

RAPID-DISSOLVING MICRONEEDLE PATCHES LOADED WITH NANO-TRANSFERSOMES: A NOVEL TRANSDERMAL DRUG DELIVERY APPROACH

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Abstract

Transdermal drug delivery offers several advantages over conventional oral and parenteral administration; however, the stratum corneum presents a major barrier to the effective delivery of many therapeutic agents. Rapid-dissolving microneedles have emerged as a minimally invasive approach capable of creating temporary microchannels in the skin and facilitating drug transport. Among advanced nanocarriers, Nano-Transfersomes are particularly attractive because of their high deformability, nanoscale size, and ability to enhance drug permeation across biological barriers. The integration of nano-transfersomes into rapidly dissolving microneedle patches combines the penetration-enhancing capability of microneedles with the drug-delivery advantages of flexible lipid vesicles. This review discusses the principles, classification, materials, fabrication techniques, mechanisms of skin penetration and drug release, and therapeutic applications of rapid-dissolving microneedle patches loaded with nano-transfersomes. Particular emphasis is placed on their potential applications in osteoporosis, cancer, vaccination, infectious diseases, dermatological disorders, and delivery of biological therapeutics. Recent advances, formulation challenges, stability considerations, manufacturing approaches, and future opportunities for personalized and targeted transdermal therapy are also discussed. Overall, nano-transfersome-loaded rapid-dissolving microneedles represent a promising next-generation platform for improving transdermal drug delivery and may facilitate the development of safer, more effective, and patient-friendly therapeutic systems.

Keywords: *Rapid-dissolving microneedles; Nano-transfersomes; Transdermal drug delivery; Nanocarriers; Skin permeation*

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1. Introduction

Transdermal drug delivery is an attractive alternative to oral and parenteral administration because it can provide controlled drug release, improve patient compliance, and avoid gastrointestinal degradation and hepatic first-pass metabolism. However, the stratum corneum acts as a major barrier, limiting the transdermal delivery of many therapeutic agents. Zafar et al. (2025) reported that microneedle-based systems can effectively overcome this barrier by creating temporary microscopic pathways in the skin.

Microneedles (MNs) are minimally invasive devices containing micron-sized projections that facilitate drug transport across the stratum corneum. Among different types, dissolving microneedles have gained considerable attention because they are fabricated from biodegradable or water-soluble materials and dissolve within the skin after application, eliminating needle removal and sharps waste. Dave et al. (2024) highlighted their potential for controlled and patient-friendly transdermal delivery.

However, the delivery of poorly soluble or unstable drugs through microneedles can remain challenging. Incorporation of nanocarriers into MN systems provides an opportunity to improve drug solubilization, stability, skin deposition, and controlled release. Zarepour et al. (2025) described microneedle-assisted nanomedicine as an emerging strategy that combines nanoscale drug carriers with minimally invasive skin penetration.

Transfersomes are highly deformable lipid vesicles composed mainly of phospholipids and edge activators. Their flexibility enables enhanced interaction with and penetration through the skin. Matharoo et al. (2024) reported that transfersomes have considerable potential for improving dermal and transdermal drug delivery.

The combination of nano-transfersomes with rapid-dissolving microneedle patches integrates the barrier-penetrating ability of microneedles with the drug-loading and skin-penetration properties of deformable nanovesicles. This approach may improve drug delivery efficiency while offering advantages such as enhanced drug deposition, controlled release, reduced invasiveness, and improved patient acceptability. However, challenges related to formulation stability, drug loading, mechanical strength, dissolution behavior, manufacturing, and regulatory translation remain. Therefore, this review focuses on the formulation, fabrication, characterization, drug-delivery mechanisms, applications, advantages, limitations, and future prospects of rapid-dissolving microneedle patches loaded with nano-transfersomes.

1.2 Overview of Transdermal Drug Delivery

Transdermal drug delivery systems (TDDS) are dosage forms designed to deliver therapeutic agents across the skin into systemic circulation or to specific skin tissues. They offer

advantages such as improved patient compliance, controlled drug release, reduced dosing frequency, and avoidance of gastrointestinal degradation and hepatic first-pass metabolism. Singh et al. (2024) reported that transdermal systems can provide prolonged therapeutic effects while offering a convenient alternative to conventional administration routes.

The major limitation of transdermal delivery is the stratum corneum, which acts as the primary barrier to drug penetration. Consequently, only drugs with suitable molecular size, lipophilicity, potency, and skin permeability are readily amenable to conventional transdermal delivery. Gaikwad et al. (2024) reviewed physical permeation-enhancement approaches, including iontophoresis, sonophoresis, electroporation, and microneedles, to overcome this barrier.

