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ADVANCED REVIEW

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Electrospun fibers as carriers for topical drug delivery and release in skin bandages and patches for atopic dermatitis treatment

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Abstract

The skin is a complex layer system and the most important barrier between the environment and the organism. In this review, we describe some widespread skin problems, with a focus on eczema, which are affecting more and more people all over the world. Most of treatment methods for atopic dermatitis (AD) are focused on increasing skin moisture and protecting from bacterial infection and external irritation. Topical and transdermal treatments have specific requirements for drug delivery. Breathability, flexibility, good mechanical properties, biocompatibility, and efficacy are important for the patches used for skin. Up to today, electrospun fibers are mostly used for wound dressing. Their properties, however, meet the requirements for skin patches for the treatment of AD. Active agents can be incorporated into fibers by blending, coaxial or side-by-side electrospinning, and also by physical absorption post-processing. Drug release from the electrospun membranes is affected by drug and polymer properties and the technique used to combine them into the patch. We describe in detail the in vitro release mechanisms, parameters affecting the drug transport, and their kinetics, including theoretical approaches. In addition, we present the current research on skin patch design. This review summarizes the current extensive know-how on electrospun fibers as skin drug delivery systems, while underlining the advantages in their prospective use as patches for atopic dermatitis.

This article is categorized under:

Implantable Materials and Surgical Technologies > Nanomaterials and Implants

Abbreviations: AD, atopic dermatitis; AgNPs, silver nanoparticles; ALG, sodium alginate; AuRNs, gold nanorods; CA, cellulose acetate; CIP, ciprofloxacin; CLOX, cloxacillin benzathine; CS, chitosan; DCF, diclofenac; DSC, differential scanning calorimetry; EC, ethyl cellulose; FA, folic acid; FTIR, Fourier-transform infrared spectroscopy; Gly, glycine; KET, ketoprofen; LCST, lower critical solution temperature; MRSA, methicillin-resistant *Staphylococcus aureus*; MTZ, metronidazole; PA6, polyamide 6; PAA, poly(acrylic acid); PAH, poly(allylamine hydrochloride); PCL, polycaprolactone; PEO, poly(ethylene oxide); PHBV, poly(3-hydroxybutyrate-co-3-hydroxyvalerate); PI, polyimide; PLA, polylactide; PLGA, poly(D,L)-lactide-*co*-glycolide; PLLA, poly-L-lactide; PNIPAAm, poly(*N*-isopropylacrylamide); PNVCL-*co*-MAA, poly(*N*-vinylcaprolactam-*co*-methacrylic acid); PPS, poly(propylene sulfide); PS, polystyrene; PU, polyurethane; PVA, poly(vinyl alcohol); PVAc, poly(vinyl acetate); PVB, poly(vinyl butyral-*co*-vinyl alcohol-*co*-vinyl acetate); PVP, poly(vinyl pyrrolidone); RosA, Rosmarinic acid; SC, stratum corneum; SEM, scanning electron microscopy; SF, silk fibroin; SG, stratum granulosum; TCH, tetracycline hydrochloride; TEWL, transepidermal water loss; VE, vitamin E.

Implantable Materials and Surgical Technologies > Nanotechnology in Tissue Repair and Replacement
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KEYWORDS
atopic dermatitis, drug delivery, electrospinning, electrospun fibers, release, skin patches

1 | INTRODUCTION

As the skin is the largest human organ and our most important protective barrier, it is exposed to many harmful conditions. A skin damaged by diseases or external factors causes a significantly reduced quality and comfort of life. Polluted environments, an aging society, trauma, and genetic factors can all lead to the development of skin problems. In 2017, 180 million persons worldwide suffered from eczema. The disability-adjusted life years-measured as the years of life lost due to premature mortality plus the years lost due to disability or its consequences-for atopic dermatitis (AD) increased worldwide from 0.27% in 1990 to 0.35% in 2017 (Urban et al., 2021). The treatment costs reported exceeded those related to cardiovascular issues or diabetes, which are usually considered examples of the most expensive health problems (Flohr & Hay, 2021; Lim et al., 2017). Therefore, medical doctors and scientists are constantly looking for new treatment possibilities to improve the efficiency of the existing ones and reduce costs (Lee et al., 2022). AD is one of the most common skin diseases. People can suffer from it at any age; however, newborns and children are the most affected. AD requires complex and diverse medication depending on the severity of the disease (Salimian et al., 2022). Topical and transdermal active substances are frequently prescribed, as they cure locally and give immediate relief (Benson et al., 2019). The main drawback of existing treatments is that they deliver drugs quickly, giving the maximum drug concentration, with the need for reapplication to keep their value constant (Souto et al., 2019). The delivery system requires a sustainable release which has been effectively obtained via electrospun fibers for topical and transdermal drug delivery (Özen & Wang, 2021), especially for wound healing cases (García-Salinas et al., 2020; Lowe et al., 2015; Zahedi et al., 2010). Electrospinning makes it possible to produce fibrous membranes, which can be loaded with various bioactive molecules (Sultana et al., 2022; Torres-Martinez et al., 2018; Wen & Jingwei, 2015). Electrospinning parameters determine fiber geometry, thus influencing drug release mechanisms (Luraghi et al., 2021). Furthermore, polymer selection also plays an important role (Theron et al., 2004). Fibrous dressings are flexible and easy to handle (C. Yang et al., 2016). Moreover, they are breathable (Keirouz et al., 2020), but also maintain skin hydration by reducing water evaporation (Costa et al., 2019). Considering the worldwide tracking costs of skin disease treatments (Flohr & Hay, 2021), the most important advantage of electrospun membranes is their low production cost (Khoshbakht et al., 2020; Z. Wang et al., 2017). This led us to think of the possibility of using fibers as topical patches for AD treatment. In this review, we describe skin problems, while focusing on AD. The requirements for topical patches have been defined. The electrospinning process has been comprehensively characterized to show the reader that an easy-looking process has many parameters that affect final materials and drug delivery system properties, which need to be carefully adjusted to the production needs. Also, we underlined the effect of bioactive molecule selection on drug release and the importance of in vitro studies. Recently published research has mainly been focused on drug delivery systems mostly for wound healing and AD itself. The design of skin bandages includes other strategies and designs, especially when using electrospun polymer fibers and membranes. Several studies on electrospun patches for skincare and AD treatment currently available are covered in this review. Furthermore, we investigated the prospect of adopting the unique electrospun fiber properties for developing skin dressings and bandages.

2 | SKIN

2.1 | Skin structure

The skin is a barrier between the environment and the organism that provides protection from physical and chemical pollution, pathogens, and unregulated water loss. It is made up of the epidermis, dermis, and a subcutaneous layer consisting of the hypodermis and muscles (see Figure 1a). The epidermis mainly consists of keratinocytes

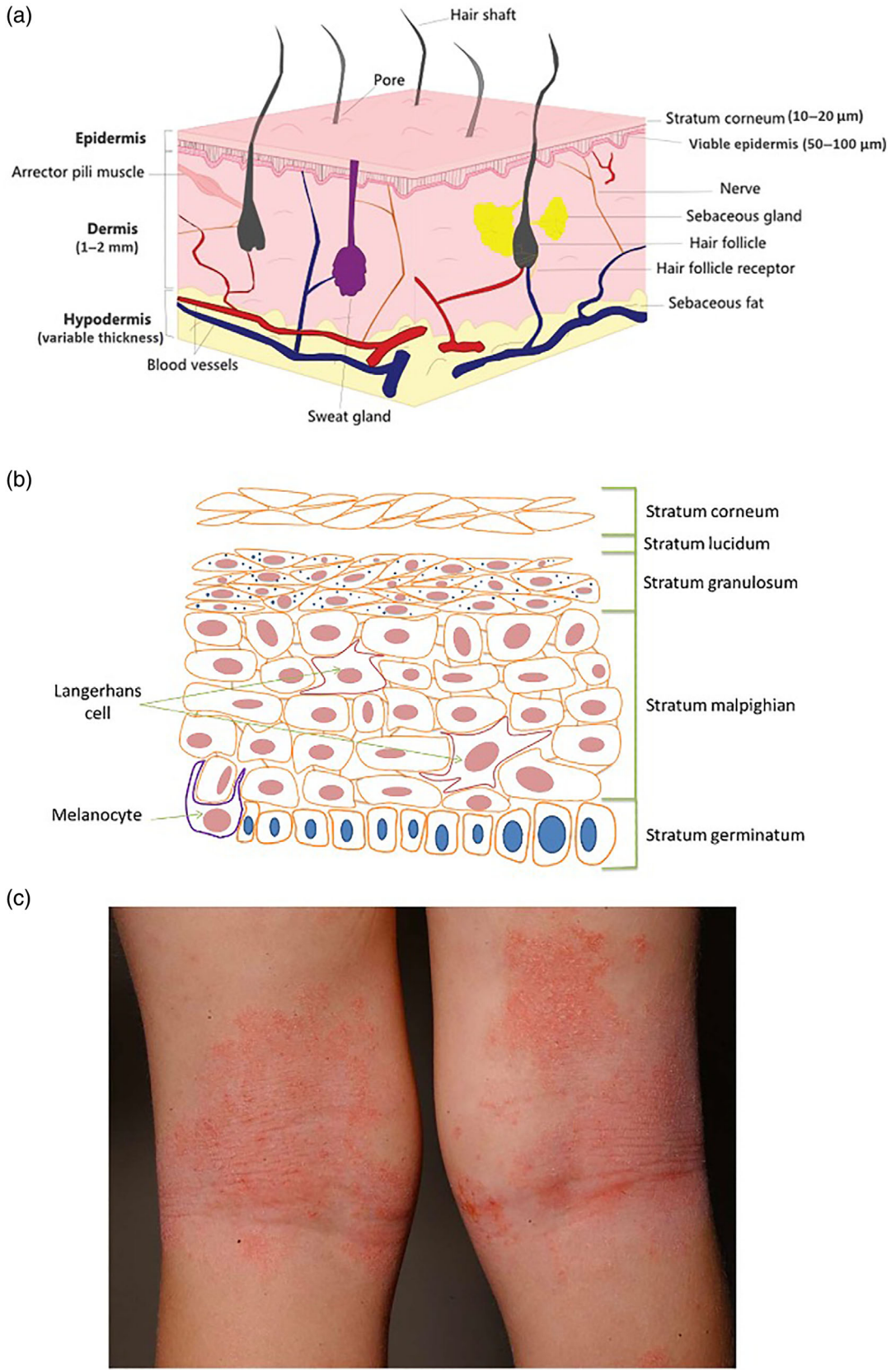

FIGURE 1 Schematic drawing of the structure of: (a) skin indicating all main components. Reproduced with permission from Moniz et al. (2020); (b) epidermis with all sub-layers and types of cells; (c) image of skin with AD shown as a red rash behind the knees. Reproduced with permission from Salava and Lauerma (2014)

(Figure 1a), but melanocytes, Langerhans cells, and Merkel cells are also found. Keratinocytes, producing keratin, are found in each layer, while the type of protein depends on the stage of cell differentiation. Cells are organized in layers and their morphology changes as they shift from the stratum germinatum to the top of the skin, becoming flatter, larger, and thinner (Lanigan & Zaidi, 2010). Melanocytes transfer melatonin via dendrites to keratinocytes to create an UV protective layer, which absorbs harmful radiation, thus protecting the skin (Gola et al., 2012). They also have a thermoregulation function (J. Y. Lin & Fisher, 2007). Langerhans cells, produced by bone marrow, protect the skin via immunological responses. This part of the skin absorbs nutrition from the dermis, as it does not have its own blood vessels (Lanigan & Zaidi, 2010). The outermost layer of skin, the stratum corneum (SC), is made up of corneocytes surrounded by lipid lamellas, which provide the main pathway for the diffusion of the active substances (Bouwstra & Honeywell-Nguyen, 2002). Corneocytes, anucleate keratinocytes, create an impenetrable layer. Cells are large, filled with keratin, and have a flat polyhedral morphology: they are held together by lipids (see Figure 1b). In addition to cells, the SC consists of ceramides, cholesterol, and free fatty acids (Menon et al., 2012; Notman et al., 2007; Sahle et al., 2015). The next epidermis layer is the stratum lucidum, but it is only present in the palms of the hands and soles of the feet. Here cells have nuclei, and their cytoplasm is densely packed. The stratum granulosum (SG) contains granules that produce different proteins which have the important role of binding SC cells and aggregating keratin filaments. The stratum malpighian, the penultimate and thickest layer of the epidermis, is responsible for keratin development and intracellular SC adhesion. In the stratum germinatum, a single layer of dividing cells with large nuclei and columnar morphology, the cytoplasm is filled with keratin filaments (tonofilaments). The disturbed permeability of the SC is a pathophysiological factor for skin diseases (Taylor, 1999). Transepidermal water loss (TEWL) is the main effect of a perturbed skin barrier, usually associated with epidermis inflammatory reactions, as it takes place in AD (Rustemeyer & Fartasch, 2012).

