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.

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...
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 exploiting 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/
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 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].

**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 \textit{in-vitro} antibacterial efficacy against \textit{S. aureus} and \textit{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 \textit{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 \textit{in-vitro} antimicrobial activity against resistant \textit{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 $127.7 \pm 43.7 \text{ nm}$ were found non-cytotoxic towards human dermal fibroblasts as revealed through confocal microscopy and they also showed excellent \textit{in-vitro} antifungal activity against different fungal strains like \textit{Epidermophyton} and \textit{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 \textit{in-vitro} antifungal activity against different fungal strains like \textit{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 ± 5.91%) followed by low \textit{in-vitro} cytotoxicity against mouse fibroblast cells. 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 ± 5.91%) followed by low \textit{in-vitro} cytotoxicity against mouse fibroblast cells. 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 ± 5.91%) followed by low \textit{in-vitro} cytotoxicity against mouse fibroblast cells. 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 ± 5.91%) followed by low \textit{in-vitro} cytotoxicity against mouse fibroblast cells. 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 ± 5.91%) followed by low \textit{in-vitro} cytotoxicity against mouse fibroblast cells. 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 ± 5.91%) followed by low \textit{in-vitro} cytotoxicity against mouse fibroblast cells. 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 ± 5.91%) followed by low \textit{in-vitro} cytotoxicity against mouse fibroblast cells. 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 ± 5.91%) followed by low \textit{in-vitro} cytotoxicity against mouse fibroblast cells.
delivery of hydroquinone and investigated the effect of chitosan on their efficacy. Optimized hydroquinone-loaded nanofibers showed a diameter of $537.24 \pm 52.5$ 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 $167 \pm 88$ 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 $331 \pm 85$ 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](image-url)
| 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 in-vitro cytocompatibility in mouse fibroblast cells                                      | [52]|
| 2     | Ciprofloxacin               | PVP                    | Not given/410±40               | SEM, ATR FT-IR, NMR, TGA/C57BL/16 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 in-vitro 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 in-vitro 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 E. coli and S. aureus in-vitro                                                                         | [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 in-vitro release of tetracycline hydrochloride and slowest release of amphotericin B in PBS (pH 7.35) followed by good antibacterial activity against S. aureus 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 given279.8                 | SEM, histology of wound tissue/Wistar rats                          | Nanofibers composed of chitosan and PVA (7:2:5) 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]|
in-vitro antioxidant effect was observed for nanofibers 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
| 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/523.66–7235.0       | SEM, FT-IR, TGA/not given                                           | Nanofibers composed of 10% (w/v) 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 in-vitro skin permeation in the reconstructed human epidermis (EpiSkin™) 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, in-vitro stability followed by high in-vitro 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 in-vitro shear adhesion followed by the extended in-vitro release of tetrahydro curcumin for 24 h | [73]  |
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 µm 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.
| 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 in-vitro 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), poly-caprolactone, gelatin | Not given/170                | SEM, Hematoxylin and eosin (HE) staining, Immuno Histochemistry/female C57BL/6 mice | Developed nanofibers showed extended in-vitro 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 in-vitro 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 in-vitro release of curcumin following non-Fickian diffusion mechanism and excellent in-vitro 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 in-vitro 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 B₁₂                   | 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 in-vitro cytocompatibility of vitamin B₁₂ loaded nanofibers in L929 cells followed by 90% in-vitro release of Vitamin B₁₂ 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 75% 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 isothiocyanate 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 in-vitro 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 in-vitro 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 ex-vivo skin permeation followed by remarkable cytotoxicity against melanoma cell lines (A-375 cell line) in-vitro | [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 in-vitro | [89] |
| Title of patent                                                                 | Brief description                                                                 | Inventors                                                                 | Patent number         | Ref  |
|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------|---------------------------------------------------------------------------|-----------------------|------|
| Method and nanofibres 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 polyporphosazene based nanofibers loaded with nanosized hydroxyapatites and their role in wound dressing | Cato T. Laurencin, Lakshmi Sreedharam Nair, Subhabrata Bhattacharyya, Harry R. Alcock, 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 Tornero Garcia, Angel Montero Carcaboso, Joan Bertran Llavi | WO2013144206A1       | [99] |
| Beauty mask based on electro spinning nano fiber                                | This patent describes 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             | KR101082038B1         | [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                                                     | CN10135833A           | [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, Keith Brandt-White, Yu Dengguang, Zheng Yan     | CN101724934B          | [103]|
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; 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
LK: conceptualization, designing of the work, writing of the original draft, and editing. SV: Writing and review. KJ: Writing and review. PU: critically reviewed the whole manuscript. SS: Writing and review. All the authors have read and approved the manuscript.

