Open Journal of Nano
ISSN: 2147-0081
(2022) 9–2
Review Article

Nano Transdermal Delivery Systems of Herbal Extracts for Dermatological Therapeutics and Skin Care

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Submission Date: 16.05.2024 Acceptation Date: 29.06.2024

Abstract
This article discusses the use of nanotechnology in the development of transdermal delivery systems for herbal extracts for dermatological therapeutics and skin care. Nanotechnology involves manipulating nanoscale materials to create nanoparticles that can penetrate the skin and deliver active ingredients more effectively. Natural products are commonly used in cosmetics because of their therapeutic properties and minimal side effects; however, the safety of nanoparticles in cosmetic products is a concern that requires further research. Chronic and nonhealing wounds pose a significant threat to patients' lives, and there is a pressing need for novel materials and approaches to wound healing. Nanomaterials exhibit unique physicochemical properties owing to their distinct structures, resulting in small size, surface, and macroscopic quantum tunnelling effects, making them ideal for use in wound dressings. Herbal transdermal patches offer advantages such as better patient tolerance, minimal side effects, renewable sources of medication, extensive availability, and cost-effectiveness; however, they also have disadvantages such as slower growth in demand, testing difficulties, and limited availability. This article concludes that by following a regimen that includes both natural ingredients and over-the-counter treatments, consumers can improve their skin health and appearance.

Keywords: herbal extracts, nanotechnology, skin care, transdermal delivery systems

1. Introduction

Nanotechnology is a rapidly growing field in the cosmetics industry that involves manipulating nanoscale materials to create nanoparticles that can penetrate the skin and deliver active ingredients more effectively [1]. Nanotechnology involves studying substances at the molecular and atomic levels, focusing on objects and structures calibrated on a nanometer scale, which is one billionth of a meter (10^{-9} m) [2]. For comparison, the diameter of the influenza virus is 100 nm, whereas that of human hair is approximately 100 µm [3].

Nanotechnology in cosmetic products has led to innovative products with improved performances [4]. Natural products are commonly used in cosmetics because of their therapeutic properties and minimal side effects [5]. Despite this, the safety of nanoparticles in cosmetic products is a concern, and further research is needed to fully understand their impact on human health and the environment [6].

Recently, there has been a significant increase in the prevalence of persistent medical conditions, including vascular dysfunction, obesity, and diabetes, which has led to an increase in the number of individuals afflicted with chronic wounds. It is estimated that patients with diabetes have a 15-25% risk of developing chronic diabetic abscesses [7]. Certainly, some skin conditions that can be transmitted, such as malignant skin tumours, sporotrichosis, autoimmune skin diseases, dermatomyositis, and physical skin diseases, can render individuals susceptible to persistent sore [8].

Chronic and nonhealing wounds expose hypodermic tissue to the external environment for a prolonged duration, resulting in an increased risk of bleeding and osteomyelitis in patients, particularly those in severe conditions. Such conditions pose a significant threat to patients' lives. In addition, the recurrence of chronic infections diminishes patients' quality of life, heightens their

DOI: 10.56171/ojn.1485463

financial burden, and triggers severe mental and psychosocial complications. The complexity of wound healing presents a continuous challenge for clinicians, and there is a pressing need for novel materials and approaches. Considerable advancements in nanotechnology, particularly in nanochemistry and nanomanufacturing, have significantly impacted the pharmaceutical and biotechnology sectors. Nanomaterials, characterized by at least one dimension below 100 nm, exhibit unique physicochemical properties owing to their distinct structures, resulting in small size, surface, and macroscopic quantum tunnelling effects.

Nanomaterials have also been extensively employed in wound healing owing to their superior adsorption capacity, antimicrobial properties, and drug-loading capabilities [9]. Wound dressings act as impermanent skin that alternates and plays an essential role in hemostasis, infection control, and wound closure. Several dressing materials have been investigated for many years. Traditionally, wound dressings such as gauze and bandages have been used to treat skin defects [10]. The development of nanomaterial dressings requires a simulation of the extracellular matrix (ECM) in a wet environment, as well as the inclusion of antimicrobial properties and the promotion of cell proliferation and angiogenesis. The significant demand for these resources in the market has contributed to the growth of nanomaterial dressings [11].

Herbal transdermal patches offer advantages such as better patient tolerance [12], minimal side effects [13], renewable sources of medication[12], extensive availability[14], and cost-effectiveness [15]. Nevertheless, it also has disadvantages such as slower growth in demand, testing difficulties and limited availability, strict manufacturing procedures, and a lack of standardization in ingredients and techniques [16]. The skin is the primary barrier that shields the body from various free radicals [17]. Various sources produce free radicals such as UV rays, dust, chemicals, and air pollution [18].

People of all ages seek premium skincare products for flawless, youthful skin. The quality and density of extracellular matrices and the provision of cells to connective tissues influence the concept of an ideal skin [19]. Skin conditions, such as acne, abnormal pigmentation, and xerosis, can indicate skin pathology [20]. Nutritional deficiencies can cause skin lesions; however, combining cosmetic skin care products and over-the-counter (OTC) treatments can help improve skin health and appearance[21]. By following a regimen that includes both products, consumers can rebuild their skin and achieve a more beautiful complexion [22]. Natural ingredients are substances derived from natural sources, such as plants or minerals, without synthetic or artificial additives, such as coconut oil, shea butter, or lavender essential oil [15]. Incorporating natural ingredients into skin care products improves skin conditions [23]. Nanotechnology is used in various ways in skincare products to provide benefits, such as UV protection [24], anti-ageing effects [25], improved moisturization [26], and wound healing [15].

Nanomaterials are increasingly used in various industries, including cosmetics [27], pharmaceuticals [28], and dermatology [29]. In cosmetics, nanomaterials are used as hair conditioners [30], serums [31], moisturizers [32], and shampoos [33] for damaged hair, skin-lightening creams, and anti-ageing creams [4].

Nanofibrous technology allows for the encapsulation of nanoparticles, which then act as a drug delivery substrate, allowing the active components to reach deeper layers of the skin where they can have the most effect [15]. Therefore, nanofibrous technology is gaining popularity in cosmetics and medicine.

In this review, we examined the recent applications of nanomaterials in skin wound healing, focusing on their potential mechanisms and the various aspects involved. By filling the existing research gap, this study aimed to elucidate the effective utilization of nanotechnology in seamlessly integrating natural ingredients into cosmetic formulations. This study offers novel insights into the application of nanotechnology and presents a fresh perspective on harnessing the potential of natural ingredients in skincare. The findings of this study hold promise for advancing our understanding of

DOI: 10.56171/ojn.1485463

Open Journal of Nano
ISSN: 2147-0081
(2022) 9–2
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how nanotechnology can revolutionize the use of natural ingredients in skincare and pave the way for innovative approaches to cosmetic and pharmaceutical product development **(Fig.1)**.

