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Nanocomposite patches for transdermal drug delivery: A review

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ABSTRACT

Transdermal drug delivery encounters limitations due to skin's barrier resistance, which restricts drug penetration. Only small, lipophilic drugs can easily cross the skin, limiting the range of deliverable compounds. Variability in skin thickness and condition further affects drug absorption and efficacy. In addition, potential skin irritation or allergic reactions present safety concerns. Overcoming these barriers requires advanced formulations and technologies to enhance drug delivery efficiency and safety. Recent advancements in transdermal drug delivery have led to the development of nanocomposite systems that integrate biocompatible polymers with nanoparticles (NPs) to optimize drug transport across the skin barrier. These nanocomposites offer controlled release kinetics, ensuring sustained therapeutic drug levels while minimizing systemic side effects. By enhancing skin permeability and overcoming challenges such as poor drug solubility and inconsistent absorption rates, they enable effective delivery of both hydrophobic and hydrophilic drugs. The versatility of nanocomposites allows for precise customization of drug release profiles, tailored to specific therapeutic needs and patient requirements. This technology shows promise in improving patient compliance and therapeutic outcomes, offering a viable alternative to conventional drug delivery methods. Ongoing research focuses on refining nanocomposite formulations to enhance efficacy, scalability, and regulatory approval, aiming to expand their clinical applications across various medical fields. This review article provides a comprehensive overview of NPs widely used in transdermal delivery, including lipid-based, polymeric-based, and inorganic NPs. It also discusses types of transdermal patches, such as reservoir, matrix, drug-in-adhesive, and hydrogel patches. In addition, biomedical applications, limitations and future perspectives are thoroughly addressed.

Keywords: nanocomposite; transdermal patches; transdermal drug delivery; nanoparticles

1. INTRODUCTION

The skin, the largest organ in the human body, performs a multitude of vital functions. These encompass sensory perception of pain, touch, and temperature; facilitation of bodily movement; synthesis of vitamin D; establishment of immune defenses against pathogens; prevention of moisture loss; regulation of body temperature; and most importantly, the formation of a protective barrier against the external environment (Swaney and Kalan, 2021).

The skin is composed of three distinct layers: the epidermis, dermis, and subcutaneous tissue layer (hypodermis) (Figure 1). The epidermis, the outermost layer of the skin, lacks blood vessels and is continually regenerated approximately every 28 days (Baroni et al., 2012). It is divided into five sublayers: stratum corneum (SC), stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale. The epidermis includes various cell types, with keratinocytes being the most dominant. These keratinocytes are produced in the basal

layer and migrate toward the surface as they undergo differentiation. During this process, keratinocytes produce the structural protein keratin, which combines with filaggrin to form flattened, tightly bundled corneocytes. The SC, the outermost layer of the skin, is composed of closely packed corneocytes surrounded by intercellular lipids. This structure is often compared to a "brick-and-mortar" model. The lipid matrix consists of a bilayer composed of ceramides, cholesterol, and fatty acids. Ceramides provide rigidity and play a crucial role in maintaining the skin's barrier function, while cholesterol enhances flexibility and fluidity. The main functions of the SC are to protect the underlying epidermis and dermis, and to serve as a barrier against water loss and the penetration of foreign substances (Woo, 2019).

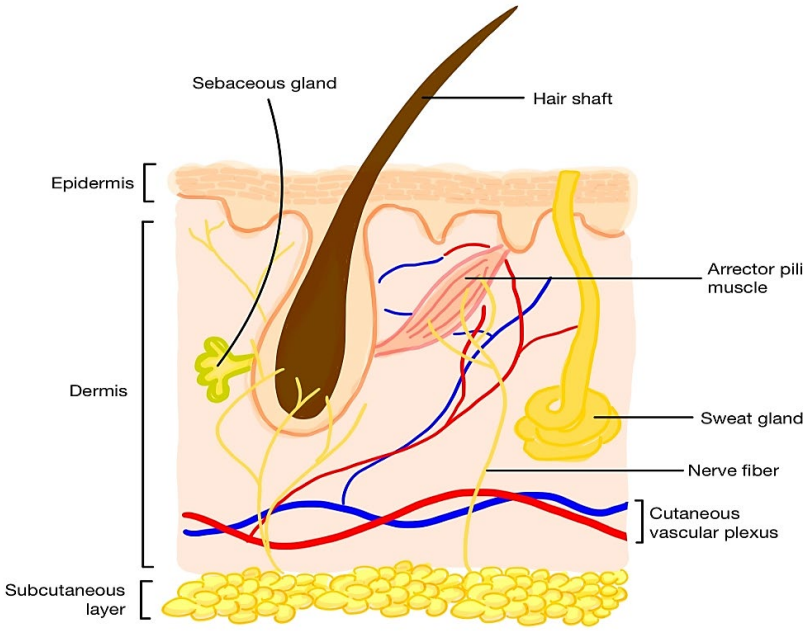

Figure 1. Illustration of skin structure

The oral route is the most common method of drug delivery due to its cost-effectiveness, patient convenience, and ease of self-administration. However, orally administered drugs are subject to hepatic first-pass metabolism. Acid-labile drugs and biomolecules, such as proteins and peptides, are particularly vulnerable to rapid degradation by gastric enzymes (McCrudden et al., 2013; Schoellhammer et al., 2014). The parenteral route offers an alternative that avoids degradation and provides rapid therapeutic action. Nevertheless, it is not widely accepted by patients due to its invasive nature and associated pain (St Clair-Jones et al., 2020). In contrast, the skin presents an appealing option for drug administration due to its ease of use, convenience, and ability to bypass first-pass metabolism in the liver. The transdermal approach offers an effective and painless way to deliver drugs to patients, making it a favorable option for drug administration. Unfortunately, transdermal delivery presents several limitations. The skin, particularly the SC, serves as a major barrier to drug absorption. Furthermore, the efficiency, stability, and skin compatibility of transdermal drug delivery systems (TDDS) remain critical concerns. Many researchers are working to address these limitations and enhance the potential of transdermal drug delivery (Jeong et al., 2021).

Drug absorption across the SC is one of the most significant challenges in transdermal drug delivery due to the formidable nature of its protective barrier. Despite its potential advantages, transdermal drug delivery has several limitations. Only drugs with a molecular weight below 500 Da can easily penetrate the SC, as diffusivity is inversely proportional to molecular size. In addition, drugs with balanced aqueous and lipid solubility (Log P value between 1 and 3) are more likely to successfully transport across the SC and reach systemic circulation (Supe and Takudage, 2021; Vaseem et al., 2024). However, transdermal delivery is unsuitable for drugs requiring high systemic concentrations (Uchechi et al., 2014). The SC permits molecules to pass through three main pathways: intercellular, intracellular, and transappendageal (Mishra et al., 2019). The intercellular pathway, the primary route for small lipophilic molecules, involves drug movement through the lipid matrix between corneocytes. The intracellular pathway enables molecules to traverse the corneocytes, transferring between the hydrophilic intracellular environment and the lipid domains between cells. However, this pathway is rarely utilized by most molecules. The transappendageal (or shunt) pathway involves penetration through hair follicles and sweat glands. This route is particularly crucial for large polar molecules, which can move through the aqueous environment of the sebaceous gland or pilosebaceous units. Although sweat glands and hair follicles make up only a small fraction (approximately 0.1%) of the total skin surface, the shunt pathway is considered practical due to its minimal associated risks (Akhtar et al., 2020). Various formulations are commonly used in transdermal delivery, including creams, gels, sprays, ointments, and patches.

Among these, hydrogels and patches are the most widely utilized. To enhance the functionality of transdermal patches, such as improving drug release kinetics, researchers have increasingly focused on designing and fabricating nanocomposite materials with specific properties and functionalities (Merino et al., 2015; Song et al., 2015). Advanced transdermal patches with enhanced properties or multifunctional capabilities have been developed. For example, nanocomposite patches incorporate nanomaterials to enhance the tensile strength, flexibility, and stability of transdermal patches (Sikandar et al., 2022). Furthermore, the encapsulation of the drug within nanomaterials and subsequent integration into the transdermal patch helps protect drug stability and enhance drug accumulation in the skin (Qindeel et al., 2020). Controlled drug release can be achieved through smart transdermal patches designed for specific targets. One example is the use of electrically responsive hydrogels, where drug release is triggered by electrical stimulation, enabling precise control of drug delivery (Yun et al., 2020). These innovations and their details will be discussed in the following sections.

