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Hydrogel Microneedles: A Breakthrough in Disease Treatment and Drug Delivery Systems

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Abstract

A revolutionary development in medication administration and illness treatment, hydrogel microneedles provide a painless, effective, and less invasive substitute for conventional techniques. These Hydrogel microneedles, which are made of hydrophilic, biocompatible polymers, expand when inserted into the skin, allowing for controlled medication release and interstitial fluid extraction for diagnostic purposes. This special feature tackles the main issues with traditional administration methods, such as hypodermic needle hazards, limited bioavailability, and patient discomfort. Because of their great versatility, hydrogel microneedles can deliver a variety of treatments, including proteins, nucleic acids, small compounds, and vaccinations. They are perfect for real-time monitoring and tailored therapy since they can be integrated with drug reservoirs and biosensors. These systems improve patient compliance, decrease the frequency of administration, and increase the effectiveness of therapies for long-term illnesses including cancer and diabetes. Advances in fabrication techniques, including photolithography, micromolding, and 3D printing, have enabled the production of robust and scalable Hydrogel microneedles designs tailored to specific applications. Beyond drug delivery, hydrogel microneedles are used in immunotherapy, glucose monitoring, insulin delivery, wound healing, and cosmetic treatments, showcasing their broad applicability. Despite their potential, challenges such as high production costs, variability in performance, and regulatory hurdles need to be addressed for widespread adoption. Ongoing research aims to improve their payload capacity, stability of sensitive biomolecules, and integration with wearable devices. Hydrogel microneedles hold immense promise for the future, combining therapeutic and diagnostic functionalities for theranostic applications. As material science and manufacturing technologies advance, hydrogel microneedles are poised to revolutionize healthcare by providing pain-free, efficient, and sustainable solutions for drug delivery and disease management.

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1. Introduction

An inventive medicine delivery method called microneedle (MN) technology was created to get beyond the drawbacks of traditional administration methods including injections and oral drugs. MNs are micron-scale structures that can penetrate the stratum corneum, the skin's outermost layer, without getting to deeper pain-sensitive neurons. They are usually between 50 and 900 micrometers in height. This feature makes it possible to distribute medicinal chemicals in a painless and less intrusive manner [1]. Because of its great versatility, the technology finds use in monitoring systems, diagnostics, cosmetic procedures, vaccine administration, and transdermal medication delivery. MNs are frequently combined with medications, vaccinations, or diagnostic sensors

and can be made of a variety of materials, including as silicon, metal, polymers, and ceramics. Based on its structure and function, the technology is divided into a number of categories, including solid, coated, dissolvable, hollow, and hydrogel-forming MNs. Each type caters to specific delivery needs, whether for systemic drug absorption, localized treatment, or sustained release [2]. The advantages of MN technology include increased patient compliance due to pain-free application, enhanced bioavailability of drugs bypassing the first-pass metabolism, and improved stability of sensitive biomolecules. Despite these benefits, challenges such as scalability, cost-effectiveness, and regulatory approval remain areas of active research and development [3].

Researchers started looking on minimally invasive drug delivery techniques in the 1970s, which is when the idea for MNs first emerged. Studies examining the viability of administering medications via the skin by interfering with the stratum corneum's barrier function established the first theoretical foundation. However, the creation of useful devices was hampered by restrictions in microfabrication processes [4]. Microfabrication breakthroughs in the 1990s gave the MN technology a boost. A groundbreaking work conducted at Georgia Tech in 1998 under the direction of Mark Prausnitz and others presented silicon-based MNs that could penetrate the skin and provide medication. This study showed that MNs have the ability to deliver drugs transdermally effectively without causing severe pain or discomfort [5]. During this period, the focus was primarily on solid and hollow MNs fabricated using microelectromechanical systems (MEMS) technology. Early prototypes aimed to test the mechanical strength, penetration efficiency, and drug delivery capabilities of MNs [6].

