REVIEW

A precise look at electrospinning parameters in fabricating the polymeric nanofibers: a review on synthetic and natural polymers

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Abstract

Background Polymeric nanofibers have been used in various applications, including drug delivery, wound dressing, tissue engineering, biosensors, and implants. A wide range of cargoes such as drugs, metal nanoparticles, proteins, cells, and herbal extracts could be loaded into these systems. Among all the different methods of fabricating fibers, the electrospinning technique has got a significant interest. Fibers could be generated from synthetic and natural polymers and even the mixture of these polymers using simple, co-axial, or side-by-side spinneret. Polymers should be either dissolved or dispersed in their solvents, making solutions or emulsions, respectively. Electrospinning processing conditions, including solution parameters (polymer molecular weight, polymer concentration, and solvent) and equipment parameters (feeding rate, applied voltage, needle-to-collector distance, and speed of collector in rotating collectors) could influence diameter, morphology, or orientation of nanofibers.

Area Covered This article highlights synthetic polymers (such as polyvinylpyrrolidone, polyvinyl alcohol, polyurethane, polyethylene oxide, poly e-caprolactone, polylactic acid, and poly(lactic-co-glycolic acid)) and natural polymers (such as gelatin, chitosan, collagen, silk fibroin, and zein) considering their electrospinning process variables. Also, the electrospinning process and formulation parameters are summarized in the most recent studies.

Expert Opinion Choosing proper electrospinning parameters is crucial in fabricating nanofibers. This article summarizes the most important electrospinning factors, including the active ingredient, molecular weight and concentration of applied polymers, solvent, voltage, etc. This article can provide a means to quickly assess the preparation conditions of nanofibers and guide formulators to choose the most suitable electrospinning conditions for nanofiber preparation.

Keywords Nanofibers · Electrospinning · Electrospinning parameters · Synthetic polymers · Natural polymers

Introduction

Nanofibers are fibers in nanoscale diameters, usually in the range of 50–1000 nm, produced from polymer solutions or polymer melts. They have numerous advantages, including large surface area, suitable physiochemical features,

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flexibility, high drug loading capacity, good mechanical performance, and ease of functionalization and surface modification (Eatemadi et al. 2016; Thakkar and Misra 2017; Nunes and Philipps-Wiemann 2018; Rasouli et al. 2019). Moreover, fibers can imitate the natural extracellular matrix (ECM) and improve the absorption and bioavailability of poorly soluble drugs (Rasouli et al. 2019; Vass et al. 2019).

Nanofibers are currently used in different biomedical, pharmaceutical, and engineering fields. Nanofibers have been studied extensively in wound healing, drug delivery, organ and tissue regeneration, implantable devices, biosensing, removal of toxins from plasma (Rasouli et al. 2019), biocatalysts, stent coating (Nirwan et al. 2022), and postoperative adhesion prevention (Babadi et al. 2022b) (Fig. 1). Moreover, nanofibers have been used for the controlled delivery of drugs, growth factors, proteins, genes, and antibiotics (Thakkar and Misra 2017; Shahriar et al. 2019).
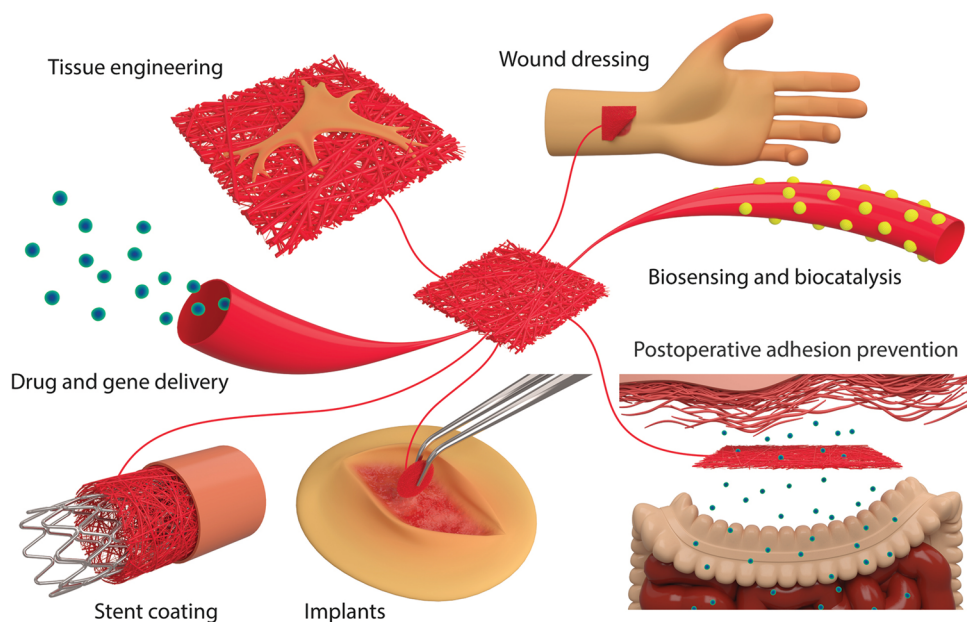
Fig. 1 Schematic representation of nanofibers application in the medical field

According to the incorporation method, fibers may have rapid, extended, or delayed release of the loaded cargoes (Chou et al. 2015; Sebe et al. 2015).

Several techniques for manufacturing nanofibrous scaffolds include electrospinning, phase separation, self-assembly, template-directed, and hydrothermal synthesis. Electrospinning, self-assembly, and phase separation are the three most important methods. Electrospinning is the most convenient, versatile, cost-effective, and widely used scaffold fabrication technique, which has emerged as an excellent method to render different kinds of polymers into multi-functional ultrafine fibers with diameters ranging from tens of nanometers to several microns (Eatemadi et al. 2016; Thakkar and Misra 2017; Shahriar et al. 2019). Therefore, in this manuscript, we have focused on this preparation technique.

A standard electrospinning machine consists of a high-voltage power supply, a syringe with a needle tip (spinneret), and a conducting collector (Eatemadi et al. 2016). During electrospinning, a polymer solution or melt in a syringe with a capillary orifice is fed through the spinneret at a constant pump rate. A sufficiently strong electrostatic field is applied to the polymer solution. Afterward, a droplet of the polymer solution forms at the tip of the capillary, which causes a deformation of the solution from a spherical to a conical shape, called a "Taylor cone" (Eatemadi et al. 2016; Vass et al. 2019). After exceeding a critical voltage value, the repulsive electrical forces overcome the surface tension of the solution, the cone becomes unstable, and fibers are extruded from the syringe tip, accelerating toward the collection plate. Simultaneously, the solvent evaporates, and the charged jets of polymer solution rapidly dry leading to the formation of a solid fiber, which is collected on the collector

with an opposite polarity (Eatemadi et al. 2016; Thakkar and Misra 2017; Vass et al. 2019).

Several parameters can affect the electrospinning process and the size and surface morphology of the resulting fibers. These factors include (1) solution factors (solvent type, polymer molecular weight, and polymer solution properties including concentration, viscosity, conductivity, polarity, and surface tension); (2) operating factors (collector type, electric field strength, needle-collector distance, nozzle gauge and geometry, and feeding rate); and (3) environmental conditions (the relative humidity and temperature) (Fig. 2) (Thakkar and Misra 2017; Bhattarai et al. 2019; Pant et al. 2019).

The electrospinning method is governed by all these various parameters, and the structural properties of obtained nanofibers notably depend on the deliberate manipulation of different parameters. Studying the effects of these parameters is helpful in optimizing the structure and function of resulting nanofibers. In this context, the optimization of solution concentration can be the first step. In the electrospinning process, a minimum concentration is required to form nanofibers. Below the minimum required concentration, the process results in a mixture of beads and fibers. When the concentration increases, beads turn to spindle-like structures and then these defects disappear. Further increase in the concentration can increase the mean diameter of fibers due to an increased viscosity resistance. Besides, there is an optimal concentration range, and when the concentration increases above the range, the flow cannot be maintained between the tip and collector, and beaded or defective nanofibers are fabricated (Bhardwaj and Kundu 2010; Haider et al. 2018).

Fig. 2 Schematic representation of electrospinning machine and process parameters
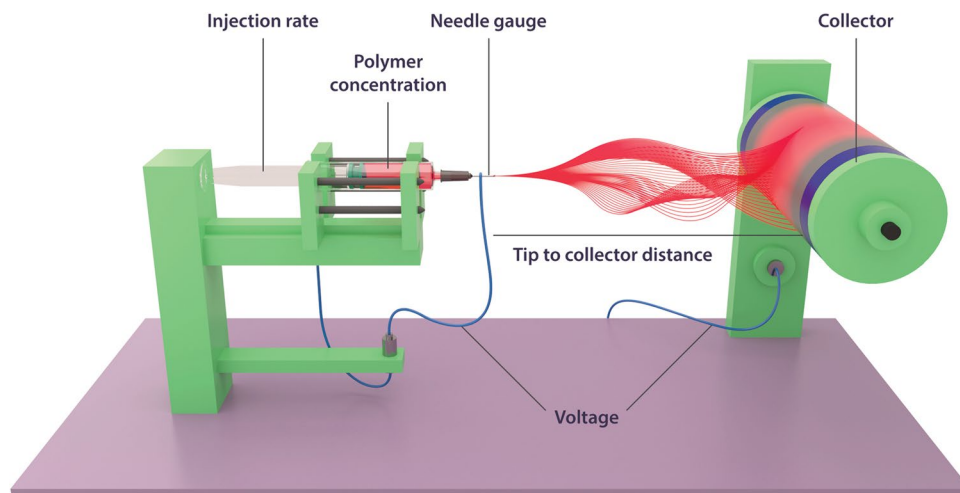
Considering other factors, most solution parameters are related to the selected polymer. The physicochemical properties of the polymer and its molecular weight determine applicable solvents, solution conductivity, and surface tension as a function of solvent composition. Besides, the molecular weight and concentration of polymers or polymers blend affect the viscosity of electrospinning solution as a considerable parameter in electrospinning. Generally, higher molecular weight can ensure the uniformity of nanofibers due to higher solution viscosity in lower concentrations. It should be kept in mind that there is an optimal point for different process parameters and an ejection difficulty for jets when the viscosity is higher than the optimum level. Also, the polymer and solvent types influence conductivity, and an increase in conductivity can decrease the mean diameter of nanofibers (Bhardwaj and Kundu 2010; Haider et al. 2018).

In a study on bioabsorbable amorphous polylactic acid (PLA), it was indicated that the nanofiber diameter and morphology depended on various electrospinning parameters. In addition to polymer concentration, the potential effect of the addition of various salts to the polymer solution was investigated. As shown in Fig. 3, solutions containing 1 wt % salts resulted in bead-free morphology. This can be due to an increase in the charge density of ejected jet's surface leading to higher elongation forces, smaller and more spindle-like beads, and less mean diameter of fibers. Also, it is worth noting that the size of ions in different salts could affect the size distribution of nanofibers and the solution containing 1 wt % NaCl showed the smallest mean nanofiber diameter. A smaller atomic radius causes higher charge density and subsequently higher elongation forces and smaller nanofiber diameter (Zong et al. 2002).

Regarding the operating parameters, applied voltage is one of the main determinative factors. Each electrospinning procedure has a threshold voltage, and the nanofiber formation occurs above this limit. While the voltage needs to be optimized for the process, the flow rate should also be optimized and kept at a minimum to give the solvent enough time to evaporate. Furthermore, optimizing tip-to-collector distance can improve the uniformity of nanofibers, and beads can be observed with less or more distance. Moreover, ambient parameters can affect the obtained nanofibers by affecting solution parameters and the electrospinning process (Bhardwaj and Kundu 2010). In a study on poly e-caprolactone (PCL), the morphology of nanofibers was investigated by electron microscopy after alterations in solution concentration, feeding rate, applied voltage, and tip-to-collector distance, and the obtained results could present the impact of different parameters (Fig. 4) (Bosworth and Downes 2012).

Classically, electrospinning systems have two types (horizontal and vertical) (Guo et al. 2022). Additionally, several electrospinning systems have been produced, such as side-by-side, co-axial, multi-jet, and emulsion electrospinning (Fig. 5). These techniques provide superior properties, including higher drug loading capabilities as well as more versatile and tunable release profiles. The co-axial (core–shell) electrospinning method can simultaneously electrospun two immiscible phases (Hu et al. 2014; Choi et al. 2015). Compared to the conventional process, this method has two aligned capillaries instead of one, which minimizes the interaction between core and shell ingredients and protects the core from exposure to harsh environments (Choi et al. 2015). The production rate is enhanced by increasing the number of nozzles through multiple-jet electrospinning. This process has greater control over fiber distribution. Another method is side-by-side electrospinning. This method loads two polymer solutions in separate spinnerets, offering a high surface area and a controlled morphology (Bhattarai et al. 2019). As one of the interesting methods, emulsion electrospinning uses emulsified polymer solutions to produce nanofibers. The

Fig. 3 Effects of variations in electrospinning parameters on the PLA nanofibrous structures determined by SEM analysis (the feeding rate: 0.02 mL/min exhibiting; the scale bar 10 μm) (reprinted with minor modification from Ref. (Zong et al. 2002), with permission). *PLA* polylactic acid, *SEM* scanning electron microscopy
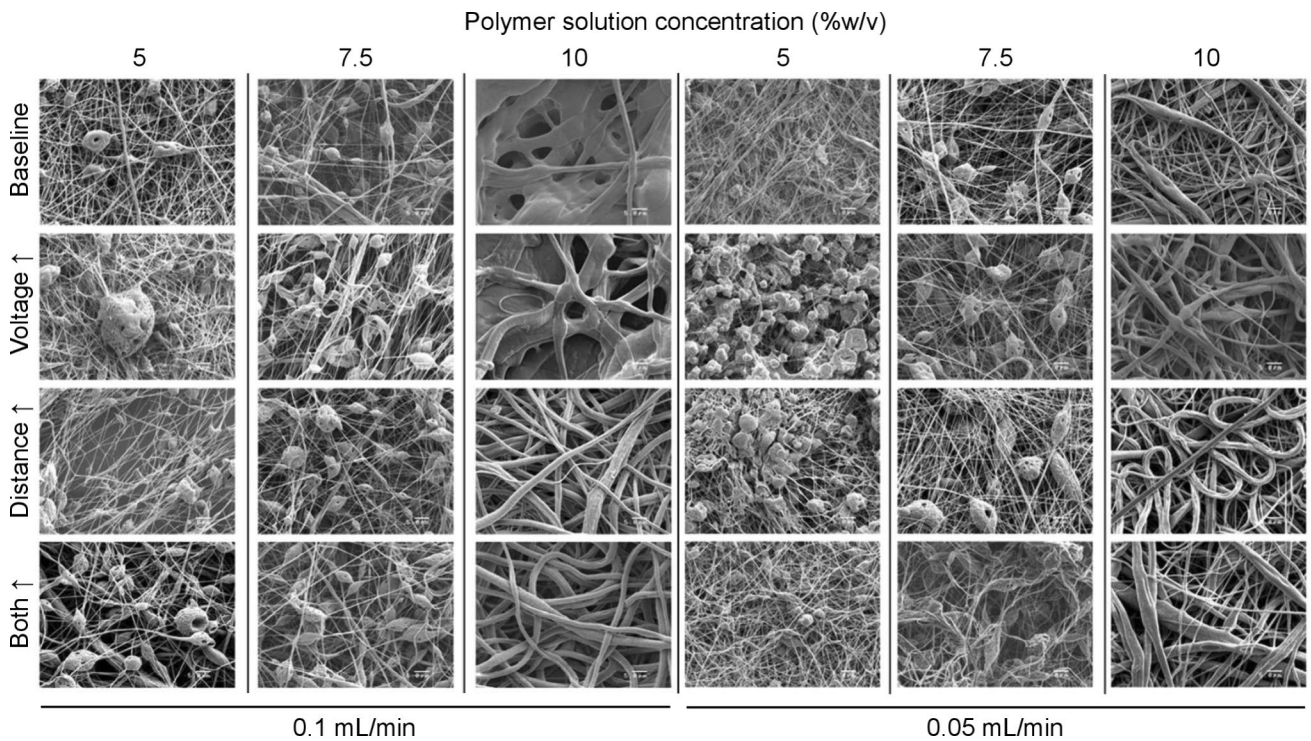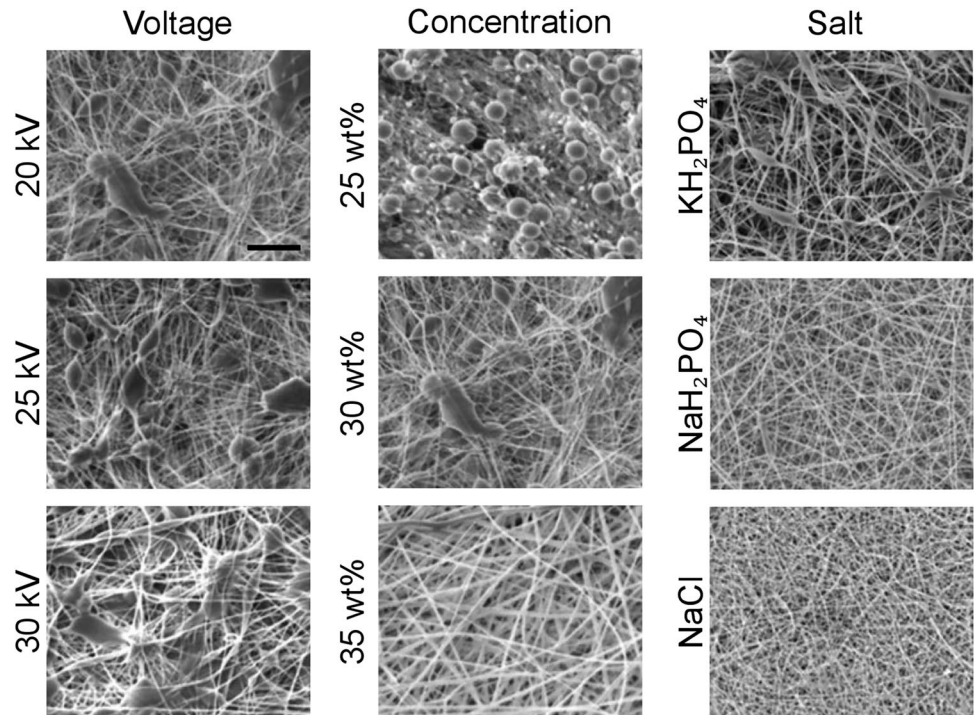
Fig. 4 Effects of variations in PCL concentration (5, 7.5, and 10%w/v), flow rate (0.1 and 0.05 mL/min), voltage (25 kV), and needle-to-collector distance (10 cm) on the PCL nanofibrous structures determined by SEM analysis, as compared to the baseline voltage and distance of 15 kV and 5 cm, respectively (scale bar 5 μm) (reprinted with minor modification from Ref. (Bosworth and Downes 2012), with permission). *PCL* poly e-caprolactone, *SEM* scanning electron microscopy

