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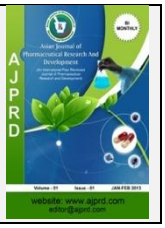

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Review Article

Hydrogel Microneedle for Controlled Delivery

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A B S T R A C T

Transdermal drug delivery (TDD) using hydrogel-forming microneedles (HFMs) is the subject of this review paper. HFMs, in contrast to traditional microneedles, are composed of cross-linked hydrophilic polymers that expand when applied topically to create microchannels for regulated and prolonged drug delivery. Their unique properties, including mechanical strength, antibacterial activity, biocompatibility, and biodegradability, make them very adaptable for both therapeutic and diagnostic applications.

The paper describes the classes of microneedles (hydrogelforming, swellable, solid, coated, hollow, and dissolving), the natural and synthetic polymers employed in their manufacture (e.g., chitosan, gelatin, hyaluronic acid, PVA, PEG, PVP), and manufacture technique's like micro-molding and 3D printing. It also points towards their mechanisms in controlled release systems, uses in chronic disease treatment, infectious disease therapy, wound healing, and drug delivery, and assessment methods. HFMs have various benefits over traditional microneedles, such as improved drug loading capacity, safe removal without residue, non-invasive fluid extraction, and single-step application.

Keywords: Hydrogel, Microneedle, Polymer, TDS, Controlled Release.

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INTRODUCTION

In the past few years, microneedles have been gaining popularity in TDD and demonstrated excellent delivery efficacy of both chemical small molecules and biomacromolecules while causing minimum insult and pain Microneedles are typically fabricated with micrometer-sized needles (in the range of 50–900 μm long) in the form of microneedle arrays, which are able to effectively penetrate the SC and deliver drugs minimally invasively underneath the SC without damage to blood vessels and nerves in the dermis enhancing patient compliance and quick absorption of drugs exposed In contrast to medical applications, microneedling devices are frequently authorised for cosmetic usage in the epidermis or dermis by surrounding capillaries and lymph nodes. Additionally, the number of clinical trials using microneedles for therapeutic purposes—such as treating diabetes, psoriasis, influenza, etc.—has been gradually rising in recent years. for extracting biofluids and delivering drugs. The MNs should expand after insertion into the skin, as the hydrogels are hydrophilic in nature. Hydrogelforming MNs are employed for TDD of drugs with drugs being loaded. The biodegradable polymer matrix or sugar-based active ingredients that make up dissolving MNs can guarantee that there won't be any medicine residue for a considerable amount of time.

Due to the unique characteristics of the skin, the microneedle (MN)-based drug delivery system is a bright prospect for traditional drug delivery systems. Its immune, inflammatory, and protective properties are perhaps reasons why it is a bright prospect. As one of the dermal drug delivery models, the MN-mediated system, or transdermal delivery of molecules without penetration, has been widely studied by business and research. It has been shown that the 100um long needles will enter the healthy epidermis through the v SC without obstructing blood vessels and nerve fibres, which are primarily found in the dermal layer. Additionally, these microneedles are less uncomfortable than standard hypodermic needles since they are thinner and smaller. They only pierce the

epidermis, the outermost layer of skin, and occasionally they pierce the dermis slightly.

A revolutionary advancement in microneedle (MN) technology, hydrogel-forming MNs have the potential to overcome some of the drawbacks typically found in conventional MNs. These encompass issues of regulating the rate and magnitude of drug release, issues of achieving adequate drug coating, and significantly decreased drug-loading capacity. These MNs are formulated from water-sensitive, biocompatible polymeric materials that gelatize upon administration to the skin. After insertion, hydrogel-forming microneedles (HFMNs) swell and form micro channels in the skin as a result of the absorption of the surrounding fluids This action preserves the structural integrity of the needle while providing controlled and sustained release of the drug, thereby creating a channel for the drug to travel into the deeper dermal layers. Their new ability to hydrate and form gel gives effective, controlled drug release, particularly of hydrophilic drugs, with no residual material remaining deposited in the skin upon removal. Hydrogel-forming microneedles (HFMs), made up of cross linked polymers, originally published in. Upon insertion into the skin, hydrogel-forming microneedles expand as they absorb interstitial fluid (ISF), which triggers the release of therapeutics from the hydrogel network, facilitating their diffusion into the dermal microcirculation. uptake and systemic absorption to occur Besides that, hydrogel-forming microneedles also have antimicrobial effects and are highly biocompatible, and thus hydrogel-forming microneedles are a controlled release of drugs over an extended period guarantees improved drug bioavailability being delivered with the prevention of drug degradation, maintaining therapeutic drug concentrations, reducing concentration fluctuation, and ultimately reducing the incidence of toxic side effects. Utilization of nonintrusive and efficient delivery approaches of drugs, such as the transdermal drug delivery system (TDDS). TDDSs are patches or devices, with the ability and capability of delivering therapeutic and effective drug amounts through the skin. They vary in advantages, mainly relating to pharmacologically unstable drugs' bioavailability. Microneedles (MNs) are small, sharp tips of microscopic dimensions stuck or unstuck to aid manufactured by different materials. In recent years, hydrogels (HGs) have become a key material used alongside microneedles (MNs) in creating transdermal drug delivery systems (TDDS). HGs can be created by crosslinking monomers inside the polymeric chain through physical (hydrogen bonds, electrostatic contacts) and chemical (covalent bonds) interactions with crosslinking agents. This will determine some of the mechanical and physical-chemical characteristics of the HGs.

