REVIEW ARTICLE

Nanofibers: Pharmaceutical, Biomedical Application, and Current Status

Vinanti R. Supare, Neha R.Binjhade, Kamlesh J. Wadher*, Milind J. Umekar

Department of Pharmaceutics, Smt. KishoritaiBhoyar College of Pharmacy, Kamptee, Nagpur, Maharashtra, India 441002.

Received: 25th August, 2020; Revised: 01th September, 2020; Accepted: 19th September, 2020; Available Online: 25th June, 2021

ABSTRACT

Nanofibers are nanosized solid polymer fibers that show improved properties compared to materials of larger dimensions. They have unique characteristics like small size and stability, making them suitable carriers for drug delivery at specific sites in the body. There are various techniques available for nanofibers preparation, but the most frequently used are self-assembly, phase separation, and electrospinning, and each one has its advantages and disadvantages. Nanofibers have wide pharmaceutical and biomedical applications and other applications such as energy generation and storage, water treatment and environmental remediation, and healthcare, biotechnology, and biomedical engineering due to their unique structural design and physicochemical properties. But there are certain limitations such as high cost, thickness, etc., to overcome such limitations, and there is a need to address formulation issues like controlled porosity, uniform drug loading, cost-effective product, and controlled fiber thickness. In the present review, we have outlined various emerging applications of nanofibers in pharmaceutical and biomedical fields along with the current status and future perspectives.

Keywords: Biomedical applications, Drug delivery, Electrospinning, Nanofibers, Pharmaceutical applications,

International Journal of Drug Delivery Technology (2021); DOI: 10.25258/ijddt.11.2.50

How to cite this article: Supare VR, Binjhade NR, Wadher KJ, Umekar MJ. Nanofibers: Pharmaceutical, Biomedical Application, and Current Status. International Journal of Drug Delivery Technology. 2021;11(2):518-523.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Nanotechnology, which includes nanoparticles, nanofibers, nano micelles, and nanosized particle formulations, greatly contributes to the different areas of pharmaceutical sciences. Nanotechnology plays an important role in identifying novel methods used to produce innovative products, alternatives to present production equipment and formulate a new formulation for improving their performance, which reduces materials and energy consumption and subsequently reduces the harm to the environment.

In nanotechnology, the materials present some unique chemical, physical, and biological properties, which are quite different than bulk material at the level of nanoscale. Considerable changes are occurring in the properties of materials as their dimensions are less than 100 nm. When compared with bulk materials, nanoparticles show higher performance when they are used for the same applications.[1,2]

Nanofibers are small, solid fibrous substances whose diameter ranges from few nanometers to 1000nm.[3] The size of nanofibers plays an important role in the therapeutic effect of any drug delivery system. Because of their small size, the drug-carrying nano vehicles can be incorporated by cells; thus, they allow the transport of drug molecules across the biological membrane. These solid fibers have the property to facilitate the release of bioactive agents, which include proteins, nucleic acid as well as drugs because of their extremely high surface area-to-volume ratio.[4-6] They have unique characteristics like small size, stability which makes them suitable carriers for drug delivery at a specific site in the body.[7]

Nanofiber works on the principle that they create a fiber mesh-like structure, which is biocompatible with the physiological conditions of the human body. This fibrous-like structure can release biochemical to give the therapeutic effect or pharmacological effect of that particular drug incorporated into the nanofiber. This results in easy modification of the drug bioavailability and targeting the specific site in the body.

Due to the fast disintegration of nanofibers, the total drug can be released within minutes.[8] Advantages of nanofiber involve their stability, high drug loading capacity, less toxicity, targeting, and thermolabile drugs can be given quickly.[9,10]chronic, inflammatory skin disease characterized by epidermal hyperplasia, proliferation of blood vessels, and infiltration of leukocytes in dermis and epidermis. Several immunosuppressants such as methotrexate (MXT The main role of nanofiber as a drug delivery system is to deliver the drug in a definite amount & release it in a controlled manner at an appropriate site in the body. Applying solid electric field produces the Nanofibers to a liquid sample, which contains polymer in dissolved form.[11] Nanofibers is a nano-formulation with a wide application in biomedicine like drug delivery and wound-healing tissue-engineering.

There are various techniques available for nanofibers' production of nanofibers, but the most frequently used

**Author for Correspondence: kamleshwadher@gmail.com*

are self-assembly, phase separation, and electrospinning. The electrospinning method is most popular used as it is used for the continuous production of nanofibers on a large scale.[12]

FABRICATION TECHNIQUES

1. Self-assembly

Self-assembly is a promising technology that involves integrating different components into a specified structure from small units. The self-assembly process is mediated by non-covalent bonds such as hydrogen bonds, electrostatic forces & van der Waals forces.[13] Biomaterials are generated by stripping down a complex entity into its component parts (for example, paring a virus particle down to its capsid to form a viral cage.[14]

2. Phase Separation

It is a process in which a single-phase homogeneous polymeric solution phase is separated into two phases i.e., polymer-rich-phase and solvent rich phase, because of the polymer solution present in a thermodynamically unstable phase. This separation results in lowering the system's free energy.[15]

Fibers are prepared by using biodegradable and biocompatible aliphatic polyesters (for example, poly(lactide) (PLA) & poly (glycolide)) and the size of these fibers ranges from 50 to 500 nm, and porosity is 98.5%, which is achieved by thermodynamically induced polymer separation.[16,17]

