Nanomed. J., 4(2): 61-70, Spring 2017

REVIEW PAPER

Electrospun polymeric nanofibers for transdermal drug delivery

Mahya Rahmani [1], Sepideh Arbabi Bidgoli [2,3], Seyed Mahdi Rezayat [1,2]*

[1]*Department of Medical Nanotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran*

[2]*Department of Toxicology and Pharmacology, Islamic Azad Universtiy, Pharmaceutical Sciences Branch (IAUPS), Tehran, Iran*

[3]*Pharmaceutical Sciences Research Center, Islamic Azad University, Pharmaceutical Sciences Branch (IAUPS), Tehran, Iran*

ABSTRACT

Conventional transdermal drug delivery systems (TDDS) have been designed for drug delivery through the skin. These systems use the permeability property of stratum corneum, the outermost surface layer of the skin. Applying polymeric micro and nanofibers in drug delivery has recently attracted great attention and the electrospinning technique is the preferred method for polymeric micro-nanofibers fabrication with a great potential for drug delivery. More studies in the field of nanofibers containing drug are divided two categories: first, preparation and characterization of nanofibers containing drug and second, investigation of their therapeutic applications. Drugs used in electrospun nanofibers can be categorized into three main groups, including antibiotics and antimicrobial agents, anti-inflammatory agents and vitamins with therapeutic applications. In this paper, we review the application of electrospun polymeric scaffolds in TDDS and also introduce several pharmaceutical and therapeutic agents which have been used in polymer nanofibrous patches.

Keywords: *Drug Delivery, Electrospinning, Nanofiber, Polymeric Scaffold, Transdermal*

How to cite this article

Rahmani M, Arbabi Bidgoli S, Rezayat SM. Electrospun polymeric nanofibers for transdermal drug delivery. Nanomed J. 2017; 4(2): 61-70. DOI:10.22038/nmj.2017.21210.1224

INTRODUCTION

Skin is typically composed of a heterogeneous membrane but the outermost layer, the stratum corneum with thicknesses of about 20 and 25 µm, plays a major role in absorption and act as a barrier for foreign materials [1].

Nevertheless, skin appendages such as hair follicle could be used as alternative routes for the entrance of drugs across skin due to the presence of blood vessels and dendritic cells surrounding hair follicle [2]. Cosmetics and skin medications use permeability property to enter into the circulatory system. Therefore, this area has great attention for drug delivery and provides the desired media for absorption of medications and entrance into the vascular system [3].

Conventional transdermal drug delivery systems (TDDS) and transdermal patches, release the medications in this manner. The patch is designed to deliver therapeutic agent across the skin and can be considered as the desired alternative to oral drug delivery [4]. Drug controlled release from TDDS with reduction of the dose fluctuations in the body can lead to the improvement of efficacy of medications, stabilization of drug diffusion profile and greater bioavailability [5]. Besides, this method can have

*Corresponding Author Email: *sepideharbabi@yahoo.com*
Tel: (+98) *021-22006221*
Note. This manuscript was submitted on December 25, 2016; approved on February 15, 2017

patients consent because of the non-invasive nature and the ease [6] but it should be considered that a few number of medications could effectively penetrate into the depth of the skin since the skin only allows to hydrophobic elements (several hundred Dalton) with low concentration (Millionths of grams per day) to influx, so entrance of large hydrophilic drugs through the skin is an unresolved issue yet [4, 5].

A wide range of polymers is used in transdermal drug diffusion vehicles as gelatinization factors in gel systems and stabilizer in emulsions and creams [7]. They could form patches matrix and wound dressings [8] and act as skin adhesives in transdermal systems and provide enhanced permeability for the improvement of treatment efficiency [2].

Application of polymeric micro and nanofibers in biomedicine has recently attracted great attentions. Nanofibers are prepared in different methods such as Phase separation, Template synthesis, Self-assembly and Electrospinning[8]. Among them, electrospinning technique is preferred for fabrication of polymer micro and nanofibers due to simplicity and cost [9, 10].

Nanofiber mats produced by this technique have considerable properties, including high surface area, nanoscale pores, unique physical and mechanical properties beside surface capability for physical and chemical activation[11-13].

The other advantages can be pointed to simple usage, inexpensive cost, adjustability, and industrialization possibility [7]. Due to these properties, electrospun nanofibers have good potential for biomedical applications, such as drug delivery, gene delivery, adhesion prevention after surgery, receptors, wound dressing and tissue engineering[4,14]. Drug release from electrospun nanofibers in comparison with polymeric films prepared with other methods makes them as proper tools for drug delivery purposes. These differences in drug release are because of their porous structures with a lot of nanofibers which provides appropriate drug molecules release from the polymer matrix [15]. Furthermore, topical drug distribution through electrospun nanofibers dramatically reduces systemic absorption of the drug, resulting in the reduction in consumed dosage [8].

Pharmaceutical ingredients which are commonly delivered using electrospun scaffolds include antibiotics, antitumor drugs, Anti-inflammatory drugs, proteins and nucleic acids [14].

However, most studies have been focused on implantable scaffolds or wound dressing, whereas transdermal patch for application in the the healthy skin has attracted less attention in researchers. But these few studies are very impressive and promising for the practical applications in future [16].

Generally, active pharmaceutical agents delivered by polymeric nanofibers have been reported in papers in two categories.

First, nanofibers preparation and characterization with loaded medications, and second investigation of therapeutic applications in outer surfaces of the human body such as transdermal drug delivery and wound dressing [4, 16]. This paper reviews the electrospun polymeric scaffolds to apply in healthy skins TDDS.