Fig. 5 Schematic representation of horizontal and vertical electrospinning systems, as well as simple, co-axial, side-by-side, and emulsion electrospinning methods
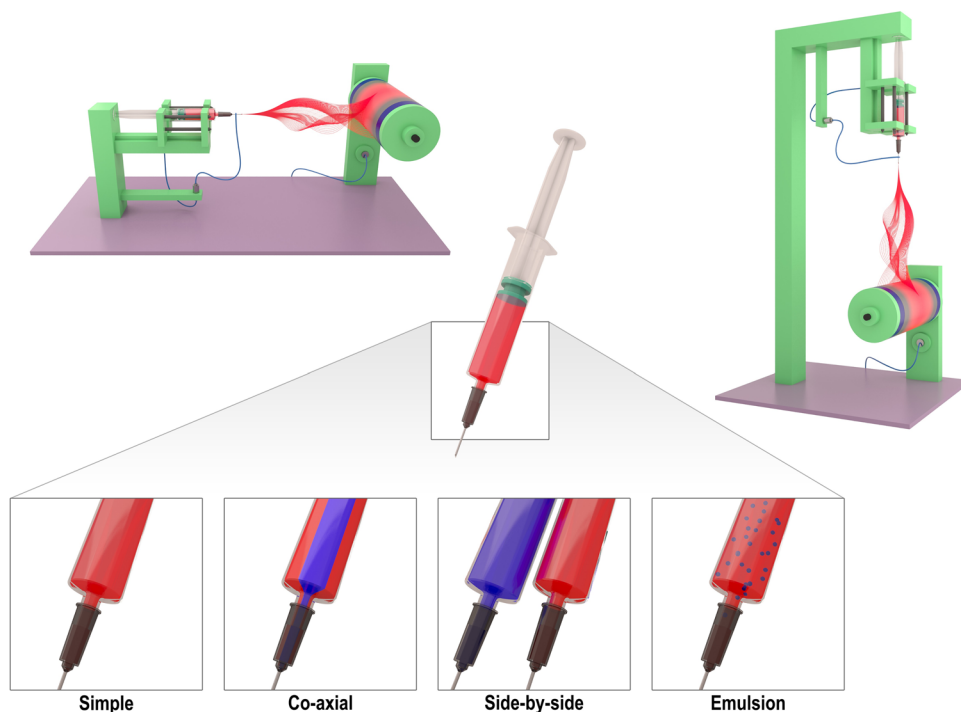
obvious difference between core–shell and emulsion electrospinning is that co-axial electrospinning works based on physical separation using two electrospinning tips and two polymer solutions. However, emulsion electrospinning is based on stretching and evaporation-induced demulsification (Hu et al. 2014).

The versatility of the electrospinning technique appears in the possibility of spinning several polymers (natural or synthetic polymers and polymeric blends) (Rasouli et al. 2019). Several synthetic polymers have been utilized to prepare nanofibers through electrospinning, such as PLA (Serio et al. 2019), poly(lactic-co-glycolic acid) (PLGA) (Yu et al. 2019), polyurethane (PU) (Balaji et al. 2016), PCL (Babadi et al. 2022a, b; Talimi et al. 2022a, b), polyethylene oxide (PEO), polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP) (Sharifi et al. 2022). Besides, a variety of natural polymers have been applied in electrospinning, such as gelatin (Okutan et al. 2014), collagen (Dhand et al. 2016), silk (Chomachayi et al. 2016), and zein (Vogt et al. 2018). Moreover, polysaccharides such as alginate (Vigani et al. 2018), chitosan (Amiri et al. 2018), dextran (Sheet et al. 2018), cellulose (Shi et al. 2013a, b; Huang et al. 2016), chitin (Moon et al. 2019), starch (Komur et al. 2017), and hyaluronic acid (Figueira et al. 2016) have recently been widely used in electrospinning techniques. Natural polymers display better biocompatibility and lower immunogenicity than synthetic ones. Yet, their physical and mechanical properties are more difficult to modify (Teixeira et al. 2019).

In this article, we summarized and explained the electrospinning parameters of various natural and synthetic polymers. Each section explains a brief description of the polymer, nanofibers characteristics, and optimized electrospinning parameters. In tables presented in each section, we tried to summarize the most important electrospinning factors including the active ingredient, molecular weight and concentration of applied polymers, solvent, and voltage. In each table, records are sorted as free and cargo-loaded polymers by simple spinneret and polymer blends using side-by-side or co-axial spinneret. The tables can provide a means to assess preparation conditions of nanofibers quickly and as a guide for nanofiber fabrication.

Synthetic polymers

Polyvinylpyrrolidone

PVP is a polymeric lactam that has US Food and Drug Administration (FDA) approval. This polymer consists of N-vinylpyrrolidone monomers, and it is characterized by its high biocompatibility, film-forming abilities, and chemical stability. All these properties along with its non-toxicity and safety have made PVP one of the most important materials in pharmaceutical technology with a wide variety of applications. This polymer has been used in numerous fields, such as food packaging, textile auxiliaries, adhesives, cosmetics, medicine, and biological engineering materials (Kurakula and Rao 2020). PVP has been used in fabricating nanofibers through the electrospinning process. The characteristics as

mentioned above are also important for the electrospinning process. Studies have shown that various molecular weights including 58 kDa (Yang et al. 2018c), 360 kDa (Dai et al. 2012), 1300 kDa (Wang et al. 2015), etc. have been used in this process. The PVP concentration in the electrospinning solution was usually 5–16% (w/v) (Table 1). This non-ionic and amorphous polymer dissolves well in various aqueous and organic solvents such as water, acids, ethanol, methanol, amines, chloroform, and dichloromethane (DCM) (Kurakula and Rao 2020). However, ethanol is mostly used in PVP nanofibers as a solvent for electrospinning (Table 1). Some recent studies on PVP nanofiber fabrication considering process variables are summarized in Tables 1 and S1 (Online Resource 1).

Emodin is a derivative of a Chinese herb that can accelerate wound healing (Dai et al. 2012). Some researchers fabricated PVP nanofibers containing emodin. 10% (w/v) polymeric solution in ethanol was prepared from PVP with a molecular weight of 360 kDa. Emodin-loaded nanofibers demonstrated shrinkage of wound area and re-epithelization in mice skin wound model (Dai et al. 2012).

In another investigation, metronidazole-loaded nanofibers were fabricated with different concentrations of PVP. They showed that the PVP content directly influenced the diameter and mechanical properties of nanofibers. On the other hand, there were no significant differences in the release patterns of metronidazole from the nanofibers with different PVP concentrations (Tuğcu-Demiröz et al. 2020).

In another study, curcumin-PVP nanofibers improved curcumin bioavailability. PVP (1300 kDa) solution at the fixed concentration of 10% (w/v) was prepared in an acetic ether medium at 40 °C. Nanofibers were fabricated through a vertical setup. The diameter of PVP and PVP-curcumin nanofibers were 888 ± 134 and 485 ± 123 nm, respectively. The presence of curcumin might increase the conductivity of the solution, therefore a decrement in nanofiber diameter was observed. Pharmacokinetic studies were conducted on two groups of mice receiving free curcumin or the novel nanofiber formulation orally. The area under the plasma concentration curve was increased by 10-fold showing an increment in bioavailability. Moreover, in vivo anticancer study revealed that nanofiber formulation inhibited tumor growth more efficiently (Wang et al. 2015).

Another research group prepared PVP nanofibers containing isosorbide dinitrate. PVP nanofibers were fabricated from a polymer solution of 8–14% (w/v) in ethanol. As this polymer concentration range did not affect nanofiber diameter, 8% (w/v) PVP (1000 kDa) was used. According to data, adding polyethylene glycol 400 (PEG-400) to the polymer solution improved characteristics (appearance and flexibility) of fibers. Furthermore, the weight ratio of PVP and PEG could alter surface characteristics. The weight ratio of PVP to PEG 8:1 was the optimum ratio, which led to bead-free fibers. Two formulations were administered sublingually to rats, including isosorbide dinitrate tablets and nanofibers. The fiber formulation showed higher and faster drug absorption. The relative bioavailability of this novel formulation to the tablet was 152% (Chen et al. 2016).

In another study, diclofenac nanofibers were prepared using the co-axial electrospinning technique. A thin layer of shellac was coated on them to protect PVP and drug nanocomposites from acidic erosion. 35% (w/v) PVP (58 kDa) and 5% (w/v) drug in ethanol (as the core fluid) with a flow rate of 0.8 mL/h and 10% (w/v) shellac (as sheath fluid) with a flow rate of 0.2 mL/h were electrospun. These core–shell nanofibers can be used as colon-targeted pulsatile drug delivery systems. For comparison, monolithic nanocomposites containing PVP, and diclofenac were prepared (the preparation method was the same as common electrospinning with a flow rate of 1 mL/h). Co-axial nanofibers had smaller diameters (570 ± 40 nm) than monolithic nanofibers (720 ± 80 nm). The ex vivo permeability study was conducted on a pig intestine. Data exhibited that permeation efficacy was improved (over 20-fold) compared to raw diclofenac particles (Yang et al. 2018c).

Polyvinyl alcohol

PVA is a synthetic polymer with an elastic nature containing hydroxyl groups in its structure. This polymer has displayed suitable properties such as inherent non-toxicity, good water solubility, non-carcinogenicity, good flexibility, bioadhesive characteristics, and gas permeability (Gaaz et al. 2015; Wali et al. 2018). It is a thermostable and semi-crystalline polymer with great transparency (Gaaz et al. 2015), which is degradable by biological organisms. PVA also has swelling capability in aqueous solutions and a gel-forming feature. These characteristics make PVA a promising candidate to be used as a supporting material in various applications including pharmaceutical uses, food packaging, paper industry, and optical polarizers (Gaaz et al. 2015). PVA with molecular weight ranging from 70 to 130 kDa has been mostly used in electrospinning studies. Almost in all these studies, water has been used as a solvent and the polymer concentration was in the range of 6–16% (w/v) (Table 2). Table 2 lists some recent publications on PVA electrospinning conditions (More information is presented in Table S2, Online Resource 1).

Coptis chinensis is a Chinese medicinal plant. Due to the presence of various alkaloids, the extract of this plant has different pharmacological effects. Accordingly, a research group fabricated PVA nanofibers containing *Coptis chinensis* extract. PVA solution (10% (w/v)) was prepared in 80 °C water. The effect of different PVA molecular weights (75 and 110 kDa) on the morphology of nanofibers was studied. Results revealed that PVA molecular weight played a critical

Table 1 Process variables of studies on PVP nanofibers

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
PVP	MPE	Drug delivery	1300	PVP/MPE 10:6	Simple	Ethanol	387–586	2	0.3	10	0.45 mm	12	–	Sriyanti et al. (2018)
PVP	Curcumin	Cancer drug delivery	1300	10	Simple	Acetic ether	485±123	4	2	15	0.5 mm	15	Ambient	Wang et al. (2015)
PVP	Metronidazole	Vaginal drug delivery	1000	10, 12.5, 15	Simple	Ethanol	PVP: 445 to 1752[b], PVP-metronidazole: 955 to 2386[b]	PVP/metronidazole: 1	1, 2.5, 10	12, 16	18 G	15	–	Tuğcu-Demiröz et al. (2020)
PVP	Diclofenac sodium	Buccal drug delivery	360	10 wt %	Simple	Water	387	–	0.3–0.8	15	22 G	25	RT, –	Sharifi et al. (2022)
PVP, PEG-400[c]	ISDN	Sublingual drug delivery	1000	8	Simple	Ethanol	–	–	1.6	9	20 G	13	23±1, 50±5	Chen et al. (2016)
PVP, hyaluronic acid	Ferulic acid, ε-polylysine	Ocular drug delivery	PVP: 360, hyaluronic acid: 600–1100	PVP: 5, hyaluronic acid: 0.8	Simple	Ethanol/water 4:6	116±48	Overnight	0.1, 0.5, 0.6	15, 18, 25	22 G	25	RT, 30–40	Grimaudo et al. (2020)
PVP, CNC	Silver nanoparticles	Antibacterial activity	40, 360 (1:1)	PVP: 16.6 wt %, CNC: 4%	Simple	DMF	131±46	24	1	18	20 G	20	–	Huang et al. (2016)
PVP, CA	Ibuprofen	Transdermal patch	PVP:1000, CA: 52	Blend solution: 15 wt % (PVP/CA 1:4)	Simple	Acetone/DMA 1:1	432±73	3	0.5	13	8 G	15	25, 40	Shi et al. (2013a)
PVP, HPβCD	Acyclovir (complexed with HPβCD)	Antiviral drug delivery	40	PVP: 50, HPβCD: 180	Simple	Ethanol/water 3:1	985±385[b]	Acyclovir/PVP/HPβCD: Overnight	0.5	15	21, 23 G	15	20, 50	Celebioglu and Uyar (2021)

Table 1 (continued)

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/ needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
PVP, PLA	Doxorubicin	Drug delivery	PVP: 1300, PLA: 111	PVP: 16, PLA: 9	Simple	DMF (for PVP), DCM/DMF 1:1 (for PLA), DMSO (for doxorubicin)	–	–	1.5	11–14	22 G	10	–	Park et al. (2018)
PVP, chitosan	Triamcinolone acetonide	Ocular drug delivery	–	PVP: 12, chitosan: 6	Simple	Acetic acid	120±30	–	0.7	22	0.6 mm	8	40, –	Mirzaeei et al. (2018)
Core: CA Shell: PVP	Artemisinin	Transdermal patch	PVP: 1000, CA: 52	PVP: 15 wt %, CA: 15 wt %	Co-axial	Core: acetone/DMA 1:1, shell: ethanol	436±125	–	0.5	13	Core: 0.8 mm, shell: 1.5 mm	20	20, 40	Shi et al. (2013b)

[a]Fibers with diameters <1000 and ≥1000 nm were considered as nanofibers and electrospun fibers, respectively

[b]Electrospun fibers

[c]As a plasticizer

–: Not provided

CA cellulose acetate, CNC cellulose nanocrystal, DCM dichloromethane, DMA dimethylacetamide, DMF dimethylformamide, DMSO dimethylsulfoxide, HPβCD hydroxypropyl-β-cyclodextrin, ISDN isosorbide dinitrate, MPE mangosteen pericarp extract, PEG-400 polyethylene glycol 400, PLA polylactic acid, PVP polyvinylpyrrolidone, RT room temperature

Table 2 Process variables of studies on PVA nanofibers

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
PVA	Diclofenac sodium	Transdermal drug delivery	~89–98	10	Simple	Water	90–250	2	1	20	23 G	15	–	Sa'adon et al. (2021)
PVA	Coptis chinensis extract	Antibacterial and antifungal activity	110	10	Simple	Water	196±36	2	0.04	15	1 mm	15	25, 60	Yang et al. (2018a)
PVA	Curcumin, (complexed with β-cyclodextrin)	Drug delivery	125	Mixture: 8, 10, 12 wt.%	Simple	Water	153±58	PVA:~4, mixture:~1	~0.5	~15	~0.5 mm	~15	–	Sharma and Satapathy (2021)
PVA, chitosan	No drug	–	–	PVA: 8 wt %, chitosan: 2 wt %	Simple	Water (for PVA), acetic acid 2 wt % (for chitosan)	117±9	–	0.13	16	–	20	~23, –	Sanchez-Alvarado et al. (2018)
PVA, silk, carbon quantum dot, silica nanoparticle	No drug	Wound dressing	–	6.25	Simple	Water	536±15	1	0.5	15	–	15	28, –	Abolghasemzade et al. (2021)
PVA, collagen	Cell-loaded nanofibers	Cornea tissue engineering	PVA: 80, collagen: 280	PVA: 15 wt %, collagen: 2.5 wt % (13:12 v/v)	Simple	Water (for PVA), HFIP/acetic acid (for collagen)	163±103	–	0.2	15	23 G	170	25, 50	Wu et al. (2018)
PVA, EHEC	Chlorhexidine	Drug delivery, tissue engineering	PVA: 75, EHEC: 1200	Blend solution:10 (PVA/EHEC 6:4)	Simple	Water	250–320	–	0.2	27	0.5 mm	15	25, –	Wali et al. (2018)
PVA, hyaluronic acid, CNCs	L-arginine	Wound dressing	PVA: 72, hyaluronic acid: ~600–750	PVA: 10, hyaluronic acid: 2	Simple	Citric acid 1.5%	122–222	Mixture: 6	0.3	30	22 G	–	Ambient, ~55	Hussein et al. (2020)
PVA, montmorillonite nanoclay	Bovine serum albumin	Drug delivery	130	8 wt %	Simple	Water/glacial acetic acid 30: 70	246±57	–	4	20	0.6 mm	20	RT, room	Ferrandez-Rives et al. (2017)
PVA, polydopamine[b]	No drug	Drug delivery, tissue engineering	85–124	15 wt %	Simple	Water	344	4	1	18	20 G	12	–	Roy et al. (2017)
PVA	Cell-loaded nanofibers	Tissue engineering	2000[c]	8.8	Simple, side-by-side	Water	–	–	1.2	12	0.6 mm	6	–	Yunmin et al. (2015)