2.2 | Inflammation of the skin

Immunologists and allergists described a variety of dermatological problems, reflecting skin conditions and people's lives (Cohen et al., 2020). Out of many, pityriasis alba was reported to be a mild form of AD frequently affecting children and teenagers. Skin erythema, plaques, scaly skin, and hypopigmentation are its main symptoms. Patients suffering from this disease often have a history of atopic skin or their relatives do. Here, climate plays an important role, since intensive sun exposure and humidity below 30% and above 50% can have a negative impact (Miazek et al., 2015). Seborrheic dermatitis is another skin disease caused by a reaction to yeast attacking the SC and generating an immune response, resulting in skin inflammation. Thus, there is an exaggerated proliferation of keratinocytes, resulting in a disturbed corneocyte differentiation, which is the cause of its characteristic symptoms. The skin around the sebaceous gland areas is that most affected by itchy scaly patches (A. K. Gupta et al., 2003). Acne vulgaris is a skin issue frequently occurring in adolescents and young adults, but may also be almost lifelong. A few pathogenesis pathways have been reported: microbial colonization, sebum overproduction, or follicular hyperkeratinization. The factors causing this illness can be either genetic or nongenetic, due to disturbed neuroendocrine regulatory mechanisms or to diet (Zaenglein et al., 2016). Rosacea is a common chronic inflammatory skin problem in adults. In this case, dry, sensitive skin with redness, flushing, and/or raised red bumps is observed. Its possible cause is often a vascular abnormality, but lifestyle—meaning diet and negative stressors—can also be an important factor in rosacea development (Culp & Scheinfeld, 2009). Lichen planus is an autoimmune inflammatory disease affecting mucous membranes and the skin, which are covered with flat-topped itchy papules (Tziotzios et al., 2018). Keratosis pilaris commonly occurs with AD in childhood and adolescence on extensor surfaces and extremities. Erythema and scaling surround keratin plugs in hair follicles (De Paepe et al., 2009). Psoriasis is a genetic, chronic, inflammatory disease, with increased proliferation and differentiation of keratinocytes. It frequently affects adults, who show scaly, dry, itchy skin which can cover either small localized patches on the scalp, knees, and elbows, or even the whole body (Gudjonsson & Elder, 2007). The skin diseases listed above are merely the most frequent ones, whereas there are many others not mentioned here, thus demonstrating the importance of delivering novel skin treatment technologies to improve people's lives. The following section focuses more in detail on AD as the main cause of skin inflammation, which is correlated with all the dermatological challenges mentioned above.

2.3 | Atopic skin characterization and treatment

AD is one of the most common inflammatory skin diseases. Its chronic, itchy (Kido-Nakahara et al., 2017), red, swollen, and cracked skin is very common in children, but may occur at any age (Fenner & Silverberg, 2018; see Figure 1c). Its main abnormalities are: increased skin pH (Proksch, 2018), penetration of allergens and microbiomes, production of proinflammatory cytokines, and skin infections mostly due to *Staphylococcus aureus* (Geoghegan et al., 2018). The expression of filaggrin and keratins is downregulated and TEWL also occurs (J. Kim et al., 2019). The immune system of patients with AD overreacts to allergens and overproduces IgE, thus leading to many diseases. AD's first manifestation is atopy, followed by food allergy, allergic rhinitis, and allergic asthma—referred to collectively as atopic march (Bantz et al., 2014). The disturbed skin barrier is a critical factor in AD; it may be caused by mutations in the gene encoding protein that builds the skin protective layer (H. Han et al., 2017). In AD, the structure of SC is changed by the distrusted lipid architecture and composition. The total number of lipids together with long chain ceramides is reduced, what leads to TEWL. The chain length of fatty acids is decreased too. Except changes in lipids, size of corneocytes is reduced. Furthermore, the SG layer is thinner or even not present in the skin (Luger et al., 2021).

AD treatment is mostly focused on improving the skin barrier by using emollients, and avoiding inflammation and infections by eliminating irritating factors. Oral anti-inflammatory therapy with topical corticosteroids and calcineurin inhibitors is usually the first-line treatment. Phototherapy is applied when other methods have failed; it can be used as a single remedy or combined with drugs. UVA light helps with collagen synthesis, as it enters the dermis, while UVBs reduce the skin colonization with *S. aureus* and the expression of cytokines responsible for immune response; the best results can be obtained with an UVA and UVB combination. Short-term doses of phototherapy may cause mild side effects such as burning, while long-term doses cause photoaging or even cutaneous malignancies (Ortiz-Salvador & Pérez-Ferriols, 2017). Wet wraps are used for AD treatment in both children and adults. These are bandages or cotton cloths soaked with emollients and sometimes with corticosteroids also, which are applied overnight (Oranje et al., 2006).

3 | TOPICAL AND TRANSDERMAL DRUG DELIVERY

The most common topical system works locally in the form of ointments or creams with a high concentration of active compounds (see Figure 2). The poor diffusion though the skin and need for controlled release present great challenges in such a treatment. Moreover, overcoming the SC barrier presents another huge problem (Ammala, 2013). Thus, penetration enhancers can be used to improve topical drug delivery systems. Different types of nanocarriers are reported to overcome the drawbacks of conventional topical systems (M. Gupta et al., 2012). Due to the skin structure, an effective

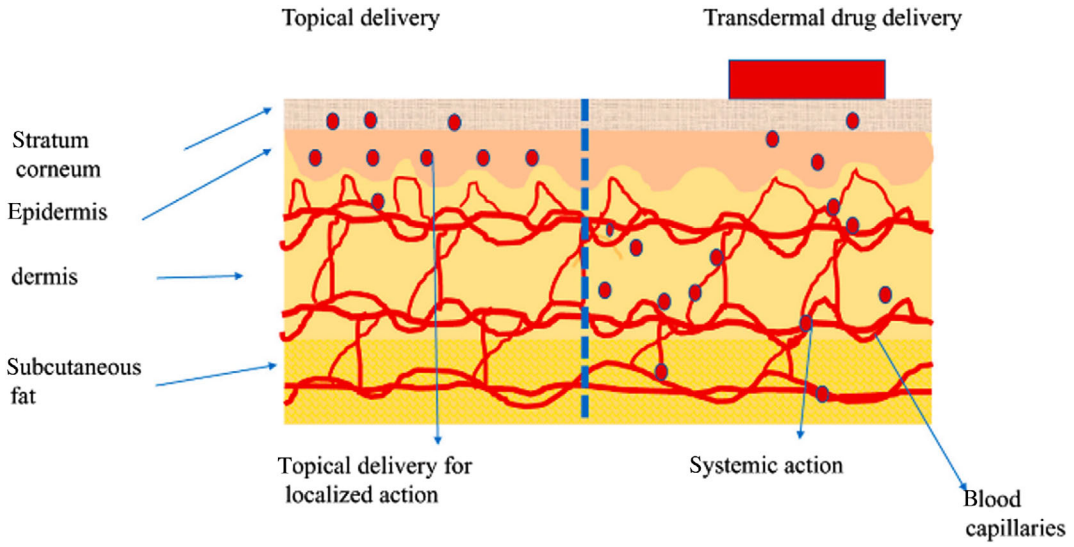

FIGURE 2 Schematic comparison of topical (dermal) drug delivery and transdermal drug delivery systems showing the different drug delivery mechanisms through the skin. Reproduced with permission from Chaturvedi and Garg (2021)

TABLE 1 The most important drug requirements for transdermal drug delivery, based on the reference Naik et al. (2000)

Specific properties	Required characteristics
Molecular weight	<500 Da
Dose deliverable	<10 mg day^{-1}
Lipophilicity	$10 < K_{o/w} < 1000$, $K_{o/w}$-oil–water partition coefficient
Aqueous solubility	> 1 mg ml^{-1}
Melting point	<200°C

drug diffusion is possible for molecules smaller than 500 kDa; enhancers are required for larger ones (Goyal et al., 2016). However, the daily drug dose should not exceed 10 mg, as it can cause diffusional resistance (Factor et al., 2013). Skin conditions change constantly even throughout a single day, and may thus alter the efficiency of topical treatments. The form of active substances affects the dispersion or absorption within the skin; lotions, emollients, and so on are used when a rapid treatment is necessary. Interestingly, some drugs, for example, antifungal ketoconazole, can only be applied onto the skin, while oral treatment is forbidden by the Food and Drug Administration and European Medicines Agency. In spite of many limitations, topical drug delivery makes it possible to use higher doses and longer treatments to obtain the required effect (Mustfa et al., 2021). Transdermal drug delivery transports medicines through the skin into the blood circulation (Figure 2). The principles of and reasons for the use of such a system are similar to those that apply to topical drug delivery. A large skin area (1–2 m^2) and its accessibility are the main enhancing factors for researching and creating new skin delivery systems. Moreover, in most cases, non-invasive and repeatable application provides an enormous opportunity for the development of effective technologies and materials for improving medical care. For many diseases, sustained medicine release is required: something that cannot be achieved by traditional oral drug administration. However, there are numerous limitations for both topical and transdermal drug delivery systems; see Table 1 (Naik et al., 2000). The SC creates a lipophilic barrier (Figure 1a), while drug dissolution occurs in the systematic circulation. Thus, the balance between medicine lipophilicity and hydrophilicity should be maintained. Otherwise, drugs may either remain in the SC layer or be unable to cross the SC. Moreover, the aqueous solubility of a drug should exceed 1 mg ml^{-1}, as the epidermal layer supporting the SC is more aqueous than the SC itself (Singh & Bali, 2016). Active substance solubility and absorption are strictly correlated with its melting point. It has been reported that a melting point lower than 200°C ensures good drug solubility (Chu & Yalkowsky, 2009; Pastore et al., 2015). Drug delivery into or across the skin shows great potential when it involves large surface areas, thus, there are numerous potential places for applying treatments. This system also reduces the necessity for dose repetition and the possible risk of toxic side effects (Verreck et al., 2003), as the pharmacokinetics process takes place evenly, with fewer peaks. Two different pathways for drug diffusion can be described: intracellular for hydrophilic and polar substances through corneocytes, and intercellular via lipid matrix for lipophilic and non-polar molecules. Medicines can also be transported by hair follicles and sweat glands (Alkilani et al., 2015). The skin drug delivery system is based on the dissolution and release from a native form, with consequent infiltration into the SC, whence drugs penetrate into subsequent layers and to the vessels and systemic circulation (Y. Chen et al., 2019). A very important issue in skin drug delivery is the distinction between desired topical and transdermal sites. The first requires a local effect, while the second distributes medicines into the systemic circulation (Cevc & Vierl, 2010).

4 | REQUIREMENTS FOR SKIN BANDAGES AND PATCHES

Transdermal patches deliver active substances to the skin by close contact and have been used for four decades. However, increasing skin problems require new solutions. The first requirement for transdermal patches is the biocompatibility of the materials, followed by the chemical and physical compatibility of the selected material with the drug or other treating substances, and the adhesive properties (Cilurzo et al., 2012). The crucial property in skin dressings is their permeability to air and fluids, as often the desired waterproof characteristics of materials can lead to skin maceration (Naseri et al., 2014; R. Xu et al., 2016). Transdermal patches are mostly pressure-sensitive adhesives and may cause chemical and mechanical skin irritation when removed (Hwang et al., 2018). Patches need to be flexible and easily removed without excessive adhesion and skin irritation (González-López et al., 2017; J. Wang & Windbergs, 2017).

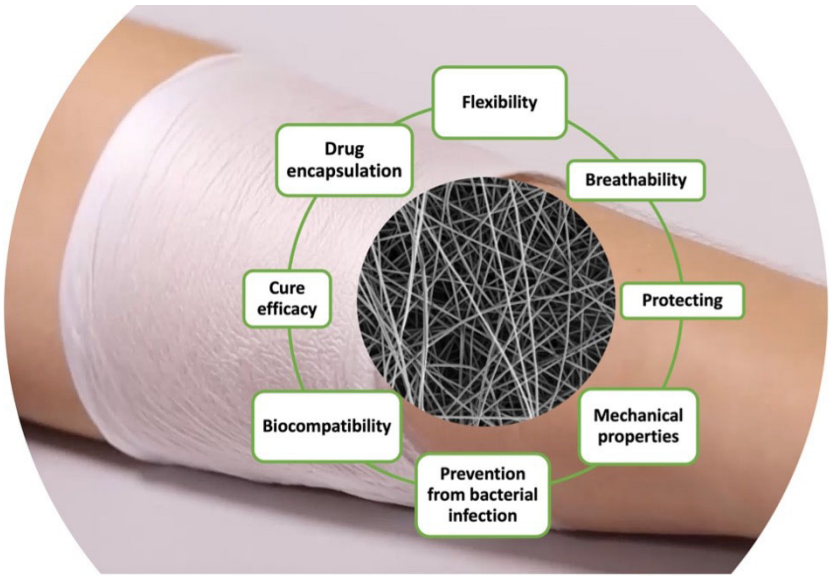

FIGURE 3 Image of an electrospun patch on forearm skin with an insert of a scanning electron microscopy micrograph of polymer fibers indicating the most important requirements and features for epidermal bandages

Tensile strength and elongation at break are required to overcome the stress exerted by body movements. Moreover, these materials have to be strong but also flexible (Peh et al., 2000). Traditional skin dressings protect from external factors but do not enhance healing, nor do they prevent bacterial infections. Modern bioactive materials optimize the process of skin healing and can be provided in different forms: foams, bandages, nanogels or microgels and scaffolds, hydrogels, and films (Teixeira et al., 2020). Transdermal patches are based on drug delivery to the systemic circulation through the skin. The poor water solubility and low chemical stability of certain medicines lead to problems with such delivery systems. Drug encapsulation responds to the expectations, by improving long-term stability, drug solubility, and sustained release. The incorporation of pharmaceutics into a polymer matrix may induce drug crystal formation, thus significantly decreasing medicinal efficiency (Vatankhah, 2018). The development method of topical drug delivery dressings depends on the skin needs. Each type of patch has different mechanical properties, breathability, and cure efficacy (see Figure 3). Generally speaking, skin dressings can be divided into three groups: passive, interactive, and bioactive; those applicable for topical drug delivery are classified as bioactive. Among the many materials used, hydrogels, hydrocolloids, thin films, and gauze-like materials are the most common (Boateng et al., 2008; B. S. Gupta & Edwards, 2019). Electrospun membrane fibers are excellent materials capable of meeting all the requirements mentioned above, thanks to their large surface area; therefore, in this review, we focus on skin patches based on fibrous structures.