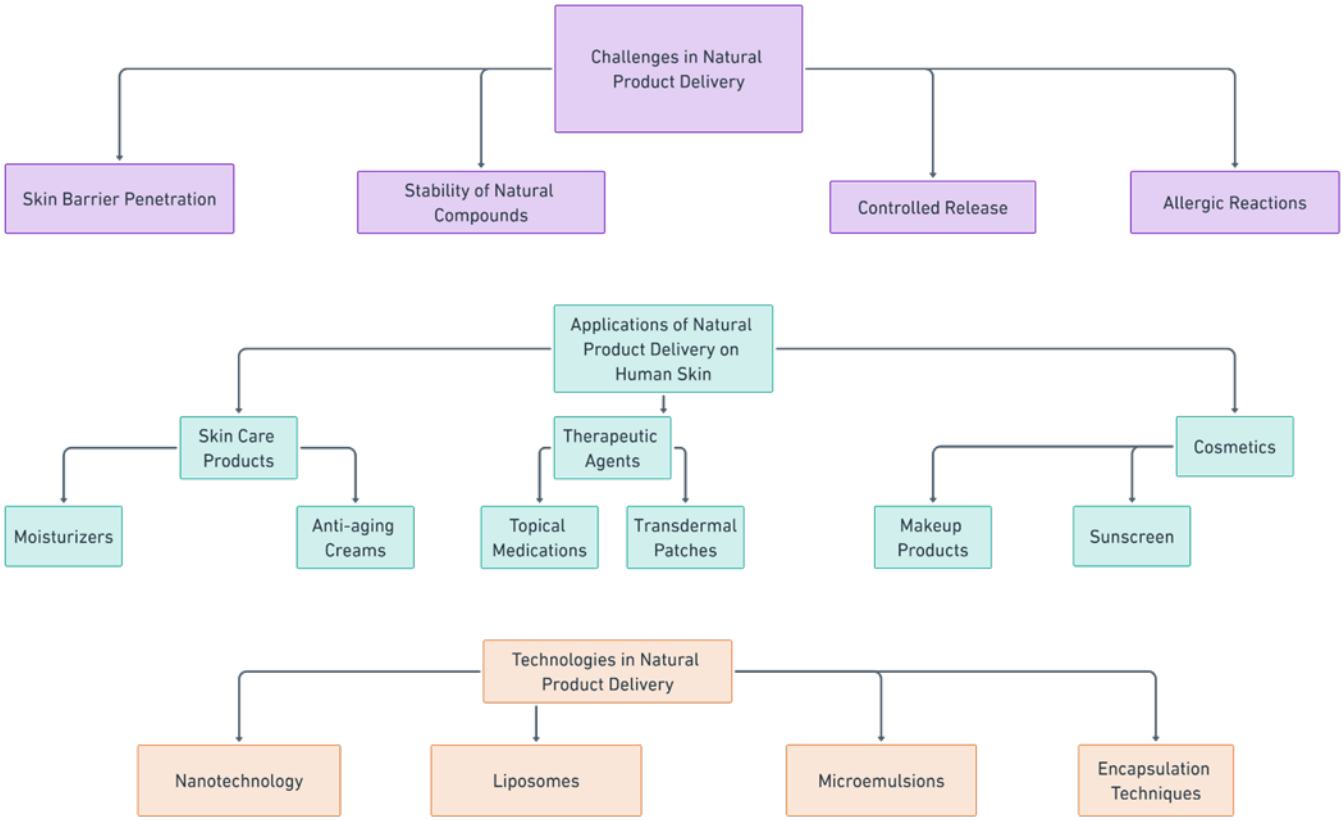

Figure 1. Applications, challenges, and technologies associated with the delivery of natural products to human skin.

2. Transdermal Patches

A transdermal patch is a medical device consisting of an adhesive layer impregnated with a specific medication. This patch is placed on the skin, where it delivers the medication through the skin and into the bloodstream [34]. One advantage of transdermal drug delivery over other routes, such as oral, topical, intravenous, or intramuscular, is that it provides a controlled release of the medication [35]. This is typically achieved through either a porous membrane covering a reservoir of medication or through body heat melting of thin layers of medication embedded in the adhesive **(Fig.2)** [36]. However, the main disadvantage of transdermal delivery systems is that the skin is a highly effective barrier, which limits the types of medications that can be delivered using this method. Only medications with molecules small enough to penetrate the skin can be administered using a transdermal patch [37]. The first prescription patch was approved by the US. In December 1979, the Food and Drug Administration administered scopolamine for motion sickness [36].

Transdermal delivery systems are self-contained and discrete dosage forms that, when applied to the skin, deliver the drug through the pores at a controlled rate to the systemic circulation. These dosage forms maintain drug absorption and concentration within the therapeutic window for an extended period, thereby ensuring that drug levels fall below the minimum effective dose (MED) or exceed the maximum tolerated dose (MTD) [38]. A drug to be used as a model for formulating transdermal drug delivery should acquire several physiochemical properties, such as short half-life and smaller molecular size for easy penetration, small dose, and minimal oral bioavailability. [39].

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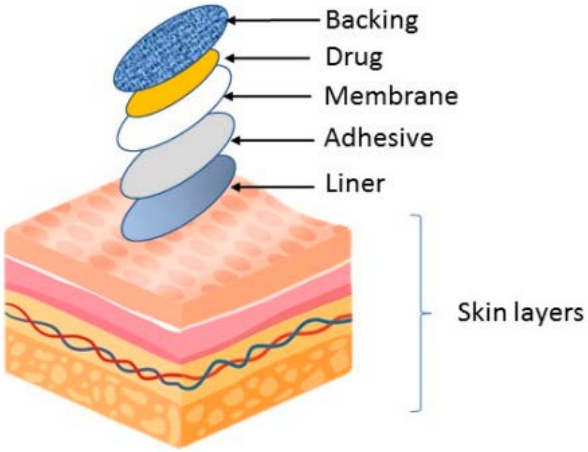

Figure 2. Basic components of a transdermal medical patch [35].

2.1. Types of Transdermal Patches

Transdermal delivery systems are self-contained and discrete dosage forms that, when applied to the skin, deliver the drug through the pores at a controlled rate to the systemic circulation. These dosage forms maintain drug absorption and concentration within the therapeutic window for an extended period, thereby ensuring that drug levels fall below the minimum effective dose (MED) or exceed the maximum tolerated dose (MTD) [38]. A drug to be used as a model for formulating transdermal drug delivery should acquire several physiochemical properties, such as short half-life and smaller molecular size for easy penetration, small dose, and minimal oral bioavailability. [39].