The skin, the largest organ of the human body, is a good barrier that defends us against external factors, such as microbes, chemicals, internal injury, and dehydration. Thus, an impaired skin barrier is a crucial element in the pathogenesis of various skin diseases, with the worst disturbance occurring as a result of direct tissue damage. So, today, the most prevalent practice is the use of biodegradable dissolving and/or swellable microneedles that are loaded with the therapeutically active drugs to be administered. These can be selected according to degradation profiles, or even according to responses to particular stimulus within the microenvironment of the wound. Hydrogels, three-dimensional cross linked polymeric chains, have attracted significant attention because of their inherent structure that replicates the extracellular matrix, combined with their tunable mechanical properties and the facile manipulability of their ability to deliver bioactive species.

Type`S of Microneedle

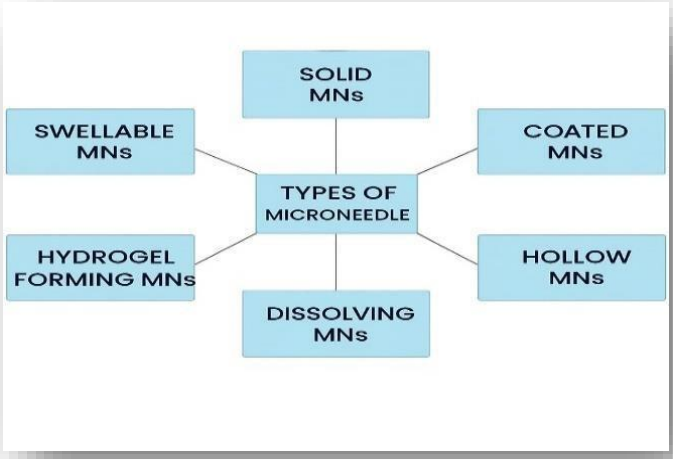

Figure 1: Type`s of Microneedles

Hydrogel Forming Microneedle`s

Fabrication of the microneedles. The polymers form the hydrophilic framework that enables it to absorb a high amount of water into its threedimensional polymeric network. These polymers swell during implantation into the skin as they have the interstitial fluid within them. This leads to channel formation between the capillary blood and the drug patch. They are used only to puncture the skin barrier before needling.During swelling, they act as a membrane that controls the rate of drug release.Size- and shape-freedom are their special features. Sterilization convenience and extraction from the skin undamaged are the special features of such microneedles.

Recent research has focused on the chemistry of hydrogels, with an aim to identify chemical linkages that will improve their properties and enable the development of responsive hydrogel microneedles for specific illnesses and conditions. They can be used to combat a variety of diseases because of their precision engineering. The extracellular matrix (ECM) can be induced using hydrogels for use in cell culture. Because of this, hydrogel microneedles are a preferred choice for cell therapy, since they may introduce therapeutic cells into injured tissues with little disruption to the tissues, enhancing the treatment's effectiveness.

1. Swellable Microneedle

Swellable MNs are a relatively new type of MN, and are synthesized from a cross-linked hydrogel and can swell but not dissolve upon the intake of interstitial fluid (IF). This kind of hydrogel MN could be loaded with drug in two modes: one is to pre-load the drug at the tip of the bottom of the MNs, and whenpiercing into the skin, the hydrogel swells by absorbing the intercellular fluid to form a gel channel.The second is that the substrate of hydrogel MN and the body of the needle are both made by mixing drugs and polymers. Upon skin penetration, the liquid infiltrates, the swelling needle expands, and releases the drug. Furthermore, the use of swellable MNs is not only applicable for drug delivery but may also be employed to draw out IF for further analysis.

2. Solid Microneedle

This type of microneedle architecture is designed to pierce the stratum corneum in order to improve drug administration to the dermis, bioavailability, and kinetic transport through the skin. The medication formulation is applied at the puncture site and enters the body through the microchannels created by the injured epidermis after the MNs have been removed.

The MNs are peeled off once the punctured epidermis creates microchannels and the drug formulation is deposited on the puncture site and subsequently diffuses into the body via the channels. The microchannels slowly shrink while the skin is healing over a period of hours before they close. This type of MN delivery process consists of two labor-intensive steps, and the amount of drugs entering the body is impossible to quantify.

3. Coated Microneedle

Coated microneedle array is made up of needle shafts used as micrometer-sized sharp needles that are fixed onto the substrate base and have on their surface drug and water-soluble inactive excipients. Diverse active materials such as peptides, small molecules viruses and micro particles are routinely considered to be delivered through coated microneedles.. The following aspects are of utmost importance when taking into consideration the usage of coated microneedles for the delivery of drugs, quality of coatings, reproducibility of the coating process and the drug delivery efficiency. Coating of a whole microneedles array along with the base substrate was achieved in one research by submerging the microneedle patches in a coating solution. Another study has documented enhanced delivery efficiencies and minimized wastage of drugs through the utilization of certain coating processes to restrict coatings to the microneedle shafts alone. A coated microneedle consists of a pointed, insoluble solid microneedle that is coated with active ingredients and water-soluble inactive excipients.

Coated microneedle consists of a solidcore sharp microneedle morphology upon which is applied a solid film of the active compound as well as watersoluble inactive excipients. Watersoluble excipients not only assist in the application of coatings to microneedles but also promote the removal of the coating film from their surfaces. To effectively coat the microneedles with drug molecules, direct physical contact between the two is required. The way in which physical contact is established dictates the classification of coating techniques, which encompass dip coating, inkjet coating, immersion coating, drop coating, and spray coating.