2. TYPE OF NANOPARTICLES IN TRANSDERMAL DRUG DELIVERY

Nanoparticles (NPs) are small colloidal particles ranging in nanoscale (1 to 100 nm). Due to their small size, NPs offer diverse functions for biomedical applications. NPs can be divided into different categories depending on the materials used for their production (Mitchell et al., 2021). To enhance the functionalities of transdermal delivery systems, such as achieving better control over drug release kinetics, NPs have gained significant interest for integration into the polymer matrix of transdermal patches, including pressure-sensitive adhesives (PSA) and hydrogels (Merino et al., 2015). In the field of biomedicine, NPs are typically constructed from biocompatible materials such as lipids, polymers, inorganic substances, and inert metals (Figure 2) (Mitchell et al., 2021).

2.1 Lipid-based NPs

Lipid-based nanosystems, such as liposomes, niosomes, ethosomes, transfersomes, nanoemulsions, solid lipid particles (SLN), and nanostructured lipid carriers (NLC), have been extensively studied as carriers for transdermal drug delivery due to their effectiveness and non-toxic nature. However, lipid-based NPs face challenges, including low encapsulation efficiency and stability issues.

2.1.1 Liposomes

In the 1980s, liposomes emerged as a groundbreaking innovation in nanotechnology. In 1986, Dior introduced liposomes into the cosmetic market, making their entry into commercial applications. Afterward, liposomes have been extensively developed for pharmaceutical products. Liposomes are spherical vesicular structures composed of phospholipid bilayers, which can be derived from natural or synthetic phospholipids, such as phosphatidylcholine and phosphatidylethanolamine, along with cholesterol. Their biocompatibility and non-toxic nature make them an ideal choice for drug delivery systems. Depending on their structural composition, liposomes can be categorized as unilamellar, multilamellar, or multivesicular vesicles (Jash et al., 2021; Kumar, 2019; Singpanna et al., 2021).

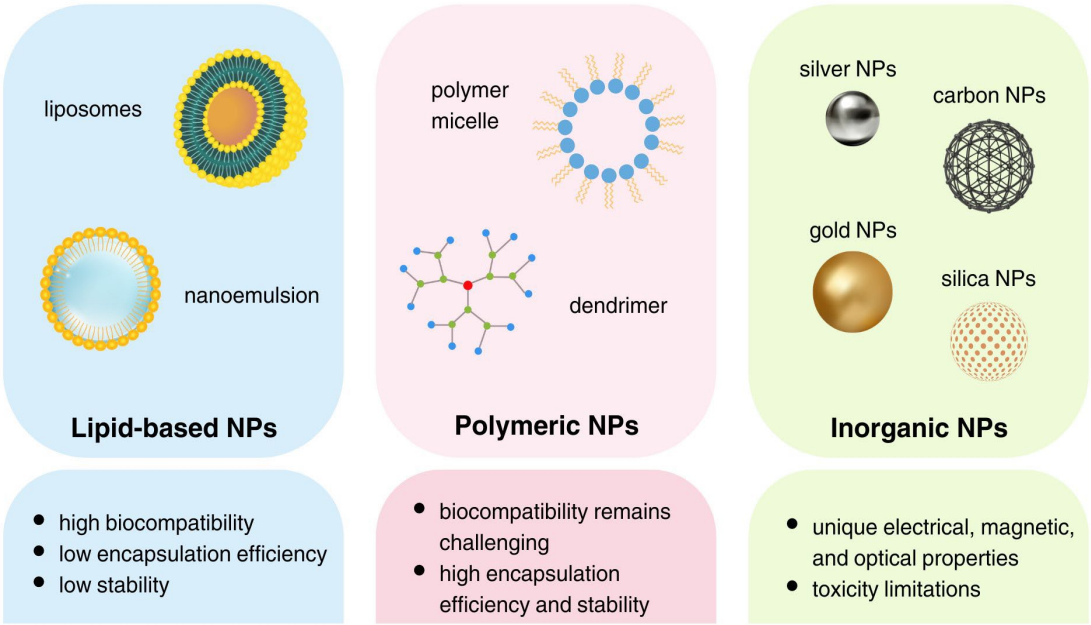

Figure 2. Examples of NPs used in transdermal drug delivery

2.1.2 Niosomes

Niosomes are lipid-based vesicles composed of cholesterol and non-ionic surfactants. They offer significant advantages in transdermal drug delivery, including enhanced drug stability, protection against degradation, and controlled release through drug encapsulation within their lipid bilayers. Additionally, niosomes improve drug absorption through the skin, resulting in increased bioavailability compared to conventional formulations. Although niosomes share a structural similarity to liposomes, their bilayers are formed from nonionic surfactants. The incorporation of surfactants in niosomes enhances drug dispersion, solubility, skin penetration, and sustained release. Furthermore, niosomes exhibit superior stability compared to liposomes over prolonged periods. As a result, they have found extensive applications in both cosmeceutical and pharmaceutical fields (Kumar, 2019).

2.1.3 Ethosomes

Conventional liposomes face several limitations, including inefficient encapsulation of hydrophilic drugs, membrane instability leading to leakage, and a short half-life. These challenges have led to the development of advanced vesicles such as niosomes, transfersomes, and ethosomes. Ethosomes, primarily composed of phospholipids, ethanol, and water, are soft and malleable vesicles. Ethanol plays a crucial role in ethosomal formulations by acting as a penetration enhancer, enabling the vehicle to overcome the SC's barrier function. The high ethanol concentration (10–45%) not only promotes deeper drug penetration but also helps maintain the nanoscale size and malleable property of the ethosomes. Ethosomes are considered more effective than liposomes due to the combined effect of ethanol, water, and phospholipids, which enables enhanced drug delivery into deeper layer of the skin. Phospholipids in ethosomes provide both hydrophilic and lipophilic properties, making them highly effective for targeted transdermal delivery (Nayak et al., 2022).

2.1.4 Transferosomes

Conventional liposomes often accumulate in the outer layer of the skin, limiting their ability to deliver drugs to deeper layers. To overcome this limitation, researchers have developed transferosomes as an advanced method for transdermal drug delivery. Transferosomes are vesicles primarily composed of phospholipids combined with membrane-softening agent such as Tween 80, Span 80, sodium cholate, and deoxycholate. This combination creates highly elastic and deformable vesicles that are significantly more flexible, enabling them to effectively penetrate the skin barrier (Opatha et al., 2020).

2.1.5 Nanoemulsions

Nanoemulsions consist of two immiscible liquids, where one phase is dispersed within the other, forming a system of small droplets. These droplets, ranging in size from 10 and 1,000 nanometers, are stabilized by emulsifiers. Deu to their small particle size, nanoemulsions are transparent. They can be formulated as oil-in-water, water-in-oil, and bi-continuous systems. Addition of surfactants and co-surfactants imparts strong thermodynamic stability to nanoemulsions. This formulation is widely used in pharmaceuticals, cosmeceuticals, and the food industry, offering numerous advantages, including improved drug bioavailability, non-toxicity, good physical stability, and enhanced drug absorption (Ashaolu, 2021; Ashfaq et al., 2023; Barradas and de Holanda e Silva, 2020; Jaiswal et al., 2015).

2.1.6 Solid lipid NPs (SLNs)

Liquid lipid nanoparticulate systems often suffer from poor stability, which significantly limit their drug delivery capability. To address this challenge, SLNs were introduced in the late 20s as a safer and more stable alternative to liposomes. SLNs consist of a solid lipid matrix stabilized by surfactants and are typically prepared from waxes, complex glycerides, and triglycerides. The use of solid lipids in place of liquid lipids in drug delivery systems provides several advantages, including controlled drug release, enhanced stability, high drug loading, compatibility with both lipophilic and hydrophilic drugs, straightforward preparation, applicability for large-scale production, and cost-effectiveness. Solid lipid NPs (SLNs) are small and biocompatible, making them suitable for transdermal, parenteral, and pulmonary drug delivery. However, the drug loading and encapsulation efficiency of SLNs is constrained by lipid crystallinity, polymorphism, and drug solubility in the solid lipids (Ghasemiyeh and Mohammadi-Samani, 2018; Scioli Montoto et al., 2020).