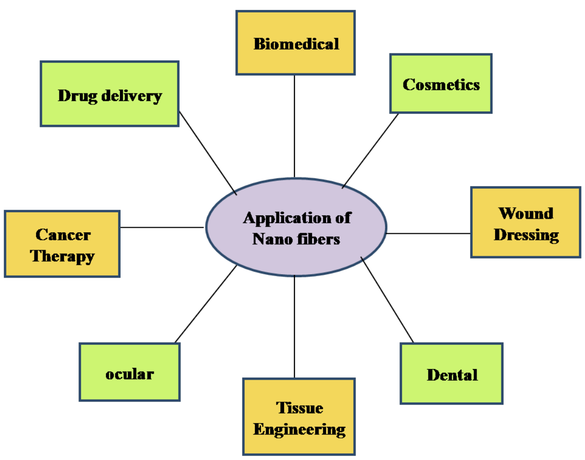

Figure 1: Application of nanofibers

3. Electrospinning Method

Electrospinning is a versatile and non-mechanical process used for the production of nanofibers with diameters ranging from nano to micron size from different types of natural proteins and various synthetic polymers.[18,19] This method produces polymeric nanofibers by exposing the syringe filled with the polymer solution to a high voltage.[20]

There are some limitations of this method, such as organic solvents' requirement to prepare a polymer solution and may not control the fiber size. Electrospun nanofibers show great promise for production of nanofibers due to their special characteristics and simple manufacturing process.[21]

The Comparative data for the three techniques are depicted in Table 1.

APPLICATION OF NANOFIBERS

Nanofibers have a wide range of applications (Figure 1) in Pharmaceutical, Biomedical, drug delivery carriers, Tissue engineering, wound dressing, Medical Prosthetics, etc., apart from other non-Pharma applications as water purification, clean energy applications, engineering, and many more.

Pharmaceutical and Biomedical Applications

Nanofibers are one of the important divisions of biomaterials because of their wide application in the biomedical field.[22] The various properties required for biomedical applications like availability of larger surface area, protein absorption, and binding sites to cell receptors are contributed significantly by the fabrication of nanofibers.[23] Due to the unique properties of nanofibers, such as high material strength, by controlling fibers alignment and orientation, they can facilitate packing of maximum volume, i.e., large amounts of material are packed within a small surface area.[24] For biomedical applications, the different properties of material like porosity, surface morphology, and geometry can be modified for application such as bioactive agents.[25] Nanofibers are functionalized with magnetic nanoparticles could be utilized for their wide applications in tissue regeneration, use in sensors, and drug delivery system.[26,27]

Scaffold for Bone Regeneration

A bone defect that occurs from tumor resection, trauma, or other skeletal abnormalities can be treated with the help of bone regeneration by tissue engineering. For bone repair, there are many

Table 1: Comparative data for the self assembly, phase separation and electrospinning techniques:

Methods	*Self-assembly*	*Phase separation*	*Electrospinning*
Principle	Organization of different components into a specified structure from small units.	single phase homogeneous polymeric solution is separated into two phase i.e. polymer rich- phase and solvent rich phase,	Fabrication of polymeric nanofibers by exposing the syringe filled with polymer solution to a high voltage.
Advantages	-Self assemble process -Can be performed without use of organic solvent	-Simple process -Batch to batch consistency -Control over pore size	-Economical process -Large scale production
Disadvantages	-Low Productivity -Complex Process	-Use of limited no. of polymers -Lab. Scale techniques	-Difficult to control pore size -Required organic solvent to prepare polymer solution
Fiber diameter	5–10 nm	50–500 nm	50 nm–2 μm
Drugs used	Camptothecin, Nucleic acid & Peptides, etc.	Paracetamol, chitosan, etc.	Doxycycline, Carvedilol, Amoxycillin, etc.

types of scaffolds investigated that are used for tissue engineering.[28] Meng *et al.* has prepared a novel nanofibrous scaffold by using the electrospun technique, which has been composed of maghemite super-paramagnetic MNPs, hydroxyapatite, and PLA.[29]

Tissue Engineering

In tissue engineering, the substitution of any human organ or tissue with artificial functional materials externally using a combination of biology, medicine, and engineering.[30] Nanofibers loaded with MNPs is used as scaffolds play an important role in the process of wound healing. Magnetic nanoparticles are helpful in wound healing because nanofiber scaffolds assemble the tissue correctly, which results in tissue formation with the help of magnetic force. By using this method, the magnetic force-based tissue engineering and mechano-transduction methods may control cellular signaling, the development of artificial blood vessels, and bone tissue formation.[31-33] Magnetic nanoparticles loaded nanofibers scaffolds have also been applicable in cell sheet engineering for skin tissue generation by forming multi-layered keratinocytes by magnetic force.[34]

Drug Delivery System

Nanofibers are potentially applicable in drug delivery systems due to their various unique properties such as high drug loading, porous structure, encapsulation efficiency, sizeable therapeutic index, localized delivery, more minor side effects, modulated drug release ability by engineering, and control the processing and solution parameters of synthesis.[35,36] Electrospun nanofibers are gaining importance as a vehicle for drug delivery systems because of their simple fabrication methods, high surface-to-volume ratio, nanoporous structure, and high permeability of drugs.[37]