Table 2 (continued)

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
Core: – Shell: PVA/dextran	Ciprofloxacin	Drug Delivery	PVA: 72, dextran: 500	PVA: 10, dextran: 10 (9:1)	Co-axial, emulsion	Water	400–600	24	Co-axial: core: 0.5, shell: 0.2 Emulsion: 0.5	Co-axial:50 Emulsion: 15	–	15	–	Moydeen et al. (2018)
Top layer: PVA, chitosan Bottom layer: PCL	Pomegranate flower extract	Wound dressing	PVA: 145, PCL: 80	PVA: 12, PCL: 8, chitosan: 2	Two-layer	Water (for PVA), acetic acid (for chitosan), DMF/DCM 1:1 v/v (for PCL)	404	PVA: 4, chitosan: overnight, PCL: 3	Top layer: 0.3, bottom layer: 0.6	Top layer: 17, bottom layer: 12	Top layer: 21 G, bottom layer: 23 G	Top layer: 14, bottom layer: 12	–	Karamat-Iradmousa et al. (2023)
Top layer: PLA Middle layer: PVA Bottom layer: PLA	Cerium oxide nanoparticles	Diabetic wound dressing	PVA: 85–124, PLA: 420	PVA: 10, PLA: 8	Multi-layer	Water (for PVA), DCM/DMF 7:3 (for PLA)	423±92, 659±154	PVA: 4, PLA: overnight	0.2	21	–	12	–	Hussein et al. (2021)
Core: PVA Shell: gelatin	No drug	Vascular tissue engineering	PVA: 89–98	PVA: 16, gelatin: 15 (1:1)	Co-axial	Ethanol/water 1:9 v/v (for PVA), ethanol/PBS 1:1 v/v (for gelatin)	–	PVA: 4, gelatin: 14	0.42	20	–	15	–	Merkle et al. (2015)

[a]Fibers with diameters <1000 and ≥1000 nm were considered as nanofibers and electrospun fibers, respectively

[b]As a coating agent

[c]Unit was not mentioned

–: Not provided

CNCs cellulose nanocrystals, *DCM* dichloromethane, *DMF* dimethylformamide, *EHEC* ethyl hydroxyethyl cellulose, *HFIP* 1,1,3,3,3-hexafluoro-2-isopropanol, *PBS* phosphate buffered saline, *PCL* poly e-caprolactone, *PLA* polylactic acid, *PVA* polyvinyl alcohol, *RT* room temperature

role in fabrication of nanofibers and only PVA with 110 kDa led to bead-free and uniform fibers. In vitro studies of loaded nanofibers exhibited antifungal and antibacterial properties (Yang et al. 2018a).

Due to the film-forming properties of PVA, this polymer has been utilized by blending with other polymers for film fabrication (Gaaz et al. 2015). However, the drug delivery application of PVA is hampered due to its poor stability in water. To overcome this drawback, the solubility of PVA has been modified by copolymerizing, cross-linking, and grafting (Jannesari et al. 2011). In another study, PVA/collagen nanofibers were electrospun as a corneal scaffold. 15% (w/v) PVA aqueous solution and 2.5% (w/v) collagen in acetic acid were mixed. Using a rotating collector (speed of 300 rpm) led to aligned fibers, which were more uniform and smaller than random fibers. For cell culture studies, phosphoric acid and glutaraldehyde vapors were used to cross-link electrospun mats and enhance water resistance ability (Wu et al. 2018). Another research group characterized PVA/ethyl hydroxyethyl cellulose nanofibers. Results showed that using tetrahydrofuran (THF)/water (2:1) as a solvent led to beaded fibers, and using water alone overcame this defect. The effect of static and rotating collectors (speed of 1000 rpm) was studied on fiber orientation. Using static and rotating collectors led to non-woven and aligned mats, respectively. Furthermore, using citric acid as a cross-linking agent led to a controlled release of chlorhexidine as an antimicrobial agent. These cross-linked nanofibers demonstrated good cytocompatibility (Wali et al. 2018).

To obtain a bead-free PVA nanofibrous mat containing curcumin-β-cyclodextrin complex, Sharma and Satapathy (2021) investigated various parameters such as PVA concentration, dimethylformamide (DMF) content, complex loading, and applied voltage. Based on the results, the mats provided using 10 wt % PVA in 100% aqueous solution and 20 kV applied voltage exhibited the minimum number of beads.

PVA/chitosan nanofibers using 8 wt % PVA/2 wt % chitosan solution were prepared to evaluate electrospinning experimental parameters. Effects of three factors, including voltage, flow rate, and tip-to-collector distance were studied, and the optimum values were 16 kV, 0.13 mL/h, and 20 cm, respectively. A saturated ethanolic solution of NaOH was used to stabilize fabricated nanofibers. This treatment led to a 44 nm decrement in the fiber diameter (Sanchez-Alvarado et al. 2018).

By a novel approach, a group of researchers fabricated ciprofloxacin-loaded PVA/dextran fibers via emulsion electrospinning. PVA 10% (w/v) and dextran 10% (w/v) aqueous solutions were mixed with the optimum volume ratio of 9:1. Dissolved ciprofloxacin in plant oil was added to a polymer mixture to prepare an emulsion, and the final sample was electrospun under voltage of 15 kV and feeding rate of 0.5 mL/min. Fibers were also prepared via co-axial process in which an aqueous solution of ciprofloxacin hydrochloride was used as the core, and a polymer mixture was used as the shell under a voltage of 50 kV with a feeding rate of 0.5 and 0.2 mL/min, respectively. Fibers were cross-linked by heating. Both procedures led to core–shell structures, although the emulsion method showed slower release rate, with only about half of the drug released within 48 h (Moydeen et al. 2018).

Polyurethane

PU is a versatile and non-immunogenic polymer having outstanding mechanical and biological properties such as elasticity, biocompatibility, and low toxicity. Moreover, it can be electrospun into nanofibrous scaffolds for biomedical and pharmaceutical purposes (Naureen et al. 2021). This synthetic polymer is compatible with blood and has been used for the preparation of vascular substitutes, adhesives, elastomers, and resins (Fathi-Karkan et al. 2022). PU with a molecular weight of 110 kDa with polymer concentration of 5–20 wt % is very common in electrospinning. 1,1,1,3,3,3-Hexafluoro-2-isopropanol (HFIP), DMF alone or mixed with either THF or methyl ethyl ketone/2-butanone (MEK) are usually used as PU solvents (Table 3). Some recent research on PU electrospinning conditions is in Tables 3 and S3 (Online Resource 1).

The superior hydrophobicity of this polymer hinders sufficient contact with the wound and adsorption of exudate when used as a wound-dressing material. Recently, PU nanofibers (12 wt %) loaded with various concentrations of silver nanoparticles (Ag NPs) and lavender oil were fabricated under a voltage of 15 kV and a flow rate of 0.5 mL/h. These cargoes improved the hydrophilicity of fibers due to the presence of silver ions and hydroxyl groups, respectively. Data also showed a synergistic antibacterial effect (Fig. 6) (Sofi et al. 2019).

The effects of three essential oils (St. John's Wort oil, lavender oil, and virgin olive oil) on the formation of thermoplastic PU electrospun were investigated in a recent study. Adding these essential oils increased the fibers' diameter and decreased the contact angle values (Arik et al. 2022).

In a recent study, PU nanofibers containing gelatin and single-walled carbon nanotubes (SWCNT) were fabricated for cardiovascular tissue engineering. Increasing gelatin content brought out smaller diameters of nanofibers and more percent elongation. Moreover, the addition of SWCNT advanced the Young's modulus and ultimate strength of nanofibers (Tondnevis et al. 2020).

Another research group developed PU nanofibers coloaded with honey and *Carica papaya* extract to manage burn injuries. The herbal extract is reported to have anti-inflammatory and antimicrobial properties. PU fibers were

Table 3 Process variables of studies on PU nanofibers

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/ needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	Reference
PU	Silver nanoparticles (in situ synthesis), lavender oil	Wound dressing	110	12 wt %	Simple	DMF/THF 1:4	943±357[b]	Overnight	0.5	15	18 G	15	27, 55	Sofi et al. (2019)
PU, gelatin, carbon nanotubes	No drug	Cardiovascular tissue engineering	260	PU: 70, 80%, gelatin: 20, 30%	Simple	HFIP	140–160	Overnight	0.3	18	23 G	12	25, 10	Tondnevis et al. (2020)
PU, chitosan, β-TCP	Amoxicillin	Bone tissue engineering	–	PU:10 wt %, chitosan: 3 wt %	Simple	DMF/THF 1:1 wt % (for PU), acetic acid (for chitosan)	140±5	1	0.8	30.5	0.8 mm	15	23, 58	Topsakal et al. (2018)
PU, dextran	Pyocyanin	Disinfectant wiping, food packaging, textile industry	PU: 110, dextran: 8.5–11.5	PU/dextran 4:1	Simple	DMF/MEK 1:1	400–600 (plain nanofibers)	72	–	22	–	–	–	Sheet et al. (2018)
TPU	Honey, *Carica papaya* extract	Burn wound dressing	–	4	Simple	DMF	190±20	24	0.75	20	18 G	15	–	Balaji et al. (2016)
TPU	Essential oils	Wound dressing, food packaging	–	5, 10, 12.5, 15 wt %	Simple	DMF	390±60 to 1870±245[b]	24	1	12.5	–	17	25, –	Arik et al. (2022)
TPU, hyaluronic acid	Propolis	Wound dressing	–	TPU: 10 wt %, hyaluronic acid: 0.5 wt %	Simple	DMF/THF 1:1 (for TPU), DMF (for hyaluronic acid)	510±45	TPU: 2, mixture: 4	0.5	18	21 G	20	25, –	Eskandarinia et al. (2020)

Table 3 (continued)

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	Reference
TPU, chitosan, carbon nanotubes	No drug	Cardiac tissue engineering	Chitosan: ~100	PU: 6 wt %, chitosan: 2 wt %	Simple	Acetic acid 90%	103–169	PU: 4, chitosan: 2, PU/chitosan: 1	1	20	23 G	10	–	Ahmadi et al. (2021)
TPU, 1-butyl-3-methylimidazolium hexafluorophosphate[c]	No drug	Biomedical and wastewater treatment	99.7	20 wt %	Simple	DMF	~450–500	–	0.02	15	0.25 mm	15	–	Xing et al. (2015)
Core: PU, NaCl[d] Shell: PET	No drug	Vascular graft	–	PU: 18 wt %, PET: 5 wt %	Co-axial	DMF/THF 1:3 v/v (for PU), TFA (for PET)	515±248	PU: overnight, PET: 24	30	18	Core: 18 G, shell: 14 G	15	25, 28	Khodadoust et al. (2018)

[a]Fibers with diameters < 1000 and ≥ 1000 nm were considered as nanofibers and electrospun fibers, respectively

[b]Electrospun fibers

[c]As an ionic liquid

[d]Prevents bead formation

–: Not provided

DMF dimethylformamide, *HFIP* 1,1,1,3,3,3-hexafluoro-2-isopropanol, *MEK* methyl ethyl ketone/2-butanone, *PET* polyethylene terephthalate, *PU* polyurethane, *β-TCP* β-tricalcium phosphate, *TFA* trifluoroacetic acid, *THF* tetrahydrofuran, *TPU* thermoplastic polyurethane
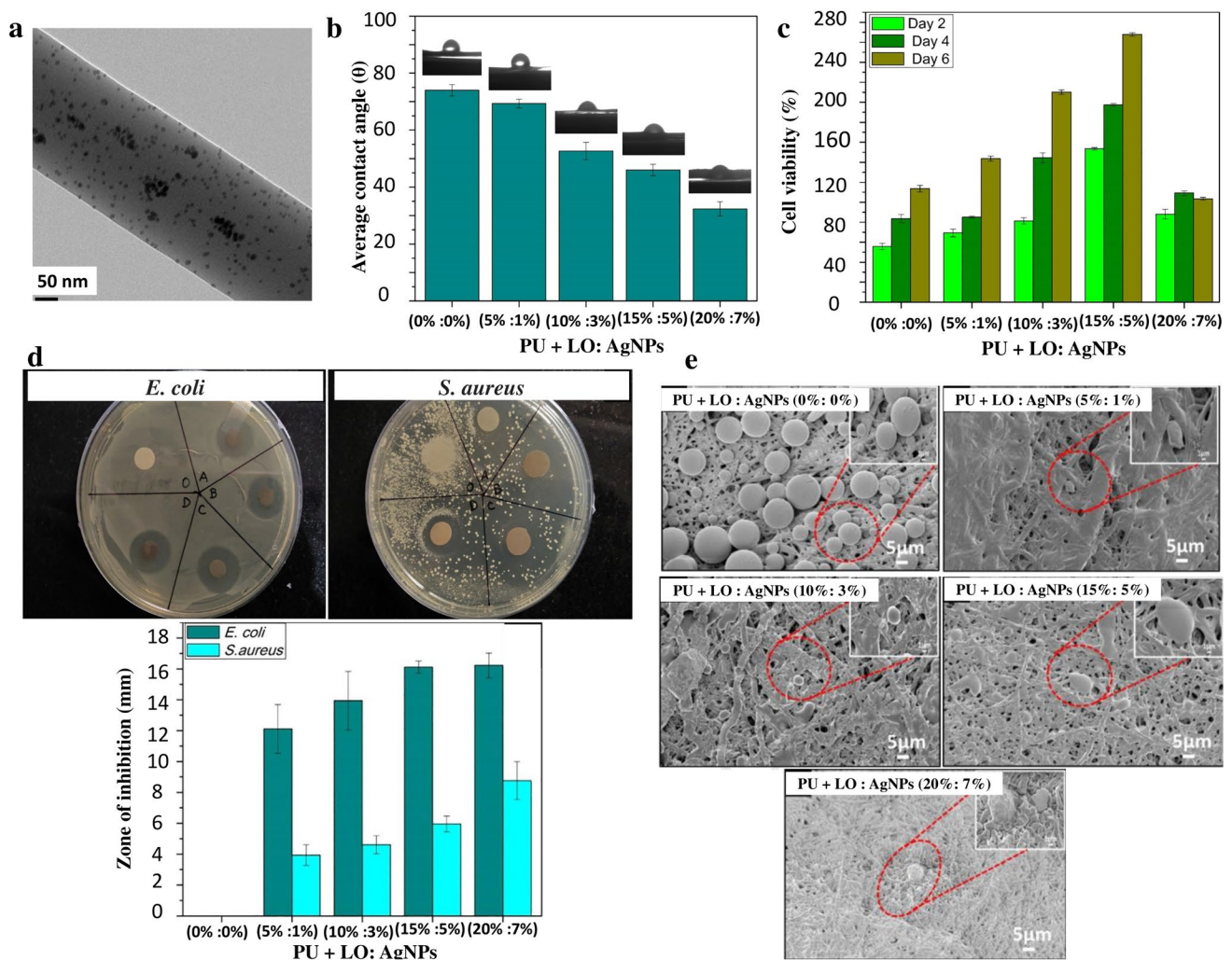
Fig. 6 **a** TEM images of PU nanofibers, **b** Average contact angle of nanofibers with various concentrations of AgNPs and LO, **c** Cell viability (%) of fibroblast cells cultured on nanofibers, **d** Zones of inhibition of nanofibers against *E. coli* and *S. aureus*, **e** SEM images of the fibroblast's morphology cultured on nanofibers (reprinted with minor modification from Ref. (Sofi et al. 2019), with permission). *AgNPs* silver nanoparticles, *LO* lavender oil, *PU* polyurethane, *SEM* scanning electron microscopy, *TEM* transmission electron microscopy

fabricated at a feeding rate of 0.7 mL/h and a voltage of 16 kV. Adding *Carica papaya* extract and honey reduced the solution viscosity. The former parameters were increased to 0.75 mL/h and 20 kV, respectively, to obtain a steady stream. Adding cargoes reduced the diameter of nanofibers and changed their morphology from smooth to ribbon-like structure due to changes in viscosity and conductivity. Moreover, exudate absorption of active nanofibers was higher than empty nanofibers, due to an enhancement in mats hydrophilicity (Balaji et al. 2016).

PU polymers are favorable in tissue engineering due to their flexibility. By a novel approach, amoxicillin nanofibers containing 10 wt % PU, 3 wt % chitosan, and 3 wt % β-tricalcium phosphate (β-TCP) were electrospun. β-TCP, similar to mineral components of bone, is widely used in bone tissue engineering. The flow rate varied between 0.8 and 2.3 mL/h and uniform and bead-free nanofibers were achieved under the lowest feeding rate and voltage of 30.5 kV (Topsakal et al. 2018).

Polyethylene oxide

In recent years, PEO has attracted much attention as an excipient for various purposes (Vanza et al. 2020). Due to the physical stability and chemical resistance of PEO, this polyether has been approved for different medical and pharmaceutical applications such as drug delivery, gene therapy, tissue engineering, and cosmetics (Theodosopoulos et al. 2017). PEO is a water-soluble polymer with good biocompatibility (Zheng and Wyman 2016; Carrasco-Torres et al. 2019). PEO can be used in pharmaceutical formulations to extend the drug release. Also, it has low toxicity, high

swelling, and thermoplastic behavior (Vanza et al. 2020). Research on nanofibers has used PEO with different molecular weights ranging from 100 to 1000 kDa (mostly 900 kDa) (Tables 4 and S4). Besides water, other solvents, such as acetic acid, chloroform, DCM, DMF, and dimethylsulfoxide (DMSO), can be used as the solvent for this polymer (Table 4). Table 4 represents some recent studies fabricating PEO nanofibers (More research is presented in Table S4, Online Resource 1).