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References

1. Jensen JM, Prokch E (2009) The skin's barrier. G Ital Dermatol Venereol 144(6):689–700
2. 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
3. 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
4. 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
5. 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
6. Forster M, Bolzinger MA, Fessl H, Brianchon S (2009) Topical delivery of cosmetics and drugs. Molecular aspects of percutaneous absorption and delivery. Eur J Dermatol 19(4):309–323
7. Bouwstra JA, Honeywell-Nguyen PL (2002) Skin structure and mode of action of vesicles. Adv Drug Deliv Rev Suppl 1:541–55
8. Jepps OG, Dancik Y, Anisimov YG, Roberts MS (2013) Modeling the human skin barrier—towards a better understanding of dermal absorption. Adv Drug Deliv Rev 65(2):152–168
9. 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):412–425
10. Rahmani M, Arbabi Bigdlo S, Rezayat SM (2017) Electrospun polymeric nanofibers for transdermal drug delivery. Nanomed J 4(2):61–70
11. 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
12. Sharma R, Singh H, Joshii 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
13. Fenot A, Cheonakis S (2003) Polymer nanofibers assembled by electrospinning. Curr Opin Colloid Interface Sci 8(1):64–75
14. Thakkar S, Misra M (2017) Electrospin polymeric nanofibers: New horizons in drug delivery. Eur J Pharm Sci 107:148–167
15. 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
16. Kamble P, Sadarang 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
17. Al-Jbour ND, Beg MD, Gimbun J, Alam AKMM (2019) An overview of chitosan nanofibers and their applications in the drug delivery process. Curr Drug Deliv 16(4):272–294
18. Torres-Martinez EJ, Cornejo Bravo JM, Serrano Medina A, Pérez González GL, Villareal 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
19. Hartgersvik JB, Beniash E, Stupp SI (2001) Self-assembly and miniaturization of peptide-amphiphile nanofibers. Science 294(5547):1684–1688
20. Martin CR (1994) Nanomaterials: a membrane-based synthetic approach. Science 266(5193):1961–1966
21. Ma PX, Zhang R (1999) Synthetic nano-scale fibrous extracellular matrix. J Biomed Mater Res 46(1):60–72
22. 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
23. Toriello M, Afshar M, Shon HK, Tjiang LD (2020) Progress on the fabrication and application of electrospun nanofiber composites. Membranes (Basel) 10(9):204
24. Kowalczyk T (2020) Functional micro- and nanofibers obtained by nonwoven post-modification. Polymers (Basel) 12(5):1087
25. Kumbar SG, Nair LS, Bhattacharyya S, Laurencin CT (2006) Polymeric nanofibers as novel carriers for the delivery of therapeutic molecules. J Nanosci Nanotechnol 6(10):2591–2607
26. Bhardwaj N, Kundu SC (2010) Electrospinning: a fascinating fiber fabrication technique. Biotechnol Adv 28(3):325–347
27. Wang A, Xu C, Zhang C, Gan Y, Wang B (2015) Experimental investigation of the properties of electrospin nanofibers for potential medical application. J Nanomater 1–8. https://doi.org/10.1155/2015/418932
28. 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
29. Yoo HS, Kim TG, Park TG (2009) Surface-functionailized electrospun nanofibers for tissue engineering and drug delivery. Adv Drug Deliv Rev 61(12):1033–1042
30. Sill TJ, von Recum HA (2008) Electrospinning: applications in drug delivery and tissue engineering. Biomaterials 29(13):1989–2006
31. Teo WE, He W, Ramakrishna S (2006) Electrospun scaffold tailored for tissue-specific extracellular matrix. Biotechnol J 1(9):918–929
32. 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
33. Castaño O, Eltahawy M, Kim HW (2012) Electrospinning technology in tissue regeneration. Methods Mol Biol 811:127–140