Recently, substantial progress has been made in the fabrication technique of electrospun nanofibers for controlled drug release delivery. The physical and chemical stimuli such as pH value, ionic strength, temperature, light, electric or magnetic fields, or a combination were used in this method to release the drug. Electrospun nanofibers have a promising approach as smart materials for oral drug delivery, transdermal drug delivery, vaginal drug delivery, and a scaffold for tissue regeneration because of their morphological similarities to the natural matrix high surface to volume ratio, mechanical properties, and high porosity.[38-43]

Electrospun nanofibers scaffolds can be used as drug delivery devices to lessen the dosage systemically. Some drugs like antimicrobial agents, analgesics, and anti-inflammatory regimens have been made by using electrospun nanofibers.[44-46]

Recently, electrospun nanofibers are applicable in implantable drugs and growth factor releasing scaffolds that help repair surgical sites by preventing infection and/or increasing the rate of Osseo integration.[47-49] PLLA fibers containing nanodiamonds loaded with growth factors are shown to possess better mechanical properties and delivery of drugs to prevent infection, reduce inflammation and accelerate bone regeneration.[50] Drug-loaded nanofibers can be employed as implants also wide application in targeted drug delivery systems. Drugs such as polysaccharides, antibiotics, and anti-cancer drugs can be loaded into nanofibers for providing sustained release.[51]

Mucoadhesives Nanofibers

Depending on the type of drugs to be administered, various delivery systems are fabricated, such as fast-dissolving polymer for a dual drug release pattern, Bi-layer drug delivery system, and three-layer mucoadhesive with a bioadhesive polymer core, a fast-dissolving drug release layer, and a water-resistant layer.[52,53] Huang *et al.* have prepared electrospun cellulose acetate phthalate (CAP) microfibers loaded with anti-HIV drugs, which showed stability in the vaginal fluid.[54] In the case of the oral cavity, mucoadhesive electrospun fibers are also used for buccal mucosa.[55-59]

The mucoadhesives microfibers have been made to deliver drugs with poor absorption because of their limited solubility. The *in vitro* and in vivo results confirmed superiority of electrospun nanofiber in release rate, compared to conventional administration.[60] Mucoadhesive nanofibers have also been reported as drug delivery systems in gastroenteric tract. Nanofibers were reported to enhance the bioavailability of the drug in GI site because of their prolonged contact time with the gastric mucosa.[61] Lee *et al.* have developed a sinonasal mucoadhesive delivery system with electrospun nanostructured carriers for nasal mucosa loaded with resveratrol. They reported improve residence time on site of action and also improved the local bioavailability of these electrospun scaffolds.[62]

Medical Prostheses

Electrospun fibers due to soft texture became excellent candidates to be utilized as a coating for hard tissue prosthetic devices and showed great potential in prosthetic devices used in surgical operations, including breast, vascular, blood vessel. Semnani *et al*. fabricated a nanofibrous scaffold for liver tissue engineering from polycaprolactone (PCL) and chitosan (CS) to improved pore size and orientation for cell infiltration.[63]

The various Polymeric nanofibers used in Pharmaceutical and Biomedical Applications are shown in Table 2.

Other Applications

Apart from Pharmaceutical Applications Electrospun nanofibers shows immense potential in wound dressing, in medicine, as protective materials, in sensor devices, as medical textile materials, cosmetics, in filtration system etc. Nanofibers are also used in transdermal delivery system.[73-77]

Electrospun scaffolds are preferable in wound dressing because they provide very high specific surface area, well inter- connectivity and nanoporous structure. Electrospun nanofibers not only remove the excess body fluid but also used for wound healing process.[78] Unnithan *et al*. reported the successful preparation of uniform nanofibers of polyurethane–dextran loaded with ciprofloxacin drug. They showed that the addition of the drug reduced the size and narrowed the distribution of electrospun nanofiber diameters due to the decrease in solution viscosity.[79]

Recently, electrospun nanofibers have shown great potential in cancer therapy also. Nanofibers play an important role to provide the sustained release of drug at the specific site loaded with anti-cancer drugs. Hence nanofibers are one of the best approach to reduce the local recurrence of cancer after surgery and can be implanted directly to the solid tumor cells for cancer treatment. Thus, nanofibers are better as compared with nanoparticles for cancer therapy.[80-82]

Electrospun nanofibers have also applicable in growth factor (GF) delivery[83] and in nucleic acid delivery. Saraf *et al.* produced the fiber mesh scaffolds using the coaxial electrospinning technique to encapsulate and release non- viral gene delivery vectors over

Table 2: Nanofibers used in pharmaceutical and biomedical applications

Application	*Types of Polymer*	*References*
Medical	Polycaprolactone (PCL)/chitosan (CS)	Semnani *et al*.[63]
	Alginate/chitin	Jayakumar *et al*.[64]
Wound dressing	CS/collagen	Wang *et al*.[65]
	Polycaprolactone (PCL)/ gelatin	Chong *et al*.[66]
	Sodium alginate (SA)/PV	Shalumon *et al*.[67]
Drug Delivery	Hydroxylpropylmethyl cellulose (HPMC)/Itraconazole	Verreck *et al*.[45]
	Zein/polyvinylpyrrolidone/ ketoprofen (KET)	Jiang *et al*.[68]
	Egg albumin/PVA	Zahedi *et al*.[69]
Tissue Engineering	CS/alginate/AHp/collagen	Yu *et al*.[70]
Bone	PCL-b-poly(acrylic acid) copolymer/PCL	Chen *et al*.[71]
	Poly (d,l-lactide)	Qu *et al*.[72]

up to 60 days.[84]

In stem cell delivery, one of the main hurdles is choosing a suitable carrier to transfer stem cells to specific tissue locations. Various materials and scaffolds have been used for the transfer of stem cells like fibrin glue for cell transfer of ocular surface, macroporous hydrogels, polymer, and collagen sponges, and self-assembling peptide nanofibers for cell-based therapy on infarcted myocardium.[85-88] We induced a myocardial infarction in 72 rats to assess the effects of different self-assembling peptides with or without platelet-derived growth factor (PDGF-BB).

