARTICLE

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ABSTRACT

Nanofibers are submicron sized fibers whose diameter is 50 - 500 nm, with the prefix nano- meaning a billionth of a basic unit (ten to the minus ninth). Often the diameter is the thickness of several atoms. Nanofibers are not visible under normal microscopes, as their diameter is smaller than the wave length of light. Such exceptionally small fibers can only be seen and photographed by electron microscopes. To help visualize this, imagine that the ratio of the average size of a nanofiber to a football is comparable to the ratio of the size of that same football to the earth. Nanofibers can be utilized in healthcare materials and in future will be utilized in filtration, the environment, cosmetics, medicine, hygiene, energy, IT, nanocomposites, and composites. The current state of electrospun nanofiber-based DDS is focused on drug-loaded nanofiber preparation from pharmaceutical and biodegradable polymers and different types of DDS. However, there are more opportunities to be exploited from the electrospinning process and the corresponding drug-loaded nanofibers for drug delivery.

KEYWORDS: Nanofibers, Electrospinning, Characterization, Applications.

INTRODUCTION[1][2]

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 body. Some properties of nanofibers which are useful for drug delivery are as follows.

• A large specific surface

• High porousness and small pore size

• Nanofiber diameter: 100 - 500 nm
• Basic weight: 0.05 - 5 g/m^2
• Transparent
• Excellent mechanical properties in relation to their weight.

The principle behind the drug delivery with polymer nanofibers that dissolution rate of a drug particulate get increased with the increase in surface area of both the drug and the corresponding carrier. In controlled drug delivery, polymer nanofibers also have been used to improve the therapeutic efficacy and safety of drugs by delivering them to the site of action at controlled rate.

Polymeric nanofibers have been studied for their ability to encapsulate and deliver bioactive molecules for therapeutic applications.

Three techniques have been successful in routinely creating nanofibrous tissue Structures, these are phase separation, self-assembly and electrospinning.

Nanofiber drug delivery systems may provide insight into the direct incorporation of bioactive growth factors into scaffolds. Drug delivery systems can be combined with implantable tissue engineering scaffolds to prevent infection while repair and regeneration occur.

MECHANISM OF ACTION[3]

Biodegradable polymers release drug in one of two ways: erosion and diffusion.

The release from the in vivo biodegradable polymers 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, having ester bonds, which repeatedly cuts the polymer chain till it is returned to monomers. Other than that, biodegradable polymers are enzymatically degradable, which is also a type of chain scissions. As water molecules break chemical bonds along the polymer chains, the physical integrity of the polymer gradually degrades and allows drug to be released.

THE TECHNIQUES USED FOR PREPARING NANOFIBERS.

Those techniques are Self-assembly, Phase Separation, and Electrospinning,

1) SELF- ASSEMBLY[4,5]

Self-assembly involves the organization of individual components into an ordered and stable structure with preprogrammed non-covalent bonds.

Nanofibers are nanoscaled supramolecular of self-assembly of natural or synthetic. Compared with electrospinning, by using self-assembly can produce much thinner nanofibers which is in several nanometers in diameter, but requires much more difficult procedures and extremely lengthy techniques. Another limitation is the low productivity of the self-assembly method.

2) PHASE SEPARATION[6]

Phase separation is a method frequently used to prepare 3-D tissue engineering scaffolds. Phase separation of an polymer solution can produce a polymer-rich domain and a solvent-rich domain, in which the morphology can be fixed by quenching under low temperature.

Porous polymer scaffolds can be produced by removal of the solvent through freeze-drying or extraction. Changing the temperature or by adding non solvent to the polymer solution can cause phase separation, thus called thermal induced or non-solvent-induced phase separation respectively. Polymer scaffolds usually have a sponge like porous morphology with microscale spherical pores. Phase separation is a simple technique that does not require much specialized equipment in contrast with self-assembly. Batch-to-batch consistency and tailoring of scaffold mechanical properties and architecture is easily achieved by varying polymer/pyrogen concentrations. But this method is limited to being effective with only a select number of polymers and is strictly a laboratory scale technique

3) ELECTROSPINNING PROCESS[7,8]

The process using electrostatic forces to form a fine filament of the polymer solution is called as electro spinning. It is an inexpensive method of nanofiber production by exposing a polymer solution to high voltage electric field, nanofiber can be formed which are 1000 times smaller in diameter than the average human hair (100nm v.100um). Electrical charge builds up on the surface on the solution when a high voltage is applied to metal syringe needle. The charge is attracted to an electrically grounded collector, a piece of aluminum foil as the charge jumps to the electrical ground, a thin jet of polymer solution is pulled from the needle.

