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SMART AND HERBAL-BASED MICRONEEDLE PATCHES FOR WOUND HEALING: RECENT ADVANCES AND FUTURE PERSPECTIVES

Kashish Sharma*, Priya Thakur, Preeti, Kirpal Singh, Navjot Kaur, Vikas Sharma, Vani, Harmeen Kaur, Sourav, Vaibhav Thakur

Department of Pharmaceutics, School of Pharmaceutical Sciences, Chandigarh College of Pharmacy Landran, Punjab 140307, India.

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***Corresponding Author**
Kashish Sharma
Department of Pharmaceutics, School of Pharmaceutical Sciences, Chandigarh College of Pharmacy Landran, Punjab 140307, India.

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ABSTRACT

Wound healing is a complex process that typically progresses through several interlated stages including hemostasis, inflammation, proliferation and tissue remodelling. The healing of chronic wounds such as diabetic ulcers, burns and pressure ulcers is often impaired by infections, extended inflammation, inadequate vascularisation and limited wound contraction. Existing treatments for chronic wounds, such as topical creams/gels, dressings, and orally administered medications, have several inherent shortcomings. Microneedle patches are comprised of micro-sized needles that penetrate through the outermost layer of skin without causing any pain or damage skin. Drugs can be delivered directly into epidermis and dermis for higher bioavailability and faster wound healing. Microneedle devices, including patch-based devices, can deliver drugs in a controlled and sustained manner to maintain optimal drug concentration in the wound site and accelerate tissue regeneration. There is a growing interest in incorporating herbal bioactive compounds and smart delivery systems into microneedle for clinical applications. Phytochemicals such as Curcumin and Aloe-emodin they possess anti-inflammatory, antimicrobial and antioxidant activities, which help tissue healing and prevent oxidative stress during wound healing. Recent advances such as dissolving microneedles, hydrogel-based microneedles and nanotechnology-based platforms for drug and stem cells delivery have been explored to

enhance drug loading, stability and penetration for wound healing. Future multifunctional microneedle patches will monitor wounds, deliver drugs and facilitate tissue repair and regeneration. In near future, wound healing patches will be constructed using a combination of nanotechnology, biodegradable biomaterials and herbal therapeutics to develop a new generation of personalized wound healing system.

KEYWORDS: Microneedle patches, Herbal drug delivery, Nanotechnology, Transdermal drug delivery, Tissue regeneration, Stimuli-responsive microneedles, Controlled drug release. release.

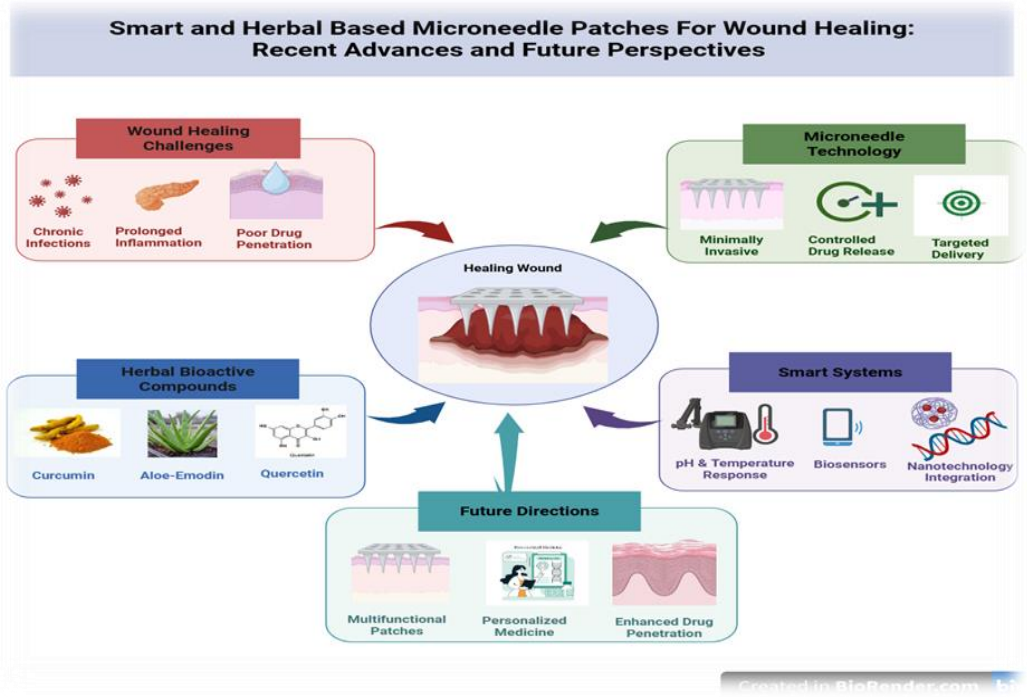


Fig.1 Smart and Herbal-Based Microneedle Patches for Wound Healing.

1. INTRODUCTION

The skin is the biggest and most intricate organ of the human body. It serves as the main protective barrier, spans an area of 1.5–2.0 $m^{2,}$ acts as first line of protection against physical and chemical assaults such as mircobes or other pathogens. It amounts for 15% of total body mass and also helps in avoiding dehydration by preventing excessive water loss.[1,2] Skin contains melatonin which helps in protecting body from harmful UV radiation of sunlight. It also shield internal organs and body fluids. The maintenance of homeostasis is facilitated by the skin through thermoregulation and perspiration.[3,4] Additionally, the skin acts as a communication channel by perceiving stimuli such as heat, cold, touch, pressure

andconveying these signals to the central nervous system. Additional the skin participates in the metabolism and excreting of substance such as xenobiotics, lipids, sodium chloride, uric acid and ammonia are excreted from the skin. Notably, the skin is a preferred site of absorption for the transdermal and intradermal distribution of different therapeutic drugs.[5,6]

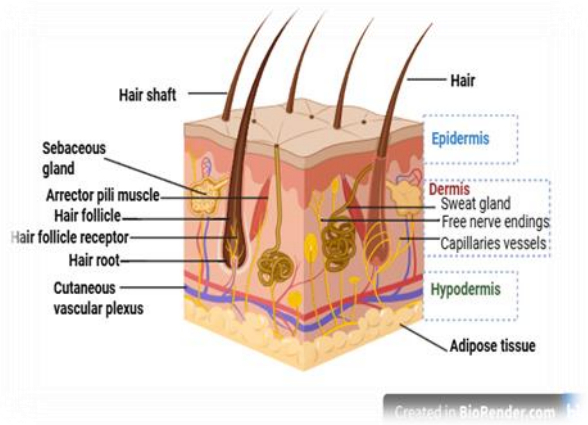


Fig.2: High quality images of the anatomy of human skin , specifically the epidermis.

The epidermis skin layer consists of five cellular layers (Fig. 2), the most superficial layer, known as the Stratum Corneum (SC), consisting of 50–20 μm thick dead corneocytes. The SC contains intercellular lipid matrix and corneodesmosomes that form a "bricks-and-mortar" structure.[7,8] The "mortar" comprises a continuous, interstitial, lipid matrix, while the "bricks" consist of plates of flattened corneocytes, up to 15 layers thick, arranged in a nearly seamless sheet. Corneocytes are actually elongated, polygonal, flat bodies and not bricks. The "mortar" is composed of water and lipids arranged in a structured water-lipid lamellar phase, where lipid moleculer may exist in gel or crystalline forms in addition to intrinsic and extrinsic protein like enzymes are also present in the extracellular matrix. In the underlying epidermal layers, the dead keratinocyte cells undergo cornification, where they form keratin proteins that assemble into the SC (also referred to as the "horny layer").[9,10] Importantly, the SC contains a complex mixture of lipid molecules, such as triglycerides, fatty acids, squalene, wax esters, ceramides, cholesterols, and their esters, forming a multi-lamellar bilayer structure. Half of the total lipid mass comprises ceramides, the primary lipid groups found in the SC, which are critical for lipid arrangement within the SC.[11,12] A notable feature of the SC is that it does not contain phospholipids, unlike most other mammalian membranes. The barrier function of skin is formed when the lipid matrix is covalently attached to the corneocytes forming a structure that only allows lipophilic molecules to pass through the skin,[13] which act as a diffusion barrier controlling the passage of topically applied drugs. For

drugs to penetrate through the skin, they have to initially pass through the SC, which is a key rate limiting step in transdermal drug delivery. The SC continuously renews itself every 2 to 4 weeks. However, it can actively reseal itself after a barrier disruption caused by various external stresses and environmental injuries.[14,15]