Conventional TDDS include reservoir systems, matrix systems, drug-in-adhesive patches, gels, creams, and films. Recent developments have expanded TDDS toward nanocarriers and active penetration-enhancement technologies. Kushwaha and Palei (2024) described the evolution of TDDS into different generations incorporating advanced approaches for improving drug permeation and dermal drug deposition.

Among these approaches, microneedles have gained particular attention because they create temporary microscopic pathways through the stratum corneum while maintaining minimally invasive administration. Nguyen and Banga (2025) highlighted microneedles as an important advancement in transdermal delivery, with applications ranging from conventional drugs to biologics and vaccines. Thus, modern TDDS increasingly combines microneedles, nanocarriers, and permeation-enhancement strategies to overcome skin barriers and improve therapeutic delivery.

1.3 Limitations of Conventional Transdermal Drug Delivery

Although conventional transdermal drug delivery systems offer controlled drug release and improved patient convenience, their application is restricted by the stratum corneum, which acts as the principal barrier to drug permeation. Gaikwad et al. (2024) reported that only a limited number of drug molecules can cross intact skin in therapeutically effective amounts, particularly because hydrophilic and high-molecular-weight drugs exhibit poor permeability.

Conventional transdermal systems are therefore mainly suitable for drugs possessing appropriate molecular size, lipophilicity, potency, and skin permeability. This restricts their application to many peptides, proteins, hydrophilic drugs, and other macromolecules. Nguyen and Banga (2025) emphasized that the barrier function of the stratum corneum substantially limits the range of drugs that can be effectively administered through conventional transdermal systems.

Other limitations include low drug flux, slow permeation, limited dose-loading capacity, variability in skin permeability, and difficulties in achieving adequate therapeutic concentrations. Conventional patches may also be affected by skin hydration, anatomical site, and individual physiological differences. Vaseem et al. (2024) highlighted the need for physical and technological permeation-enhancement approaches to overcome these limitations.

These limitations have encouraged the development of advanced approaches such as microneedles, nanocarriers, iontophoresis, sonophoresis, and other penetration-enhancement technologies. Among them, microneedles can bypass the stratum corneum by creating temporary microscopic pathways, thereby expanding the range of drugs suitable for transdermal delivery.

1.4 Microneedle-Based Drug Delivery Systems

Microneedle (MN)-based drug delivery systems are minimally invasive platforms designed to enhance drug transport across the skin by creating microscopic pathways through the stratum corneum. They combine the convenience of transdermal patches with the penetration capability of conventional needles, while generally causing less pain and tissue damage. Nguyen and Banga (2025) described MNs as an important advancement in transdermal delivery, with applications involving small molecules, biologics, vaccines, and other therapeutic agents.

MNs are broadly classified into solid, coated, hollow, dissolving, hydrogel-forming, and biodegradable microneedles, depending on their structure and drug-release mechanism. Each type offers different advantages in terms of drug loading, release profile, manufacturing, and therapeutic application. Xue et al. (2024) highlighted the expanding applications of different MN designs in transdermal and intradermal drug delivery.

Among these systems, dissolving microneedles (DMNs) are particularly attractive because they are prepared using water-soluble or biodegradable materials and dissolve after insertion into the skin, eliminating the need for needle removal and reducing sharps waste. Dave et al. (2024) reported that DMNs provide opportunities for controlled and minimally invasive delivery of therapeutic agents.

MNs can also be combined with nanocarriers, including liposomes, nanoparticles, nanoemulsions, and deformable vesicles, to improve drug solubility, stability, skin deposition, and controlled release. Kheirieh et al. (2025) highlighted the potential of combining nanocarriers with dissolving MNs to enhance localized drug delivery.

Despite their potential, MN systems face challenges including dose-loading limitations, mechanical strength, fabrication reproducibility, sterilization, safety, scale-up, and regulatory requirements. Moawad et al. (2025) particularly emphasized poor drug-loading capacity, dose inconsistency, manufacturing complexity, and regulatory barriers as important challenges for the clinical translation of dissolving MNs.

1.5 Types and Classification of Microneedles

Microneedles (MNs) can be classified according to their structure, composition, drug-loading strategy, and mechanism of drug release. The major types include solid, coated, hollow, dissolving, and hydrogel-forming microneedles. Each type possesses distinct characteristics that influence drug loading, release, fabrication, and therapeutic applications. Nguyen and Banga (2025) described these major MN platforms and highlighted their increasing use in transdermal and intradermal drug delivery.

