

REVIEW

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Nanofiber as a novel vehicle for transdermal delivery of therapeutic agents: challenges and opportunities

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Abstract

Background: Transdermal delivery of drugs is a quite challenging task for pharmaceutical scientists. The transdermal route is preferred over the oral route due to various advantages like avoidance of the first-pass effect, non-invasiveness, and high patient compliance. Therefore, it is necessary to develop an effective carrier system that enables the effective passage of the drug through the dermal barrier.

Main body of abstract: Various novel drug delivery systems are used to enhance the permeation of a variety of drugs through the skin barrier. Researchers around the globe have explored nanofibers for the transdermal delivery of various therapeutic agents. Nanofibers are designed to have a high concentration of therapeutic agents in them promoting their flux through various skin layers. Polymeric nanofibers can be explored for the loading of both hydrophilic and lipophilic drugs. Biopolymer-based nanofibers have been also explored for transdermal delivery. They are capable of controlling the release of therapeutic agents for a prolonged time.

Short conclusion: The literature presented in this review paper provides significant proof that nanofibers will have an intense impact on the transdermal delivery of different bioactive molecules in the future.

Graphic abstract:

Keywords: Flux, Nanofibers, Permeation, Skin barrier, Transdermal

Background

Skin is the outermost lipidic barrier of the body with a thickness of 20–25 μm [1]. Besides the barrier function, it also helps in the absorption of various therapeutic and non-therapeutic molecules [2]. The presence of skin appendages like hair follicles can also be responsible for the passive absorption of drug molecules through the transdermal route (Fig. 1) [3]. Since drug molecules can directly enter into the systemic circulation after crossing this barrier, therefore, this route has attracted pharmaceutical scientists to perform research in the field of

drug delivery for the last two decades [4]. The transdermal route is considered a better alternative to the oral route of drugs due to the prevention of dose fluctuations, first-pass hepatic metabolism, and increased bioavailability [5]. Moreover, the non-invasive nature and ease of application of dosage form through this route have helped to gain popularity among patients [6]. Numerous factors should be considered before developing transdermal delivery systems of drugs like skin barrier only allows penetration of hydrophobic drug molecules through it with molecular weight less than 500 kDa (kilodaltons) [7]. The rate of influx of drugs is very slow through this barrier. However, the effective delivery of hydrophilic drugs through the skin is still a challenging task [8].

There are various nanocarrier systems like liposomes, niosomes, solid lipid nanoparticles, nanostructured

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lipid carriers, ethosomes, and polymeric nanoparticles which are explored for effective transdermal delivery of drugs [9]. However, polymeric micro or nanofibers have gained special attention for effective transdermal delivery of drugs for the last decade [10]. Various methods explored for the production of nanofibers are electrospinning, template synthesis, and phase separation [11]. However, electrospinning is the most widely used technique among all of them due to its cost-effectiveness and simplicity [12]. Nanofibers are generated in the form of the mat from electrospinning (Fig. 2) revealing various advantages like high surface area, nanopore size, and unique physicochemical properties [13]. These characteristic traits of nanofibers make them a suitable candidate for the delivery of drugs and genes [14]. Nanofibers may be an excellent choice for tissue engineering and dressing wounds due to their capability to produce a local effect [15]. There are various categories of drugs like anticancer, NSAIDs (Non-steroidal anti-inflammatory drugs), and antibiotics which are delivered through the transdermal route exploring nanofibrous mats [16]. This paper summarizes the utility of nanofibrous mats/scaffolds for transdermal delivery of various categories of bioactive molecules.

Main text

Methods of production of nanofibers

Nanofibers come under the category of nanostructured vehicles having a diameter of individual fiber below 100 nm [17]. Although developed fibers with a diameter in the range of 100–1000 nm are also designated as nanofibers and they are generally manufactured using a technique known as electrospinning [18]. Various

methods explored for the production of nanofibers are shown in Fig. 3.

Self-assembly method

There is a spontaneous arrangement of atomic/molecular aggregates into structurally defined nanofibrous form in this method. This method leads to the production of nanofibers of a size range up to 100 nm. This method requires a higher time to generate nanofibers, therefore, less commonly implemented. However, nanofibers manufactured through a self-assembly method can mimic natural materials like chitin (polysaccharide) very closely that has been explored in tissue engineering [19].

Template synthesis method

Template synthesis involves the use of nanoporous membranes that are available in the form of templates to extrude available fibers of different sizes into the nanoscale size range. The size of nanofibers produced lies in the range of 200–400 nm [20].

Phase-separation method

This method involves lyophilization of polymeric blend resulting in the formation of the nanofibrous mat. However, this method is very time-consuming and nanofibers obtained through this method are shorter in length with a size range of 50–500 nm [21].

Melt-blown technology

Melt blown method involves extrusion of polymer blend across a minute orifice followed by passage through heated air stream with a very high velocity. The size of nanofibers produced exploring this method is 150–1000 nm [22].

Electrospinning

Electrospinning is the most widely used technique for nanofiber production. Fibers generated through the electrospinning method may lie in the nanometer to the micrometer size range. It is considered a cheap and scalable technique for the production of nanofibers [23]. Nanofibers are also produced by a modified electrospinning technique known as ‘nanospider’. This technique generates nanofibers in the form of nonwovens with a diameter range of 50–300 nm [24]. Nanofibrous nonwovens are widely explored in various fields of biomedical engineering like wound dressing and tissue engineering, transdermal drug delivery, and enzyme immobilization [25]. Electrospinning involves the preparation of polymeric melt/solution initially followed by application of electric charge on it after its extrusion from nozzle/

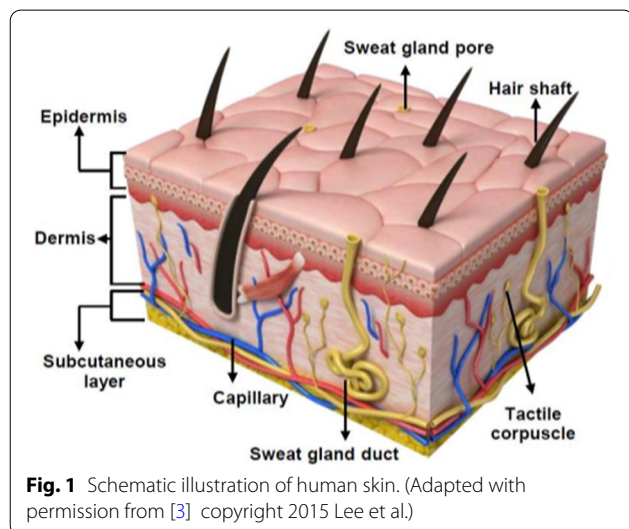


Fig. 1 Schematic illustration of human skin. (Adapted with permission from [3] copyright 2015 Lee et al.)

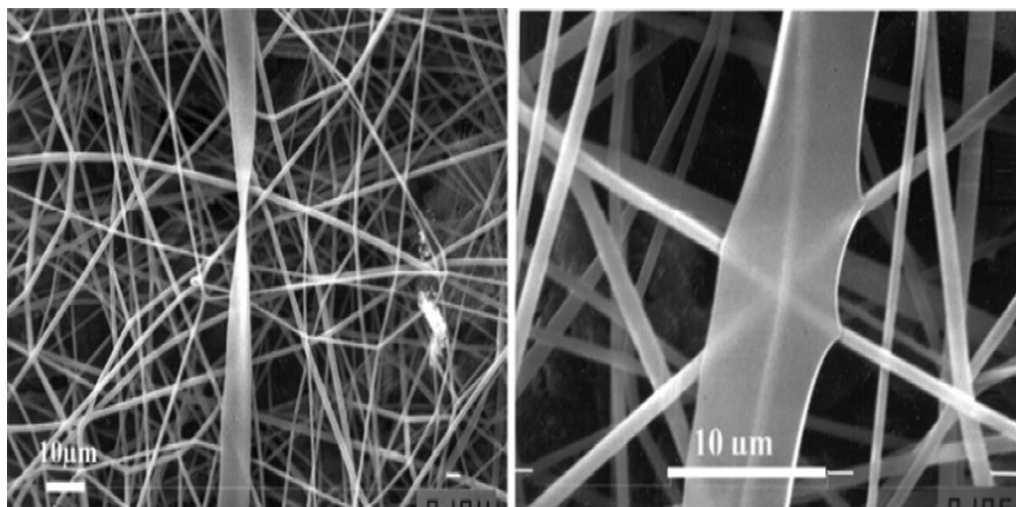


Fig. 2 Scanning electron micrographs showing flat ribbons formation during electrospinning of PET (polyethylene terephthalate) from a solution of 13 wt.% in 1:1 dichloromethane and trifluoroacetic acid. Left magnification $\times 1000$, right: an enlarged image with magnification $\times 3500$. (Adapted with permission from [13] copyright 2003 Frenot and Chronakis)

syringe/pipette [26]. Finally, the developed nanofibers are collected on the aluminum wall due to electrostatic attraction between polymer and wall (due to the presence of opposite charge on both) (Fig. 4) [27].