5 | ELECTROSPINNING

The most common method of producing fibrous membranes is electrospinning. The electrospinning setup consists of a high-voltage power supply and grounded collector, polymer solution in the syringe, a pump which doses and determines the flow rate of the polymer solution, and spinneret (see Figure 4a,b). Some of them can control the temperature and humidity, when the setup consists of a climate-controlled chamber. The principle of electrospinning consists of the application of a voltage sufficient to stretch a polymer droplet by electrostatic repulsion, which counteracts the surface tension of the liquid. The solution droplet is then elongated into a cone shape, forming a polymer jet at the cone apex, which starts to spin in the electric field; lastly, fibers are deposited on the collector (Keirouz et al., 2020; Sandri et al., 2020). In particular, electrospinning is based on fast solvent evaporation leading to the production of solid fibers, thus indicating the solvent selection for preparing polymer solutions (Luo et al., 2010). Membranes made of electrospun fibers have a high surface area-to-volume ratio and high porosity (Hong, 2006; Kaniuk et al., 2020); thus, they provide satisfactory gas exchange (Shi et al., 2013) and high absorption capacity (Ma et al., 2018; Mofidfar & Prausnitz, 2019; Sandri et al., 2020). Electrospun fibers can be produced using single- or multiaxial nozzles (D. Han & Steckl, 2013;

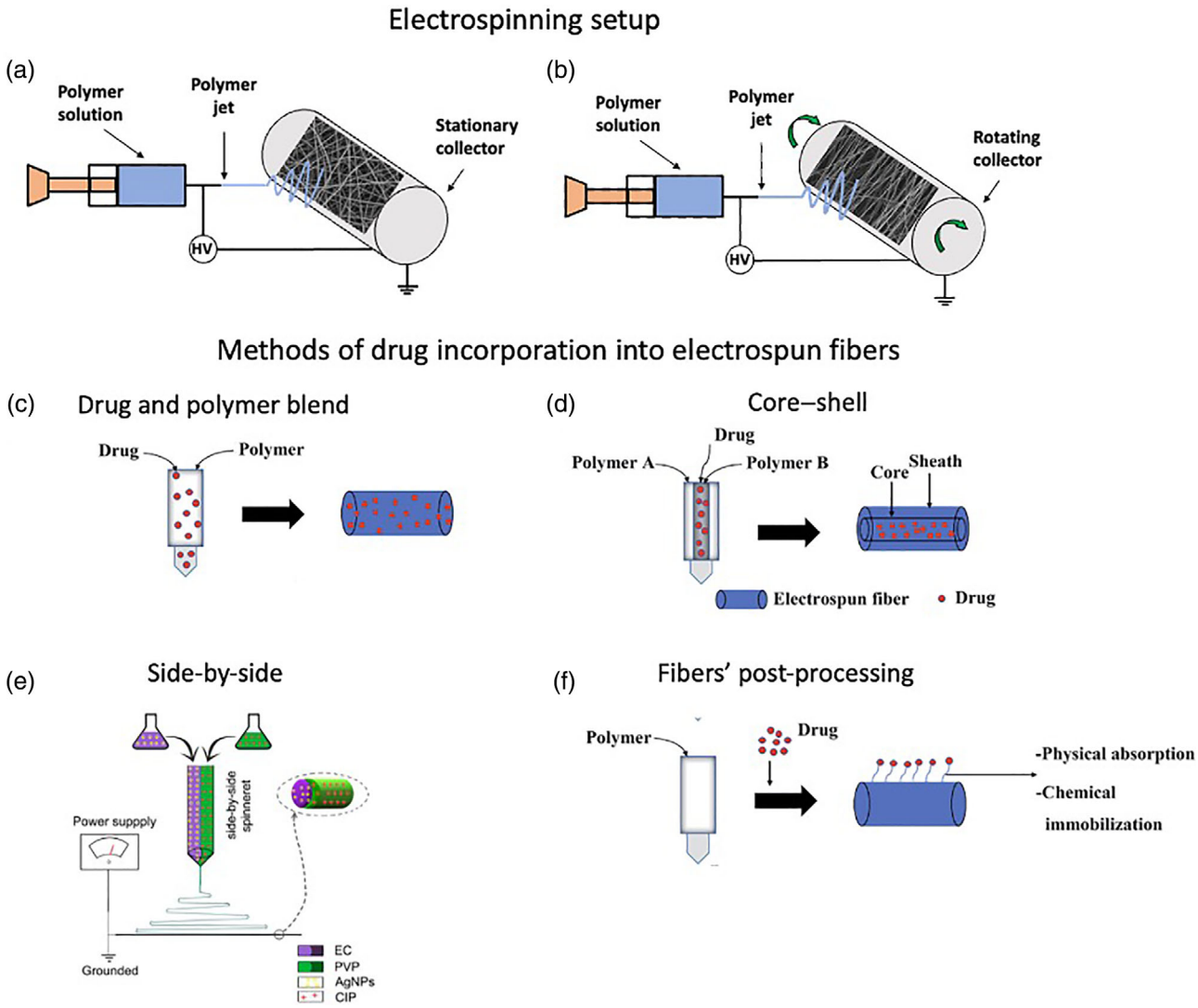

FIGURE 4 Electrospinning setup consisting of a syringe filled with polymer solution, stainless needle, and grounded collector: (a) stationary to obtain random fibers, and (b) rotating for aligned fibers. Schematics of drug incorporation into electrospun fibers: (c) polymer and drug blend in a solution, (d) core–shell fibers, where a drug can be loaded in both the core and shell into a coaxial needle. Reproduced with permission from Y. Sun et al. (2019), (e) side-by-side electrospinning, where a drug can be loaded into one or two sides of a divided needle. Reproduced with permission from J. Yang, Wang, et al. (2020), (f) physical absorption or chemical immobilization of a drug on the fiber surface. Reproduced with permission from Y. Sun et al. (2019)

Khalf & Madihally, 2017), obtaining porous membranes with random or oriented fibers (Z. Yang et al., 2010). Aligned fibers are obtained when deposited on the fast rotating collector (see Figure 4b; Kiselev & Rosell-Llompart, 2012; Truong et al., 2010). High humidity during electrospinning leads to a disturbed solvent evaporation and porous fiber formation (Szewczyk & Stachewicz, 2020). Fiber morphology depends on electrospinning parameters and polymer and solvent selection (Koski et al., 2004; Szewczyk, Ura, et al., 2019). The fiber size can be decreased as the distance between needle and collector increases (Al-Hazeem, 2020). Moreover, the flow rate of the polymer solution affects fiber diameter, while reduced smaller fibers are obtained (Zargham et al., 2012). The surface chemistry of fibers can be changed by applying a positive or negative voltage polarity (Stachewicz et al., 2012; Szewczyk et al., 2020). Voltage polarity plays an important role in the dynamics of the electrospinning process (Ura & Stachewicz, 2022). Also, as the voltage increases, the fibers formed have smaller diameters (Zanto et al., 2011). Generally speaking, manufactured structures have small diameters ranging from hundreds of nanometers to a few micrometers (Fridrikh et al., 2003; Ura et al., 2019; Z. Wang et al., 2017; see Figure 5). The higher the molecular weight of a polymer, the larger the fiber diameter, for the same polymer (Krysiak, Kaniuk, et al., 2020). Both natural and synthetic polymers can be used for electrospinning (Zahedi

et al., 2010). Also, hydrophilic, hydrophobic membranes (C. H. Kim et al., 2005) or their combination can be produced via electrospinning (Knapczyk-Korczak, Ura, et al., 2020; Krysiak, Gawlik, et al., 2020). The mechanical properties of electrospun mats are mostly related to the fiber diameter, thus they can be adjusted depending on the requirements (Rashid et al., 2021). Electrospun fibers are used in piezoelectric nanogenerators (Szewczyk et al., 2020), smart textiles (Busolo et al., 2019), systems for water harvesting (Knapczyk-Korczak et al., 2021; Knapczyk-Korczak, Szewczyk, et al., 2020) and purification from oil (Brown & Bhushan, 2016; Jiang et al., 2022; F. Li, Bhushan, et al., 2019), or systems for separation of antibiotics (K. Zhao et al., 2021). Due to the possibility of using various non-toxic, biodegradable polymers for electrospinning, this method makes it possible to use polymer fibers for food packaging (H. Huang et al., 2022; Razavizadeh & Niazmand, 2020; C. Zhang et al., 2019) and tissue engineering purposes (Angel et al., 2022; Sell et al., 2010; X. Wang et al., 2013). In particular, fibrous membranes are commonly used for wound healing (D. W. C. Chen et al., 2012; H. Li, Zhang, et al., 2019; J. Wang & Windbergs, 2017; J. Yang, Wang, et al., 2020), as they are highly permeable and their structural properties aid in the skin regeneration processes (Kataria et al., 2014; Naseri et al., 2014; Shi et al., 2013; R. Xu et al., 2016). Electrospun fibers create 3D, interconnected porous structures that mimic an extracellular matrix (Soliman et al., 2011; Z. Wang et al., 2014), resulting in their excellent regeneration properties. Furthermore, fibers can be used as a drug delivery system (El-Newehy et al., 2012; Kyzioł et al., 2017; Shoba et al., 2014), thanks to their high loading capacity (Vatankhah, 2018). Treatment substances and drugs can be incorporated into the fiber membrane (Mustfa et al., 2021) by blend electrospinning, covalent immobilization (Feng et al., 2019; Nada et al., 2016), physical adsorption, or coaxial or side-by-side electrospinning (Z. Sun et al., 2003; Zare et al., 2021; see Figure 4c–f). Depending on the method chosen for incorporation of the medicine into the fibers and the different materials selected to manufacture them, the drug release rate can be controlled, and consequently, fibrous drug delivery systems are used for various applications (Schneider et al., 2018; Wu et al., 2020). In addition, post-processing steps on fibers and membranes also make it possible to incorporate medical substances or drugs (Paquin et al., 2015; Teixeira et al., 2020). In short, electrospinning is a beneficial method for the production of porous membranes that can be successfully used as patches.

5.1 | Drug delivery systems obtained via various types of electrospinning

Electrospun fibers are used as drug delivery systems because their release properties can be conveniently adjusted. Many drawbacks of medicine release kinetics can be overcome when loaded into electrospun meshes. For instance, poorly water-soluble drugs cause difficulties when used in drug delivery systems. But when they are encapsulated within electrospun fibers, their availability for aqueous media increases. This approach is used in amorphous solid dispersion materials, where the liquid carrying the drug is solidified by the applied energy. Electrospinning provides fast solvent evaporation and fiber solidification, thus, drug mobility within fibers is reduced. Drug molecules are homogenously "frozen" within polymer fibers and there is little possibility for their crystallization (Yu et al., 2018). In other words, drug dissolution and solidification can provide changes in the drug's crystal structure, leading to its amorphization, and thus enhance dissolution (Hemati Azandaryani et al., 2018; Potrč et al., 2015; Siafaka et al., 2016). The release from nanomaterials loaded with drugs can be controlled by the polymer response to environmental factors such as pH (Okuda et al., 2010; Schneider et al., 2018; Schoeller et al., 2021), oxidative stress, or temperature (X. Lin et al., 2013; Ziaee et al., 2016), and also to issues generated externally: magnetic field, light, or ultrasound (Pillai &

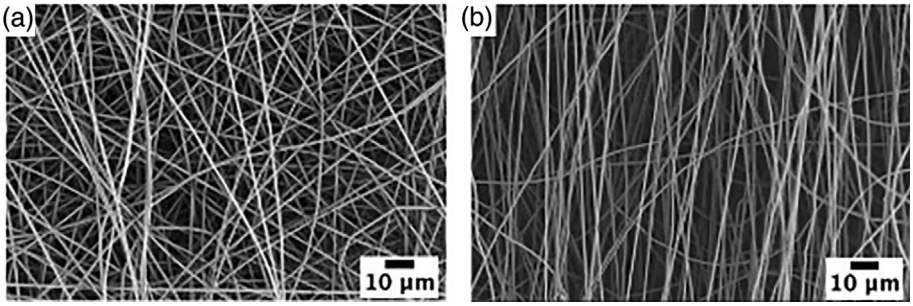

FIGURE 5 Scanning electron microscope (SEM) micrographs of (a) random, and (b) aligned poly(vinyl butyral-*co*-vinyl alcohol-*co*-vinyl acetate) (PVB) fibers

Panchagnula, 2001). These properties promote the use of electrospun fibers as a drug delivery system that is tunable via external factors (X. Zhao et al., 2015). Different approaches are related to drug release times and amounts, which can be controlled by manufacturing techniques. The easiest way to incorporate drugs into fibers is by blending the medicine with a polymer solution before electrospinning (Figure 4c). Another method is coaxial or side-by-side electrospinning (Zheng et al., 2021), when a drug can be dissolved in its solvent or in a polymer solution (Figure 4d,e). Active agents can be incorporated post-processing by physical absorption to create the drug delivery system (Figure 4f). Electrospraying is an alternative approach for depositing medicine on the electrospun membrane. In the following sections, blend, coaxial and side-by-side electrospinning are described within the mentioned processing methods and post-processing steps.

