International Journal of Farmacia (IJF)
IJF |Vol.11 | Issue 2 | Apr - Jun -2025
www.ijfjournal.com
DOI : https://doi.org/10.61096/ijf.v11.iss1.2025.25-33
ISSN: 2455-8109

Review

Curcumin Microneedle Patches: Innovations In Transdermal Drug Delivery For Enhanced Therapeutic Efficacy

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Published on: 06 May 2025

Published by:
DrSriram Publications

Abstract

Curcumin a natural polyphenol with strong anti-inflammatory, antioxidant, and anticancer properties, but face challenges in clinical application due to its low bioavailability, rapid metabolism, poor water solubility. To address these issues, Curcumin loaded microneedle (MN) patches have emerged as an innovative transdermal drug delivery platform. These patches create microchannels in the skin, enabling efficient delivery of curcumin while bypassing gastrointestinal degradation and first-pass metabolism. Additionally, microneedles offer a painless and patient- friendly alternative to oral and injected route, with the potential for sustained and controlled drug release. Recent advancement in studies indicate that these systems can enhances therapeutic outcomes in various condition including chronic inflammation, wound healing and cancer therapy. This review article highlights the curcumin detailing its pharmacological properties, limitation and challenges. Additionally, it focuses on microneedle technology including material employed in their fabrication and different types of microneedle available. The article also discusses recent advance and therapeutic use of curcumin loaded microneedle patch for transdermal drug delivery, which can be used to treat various medical conditions.

Keywords: Microneedle, curcumin, transdermal drug delivery, therapeutic application

INTRODUCTION

The curcumin compound derived from the rhizome of the turmeric plant (Curcuma longa) has garnered considerable scientific attention due to its diverse range of medical application, which includes anti-inflammatory, antioxidant, antimicrobial, and anticancer properties.[1] However, despite its pharmacological benefits, curcumin's clinical application remains limited due to its poor water solubility, rapid metabolism, and low bioavailability when administered through conventional routes such as oral or topical formulations.[2] For example, when curcumin administered orally, it undergoes rapid degradation within the gastrointestinal tract and liver, leads to reach minimal amounts in the systemic circulation. Due to these challenges, novel delivery methods are required in order to improve its therapeutic poteinal.[3,4]

Transdermal drug delivery (TDD) is a method of administering medications through the skin, allowing them to permeate into deeper layers and enter the bloodstream. This approach bypasses first-pass metabolism, enables sustained release of drugs with short half-lives, stabilizes blood concentration levels, minimizes side effects, and enhances patient compliance.[5] In recent years, microneedles have gained recognition as one of the most effective and reliable techniques for improving the efficiency of TDD. The length of microneedles, which usually ranges from hundreds of micrometers to a few millimeters, allows these microneedle arrays to effectively penetrate the stratum corneum to deliver medications in a minimally invasive way beneath this outer layer, while preserving the integrity of blood vessels and nerves within the dermis. This approach enhances patient compliance and facilitates the rapid absorption of drugs present in the epidermis or dermis by adjacent capillaries and lymph nodes.[6,7] Researchers have explored various types of microneedles for the transdermal delivery of curcumin, including solid, coated, dissolving, and hydrogel-forming microneedles showed in (figure 1). Each type offers distinct advantages in terms of drug loading capacity, release kinetics, and ease of administration, allowing for tailored approaches to meet specific therapeutic requirements.[8] Curcumin-loaded microneedle patches represent a promising advancement in TDD, addressing the challenges associated with curcumin's poor water solubility, rapid metabolism, and low bioavailability. These patches offer targeted drug delivery, improved absorption, controlled release, and a patient-friendly approach to treating conditions like blood cancers. They minimize systemic exposure and side effects, bypass metabolic degradation, and are painless, self-administered, and eliminate the need for intravenous infusions or oral administration.[9,11] Figure 01 illustrate of microneedle diagram and its biomedical applications.