- **Solid Microneedles:** These are primarily used to create microscopic pores in the stratum corneum before application of a drug formulation. They are commonly associated with the “poke-and-patch” approach and can improve skin permeability.
- **Coated Microneedles:** In this system, the drug is coated onto the surface of solid MNs. After insertion, the coating dissolves or releases the drug into the skin. This approach provides relatively rapid drug delivery but generally has limited drug-loading capacity.
- **Hollow Microneedles:** Hollow MNs contain internal channels through which liquid formulations can be delivered directly into the skin. They can provide controlled delivery but require more complex fabrication and may be susceptible to blockage.
- **Dissolving Microneedles:** These MNs are prepared using water-soluble or biodegradable polymers, sugars, or other biocompatible materials. After insertion, the MN matrix dissolves within the skin and releases the incorporated drug. Dave et al. (2024) reported that dissolving MNs are particularly attractive because they eliminate needle recovery and reduce sharps waste.
- **Hydrogel-Forming Microneedles:** These MNs absorb interstitial fluid after insertion and swell to form aqueous pathways through which drug molecules can diffuse from an attached drug reservoir. They can provide sustained drug delivery without leaving insoluble materials in the skin.
- **Hybrid and Nanocarrier-Loaded Microneedles:** Advanced systems combine MNs with nanoparticles, liposomes, transfersomes, nanoemulsions, or other nanocarriers. Such combinations can improve drug solubility, stability, skin deposition, and controlled

release. Kheirieh et al. (2025) highlighted the growing interest in combining nanocarriers with dissolving MNs for enhanced topical and transdermal delivery.

Overall, dissolving microneedles are particularly relevant to the present review because their biodegradable matrix can be used to incorporate nano-transfersomes and provide minimally invasive delivery while avoiding conventional needle disposal.

1.6 Rapid-Dissolving Microneedles: Principle and Mechanism

Rapid-dissolving microneedles (RDMNs) are minimally invasive drug-delivery systems designed to penetrate the stratum corneum and rapidly dissolve after insertion into the skin. They are generally fabricated from water-soluble or biodegradable polymers and other biocompatible materials, within which the drug or nanocarrier is incorporated. Dave et al. (2024) reported that polymer selection strongly influences the mechanical strength, insertion ability, dissolution behavior, and drug-release characteristics of dissolving microneedles.

The delivery process begins when the microneedle projections penetrate the stratum corneum, producing temporary microscopic channels. After insertion, interstitial fluid hydrates the polymeric matrix, resulting in rapid dissolution of the microneedle tips and release of the incorporated therapeutic agent into the viable epidermis and dermis. Zhuo et al. (2025) described this process as a simple mechanism in which the dissolving matrix releases the drug directly within the skin following insertion.

The rate of dissolution depends on factors such as polymer type and molecular weight, polymer concentration, needle geometry, water uptake, drug loading, and formulation composition. Hydrophilic materials such as polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), hyaluronic acid, and carboxymethyl cellulose are frequently investigated because of their ability to hydrate and dissolve in the aqueous skin environment. Kolekar et al. (2025) highlighted the importance of polymer selection and formulation design in achieving effective dissolution and delivery of therapeutic molecules.

In rapid-dissolving systems, drug release generally occurs through hydration, polymer dissolution, and diffusion. The temporary microchannels created during insertion also reduce the barrier function of the stratum corneum, allowing the released drug to reach deeper skin layers. Madhusoodanan et al. (2025) reported that advances in polymeric microneedle design and fabrication are being used to control dissolution and improve transdermal drug delivery.

For nano-transfersome-loaded RDMNs, the mechanism involves two complementary processes: the microneedle matrix provides mechanical penetration through the stratum corneum, while nano-transfersomes serve as deformable nanocarriers for transporting the drug within the skin. Thus, the combination can potentially improve drug deposition, protect

the incorporated drug, and provide controlled or localized delivery. Xiang et al. (2024) emphasized the potential of dissolving microneedles as platforms for incorporating advanced drug-delivery systems and therapeutic agents.

1.7 Transfersomes as Advanced Nanocarriers

Transfersomes are ultra-deformable lipid nanovesicles designed to improve topical and transdermal drug delivery. They generally consist of phospholipids, an aqueous phase, and an edge activator, which increases membrane flexibility and allows the vesicles to deform during skin penetration. Manchanda et al. (2025) reported that the flexible bilayer of transfersomes enables the incorporation of both hydrophilic and lipophilic drugs and supports enhanced transdermal delivery.