Current Status of Drug Loaded Nanofibers

Pranabeshsasmal *et al*.,[89] have researched tranexamic acid-loaded chitosan electrospun nanofibers as a drug delivery system for hemorrhage control application and reported that TXA incorporation into chitosan nanofibers could be an attractive strategy to obtain hemostatic membranes for a wide variety of battlefield and clinical applications. Ze -yuquin *et al.,* worked on fast dissolving oral films for drug delivery prepared from chitosan/ pullulan electrospinning nanofibers. They were prepared chitosan/ pullulan composite nanofiber fast dissolving oral films (FDOFs) via electrospinning technique.[90]

Motahirahashmi *et al.,* was done work on Copper oxide (CuO) loaded polyacrylonitrile (PAN) nanofiber membranes for antimicrobial breath mask applications.[91]

Essam A. *et al*., worked on Dual drug-loaded coaxial nanofibers for the treatment of corneal abrasion. They investigated an oval approach to co-administer an anti-scarring agent and an antibiotic, both being incorporated into one dosage form to accelerate wound closure and treat any associated infection. The fibers could extend the release of both drugs, hence raising the possibility of a single daily dose of the drug-loaded coaxial fibers to treat corneal abrasion.[92]

Jiangsong Hou *et al.* performed a nanofiber-based drug depot with high drug loading for sustained release. They prepared a core-shell fiber-based nano depot (ND) to achieve a high drug loading while ensuring a zero-order drug sustained-release profile. With cellulose acetate (CA) as a filament-forming polymeric matrix and ferulic acid (FA) as a model drug, triaxial electrospinning was implemented to generate the ND.[93]

CONCLUSION AND FUTURE ASPECTS OF DRUG LOADED NANOFIBERS

During the past few decades, nanofibers have been widely used to prepare drug-loaded scaffolds for various applications such as biomedical, tissue engineering, wound healing, etc. Nanofibers are the promising approach for drug delivery systems because of their unique characteristics such as high specific surface area, ease of fabrication methods, nanoporous structure etc. But there are certain limitations such as high cost, thickness, etc. to overcome such limitations, and there is a need to address formulation issues like controlled porosity, uniform drug loading, cost-effective product, and controlled fiber thickness. There is also a need to scale up nanofibers' manufacturing process for commercial scale and advancement in electrospinning technique.

REFERENCES

1. Pelipenko J, Kocbek P, Kristl J. Critical attributes of nanofibers: Preparation, drug loading, and tissue regeneration. *Int J Pharm*. 2015;484(1-2):57-74. doi:10.1016/j.ijpharm.2015.02.043
2. Hu X, Liu S, Zhou G, Huang Y, Xie Z, Jing X. Electrospinning of polymeric nanofibers for drug delivery applications. *J Control Release*. 2014;185(1):12-21. doi:10.1016/j.jconrel.2014.04.018
3. Braghirolli DI, Steffens D, Pranke P. Electrospinning for regenerative medicine: A review of the main topics. *Drug Discov Today*. 2014;19(6):743-753. doi:10.1016/j.drudis.2014.03.024
4. Li C, Vepari C, Jin HJ, Kim HJ, Kaplan DL. Electrospun silkBMP-2 scaffolds for bone tissue engineering. Biomaterials 2006; 27: 3115–3124 doi:10.1016/j.biomaterials.2006.01.022
5. Kenawy ER, Bowlin GL, Mansfield K *et al*. Release of tetracycline hydrochloride from electrospunpoly (ethylenecovinylacetate), poly (lactic acid), and a blend. J. Control. Release.2002; 81: 57–64.doi: 10.1016/ s0168-3659(02)00041-x.
6. Luu YK, Kim K, Hsiao BS, Chu B, Hadjiargyrou M. Development of a nanostructured DNA delivery scaffold via electrospinning of PLGA and PLA-PEG block copolymers. J. Control. Release.2003; 89: 341–353. DOI: 10.1016/s0168-3659(03)00097-x
7. Charles PP Jr, Owens F. Introduction to Nanotechnology. Hoboken, NJ: A-Wiley Interscience Publication.2004; 43: 2196-2197.https://doi. org/10.1002/anie.200385124
8. Akhgari A, Shakib Z, Sanati S. A review on electrospunnanofibers for oral drug delivery.Nanomedicine J 2017;4:197–207. doi:10.22038/ nmj.2017.9428)
9. Garg T, Singh S, Goyal AK. 2013. Stimuli-sensitive hydrogels: an excellent carrier for drug and cell delivery. Crit Rev Ther Drug Carrier Syst. 2020; 30:369–409. doi:10.1615/critrevtherdrugcarriersyst.2013007259
10. Parnami N, Garg T, Rath G, Goyal AK. Development and characterization of nanocarriers for topical treatment of psoriasis by using combination therapy. *Artif Cells, Nanomedicine Biotechnol*. 2014;42(6):406-412. doi :10.3109/21691401.2013.837474
11. Hu X, Liu S, Zhou G, Huang Y, Xie Z, Jing X. Electrospinning of polymeric nanofibers for drug delivery applications. *J Control Release*. 2014;185(1):12-21. doi:10.1016/j.jconrel.2014.04.018
12. Samprasit W, Akkaramongkolporn P, Ngawhirunpat T, Rojanarata T, Kaomongkolgit R, Opanasopit P. Fast releasing oral electrospun PVP/ CD nanofiber mats of taste-masked meloxicam. *Int J Pharm*. 2015;487(1-2):213-222. doi:10.1016/j.ijpharm.2015.04.044
13. Zhang S. Fabrication of novel biomaterials through molecular self-assembly. *Nat Biotechnol*. 2003;21(10):1171-1178. doi:10.1038/nbt874
14. Hartgerink JD, Beniash E, Stupp SI. Peptide-amphiphile nanofibers: a versatile scaffold for the preparation of self-assembling materials. Proc Natl