A research group developed nanofibers with aqueous electrospinning solutions of PEO and low molecular weight sunflower pectin (with a total polymer concentration of 8 wt %). The effect of PEO content and molecular weight (1000 and 5000 kDa) on the fabrication of nanofibers was investigated. Data exhibited that PEO content in polymeric solution had a crucial role in the uniformity and formation of nanofibers. Uniform nanofibers were achieved with 10% PEO (5000 kDa). However, PEO (1000 kDa) content lower than 20% resulted in no fiber, and bead-free fibers could only be observed at 50%. Triton X-100 as a surfactant formed uniform nanofibers even at 30–50% PEO (1000 kDa) content. The presence of DMSO, DMF, or glycerol as a cosolvent could improve nanofibers generation even at lower PEO (1000 kDa) content (20%). It should be noted that even with 5000 kDa PEO, no fibers were generated at 5% PEO (Cui et al. 2017).

In another work, hesperidin was loaded in polyacrylonitrile/PEO electrospun nanofibers for wound healing application. PEO, hesperidin, and total polymer amounts were the independent variables in this experiment, and morphology, fiber diameter, and swelling percent were the responses. The amount of PEO had a major effect on swelling, so a 20 wt % to 40 wt % increase in the amount of PEO resulted in a significantly higher percentage of swelling and release. The optimized formulation of nanofiber mats was non-beaded and smooth with a diameter of 126 ± 24 nm (Taymouri et al. 2021).

In another study, the effects of silk fibroin/PEO polymer ratio variations on the morphology and size distribution of nanofibers were investigated. Results indicated that nanofibers prepared from ratios below 5:5 exhibited uniform thickness and smooth surface with a 400–600 nm diameter. Whereas, in ratios greater than 5:5, the nanofibers demonstrated uneven thickness, clear fractures, and many bubbles with a size distribution of 500–800 nm. The article suggests that the high crystalline nature of silk fibroin explains fiber breaks. In addition, the unsuitable viscosity of the electrospinning solution could lead to uneven fibers and a great number of bubbles due to partial volatilization of the spinning solution (Lan et al. 2022).

Egg albumen protein could stabilize emulsions. Using this component as a carrier led to a controlled delivery of cargoes. However, the pure component could not be electrospun due to its globular structure and lack of entanglement. Incorporating polymers such as PEO could overcome this issue. Recently, PEO/egg albumen fibers were fabricated. Investigating the effect of pH on fiber morphology showed that uniform fibers were generated at neutral conditions. Acidic conditions led to irregular and beaded fibers. Data showed that these structures were formed due to egg white albumen and its conformational changes (Martin-Alfonso et al. 2018).

Polycaprolactone

PCL is a semi-crystalline aliphatic polymer and exhibits so many advantages such as superior mechanical strength, acceptable biocompatibility, and slow degradation rate (Bharadwaz and Jayasuriya 2020). In almost all publications on PCL nanofibers, PCL with a mean molecular weight of 80 kDa was used (Table 5). This polymer shows considerable solubility in many solvents, like acetone, DCM, DMF, HFIP, and chloroform alone or mixed with methanol (Table 5). Tables 5 and S5 (Online Resource 1) summarized some recent publications investigating PCL nanofibers.

A research group evaluated the effect of PCL concentration on nanofiber morphology. Two polymer solutions in acetone (7.5 and 15% (w/v)) were electrospun under the feeding rate of 6 mL/h and voltage of 7 kV. Increasing PCL concentration led to an increment in nanofiber diameter (from 295 to 701 nm) and pore area (about 3.5-fold), though surface porosity was similar in both scaffolds (Rabionet et al. 2017).

In another study, PCL solutions were prepared in different solvent mixtures (THF/DMF and chloroform/DMF). Fibers were fabricated under a voltage of 16–18 kV and the flow rate of 3 mL/h. Random, semi-aligned, and aligned fibers were prepared with collector speeds of 60, 2000, and 3000 rpm, respectively. Data showed that aligned nanofibers can be used as a cell culture scaffold and guide the orientation of human mesenchymal stem cells (Fotticchia et al. 2013).

In a novel approach, PCL solutions were prepared in trichloromethane and trichloromethane/ethanol at a concentration of 17.5% and 15% (w/v), respectively. Polymer solutions were electrospun, leading to fiber diameters of 10 and 2 μm, respectively. Thinner fibers were easily coated with norepinephrine via immersion of fibers in a norepinephrine solution. This membrane showed the potential for muscle regeneration in injuries (Liu et al. 2017b).

In another research, the effect of the PCL/keratin ratio on the conductivity and diameter of nanofibers was investigated. Since amine and carboxyl moieties are responsible for keratin's high polarity and conductivity, an increase in the keratin ratio of the polymeric mixture resulted in higher conductivity and consequently, thinner nanofibers. A PCL/

Table 4 Process variables of studies on PEO nanofibers

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/ needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	Reference
PEO	Streptomycin, pyrazinamid, isoniazid, clarithromycin	Drug delivery	300	11 wt %	Simple	Water	130 ± 25	–	1	15	18 G	15	–	Hassounah et al. (2014)
PEO, pectin, Triton X-100[c]	No drug	–	PEO: 1000, 5000, LMW pectin: 15.6	PEO: 10 wt %, LMW pectin: 15 wt %	Simple	Water, DMSO[d], DMF[d] or glycerol[d]	60–500	–	0.8–1.0	5–7	8 G	15	25–30, 25–30	Cui et al. (2017)
PEO, polyacrylonitrile	Hesperidin	Wound dressing	300	Polyacrylonitrile and PEO: 12–15 wt %	Simple	DMF	126 ± 24	Mixture: 0.5	0.2	13	27 G	17.2	–	Taymouri et al. (2021)
PEO, silk fibroin	Gentamicin sulfate	Antibacterial activity	Silk fibroin: 10–30, PEO: 300	Silk fibroin/ PEO 3:7 wt %	Simple	Water/ethanol 1:1 v/v	470 ± 107	Silk fibroin, PEO: 8	1.25	15	–	20	–	Lan et al. (2022)
PEO, egg albumen	No drug	–	900	PEO: 4 wt %, albumen: 25, 50, 75 wt %	Simple	Water or buffer (pH: 7)	235–264	–	0.3	16	0.6 mm	15	24, 50	Martin-Alfonso et al. (2018)
Top layer: PCL Bottom layer: chitosan, PEO	Aloe vera	Wound dressing	PCL: 80, chitosan: 50–190	PCL: 7, chitosan: 7, PEO: 8	Two-layer	TFE/water 4:1 v/v (for top layer)	Top layer: 385 ± 134, bottom layer: 152 ± 54	–	Top layer: 2.5, bottom layer: 4	Top layer: 25, bottom layer: 28	21 G	Top layer: 15, bottom layer: 12	–	Miguel et al. (2017)
Core: PEO Shell: TCMC	Tetracycline hydrochloride	Drug delivery	900	PEO: 1, TCMC: 3	Co-axial	DMF (for TCMC), chloroform (for PEO)	86	–	3	15	Core: 22 G, shell: 16 G	18	25, –	Esmaeili and Haseli (2017)

Table 4 (continued)

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/ needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	Reference
Core: PEO Shell: PCL, JFA	Horseradish peroxidase	Protein delivery	PEO: 200, PCL: 80, JFA: 1.9	PEO: 16, PCL, PCL/ JFA: 10	Co-axial	Water (for PEO), chloroform/ DMF 8:2 (for PCL)	1400[b]	Overnight	Core: 0.2, shell: 1.4	13	–	13	–	Adala et al. (2021)

[a] Fibers with diameters <1000 and ≥1000 nm were considered as nanofibers and electrospun fibers, respectively

[b] Electrospun fibers

[c] As a surfactant

[d] As a cosolvent

–: Not provided

DMF dimethylformamide, *DMSO* dimethylsulfoxide, *JFA* O,O'-bis(2-aminopropyl)polypropylene glycol-block-polyethylene glycol-block-polypropylene glycol (Jeffamine), *LMW* low molecular weight, *PCL* poly e-caprolactone, *PEO* polyethylene oxide, *RT* room temperature, *TCMC* graft copolymerization of sodium carboxymethyl cellulose with methyl acrylate, *TFE* trifluoroethanol

keratin ratio of 7:3 was considered an optimized ratio to preserve the mechanical features (Li et al. 2020).

Despite all its advantages, PCL also has some negative points like a slow degradation rate and high hydrophobicity (Sims-Mourtada et al. 2014; Babadi et al. 2022a). Combining with some natural biomaterials, including gelatin (Lim and Sultana 2016), collagen (Babadi et al. 2022a), and chitosan (Sims-Mourtada et al. 2014) could help to solve the problem. Recently, our team fabricated piperine-loaded PCL/collagen nanofibers for the postsurgical treatment of breast cancer. Increasing collagen content in polymer solution led to an increment in conductivity and a decrement in viscosity of the solution and, consequently, thinner fibers. PCL/collagen fibers exhibited higher drug release due to the higher swelling degree and hydrophilicity than PCL fiber (Babadi et al. 2022a).

A group of researchers developed a three-layer PCL mat for tissue engineering connecting bone and soft tissue. Two microfiber layers were separated by a nanofiber layer and fibroblasts and mesenchymal cells were seeded on either side. Under a voltage of 17 kV, feeding rate of 2.4 mL/h, and collector speed of 300 rpm, 10 wt % PCL in DCM (tip-to-collector distance of 17 cm) and 5 wt % PCL in DCM/ methanal (tip-to-collector distance of 10 cm) led to microfiber and nanofiber production, respectively (Puwanun et al. 2016).

In another study, a PCL scaffold containing ibuprofen was electrospun using the co-axial method as a treatment for periodontal inflammation. The ibuprofen was dispersed in a PCL solution (in DCM/DMF) containing hydroxyapatite. The feeding rate of 0.5 mL/h was fixed for both the outer and inner membranes. The outer needle was connected to a 13.3 kV voltage, while the collector was connected to -2.7 kV (Batool et al. 2018).

In a recent study, PEO/PCL fibers containing doxycycline were fabricated, and the effect of flow rates (0.1–0.6 mL/h), applied voltages (10–30 kV), and tip-collector distances (10–20 cm) were optimized. The optimized parameters were 0.1 mL/h, 15 kV, and 12.5 cm, respectively, leading to uniform and bead-free mats (Eskitoros-Togay et al. 2019).

Another research group fabricated collagen-PCL nanofibers using different proportions of polymers. This study used PCL to collagen ratios of 3:7, 6:4, and 9:1 w/w as precursor solutions for artemisinin-loaded electrospun nanofibers. The results demonstrated that the increase of PCL increased the viscosity, mass density, and hydrophobicity of the solution. Moreover, with increasing the PCL ratio, the nanofibers' mean diameter increased, and bead formation decreased (Huo et al. 2021).

In another study, PU/PCL nanofibers were characterized as vascular grafts. 15 wt % PU in THF/DMF and 10 wt % PCL in chloroform/ethanol solutions were prepared and electrospun individually by the co-electrospinning

Table 5 Process variables of studies on PCL nanofibers

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
PCL	No drug	Breast cancer 3D culture	80	15	Simple	Acetone	701±402[b]	–	6	7	18 G	15	–	Rabionet et al. (2017)
PCL	No drug	Tissue engineering	70–90	11 wt %	Simple	Chloroform/DMF 1:1	400±140	–	3	16–18	1 mm	16	–	Fotticchia et al. (2013)
PCL	Norepinephrine	Muscle engineering	80	15	Simple	Trichloromethane/ethanol 7:3	2000[b]	Overnight	10	20	20 G	20	–	Liu et al. (2017b)
PCL	*Lavandula lusieri* essential oil	Bioactive packaging	45	15	Simple	Ethanol/chloroform 32.5:17.5	367±203	PCL: 0.5	–	80	–	13	20, –	Ferreira et al. (2022)
PCL, keratin	No drug	Vascular tissue engineering	80	PCL/keratin: 7:3	Simple	HFIP	485±151	–	2	20	23 G	15	–	Li et al. (2020)
PCL, PVP	ZnO nanoparticles, silver nanoparticles	Antibacterial activity	360	Blend solution: 12 (PVP/PCL 1:3)	Simple	TFE	368±124	24	0.8	15	0.8 mm	15	–	Hu et al. (2018)
PCL, gelatin	Zinc (II) quercetin complex	Bone tissue engineering	–	PCL: 10, gelatin: 10 (5:5 v/v)	Simple	TFE (for PCL and gelatin), ethanol (for zinc (II) quercetin complex)	260–500	PCL: 3, gelatin: 3	0.8	15	24 G	12	25, 45	Raj Preeth et al. (2021)
PCL, PEO	Doxycycline	Drug delivery	PEO: 100, PCL: 80	PEO: 12, PCL: 12	Simple	DCM/DMF 80:20 v/v	670±226	Overnight	0.1	15	–	12.5	RT, –	Eskitoros-Togay et al. (2019)

Table 5 (continued)

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/ needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
PCL, aniline tetramer	No drug	Tissue engineering	PCL: 70–90	–	Simple	Chloroform/methanol 9:1, phytic acid 0.02 M	300±100	–	1.2	15	–	15	–	Guex et al. (2017)
PCL, collagen	Piperine	Breast cancer treatment	80	PCL: 8, collagen: 8 (75:25)	Simple	HFIP	377±10	–	0.4	12	23 G	15	–	Babadi et al. (2022a)
PCL, soy phosphatidylcholine	Curcumin	Postoperative adhesion	80	PCL: 15	Simple	DCM/DMF 1:1	371±12	2	0.4	12	23 G	15	RT, –	Babadi et al. (2022b)
PCL, Zinc-doped bio active glass	No drug	Nasal implant	80	PCL: 10, A2Zn5 BG: 4 wt %	Simple	Chloroform/methanol 1:1	2950±1640[b]	–	3	25	0.22 mm	20	–	Rajzer et al. (2019)
PCL, silk fibroin	Estradiol	Treatment of osteoporotic fractures	PCL: 80	Blend solution: 8 wt %	Emulsion	HFIP	2690±470[b]	Mixture: 24	5	12	24 G	16	–	Steffi et al. (2018)
PCL, PU	No drug	Vascular graft	PCL: 80	PU: 15 wt %, PCL: 10 wt % (1:3 wt %)	Co-electrospinning	DMF/THF 1:3 v/v (for PU), chloroform/ethanol 7:3 v/v (for PCL)	420±75	PU: 12, PCL: 3	PU: 0.5, PCL: 1.5	25	18 G	25	25, 28	Jirofti et al. (2018)
First layer: PCL Second layer: PVA/PCL Third layer: PCL	Curcumin	Wound dressing	PVA: 85–124, PCL: 80	PVA: 8, PCL: 12.5	Multilayer	Water (for PVA), DMF/DCM 2:1 (for PCL)	–	PVA: 3, PCL: 4	1	17.8	–	16	–	Saeed et al. (2017)

Table 5 (continued)

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/ needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
PCL (two microfiber layers separated by a layer of nanofibers)	No drug	Bone tissue engineering	80	Microfiber: 10 wt %, nanofiber: 5 wt %	Multi-layer	DCM (for microfiber), DCM/methanol 10.5:89.5 (for nanofiber)	Top layer: 8400±500[b], middle layer: 3600±400[b], bottom layer: 7700±400[b]	24	2.4	17	–	Microfiber: 17, nanofiber: 10	RT, –	Puwanun et al. (2016)
Top layer: Collagen, PCL Middle layer: Chitosan, PEO Bottom layer: PCL	Silver sulphadiazine, growth factors	Wound dressing	PCL: 80, PEO: 900	Top layer: collagen/PCL 2:15 wt %, middle layer: chitosan: 2 wt %, PEO: 5 wt %, bottom layer: PCL: 15 wt %	Multi-layer	Acetic acid 90% (for collagen and PCL), acetic acid 2% (for chitosan), water (for PEO)	Top layer: 121, middle layer: 96, bottom layer: 116	Top layer: 24, middle layer: 16–18, bottom layer: overnight	Top layer: 0.6, middle layer: 0.2, bottom layer: 0.5	Top layer: 17, middle layer: 19, bottom layer: 17	–	Top layer: 17, middle layer: 10, bottom layer: 17	–	Nejad-dehbashi et al. (2019)
Top layer: PCL, collagen Middle layer: PCL Bottom layer: PCL	Sirolimus	Vascular drug delivery	80	PCL: 10 wt %, collagen: 8 wt %	Multi-layer	DCM/DMF 1:1 v/v (for PCL), HFIP (for collagen)	Top layer: 469, middle layer: 353, bottom layer: 343	PCL: 3, collagen: 3, mixture: 1	0.7	12.5	21 G	15	–	Talimi et al. (2022a)
Core: PCL Shell: PEO, chitosan	Curcumin, lidocaine hydrochloride	Wound dressing	PEO: 1000, PCL: 8	Chitosan/PEO 95:5 wt %, chitosan: 5, PCL: 10	Co-axial	–	325±52	Overnight	Core: 0.2, shell: 0.4	Core: 15	Core: 0.34 mm, shell: 1.12 mm	20	25, 20–30	Guo et al. (2020)

Table 5 (continued)

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
Core: PCL Shell: PCL, chitosan	Sirolimus	Breast cancer treatment	80	PCL: 10 wt %, chitosan: 2 wt %	Co-axial	HFIP (for PCL), TFA (for chitosan)	725	PCL: 3, chitosan: 14, PCL/chitosan: 3	Core: 0.6, shell: 0.7	20	Core: 0.6 mm, shell: 1.19 mm	15	–	Talimi et al. (2022b)
Core: PLA, PCL Shell: PCL	No drug	Differentiation of stem cells	PLA: 59–101, PCL: 70–90	PLA: 6.6, PCL: 13.3	Co-axial	TFE	1928[b]	–	3	–	–	–	–	Baudequin et al. (2017)
Core: PCL, HAnC, Tween 80 Shell: PCL, PVAc	Ibuprofen	Periodontal engineering	–	PCL: 10 wt %, PVAc: 10 wt %	Co-axial	DCM/DMF 1:1 (for PCL), DMF (for PVAc)	374±89	Overnight	0.5	16	Core: 0.9 mm, shell: 1.7 mm	19	–	Batool et al. (2018)

[a]Fibers with diameters <1000 and ≥1000 nm were considered as nanofibers and electrospun fibers, respectively

[b]Electrospun fibers

–: Not provided

DCM dichloromethane, *DMF* dimethylformamide, *HAnC* non-commercial hydroxyapatite, *HFIP* 1,1,1,3,3,3-hexafluoro-2-isopropanol, *PCL* poly e-caprolactone, *PCL* poly e-caprolactone, *PEO* polyethylene oxide, *PLA* polylactic acid, *PVA* polyvinyl alcohol, *PVAc* polyvinyl acetate, *PVP* polyvinylpyrrolidone, *RT* room temperature, *TFA* trifluoroacetic acid, *TFE* trifluoroethanol, *THF* tetrahydrofuran, *ZnO* zinc oxide

method under the voltage of 25 kV and flow rates of 0.5 and 1.5 mL/h, respectively. On one hand, the presence of PU improved the elasticity of the scaffold. On the other hand, adding PCL to PU enhanced the strength of scaffolds, making it proper in tissue grafting. In vivo implantation in sheep carotid exhibited complete patency (Jirofti et al. 2018).