The major advantage of transfersomes is their high deformability. Their flexible membranes can adapt to narrow intercellular pathways within the stratum corneum, while the hydration gradient across the skin provides a driving force for their movement. Matharoo et al. (2024) reported that this combination of flexibility and hydration-gradient-driven transport can improve drug permeation and facilitate delivery into different skin layers.

The composition of transfersomes also influences their physicochemical and delivery characteristics. Phospholipid concentration, type and concentration of edge activator, drug properties, vesicle size, surface characteristics, and preparation method can affect entrapment efficiency, deformability, stability, and skin permeation. Simrah et al. (2024) emphasized the importance of formulation composition and physicochemical characteristics in obtaining efficient transfersomal systems.

Transfersomes can accommodate a broad range of therapeutic molecules, including small hydrophilic and lipophilic drugs, peptides, proteins, and other bioactive compounds. Their ability to protect incorporated drugs from environmental degradation and improve localized skin delivery makes them attractive alternatives to conventional vesicular systems. Matharoo et al. (2024) highlighted their potential for delivering molecules that are difficult to transport through intact skin.

Compared with conventional liposomes, transfersomes provide greater membrane flexibility and are therefore particularly suited to overcoming the skin barrier. Jain et al. (2021) described transfersomes as elastic liposomes whose deformability can enhance penetration through narrow skin pathways.

Recent research has further explored transfersomal patches, hybrid nanocarriers, surface-modified transfersomes, and microneedle-assisted transfersomal delivery. These approaches aim to improve stability, drug loading, penetration, and therapeutic targeting. Manchanda et

al. (2025) highlighted clinical studies and emerging applications of transfersomes, while recent research has also investigated their combination with microneedle systems.

Thus, transfersomes represent an important lipid-based nanocarrier platform for overcoming the limitations of conventional transdermal delivery. Their deformability, biocompatibility, drug-loading versatility, and enhanced skin interaction make them particularly suitable for incorporation into rapid-dissolving microneedle patches.

1.8 Nano-Transfersomes: Composition

Nano-transfersomes are nanosized, ultra-deformable lipid vesicles designed to improve dermal and transdermal drug delivery. Their basic structure consists of a phospholipid bilayer containing an edge activator, with an aqueous internal phase that can accommodate hydrophilic drugs, while lipophilic drugs can be incorporated within the lipid bilayer. Manchanda et al. (2025) described phospholipids and edge activators as the principal components responsible for the structural and functional properties of transfersomes.

Phospholipids such as phosphatidylcholine, soya phosphatidylcholine, and egg phosphatidylcholine form the main vesicular membrane. They provide structural integrity and determine the ability of the vesicle to encapsulate and retain the drug. Matharoo et al. (2024) reported that the choice and concentration of phospholipid can significantly influence vesicle characteristics, drug incorporation, stability, and skin delivery.

Edge activators are generally surfactants or bile salts, including Tween 20, Tween 80, Span 80, sodium cholate, and sodium deoxycholate. They are incorporated into the phospholipid bilayer to reduce lipid-packing rigidity and increase membrane flexibility. Simrah et al. (2024) emphasized that the type and concentration of edge activator are critical formulation variables because they influence deformability, vesicle size, entrapment efficiency, and permeation.

Alcohols or co-solvents, particularly ethanol, may also be incorporated into some transfersomal formulations. They can modify membrane fluidity and may contribute to enhanced skin permeation. Ascenso et al. (2020) reported that surfactants and alcohols can significantly alter the fluidity and penetration properties of phospholipid vesicles.

Cholesterol may be included as an optional membrane-modifying component. It can influence membrane packing, rigidity, permeability, and stability; however, its concentration must be optimized because excessive membrane rigidification may reduce the deformability that characterizes transfersomes. The recent formulation-focused review by Méndez-Gurabo et al. (2026) identifies cholesterol as an optional component alongside phospholipids and edge activators.

Thus, the performance of nano-transfersomes depends on the balance between phospholipids, edge activators, aqueous phase, drug, and optional membrane modifiers. Optimization of these components is essential to obtain small, stable, highly deformable vesicles with adequate drug loading and skin permeation.