Nanofiber fabrication via electrospinning

Nanofibers production using electrostatic force process has been known as electrospinning which is a simple method to make fibers from some microns to few ten nanometers [13]. Various polymers including synthetics, natural, and synthetic-natural combination can are electrospun (Table 1) [16].

Properties such as high surface to volume ratio, flexible surface functional groups, adjustable surface properties and excellent mechanical performanceintroducenanofibers as an appropriate option for different applications [8].

Basic electrospinning systems are composed of three main components: a high voltage power source, a pipette like a spinneret, and plate or cylinder rotating (collector) covered with aluminum foil. Pumping polymer solution and the appearance of a drop at the tip of the syringe to lead Taylor cone when the electrostatic force is enough to overcome the surface tension of the solution.

The potential difference between the needle and the collector creates a thin jet from polymer solution to collector plate [34]. The solvent evaporation and cooling the molten polymer create a nonwoven fibrous mat on the collector surface [35]. Fig. 1 schematically illustrates the components of an electrospinning set.

Nowadays, electrospun nanofibers loaded with drug are used in the treatment of various diseases. Electrospun membranes are applied to local drug delivery systems or implants, cancer treatment, DNA

Table 1. Some of the electrospun polymers and their solvents

Polymer name	Type of polymer	Solvent	Ref.
Cellulose acetate	Biopolymer	Acetone/DMAC	[17]
Gelatine	Biopolymer	Formic acid, DMSO, Glacial acetic acid, TFE	[18,19]
Polyvinyl chloride (PVC)	Synthetic polymer	DMF, THF	[20]
Polyurethane (PU)	Synthetic polymer	DMF, DMAC, MEK	[21,22]
Polystyrene	Synthetic polymer	DMF, Diethyl formamide	[23]
Poly-L-lactic acid (PLLA)	Biopolymer	Chloroform	[24]
PLGA	Biopolymer	DCM, DMF	[25,26]
Chitosan (CS)	Biopolymer	Acetic acid, TFA	[27,28]
Polyvinyl alcohol (PVA)	Biopolymer	Deionized water	[29,30]
Polycaprolactone (PCL)	Biopolymer	Dichloromethane/DMF, DCM/Methanol	[31,32]
Poly (methyl methacrylate) (PMMA)	Synthetic polymer	Toluene/DMF	[33]

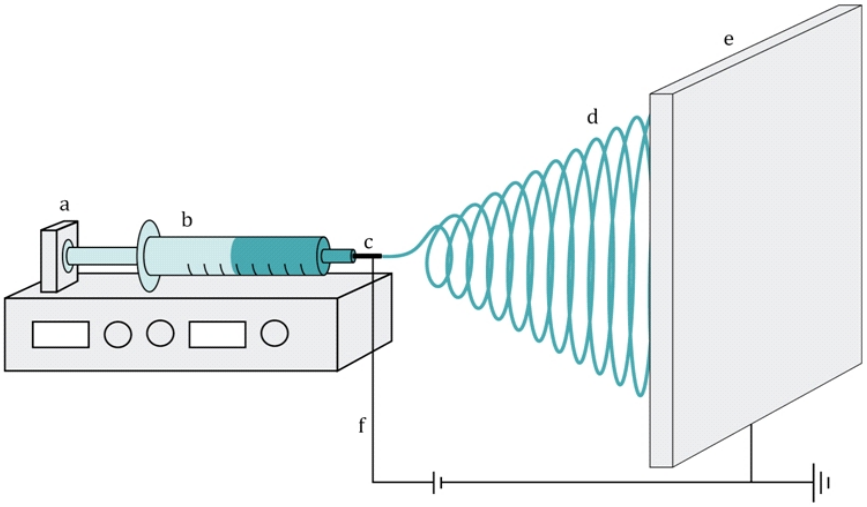

Fig. 1. Schematic picture of a typical electrospinning setup
a.syringe pump; b.syringe containing polymer solution; c. spinneret needle; d. Nanofibers formation; e. collector plate; f. high-voltage supply

and or siRNA distribution, and growth factor delivery [3].

Here, we have an overview of drug incorporation methods into electrospun nanofibers for the transdermal drug delivery systems for healthy skin, and drugs which have been studied for this purpose.

Drug loading procedures in Electrospun nanofibers

In order to construct the electrospun micro and nanofibers using in drug delivery, a variety of methods have been used. They can be divided into several categories [36]:

Blending

In this mode, the drug is dissolved or dispersed in a polymer solution to be encapsulated by fibers. This method is simpler than the other techniques, but to achieve desired results needs some supplies. For example, drug release profile is strongly affected by the distribution of drug molecules and morphology of nanofibers. In addition, it is also important for drug and polymer to be hydrophilic and or hydrophobic. For this reason, in order to achieve an anoptimal mode of drug encapsulation in the fiber, lipophilic drugs such as Rifampicin and Paclitaxel

should be electrospun with hydrophobic polymers, and hydrophilic drugs such as Doxorubicin Hydrochloride, electrospinning process should be done in blend with hydrophilic polymers [36].

Core-shell electrospinning (Coaxial)

This method is a modified technique for the production of Core-Shell electrospun fibers. The solution containing a drug or biological molecule formed by the inner jet and Polymer solution would be Electrospun from the outer jet which is concentric with inner jet simultaneously [7,37,38].