Second layer of epidermal layer of skin followed by stratum corneum is called the viable epidermis. This layer is 130-180m thick, cellular and avascular. Viable layer, also known as stratum lucidum, is mostly consist of keratinocytes containing 40% proteins, 40% water and 15-20% lipids.[16,17] Stratum lucidum is consists of 2-3 layers of keratinocyte cells which supply dead corneocytes to stratum corneum. Stratum granulosum, below stratum lucidum, have thicker cell membranes than other outer layers, is created from granules in living cells through accumulation of keratoohyalin.[18,19] Below it, stratum spinosum layer, also known as spinny layer consists of 8-10 keratinocyte layers. This layer have a abundance of Langerhans cells. The innermost cell layer, stratum basale, connects with the dermis by collagen fibers. This is where all skin cell proliferation occurs and where the lower keratinocytes of the epidermis are produced. This is the location of the melanocytes, responsible for producing skin pigment and the Merkel cells associated with skin sensation. The cells of stratum basale form the basement membrane which is a connection to the lower dermis layer. The dermis layer, which is located beneath the epidermis and is about 2,000 μm thick, is composed of the papillary and reticular layers. The top papillary layer, which is 100–200 μm thick, contains collagen fiberd, elastin filaments, fibroblast cells, fat cells, blood vessels and lymph vessels.[20–22] Fluids, ions, blood proteins and carbohydrate-protein complexes are also plentiful in this layer. The compact reticular layer is rich in coarse elastic fibers and collagen bundles.[23] The dermis is a layer of tissue composed of collagen fibres, fibrous proteins and elastic tissue, which gives skin its tensile strength and elasticity. The dermis contains fewer cells than the epidermis and more fibres, primarily collagen which forms a dense mesh-like structure and elastin that stores energy in stretched skin allowing it to spring back. The epidermal–dermal junction is found between the basement membrane of the epidermis and the papillary dermis, forming a tight conjunction of complex glycoproteins some 50 nm thick, the barrier to drug penetration through the epidermis.[24-25] Numerous immune cells, such as fibroblasts, leukocytes, mast cells and phagocytes are found in this dermis layer.[26, 27] Sebum and sweat glands, hair follicles, nociceptors and nerve fibers are also found in the dermis. Blood vessels originating from the arterial and venous systems extend into the dermal layer of the skin without penetration the epidermis. Consequently once drugs traverse the

epidermal barrier and reach the dermis, they can rapidly enter the systemic circulation.[28–30] Skin appendages, including sebaceous glands, sweat glands and hair follicles, play important physiological roles. Hair follicles containthe hair shift which is composed of densed packed keratinocyten. The sebaceous glands secrete sebum which lubricates the skin and help maintain an acidic surface pH of approximately 5.[31] The trans follicular pathway is considered a significant route for transdermal drug delivery. Additionally, thermoregulation through sweating is primarily mediated by coiled tubular eccrine glands located in the dermis. Human skin contain approximately 3-4 million eccrine glands, capable of producing up to 3 liters of sweat per hour under extreme conditions.[32] Below it, subcutaneous layer or hypodermis, which is consist of proteoglycans and glycosaminoglycans. This layer connects skin, muscles and bones. It also contains adipose tissue, that assists skin in thermoregulation function.[33,34]

1.1.Wound healing

Wound healing is a complex, highly coordinated process by which the body fast tracks the tissue's return to a fully functional state following injury to skin or other tissues.[35, 36] The process consists of four interrelated and connected stages: hemostasis, inflammation, proliferation and tissue remodeling. The hemostasis phase, which starts right after damage, The primary aim of the initial phase of healing, i.e. hemostasis, is to cease excessive bleeding and create an appropriate substrate for cell migration, a process which is facilitated by a variety of growth factors and cytokines released by platelets.[37] Followed by inflammatory phase, when immune cells like neutrophils and macrophages go to the wound site to eliminate debris, infections and injured cells. Prolonged or severe inflammation can seriously impede tissue repair, even though inflammation is essential for healthy healing.[38] Next, proliferation phase, is marked by the production of new tissue via angiogenesis (creation of new blood vessels), fibroblast activity, collagen synthesis and re-epithelialization.[39] Granulation tissue develops and aids in filling the wound bed during this phase. Collagen fibers finally realign and strengthen during the remodeling or maturation phase, which restores tissue structure and function. Depending on how severe the wound is, this phase may extend for a few weeks or even months.[40]

Even with the natural healing ability of the body many wounds such as Chronic wounds, including diabetic ulcers, burn injuries and pressure ulcers fails to heal, and are regarded as a major clinical and healthcare challenge worldwide.[41,42,43] The healing process of these

wounds are affected by different factors such as microbial infection, impaired immune response, prolonged inflammation, poor blood circulation and reduced oxygen supply to the affected tissue. Other medical conditions such as diabetes, vascular complications and neuropathy, also impair the wound healing process.[44]

Conventional wound healing treatments involves the use of antiseptic creams, topical ointments, gauze dressings and systemic medications like antibiotics and anti-inflammatory drugs. These conventional approaches faced many limitations.[45,46] Usually, topic treatments fails to penetrate deeply into the skin layers, resulting in insufficient drug concentration at the wound site. Also, frequent dressing and repeated drug applications can increase the risk of secondary infection.[47,48] Therefore, there is a growing need for advanced and targeted drug delivery systems that can enhance drug penetration, maintain controlled drug release, and provide a more efficient therapeutic approach.[49,50] Innovative technologies such as microneedle-based delivery systems have emerged as promising solutions to overcome the limitations of conventional wound treatments and improve the overall healing process.[51-53]

1.2.Microneedles

However, Microneedle technology have been the most popular and promising approach in terms of drug delivery via transdermal route, receiving tremendous attention in both academic and industrial sectors during the last decade.[54-57] World Economic Forum also recognized microneedle technology as one of the ten leading technologies in 2020. The word microneedle itself refers to tiny needles typically made from metals like brass or from biodegradable materials like polylactic acid (PLA). The length of such needles usually varies from 25 μm to 2,000 μm and create transient, and reversible, hydrophilic, micrometer-sized channels in the stratum corneum and upper skin-layer by self-controlled, precise fashion. The technology has been evolving over 40 years.

1976: The first patent describing the basic design of microneedles was filed by gerstel and place under the title“Drug delivery device”.[61]

* 1996: Gross and Kelly patented hollow microneedle device for intradermal drug delivery.
* 1997: Jang developed a skin-perforating device to enhance transdermal delivery.
* 1998: Silicon solid microneedles were developed to improved the delivery of calcein.
* 2000: Zahn introduced hollow microneedles designed for the injection of drug solutions into the skin.

* 2004: Cormier developed coated microneedles for transdermal delivery of desmopressin to the upper skin layers, aimed to treating bedwetting.
* 2006: Drug-loaded dissolving microneedles were fabricated using PLGA for dermal delivery of compounds such as calcein and bovine serum albumin.
* 2012: Donnelly introduced hydrogel- forming microneedles a novel system capable of absorbing interstation fluid, swelling and creating microchannels to facilitate drug delivery through the skin.

Interestingly, during the 10 years between 2004 and 2013, the number of publications about microneedles incresed by 77.9%, although since 1970, the increment rate has only been 14.9%.[62] Also, thirty percent of all papers on transdermal delivery methods are related to microneedles.[63] More research and development of microneedle-based devices is anticipated in the future years. Numerous review articles have been written on various aspects of microneedles, including clinical trials, ethical studies, delivery-enhancement applications, fabrication techniques and microneedle design.[64,65] Is has been successfully reported that microneedles these microneedles create microscopic openings in the skin that allow topical products to penetrate deep into skin, but do not penetrate through to reach nerve endings, blood capillaries, etc. to cause pain, irritation or bleeding.[66] In addition to biosignal sensing, therapeutic and cosmetic applications are possible with microneedles. Studies have demonstrated effective transdermal delivery of numerous therapeutic agents, including both small molecules (hydrophilic and lipophilic) and macromolecules (e.g. peptides and proteins), cosmeceuticals and micro- or nano-structured delivery systems containing micro- or nanoparticles. Examples of substances administered with microneedles include oligonucleotides, desmopressin, human growth hormone, insulin, DNA or protein antigens and other immunobiological agents.[67–70] In general, substances can be administered using microneedles without regard to their size or molecular weight. Various geometries, dimensions, designs, densities and materials have been used in the development of microneedles. Glass, sugar, metal, silicon, solid polymers, aqueous hydrogel and dissolving polymers are among the materials used to manufacture microneedles.[71,72] Microneedles have been made using a variety of manufacturing processes; including ion sputter coating, light-based lithographic techniques, chemical and physical etching methods, photo-induced polymer formation, laser-based material removal, micro-molding, sequential layer deposition, droplet- assisted air- blowing and mechanical machining.[73–75] Recent studies havedemonstrated the expanding applications of microneedles in HIV treatment, hormonal

contraception, drug monitoring, diabetes care, cosmetic treatements, cancer therapy, osteoporosis management and vaccination, including COVID-19. Transdermal medication administration is the primary application for microneedles.[76,77] Fig 3. Five different kinds of microneedles.