After the solution finally leaves the syringe, the solvent evaporates and a very thin stream of polymer is completing a circuit started by the voltage power source. Finally nanofibers are collected and patterned on a grounded plate.

The benefits of electro spinning technology are

a) High Rate Of Nanofiber Can Be Produced.

b) It Is Very Simple To Set Up And Production Costs Is Low.

One of the most important quantities related with electrospinning is the fiber diameter. Since nanofibers are be used in drug delivery systems to improve the control drug delivery of drugs via nanofiber resulted from evaporation or solidification of polymer fluid jets, the fiber diameters of nanofiber will depend only on the jet sizes, the polymer content in the jets and solution viscosity. It has been recognized that during the traveling of a solution jet from the pipette onto the metal collector, primary jet may or may not be split into multiple jets, resulting in different nanofiber diameters. As long as no splitting is involved, one of the most important parameters influencing the fiber diameter is the solution viscosity. An increase in viscosity will result in a larger fiber diameter. But, when a solid polymer is dissolved in a solvent, the solution viscosity is directly proportional to the polymer concentration. Thus the increase in the polymer concentration, resulting nano fiber diameters will be larger. Deitzel et al. pointed out that the fiber diameter is high with increasing polymer concentration according to a power law relationship**.** He further found that the fiber diameter was directly proportional to the cube of the polymer concentration. Another significant parameter which affects the fiber diameter is the applied electrical voltage. In short, an increase in applied voltage ejects more fluid in a jet, resulting in an increase in fiber diameter.

DRUG LOADING[3]

One method to incorporate therapeutic drugs into nanofibers involves solubilizing the drug into the polymer solution to be spun. Using the same method, a loading efficiency of 90% into PDLA nanofibers was reported for the antibiotic drug Mefoxin. Covalent conjugation to polymers is another method to modulate drug release.

It has been found out that the high porosity of nanofibers allows for rapid diffusion of degradation by products. But, the burst release may indicate that the drug being attached only on the surface. The drug and carrier materials can be mixed together for electrospinning of nanofibers, the resulting nanofiber can be formed in four ways.

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

DRUG RELEASE[3]

There are different types of release is relevant in drug delivery systems; This are immediate release, extended release and triggered or delayed release.

Immediate release

1. The drugs are available within a relatively short time.
2. This type of release is required in situations where immediate action is essential.

Extended release

1. The availability of drugs is maintained at a lower concentration and for a prolonged time compared to immediate release systems.
2. The drug is delivered at a (very) slow rate and for a prolonged period of several hours, days or possibly years, thereby usually reducing dosing frequency.

Triggered or delayed release

1) The release of drugs from triggered or delayed release systems is done by an (external) trigger/stimulus or time. The final resulting release can be of the immediate type or slow-release type.
2) The release of the drug from the delivery system might also be triggered by a specific event, or by change in the environment such as a change in temperature, pH, ionic strength, or by an externally controllable trigger-like ultrasound.

CHARACTERIZATION[9]

Molecular structure of a nanofiber can be characterized by nuclear magnetic resonance (NMR) techniques and Fourier transform infrared (FTIR).

If two polymers were blended together for the fabrication of nanofibers, the structure of the two materials can be detected and the inter-molecular interaction can be determined. When

the collagen and PEO blend used for electrospinning of nanofibers, the NMR spectrum showed a new phase structure which is formed by the hydrogen bond formation between protons of the amino and hydroxyl groups in collagen and the ether oxygen of PEO. Supermolecular structure describes the configuration of the macromolecules in a nanofiber, and can be characterized by small angle X-ray scattering (SAXC), Optical birefringence, Differential scanning calorimeter (DSC) and wide angle X-ray diffraction (WAXD)

APPLICATIONS OF NANOFIBERS AS DRUG DELIVERY SYSTEM[10]

Nanofibers protect the drugs in the case of systemic application from decomposition, example:- in the blood circulation. They should be able to allow controlled release of the drug at a release rate which is constant as possible over a longer period of time, depending on the field of application. It permeates Blood Brain Barrier (BBB). They are able concentrate the drug release only on the targeted body. Nanofibers have potential medical applications like drug and gene delivery, artificial organs, medical facemasks and artificial blood vessels. Carbon and hollow nanofibers are smaller than blood cells, have good potential to carry drugs in to blood cells. Nanofibers are able to deliver medicines directly to internal tissues. This nanofiber can be used as medical applications such as bandages or sutures that ultimately dissolve into body. This nanofiber lessens infection rate, blood lost and is adsorbed by the body. Using electrospun nanofibers as drug delivery vehicles has been based on inherent nanoscale morphological characteristics and their unique functionally.