Transportation of active pharmaceutical ingredients across the skin is affected by various factors such as skin permeability, area, and duration of application, as well as the metabolic activity of the skin (i.e., first-pass metabolism) [40]. Every drug has unique properties that can affect transdermal delivery. In order to achieve adequate skin absorption and penetration, the drug should be nonionic and relatively lipophilic to cross the skin barrier [41]. Molecules larger than 500 Da make it difficult to cross the stratum corneum, and ideally, the therapeutic dose of the drug should be less than 10 mg/day [42].

Transdermal patches typically consist of several layers designed to deliver medication through the skin and into the bloodstream [35]. Figure 2 illustrates the basic components of the medicated patch. The specific composition and structure of the patch may vary depending on the drug being delivered and the desired rate of drug release [43].

The outermost layer of the patch, known as the backing layer, protects other layers from external influences. It is commonly composed of flexible waterproof materials, such as polyethene or polypropylene. The adhesive layer was responsible for securely affixing the patch to the skin and ensuring its retention. It is typically comprised of a potent hypoallergenic adhesive that is gentle on the skin. The drug layer contains medication that is delivered through the skin and formulated to release the medication at a consistent rate over a predetermined period. The rate-controlling membrane regulates the release of drugs from the patch and is typically constructed of a semipermeable material that allows the medication to pass through at a controlled rate. The protector and adhesive layer act as barriers for the patch. It is necessary to remove the patch before its application to the skin.

DOI: 10.56171/ojn.1485463

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2.1.1. Single-layer Drug-in-adhesive

The present system incorporated an adhesive or gummy layer that served the dual purpose of securing the transdermal patch onto the porous membrane and facilitating the release and penetration of the drug into the skin. The patch comprises a single-layer film, which houses the active pharmaceutical ingredient (API) along with all other excipients blended within a single layer [44].

2.1.2. Multilayer Drug-in-Adhesive

The Multilayer Drug in the gummy layer functions in a manner similar to that of the single/solo layer patch. However, it employs the unique feature of utilizing multiple layers of adhesive to achieve controlled and predetermined drug release. Specifically, one layer is designed for immediate release, whereas the other layer regulates the controlled and predetermined release of the drug [45]. The Multilayer Drug in Adhesive possesses the ability to accommodate two distinct classes of pharmaceuticals.

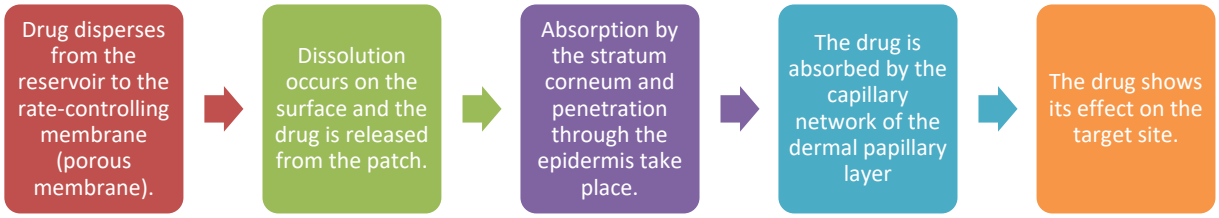
2.1.2.1. Reservoir system: The Reservoir transdermal system incorporates a unique layer specifically designed for the Active Pharmaceutical Ingredient (API). This layer consists of a solution or suspension of the medication in a separate liquid compartment, which is separated from the outer layer by a semipermeable membrane and an adhesive layer. The adhesive layer functions as a continuous coating, establishing a connection between the skin and the release liner [46].

2.1.2.2. Matrix system: The matrix system is characterized by a semi-solid matrix, which incorporates a drug suspension and solution. This matrix is encased in an adhesive layer that affixes the system to the skin and forms a semi-solid matrix [37]. This particular type of system is commonly known as a "monolithic system."

2.1.2.3. Micro-Reservoir System: This system combines reservoir and matrix dispersion technologies. The drug is formulated by suspending drug solids in an aqueous solution of a water-soluble liquid polymer, which is then uniformly dispersed in a lipophilic polymer to generate a vast array of non-leaching microscopic drug reservoirs [47].

3. Mechanism of Actions Transdermal Patches

A transdermal patch serves as the primary means of delivering the drug that it holds in place. Upon application, the adhesive secures the patch on the skin, enabling it to adhere to the surface and facilitate drug release [48,49].



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Open Journal of Nano
ISSN: 2147-0081
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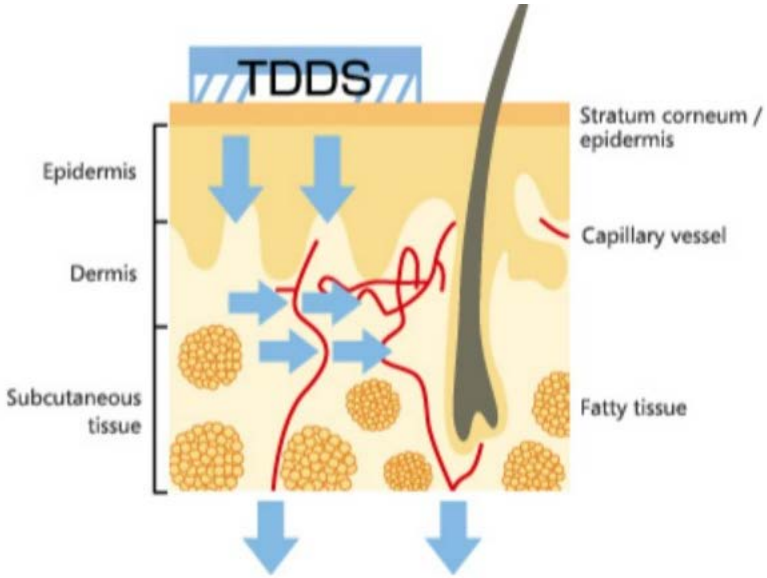

Figure 3. Mechanism of action transdermal patches [50]

Understanding the dynamics of skin permeation is of the utmost importance for the development of effective topical drug delivery (TDD) systems. To evaluate any TDD, assessing the percutaneous absorption of molecules is a vital step, as it pertains to the penetration of substances into the various layers of the skin and their subsequent permeation through the skin into the systemic circulation [51]. Percutaneous absorption of molecules is a multistep process that includes **(Fig.3)** [52]:

i. Penetration: entry of a substance into a specific layer of the skin.
ii. Partitioning: redistribution of the substance from the stratum corneum to the aqueous viable epidermis.
iii. Diffusion: Movement of the substance through the viable epidermis and into the upper dermis.
iv. Permeation: The passage of molecules from one layer to another is distinct in terms of both structure and function from the initial layer.
v. Absorption: uptake of the substance into the systemic circulation.