Methodologies of drug loading in nanofibers

Various methodologies of loading drugs into nanofibers are discussed below:

Co-electrospinning

This approach involves the simple mixing of the polymeric solution with the drug before the initiation of electrospinning. A homogeneous solution of drug and polymer in a single solvent is further subjected to electrospinning and this type of electrospinning is called co-electrospinning [28]. This technique shows high loading efficacy and homogeneous drug distribution within the nanofibrous network [29]. The loading efficiency of nanofibers produced through this method depends on the physicochemical properties of the polymer used followed by the interaction of polymers with drug molecules [30]. The morphology of nanofibers and the distribution of drug molecules within them may affect their release kinetics [31]. Various natural polymers like gelatin, collagen, and chitosan are used to develop nanofibers loaded with hydrophilic drugs due to their complete dissolution in the aqueous phase [32]. Nanofibers produced through this method collapse during the cross-linking process creating problems in the electrospinning process. This can be due to the reduced viscosity of the solution and this problem can be overcome by using synthetic

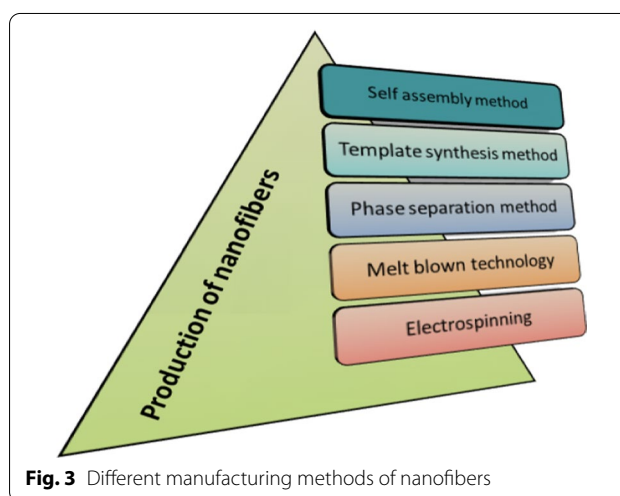


Fig. 3 Different manufacturing methods of nanofibers

hydrophilic polymers like PEO (Polyethylene oxide) additionally. Nanofibers developed through this method can lead to a burst release effect also [33].

Immobilization of drug molecules on the surface of nanofibers

Various therapeutic drug molecules can be loaded in nanofibers following the surface immobilization method through various physical and chemical mechanisms. Various forces involved in physical immobilization are electrostatic forces, hydrogen bonding, or weak *van der Waals* forces [34]. Chemical immobilization involves the direct attachment of drug molecules over the nanofiber

surface through functionalization with various groups like thiol, carboxyl, hydroxyl, and amine [35]. The surface immobilization method does not cause denaturation of drug molecules as observed in the case of the co-electrospinning method due to excessive use of organic solvents and high voltage [36]. The amount of drug to be immobilized on the surface of nanofibers can also be controlled by using this technique through optimization of drug feeding ratio. This approach is also capable of blocking initial burst release from nanofibers promoting slow release kinetics [37].

Co-axial electrospinning

Immiscibility between drug molecules and the polymer may create problems in the co-electrospinning process. Therefore, for loading different kinds of drugs having a difference in solubilities in polymers a new technique named 'co-axial electrospinning' is used [38]. Co-axial electrospinning is done with the help of a spinneret needle having one inner and one outer nozzle organized concentrically. There is the presence of two different chambers for the handling of sheath solution and core solution. The final solution is ejected from the co-axial cone (Fig. 5) [39]. This technique enables the electrospinning of two non-miscible polymers having therapeutic agents in core and sheath as well [40]. Electrospinning through this technique results in high drug loading capacity and prevention of initial burst release due to the presence of a stagnant sheath [41]. Generally, hydrophilic polymers and therapeutic agents like proteins are enclosed in the core portion while hydrophilic elements remain in the sheath. Co-axial electrospinning requires controlling a large number of factors like the feeding speed of polymeric solution, voltage application, and concentration of therapeutic agents for the production of nanofibers with proper core and sheath structure [42].

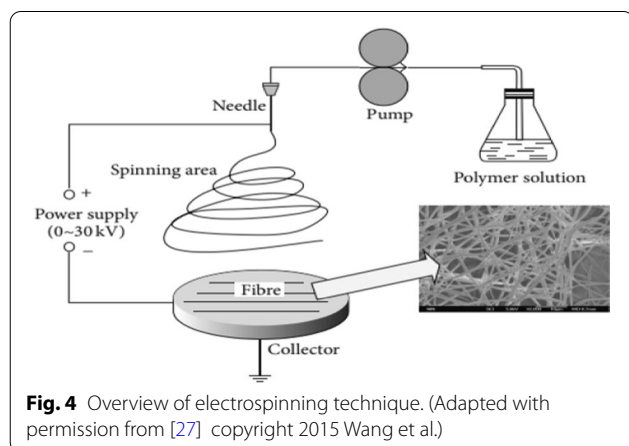


Fig. 4 Overview of electrospinning technique. (Adapted with permission from [27] copyright 2015 Wang et al.)

Emulsion electrospinning

Emulsion electrospinning involves the emulsification of an aqueous solution of a therapeutic agent or protein with a lipophilic polymeric solution [43]. Furthermore, the drug-loaded phase is disseminated in the nanofibers at the termination of electrospinning (Fig. 6). While using this method, the distribution of drug molecules within the nanofiber is totally dependant on the ratio of hydrophilic to the lipophilic solution used [44].

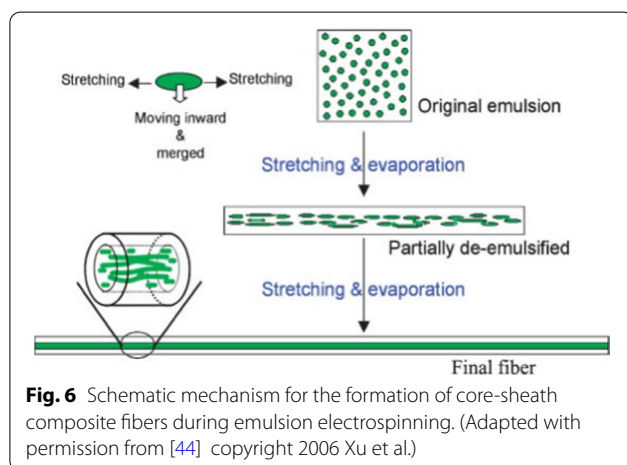
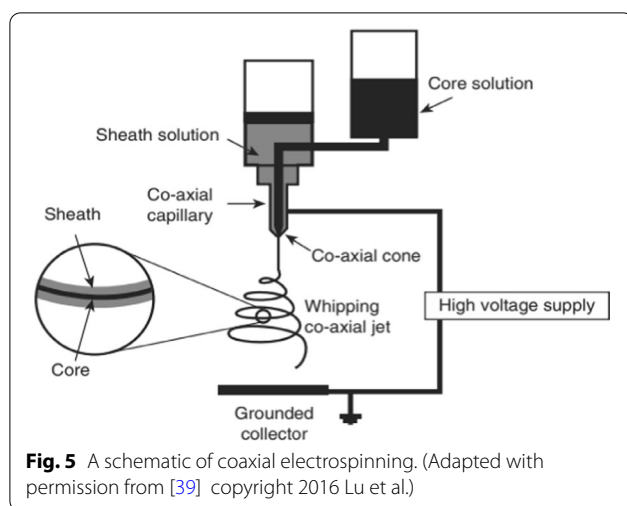
Therapeutic agents and polymers can be dissolved in suitable solvents using this technique. This method involves minimal exposure to the therapeutic agent with an organic solvent [45]. The emulsion electrospinning method allows the use of a variety of hydrophilic drugs and lipophilic polymer combinations [46]. The existence of interfacial tension and strong shearing forces between two phases of the emulsion can degrade the proteinaceous drug molecules due to their high sensitivity [47]. The use of ultrasonication methodology in this electrospinning technique can damage the drug molecules reducing the efficacy of nanofiber produced [48].

Applications of nanofibers in transdermal delivery of various therapeutic agents

Various categories of drugs that are delivered through a transdermal route using nanofibers are discussed below:

Antibiotics or antimicrobial drugs

Cutaneous wounds infection may be responsible for increased healing duration, a longer period of hospitalization, and death of the patients many times [14]. Skin infections can be effectively treated by using antibiotics/antimicrobial drugs locally. Pharmaceutical scientists have investigated various antibiotics/antimicrobial drugs impregnated into nanofibers for the treatment of cutaneous wounds [16]. Kataria et al. [49] investigated ciprofloxacin-loaded polyvinyl alcohol and sodium alginate-based nanofibers for localized delivery and to treat the wound in rabbits. Ciprofloxacin-loaded nanofibers showed drug release *in-vitro* following Higuchi and Korsmeyer-Peppas model. The wound healing capacity of nanofibers was determined using hydroxyproline assay in wounds. Ciprofloxacin-loaded nanofibers showed the highest amount of hydroxyproline (8.39/100 mg of wound bed) in the animal wound after twenty days compared to the marketed formulation of ciprofloxacin (7.91/100 mg of wound bed) indicating their high effectiveness [49]. Furthermore, nanofibers composed of polymers poly(vinyl alcohol) and lysine and impregnated with ibuprofen (an anti-inflammatory agent) and lavender oil (anti-bacterial agent) were



investigated by Sequeira et al. [50] for the acceleration of the wound healing process. Ibuprofen was loaded using the co-electrospinning technique while lavender oil was loaded using the surface adsorption technique in nanofibers. Nanofibers loaded with ibuprofen displayed a reduction in the time scale of the wound healing inflammatory phase. However, lavender oil-loaded nanofibers showed a very high *in-vitro* antibacterial efficacy against *S. aureus* and *P. aeruginosa* compared to nanofibers loaded with ibuprofen without affecting dermal fibroblasts [50] (Fig. 7).

Later on, Iqbal et al. [51] determined the efficacy of chitosan/poly(vinyl alcohol) nanofibers loaded with cefadroxil monohydrate against resistant gram-positive bacteria *S. aureus* responsible for chronic skin fungal infection. Nanofibers with 30:70 of chitosan/poly(vinyl alcohol) were considered as optimized and these developed nanofibers showed high *in-vitro* antimicrobial activity against resistant *S. aureus* followed

by low toxicity towards epidermal keratinocytes as depicted in MTT assay. They were considered a better alternative for the treatment of chronic skin fungal infections [51]. Table 1 gives a brief overview of nanofibers for transdermal delivery of various antimicrobial/antibiotic drugs.