As of right now, there are five different kinds of microneedles: solid, hollow, coated, dissolving, and swelling.[78–81] Microneedles' primary function is to effectively microporate the skin to a specific penetration depth, breaking down the skin barrier and creating new channels for improved drug delivery.[82,83] Various studies have shown that the preferred and main route of medication diffusion into the skin is through channels made by microneedles. When solid microneedles such as glass, silicon, metal and polymeric microneedles are introduced to pierce the skin, they leave behind numerous microchannels. On the site treated by microneedles, drug-loaded pharmaceutical preparations (such as a patch, semisolid formulation, or solution) are applied.[84] The medication then enters the skin through the usual passive diffusion process through the hydrophilic channels that are open and filled with skin fluid.[85] Fundamentally, hollow microneedles are micrometer-sized hypodermic needles that function similarly to traditional needles. To pierce the skin tissue, mechanically sharp microneedles are first placed.[86] Then, by using passive diffusion or external pressure, the drug formulation—solution or formulation with regulated viscosity is delivered via the needle bore into the skin. A desirable drug delivery profile depends on maintaining a steady and adequate drug injection flow rate. Changing the amount of applied pressure could change the delivery rate.[87,88] Coated microneedles consist of solid microneedles with a drug- loaded layer applied to their surface. Upon insertion into the skin, the coating detaches from the needle surface, dissolves in the interstitial fluid and releases the drug into the skin layers. In contrast, dissolving microneedles- als referred to as polymeric micro needles- encapsulated the drug within a biodegradable polymer matrix. Following insertion, the micro needles dissolve within the skin, enable controlled and efficient drug release.[89, 90] Without leaving any sharp waste behind, the needles pierce the skin, gently disintegrate there, and release the medication payload. Swelling microneedles are strong enough to pierce flesh. After skin insertion, the needles inflate and absorb skin fluid to create a porous hydrogel structure that makes it easy for permeant to permeate skin tissue.[91,92]

Numerous benefits and drawbacks of microneedles have been documented in the literature.

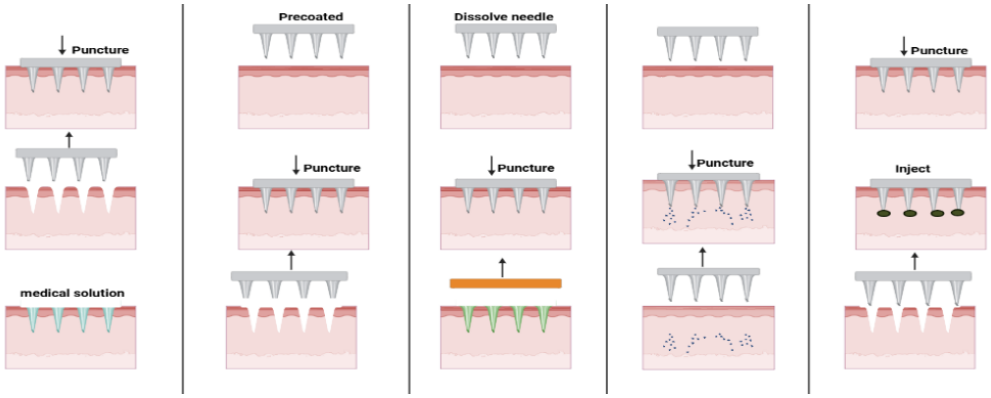


Fig. 3: Five different kinds of microneedles for improved transdermal medication administration are shown.

(A) Solid micro needles: Act by forming transient pores in the skin barrier, solid micro needles improve medication diffusion from topically applied formulations.
(B) Coated micro needles: Enable drug delivery as the surface applied coating quickly dissolves in the skin.
(C) Dissolving micro needles: Deliver drug through degradation of the polymeric matrix after insertion into the skin.
(D) Hollow microneedles: Deliver drug solutions into the skin through needle bores created upon skin penetration.
(E) Swelling microneedles: skin interstitial fluids are absorbed by hydrogel-forming swelling microneedles, which then expand to produce porous channels that enhance medication penetration. Images reprinted with permission from.[93-96]

2. Microneedle-Based Delivery Approaches

Because of the large surface area and specific position of skin it becomes acceptable and non-invasive for dermal ISF sampling as well as delivering medicinal agents. Delivery and sampling by microneedle are generally non-invasive, pain free, and self-administered method impart more patient compliance because of the replacement of the hypodermic needles. In the last few decades, there is increasing research activities in which microneedles of various designs and shapes are made with different material such as metals, glass, polymers and hydrogels in combination with different delivery systems. Initially, four main microneedle-based delivery strategies were introduced.[97, 98] poke and patch (Solid microneedles), coat and poke (Coated microneedles), poke and dissolve (Dissolving microneedles). Figure 4

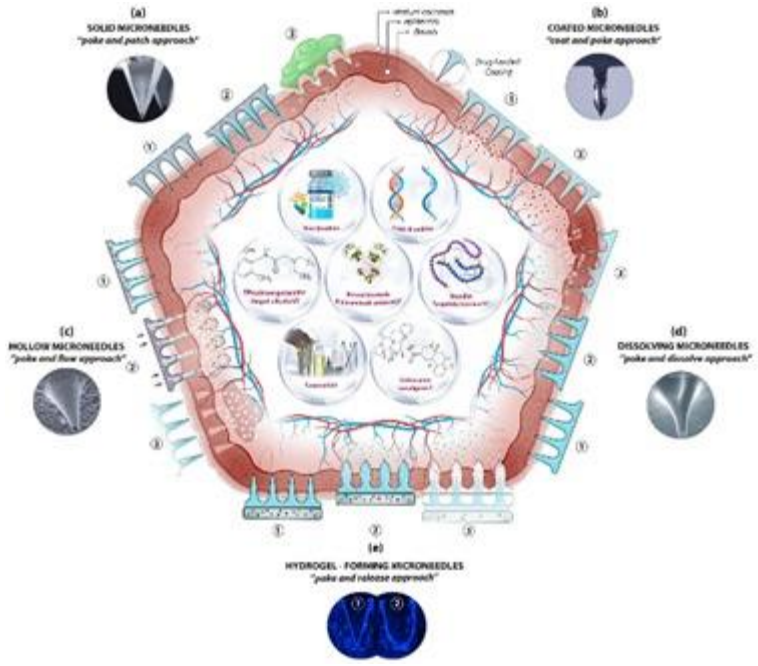


Fig. 4: Figure represents various microneedle-based drug delivery methods with a cross-sectional demonstration of the upper skin layers.

A Figure represents various microneedle-based drug delivery methods with a cross-sectional demonstration of the upper skin layers. These methods include (a) Solid microneedles, (b) coated microneedles, (c) hollow microneedles, (d) dissolving microneedles and (e) hydrogel-forming microneedles. Each method follows a sequence of steps, typically labelled from 1 to 3, to demonstrate how the drug is delivered through the skin. The figure also includes microscopic images of various microneedle types and examples of substances that can be delivered, such as conventional drugs and larger biomolecules.[99]

In the poke and patch method, firstly the solid microneedles are applied on the skin to form tiny microchannels. Then formulation containing drug is applied on these areas, after this pre-treatment step which permit the drug to diffuse via created pores. Silicon-based solid microneedles are used in early studies used to deliver compounds like calcein across excised human skin under laboratory conditions.[100] But high cost, brittleness, limited biocompatibility, and complicated fabrication methods are the challenges that encourage the use of alternative materials like metals, ceramics, and polymers. Although solid microneedles are comparatively easy to manufacture as they do not require drug loading or coating, but they have certain drawbacks such as need for two-step application process and difficulty in achieving precise dosing. In addition, safety concerns remain an important consideration.