The 2000s witnessed significant progress in MN technology, driven by interdisciplinary collaborations among material scientists, engineers, and pharmaceutical researchers. Diverse MN designs emerged, including coated and dissolvable MNs, expanding the scope of applications. The use of biocompatible polymers for dissolvable MNs marked a major innovation, enabling the delivery of vaccines and biologics without leaving residual material in the skin [7]. Notable achievements during this period included the development of MNs for vaccine delivery, such as influenza and polio vaccines, demonstrating enhanced immune responses compared to traditional methods. Companies like 3M began investing in MN technology, furthering its commercialization [8]. The 2010s saw the maturation of MN technology, with a surge in clinical trials and commercial products. Hydrogel-forming MNs emerged as a breakthrough, enabling sustained drug release and real-time monitoring of biomarkers. Advances in 3D printing and nanotechnology enhanced the precision and functionality of MN fabrication [9]. The COVID-19 pandemic underscored the potential of MNs for vaccine delivery, with studies exploring their role in rapid and scalable immunization strategies. Companies like Micron Biomedical and academic institutions have spearheaded efforts to bring MN-based products to market [10].

2. Comparison of Hydrogel MNs with Traditional Drug Delivery Systems

Hydrogel MNs represent a significant advancement over traditional drug delivery systems (DDS), offering unique benefits that address longstanding limitations of conventional approaches such as oral administration and hypodermic injections [11]. Below is a comparative analysis:

2.1. Invasiveness and Patient Comfort

Hypodermic needles are invasive, causing pain, anxiety, and discomfort for many patients, especially children and needle-phobic individuals. Oral drugs may have side effects due to systemic exposure. These are minimally invasive, penetrating only the outermost skin layers, thus avoiding pain and improving patient compliance [12].

2.2. Drug Bioavailability

Oral drugs often suffer from poor bioavailability due to first-pass metabolism in the liver. Hypodermic injections bypass this but may not offer controlled release. They bypass the first-pass metabolism, enhancing bioavailability, and allow for controlled or sustained drug release, improving therapeutic outcomes [13].

2.3. Precision and Control

Oral and injectable drugs may lead to inconsistent dosing and challenges in maintaining therapeutic drug levels. Offer precise and localized delivery, reducing systemic side effects and allowing real-time adjustments in dosage through integrated biosensors [14].

2.4. Safety and Infection Risks

Reusable hypodermic needles pose risks of needle-stick injuries and infections. Single-use and dissolvable designs eliminate residual waste, reducing contamination risks and ensuring safety [15].

2.5. Versatility and Applications

Limited applications, with oral drugs unsuitable for large biomolecules and hypodermic needles restricted to liquid formulations. Versatile, delivering a wide range of therapeutics, including large biomolecules like proteins and nucleic acids, as well as enabling diagnostics and theranostics [16].

2.6. Patient Compliance

Frequent injections or dosing regimens can lower patient adherence. Improved convenience through pain-free application, self-administration, and reduced dosing frequency encourages adherence [17].

2.7. Scalability and Cost

Oral drugs are cost-effective to manufacture at scale, whereas hypodermic needles require sterilization and safe disposal systems. While fabrication techniques like 3D printing have improved, scalability and cost remain challenges that need to be addressed for widespread use [18].

3. Hydrogel MNs

Hydrogel MNs are an innovative class of MN technology designed for minimally invasive drug delivery and diagnostic applications. Composed primarily of hydrophilic polymer networks, hydrogel MNs exhibit the ability to swell upon contact with bodily fluids, enabling the controlled release of therapeutic agents or the extraction of interstitial fluid for biomarker analysis. This unique functionality positions hydrogel MNs as a versatile and patient-friendly platform in modern healthcare [19].

