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Review Article

Dissolving and Hydrogel-Forming Microneedles for Transdermal Delivery of Biologics: Formulation Parameters, Mechanical Strength, and Stability

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ABSTRACT

Transdermal delivery of biologics such as proteins, peptides, vaccines, and nucleic acids is challenging because of their large molecular size, poor skin permeability, and susceptibility to degradation. Microneedle-based delivery systems are among newest pharmaceutical delivery systems that scientifically are formulated with components released on the attachment to the skin that minimizes the barrier of penetration upon the structure of the skin. Among the different microneedle platforms, dissolving microneedles (DMNs) and hydrogel-forming microneedles (HFMNs) have received considerable attention because of their potential for efficient, patient-friendly, and controlled drug delivery. This review focuses on the formulation strategies, mechanical strength, and stability considerations governing the performance of DMNs and HFMNs for transdermal delivery of biologics. Particular emphasis is placed on the selection and concentration of polymers, molecular weight, drug–polymer interactions, plasticizers, crosslinking agents, microneedle geometry, drug loading, and fabrication techniques. The role of mechanical strength in ensuring successful skin penetration without needle deformation or fracture is discussed, along with methods used to evaluate insertion efficiency and mechanical performance. Furthermore, the stability of biologics during formulation, fabrication, storage, and application is examined, considering factors such as temperature, moisture, polymer composition, and processing conditions. A comparative discussion of DMNs and HFMNs is presented in terms of drug-loading capacity, release behaviour, mechanical properties, stability, and potential for sustained delivery. The review also highlights current challenges, including dose limitations, preservation of biologic activity, standardization of mechanical testing, storage stability, sterilization, and scale-up. Overall, rational optimization of formulation and device

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characteristics is essential for developing mechanically robust and stable microneedle systems capable of translating biologic transdermal delivery from laboratory research to clinical applications.

INTRODUCTION

1.1 Overview of Biologics.

Biologics, including peptides, proteins, monoclonal antibodies, vaccines, and nucleic acid-based therapeutics, have revolutionized the treatment of numerous chronic and life-threatening diseases. Their high specificity, potency, and ability to target complex biological pathways have significantly advanced modern medicine. However, the delivery of biologics remains challenging because these macromolecules are susceptible to enzymatic degradation, exhibit poor membrane permeability, and often require parenteral administration to achieve therapeutic efficacy. Conventional injections are associated with pain, needle phobia, poor patient compliance, generation of sharps waste, and dependence on trained healthcare personnel. Furthermore, many biologics are thermolabile and require strict cold-chain storage conditions, increasing distribution costs and limiting accessibility.

1.2 Transdermal Drug Delivery

Transdermal drug delivery offers an attractive alternative to conventional administration routes due to its non-invasive nature, avoidance of first-pass metabolism, and potential for self-administration. Nevertheless, the skin's outermost layer, the stratum corneum, acts as an effective barrier that restricts the permeation of most therapeutic agents, particularly large hydrophilic molecules such as biologics. As a result, only a limited number of drugs can be delivered effectively through traditional transdermal systems [1,2]

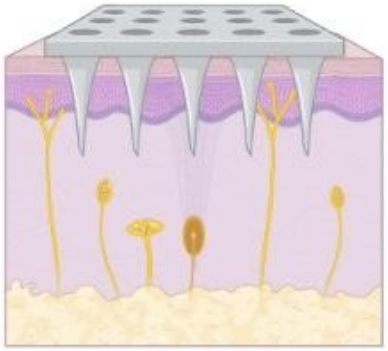

Figure 1: ***STRATUM CORNEUM ALONG WITH THE MICRONEEDLE PATCH***

1.3 Microneedle Technology

Microneedle (MN) technology has emerged as a promising strategy to overcome this barrier. Microneedles are micron-scale projections capable of creating transient microchannels in the skin, enabling painless and causes less damage to its penetration towards the epidermis and dermis part of the skin. By bypassing the skin as it prevents the damaging of deep nerve endings and blood vessels, MNs combine the advantages of hypodermic injections with improved patient comfort and safety. Microneedle systems have demonstrated significant potential for the delivery of both small molecules and biologics, including proteins, peptides, vaccines, and antibodies.

Among the various microneedle platforms, dissolving and hydrogel-forming microneedles have attracted considerable attention due to their biocompatibility, biodegradability, and ability to encapsulate sensitive biological therapeutics. Dissolving microneedles are generally fabricated from water-soluble polymers that encapsulate drugs within the needle matrix and release them upon dissolution in interstitial fluid. In contrast, hydrogel-forming microneedles absorb interstitial fluid after insertion, swell to form hydrogel networks, and facilitate controlled drug diffusion without leaving polymer residues in the skin. These systems eliminate the risks associated with sharps waste and offer opportunities for sustained, controlled, and targeted delivery of biologics.[3,4]

1.4 Aim and Scope of the Review

The successful development of dissolving and hydrogel-forming microneedles depends on several critical factors. Formulation parameters, including polymer selection, polymer concentration, crosslinking density, drug loading, and excipient incorporation, directly influence drug encapsulation, release behavior, and biocompatibility. Equally important is mechanical strength, as microneedles must possess sufficient robustness to penetrate the skin without bending or fracturing during application. Additionally, stability remains a major concern, particularly for biologics that are highly sensitive to temperature, moisture, processing conditions, and long-term storage. Preservation of structural integrity and biological activity throughout fabrication, storage, and administration is essential for successful clinical translation.[5]

This review aims to provide a comprehensive overview of dissolving and hydrogel-forming microneedles for transdermal delivery of biologics, with particular emphasis on formulation parameters, mechanical performance, and stability considerations. Furthermore, recent advances, challenges, and future perspectives associated with the clinical translation and commercialization of these microneedle-based delivery systems are discussed.[6]

2. Dissolving and Hydrogel-Forming Microneedles

Principle and mechanism of action of Microneedles;

Microneedles work by using tiny,microscopic needles about 20-1500 micrometers long mounted on a patchto pierce the outer layer of the skin-stratum corneum.

They act by overcoming/bypass the outer skin barriers so that drug that normally cannot pass through the skin outer layer (stratum corneum) can be delivered more effectively.

They create tiny temporary pathways that are painless micro-channels that deliver drugs directly into the tissue fluid or capillaries without reaching deep nerve endings or causing bleeding.[16]

2.1 Dissolving Microneedles

(a) Principle of and mechanism of action of Dissolving Microneedles

Dissolving microneedles are drug delivery formulations that are comprised and obtained from water-soluble polymers that penetrate the skin and absorb moisture from skin layers,its needle structure gradually dissolves,biological drug incorporated inside the microneedle and released into the skin.[16,17]

Basic principle of this microneedle;

Insertion → Skin penetration→ Polymer dissolution → Drug release → Drug diffusion into viable skin.

(b) Materials commonly used.

Microneedles are composed of different materials commonly classified in table 1 as follows:

Table 1: ***Different types of different materials used in Dissolving Microneedles***

Category	Polymer/Compound	Description / Key Features
Natural and Biodegradable	Hyaluronic Acid (HA)	Natural tissue component; excellent for skin compatibility and cosmetic or intradermal drug delivery.
	Chitosan	Derived from chitin; good biocompatibility and natural mucoadhesive properties.
	Silk Fibroin	Protein-based polymer; great mechanical strength and tunable dissolution rates.
Synthetic and Semi-Synthetic	Polyvinylpyrrolidone (PVP)	Water-soluble, amorphous polymer; forms clear, hard structures that trap fragile biologics well.

Category	Polymer/Compound	Description / Key Features
	Carboxymethyl Cellulose (CMC)	Cellulose derivative; provides stable mechanical properties during skin insertion.
	Polyvinyl Alcohol (PVA)	Strong film-forming polymer; easily tailored for different degradation speeds.
Sugars and Carbohydrates	Maltose and Trehalose	Natural disaccharides; used to stabilize delicate proteins and vaccines during rapid manufacturing and storage.