2.1.7 Nanostructured lipid carriers (NLCs)

Liposomes, a traditional form of lipid-based NPs, face limitations such as instability and challenges in large-scale production (Kumar, 2019). To overcome these issues, SLNs and NLCs were developed. Both systems use a lipid matrix that is more stable and better tolerated by the skin compared to liposomes. However, SLNs have notable drawbacks, including low drug loading capacity and drug expulsion, which are attributed to their highly ordered lipid structure. To address this, NLCs were created by incorporating a low-melting-point liquid lipid into the solid lipid matrix, resulting in a less ordered lipid structure, allowing for higher drug encapsulation efficiency and greater drug loading capacity (Borges et al., 2020).

2.2 Polymeric NPs

Polymeric NPs have emerged as versatile carriers in TDDS, offering unique advantages over traditional formulations. They can be fabricated from both natural and synthetic polymers. Synthetic polymers are generally preferred for their superior consistency and purity. These NPs are typically composed of biocompatible and biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), or polylactic acid (PLA) (Jiang et al., 2017). Their ability to encapsulate a wide range of drugs, protect them from degradation, and control their release kinetics makes them promise to enhance drug delivery through the skin. The majority of polymeric NPs are impeded from traversing the SC due to their elevated molecular weight, thereby necessitating their utilization of the transfollicular pathway (Zhang et al., 2013; Zhou et al., 2018). One significant advantage of polymeric NPs is their capacity to encapsulate both hydrophobic and hydrophilic drugs. The polymer matrix provides a stable environment for drug molecules, protecting them from enzymatic degradation and enhancing their solubility. This versatility allows for the delivery of diverse therapeutic agents, from small to large molecules, which may otherwise face challenges in permeating the skin barrier (Nunes et al., 2022).

2.3 Metallic and inorganic NPs

Recently, inorganic NPs have gained popularity in drug delivery due to their ability to facilitate photothermal therapy and bioimaging. Certain inorganic nanostructures, particularly those with a positive charge and lipophilic functionalization, have shown the potential to penetrate the SC, making them suitable candidates for transdermal delivery. Their exceptional stability and the potential for surface functionalization further enhance their appeal in this application (M. Wang et al., 2016). Inorganic NPs investigated for transdermal applications encompass gold, silver, iron oxide, and carbon. Among these, gold and silver NPs have been widely explored as therapeutic agents (Gao et al., 2016; Ko et al., 2021; Pangli et al., 2021).

2.3.1 Evaluating the effectiveness of nanoparticulate systems

NPs are extensively utilized to advance transdermal drug delivery. Various methodologies, including microscopic, spectroscopic, and structural analyses, are employed to evaluate the efficacy of functional nanosystems in enhancing transdermal drug delivery. Both label-free and label-based instrumental approaches are used to examine the characteristics of these nanosystems and their permeation through the skin. Label-free techniques include methods such as the diffusion cell method, transmission electron microscopy (TEM), scanning electron microscopy (SEM), cryo-electron microscopy, X-ray spectromicroscopy, Raman microscopy, atomic force microscopy (AFM), surface-enhanced Raman scattering (SERS), Fourier transformed infrared (FTIR), and infrared microscopy (IR). In contrast, label-based techniques involve fluorescent molecules to monitor skin permeation, employing techniques such as fluorescence spectroscopy, multiphoton microscopy, and electron paramagnetic resonance (EPR) (Liu et al., 2023).

3. TYPE OF TRANSDERMAL PATCHES IN TRANSDERMAL DRUG DELIVERY

Transdermal patches provide a favorable option for drug administration, overcoming challenges associated with other delivery methods. These patches eliminate issues such as gastrointestinal upset, enzymatic degradation, first-pass metabolism, and susceptibility to acidic conditions. Moreover, they improve patient adherence as they are easy to self-apply, enabling localized or systemic drug absorption through the skin over a predetermined period (Al Hanbali et al., 2019). Transdermal patches are generally categorized into three types: reservoir (Figure 3a), matrix (Figure 3b), and drug-in-adhesive (Figure 3c) systems. The essential elements of transdermal patches consist of the backing, membrane, adhesive, and liner. The backing serves as the impermeable layer that protects the patch from environmental exposure while providing flexibility. Meanwhile, the membrane regulates drug release and is typically made from natural or synthetic polymers. The adhesive binds components together and ensure the patch adheres to the skin. Adhesives are commonly made from silicone, rubber, polyvinyl acetate, or polyisobutylene, depending on the desired skin adhesion properties. This layer may also contain permeation enhancers to facilitate drug permeation through the skin. Lastly, the liner protects the patch during storage and needs to be removed before use (Bird and Ravindra, 2020).

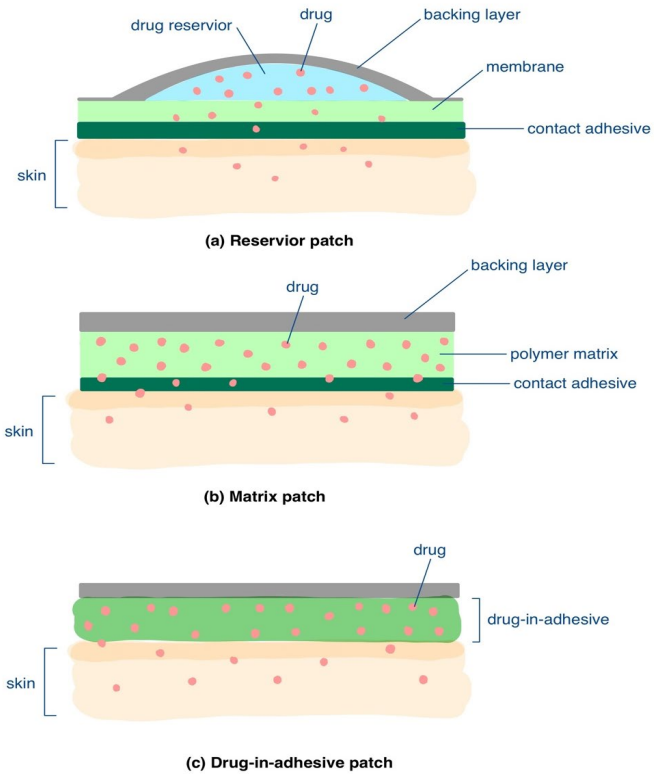

Figure 3. Three types of transdermal patch systems: (a) reservoir patch, (b) matrix patch, and (c) drug-in-adhesive patch

3.1 Reservoir patches

Reservoir patches (Figure 3a) comprise an adhesive layer, a rate-controlling membrane, and a drug reservoir. They are commonly used when the drug is either incompatible with or insufficiently soluble in a transdermal device. Typically, the drug reservoir includes a rate-controlling membrane made from polymeric materials such as ethyl vinyl acetate, along with an impermeable backing membrane, the drugs, and excipients. Drug release occurs through the rate-controlling membrane, which can be microporous or nonporous. Within the drug reservoir, the drug may be present in the form of a solution, suspension, gel, or dispersion in a solid polymer matrix. These patches are characterized by a separate drug reservoir sandwiched between a backing layer and a rate-controlling membrane. The membrane acts as a gatekeeper, regulating the drug's flow from the reservoir into the skin and ensuring a consistent controlled release profile. The drug permeates the skin by passing through both the adhesive layer and the membrane (Kesarwani et al., 2013; Kim and Choi, 2021).

3.2 Matrix patches

Matrix patches (Figure 3b) are the simplest and most cost-effective type, characterized by the drug being uniformly distributed within the adhesive layer. These patches store the drug within a hydrophilic or lipophilic polymer matrix, which plays a major role in controlling the drug release. This design enables passive diffusion of the drug molecules from the patch through the skin and into the bloodstream. Although cost-effective and discreet, matrix patches have limitations in controlling the rate of drug release and are best suited for potent drugs that easily penetrate the skin (Adepu and Ramakrishna, 2021; Nandi and Mondal, 2022).

3.3 Drug-in-adhesive patches

Drug-in-adhesive patches (Figure 3c) represent a significant advancement in transdermal drug delivery technology, offering a convenient and effective method for administering medications through the skin. These patches consist of a drug reservoir embedded within an adhesive matrix that adheres to the skin, allowing controlled drug release of the drug over an extended period. These patches are utilized when a drug can easily permeate the skin and matrix. The drug-in-adhesive patch is produced by blending an adhesive polymer with the drug and then applying the medicated polymer onto a backing membrane layer (Pastore et al., 2015). Pressure-sensitive adhesives (PSAs) are viscous, rubbery polymers that strongly adhere to surfaces when gentle external pressure (e.g., light touch with a finger) is applied for a few seconds (Creton and Fabre, 2002). PSAs must be chemically inert, non-irritating, and non-sensitizing to the skin. In addition, they should be biocompatible and must not degrade or interact with the drug and other formulation components (Tan and Pfister, 1999). PSAs create a temporary adhesive bond that can be removed without leaving any residue on the surface. Traditional PSAs are usually made from acrylates, silicones, or polyisobutylenes (PIBs). Among these, acrylates are often preferred because they can be tailored to meet different performance requirements for various drugs, excipients, and specific product needs (Chalykh et al., 2002).