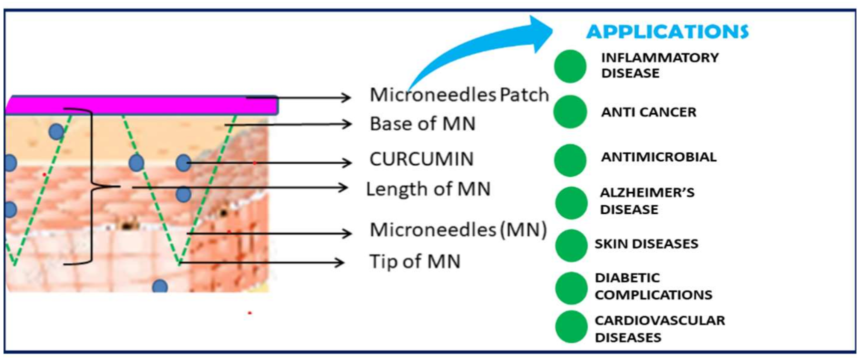

Fig 1: Microneedle in biomedical application

Curcumin

Curcumin also known as diferuloylmethane (1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) (Figure 2), is a prominent polyphenol derived from the rhizome of *Curcuma longa* widely recognized as turmeric and other species within the *Curcuma* genus. Figure 02 illustrate of chemical structure diagram of Curcumin.For centuries, *Curcuma longa* has been used medicinally in traditional practices across Asian countries.[9,10,11] As the primary source of curcumin, turmeric is highly esteemed among herbal remedies, particularly in traditional Chinese and Indian (Ayurvedic) medicine, where it has been used for various therapeutic purposes. Curcumin is a brightly yellow-colored phytochemical extracted from the *Curcuma longa* rhizome, part of the Zingiberaceae family. In addition to curcumin, turmeric contains other curcuminoids, including bis-desmethoxycurcumin and desmethoxycurcumin. Curcumin is available various forms such as tablets, ointments, capsules, soaps and cosmetics.[11,12] Curcumin is recognized for its safety and non-toxic chactericstics, making it one of the most widely used natural edible colorings globally, with approval by the U.S. Food and Drug Administration (FDA) as a food additive in many countries.[13] Over the past few decades, thousands of studies have investigated the pharmacological effects of curcumin, confirming its efficacy in traditional uses and revealing exciting new therapeutic potentials.[14]

Pharmacoligical properties of curcumin

Traditional and alternative medicine significantly shapes the trends in both preclinical and clinical research concerning medicinal plants and natural active compounds. Curcumin, the principal active ingredient in turmeric, demonstrates a broad spectrum of pharmacological effects attributed to its capacity to influence various molecular pathways.[14,15] Consequently, numerous studies indicate that curcumin possesses diverse pharmacological properties, including antioxidant, anti-inflammatory, anti-arthritic, antimicrobial, cardioprotective, antithrombotic, hepatoprotective, hypoglycemic, and wound healing properties. In terms of its antioxidant properties, curcumin effectively neutralizes free radicals by scavenging reactive oxygen species (ROS) and reactive nitrogen species (RNS), thereby protecting cells from oxidative damage. Additionally, it enhances the sensitivity of cancer cells to chemotherapy and radiation, making it a promising adjunct in cancer therapy.[18,21] Furthermore, curcumin's cardio protective effects stem from its capacity to regulate lipid metabolism, lower low-density lipoprotein (LDL) cholesterol levels, and inhibit the development of atherosclerotic plaques. It also enhances endothelial function, which is crucial in preventing cardiovascular diseases such as atherosclerosis and hypertension. Moreover, its anti-inflammatory and antioxidant characteristics contribute to the reduction of myocardial injury and it improves cardiac function.[14,22] In metabolic disorders, curcumin improves insulin sensitivity and reduces blood glucose levels, offering potential benefits in the management of type 2 diabetes. Therefore, At the molecular level, the extensive effects of curcumin are attributed to its interactions with various cellular targets, including transcription factors, growth factors, enzymes, and receptors.[15,23]

Limitations and challenges in curcumin delivery:

The physicochemical and pharmacokinetic characteristics of curcumin present significant challenge for its systemic delivery. Being a highly lipophilic substance, curcumin exhibits extremely low solubility in water. This limitation affects the dissolution of curcumin and significantly reduced its absorption and oral bioavailability. This poor solubility makes it difficult for curcumin to dissolve adequately in gastrointestinal fluid limiting the amount that can be absorbed into the bloodstream after oral administration.[24,25] This rapid metabolism and extensive elimination significantly lower its bioavailability, limiting its therapeutic efficacy in clinical application. As a result, curcumin poor oral bioavailability remains a critical obstacle to maximizing its potential as a therapeutic agent.[2,26]