Microneedles composed of hyaluronic acid integrated with pH-sensitive dextran nanoparticles that encapsulate a PD1and glucose oxidase (GOx), which converts blood glucose to gluconic acid. The resulting acidic environment promotes the self-dissociation of the nanoparticles and results in the release of aPD1 for treatment of melanoma

(c) Drug loading and release mechanisms

Drug loading in dissolving microneedles involves mixing active pharmaceutical ingredients into a water-soluble, biodegradable polymer matrix. The mixture is cast into micro-molds using solvent casting or centrifugation. Upon skin insertion, the needles absorb interstitial fluid, rapidly dissolve, and release the cargo painlessly without sharp waste.

Table 2: ***Polymers Used in Dissolving Microneedles***

Polymer	Key Properties	Role/Advantage in Microneedles
Hyaluronic Acid (HA)	Biocompatible, highly soluble, and naturally occurring	Excellent skin compatibility and supports efficient skin penetration.
Polyvinylalcohol (PVA)	Good film-forming ability,water solubility and chemical stability	Provides safety at skin application and biodegradability.
Polyvinylpyrrolidone (PVP)	Highly water-soluble and rapidly dissolving	Enables fast microneedle dissolution and helps stabilize macromolecules.
Carboxymethyl Cellulose (CMC)	Natural, water-soluble, biodegradable polymer	Provides a safe biodegradation profile and suitable matrix formation.
Chitosan	Natural, biodegradable, biocompatible, and mucoadhesive	Offers safe biodegradation and can enhance drug delivery properties.

Table 3: ***rug Loading Strategies and Limitations of Microneedles***

Category	Description	Key Advantage / Limitation
Tip-Loading (Two-Step Casting)	Drug is concentrated primarily within the microneedle tips using a two separate operations casting process.	Minimizes drug wastage and promotes delivery beyond the stratum corneum.
Bulk-Loading	Drug is distributed uniformly throughout the needle and base matrix.	Suitable for broader drug distribution and higher drug-loading requirements.
Nanoparticle/Liposome Incorporation	Hydrophobic or sensitive biologic drugs are encapsulated in nanoparticles or liposomes before incorporation into the hydrophilic polymer matrix.	Protects fragile drugs and can provide controlled or sustained release.
Capacity Bounds	The small volume of individual microneedles limits the total amount of active constituents that can be formulated into a patch.	Limits the drug deliverance at the site of action when required at high doses.
Mechanical Trade-Offs	High drug concentrations may alter polymer properties of the microneedle matrix.	May result in inadequate skin penetration or needle deformation/fracture.

Category	Description	Key Advantage / Limitation
Stability Issues	Manufacturing conditions such as heat and solvent exposure may affect sensitive biologics.	Can cause degradation or loss of activity of vaccines, peptides, and proteins.

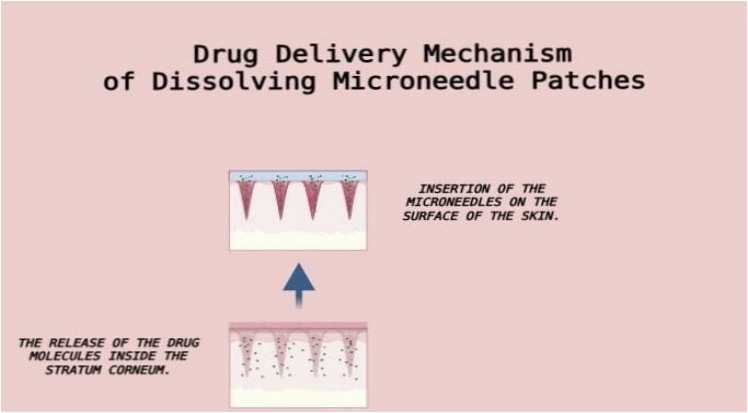

Figure 2: ***Drug delivery mechanism of dissolving microneedle patches***

2.2 Hydrogel-Forming Microneedles

(a) Principle and mechanism of action of Hydrogel forming microneedles

Hydrogel forming microneedles are microneedles made from water-absorbing,hard, cross-linked polymeric materials that swell when they come into contact with the interstitial fluid of the skin and are painless when pierced on the skin.[26]

The basic principle of this microneedle;

Drug reservoir → Hydrogel-forming microneedle → Skin fluid enters → Microneedle swells → Drug diffuses → Skin → Systemic circulation

(b) Swelling behavior and drug diffusion

Hydrogel forming microneedle since is hard and water absorbing polymer when in contact with skin they will absorb the interstitial fluids and swells to that forming a continuous and unblockable fluid-filled pathways created through the skin's outermost barrier (the stratum corneum).

The intensity of swelling of the Hydrogel forming microneedles depends on degree of polymer cross linkage,type and concentration of the polymer,porosity of the hydrogel,polymer molecular weight and amount of fluid available in the skin.

Process of transporting materials (ie drug molecules)from the region of higher concentration towards the region of lower concentration through a semi permeable membrane until the equilibrium is reached is called Diffusion. In hydrogel-forming microneedles the drug diffusion occurs when the dry polymer needle pierces the stratum corneum,absorb fluid and swell to create a continuous, water-filled channel. This channel connects the drug patch on the surface of your skin directly to the deeper layers of tissue, allowing the medication to flow straight through.[26,27]

(c) Materials used in fabrication

Microneedles (MNs) facilitate drug delivery by transiently penetrating the skin or mucosal barriers; therefore, the materials used in fabrication must exhibit adequate biocompatibility and safety. Hydrogels are particularly suitable for this purpose due to their inherent biocompatibility and ability to interact with biological tissues with minimal irritation or adverse effects. Various polymers used in fabrication of hydrogel-forming microneedles (HFMNs) have been extensively investigated for pharmaceutical, medical, and dermatological applications. These polymers possess desirable characteristics, including biocompatibility, biodegradability, and favorable biological safety profiles, making them promising materials for HFMN-based drug delivery systems.[34,35]

Hydrogel-forming microneedles use crosslinked natural or synthetic polymers that absorb body fluids and swell without dissolving into the skin.[35]

Table 4: ***Types of Polymers Used in Hydrogel-Forming Microneedles and Their Key Characteristics***

Polymer Type	Examples	Key Features	Application in Hydrogel Microneedles
Natural Polymers	- Hyaluronic Acid (HA)	Biocompatible, biodegradable, hydrophilic	Excellent swelling, skin-friendly, promotes healing
	- Chitosan	Biodegradable, antimicrobial	Enhances mechanical strength and bioactivity
	- Gelatin	Biocompatible, biodegradable	Good film forming, supports cell adhesion
	- Alginate	Biocompatible, forms ionic crosslinks	Provides structural stability and swelling
Semi-Synthetic Polymers	- Carboxymethyl Cellulose (CMC)	Water-soluble, biocompatible	Forms flexible, swellable hydrogel matrix
	- Hydroxypropyl Methylcellulose (HPMC)	Good mechanical properties, biocompatible	Enhances mechanical strength, controls drug release
	- Ethyl Cellulose	Hydrophobic derivative of cellulose	Used for controlled swelling and mechanical integrity
Crosslinking Polymers	- Polyethylene Glycol Diacrylate (PEGDA)	Synthetic, photo-crosslinkable	Enables tunable mechanical properties, stable hydrogel formation
	- Polyvinyl Alcohol (PVA)	Water-soluble, chemically crosslinkable	Provides hydrogel stability and durability
	- Methacrylated Polymers	Photo-crosslinkable, synthetic	Used for precise control over microneedle structure and mechanics

2.3 Comparison Between Dissolving and Hydrogel-Forming Microneedles

Table 5: ***Comparison Between Dissolving and Hydrogel-Forming Microneedles***

Parameter	Dissolving Microneedles	Hydrogel-Forming Microneedles
Drug Release	Rapid	Sustained
Needle Fate	Dissolves in skin	Removed after use
Drug Loading	Limited	Higher capacity
Stability	Moderate	Better
Safety	High	High

3. Formulation Parameters Affecting Microneedle Performance

Formulation variables directly dictate how effectively microneedle (MN) systems perform by controlling critical factors such as mechanical strength, insertion success, drug capacity, dissolution or swelling properties, release rates, and overall stability.