3.4 Hydrogels

Traditional PSAs have typical limitations, such as inadequate wetting properties, insufficient adhesion capacity, and problems related to the disposal of organic solvent residues. To address these issues, hydrogels or hydrophilic PSAs, which rely on water-absorbing polymers, are increasingly used (Feldstein et al., 2015). Hydrogels are produced from hydrophilic polymers that can swell and dissolve in water. The hydrophilic nature of the polymer used in hydrogel PSAs allows them to retain a large amount of water within their 3D structures. Additionally, due to their high-water content, hydrogel PSAs are highly compatible with living tissue and can be used as biomaterials. Their similarity to natural tissue makes them suitable for a wide range of biomedical applications (Ahmad et al., 2022).

4. NANOCOMPOSITE PATCHES IN TRANSDERMAL DRUG DELIVERY

Nanocomposite patches are innovative drug delivery systems that incorporate NPs into the patch matrix to achieve specific therapeutic goals. By leveraging the unique properties of NPs—such as their high surface area, tunable surface chemistry, and ability to encapsulate drugs—nanocomposite patches offer several advantages over traditional transdermal patches. These advantages include enhanced drug permeation through the skin, sustained drug release, improved stability of active ingredients, and targeted delivery to specific skin layers or tissues (Parhi, 2018).

The effectiveness of nanocomposite patches in transdermal drug delivery relies on the synergistic interactions among their key components. NPs, as versatile carriers, play a pivotal role in enhancing drug bioavailability and enabling targeted delivery. Encapsulating drugs within NPs allows for precise control over drug release kinetics and improved drug stability (Liu et al., 2024). Moreover, NPs can be functionalized to enhance skin permeation, bypass the skin barrier, and enable localized drug delivery to specific skin layers or tissues (Chang et al., 2023). The polymeric matrix of nanocomposite patches serves as a scaffold, supporting NPs and drug molecules. Biocompatible polymers are carefully selected to ensure skin compatibility, minimal irritation, and controlled drug release. The polymer matrix can be engineered to modulate drug diffusion rates, tailor release profiles, and optimize drug delivery efficiency. Additionally, the mechanical properties of the polymeric matrix influence the flexibility, adhesion, and wearability of the patch, ensuring patient comfort and ease of application (Thang et al., 2023).

The drug delivery system integrated within nanocomposite patches is designed to encapsulate drugs and regulate their release over time. By leveraging the unique properties of NPs, such as their high drug-loading capacity and tunable release kinetics, researchers can develop innovative drug delivery systems with enhanced therapeutic outcomes. These systems can be tailored to achieve sustained release, pulsatile release, or triggered

release in response to specific stimuli, offering personalized treatment options for various medical conditions (Kashkooli et al., 2020; Petrovic et al., 2024; Rahim et al., 2021). The adhesive layer of nanocomposite patches plays a critical role in ensuring proper attachment to the skin surface. The adhesive material must exhibit strong adhesion properties, skin compatibility, and minimal skin irritation to enable continuous drug delivery. The adhesive layer not only secures the patch in place but also facilitates drug permeation through the skin barrier, promoting efficient drug absorption and bioavailability. Patient compliance and comfort are key considerations in designing the adhesive layer, as these factors directly affect the usability and effectiveness of the patch (Alex et al., 2024). The backing layer of nanocomposite patches provides structural support and protection for the system. This layer acts as a barrier against external factors such as moisture, light, and oxygen, which could degrade the drug or impair patch performance. By shielding the patch from environmental influences, the backing layer ensures the integrity and stability of the drug delivery system, prolonging shelf life and maintaining consistent drug release kinetics. Additionally, the backing layer contributes to the patch's overall durability and functionality (Wong et al., 2023).

The improvement of transdermal patches requires a comprehensive understanding of a drug's properties. Key factors such as hydrophobicity and ionization status play a crucial role in drug selection. Other important characteristics that influence skin penetration—such as water solubility, melting point, molecular weight, partition coefficient, drug concentration, absorbability, permeability, saturation, and diffusion rate across the SC— must also be considered (Jayaprakash et al., 2017). Various enhancement methods have been researched and integrated into patches to address challenges associated with the SC, leading to a substantial enhancement in the transdermal flux (Pastore et al., 2015). NPs possess unique multifunctional properties; however, their inherent instability and rapid clearance often limit their effectiveness in drug delivery. This has driven growing interest in incorporating NPs into the polymer matrix of transdermal patches to enhance delivery functions, including improved drug release, high drug loading capacity, and targeted drug delivery (Merino et al., 2015). Nanocomposites are materials that integrate nanoscale particles, ranging from 1 to 100 nanometers, into a matrix material (Figure 4) (Di Ventra et al., 2004; Rhim, 2011). These materials consist of two main components: the continuous phase and the discontinuous phase (also known as the reinforcing phase). The continuous phase, which serves as the primary building block of the nanocomposite, can be a metal, polymer, or ceramic. Based on the type of building blocks, nanocomposites are classified into polymeric, metallic, and ceramic groups. The discontinuous phase, or nano-fillers, consists of various types of nanosized materials dispersed within the continuous phase (Lateef and Nazir, 2017).

Designing nanocomposite patches requires careful consideration of several key factors to ensure their effectiveness, durability, and practicality for various applications. Material selection is a crucial step, involving the choice of base materials and NPs that are compatible and capable of providing the desired mechanical, electrical, or optical properties. The type and loading of NPs must be carefully evaluated. Different types of NPs offer specific advantages; for example, clay NPs can enhance barrier properties in protective coatings. The NP loading in the matrix should be optimized to enhance performance without compromising the structural integrity of the patch. Mechanical properties are another key consideration. Nanocomposite patches must exhibit adequate strength, flexibility, and toughness for their intended applications. NPs should improve these properties without causing brittleness or increasing weight excessively. Also, biocompatibility and safety are paramount for biomedical applications or patches in contact with the skin (Kim and Choi, 2021). In transdermal delivery applications, polymeric matrix nanocomposites are extensively utilized due to their flexibility, ease of processing, and ability to host NPs effectively. The polymer matrix not only provide mechanical support but also ensure uniform dispersion of NPs, which is crucial for consistent performance. This review focuses on various types of transdermal patches, including hydrogels, membranes and films, PSAs and microneedles patches.

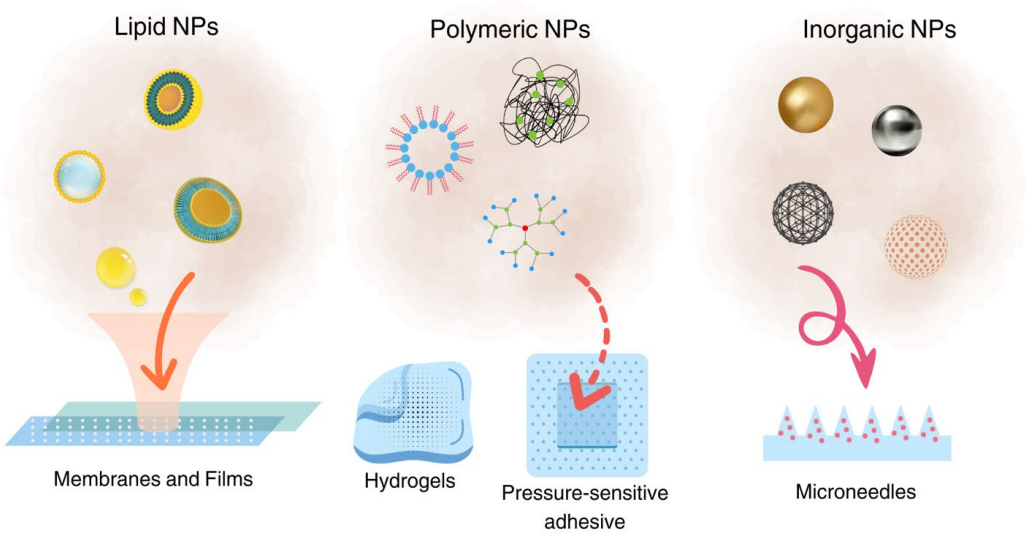

Figure 4. Integration of different NPs into a matrix of transdermal patch

4.1 Nanocomposite hydrogels

Hydrogels play a crucial role in the pharmaceutical sector, particularly in advancing TDDS. Innovations in adhesive technology for these applications focus on enhancing drug-diluent compatibility, skin permeation, and adhesive performance. Nanocomposite hydrogels are three-dimensional networks that are physically or chemically cross-linked with nanostructures. These hydrogels have the ability to swell in water or other compatible solvents. Incorporating various types of nano-fillers—such as polymeric NPs, metal NPs, and inorganic NPs—into the polymeric network produce nanocomposite hydrogels with specific properties and functions (Merino et al., 2015; Vashist and Ahmad, 2013).