Antifungal drugs

Polymeric electrospun nanofibers are also explored for transdermal delivery of various antifungal drugs. Harini et al. [61] investigated the antifungal potential of polycaprolactone (PCL)/egg lecithin-based nanofibers impregnated with terbinafine hydrochloride to treat skin fungal infections. Developed nanofibers with diameter 127.7 ± 43.7 nm were found non-cytotoxic towards human dermal fibroblasts as revealed through confocal microscopy and they also showed excellent *in-vitro* antifungal activity against different fungal strains like *Epidermophyton* and *Trichophyton mentagrophytes* responsible for topical fungal infections [61]. Furthermore, Paskiabi et al. [62] formulated nanofibers loaded with terbinafine hydrochloride (TFH) using polymers polycaprolactone (PCL) and gelatin (50:50 w/w) using glutaraldehyde (GTA) as a cross-linking agent. TBH-loaded nanofibers showed non-cytotoxic behavior as evaluated in L929 cells. Cross-linked nanofibers loaded with TBH showed 100% drug loading followed by a high *in-vitro* antifungal activity against *T. mentagrophytes* and *A. fumigates* and less effective against *C. albicans* (Fig. 8) [62]. Later on, voriconazole impregnated polyvinyl alcohol (PVA)/sodium alginate nanofibers were formulated by Esentürk et al. [63] and further cross-linked with glutaraldehyde (GTA) for effective delivery through the transdermal route. Cross-linked polymer composite nanofibers loaded with voriconazole showed high drug loading ($96.45 \pm 5.91\%$) followed by low *in-vitro* cytotoxicity against mouse fibroblast cells. Voriconazole impregnated polyvinyl alcohol (PVA)/sodium alginate nanofibers showed high *in-vitro* antifungal activity against *C. albicans* and deeper penetration of drug in the lower skin layer compared to the solution of voriconazole in propylene glycol [63]. Esenturk et al. [64] explored polyurethane/polyvinylpyrrolidone/silk nanofibrous mats loaded with sertaconazole nitrate for transdermal treatment of fungal infection caused by *C. albicans*. Developed nanofibers showed approximately $89.97 \pm 1.40\%$ loading of sertaconazole nitrate and sustained its release for up to 168 h *in-vitro*. Sertaconazole nitrate loaded in nanofibers showed fungistatic action towards *C. albicans* and excellent *in-vitro* biocompatibility for mouse fibroblast cell lines as revealed in the CCK-8 assay [64].

Later on, Azarbayani et al. [65] developed nanofibers of Polyvinyl alcohol and chitosan for transdermal

delivery of hydroquinone and investigated the effect of chitosan on their efficacy. Optimized hydroquinone-loaded nanofibers showed a diameter of 537.24 ± 52.5 nm and drug loading of 4.4%. Increasing the concentration of chitosan up to 2% in the formulation did not cause any significant changes in nanofiber diameter, loading percentage, and *in-vitro* antifungal activity against *Candida albicans*, however, it was able to increase the *in-vitro* release of hydroquinone at 32 °C compared to 25 °C [65].

Anti-inflammatory drugs

Electrospun nanofibers have also been investigated by pharmaceutical scientists for the transdermal delivery of many anti-inflammatory drugs. Shi et al. [66] investigated Cellulose acetate/poly(vinyl pyrrolidone) based nanofibers impregnated with ibuprofen for transdermal delivery. Optimized nanofibers showed a diameter of 167 ± 88 nm

and X-Ray Diffraction analysis of nanofibers revealed uniform distribution of ibuprofen in the nanofibrous network in amorphous form. Developed nanofibers showed better *in-vitro* skin permeation of the drug followed by increased water vapor permeability compared to the conventional transdermal patch of the same drug indicating their high thermodynamic stability [66]. Furthermore, rosmarinic acid (RosA) loaded cellulose acetate (CA) nanofibers were evaluated by Vatankhah [67] for *in-vitro* anti-inflammatory activity (determination through protein denaturation assay), cytotoxicity, and antioxidant effect. Nanofibers formulated using 10% rosmarinic acid were considered as optimized and they showed diameter 331 ± 85 nm and drug loading (%) $84 \pm 4\%$. These nanofibers were capable of extending the release of rosmarinic acid up to 64 h through the Fickian diffusion mechanism and higher *in-vitro* anti-inflammatory activity compared to the ibuprofen solution. A promising

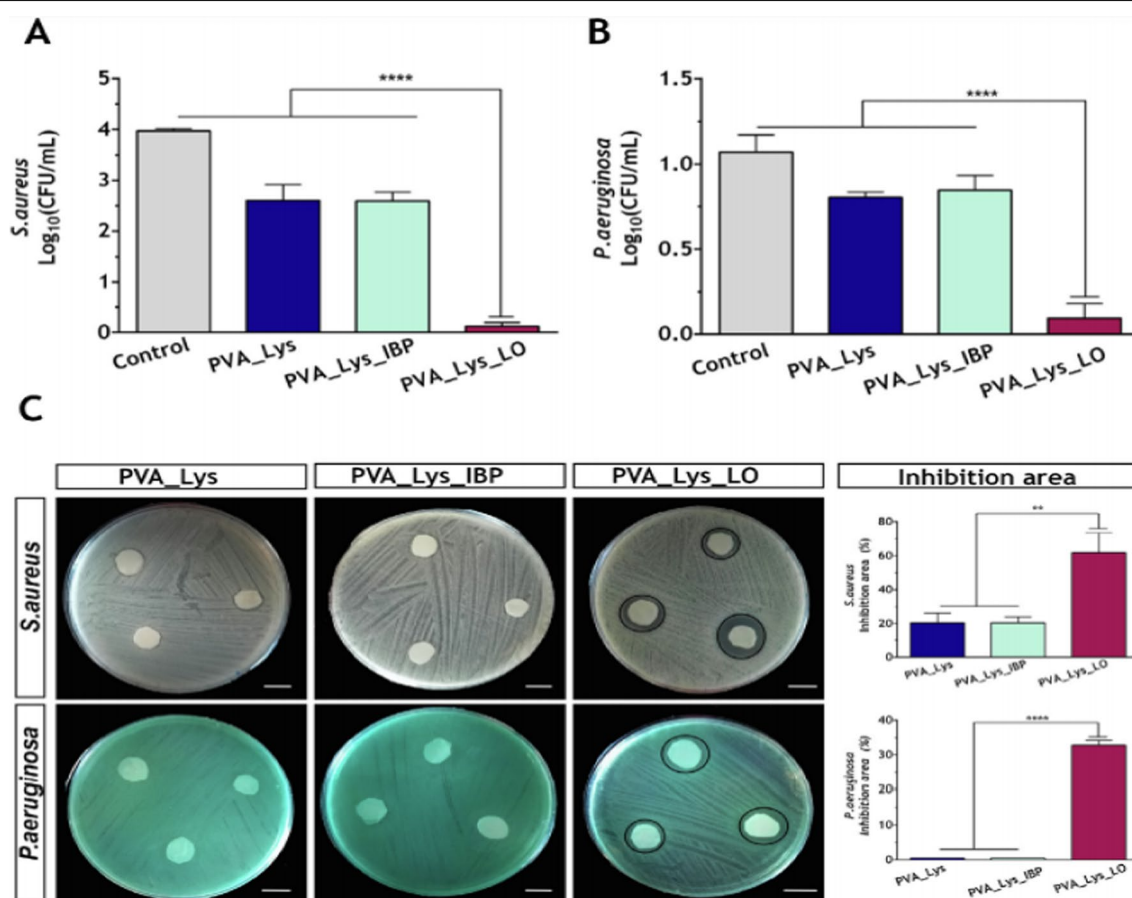


Fig. 7 Evaluation of the produced PVA_Lys electrospun membranes' antibacterial properties. Determination of the CFU/mL of *S. aureus* (A) and *P. aeruginosa* (B), when seeded in contact with the membranes. Macroscopic images and analysis of the inhibitory halos against *S. aureus* and *P. aeruginosa* (C). Data are presented as the mean \pm standard deviation, $n = 5$, ** $p < 0.001$, **** $p < 0.0001$. PVA_Lys blank poly(vinyl alcohol) and lysine nanofibers, PVA_Lys_IBP Ibuprofen loaded nanofibers, PVA_Lys_LO Lavender oil loaded nanofibers). (Adapted with permission from [50] copyright 2019 Sequeira et al.)

Table 1 Role of nanofibers for transdermal delivery of various antibiotics/antimicrobial drugs

S. No	Drug	Polymer	Drug loading (%) / diameter (nm)	Sophisticated techniques used for characterization/animal model used	Key findings	Ref
1	Tetracycline hydro chloride	PLGA	42.65/519 ± 133	SEM, Cytocompatibility assay/not given	Halloysite nanotubes/PLGA nanofibers impregnated with tetracycline hydrochloride showed release of drug up to 42 days followed by excellent <i>in-vitro</i> cytocompatibility in mouse fibroblast cells	[52]
2	Ciprofloxacin	PVP	Not given/410 ± 40	SEM, ATR FT-IR, NMR, TGA/C57BL/6 J mice	Ciprofloxacin loaded nanofibers showed quick wound resorption and speedy healing of the wound in experimental animals compared to a transparent polymeric film	[53]
3	Ciprofloxacin	PVA/Dextran	Not given/200–300	SEM, FT-IR, TGA/not given	Ciprofloxacin loaded nanofibers showed <i>in-vitro</i> drug release through a non-Fickian diffusion mechanism indicating their effectiveness to deliver ciprofloxacin transdermally	[54]
4	Teicoplanin	Chitosan/PEO	63.06 ± 0.19/272.57 ± 54.15	SEM, FT-IR, DSC/Wistar rats	Nanofibers loaded with 4% teicoplanin showed its sustained release up to twelve days, high <i>in-vitro</i> antibacterial effect and cytocompatibility, and significant wound reduction in experimental animals	[55]
5	Tetracycline	Dextran, PCL, GO	42/30–50	SEM, FT-IR/not given	Tetracycline loaded nanofibers containing 50% (w/w) dextran showed its sustained release for three days followed by high therapeutic activity against <i>E. coli</i> and <i>S. aureus in-vitro</i>	[56]
6	Chloro tetracycline hydro chloride, Tetracycline hydro chloride, Amphotericin B	PCL, PLA	Not given/300–400	SEM/not given	Nanofibers composed of polymers PCL: PLA (3:1) showed the quickest <i>in-vitro</i> release of tetracycline hydrochloride and slowest release of amphotericin B in PBS (pH 7.35) followed by good antibacterial activity against <i>S. aureus</i> indicating their suitability for transdermal drug delivery	[57]
7	Ciprofloxacin hydro chloride	Sodium alginate, PEO, Pluronic F-127	51.0 ± 6.7/161	SEM, FT-IR/not given	Developed nanofibers released 24% ciprofloxacin hydrochloride for the first twenty hours of study through the mechanism of Fickian diffusion indicating their efficacy for transdermal drug delivery for treating wounds	[58]
8	Not given	Chitosan, PVA	Not given/279.8	SEM, histology of wound tissue/Wistar rats	Nanofibers composed of chitosan and PVA (75:25) showed speedy wound recovery in diabetic rats compared to the control group of the animals	[59]
9	Neomycin	PSSA-MA, PVA	46/250 ± 21	FT-IR, cytotoxicity analysis/Wistar rats	Neomycin loaded PSSA-MA and PVA nanofibers effectively reduced the size of wound in Wistar rats during the first week of treatment compared to polymeric gauze and blank nanofibers composed of the same polymers	[60]