3.1 Polymer Selection

The choice and concentration of polymer are critical for determining microneedle (MN) morphology, mechanical strength, flexibility, swelling, and drug-release behavior. Hydrophilic polymers such as PVP, PVA, PVP/VA, hyaluronic acid, and polyacrylic synthetic polymer acid are commonly used. Increasing polymer concentration generally enhances mechanical strength

and structural integrity but may reduce dissolution rate and drug diffusion.[36,37]

a) Natural polymer

Natural biopolymers like hyaluronic acid, carboxymethyl cellulose, chitosan, sodium alginate, and gelatin are widely used in transdermal microneedle patches due to their safety and ability to break down naturally in the body. These materials have a crucial importance in shaping how microneedle patches are designed and how effectively they perform.

b) Synthetic polymer

Synthetic polymers directly control the essential quality standards of microneedle patches. By carefully adjusting key formulation variables, developers can optimize critical performance factors, including how easily the needles penetrate the skin, the quantity of active drug incorporated in the needle, and the timing of the drug release.Synthetic polymers directly control the essential quality standards of microneedle patches. By carefully adjusting key formulation variables, developers can optimize critical performance factors, including how easily the needles penetrate the skin, the quantity of drug they hold, and the timing of the drug release.

Table 6: ***Effect of Polymer Concentration and Molecular Weight on Microneedle Performance***

Parameter	Effect on Microneedle Performance	Impact / Outcome
Polymer Concentration	Determines the proportion of solid polymer in the liquid casting formulation.	Directly influences mechanical strength, dissolution, drug release, and manufacturing quality.
Structural Integrity	Higher polymer concentration increases needle stiffness and mechanical strength, whereas insufficient polymer may produce brittle or blunt tips after drying.	Adequate concentration improves penetration through the stratum corneum and reduces needle failure.
Release Kinetics	Increased polymer density forms a tighter molecular network, reducing hydration and dissolution in skin fluid.	Promotes slower, prolonged drug release rather than immediate release.
Manufacturing Quality	Excessive polymer concentration increases formulation viscosity, which can hinder complete filling of micromolds and promote air entrapment at needle tips.	May result in incomplete or defective microneedle formation during vacuum or centrifugal processing.
Molecular Weight – Skin Microporation	High-molecular-weight natural polymers exhibit greater chain entanglement and tensile strength.	High-MW HA or CMC can produce stronger, more rigid needles capable of effectively piercing the stratum corneum.
Molecular Weight – Drug Release	Low-molecular-weight polymers generally hydrate and dissolve more rapidly, whereas high-molecular-weight polymers dissolve more slowly.	Low MW is suitable for rapid/bolus delivery, while high MW or a more strongly networked formulation can support sustained or delayed release.

3.2 Fabrication Techniques

Microneedle fabrication is strongly influenced by their geometry, structural design, and constituent materials.A range of microfabrication techniques has been developed for producing solid microneedles, including dry etching,wet etching, three-dimensional (3D) printing, laser ablation, micromolding, magnetorheological drawing lithography, and electroplating. However, these approaches generally **C**exhibit limited drug-loading capacity and are less suitable for sustained drug release, although they provide moderate delivery efficiency.[38]

A. Casting

This is a fabricating technique that is a widely used for the developing of hydrogel-forming microneedles.The

process involves liquid polymer or hydrogel solutions that are contained with amount of active ingredients poured in a master mold and an application of the centrifugation process where solidification occurs through crosslinking that is achieved by UV exposure, chemical agent or heat, then vaccum filling or drying will form dissolving microneedles.

Following solidification, the microneedle (MN) arrays are carefully demolded. The casting approach enables precise fabrication of MNs with customized geometries and dimensions tailored to specific therapeutic applications. Furthermore, bioactive molecules, including drugs, peptides, and growth factors, can be incorporated into the hydrogel matrix, facilitating their controlled and sustained release following insertion into the skin.This technique is said to be cost effective,scalability and making suitable variety of biomedical applications.[9,10]

B. Micro-Molding Method

Microneedles are fabricated using a negative mold containing defined cavities that are filled with the selected formulation. Following material filling and appropriate curing or solidification, the microneedle structures are demolded to obtain the final product. This approach is compatible with a broad range of materials,such as polymers and hydrogels. Depending on the physicochemical characteristics of the material, different solidification techniques, such photochemical and chemical crosslinking, melt solidification, sintering, freezing, and freeze–thaw treatment, may be employed. Biodegradable polymeric microneedles prepared from both natural and synthetic polymers have also been developed, exhibiting optimized geometries and sufficient mechanical strength for effective skin penetration.

Micro-molding method is important because it is a less complicated,less costful, and is highly reproducible technique. At that extent,a hydrogel microneedle can be readily created by simultaneously involving different components added into the same mold.

C. Cross-Linking Method

The microneedles are usually fabricated using both chemical and physical cross-linking techniques.Chemical cross-linking of polymers can be achieved through high-energy ionizing radiation, chemical cross-linking agents, or thermal treatment. In chemically induced cross-linking, reagents such as borax promote the formation of covalent bonds between PVA chains or between PVA and other polymers, resulting in a stable three-dimensional polymer network. Thermal cross-linking involves enhanced molecular mobility at elevated temperatures, increasing the probability of intermolecular interactions and covalent bond formation. Increasing the temperature or duration of thermal treatment generally enhances the cross-linking density and the number of cross-linking points within the polymer network. Owing to the presence of stable covalent bonds, cross-linked polymeric microneedles primarily undergo hydration when contact with skin fluids rather than dissolving within the skin barriers making PVA-based hydrogel-forming microneedles (HFMNs) attractive for applications of transdermal drug delivery[11]. However, despite the effectiveness of chemical cross-linking, its pharmaceutical application may be restricted by the potential toxicity and residual effects of certain cross-linking agents.

Physical cross-linking of PVA is commonly achieved through repeated freeze–thaw cycles, producing hydrophilic yet water-insoluble hydrogels with high elasticity and mechanical strength without the need for potentially toxic chemical cross-linking agents. The aliphatic polymer backbone of PVA and the ability of its hydroxyl groups to form extensive hydrogen bonds contribute to the favorable mechanical and physicochemical properties of the resulting hydrogel. During successive freeze–thaw cycles, polymer chain rearrangement promotes the formation of new physical junctions and crystalline micro- or submicron domains that function as cross-linking points. The density and extent of these domains influence hydrogel swelling behavior and, consequently, drug-release kinetics. Thus, the degree of physical cross-linking can be controlled by varying the number of freeze–thaw cycles. However, the requirement for repeated freezing and thawing increases processing complexity and may prolong fabrication time[12].

3.3 Drug Incorporation Strategies

Drug incorporation strategies encompass the approaches employed to load and uniformly distribute

therapeutic agents within microneedle matrices, particularly dissolving and hydrogel-forming microneedles, to facilitate efficient transdermal delivery and controlled drug release. These approaches include incorporation into the polymer matrix, surface coating, encapsulation, and post-fabrication loading. The selected method can significantly affect drug-loading efficiency, content uniformity, stability, release kinetics, and biological activity. For biologics, the incorporation process should additionally minimize exposure to conditions that may compromise their structural integrity or therapeutic activity.

A. Encapsulation

Microneedle encapsulation involves incorporating pharmaceuticals, biological compounds, or cosmetic actives inside microscopic needle arrays. This technique shields delicate compounds from breakdown, enables precise transdermal administration past the skin barrier, and facilitates regulated or extended substance release.The technique of encapsulation of microneedles depends on the design of the microneedle and stability of the active ingredient.

The following table shows the drug incorporation strategy by encapsulation technique;

Table 7: ***Drug incorporation strategy by encapsulation technique***

Drug Incorporation Strategy	Description	Key Advantage / Application
Matrix Encapsulation (Dissolving Microneedles)	Active agents are directly incorporated into a water-soluble polymer matrix, such as hyaluronic acid, PVA, PVP, or carboxymethylcellulose. Following skin insertion, the polymer dissolves in interstitial fluid and releases the therapeutic payload.	Simple incorporation and rapid drug release; suitable for drugs and biologics requiring dissolution-mediated delivery.
Core–Shell / Layered Encapsulation	The active ingredient is incorporated within the core of the microneedle, while an outer shell provides mechanical strength and/or regulates drug release.	Protects fragile biological molecules and enables controlled or biphasic release profiles.
Nanoparticle / Microparticle Encapsulation	Drugs are first encapsulated within carriers such as liposomes, PLGA nanoparticles, or hydrogel microparticles and subsequently incorporated into the microneedle matrix.	Provides protection for sensitive proteins, mRNA, and vaccines while enabling multi-stage or sustained drug release.
Surface Coating (Coated Microneedles)	The drug formulation is prepared in a suitable buffer and incorporated into the surface of microneedles by techniques such as dip-coating or spray-coating.	Enables rapid delivery of surface-loaded drugs and is compatible with metal, silicon, and rigid polymeric microneedles.