Acad Sci.2002; 99:5133–5138.https://doi.org/10.1073/pnas.072699999
15. Ma PX. Biomimetic materials for tissue engineering.Adv. Drug Deliv. Rev.2008; 60: 184–198 doi: 10.1016/j.addr.2007.08.041
16. Barnes CP, Sell SA, Bol and ED, Simpson DG, BowlinGL.Nanofiber technology: designing the next generation of tissue engineering scaffolds. Adv. Drug Deliv.Rev.2007; 59(14), 1413–1433 doi: 10.1016/j.addr.2007.04.022.
17. Vasita R, Khatti DS.Nanofibers and their applications in tissue engineering. Int. J. Nanomedicine . 2006; 1(1): 15–30 doi: 10.2147/nano.2006.1.1.15
18. Matthews JA, Wnek GD, Simpson DG, Bowlin GL. Electrospinning of collagen nanofibers. Biomacromolecules 2002; 3(2), 232–238 . doi:10.1021/bm015533u
19. Boland ED, Matthews JA, Pawlowski KJ, Simpson DG, Wnek GE, Bowlin GL. Electrospinning collagen and elastin: Preliminary vascular tissue engineering. *Front Biosci*. 2004;9:1422-1432. doi:10.2741/1313
20. Reneker DH, Chun I. Nanometre diameter fibres of polymer, produced by electrospinning. *Nanotechnology*. 1996;7(3):216-223. doi:10.1088/0957-4484/7/3/009
21. Seigel RA, Langer R. Mechanistic studies of macromolecular drug release from macroporous polymers. II. Models for the kinetics of drug release. J. Control. 1990; 14: 153–167. doi: 10.1016/0168-3659(90)90152-J
22. Zhang Y, Chwee TL, Ramakrishna S, Huang ZM. Recent development of polymer nanofibers for biomedical and biotechnological applications. *J Mater Sci Mater Med*. 2005;16(10):933-946. doi:10.1007/s10856-005-4428-x
23. Stevens MM, George JH. Exploring and engineering the cell surface interface. Science. 2005 Nov 18;310(5751):1135-1138. doi: 10.1126/science.1106587
24. Bosworth LA, Downes S. Electrospinningfor TissueRegeneration; Bosworth, L., Downes, S., Eds.; Woodhead Publishing in Materials; Woodhead Publishing: Oxford, UK, 2011; p. 409.
25. Liang D, Hsiao BS, Chu B. Functional electrospun nanofibrous scaffolds for biomedical applications. *Adv Drug Deliv Rev*. 2007;59(14):1392-1412. doi:10.1016/j.addr.2007.04.021
26. Alexiou C, Arnold W, Klein RJ, Parak FG, Hulin P, Bergemann C, Erhardt W, Wagenpfeil S, Luebbe AS. Locoregional cancer treatment with magnetic drug targeting. Cancer research. 2000 Dec 1;60(23):6641-6648.
27. Ahn BW, Kang TJ. Preparation and characterization of magnetic nanofibers with iron oxide nanoparticles and poly(ethylene terephthalate). *J Appl Polym Sci*. 2012;125(2):1567-1575. doi:10.1002/app.34953
28. Bueno EM, Glowacki J. Cell-free and cell-based approaches for bone regeneration. *Nat Rev Rheumatol*. 2009;5(12):685-697. doi:10.1038/nrrheum.2009.228
29. Meng J, Xiao B, Zhang Y, *et al*. Super-paramagnetic responsive nanofibrous scaffolds under static magnetic field enhance osteogenesis for bone repair in vivo. *Sci Rep*. 2013;3(1):2655. doi:10.1038/srep02655
30. Preslar AT, Parigi G, McClendon MT, *et al*. Gd(III)-Labeled Peptide Nanofibers for Reporting on Biomaterial Localization *in Vivo*. *ACS Nano*. 2014;8(7):7325-7332. doi:10.1021/nn502393u
31. Kasoju N, Bora U. Silk fibroin in tissue engineering. *Adv Healthc Mater*. 2012;1(4):393-412. doi:10.1002/adhm.201200097
32. Shan D, Shi Y, Duan S, Wei Y, Cai Q, Yang X. Electrospun magnetic poly(l-lactide) (PLLA) nanofibers by incorporating PLLA-stabilized Fe3O4 nanoparticles. *Mater Sci Eng C*. 2013;33(6):3498-3505. doi:10.1016/j.msec.2013.04.040
33. Bueno, E.M.; Glowacki, J. Cell-free and cell-based approaches for bone regeneration. Nat. Rev. Rheumatol. 2009, 5, 685–697. doi: 10.1038/nrrheum.2009.228
34. Gloria A, De Santis R, Ambrosio L. Polymer-based composite scaffolds for tissue engineering. *J Appl Biomater Biomech*. 2010;8(2):57-67. doi:10.1177/228080001000800201
35. Sundararaj SC, Thomas MV, Peyyala R, Dziubla TD, Puleo DA. Design of a multiple drug delivery system directed at periodontitis. Biomaterials. 2013 Nov 1;34(34):8835-8842.
36. Nagarajan S, Soussan L, Bechelany M, Teyssier C, Cavaillès V, Pochat-Bohatier C, Miele P, Kalkura N, Janot JM, Balme S. Novel biocompatible electrospun gelatin fiber mats with antibiotic drug delivery properties. Journal of Materials Chemistry B. 2016;4(6):1134-1141.