4. Hollow Microneedle

Hollow microneedles (HM) are capable of delivering a considerable amount of therapeutic agents via microchannels that offer essentially a micron-sized hypodermic needle, which better the quality of life of numerous patients. For example, substituting the hypodermic injection of insulin in type 1 diabetes may bring much relief to the patients. In a study, Davis et al. An array of hollow metal microneedles was developed to deliver a therapeutically significant dose of insulin. The most straightforward method of drug delivery through hollow microneedles is passive diffusion. The capacity of hollow microneedles to deliver a large and accurate dose of medication into the skin is a well-known advantage. In order to minimise the risk of bore obstruction, a major issue with hollow microneedles, and to prevent needle fracture upon skin penetration, an optimised microneedle design should have a respectable mechanical strength.

Hollow microneedles can be made from materials such as metal, silicon, and polymers, among others. One of their main advantages is the ability to precisely control both the amount and the rate of drug release. This makes them particularly effective for administering biological macromolecules and for delivering higher

doses of therapeutic agents. Hollow microneedles are a powerful approach for delivering conventional injectable preparations, hence widening the scope of their applications to fluid drug micro-injection and minimally invasive tissue/blood sampling.

5. Dissolving Microneedle

One major breakthrough in μND research has been the development of dissolvable μNDs. The new generation of μNDs is composed of biodegradable or soluble materials, which usually incorporate the drug payload into their structure.Dissolvable μNDs have overcome two of the drawbacks of their non-dissolvable counterparts, i.e., the development of sharp and harmful waste and the ability to encapsulate molecules of varying molecular weights. Architecture of disintegratable μNDs can be engineered to manage release kinetics, drug dissolution profile, skin penetration and skin clamping, dissolution rate of μNDs, and enhance biocompatibility in the skin tissue.

The two most critical parameters to consider while selecting a dissolving MN are the suitable polymer, and the release kinetics. The most widely used techniques are solvent casting, dropletborn air blowing, laser machining, hot embossing, microinjection molding, and ultrasonic welding. The function of MNs is impacted by their hygroscopic tendency. If the DMN dissolves too rapidly, the body cannot be able to absorb the medication. If it dissolves too slowly, discomfort and irritation of the skin can result. Researchers are continually striving to create MNs that dissolve at the optimal rate of delivery. Another problem in designing DMNs is degradation. The biodegradable materials used are prone to degradation through the actions of pathogens, which can affect the stability of the MN.

Polymer Use In Hydrogel Microneedle

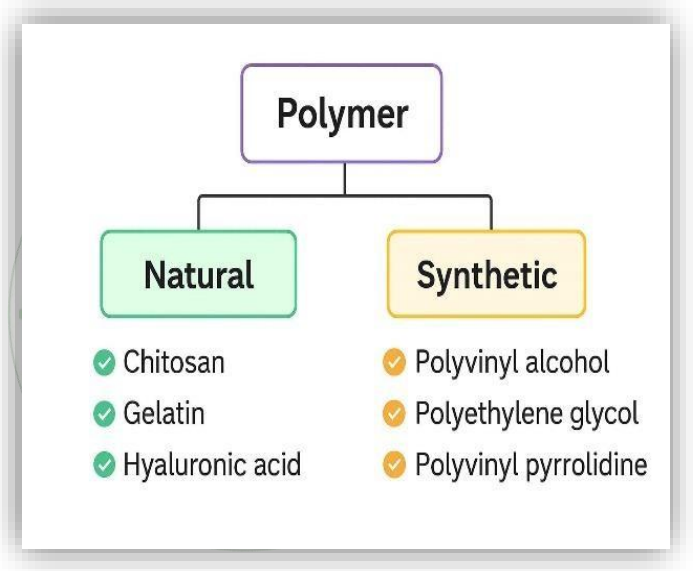

Figure 2: Polymer Use In Hydrogel Microneedle

1. Natural polymer`s

a) **Chitosan:** The cationic biodegradable natural polymer chitosan is produced when chitin in the cell walls of different microorganisms, such as yeast and fungi, and animal organs, such as oysters, squid pens, and the exoskeleton of crustaceans, is Ndeacetylated. One of the best natural polymers is chitosan, which is primarily used in the production of controlled-release medication formulations. This is because chitosan is a polymer with many advantages, including high swelling, gel formation, biodegradability, biocompatibility, and nontoxicity. These polymers are frequently combined with crosslinking agents, such as glutaraldehyde, which interacts with the protein or polysaccharide amino groups in chitosan (group –NH2) to generate Schiff bases.

Herein, a controlled drug release biomass chitosan hydrogel microneedle array patch is proposed for facilitating wound healing,. Chitosan (CS), a chitin derivative from arthropod, is the only alkaline polysaccharide in nature due to its free amino group with positive charge. The CS extraction process is also mild-operated, non-toxic, mild and friendly. These aspects render CS significantly useful in biomedical applications with the properties of biodegradation, nontoxicity, biocompatibility, antimicrobial and hemostasis. Additionally, microneedles (MN) may have uniform nano or microstructures with various types of natural materials and synthetic polymers, and penetrate the skin conveniently in a minimally invasive nature to deliver drugs efficiently to the targeted sites and achieve long-term local drug concentration. Taking advantage of these merits, MN has been shown to be valuable in numerous medical applications ranging from cancer treatment, biomedical sensors, to sampling.

Herein, we combined the antibacterial CS hydrogel with the MN array to produce a multifunctional kind

of patch for wound healing promotion, which was capable of directly and controllably releasing drugs into damaged tissues. In addition, the microstructure of MN may release the loaded drugs to the target area more efficiently and avoid the excessive adhesion of the skin with the patch.

b) **Gelatin:** Gelatin is a biopolymer obtained through the hydrolysis of purified collagen, typically sourced from bovine or porcine skin. The optimal microneedle should possess good functionalization properties like good mechanical properties for insertion in stratum corneum, biocompatibility, biodegradability, without crosscontamination, easy fabrication procedure, and high reproducibility. Gelatin can be regarded as an appropriate material to produce an MN patch since it contains a large number of functional side groups that can control the corresponding mechanical characteristics through chemical crosslinking and have biocompatible and biodegradable qualities. Furthermore, the gelatin contains a vast array of ArgGly-Asp peptides (RGD) that can serve as cellular binding sites to increase the affinity between the cell and the carrier. Additionally, gelatin can be chemically conjugated with various organic compounds to create an amphiphilic gelatin that can encapsulate hydrophobic drugs thanks to the abundance of functional groups in its backbone.