Despite these limitations, solid microneedles have been widely explored for delivery proteins, hormones, and vaccines in various studies.[101]

Coated MNs can be formulated by coating drugs on the surface of microneedles (e.g., solid MNs—metallic, silica, or polymeric, hence the "coat and poke" approach). Drugs can be uniformly distributed on the surface of MNs to enable the "coat and poke" approach for stable and effective drug delivery. Water-soluble compounds that can form an effective coating layer on the surface of MNs are suitable for the "coat and poke" approach. Choosing a suitable coating technique for the successful generation of coated MNs is an critical step. The "coat and poke" approach has been applied for the delivery of vaccines[102], insulin[103], hormones[104] and other macromolecules. The coated MNs can be used in an immunised mouse model for ultra-sensitive detection of protein biomarkers.[105] Arrays of polystyrene microneedles with detecting inflammatory biomarkers in interstitial fluid with improved sensitivity (i.e., an improved limit of detection) were made using a primary antibody as bioactive compound coating on the surface of MNs. Coating is the easiest and most controlled way of enabling bioactivity of bioactive compounds throughout the MN manufacturing process. Bioactive coating enables sampling and isolation of biospecimens, in particular for MNs that have detecting capabilities. Challenges include small doses and low strength of the MNs (i.e., decreasing strength of MNs due to loaded cargo).

In the poke and flow strategy hollow microneedle and used to deliver high doses of therapeutic agents into the skin, effectively overcoming the limitations of conventational solid microneedles.[106] The delivery mechanism via hollow MNs can be governed by the diffusion mechanism, mechanical compressions, or even electrical pumps to modulate the dispensing of fluid. Furthermore, integrating hollow MNs into a lab-on-chip device offers immense opportunities for advanced point-of-care applications that require analytical diagnostics. Hollow MNs can facilitate the delivery of biomacromolecules (e.g., proteins and mRNA) and biotherapeutic vaccines, as well as diagnostic compounds[107] (e.g., bio-markers and glucose)[108] for real-time monitoring of ECG signals.[109] While this approach offers numerous advantages, challenges associated with the fabrication of hollow MNs (e.g., clogging, leakage, device fragility, and larger needle tips for efficient skin penetration) remain to be overcome.

A poke-and-dissolve approach has been employed to fabricate microneedles (MNs) from bioabsorbable and biocompatible materials. The majority of devices were made from

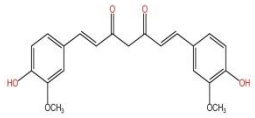
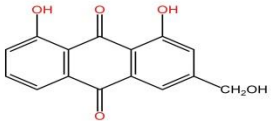
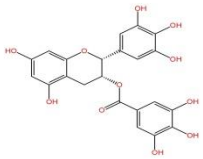
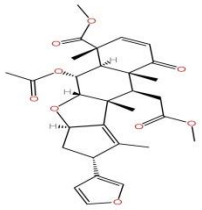
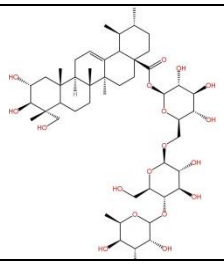
biodegradable polymer PLA/PGA, as well as from various polysaccharides such as hyaluronic acid, sucrose and chitosan. These devices dissolve into the interstitial fluid within the skin to release the contained drug for either localized or systemic effect, not generating any hazardous sharp waste. Dissolving MNs can be made using standard casting or micromolding techniques employing a variety of polymers and sugars.[110] Typically, the drug of choice is incorporated into the needle-like structure of MNs, being released gradually during degradation of the solidified device. While metal and silicon MNs have been studied and applied, MNs made from natural polymers offer an attractive alternative. Pilot studies and clinical trials indicated that dissolving MNs, incorporated into patches, and arrays can act as efficient platforms for delivery of vaccine and related bioactive agents, such as proteins and oligonucleotides.[111] In particular, MN patches that incorporated influenza vaccines provided a safe and effective method to induce specific immune response in clinical studies. The approach overcomes numerous potential disadvantages associated with conventional MNs, for example, they eliminate sharp waste generation, are not needed to contain pumps, provide cost-effective fabrication and do not require complex coatings. However, lower mechanical strength and limited drug-loading capacity, as well as skin penetration issues, could be major concerns in MN device fabrication.[112]

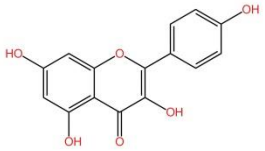
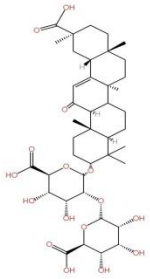
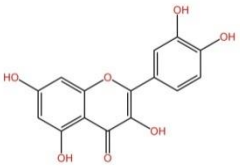
The Microneedles based on hydrogel-forming materials, which are made of swellable polymers.[113] like poloxamers, PEG-crosslinked polymers and modified silk fibroin, are implemented to release drugs into skin.[114] Following insertion into skin, these materials quickly absorb interstitial fluid to form a 3D network of polymer chains and, as the network swells, open microchannels between them that allow drug to permeate through the structure. These devices can also support self-regulated injection by modules that automatically sense glucose and release insulin, for example, reducing the need for constant monitoring by the user. They can also function as diagnostic tools to monitor glucose.[115] and lithium levels.[116] The lifetime of release is easily controlled by modifying the properties of the polymer to release drugs within a time frame ranging from a few minutes to several days. Similar to other soft microneedle devices, however, higher mechanical strength and greater drug-loading capacity are required for improved clinical application.

3. Herbal Materials and Polymers Used in Microneedle Patch Formulation for Wound Healing

Herbal bioactive compounds and biodegradable polymers are widely used in microneedle patch formulations to enhance wound healing. The inclusion of herbal phytochemicals in therapy has gained popularity as a result of their anti-inflammatory, antimicrobial, antioxidant and tissue regenerative actions, etc. in contrast, the polymers are used as the matrix system to fabricate and control release of these bioactive agents through microneedle device. This volume explores the exploitation of herbal materials combined with the polymers microneedle technology. Herbal devices and systems edited by, Madhu Chandra.

Table 1: Herbal Materials and Polymers Used in Microneedle Patch Formulation for Wound Healing.

S. No.	Herbal Material	Major Active Compound	Chemical structure	Role in Wound Healing	References
1	Curcuma longa	Curcumin		Anti-inflammatory, antioxidant, promotes collagen formation	117
2	Aloe vera	Aloe-emodin		Accelerates skin regeneration and reduces inflammation	118-119
3	Camellia sinensis	Epigallocatechin gallate		Antioxidant and antimicrobial activity	120-1 21
4	Azadirachta indica	Nimbidin		Strong antibacterial and anti-inflammatory effect	122 -123
5	Centella asiatica	Asiaticoside		Stimulates collagen synthesis and tissue regeneration	124

6	Calendula officinalis	Flavonoids		Anti-inflammatory and promotes wound contraction	125-126
7	Glycyrrhiza glabra	Glycyrrhizin		Anti-inflammatory and antimicrobial	127-128
8	Moringa oleifera	Quercetin		Antioxidant and promotes tissue repair	129-130

3.1 Polymers Used in Microneedle Patch Formulation

The role of polymers in microneedle patch design and fabrication is highlighted in this review, encompassing materials used to manufacture arrayed microneedle devices as well as for coating individual needles or forming drug-loaded hydraulic microarrays. Assessing the mechanical, biocompatibility and drug release characteristics of the system. Both are natural and synthetic polymers have been used to prepare microneedles. The new polymers are suitable for a variety of applications. They make stable needles, which can adhere firmly to surfaces. These devices, designed to penetrate the skin in a safe and controlled manner, require the use of suitable polymers to efficiently deliver therapeutic agents; importantly, the choice of polymer must allow sufficient drug loading. dissolution, and overall performance of microneedle patches.

Table 2: Polymers Used in Microneedle Patch Formulation.