34. Ingavle GC, Leach JK (2014) Advancements in electrospinning of polymeric nanofibrous scaffolds for tissue engineering. Tissue Eng Part B Rev 20(4):277–293
35. Pilehvar-Soltanamadh Y, Akbarzadeh A, Moazzam-Lalakoo N, Zarhagni H (2016) An update on clinical applications of electrospun nanofibers for skin bioengineering. Artif Cells Nanomed Biotechnol 44(6):1350–1364
36. Norouzi M, Boroujeni SM, Omidvarkhodouei N, Soleimani M (2015) Advances in skin regeneration: application of electrospin scaffolds. Adv Healthc Mater 4(8):1114–1133
37. 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
38. 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
39. Lu Y, Huang J, Yu G, Cardenas R, Wei S, Wujick KE, Guo Z (2016) Coaxial electrospun fibers: applications in drug delivery and tissue engineering. Wiley Interdiscip Rev Nanomol Biotechnol 8(5):654–677
40. Pant B, Park M, Park SJ (2019) Drug delivery applications of core-sheath nanofibers prepared by coaxial electrospinning: a review. Pharmaceutics 11(7):305
41. McCullough P, Landis WI (2016) Recent applications of coaxial and emulsion electrospinning methods in the field of tissue engineering. Biores Open Access S(1):212–227
42. Su Y, Su Q, Liu W, Jin G, Mo X, Ramakrishn S (2012) Dual-drug encapsulation and release from core-shell nanofibers. J Biomat Sci Polym Ed 23(7):861–871
43. Ye K, Huang 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 Commun 27(19):1657–1662
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 break up during electrospinning. Polym Adv Technol 19(7):728–733
47. Ajalloueian F, Tavanai H, Hillborn J, Donzel-Gargand O, Leifer K, Wickham A, Arpaneaei A (2014) Emulsion electrospinning as an approach to fabricate PLGA/chitosan nanofibers for biomedical applications. Bio Med Res Int 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. Katania 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 I (2019) Development of a poly (vinyl alcohol)/lysine electrospun membrane-based drug delivery system for improved skin regeneration. Int J Polym Anal Charat 24(3):227–235
51. Iqbal H, Khan BA, Khan ZU, Razzaq A, Khan NU, Menaa B, Menaa F (2018) 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, Valentinii P, Pompa PP, Spanò R, Goldoni L, Bertorelli R, Athanassiou A, Bayer IS (2017) Transpar- ent 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, Aboelfetoh EF, Al-Deyab SS, El-Newehy MH (2018) Fabrication of electrospun poly(vinyl alcohol)/dextan 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 N (2019) Chitosan/poly(lactic-co-glycolic acid)/cobalt ferrite/titanium oxide nanofibers for topical treatment and controlled drug release. Int J Biol Macromol 116:378–384
56. Nematpour N, Farhadian N, Ebrahimi KS, Arkan E, Seyedi F, Khaledian S, Nematpour N, Farhadian N, Ebrahimi KS, Arkan E, Seyedi F, Khaledian S (2017) Preparation and application: preparation, characterization and antifungal activity studies against Candida species. Pharm Dev Technol 25(4):440–453
57. Esenturk I, Gumrukcu S, Özdağbak Sert AB, Kök FN, Döjles S, Gungor S, Erdal MS, Sarac AS (2020) Silk-fibrin-containing nanofibers for topical sertaconazole delivery: preparation, characterization, and antifungal activity. Int J Polym Mater 1–8. https://doi.org/10.1080/00904307.2020.1740992
58. Azarbayaji 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
59. Shi Y, Wei Z, Zhao H, Liu J, Jiang J (2013) Electropinning of ibuprofen-loaded composite nanofibers for improving the performances of transdermal patches. J Nanosci Nanotechnol 13(6):3855–3863
60. Vatanakhi R, Esfandiarian T, Khatami A, Massoumi B, Haji Z, Nabi H (2017) Electrospinning of PLGA/chitosan nanofibers for the development of new nanofibrous membranes. J Biomed Mater Res A 105:1512–1520