The release of drugs from the transdermal patches can be evaluated by determining the maximum flux of the drug compound across the skin, which is typically expressed in units of μg/cm²/h (Equation 1). This flux is governed by Fick's law of diffusion, which states that the transport of therapeutic molecules across the skin continues until the concentration gradient no longer exists. Transdermal patches can be classified into two types: those that use a solid polymer as a rate-controlling membrane (reservoir type) and those that use a liquid or gel-based reservoir (matrix type) [53].

$$J = -D\frac{dc}{dl} \quad (1)$$

where J is the molecular flux, D is the diffusion coefficient, L is the cross-sectional thickness of the diffusion, and dc/dt is the concentration gradient. The equation indicates Fick's law of diffusion [53].

3.1. Brief of Skin Structure

The skin is the body's largest and most accessible organ, spanning an area of 1.7 m^2 and accounting for approximately 16% of the average individual's total body mass [53]. The primary role of the skin is to act as a barrier that protects the body against external threats such as microorganisms, penetration of ultraviolet (UV) radiation, chemicals, allergens, and dehydration [54]. The skin can be

DOI: 10.56171/ojn.1485463

Open Journal of Nano
ISSN: 2147-0081
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classified into three primary regions: the outermost layer, the epidermis, which comprises the stratum corneum; the middle layer, the dermis; and the innermost layer, the hypodermis [55–57]. **Figure 4** shows the structure of the skin.

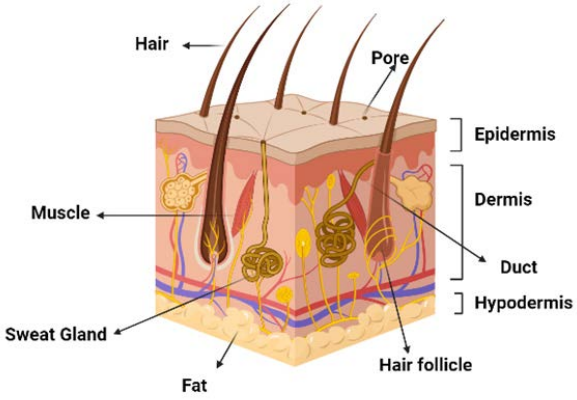

Figure 4. Skin anatomy [58].

3.1.1. Epidermis

The epidermis constitutes the outermost layer of the skin, and its thickness is not uniform, measuring approximately 0.8 millimetres on the palms of the hands and soles of the feet [59]. The epidermis is composed of multiple layers of epithelial cells, with the living tissue below the outermost layer, the stratum corneum, commonly referred to as the epidermal layer [60,61]. The cellular composition of the epidermis primarily comprises keratinocytes, which account for nearly all (95%) of the cells. In addition, other cell types present in the epidermis include melanocytes, Langerhans cells, and Merkel cells [62]. The stratum corneum is the most superficial layer of the stratum corneum [53,63,64]. The stratum corneum is in direct contact with the external environment, and its barrier properties may be partly related to its high density (1.4 g/cm^3 in the dry state) and low hydration level (15%-20%) [53]. The stratum corneum cells are primarily composed of insoluble keratins (70%) and lipids (20%). Water in the stratum corneum is associated with keratin in corneocytes [65].

3.1.2. Dermis

The dermis measures approximately 2-3 millimetres in thickness and is composed of collagenous (70%) and elastin fibres, which endow the skin with strength and flexibility. The presence of blood vessels within the dermis ensures the provision of essential nutrients to both the dermis and epidermis [66].

3.1.3. Hypodermis

The hypodermis, also known as the subcutaneous layer, is the deepest layer of skin and is characterized by a network of fat cells. It serves as the interface between the skin and underlying tissues of the body, such as muscles and bones [67]. The primary functions of the hypodermis include protection against physical impact, insulation against heat, and facilitation of vascular and neural signal transmission. Approximately 50% of the body's fat is stored in hypodermis-resident fat cells, while the remaining predominant cells in this layer include fibroblasts and macrophages [68].

4. Natural Bioactive Ingredients in Transdermal Applications

The absorption of percutaneous drugs or active ingredients is a complex phenomenon that is influenced by several factors, such as molecular size, hydrophile/lipophilic balance, melting point, and water solubility of the drug. Natural product compounds are commonly used in the clinical setting. **Table 1** presents a compilation of scientifically supported active ingredients derived from natural sources, curated for their potential effectiveness in addressing various skin types. Specifically, for individuals with dry skin, the following ingredients are recommended: aloe vera *(Aloe*

DOI: 10.56171/ojn.1485463

barbadensis), chamomile *(Matricaria chamomilla)*, calendula *(Calendula officinalis)*, lavender *(Lavandula angustifolia)*, coconut oil *(Cocos nucifera)*, jojoba oil *(Simmondsia Chinensis)*, shea butter *(Butyrospermum parkii)*, olive oil *(Olea europaea)*, rosehip oil *(Rosa canina)*, and witch hazel *(Hamamelis virginiana)*. These ingredients have been identified for their potential soothing, moisturizing, and hydrating effects, offering a natural approach to alleviate dryness and improve skin health [69]. Furthermore, cosmeceuticals can regulate the distribution of their active ingredients by forming thin films on the skin, facilitating targeted and precise delivery [13]. This controlled release mechanism enables the recommended ingredients for normal, oily, and combination skin types, such as niacinamide, vitamin C, hyaluronic acid, green tea extract, salicylic acid, tea tree oil, zinc, witch hazel, alpha hydroxy acids, jojoba oil, to exert their beneficial effects in specific areas as needed. By incorporating such advanced delivery systems, cosmeceuticals can optimize the efficacy of these ingredients, ensuring their effective penetration into the skin and enhancing desired outcomes [30].

Monton et al. developed controlled-release herbal transdermal patches using a microwave-assisted extraction of *Lysiphyllum strychnifolium* stem extract, which, when incorporated into a polyvinyl alcohol matrix, displayed potent antioxidant properties and efficacious skin permeation of astilbin, fitting Korsmeyer–Peppas and zero-order kinetic models, showing promise for herbal medicinal applications [70]. Kanjani et al. explored the transdermal delivery of *Azadirachta indica*, formulating a transdermal patch via solvent casting and assessing its properties, including SEM analysis and in-vitro release kinetics, with the patch showing 74.89% cumulative drug release over 24 hours and indicating a novel herbal application in transdermal delivery technologies [71]

Traditional topical skin care formulations may have limitations that affect their safety and efficacy [72]. Researchers have developed various nanomaterials to overcome these limitations and facilitate drug delivery [73]. Using nanomaterials to develop skin care products is an ongoing process in the healthcare and cosmetics industries, potentially creating new opportunities and positive impacts on society and various industries [74].