Gelatin is a natural polymer with properties highly comparable to the extracellular matrix and has thus been utilized for a multitude of tissue engineering applications due to the high biocompatibility This and the simplicity of tunable functionalization. As with HA, gelatin also dissolves readily in the skin, but through functionalization with methacrylate groups through reactive amine and hydroxyl groups of the amino acid residues, the resulting gelatin methacryloyl (GelMA) A novel method of tuning swelling of GelMA is possible with UV irradiation and DM. The smaller the DM, the more swollen a hydrogel becomes with greater UV exposure. The characteristics of GelMA are tunable by varying factors such as the extent of methacrylation and UV exposure time/intensity, while the animal source of the gelatin and photoinitiator concentration and polymer also need to be taken into account. Numerous variables, such as GelMA concentration, UV exposure duration, methacrylation amount, and synthesis circumstances, influence how the mechanical properties of GelMA are modulated.

c) **Hyaluronic acid** Hyaluronic acid (HA), or hyaluronan, is a type of sugar molecule made up of two components: d-glucuronic acid and Nacetyl-d-glucosamine, which are linked together by special chemical bonds. It is a plain, water-soluble polysaccharide.

It's naturally found in the skin and in the fluid that lubricates our joints.

Alternatively, it can also be derived from rooster combs, shark skin, and certain microorganisms. It is employed to produce dissolving microneedles, which disintegrate after piercing the skin and deliver the drug. It also supports high levels of a drug, producing better delivery and faster action. In designing insulin delivery with the help of hyaluronic acid microneedles in a study, microneedles completely dissolved into rat skin after applying it for 1 h. This demonstrated the self-dissolving property into the skin and release of loaded molecules to the site of action. Plasma peak levels were also compared with microneedles and subcutaneous injection, where an enhanced level of insulin was obtained with microneedles. This study brought the potential of hyaluronic acid into dissolving microneedle formulation for transdermal drug delivery into the limelight. Hyaluronic acid also possesses good mechanical properties that permeate psoriasis-induced mouse epidermis. Dissolving in microneedles via hyaluronic acid was more effective than oral administration in curing psoriasis, and this set the dissolving microneedle patch as a superior technique to effective delivery of the drug. Hyaluronic acid-coated dissolving microneedles were also researched for the delivery of molecules of drugs with a high molecular weight. High molecular weight4000 Da fluorescein isothiocyanate-conjugated dextran was employed and studied for skin penetration and deposition.

Transcutaneous electrical resistance and trans-epidermal water loss were found to rise, indicating the piercing character of hyaluronic acid microneedles.

2. Synthetic Polymer`s

a) Polyvinyl Alcohol PVA is a very convenient polymer to be used in blending since it is non-toxic, biodegradable, and is highly soluble in water. It can also be compatible with other polysaccharides like chitosan, alginate, and cellulose derivatives due to its ability to create intermolecular hydrogen bonds with the other bonds. PVA contains hydroxyl groups. Sacran is also hydroxyl group-rich. Thus, sacran and PVA are able to form strong hydrogen bonds with each other because of the availability of rich hydroxyl groups and, resulting in a physically cross-linked strong polymer blend.Polyvinyl alcohol (PVA) has been used to create coated and dissolving microneedles, with studies showing that PVA-based microneedles perform better than other dissolving materials like trehalose, raffinose, polyvinylpyrrolidone, and carboxymethylcellulose.

b) Poly Ethylene Glycol PEG is a hydrophilic carrier that can raise the solubility of drugs with low toxicity compared to other polymers. PEG was identified as a good reservoir medium for improving the transdermal delivery of hydrophobic drugs. This shape can be incorporated rapidly for release, dissolved and dispersed drugs.

With this reservoir shape, the onset time of ABZ reservoir can be prolonged using PEG so that it has the potential to enhance its bioavailability.

Amphiphilic solid poly(ethylene glycol) (PEG), which has a melting point of approximately 67°C, is soluble in water as well as in a range of organic solvents, including acetonitrile, aliphatic ketones, alcohols, chloroform, dimethylformamide, glycol ethers, esters, and aromatic hydrocarbons. It is non-toxic and FDA-approved as excipient or carrier in a range of pharmaceutical preparations, food, and cosmetics.

c) Poly Vinyl Pyrrolidone PVP has the benefit of being in stable form since it is well soluble in drugs with poor solubility and is not much affected by pH in the water solution. Gold or silver-plated PVP-based MNPs (PVP-MNPs) exhibited higher electrical conductance and thermal conductance, and were synthesized using gamma irradiation to achieve maximum efficiency of drug release. Sharp needleshaped tips of the arrowheads of the radiation crosslinking PVP-MNPs allow effective penetration of the skin and effective drug delivery. The other side of every PVP-MNP was also goldcoated or silver-coated via thermal evaporation to provide good thermal and electrical conductivity and to improve drug efficiency to the maximum extent.

PVP, on the other hand, suffers from a drawback of being prone to deformation or breaking and having low

biocompatibility for use as MNs. kcarrageenan (k-C) and locust Bean Gum (LBG) are polysaccharides which can render the hydrogel more compliant and biocompatible through an improvement in the viscosity of the PVP solution Additionally, the PVP-polysaccharides were combined with graphene oxide (GO) to enhance the efficiency of drug delivery using electrical stimulation.