1.9 Integration of Nano-Transfersomes with Dissolving Microneedles

The integration of nano-transfersomes with dissolving microneedles (DMNs) combines the skin-penetrating ability of microneedles with the deformability and drug-carrying capacity of transfersomes. In this approach, nano-transfersomes containing the therapeutic agent are incorporated into a water-soluble or biodegradable microneedle matrix. Following skin insertion, the microneedles dissolve and release the nanovesicles within the skin, potentially improving drug deposition and localized delivery. Kheirieh et al. (2025) identified nanocarrier-loaded dissolving microneedles as an emerging strategy for improving topical and transdermal delivery.

The integration generally involves preparation of nano-transfersomes followed by incorporation into the microneedle-forming polymeric solution. The resulting formulation must maintain adequate vesicle integrity while providing sufficient mechanical strength for skin penetration. Dave et al. (2024) emphasized that polymer composition, viscosity, drug loading, microneedle geometry, and drying conditions are important factors affecting the performance of dissolving microneedles.

After application, the microneedles penetrate the stratum corneum and rapidly hydrate in the aqueous skin environment. The polymeric matrix subsequently dissolves, releasing the incorporated nano-transfersomes into the viable skin layers. The released vesicles can then interact with the surrounding tissue and facilitate drug transport. Matharoo et al. (2024) reported that the deformability of transfersomes contributes to their ability to interact with and penetrate skin barriers, making them suitable candidates for combination with advanced transdermal platforms.

This combination may provide several advantages, including enhanced skin penetration, improved drug deposition, protection of the drug within the nanocarrier, reduced systemic exposure for locally acting drugs, and controlled drug release. Furthermore, dissolving MNs eliminate the need to remove intact needles after application. Zarepour et al. (2025) highlighted the potential of integrating nanomedicine with microneedle technology to overcome limitations associated with conventional transdermal delivery.

However, successful integration requires careful optimization because the fabrication process may affect nano-transfersome size, deformability, encapsulation efficiency, and stability.

Excessive drying, mechanical stress, or inappropriate polymer–surfactant interactions may compromise nanovesicle characteristics. Therefore, parameters such as vesicle size, PDI, zeta potential, entrapment efficiency, deformability, microneedle mechanical strength, insertion ability, dissolution time, drug content, and skin permeation should be evaluated.

Overall, nano-transfersome-loaded dissolving microneedles represent a multifunctional transdermal platform in which microneedles temporarily overcome the skin barrier while nano-transfersomes facilitate efficient drug transport. Further research is required to establish optimal formulation strategies, long-term stability, scalability, safety, and clinical translation.

1.10 Mechanism of Skin Penetration and Drug Release

The skin-penetration mechanism of nano-transfersome-loaded dissolving microneedles involves microneedle insertion, formation of temporary microchannels, polymer dissolution, nano-transfersome release, and subsequent drug diffusion. When the patch is applied, the microneedle tips mechanically penetrate the stratum corneum and create microscopic pathways, temporarily reducing the barrier effect of the skin. Nguyen and Banga (2025) described microchannel formation as the fundamental mechanism by which microneedles enhance transdermal drug transport.

Following insertion, the dissolving microneedle matrix absorbs interstitial fluid and gradually dissolves. This process releases the incorporated nano-transfersomes within the viable skin layers. The rate of dissolution is influenced by the polymer composition, molecular weight, microneedle geometry, skin hydration, and environmental conditions. Limcharoen et al. (2024) demonstrated that skin hydration and barrier condition can significantly influence the dissolution behavior of dissolving microneedles.

The released nano-transfersomes subsequently facilitate drug transport through the skin. Their high membrane deformability and hydration-gradient-driven movement enable them to interact with the lipid structures of the stratum corneum and improve drug permeation. Matharoo et al. (2024) reported that the flexible structure and surface properties of transfersomes contribute to enhanced dermal penetration and controlled drug release.

Drug release from the nano-transfersomes may occur through vesicle diffusion, membrane partitioning, and gradual drug release from the lipid bilayer or aqueous compartment, depending on the physicochemical properties of the drug and vesicle composition. The edge activator increases membrane flexibility and influences drug release and skin interaction. Manchanda et al. (2025) emphasized that the phospholipid–edge-activator structure is central to the transdermal performance of transfersomes.

1.11 Materials Used in Rapid-Dissolving Microneedle Patches

The performance of rapid-dissolving microneedle patches largely depends on the selection of biocompatible, water-soluble or biodegradable polymers that provide sufficient mechanical strength for skin insertion while allowing rapid dissolution after application. Commonly investigated materials include natural polymers, synthetic polymers, and their blends.