5.1.1 | Blend electrospinning

Blend electrospinning is one of the methods most often used to incorporate drugs into a polymer matrix (Buzgo et al., 2018). An active molecule is added to the polymer solution before electrospinning and then fibers are produced (see Figure 4c). Cellulose acetate (CA) fiber mats with incorporated retin-A and vitamin E (VE) have been reported to be used as a dermal and transdermal drug delivery system. Lipid soluble substances (vitamins) were added to the polymer solution before electrospinning. The release was examined in vitro and was compared with cellulose solution-cast films. Fibrous systems made possible a slower, more even release of retin-A and VE, compared with the films (Taepaiboon et al., 2007). A water-soluble derivative of VE was combined with silk fibroin (SF) for fiber fabrication. The beneficial effects of both VE and SF on the skin are well known. They stabilize the skin barrier, alleviate atopic skin, and reduce scarring (Sheng et al., 2013). Vitamin B_{12} was dissolved in a hydrophobic polycaprolactone (PCL) solution and electrospun to produce fibers which underwent plasma treatment post-production to obtain hydrophilic fibers. This research was conducted to verify the difference in the water-soluble vitamin release profile of electrospun mats. Vitamin release from hydrophobic fibers is slower than from hydrophilic ones, thus suggesting that an active compound release could be manipulated by the wetting properties of a material (Madhaiyan et al., 2013). Electrospun fiber mats could be used as an alternative facial mask; for this purpose polyvinyl alcohol (PVA) was mixed with randomly methylated β-cyclodextrins, ascorbic acid, retinoic acid, collagen, and gold to manufacture nanofibers via electrospinning. The material was delivered to the skin in the dry form and wetted with water once on the skin. The advantage over commercially used facial masks is an increased stability of the incorporated active substances. In addition, the unique characteristic of electrospun mats, such as their high surface area-to-volume ratio, also make this an advantageous material (Fathi-Azarbayjani et al., 2010). Layered systems made of PCL/shellac/PCL electrospun fibers were reported to be a mechanically strong material with a slow drug release profile, which is ideal for overnight skin care products. Salicylic acid was added to both PCL and shellac solutions prior to electrospinning. Different types of fibers were overlaid layer by layer to obtain PCL/shellac/PCL membranes. The drug release process took from 8 to 10 h to obtain a 70% cumulative release of salicylic acid, thus making it usable for overnight products (Ma et al., 2018). Another possible application of electrospun fibers is a long-acting contraceptive patch. PCL was mixed with levonorgestrel and then electrospun to fabricate microfiber mats which were homogenously loaded with a drug. Both the lack of chemical interactions between PCL and the drug and the uniformity of the levonorgestrel incorporation ensure a steady release rate. Moreover, ex vivo skin studies showed that a 1 cm^2 fibrous mat provides a daily dose of human contraception for 5 days (Mofidfar & Prausnitz, 2019). PCL was also blended with tretinoin and used for acne treatment in the form of topically applied substances. Nanofibers were produced via electrospinning, resulting in enhanced stability and sustained drug release (Khoshbakht et al., 2020). Transdermal patches made of CA and poly (vinyl pyrrolidone) (CA/PVP) in the form of nanofibers and cast membranes were loaded with ibuprofen to compare their drug release. Both in vitro and ex vivo (using porcine skin) studies showed the advantage of electrospun fibers over cast membranes in obtaining a faster drug release and efficient permeation through the skin (Shi et al., 2013). Propolis, a natural substance produced by bees, boasts some anti-inflammatory and antimicrobial properties which can be applied to the biomedical field (Adomavičiūtė et al., 2018). Propolis was blended with polyurethane (PU) and electrospun, producing smooth nanofibers with increased antibacterial activity (J. I. Kim et al., 2014; Razavizadeh & Niazmand, 2020). Anti-inflammatory poly(propylene sulfide) (PPS) nanoparticles were added to poly(ethylene oxide) (PEO) and electrospun to produce patches for skin diseases such as AD and psoriasis. The biocompatibility of the manufactured materials was examined with human dermal fibroblasts. The enzyme-linked immunosorbent assay for tumor necrosis factor confirmed the anti-inflammatory properties of PPS nanoparticles (Willcock et al., 2021). Antibiotic therapies require high

doses, resulting in adverse effects such as instance nephrotoxicity. Drug encapsulation makes it possible to use high concentrations of drugs, thus obtaining a more efficient therapy without side effects. Methicillin-resistant *Staphylococcus aureus* (MRSA) causes skin infections which may be life-threatening. PEO and sodium alginate (ALG) were mixed and electrospun with vancomycin for MRSA treatment. The material produced can be applied directly to the skin for precise drug release, without causing any adverse effects. Cytotoxicity was examined in four different cell lines. In vitro and in vivo antibacterial tests showed the superiority of electrospun fiber over vancomycin solution (Fathi et al., 2020). Non-antibiotic therapies for acne vulgaris, a common chronic inflammatory skin disease, continue to be investigated. Herbal extracts are known to have properties that reduce inflammation by regulating cytokine secretion. PVA and chitosan (CS) were both blended with multiple herbal extracts, with possible synergistic effects, and electrospun. The produced patches were examined for their prospective use as drug delivery systems for acne treatment. The reported results confirmed their in vitro and in vivo antibacterial effect (Tang et al., 2021).

5.1.2 | Coaxial electrospinning

Coaxial nozzles are used for electrospinning core–shell fibers, where drugs can be incorporated into either the core or the shell polymer solution (see Figure 4d). Core–shell structures are used for deliberate drug release, where the pharmaceutical concentration can vary between the core and the shell (H. H. Huang et al., 2009; C. Yang et al., 2016). PCL or poly(D,L)-lactide-*co*-glycolide (PLGA) was electrospun as the shell, while tetracycline hydrochloride (TCH) with the sheath polymer was loaded into the core. Both polymers underwent erosion due to hydrolysis and pore formation, thus creating the pathway for drug diffusion. First the TCH on the core surface and between the core and shell was released as it was available for the buffer. Then the driving force was the TCH concentration gradient. Lastly, the release rate decreased, as the concentration was reduced, and the diffusion pathway increased. The described TCH delivery system presented a sustained release, compared with the typical fiber blend made of the above-mentioned polymer and drug (Maleki et al., 2013, 2014). Exactly 1 and 5 wt% TCH-loaded shell fibers, with a constant drug concentration in the core, were compared. The cumulative burst release reached 44% and 73%, respectively. In this case, the driving force of TCH diffusion was the concentration gradient. When the difference in drug concentration between the release medium and fibers is great, it starts to achieve an equilibrium state, and burst release occurs. When a drug is also incorporated in the shell, however, it creates a protective barrier, because the concentration gradient is smaller (Maleki et al., 2013). In addition to core–shell fibers, tri-layered nanofibers were electrospun (M. Wang, Hou, et al., 2020). In the inner part of the fiber, CA was blended with ketoprofen (KET), then CA was covered with the outermost layer of PVP mixed with KET. Fibers with three different coaxial layers were created. The KET release profiles from the core–shell and tri-layer structure were compared. The only difference between these two-drug delivery systems was CA coating. The role of the CA middle layer was to retard KET diffusion from the core (Y. Yang, Wang, et al., 2020; see Figure 6). Another approach to controlled drug elution is to create thin coatings on the electrospun fiber surfaces. Polymers can be absorbed on the material surface by electrostatic forces, acid–base interactions, and hydrogen bonds. Poly(acrylic acid)

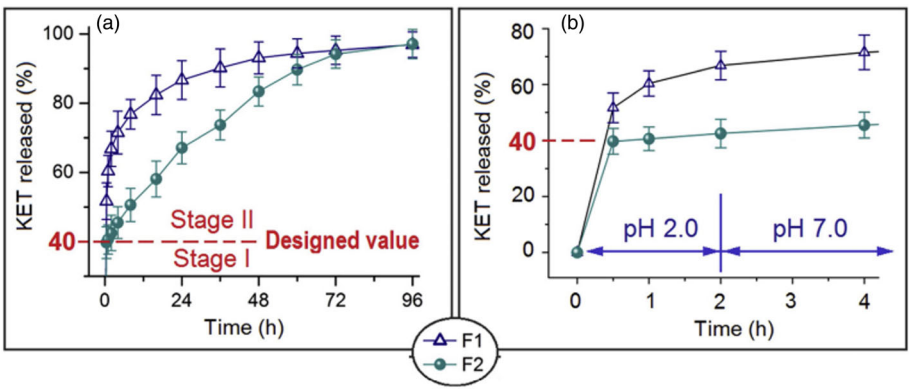

FIGURE 6 Drug release from: F1-core–shell nanofibers where the core was CA + KET and the shell PVP + KET, and F2-tri-layered nanofibers, where the outer layer was PVP + KET, middle CA, and inner CA + KET. (a) Cumulative release of KET over 4 days, (b) 4 h release in the first stage. Reproduced with permission from Y. Yang, Chang, et al. (2020)

(PAA) and poly(allylamine hydrochloride) (PAH) fibers blended with model drug-methylene blue were hydrophobic-coated with perfluorosilane to obtain drug elution in a controlled manner (Chunder et al., 2007). Hydrophobic layers act like the previously described hydrophobic shell, which retards medicine release due to the difficult access of water to the drug delivery system.

5.1.3 | Side-by-side electrospinning

Another approach is creating side-by-side fibers, so-called Janus fibers, with a hydrophilic and a hydrophobic part (see Figure 7; M. Wang, Li, et al., 2020; J. Yang, Wang, et al., 2020). PVP-zein fibers loaded with ferulic acid provide a two-stage release profile. First, the medicine from water-soluble PVP was available due to the polymer dissolution and burst release which occurred, followed by a more sustained one, as the zein did not dissolve in the aqueous medium. Here, the drug is released within polymer erosion in the early stage, and then, by a diffusion mechanism (M. Wang, Li, et al., 2020). This system could be used, when an intensive release is required at the beginning, with a further constant quantity of released medicine. For instance, PVP mixed with ciprofloxacin (CIP) and ethyl cellulose (EC) with silver nanoparticles (AgNPs) were used for electrospinning side-by-side fibers. A fibrous membrane produced was used for wound healing, where immediate antibacterial treatment is necessary. In the initial stage, CIP was intensively released to inhibit bacteria growth, then followed by a sustained release of AgNPs, which offers a long-term antibacterial protection (J. Yang, Wang, et al., 2020).

5.1.4 | Physical absorption of drug on electrospun fibers

The immobilization of drugs on fibers after electrospinning via absorption prevents active agent degradation, because the contact between solvent and medicine is avoided (Luraghi et al., 2021). Cellulose microfibers were immersed in an ibuprofen solution, and then the fibers were dried. The drug presence was confirmed by Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). A burst release of ibuprofen was observed due to its dissolution from the fibers' surface. Furthermore, it was slightly reduced, as the remaining drug was entrapped in the porous structure of the electrospun membrane. The release time (300 min) was short, compared with the drugs incorporated via blend or coaxial electrospinning (Y. Liu et al., 2017). An ornidazole solution was dropped onto the electrospun PCL membrane. The dressing produced was elastic and easy to handle. Due to PCL biodegradability, the material produced could potentially be used for abdominal adhesion reduction. As previously described, in this case, also, the drug absorbed into the fiber surface was released rapidly (Bölgen et al., 2007). PU was mixed with keratin, and nanofibers were produced via electrospinning. AgNPs were fabricated in situ by immersing the fibrous mesh first in the silver nitrate solution, and then in the ascorbic acid for nanoparticle formation. This dressing had antibacterial properties and

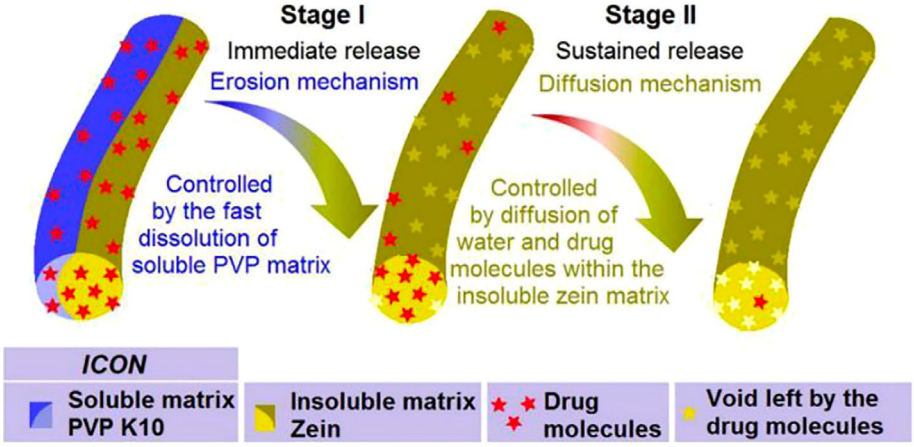

FIGURE 7 Biphasic drug release profile from Janus fibers. First, an erosion mechanism occurred due to PVP dissolution, followed by medicine diffusion from the insoluble part of fibers. Reproduced with permission from M. Wang, Li, et al. (2020)

a potential to repair wounds (Y. Wang et al., 2016). Similarly, SF electrospun nanofibers were coated with AgNPs by dropping the nanoparticle solution onto the membrane, and showed an inhibitory effect against the most common skin bacteria species (Uttayarat et al., 2012). There are a few examples of electrospun fibers used as patches for skin care, except for wound healing dressings. These fibers were loaded with oils blackcurrant seed (Sroczyk et al., 2021), hemp seed (Metwally et al., 2020), borage, black cumin seed, and evening primrose (Krysiak, Kaniuk, et al., 2020; Krysiak, Knapczyk-Korcak, et al., 2020) by simple absorption and used as a moisturizing bandage for dry skin. A nanosized polyamide 6 (PA6) fiber-based dressing was compared with polystyrene (PS) microfibers to verify borage oil delivery to the dry skin. Both materials behaved as slow-release oil reservoirs. Nanofibers, however, showed a more significant skin moisture than PS fibers (Krysiak, Knapczyk-Korcak, et al., 2020). Moreover, PVB patches loaded with evening primrose oil showed a similar behavior. The release of the oil absorbed in the electrospun fibers depends on the fiber diameter (Krysiak et al., 2022).