B. Surface Coating

Variety of several active ingredients of drugs can be deposited onto microneedle surfaces using techniques such as dip coating, spray coating, and inkjet printing. Among these, dip coating is a simple and widely applicable method in which microneedles are immersed in a drug-containing coating formulation and subsequently withdrawn and dried to form a solid therapeutic layer on the needle surface. However, capillary forces during immersion may cause the formulation to spread onto the base of the microneedle patch. Since only the needle projections penetrate the skin, drug deposited on the patch base remains undelivered, potentially reducing dose utilization. As microneedles typically penetrate approximately 10–80% of their total length into the skin, selectively coating the skin-penetrating region can improve the proportion of the applied therapeutic dose that reaches the target site[13].Various dip-coating strategies are used to target only the tips of microneedles. Key techniques include using high-viscosity formulations to minimize capillary spreading, inserting microneedles into matching solution-filled arrays, and employing micropositioning equipment for

precision-depth dipping into open reservoirs. Alternatively, micropositioners can insert the needles through perforated covers placed over the solution reservoirs. This covered-reservoir method is particularly advantageous because the protective top serves as a physical barrier against the microneedle base, preventing unwanted coating and reducing drug waste.

C. Matrix Loading

This is a drug incorporated strategy that involves incorporating the therapeutic agent directly into the polymeric matrix during microneedle fabrication, resulting in its distribution throughout the microneedle structure. Following insertion into the skin, dissolution or degradation of the matrix facilitates drug release and subsequent transdermal delivery.

The following is a table summary showing the manufacturing materials for Matrix loading;

Table 8: ***Manufacturing materials for Matrix loading***

Manufacturing method	Principle / Process	Key advantage	Application / Suitability
Two-Step Solvent Casting & Centrifugation	The API is incorporated into a concentrated polymer gel and introduced into PDMS negative molds. Centrifugation or vacuum fills the drug –polymer mixture preferentially into the microneedle tips, followed by removal of excess material. A drug-free polymer layer is then added to form the flexible base plate.	Localizes the therapeutic agent within the microneedle tips and improves drug-use efficiency.	Suitable for **targeted drug delivery**, particularly when drug localization in the penetrating tips is desired.
Emulsion-Based Matrix Loading	Sensitive peptides or biomolecules are incorporated into hydrophobic polymers such as PLGA using a **water-in-oil (W/O) emulsion** during the molding process.	Helps protect sensitive active ingredients from interfacial stresses and avoids harsh post-loading procedures.	Particularly suitable for **peptides, proteins, and other sensitive biomolecules**.
3D Bioprinting & Photopolymerization	Liquid monomer–drug formulations are selectively solidified using light-based techniques such as **UV digital light processing (DLP)** or **two-photon polymerization (TPP)** to produce precisely defined microneedle structures.	Enables high geometric precision and localized fabrication, with potential for incorporating sensitive therapeutics.	Useful for **complex microneedle architectures** and advanced drug-delivery systems.

3.4 Geometrical Parameters

Five linear arrays, each containing 10 square pyramids with a 0.5 mm base length, a 0.5 mm height, and 2.5 mm center-to-center spacing, were modeled in SolidWorks. The needles were designed with a 60° nominal tip angle and a 0 µm tip radius. A simplified linear configuration was chosen over a standard matrix array to make measuring the geometrical features easier.- Surface topography and geometry were evaluated using an Alicona InfiniteFocus XL200 focus variation microscope fitted with a 10× objective lens, operating at an exposure time of 20 ms, a vertical resolution of 0.1 µm, and a lateral resolution of 4.0 µm. The system's profile form measurement module quantified key dimensions, including needle height (Hn), base length (Lb), tip radius (Rt), and tip angle (θ). To measure surface roughness (Ra), microneedles were positioned at a 90° angle, using a cutoff length (Lc) of 800 µm

along a 4 mm evaluation path. Dimensional evaluations were carried out at intervals of every ten microneedles, sampling up to 50 microneedles in total[41]

A. Needle Height (Length)

Lengths generally range between 100 and 2000 μm, allowing penetration through the outer stratum corneum (10–20 μm) into the epidermis or upper dermis while avoiding deep pain receptors.Penetration Depth & Skin Layer Targeting,the primary purpose of varying needle height is to reach specific physiological layers of the skin 250–500 μm,reaches the barriers of the skin and then to the epidermis. This is typically used for superficial drug delivery, localized skin rejuvenation, or cosmetic treatments 500–1000 μm (1 mm).Reaches the upper dermis. This is optimal for systemic drug delivery, vaccines, or stimulating collagen production >1000 μm: Reaches deeper into the dermis or dermal-subcutaneous junction for larger molecule delivery or thicker skin regions (e.g., psoriatic plaques). Sensation and Nerve Activation,shorter microneedles (<500 μm) generally avoid contact with nerve endings (nociceptors) in the dermal layer, enabling painless application. As needle height increases beyond 750–1000 μm, the likelihood of contacting dermal nerve fibers rises, which can cause mild pain or discomfort.Bleeding and Vascular Access: The epidermis is avascular (lacks blood vessels). Shorter needles that remain in the epidermis do not cause bleeding. Increasing the height past ~600 μm allows the needle to penetrate into the vascularized dermal layer, which is necessary for sampling biological fluids (e.g., continuous glucose monitoring) or systemic absorption, but can cause minor micro-bleeding. Drug Delivery Kinetics: Taller needles create microchannels that extend deeper into the dermis, increasing the surface area for diffusion. This accelerates the rate of systemic absorption for therapeutics and enables higher volumetric loading for larger molecule delivery. Mechanical Strength & Bending Risk as height increases, the aspect ratio (height-to-width ratio) of the microneedle grows. Taller needles experience higher bending moments and lateral shear stress upon insertion. Without increasing the base diameter, taller microneedles are more prone to buckling, bending, or fracturing during penetration. "Bed-of-Nails" Effect: Taller needles require higher insertion force per needle to puncture the elastic skin. If needles are packed too closely together on an array, taller heights can amplify skin deformation (elastic stretching without puncture) unless sufficient force or pre-stretching is applied[15].

B. Base Diameter

Typically spanning 100 to 300 μm, the base diameter has been identified by research as a primary factor influencing puncture.The mechanical strength and buckling resistance is that axial bending and tip fracture are major failure modes during microneedle insertion. According to Euler's buckling principle, structural resistance to deformation is influenced by the cross-sectional geometry of the needle. An increased base diameter enhances the moment of inertia, thereby improving mechanical strength and enabling the microneedle to withstand greater insertion forces. Puncture forces and penetration depth as well has an increased base diameter produces a broader transition from the tip to the needle base. Although this can improve structural stability, the larger surface area in contact with tissue increases friction and tissue displacement during insertion. Consequently, at a constant applied force, excessive base diameter may increase insertion resistance and reduce the achievable penetration depth beyond the stratum corneum.Drug capacity and loading**,**For solid-coated and dissolving polymeric microneedles, increasing the base diameter increases the overall needle volume, approximately following the relationship (V \propto r^2h). Therefore, a larger base can accommodate a greater quantity of therapeutic agent without necessarily increasing microneedle height.Bed -of-Nails effect is in densely packed microneedle arrays, increasing the base diameter reduces the inter-needle spacing and intensifies collective skin deformation. This bed-of-nails effect distributes the applied force across multiple needles, potentially increasing the force required per needle to achieve effective skin puncture[16].