Due to their high biocompatibility and moisture content, hydrogels are widely used in wound care and are of significant interest for their therapeutic potential. Metal and metal oxide-based NPs, such as silver, gold, copper, zinc oxide (ZnO), titanium oxide, and cerium oxide, are frequently used in hydrogels for their antipathogenic properties, promoting wound healing (Dam et al., 2023). Among these, silver NPs (AgNPs) are particularly common due to their antibacterial, antiviral, and antifungal properties. AgNPs can penetrate bacterial cell walls, modify the structure of cell membranes, and induce cell death (Yin et al., 2020). For instance, AgNPs incorporated into chitosan–PVA-based hydrogel exhibited good antibacterial activity against *Escherichia coli* (*E. coli*) (Agnihotri et al., 2012). Similarly, AgNPs nanocomposite carrageenan-based hydrogels effectively inhibited bacterial growth against both *Bacillus* and *E. coli* (Jayaramudu et al., 2013). In addition to bacterial infections, AgNPs hydrogels have shown potential in treating viral infections. An AgNP hydrogel modified with tannic acid demonstrated a substantial reduction in the infectivity of herpes simplex virus type 1 and 2 after 24 h of exposure (Szymańska et al., 2018). Nanocomposite hydrogels containing ZnO modified with poly(ethylene glycol) methyl ether methacrylate (PEGMA) demonstrated strong bactericidal activity against *E. coli* and *Staphylococcus aureus* while maintaining biocompatibility, suggesting their suitability for wound dressing (J. Wang et al., 2016). Other innovative examples include chitosan-based hydrogels with chondroitin sulfate encapsulated in selenium NPs, which have shown to effectively promote vascular regeneration, induce tissue remodeling, and accelerate wound healing in animal models (Zhao and Yuan, 2023). Gelatin-based hydrogel nanocomposite surgical sealant composed of polydopamine functionalized nano-silicate (Laponite) has demonstrated improved adhesion, controlled swelling, and biodegradability. These hydrogel also exhibited excellent recovery ability, strong tissue adhesiveness, and reduced blood clotting time, making them a promising option for surgical sealants (Rajabi et al., 2020). Moreover, a new moldable hydrogel composed of PEG-dopamine and nano-silicate (Laponite) has been developed as an injectable surgical sealant. The inclusion of NPs allows the hydrogel to be reshaped and solidified to close tissue defects (Liu et al., 2017).

Hydrogels can be functionalized, making them ideal for controlled drug delivery (Wei et al., 2020; Wu et al., 2020). A novel HPMC-based PLGA nanoparticulate hydrogel infused with *Croooandra infundibuliformis* leaf extract demonstrated favorable viscosity and spreadability. The hydrogel exhibited an initial burst release followed by sustained drug release over 24 h (Jyothi et al., 2017). Nanocomposite hydrogels have also been utilized for improving transdermal drug delivery. Jose et al. (2016) fabricated an HPMC-based hydrogel embedded with pirfenidone encapsulated in liposomes, combined with various penetration enhancers, including oleic acid and isopropyl myristate. The nanocomposite hydrogels demonstrated enhanced skin permeation, exhibiting a transdermal flux approximately 5 times greater than hydrogels containing free drugs (Jose et al., 2016). Hydrogels can also be modified for on-demand drug delivery, where internal or external stimuli trigger drug release. When NPs integrated into a hydrogel respond to specific stimuli, the material is referred to as an intelligent nanocomposite hydrogel. The type of stimulus required to release a drug from the hydrogel is determined by the properties of the NPs. Stimuli such as pH, temperature, enzymes, ionic strength, light, electric field, and magnetic field can induce reversible change in the hydrogel's structure. These changes regulate drug release by altering the swelling, dissolution, or erosion of the hydrogel network. Intelligent nanocomposite hydrogels are the basis of self-regulated and site-specific drug delivery systems (Zhao et al., 2015). For instance, polyacrylamide (PAAm)-based nanocomposite hydrogel incorporating polyaniline (PAL) nanofibers was fabricated using amoxicillin as a model drug. PAL formed a three-dimensional nanofiber network within the hydrogel matrix and acted as a regulator for drug delivery through electrical stimulation. The nanocomposite hydrogel demonstrated sustained drug release when exposed to cathodic electrical stimulation. Moreover, it exhibited an "on-off" drug release pattern, controlled by the activation and deactivation of the PAL's electrochemical reduction properties. These adjustable properties highlight the suitability of nanocomposite hydrogels for electrically regulated drug delivery applications, such as implantable devices and TDDS (Pérez-Martínez et al., 2016). An alginate-graphene oxide nanosheet hydrogel nanocomposite was also developed as an electrically responsive hydrogel for the transdermal delivery of methotrexate (MTX). Electrical stimulation increased the cumulative release of the drug due to enhanced electrostatic repulsion (Yun et al., 2020). In addition, Carbopol 934-based hydrogel containing nanomicelles was developed for skin application. MTX loaded into polycaprolactone-polyethylene glycol-polycaprolactone (PCL-PEG-PCL) nanomicelles showed greater drug accumulation in inflamed joints of rats. The hydrogel also enhanced the pharmacokinetic parameters (e.g., half-life, AUC, residence time) and pharmacodynamic profile while reducing hepatotoxicity and avoid immune system activation. This indicates its potential as a therapeutic option for rheumatoid arthritis (Qindeel et al., 2020). The applications of nanocomposite hydrogels are summarized in Table 1.

Table 1. Application of nanocomposite hydrogels

References	Application	Matrix	Nano-filler	Drug	Findings
Agnihotri et al. (2012)	Antimicrobial wound dressing	Chitosan-PVA	AgNPs	N/A	The AgNPs-chitosan-PVA hydrogel exhibited good antibacterial activity against *E. coli.*
Jayaramudu et al. (2013)	Antimicrobial wound dressing	Carrageenan	AgNPs	N/A	The AgNPs nanocomposite carrageenan-based hydrogels effectively inhibited bacterial growth against both *Bacillus* and *E. coli.*
Szymańska et al. (2018)	Mucoadhesive hydrogels	Carbopol 974P	AgNPs	N/A	AgNPs hydrogels demonstrated a substantial reduction in the infectivity of herpes simplex virus type 1 and 2.
J. Wang et al. (2016)	Antimicrobial wound dressing	Agarose	ZnO-PEGMA	N/A	The hydrogels demonstrated strong bactericidal activity against *E. coli* and *S. aureus*, while maintaining biocompatibility, suggesting the potential application for wound dressing.
Zhao and Yuan (2023)	Wound dressing	Carboxymethyl chitosan	Selenium NPs	N/A	The developed hydrogels effectively promoted vascular regeneration, induced tissue remodeling, and accelerated wound healing in animal models.
Rajabi et al. (2020)	Surgical sealants	Thiolated gelatin and gelatin methacrylate	Polydopamine functionalized Laponite	N/A	The nanocomposite hydrogel demonstrated improved adhesion, controlled swelling, and biodegradability, exhibited excellent recovery ability, strong tissue adhesiveness, and decreased blood clotting time.
Liu et al. (2017)	Surgical sealants	Dopamine-PEG	Nano-silicate (Laponite)	N/A	The moldable nanocomposite hydrogel can be reshaped and solidified into a new shape, effectively closing defects in the tissue.
Jyothi et al. (2017)	Sustained release drug delivery	HPMC	PLGA-NPs	*Croooandra infundibuliformis* leaf extract	Nanocomposite hydrogel exhibited sustained release kinetic over 24 h.
Jose et al. (2016)	Enhanced transdermal drug delivery	HPMC	liposomes	pirfenidone	Nanocomposite hydrogels demonstrated better skin permeation (5 times greater in transdermal flux) compared with hydrogel with free drug.
Pérez-Martínez et al. (2016)	Electrical responsive hydrogel	Polyacrylamide	polyaniline nanofibers	amoxicillin	The nanocomposite hydrogel released amoxicillin in a sustained release manner when exposed to cathodic electrical stimulation and showed a pattern of turning drug release on and off upon the application and removal of electrical stimulation.
Yun et al. (2020)	Electrical responsive hydrogel	Sodium alginate	Graphene oxide nanosheet	methotrexate	An electrical-responsive hydrogel could significantly enhance cumulative drug release when exposed to the electrical stimulation.
Qindeel et al. (2020)	Enhanced transdermal drug delivery	Carbopol 934	PCL-PEG-PCL nanomicelles	methotrexate	Hydrogel with PCL-PEG-PCL nanomicelles showed greater drug accumulation in rats' inflamed joints, and improved pharmacokinetic and pharmacodynamic profile. As compared with the free drug, nanomicelles significantly improved the pharmacokinetic with 4.34-fold greater half-life, 3.68-fold higher AUC_{0-t}, and 3.15-fold higher mean residence time. The nanocomposite hydrogel also reduced hepatotoxicity and did not activate the immune system, indicating its potential as a treatment for rheumatoid arthritis.