Polylactic acid

PLA is an FDA-approved synthetic polymer (Bharadwaz and Jayasuriya 2020). Lactic acid (LA) monomers are polymerized to construct PLA. There are two methods to produce LA: microbial fermentation and chemical synthesis. The former process can lead to L- or D-LA (two optical enantiomers of LA), while the latter led to a racemic mixture. These isomers could affect the properties of the resultant polymer, such as biodegradability and crystallinity (Singhvi et al. 2019). PLA is a degradable and biocompatible polymer often used in various tissue regeneration studies, bone tissue engineering, and drug delivery systems (Santoro et al. 2016; Bharadwaz and Jayasuriya 2020). PLA with various molecular weights has been used in electrospinning (Table 6). Chloroform, DCM, HFIP, DMF, acetone, and trifluoroethanol (TFE) are suitable solvent examples for PLA (Table 6). In Table 6, some recent studies on PLA fibers are summarized (More studies are listed in Table S6, Online Resource 1).

Recently, PLA filaments containing bioactive glass particles were generated to enhance mineralization, especially in bones. Bioactive glass particles based on silica are bulky bone cement with antibacterial properties. These particles were added to 20% (w/v) PLA (85–160 kDa) in DCM/acetone and electrospun at 12 kV and 0.8 mL/h. Random and aligned fibers were collected on the static and rotating collector (5000 rpm), respectively. The presence of glass particles increased fiber roughness and reduced fiber diameter due to the changes in solution properties (rheology and conductivity) (Serio et al. 2019).

In another study, PLA/polybutylene succinate mats were developed, and the effect of electrospinning parameters on fabricated fibers was evaluated. Data exhibited that a minimum of 6 wt % polymer concentration is needed to obtain bead-free fibers. Furthermore, the voltage had a great impact on the fiber formation. It was shown that increasing voltage from 20 to 24 kV led to the beaded structure. Optimum parameters to obtain uniform and smooth fibers were reported as: flow rate of 0.5 mL/h, needle-to-collector distance of 12 cm, and voltage of 20 kV (Abudula et al. 2018).

The surface morphology of PLA/PCL nanofibrous mats was investigated in a recent study. PCL content (10–30 wt %), DMF content (10–30 wt %), and solution concentration (8–12 wt %) could affect bead formation in the fibers. Results indicated noticeable bead defects due to either PCL content of ~ 30 wt %, DMF content of ~ 30 wt %, or solution

concentration of ~ 8 wt % due to the elevated electrical conductivity of the electrospinning solution and instability of the charged jet. A minimum number of beads were exhibited with either PCL content of ~ 10 wt %, DMF content of ~ 10 wt % or solution concentration of ~ 12 wt % due to the formation of a stable Taylor cone and a constantly charged jet (Sharma et al. 2021).

Poly(lactic-co-glycolic acid)

PLGA is a well-known and widely used polymer with many applications (Naves et al. 2017). PLGA contains PLA and polyglycolic acid (PGA) as constituent monomers. PLGA is a biocompatible and biodegradable polymer, making it appropriate for vast medical usage. It also offers other remarkable properties, such as swelling behavior, controlled degradation rate, and mechanical strength (Naves et al. 2017; Bharadwaz and Jayasuriya 2020). PLGA consisting of different PLA-to-PGA ratios is used in fiber development, and 75:25 is mostly used. Moreover, different molecular weights of PLGA ranging from 20 to 240 kDa are used in this field, and molecular weights less than 120 kDa are more common (Tables 7 and S7). Most common solvents, such as chloroform, DMF, HFIP, and THF, could be used for PLGA electrospinning. However, HFIP is mostly used (Table 7). Some recent publications on PLGA fibers are summarized in Table 7 and Table S7 (Online Resource 1).

The hydrophobicity of PLGA can limit its application (Li et al. 2017). To overcome these problems, inorganic materials such as hydroxyapatite (Yang et al. 2018b) and bioactive glass (Chen et al. 2015) have been combined with PLGA. Also, functionalizing PLGA scaffolds could be a good way to increase their hydrophilicity (Campos et al. 2014).

In a recent study, aligned and random PLGA fibers were embedded in polymethyl methacrylate-based microfluidic chips. Fibers were coated with biotin-(PEG)$_7$-amine to conjugate to a specific antibody to capture circulating tumor cells. Electrospinning was carried out at a voltage of 15 kV, a flow rate of 0.1–0.5 mL/h, and a tip-to-collector distance of 15 cm with 10 wt % PLGA in HFIP. Random and aligned fibers were collected on the static and rotating collector (3000 rpm), respectively. It is noticeable that random fibers were thicker than aligned fibers, about 1.7-fold, due to a drafting force in the rotating drum. Also, cell release efficacy was higher in random fibers, suggesting a suitable device for capturing circulating tumor cells (Yu et al. 2019).

The surface tension, viscosity, and conductivity of PLGA solution could be altered by different solvents. Some researchers inquired about the effects of electrospinning solvent on the morphology and diameter of PLGA nanofibers. Using HFIP as the solvent resulted in forming bead-free and smooth surface nanofibers. Whereas nanofibers of PLGA solution with DCM/DMF as the solvent mixture had

Table 6 Process variables of studies on PLA nanofibers

Composition (isomer)	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/ needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
PLA (L)	No drug	Tissue engineering and antibacterial dressing	732±222	10	Simple	Chloroform	–	–	1.2	18	–	10	40, 45	Shen et al. (2018)
PLA (L)	SBA2	Bone and soft tissue engineering	85–160	20	Simple	DCM/acetone 4:1	1000±200[b]	Overnight	0.8	12	21 G	15	20, 40	Serio et al. (2019)
PLA	Chitosan-calcium silicate mixture	Bone tissue engineering	146	6	Simple	Chloroform/DMSO 3:1	–	24	0.5	21	23 G	18	–	Su et al. (2017)
PLA	Tranexamic acid, ZnO nanoparticles	Wound dressing	70–90	10 wt %	Simple	DCM	90	–	0.6	20	0.8 mm	10	–	Molapour Rashedi et al. (2021)
PLA	Birch bark triterpene extract	Wound dressing	–	6.4	Simple	DCM/DMSO 4:1 v/v	927±214[b]	–	0.7	9	0.8 mm	10	RT, –	Fan and Daniels (2021)
PLA, PCL	No drug	Suture	PLA: 116, PCL: 80	Blend solution: 12 wt %	Simple	Chloroform/DMF 9:1	310±60	–	1	20	~0.5 mm	–	–	Sharma et al. (2021)
PLA, PTMC	Dexamethasone	Functional delivery of osteogenic molecules	PLA: 2000, PTMC: 10	PTMC: 50 wt %	Simple	Chloroform/methanol 3:1 (for PLA), DCM (for PTMC)	740±150	–	1	18–20	–	15	–	Zhang et al. (2018)

Table 6 (continued)

Composition (isomer)	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/ needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
PLA (L), silk fibroin, collagen	Polypyrrole nanoparticles	Construct piezoresistive devices	PLA: 150, silk fibroin: 50, collagen: 120	PLA: 4, silk fibroin: 2, collagen: 2	Simple	HFIP	122±28	Mixture: 6	0.5	20	0.6 mm	20	–	Zhao et al. (2018)
PLA, poly-butylene succinate	No drug	–	–	Blended solution: 6 wt %	Simple	Chloroform/acetone 3:1	409±55	Mixture: 3	0.5	20	27 G	12	–	Abudula et al. (2018)
PLA, starch	Arginine-glycine-aspartic acid peptides	Bone tissue engineering	12–15	8 wt %	Simple	Chloroform	>1000[b]	Mixture: 24	2	6	0.41 mm	15	–	Gutierrez-Sanchez et al. (2019)
PLA (L)	Cisplatin	Prevention of local liver cancer recurrence after surgery	13.8	6 wt %	Multi-layer	Chloroform/methanol/DMSO 82:14:4 v/v/v	–	–	1–2	27–30	0.4 mm	15	RT, –	Zhang et al. (2014)

[a]Fibers with diameters <1000 and ≥1000 nm were considered as nanofibers and electrospun fibers, respectively

[b]Electrospun fibers

–: Not provided

DCM dichloromethane, DMF dimethylformamide, DMSO dimethylsulfoxide, HFIP 1,1,1,3,3,3-hexafluoro-2-isopropanol, PCL poly e-caprolactone, PHB poly 3-hydroxybutyrate, PLA polylactic acid, PTMC three-armed methacrylate-ended, RT room temperature, SBA2 bioactive silica-based glass, ZnO zinc oxide

Table 7 Process variables of studies on PLGA nanofibers

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
PLGA	Linezolid	Antibacterial activity	75:25: 66–107	10	Simple	HFIP	371 ± 11	–	0.75	11.5	21 G	14	–	Boncu et al. (2020)
PLGA	No drug	Cancer diagnosis and monitoring	85:15: 100	30	Simple	DMF/THF 7:3	503 ± 103	–	0.5	18	22 G	10	–	Wu et al. (2021b)
PLGA	No drug	Cancer cell isolation	50:50	10 wt %	Simple	HFIP	700 ± 63	6	0.1–0.5	15	27 G	15	Ambient, <40	Yu et al. (2019)
PLGA, HA, collagen	No drug	Bone tissue engineering	PLGA: 75:25: 50	PLGA: 20	Simple	HFIP	200–400	–	0.6	18	27 G	12	–	Yang et al. (2018b)
PLGA, HA	No drug	Cancer cell capture and culture	–	25	Simple	DMF/THF 1:3	908 ± 132^{b}	~6	0.3	15	21 G	15	20–25, 40–50	Xu et al. (2017)
PLGA, PCL	Tenofovir	–	PLGA: 50:50: 100, PCL: 80	PLGA: 15, PCL: 15	Simple	HFIP	–	Overnight	1.2	10	21 G	15	–	Chou and Woodrow (2017)
PLGA	Povidone-iodine	Postoperative adhesion	75:15	20 wt %	Simple	HFIP	–	–	0.5 mm/min	13	–	15	–	Wang et al. (2019)
PLGA, PLA (L), PLA (D, L)	Naringin	Guided bone engineering	PLGA: 75:25: 48, PLA (L): 100, PLA (D,L): 50	–	Simple	DCM/HFIP 2:3	1100 ± 500^{b}	–	2	15	0.57 mm	10	–	Guo et al. (2018)
PLGA, PLA	No drug	Guided tissue engineering	50:50	16	Simple	Chloroform/DMF 9:1	2900 ± 700^{b}	–	7	15–20	0.7 mm	20	RT, –	Zhang et al. (2016a)

Table 7 (continued)

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
PLGA, Silk fibroin	ZnO nanoparticles	Wound dressing	50:50	PLGA: 18, silk fibroin: 18	Simple	HFIP	1503±608[b]	PLGA: 12, silk fibroin: 12, PLGA/silk fibroin/ZnO: 12	1	12–14	21 G	10–12	25, 50	Khan et al. (2021)
PLGA	Metronidazole, amoxicillin	Periodontitis treatment	20	PLGA: 13	Co-electrospinning	DCM/EA 9:1	240±48	PLGA: 5, metronidazole/PLGA: 2, amoxicillin/PLGA: 2	1	17	–	10	16 to 20, –	Mirzaeei et al. (2021a)
PLGA, CNT	No drug	Neural tissue engineering, biosensor	PLGA: 50:50: 50	PLGA: 17, CNT: 0.5	Co-electrospinning	HFIP (for PLGA), ethanol (for CNT)	855±271[b]	–	PLGA: 1, CNT 1.5	17	21 G	19	–	Nazeri et al. (2018)
Core: PEI Shell: PLGA	pBMP2	Gene delivery to periodontal ligament stem cells	PLGA: 75:25: 100	PEI: 0.0375, PLGA: 12 wt %	Co-axial	HFIP (for PLGA), water (for PEI)	481±103	Core: 0.083, shell: overnight	Core: 0.6, shell: 2	25	Core: 25 G, shell: 16 G	15	–	Xie et al. (2016)

[a]Fibers with diameters <1000 and ≥1000 nm were considered as nanofibers and electrospun fibers, respectively

[b]Electrospun fibers

-: Not provided

CNT carbon nanotubes, *DMF* dimethylformamide, *EA* ethyl acetate, *HA* hydroxyapatite, *HFIP* 1,1,1,3,3,3-hexafluoro-2-isopropanol; *pBMP2* bone morphogenetic protein-2 plasmid, *PCL* poly e-caprolactone, *PEI* polyethylen imine, *PLA* polylactic acid, *PLGA* poly(lactic-co-glycolic acid), *RT* room temperature, *THF* tetrahydrofuran, *ZnO* zinc oxide

generally beaded morphology due to the high volatility and surface tension of DMF. Moreover, the high content ratio of DMF reduced the viscosity of the PLGA solutions and the average nanofiber diameter (Boncu et al. 2020). Another research group also confirmed that an increase in the DMF ratio results in an elevation in the surface tension of PLGA solutions even higher than the surface tension created by THF and chloroform (Liu et al. 2017a). HFIP is an appropriate solvent for the electrospun process with a suitable boiling point and low surface tension (Boncu et al. 2020).

Unlike PLA, PLGA exhibits rapid degradation (Kim et al. 2003). Therefore, different polymer ratios were studied for a balanced degradation rate-hydrophilicity. Accordingly, some researchers designed PLGA/PLA membranes with different ratios of polymeric solution (in chloroform/DMF). Randomly oriented fibers were generated at a 15–20 kV voltage, a flow rate of 7 mL/h, and a collector speed of 180 rpm. The stability of fibers was evaluated in phosphate buffer saline (PBS) at 37 °C. Data demonstrated that PLGA/PLA 50:50 had a reasonable degradation profile and ductility rather than other mixtures (Zhang et al. 2016a).

By a novel approach, nanofiber mats of PLGA/multi-walled carbon nanotubes (MWCNT) were fabricated using three methods, including 1) blend electrospinning, 2) PLGA electrospinning-MWCNT electrospraying, and 3) adsorption of MWCNT on PLGA nanofiber via ultrasound. The first method was conducted at a voltage of 14 kV, needle-to-collector distance of 17 cm, and flow rate of 0.7 mL/h consisting of PLGA (17 wt %) and MWCNT solution in HFIP. The second method was performed at a voltage of 17 kV, a distance of 19 cm, and a feeding rate of 1 and 1.5 mL/h for PLGA solution (17 wt % in HFIP) and 0.5% (w/v) MWCNTs in ethanol, respectively. In the last method, nanofibers were immersed in ethanolic MWCNT solution followed by ultrasonication. Data showed a rough surface after the sonication of fibers. These methods led to mats with different properties, making electrospinning/electrospray mats suitable for tissue engineering and ultrasonicated fibers for biosensors due to the highest biocompatibility and lowest electrical resistance, respectively (Nazeri et al. 2018).

Natural polymers

Gelatin

Gelatin is a natural polymer derived from collagen and composed of arginine-glycine-aspartate (RGD) sequences (Tan et al. 2023; Zhai et al. 2023). Gelatin is a non-toxic, biodegradable, inexpensive, and easily available polymer. In light of its good biocompatibility (Tan et al. 2023), it has been successfully electrospun with different solvents such as acetic acid, formic acid, and TFE (Table 8). This polymer

can incorporate both hydrophilic and hydrophobic agents (Sahoo et al. 2015). Despite its good merits, gelatin has weak mechanical properties, poor water resistance, and rapid degradation that have restricted its application in different biomedical fields (Gomes et al. 2015; Morsy et al. 2017). Glutaraldehyde (Gomes et al. 2015), tannic acid (Tavassoli-Kafrani et al. 2018), glycerol, glucose (Morsy et al. 2017), genipin (Baiguera et al. 2014), and PEG diacrylate (Dongargaonkar et al. 2013) are some suitable cross-linking agents to overcome the problem. Photo-cross-linking under ultraviolet (UV) light is another option (Coimbra et al. 2017).

Tables 8 and S8 (Online Resource 1) summarized recent publications investigating gelatin nanofibers. A research team characterized gelatin nanofibers and investigated the effect of polymer concentration (7 and 20% (w/v)), voltage (28 and 35 kV), and feeding rate (0.1 and 1 mL/h) on electrospun fibers. The polymer solution in acetic acid was prepared at 40 °C. According to the data, gelatin 7% (w/v) could not generate nanofibers, and instead, some fibrous structures and droplets were obtained due to the low viscosity of the solution. Increasing voltage and decreasing flow rate simultaneously led to more fibrous structures and fewer drops. Interestingly, 20% (w/v) gelatin could fabricate nanofibers under all electrospinning conditions. The results also showed that voltage was a key factor in developing bead-free fibers. However, the flow rate influenced fiber diameter and thinner nanofibers were obtained at lower feeding rates. Also, electrospinning changed the zeta potential of gelatin from negative to positive, probably due to the applied voltage (Okutan et al. 2014).