Microneedle techonogy in transdermal drug delivery system

An improvement in transdermal drug administration can be achieved through various approaches, such as the use of penetration enhancers, advanced formulation designs, and physical methods. Recently, microneedles have been identified as the most efficient and dependable technique for transdermal drug delivery, as supported by numerous studies conducted in both academic and industrial settings.[27,28] These micron-sized needles, ranging from 25 to 2000 µm in length, have been shown to penetrate the skin layers, effectively and reversibly compromising the skin barrier function, thereby generating multiple microchannels within the skin.[29] Microneedles are an ideal platform for transdermal delivery of medication because they are easy to administer and have a high drug bioavailability. Subsequently, in 2006, drug-loaded dissolving microneedles were developed for the transdermal administration of bovine serum albumin and calcein. Figure 03 illustrate of Adavantage of microneedle technology in transdermal drug delivery.In 2012, hydrogel-forming swelling microneedles were invented, marking the most current innovation in microneedle technology.[32,33] Transdermal delivery has seen considerable improvement through the use of microneedle technology, which broadens the spectrum of possible transdermal candidates, including macromolecule, small molecules, particulate systems, and cosmeceuticals. Generally, microneedles can facilitate the transport of molecules regardless of their size or molecular weight. Numerous microneedle systems have been developed, each characterized by distinct geometries, designs, sizes, layouts, materials and compositions.[34,35]

Fig 3: Adavantage of microneedle technology in transdermal drug delivery

Material and fabrication

Microneedles can be produced from a wide range of materials, including glass, silicon, metal, sugar , ceramics and polymers. Each of these materials must adhere to specific criteria to ensure successful microneedle production such as biocompatibility, mechanical strength, and safety consideration.[36,37] The utilization of biodegradable and biocompatible polymers has garnered considerable interest in the scientific community, primarily due to their favourable safety characteristics. These polymers have demonstrated versatility, rendering them suitable for the fabrication of a diverse array of microneedle designs, including solid, dissolvable, coated, and hollow variants.[38] The most frequently employed polymeric materials in microneedle include poly lactic-co-glycolic acid, polyvinyl alcohol , PVP, polycarbonate, polyglycolic acid, polylactic acid, polystyrene, cyclic-olefin copolymer, polymethyl methacrylate, and sodium carboxymethyl cellulose. Among these, PLGA, hyaluronic acid, chitosan have been the most commonly utilized. Recent research has explored different materials for microneedle fabrication, including natural, synthetic, and composite polymers.[27,39] Microneedles crafted from natural source are particularly noteworthy due to their excellent compatibility and low potential for skin irritation. Dabholkar, conducted an in-depth analysis of the utilization of naturally occurring polymers, including polysaccharides, proteins, polypeptides for the development of biodegradable microneedles.[40] This study highlighted the potential of carbohydrate-based materials, such as cellulose and its derivatives, starch, as well as carbohydrate polymers like chitosan ,alginates, chitin, hyaluronic acid., xanthan gum, as viable alternatives for the production of these advanced drug delivery systems. In the realm of biomaterials, protein-based polymers such as gelatin, collagen, zein, and silk fibroin.[41] Additonally, Damiri et al. have conducted a comprehensive review of the diverse carbohydrates employed in the fabrication of microneedle systems.[42]

Researchers from both academic and industrial sectors have used numerous approaches for the fabrication of microneedle at various scales. The methods for producing microneedles include microelectromechanical systems (MEMS), micromolding, and various additive manufacturing techniques such as fused deposition modeling , digital light processing, stereolithography and two-photon polymerization.[43] Other methods involve atomized spraying, X-ray techniques, laser-based techniques like laser cutting and ablation, droplet-born air blowing, pulling pipettes, drawing lithography, and micro-injection molding. Among these, micromolding is the most commonly utilized technique for microneedle production in both academic and industrial applications. Techniques for coating microneedles include spray coating ,immersion coating, , layer-by-layer coating, dip coating, drop coating, gas-jet drying, electrohydrodynamic atomization and piezoelectric inkjet printing.[44] Also 3D printing, which has recently gained significant attention as a promising method for microneedle fabrication. Once fabricated, microneedles are rigorously evaluated in various studies. Researchers assess several factors such as the formulation of microneedle which encompasses drug solubility, compatibility between the drug and excipients; additionally they analyze rheological and interfacial charactertics as along with geometry and morphology of the microneedles both before and after insertion.[45,76,] Along with microneedle disintegration, drug-loading capacity, drug release, and distribution. Mechanical characteristics, such as axial and transverse forces, skin penetration force, base strength are also analyzed. Furthermore, studies focus on effectiveness of skin penetration, skin irritation, safety and recovery, as well as physicochemical stability parameters such as water content, and solid-state properties, hygroscopicity, swelling behaviour.[32,35]

Types of microneedle used in transdermal drug delivery:

Four types of microneedles have been employed in transdermal drug delivery, namely solid, hollow, coated, dissolving microneedles. Table 1 shows the overview of different types of microneedle used in transdermal drug delivery.