Shell polymer not only causes a slow and delayed release of the drug but also plays a vital role in the protection of the drug from the surrounding environment [39]. This technique is used in Transdermal drug delivery (e.g. Antibiotics) and Tissue Engineering [38-40].

Emulsion electrospinning

In this technique, a hydrophilic drug with polymer solution (As the oil phase) makes an emulsion. After electrospinning process, a drug with low molecular weight is distributed into nanofibers prevent their accumulation on the nanofibers surface [41].

If macromolecules with high weights are applied, fibers are shaped into the core-shell structure and the drug placed in the the aqueous phase of thecore[42,43]. However, there is a risk of damage or destruction in some macromolecules such as DNA, which can be due to shear or tension force between the aqueous phase and the organic emulsion. This problem resolves with modifications such as DNA condensing [42, 43].

Surface modification

Another form for loading a drug in electrospun nanofibers is their chemical or physical surface modification. In this technique, drug agent is immobilized chemically on the nanofibers surface, resulting in drug release reduction and its stability on Electrospun nanofibers surface due to strong bonding. This method is appropriate for delivery of genes, growth factors, and enzymes.

Other drug delivery approaches via electrospinning

One of the recent advances in effective drug delivery systems is complex treatment, such as multidrug delivery with the same or different therapeutic effects. The most important factor in

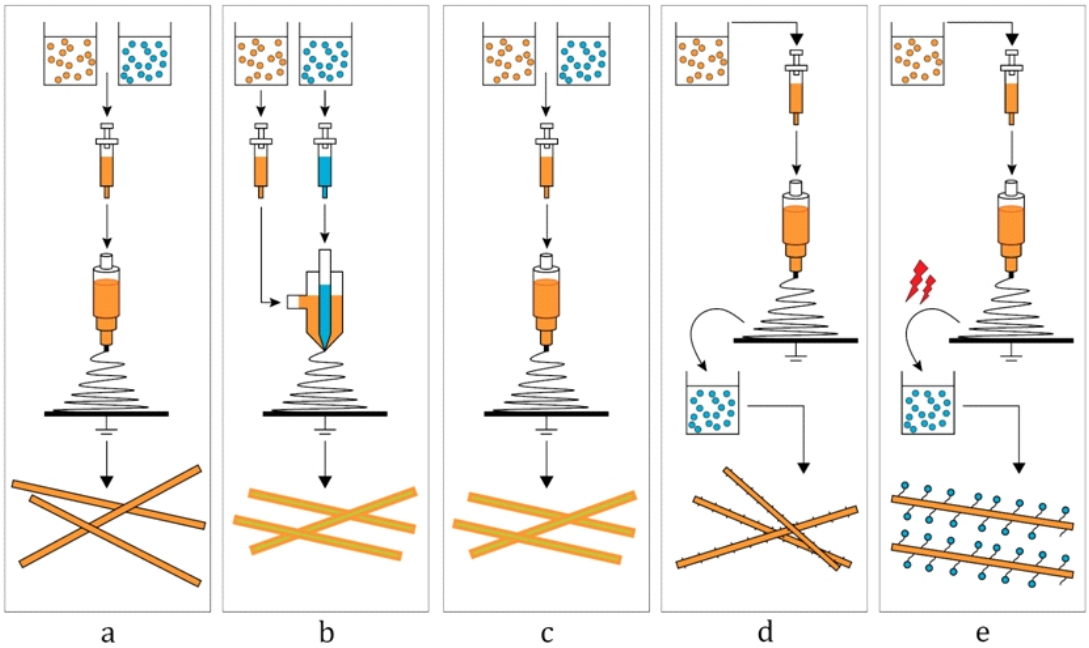

Fig. 2. Schematic picture of different methods of drug incorporation into nanofibers
a. blending; b. coaxial electrospinning; c. emulsion electrospinning; d. surface modification (physical adsorption); e. surface modification (chemical immobilization)

multidrug distribution systems is the autonomous drug controlled release, which is effective in the prevention of multidrug resistance, cancer and or other complex diseases. It is not a simple process for researchers to access the independently controlled release of drugs in a carrier, and it is obtained with drug release profile pre-regulation in all pharmaceutical compounds. It can be an approach to electrospun polymer solutions containing drug consecutively for this type of drug delivery. Fiber size and layer thickness are effective variables in rate and release time can be controlled this way [44].

Nanoparticles containing various drugs could be electrospun with the desired polymer solution. For example, Wang and coworkers dissolved chitosan nanoparticles containingNaproxen, (a nonsteroidal anti-inflammatory drug; NSAID) and Rhodamin B (a chemical dye) in polycaprolactone (PCL) solution and they produced a chain of nanoparticles in nanofibers core with electrospinning technique [44, 45]. In a similar study with Xu research team, it was observed as the same result[46].

Furthermore, multilayer coated nanofibers are the other construction method of electrospun nanofibrous drug delivery systems [47, 48]. Using hydrogel polymers, such as polyvinyl alcohol (PVA) and cellulose acetate can be produced electrospun nanofibers containing vitamins, Anti-inflammatory agents and antioxidants [3]. PVA nanofibers in comparison with PVA film show protuberances reduced weight and an increase in the amount of drug release. Transdermal distribution experiment on pigs skin showed that molecular weight of the pharmaceutical agents plays a much better role than the properties of water absorption in drug release [49].A drug delivery system model is composed of a formulation and or a mechanism, which improves efficacy and safety of drug concurrent with the drug release into the body. This system supports transmission and storage of the appropriate amount of drug in a determined period. In addition, it is expected that drug delivery system prevents the destruction of non-released drugs from fibers. During recent decades, drug delivery systems based on micro and nano polymeric structures have attracted great attention. Drug delivery using polymeric micro and nanostructures is based on the principle that increasing levels of drug carrier surface leads Tomo redissolution rate [3].