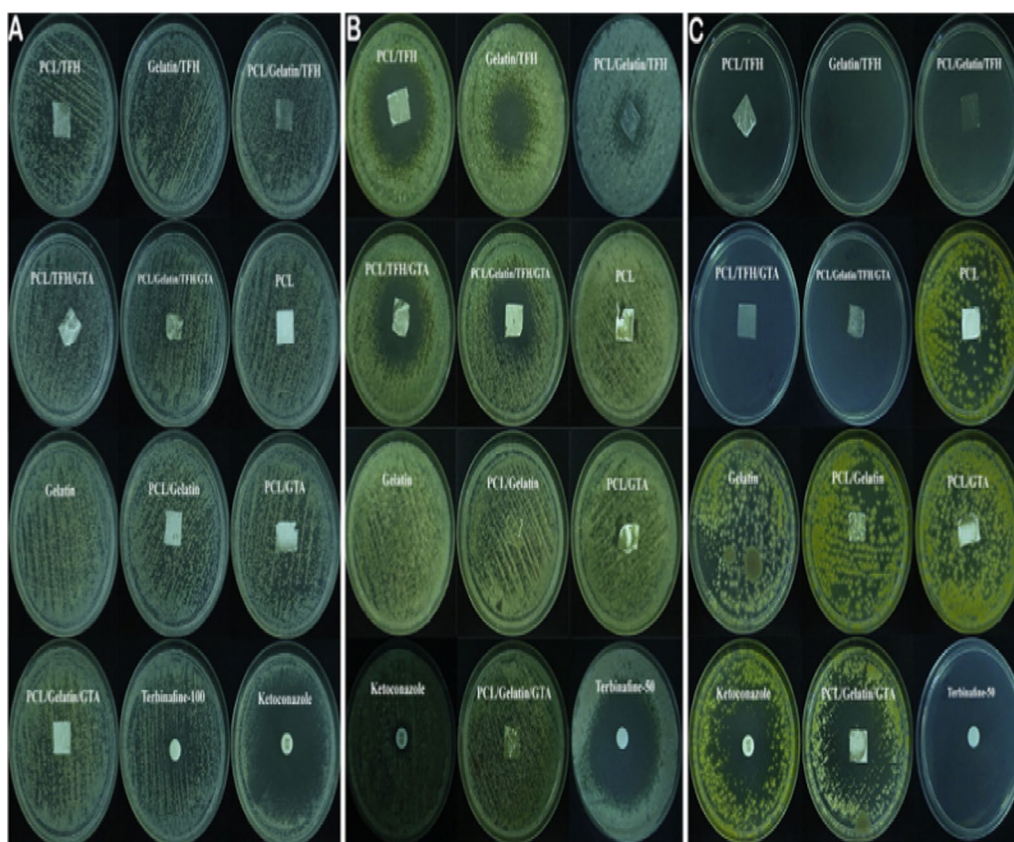


Fig. 8 Antifungal effects of nanofibers and antifungal disks on *C. albicans* after 48 h (A), on *A. fumigatus* after 72 h (B), and on *T. mentagrophytes* at 144 h of treatment (C). PCL/TFH terbinafine hydrochloride loaded polycaprolactone nanofibers; Gelatin/TFH terbinafine hydrochloride loaded gelatin nanofibers; PCL/Gelatin/TFH terbinafine hydrochloride loaded polycaprolactone/gelatin nanofibers; PCL/Gelatin/TFH/GTA terbinafine hydrochloride loaded polycaprolactone/gelatin/glutaraldehyde cross-linked nanofibers. (Adapted with permission from [62] copyright 2017 Paskiabi et al.)

in-vitro antioxidant effect was observed for nanofibers

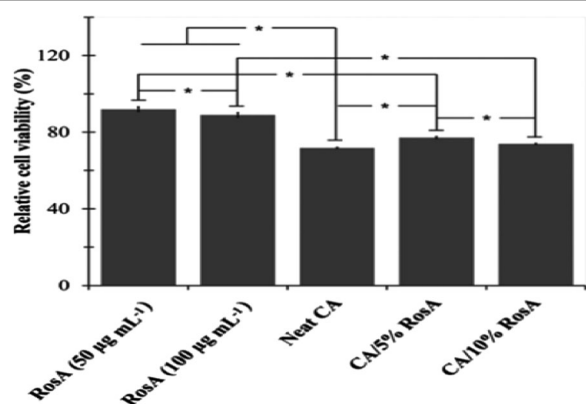


Fig. 9 Relative cell viability of epithelial cells cultured with RosA containing media and extraction media from neat and RosA loaded CA nanofibers (The relative cell viability of the control was defined as 100%).* indicates significant differences. (Adapted with permission from [67] copyright 2018 Vatankhah)

followed by very low cytotoxicity in epithelial cells (Fig. 9) [67].

Later on, an evaluation of poly(vinyl alcohol) based nanofibers loaded with diclofenac enclosed in zein nanoparticles was carried out by Ghalei et al. [68]. Developed nanofibers showed a diameter of 324.42 ± 72.80 nm and good tensile properties for topical application. Nanofibers containing diclofenac loaded inside zein nanoparticles were considered best for wound healing due to their better *in-vitro* attachment in fibroblasts followed by the promotion of their proliferation [68]. The utility of nanofibers for transdermal delivery of various anti-inflammatory drugs is given below in Table 2.

Anticancer drugs

The local effect of anticancer drugs in the skin can be improved by loading them into a nanofibrous mat. Rengifo et al. [74] developed pyrazoline H3TM04 loaded nanoparticles and further impregnated them into nanofibers composed of polyethylene oxide-chitosan for

Table 2 A brief overview of research work done on nanofibers for transdermal delivery of anti-inflammatory drugs

S. No	Drug	Polymer	Drug loading (%) / diameter (nm)	Sophisticated techniques used for characterization / animal model used	Key findings	Ref
1	Naproxen	Thermo plastic polyurethane	Not given/523.66–723.50	SEM, FT-IR, TGA/not given	Nanofibers composed of 10% (w/w) solution of thermoplastic polyurethane showed smooth texture and release of naproxen from nanofibrous mat was greatly affected by its thickness	[69]
2	Plai oil	Poly (lactic) acid	29.95 ± 1.25/0.38 µm	SEM, FT-IR, TGA, DSC, XRD/not given	Nanofibers containing 30% weight plai oil showed the highest <i>in-vitro</i> skin permeation in the reconstructed human epidermis (EpSkin™) followed by minimum skin irritation indicating their suitability for transdermal delivery	[70]
3	Diclofenac sodium	Cellulose acetate	Not given/0.5 µm	Not given/not given	Cellulose acetate based nanofibers showed uniform distribution of diclofenac sodium and high wettability followed by the release of only 30% diclofenac sodium during the first three hours of the release study	[71]
4	Sulindac	Polyvinyl alcohol-co-polyethylene	92/461	SEM, FT-IR, TGA, DSC/not given	Sulindac loaded nanofibers showed high drug loading, <i>in-vitro</i> stability followed by high <i>in-vitro</i> skin permeation of sulindac compared to patch available in the market	[72]
5	Tetrahydro curcumin	Poly caprolactone, polyethylene glycol	95/400 ± 20	SEM, FT-IR, TGA, DSC, XRD/not given	Nanofibers composed of polycaprolactone (10% w/v) and polyethylene glycol (5% w/v) in a 2:1 ratio showed excellent morphology and high <i>in-vitro</i> shear adhesion followed by the extended <i>in-vitro</i> release of tetrahydro curcumin for 24 h	[73]

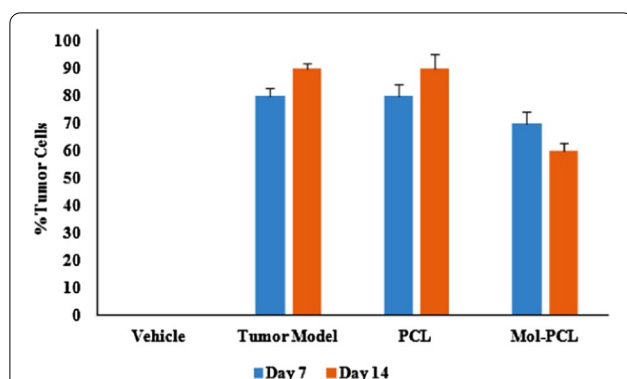


Fig. 10 Percentage of tumor cells in PCL and Mol-PCL treated zebrafish on Day 7 and Day 14. PCL Blank polycaprolactone nanofibers; Mol-PCL polycaprolactone nanofibers loaded with molybdenum oxide nanoparticles. (Adapted with permission from [75] copyright 2018 Janani et al.)

