Microneedling as a Mode of Delivery of Topical Medications:
A Comprehensive Review
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ABSTRACT
Background: Microneedling has emerged as a promising technique for transdermal drug delivery, offering a minimally invasive method to enhance the permeation of topical medications. Despite its increasing application in dermatological treatments, comprehensive reviews of its mechanisms, advantages, and therapeutic uses are scarce.
Objective: This review aimed to provide a comprehensive overview of microneedling as a mode of delivery for topical medications, encompassing its mechanism of action, advantages, disadvantages, and applications in cosmetic and therapeutic delivery.
Methods: An extensive literature search was conducted across multiple databases, including PubMed, Scopus, and Web of Science, to identify studies related to microneedling and its applications in drug delivery. The review focused on articles published in the last two decades. Documents in languages other than English were disqualified due to lack of translation-related sources.
Conclusion: Microneedling represents a versatile and effective method for transdermal drug delivery, with a wide range of applications in both cosmetic and therapeutic contexts. Ongoing research and technological advancements are expected to further enhance its efficacy and safety, solidifying its role in modern dermatological treatments.
Keywords: Microneedling, Transdermal drug delivery, Cosmetic dermatology, Therapeutic delivery, Topical medications, Skin rejuvenation, Vaccine delivery.

INTRODUCTION
Microneedling is a novel type of transdermal drug delivery technique that improves drug permeation through the toughest barrier of the skin. Microneedles can be defined as solid or hollow cannula with an approximate length of 50–900 mm and an external diameter of not more than 300 mm [1].

Microneedles can be fabricated within a patch for transdermal drug delivery. Patches containing microneedles have been evaluated in the delivery of drugs, biopharmaceuticals and vaccines, etc. A quick response can be observed due to disruption of stratum corneum by microneedles. Although microneedles were first proposed in 1976, the technology needed to make needles of micron dimensions was not widely available until 2000s [2].

Using the low-cost mass production tools of the microelectronics industry, needles have been fabricated out of silicon, metals and other materials [3]. Microneedles have been designed to penetrate through the epidermis up to a depth of 70–200 mm. Microneedles are thin and short and do not penetrate the dermis layer with its nerves; hence painless application is possible [4]. Microneedles are more capable of enhancing the transport of drug across the skin as compared with other transdermal delivery methods.

The mechanism involves the creation of a larger pathway of transport of drug molecules through micron size hypodermic needles, which can disrupt the stratum corneum and directly deliver the drug into the epidermis or dermis layer. “Collagen induction therapy”, “derma rolling”, “skin needling” and “percutaneous collagen induction” are all terms used to describe microneedling process [5,6].

Patients who are concerned about aesthetic changes caused by injury, sickness or aging have recently been treated using this technique [7].

Solid, dissolving, hydrogel-coated, and hollow microneedles are some of the varieties of microneedles. This technique has a long list of benefits in the treatment of acne vulgaris, scars, facial rejuvenation, dyspigmentation, alopecia, hyperhidrosis and transdermal medication administration, as well as the treatment of diseases other than skin. It is a low-cost and minimally invasive tool for transdermal drug delivery [8].

Advantages of microneedles:
The advantages of microneedles are that large molecules can be administered, painless administration of active pharmaceutical ingredients, first-pass metabolism is avoided, faster healing at injection site than with a hypodermic needle, no fear of needle, ease of administration, decreased microbial penetration as compared to a hypodermic needle. The microneedle punctures only the epidermis, specific skin area can be targeted for desired drug delivery, enhanced drug efficacy may result in dose reduction, good tolerability without long-term oedema or erythema and rapid drug delivery can be achieved by coupling the microneedles with an electrically controlled micropump. Additionally, the rate of drug delivery can be controlled more effectively by this system as compared to drug delivery via the stratum corneum [9,10].

Disadvantages of microneedles:
The disadvantages of microneedles are dosage accuracy may be less than with hypodermic needles,
careful use of the device may be needed to avoid particles ‘bouncing off’ the skin surface. If the device is not held vertically, the dose may escape or can penetrate the skin to differing degrees, the thickness of the stratum corneum and other skin layers varies between individuals and so penetration depth of particles could vary too, the external environment, like hydration of the skin, could affect delivery, repetitive injection may collapse the veins, the tip of the microneedle may break off and remain within the skin on removal of the patch, a small amount of drug (less than 1 mg) can be given by bolus and compressed dermal tissue can block hollow microneedles [4].

Drug delivery mechanism of microneedling:
Drug delivery through microneedling is primarily based on damaging the skin barrier and then release of drugs in the upper dermis layer for systemic absorption [11]. After crossing the skin barrier, the release of the drug into the body is dependent on the type of microneedle, which can be classified as dissolution-based and diffusion-based drug delivery. Nonbiodegradable solid microneedle usually deliver the drug through diffusion, while coated and biodegradable microneedle exhibit dissolution-based drug release [12, 13].

Applications of microneedles in cosmetic and therapeutic delivery:
- Microneedling as an adjunct therapy for facial melasma
  Lima et al. [14] did an open pilot study with women who had faced refractory melasma. They were not allowed to receive any treatment for the previous 30 days other than sunscreen. Patients were given two microneedling sessions with Dr. Roller TM (1.5 mm). After two sessions of microneedling, all participants reported a reduction in melasma, as well as a subjective improvement in facial skin smoothness and brightness. Histologically, epithelial thickening, decreased epithelial melanin pigmentation and densification of upper dermis collagen were all seen. They have reported that to maximize the efficacy of microneedling treatment and fixation of the regimens to ensure long-term results, further randomized controlled trials were needed.