61. Guo M, Zhou G, Liu Z, Liu J, Tang J, Xiao Y, Wu L, Liu Y, Chen C (2018) Electrospun poly (lactic acid) nanofiber mats for treating local muscular pain. Ther Deliv 9(6):405–407
62. Sheng S, Yin X, Chen F, Lv Z, Zhang L, Cao M, Sun Y (2020) Preparation and Characterization of naproxen-loaded electrospun thermoplastic polyurethane nanofibers as a drug delivery system. Mater Sci Eng C Mater Biol Appl 104:383–390
63. Nitanan T, Akkaramongkolporn P, Nooeaid P, Techasakul S, Chuenchom L, Dechtirat D (2020) Electrospun poly (actic) nanofiber mats for controlled transdermal delivery of essential oil from Zingiber cassumunar Roxb. Mat Res Exp 7(5):055305
64. Sharma CS, Khandelwal M (2018) A novel transdermal drug delivery patch for treating local muscular pain. Ther Deliv 9(6):405–407
65. Eng Asp 586:124267
66. Shi Y, Wei Z, Zhao H, Liu J, Jiang J (2013) Electropinning of ibuprofen-loaded composite nanofibers for improving the performances of transdermal patches. J Nanosci Nanotechnol 13(6):3855–3863
67. Vatanakhi R, Esfandiarian T, Khatami A, Massoumi B, Haji Z, Nabi H (2017) Electrospinning of PLGA/chitosan nanofibers for the development of new nanofibrous membranes. J Biomed Mater Res A 105:1512–1520
68. Guo M, Zhou G, Liu Z, Liu J, Tang J, Xiao Y, Wu L, Liu Y, Chen C (2018) Electrospun poly (lactic acid) nanofiber mats for treating local muscular pain. Ther Deliv 9(6):405–407
69. Patel G, Yadav BM (2019) Formulation, characterization and in vitro cytotoxicity of S-fluorouracil loaded polymeric electrospun nanofibers for the treatment of skin cancer. Recent Pat Nanotechnol 13(2):114–128
70. Sampaath M, Lakra R, Korrapati PS (2018) Selectivity and sensivity of molybdenum oxide-polyacrylamide nanofibers composites on skin cancer: preliminary in-vivo and in-vivo implications. J Trace Elem Med Biol 49:60–71
71. Balabhanmugam P, Suchanthra G (2020) Efficacy of biopolymeric PVA-AuNPs and PCL-curcumin loaded electrospun nanofibers in the treatment of skin cancer activity against A431 skin cancer cell line. Mater Today Commun 101276. https://doi.org/10.1016/j.mtcom.2020.101276
72. Guo M, Zhou G, Liu Z, Liu J, Tang J, Xiao Y, Wu L, Liu Y, Chen C (2018) Electrospun poly (lactic acid) nanofiber mats for treating local muscular pain. Ther Deliv 9(6):405–407
73. Patel G, Yadav BM (2019) Formulation, characterization and in vitro cytotoxicity of S-fluorouracil loaded polymeric electrospun nanofibers for the treatment of skin cancer. Recent Pat Nanotechnol 13(2):114–128
74. Madhjayan K, Sridhar R, Sundararajan S, Venugopal JR, Ramakrishna S (2013) Vitamin B12 loaded polyacrylonitrile nanofibers: a novel transdermal route for the water soluble energy supplement delivery. Int J Pharm 444(1–2):70–76
75. Hemati Azandaryani A, Derakhshandeh K, Arkan E (2018) Electrospun nanobandage for hydrocortisone topical delivery as an anti-inflammatory candidate. Int J Poly Mater 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. Abd 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(1):6387–6411
85. Phiriyawirut M, Phaechamud T (2012) Gallic acid-loaded cellulose acetate electropun 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, Lofti R, Shalagh Y, Shokroozar MA, Tamjed 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. Mbohau 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, Deradj M, Hamidon TS, Masruchin N, Bross N, Hussin NH (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/phytochemicals 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, Cenize NNP, Velasco MVR, Baby AR (2014) Method and nanofibers produced by electrospinning containing active substances for controlled release cosmetic application. WPO 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, Llaví 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 101749544A, 9 June 2010

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