Solid microneedles

The design of this microneedles structure is intended to penetrate the stratum corneum, thereby enhancing the delivery of drugs to the dermis and improving both bioavailability and kinetic transport through the skin. These microneedles function based on a "poke and patch" methodology. The Solid microneedles can be produced from a range of materials, including glass, metal, silicon, and various polymers and the types of designs that are commonly used such as solid arrays, roller types and flexible patches.[46] The administration of drugs using solid microneedles generally follows a two-step procedure. Initially, the microneedles are inserted into the skin and then removed, which leads to limited hydrophilic microchannels. Following this, a drug-laden formulation such as a gel, lotion, cream, ointment, or transdermal patch subsequently applied to the microchannels to facilitate the diffusion of drug into the skin.[47] These microchannels facilitate passive drug transport into the deeper layers of the skin, with the delivery process continuing until the drug is completely absorbed or the channels naturally close. It shows the operational mechanism of solid microneedles (Figure 4). In comparison to hollow microneedles, solid microneedles are simpler to manufacture and demonstrate superior mechanical properties, rendering them more durable for clinical applications.[27]

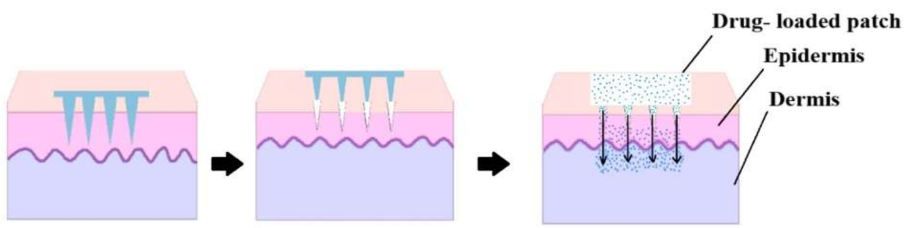

Fig 4: Operational mechanism of solid microneedles.

Dissolving microneedle

The Dissolving microneedles (MNs) have gained significant attention due to their user-friendly "poke-and-release" mechanism. These microneedles encapsulate therapeutic substance within their polymeric matrix.[48,49] Generally, These MNs are primarily fabricated using water-soluble, biodegradable polymers through solvent casting technique. The most Common materials used in dissolving microneedles are carboxymethylcellulose, maltose, hyaluronic acid, polyvinyl alcohol, chitosan, and Polyvinylpyrrolidone. After application, the conjugated therapeutic substance is released when the microneedles dissolve into the skin.

Coated microneedles

The coated microneedles consist of a solid base coated with drug solutions or dispersions, by following a "coat and poke" principle. When these microneedles are inserted into the skin, the coating layer dissolves quickly, facilitating the delivery of the drug to the targeted layer.[52]It is essential to remove the microneedles from the skin after the coating has detached completely.[27,47]

Hallow microneedles

The hallow microneedles are designed with a hollow core or chamber that stores or injects drug fluids, similar to a traditional hypodermic syringe. These microneedles have openings at the tips, allowing drug solutions to be released directly into the epidermis or upper layers of dermal upon insertion. Despite their potential, hollow microneedles receive less attention than solid ones due to their weaker structure, which requires careful design and insertion techniques. They also face challenges like leakage and clogging during injection procedure.[55]

Table 1: An overview of different type of microneedle used in transdermal drug delivery

Types Of Microneedle	Features	Advantage	Disadvantage	Uses	Reference
Solid Microneedle	This microneedle makes channels in the skin, and allowing the medication to reach deeper layers. Also they have sufficient mechanical strength and sharp tip for effective penetration	Easily fabricatable makes it easier to create and permits more mediations to enter the skin.	Microneedle creates fracture beneath the skin, resulting in a limited surface area for drug absorption. Skin damage and micro incisions must be kept close together to minimize the risk of infection.	Cosmetics and delivery of medication.	6
Dissolving Microneedle	The system facilitates the swift release of macromolecules, utilizing biocompatible polymers or sugar that fully dissolve thereby liberating	Administration to patients can be accomplished effortlessly with a single step application.	Manufacturing requires techniques expertise and the process may take time to dissolve. Additionally, only biodegrable	Delivery of medication, vaccines and cosmetics.	52

	the encapsulated medication.		materials are permissible.		
Coating Microneedle	The design facilitates a decreased volume of drug administration .It is equipped to delivery proteins and DNA	Ensure rapid delivery of the medication to the skin and is suitable for potent drug with minimal dosage requirements	Linked to the loss of drugs during production , temperature constraints and susceptibility to infections.	Delivery of medication and vaccines.	44
Hallow Microneedle	It has hallow structure to hold the medication and Capability to regulate the release of drug over a specific duration.	Manages a significant dosage or volume of drug solution .	Weak needles necessitate careful attention regarding their design and insertion techniques, as improper handling may lead to issue such as leakage and clogging.	Identification of medication conditions.	35