C. Tip Sharpness

The engineering of the microneedle relies heavily on its tip sharpness, which dictates how easily it penetrates the skin, how comfortable it feels for the patient, whether it maintains its structural strength, and how

effectively it delivers medication.The effect of Tip sharpness on microneedle drug incorporation as Minimizes Insertion Force because the force needed to pierce the skin's tough outer layer (stratum corneum) directly depends on the tip's contact area, ultra-sharp needles with tip radii under 5–10 µm concentrate applied pressure far more effectively than blunter tips (over 20–30 µm), drastically lowering the force required for penetration[17].Prevents Skin Deformation,the skin's elastic, viscoelastic nature causes it to stretch inward under pressure before puncturing. A sharper needle pierces the skin barrier cleanly with minimal surface indentation, guaranteeing that it reaches its full target depth instead of merely pushing the tissue downward.Enhances Patient Comfort,nerve endings (nociceptors) signal pain when exposed to mechanical pressure and tissue strain. By decreasing both insertion force and skin deflection, sharp tips minimize stress on surrounding nerves, making application virtually painless and improving patient adoption. Ensures Consistent Array Penetration,multi-needle patches often encounter a "bed-of-nails" effect, where force spreads across the patch surface and skin elasticity prevents complete insertion. Ultra-sharp tips overcome this surface resistance, allowing large arrays to reliably breach the skin barrier even with simple manual pressure.Navigates the Sharpness–Strength Trade-off,while fine tips penetrate effortlessly, extremely thin or high-aspect-ratio geometries compromise structural integrity. Needles made from polymers or dissolving materials risk bending, curling, or snapping during application, requiring designers to carefully calibrate tip radius against material yield strength to prevent fracture.

4. Mechanical Strength of Microneedles

4.1 Importance of Mechanical Strength

The structural integrity of microneedle transdermal patches is an essential design priority. Because these micro-structures must penetrate the resilient stratum corneum without breaking or bending, their mechanical resilience determines how safely, accurately, and reliably the patch delivers its treatment.Mechanical strength is such important to reasons crucial in microneedle drug incorporation.Prevention of Structural Failure (Buckling and Fracture),During insertion, microneedles experience high axial compression and lateral shear forces. If the material or geometry lacks sufficient yield strength, the needles will either buckle (bend sideways under axial load) or fracture (snap off). Mechanical strength ensures the needle maintains its structural integrity throughout application. Patient Safety and Biocompatibility Concerns,If a microneedle fractures during application, broken fragments can remain embedded under the skin. In non-dissolving systems (such as silicon, glass, or certain metals), retained micro-fragments can cause foreign-body reactions, inflammation, or granulomas. High mechanical strength prevents structural breakage and mitigates biocompatibility risks. Guaranteed Drug Delivery Efficiency and Depth,Microneedles must reach a specific target depth (typically the viable epidermis or upper dermis) to deliver active pharmaceutical ingredients (APIs) or biofluids effectively. Bending or blunting upon initial impact prevents the needle from penetrating fully, leading to incomplete dosing or drug leakage on the skin surface. Overcoming Skin Viscoelastic Resistance and "Bed-of-Nails" Effect,Human skin is highly elastic and deformable. When applying a microneedle array with dozens or hundreds of tips, the force spreads across the surface, requiring each individual needle to withstand higher force thresholds before breaching the barrier. High mechanical strength ensures every needle in an array punctures cleanly without collapsing under collective resistance.Margin of Safety Against Application Variability,In real-world use, patients apply patches with varying degrees of force, angles, and speed (manual thumb pressure versus spring-loaded applicators). Sufficient mechanical strength ensures a wide margin of safety—defined as the ratio of failure force (fracture force) to insertion force—so the patch performs reliably despite non-uniform user handlin.[[42,43]

4.2 Mechanical Testing Methods

The transdermal delivery microneedles are faced with mechanical strength during its application to the stratum corneum to release the drug to the body.For that there are testing methods mechanically applied to approve the withstanding ability of microneedles on application of mechanical strength.

A. Compression Testing

In microneedle engineering, compression testing serves as the main technique for assessing axial mechanical strength by measuring the peak vertical force a single needle or array can handle before bending, deforming, or snapping. Since skin application mainly subjects needles to downward force along their length, this testing directly verifies whether a design offers a sufficient safety margin for safe patient use.The principle of testing is with different parameters as follows;The test is performed using a universal testing machine (UTM) or a specialized micro-force mechanical analyzer equipped with a sensitive load cell (typically in the range of 10 N to 100 N) and a high-resolution displacement sensor. Specimen Placement: The microneedle array or a single isolated needle is mounted flat on a rigid, stationary lower platen.Axial Loading: A flat metal or ceramic probe moves downward vertically at a controlled, constant velocity (typically between 0.1 mm/min and 1.0 mm/min) against the tips. Data Capture: The instrument continuously records the applied compressive force (F) against vertical displacement (\delta) to generate a characteristic Force –Displacement curve.[44,45]

B. Insertion Studies

Insertion studies analyze the mechanical forces and structural integrity necessary for microneedles to penetrate the skin's outer barrier—the stratum corneum—without buckling or snapping. Because these devices combine the advantages of traditional needles and transdermal patches, achieving dependable skin penetration is essential for effective drug delivery, vaccination, and biosensing applications.When evaluating microneedle insertion, researchers focus on several core mechanical parameters;Insertion Force: The baseline compressive force needed for a needle tip to puncture the skin, generally falling between 0.1 N and 3.0 N for individual microneedles based on their shape.Fracture Force**:** The critical load at which a microneedle suffers structural failure, such as shearing, bending, or buckling.Margin of Safety**:** The ratio comparing fracture strength to required insertion force. A safety margin substantially higher than 1 (ideally exceeding 5) ensures the needle enters safely without breaking in the skin.Penetration Efficiency**:** The proportion of microneedles within an array that effectively reach their target depth in the skin.A standard insertion study measures force versus displacement during the application process, yielding a distinct multi-stage curve by the following table;

Table 9: ***Stages of Microneedle Insertion into the Skin and Corresponding Force–Displacement Behaviour***

Stage of Insertion	Skin/Tissue Response	Force–Displacement Behavior
1. Elastic Deformation (Skin Indentation)	The microneedle tip contacts the skin, causing the elastic stratum corneum to deform and stretch without immediate rupture.	The insertion force increases sharply as the skin resists deformation.
2. Skin Puncture	Localized stress beneath the microneedle tip exceeds the tensile strength of the stratum corneum, resulting in tissue penetration.	A characteristic sudden decrease in force or a reduction in the slope of the force–displacement curve occurs after puncture.
3.Subdermal Advancement	The microneedle advances through the softer epidermal and dermal layers.	Force increases gradually due to friction and resistance between the needle shaft and surrounding tissue.

4.3 Factors Affecting Mechanical Strength;

a) Polymer Composition

The choice of polymer backbone and its molecular weight directly governs the mechanical performance and insertion efficiency of microneedle arrays.Molecular Weight, Higher molecular weight polymers increase dynamic viscosity and chain entanglement, yielding higher Young's modulus, tensile strength, and fracture resistance. Higher molecular weight prevents premature bending or fracture upon skin penetration. However, excessively high molecular weight slows down the dissolution rate of dissolving microneedles.Polymer Blends & Copolymers**:** Monopolymers

often suffer from a trade-off between stiffness and dissolution speed (e.g., highly rigid polymers dissolve slowly). Combining flexible/rapidly-dissolving polymers (such as Polyvinylpyrrolidone [PVP] or Hyaluronic Acid [HA]) with structural polymers (such as Carboxymethylcellulose [CMC] or Polyvinyl Alcohol [PVA]) balances structural integrity during skin insertion with quick drug dissolution upon insertion.

b) Polymer Concentration

Polymer concentration dictates the precursor formulation's viscosity and the final matrix density after drying or curing.Viscosity vs. Mold Filling**:** Low polymer concentrations (<2% w/v) flow easily into high-aspect-ratio micro-cavities (silicone/PDMS molds). However, low concentration yields a porous or fragile matrix upon drying, leading to low buckling force and failure to pierce the *stratum corneum*.Mechanical Integrity vs. Processability**:** Increasing polymer concentration produces a denser polymer network that resists compressive loads during skin insertion. However, high concentrations cause high solution viscosity, hindering bubble removal and preventing complete filling of micro-cavities, often requiring vacuum-assisted or centrifugal casting techniques to avoid tip defects.