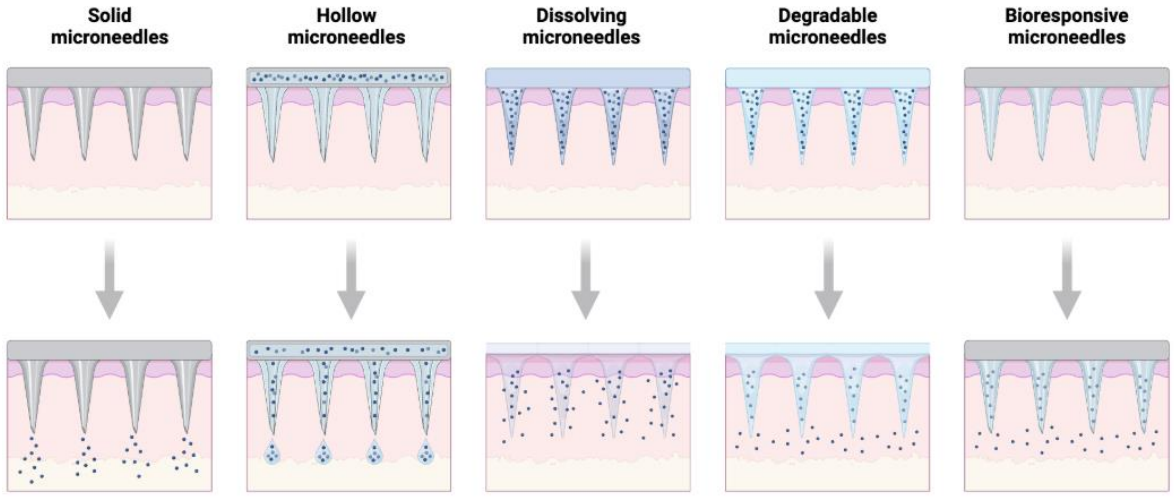

Figure 01: Hydrogel MNs Designed for Transdermal Drug Delivery

4. Definition And Unique Properties of Hydrogels

Three-dimensional polymeric polymers called hydrogels can absorb and hold onto a lot of water without losing their structural integrity. These materials are perfect for biological applications since they are very biocompatible. Important characteristics of hydrogels that improve their performance in MN systems include their high absorption capacity, which enables them to efficiently interact with biological fluids [20]. Hydrogel MNs expand after being inserted into the skin because they absorb interstitial fluid, enabling sustained drug release or sampling. Hydrogels can be engineered to possess sufficient strength for skin penetration while remaining soft enough to minimize tissue damage. Hydrogels are safe for use in humans and can be designed to degrade naturally, leaving no residues. Hydrogels can be functionalized with drugs, nanoparticles, or biosensors to meet specific therapeutic or diagnostic needs [21].

5. Advantages Of Hydrogel MNs Over Other Types

Compared to other forms of MNs, such as solid, coated, dissolvable, or hollow MNs, MNs have a number of clear benefits. One of the key benefits is their ability to provide controlled and sustained drug release, unlike solid or coated MNs, which deliver drugs immediately. The swelling properties of

hydrogel MNs enable programmable drug release, ensuring more precise and longer-lasting therapeutic effects [22]. Additionally, hydrogel MNs can be integrated with biosensors for real-time biomarker analysis, a feature not typically found in other MN types, enabling continuous monitoring of patient conditions. Another advantage is their clean removal after use, as hydrogel MNs do not leave behind polymer residues like dissolvable MNs. These MNs also have a high payload capacity, allowing for the encapsulation of larger quantities of therapeutic agents or hydrophilic drugs, which is not possible with coated MNs. Furthermore, hydrogel MNs offer a pain-free application, as they only penetrate the stratum corneum without reaching pain-sensitive nerves, enhancing patient comfort. Finally, their versatility extends beyond drug delivery, as hydrogel MNs are ideal for theranostic applications, combining diagnostic and therapeutic functions in a single system [23].

6. Importance of the Review

The rapidly growing interest in hydrogel MNs underscores the need for a comprehensive review to consolidate current knowledge and address gaps in the literature. Hydrogel MNs have demonstrated immense potential in improving DDS and diagnostic tools, but several aspects remain underexplored or fragmented across various studies. This review serves as a critical resource to guide future research, highlight advancements, and accelerate their integration into clinical and commercial applications [24].

7. Addressing

To fully utilize MNs' promise in medication delivery and illness treatment, a number of holes in the current research must be filled. One key area that has received limited attention is the optimization of hydrogel materials, particularly in terms of their mechanical properties, swelling behavior, and drug-loading capacities. While many studies highlight the biocompatibility of hydrogels, there is a lack of detailed investigations into improving these critical aspects. This review aims to bridge these gaps by analyzing recent advancements in hydrogel formulations and fabrication techniques [25]. Another area often overlooked is the scalability and economic feasibility of hydrogel MN production. Although laboratory results show promising outcomes, few studies address the challenges related to large-scale manufacturing and cost-effectiveness. This review identifies emerging technologies, such as 3D printing, which could help overcome these obstacles. Furthermore, while much of the current research is based on preclinical studies and laboratory experiments, there is a notable lack of clinical trial data and real-world evidence regarding the safety, efficacy, and user acceptance of hydrogel MNs [26]. By compiling available data, this review seeks to provide a clearer pathway for clinical translation. Lastly, the integration of hydrogel MNs with wearable technology for continuous monitoring and therapy remains an underexplored area. This review highlights emerging trends and opportunities in this field, which could significantly enhance the capabilities of hydrogel MNs for personalized, real-time medical applications [27].