- Microneedling in skin rejuvenation
  For face rejuvenation, microneedling has proven to be a precise and safe solution. Dyspigmentation, rhytids, elasticity loss and collagen loss are all symptoms of aging skin. The extracellular and cellular components of the skin are changed by cumulative intrinsic and external forces. Microneedling allows collagen and elastin neogenesis by mechanically stimulating the dermis while avoiding harm to the epidermis. Clinically, skin rejuvenation is defined as a reorganization of dermal architecture. Microneedling disrupts dermal collagen and scar anchoring, resulting in a pro-inflammatory response with subsequent collagen and elastin remodeling. The variation in the needle length from 0.5-3 mm can cause mechanical damage from the stratum corneum to the papillary dermis, hence they can deliver medicine to any layers of skin. Microneedling reduces the incidence of post inflammatory hyperpigmentation, infection, scarring, and milia by maintaining the epidermis and dermal epidermal melanocytes [15].

El-Domyati and colleagues [16] reported a significant clinical improvement in photoaged skin. Microneedling has demonstrated promising outcomes in facial rejuvenation. Clinical and histological alterations that aid in the reduction of wrinkles and skin laxity have been identified in previous studies. It has a positive safety profile due to its low invasiveness. Microneedling is a rejuvenation technique that reduces the likelihood of hyperpigmentation and is a safe and effective treatment option that can be used alone or in conjunction with other agents or treatments [16].

- Vitiligo
  The effectiveness of microneedles as part of a vitiligo treatment regimen is unknown. Neinaa et al. [17] explored the use of narrow-band ultraviolet B and topical 0.005% latanoprost solution for the treatment of vitiligo, with and without derma roller. The results were promising and the therapeutic efficacy of latanoprost was enhanced significantly in the treatment of nonsegmental vitiligo.

- Verruca
  Konicke and Olasz [18] showed the usefulness of microneedle as a technique of transdermal delivery of bleomycin for the treatment of verruca vulgaris, without tissue necrosis. The cure rates with the application of this technique were found to be a promising approach for ensuring 100% cure rates in plantar warts. The findings prompted a requirement for a large-scale clinical trial to establish the efficacy of microneedles in the treatment of wart.

- Anti-aging
  Microneedling is becoming increasingly popular to arrest the aging of the skin. The use of microneedle rollers to improve facial cosmesis by inducing collagen and increasing the penetration of topical cosmeceuticals has been widely studied. This therapy doesn’t cause epidermal harm like laser therapy. This provides a less expensive treatment. The procedure can be carried out in a doctor’s office and does not necessitate any lengthy special training or costly equipment [19]. MicroHyala®, an FDA-approved product of dissolving hyaluronic acid microneedles is prescribed for wrinkle treatment. Dermaroller®, solid metallic microneedles are used for improving the texture of skin [20, 21].
Aesthetic uses
The fact that microneedling may be used for a variety of aesthetic treatments is one of the key reasons for its growing popularity. This comprises the treatment of: anti-ageing/skin rejuvenation – revive microneedle procedure kit consists of moisturizer, cleanser and topical serum used to improve post-operative healing of the skin. Hyper-pigmentation was found to improve skin pigmentation and laxity and hair loss by inducing stem cells in the scalp. Dhurat et al. reported the positive use of minoxidil lotion with dermaroller device for the treatment of alopecia. Scarring and stretch marks, dermapen® and dermastamp® are claimed to be effective for scar, wrinkles and skin lesions.

Insulin delivery
Insulin is one of the most challenging medications to deal with for drug delivery technologists. Martano et al. used microarrays to deliver insulin to hairless diabetic rats. Solid stainless-steel microneedles with a length of 1 mm and a tip width of 75 m were implanted into the rat skin and employed with poke and patch procedure. Over four hours, blood glucose levels dropped by as much as 80%

Vaccine delivery
Conventional delivery of vaccines is painful and requires cold storage. Microneedles can be used effectively for vaccination without the requirement of cold storage and reduce medical waste. Intramuscular administration of DNA vaccines exhibits a weaker immune response due to the inefficent delivery of plasmid DNA into host cell. A suitable delivery system is of prime importance to improve immunization of DNA vaccines. DNA vaccines were loaded in microneedles and studies revealed that they could deliver plasmid DNA effectively into the host cell. Hence, it can be considered an optimistic delivery method for DNA vaccines.

CONCLUSION
The transdermal delivery of drugs is restricted to a particular class of drugs due to their physicochemical and molecular characteristics. The application of microneedling has significantly transformed the field of transdermal delivery, surpassing any limitations imposed by drug properties. It had extensively effective applications including the delivery of peptides, hormones and vaccines, in addition to cosmetic use. The advancement and oversight of microneedles are becoming increasingly significant in the current era. The current review focuses on the scientific and design aspects of microneedles, as well as their diverse range of applications. Similar to any innovative procedure, the implementation of microneedling for transdermal drug delivery is accompanied by clinical challenges and concerns regarding scalability, including skin irritation, redness and allergic reactions. Therefore, further investigation into the properties and fabricating material, as well as an extensive series of clinical trials, are required to solidify the promising concepts behind microneedles.

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