The shape, size, morphology and combination of micro and nanostructures can be changed by variable parameters of electrospinning and material choice, resulting in optimization of drug release profile.

Drug Release from ElectrospunNanofibers

A wide range of polymers has been used to fabricate Electrospun scaffolds. Natural polymers are collagen, chitosan, gelatin, hyaluronic acid, and famous synthetic polymers like polylactic acid (PLA), polycaprolactone (PCL), polyethylene oxide (PEO) and other similar copolymers[3,50].

For Drug delivery purposes using electrospun nanofibers, it is more demanded to use biodegradable polymers.

This category of a polymer containing drugs releases their cargo with one of two methods which are erosion and diffusion (Fig. 3).

However, in relation to the speed ratio of each of two methods, drug release from these polymers can be controlled by a combination of both of them in vivo. Most of the biodegradable polymers in drug delivery are degradable by hydrolysis process and some polymers are mediated by enzymatic catalytic activity[49]. It should be noted that drug release occurs simultaneously with the degradation of biodegradable polymers and this may cause the toxicity resulting from a sudden increase in drug concentration into the body.

Thus, in the selection of materials for drug delivery and polymer fibers, the drug release rate and degradation rate of the polymer both should be optimized simultaneously[49]. Both hydrophilic drugs (such as tetracycline hydrochloride and doxorubicin hydrochloride) and hydrophobic ones (such as Rifampin and Paclitaxel), and biomacromolecules (such as proteins and DNAs) can be encapsulated in electrospun nanofibers. For drug delivery using electrospun nanofibers [51].

The pharmaceutical agent should be taken on the patch in amorphous or non-ionic form to optimize drug into the skin. The restrictions on drug release reduce due to high surface to volume ratio and three-dimensional porous structure of nanofibers [52].

On the other hand, localized drug delivery via electrospun nanofibers can lead to a reduction of the minimum required dose of a drug which provides decreased systemic absorption and unwanted side effects of drugs.In comparison with other forms of

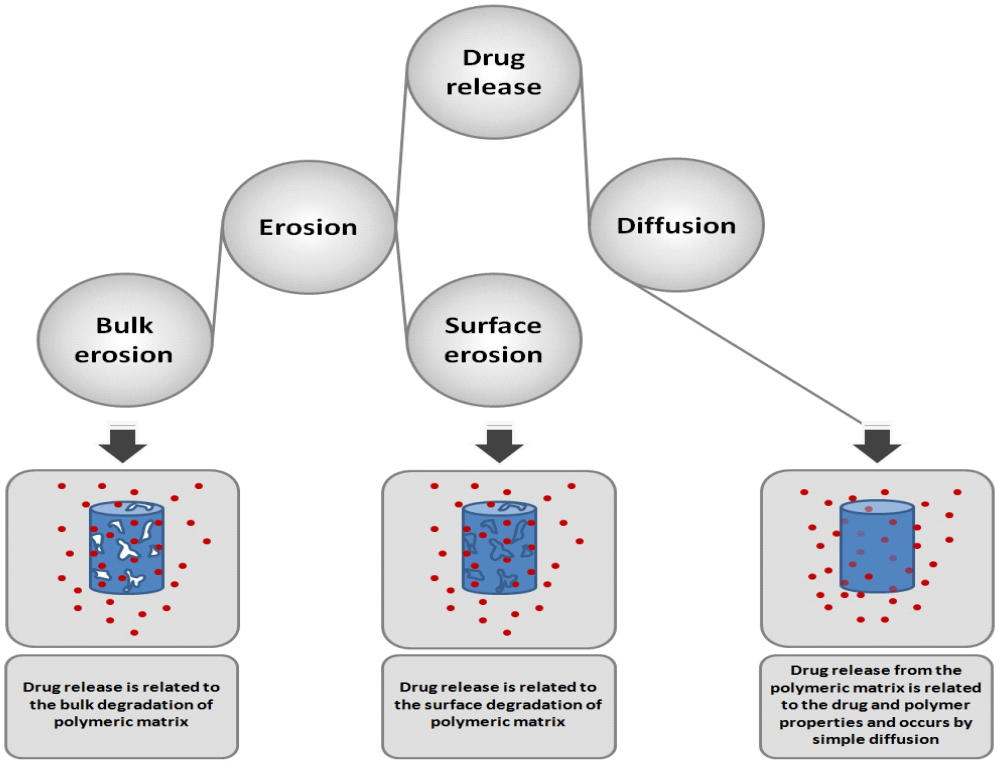

Fig. 3. Schematic drug release manners from electrospun nanofibers

drug carriers such as liposomes, hydrogels, and micro-nano structures produced by common methods, electrospun nanofibers have superior efficiency in encapsulating drugs and decreasing burst effect in the body. Furthermore, electrospun dressings over films prepared by casting methods lead to facilitation of the distribution of drug molecules to the surrounding environment [36,53].

Medications and or therapeutic agents loaded in electrospun nanofibers

As yet, transdermal patches have been used for the limited number of pharmaceutical agents' delivery which are steroid hormones, nicotine, nitrogly- cerine, analgesics such as Fentanyl(Opioid Analgesic) and Buprenorphine(Opioid Anal- gesic)(Madhaiyan, Sridhar, Sundarrajan, & Ramakrishna, 2013).