8. Significance In Advancing Medical Applications

MNs hold significant promise in advancing medical applications by offering pain-free, efficient, and sustainable solutions across a variety of therapeutic areas. In drug delivery, hydrogel MNs enhance bioavailability, enable sustained drug release, and improve patient compliance, making them particularly advantageous for the treatment of long-term illnesses such diabetes, cancer, and autoimmune disorders [28]. In vaccination, hydrogel MNs simplify the administration process, ensuring better distribution and uptake of vaccines, which is especially valuable in low-resource settings. Their ability to extract interstitial fluid also positions hydrogel MNs as a powerful tool for diagnostics, enabling real-time biomarker analysis and paving the way for more personalized medicine approaches. Moreover, hydrogel MNs serve as a versatile platform for theranostics, combining both therapeutic and diagnostic functions to support tailored treatments, particularly for chronic and complex diseases. These advancements highlight the potential of hydrogel MNs to revolutionize medical practices, providing more effective, accessible, and patient-friendly healthcare solutions [29].

9. Design And Fabrication of Hydrogel MNs

MNs are designed and manufactured by integrating materials science, engineering, and pharmaceutical technology to create devices that are effective, safe, and scalable. This process is critical in tailoring hydrogel MNs for specific medical applications, such as drug delivery, diagnostics, or theranostics [30].

10. Material Composition of Hydrogel MNs

The material composition of MNs is critical for their performance in drug delivery, diagnostics, and other

biomedical applications. These materials are typically composed of hydrophilic polymers that absorb water and swell upon insertion into the skin, enabling controlled drug release or fluid extraction. The selection of materials affects hydrogel MNs' mechanical characteristics, biocompatibility, swelling behavior, and drug-loading ability [31].

Table 01: Common Hydrogels used in MNs.

S. No.	Hydrogel	Properties	Advantages	Applications	References
a)	**Polyvinyl Alcohol**	PVA is a water-soluble, synthetic polymer that is non-toxic and extremely biocompatible. When crosslinked, it takes on the consistency of gel.	a) Excellent mechanical properties when crosslinked, making it suitable for MN fabrication. b) Good water absorption and swelling capacity, ideal for controlled drug release.	PVA is widely used in both solid and dissolvable MNs, particularly for both wound healing and medication distribution.	[32]
b)	**Gelatin**	Derived from collagen, gelatin is a naturally occurring polymer that is biocompatible and biodegradable. It is quite adjustable and produces hydrogels at physiological temperatures.	a) Biodegradable and non-toxic, making it ideal for medical applications. b) Capable of encapsulating a wide range of drugs, including proteins and peptides, without compromising stability.	Gelatin is frequently used in dissolvable hydrogel MNs for drug delivery and tissue regeneration.	[33], [34]
c)	**Hyaluronic Acid**	Connective tissues naturally contain HA, a polysaccharide that is well-known for its excellent water retention capacity and biocompatibility. For improved mechanical qualities, it is frequently combined with other materials.	a) Excellent biocompatibility and skin compatibility, reducing the risk of irritation. b) Promotes tissue repair and regeneration, making it ideal for wound healing applications.	HA is used in hydrogel MNs for drug delivery, skin rejuvenation, and cosmetic applications.	[35]

d)	**Chitosan**	A naturally occurring biopolymer made from chitin is called chitosan. It has antibacterial qualities and is non-toxic and biodegradable.	a) Provides excellent mechanical strength and is highly suitable for skin penetration. b) Offers controlled drug release and can be modified for use in both non-dissolvable and dissolvable MNs.	Because of its antibacterial qualities and biocompatibility, chitosan is frequently utilized in medication delivery and wound healing MNs.	[36], [37]
e)	**Polyethylene Glycol (PEG)**	PEG is a synthetic polymer that dissolves in water and has exceptional hydrophilicity. It is frequently combined with other polymers to improve biocompatibility and swelling characteristics.	a) Water absorption and swelling behavior make it ideal for controlled drug release. b) PEG's hydrophilic nature improves the solubility and stability of many drugs, particularly biologics.	PEG is used in both dissolvable and solid MNs for drug delivery and bioactive compound stabilization.	[38], [39]