c) Cross-Linking

Cross-linking transforms linear polymer chains into a 3D insoluble network, primarily used for hydrogel-forming or swellable MN systems.Mechanical Resilience**:** Chemical (e.g., covalent bonds via UV photocrosslinking or glutaraldehyde) or physical (e.g., freeze-thaw cycles, ionic interactions) cross-linking increases cross-link density, improving the elastic modulus, yield strength, and shear resistance needed for skin insertion.Swelling Capacity & Kinetics**:** Higher cross-linking density restricts mesh size, limiting water uptake and swelling capacity. Hydrogel MNs designed for interstitial fluid (ISF) sampling or sustained drug release require an optimal cross-linking density to maintain structural integrity under mechanical stress without suppressing fluid absorption.

d) Moisture Content

Water acts as a plasticizer in hydrophilic polymer systems, altering their viscoelastic properties.Plasticization Effect: Residual moisture penetrates polymer chains, disrupting inter-chain hydrogen bonds, increasing chain mobility, and lowering the glass transition temperature. This reduces stiffness (Young's modulus) and failure force, causing microneedle tips to bend or undergo plastic deformation rather than penetrating the skin.Storage & Stability: High ambient humidity during storage leads to water uptake, causing loss of needle sharpness and premature degradation in dissolving microneedles. Proper packaging with desiccants or controlled relative humidity (RH < 30%) storage conditions is critical to maintain structural sharpness and insertion capacity over time.

e) Needle Geometry

The physical geometry of a microneedle array directly influences its stress distribution and resistance to mechanical failure (buckling vs. fracture).Aspect Ratio & Base Width**:** Slender microneedles with high aspect ratios (height-to-base diameter ratio > 4:1) are prone to Euler buckling under axial compression forces during skin insertion. Decreasing the aspect ratio—by reducing needle height or increasing base diameter—lowers stress concentration at the base and significantly raises the critical buckling load.Tip Sharpness & Shape**:** Sharp tip radii (<10–15 \mum) minimize the force required to fracture the *stratum corneum*, reducing the total insertion force needed. Conical and pyramidal geometries provide a wider, structurally reinforced base while maintaining a sharp tip, offering superior resistance to mechanical failure compared to cylindrical or uniform structures.

4.4 Comparative Analysis of Dissolving and Hydrogel-Forming Microneedles

Dissolving microneedles and hydrogel-forming microneedles are two important classes of polymer-based transdermal drug-delivery systems. Although both systems facilitate minimally invasive penetration of the stratum corneum with minimal pain, they differ substantially in their behavior following skin insertion. These differences arise primarily from their polymeric structure, interaction with interstitial fluid, drug-loading strategy, drug-release mechanism, and potential therapeutic applications. A comparative evaluation of

these characteristics is presented in the core compari- son matrix below.

Table 10: ***Comparative Evaluation of Dissolving and Hydrogel-Forming Microneedles: Principles, Characteristics, Drug Release and Applications***

Parameter	Dissolving Microneedles (DMNs)	Hydrogel-Forming Microneedles (HFMNs)
Basic principle	Microneedles dissolve or biodegrade after insertion into the skin, releasing the incorporated drug.	Microneedles absorb interstitial fluid, swell, and form a hydrated pathway for drug diffusion.
Matrix composition	Generally composed of water-soluble or biodegradable polymers, sugars, and other biocompatible materials.	Primarily composed of crosslinked hydrophilic polymers capable of swelling without dissolving.
Interaction with skin fluid	Skin fluid facilitates dissolution of the polymeric matrix and subsequent drug release.	Skin fluid is absorbed into the crosslinked polymer network, causing swelling.
Drug-loading mechanism	Drug is incorporated directly within the dissolving microneedle matrix or concentrated in the needle tips.	Drug is generally loaded into a separate drug reservoir or attached to the hydrogel-forming system.
Drug release mechanism	Drug release occurs mainly through dissolution or degradation of the microneedle matrix.	Drug diffuses through the swollen hydrogel matrix and hydrated microchannels.
Drug-loading capacity	Can provide relatively high loading, depending on polymer properties and drug stability.	Drug capacity is often determined by the associated drug reservoir rather than the needle matrix itself.
Mechanical strength	Must possess sufficient strength to penetrate the stratum corneum before dissolving.	Crosslinking provides structural integrity and mechanical strength during insertion.
Needle dissolution/swelling	Dissolves progressively after insertion.	Swells substantially but remains structurally intact.
Insertion requirement	Requires adequate mechanical strength for successful skin penetration.	Requires adequate mechanical strength and appropriate swelling characteristics.
Drug release duration	Generally suitable for rapid to moderately sustained drug delivery, depending on formulation.	Can provide prolonged and controlled drug delivery through the swollen hydrogel matrix.
Biologics compatibility	Potentially suitable for peptides, proteins, vaccines, and other biologics when formulation stability is maintained.	Particularly useful for controlled delivery of macromolecules through a hydrated pathway.
Residual material after application	Leaves little or no solid microneedle structure after dissolution.	The hydrogel microneedle remains within or near the skin during application and is subsequently removed.
Patient acceptability	Minimally invasive, generally painless, and leaves no sharp needle waste.	Minimally invasive and painless, with removal of the intact swollen microneedle system after drug delivery.
Major advantage	Combines painless skin penetration with direct incorporation and delivery of the therapeutic agent.	Enables controlled delivery and can accommodate drug reservoirs for sustained release.
Major limitation	Drug stability and loading capacity may be affected by polymer dissolution and manufacturing conditions.	More complex design and manufacturing; swelling and drug diffusion must be carefully controlled.

Parameter	Dissolving Microneedles (DMNs)	Hydrogel-Forming Microneedles (HFMNs)
Typical applications	Vaccines, peptides, proteins, hormones, and other biologics requiring minimally invasive delivery.	Sustained transdermal delivery of macromolecules and other therapeutics requiring controlled release.

5.Stability Consideration.

5.1 Stability of Biologics

The inherent vulnerability of proteins and peptides to degradation makes stability a critical requirement for microneedle-based biologic delivery systems.Because proteins and peptides easily break down, maintaining structural integrity is essential when delivering biologics via microneedles.Preserving stability is vital in the microneedle administration of biologics to prevent the deterioration of sensitive peptides and proteins.Given that peptides and proteins degrade rapidly, ensuring stability is a top priority for biologic delivery using microneedles.Maintaining stability is critical for microneedle delivery systems, as the device's therapeutic efficacy depends on the structural integrity of both the polymer matrix and the active pharmaceutical ingredient.Throughout storage, exposure to ambient humidity, thermal fluctuations, moisture, and specific formulation components can negatively impact the array's physical structure, mechanical performance, skin insertion capability, release profiles, and active ingredient potency. This vulnerability is especially prominent in dissolving microneedles and hydrogel-forming microneedles, as their hydrophilic matrices rapidly absorb environmental water.[46,47]

5.2 Stability of Microneedle Systems

A. Physical Stability

Physical stability requires the microneedle system to retain its structural dimensions and operational functionality across its shelf life. Key physical properties include needle geometry, tip morphology, mechanical durability, matrix dissolution rate, swellability, and uniform drug distribution across the array.Dissolving Microneedles: Absorbing ambient moisture plasticizes and hydrates the polymer matrix, resulting in needle softening, tip deformation, and decreased fracture strength. Consequently, the needles may fail to penetrate the *stratum corneum*. Excessive moisture also alters dissolution rates, leading to uncontrolled or premature drug release.Hydrogel-Forming Microneedles;Moisture fluctuations disrupt the cross-linked polymer network, altering swelling capacity, hydration kinetics, structural integrity, and diffusion-mediated release. Controlling internal moisture levels is therefore essential to preserving the functional performance of both DMN and HFMN platforms.Key Physical Stability Evaluation Metrics:Array dimensions, needle height, and geometric symmetry,Tip sharpness and microscopic surface morphology,Axial compression, bending, and fracture strength,Skin insertion efficiency and depth,Dissolution behavior (DMNs) vs. Swelling capacity and hydration rates (HFMNs),Content uniformity and API release profiles.

B. Chemical Stability

Chemical stability is vital when delivering delicate biologics (e.g., proteins, peptides, vaccines, and enzymes) susceptible to deamidation, oxidation, hydrolysis, aggregation, fragmentation, or conformational denaturation during processing and storage.The microenvironment within the polymer matrix directly impacts biologic stability through localized pH shifts, residual moisture, polymer-drug molecular interactions, and manufacturing stress. For instance, dehydration processes during DMN casting can alter protein tertiary structure, whereas harsh cross-linking environments during HFMN synthesis may degrade sensitive therapeutics. Therefore, maintaining functional biological activity is far more critical than simply tracking total chemical content.