37. He C, W. Nie W. Feng. Engineering of biomimetic nanofibrous matrices for drug delivery and tissue engineering. J. Mater. Chem. B 2014; 2: 7828.
38. Yu DG, Shen XX, Branford-White C, White K, Zhu LM, Bligh SW. Oral fast-dissolving drug delivery membranes prepared from electrospun polyvinylpyrrolidone ultrafine fibers.*Nanotechnology*. 2009;20(5):055104. doi:10.1088/0957-4484/20/5/055104
39. Bhandari J, Mishra H, Mishra PK, Wimmer R, Ahmad FJ, Talegaonkar S. Cellulose nanofiber aerogel as a promising biomaterial for customized oral drug delivery. *Int J Nanomedicine*. 2017;12:2021-2031https://doi.org/10.2147/IJN.S124318
40. Ngawhirunpat T, Opanasopit P, Rojanarata T, Akkaramongkolporn P, Ruktanonchai U, Supaphol P. Development of meloxicam-loaded electrospun polyvinyl alcohol mats as a transdermal therapeutic agent. Pharmaceutical development and technology. 2009 Jan 1;14(1):73-82.
41. Yun J, Im JS, Lee YS, Kim HI. Electro-responsive transdermal drug delivery behavior of PVA/PAA/MWCNT nanofibers. European Polymer Journal. 2011 Oct 1;47(10):1893-1902.
42. Blakney AK, Ball C, Krogstad EA, Woodrow KA. Electrospun fibers for vaginal anti-HIV drug delivery. Antiviral Research. 2013 Dec;100 Suppl:S9-16. doi: 10.1016/j.antiviral.2013.09.022.
43. O. S. Manoukian, R. Matta, J. Letendre, P. Collins, A. D. Mazzocca, S. G. Kumbar, in Biomedical Nanotechnology: Methods and Protocols, Springer 2017, p. 261.
44. Kim K, Luu YK, Chang C, Fang D, Hsiao BS, Chu B, Hadjiargyrou M. Incorporation and controlled release of a hydrophilic antibiotic using poly (lactide-co-glycolide)-based electrospun nanofibrous scaffolds. Journal of controlled release. 2004 Jul 23;98(1):47-56. doi:10.1016/j.jconrel.2004.04.009
45. Verreck G, Chun I, Peeters J, Rosenblatt J, Brewster ME. Preparation and characterization of nanofibers containing amorphous drug dispersions generated by electrostatic spinning. *Pharm Res*. 2003;20(5):810-817. doi:10.1023/A:1023450006281
46. Kenawy ER, Bowlin GL, Mansfield K, Layman J, Simpson DG, Sanders EH, Wnek GE. Release of tetracycline hydrochloride from electrospun poly (ethylene-co-vinylacetate), poly (lactic acid), and a blend. Journal of controlled release. 2002 May 17; 81(1-2):57-64.
47. Kim K, Luu YK, Chang C, Fang D, Hsiao BS, Chu B, Hadjiargyrou M. Incorporation and controlled release of a hydrophilic antibiotic using poly (lactide-co-glycolide)-based electrospun nanofibrous scaffolds. Journal of controlled release. 2004 Jul 23;98(1):47-56.
48. Vacanti NM, Cheng H, Hill PS, *et al*. Localized delivery of dexamethasone from electrospun fibers reduces the foreign body response. *Biomacromolecules*. 2012;13(10):3031-3038. doi:10.1021/bm300520u
49. Kenawy ER, Bowlin GL, Mansfield K, Layman J, Simpson DG, Sanders EH, Wnek GE. Release of tetracycline hydrochloride from electrospun poly (ethylene-co-vinylacetate), poly (lactic acid), and a blend. Journal of controlled release. 2002 May 17;81(1-2):57-64.
50. Zhang Q, Mochalin VN, Neitzel I, Knoke IY, Han J, Klug CA, Zhou JG, Lelkes PI, Gogotsi Y. Fluorescent PLLA-nanodiamond composites for bone tissue engineering. Biomaterials. 2011 Jan 1;32(1):87-94.
51. Nguyen TT, Ghosh C, Hwang SG, Chanunpanich N, Park JS. Porous core/sheath composite nanofibers fabricated by coaxial electrospinning as a potential mat for drug release system. Int J Pharm. 2012 Dec 15; 439(1-2):296-306
52. Brako F, Raimi-Abraham B, Mahalingam S, Craig DQM, Edirisinghe M. Making nanofibres of mucoadhesive polymer blends for vaginal therapies. *Eur Polym J*. 2015;70:186-196. doi:10.1016/j.eurpolymj.2015.07.006
53. Rossi S, Sandri G, Caramella CM. Buccal drug delivery: A challenge already won? *Drug Discov Today Technol*. 2005;2(1):59-65. doi:10.1016/j.ddtec.2005.05.018
54. Huang Z-M, Zhang Y-Z, Kotaki M, Ramakrishna S. A review on polymer nanofibers by electrospinning and their applications in nanocomposites. *Compos Sci Technol*. 2003;63(15):2223-2253. doi:10.1016/S0266-3538(03)00178-7
55. Nguyen S, Hiorth M. Advanced drug delivery systems for local treatment of the oral cavity. *Ther Deliv*. 2015;6(5):197-210. doi:10.4155/tde.15.5
56. Colley HE, Said Z, Santocildes-Romero ME, *et al*. Pre-clinical evaluation