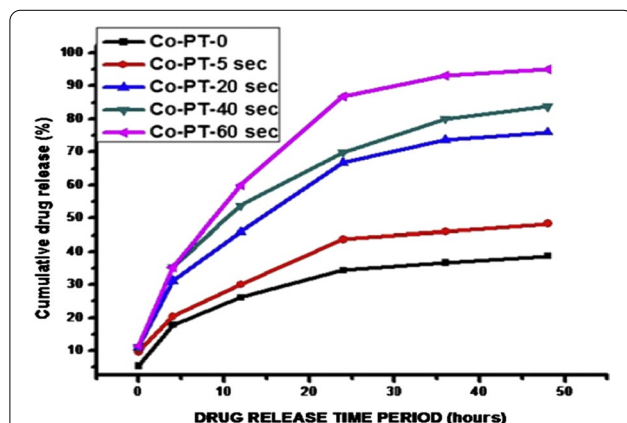


Fig. 11 Cumulative drug release measurements using UV spectrophotometer showing 35–95% release of vitamin B₁₂ with plasma treatment. (Adapted with permission from [81] copyright 2018 Madhaiyan et al.)

the treatment of skin cancer. Optimized nanoparticles loaded nanofibers showed a diameter of 197.8 ± 4.1 nm and uniform distribution of nanoparticles throughout the nanofiber matrix followed by the extended-release of pyrazoline H3TM04 up to 120 h. Developed nanofibers also enhanced *in-vitro* transport pyrazoline H3TM04 across the epidermal skin layer followed by excellent *in-vitro* cytotoxicity against B16F10 melanoma cells [74]. Furthermore, molybdenum oxide-loaded nanoparticles were prepared by Janani et al. [75] and impregnated into polycaprolactone (PCL) nanofibers for evaluation of their skin anticancer potential in zebrafish. Nanofibrous mat loaded with molybdenum oxide nanoparticles showed an average diameter of 200 nm and a significant reduction in *in-vitro* cell viability (> 50%) in A431 cells through

mitochondrial dependant apoptosis. Nanofibers loaded with molybdenum oxide nanoparticles showed reduced skin cancer progression in zebrafish by more than 30% within two weeks (Fig. 10) [75].

Table 3 discloses the role of polymeric nanofibers in the transdermal delivery of various antineoplastic drugs.

Other categories of drugs

There are other categories of drugs other than those discussed above which can be delivered through the transdermal route exploring nanofibers for producing the evident pharmacological effect. Madhaiyan et al. [81] investigated polycaprolactone polymer-based nanofibers loaded with Vitamin B₁₂ for effective delivery through the transdermal route. Vitamin B₁₂ loaded nanofibers showed an average diameter of 1.226 ± 0.108 μ m and 89% drug loading capacity followed by high mechanical strength and excellent surface wettability. Surface treatment of Vitamin B₁₂ loaded nanofibers with plasma greatly affected *in-vitro* release rate of Vitamin B₁₂ from nanofibers. Nanofibers treated with plasma for 60 s showed the highest release of Vitamin B₁₂ within 50 h (Fig. 11). This could be due to the increased hydrophilicity of the nanofiber membrane after treatment with plasma [81]. Furthermore, hydrocortisone-loaded polyacrylonitrile-based nanofibers were formulated by Hemati Azandaryani et al. [82] and were investigated for topical treatment of psoriasis by varying amounts of surfactant Tween 80 in nanofiber composition. Nanofibers produced using polyacrylonitrile polymer along with 5% Tween 80 surfactant showed the lowest diameter (160.11 ± 30.11 nm) and maximum tensile strength (15.35 MPa) followed by the highest *in-vitro* drug release for 12 h and minimum cytotoxic effect against HUVEC cell lines indicating their efficacy in transdermal drug delivery for the treatment of psoriasis [82].

The role of polymeric nanofibers in transdermal drug delivery of various therapeutic agents is given in Table 4.

Biopolymer based nanofibers in transdermal delivery

Biopolymers are polymeric materials that are manufactured from natural provenance. Biopolymers are chemically produced from biological materials or their complete biosynthesis can be done by living organisms [90]. Various examples of biopolymers are cellulose, chitosan, hemicellulose, silk, and lignin. These biopolymers may be biocompatible and biodegradable promoting their use in drug delivery [91]. Nanomaterials that are derived usually derived from cellulose are called nanocellulose materials. These materials can be classified into three categories namely nanofibrillated cellulose, bacterial nanocellulose, and nanocrystalline cellulose

Table 3 Utility of nanofibers in transdermal delivery of anticancer therapeutic agents

S. No	Drug	Polymer	Drug loading (%) / diameter (nm)	Sophisticated techniques used for characterization/animal model used	Key findings	Ref
1	Gold nanoparticles (AuNPs) and curcumin	Polyvinyl alcohol (PVA), poly caprolactone (PCL)	95.60 for PCL + curcumin nanofibers/300 (PVA + gold nanoparticles nanofibers), 600 (for PCL + curcumin nanofibers)	SEM, FT-IR, DNA Fragmentation Assay, Fluorescence Microscopy/ not given	Gold nanoparticles loaded nanofibers showed better <i>in-vitro</i> cytotoxicity against 3T3 fibroblast and A431 skin cancer cells compared to curcumin loaded nanofibers and marketed antineoplastic agents	[76]
2	Doxorubicin	Poly(lactic co-glycolic acid), polycaprolactone, gelatin	Not given/170	SEM, Hematoxylin and eosin (HE) staining, Immuno Histochemistry/female C57BL/6 mice	Developed nanofibers showed extended <i>in-vitro</i> release of doxorubicin for 360 h followed by a significant reduction in tumor volume and side effects of drug compared to marketed injection of doxorubicin in experimental animals	[77]
3	5-fluorouracil	Polyvinyl alcohol, chitosan	78.90 ± 3.1/162.7	SEM, Fluorescence Microscopy/ not given	Developed nanofibers were capable to sustain the release of drug and reduce <i>in-vitro</i> tumor cell viability up to 10% after 48 h of application	[78]
4	Curcumin	Poly(dl-lactic-co-glycolic) acid	81.1 ± 0.97/160 ± 10	SEM, FT-IR, XRD/not given	Nanofibers showed <i>in-vitro</i> release of curcumin following non-Fickian diffusion mechanism and excellent <i>in-vitro</i> cytotoxic effect against A431 cells	[79]
5	Titanium oxide nanoparticles mixed with cobalt ferrite, Doxorubicin hydro chloride	Chitosan	96.5 ± 1/110	SEM, XRD, FESEM/not given	Doxorubicin hydrochloride loaded magnetic nanofibers showed its quick release in the acidic medium after application of an external magnetic field and high anticancer activity against B16F10 cells <i>in-vitro</i> under similar condition	[80]

Table 4 A brief overview of research work done for transdermal delivery of various categories of drugs using nanofibers

S. No	Drug	Polymer	Drug loading (%) / diameter (nm)	Sophisticated techniques used for characterization/animal model used	Key findings	Ref
1	Vitamin B ₁₂	Chitosan mixed with phospho-lipids	82.5/1.1 ± 0.4 µm	SEM, Illumination fluorescence microscopy, FT-IR/not given	Illumination fluorescence microscopy revealed high <i>in-vitro</i> cytocompatibility of vitamin B ₁₂ loaded nanofibers in L929 cells followed by 90% <i>in-vitro</i> release of Vitamin B ₁₂ within 24 h	[83]
2	Gabapentin and acetaminophen	Polyethylene oxide, polyvinyl alcohol, sodium alginate	95.44 (for gabapentin in polyethylene oxide nanofibers), 93.67 (for acetaminophen in polyvinyl alcohol and sodium alginate nanofibers)/252 (for gabapentin in polyethylene oxide nanofibers), 220 (for acetaminophen in polyvinyl alcohol and sodium alginate nanofibers)	SEM, FT-IR, TGA/not given	The first layer of developed bilayered nanofibers showed an initial burst release of gabapentin followed by controlled release of gabapentin plus acetaminophen through the second layer due to the presence of calcium alginate enhancing activity of gabapentin as a pain killer	[84]
3	Gallic Acid	Cellulose acetate	Not given/701 ± 162	SEM, DSC/not given	Nanofibers loaded with 7.5% w/w gallic acid showed the quickest release within 24 h period along with smooth surface morphology and was considered effective for transdermal drug delivery	[85]
4	Fluorescein iso-thiocyanate loaded on ethosomes	Polyvinyl alcohol and hydroxyl ethyl-cellulose	Not given/479; 14 ± 37	SEM, DSC, FT-IR, XRD/not given	Ethosomes loaded with fluorescein isothiocyanate were effectively distributed in the nanofibrous scaffold as predicted in XRD and FT-IR analysis and nanofibers also showed higher <i>in-vitro</i> release of fluorescein isothiocyanate (43.5%) compared to ethosomes (26.5%)	[86]
5	Epidermal growth factors (EGF)	Gelatin, laponite	Not given/98.1 ± 1.3	SEM/not given	Nanofibers explored in the form of hydrogel showed high <i>in-vitro</i> adhesion and 93.1 ± 1.5% wound closure after 14 days of application compared to control groups	[87]
6	Colchicine	Chitosan	84.51 ± 2.1/112 ± 1.9	SEM, FT-IR, XRD/not given	Colchicine loaded nanofibers showed its excellent <i>ex-vivo</i> skin permeation followed by remarkable cytotoxicity against melanoma cell lines (A-375 cell line) <i>in-vitro</i>	[88]
7	Citrulline Malate	Poly (vinyl alcohol) (PVA)	Not given/168	SEM, FT-IR, Raman spectroscopy	The flexibility of citrulline malate loaded nanofibers increased with an increasing amount of citrulline malate in formulation followed by its extended-release up to 20 h <i>in-vitro</i>	[89]

Table 5 List of patents granted related to the use of nanofibers for transdermal drug delivery