Common Fabrication Techniques In Hydrogel Microneedle

1. **Micro Molding technology** Micro-molding technology is among the most popular techniques used to fabricate hydrogel microneedles, and it has advantages like good reproducibility and compatibility with large-scale production. The technique consists of producing target microneedles on micro-molds, where in the design of the mold, consideration should be given to parameters like needle density, diameter, and depth to guarantee that the microneedles are suitable for the targeted application. Once the hydrogel-based microneedle matrix has been constructed and conditioned in the mold, it is usually freeze-dried or subjected to other requisite drying processes to dissipate excess liquid and excess mold material.

Since the molds are reusable, a number of hydrogel microneedles may be readily and rapidly fabricated, making micro-molding technology viable for optimization and production on a large scale. Micro-molds may be applied to micro-molding technology by means of polymer casting, laser drilling, injection molding, and hot-press molding.

One of the common methods used is the preparation of hydrogel MNs by micromolding. PDMS casts, which are cast onto a solid master template and cured for two hours at 70 °C, are occasionally used. For HFM fabrication, the master template can be used to create a negative micro-mold. The reusable nature of the micro-mold makes it possible to swiftly and easily build large numbers of HFM arrays, which is crucial for parameter optimisation. A common technique for creating MNs for drug administration is two-step fabrication, in which active medications are concentrated on the MN.

2. **3D Printed Microneedle** Material deposition and vat polymerisation are the two main 3D printing techniques used in MN construction. When choosing which 3D-printing fabrication technique to use, the choice of material is crucial. Because of its temperature-dependent deposition process, FDM uses thermoplastic polymers as feedstock in enormous quantities. While PVA is frequently used because of its excellent mechanical strength in dry form, ability to contain solute in the form of a gel after being inserted into the skin, maintenance of short-term gel stability, and eventual dissolution and absorption in the skin, polylactic acid (PLA) is used because of its relatively low melting point, biocompatibility, and hydrolytic degradability.

In the field of 3D printing, polymeric materials in liquid form and low-melting-point materials are preferred for being inexpensive, light in weight, processable with versatility, and capable of providing mechanical support. Despite this, there has been an increased use of higher-melting-point materials like polyetheretherketone (PEEK) and polymethyl methacrylate (PMMA).

Most of these polymer-based microneedles are typically produced using template-driven manufacturing. This approach produces microneedles with a consistent design and easily modifiable substance. However, it is difficult to determine whether any changes should be made to the MNs because creating a template is expensive.

Micro-nano 3D technologies can fabricate materials into free shapes and have been used to directly produce MNs without template. The 3D printing principles include fused deposition modeling (FDM), selective laser sintering (SLS), and stereolithography (SLA). The smallest feature size for both SLS and SLA is more than 100 microns, and they also have comparable constraints. Additionally, SLS requires a high power supply and printing temperature, which would raise manufacturing costs. Despite being commonly used in SLA, ultraviolet (UV) photosensitive resin has poorer biocompatibility

Mechanismof Hydrogel Forming Microneedles In Controlled Drug Release System

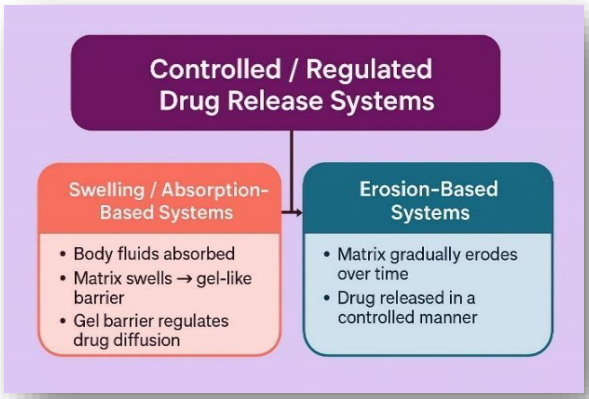

Figure 3: Mechanism of Hydrogel Forming Microneedles In Controlled

Drug Release System

These regulated or controlled release systems consist of the absorption and swelling of drug molecules by body fluids that create a gel-like barrier regulating drug diffusion. Others HFMNs also include erosion-based systems, where the matrix erodes with time for the drug to be released in a controlled manner.

APPLICATION

Chronic Disease Management HMNs are also essential in the control of chronic diseases through the sustained delivery of drugs, better systemic absorption, and patient compliance. NIR-responsive black phosphorus microneedles release insulin in a glucose-sensitive manner for diabetes control with fewer, less frequent injections.

Phenylboronic acidbased crosslinked HMNs exhibit glucose-responsive delivery of insulin with improved glycemic control with less injection frequency.

1. **Treatment Of Infectious Disease`s** With their localised drug diffusion, long-lasting effects, and reduced systemic toxicity, HMNs provide a potent transdermal approach for antibacterial, antiviral, and antiparasitic therapy. Rifampicin-loaded SmartFilm-based HMNs have demonstrated effective transdermal drug release in bacterial illness, offering a potential alternative to traditional antibiotic administration.

   Similarly, polymer-blend acyclovir-loaded HMNs promote sustained antiviral effects, especially for the treatment of herpes simplex virus.

   A combination of rifampicin, isoniazid, pyrazinamide, and ethambutol made using microneedles quickly improves skin penetration for the treatment of tuberculosis, reducing the requirement for oral medication administration. Additionally, HMNs exhibit a very potent parasitic infection effect by improving albendazole solubility and systemic absorption.