of novel mucoadhesive bilayer patches for local delivery of clobetasol-17-propionate to the oral mucosa. *Biomaterials*. 2018;178:134-146. doi:10.1016/j.biomaterials.2018.06.009

57. Muzzarelli RAA, El Mehtedi M, Bottegoni C, Aquili A, Gigante A. Genipin-crosslinked chitosan gels and scaffolds for tissue engineering and regeneration of cartilage and bone. *Mar Drugs*. 2015;13(12):7314-7338. doi:10.3390/md13127068
58. Mašek J, Lubasová D, Lukáč R, *et al*. Multi-layered nanofibrous mucoadhesive films for buccal and sublingual administration of drug-delivery and vaccination nanoparticles - important step towards effective mucosal vaccines. *J Control Release*. 2017;249:183-195. doi:10.1016/j.jconrel.2016.07.036
59. Malik R, Garg T, Goyal AK, Rath G. Polymeric nanofibers: targeted gastro-retentive drug delivery systems. *J Drug Target*. 2015;23(2):109-124. doi:10.3109/1061186X.2014.965715
60. Ignatious F, Sun L, Lee C-P, Baldoni J. Electrospun Nanofibers in Oral Drug Delivery. *Pharm Res*. 2010;27(4):576-588. doi:10.1007/s11095-010-0061-6
61. Malik R, Garg T, Goyal AK, Rath G. Diacerein-Loaded novel gastroretentive nanofiber system using PLLA: Development and in vitro characterization. *Artif Cells, Nanomedicine Biotechnol*. 2016;44(3):928-936. doi:10.3109/21691401.2014.1000492
62. Lee M, Park CG, Huh BK, *et al*. Sinonasal Delivery of Resveratrol via Mucoadhesive Nanostructured Microparticles in a Nasal Polyp Mouse Model. *Sci Rep*. 2017;7(1):40249. doi:10.1038/srep40249
63. Semnani D, Naghashzargar E, Hadjianfar M, *et al*. Evaluation of PCL/chitosan electrospun nanofibers for liver tissue engineering. *Int J Polym Mater Polym Biomater*. 2017;66(3):149-157. doi:10.1080/00914037.2016.1190931
64. Jayakumar R, Menon D, Manzoor K, Nair S V., Tamura H. Biomedical applications of chitin and chitosan based nanomaterials - A short review. *Carbohydr Polym*. 2010;82(2):227-232. doi:10.1016/j.carbpol.2010.04.074
65. Wang CC, Su CH, Chen CC. Water absorbing and antibacterial properties of N-isopropyl acrylamide grafted and collagen/chitosan immobilized polypropylene nonwoven fabric and its application on wound healing enhancement. *J Biomed Mater Res - Part A*. 2008;84(4):1006-1017. doi:10.1002/jbm.a.31482
66. Evaluation of electrospun PCL/gelatin nanofibrous scaffold for wound healing and layered dermal reconstitution. Chong EJ, Phan TT, Lim IJ, Zhang YZ, Bay BH, Ramakrishna S, Lim CT Acta Biomater. 2007 May; 3(3):321-30. -
67. Shalumon KT, Anulekha KH, Nair S V., Nair S V., Chennazhi KP, Jayakumar R. Sodium alginate/poly(vinyl alcohol)/nano ZnO composite nanofibers for antibacterial wound dressings. *Int J Biol Macromol*. 2011;49(3):247-254. doi:10.1016/j.ijbiomac.2011.04.005
68. Electrospun drug-loaded core-sheath PVP/zein nanofibers for biphasic drug release. Jiang YN, Mo HY, Yu DG Int J Pharm. 2012 Nov 15; 438(1-2):232-9.
69. Zahedi P, Fallah-Darrehchi M. Electrospun egg albumin-PVA nanofibers containing tetracycline hydrochloride: Morphological, drug release, antibacterial, thermal and mechanical properties. *Fibers Polym*. 2015;16(10):2184-2192. doi:10.1007/s12221-015-5457-9
70. Yu C.-C., Chang J.-J., Lee Y.-H., Lin Y.-C., Wu M.-H., Yang M.-C., Chien C.-T. Electrospun scaffolds composing of alginate, chitosan, collagen and hydroxyapatite for applying in bone tissue engineering. Mater. Lett. 2013;93:133–136. doi: 10.1016/j.matlet.2012.11.040.
71. Chen X, Gleeson SE, Yu T, *et al*. Hierarchically ordered polymer nanofiber shish kebabs as a bone scaffold material. *J Biomed Mater Res Part A*. 2017;105(6):1786-1798. doi:10.1002/jbm.a.36039
72. Qu Y, Wang B, Chu B, *et al*. Injectable and Thermosensitive Hydrogel and PDLLA Electrospun Nanofiber Membrane Composites for Guided Spinal Fusion. *ACS Appl Mater Interfaces*. 2018;10(5):4462-4470. doi:10.1021/acsami.7b17020
73. Riboldi SA, Sampaolesi M, Neuenschwander P, Cossu G, Mantero S. 2005. Electrospun degradable polyesterurethane membranes: potential scaffolds for skeletal muscle tissue engineering. Biomaterials. 26:4606–4615 -