S. No.	Polymer	Type	Key Properties	Application in Microneedles	Ref
1	Hyaluronic Acid	Natural	Biocompatible, biodegradable, high water retention	Dissolving microneedles for drug delivery	144
2	Chitosan	Natural	Antimicrobial, biodegradable, biocompatible	Wound healing microneedles	145
3	Gelatin	Natural	Biodegradable, flexible	Drug-loaded dissolving microneedles	146

4	Alginate	Natural	High swelling ability, biocompatible	Hydrogel microneedles	147
5	Polyvinyl Alcohol	Synthetic	Good mechanical strength, film-forming ability	Dissolving microneedles	148
6	Polyvinylpyrrolidone	Synthetic	Water-soluble, good drug loading	Fast dissolving microneedles	149
7	Poly(lactic-co-glycolic acid)	Synthetic	Regulated drug release, biodegradable	Prolonged release micro needle system	150
8	Carboxymethyl Cellulose	Natural	High viscosity, biocompatible	Dissolving microneedles	151
9	Polyethylene Glycol	Synthetic	Improves drug solubility and stability	Hydrogel microneedles	15
10	Polylactic Acid	Synthetic	Strong mechanical properties	Solid microneedles	153

4. Formulation Methods of Microneedle Patches

Microneedle (MN) patches are fabricated using various micro fabrication and polymer melding techniques to achieve precise needle geometry, adequate mechanical strength, and efficient drug delivery.[131] Several fabrications methods have been depending on the type of microneedle; materials usesd, and intended therapeutic application. Among these techniques, micro-molding, solvent casting, droplet-born air blowing, photolithography, and 3D printing are the most common methods.[132]

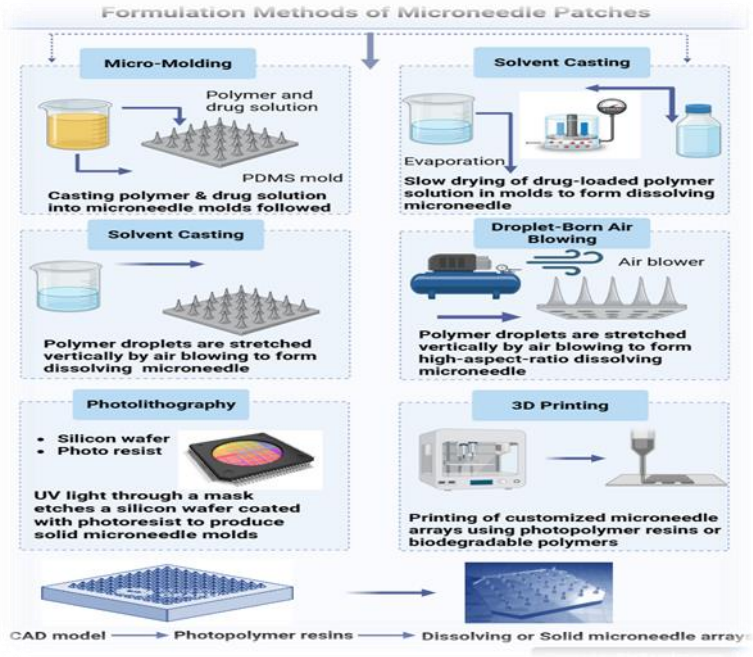


Fig 5. Formulation Methods of Microneedle Patches.

4.1. Micro-molding method

The micro-molding method is the most widely used technique for the fabrication of dissolving and biodegradable micro needle patches. In this method, biocompatible polymers such as chitosan, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), hyaluronic acid, or gelatin are dissolved in distilled water to prepare a polymer solution.[133] Subsequently, herbal bioactive compounds such as curcumin, quercetin, or asiaticoside, or other therapeutic drugs are incorporated into the polymer matrix and mixed thoroughly. The prepared formulation is then poured into microneedle molds, typically made of polydimethylsiloxane (PDMS). To ensure complete filling of the microneedle cavities and removal of air bubbles, the mold is subjected to vacuum or centrifugation. The filled molds are dried at room temperature or at controlled temperatures (approximately 37–40 °C) until solidification occurs.[134] After the formation of the microneedle tips, a second polymer layer is applied to form the backing layer of the patch. Finally, the dried microneedle patch is carefully removed from the mold. This method is widely preferred due to its simplicity, cost-effectiveness, and compatibility with heat-sensitive drugs.[135]

4.2 Solvent casting method

Another commonly used technique is the solvent casting method, which is particularly suitable for polymer-based dissolving microneedles. In this process, polymers such as PVA, PVP, or gelatin are dissolved in an appropriate solvent to form a uniform solution. The active pharmaceutical ingredient or herbal extract is then dissolved or dispersed within the polymer solution. The resulting mixture is poured into microneedle molds and allowed to undergo slow solvent evaporation under controlled temperature conditions.[136] After complete drying, the formed microneedle patch is carefully peeled off from the mold. This method is relatively simple and requires minimal equipment, making it suitable for laboratory-scale fabrication.[137]

4.3. Droplet-born air blowing method

The droplet-born air blowing method represents an alternative technique for producing high-aspect-ratio dissolving microneedles. In this method, droplets of a polymer solution containing the therapeutic agent are deposited onto a substrate.[138] An air-blowing force is applied to stretch the droplets vertically, forming elongated needle-like structures. As the solvent evaporates, the droplets solidify into microneedles. This method eliminates the need for molds and allows rapid fabrication with relatively uniform needle formation.[139]

4.4. Photolithography method

The photolithography method is an advanced microfabrication technique mainly employed for the preparation of solid microneedles and microneedle molds. In this process, a photoresist material is first coated onto a silicon wafer. The coated wafer is then exposed to ultraviolet (UV) light through a patterned mask, which defines the microneedle geometry.[140] The exposed regions undergo chemical etching to produce microneedle structures on the silicon substrate. The resulting structures can serve directly as microneedles or as master molds for polymer microneedle fabrication. Photolithography provides high precision and excellent control over needle dimensions, making it suitable for large-scale manufacturing.[141]

4.5.3D printing technology

Recently, 3D printing technology has emerged as a promising method for the fabrication of customized microneedle patches. In this approach, computer-aided design (CAD) software is used to design the microneedle array with precise dimensions and geometry. The design is then printed using 3D printers with biocompatible photopolymer resins or biodegradable polymers. Following printing, drug-loaded polymers or coatings can be incorporated into the microneedle structures.[142] This technique allows rapid prototyping, personalized design, and the creation of complex structure that are difficult to achieve using tradition alfabrication methods.[143]

5. Characterization of Micro needle Patches

Characterizations of Micro needle Patches are important to determine the quality, safety, mechanical strength, drug loading, and performance of microneedle formulations. These tests allow microneedles to effectively penetrate the skin and release drugs appropriately.

Table 3: Evaluation Parameters of Microneedle Patches.

S. No.	Evaluation Parameter	Method / Description	Purpose	Ref
1	Microneedle morphology	Observed using Scanning Electron Microscopy or optical microscopy.	To evaluate needle shape, size, and structural uniformity.	154
2	Needle height and diameter	Measured using microscopy or image analysis software.	To ensure proper penetration into the skin.	155
3	Mechanical strength	Compression or fracture test using texture analyzer.	To determine the ability of micro needles to tolerate applied insertion stress without breaking.	156

4	Insertion capability	Tested using Parafilm® layers or excised animal skin.	To verify the ability of micro needles to penetrate the skin	157
5	Drug content uniformity	Measured using UV-spectrophotometry or HPLC.	To ensure even drug distribution within the patch.	158
6	Drug release study	Conducted using a frans diffusion cell.	To assess the drug release pattern from microneedles	159
7	Skin penetration study	Conducted using animal skin or artificial skin models.	To study depth of penetration and drug delivery efficiency.	160
8	Dissolution / degradation test	Observed in simulated skin conditions.	To evaluate dissolving behavior of microneedles.	161
9	Biocompatibility study	Cell viability assay (MTT assay).	To confirm safety and non-toxicity of materials.	162
10	Stability study	Performed under different temperature and humidity conditions.	To evaluate shelf life and formulation stability.	163

6. Applications of Microneedle Patches in Wound Healing

Wound healing is made easier with the use of microneedle patches. These advanced skin patches create microscopic holes in the upper layer of the skin to allow medication to reach deep into the lesions. Antibiotics, growth factors and anti-inflammatory drugs such as triamcinolone acetonide can be applied topically to soothe wounds and help them heal faster. These microneedle patches are designed for controlled release and are made from biodegradable materials. They may be the future of wound care.