In another study, gelatin/PCL fibers were electrospun and the effect of solvent on polymer degradation was investigated by considering gelatin leaching. The study showed faster erosion in nanofibers electrospun from acetic acid/formic acid than from HFIP, probably due to the high tendency to phase separation in the former system (Dulnik et al. 2016).

By a novel approach, ketoprofen-loaded gelatin/PCL mats were designed using the emulsion method. PCL solution in chloroform/methanol containing ketoprofen was dispersed in gelatin solution (in acetic acid), making an oil-in-water system using Span 80 as the surfactant. Electrospinning conditions such as flow rate and voltage were set at 1.08 mL/h and 18 kV, respectively. Nanofibers were cross-linked with glutaraldehyde vapor. Based on the results, treatment with glutaraldehyde developed continuous structures having high porosity and less fibrous morphology. Moreover, this treatment changed the hydrophilicity of fibers to a moderate level, leading to a sustained release profile for ketoprofen (Basar et al. 2017).

In a recent study, chitosan/gelatin nanofibers with various polymer ratios were fabricated using acetic acid 90% (v/v) as a safer alternative solvent compared to trifluoroacetic

Table 8 Process variables of studies on gelatin nanofibers

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/ needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
Gelatin	No drug	–	–	20	Simple	Acetic acid 20%	45–49	4	0.1	28	–	10	RT, –	Okutan et al. (2014)
Gelatin, PU	Silver sulfadiazine	Burn wound dressing	110	PU: 2, gelatin: 4 (1:1 v/v)	Simple	HFIP	–	–	1	20	18 G	15	–	Heo et al. (2013)
Gelatin, silk fibroin	Thyme essential oil, doxycycline	Drug delivery	–	Blend solution: 10	Simple	Formic acid 98–100%	248±42	4	0.3	20	18 G	10	–	Chomachayi et al. (2018)
Gelatin, zein	Perillaldehyde	Food packaging	–	Zein: 2.5, gelatin: 12.5	Simple	Acetic acid/ water 80:20 v/v	71±39	Gelatin: 0.25, gelatin, zein: 0.25–0.5, mixture: 24	0.03 mm/min	22	18 G	10	RT, –	Wang et al. (2021)
Vinyl benzylated gelatin, PCL dimethacrylate	No drug	Regenerative devices	PCL dimethacrylate: 4	Gelatin: 25, PCL: 25	Simple	Acetic acid 90%	140±45	5	–	80	–	20	25, 30	Bazbouz et al. (2018)
Gelatin, chitosan, PEO	No drug	–	Chitosan: LMW, PEO: 900	Chitosan: 2.5 wt %, gelatin: 10 wt %, PEO: 3 wt %, chitosan/gelatin: 7:3	Simple	Acetic acid 90%	270±38	–	0.75	10	18 G	20	–	Amiri et al. (2018)
Gelatin, PLA	MTS functionalized cerium oxide nanoparticles	Angiogenesis related diseases	PLA: 10	PLA/Gelatin 5:5 wt %	Simple	HFIP	3007±798[b]	–	2	14	19 G	20	–	Xu et al. (2020)

Table 8 (continued)

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
Gelatin-copolymer-chitosan	Tetracycline	Wound dressing	Copolymer: 21	Chitosan: 1 wt %, copolymer: 15 wt %, gelatin: 8 wt % (50:40:10 v/v)	Simple	HFIP/formic acid 2:1 v/v (for chitosan), HFIP (for copolymer, gelatin)	86–225	Chitosan: 48, copolymer/tetracycline: 24, gelatin: 2, copolymer/gelatin/chitosan: 1	2	25	0.8 mm	17	Ambient condition	Ulker Turan and Guvenilir (2022)
Gelatin, PCL	Ketoprofen	Wound dressing	PCL: 80	Gelatin: 32.5, PCL: 8	Emulsion	Acetic acid 25 wt % (for gelatin), chloroform/methanol 4:1 (for PCL)	272	–	1.08	18	–	13	–	Basar et al. (2017)
Gelatin	Orange essential oil	Drug delivery	–	15 wt %	Emulsion	Acetic acid 40%	135–194	0.5	0.3	13	20 G	15	25, 33	Tavassoli-Kafrani et al. (2018)
Gelatin, PCL	No drug	Tissue engineering	PCL: 80	Blend solution: 5, 15 wt %	Co-electrospinning	HFIP (for 5% polymer), acetic acid/formic acid 9:1 (for 15% polymer)	–	Mixture: 24	0.6	12–14	0.34 mm	15	22–24, 50–55	Dulnik et al. (2016)

Table 8 (continued)

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
Core: PCL Shell: gelatin-methacrylic anhydride	No drug	Vascular tissue engineering	PCL: 80	Gelatin: 12.5, PCL: 9.4	Co-axial	TFE/acetic acid 4:1 (for gelatin), TFE (for PCL)	~600	–	Core: 1 or 2, shell: 0.5, 1.5, or 2.25	16–17	Core: 0.6 mm, shell: 1.6 mm	15–20	–	Coimbra et al. (2017)
Core: PCL Shell: gelatin	Ciprofloxacin, tetracycline	Wound dressing	PCL: 80	Gelatin: 10, PCL: 9	Co-axial	TFE/water 3:1 (for gelatin), TFE (for PCL)	158 ± 33	PCL: overnight, gelatin: overnight	Core: 0.02 mm/min, shell: 0.04 mm/min	8.5	Core: 21 G, shell: 15 G	15	–	Lin et al. (2022)

[a]Fibers with diameters < 1000 and ≥ 1000 nm were considered as nanofibers and electrospun fibers, respectively

[b]Electrospun fibers

–: Not provided

copolymer poly(ο-pentadecalactone-co-ε-caprolactone), *HFIP* 1,1,1,3,3,3-hexafluoro-2-isopropanol, *LMW* low molecular weight, *MTS* (6-(2-(2-(2-methoxy-ethoxy)-ethoxy)-ethoxy)-hexyl) triethoxysilane, *PCL* poly ε-caprolactone, *PEO* polyethylene oxide, *PLA* polylactic acid, *PU* polyurethane, *RT* room temperature, *TFE* trifluoroethanol

acid (TFA), HFIP, or DCM. To facilitate electrospinning, 3 wt % PEO as a film-forming additive was added to polymer solutions. Processing parameters, including flow rate, applied voltage, and tip-to-collector distance in the respective range of 0.5–1.5 mL/h, 10–25 kV, and 15–25 cm, were optimized in each polymer ratio. Increasing the applied voltage or needle-to-collector distance lowered fiber diameter due to increased electrostatic forces and more time for fibers stretching, respectively. However, the high feeding rate led to higher fiber diameter since the volume of the Taylor cone increased. To obtain uniform and bead-free structures with minimum diameter, processing parameters were fixed at 10 kV, 0.75 mL/h, and 20 cm for the chitosan/gelatin ratio of 7:3. Data demonstrated that the gelatin content could alter fibers diameter and at lower chitosan/gelatin ratios, higher fiber diameters were obtained. Moreover, glutaraldehyde vapor as a cross-linking agent was used to stabilize nanofibers in physiological environments (Amiri et al. 2018).

In another study, dendrimers were conjugated to gelatin. The conjugate and silver acetate were electrospun under the fixed condition of a flow rate of 5 mL/h, a voltage of 25 kV, and a speed of rotating collector of about 500 rpm. PEG diacrylate was used as a cross-linking agent to enhance the mechanical properties and stability of fibers. The presence of dendrimer enhanced drug loading capacity and led to controlled drug delivery. Furthermore, there would be functional sites for drug attachment, and multi-functional fibers as dressing materials could be electrospun. These fiber constructs showed sustained release of silver and antimicrobial properties against two wound pathogens (Dongargaonkar et al. 2013).

A recent study produced a core–shell drug-loaded nanofibrous mat using co-axial electrospinning. The core and shell layers contained ciprofloxacin/PCL and tetracycline/gelatin, respectively. The core–shell structure makes it possible to deliver various drugs with different release profiles. The in vitro release curve of tetracycline exhibited a rapid release, reaching 84% during 2 h due to the hydrophilic nature of gelatin. The cumulative release of ciprofloxacin reached only 30% within 2 h due to the hydrophobic properties of PCL, and consequently, slow destruction of fibers (Lin et al. 2022).

Collagen

Collagen is a major protein of the natural ECM and is mainly responsible for ECM tension-resisting (Wang 2021). Since collagen provides structural support and tensile strength to tissues, it supports the attachment, proliferation, and differentiation of cells (Zhu et al. 2015). In addition, it shows low antigenicity and good biocompatibility (Wang 2021). Collagen electrospinning is mostly possible by dissolving it in HFIP, TFE, and acetic acid solutions (Table 9). Poor

mechanical properties and rapid biodegradability limit the unmodified collagen usage as a single electrospinning component. Chemical cross-linking is a solution to stabilize collagen (Delgado et al. 2015). The most used cross-linking reagents are genipin, glutaraldehyde, N-(3-Dimethyl aminopropyl)-N'-ethyl carbodiimide hydrochloride (EDC), EDC with N-hydroxysulfosuccinimide (EDC-NHS), and hexamethylene diisocyanate (Delgado et al. 2015; Huang et al. 2015). Also, physical cross-linking via dehydrothermal treatment and UV irradiation is considered as another methods for modification of polymers (Delgado et al. 2015). Some recent research involving collagen nanofiber fabrication considering process variables is listed in Tables 9 and S9 (Online Resource 1).

By a novel approach, collagen nanofibers were electrospun under an electrospinning condition of 0.8 mL/h and 17 kV using 8% (w/v) polymer in HFIP/water solution. Mats contained calcium chloride and catecholamines such as dopamine and norepinephrine. Collagen cross-linking via catecholamine oxidative polymerization was induced in the presence of calcium ions. Furthermore, fiber diameter was decreased about 3-fold, and welded junctions were formed. Based on the data, seeding human osteoblasts on the scaffold enhanced cell adhesion, differentiation, and proliferation (Dhand et al. 2016).

HFIP and TFE are corrosive and could change collagen's third configuration. A less corrosive acidic solvent consisting of ethanol and water has been developed to avoid using these solvents. Citric acid and glycerol were used as a cross-linking agent and cross-linking extender, respectively. Nanofibers were fabricated under a voltage of 20 kV, an injection rate of 1 mL/h, and a rotating drum with a speed of 1200 rpm. It should be noted that using citric acid did not develop major fiber deformation while using glutaraldehyde led to fused fibers. Furthermore, mats cross-linked with citric acid maintained their structure for one month in PBS at 37 °C. Results demonstrated that cell adhesion and proliferation on citric acid cross-linked fibers were better than on glutaraldehyde cross-linked fibers (Jiang et al. 2013).

Recently, collagen/poly(lactide-co-e-caprolactone) (PLCL) scaffold was electrospun by a co-spinning approach using PVP as a polymer sacrificing agent. 1% collagen in acidified water (acetic acid 0.1 M) was mixed with 15 wt % PVP aqueous solution and 10 wt % PLCL was dissolved in DCM/DMF. The collagen/PVP/PLCL hybrid mat was fabricated at a voltage of 30 kV and a flow rate of 2.5 mL/h and 3 mL/h for collagen/PVP and PLCL, respectively. Smooth and bead-free fibers were fabricated after the co-electrospinning of polymers. PVP was removed from the scaffold via fiber immersion in water. This hybrid mat showed the highest tensile strength due to the intramolecular bonding of collagen and its reinforcing effect on PLCL. Also, reasonable cell adhesion and proliferation were obtained. This scaffold

Table 9 Process variables of studies on collagen nanofibers

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
Collagen	Dopamine, norepinephrine	Bone tissue engineering	–	8	Simple	HFIP/water 9:1	331±46 (dopamine), 323±43 (norepinephrine)	–	0.8	17	27 G	13	RT, ~25	Dhand et al. (2016)
Collagen, PCL	Artemisinin	Drug delivery	PCL: 80	Collagen: 5, PCL: 10	Simple	Acetic acid	60	–	1	20	0.41 mm	10	RT, 30	Huo et al. (2021)
Collagen, PET	No drug	Various biomedical applications	–	Collagen: 10, PET: 10	Simple	HFIP	347–780	Mixture: 2	0.12	12.5	–	10	RT, –	Drobota et al. (2020)
Collagen, PVDF	PRP	Bone tissue engineering	–	Collagen: 7.2, PVDF: 10	Simple	TFE (for collagen), DMA-acetone (for PVDF)	785±438[b]	–	0.4	21	–	18	25, –	Abazari et al. (2019)
Collagen, PLCL	No drug	3D cell culture, tissue engineering	–	Collagen: 1, PLCL: 10 wt %	Co-electrospinning	Acidified water (for collagen), DCM/DMF 9:1 (for PLCL)	1500±210[b]	PLCL: overnight	Collagen/PVP: 2.5, PLCL: 3	30	20 G	10.5	–	Turker et al. (2019)
Core: TPU Shell: collagen	No drug	Tissue engineering	Collagen: 80–100	TPU: 6 wt %, collagen: 8 wt %	Co-axial	HFIP	960±163[b]	–	Core: 0.8, shell: 1.2	20	–	Core: 130, shell: 50	Ambient, 55	Chen et al. (2010)
Core: PLA Shell: collagen	No drug	Meniscal tissue engineering	PLA: 100	Collagen: 10, PLA: 5	Co-axial	HFIP	240±12 (not crosslinked), 320±16 (crosslinked)	–	1–2	15–20	–	–	–	Baek et al. (2019)

[a]Fibers with diameters <1000 and ≥1000 nm were considered as nanofibers and electrospun fibers, respectively

[b]Electrospun fibers

–: Not provided

DCM dichloromethane, *DMA* dimethylacetamide, *DMF* dimethylformamide, *HFIP* 1,1,1,3,3,3-hexafluoro-2-isopropanol, *PCL* poly e-caprolactone, *PET* polyethylene terephthalate, *PLA* polylactic acid, *PLCL* poly(lactide-co-e-caprolactone), *PRP* platelet-rich plasma, *PVDF* polyvinylidene fluoride, *PVP* polyvinylpyrrolidone, *RT* room temperature, *TFE* trifluoroethanol, *TPU* thermoplastic polyurethane
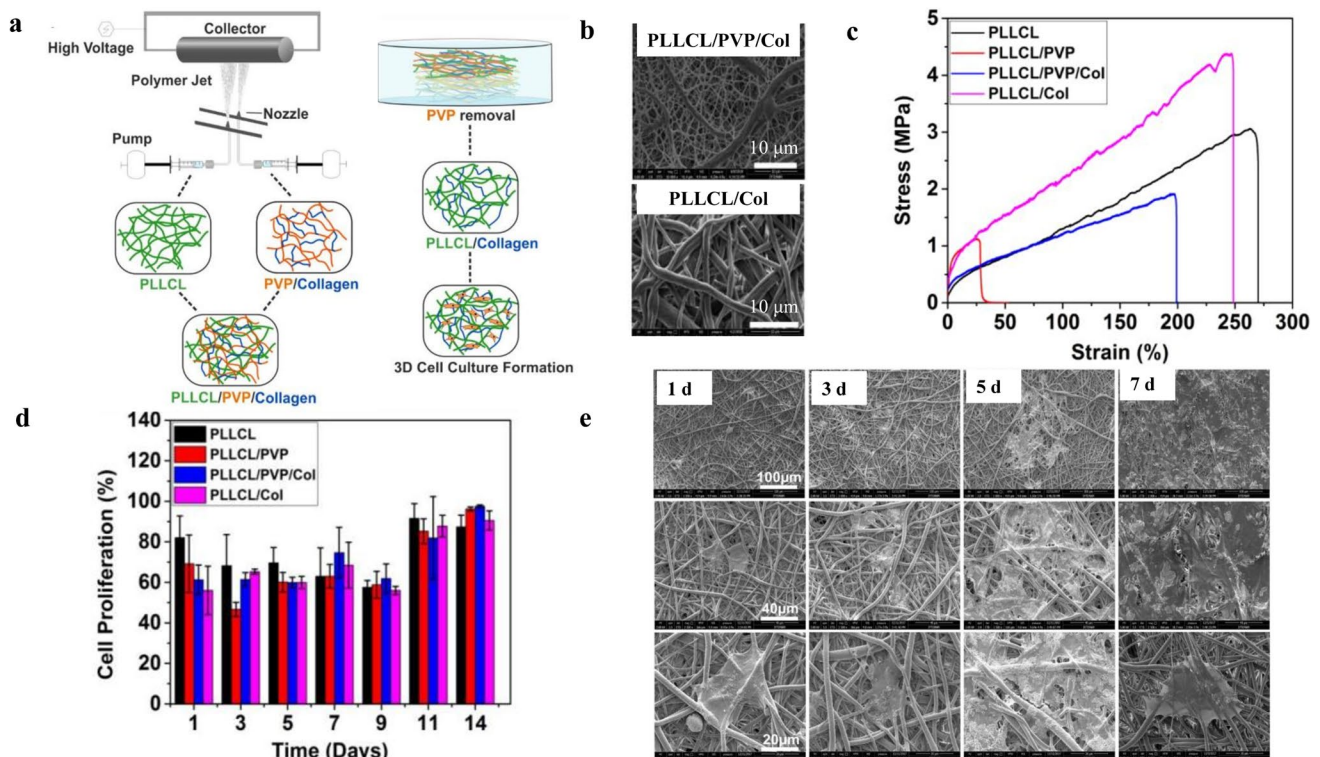
Fig. 7 a Schematic representation of nanofiber fabrication, **b** SEM images of fibers, **c** Stress–strain curve of scaffolds, **d** Cell proliferation of fibroblast cells on nanofiber mats after various time intervals, **e** SEM images of fibroblast cells proliferation on fibers containing Col and PLLCL (reprinted with minor modification from Ref. (Turker et al. 2019), with permission). *Col* collagen, *PVP* polyvinylpyrrolidone, *PLCL* poly(L-lactide-co-e-caprolactone), *SEM* scanning electron microscopy

could be used for tissue engineering due to its high biocompatibility (Fig. 7) (Turker et al. 2019).