Four major categories of drugs or biological agents with distinct pharmacological applications consist of antibiotics and antimicrobial agents, antioxidants and antitumors, Anti-inflammatory drugs and vitamins. In addition to proteins with medical applications (such as enzymes and hormones), material such as ions, metals, and oxides, and natural materials obtained from plants or animals have an effective therapeutic potential if loaded in the patches [14].

an overview of the pharmacological agents in the electrospinning of polymeric patches and their application particularly in transdermal patches is presented in this section.

Table 2 shows an overview of medications loaded on/into electrospun nanofibers with the applications of transdermal drug delivery.

Antibiotics and antimicrobial agents

Among electrospun nanofibers containing antibiotics, Amoxicillin, Chlorhexidine, Ciprofloxacin HC1, Ornidazole, and Tetracycline Hydrochloride can be pointed out. In a study, core-shell patches, cellulose acetate (CA) and polyvinylpyrrolidone (PVP) were prepared by electrospinning method to investigate controlled the release of loaded Amoxicillin into the nanofibers

Table 2. Drugs and therapeutic agents loaded in electrospun matrices for transdermal drug delivery

Drug name	Drug category	Electrospun polymer	Loading technique	Ref.
Amoxicillin	Antibiotic	Cellulose acetate (CA)/ PVP	Coaxialelectrospinning	[54]
Tetracycline hydrochloride	Antibiotic	Poly(ethylene-co-vinyl acetate) (PEVA)/ Poly(lactic acid) (PLA)	Drug containing polymer solution electrospinning	[55]
Ornidazole	Antibiotic	Cellulose acetate (CA)/ PVP Polycaprolactone (PCL)	the drug containing polymer solution electrospinning Surface adsorption	[56,57]
N-halamin (CI-BTMP)	Antimicrobial agent	Cellulose acetate (CA)	the drug containing polymer solution electrospinning	[58]
Chlorhexidine	Topical Disinfectant	Cellulose acetate (CA)	Immobilization on nanofibers surface	[59]
Vitamin A	Vitamin	Cellulose acetate (CA)	immobilized on nanofibers	[60]
Vitamin E	Vitamin	Cellulose acetate (CA)	immobilized on nanofibers	[60]
Vitamin B12	Vitamin	Polycaprolactone (PCL)	drug containing polymer solution electrospinning	[61]
Naproxen	Antiinflammatory drug (NSAID)	Cellulose acetate (CA)	drug containing polymer solution electrospinning	[17]
Indomethacin	Anti-inflammatory drug (NSAID)	Cellulose acetate (CA)	the drug containing polymer solution electrospinning	[17]
Ibuprofen	Anti-inflammatory drug (NSAID)	Cellulose acetate (CA)	the drug containing polymer solution electrospinning	[17]
Sulindac	Anti-inflammatory drug (NSAID)	Cellulose acetate (CA)	the drug containing polymer solution electrospinning	[17]

for application on the gastrointestinal tract and transdermal patches [54].

In another work, by treatment with organic Titanate in the presence of water vapor, Chlorhexidine on electrospun cellulose acetate nanofibers was immobilized. Then the antibacterial activity of surface (by the inhibition region) against E.coli and S.epidermis bacteria with a simple diffusion model was observed [59].

The other study, electrospun cellulose acetate nanofiberscontainingN-halamine, an antimicrobial agent by (N-choloro-2, 2, 6, 6-tetramethyl-4-piperidinyl) sebacate (CI-BTMP), showed desired antibacterial performance over the films prepared by casting solution method. Furthermore, composite fibers showed an excellent bioavailability in mammalian cells [58]. Besides, Kenya yet al reported the release of 5% tetracycline hydrochloride from electrospun poly(ethylene-co-vinyl acetate) ¡poly(lactic acid) fibers and their blends [55].

Anti-inflammatory agents

most drugs, consumed in the world, are non-steroidal anti-inflammatory drugs (NSAIDs). This class of the drug is a desirable candidate for preliminary studies on controlled release processes [31].

In a study, four groups of these drugs including Naproxen, Indomethacin, Ibuprofen, and Sulindac (with different solubilities in water) were electrospun with CA and nanofibers with the diameter of 263-297 nm were produced. Drug release profile in CA nanofibers and CA film containing drugs was evaluated.

The result showed that no accumulation of drug crystals in nanofibers surface occurred, and appropriate encapsulation of drug molecules in fibers formed against the CA film with drug accumulation on its surface and the drug release in electrospun nanofibers was better than CA polymericfilm [17].

Vitamins in therapeutic applications

Vitamins are important elements for human health , but a limited number of investigations have been done on loaded vitamin in electrospun polymeric fibers. Among them, most studies have been on vitamin A and E [62], because vitamin A and E display various biological activities and protective functions [60].

In a study, these two vitamins immobilized on CA nanofibers with the diameter of 247–265 nm produced by electrospinning process.

Vitamin A was used in Trans retinoic acid or vitamin An acid (Retin-A) form that is a derivative of vitamin A or retinol, and vitamin E was used in a-tocopherol (Vit-E) form. A steady and gradual increase in the vitamin release from nanofibers was observed in this research, whereas a burst release from CA cast films was seen [60, 63, 64].

Other therapeutic agents loaded in electrospun nanofibers

There are some enzymes, hormones, nucleic acids and chemicals investigated for loading in electrospun nanofibers [34], but there has not been any promising result indicating that their transdermal application possibility, yet.