Hyaluronic acid (HA) is widely used because of its biocompatibility, biodegradability, high water-binding capacity, and ability to form dissolving microneedles. Its hydration properties facilitate rapid dissolution within the skin. PVP and PVA are synthetic water-soluble polymers frequently used because their molecular weight and concentration can be adjusted to control mechanical strength, dissolution rate, and drug release.

Other natural and semi-synthetic materials include chitosan, gelatin, alginate, carboxymethyl cellulose (CMC), dextran, and chondroitin sulfate. These materials can provide good biocompatibility and can be combined with synthetic polymers to improve mechanical properties and formulation stability.

For nano-transfersome-loaded microneedles, the polymer matrix must additionally be compatible with the nanovesicles and should not adversely affect their size, deformability, encapsulation efficiency, or stability during fabrication. PVP, PVA, HA, and CMC are therefore particularly relevant as matrix materials for incorporating nano/microparticles into dissolving microneedles.

Table 1: The major materials can be summarized as follows:

Material	Major role/properties
Hyaluronic acid (HA)	Biocompatible, biodegradable, rapid dissolution
PVP	Water-soluble, good film formation, adjustable dissolution
PVA	Good mechanical strength and flexibility
CMC	Biocompatible, water-soluble polysaccharide
Chitosan	Biocompatible, biodegradable, mucoadhesive properties
Gelatin	Biodegradable and good film-forming ability
Dextran	Water-soluble polysaccharide suitable for rapid dissolution
Chondroitin sulfate	Biocompatible polysaccharide used in dissolving matrices

Thus, the choice of polymer should provide an appropriate balance between needle strength, rapid dissolution, drug/nanocarrier compatibility, drug loading, and release characteristics. For nano-transfersome-loaded rapid-dissolving patches, polymer blends may be particularly

useful because combining materials can improve mechanical strength while maintaining rapid dissolution.

1.12 Fabrication Techniques

Fabrication of rapid-dissolving microneedles requires techniques that produce sharp, mechanically strong, reproducible needle structures while preserving the stability of the incorporated drug or nanocarrier. Micromolding or solvent casting is the most widely used approach for dissolving microneedles. In this method, a polymeric solution containing the drug or nano-transfersomes is introduced into a microneedle mold, followed by vacuum or centrifugation to improve cavity filling and subsequent drying. Dave et al. (2024) reported that vacuum-assisted filling, centrifugation, spin coating, and related approaches can improve mold filling at the microscale.

Centrifugal lithography uses centrifugal force to drive the formulation into the microneedle cavities and can produce multilayered structures with good mechanical characteristics. However, material loss and restrictions on formulation properties can limit its application. Dave et al. (2024) discussed centrifugal lithography as an alternative technique for producing complex dissolving microneedle structures.

Lithography and microelectromechanical systems (MEMS) techniques involve processes such as deposition, patterning, and etching to generate microscale structures with high dimensional precision. These techniques are particularly useful for producing master molds and complex microneedle geometries, although they can involve relatively high fabrication costs and specialized equipment. Narasimman et al. (2024) reviewed MEMS-based fabrication among the established approaches for microneedle production.

More recently, 3D printing has emerged as a promising technique for microneedle fabrication because it enables rapid prototyping, precise control of geometry, and production of customized structures. Different printing technologies can potentially overcome some limitations of conventional molding, although print resolution, material compatibility, and scalability remain important considerations. Madhusoodanan et al. (2025) reviewed the growing application of 3D printing for self-dissolving polymeric microneedles.

For nano-transfersome-loaded rapid-dissolving microneedles, micromolding is particularly relevant because the nano-transfersome dispersion can be incorporated into the polymeric matrix before mold filling. The fabrication conditions should be carefully controlled to minimize changes in vesicle size, deformability, encapsulation efficiency, and drug stability. Zhuo et al. (2025) emphasized that fabrication method and processing conditions strongly influence the structural and functional characteristics of dissolving microneedles.

Overall, the major fabrication approaches include micromolding/solvent casting, vacuum-assisted molding, centrifugation, centrifugal lithography, lithography/MEMS, and 3D printing. Among these, micromolding remains the most commonly employed method for dissolving microneedles because of its relative simplicity, reproducibility, and compatibility with water-soluble polymeric materials.