Chitosan

Chitosan is a natural linear polysaccharide, a chitin derivative obtained through a deacetylation process (Aranaz et al. 2021). Chitosan is well known for its good biocompatibility, desirable biodegradability, intrinsic anti-bacterial nature, and nontoxicity (Aranaz et al. 2021; Thambiliyagodage et al. 2023). Due to chitosan's polycationic nature, common solvents are not appropriate for the electrospun procedure (Thambiliyagodage et al. 2023). Thus, acetic acid, TFA, HFIP, DCM or their combinations are being replaced (Qasim et al. 2018). The concentration of prepared chitosan solutions and flow rates were 2–8% (w/v) and ≤ 1 mL/h, respectively (Table 10). Despite the benefits of chitosan, it has poor mechanical properties, weak electrospinnability, and a fast degradation rate (Gomes et al. 2015; Adamski and Siuta 2021). Combining chitosan with other polymers, such as PVA (Habiba et al. 2017), PEO (Yuan et al. 2018), PCL (Li et al. 2018), and gelatin (Amiri et al. 2018), or using cross-linking agents such as glutaraldehyde (Amiri et al. 2018) and EDC (Pezeshki-Modaress et al. 2018) could help

to stabilize the electrospinning process and lead to defect-free fibers (Qasim et al. 2018; Han et al. 2023). Some recent studies on chitosan fibers are listed in Tables 10 and S10 (Online Resource 1).

In a recent work, three steps were carried out to fabricate chitosan-based nanofibers with remarkable antibacterial activity. For this, 1) NaOH hydrolysis was utilized to reduce the molecular weight of chitosan, 2) PVA and PVP were used as carrying polymers, and 3) in-situ synthesized AgNPs were incorporated in nanofibers. Increasing of hydrolyzed chitosan fraction decreased the diameter of fibers. The lowest fiber diameter and best antibacterial activity were observed in the nanofibers containing AgNPs, and the optimizations mentioned above improved the electrospinning performance (Bandatang et al. 2021).

The effects of physical and chemical cross-linking on the mechanical and biological properties of chitosan-based nanofibers were investigated. In this regard, phosphate ions and ethylene glycol diglycidyl ether were used for physical and chemical cross-linking, respectively. Based on the results, physical cross-linking led to smooth nanofibers, whereas chemical cross-linking provided rougher and bigger nanofibers. Moreover, physically cross-linked nanofibers

Table 10 Process variables of studies on chitosan nanofibers

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
Chitosan, PVA	Zeolite	Water treatment	Chitosan: 896, PVA: 60	Chitosan: 7 wt %, chitosan/PVA 1:1	Simple	Acetic acid (for chitosan), water (for PVA)	70±19	–	0.4	10	19 G	10	–	Habiba et al. (2017)
Chitosan, PVA	No drug	Tissue engineering	Chitosan: LMW, PVA: 72	Chitosan: 2 wt %, PVA: 10 wt %	Simple	0.5 M acetic acid	105	–	0.48	20	0.514 mm	10	–	Mahdian-Dehkordi et al. (2021)
Chitosan, PEO	Cefazolin, fumed silica	Wound dressing	400	Blend solution: 4 wt % (PEO/chitosan 1:4)	Simple	Acetic acid 50% (v/v)	70±15	Overnight	1	21	20 G	10	25–35, 35–42	Fazli and Shariatinia (2017)
Chitosan, PEO	Teicoplanin	Wound dressing	~900	Chitosan: 2.5, PEO: 0.5	Simple	Aqueous acetic acid	2% Teicoplanin: 585±94, 4% Teicoplanin: 602±136	–	0.5	10, 12	–	20	–	Amiri et al. (2020)
Chitosan, PVA, Eudragit RL100	Ofloxacin	Ocular drug delivery	PVA: 89–98	Chitosan: 2, PVA: 4	Simple	Acetic acid (1% v/v)/water (1:1)	No crosslinking: 123±23, crosslinked: 159±30	–	No crosslinking: 0.5, crosslinked: 2	28	–	15	25, 25	Mirzaeei et al. (2021b)
Chitosan, collagen, PEO	Curcumin	Wound dressing	PEO: 900	Collagen: 2.5, chitosan: 2.5, PEO: 2.5	Simple	Acetic acid 80%	371±46	Chitosan/PEO: 12, Chitosan/PEO/collagen: 2, mixture: 0.33	0.5	6–8	18 G	20	28, 30	Jirofti et al. (2021)

Table 10 (continued)

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/ needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
Hydrolyzed chitosan, PVP, PVA	Silver nanoparticles	Antibacterial activity	Chitosan: 100–300, PVP: 1300, PVA: 85–120	Chitosan: 4, PVP: 20 wt. %, PVA: 15 wt. %	Simple	50% NaOH (for chitosan), acetic acid 0.35 M (for PVP and PVA)	139±17	Chitosan: 24, PVP and PVA: 24	1	22	0.8 mm	15	RT, –	Bandatang et al. (2021)
Chitosan, collagen, PEO, polypyrrole	No drug	Tissue engineering	–	Collagen: 0.66, chitosan: 2.64, PEO: 2.1, polypyrrole: 10 wt. %	Simple	Acetic acid/ water 1:1	92	PEO: 3, PEO/chitosan: 4, PEO/chitosan/collagen: 2, mixture: 4	0.4	18	–	12	–	Zarei et al. (2021)
Chitosan, PEO	No drug	Wound dressing	Chitosan: LMW, PEO: 900	Chitosan: 3.5 wt. %, PEO: 3.5 wt. %	Simple	Acetic acid 5% v/v	Physical crosslinking: 190, chemical crosslinking: 270	Chitosan: 24, Chitosan/PEO: 24	0.15	17.5	22 G	20	25, 50	Dodero et al. (2021)
Chitosan, gelatin, PVA	No drug	Tissue engineering	Chitosan: 300	Chitosan: 2 wt %, gelatin: 2 wt %, PVA: 4 wt %	Simple	Acetic acid 20%	~150	–	0.3	20	23 G	15	30, 40	Tsai et al. (2014)
Chitosan, gelatin, PVA, arabic gum	No drug	Tissue engineering	Chitosan: ~300, PVA: 75	Chitosan: 8 wt %, gelatin: 8 wt %, PVA: 2 wt %, arabic gum: 0.5 wt %	Simple	Acetic acid 20%	143±31	–	0.3	25	23 G	15	30, 40	Tsai et al. (2015)

Table 10 (continued)

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/ needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
Chitosan, PEO, fibrinogen	PDGF	Wound dressing	Chitosan: LMW, PEO: 300	Blend solution (Chitosan/PEO 2:1 wt%): 5.5 wt %, fibrinogen: 11	Co-electrospinning	Acetic acid/ BSA/DMSO 1:0.5:10 (for chitosan and PEO), EMEM/HFIP 1:9 (for fibrinogen)	202 ± 113	–	Chitosan-PEO: 0.7, fibrinogen: 1	Chitosan-PEO: 28, fibrinogen: 22	18 G	Chitosan-PEO: 22, fibrinogen: 12.5	RT, 35–45	Yuan et al. (2018)
First layer: PCL Second layer: chitosan	Mupirocin, lidocaine	Wound dressing	Chitosan: MMW	Chitosan: 8, PCL: 10	Two-layer	TFA/DCM 7:3 (for chitosan), HFIP/DCM 1:3 (for PCL)	First layer: 1031 ± 227[b], second layer: 735 ± 152	Chitosan: 48, PCL: 24	1	First layer: 15, second layer: 17	25 G	First layer: 15, second layer: 13	RT, 30–40	Li et al. (2018)

[a]Fibers with diameters < 1000 and ≥ 1000 nm were considered as nanofibers and electrospun fibers, respectively

[b]Electrospun fibers

–: Not provided

BSA bovine serum albumin, *DCM* dichloromethane, *DMSO* dimethylsulfoxide, *EMEM* Eagle's minimum essential media, *HFIP* 1,1,1,3,3,3 hexafluoro-2-isopropanol, *LMW* low molecular weight, *MMW* medium molecular weight, *PCL* poly e-caprolactone, *PDGF* platelet-derived growth factor, *PEO* polyethylene oxide, *PVA* polyvinyl alcohol, *PVP* polyvinylpyrrolidone, *RT* room temperature, TFA trifluoroacetic acid

Table 11 Process variables of studies on silk fibroin nanofibers

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
Silk fibroin	No drug	–	–	10	Simple	Formic acid 98–100%	134	1	0.1	20	18 G	12	–	Chomachayi et al. (2016)
Silk fibroin	Laponite® nanoplatelets	Bone tissue engineering	–	16 wt %	Simple	Water	820	–	0.5	20	20 G	15	–	Wu et al. (2021a)
Silk fibroin, PLCL	CPL	Diabetic wound dressing	PLCL: 50:50, 450	Silk fibroin /PLCL 60:40 wt. %, blend solution: 10	Simple	HFIP	199±31	Silk fibroin, PLCL: overnight, mixture: 12	1	12	–	10	–	Xu et al. (2021)
Silk fibroin, PCL	No drug	Tissue engineering	PCL: 80	Silk fibroin /PCL 50:50, blend solution: 25	Simple	Formic acid 98%/acetic caid 33:7	190±40	Silk fibroin, PCL: 2, Silk fibroin, PCL: 5	0.3	17	22 G	15	–	Zhu et al. (2016)
Silk fibroin, PLA	No drug	Cartilage tissue engineering	PLA: 300	Silk fibroin/ PLA 50:50	Simple	TFA (for silk fibroin), HFIP (for PLA)	1130±130[b]	–	–	15	0.4 mm	20	–	Liu et al. (2016)
Silk fibroin, PVA	CP, GSNO	Treatment of ischemic chronic wounds	PVA: 60–125	Silk fibroin: 3, PVA: 11	Simple	–	115±37	–	48	25±3	21 G	15	–	Ramadass et al. (2019)
Core: PVA Shell: Silk fibroin	Rosuvastatin	Enhancement of osteogenesis of human adipose-derived stem cells	–	Silk fibroin: 13, PVA: 10	Co-axial	Formic acid	206±5	Silk fibroin: 3, PVA: 1	Core: 0.25, shell: 0.2	18	Core: 22 G, shell: 14 G	12	–	Kalani et al. (2019)

[a]Fibers with diameters <1000 and ≥1000 nm were considered as nanofibers and electrospun fibers, respectively

[b]Electrospun fibers

–: Not provided

CP type I collagen peptide, CPL compound phellodendron liquid, GSNO s-nitrosoglutathione, HFIP 1,1,1,3,3,3-hexafluoro-2-isopropanol, PCL poly e-caprolactone, PLA polylactic acid, PLCL poly(lactide-co-e-caprolactone), PVA polyvinyl alcohol, TFA trifluoroacetic acid
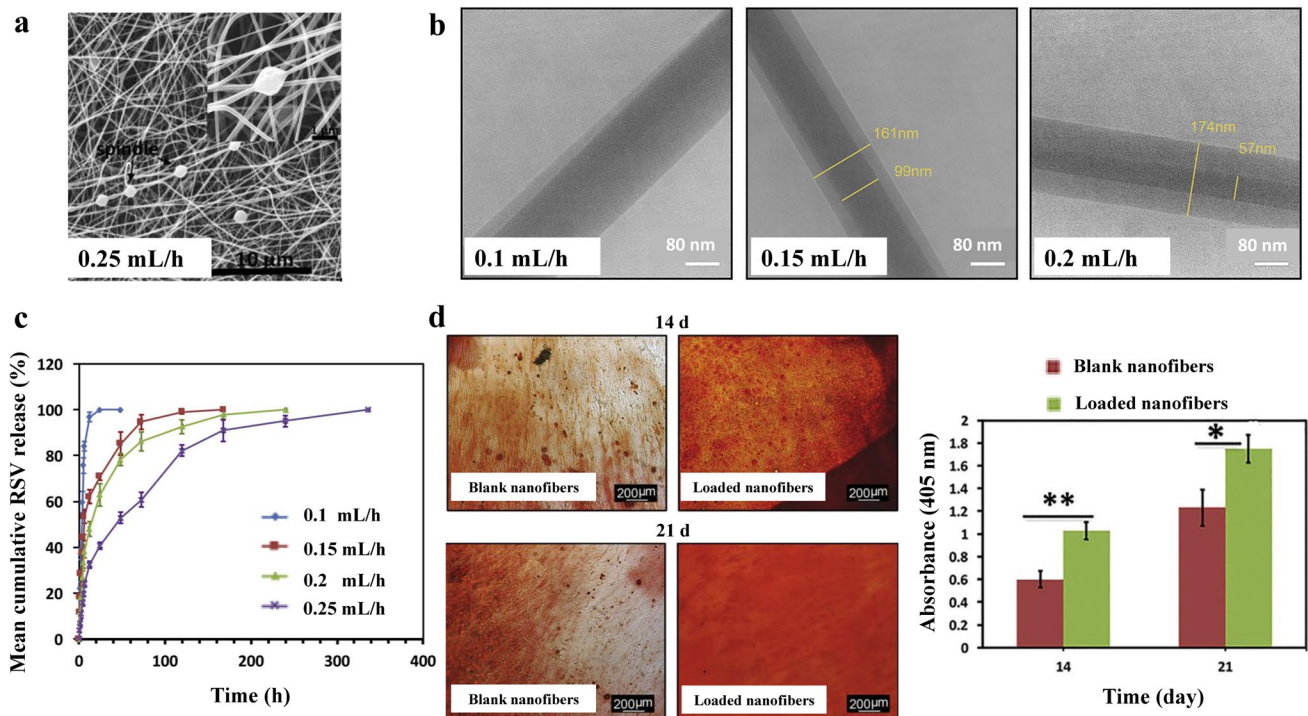
Fig. 8 **a** SEM image of nanofibers fabricated at the flow rate of 0.25 mL/h, **b** TEM images of fibers prepared at different flow rates, **c** Rosuvastatin release profile of fibers electrospun under different flow rates, **d** Formation of extracellular matrix on fibers following differentiation of stem cells which were seeded on them (reprinted with minor modification from Ref. (Kalani et al. 2019), with permission). *SEM* scanning electron microscopy, *TEM* transmission electron microscopy

showed better results in cell viability analysis (Dodero et al. 2021).

In a study, a chitosan/gelatin scaffold using PVA as a film-forming agent was electrospun using acetic acid as the solvent. The effect of different concentrations of acetic acid (2, 20, and 70 wt %) was investigated. Changing acetic acid concentration from 2 to 70 wt % decreased electrical conductivity. However, acetic acid 2 and 20 wt % were not electrospinnable, and beaded structures were obtained rather than fiber. Nevertheless, acetic acid 70 wt % is not environmentally safe. Hence, 4 wt % PVA was used to improve spinnability and reduce the acetic acid concentration to 20 wt %, generating bead-free mats. The hybrid mat was cross-linked via glutaraldehyde vapor. The better proliferation of mesenchymal stem cells on mats was obtained than on sponges (Tsai et al. 2014).

In another experiment, different weight percentages of polypyrrole, a conductive polymer, were used in electrospun nanofibers containing collagen, chitosan, and PEO. The increase in polypyrrole content enhanced the conductivity and reduced the mean diameter. In addition, better cell growth and proliferation properties were observed in nanofibers with 10 wt % polypyrrole (Zarei et al. 2021).

Silk fibroin

Silk fibroin is a structural protein extracted from silkworm cocoons. This process leads to an aqueous solution, which makes silk fibroin self-assemble and form both an amorphous and a crystalline form. These two forms have different physicochemical features. While the amorphous type is soluble in water, the crystalline type is insoluble (Lu et al. 2010). Also, elasticity and flexibility contributed from the amorphous part, meanwhile toughness and strength contributed from the crystalline part (Vepari and Kaplan 2007). Silk fibroin has been used as a biopolymer due to its superiorities, including high biocompatibility, nontoxicity, controllable biodegradability, ease of processing, adequate supply, excellent mechanical strength, and good cellular response (Ju et al. 2016; Qi et al. 2017; Onder et al. 2022). Solvents including HFIP, TFA, formic acid, and water can be used as a solvent for electrospinning of silk fibroin (Table 11). Some recent research on silk electrospinning conditions is listed in Tables 11 and S11 (Online Resource 1).