Table 4: Applications of Microneedle Patches in Wound Healing.

S. No.	Applications	Descriptions	Therapeutic Benefit	Ref
1	Drug delivery for wound treatment	Microneedles deliver antibiotics, anti-inflammatory drugs and analgesic directly into the wound area.	Improves drug penetration and reduces systemic side effects.	164
2	Antibacterial wound management	Microneedle patches loaded with anti-microbial agents such as silver nanoparticles or antibiotics.	Prevents bacterial infection and promotes faster healing.	165
3	Diabetic wound healing	Controlled drug delivery of growth factors, insulin, or anti-inflammatory agents in diabetic ulcers.	Accelerates healing of chronic diabetic wounds.	166
4	Burn wound treatment	Delivery of anti-inflammatory and regenerative compounds into burn-damaged skin.	Reduces inflammation and enhances skin regeneration.	167
5	Growth factor delivery	Microneedles delivery growth factors such as VEGF, EGF, and PDGF to stimulate tissue regeneration.	Enhances angiogenesis and collagen formation.	168

6	Stem cell therapy	Microneedle patches can deliver stem cells or exosomes into damaged tissue.	Promotes tissue repair and regeneration.	169
	Scar prevention	Controlled delivery of antifibrotic agents to regulate collagen deposition.	Reduces scar formation during wound healing.	
8	Smart wound monitoring	Microneedles integrated with sensors to detect pH, temperature, and infection markers.	Enables real-time monitoring of wound healing.	170
9	Herbal drug delivery	Delivery of plant-based bioactive compounds such as curcumin, aloe-emodin, or other phytochemicals.	Provides natural anti-inflammatory and antioxidant effects.	171
10	Gene therapy delivery	Microneedles deliver DNA, RNA, or siRNA to regulate wound-healing pathways.	Enhances tissue regeneration and controls inflammation.	172

6.1. Marketed Microneedle Products

From laboratory bench to commercial products on the global market shelves Microneedle technology has matured. Cosmetics and dermatology products as well as drugs are available on the global market containing minipores or minichannels that create a minimally invasive pathway for increased transdermal delivery of active ingredients.

Table 5: Marketed Microneedle Products.

S. No.	Product Name	Company	Application	Ref
1	MicronJet®	NanoPass Technologies	Intradermal drug and vaccine delivery	173
2	AdminPatch®	AdminMed NanoBioSciences	Cosmetic and drug delivery	174
3	Dermapen®	Equipmed	Skin rejuvenation and dermatological treatments	175
4	MicroHyala®	CosMED Pharmaceutical	Cosmetic microneedle patch with hyaluronic acid	176

7. Obstacles of Micro needle Drug Delivery System

The shifting of MNs from lab scale to the large-scale production is thrilling but arduous upcoming task. Various crucial obstacles must be systematically handled to enable large scale production. The major limitations that determine the applications and future of this technology and various strategies to overcome these barriers are described below.

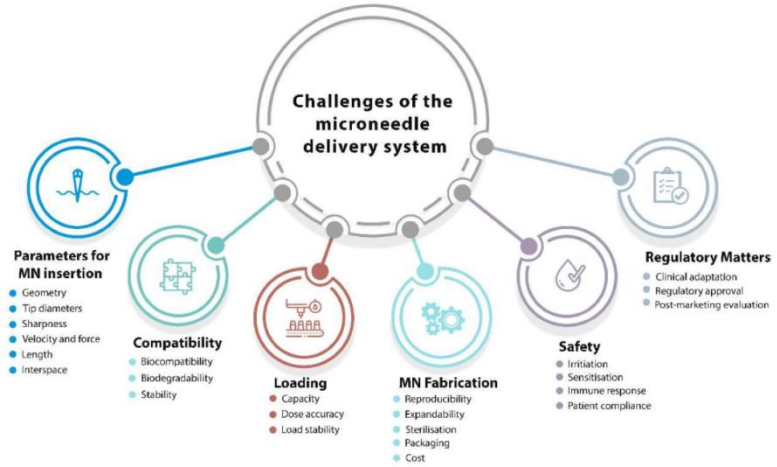


Fig.6: Challenges of Microneedle Delivery.

7.1. Parameters Affecting Micro needle Insertion

Microneedle's ability to trace pass the skin barriers is fundamental property. However, difference in skin's properties at various anatomical sites and person to person variations may affect the insertion efficiency critically. Key design parameters that play a critical part in MNs penetration behaviour measurement and skin elasticity overcoming ability are base and tip diameter, geometry, interspacing (centre-to-centre distance) and length.[177,178] Thus, "one-size-fits-all" approach is not applicable here. Key parameters upon which MNs insertion and drug delivery ability reliant on are skin characteristics, application technique, needle geometry, and material composition.[179] To use MNs as per the intended therapeutic application, the pinpoint tuning of parameters such as insertion depth, mechanical strength, and drug release kinetics must be done by altering the formulation and design of microneedle.

Geometry: For early stage of development, geometry is critical design factor that must be considered. Penetration efficiency and mechanical robustness of microneedle array is majorly affected by the structural configurations as per the recent studies.[180] Proportional relationship is obtained amongst the tensile strength and the number of vertical corner points of polygon base (e.g. Hexagonal micro needle bases) from simulation studies which demonstrate that three-lateral-face pyramidal and square pyramidal microneedles have superior penetration than hexagonal structures due to their sharp edges. Vaccine delivery such as ovalbumin-based immunization can be achieved by Cone-shaped microneedles due to their optimal balance between fast dissolution and insertion efficiency.[181] To enhance drug flux and decrease inconsistencies in delivery medications, various design innovations such as hemispherical convexities incorporation in dissolving MNs have been purposed additionally.[182]

Tip diameter and Sharpness: Another determinant of insertion efficiency is tip diameter and sharpness. Because of increased front surface area, MNs with larger tip diameter (60-160 µm) need higher force of insertion.[183] On the other hand, Sharpe microneedles with small tip diameter ((<15 µm) promote smooth penetration with lesser force. High risk of needle brakeage/leakage and structural comptonizations are the limitations of increasing sharpness of microneedles. In vaccine delivery it is crucial to gain a dominance on skin depth of MNs, where targeting immune cells such as Langerhans cells in the epidermis and dendritic cells in the dermis is important for producing and effective immune response.[184]

Application velocity and force: The force and applied velocity are other parameters related closely with the tip diameter that significantly influence the penetration depth from 10% to 80% depending upon the conditions and must be considered carefully.[185] For effective insertion microneedle with tip radius less than 100 nm need approx. 10mN fore as per the studies. For array containing 10-100 needles insertion force per needle of 15-30mN rang is enough, corresponding to total implementation force of 0.1-3 N. Investigation of a wide range of MN patch designs is carried out which demonstrate per-needle basis comparable penetration force requirements.[186] Reported findings from independent studies shows that under optimal conditions the insertion force in range of 15–20 mN.[187] and 15–30 mN[188] per microneedle is sufficient to achive effective penetration of skin.

Length: The particles insertion depth may be vary, as density of stratum coronium and various skin layers differs across individuals. Microneedle length determines depth of penetration and drug delivery pathway. For rapid systemic delivery deeper penetration into the dermis is required, whereas superficial pores may be sufficient for small molecules with high diffusivity. Thus, longer microneedles (up to 1000 µm long) have been used to enhance insulin skin permeability.[189]

Interspace (centre-to-centre spacing): Spacing between microneedles in an array also affects insertion efficiency. High-density arrays (more than 500/cm^2) required greater force due to “bed=-of-nails” effect, where skin deformation distributes the applied force across the needles and results in reduction of individual penetration effiviency. By creatin more microchannels, MNs with enhanced microneedle density may increase drug delivery, but effective insertion may be hindered by excessive crowding.[185]

7.2. Biocompatibility, Biodegradability, and Stability

Bio-acceptability is major safety parameters of microneedles in clinical use. To ensure the microneedle products are acceptable for clinical use, on the basis of contact period upto 24h,24-30h and beyond 30h are carried out to analyse there bio-accessibility.[190] Standard biological test includes cytotoxicity, irritation, intracutaneous reactivity, and sensitisation tests, Analysis on the basis of genotoxicity and subacute or sub chronic systematic toxicity are also recommended for extended exposure duration. Due to their easy degradation and safely elimination from the body, the use of biodegradable material is described for microneedles. Therefore, in recent years polymer-based microneedles gain significant attention.