Title of patent	Brief description	Inventors	Patent number	Ref
Method and nanofibers produced by electrospinning containing active substances for controlled release cosmetic application	This invention discloses a method of preparation of nanofibers loaded with nitrogenated organic compounds of the xanthine and their activity against cellulite	Maria Helena Ambrosio Zanin, Adriano Marim De Oliveira, Natália Neto Pereira Cerize, Maria Valéria Robles Velasco, André Rolim Baby	WO2014089650A1	[96]
Polymeric nanofibers for tissue engineering and drug delivery	This patent describes a method of production of polyphosphazene based nanofibers loaded with nanosized hydroxyapatites and their role in wound dressing	Cato T. Laurencin, Lakshmi Sreedharan Nair, Subhabrata Bhattacharyya, Harry R. Allcock, Jared D. Bender, Paul W. Brown, Yaser E. Greish	US7235295B2	[97]
A hollow fiber-based biocompatible drug delivery device with one or more layers	This patent describes a production method of a hollow fiber-based drug delivery system with pore size below 100 µm with multiple layers and its role in transdermal drug delivery	Semali Priyanthi Perera	WO2007052042A2	[98]
Nonwoven membrane as a drug delivery system	This invention discloses the preparation method of electrospun nanofibers for effective transdermal delivery of a therapeutic agent with low water solubility	José Antonio Tórnero García, Angel Montero Carcaboso, Joan Bertran Llavi	WO2013144206A1	[99]
Beauty mask based on electro spinning nano fiber	This patent discloses the method of loading medicinal agent/cosmetic agent in concentration 0.01–50% in a biodegradable nanofibrous scaffold	Gu Zhongze, Xu Qian	CN101390814A	[100]
Medical skin-patch fabricated by using multilayer nanofiber sheet	This invention describes a method of preparation of multilayered skin adhesive nanofibrous patch composed of biodegradable polymer for the treatment of diabetic skin cancer	Cho Jae-yong, Lee Hyun-wook, Park So-young, Jeong Se-young	KR101080203B1	[101]
Alkanna tinctoria drug loading nanofiber, preparation and application thereof	This patent discloses about development method of lithospermum loaded biodegradable nanofibers for the treatment of skin injuries or cancer	Zhu Limin, Han Jie	CN101358383A	[102]
Medicinal fiber used for treating cutaneous inflammation and pain, preparation and application thereof	This invention describes a loading method of ketoprofen in cellulose acetate nanofibers and their role in the treatment of cutaneous inflammation and pain	Zhu Limin, Wu Xiaomei, Kreith Brandt-White, Yu Deng-guang, Zheng Yan	CN101724934B	[103]

[92]. nanocellulose based materials show elevated surface area, ease of chemical modification, and a higher value of specific strength. Hence, nanocellulose can be explored as a good candidate for various biomedical utilities [93]. El-Wakil et al. [94] investigated the wound healing potential of coffee extract impregnated into bacterial cellulose (produced from kombucha tea fungus) biocomposites. Biocomposites composed of minimum coffee extract and cellulose amount disclosed maximum tensile strength (3.35 MPa) and transmission of water vapors (3184.94 ± 198.07 g/m²/day) followed by least release of polyphenols *in-vitro* in PBS (pH 7.4) considered suitable for wound healing [94]. Furthermore, Shan et al. [95] developed cellulose nanocrystal incorporated calcium cross-linked sodium alginate/gelatin nanofibers for efficient wound healing. Developed nanofibers showed *in-vitro* non-toxicity against mouse embryonic fibroblast and improved cell adhesion. The cellulose nanocrystal incorporated calcium cross-linked sodium alginate/gelatin nanofibers showed excellent wound healing in Sprague Dawley rats through a re-epithelialization mechanism compared to the control group [95].

Description of patents related to the use of nanofibers for transdermal delivery of various therapeutic agents

A detailed literature investigation revealed the excellent therapeutic potential of nanofibers to treat various abnormal conditions of the skin. These nanofibrous scaffolds can be explored as a better alternative to conventional drug delivery systems for the transdermal treatment of various skin disorders. Hence, pharmaceutical researchers are filing patents regarding the use of nanofibers for transdermal drug delivery of various therapeutic agents. Table 5 discloses the list of patents granted regarding this context.

Limitations and challenges in the exploration of nanofibers for transdermal drug delivery

Polymeric nanofibers have shown promising potential in transdermal drug delivery, however, many significant challenges must be taken into consideration. All the research investigations available in the literature describe either *in-vitro* or *in-vivo* (in different animal models) efficacy of transdermal nanofibers. However, the clinical efficacy determination of nanofibers explored through the transdermal route is still a challenge. Clinical evaluation of nanofibers will be exorbitant and laborious. It will require high speculation by the industries or government funding agencies of the countries. The second major concern will be regarding the scale-up of transdermal nanofibers. Nanofibers are effectively produced through the electrospinning process following a low flow rate of polymeric solution, making the production process more

time-consuming. Nanofibers production is also affected by humidity, hence it might be a challenging factor for bulk processing and scale-up of nanofibers. Furthermore, the production of transdermal nanofibers with GMP (Good manufacturing practices) standards will be required. The development of standard and universally accepted electrospinning protocol will govern their quick entrance into the pharmaceutical market.

Conclusions

Nanofibers have been explored for transdermal drug delivery due to their various merits like high drug loading, surface-to-volume ratio, and similarity with the extracellular matrix. Successful production of the nanofibrous mat is dependent on appropriate polymers and solvent selection for electrospinning. A nanofiber suitable for transdermal drug delivery can be produced using multiple polymer blends for electrospinning. Polymeric nanofibrous mat loaded with a therapeutic agent has the caliber to control/prolong its release transdermally. Transdermal nanofibers have shown their therapeutic potential in various preclinical investigations carried out by various pharmaceutical scientists. However, their entrance into the pharmaceutical market will be governed by developing effective scale-up technologies and detailed clinical evaluation.

Abbreviations

FT-IR: Fourier transform infrared spectrometer; SEM: Scanning electron microscopy; XRD: X-ray diffraction analysis; DSC: Differential scanning calorimetry; TGA: Thermogravimetric analysis; FESEM: Field emission scanning electron microscopy; PLGA: Poly(lactic-co-glycolic acid); PVP: Polyvinylpyrrolidone; ATR FT-IR: Attenuated total reflectance coupled with Fourier Transform Infrared spectrometer; NMR: Nuclear magnetic resonance spectroscopy; PVA: Poly(vinyl alcohol); PEO: Polyethylene oxide; PCL: Polycaprolactone; GO: Graphene oxide; PLA: Poly(L-lactic acid); PSSA-MA: Poly(styrene sulfonic acid-co-maleic acid); MPa: Megapascals; PBS: Phosphate buffer saline.