A research group fabricated silk nanofibers using mathematical models considering polymer concentration (10 and 12% (w/v)), feeding rate (0.1–0.6 mL/h), needle-to-collector distance (8–12 cm), and speed of collector (200–2500 rpm) as variables. The polymer solution was prepared using

Table 12 Process variables of studies on zein nanofibers

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
Zein	PGS	Soft tissue engineering	–	30 wt %	Simple	Acetic acid	200 ± 100	Zein: 0.25, mixture: 1.5	0.3	20	–	15	23–26, 36–64	Vogt et al. (2018)
Zein	No drug	–	–	45 wt %	Simple	Choline chloride/furfuryl alcohol 1:2 molar ratio	350 ± 50	2	0.2	10	0.6 mm	14	–	Khatri et al. (2020)
Zein, PEO, chitosan	No drug	Mucoadhesive delivery system	PEO: 300, chitosan: 900	Zein: 40 wt %, PEO: 3, chitosan: 1	Simple	Ethanol 85% and 90% (for zein and PEO), acetic acid 50%+Tween 2 wt % (for chitosan)	357 ± 87	Zein, PEO: 1, chitosan: 12, mixture: 0.12	–	15–20	0.69 mm	18	–	Wongsasulak et al. (2013)
Zein, nylon-6	No drug	Hexavalent chromium removal	nylon-6: ~25	Zein: 38, nylon-6: 22	Co-electrospinning	DMF (for zein), formic acid (nylon-6)	100–200	Zein: 2, nylon-6: 2.5	0.05	18	–	1.5	–	Ansari et al. (2022)
Core: PLA Shell: zein	RCSPs	Wound dressing	Zein: 35, PLA: 180	Zein: 25.1, PLA: –	Co-axial	HFIP	335 ± 101	–	Core: -0.36, shell: 0.48	15	–	12	–	Zhang et al. (2016b)

Table 12 (continued)

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
First layer: zein, PCL, arabic gum Second layer: PCL Third layer: zein, PCL, arabic gum	Calendula officinalis extract	Skin tissue engineering	PCL: 80, arabic gum: 0.0014	Zein: 15, PCL: 20, arabic gum: 6	Multi-layer	Acetic acid 95% (for zein and PCL), formic acid (for arabic gum)	371 ± 253	Zein, PCL, arabic gum: 2, zein, PCL, arabic gum, Calendula officinalis extract: 1, PCL: 5, PCL, Calendula officinalis extract: 1	0.2	18	23 G	15	–	Pedram Rad et al. (2019)
Core: zein Shell: PVP	Ketoprofen	Drug delivery	360	PVP: 10, zein: 28	Co-axial	Core: ethanol 80%, shell: DMA/ethanol 1.5:8.5	730 ± 190	–	0.5	15	–	15	21 ± 3, 58 ± 5	Jiang et al. (2012)
Core: PCL Shell: Zein	Metronidazole	Guided tissue engineering	PCL: 80	Zein 20 wt %, PCL: 10 wt %	Co-axial	Acetic acid (for zein), TFE (for PCL)	560–790	PCL, metronidazole: 12, zein: 12	Core:0.7–1.4, shell: 3	23–25	–	18	–	He et al. (2016)

Table 12 (continued)

Composition	Drug	Indication	Polymer molecular weight (kDa)	Polymer concentration (% w/v)	Method of electrospinning	Solvent	Fiber diameter (nm)[a]	Time of stirring (h)	Rate of injection (mL/h)	Voltage (kV)	Nozzle gauge (G)/needle inner diameter (mm)	Needle-collector distance (cm)	Temperature (°C), humidity (%)	References
Top layer: PCL, hyaluronic acid Bottom layer: zein, chitosan	SA	Wound dressing	chitosan: LMW, hyaluronic acid: 1500–2200	Zein: 40, chitosan: 7, PCL:7, hyaluronic acid: 1	Two-layer	Ethanol 80% (for zein), acetic acid 70% (for chitosan), TFE 80% (for PCL), NaOH 5 M/DMF 4:1 (for hyaluronic acid)	Top layer: 472±192, bottom layer: 530±180	Zein, chitosan: 0.25	Top layer: 2.5, bottom layer: 3	Top layer: 25, bottom layer: 28	21 G	15	–	Figueira et al. (2016)

[a]Fibers with diameters <1000 and ≥1000 nm were considered as nanofibers and electrospun fibers, respectively

–: Not provided

DMA dimethylacetamide, *DMF* dimethylformamide, *HFIP* 1,1,1,3,3,3-hexafluoro-2-isopropanol, *LMW* low molecular weight, *PCL* poly e-caprolactone, *PEO* polyethylene oxide, *PGS* poly(glycerol sebacate), *PLA* polylactic acid, *PVP* polyvinylpyrrolidone, *RCSPs* Rana chensinensis skin peptides, *SA* salicylic acid, *TFE* trifluoroethanol

formic acid as a solvent. According to data, changing polymer concentration from 10 to 13% (w/v) increased fiber diameter about 2.2-fold probably due to an increment in polymer amount in the electrospinning jet. Increasing flow rate had a direct influence on diameter, generating thicker fibers. Flow rate affects the formation of Taylor cone and consequently, the structure of fibers. An increment in distance lowered fiber diameter due to more solvent evaporation. However, this change did not affect the morphology of fibers. Moreover, higher speeds of collector decreased nanofiber diameter. Altogether, optimized parameters generating fibers with minimized diameter were 10% (w/v), 0.1 mL/h, 12 cm, 20 kV, and 200 rpm (Chomachayi et al. 2016).

The high cost of HFIP made this solvent unfavorable, especially in large-batch preparations of fibers. Thus, formic acid as an alternative solvent gathered much attention; however, this solvent could lead to phase separation in polymer solution after being left for a few hours. Accordingly, acetic acid was added to the solution to obtain a homogenous solution of silk fibroin/PCL in formic acid. Acetic acid concentration could alter phase separation. Formic acid/acetic acid 33:7 containing 17.5% (v/v) acetic acid resulted in no phase separation after 24 h. Phase separation could lead to inhomogeneous morphology of scaffolds and consequently affect the adhesion and proliferation of cells (Zhu et al. 2016).

In a study, some researchers developed rosuvastatin-loaded silk fibroin/PVA for enhancing osteogenesis via the co-axial method. The core and shell consisted of a PVA solution containing rosuvastatin and silk fibroin, respectively. Both core and shell solutions were prepared in formic acid. While the feeding rate of the core was fixed at 0.25 mL/h, the shell went through different flow rates ranging from 0 to 0.25 mL/h. Results exhibited larger fibers were formed by increasing the shell flow rate. At the highest shell injection rate, wet fibers deposited on the collector, and a few spindles were observed (Fig. 8A). At lower rates, shell material would be insufficient and axial asymmetry was occurred. Increasing the shell feeding rate from 0.15 to 0.2 mL/h resulted in thicker shell fibers. Based on the data, the 0.2 mL/h shell flow rate was properly giving smooth nanofibers (Fig. 8B). Moreover, increasing the shell flow rate contributed to a sustained drug release (Fig. 8C). Also, using nanofibers led to an enhancement in osteogenic differentiation and proliferation (Fig. 8D). To stabilize developed scaffolds, mats were cross-linked with glutaraldehyde and hydrochloric acid solution (Kalani et al. 2019).

Zein

Zein is a natural polymer, accredited as a safe ingredient by the FDA. Zein is a prolamine in a corn maize and is widely known for its biodegradability, biocompatibility (Berardi et al. 2018), biological function to enhance cell attachment

Table 13 Properties of marketed nanofiber products

Product name	Company	Indication	Composition	Administration route	References
ActiVLayr®	Revolution Fibers	Skincare	Marine collagen, a mixture of grapefruit and kiwifruit bioactives (Vinanza)	Dermal (under-eyes patch)	Zheng et al. (2020)
AVflo™ Vascular Access Graft	Nicast	Vascular access in hemodialysis	PU	Surgery (implant)	Stoddard et al. (2016), Omer et al. (2021), Hiwrale et al. (2023)
Chito-Flex® PRO	Tricol Biomedical	Wound dressing	Chitosan	Dermal	Tien et al. (2021)
HealSmart™	PolyRemedy	Antimicrobial wound dressing	Hyaluronic acid, PHMB	Dermal	Fadil et al. (2021), Omer et al. (2021), Hiwrale et al. (2023)
Kerlix™ AMD	Kendall	Decrease in wound and surgical site infections	PHMB	Dermal (gauze)	Kattamuri et al. (2012)
NeoDura™	Medprin Biotech GmbH	Absorbable dural repair	PLA (L), gelatin	Dural (patch)	Fadil et al. (2021)
PK Papyrus®	Biotronik	Stent covering	PU	Surgery (implant)	Stoddard et al. (2016), Omer et al. (2021), Hiwrale et al. (2023)
ReBOSSIS®	Ortho ReBirth	Filling gaps and voids in bone	Bioabsorbable polymer, β-TCP, silicone, calcium carbonate	Surgery (bone substitution)	Omer et al. (2021), Hiwrale et al. (2023)
ReDura®	Medprin	Similar to ECM, rapid repair and regeneration	PLA (L)	Dural (patch)	Fadil et al. (2021), Omer et al. (2021)
Surgiclot®	ST. Teresa Medical	Bone bleeding	Dextran	Dermal	Omer et al. (2021), Hiwrale et al. (2023)
Tromboguard®	TRICOMED S.A	Wound dressing	Chitosan, alginate	Dermal	Tien et al. (2021)
Zeus Bioweb™	Zeus	Stent covering	PTFE	Surgery (implant)	Fadil et al. (2021), Omer et al. (2021)

ECM extracellular matrix, *PHMB* polyhexamethylene biguanide, *PLA* polylactic acid, *PTFE* polytetrafluoroethylene, *PU* polyurethane, *β-TCP* β-tricalcium phosphate

and viability (He et al. 2016), high degree of microbial resistance (Pedram Rad et al. 2019), low cytotoxicity, toughness, flexibility, and water swelling (Rahman et al. 2023). Due to a significant proportion of nonpolar groups, zein cannot be dissolved in water (Berardi et al. 2018). Still, it can be dissolved in organic solvents like DMF, HFIP, ethanol, and acetic acid (Table 12). Electrospinning feeding rates and applied voltages range from 0.05 to 3 mL/h and from 10 to 28 kV, respectively. Zein has an amphiphilic polymeric nature; hence it could be blended with hydrophilic and hydrophobic solvents (Berardi et al. 2018). Some recent research on electrospinning conditions of zein is summarized in Tables 12 and S12 (Online Resource 1).

It is shown that the humidity of the electrospinning chamber can alter electrospinnability and fiber morphology due to the change in solvent removal and solidification rate. Recently, zein nanofibers were generated under the relative humidity of 25 and 50%, and circular cross-section, defect-free, and bead-free structures were developed. The authors also used either ethanol or acetic acid as the solvent, and

based on the data, acetic acid led to a higher yield (Vogt et al. 2018).

Another study tested the effect of ethanol concentration (85 and 90%) on the fiber morphology. By increasing the ethanol percentage, nonpolarity increased, leading to decreased electrical conductivity. Lower ethanol concentration decreased viscosity, meanwhile increased surface tension. Altogether, low ethanol concentration with high solution conductivity and low viscosity yielded disintegrating fibers. Furthermore, lower ethanol concentration decreased solvent evaporation rate, generating spider-web structures (Wongsasulak et al. 2013).

Recently, zein nanofibers were fabricated using deep eutectic solvent (DES) electrospinning. DES consisted of furfuryl alcohol and choline chloride with a ratio of 2:1. Compared to the hydrophobic zein nanofibers, DES-zein nanofibers showed hydrophilic properties and less average diameter. The average diameter of DES-zein nanofibers partially increased following a decrease in the tip-collector

Table 14 Properties of nanofibers under clinical trials

Product name	Active ingredient	Administration route	Study title	Status	Polymer	Clinical trial identifier	References
BioFiber™	Polymer	Surgery (soft tissue repair)	BioFiber and BioFiber-CM Absorbable biologic scaffold for soft tissue repair and reinforcement post-market surveillance clinical study	Not applicable	Collagen	NCT01849458	Brockmeier et al. (2013)
Neuro-Spinal scaffold™	Polymer	Surgery (spinal cord)	The INSPIRE study: in vivo study of probable benefit of the neuro-spinal scaffold for safety and neurologic recovery in subjects with complete thoracic AIS A spinal cord injury	Not applicable	PLGA-b-PLL	NCT02138110	Toselli (2014)
Rotium nanofiber graft	Polymers	Surgery (graft)	A prospective randomized multicenter evaluation of rotator cuff healing using a nanofiber scaffold in patients greater than 55 years	Not applicable	PLCL, PGL	NCT04325789	Badman (2020)
PCL-TCP scaffold	Polymer, TCP	Surgery (dental implantation)	3D printed scaffold device for ridge preservation after tooth extraction-A randomized	Not applicable	PCL	NCT03735199	Goh (2019)
EktoTherix™	–	Surgery	EktoTherix™ regenerative tissue scaffold for repair of surgical excision wounds	Not applicable	Not provided	NCT02409628	Lyon (2015)
TAP nanofibers	Ciprofloxacin, metronidazole, minocycline	Intracanal (endodontics)	Evaluation of the antimicrobial effect of pre-synthesized novel antibiotic electrospun nanofibers as an intracanal delivery strategy for regenerative endodontics-A randomized clinical trial	Not applicable	Not provided	NCT03690960	Ahmed (2018)
PLCL-porcine fibrinogen dressing	Porcine fibrinogen	Topical	Study on regeneration of skin defects in diabetic ulcers treated with new electrospun material poly (L-lactide-co-caprolactone) and formulated porcine fibrinogen	Phase 4	PLCL	NCT06014437	Dong (2023)

Table 14 (continued)

Product name	Active ingredient	Administration route	Study title	Status	Polymer	Clinical trial identifier	References
Spincare® Matrix	–	Topical	A pilot study to evaluate a temporary skin substitute (Spincare® Matrix) for wound healing in RDEB patients	Not applicable	Not provided	NCT05944250	Tang (2023)
Restrata®	–	Surgery (graft)	Prospective randomized controlled trial comparing infection rates and wound closure following transmetatarsal amputation with aid of electrospun fiber matrix	Not applicable	Not provided	NCT06063694	Brookshier (2023)

PCL-TCP polycaprolactone-tricalcium phosphate, *PGL* polyglycolide, *PLCL* poly(lactide-co-e-caprolactone), *PLGA* poly(lactic-co-glycolic acid), *PLL* poly(L-lysine), *RDEB* recessive dystrophic epidermolysis bullosa, *TAP* electrospun triple antibiotic mixture

distance, while the voltage did not affect their morphology (Khatri et al. 2020).

Different electrospinning methods could generate nanofibers with different properties (Pedram Rad et al. 2019). For example, a wound dressing patch was fabricated using zein/PLA mats loaded with skin peptides. Nanofibers were obtained by blend and co-axial (core: PLA and shell: zein) methods. Fibers from the co-axial technique had lower diameters and more hydrophobic nature, while blend mats showed hydrophilic properties and lower mechanical characteristics (Zhang et al. 2016b).

By a novel approach, *Calendula officinalis* extract was loaded into zein/PCL/Arabic gum nanofibers for skin tissue engineering using suspension, two-nozzle, and multilayer fabrication methods. In the suspension method, one solution containing all ingredients was electrospun. While in the other methods, two solutions containing zein/PCL/ Arabic gum and PCL/*Calendula* extract were electrospun, individually. All methods resulted in bead-free and smooth fibers. The multilayer mat had finer fibers, while fibers from the suspension method had lower strength. Multilayer fibers had more Arabic gum content, hence higher strength than fibers fabricated from the two-nozzle method. Both multilayer and two-nozzle techniques developed fibers with similar porosity, which is lower than fibers generated from the suspension technique. All nanofibers showed moderate biodegradability (Pedram Rad et al. 2019).

Marketed nanofibers and nanofibers under clinical trials

Electrospinning is known as the most efficient technology for the large-scale production of polymeric filaments (Shahriar et al. 2019). Some of these electrospun nanofiber-based products have been commercialized (Table 13), and some are under clinical trials (Table 14) for various biomedical applications, including wound dressings, drug delivery, and tissue engineering.

Electrospun nanofibrous scaffolds are promising in the wound dressings area as they can mimic the ECM regarding the structure and accordingly assign an effective microenvironment for cell adhesion, proliferation, and differentiation. In addition, nanofibrous materials also retain a large amount of water due to their porous structures (Rasouli et al. 2019).

Electrospun nanofibers are superior platforms for drug delivery because of their unique properties (Shahriar et al. 2019). The aim of exploiting the nanofibers in tissue engineering is to mimic tissue properties by designing scaffolds with exclusive features of that specific tissue (Gao et al. 2019). For example, polycarbonate-urethane was electrospun with silicone copolymers in the multilayered

form to fabricate AVflo™ for use as a vascular access graft. Biotronik® produced a coronary stent system using PU (named PK papyrus™) as the stent coating. AVflo™ mostly consists of electrospun fibers, but PK papyrus™ just covers the coronary metal stent. Both products obtained Conformitè Europèenne (CE) certification (Stoddard et al. 2016). Details on other marketed products and those under clinical trial are summarized in Tables 13 and 14.

Conclusion

Various techniques, such as phase separation, electrospinning, and self-assembly are used to fabricate fibers. To date, the electrospinning process has gathered much interest in the field of medical applications (wound dressing, biosensors, drug delivery, tissue engineering, regenerative medicine, etc.) (Bhattarai et al. 2019; Keirouz et al. 2023) due to its simplicity, cost-effectiveness, potential to scale up, generating scaffolds with high surface-volume ratio, tunable porosity, controlled drug delivery, obtaining desirable mats morphology, scaffolds ability to mimic natural tissues (Nangare et al. 2020), ability to coat materials such as implants, and antimicrobial properties (Sousa et al. 2020). Both nanofibers and microfibers could be fabricated using different electrospinning methods (simple, side-by-side, co-axial, and emulsion) by manipulating critical parameters. Various electrospinning techniques and their developments lead to the use of different synthetic and natural polymers, considering polymer blends that have the advantage of all polymeric components. Most natural polymers are biocompatible and biodegradable, which makes them favorable in drug delivery and biomedical applications; however, generating nanofibers from these polymers is hampered due to poor mechanical properties. The combination of both natural and synthetic polymers improved the characteristics of scaffolds. Furthermore, a wide range of cargoes can be loaded into these systems, including drug molecules, peptides, proteins, cells, inorganic composites, nanostructures, and herbal extracts. Also, there are commercialized fibers available in the market.

Solution properties (polymer concentration, solvents used to dissolve polymers and drugs, viscosity and conductivity of spinning solution, etc.), process factors (applied voltage, flow rate, distance between needle and collector), and environmental conditions (humidity and temperature) are the three main parameters which play crucial roles in fibers morphology, orientation, porosity, mechanical strength, cell attachment, and drug release. To fabricate scaffolds with desirable properties, the mentioned parameters should be optimized. This article reviewed electrospinning variable parameters in different nanofibers composed of single polymer and polymer blends.

Numerous studies have covered the potential of fibers; however, future research should address more preclinical and clinical studies, identifying the relationship between cargo concentration, formulation design, and efficacy. Scale-up methods should also be mentioned as a path to commercializing products.

Declarations

Conflicts of interest The authors F. Bayat, Y. Hashtrodylar, H. Karimi, F. Mehryab, and A. Haeri declare no conflicts of interest.

Statement of human and animal rights This article does not contain any studies with human and animal subjects performed by any authors.

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