5.1.5 | Electrospinning fibers combined with drug electrospraying

Apart from simple fiber immersion in the bioactive molecule solution, drug immobilization into the electrospun membrane by electrospraying is also possible (Sridhar et al., 2015). The principle of this technique is similar to electrospinning; however, the solution flowing out from the needle is dispersed in very small droplets. CA nanofibers were covered with the lysosome-antibacterial enzyme by electrospraying, thus creating an antimicrobial dressing (W. Li et al., 2014). A layer-by-layer system was produced with electrospun CA fibers coated with CS via electrospraying, for prospective use as a patch for wounds (W. Li et al., 2012). Different water-soluble polymers were combined with folic acid (FA) for the production of transdermal drug delivery systems and beauty masks. PVA, PVA-gelatin, and PVA-ALG fibers were produced and sprayed with an FA solution. Due to the hydrophilic character of the mentioned polymers and drug, the latter was integrated within fibers rather than deposited onto the fiber surface. Thus an initial burst release was observed, which is beneficial for a rapid action on the skin (Parın et al., 2021). Electrospraying was combined with electrospinning to manufacture core–shell fibers loaded with KET. Since the shell layer was made of electrosprayed hydrophilic microparticles, an initial burst release of drug was observed, followed by sustained medicine dissolution, which was entrapped in the electrospun fibers. This approach demonstrated the possibility to create drug delivery systems with a dual release profile, based on two manufacturing methods (Yu, Williams, et al., 2013).

Table 2 summarizes various electrospinning methods for the design of drug delivery systems. Depending on the needs, a different production approach is applied. The type of incorporated drug or active substance defines the application of a fibrous membrane as a drug delivery material. Blend electrospinning is the most popular method for drug incorporation into fibers (Chou & Woodrow, 2017). Electrospinning parameters have to be adjusted to the one drug–polymer solution, while the release behavior depends on fewer parameters: mostly fiber size, polymer and drug solubility, and concentration (Ziaee et al., 2016). Coaxial and side-by-side electrospinning require the proper selection of solvents if different polymers are used for core and shell or sides for fiber production. Solvents have to be miscible with each other (Yan et al., 2021). Core–shell fibers enable drug entrapment in the inner layer and retard drug release. Moreover, both core–shell and side-by-side electrospinning lead to drug delivery systems with a dual release profile (first a burst followed by a more sustained release) (Chunder et al., 2007; M. Wang, Li, et al., 2020). Medicine deposition on the surface of fibrous membranes by physical absorption or electrospraying causes a fast release, as the drug is not permanently bound to the polymer (Parın et al., 2021; Y. Wang et al., 2016). In summary, by choosing the production procedure for fibrous drug delivery systems, the release behavior can be adjusted to the treatment requirements.

6 | MECHANISM OF DRUG RELEASE FROM FIBERS

Numerical models for drug release kinetics usually take into consideration only one or two variables, thus for more expanded systems experimental results may differ from simplified theoretical approaches. Computational models, however, often provide good estimates of the requirements for drug delivery systems, thus helping to create the most efficient and suitable devices (Siepmann & Siepmann, 2008). The aim is to find the ideal drug concentration to obtain a fair effectiveness with less than the minimum toxic dose. A drug should be beneficial and without side effects. In vitro studies of drug release help to understand and predict in vivo behaviors (Laracuente et al., 2020). Nevertheless, real physiological conditions have not yet been described by numerical models, as many factors have to be taken into

TABLE 2 Summary of the electrospun fibers used as a drug delivery system, including the type of polymer, drug, and the application of the proposed system and references

Type of system	Polymer	Drug/active substance	Application	Reference
Blend	CA	Curcumin	Topical, transdermal, wound healing	Suwantong et al. (2007)
	CA	Rosmarinic acid	Anti-inflammatory	Vatankhah (2018)
	CA	VE/vitamin A	Acne treatment, antioxidant activity	Taepaiboon et al. (2007)
	PVA and CS	Herbal extracts	Topical treatment of acne vulgaris	Tang et al. (2021)
	PVA	Ascorbic acid/ retinoic acid/ collagen/gold	Anti-wrinkle facial mask	Fathi-Azarbayjani et al. (2010)
	PAN	Hydrocortisone	Topical treatment of psoriasis	Hemati Azandaryani et al. (2018)
	Ecovio® (blend of poly(butylene adipate-*co* terephthalate and PLA)	CLOX	Antibacterial topical application	Schneider et al. (2018)
	PCL	Tretinoin and Erythromycin	Topical treatment of acne vulgaris	Khoshbakht et al. (2020)
	PCL	Acyclovir and omega-3 fatty acids	Herpes treatment	Costa et al. (2019)
	PLA	DCF	Topical treatment of actinic keratosis	Piccirillo et al. (2017)
	PEO	PPS nanoparticles	Wound healing and treatment of inflammatory skin disorders	Willcock et al. (2021)
	PEO and ALG	Vancomycin	Antibacterial topical application	Fathi et al. (2020)
	PVP	Aloe vera	Antimicrobial, anti-inflammatory	Aghamohamadi et al. (2019)
	Gelatin	Chloramphenicol	Antibacterial topical application	Nada et al. (2016)
	SF	VE	Skin care	Sheng et al. (2013)
	SF	Manuka honey	Antimicrobial, anti-inflammatory, and antioxidant	X. Yang et al. (2017)
Layer-by-layer	PCL and shellac	Salicylic acid	Skin care	Ma et al. (2018)
	CA	CS	Wound patch	W. Li et al. (2012)
Coaxial	CA	Acyclovir	Antiviral application	M. Wang, Hou, et al. (2020)
	CA	KET	Anti-inflammatory	Yu, Li, et al. (2013)
	CA and PVP	KET	Anti-inflammatory	Y. Yang, Chang, et al. (2020)
	PLGA	Tetracycline hydrochloride	Antibacterial	Maleki et al. (2013)
	PCL	Ampicillin	Antibacterial	Sultanova et al. (2016)

TABLE 2 (Continued)

Type of system	Polymer	Drug/active substance	Application	Reference
	Methacrylic acid/methyl methacrylate copolymer	DCF and lecithin	Anti-inflammatory	C. Yang et al. (2016)
Side-by-side fibers (Janus fibers)	Zein and PVP	Ferulic acid	Skin care	M. Wang, Li, et al. (2020)
	EC and PVP	AgNPs and CIP	Antibacterial	J. Yang, Wang, et al. (2020)
Absorption	PA6, PS	Borage oil	Skin moisture	Krysiak, Knapczyk-Korcak, et al. (2020)
	PCL	Hemp oil	Skin moisture	Metwally et al. (2020)
	PCL	Ornidazole	Antibacterial	Bölgen et al. (2007)
	PVB	Evening primrose oil	Skin moisture	Krysiak, Kaniuk, et al. (2020)
	Polyimide (PI)	Blackcurrant seed oil	Skin moisture	Sroczyk et al. (2021)
	Cellulose	Ibuprofen	Anti-inflammatory	Y. Liu et al. (2017)
	PU and keratin	AgNPs	Antibacterial	Y. Wang et al. (2016)
	SF	AgNPs	Antibacterial	Uttayarat et al. (2012)
	CA	Lysozyme	Antibacterial	W. Li et al. (2014)
	PVA, PVA-gelatin, PVA-ALG	FA	Beauty masks	Parın et al. (2021)

consideration, such as protein binding, active and passive drug uptake into cells, enzymatic degradation, and many others (Fu & Kao, 2010; Siepmann & Siepmann, 2008). The mechanism of drug release profiles relies on the analysis of in vitro results plotted in various kinetics model-dependent methods: zero- or first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell (Dash et al., 2010).

In the zero-order model, the drug is released without disaggregation at a constant rate, and it is described as:

$$Q_t = Q_0 + k \cdot t \tag{1}$$

First-order model

$$Q_t = Q_0 + \left(1 - e^{-k(t-t_o)}\right) \tag{2}$$

Higuchi model

$$Q_t = Q_0 + k \cdot (t - t_0)^{\frac{1}{2}} \tag{3}$$

Hixson–Crowell model

$$(Q_0 - Q_t)^{\frac{1}{3}} = k \cdot t \tag{4}$$

The Korsmeyer–Peppas model assumes that the drug is homogenously distributed in the polymer matrix.

$$Q_t = k \cdot t^n \tag{5}$$

where, Q_0 is the initial drug quantity in the time t_0, Q_t is the drug quantity dissolved in the time t, and K is the release constant.

Zero-order release model is independent of the drug concentration. In the Korsmeyer–Peppas model, n release exponent for cylindrical shape describes the mechanism. For $n < 0.45$ release represents Fickian diffusion, $0.45 < n < 0.89$ non-Fickian. When n exceeds 0.89, matrix dissolution occurs (Amoli-Diva & Pourghazi, 2017; Wu et al., 2020).

Most frequently, a drug release mechanism is quantitatively examined in vitro using the spectrophotometric method. A new drug delivery system must be examined from the standpoint of medicine release behavior. Firstly, it helps predict the doses required for in vivo studies. Also, it makes possible to modify the system produced to obtain the desired release kinetics. In vitro studies are the initial step in material characterization and make it possible to reduce the expenses for in vivo research (Zahedi et al., 2010). Drug release is described as a process in which drug solutes migrate from the polymer matrix to the release medium. It is affected by the physicochemical properties of solutes and polymer, release environment, and structure of the drug delivery material (Fu & Kao, 2010). The understanding of drug release mechanisms is essential for the proper development of controlled release systems. Among many mechanisms, erosion, diffusion, and swelling are the most common for electrospun drug delivery systems (Bruschi, 2015; Grassi & Grassi, 2005; Pillay et al., 2013; see Figure 8). The most common release mechanism is based on diffusion through the water-filled pores; Figure 8d (Fredenberg et al., 2011). Fick's law of diffusion describes solute transport through the polymer matrix. The transport in the polymer matrix can follow both Fickian and non-Fickian diffusion. In the case,

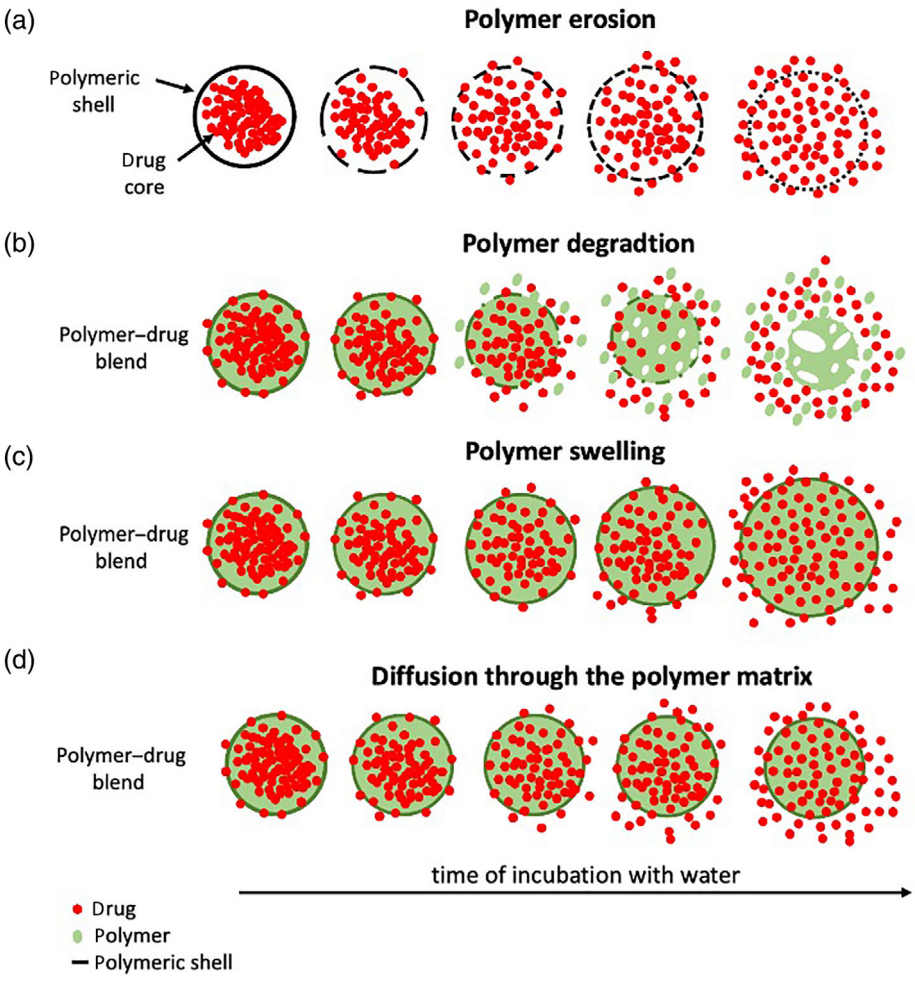

FIGURE 8 Drug release mechanism from electrospun fibers through a polymer (the cross section of fibers): (a) erosion, (b) degradation, (c) swelling, and (d) diffusion through the polymer matrix

when polymer relaxation time (t_r) is much greater than solvent diffusion time (t_g), the transport refers to Fickian diffusion. Non-Fickian model is applied, when t_g value is similar to t_r (Fu & Kao, 2010). The erosion mechanism can be described for fibers electrospun from water-soluble polymers (Figure 8a). Nanofiber membranes, when brought to the aqueous solution, start swelling, and polymeric chains are solvated, resulting in drug dissolution (Jannesari et al., 2011; Schneider et al., 2018).