74. Fujihara K, Kotaki M, Ramakrishna S. 2005. Guided bone regeneration membrane made of polycaprolactone/calcium carbonate composite nanofibers. Biomaterials. 26:4139–4147 -
75. Blanco E, Shen H, Ferrari M. 2015. Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nature Biotechnol. 33:941–951 -
76. Yang Y, Nikkola L, Ylikauppila H, Ashammakhi N. 2006. Investigation of cell attachment on the scaffolds manufactured by electrospun PCLhyaluronan blend. Paper presented at: TNT2006' "Trends in Nanotechnology"' Conference (pp. 4–8)
77. Li WJ, Laurencin CT, Caterson EJ, Tuan RS, Ko FK. Electrospun nanofibrous structure: A novel scaffold for tissue engineering. *J Biomed Mater Res*. 2002;60(4):613-621. doi:10.1002/jbm.10167
78. Garg T, Kumar Goyal A. 2012. Iontophoresis: drug delivery system by applying an electrical potential across the skin. Drug Delivery Lett. 2:270–280.
79. Unnithan AR, Barakat NA, Pichiah PB, Gnanasekaran G, Nirmala R, Cha YS, Jung CH, El-Newehy M, Kim HY Carbohydr Polym. 2012 Nov 6; 90(4):1786-93
80. Sridhar R, Sundarrajan S, Venugopal JR, Ravichandran R, Ramakrishna S. Electrospun inorganic and polymer composite nanofibers for biomedical applications. Journal of Biomaterials Science, Polymer Edition. 2013 Mar 1;24(4):365-385.
81. Luo X, Xie C, Wang H, Liu C, Yan S, Li X. Antitumor activities of emulsion electrospun fibers with core loading of hydroxycamptothecin via intratumoral implantation. *Int J Pharm*. 2012;425(1-2):19-28. doi:10.1016/j.ijpharm.2012.01.012
82. Weinberg BD, Blanco E, Gao J. Polymer implants for intratumoral drug delivery and cancer therapy. *J Pharm Sci*. 2008;97(5):1681-1702. doi:10.1002/jps.21038
83. Varkey M, Gittens SA, Uludag H. Growth factor delivery for bone tissue repair: An update. *Expert Opin Drug Deliv*. 2004;1(1):19-36. doi:10.1517/17425247.1.1.19
84. Schneider A, Wang XY, Kaplan DL, Garlick JA, Egles C. 2009. Biofunctionalized electrospun silk mats as a topical bioactive dressing for accelerated wound healing. Acta Biomater. 5:2570–2578
85. Schwab IR, Johnson NT, Harkin DG. 2006. Inherent risks associated with manufacture of bioengineered ocular surface tissue. Arch Ophthalmol. 124:1734–1740 -
86. Sykova E, Jendelova P, Urdzıkova L, Lesny P, Hejcl A. 2006. Bone marrow stem cells and polymer hydrogels—two strategies for spinal cord injury repair. Cell MolNeurobiol. 26:1111–1127 - Google Search. Accessed August 23, 2020.
87. Rama P, Bonini S, Lambiase A, Golisano O, Paterna P, De Luca M, Pellegrini G. 2001. Autologous fibrin-cultured limbal stem cells permanently restore the corneal surface of patients with total limbal stem cell deficiency1. Transplantation. 72:1478–1485
88. Dubois G, Segers VFM, Bellamy V, *et al*. Self-assembling peptide nanofibers and skeletal myoblast transplantation in infarcted myocardium. *J Biomed Mater Res - Part B Appl Biomater*. 2008;87(1):222-228. doi:10.1002/jbm.b.31099
89. PranabeshSasmal, PallabDatta; Tranexamic acid-loaded chitosan electrospun nanofibers as drug delivery system for hemorrhage control applications; Journal of Drug Delivery Science and Technology 52 (2019) 559–567
90. Ze-yu Qin, Xi-Wen Jia, Qian Liu, Bao-hua Kong, Hao Wang; Fast dissolving oral films for drug delivery prepared from chitosan/ pullulan electrospinning nanofibers; Int J BiologicalMacromolecules137 (2019) 224–231
91. Hashmi M, Ullah S, Kim IS. Copper oxide (CuO) loaded polyacrylonitrile (PAN) nanofiber membranes for antimicrobial breath mask applications. *Curr Res Biotechnol*. 2019;1:1-10. doi:10.1016/j.crbiot.2019.07.001
92. Tawfik EA ,Craig DQM, Barker SADual drug-loaded coaxial nanofibers for the treatment of corneal abrasion,International Journal of Pharmaceutic.2020;581, 119296 doi: 10.1016/j.ijpharm.2020.119296.
93. Jiangsong Hou, Jinke Yang, Xiaolu Zheng, Menglong Wang, Yanan Liu, Deng-Guang Yu. A nanofiber-based drug depot with high drug loading for sustained release,International Journal of Pharmaceutics.2020;583 : 119397. doi: 10.1016/j.ijpharm.2020.119397.