C. Environmental Factors

Environmental factors—particularly temperature and relative humidity (RH)—heavily dictate the shelf-life stability of polymeric microneedles.Temperature: High temperatures accelerate chemical degradation of APIs and alter polymer matrix mechanics. Thermal variations also trigger internal moisture migration, compromising the structural performance of the needles.Relative Humidity: Hydrophilic MN materials

absorb atmospheric water, which acts as a plasticizer. This lowers the glass transition temperature (T_g) and reduces mechanical stiffness. Elevated RH leads to premature softening and altered dissolution in DMNs, while disrupting swelling and uptake kinetics in HFMNs.Light and Oxygen: Photolytic exposure and atmospheric oxygen induce oxidative degradation in sensitive biologics, requiring specialized barrier packaging.Packaging Solutions: High-barrier packaging, protective pouches, desiccant inserts, and hermetic seals maintain a controlled microenvironment around the patch, isolating it from external ambient conditions.

5.3 Strategies to Improve Stability

Multiple formulation and processing techniques can be applied to preserve the functional and structural stability of biologic-loaded MN systems:

Excipient Stabilization: Adding sugars, polyols, amino acids, or surfactants prevents protein aggregation and conformational changes.pH Optimization: Tuning formulation pH minimizes deamidation, hydrolysis, and self-aggregation without compromising polymer compatibility.Cryoprotective Sugars: Incorporating sucrose or trehalose creates a protective glassy matrix that stabilizes biologics during drying and storage.Controlled Drying & Lyophilization: Dehydrating under optimized conditions limits hydrolytic degradation while preventing the polymer network from becoming overly brittle.High-Barrier Packaging & Storage: Employing moisture-impermeable packaging combined with temperature-controlled storage preserves both matrix mechanics and API potency.Gentle Manufacturing Conditions: Utilizing low-temperature, aqueous processing reduces thermal degradation and avoids exposure to harsh organic solvents.[48]

6.Applications in Biologic Delivery

Microneedle (MN) systems have emerged as promising platforms for the transdermal administration of biologics that are poorly absorbed through intact skin. By creating microscopic pathways across the stratum corneum, MNs facilitate the delivery of macromolecules into the viable epidermis and dermis while minimizing tissue damage and pain. Depending on their design, dissolving microneedles release the incorporated biologic through dissolution of the polymeric matrix, whereas hydrogel-forming microneedles absorb interstitial fluid, swell, and form aqueous pathways that facilitate drug diffusion from an attached drug reservoir. These systems have been investigated for the delivery of proteins, peptides, vaccines, enzymes, antibodies, and nucleic-acid-based therapeutics.[49]

6.1 Protein Delivery

Proteins generally exhibit poor passive transdermal permeability because of their high molecular weight, hydrophilicity, and complex three-dimensional structures. MNs overcome the barrier function of the stratum corneum by creating microscopic channels that enable proteins to reach the viable skin layers.Dissolving microneedles can incorporate proteins within water-soluble polymeric matrices such as hyaluronic acid, polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), and carboxymethyl cellulose (CMC). Following insertion into the skin, the polymer dissolves and releases the protein locally.Hydrogel-forming microneedles, in contrast, swell following contact with interstitial fluid and facilitate controlled transport of protein molecules from a drug-containing reservoir.Potential protein therapeutics include insulin, growth factors, recombinant proteins, and other therapeutic proteins. An important formulation consideration is maintaining protein structural integrity during drying, molding, sterilization, and storage, as aggregation or denaturation can reduce biological activity.

6.2 Peptide Delivery

Peptides are attractive candidates for MN-mediated transdermal delivery because their hydrophilic nature and relatively large molecular size restrict their penetration through the stratum corneum. MNs provide a physical route for peptide transport while avoiding the gastrointestinal degradation and, in some cases, the extensive first-pass metabolism associated with oral administration.Insulin is one of the most extensively investigated peptide therapeutics for MN delivery. Dissolving MNs can provide rapid deposition of insulin within the skin, while hydrogel-forming MNs can support sustained transport from a drug reservoir. Other peptides investigated for MN-based delivery include peptide hormones and therapeutic peptide

molecules.The performance of peptide-loaded MNs depends on factors such as polymer concentration, drug loading, needle geometry, mechanical strength, dissolution/swelling behavior, peptide stability, and insertion efficiency.

6.3 Vaccine Delivery

The skin is an attractive site for vaccination because it contains numerous immune cells, including Langerhans cells and dermal dendritic cells, which can efficiently capture and process antigens. MN arrays can deliver vaccine antigens directly into the epidermal and dermal layers, potentially enhancing immune recognition.Dissolving MNs are particularly useful for vaccine delivery because the antigen can be incorporated directly into the biodegradable or water-soluble needle matrix. Upon insertion, the needles dissolve and release the antigen without leaving a sharp biohazardous needle. MN-based vaccination has been investigated for influenza**,** measles, rubella, COVID-19, hepatitis B, and other vaccine antigens.Additional advantages include minimally invasive administration, reduced pain, improved patient acceptability, and potential for simplified administration. However, maintaining antigen stability during fabrication and storage remains an important challenge.

6.4 Enzyme Delivery

Enzymes are highly sensitive biological molecules whose therapeutic activity depends on maintaining their native structure. Conventional transdermal delivery is difficult because enzymes are large and cannot readily cross the stratum corneum.Microneedle systems can provide a minimally invasive pathway for delivering enzymes into the skin. Dissolving Microneedles encapsulate enzymes within polymeric matrices, whereas hydrogel-forming MNs can provide a diffusion pathway between the reservoir and skin.-During formulation, parameters such as pH, temperature, solvent exposure, polymer–enzyme interactions, drying conditions, and moisture content must be carefully controlled to prevent enzymatic inactivation. Stabilizing excipients such as sugars or other protective agents may also be incorporated to maintain enzyme activity during processing and storage.

6.5 Monoclonal Antibodies and Advanced Biologics

Monoclonal antibodies (mAbs) and other advanced biologics have high molecular weights and complex structures, making their passive transport across the skin extremely limited. MN technology provides a physical route through the stratum corneum and therefore offers potential for minimally invasive administration of these macromolecules.Hydrogel-forming MNs are particularly interesting for large biologics because their swollen hydrogel network can provide an aqueous pathway for transport from an external drug reservoir. Dissolving MNs may also be used when sufficient drug loading and maintenance of antibody stability within the polymer matrix can be achieved.However, the delivery of mAbs presents significant challenges, including high dose requirements, molecular instability, aggregation, limited drug loading capacity, and sensitivity to manufacturing and sterilization conditions. Development of high-capacity, biocompatible polymeric matrices and optimized fabrication processes is therefore essential for the successful translation of MN-based mAb delivery.

6.6 Nucleic Acid Delivery

Microneedles are also being investigated for the delivery of DNA, mRNA, siRNA, and other nucleic-acid-based therapeutics. These molecules are highly hydrophilic and susceptible to enzymatic degradation, making conventional transdermal delivery inefficient. MN-mediated skin penetration can bypass the stratum corneum and facilitate deposition within viable skin tissues.Dissolving MNs can incorporate nucleic acids into polymeric matrices or nanocarriers, while hydrogel-forming systems can provide controlled transport from an attached reservoir. Nanoparticles, liposomes, and other delivery vehicles may be combined with MNs to improve nucleic-acid protection and cellular uptake.

7. Recent Advances and Clinical Progress

Recent studies have advanced from merely confirming microneedle skin penetration to rationally optimizing formulation and device parameters.For hydrogel-forming microneedles, key research priorities include tuning polymer chemistry and structural design to control swelling kinetics, drug release rates,

mechanical strength, and treatment longevity, while establishing standardized testing to boost reproducibility and clinical translation. Concurrently, increasing focus is directed toward industrial scale-up, quality assurance, and regulatory approval. A critical challenge for biologic-loaded systems is sterilization: standard thermal or chemical methods can degrade delicate biological drugs, necessitating aseptic production or specialized alternative sterilization techniques according to the formulation.