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Authors' contributions

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References

- Jensen JM, Proksch E (2009) The skin's barrier. *G Ital Dermatol Venereol* 144(6):689–700
- Alonso C, Carrer V, Espinosa S, Zanuy M, Córdoba M, Vidal B, Domínguez M, Godessart N, Coderch L, Pont M (2019) Prediction of the skin permeability of topical drugs using in silico and in vitro models. *Eur J Pharm Sci* 136:104945
- Lee H, Song C, Baik S, Kim D, Hyeon T, Kim DH (2018) Device-assisted transdermal drug delivery. *Adv Drug Deliv Rev* 127:35–45
- Antunes AF, Pereira P, Reis C, Rijo P, Reis C (2017) Nanosystems for skin delivery: from drugs to cosmetics. *Curr Drug Metab* 18(5):412–425
- Li J, Xu W, Liang Y, Wang H (2017) The application of skin metabolomics in the context of transdermal drug delivery. *Pharmacol Rep* 69(2):252–259
- Förster M, Bolzinger MA, Fessi H, Briançon S (2009) Topical delivery of cosmetics and drugs. Molecular aspects of percutaneous absorption and delivery. *Eur J Dermatol* 19(4):309–323
- Bouwstra JA, Honeywell-Nguyen PL (2002) Skin structure and mode of action of vesicles. *Adv Drug Deliv Rev* 54(Suppl 1):S41–55
- Jepps OG, Dancik Y, Anissimov YG, Roberts MS (2013) Modeling the human skin barrier—towards a better understanding of dermal absorption. *Adv Drug Deliv Rev* 65(2):152–168
- Kurmi BD, Tekchandani P, Paliwal R, Paliwal SR (2017) transdermal drug delivery: opportunities and challenges for controlled delivery of therapeutic agents using nanocarriers. *Curr Drug Metab* 18(5):481–495
- Rahmani M, Arbabi Bidgoli S, Rezayat SM (2017) Electrospun polymeric nanofibers for transdermal drug delivery. *Nanomed J* 4(2):61–70
- Hu X, Liu S, Zhou G, Huang Y, Xie Z, Jing X (2014) Electrospinning of polymeric nanofibers for drug delivery applications. *J Control Release* 185:12–21
- Sharma R, Singh H, Joshi M, Sharma A, Garg T, Goyal AK, Rath G (2014) Recent advances in polymeric electrospun nanofibers for drug delivery. *Crit Rev Ther Drug Carrier Syst* 31(3):187–217
- Frenot A, Chronakis IS (2003) Polymer nanofibers assembled by electrospinning. *Curr Opin Colloid Interface Sci* 8(1):64–75
- Thakkar S, Misra M (2017) Electrospun polymeric nanofibers: New horizons in drug delivery. *Eur J Pharm Sci* 107:148–167
- Gao X, Han S, Zhang R, Liu G, Wu J (2019) Progress in electrospun composite nanofibers: composition, performance and applications for tissue engineering. *J Mater Chem B* 7(45):7075–7089
- Kamble P, Sadarani B, Majumdar A, Bhullar S (2017) Nanofiber based drug delivery systems for skin: a promising therapeutic approach. *J Drug Del Sci Tech* 41:124–133
- Al-Jbour ND, Beg MD, Gimbin J, Alam AKMM (2019) An overview of chitosan nanofibers and their applications in the drug delivery process. *Curr Drug Deliv* 16(4):272–294
- Torres-Martínez EJ, Cornejo Bravo JM, Serrano Medina A, Pérez González GL, Villarreal Gómez LJ (2018) A summary of electrospun nanofibers as drug delivery system: drugs loaded and biopolymers used as matrices. *Curr Drug Deliv* 15(10):1360–1374
- Hartgerink JD, Beniash E, Stupp SI (2001) Self-assembly and mineralization of peptide-amphiphile nanofibers. *Science* 294(5547):1684–1688
- Martin CR (1994) Nanomaterials: a membrane-based synthetic approach. *Science* 266(5193):1961–1966
- Ma PX, Zhang R (1999) Synthetic nano-scale fibrous extracellular matrix. *J Biomed Mater Res* 46(1):60–72
- Wang FF, Wang Q, Zhang Y, Zhao ZX, Wang P, Zhang DT (2019) The study on semi-blunt puncture behavior of nanofiber membrane/non-woven composite material. *Recent Pat Nanotechnol* 13(1):70–76
- Toriello M, Afsari M, Shon HK, Tijing LD (2020) Progress on the fabrication and application of electrospun nanofiber composites. *Membranes (Basel)* 10(9):204
- Kowalczyk T (2020) Functional micro- and nanofibers obtained by nonwoven post-modification. *Polymers (Basel)* 12(5):1087
- Kumbar SG, Nair LS, Bhattacharyya S, Laurencin CT (2006) Polymeric nanofibers as novel carriers for the delivery of therapeutic molecules. *J Nanosci Nanotechnol* 6(9–10):2591–2607
- Bhardwaj N, Kundu SC (2010) Electrospinning: a fascinating fiber fabrication technique. *Biotechnol Adv* 28(3):325–347
- Wang A, Xu C, Zhang C, Gan Y, Wang B (2015) Experimental investigation of the properties of electrospun nanofibers for potential medical application. *J Nanomat* 1–8. <https://doi.org/10.1155/2015/418932>
- Lee MW, An S, Yoon SS, Yarin AL (2018) Advances in self-healing materials based on vascular networks with mechanical self-repair characteristics. *Adv Colloid Interface Sci* 252:21–37
- Yoo HS, Kim TG, Park TG (2009) Surface-functionalized electrospun nanofibers for tissue engineering and drug delivery. *Adv Drug Deliv Rev* 61(12):1033–1042
- Sill TJ, von Recum HA (2008) Electrospinning: applications in drug delivery and tissue engineering. *Biomaterials* 29(13):1989–2006
- Teo WE, He W, Ramakrishna S (2006) Electrospun scaffold tailored for tissue-specific extracellular matrix. *Biotechnol J* 1(9):918–929
- Liao S, Li B, Ma Z, Wei H, Chan C, Ramakrishna S (2006) Biomimetic electrospun nanofibers for tissue regeneration. *Biomed Mater* 1(3):R45–53
- Castaño O, Eltohamy M, Kim HW (2012) Electrospinning technology in tissue regeneration. *Methods Mol Biol* 811:127–140
- Ingavle GC, Leach JK (2014) Advancements in electrospinning of polymeric nanofibrous scaffolds for tissue engineering. *Tissue Eng Part B Rev* 20(4):277–293
- Pilehvar-Soltanahmadi Y, Akbarzadeh A, Moazzzez-Lalaklo N, Zarghami N (2016) An update on clinical applications of electrospun nanofibers for skin bioengineering. *Artif Cells Nanomed Biotechnol* 44(6):1350–1364
- Norouzi M, Boroujeni SM, Omidvarkordshouli N, Soleimani M (2015) Advances in skin regeneration: application of electrospun scaffolds. *Adv Healthc Mater* 4(8):1114–1133
- Sridhar R, Sundarajan S, Venugopal JR, Ravichandran R, Ramakrishna S (2013) Electrospun inorganic and polymer composite nanofibers for biomedical applications. *J Biomater Sci Polym Ed* 24(4):365–385
- Chen S, Liu B, Carlson MA, Gombart AF, Reilly DA, Xie J (2017) Recent advances in electrospun nanofibers for wound healing. *Nanomedicine (Lond)* 12(11):1335–1352
- Lu Y, Huang J, Yu G, Cardenas R, Wei S, Wujcik EK, Guo Z (2016) Coaxial electrospun fibers: applications in drug delivery and tissue engineering. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 8(5):654–677
- Pant B, Park M, Park SJ (2019) Drug delivery applications of core-sheath nanofibers prepared by coaxial electrospinning: a review. *Pharmaceutics* 11(7):305
- McClellan P, Landis WJ (2016) Recent applications of coaxial and emulsion electrospinning methods in the field of tissue engineering. *Biores Open Access* 5(1):212–227
- Su Y, Su Q, Liu W, Jin G, Mo X, Ramakrishna S (2012) Dual-drug encapsulation and release from core-shell nanofibers. *J Biomater Sci Polym Ed* 23(7):861–871
- Ye K, Kuang H, You Z, Morsi Y, Mo X (2019) Electrospun nanofibers for tissue engineering with drug loading and release. *Pharmaceutics* 11(4):182

44. Xu X, Zhuang X, Chen X, Wang X, Yang L, Jing X (2006) Preparation of core-sheath composite nanofibers by emulsion electrospinning. *Macromol Rapid Comm* 27(19):1637–1642
45. Zhang C, Feng F, Zhang H (2018) Emulsion electrospinning: Fundamentals, food applications and prospects. *Trends Food Sci Technol* 80:175–186
46. Angeles M, Cheng HL, Velankar SS (2008) Emulsion electrospinning: composite fibers from drop breakup during electrospinning. *Polym Adv Technol* 19(7):728–733
47. Ajalloueiian F, Tavanai H, Hilborn J, Donzel-Gargand O, Leifer K, Wickham A, Arpanaei A (2014) Emulsion electrospinning as an approach to fabricate PLGA/chitosan nanofibers for biomedical applications. *Bio Med Res* 2014:475280. <https://doi.org/10.1155/2014/475280>
48. Elahi MF, Lu W, Guoping G, Khan F (2013) Core-shell fibers for biomedical applications—a review. *J Bioeng Biomed Sci* 3(1):1–4
49. Kataria K, Gupta A, Rath G, Mathur RB, Dhakate SR (2014) In vivo wound healing performance of drug loaded electrospun composite nanofibers transdermal patch. *Int J Pharm* 469(1):102–110
50. Sequeira RS, Miguel SP, Cabral CSD, Moreira AF, Ferreira P, Correia IJ (2019) Development of a poly (vinyl alcohol)/lysine electrospun membrane-based drug delivery system for improved skin regeneration. *Int J Pharm* 570:118640
51. Iqbal H, Khan BA, Khan ZU, Razzaq A, Khan NU, Menaa B, Menaa F (2020) Fabrication, physical characterizations and in vitro antibacterial activity of cefadroxil-loaded chitosan/poly(vinyl alcohol) nanofibers against *Staphylococcus aureus* clinical isolates. *Int J Biol Macromol* 144:921–931
52. Qi R, Guo R, Zheng F, Liu H, Yu J, Shi X (2013) Controlled release and antibacterial activity of antibiotic-loaded electrospun halloysite/poly(lactic-co-glycolic acid) composite nanofibers. *Colloids Surf B Biointerfaces* 110:148–155
53. Contardi M, Heredia-Guerrero JA, Perotto G, Valentini P, Pompa PP, Spanò R, Goldoni L, Bertorelli R, Athanassiou A, Bayer IS (2017) Transparent ciprofloxacin-povidone antibiotic films and nanofiber mats as potential skin and wound care dressings. *Eur J Pharm Sci* 104:133–144
54. Moydeen AM, Ali Padusha MS, Aboufetooh EF, Al-Deyab SS, El-Newehy MH (2018) Fabrication of electrospun poly(vinyl alcohol)/dextran nanofibers via emulsion process as drug delivery system: Kinetics and in vitro release study. *Int J Biol Macromol* 116:1250–1259
55. Amiri N, Ajami S, Shahroodi A, Jannatabadi N, Amiri Darban S, Fazly Bazzaz BS, Pishavar E, Kalalinia F, Movaffagh J (2020) Teicoplanin-loaded chitosan-PEO nanofibers for local antibiotic delivery and wound healing. *Int J Biol Macromol* 162:645–656
56. Nematpour N, Farhadian N, Ebrahimi KS, Arkan E, Seyed F, Khaledian S, Shahlaei M, Moradi S (2020) Sustained release nanofibrous composite patch for transdermal antibiotic delivery. *Colloids Surf A Physicochem Eng Asp* 586:124267
57. Buschle-Diller G, Cooper J, Xie Z, Wu Y, Waldrup J, Ren X (2007) Release of antibiotics from electrospun bicomponent fibers. *Cellulose* 14(6):553–562
58. Kyziol A, Michna J, Moreno I, Gamez E, Irueta S (2017) Preparation and characterization of electrospun alginate nanofibers loaded with ciprofloxacin hydrochloride. *Eur Polym J* 96:350–360
59. Ahmadi Majd S, Rabbani Khorasgani M, Moshtaghian SJ, Talebi A, Khezri M (2016) Application of chitosan/PVA Nano fiber as a potential wound dressing for streptozotocin-induced diabetic rats. *Int J Biol Macromol* 92:1162–1168
60. Nitanan T, Akkaramongkolporn P, Rojanarata T, Ngawhirunpat T, Opanasopit P (2013) Neomycin-loaded poly(styrene sulfonic acid-co-maleic acid) (PSSA-MA)/polyvinyl alcohol (PVA) ion exchange nanofibers for wound dressing materials. *Int J Pharm* 448(1):71–78
61. Harini S, Venkatesh M, Radhakrishnan S, Fazil MH, Goh ET, Rui S, Dhand C, Ong ST, Barathi VA, Beuerman RW, Ramakrishna S (2016) Antifungal properties of lecithin and terbinafine-loaded electrospun poly (ε-caprolactone) nanofibers. *RSC Adv* 6(47):41130–41141
62. Paskiabi FA, Bonakdar S, Shokrgozar MA, Imani M, Jahanshiri Z, Shams-Ghahfarokhi M, Razzaghi-Abyaneh M (2017) Terbinafine-loaded wound dressing for chronic superficial fungal infections. *Mater Sci Eng C Mater Biol Appl* 73:130–136
63. Esentürk İ, Balkan T, Özhan G, Döşler S, Güngör S, Erdal MS, Sarac AS (2020) Voriconazole incorporated nanofiber formulations for topical application: preparation, characterization and antifungal activity studies against *Candida* species. *Pharm Dev Technol* 25(4):440–453
64. Esentürk I, Gumrukcu S, Özdebak Sert AB, Kök FN, Döşler S, Gungor S, Erdal MS, Sarac AS (2020) Silk-fibroin-containing nanofibers for topical sertaconazole delivery: preparation, characterization, and antifungal activity. *Int J Polym Mater* 1–8. <https://doi.org/10.1080/00914037.2020.1740992>
65. Azarbayjani AF, Talebi N, Diba K (2019) Development and characterization of hydroquinone-loaded nanofiber for topical delivery: effect of chitosan. *Int J Polym Anal Charat* 24(3):227–235
66. Shi Y, Wei Z, Zhao H, Liu T, Dong A, Zhang J (2013) Electrospinning of ibuprofen-loaded composite nanofibers for improving the performances of transdermal patches. *J Nanosci Nanotechnol* 13(6):3855–3863
67. Vatankhah E (2018) Rosmarinic acid-loaded electrospun nanofibers: in vitro release kinetic study and bioactivity assessment. *Eng Life Sci* 18(10):732–742
68. Ghalei S, Asadi H, Ghalei B (2018) Zein nanoparticle-embedded electrospun PVA nanofibers as wound dressing for topical delivery of anti-inflammatory diclofenac. *J Appl Polym Sci* 135(33):46643
69. Akduman C, Özgüney İ, Kumbasar EPA (2016) Preparation and characterization of naproxen-loaded electrospun thermoplastic polyurethane nanofibers as a drug delivery system. *Mater Sci Eng C Mater Biol Appl* 64:383–390
70. Wongkanya R, Teeranachaiideekul V, Makarasin A, Chuysinuan P, Yingyud P, Nooeaid P, Techasakul S, Chuenchom L, Dechtrirat D (2020) Electrospun poly (lactic acid) nanofiber mats for controlled transdermal delivery of essential oil from *Zingiber cassumunar Roxb*. *Mat Res Exp* 7(5):055305
71. Sharma CS, Khandelwal M (2018) A novel transdermal drug-delivery patch for treating local muscular pain. *Ther Deliv* 9(6):405–407
72. Sheng S, Yin X, Chen F, Lv Y, Zhang L, Cao M, Sun Y (2020) Preparation and Characterization of PVA-Co-PE Drug-Loaded Nanofiber Membrane by Electrospinning Technology. *AAPS Pharm Sci Tech* 21(5):199
73. Ravikumar R, Ganesh M, Senthil V, Ramesh YV, Jakki SL, Choi EY (2018) Tetrahydro curcumin loaded PCL-PEG electrospun transdermal nanofiber patch: preparation, characterization, and in vitro diffusion evaluations. *J Drug Del Sci Tech* 44:342–348
74. Rengifo AF, Stefanos NM, Toigo J, Mendes C, Argenta DF, Dotto ME, da Silva MC, Nunes RJ, Caon T, Parize AL, Minatti E (2019) PEO-chitosan nanofibers containing carboxymethyl-hexanoyl chitosan/dodecyl sulfate nanoparticles loaded with pyrazoline for skin cancer treatment. *Eur Pol J* 119:335–343
75. Janani I, Lakra R, Kiran MS, Korrapati PS (2018) Selectivity and sensitivity of molybdenum oxide-polycaprolactone nanofiber composites on skin cancer: preliminary in-vitro and in-vivo implications. *J Trace Elem Med Biol* 49:60–71
76. Balashanmugam P, Sucharithra G (2020) Efficacy of biopolymeric PVA-AuNPs and PCL-curcumin loaded electrospun nanofibers anticancer activity against A431 skin cancer cell line. *Mater Today Commun* 101276. <https://doi.org/10.1016/j.mtcomm.2020.101276>
77. Guo M, Zhou G, Liu Z, Liu J, Tang J, Xiao Y, Xu W, Liu Y, Chen C (2018) Direct site-specific treatment of skin cancer using doxorubicin-loaded nanofibrous membranes. *Sci Bull* 63(2):92–100
78. Patel G, Yadav BKN (2019) Formulation, characterization and *in vitro* cytotoxicity of 5-fluorouracil loaded polymeric electrospun nanofibers for the treatment of skin cancer. *Recent Pat Nanotechnol* 13(2):114–128
79. Sampath M, Lakra R, Korrapati P, Sengottuvelan B (2014) Curcumin loaded poly (lactic-co-glycolic) acid nanofiber for the treatment of carcinoma. *Colloids Surf B Biointerfaces* 117:128–134
80. Radmansouri M, Bahmani E, Sarikhani E, Rahmani F, Sharifianjazi F, Irani M (2018) Doxorubicin hydrochloride—loaded electrospun chitosan/cobalt ferrite/titanium oxide nanofibers for hyperthermic tumor cell treatment and controlled drug release. *Int J Biol Macromol* 116:378–384
81. Madhaiyan K, Sridhar R, Sundarajan S, Venugopal JR, Ramakrishna S (2013) Vitamin B12 loaded polycaprolactone nanofibers: a novel transdermal route for the water soluble energy supplement delivery. *Int J Pharm* 444(1–2):70–76
82. Hemati Azandaryani A, Derakhshandeh K, Arkan E (2018) Electrospun nanobandage for hydrocortisone topical delivery as an antipsoriasis candidate. *Int J Poly Mater Polym Biomater* 67(11):677–685