Nano-sized drug delivery systems are being studied to improve the delivery of active pharmaceutical ingredients (APIs) in nano-products such as cosmetics and pharmaceuticals [75]. The skin is a barrier, and the administration of APIs can be challenging because of the complex physiological layers with different polarities [76]. Various active ingredients in cosmetic products can prevent, delay, and treat skin ageing [77]. Nanofibers have been studied as potential solutions to address the challenges of transdermal drug delivery [78]. Skin care products that use nanotechnology, including nano-products, have demonstrated promising results in delivering active ingredients to the skin [12,14,79,80].

DOI: 10.56171/ojn.1485463

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ISSN: 2147-0081
(2022) 9–2
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Table 1. Active Ingredients from Natural Sources for Different Skin Types

Skin Type	Active Ingredient	Benefits	References
Dry skin	Aloe vera	Moisturises and soothes dry skin and helps restore the natural skin moisture barrier.	[81]
	Chamomile	It has anti-inflammatory properties and soothes dry, irritated skin.	[82]
	Calendula	Helps to hydrate and heal dry, damaged skin.	[83]
	Lavender	Has calming properties and soothes dry, itchy skin.	[84]
	Coconut oil	Has moisturizing properties and helps to soothe and hydrate dry skin.	[85]
	Jojoba oil	Helps to moisturize dry skin without leaving a greasy residue	[86]
	Shea butter	Has deeply moisturizing properties, helps to soothe and nourish dry skin	[87]
	Olive oil	Contains antioxidants and moisturizing properties, helps to hydrate and protect dry skin	[88]
	Rosehip oil	Contains essential fatty acids and vitamin A, helps to hydrate and rejuvenate dry skin	[89]
	Witch hazel	Has astringent properties, helps to tighten and tone dry, ageing skin	[90]
Normal skin	Niacinamide	Helps improve skin texture and tone, reduces the appearance of fine lines and wrinkles, and strengthens the skin barrier	[91]
	Vitamin C	Helps brighten and even out skin tone, promotes collagen synthesis, and protects against environmental damage	[92]
	Hyaluronic acid	Provides deep hydration and helps retain moisture in the skin, improving skin elasticity and firmness.	[93]
	Green tea extract	Has anti-inflammatory and antioxidant properties, helps protect against UV damage, and promotes healthy skin ageing	[79]
	Retinoids	Helps stimulate collagen production, improves skin texture and tone, and reduces the appearance of fine lines and wrinkles	[94]
Oily skin	Salicylic acid	Helps unclog pores, reduces oiliness, and prevents breakouts	[95]
	Tea tree oil	Has anti-inflammatory and antimicrobial properties, helps reduce acne and oiliness	[96]
	Zinc	Helps regulate sebum production, has anti-inflammatory and antimicrobial properties, and promotes wound healing.	[97]
	Witch hazel	Has astringent properties that can help tighten and tone oily skin, reduce inflammation and irritation	[90]
Combination	Niacinamide	Helps regulate sebum production, improves skin texture and tone, and strengthens the skin barrier.	[91]
	Hyaluronic acid	Provides deep hydration to dry areas while being lightweight enough not to exacerbate oiliness in the T-zone	[93]
	Vitamin C	Helps brighten and even out skin tone, promotes collagen synthesis, and protects against environmental damage	[92]
	Alpha-hydroxy acids (AHAs)	Help exfoliate dead skin cells, improve skin texture and tone, and reduce the appearance of fine lines and wrinkles.	[91]
	Jojoba oil	A similar structure to the natural skin sebum helps regulate oil production and hydrates dry areas.	[86]

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Traditional topical skin care formulations may have limitations that affect their safety and efficacy [72]. Researchers have developed various nanomaterials to overcome these limitations and facilitate drug delivery [73]. Using nanomaterials to develop skin care products is an ongoing process in the healthcare and cosmetics industries, potentially creating new opportunities and positive impacts on society and various industries [74]. Nano-sized drug delivery systems are being studied to improve the delivery of active pharmaceutical ingredients (APIs) in nano-products such as cosmetics and pharmaceuticals [75]. The skin is a barrier, and the administration of APIs can be challenging because of the complex physiological layers with different polarities [76]. Various active ingredients in cosmetic products can prevent, delay, and treat skin ageing [77]. Nanofibers have been studied as potential solutions to address the challenges of transdermal drug delivery [78]. Skin care products that use nanotechnology, including nano-products, have demonstrated promising results in delivering active ingredients to the skin [12,14,79,80].

The transdermal drug delivery system (TDDS) represents a cutting-edge approach to drug delivery that transcends the limitations of traditional methods. Our country is fortunate to possess an extensive repository of Ayurvedic knowledge, which has been increasingly recognized and utilized in recent times. Nevertheless, the conventional means of administering herbal remedies to patients is antiquated and ineffective, which restricts the therapeutic potential of the drug. Given its application in herbal medicine, TDDS offers a promising solution to improve efficacy and reduce the adverse effects associated with various herbal remedies and plant-based treatments [98]. The problem of the ineffectiveness of oral medications, which account for 90% of medications taken in comparison to their high cost, can be addressed by exploring the use of a transdermal drug delivery system (TDDS). TDDS has several benefits, such as increased bioavailability, controlled absorption, higher plasma levels and half-life, ease of use without causing pain or side effects, and the convenience of discontinuing drug administration by simply removing the patch from the skin [72,99,100].

Recently, the use of herbal remedies has gained popularity worldwide owing to their remarkable healing properties and minimal side effects. Nevertheless, the creation of herbal medications requires adjustments to ensure the effective and sustained release of active pharmaceutical ingredients (APIs).

The oral administration of medication presents various concerns, such as unpleasant taste and colour. In contrast, the transdermal patch offers a non-irritating and non-invasive means of delivering medication with a precise time of action, making it a more appealing option for systematic drug administration than traditional approaches. However, patients may still become noncompliant during recovery, and the use of pills can cause additional complications [101]. The transdermal drug delivery system involves the application of medication through the skin to elicit a systemic response rather than employing conventional topical methods [81]. To deliver therapeutic agents across the human dermal layer for systemic effects, it is imperative to consider the detailed morphological, biophysical, and physiochemical properties of the dermal layer. Among the various drug delivery methods, transdermal drug delivery systems offer the most significant advantage over oral and injectable routes, particularly in terms of circumventing first-pass metabolism and promoting patient compliance [102]. Transdermal drug delivery systems are self-contained discrete dosage forms that deliver medication to the systemic circulation at a regulated and controlled rate when applied to healthy skin [59]. This mode of delivery offers several advantages, including controlled and consistent drug administration, continuous input of medications with limited biological half-lives, and prevention of pulsed entry into the systemic circulation, which may result in unwanted side effects [103]. Consequently, various novel and innovative drug delivery systems have been developed, including transdermal, controlled and predetermined release, and transmucosal delivery systems. Table 2 encompasses a range of herbal remedies for the treatment of diverse ailments through the administration of herbal medications.