CA nanofibers were electrospun with KET. At the beginning the drug release was bursting followed by a high cumulative percentage. It was analyzed using the Peppas equation, demonstrating the Fickian diffusion mechanism:

$$Q = 12.5 \cdot t^{0.4} \tag{6}$$

To retard KET diffusion from the CA matrix to the medium, coaxial electrospinning was applied. CA drug-loaded fibers were coated with pure CA. Release kinetics was represented by a zero-order model within a small tailing-off. Furthermore, when the Peppas equation was applied, the release exponent was equal to 0.84, thus suggesting an erosion/diffusion mechanism (Figure 8a,d). This approach shows that a drug release mechanism can be easily modified depending on the requirements, for instance in transdermal and topical delivery systems (Yu, Li, et al., 2013). Also, when comparing drug release kinetics from core–shell and tri-layer systems made of the same polymer and medicine, a different mechanism appeared (see Figure 6). CIP was homogenously distributed in the PLGA-based fibrous meshes, as all delivery system components were dissolved in the same solvent. Drug release was studied in detail and three stages were characterized. Initially, as with most drug-loaded electrospun fibers, the initial burst release was observed in correspondence with the first-order model, due to fiber swelling and polymer hydrophobicity. Within the swelling, fiber diameter increased (Figure 8c), fibers linked together, and the electrospun membrane grew denser. There were fewer release channels, thus slowing down the medicine release. At this stage, as the sustained release is independent of concentration, a zero-order model could be applied. Lastly, the polymer matrix became degraded, and the large release was characterized as Higuchi. Moreover, the drug release mechanism from the complex delivery system made of two polymers is divided into different stages. This makes it possible to adjust the release duration and the dose of medicine. Also, complex drug release systems described by the one mechanism may be incorrect: in these cases the Peppas equation should be applied (Wu et al., 2020). PVA was blended with poly(vinyl acetate) (PVAc) and loaded with 5% or 10% CIP. The high initial drug release (up to 72 h) characteristic was defined by the Higuchi model, where the medicine was diffused from the fiber surfaces. The later stage of drug release can be ascribed to the Hixson–Crowell model, due to the erosion of PVAc (Jannesari et al., 2011). PLGA was electrospun on commercially available vascular grafts together with vancomycin. Moreover, its non-topical application showed a difference between in vitro and in vivo drug release: something which should be taken into consideration in all studies on drug delivery materials (K. S. Liu et al., 2015). An antibiotic, cloxacillin benzathine (CLOX), was mixed with Ecovio® (polymer blend) and nanofibers were electrospun. The drug release profile was determined in vitro in a medium with two different pH values: 7.3—physiological and 5.5—inflammatory. An initial burst release, characteristic for non-Fickian kinetics, was obtained for the higher pH, while for the slightly acidic medium, the first intense release was followed by the more sustained-Fickian diffusion. Post-release SEM images of a nanofiber membrane soaked in physiological solution showed eroded structures with pores and capillaries. This indicates CLOX dissolution and diffusion from the polymer, which enhance the medium penetration into fibers, thus further inducing the linear drug release. On the other hand, an acidic buffer can induce the negative charge density of CLOX and, consequently, the electrostatic interaction between polymer and drug, thus decreasing the release (Schneider et al., 2018). Rosmarinic acid (RosA), an anti-inflammatory and antioxidant substance, was blended with CA, and fibers for chronic pain treatment patches were manufactured via electrospinning. The in vitro release of RosA in a sodium acetate buffer (pH = 5.5) stimulating the skin environment, was elevated (almost total release after 64 h) due to no drug aggregation in the fiber matrix. The patches presented had a semi-crystalline structure, thus showing a limited drug diffusion and little fiber erosion, which were ascribed to a Fickian diffusion (Vatankhah, 2018). Anti-inflammatory and non-steroidal diclofenac (DCF) was combined with glycine (Gly) to obtain a derivative suitable for daily skin treatments. This synthesized drug (DCF-Gly) has an acidic form, and is characterized by low solubility in water and high hydrophobicity, compared with pure DCF. A hydrophobic poly-L-lactide (PLA) was mixed with DCF-Gly and electrospun to create transdermal drug delivery systems. The drug release profile was ascribed to the Fickian diffusion, as both the active agent and the polymer have a hydrophobic character (Piccirillo et al., 2017).

7 | FACTORS AFFECTING DRUG RELEASE

Drug release profiles depend on the chemical and physical factors of a drug delivery system. In particular: hydrophobicity, molecular weight (Huma et al., 2013; Tallury et al., 2008), and crystallinity of the polymer and drug. Also, the degradation rate of a polymer, drug concentration, and structure of electrospun membranes affect the drug release profile (Cui et al., 2006; Demirci et al., 2014; L. Liu et al., 2016). The pH of pathological tissue can modulate the release mechanism by drug solubility (C. Yang et al., 2016; X. Zhao et al., 2015), polymer–drug interactions, and different effectiveness of water penetration into the fibrous membrane. Variable skin problems and diseases require different drug release profiles. Bacterial infections require an initial burst in drug release to quickly inhibit bacteria proliferation and then a sustained release to prolong treatment (Jannesari et al., 2011). A burst medicine release can have both a desirable and undesirable effect at the same time. In particular, it can take a drug to its toxic level without being sufficiently metabolized, and thus be wasted. On the other hand, a burst release either contributes to the immediate bacterial growth inhibition or kills the pain quickly (X. Huang & Brazel, 2001). All parameters affecting the drug release from electrospun fibers are summarized in Table 3 and are also described in more detail in the sections below.

7.1 | Polymer properties

The selection of polymers is crucial when designing a drug delivery system, as they make it possible to determine the chemical, mechanical, biological, and surface properties of the drug-releasing material for a predictable release. Hydrophilicity influences the permeability, water sorption capacity, and degradability of materials and, consequently, the release mechanism. Water-soluble polymers are characterized by an initial burst drug release (M. Zhang et al., 2016). Furthermore, hydrophilic polymer carriers used as the shell in core–shell systems lead to an initial intensive release. However, blending with a hydrophobic polymer or crosslinking such a material makes it possible to control degradability, due to the reduced drug diffusion rate through fibers (El-Newehy et al., 2012; Kyzioł et al., 2017; Moreno et al., 2011). Furthermore, the molecular weight of a polymer and its solubility significantly affect drug delivery kinetics (Miyajima et al., 1997; Pillai & Panchagnula, 2001). Drug release increases as the molecular weight decreases, while comparing the same polymer. The chain entanglement is lower and the diffusion of drug molecules through the

TABLE 3 Parameters affecting drug transport in delivery systems

Drug/ polymer	Parameter	References
Polymer	Hydrophobicity/hydrophilicity	Amoli-Diva and Pourghazi (2017); Huma et al. (2013); Jannesari et al. (2011); Maleki et al. (2014); Pillai and Panchagnula (2001); Siepmann and Siepmann (2008); Wu et al. (2020)
	Molecular weight, copolymer ratio	Jeong et al. (2003); Miyajima et al. (1997); Sung et al. (1998)
	Form (amorphous, crystalline)	Jeong et al. (2003); Kamath et al. (2020); Karavelidis et al. (2011); Miyajima et al. (1998); Sackett and Narasimhan (2011); Vollrath et al. (2021); Zamani et al. (2010)
Polymer and drug	Chemical reactions/ physical interaction of polymer, drug, and release medium	Fredenberg et al. (2011); Göpferich (1996); Kamath et al. (2020); Karavelidis et al. (2011); Klose et al. (2008); Y. Yang et al. (2008)
Drug	Hydrophobicity/Hydrophilicity	Karavelidis et al. (2011); Sung et al. (1998)
	Molecular weight	X. Huang and Brazel (2001); Naik et al. (2000); Potrč et al. (2015)
	Form (amorphous, crystalline)	Natu et al. (2010)
	Concentration	X. Chen et al. (2009); H. H. Huang et al. (2009); Maleki et al. (2013)
	Distribution in the polymer matrix	Fredenberg et al. (2011); X. Huang and Brazel (2001); Maleki et al. (2013)
Release medium	pH, ionic strength, LCST	Amoli-Diva and Pourghazi (2017); Demirci et al. (2014); Göpferich (1996); X. Huang and Brazel (2001); L. Liu et al. (2016); Miyajima et al. (1998); C. Yang et al. (2016); Z. Zhang et al. (2020); Ziaee et al. (2016) Nakielski et al. (2020)

polymer matrix is simplified. Copolymers made of hydrophilic and hydrophobic monomers can be applied for a controlled drug delivery. The changing ratio between monomers affects polymer properties, resulting in different drug release mechanisms (X. Huang & Brazel, 2001; Sung et al., 1998; Wu et al., 2020). Also, the blending of two polymers, hydrophilic and hydrophobic in various proportions, affects release kinetics. A fibrous drug delivery system made of PCL and PEO showed a significantly faster medicine release, when the hydrophilic PEO was the majority blend component (Pillay et al., 2013). Huma et al. suggested that poly(*N*-vinyl pyrrolidone-*co*-*n*-hexyl methacrylate) loaded with dexamethasone could have diverse release mechanisms, when changing the monomer ratio and molecular weight (Huma et al., 2013; Natu et al., 2010). Polymer crystallinity significantly affects the delivery of the incorporated drug. The molecular mobility of polymer chains is reduced in the crystalline part of the chain, thus retarding degradation and causing a slow drug release. The arranged chains (crystallites) create a barrier against aqueous medium penetration (Frank et al., 2005; Kamath et al., 2020). Furthermore, amorphous polymers are used for enhancing the dissolution of insoluble drugs (Vollrath et al., 2021). Some research, however, has reported that high crystallinity causes a microchannel development in the polymer matrix, thus enlarging the surface area of the polymer matrix and creating an additional pathway for drug release (Karavelidis et al., 2011). Semi-crystalline materials are characterized by an initial burst release as the medicine located on the fiber surface is immediately dissolved. Additionally, polymer bulk degradation is retarded by limited water access to the semi-crystalline regions. Polymer degradation may help with drug release in such a case (Natu et al., 2010). Thus polymer degradability has a huge impact on drug release kinetics (Klose et al., 2008). Application of a biodegradable polymer on electrospun fibers or coaxial electrospinning resulting in core–shell fibers can prevent an initial burst effect (Cui et al., 2006; Z. M. Huang et al., 2006; Maleki et al., 2014; Y. Yang et al., 2008; M. Zhang et al., 2016). Biodegradable PLGA fibers were loaded with vancomycin for a slow and sustained release, which took more than 30 days both in vitro and in vivo. The release rate was related to the polymer degradation, which is reported to take approximately 2 months (K. S. Liu et al., 2015).

Thermo-sensitive polymeric drug carriers can be applied for a deliberate pharmaceutical release profile. Poly(*N*-vinylcaprolactam-*co*-methacrylic acid) (PNVCL-*co*-MAA) has different properties with regard to low critical solution temperature (LCST). Therefore, it was electrospun within captopril or KET to create a thermo-sensitive drug carrier. Below LCST (33°C), the components of a mixture are miscible for all compositions and PNVCL-*co*-MAA can easily dissolve in water. Furthermore, LCST is a critical value for a drug release profile. At 20°C, that is, below LCST, both captopril and KET loaded in the PNVCL-*co*-MAA electrospun fibers had an initial burst release-Fickian mechanism. On the other hand, at 40°C, when the temperature exceeded LCST, a non-Fickian behavior was observed and the drug dissolved and diffused slowly (L. Liu et al., 2016). The chemical properties of thermo-responsive poly(*N*-isopropylacrylamide) (PNIPAAm) blended with PU depend on temperature. The material's character changes from hydrophilic to hydrophobic when the temperature exceeds the LCST value. Consequently, drug release was significantly more effective in the case of hydrophilic materials (below LCST), as the water can easily diffuse into fibers and dissolve the drug (X. Lin et al., 2013). Also, PNIPAAm blended with hydrophobic PCL reduced ibuprofen burst elution in release tests conducted below and above LCST (see Figure 9). PCL was used as a boundary layer and reduced medicine release (Tran et al., 2015). Furthermore, drug release on demand is possible with thermoresponsive polymer. P(NIPAAm-*co*-NIPMAAm) hydrogel containing gold nanorods (AuNRs) was encapsulated between fibrous layers manufactured via electrospinning of poly-L-lactide (PLLA) combined with Rodamine B. Cascade-stimuli drug release was activated by Near-infrared light, which is absorbed by AuRNs and converted to the heat. The hydrogel structure is changed leading to the drug release. Thus thermo-sensitive polymers can be used for controlled and switchable drug delivery systems (Nakielski et al., 2020).