2. **Wound Healing**

   HFMs have particularly been tailored to assist with the closure of wounds by mechanically interlocking upon insertion; this is induced by the swelling of the HFMs. The interlocking HFMs contribute to wound healing through the prevention of mechanical stress on the tissue and facilitation of wound closure. Engineered HFMs consisting of a PSb-PAA swellable tips and nonswellable polystyrene core. PS-bPAA is a common absorbance polymer material and polystyrene offers mechanical strength but no swelling. When applied, the tips of the HFMs swell and result in attachment of the proboscis on the wound inner wall leading to a mechanical interlock. They achieved a 3.5 enhancement in adhesion strength relative to the normal staples utilized in skin graft fixations. Dveloped a double layer adhesive HFM patch with a swellable muscle adhesive protein shell and a nonswellable silk fibroin-based core.

3. **Transdermal Drug Delivery** Hydrogel-based film matrices (HFMs) have shown promise in enhancing the transdermal absorption of smallmolecule drugs, including donepezil, caffeine, lidocaine hydrochloride, ibuprofen, and metformin HCl. By improving the skin's permeability, these systems offer a more effective route for delivering various therapeutic agents. An instance where HFMs have been employed is in the treatment of mild dementia of Alzheimer's disease,

   At the time of drug delivery, the preloaded drug also need not be trapped within the needles but can be loaded in a distinct reservoir, as the swelling enables the drug to diffuse through the hydrogel material when pore size becomes larger.(4)

Evaluation Method for Hydrogel Forming Microneedles

1. **Appearance and Morphology**

   The tip radius, height, width, length and spacing of HFMs can be described by optical microscopy, scanning

electron microscopy (SEM) or optical coherence tomography (OCT), confocal laser scanning microscopy (CLSM), and multiphoton microscopy (MPM). OCT imaging is precise, has a specific imaging depth and imaging speed, and is frequently utilized for observing, in situ, the penetration depth of microneedle patches after piercing into isolated or in vivo skin or for capturing the process of microneedle transformations within the skin. By loading the microneedles with fluorescent dyes that mimic the drug's physicochemical characteristics, the distribution of the drug among the microneedles can be assessed using CLSM.

2. **Mechanical strength tests**

Enzyme-catalyzed cross-linking of polymers (such as hyaluronic acid) has become a novel method to modulate the mechanical strength and pore size of hydrogel materials that may be used as a good candidate for the synthesis of dissolving microneedles. More specifically, hyaluronic acid-tyramine hydrogels (labeled as HAT hereafter) have shown tunable mechanical characteristics through variations in the concentrations of cross-linking reagents like hydrogen peroxide (H2O2) and horseradish peroxidase. Extensive research has been conducted on the application of HAT hydrogels in drug delivery and tissue engineering.

However, their use in the fabrication of microneedles (MNs) has not yet been reported in the literature.

Nanocomposite hydrogel is a group of multifunctional materials that presents superior mechanical properties, adjustable drug release behaviors, and multiple bioactivities. Nevertheless, they present low transdermal efficiency when encountering skin barriers. The integration of nanocomposite hydrogels with MN technology is an innovative potential in the fields of transdermal drug deliveryTo develop a novel microneedle (MN) system for sustained drug release, we propose the formulation of a nanocomposite hydrogel incorporating HAT hydrogels as the outer matrix and PLGA nanoparticles (NPs) as the inner phase. PLGA is a FDA-approved excipient that has been widely utilized in different drug formulations. It. shows tunable degradability profiles in vivo and in vitro with the controlled release of drug payload. The incorporation of PLGA NPs and HAT hydrogels in the MNs has the following advantages: (i) HAT hydrogels with various cross-linking density, offer adjustable mechanical strength for best transdermal performances of MNs; (ii) sustained release of drug cargoes is contributed by

PLGA NPs and cross-linked HAT network; (iii) transdermal delivery of PLGA NPs by MNs maximizes drug therapeutic efficiency.

ADVANTAGES

1. HFMs have proven to surpass the limitations of other MN forms, such as enhanced loading (swelling) capacity, transcending the challenge of coating MNs, and targeted, controlled drug release.
2. The polymers utilized in HFMs are extremely biocompatible, possess good degradability, and are non-toxic, eliminating such risks upon application.
3. HFMs, when applied to the skin, may be stripped off in their entirety without depositing any polymer or, if there is some residue left behind as a result of breakage then the polymer can be easily managed due to their biocompatibility and biodegradability. However, breakage is a major issue with solid MNs if there is residual metal deposited behind when applied.
4. HFMs also do not clog with the compression of dermal tissue upon application, as is the case with most hollow MNs.
5. HFMs offer the advantage of a simplified, one-step application process for drug delivery or interstitial fluid (ISF) extraction, in contrast to the two-step procedures typically required with solid and hollow microneedles.
6. One of the primary benefits of HFMs is that they are not only confined to drug delivery but can also passively uptake ISF that cannot be done by other MNs.

Challenge and Future Prospect of HFMS

Although the creation of HFMs with integrated NPs has advanced significantly, there are still a number of obstacles to overcome in the production and in vivo use of this particular type of nanocomposite. When the encapsulated medicine is fully discharged, the structure's clearance is especially crucial.

Even though the individual components are highly biocompatible, their extended retention can lead to undue effects, including foreign body reactions. The problem can be solved by employing more advanced controlled degradation strategies, possibly encompassing the simultaneous control of polymer cleavage rates, crosslinker variation, and utilization of homogenous polymer networks. Gelation at the appropriate time, either in situ or prior to implantation, is another issue. Early gelation increases the possibility of low or uneven NP incorporation in the structure, which results in less-than-ideal therapeutic payload delivery.