DOI: 10.56171/ojn.1485463

Open Journal of Nano
ISSN: 2147-0081
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Table 2. Transdermal Delivery of Herbal Bioactive Compounds for the Treatment of Various Ailments[104–109].

Active Constituent	Biological Source	Method of Preparation of Patch	Pharmacological Activity
Zingiber, Podina (Mentha arvensis), and Sirka (Vinegar) were envisaged	Brassica nigra, Zingiber officinale, Mentha arvensis and Vinegar	Solvent evaporation technique	Antiemetic Therapy
Extract of Hibiscus	Hibiscus sassiness	Two different polymers in the ratio of (1:4) are used for its preparation	Antidiabetic activity
Ginger, Turmeric, Lavender, Clove oil, Wintergreen, Camphor, Menthol, aloe Vera, Turpentine	rhizomes of Zingiber officinale, Curcuma longa, Lavandula angustifolia, Aloe barbadense	Matrix diffusion-controlled systems, Solvent casting Technique	Anti-inflammatory
Neem oil	Azedarach indica	Solvent casting method	Antimicrobial

5. Nanofiber-Based Transdermal Drug Delivery: Prospects and Challenges

5.1. Methods of production of nanofibers

Nanofibers are nanostructured vehicles with an individual diameter below 100 nm [17]. Developed fibres with diameters in the range of 100–1000 nm are also designated as nanofibers and are generally manufactured using a technique known as electrospinning [18].

5.1.1. Self-assembly method

In this method, there is a spontaneous arrangement of atomic/molecular aggregates into structurally defective nanofibrous forms. The Tis method leads to the production of nanofibers with sizes of up to 100 nm. The Tis method requires a longer time to generate nanofibers; therefore, it is less commonly used. However, nanofibers manufactured through self-assembly can very closely mimic natural materials such as chitin (polysaccharide), which has been explored in tissue engineering [19].

5.1.2. Template synthesis method

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

5.1.3. Phase-separation method

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

5.1.4. Melt-blown technology

The melt-blowing method involves the extrusion of the polymer blend across a minute orifice followed by passage through a heated air stream with a very high velocity. The Te size of the nanofibers produced using this method was 150– 1000 nm [22].

5.1.5. Electrospinning methods

Electrospinning is a scientifically established process that uses an electric field to induce the transformation of a charged polymer solution or melt into finely spun fibres [110]. The process commences with the preparation of a polymer solution that is subsequently loaded into a syringe or spinneret apparatus [111]. The polymer solution was carefully extruded through a needle or spinneret orifice, subsequently experiencing the influence of a high-voltage electric field [110]. This causes the solution to become charged and form a Taylor cone at the tip of the needle [112]. As the electric field strength increases, the surface tension of the solution is overcome, and a charged jet is ejected from the cone [113]. The jet undergoes a whipping motion as it travels towards a grounded collector, and

DOI: 10.56171/ojn.1485463

Open Journal of Nano
ISSN: 2147-0081
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as it dries, it solidifies into a continuous nanofiber [114]. The diameter of the fibres can be controlled by adjusting the concentration of the polymer solution [115], flow rate [116], and the strength of the electric field [111]. Electrospinning is versatile and can be used with various polymers, including synthetic and natural materials. They have numerous applications in tissue engineering [117], drug delivery [118], filtration [119], energy storage [120], and sensors [3]. Several electrospinning approaches that can be used to encapsulate active ingredients and produce nanofibers are shown in **Figure 5**.

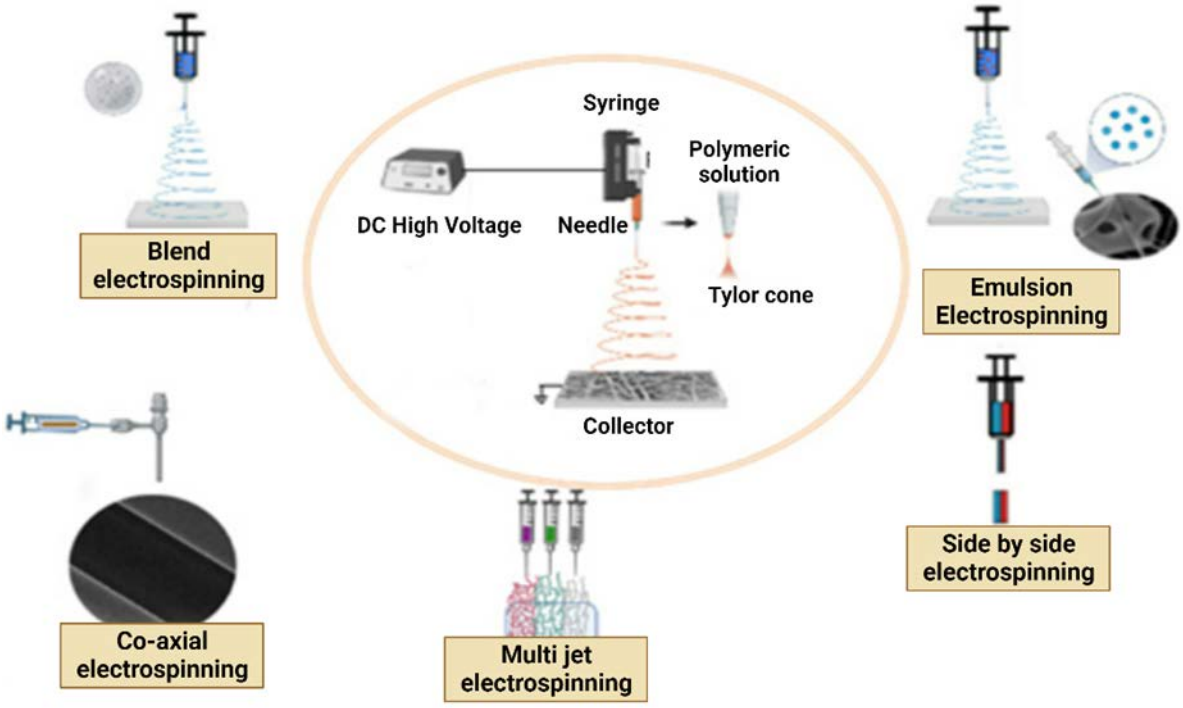

Figure 5. Schematic representation of various methods for incorporating drugs into polymer-carriers using electrospinning.