Conclusion and future outlook

TDDS have attracted great attention due to the delivery of therapeutic agent across the skin and the absorption of medications and entrance into the vascular system [1-3].

Controlled Drug release from TDDS reducing the dose fluctuations in the body can lead to the improvement of efficacy of pharmaceutical agents, stabilization of drugs diffusion profile, and greater bioavailability.

As the passage of hydrophilic drugs is limited into the deeper layers of skin, incorporation of these drugs with electrospun nanofibers has been suggested due to the advantages such as reduction in consumed dosage and systemic absorption of the drug, [8] but using electrospun nanofibers in TDDS is still in its early stages and it requires more studies.

ACKNOWLEDGMENTS

Authors are thankful to the School of advanced technologies in medicine, Tehran University of Medical Sciences, Tehran, Iran.

CONFLICT OF INTEREST

The authors confirm that this article content has not any conflicts of interest.

REFERENCES

1.Prausnitz MR, Langer R. Transdermal drug delivery. Nature Biotechnol. 2008; 26(11): 1261-1268.

2.Wokovich A, Prodduturi S, Doub W, Hussain A, Buhse L. Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute. European J Pharm Biopharm. 2006; 64(1): 1-8.

3. Seeram R, Zamani M, Molamma PP. Advances in drug delivery via electrospun and electrosprayed nanomaterials. Int J Nanomed. 2013: 2997.

4.Paskiabi FA, E, Amani A, Shokrgozar MA, Saber R, Faridi-Majidi R. Optimizing parameters on alignment of PCL/PGA nanofibrous scaffold: An artificial neural networks approach. Int J Biol Macromol. 2015; 81: 1089-1097.

5. Valenta C, Auner BG. The use of polymers for dermal and transdermal delivery. European J Pharm Biopharm. 2004; 58(2): 279-289.

6.Yun J, Im JS, Lee Y-S, Kim H-I. Electro-responsive transdermal drug delivery behavior of PVA/PAA/MWCNT nanofibers. European Polym J. 2011; 47(10): 1893-1902.

7.Faridi-Majidi R, Madani M, Sharifi-Sanjani N, Khoee S, Fotouhi A. Multi-Phase Composite Nanofibers via Electrospinning of Latex Containing Nanocapsules with Core-Shell Morphology. Polym Plast Technol Eng. 2012; 51(4): 364-368.

8.Kontogiannopoulos KN, Assimopoulou AN, Tsivintzelis I, Panayiotou C, Papageorgiou VP. Electrospun fiber mats containing shikonin and derivatives with potential biomedical applications. Int J Pharm. 2011; 409(1-2): 216-228.

9. Faridi-Majidi R, Sharifi-Sanjani N. In situ synthesis of iron oxide nanoparticles on poly(ethylene oxide) nanofibers through an electrospinning process. J Appl Poly Sci. 2007; 105(3): 1351-1355.

10.Madani M, Sharifi-Sanjani N, Hasan-Kaviar A, Choghazardi M, Faridi-Majidi R, Hamouda AS. PS/TiO 2 (polystyrene/titanium dioxide) composite nanofibers with higher surface-to-volume ratio prepared by electrospinning: Morphology and thermal properties. Polym Eng Sci. 2013;53(11):2407-2412.

11. Faridi-Majidi R, Sharifi-Sanjani N. In situ synthesis of iron oxide nanoparticles on poly(ethylene oxide) nanofibers through an electrospinning process. J Appl Polym Sci. 2007; 105(3): 1351-1355.

12.Abbasi A, Nasef MM, Takeshi M, Faridi-Majidi R. Electrospinning of nylon-6,6 solutions into nanofibers: Rheology and morphology relationships. Chinese J Polym Sci. 2014; 32(6): 793-804.

13. Sill TJ, von Recum HA. Electrospinning: Applications in drug delivery and tissue engineering. Biomet. 2008; 29(13): 1989-2006.

14.Pillay V, Dott C, Choonara YE, Tyagi C, Tomar L, Kumar P. A Review of the Effect of Processing Variables on the Fabrication of Electrospun Nanofibers for Drug Delivery Applications. J Nanomat. 2013; 2013: 1-22.

15. Suwantong O, Ruktanonchai U, Supaphol P. Electrospun cellulose acetate fiber mats containing asiaticoside or Centella asiatica crude extract and the release characteristics of asiaticoside. Polym. 2008; 49(19): 4239-4247.

16.Shen X, Yu D, Zhu L, Branford-White C, White K, Chatterton NP. Electrospun diclofenac sodium loaded Eudragit® L 100-55 nanofibers for colon-targeted drug delivery. International J Pharm. 2011; 408(1-2): 200-207.

17. Tungprapa S, Jangchud I, Supaphol P. Release characteristics of four model drugs from drug-loaded electrospun cellulose acetate fiber mats. Polym. 2007; 48(17): 5030-5041.

18.Choktaweesap N, Arayanarakul K, Aht-ong D, Meechaisue C, Supaphol P. Electrospun Gelatin Fibers: Effect of Solvent System on Morphology and Fiber Diameters. Polym J. 2007; 39(6): 622-631.

19.Yang D, Li Y, Nie J. Preparation of gelatin/PVA nanofibers and their potential application in controlled release of drugs. Carb Polym. 2007; 69(3): 538-543.