7.2 | Drug properties

The hydrophilicity of drugs plays an important role in the release mechanism (Sung et al., 1998). Water-soluble pharmaceuticals loaded into electrospun fibers are characterized by an initial burst release, as the drug located on the fiber surface can be easily dissolved (L. Liu et al., 2016). Moreover, the high ionic strength of drugs leads to their deposition on the fiber surface (K. Kim et al., 2004). The burst release of low molecular weight medicines is more likely due to their small size and high solubility in aqueous solutions (X. Huang & Brazel, 2001). The form of the medicine determines its location in fibers: a crystalline drug is generally located on the fiber surface, while an amorphous drug enters the fiber structure. Obviously, easily available pharmaceuticals trigger an initial burst release (Natu et al., 2010; Thakur et al., 2008). PCL blended with Lutrol F127 and timolol or acetazolamide had a three-stage release profile. At the

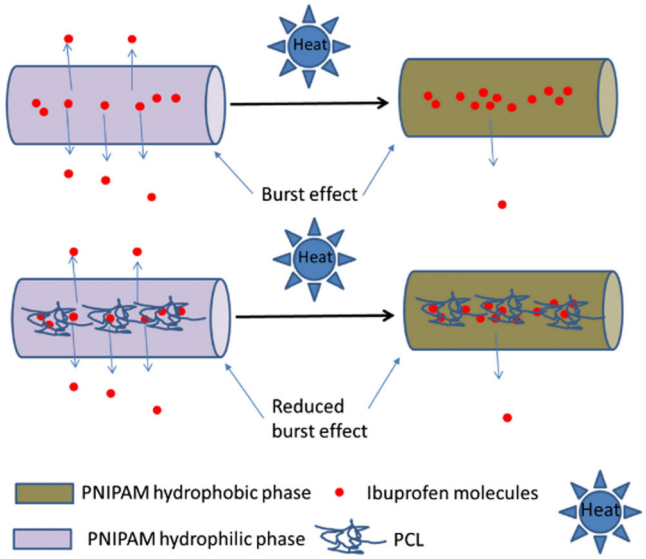

FIGURE 9 Mechanism of reduced burst effects from thermo-sensitive pNIPAM blended with ibuprofen IP and hydrophobic PCL, which prevent the initial fast drug release. Reproduced with permission from Tran et al. (2015)

beginning, a crystalline drug was dissolved, as it was not fully entrapped within the polymer. Next there was an erosion of the hydrophilic Lutrol, followed by degradation of the hydrophobic PCL (Natu et al., 2010). A drug acidic form has a lower water solubility, compared with salt formulas; consequently, its diffusion rate is slower and can be controlled depending on the form of the drug (Piccirillo et al., 2017). Moreover, the drug content in the fibers has an impact on its release. A greater quantity of medicine stimulates a burst release, as the drug crystals were not fully encapsulated within the polymer matrix and were immediately dissolved. Conversely, a smaller quantity of medicine was totally encapsulated in the fibers, thus causing the release to be more sustained. Both drug and polymer characters affect their behavior in the aqueous environment; since they are hydrophobic, medicine release has a low burst and sustained release (Zamani et al., 2010). Therefore, for a sustained release, a lipophilic drug should be loaded into a lipophilic polymer, and for hydrophilic drugs the relationship is the same. Otherwise, the medicine would be dispersed on the fiber surface (Demirci et al., 2014; Zeng et al., 2005). Low medicine solubility in the polymer matrix, together with an excellent water solubility, results in a high percentage of total release. Drug release is strictly correlated with the polymer solubility limits; when the quantity of the drug is above the limit, it forms crystals. On the other hand, when it is below the limit, its form is amorphous. Pharmaceutical release profiles may be designed by their quantity incorporated into the polymer (Z. M. Huang et al., 2006; Natu et al., 2010; Zamani et al., 2010). Furthermore, a large amount of pharmaceuticals added to the polymer decreases its crystalline structure (Chou & Woodrow, 2017). This happens when a drug is homogenously spread in the material matrix and disturbs hydrogen bonding within polymer chains (Vatankhah, 2018). In addition, a low drug concentration loaded into the fibers creates fewer pores within the structure during the initial release, compared with higher concentrations. The porosity created is crucial for any additional medicine dissolution and release (Cui et al., 2006).

7.3 | Fiber properties

Fiber size, morphology, porosity, and geometry affect the drug release behavior (Peng et al., 2008; Pillay et al., 2013). Mechanically stretched electrospun membranes loaded with a drug showed a faster release compared with non-stretched ones. Elongated fibers have thinner diameters, therefore the drug diffusion distance is shorter (Chou & Woodrow, 2017; Yu, Li, et al., 2013). In the presence of smaller fiber diameter and higher surface area, drug release is faster due to the short diffusion pathway. In other words, a medicine encapsulated in thin fibers is more available through the surface (Fathi et al., 2020; Kyzioł et al., 2017; K. S. Liu et al., 2015; Okuda et al., 2010; Pillay et al., 2013; Zamani et al., 2010). In Figure 10, the schematics of drug release from electrospun fibers is illustrated, indicating that the initial burst release can be reduced by entrapping the drug in the core, when the shell of fibers is polymeric.

Increasing fiber size for both core–shell and blend material would reduce the initial drug release and provide a more sustained process. A shell covering the drug in the fibers creates a boundary layer, which slows down drug diffusion (Sultanova et al., 2016). A thinner core part also delays medicine release, when fibers with the same diameter but a different shell size are compared, since the drug has to cover a larger distance to reach the release medium and become dissolved. Interestingly, a medicine addition to the polymeric shell layer may decrease the burst release. The thickness of a membrane can also affect the release kinetics for a single-drug delivery system (Blakney et al., 2014; Cui et al., 2008). The thickness of the electrospun membranes is usually controlled by the electrospinning time; when fiber production is longer, more fibers are deposited. Therefore, metronidazole (MTZ) was blended with PCL, and fibers were manufactured with various electrospinning times. The longer the process, the more fibers were produced, and the more the membrane thickness increased. MTZ release took longer in the case of fibers produced within 8 h, compared with the thinner samples, which are related to the shorter electrospinning time (see Figure 10d). The thicker the fiber mat, the smaller the swelling is, and both the initial and total time for drug release are longer (Okuda et al., 2010). Buffer uptake by the membrane is strictly correlated with wettability. Generally speaking, superhydrophobic materials are perfect for a prolonged and sustained drug elution, as it occurs at the interface between material and water. The high hydrophobicity of electrospun membranes is associated with the air entrapped in the fiber pores which reduce water

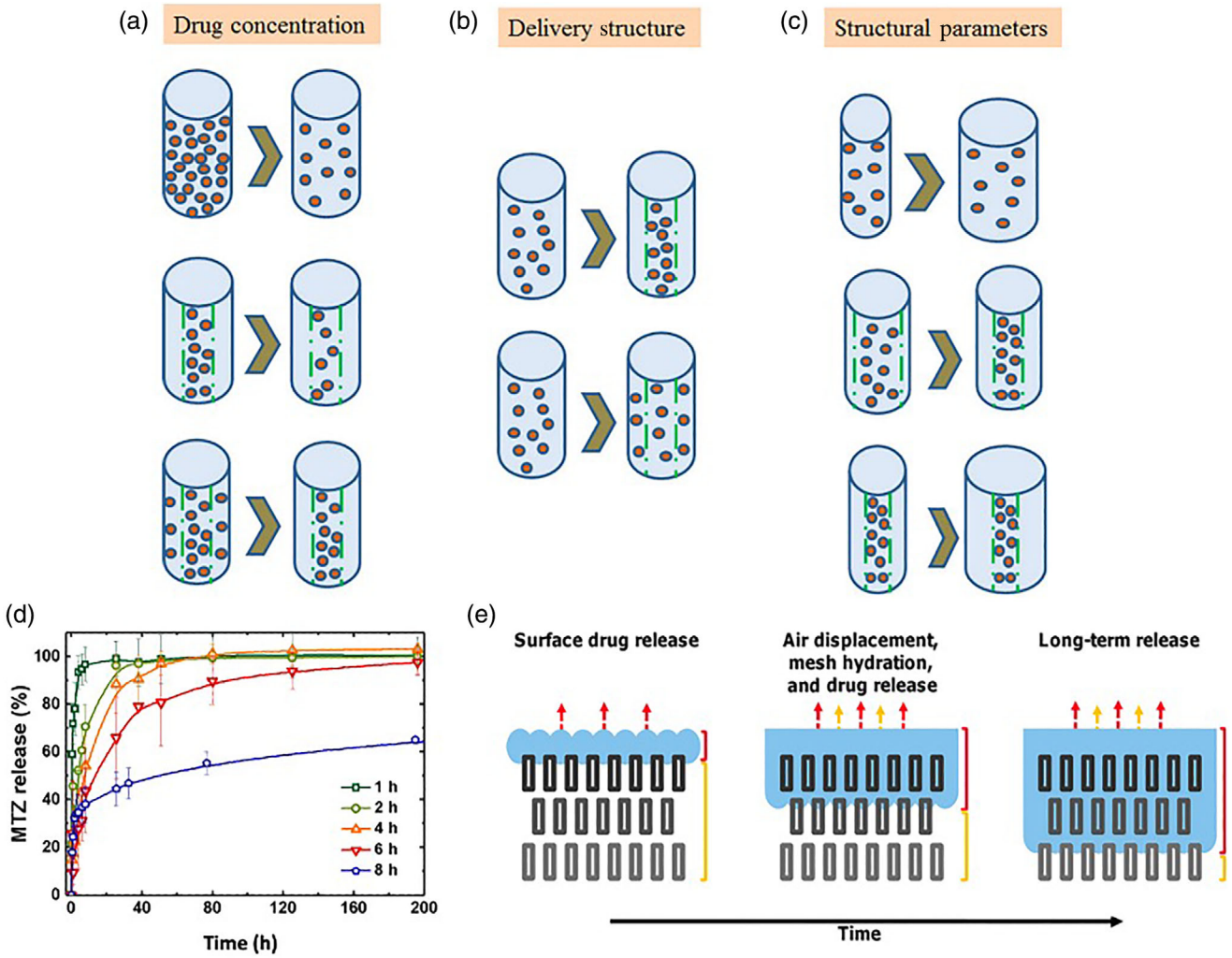

FIGURE 10 Scheme of drug release depending on: (a) drug concentration, (b) fiber structure, and (c) structural parameters for both core–shell and blend drug delivery systems. Reproduced with permission from Maleki et al. (2013). (d) Drug release from nanofibers with different thicknesses related to blend electrospinning time. Reproduced with permission from Zupančič et al. (2018). (e) Mechanism of drug-eluting release from superhydrophobic materials. Water diffuses into the superhydrophobic structure within displacement entrapped air, thus regulating the drug release by controlling the rate at which the internal polymer surface area is exposed to the release medium. Reproduced with permission from Yohe et al. (2012)

contact with their surface (Yohe et al., 2012; see Figure 10e). For the PCL-MTZ blend, the medicine was immediately released after an in vitro buffer uptake. Moreover, the thicker the fibrous membrane, the longer the buffer penetration is, resulting in a prolonged drug release (Zupančič et al., 2018).

8 | EXAMPLES OF ELECTROSPUN SKIN PATCHES

As we mentioned in the introduction, so far only a few designs of electrospun patches have been proposed. PCL was blended with acyclovir and omega 3-fatty acids and electrospun to produce a skin dressing for orofacial herpes treatment (see Figure 11). Fibrous material created an occlusive bandage with antiviral properties and the ability to heal herpes infections. This bandage showed the possibility to overcome many of the limitations existing with commercially available herpes treatments. Electrospun fibers can provide single dosage with controlled release, thus eliminate daily reapplications. The contact between the active agent and epidermis is undisturbed and there was no physiological removal of the formulation. A large fiber surface area leads to a slow acyclovir release in a controlled manner. Furthermore, omega 3-fatty acids were also incorporated into PCL fibers to help the healing process, whereas the only products available on the market are mainly antivirals. Fibrous dressings prevent water evaporation from the skin, while at the same time they are permeable for oxygen and make it possible to drain wound exudates. In particular, the designed material was flexible and durable during application, its mechanical properties being similar to already-available medical textiles (Costa et al., 2019).

A portable electrospinning device was used for the production of antimicrobial bandages. Electrospun fibers made of a PEO solution combined with antibiotics and gold nanoparticles which showed a great potential for killing bacteria. The main advantage of this system is the possibility to place the fiber directly on the affected skin area, thus enabling fiber collection on nonconductive surfaces (Huston et al., 2019).