5.1.5.1. Single Fluid Electrospinning_Blend Electrospinning: This approach involves dissolving the drug and the polymer carrier in a suitable solvent to create a homogenous spinning solution. Electrospinning this solution can achieve a wide range of drug release profiles, ranging from rapid (within seconds) to sustained release over weeks or even months. The choice of solvent, polymer, and processing conditions can be optimized to achieve the desired release profile for a particular drug and delivery application [47]. The main weakness of this approach is the commonly observed burst release phenomenon [30].

5.1.5.2. Emulsion Electrospinning: Emulsion electrospinning is a scientifically established technique for fabricating core-shell nanofibers, enabling the encapsulation of growth factors, proteins, and drugs within the core region to enhance drug stability and improve bioavailability [121]. Forming a stable emulsion requires three crucial components: an oil phase, a water phase, and surfactants/emulsifiers, all of which influence the drug-release properties of the resulting fibres based on their respective compositions [122]. Typically, a hydrophobic polymer is dispersed in an organic solvent (oil phase), whereas hydrophilic compounds are dispersed in water, ensuring the desired characteristics of the emulsion for successful electrospinning. [20]. Tao et al. successfully manufactured polycaprolactone/carboxymethyl chitosan/sodium alginate fibres by emulsion electrospinning with minimal organic solvents. The resulting fibres positively affected osteoblast viability and osteogenesis [41].

DOI: 10.56171/ojn.1485463

5.1.5.3. Multifluid Electrospinning Multijet Electrospinning: Multijet electrospinning can be implemented using two distinct methods: needleless and needle-based configurations [123]. This technique offers substantial advantages for large-scale nanofiber fabrication because it considerably enhances the throughput. The production rate can be significantly increased by enabling simultaneous electrospinning of multiple jets, thereby facilitating the efficient manufacturing of nanofibers on a larger scale [124]. Moreover, it enables the preparation of multi-component fibre mats, wherein diverse populations of fibres fabricated from distinct materials are seamlessly integrated into a unified scaffold. This capability facilitates the development of complex and versatile structures with tailored properties, opening up possibilities for a wide range of applications in tissue engineering, filtration systems, and other fields [125]. This feature is valuable in cases where the inclusion of multiple polymers in a formulation is necessary; however, they cannot be dissolved within the same solution because of their incompatible solubilities. By employing multi-component fibre mats produced through this technique, the simultaneous incorporation of diverse polymers can be achieved, offering enhanced flexibility in designing materials with desired characteristics and functionalities [126]. The resulting fibre mat can deliver multiple drugs at varying rates, and different fibre populations can also influence the mechanical and cell adhesion properties [127]. However, there are some drawbacks to multijet spinning in the needle modality. The electric fields around different needles can interact with each other, which can cause spinning to be erratic [128]. Determining the optimal needle arrangement is a significant challenge in the electrospinning process. However, this obstacle can be overcome by using needleless or auxiliary electrodes. These approaches contribute to the enhanced stability of the spinning process, thereby improving the overall quality and consistency of the resulting fibre mats [78].

5.1.5.4. Side-by-Side Electrospinning: The side-by-side electrospinning technique involves the extrusion of multiple spinning solutions through adjacent spinnerets. This method offers a notable advantage in the form of side-by-side Janus morphology, enabling both compartments to establish physical contact with the biological microenvironment. The efficacy of this approach relies on the precise design of the spinneret and meticulous optimization of the electrospinning parameters [129,130]. Zheng et al., in 2021, tamoxifen, a chemotherapeutic drug, was incorporated into polymer matrices of PVP and Ethyl cellulose (EC). The research findings highlight the significance of shape, structure, and composition in the design of functional nanomaterials. By precisely manipulating these factors, novel materials with enhanced drug release profiles and other desirable properties can be developed for biomedical applications [131].

5.1.5.5. Coaxial/Multiaxial Electrospinning: Coaxial or multiaxial electrospinning enables the fabrication of nanofibers with core-shell or multilayered structures. This technique involves simultaneous electrospinning of two or more spinning solutions through concentric or parallel spinnerets [132]. The outer layer of the fibre is formed by the polymer solution dispensed from the outer spinneret, whereas the inner layer (core) is formed by the solution dispensed from the inner spinneret [133]. Core-shell nanofibers offer the incorporation of various drugs and biomolecules, enabling precise modulation of drug release rates and durations for advanced drug delivery [132]. Their structure enhances their mechanical properties and biocompatibility, making them suitable for biomedical applications such as drug delivery, tissue engineering, and wound healing [134]. Coaxial electrospinning allows for the precise control of small drug molecule release rates from a hydrophobic matrix and enables the encapsulation of liquids within the nanofiber cores [135]. Baykara and Taylan fabricated core-shell fibres using a polyvinyl alcohol (PVA) shell and a core containing Nigella sativa seed oil, renowned for its antimicrobial properties. This core-shell structure effectively regulated the release of oil, preventing sudden bursts of release [93]. This approach can be extended to various drugs or biomolecules that require controlled release rates or encounter compatibility issues with the matrix material, offering a versatile solution for tailored drug delivery systems and overcoming formulation limitations [136]. Triaxial spinning, which involves three fluids, allows the production of multilayer nanofibers [137]. Liu et al. demonstrated the application of triaxial electrospinning to

DOI: 10.56171/ojn.1485463

encapsulate ferulic acid within cellulose acetate nanofibers, resulting in a multilayer structure. The in vitro drug release from these fibres exhibited nearly zero-order kinetics, indicating a controlled and steady release rate. This technique can be used to encapsulate various drugs with varying properties, and the number of layers can be adjusted to achieve the desired release profile. Triaxial electrospinning holds promise for the development of drug delivery systems with improved efficacy and reduced toxicity [138]. Quad-axial electrospinning fabricates nanofibers using four simultaneous fluids, enabling precise control over their composition and functionality [139]. Quad-axial electrospinning enables the fabrication of intricate, multilayered structures with improved properties and customized release profiles, thereby revolutionizing drug delivery, tissue engineering, and biomedical applications [140]. Zhang et al. [141] utilized this approach to encapsulate the antimicrobial moxifloxacin in polycaprolactone and gelatine nanofibers with a quad-axial structure. By incorporating moxifloxacin into the nanofibers, quad-axial electrospinning facilitated controlled release kinetics over an extended duration, highlighting the adaptability of this technique in the design of drug delivery strategies. With its precise control over nanofiber composition and structure, quad-axial electrospinning presents a promising avenue for developing advanced drug delivery systems with tailored release profiles [141].