Table 2: Therapeutic Applications

Therapeutic application	Representative therapeutic agents	Role of rapid-dissolving microneedles	Key evidence
Osteoporosis	Alendronate, risedronate, ursolic acid, teriparatide, calcitonin, minodronic acid	Bypass gastrointestinal limitations, improve systemic delivery and potentially reduce dosing-related problems	Katsumi et al. (2017); Iqbal et al. (2023); Pan et al. (2024)
Osteoporosis nano-transfersome delivery	Risedronate sodium + ursolic acid	Combines dissolving MN penetration with nanotransfersome-mediated drug delivery and sustained release	Iqbal et al. (2023) developed a dissolving MN patch containing risedronate sodium/ursolic acid nanotransfersomes, with >80% ex vivo permeation within 24 h.
Osteoporosis – peptide therapy	Teriparatide	Provides a non-invasive alternative to repeated subcutaneous administration	Teriparatide-loaded dissolving MNs demonstrated transdermal delivery and anti-osteoporotic activity in preclinical studies.
Osteoporosis – bisphosphonate delivery	Alendronate, minodronic acid	Enhances transdermal bioavailability while avoiding oral gastrointestinal exposure	Alendronate MNs achieved approximately 96% bioavailability in mice; minodronic-acid MNs showed markedly improved exposure compared with oral administration.
Osteoporosis – calcitonin delivery	Salmon calcitonin	Enables transdermal peptide delivery and controlled release	Microneedle systems containing salmon calcitonin have demonstrated improved bone outcomes in experimental osteoporosis models.
Cancer therapy	Anticancer drugs, immunotherapeutics,	Localized drug delivery and enhanced	Aljohani et al. (2025)

	nucleic acids	skin/tumor exposure	
Vaccination	Protein, peptide and nucleic-acid vaccines	Minimally invasive intradermal delivery and interaction with skin immune cells	Sanjanwala et al. (2025)
Diabetes	Insulin and other peptide therapeutics	Facilitates transdermal delivery of macromolecules and may reduce repeated injections	Kolekar et al. (2025)
Infectious diseases	Vaccines and antimicrobial agents	Enhances delivery through the skin while avoiding conventional injections	Sen et al. (2025)
Dermatological diseases	Anti-inflammatory, antimicrobial and other topical drugs	Direct and localized delivery into skin tissues	Zhuang et al. (2025)
Wound healing	Growth factors, peptides and bioactive molecules	Localized delivery to damaged tissue and potential controlled release	Zhuang et al. (2025)
Biological macromolecules	Proteins, peptides and nucleic acids	Provides a route for molecules with poor conventional transdermal permeability	Kolekar et al. (2025)

1.13 Advantages and Limitations of Rapid-Dissolving Microneedle Patches

1.13.1 Advantages

- **Enhanced skin penetration:** Rapid-dissolving microneedles temporarily bypass the stratum corneum and create microscopic pathways, facilitating drug transport into deeper skin layers.
- **Minimally invasive delivery:** Their micron-sized projections generally cause less pain and tissue damage than conventional hypodermic needles. **Nguyen and Banga (2025)** highlighted their minimally invasive nature as a major advantage.
- **Rapid dissolution:** The microneedles are prepared from water-soluble or biodegradable materials that dissolve after insertion, eliminating the need for needle removal. **Dave et al. (2024)** reported this as an important benefit of dissolving microneedles.
- **Improved patient compliance:** Patch-based administration is convenient and may improve acceptance compared with repeated injections.

- **Improved delivery of poorly permeable drugs:** Temporary microchannels facilitate delivery of drugs that cannot efficiently cross intact skin.
- **Compatibility with nanocarriers:** Nano-transfersomes can be incorporated into dissolving microneedles to improve drug solubilization, stability, skin interaction, and drug deposition. **Kheirieh et al. (2025)** discussed the potential of combining nanocarriers with dissolving microneedles.
- **Controlled drug release:** Polymer composition, microneedle structure, and nanocarrier characteristics can be optimized to modify the rate and duration of drug release.
- **Localized drug delivery:** The system can deliver drugs directly into the skin or underlying tissues, which is particularly useful for dermatological and localized therapies.
- **Reduced sharps waste:** Since the microneedles dissolve after insertion, intact needles do not remain for disposal, reducing the risk associated with conventional sharps.
- **Potential in osteoporosis therapy:** Dissolving microneedles have been investigated for transdermal delivery of **risedronate, alendronate, minodronic acid, teriparatide, and calcitonin**, providing a potential alternative route for osteoporosis treatment. **Iqbal et al. (2023)** specifically investigated risedronate sodium/ursolic acid nanotransfersome-loaded dissolving microneedles.