20. Lee KH, Kim HY, La YM, Lee DR, Sung NH. Influence of a mixing solvent with tetrahydrofuran andN,N-dimethylformamide on electrospun poly(vinyl chloride) nonwoven mats. Journal of Polymer Science Part B: Polym Phys. 2002; 40(19): 2259-2268.

21.Nirmala R, Nam KT, Navamathavan R, Park S-J, Kim HY. Hydroxyapatite Mineralization on the Calcium Chloride Blended Polyurethane Nanofiber via Biomimetic Method. Nanoscale Res Let. 2010.

22.Verreck G, Chun I, Rosenblatt J, Peeters J, Dijck AV, Mensch J. Incorporation of drugs in an amorphous state into electrospun nanofibers composed of a water-insoluble, nonbiodegradable polymer. J Control Release. 2003; 92(3): 349-360.

23. Wannatong L, Sirivat A, Supaphol P. Effects of solvents on electrospun polymeric fibers: preliminary study on polystyrene. Polym Int.2004; 53(11): 1851-1859.

24. Maretschek S, Greiner A, Kissel T. Electrospun biodegradable nanofiber nonwovens for controlled release of proteins. J Control Release. 2008; 127(2): 180-187.

25.Kim K, Luu YK, Chang C, Fang D, Hsiao BS, Chu B. Incorporation and controlled release of a hydrophilic antibiotic using poly(lactide-co-glycolide)-based electrospun nanofibrous scaffolds. J Control Release. 2004; 98(1): 47-56.

26.Ranganath SH, Wang C-H. Biodegradable microfiber implants delivering paclitaxel for post-surgical chemotherapy against malignant glioma. Biomat. 2008; 29(20): 2996-3003.

27.Rošic R, Pelipenko J, Kocbek P, Baumgartner S, Bešter-Rogaè M, Kristl J. The role of rheology of polymer solutions in predicting nanofiber formation by electrospinning. European Polym J. 2012; 48(8): 1374-1384.

28. Sangsanoh P, Supaphol P. Stability Improvement of Electrospun Chitosan Nanofibrous Membranes in Neutral or Weak Basic Aqueous Solutions. Biomacromol. 2006; 7(10): 2710-2714.

39.Kenawy E-R, Abdel-Hay FI, El-Newehy MH, Wnek GE. Controlled release of ketoprofen from electrospun poly(vinyl alcohol) nanofibers. Mat Sci Eng A. 2007; 459(1-2): 390-396.

30.Moradzadegan A, Ranaei-Siadat S-O, Ebrahim-Habibi A, Barshan-Tashnizi M, Jalili R, Torabi S-F. Immobilization of acetylcholinesterase in nanofibrous PVA/BSA membranes by electrospinning. Eng Life Sci. 2010; 10(1): 57-64.

31.Luong-Van E, Grøndahl L, Chua KN, Leong KW, Nurcombe V, Cool SM. Controlled release of heparin from poly(å-caprolactone) electrospun fibers. Biomat. 2006; 27(9): 2042-2050.

32.Wutticharoenmongkol P, Sanchavanakit N, Pavasant P, Supaphol P. Preparation and Characterization of Novel Bone Scaffolds Based on Electrospun Polycaprolactone Fibers Filled with Nanoparticles. Macromol Biosci. 2006; 6(1): 70-77.

33. Pornsopone V, Supaphol P, Rangkupan R, Tantayanon S. Electrospinning of methacrylate-based copolymers: Effects of solution concentration and applied electrical potential on morphological appearance of as-spun fibers. Polym Eng Sci. 2005; 45(8): 1073-1080.

34. Konwarh R, Karak N, Misra M. Electrospun cellulose acetate nanofibers: The present status and gamut of biotechnological applications. Biotechnol Adv. 2013; 31(4): 421-437.

35. Beachley V, Wen X. Polymer nanofibrous structures: Fabrication, biofunctionalization, and cell interactions. Prog Polym Sci. 2010; 35(7): 868-892.

36.Zeng J, Yang L, Liang Q, Zhang X, Guan H, Xu X. Influence of the drug compatibility with polymer solution on the release kinetics of electrospun fiber formulation. J Control Release. 2005; 105(1-2): 43-51.

37.Naderi N, Sharifi-Sanjani N, Khayyat-Naderi B, Faridi-Majidi R. Preparation of organic–inorganic nanocomposites with core-shell structure by inorganic powders. J Appl Polym Sci. 2006; 99(6): 2943-2950.

38. Liao IC, Chen S, Liu JB, Leong KW. Sustained viral gene delivery through core-shell fibers. J Control Release. 2009; 139(1): 48-55.

39. Saraf A, Baggett LS, Raphael RM, Kasper FK, Mikos AG. Regulated non-viral gene delivery from coaxial electrospun fiber mesh scaffolds. J Control Release. 2010; 143(1): 95-103.

40.Liao IC, Leong KW. Efficacy of engineered FVIII-producing skeletal muscle enhanced by growth factor-releasing co-axial electrospun fibers. Biomat. 2011; 32(6): 1669-1677.

41.Xu X, Yang L, Xu X, Wang X, Chen X, Liang Q. Ultrafine medicated fibers electrospun from W/O emulsions. J Control Release. 2005; 108(1): 33-42.

42. He S, Xia T, Wang H, Wei L, Luo X, Li X. Multiple release of polyplexes of plasmids VEGF and bFGF from electrospun fibrous scaffolds towards regeneration of mature blood vessels. Acta Biomaterialia. 2012; 8(7): 2659-2669.