5.2. Applications of Nanofibers in Transdermal Delivery of Various Therapeutic Agents

Electrospinning has opened new avenues for investigating the efficacy of nanofibers in enhancing the properties of matrix materials used in cosmetic applications [153]. The integration of composites offers a distinct advantage by combining the strength of the reinforcement with the toughness of the matrix, resulting in exceptional properties that surpass those of conventional single materials [103]. The emergence of electrospinning techniques employing biopolymers has led to innovative nano-biocomposites distinguished by their multifaceted nature, superior functionality, and commendable environmental sustainability, making them highly promising for future applications [154]. Table 3 summarizes the active ingredients electrospun into nanofibrous scaffolds for a specific skin care product, outlining their benefits for the skin. This information can aid in the selection of skincare products tailored to address specific skin concerns. Enzymes are commonly used in the cosmetic industry because of their ability to improve skin texture, reduce wrinkles, and enhance skin hydration [142]. Enzyme immobilization is a well-established technique used in various fields because of its ability to improve the stability, activity, and reusability of enzymes [143]. However, using free enzymes in cosmetic formulations can be challenging because of their instability and susceptibility to degradation [144].

The utilization of nanofibers for transdermal drug delivery has gained attention because of several advantages, such as high drug loading capacity, high surface-to-volume ratio, and resemblance to the extracellular matrix. The successful production of nanofibrous mats depends on the appropriate selection of polymers and solvents for electrospinning. Nanofibers suitable for transdermal drug delivery can be produced using multiple polymer blends for electrospinning. A polymeric nanofibrous mat loaded with a therapeutic agent has the capacity to control and prolong its transdermal release. Transdermal nanofibers have demonstrated therapeutic potential in preclinical studies conducted by pharmaceutical scientists. However, their entry into the pharmaceutical market is governed by the development of effective scale-up technologies and comprehensive clinical evaluation.

DOI: 10.56171/ojn.1485463

Open Journal of Nano
ISSN: 2147-0081
(2022) 9–2
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Table 3. The sum of bioactive ingredients and their benefits to skin.

Electrospun polymers	Ingredients	Benefits for skin	Personal Care Category	References
Silk fibroin	Lanolin	Occlusive, emollient	Lipophilic	[145–147]
Chitosan, PVA	Glycerine	Anti-inflammatory, barrier recovery	Humectant, moisturizer	[148–150]
Chitosan, Gelatin, and PVA	Hyaluronic Acid	Humectant, anti-aging	Humectant, moisturizer	[93,151]
Silk fibroin	Vitamin B5 (Pantothenic Acid/Dexpanthenol)	Hydration, barrier protection, reduction of trans-epidermal water loss (TEWL), fibroblast stimulation, and re-epithelialization.	Humectant, emollient, antiinflammatory	[152–155]
Chitosan,Gelatin, and PVA	Aloesin	Tyrosinase inhibition, antioxidant, anti-inflammatory	Depigmenting, sun protective (UVB)	[156,157]
PVA, PCL, Chitosan	Mulberry Extract	Antityrosinase, antihyperglycemic, antitumorigenic, anti-inflammatory, antipyretic, antioxidant, anti-atherogenic, antimicrobial chemo-preventive, neuro-protective	Depigmenting	[158–160]
PVA	Niacinamide	PAR-2 inhibition, anti-inflammatory, antioxidant, anti-ageing, photoprotective	Depigmenting, exfoliant	[158,161,162]
PVA, Chitosan	Green Tea	Antioxidant, anti-ageing, antiacne, antiangiogenic, anticarcinogenic, anticarcinogenic, anti-inflammatory, antimicrobial, chemo-preventive, immunomodulatory,2photoprotective	Anti-ageing, moisturizing, antiacne, anogenital wart treatment	[79,163,164]
PVA, PLGA.Chitosan	Flaxseed Oil	Antioxidant, anti-ageing, anti-inflammatory, and antiapoptotic	Antioxidant, anti-ageing	[165–167]
PVA, PLGA	Caffeic Acid	Antioxidant, anticarcinogenic, anti-inflammatory, antimicrobial, immunostimulatory, neuroprotective, photoprotective	Antioxidant, anti-ageing	[168–171]
PLGA.PEO	Ferulic Acid	Antioxidant, anticancer, anti-inflammatory, antimicrobial, cardioprotective, neuroprotective, hepatoprotective, photoprotective, skin-lightening	Antioxidant, anti-ageing, photoprotection	[170,172,173]
Cellulose acetate	Tocopherol (Vitamin E)	Antioxidant, photoprotection, wound healing	Antioxidant, moisturizing, anti-ageing	[174–176]
Hyaluronic acid, PEO	Honey/Propolis/Royal Jelly	Analgesic, antioxidant, antiinflammatory, antimicrobial, antitumor, antiseptic, antipyretic, antiulcer, hepatoprotective, immunomodulatory	Antioxidant, anti-ageing, photoprotection, antiseptic, wound healing	[177–180]
Chitosan, Polycaprolactone,PVA	Melatonin	Antioxidant, anticarcinogenic, anti-ageing, anti-inflammatory, anxiolytic, immunomodulatory	Antioxidant, anti-ageing	[181–183]
Pullulan	Aloe Vera	Anti-inflammatory, antioxidant, antimicrobial, immunomodulatory, laxative, wound healing	Moisturizing, soothing, cooling, burning, healing	[81,184,185]

DOI: 10.56171/ojn.1485463

6. Conclusions and Future Challenges

Transdermal patches represent a strategic advancement in medicinal treatment, offering enhanced safety and efficiency. These patches, equipped with a drug reservoir, penetration enhancer, and various layers integral to their function, facilitate a crucial drug release mechanism. Diffusion from the patch through the skin to the underlying blood capillaries is pivotal for its efficacy. The advantages of transdermal patches include their ability to control drug release, their non-invasive nature, diminished side effects, bypassing of hepatic first-pass metabolism, and a quicker and more potent onset of action. Nevertheless, challenges such as the risk of self-toxicity, adhesion issues, suboptimal drug penetration, skin irritation, and patch malfunction necessitate further innovation and exploration to refine these delivery systems. Notably, transdermal applications present an opportunity to enhance the delivery of natural products, although the complexity of herbal medicine constituents and dosage discrepancies between traditional uses and nanotechnological limitations pose significant research areas. Addressing these complexities, particularly the authentic effects of natural products via nanocarriers and systemic mechanisms underlying their efficacy, is critical. Future studies should focus on developing suitable transdermal methods and proper evaluation techniques for natural products to fully harness their potential in this domain. The current work encapsulates these aspects and has published research in this field.

Abbreviations

MED: Minimum Effective Dose
MTD: Maximum Tolerated Dose
FDA: US Food and Drug Administration
API: Active Pharmaceutical Ingredient
TDD: Topical Drug Delivery
J: Molecular Flux (mol/s·m²)
D: Diffusion Coefficient (m²/s)
L: Cross-Sectional Thickness of Diffusion (m)
dc/dl: Concentration Gradient (mol/m⁴)

Peer-review: Externally peer - reviewed.

Author contributions: -

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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