Furthermore, there are a few examples of the use of electrospun fibers as skin moisturizing patches. The principle is based on using oil-loaded fibrous membranes as slow-release reservoirs applied on the dry skin in order to increase its moisture, as presented by Krysiak, Kaniuk, et al. (2020). Prior to electrospinning, poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV) was blended with evening primrose oil (EPO) and fibers were produced. The patches created with extra EPO drops were applied on the skin and left for 6 h. Skin moisture was measured before and after patch

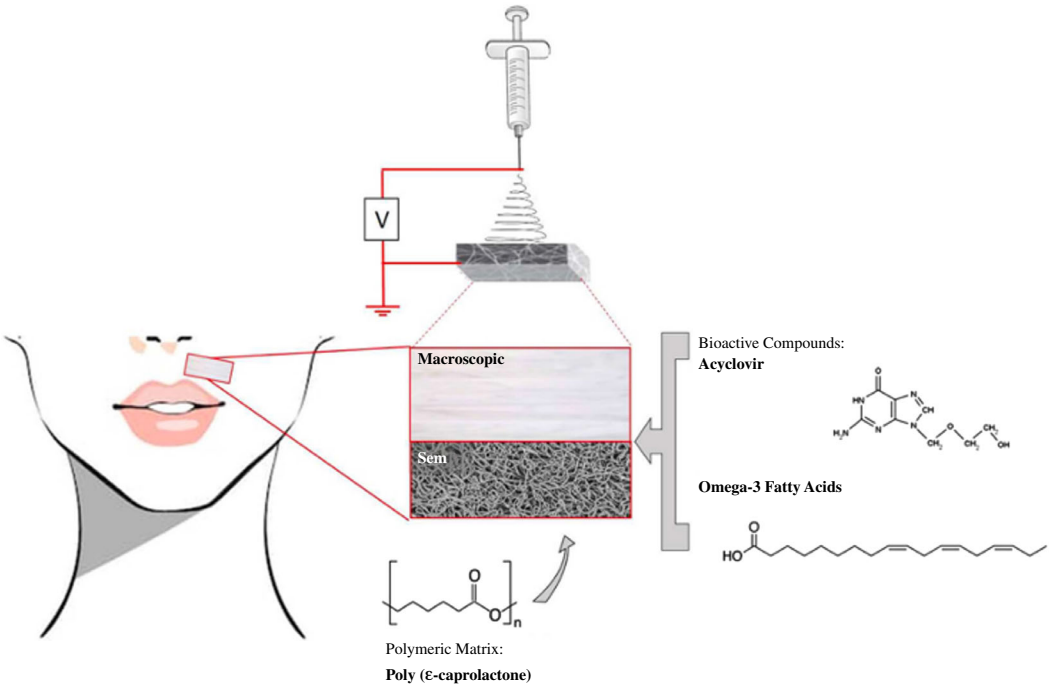

FIGURE 11 Example of a skin dressing for the healing of herpes infections made of PCL electrospun fibers blended with acyclovir and omega-3 fatty acids. Reproduced with permission from Costa et al. (2019)

application. The results obtained were compared with pure PHBV fibers soaked with EPO and dry PHVB fibers used as a control. The skin moisture increased about 20% on patches soaked with oil when a blended (PHVB + EPO) membrane was used, as it was more hydrophilic than a pure PHBV membrane, thus permitting faster oil transport thorough fibrous material to the skin (Kaniuk et al., 2022). Another study comparing hydrophilic and hydrophobic skin patches indicated similar results. PA6-hydrophilic, PS-hydrophobic, and composite membranes based on PS and PA6 fibers were manufactured to be used as skin patches in the sandwich system, that is, with one membrane on the other (see examples of the layer configurations in Figure 12a–e). The patches containing PA6 fibers showed better skin hydration with borage oil, compared with PS-based materials. Apart from hydrophilicity, the structure of the fibrous membrane played an important role. Borage oil incorporated within the PS cotton-like membrane could be released with difficulty (Krysiak, Knapczyk-Korcak, et al., 2020). For electrospun PLC with different fiber arrangements, random and aligned, both porous and smooth fibers were used with hemp oil to improve skin moisturization. Here, PCL patches showed that skin hydration increased by about 20% after a 6 h experiment. The designed sandwich system made of porous random and smooth aligned PCL fibers showed the greatest oil release and best mechanical properties (see example in Figure 12f; Metwally et al., 2020). In addition, the topical electrospun polyimide (PI) patches loaded with blackcurrant seed oil were tested to verify the effective gamma linoleic acid transport and skin hydration. PI fibrous membranes were also soaked in oil, as described in previous studies, and a 6 h skin hydration test was also performed. Remarkably, this study showed how the skin moisture changed every 1 h. After 3 h, skin test results showed the beginning of a plateau level when SC became saturated with blackcurrant seed oil (see Figure 12g,h; Sroczyk et al., 2021). An additional analysis of skin treatment with the electrospun patches was performed with thermal camera images. The skin test with PHBV + EPO fibers soaked in EPO showed an efficient oil release after 3 h. After patches were applied to the skin, their temperature was similar to that of the body, whereas—after 3 h fibrous membrane release—the oil and patch temperature was lower than the skin (Figure 12i; Kaniuk et al., 2022). All the mentioned patches, based on PHBV, PA6, PS, PCL, and PI electrospun fibers loaded with oils, behave as reservoirs with a slow oil release, and therefore can be used as skin moisturizing bandages in AD. Moreover, these materials are flexible, very stretchable, provide thermal insulation, and protect the skin from scratching and external infections.

9 | PROSPECTIVE APPLICATION OF ELECTROSPUN FIBERS AS PATCHES FOR TOPICAL SKIN TREATMENT

Up to now, in the biomedical field, electrospun fibers are mostly used in regenerative medicine (Sell et al., 2007; Szewczyk, Metwally, et al., 2019) as drug delivery systems (X. Lin et al., 2013; L. Liu et al., 2016) and dressings for wound healing (Gizaw et al., 2018; Paquin et al., 2015; Teixeira et al., 2020). The growing number of skin problems has led to a search for new treatment methods and materials. In this review, we showed the properties of electrospun membranes and compared them with the requirements for skin patches or bandages. The high surface area-to-volume ratio (Stachewicz et al., 2015), porosity (Eichhorn & Sampson, 2010), and high loading capacity (Aragón et al., 2019) are significant factors advising the use of electrospun membranes for topical skin treatments. Expect single-nozzle electrospinning, side-by-side and co-axial nozzles are applied for manufacturing modified drug delivery systems (Z. M. Huang et al., 2006; H. Xu et al., 2022). Moreover, by selecting suitable polymers, biocompatible (Y. Wang et al., 2016), and even biodegradable (J. Li et al., 2009) materials can be manufactured. Depending on the type of drug or active agent incorporated into electrospun fibers, the latter can be used for different applications. Both antibiotics (Turan & Guvenilir, 2022) and moisturizing substances (Sroczyk et al., 2021) can be combined within fibers. In AD, the skin is dry with some lesions, usually with bacteria colonies; therefore the possibility of using electrospun fibers as drug delivery systems is promising for AD treatment. Furthermore, electrospun membranes provide an opportunity to control and predict their medicine release (Hu & Cui, 2012); therefore patches can be designed according to AD requirements. Stimuli responsive polymers are excellent materials for drug release on demand activated by external factors, like light or heat (Nakielski et al., 2020). In addition to the beneficial effect of the incorporated substances, the electrospun membrane itself showed many valuable aspects. First, it reduces the water vapor transmission rate in vitro, being permeable to air, thus maintaining a proper level of skin hydration and preventing maceration. Electrospinning can be used to produce side-by-side fibers, which are both hydrophobic and hydrophilic (Knapczyk-Korczak et al., 2021). Their asymmetric wettability makes it possible to transport the fluids in one direction, from the hydrophilic to hydrophobic side. Thus the sweat or possible wound exudates would be removed from the skin surface and prevent fibrous membrane adhesion to the skin (Shao et al., 2021). Moreover, these membranes are easily stretchable, so they

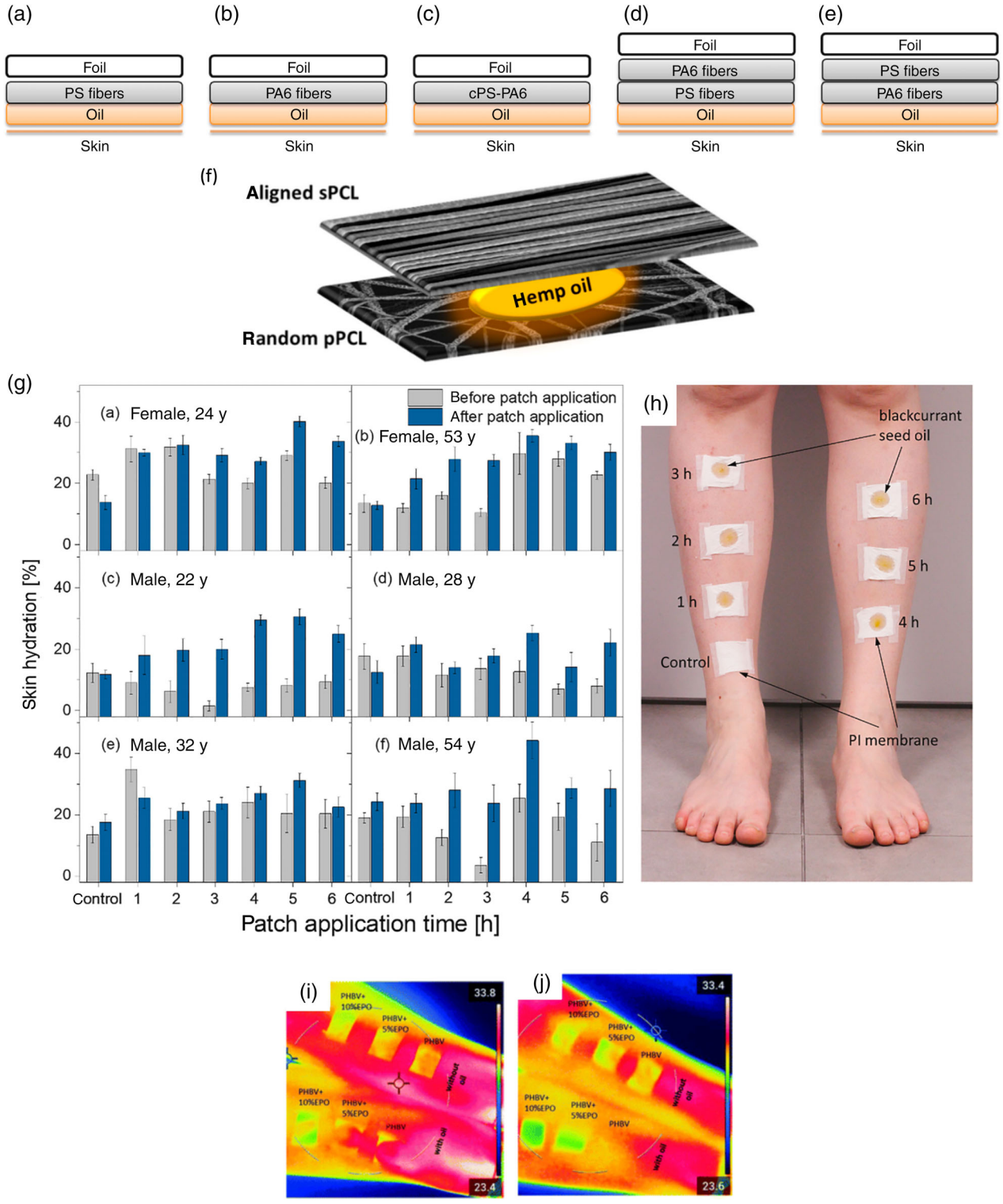

FIGURE 12 Scheme of patches used for skin moisture tests: (a) single PS membrane, (b) single PA6 membrane, (c) composite PS-PA6 membrane; sandwich system made of: (d) PS membrane placed on skin and PA6 membrane on top, (e) PA6 membrane placed on skin and PS membrane on top. Reproduced with permission from Krysiak, Knapczyk-Korcak, et al. (2020). (f) Schematic of the smooth PCL (sPCL) and porous PCL (pPCL) sandwich patches with hemp oil. Reproduced with permission from Metwally et al. (2020). (g) Skin hydration before and after 6 h fibrous patches were soaked in blackcurrant seed oil. (h) Representative image of the experimental arrangements of patches on volunteers. Reproduced with permission from Sroczyk et al. (2021). Heat transmission rates through PHBV, PHBV + 5%EPO, and PHBV + 10%EPO electrospun fibers and samples with an additional EPO: (i) just after patch and oil application, (j) after 3 h of wearing the patch. Reproduced with permission from Kaniuk et al. (2022)

adjust to movement and handling and are comfortable (Krysiak, Kaniuk, et al., 2020; Krysiak, Knapczyk-Korcak, et al., 2020; Metwally et al., 2020; Sroczyk et al., 2021). Currently, AD treatment is focused on topical treatments with lotions, emulsions, or ointments being applied to the skin several times a day (Parekh et al., 2021). The topical drug delivery system based on electrospun fibers is able to provide a sustained release, reducing dose frequency and preventing many side effects.

10 | CONCLUSION

In this review, we showed some widespread skin problems, with a focus on eczema, which are affecting more and more people all over the world. We focused on AD and its topical treatment with electrospun patches. There are numerous requirements for materials to be used for dermal dressings. These patches must be biocompatible, breathable, and reduce TEWL. Besides the material properties themselves, the possibility of drug loading is much appreciated. Electrospun fibers have all the advantages mentioned above, which are widely described in this review. The method for the incorporation of bioactive molecules into fibers determines both the drug release and the treatment effect. Electrospinning provides many opportunities to entrap the drug into the fiber structure and, by changing the polymer or process itself, to control the medicine release. We also underlined the importance of in vitro release studies, as well as characterizing the release models and kinetics which are practical for dose prediction for in vivo tests. Moreover, all the factors affecting the active agent release were correlated and the complexity of designing topical drug delivery patches was emphasized. We showed various examples of electrospun fibrous membrane application in topical and transdermal drug delivery, and also suggested their use for wound healing materials. Lastly, we combined the AD requirements for dressings with electrospun fiber properties to demonstrate the prospect of using these materials for eczema treatment.

AUTHOR CONTRIBUTIONS

Zuzanna J. Krysiak: Conceptualization (lead); validation (equal); visualization (lead); writing – original draft (lead); writing – review and editing (equal). **Urszula Stachewicz:** Conceptualization (supporting); project administration (lead); resources (lead); supervision (equal); validation (equal); visualization (supporting); writing – original draft (supporting); writing – review and editing (equal).

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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