4.2 Nanocomposite membranes and films

Drug delivery through transdermal membranes is becoming increasingly popular. Unlike orally administered drugs, TDDS can reduce systemic side effects, especially during prolonged use. TDDS also exhibits excellent compatibility with human skin offering benefits such as moisture retention and oxygen permeability. The physicochemical properties of a transdermal film—including thickness, permeability, composition, rigidity, and stability—can be modified to influence the drug release rate and enhance overall functionalities (Picart, 2008; Wang et al., 2008). For example, a transdermal matrix patch made from ethyl cellulose and polyvinylpyrrolidone (PVP), containing piroxicam-SLN, was developed to enhance skin permeation and reduce systemic adverse effects, such as gastrointestinal toxicity. The piroxicam-SLN patch exhibited a higher transdermal flux of 17.16 μg/cm^2/h compared to 4.6 μg/cm^2/h for a piroxicam patch without SLN. Moreover, the patch cause no signs of skin irritation, and kinetic studies suggested enhanced transdermal bioavailability when incorporating SLN into the formulation (Mangesh et al., 2016). Likewise, da Silva et al. (2020) developed a nanoemulsion incorporated into chitosan films for delivering methylsalicylate. The nanoemulsion increased the drug loading capacity in the hydrophilic film, improved moisture content and film stability, and prevented phase separation. Besides, the nanoemulsion enhanced drug release compared to a physical mixture film (da Silva et al., 2020). Nanofillers not only enhance skin permeation and drug release but also improve the mechanical properties of transdermal films. For example, chitosan transdermal films incorporated with cellulose nanofibrils improved mechanical strength upon nanofibril loading (Ojo et al., 2024). Clay-based transdermal films have gained attention due to their unique structure and properties. Propranolol-incorporated nanocomposite PVA films containing alumina-silicate clay (halloysite nanotubes; HNTs) exhibited good appearance, mechanical stability, uniform drug content, controlled drug release profile and enhanced skin permeation. The optimized films were safe, non-irritating, and could lead to a cost-effective and commercially viable for TDDS applications (Sikandar et al., 2022). In addition, a nanocomposite PVA film incorporating cellulose nanofiber and titania NPs, which encapsulate diclofenac sodium, D-penicillamine, and phosphomycin. These films exhibited delayed and controlled drug release kinetics due to the interaction between titania NPs and cellulose nanofiber (Galkina et al., 2015). Moreover, macroporous PVA films reinforced with graphene oxide were fabricated to modulate the ketoprofen delivery. The graphene oxide sheets reduced drug release rates by lowering permeability and increasing diffusion distance (Kurniawan et al., 2019). Biocompatible nanocomposite membranes integrating nanosilica with guar gum-graft-polyacrylamide (GG-g-PAM) copolymer demonstrated efficient and sustained delivery of diltiazem through the skin. Membranes containing 1% nanosilica exhibited the best performance, with approximately 24.76% drug release within 20 h. These membrane were non-irritating and non-cytotoxic, suggesting their potential for transdermal drug delivery (Dutta et al., 2017). A novel transdermal membrane utilizing polyethersulfone (PES), and PVP, combined with mesoporous nanosilica, was developed to enhance the transdermal delivery of azithromycin. The addition of mesoporous nanosilica augmented membranes durability, flexibility and water vapor transmission. The porous structure functioned as a drug reservoir, enabling sustained drug release following zero-order kinetics. The membranes displayed a commendable safety profile, making them promising candidates for transdermal drug delivery (Samari et al., 2024). Lastly, polyurethane nanocomposite films incorporating montmorillonite (Mt) clay, and reduced graphene oxide (rGO) were fabricated for transdermal delivery of progesterone. XRD and NMR analyses revealed modification in the polymer structure due to nanofillers. The nanoclay provided sustained drug release and controlled skin permeation, attributed to the chemical and/or physical interactions between the NPs and polymer chains, or the physical obstruction of drug diffusion by NPs (Vieira et al., 2020). The applications of nanocomposite membranes and films are summarized in Table 2.

4.3 Nanocomposite pressure-sensitive adhesives (PSAs)

Among the various types of TDDS, the drug-in-adhesive system is particularly popular due to its ease of formulation and convenience for patient self-application. This system incorporates the drug dispersed or dissolved within the polymer matrix, which also serves as the adhesive layer. Pressure-sensitive adhesives (PSAs) are a key component of the drug-in-adhesive system, functioning as a drug-containing matrix while also providing strong adhesion. PSAs are viscoelastic materials that adhere firmly to smooth surfaces with minimal pressure and can be removed without leaving any residue (Bozorg and Banga, 2020). In recent decades, researchers have investigated various techniques to improve the mechanical properties and stability of PSAs, and to regulate drug delivery over specific durations. The integration of nanocomposites into PSAs has highly effective in achieving these goals. For example, a PSA nanocomposite was fabricated using PAAm and poly(acrylamide-hydroxyethyl methacrylate) (HEMA) reinforced with polystyrene (PS) nano-fillers. This formulation demonstrated increased elasticity and tackiness while retaining high water content, enabling compatibility with liquid excipients without altering adhesive properties (Baït et al., 2011). Nanocomposite filler particles can reinforce PSAs by cross-linking multiple polymer chains through their large surface area-to-volume ratios. Filler particles that create strong physical and chemical interactions with the surrounding polymer matrix, while maintaining dispersion and preventing aggregation, could lead to significant advancement in PSA performance. For instance, nanocomposite PSAs comprising poly(n-butyl acrylate-co-acrylic acid) chains attached to SiO2 NPs (PGNPs) demonstrated enhanced shear resistance while maintaining adhesive properties (Ojo et al., 2024). Furthermore, PSA patches incorporating NLCs have been developed to enhance capsaicin delivery through the skin. An optimal NLC formulation containing 0.3% capsaicin, with particle sizes below 200 nm and excellent stability, was used to create these patches. The patches composed of 7% polyacrylic acid as the polymer base, provided strong adhesion and sustained release of capsaicin. Additionally, the capsaicin-loaded NLC PSA delivered more capsaicin into the deeper skin layers compared to traditional capsaicin patches, improving transdermal delivery. A human study showed that NLC-loaded patches reduced skin side effects of capsaicin, such as burning and irritation, suggesting the efficacy of NLC in facilitating transdermal delivery with minimal skin irritation (Arunprasert et al., 2022).