8. Challenges and Future Perspectives

Apart from microneedle (MN) technology being advantageous with higher theraupical revolutions, several formulation, mechanical, manufacturing, stability, and regulatory challenges must be addressed before dissolving microneedles (DMNs) and hydrogel-forming microneedles (HFMNs) can achieve widespread clinical and commercial application. The delivery of biologics presents additional challenges because these molecules require protection against degradation while maintaining adequate dose loading and achieve therapeutic effects.

8.1 Limited Drug Loading

Among of the major limitations of polymeric microneedles is the relatively limited amount of drug that can be incorporated into the needle matrix. This is particularly significant for biologics that require relatively high therapeutic doses. Increasing the drug concentration may alter the viscosity, mechanical strength, dissolution behavior, and structural integrity of the polymeric matrix.In Dissolving microneedles excessive drug loading may interfere with polymer–polymer interactions and reduce the mechanical strength required for skin penetration. Hydrogel-forming microneedles can overcome some of this limitation by incorporating the drug into a separate reservoir rather than loading the entire dose into the microneedle matrix. Future research should focus on high-capacity drug-loading strategies, localized tip loading, multilayer structures, and reservoir-integrated microneedle systems.

8.2 Mechanical Failure and Insertion Efficiency

Adequate mechanical strength is essential for successful MN insertion. During application, microneedles are subjected to compressive forces that may cause bending, buckling, deformation, or fracture. Insufficient mechanical strength can result in incomplete penetration of the stratum corneum and consequently reduce drug delivery efficiency.For Dissolving microneedles,the formulation must provide sufficient strength before insertion while retaining an appropriate dissolution rate after insertion. Similarly, HFMNs require adequate structural integrity before and during swelling. Increasing polymer concentration or network density may improve strength but can also reduce dissolution or swelling and drug diffusion.Therefore, future MN designs should optimize needle geometry, polymer composition, polymer concentration, aspect ratio, tip sharpness, array density, and network structure simultaneously rather than optimizing each parameter independently.

8.3 Biologic Stability

Maintaining the structural integrity and biological activity of proteins, peptides, vaccines, and other biologics throughout formulation, fabrication, drying, sterilization, and storage remains a major challenge.Biologics may undergo aggregation, oxidation, hydrolysis, deamidation, fragmentation, or denaturation when exposed to unfavorable temperature, pH, moisture, solvents, or mechanical stresses. Fabrication processes such as drying, solvent exposure, heating, and polymer processing must therefore be carefully controlled.The incorporation of stabilizing excipients, protective sugars, suitable buffers, surfactants, and optimized drying conditions may help preserve biological activity. Future research should also investigate formulations that provide protection against both processing-related and storage-related degradation.

8.4 Manufacturing Scale-Up and Reproducibility

Many microneedle technologies have demonstrated promising results at laboratory scale; however, transferring these processes to large-scale manufacturing remains challenging. Consistent production of thousands or millions of microneedle arrays requires precise control over needle height, base diameter, tip

geometry, array density, polymer composition, drug distribution, and mechanical strength.Micromolding and casting processes may experience variations in cavity filling, drying, polymer distribution, and demolding during scale-up. Such variations can result in differences between individual patches and affect dose uniformity and insertion performance.Future manufacturing approaches should therefore incorporate automated production, process analytical technology, quality-by-design principles, and in-process monitoring to achieve reproducible microneedle products.

8.5 Standardization of Characterization Methods

A lack of universally standardized methods for evaluating microneedles makes comparison between different studies difficult. Researchers may use different testing conditions for mechanical strength, insertion efficiency, dissolution time, swelling behavior, drug release, and skin penetration.For example, differences in compression force, loading rate, skin model, application time, and analytical method can produce different mechanical or insertion results even for similar microneedle formulations.Standardized protocols should therefore be established for evaluating:Mechanical strength and fracture force,Skin insertion efficiency,Needle dissolution time,Hydrogel swelling behavior,Drug-loading capacity,Drug-content uniformity,In vitro and ex vivo drug release,Biologic integrity and activity,Stability under different temperature and humidity conditionsStandardization would improve reproducibility and facilitate comparison between formulations and research groups.

8.6 Regulatory Translation

DMNs and HFMNs may involve characteristics of both a pharmaceutical formulation and a medical device. Consequently, regulatory evaluation may require consideration of drug quality, device performance, manufacturing controls, biocompatibility, sterility, stability, and clinical efficacy.Important critical quality attributes may include microneedle dimensions, mechanical strength, drug content, content uniformity, dissolution or swelling behavior, drug-release characteristics, residual solvents, microbial quality, and packaging integrity.For biologic-loaded MNs, regulators must also consider preservation of biological activity throughout the product's shelf life. Establishing appropriate specifications and validated analytical methods will therefore be essential for successful regulatory approval.

8.7 Sterilization and Microbial Safety

Sterilization is an additional challenge for MN-based biologic delivery systems. Conventional sterilization techniques involving high temperature, radiation, or reactive chemicals may adversely affect polymeric materials or sensitive biologics.Furthermore, the microneedle array must maintain its mechanical and structural properties after sterilization. Therefore, sterilization conditions should be selected based on the composition of the polymer, therapeutic agent, backing material, and packaging system.Future research should focus on sterilization-compatible formulations and manufacturing under controlled or aseptic conditions while maintaining biologic activity and MN performance.

8.8 Patient Application and Dose Delivery

Although microneedles are designed for minimally invasive administration, consistent skin penetration may depend on the force, duration, and method of application. Variability in application by different users can result in differences in insertion depth and consequently affect drug delivery.Factors such as skin thickness, age, hydration, anatomical site, and skin condition may also influence MN performance. Applicator-assisted systems could improve the consistency of insertion force and penetration depth.Future MN platforms should therefore consider user-friendly applicators, controlled insertion mechanisms, and clear administration procedures to improve dose reproducibility, particularly for self-administration.

8.9 Long-Term Storage and Packaging

The stability of hydrophilic polymeric MNs can be strongly influenced by moisture uptake during storage. Exposure to humidity may soften DMNs, alter their dissolution characteristics, or modify the mechanical strength of HFMNs.Protective packaging, moisture-barrier films, desiccants, and optimized storage conditions may help maintain the physical and chemical stability of the product. Stability studies should

evaluate both the biologic and the MN device throughout the proposed shelf life.

8.10 Future Perspectives

Future development of MN-based biologic delivery should focus on integrating pharmaceutical formulation, polymer science, microneedle engineering, and advanced manufacturing technologies. High-dose and high-capacity systems, optimized hydrogel networks, multilayer or core–shell architectures, and intelligent drug-release systems may expand the therapeutic applications of MNs.The development of standardized characterization methods and scalable manufacturing processes will be equally important for clinical translation. In addition, greater emphasis should be placed on long-term stability, preservation of biologic activity, patient-friendly application, and regulatory requirements.Ultimately, successful translation of DMNs and HFMNs will depend on achieving an appropriate balance between drug loading, mechanical strength, skin insertion, dissolution or swelling, controlled drug release, biologic stability, manufacturability, and patient acceptability. Addressing these challenges could establish microneedle systems as practical alternatives to conventional injectable administration of selected biologic therapeutics.[49,50]

CONCLUSION

Dissolving and hydrogel-forming microneedles provide a minimally invasive alternative to traditional injections for delivering large biologic molecules—such as vaccines, proteins, and enzymes—by bypassing the outer layer of the skin.Dissolving Microneedles: Embed therapeutics within a water-soluble matrix that dissolves directly inside the skin to release the drug.Hydrogel-Forming Microneedles: Use a cross-linked polymer array that absorbs fluid and swells upon skin insertion, drawing the therapeutic from an attached reservoir for controlled delivery.The efficacy of both approaches depends heavily on needle geometry, production techniques, choice of polymer, cross-linking density, and drug concentration. Successful formulations must strike a balance between structural strength (to penetrate the skin without failing), drug capacity, release rate, and preserving the delicate stability of the biologic payload.While promising, clinical translation still faces hurdles in scaling up manufacturing, standardizing production, ensuring sterility, maximizing drug load, preventing mechanical failure, and securing regulatory approval. Bridging the gap between laboratory research and clinical adoption requires combining pharmaceutical formulation expertise with microneedle engineering.

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