A rich variety of therapeutic agents such as antibiotics, polysaccharides proteins, anticancer drugs and growth factors have been chemically or physically formulated within the bulk phase of electrospun nanofibers and on their surface for accomplishing controlled topical release within the certain period of time. Such medicated Nanofibers could be could be applied like tissue engineering scaffolds

1) TOPICAL DRUG DELIVERY[14]

Electrospun nanofibers for drug and gene delivery application have been used to improve therapeutic efficacy for tissue engineering. It has been observed that the fibrous surface structure shows a strong adhesiveness to mucous layers because of their nanoporous structures which instantly absorb moisture at mucous layers through nano-void volumes. The superior adhesiveness to biological surfaces makes nanofibers to be an ideal candidate for topical drug delivery.

2) VITAMINS[11]

Electrospun nanofibers can be used as carriers for delivery of vitamins to the skin. Vitamins are applied to the skin in the form of topical lotions, creams or ointments.

Vitamin E and vitamin A, were chosen as the model vitamins, because of their benefits in cosmetics. Vitamin –A is naturally occurring and lipid soluble substances, known to be used for the treatment of acne, leukemia and other skin disorders. Vitamin-E is also lipid soluble vitamin which shows potent antioxidant ability, due to the presence of an hydroxyl group on its chromanol ring which can readily donate a proton to reduce free radicals.

3) PROTEIN DELIVERY[11]

Nanofibers are used to control the release of the encapsulated proteins in core. A platelet derived growth factor-bb (PDGF-bb) with zero order release can be produced with no burst release. In addition to it, PDGF-bb aligned loaded nanofibers are fabricated. These aligned drug loaded fibers may both provide biochemical and topographical cues to the seeded cells at same time, provision that should prove beneficial for many tissue engineering applications.

4) NUCLEIC ACID[12]

Luu et al. describe the encapsulation of plasmid DNA in a polylactic acid –Polyethylene glycol(PLA-PEG) block co-polymer nanofibrous matrix for tissue engineering purposes. 80% of the ß-galactocidase receptor gene has been observed to be release in 20 days. Transfection experiments performed on the MC3T3-E1 osteoblastic cells line demonstrate an increase in transfection efficiency of the fiber-encapsulated DNA than naked plasmid added to the medium, but which is lower than that with a commercial transecting reagent. To improve the stability of DNA during the electrospinning processes, Liang et al. have incorporated solvent-induced compacted DNA in Polylactic acid-Polyethylene glycol-Polylactic acid (PLA-PEG-PLA) triblock copolymer.

5) DELIVERY OF CHEMOTHERAPEUTIC AGENTS[13]

Nanofibers have been used to the lesser extent as an anti-neoplastic drug delivery. This is because of 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 visualised for the treatment of malignant gliomas. The current Drug Delivery System of choice is post tumor-resection implantation of a drug-eluting wafer. Thus, all these studies have tried to find the benefits of implantation of a drug-eluting wafer.

Doxorubicin Hcl, a hydrophilic anti-neoplastic agent is electronspun as a aqueous emulsion in a solution of Polyethylene glycol - Poly-L-lactide acid (PEG-PLLA) copolymer. This method gives uniform distribution of the drug inside the fiber and an administered burst release.

Drug already prepared for nanofiber are summarized as below

DRUG	POLYMER	TECHNIQUE
Indomethacin	Eudragit ERS and Eudragit S100 (ES)	Electrospinning
Plasmid DNA	PLA-PEG block co-polymer	Electrospinning
Doxorubicin HCl	PEG-PLLA copolymer	Electrospinning
Heparin	poly (e-caprolactone) fiber	Electrospinning
human ß-nerve growth factor (NGF) in carrier protein bovine serum albumin (BSA)	e-caprolactone and ethyl ethylene phosphate.	Electrospinning
Naproxen (NAP),	PVA Polymer	Electrospinning
Sodium salicylate	PVA Polymer	Electrospinning
Resveratrol and Gentamycin Sulfate,	Polycaprolactone	Electrospinning
Paclitaxel	PLLA fiber mats	Electrospinning
Ketoprofen	poly(vinyl alcohol) fiber mats	Electrospinning

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. 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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