43.Yang Y, Li X, Qi M, Zhou S, Weng J. Release pattern and structural integrity of lysozyme encapsulated in core–sheath structured poly(dl-lactide) ultrafine fibers prepared by emulsion electrospinning. European J Pharm Biopharm. 2008; 69(1): 106-116.

44. Wang Y, Wang B, Qiao W, Yin T. A Novel Controlled Release Drug Delivery System for Multiple Drugs Based on Electrospun Nanofibers Containing Nanoparticles. J Pharm Sci. 2010; 99(12): 4805-4811.

45. Ranjbar-Mohammadi M, Rabbani S, Bahrami SH, Joghataei MT, Moayer F. Antibacterial performance and in vivo diabetic wound healing of curcumin loaded gum tragacanth/poly(å-caprolactone) electrospun nanofibers. Mat Sci Eng C. 2016; 69: 1183-1191.

46. Xu J, Jiao Y, Shao X, Zhou C. Controlled dual release of hydrophobic and hydrophilic drugs from electrospun poly(l-lactic acid) fiber mats loaded with chitosan microspheres. Mat Let. 2011; 65(17-18): 2800-2803.

47.Chunder A, Sarkar S, Yu Y, Zhai L. Fabrication of ultrathin polyelectrolyte fibers and their controlled release properties. Colloids Surf B Biointerfaces. 2007; 58(2): 172-179.

48. Im JS, Lee SK, Bai BC, Lee Y-S. Prediction and characterization of drug release in a multi-drug release system. J Ind Eng Chem. 2012; 18(1): 325-330.

49.Taepaiboon P, Rungsardthong U, Supaphol P. Drug-loaded electrospun mats of poly(vinyl alcohol) fibres and their

release characteristics of four model drugs. Nanotechnol. 2006; 17(9): 2317-2329.
50. Mendes AC, Gorzelanny C, Halter N, Schneider SW, Chronakis IS. Hybrid electrospun chitosan-phospholipids nanofibers for transdermal drug delivery. Int J Pharm. 2016; 510(1): 48-56.
51. Liang D, Hsiao BS, Chu B. Functional electrospun nanofibrous scaffolds for biomedical applications. Adv Drug Deliv Rev. 2007; 59(14): 1392-1412.
52. 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.
53. Meng ZX, Xu XX, Zheng W, Zhou HM, Li L, Zheng YF. Preparation and characterization of electrospun PLGA/gelatin nanofibers as a potential drug delivery system. Colloids Surf B Biointerfaces. 2011; 84(1): 97-102.
54.Castillo-Ortega MM, Nájera-Luna A, Rodríguez-Félix DE, Encinas JC, Rodríguez-Félix F, Romero J. Preparation, characterization and release of amoxicillin from cellulose acetate and poly(vinyl pyrrolidone) coaxial electrospun fibrous membranes. Mat Sci Eng C. 2011; 31(8): 1772-1778.
55. Kenawy E-R, Bowlin GL, Mansfield K, Layman J, Simpson DG, Sanders EH. Release of tetracycline hydrochloride from electrospun poly(ethylene-co-vinylacetate), poly(lactic acid), and a blend. J Controlled Release. 2002; 81(1-2): 57-64.
56.Meinel AJ, Germershaus O, Luhmann T, Merkle HP, Meinel L. Electrospun matrices for localized drug delivery: Current technologies and selected biomedical applications. European J Pharm Biopharm. 2012; 81(1): 1-13.
57. Bölgen N, Vargel Ý, Korkusuz P, Menceloðlu YZ, Piþkin E. In vivo performance of antibiotic embedded electrospun PCL membranes for prevention of abdominal adhesions. J Biomed Mat Res B Appl Biomat. 2007; 81B (2): 530-543.
58. Sun X, Zhang L, Cao Z, Deng Y, Liu L, Fong H. Electrospun Composite Nanofiber Fabrics Containing Uniformly Dispersed Antimicrobial Agents As an Innovative Type of Polymeric Materials with Superior Antimicrobial Efficacy. ACS Appl Mat Interfaces. 2010; 2(4): 952-956.
59. Chen L, Bromberg L, Hatton TA, Rutledge GC. Electrospun cellulose acetate fibers containing chlorhexidine as a bactericide. Polym. 2008; 49(5): 1266-1275.
60.Taepaiboon P, Rungsardthong U, Supaphol P. Vitamin-loaded electrospun cellulose acetate nanofiber mats as transdermal and dermal therapeutic agents of vitamin A acid and vitamin E. European J Pharm Biopharm. 2007; 67(2): 387-397.
61. Madhaiyan K, Sridhar R, Sundarrajan S, Venugopal JR, Ramakrishna S. Vitamin B12 loaded polycaprolactone nanofibers: A novel transdermal route for the water soluble energy supplement delivery. Int J Pharm. 2013; 444(1-2): 70-76.
62.Paneva D, Manolova N, Argirova M, Rashkov I. Antibacterial electrospun poly([-caprolactone)/ascorbyl palmitate nanofibrous materials. Int J Pharm. 2011; 416(1): 346-355.
63. Cao H, Jiang X, Chai C, Chew SY. RNA interference by nanofiber-based siRNA delivery system. J Control Release. 2010; 144(2): 203-212.
64.Arthanari S, Mani G, Jang JH, Choi JO, Cho YH, Lee JH. Preparation and characterization of gatifloxacin-loaded alginate/poly (vinyl alcohol) electrospun nanofibers. Artificial Cells, Nanomed Biotechnol. 2014: 1-6.