Recent advance and therapeutic application of curcumin loaded microneedle patch in transdermal drug delivery system

The Curcumin-loaded microneedle (MN) patches have emerged as a significant advancement in transdermal drug delivery systems by utilizing the therapeutic benefits of curcumin, including its anti-inflammatory and antioxidant effect, while effectively addressing the issue of its poor bioavailability. By combining the unique capabilities of microneedles with the therapeutic benefits of curcumin, these patches enhance skin absorption and offer a minimally invasive alternative to conventional drug delivery methods, including oral ingestion and intravenous administration.[27,28] Recent research has focused on the integrating solid lipid nanoparticles (SLNs) containing curcumin in microneedle arrays using a microemulsion process with glyceryl monostearate and Tween 80.

Furthermore, C57BL/6 mice treated with a curcumin-zinc structure targeting hair loss have shown promise for treating oxidative stress and zinc deficiency, promoting hair growth and accelerating wound healing. Histological analysis confirmed significant improvements in hair follicle density and cell proliferation.curcumin via amorphous solid dispersions that retained structural integrity and effective penetration of skin layers in in vitro and ex vivo models. Furthermore, a biodegradable MN patch made of gelatin methacryloyl (GelMA) and β-cyclodextrin (β-CD) improved the stability, solubility, and skin penetration of curcumin, showing therapeutic efficacy and deeper penetration compared to the potential non-transdermal patch of such systems for more efficient delivery of water-insoluble drugs.[54,55]

The inclusion of curcumin in nanosuspension technology has been shown to improve its solubility and facilitate intradermal administration. Abdelghani et al. used a modified nanoprecipitation technique to produce curcumin as a nanosuspension (CU-NS), which was integrated into soluble microneedle arrays (CU-MN) composed of polyvinyl alcohol (PVA). These microneedles effectively penetrate the stratum corneum, allowing the delivery of curcumin to the epidermal and upper dermal layers of the skin. Additionally, a novel approach that combines a new approach combining albumin binding, extracellular vesicles (EVs) and dissloving microneedle arrays (dMNA) was developed to overcome the challenges of curcumin's low solubility and stability, highlighting its significant anti-inflammatory in preclinical studies. Hyaluronidase has been shown to improve the penetration of therapeutic agents through the skin. Similarly, Xiang *et al.* (2022) found that smaller particle sizes improved transdermal and transfollicular absorption due to increased surface area and solubility of curcumin nanocrystals with disintegrating microneedles. This suggests that fine-tuning of particle size and matrix materials can improve controlled therapeutic release for local and systemic uses.[24] it shows the therapeutic application of curcumin-loaded microneedle patch in transdermal delivery. Therefore, these advances in microneedle technology highlight the versatility of curcumin-MNs in various therapeutic applications, providing a promising form of platform for drug delivery systems.[24,53]

CONCLUSION

Curcumin microneedle patches present a novel and promising strategy for transdermal drug delivery, by addressing the key challenges associated with curcumin’s low bioavailability and poor solubility. By utilizing microneedle technology, these patches allow for controlled and targeted release of curcumin directly into skin, bypass gastrointestinal tract and enhance drug absorption and bioavailability. This approach not only improve curcumin therapeutic efficacy but also offers a painless, non-invasive method which is alternative to traditional drug delivery methods. The development of curcumin microneedle patch could pave the way for more effective treatments for various condition, including anti-inflammatory, antioxidant, anticancer properties, skin disease etc., thereby expanding the potential application of curcumin in modern medicine. However to release their full potential, further research and optimization are necessary. Key area for development include refining microneedle design such as improving needle geometry for better skin penetration and incorporating synergistic agents to enhances curcumin therapeutic effect. Additionally, Scaling up production to ensure affordability and regulatory compliance will be critical for future commerlization. With continuous innovation and clinical validation, curcumin microneedle patch could offer highly effective patient – friendly alternative to conventional drug delivery system unlocking new possibilities in the treatment of various disease.

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