Microneedles formed from aqueous polymeric solutions at ambient temperature, without need of thermal processing, offers advantage in preserving incorporated therapeutics, In case of temperature-sensitive biomolecules such as proteins and peptides this becomes critical. To ensure therapeutic efficiency of easily brittle and decomposable drugs, stability if microneedles during storage is very crucial. The stability and shelf-life of protein-based formulations is enhanced due to rigid, glassy structure of microneedle matrices by hindering the mobility and decrease the atmospheric oxygen exposure.[191] Furthermore, to protect labile compounds, stabilizers such as trehalose and sucrose are also incorporated. Under non-vacuum storage conditions both the stability of drug and mechanical strength of microneedle are adversely affected by elevated water levels. Thus, moister content plays a critical role during storage.[192] To ensure prolonged stability and maintain product performance in case of dissolvable microneedles, it is essential to store them under controlled conditions, preferably in cool and low-humidity environment.

7.3. Loading Efficiency and Dose Uniformity

Loading capacity: Only bolus dose of around 1 mg of medicine can be administered via coated microneedles. Although, continuous infusion is possible with hollow microneedles, after microneedle insertion central exits likely be hindered by thickened skin tissue. Although the MN tend to counter the barriers of sikn, but the success of MNs is relay on drug's passive diffusion into the skin, due to which the only small dose of drug can be administered and most of the drug amount can be vanished on surface of skin. Use of this technology for clinical application is obstacle by the time of implementation and the lack of dose delivery monitoring e.g.; dose constancy is critical in case of vaccine distribution. Recent studies

demonstrated that the direct administration of vaccines through dermis and epidermis and dermis has tendency to produce immunological responses with comparatively low amount vaccine than standard IM injection, but this advantage is useless if a very small amount of drug reaches the skin. However, this is not unavoidable barrier to this technology, but vaccine delivery required a threshold dose to produce immune response but this is hard to achieve with passive diffusion.

Dosage accuracy: In sustained drug delivery system, problem that needs close investigation is dosage accuracy of MN delivery system. To reduce the patching time and fast elimination of drug from MNs various methods have been purposed using separable needles.[193,194] As large biological molecules are susceptible to fast deterioration the proteinases drugs for instance, insulin, erythropoietin, glucagon, parathyroid hormones and growth homones are sensitive and difficult to store property deliver via this technology. Considering all the parameters of MN formulation such storage and formulation temperatures, conditions of drying, sterilisation, packaging along with incorporating the stabilizer, and polymer concentration can overcome this obstacle. Accurately control of drug delivery efficiency is difficult with solid MNs. To deliver precise amount of drug, coated MNs are used but due to their compact area of coating only small quantity of therapeutics can be loaded. Dissolvable microneedle can encapsulate the drug in MNs matrix which are formulate from water loving, bio accessible, and bio composable materials. By using dissolvable MNs large dose and controlled release of different medicines can be achieved without any reservoir leakage. To give protection and stability to nano-sized formulations along with enhancing SC barrier penetration of nanoparticles dissolvable in micro needles and it can be efficient approach. To monitor or evaluate the in vivo progression nanomaterials along with the loaded drugs, modern tracing and tracking approaches are essential.[195,196]

7.4. Skin Irritation and Recovery

In microneedle mediated drug delivery, the immunologically active nature of skin plays a critical role, and makes it a responsible organ. Depending upon the factors such as physicochemical properties, type of administered drug, molecular size mild side effects such as temporary erythema may develop. Thus, on the time of clinical trials the safety assessment of MN products must evaluate the skin irritation, sensitisation, and immune response. Prior to human trials, these safety aspects must be examined through animal studies. Once the key

challenges are countered adequately, this technology have great potential to develop MN-based vaccine delivery system.

7.5. Cost of Microneedle Fabrication

To enable the development of microchip-based micro needles for clinical use and achieve large-scale production, improvements are required in current micro needle manufacturing processes. Although the comprehensive economic assessment of this technology is not quantified yet, but it can be anticipated that, like other new technologies, initial clinical development of MN system suffers from high cost, because of complex manufacturing and storage procedure along with long approval process.

Here is a lack of assessment of economic and epidemiological implications of MN-based systems for clinical use in populations (with the exception of pilot-scale studies and trials). However, some first cost calculations have been made and are presented in this study. We attempted to estimate economic efficiency of one type of MN patches developed in our group for measles vaccine (MV) delivery in comparison with standard SC administration, using a typical national measles vaccination program as an example.[197] Data showed that cost per dose for vaccination of one million children were about USD 0.95 for MN patches against USD 1.65 for SC injections preserving advantage in terms of thermostability and in reduction of the cold chain use.[80] Overall, the costs for one-year vaccination program based on MN patches would constitute USD 1.5 million as against USD 2.5 million for traditional SC regime.[198] Economic modeling of MN-based seasonal influenza vaccination showed that this technology could be cost-effective or even dominant at USD 9.50 when administered by healthcare professionals. Moreover, as long as vaccine efficacy increased by 3% or more, MN-based vaccine would remain cost-effective for all scenarios at price up to USD 30. Therefore, cost-effectiveness analysis must be performed at early stages of development, especially when global healthcare expenditure is escalating. For MN systems to achieve successful commercialization, their commercial viability must be paralleled with advances in fabrication methodologies and the selection of materials. The fabrication of MN systems requires reproducibility and precision in their manufacture. Moreover, the methodology must be amenable to up-scale manufacturing to generate high yields in a timely manner, and be applicable to a variety of clinical applications.[199] Furthermore, the selection of materials must confer therapeutically relevant stability, activity, and delivery to the encapsulated drugs.

The ultimate manufacturing approach must enable rapid, flexible, and cost-efficient production, enabling optimization of material composition and MN geometry.

7.6. Sterilization Challenges of Microneedle Patches

Sterilization is a significant issue for MN-based delivery systems and needs to be addressed at the early stages of product design. An appropriate method of sterilization has to be selected, as conventional methods like moist heat, gamma irradiation, microwave treatment or ethylene oxide sterilization can potentially affect the stability of the vaccine, peptides or other biomolecules, as well as the integrity of the MN structure.[200] Unlike traditional hypodermic needles, the risk of microbial contamination from microneedles (MNs) is perceived to be lower; however, from a regulatory perspective, complete sterilization of MNs is required to guarantee patient safety. The method of sterilization is influenced by the type of materials used in MNs fabrication. Solid MNs constructed from metals, silicon or glass can be efficiently sterilized via dry heat, moist heat or gamma radiation techniques.[201] Developing Micro-Nano (MN) systems for the delivery of biologically sensitive bio-therapeutic agents is more challenging than making MN systems for non-sensitized dosage forms. Coated, dissolving, or hydrogel forming MN systems require careful aseptic preparation to minimize the risk of contamination (bioburden) and the presence of endotoxins. However, the commonly used heat-based sterilization methods for MNs can alter the properties of MNs and their formulations, affecting both the stability of encapsulated drugs and the functionality of MN systems. Sterilization of dissolving or hydrogel forming MN systems using model drugs, such as ibuprofen or ovalbumin, resulted in acceptable levels of bioburden and endotoxin (below 100 CFU/g or 0.2 EU/g), respectively.[202] Using appropriate sterility assurance level (SAL 10^{-6}), gamma sterilization also could prepare aseptic MN systems that retained their integrity and functionality. However, it should be noted that gamma sterilization may not be suitable for all bio-therapeutic agents and require formulation dependent optimization.[203,204] Except for gamma irradiation, alternative sterilization methods like ethylene oxide or electron beam irradiation have been developed which less severely compromise MN performance. Moreover, novel strategies for sterilizing MN have been proposed, as for instance incorporating antimicrobial agents such as silver nanoparticles into the MN carrier material to achieve self-sterilization properties, thus preventing any microbial contamination when applying the MN to the skin.[205]

Although there are some available solutions and approaches reported in the literature for achieving the necessary sterilization of Microelectronic Networks (MN), there is still a lack of sufficient information regarding different approaches and techniques to achieve sterilization. Moreover, there is a need for more research in order to establish protocols that are cost effective, reproducible, reliable and generally applicable. In particular, the process of terminal sterilization is inherently difficult to achieve due to the complexities of maintaining aseptic manufacturing processes and environments.