83. Mendes AC, Gorzelanny C, Halter N, Schneider SW, Chronakis IS (2016) Hybrid electrospun chitosan-phospholipids nanofibers for transdermal drug delivery. *Int J Pharm* 510(1):48–56
84. Abid S, Hussain T, Nazir A, Zahir A, Khenoussi N (2019) A novel double-layered polymeric nanofiber-based dressing with controlled drug delivery for pain management in burn wounds. *Polym Bull* 76(12):6387–6411
85. Phiriyawirut M, Phaechamud T (2012) Gallic acid-loaded cellulose acetate electrospun nanofibers: thermal properties, mechanical properties, and drug release behavior. *Open J Polym Chem* 2:21–29
86. El Fawal G, Hong H, Song X, Wu J, Sun M, Zhang L, He C, Mo X, Wang H (2020) Polyvinyl alcohol/hydroxyethylcellulose containing ethosomes as a scaffold for transdermal drug delivery applications. *Appl Biochem Biotech* 191(4):1624–1637
87. Zandi N, Dolatyar B, Lotfi R, Shallageh Y, Shokrgozar MA, Tamjid E, Annabi N, Simchi A (2021) Biomimetic nanoengineered scaffold for enhanced full-thickness cutaneous wound healing. *Acta Biomater* 124:191–204
88. Morad H, Jahanshahi M, Akbari J, Saeedi M, Gill P, Enayatifard R (2021) Novel topical and transdermal delivery of colchicine with chitosan based biocomposite nanofibrous system; formulation, optimization, characterization, ex vivo skin deposition/permeation, and anti-melanoma evaluation. *Mater Chem Phys* 263:124381
89. López-Ramírez E, Chapa-González C, Perez CA, Escobedo-González R, Vázquez MI, Medellín-Rodríguez F, García-Casillas PE (2021) Citrulline Malate transdermal delivery through integrating into polyvinyl alcohol (PVA) nanofibers. *J Drug Deliv Sci Tech* 102630. <https://doi.org/10.1016/j.jddst.2021.102630>
90. Moohan J, Stewart SA, Espinosa E, Rosal A, Rodríguez A, Larrañeta E, Donnelly RF, Domínguez-Robles J (2020) Cellulose nanofibers and other biopolymers for biomedical applications. A review. *Appl Sci* 10(1):65
91. Sivakanthan S, Rajendran S, Gamage A, Madhujith T, Mani S (2020) Antioxidant and antimicrobial applications of biopolymers: a review. *Food Res Int* 136:109327
92. Trache D, Tarchoun AF, Derradji M, Hamidon TS, Masruchin N, Brosse N, Hussin MH (2020) Nanocellulose: from fundamentals to advanced applications. *Front Chem* 8:392
93. Kargarzadeh H, Mariano M, Huang J, Lin N, Ahmad I, Dufresne A, Thomas S (2017) Recent developments on nanocellulose reinforced polymer nanocomposites: a review. *Polymer* 132:368–393
94. El-Wakil NA, Hassan EA, Hassan ML, Abd El-Salam SS (2019) Bacterial cellulose/phytochemical's extracts biocomposites for potential active wound dressings. *Environ Sci Pollut Res Int* 26(26):26529–26541
95. Shan Y, Li C, Wu Y, Li Q, Liao J (2019) Hybrid cellulose nanocrystal/alginate/gelatin scaffold with improved mechanical properties and guided wound healing. *RSC Adv* 9(40):22966–22979
96. Zanin MHA, Oliveira AMD, Cerize NNP, Velasco MVR, Baby AR (2014) Method and nanofibres produced by electrospinning containing active substances for controlled release cosmetic application. WIPO Patent 2014089650A1, 19 June 2014
97. Laurencin CT, Nair LS, Bhattacharyya S, Allcock HR, Bender JD, Brown PW, Greish YE (2007) Polymeric nanofibers for tissue engineering and drug delivery. US Patent 7235295B2, 26 June 2007
98. Perera SP (2007) A hollow fiber-based biocompatible drug delivery device with one or more layers. WIPO Patent 2007052042A2, 23 Aug 2007
99. Garcia JAT, Carcaboso AM, Llavi JB (2013) Nonwoven membrane as a drug delivery system. WIPO Patent 2013144206A1, 3 Oct 2013
100. Zhongze G, Qian X (2009) Beauty mask based on electro spinning nano fiber. CN Patent 101390814A, 25 Mar 2009
101. Jae-yong C, Hyun-wook L, So-young P, Se-young J (2011) Medical skin-patch fabricated by using multilayer nanofiber sheet. KR Patent 101080203B1, 7 July 2011
102. Limin Z, Jie H (2009) Alkanna tinctoria drug loading nanofiber, preparation and application thereof. CN Patent 101358383A, 4 Feb 2009
103. Limin Z, Xiaomei W, Brandt-White K, Dengguang Y, Yan Z (2010) Medicinal fiber used for treating cutaneous inflammation and pain, preparation and application thereof. CN Patent 101724934A, 9 June 2010

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