Table 2. Application of nanocomposite membranes and films

References	Application	Matrix	Nano-filler	Drug	Findings
Mangesh et al. (2016)	Enhancing transdermal delivery	Ethyl cellulose and PVP	SLN	Piroxicam	The drug release from patch incorporated with SLNs was found 66.6% up to 24 h, significantly less as compared to plain piroxicam patch having release of 88.01%. Piroxicam-SLN patch can improve drug skin permeability with satisfactory flux of 17.16 μg/cm^2/h compared with that of plain piroxicam patches (4.6 μg/cm^2/h), and transdermal bioavailability without causing skin irritation.
da Silva et al. (2020)	Enhancing drug release	Chitosan	Nanoemulsion	Methyl salicylate	The addition of nanoemulsion could increase loading capacity of oily drug. Also, the nanocomposite films exhibited enhanced drug release compared with physical mixture film. At least 30% of drug was released in the first 6 h of the experiment, suggesting the burst release effect.
Ojo et al. (2024)	Transdermal film with improved mechanical strength	Chitosan	Cellulose nanofibrils	Aspirin	The incorporation of cellulose nanofibrils could improve mechanical properties of the transdermal film.
Sikandar et al. (2022)	Controlled drug release and enhanced skin permeation	PVA	Halloysite nanotubes (HNTs)	Propranolol	The nanocomposite films exhibited good appearance, mechanical stability, consistent drug content, controlled drug release profile (80% in 4 h) and enhanced skin permeation with maximum flux of 145.812 μg/cm^2/h. Also, the optimized film was safe, non-irritating, and stable.
Galkina et al. (2015)	Sustained drug release	PVA	Titania NPs and cellulose nanofiber	Diclofenac sodium, D-penicillamine, and phosphomycin	The nanocomposite transdermal film exhibited delayed and controlled drug release kinetics, with only 25% of drug was released in 25 h.
Kurniawan et al. (2019)	Sustained drug delivery	PVA	Graphene oxide sheet	Ketoprofen	Macroporous PVA transdermal films loaded with graphene oxide could provide a delayed drug release rate of ketoprofen over a period at least 12 h.
Dutta et al. (2017)	Sustained drug delivery	Guar gum-graft-polyacrylamide (GG-g-PAM)	Nanosillica	Diltiazem	The GG-g-PAM nanocomposite membrane demonstrated a sustained delivery of diltiazem through the skin. The nanocomposite containing 1 wt% nanosilica provides the best result with 8.58 and 24.76% drug release after 5 and 20 h, respectively. The developed membrane also exhibited favorable performance, non-irritation and non-cytotoxicity.
Samari et al. (2024)	Sustained drug delivery	polyethersulfone (PES), and polyvinylpyrrolidone (PVP)	Nanosilica	Azihromycin	The nanocomposite membrane containing mesoporous nano silica had increased durability, flexibility, and higher water vapor transmission rate. The optimized membranes demonstrated a substantial increase in drug release (906 mg/L) compared to the unmodified membrane (440 mg/L).
Vieira et al. (2020)	Sustained drug delivery	Polyurethane	montmorillonite (Mt) clay and reduced graphene oxide (rGO)	Progesterone	Nanofiller incorporation can cause a structural change of polymer material and provided a controlled drug release and skin permeation. Drug release was decreased from 99% for film without nano-clay to 53% for films containing nanoclay.

4.4 Nanocomposite microneedles (MNs)

Nanocomposite MNs are gaining attraction in medical research for their potential in drug delivery and diagnostics. These tiny needles, composed of nanomaterials, can penetrate the skin painlessly. Recent studies highlight their effectiveness in vaccine delivery, where researchers are exploring biocompatible and biodegradable materials to improve safety. For example, nanocomposite MNs made from poly(lactide-co-glycolide) were developed to carry lipid nanocapsules loaded with antigens for transcutaneous immunization. These MNs could remain in the skin for over 24 h, enabling the lipid nanocapsules to be uptaken by antigen-presenting cells, resulting in effective immunization. This indicates the potential of lipid nanocapsules delivered by MNs as a promising noninvasive vaccine delivery method (DeMuth et al., 2012). Additionally, nanocomposite hydrogel MNs show great promise in cancer therapy, especially in combined treatments such as chemotherapy, immunotherapies, and other anticancer treatments. Their relevance in treating melanoma lies in their ability to penetrate the skin at an appropriate depth for treating superficial lesions, making them ideal for dermatology and skin cancer treatment (Y. Huang et al., 2022). By targeting affected skin area with appropriate therapeutic agents, systemic exposure is minimized, reducing side effects. For solid and superficial cancers, combining chemotherapy with photothermal therapy (PTT) enhances treatment effectiveness. Chemotherapy addresses both primary tumors and distant metastases, while PTT uses light-absorbing sensitizers, such as molecules or plasmonic NPs, to focus treatment at the tumor site (Nam et al., 2019). For instance, nanocomposite MNs fabricated from hyaluronic acid and loaded with gold nanorods (AuNRs) and doxorubicin (DOX) combined photothermal effects with chemotherapy, showing significant tumor reduction without recurrence after a single treatment (Hao et al., 2018). Another example is nanocomposite MN patch loaded with tumor-targeted lipid NPs, designed for precise co-delivery of immunotherapeutic agents and the chemotherapeutic agent cisplatin to cancer tissues. These MNs enabled localized delivery of nano-encapsulated chemotherapeutic and immunotherapeutic agents at tumor skin sites, providing a novel treatment strategy for delivering anticancer drug directly to tumor sites (Lan et al., 2020). Furthermore, combining MNs with nanomaterials can create theranostic systems that integrates therapy, imaging, and diagnostics into a single smart platform. These systems enhance treatment effectiveness while allowing real-time monitoring of therapeutic responses (Farokhzad and Langer, 2006; Martins et al., 2024). Despite significant progress in developing hydrogel MNs with embedded NPs, challenges remain in synthesis and in vivo applications. Issues include structure clearance after therapeutic release and risks associated with prolonged retention, which may cause adverse effects. Future strategies should focus on controlled degradation and the gelation, development of smart polymer systems to optimize and ensure safety during therapeutic applications. Enhancing interfaces between biomedical devices and the body, coupled with optimizing needle design and material properties, can minimize tissue damage and immune reactions. Integrating various NPs into MNs can add functionalities such as monitoring tissue parameters and modulating the tumor microenvironment, thereby enhancing treatment effectiveness. Examples of nanocomposite MNs applications are illustrated in Figure 5.

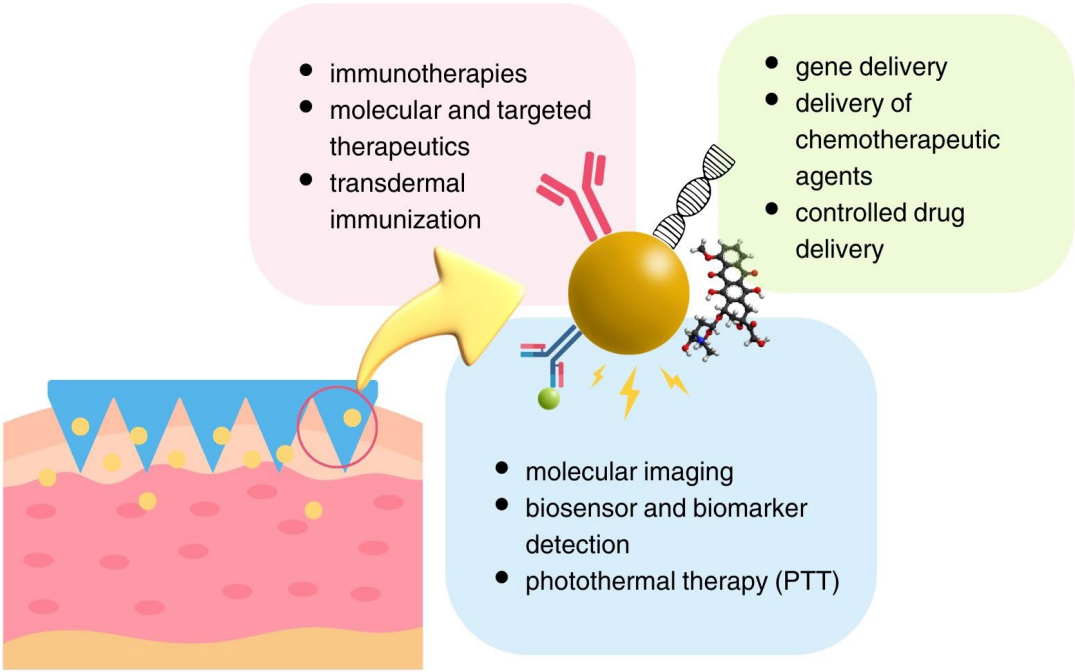

Figure 5. Applications of nanocomposite MNs

5. BIOMEDICAL APPLICATIONS OF NANO-COMPOSITE PATCHES IN TRANSDERMAL DRUG DELIVERY

Nanocomposite patches hold immense potential in biomedical applications for transdermal drug delivery, offering innovative solutions to improve therapeutic outcomes and patient care. These patches integrate NPs within polymeric matrices to enhance drug stability, control drug release kinetics, improve skin permeation, and enable targeted delivery. Considering its ability to enhance drug delivery efficiency, nanocomposite patches are designed to overcome barriers such as the SC and enhance drug permeation. This capability is particularly advantageous in delivering therapeutics requiring sustained release or precise dosing over extended periods. Incorporating NPs such as liposomes, metal, or polymer-based nanocarriers optimizes drug distribution and improve therapeutic efficacy (Kim and Choi, 2021; Parhi, 2018).