1.13.2 Limitations

- **Limited drug-loading capacity:** The small dimensions of microneedle projections restrict the quantity of drug that can be incorporated into a patch.
- **Requirement for adequate mechanical strength:** Microneedles must be strong enough to penetrate the stratum corneum without bending or breaking. **Nguyen and Banga (2025)** identified mechanical performance as an important design consideration.
- **Nanocarrier instability:** Fabrication and drying conditions may affect nano-transfersome size, deformability, encapsulation efficiency, and drug stability.
- **Variable dissolution rate:** Dissolution depends on polymer composition, molecular weight, microneedle geometry, drug loading, and skin hydration.
- **Skin variability:** Differences in skin thickness, hydration, age, anatomical site, and physiological condition can influence microneedle insertion and drug delivery.

- **Manufacturing challenges:** Producing microneedles with uniform dimensions, consistent drug distribution, and reproducible mechanical properties on a large scale remains challenging.
- **Storage and stability issues:** Moisture absorption and changes in polymer or nanocarrier characteristics may affect the stability and shelf life of the final patch.
- **Application variability:** Differences in the force, duration, and angle used by patients during patch application may influence insertion depth and drug delivery.
- **Formulation compatibility:** Interaction between the microneedle-forming polymer and nano-transfersomes may alter vesicle characteristics or drug-release behavior.
- **Regulatory challenges:** Drug–nanocarrier–microneedle systems are complex combination products and require comprehensive evaluation of quality, safety, efficacy, manufacturing consistency, and long-term stability.

Overall, rapid-dissolving microneedles provide an attractive platform for minimally invasive transdermal delivery, while integration with nano-transfersomes may further improve drug transport and therapeutic performance. Nevertheless, drug-loading limitations, mechanical strength, nanocarrier stability, manufacturing reproducibility, and regulatory translation remain important challenges.

1.14 Future Perspectives

Rapid-dissolving microneedle patches loaded with nano-transfersomes have considerable potential as advanced transdermal drug-delivery systems. Future research should focus on optimizing phospholipid composition, edge activators, vesicle size, deformability, polymer selection, drug loading, and dissolution behavior to achieve stable and reproducible formulations. The use of advanced manufacturing approaches such as 3D printing may enable better control of microneedle geometry and personalized drug delivery. Madhusoodanan et al. (2025) highlighted the growing potential of 3D-printed polymeric microneedles for advanced transdermal applications.

Particular attention may be given to osteoporosis therapy, where nano-transfersome-loaded dissolving microneedles could provide an alternative route for drugs such as bisphosphonates, calcitonin, and other therapeutic agents. Iqbal et al. (2023) demonstrated the feasibility of risedronate sodium and ursolic acid-loaded nanotransfersomes incorporated into dissolving microneedles for osteoporosis treatment. Further studies should establish their pharmacokinetic, pharmacodynamic, safety, stability, and long-term therapeutic performance. The future development of these systems is also likely to involve targeted, stimuli-responsive, combination, and personalized drug-delivery approaches. However, large-scale

manufacturing, formulation stability, dose limitations, reproducibility, regulatory requirements, and clinical validation remain important challenges. Recent GJPSR publications on advanced vesicular and topical drug-delivery systems, such as Singh et al. (2026) and Kumar et al. (2026), further demonstrate the growing interest in nanocarrier-based approaches for improving topical and transdermal therapy. Overall, successful translation will require standardized manufacturing, comprehensive safety evaluation, and well-designed clinical studies to establish the therapeutic value of nano-transfersome-loaded rapid-dissolving microneedle patches.

1.15 Conclusion

Rapid-dissolving microneedle patches loaded with Nano-Transfersomes represent a promising approach for overcoming the limitations of conventional transdermal drug delivery. Microneedles temporarily bypass the stratum corneum, while Nano-Transfersomes provide a flexible nanocarrier system capable of improving drug loading, skin penetration, and drug release. The combined system offers advantages such as minimally invasive administration, improved patient compliance, localized delivery, and reduced sharps waste. Its potential application in osteoporosis therapy, particularly for the delivery of drugs such as risedronate, calcitonin, and other poorly permeable therapeutic agents, is especially noteworthy. However, challenges related to drug-loading capacity, nanocarrier stability, mechanical strength, fabrication, storage, scale-up, and regulatory approval must be addressed. Continued research and clinical validation may facilitate the development of stable, reproducible, and patient-friendly nano-transfersome-loaded microneedle patches for transdermal therapy.

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1.17 Conflict of Interest

The authors declare that they have no conflict of interest related to the publication of this review article.

1.18. References

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