On the other hand, late gelation yields risks of delivery to unwanted regions, as opposed to specific targeted delivery. Using smart polymer systems capable of rapidly developing gel on exposure to a particular stimulus could be a feasible solution for overcoming this problem. The intricacy of the biological environment must also be considered while using NP-loaded HFMs. The platform's ability to engage with individual cells and the milieu, both close to and inside the structure itself, is essential for tissue engineering applications and immune regulation. Platforms must have parts that can effectively interface with the body for these reasons. Therefore, it is crucial to improve the interface between biomedical devices, such as HFMs, and the human body in order to increase patient comfort, safety, and device performance. Some strategies to be taken into consideration include altering the needles' surfaces to improve tissue interactions and lower immunological responses, which will promote biocompatibility.

In order to reduce the risk of long-term implantation or foreign body reactions, sterilisation and packing are also essential for preventing contamination and biodegradability. Combining different NPs with hydrogel platforms to create superstructures like HFMs is generally a promising way to get around and combat the drawbacks of current conventional therapies. We anticipate that as study and understanding continue, superstructure platforms will become more widely used. In addition to improving the material's biocompatibility with the body, including several NP classes may enable hybrid HFMs to convey special functions. For instance, adding pH sensors or photoluminescent rare earth-based nanothermometers will enable real-time monitoring of the therapeutic action.

In addition, the blending of various NPs in a single system is promising in terms of multimodal sensing and imaging functionalities. On the other hand, HFMs can be used to adjust the mechanical characteristics of the tumour microenvironment by introducing piezoelectric particles. This could change the behaviour of the cancer cells and control their mechanobiology.

CONCLUSION

Hydrogel-forming microneedles are a promising development in transdermal drug delivery systems that incorporate the benefits of hydrogels and microneedle technology. With their potential to give controlled, sustained, and minimally invasive drug delivery along with their biocompatibility and safety, they are better options compared to traditional microneedle structures. Challenges still persist in controlled degradation, timing of gelation, largescale production, and long-term biocompatibility. Future directions involve the use of nanocomposites, intelligent polymers, and multifunctional materials to improve therapeutic effectiveness, biocompatibility, and diagnostic potential. With advancing research and development, HFMs have tremendous potential to revolutionize the field of personalized medicine, management of chronic diseases, and healing therapies of wounds.

REFERENCES

1. Hou X, Li J, Hong Y, Ruan H, Long M, Feng N, Zhang Y. Advances and prospects for hydrogel-forming microneedles in transdermal drug delivery. Biomedicines. 2023 Jul 27;11(8):2119.
2. Ebrahiminejad, V., Malek-khatabi, A., & Faraji Rad, Z. (2024). Influence of lowfrequency vibration and skin strain on insertion mechanics and drugdiffusion of PVA/PVP dissolving microneedles. Advanced Materials Technologies, 9(4), 2301272.
3. Mohite P, Puri A, Munde S, Ade N, Kumar A, Jantrawut P, Singh S, Chittasupho C. Hydrogel-forming microneedles in the management of dermal disorders through a non invasive process: a review. Gels. 2024 Nov 7;10(11):719.
4. Mohite P, Puri A, Munde S, Ade N, Kumar A, Jantrawut P, Singh S, Chittasupho C. Hydrogel-forming microneedles in the management of dermal disorders through a non invasive process: a review. Gels. 2024 Nov 7;10(11):719.
5. Pires PC, Renca A, Amaro I, Parreiras L, Anselmo M, Ferreira M, Veiga F, Paiva-Santos AC. From stimuli responsive polymers to nanosystems and electrocircuits: An update on the current state of polymeric hydrogel microneedles for wound healing. Journal of Drug Delivery Science and Technology. 2024 Dec 1;102:106395.
6. Waghule T, Singhvi G, Dubey SK, Pandey MM, Gupta G, Singh M, Dua K. Microneedles: A smart approach and increasing potential for transdermal drug delivery system. Biomedicine & pharmacotherapy. 2019 Jan 1;109:1249-58.
7. Wu C, Yu Q, Huang C, Li F, Zhang L, Zhu D. Microneedles as transdermal drug delivery system for enhancing skin disease treatment. Acta Pharmaceutica Sinica B. 2024 Dec 1;14(12):5161-80.
8. Zhang W, Zhang W, Li C, Zhang J, Qin L, Y. Recent advances of microneedles and their application in disease treatment. International Journal of Molecular Sciences. 2022 Feb 22;23(5):2401.
9. Jirole UD, Jirole DU, Shaikh SM, Shelake YP, Kadam SS, Hajare SS, Kulkarni AS. Microneedles: A Smart Approach for Transdermal Drug Delivery System. International Journal of Scientific Research in Science and Technology. 2023 Jan;7(3):612-23.
10. Mdanda S, Ubanako P, Kondiah PP, Kumar P, Choonara YE. Recent advances in microneedle platforms for transdermal drug delivery technologies. Polymers. 2021 Jul 22;13(15):2405.
11. Ingrole RS, Gill HS. Microneedle coating methods: A review with a perspective. The pharmacology and journal of experimental therapeutics. 2019 Sep 1;370(3):555 69.
12. Lim DJ, Vines JB, Park H, Lee SH. Microneedles: A versatile strategy for transdermal delivery of biological molecules. International journal of biological macromolecules. 2018 Apr 15;110:30-8.
13. Oliveira C, Teixeira JA, Oliveira N, Ferreira S, Botelho CM. Microneedles' device: design, fabrication, and applications. Macromol. 2024 May 15;4(2):320-55.
14. Ali M, Namjoshi S, Benson HA, Mohammed Y, Kumeria T. Dissolvable polymer microneedles for drug delivery and diagnostics. Journal of Controlled Release. 1;347:561-89.
15. Kulkarni D, Gadade D, Chapaitkar N, Shelke S, Pekamwar S, Aher R, Ahire A, Avhale M, Badgule R, Bansode R, Bobade B. Polymeric microneedles: an emerging paradigm for advanced biomedical applications. Scientia Pharmaceutica. 2023 May 31;91(2):27.
16. Mahfud MA, Fitri AM, Elim D, Sultan NA, Saputra MD, Afika N, Friandini RA, Himawan A, Rahman L, Permana AD. Combination of synthetic and natural polymers on the characteristics and evaluation of transdermal hydrogel-forming microneedles preparations integrated with direct compressed tablets reservoir sildenafil citrate. Journal of Drug Delivery Science and Technology. 2023 Aug 1;85:104611.
17. Chi J, Zhang X, Chen C, Shao C, Zhao Y, Wang Y. Antibacterial and angiogenic chitosan microneedle array patch for promoting wound healing. Bioactive materials. 2020 Jun 1;5(2):253-9.
18. Chen YJ, Cheng HW, Yen WY, Tsai JH, Yeh CY, Chen CJ, Liu JT, Chen SY, Chang SJ. The treatment of keloid scars via modulating heterogeneous gelatin structured composite microneedles to control transdermal dual-drug release. Polymers. 2022 Oct 20;14(20):4436.
19. Aroche AF, Nissan HE, Daniele MA. Hydrogel-Forming Microneedles and Applications in Interstitial Fluid Diagnostic Devices. Advanced Healthcare Materials. 2025 Jan;14(1):2401782.
20. Damiri F, Kommineni N, Ebhodaghe SO, Bulusu R, Jyothi VG, Sayed AA, Awaji AA, Germoush MO, Al-Malky HS, Nasrullah MZ, Rahman MH. Microneedle-based natural polysaccharide for drug delivery systems (DDS): progress and challenges. Pharmaceuticals. 2022 Feb 3;15(2):190.
21. Supachettapun C, Ali MA, Muangsin N, Nguyen LV, Ho VA, Okajima MK, Kaneko T, Matsumura K. Poly (vinyl alcohol)/sacran