Nanocomposite patches are useful in the treatment of various disorders. In dermatology, these patches offer targeted delivery of medications for treating various skin conditions. For instance, patches formulated with lipid-based NPs can deliver drugs directly to affected areas, alleviating symptoms of conditions like psoriasis (C. Huang et al., 2022; Wang et al., 2022) or alopecia (Zhang et al., 2023). The controlled release provided by nanocomposite patches helps maintain therapeutic drug levels in the skin, enhancing treatment outcomes while minimizing systemic side effects. In wound healing and tissue regeneration, nanocomposite patches play a crucial role by delivering growth factors, antimicrobial agents, or regenerative biomolecules directly to wounds. NPs embedded within the patch matrix facilitate the controlled release of therapeutic agents, promoting faster wound healing, reducing infection risks, and supporting tissue regeneration. These patches can be tailored to provide localized therapy, addressing specific wound characteristics and patient needs for improved clinical outcomes (Dam et al., 2023).

Transdermal nanocomposite patches are increasingly used for delivering analgesic drugs to manage acute and chronic pain. Lipid NPs encapsulate pain-relieving medications, allowing sustained release over hours to days. This approach provides continuous pain relief, improves patient comfort, reduces reliance on systemic adverse effects, and enhances pain management strategies (Gaur et al., 2013). Nanocomposite patches have also shown significant promise in cancer therapy and localized treatments. These patches deliver chemotherapeutic agents directly to tumors or cancerous lesions through the skin. NPs can be functionalized to target specific cancer cells or tumor microenvironments, enhancing drug accumulation at the site of action while minimizing systemic exposure and off-target effects. This targeted delivery approach improves therapeutic efficacy, reduces treatment-related toxicity, and supports personalized cancer treatment strategies (Nazir et al., 2021; Sharma and Otto, 2024).

6. LIMITATIONS AND PERSPECTIVES

Nanocomposite patches have emerged as a promising solution for transdermal drug delivery, offering enhanced drug permeation, controlled release, and improved patient compliance. However, several limitations hinder their widespread clinical adoption.

1. Potential toxicity of nanomaterials: While nanomaterials enhance functionality, their long-term effects remain concern. The accumulation of NPs in the body and their potential interactions with organs are not fully understood. Rigorous toxicological studies are crucial to ensure their safety for human use (Xuan et al., 2023).
2. Risk of skin irritation and allergic reactions: Although hydrogels are generally biocompatible, inclusion of NPs can alter their surface properties, potentially causing adverse reactions in sensitive individuals. Careful selection of biocompatible nanomaterials and surface modifications is essential to mitigate these risks (Sanità et al., 2020).
3. Challenges in scalable manufacturing: Manufacturing nanocomposite patches on a large scale with reproducible characteristics and cost-effectiveness pose significant challenges. Ensuring uniform NPs dispersion within the hydrogel matrix and maintaining patch integrity during storage and application require sophisticated and scalable fabrication techniques (Martins et al., 2024).
4. Optimization of drug loading and release profiles: Achieving optimal drug loading and desired release profiles presents another challenge. Parameters such as NP size, surface charge, and interactions with the drug and hydrogel matrix can significantly influence drug loading capacity and release kinetics. Researchers are continually refining these parameters to achieve desired therapeutic outcomes (Parhi, 2018).
5. Regulatory hurdles for approval: As a relatively new technology, nanocomposite patches face stringent regulatory requirement for approval. Demonstrating long-term safety, efficacy, and manufacturing consistency is essential for regulatory acceptance. Comprehensive preclinical and clinical studies are needed to build a robust safety and efficacy profile, paving the way for widespread clinical adoption (Ramezani and Ripin, 2023).

Despite the existing limitations, nanocomposite patches for transdermal drug delivery exhibits substantial potential for advancement. Transitioning nanocomposite transdermal patches from laboratory-scale development to clinical implementation and real-world application necessitates concerted collaborative efforts and the establishment of robust supporting data. To expedite the translation of this nanotechnology from experimental settings to clinical application, extensive and rigorous preclinical and clinical research is imperative. During the development process, computational modeling and simulation techniques can be employed to optimize patch design, predict drug release kinetics, and assess potential toxicity risks. This in silico approach accelerates development process and reduces reliance on costly and time-consuming in vitro and in vivo experiments. Given the paramount importance of safety and toxicity in pharmaceutical development, the use of well-established biocompatible materials such as natural polymers and lipid-based NPs is a sensible strategy to prioritize safety. Furthermore, conducting in-depth and comprehensive

investigations of the skin penetration mechanism of nano-systems to gain insightful information regarding efficacy and safety is pivotal for successful clinical translation. Before human application, rigorous quality control measures are essential to ensure product efficacy, quality, and safety. It is mandatory to conduct thoughtfully designed quality tests that adhere to the standard guidelines established by regulatory bodies.

6.1 Potential research direction and technological advancements

In the context of future developments, nanocomposite transdermal patches not only facilitate improved drug delivery but also exhibit potential for personalized medicine and multifunctionality. These innovations include customized treatment, combination therapy, and patches integrated with biosensors to monitor physiological parameters and offer real-time feedback. Such advancements are expected to enhance therapeutic effectiveness, reduced adverse effects, and improved patient adherence. Potential areas for research may involve the exploration and advancement of novel nanomaterials and transdermal patch components, with the goal of enhancing their physicochemical properties while ensuring safety. Advancements in nanotechnology and material science also enable the development of personalized nanocomposite patches tailored to individual patient needs. This includes customizing drug release profiles and patch size and even incorporating diagnostic sensors for real-time monitoring, ushering in a new era of personalized medicine. Smart TDDS have emerged as an exciting innovation. These systems incorporate stimuli-responsive elements into nanocomposite patches, enabling on-demand drug release triggered by external stimuli such as temperature, pH, or ultrasound. This targeted delivery approach improves drug efficacy and reduces side effects, opening new possibilities for personalized treatment approaches. Future research should also prioritize toxicology studies, particularly focusing on long-term toxicity assessment and addressing regulatory requirements to ensure patient safety. Developing scalable and cost-effective manufacturing techniques is important for commercial success. Research in this area will focus on streamlining production processes while maintaining high product quality. Advanced technologies, such as 3D printing, have been integrated to revolutionize the production of transdermal patches. 3D printing technology offers precise, customizable, and optimized complex designs. In summary, the future of nanocomposite transdermal patches lies in enhancing drug delivery efficiency, personalization, and multifunctionality. Supported by advances in nanomaterial research, smart systems, biocompatibility, scalable manufacturing, and cutting-edge technologies, these patches promise to deliver more effective, safe, and user-friendly TDDS, revolutionizing patient care.

7. CONCLUSION

Integrating nano-fillers into polymeric matrices has created multicomponent systems with enhanced functionalities due to advancements in polymer science and nanotechnology. Biodegradable and biocompatible polymers have demonstrated great potential in drug delivery, particularly in transdermal drug delivery, making them preferred choice for new product development. Nanocomposite materials have been utilized in the fabrication of transdermal patches, offering enhancement in mechanical strength, drug loading capacity, and controlled drug release over prolonged periods. The ongoing modification and incorporation of functional nanofillers are expected to drive further advancement in this field. Biocompatible nanomaterials, such as lipids and hydrophilic polymers are promising choices for use in nanocomposite transdermal patches. However, the safety of metal and inorganic NPs is still questionable, necessitating robust toxicity assessment to ensure their safe application. Another challenge lies in achieving proper dispersion and alignment of reinforcing agents within the polymer matrix. NPs tend to form macro-sized agglomerates, which can compromise the desired properties of nanocomposites. Ensuring excellent dispersion and morphology control of NPs within the matrix is crucial for optimizing nanocomposite performance. Employing advance characterization techniques can help to address these issues and enhance the overall functionality of nanocomposite system.

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