7.7. Regulatory Considerations for Microneedle Patches

Regulatory approval of microneedle-based products is becoming increasingly complex. Despite advances in MN technology, agencies such as the US FDA consider current submissions for MN-based combination products to be of poor quality, particularly with respect to stability testing, dose uniformity, risk management, sterility, and manufacturing consistency. Microneedles provide a promising delivery technology for a variety of drugs like vaccines, hormones and enzymes, nucleic acids and small molecules with poor bioavailability for transdermal administration. Translation of microneedles to clinical use, however, requires robust evidence from in vitro studys, preclinical animal study, clinical studies and understanding of human physiology, clinical needs and user-friendly aspects. Current practices allow MN-based products to receive regulatory clearance on a case-by-case basis with product specific timelines to market. However, these processes are often time consuming and could benefit from streamlined product development. Harmonized federal and state level guidelines outlining appropriate cGMP manufacturing practices, quality control strategies and clear product classification (based on MN design, product formulation, sterilization methodology and packaging configuration) could significantly enhance MN-based product commercialization.[190] MN devices may be regulated as medical devices, e.g. for diagnostic/monitoring functions, distinct from drug- delivery systems which are combination products or drug products. However, clear regulatory pathways need to be established to encourage investment in this field. There is also the possibility that MN devices can be developed independently of a drug formulation, and easily incorporated into existing pharmaceutical supply chains. In some cases, particularly for diagnostic/monitoring functions, MN devices are regulated as medical devices as opposed to drug- delivery systems which are classified as combination products or drug products.[206,207] Investment in this field would be facilitated by establishment of clear regulatory pathways to foster product

development. Independently developing MN devices that can be easily incorporated into existing supply chains also has the potential to stimulate investment.

Here we see another example of progress in the field as Zosano Pharma recently submitted their new drug application to the FDA in 2020 for Qtrypta (zolmitriptan), a Microneedle-based product for treating acute migraine. This innovative device contains titanium Microneedles that are coated with a liquid solution containing zolmitriptan, a powerful medication for treating and preventing migraine headaches. This product marks an important milestone for MN technology, demonstrating new clinical and commercial possibilities.

8. Future outlook of Microneedle-Assisted Wound Healing Strategies

Topical drug delivery systems based on 'microneedle' patches have been recently explored and demonstrated as emerging technologies for advanced wound care and management. In such patches, micron-sized needles create micro-pores in the skin allowing harmless penetration, and provide a delivery route for active pharmaceutical or biomaterial agents to promote healing to the wounded area, prevent infection, and enhance tissue regeneration. The future for microneedle patches as drug and biomaterial delivery systems for wound healing is promising.[208]

8.1. Advanced Drug Delivery Systems

Future microneedle patches will function as micro-scale drug delivery devices that deliver antibiotics, anti-inflammatories, growth factor and herbal bioactive molecules directly into skin wound tissue, improving efficacy and reducing systemic side effects and dosage requirements the enhancing efficacy therapeutic effectiveness and reducting systemic adverse effects products.

8.2. Integration with Smart and Responsive Systems

Future microneedle patches could comprise of smart materials or stimuli-responsive materials that could automatically release drugs upon environmental change such as pH, temperature or infection markers. This approach enables real-time drug delivery to wounds, making it possible to combat an infection as it occurs through the release of active ingredients.[210]

8.3. Use of Natural and Herbal Bioactive Compounds

Current research has examined the application of herbal extracts and phytochemicals in the development of microneedle patches for wound healing. Extracts from medicinal herbs have

exhibited notable antimicrobial, antioxidant and anti-inflammatory effect which can facilitate faster tissue repair and aid in preventing the formation of scars. Incorporating herbal therapeutics with nanotechnology-based platforms could derive the development of safer and more effective wound healing technologies.[211]

8.4. Nanotechnology-Based Microneedle Systems

Nanoparticles, like Fe_3O_4 (magnetite) nanoparticles or polymeric nanocarriers, containing drugs can increase the loading capacity and achieve sustained release, alongside enabling stimulus-responsive, externally controlled drug delivery, like into deep wound tissues, through magnetic or responsive properties.[212]

8.5. Biodegradable and Biocompatible Materials

Future formulations will be biodegradable so that the polymers dissolve within the skin delivering dose, future candidates for biodegradable polymer formulations include PVP, Hyaluronic Acid, PVA and others.

8.6. Personalized and 3D-Printed Microneedle Patches

Technological innovations in 3D printing and microfabrication will enable the development of personalised patches comprised of micron sized needles to deliver targeted treatments. Custom made to taking into accound wound dimensions, penetration depth and wound type, these advancements offer improved outcomes in chronic wound management such as diabetic ulcers and some burn injuries for the millions of patients worldwide suffering from them.[214]

8.7. Clinical Translation and Commercialization

Although promising, further clinical trials and regulatory approval are required before widespread clinical use of microneedle technology. Future work will focus on optimisation of manufacturing, stability and clinical use for wound care.

Table 6: Future Prospects of Microneedle Patches.

Future Direction	Description	Expected Benefit
Smart microneedle patches	Utilization of biosensors for continuous monitoring of wound biomarkers like pH, glucose, temperature, and infection markers.	Dynamic monitoring of wound status and personalized treatment.
Nanoparticle-loaded microneedles	Incorporation of nanoparticles (silver, gold, polymeric, magnetic) into microneedles.	Improved antimicrobial activity, enhanced drug penetration, and sustained drug release.
Growth factor	Microneedles delivering various growth-	Stimulates angiogenesis, collagen

delivery	promoting factors such as VEGF, TGF-β and EGF.	synthesis, and faster tissue regeneration.
Stem cell / exosome delivery	Microneedle patches delivering stem cells or stem-cell-derived extracellular vesicles directed to wound sites.	Accelerates tissue regeneration and improves healing of chronic wounds.
Hydrogel microneedles	Use of hydrogel-based microneedles with high biocompatibility and moisture retention.	Maintains moist wound environment and enhances drug stability.
Stimuli-responsive microneedles	Microneedles that release drugs as a result of stimuli such as variations in pH,temperature or infection	Controlled or targeted drug release for better treatment outcomes.
3D-printed microneedles	Use of 3D printing technology to design customizable microneedle arrays.	Personalized wound therapy and precise drug delivery.
Gene therapy delivery	Microneedles delivering genes or siRNA to regulate wound-healing pathways.	Enhanced regulation of inflammation and tissue repair.
Combination therapy systems	Microneedles delivering multiple agents (antibiotics + anti-inflammatory drugs + growth factors).	Simultaneous control of infection, inflammation, and tissue repair.
Scar-free wound healing systems	Microneedle systems designed to control collagen deposition and prevent scar formation.	Improved cosmetic and functional healing outcomes.

9. CONCLUSION

Bioactive herbal compounds or plant extracts are increasingly being explored as active agents for development of microneedle-based wound healing products. Many phytochemicals have proven to possess excellent antioxidant, antimicrobial and anti-inflammatory bioactivities. Antioxidants such as EGCG (epigallocatechin gallate) and glycyrrhizin combat oxidative stress, antimitobials such as ellagic acid inhibit microbial infections. The anti-inflammatories decrease inflammation to increase collagen deposition and tissue regeneration thereby facilitating wound healing.

Delivery of herbal medicinal ingredients by using microneedle patches provides several advantages to conventional wound therapies. Microneedle patches provide an alternate route of minimally invasive transdermal delivery, enhancing drug penetration reaching the inner layers of the skin,namely the epidermal and dermal regions. Microneedle patches are also capable in controlling or releasing therapeutic amounts of active ingredients to the wound site for prolonged durations, resulting in enhanced bioavailability of the delivered herbal bioactive compoundsreduced toxicity and greater patient acceptance.

Advances in fabrication technology for polymeric microneedles and nanotechnology have led to the enhanced stability, loading efficiency, and bioactivity of herbal materials. The use of

biodegradable polymeric systems for loading herbal bioactives forms the basis of novel, safe, efficacious, and patient-friendly wound care products.

This article focuses on recent developments utilizing herbal compounds, which are incorporated into microneedle patches to promote wound healing. Future directions, including optimization of the novel formulation, long-term toxicity studies, and clinical trials, are discussed. Based on these attributes, future-generation wound healing systems could consist of herbal-loaded microneedle patches to promote efficient tissue repair and improve patient outcomes.

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