hydrogel microneedles for anticancer transdermal drug delivery. Journal of Materials Chemistry B. 2025.

22. Nguyen HX, Bozorg BD, Kim Y, Wieber A, Birk G, Lubda D, Banga AK. Poly (vinyl alcohol) microneedles: Fabrication, characterization, and application for transdermal drug delivery of doxorubicin. European journal of pharmaceutics and biopharmaceutics. 2018 Aug 1;129:88-103.
23. Mahfufah U, Sultan NA, Fitri AM, Elim D, Mahfud MA, Wafiah N, Friandini RA, Chabib L, Permana AD. Application of multipolymers system in the development of hydrogel forming microneedle integrated with polyethylene glycol reservoir for transdermal delivery of albendazole. European Polymer Journal. 2023 Jan 19;183:111762.
24. Ko PT, Lee IC, Chen MC, Tsai SW. Polymer microneedles fabricated from PCL and PCL/PEG blends for transdermal delivery of hydrophilic compounds. Journal of the Taiwan Institute of Chemical Engineers. 2015 Jun 1;51:1-8.
25. Yang SJ, Jeong JO, Lim YM, Park JS. Synthesis and characterization of PVP microneedle patch using metal bioelectrodes for novel drug delivery system. Materials & Design. 2021 Mar 1;201:109485.
26. Jeong JO, Lim YM, Lee JY, Park JS. Polyvinylpyrrolidone based graphene oxide hydrogels by radiation crosslinking for conductive microneedle patches. European Polymer Journal. 2023 Feb 7;184:111726.
27. Cao J, Wu B, Yuan P, Liu Y, Hu C. Advances in Research of Hydrogel Microneedle-Based Delivery Systems for Disease Treatment. Pharmaceutics. 2024 Dec 9;16(12):1571.
28. Li Y, Bi D, Hu Z, Yang Y, Liu Y, Leung WK. Hydrogel-forming microneedles with applications in oral diseases management. Materials. 2023 Jul 3;16(13):4805.
29. Loh, J. M., Lim, Y. J. L., Tay, J. T., Cheng, H. M., Tey, H. L., & Liang, K. (2024). Design and fabrication of customizable microneedles enabled by 3D printing for biomedical applications. Bioactive Materials, 32, 222-241.
30. Yao W, Li D, Zhao Y, Zhan Z, Jin G, Liang H, Yang R. 3D printed multi functional hydrogel microneedles based on high-precision digital light processing. Micromachines. 2019 Dec 23;11(1):17.
31. Omidian H, Dey Chowdhury S. Multifunctional Hydrogel Microneedles (HMNs) in drug delivery and diagnostics. Gels. 2025 Mar 15;11(3):206.
32. Hou X, Li J, Hong Y, Ruan H, Long M, Feng N, Zhang Y. Advances and prospects for hydrogel-forming microneedles in transdermal drug delivery. Biomedicines. 2023 Jul 27;11(8):2119.
33. Chi Y, Zheng Y, Pan X, Huang Y, Kang Y, Zhong W, Xu K. Enzyme-mediated fabrication of nanocomposite hydrogel microneedles for tunable mechanical strength and controllable transdermal efficiency. Acta Biomaterialia. 2024 Jan 15;174:127-40.
34. Martins, C. F., Garcia-Astrain, C., Conde, J., & Liz-Marzan, L. M. (2024). Nanocomposite hydrogel microneedles: a theranostic toolbox for personalized medicine. Drug Delivery and Translational 22622275. Research, 14(8).