11. Role of Crosslinking in Structural Stability

In order to improve MNs' overall performance and structural stability, crosslinking is essential. Crosslinking offers a number of significant benefits by chemically joining polymer chains, which are necessary for the efficient application of hydrogel MNs in drug administration. In the first place, it increases the hydrogel's mechanical strength, which makes the network more rigid and enables MNs to keep their shape after skin insertion without breaking or deforming. This is essential to guaranteeing optimal medication administration and efficient skin penetration [40]. Furthermore, crosslinking affects how the hydrogel swells in reaction to water absorption. For controlled release applications, hydrogel MNs must be properly crosslinked to provide predictable swelling and avoid premature degradation. Additionally, by maintaining therapeutic agent encapsulation and preventing uncontrolled diffusion, crosslinking improves drug loading and release characteristics [41]. This increases the effectiveness of therapies by allowing for prolonged, sustained medication release. Additionally, the degree of crosslinking can affect how quickly hydrogel MNs biodegrade, enabling degradation to be adjusted to meet the therapeutic agent's desired release profile. For example, slow crosslinking in dissolvable MNs guarantees that the MNs break down gradually following insertion. Lastly, crosslinking ensures that medications are only released when the MNs come into touch with the interstitial fluids in the skin, preventing premature drug leakage. Crosslinking is essential to the creation of efficient hydrogel MNs because it improves medication delivery accuracy and reduces adverse effects [42].

12. Mechanical Properties and Considerations of Hydrogel MNs

MNs are made to effectively transport medications or other therapeutic substances via the skin. The performance of these MNs is largely determined by their mechanical characteristics. MNs need to be strong enough mechanically to pierce the stratum corneum, the outermost layer of the skin, without breaking or cracking. The needles must be robust enough to stay in place during insertion while still being sharp enough to make microscopic channels in

the skin. Because it needs to be carefully adjusted, the MNs' stiffness is crucial to penetration efficiency [43]. If the needles are too stiff, they can cause excessive pain or tissue damage, whereas if they are too soft, they may not penetrate deep enough to deliver the desired drug or biomolecule. Additionally, the height and diameter of the MNs significantly affect their mechanical properties. Shorter, thinner needles may offer higher comfort during insertion but may require higher forces to penetrate deeper tissue layers, potentially limiting their effectiveness. On the other hand, longer, thicker needles may penetrate the skin more effectively but could result in more discomfort during use. Therefore, optimizing these factors is crucial to ensure a balance between effective drug delivery and patient comfort [44]t.

13. Optimization For Skin Penetration

The efficiency of MNs depends on efficient skin penetration, which requires careful optimization of a number of factors. In the first place, the MNs' geometry is crucial. The needles' length should be just right to pierce the stratum corneum, the outermost layer of skin, without injuring or causing undue discomfort to the deeper layers of skin. MN lengths typically fall between 100 μm to 1 mm. Additionally important is the needle tips' sharpness, as sharper tips limit pain and require less power to penetrate the skin [45]. Additionally, the density and arrangement of the MNs can significantly impact penetration effectiveness. A higher density of MNs increases the surface area in contact with the skin, improving drug delivery efficiency and reducing the force needed for insertion. Material choice is equally important for skin penetration. Hydrophilic materials, such as the hydrogels commonly used in MNs, facilitate smoother insertion by enhancing the interaction between the MNs and the skin. Materials like polyvinyl alcohol (PVA), gelatin, and hyaluronic acid are known to improve skin adhesion and reduce friction during penetration. While softer materials may be easier to insert, they may not be suitable for deeper tissue penetration. Therefore, optimizing the balance between softness for patient comfort and hardness for effective penetration is crucial for achieving the desired therapeutic outcomes [46].

14. Swelling Behaviour and Its Role in Drug Release

Swelling behavior is a crucial feature of MNs, as it directly impacts their drug release characteristics. Hydrogels are known for their ability to absorb water and swell, and this property plays a pivotal role in controlled drug delivery. Hydrogel MNs expand after being inserted into the skin because they absorb interstitial fluid. The MNs' increased surface area as a result of this swelling improves the effectiveness of drug release from the hydrogel matrix. As the hydrogel swells, it can gradually release the encapsulated drug over time, providing a sustained drug release that is beneficial for therapies requiring a constant drug concentration over a prolonged period [47]. By altering variables including the crosslinking density, polymer composition, and the addition of additional agents that regulate water absorption, the pace of swelling may be managed. One important factor is the hydrogel material's degree of crosslinking in its swelling behavior. A higher degree of crosslinking generally leads to reduced swelling, as the polymer network becomes more rigid and less able to absorb water. Conversely, lower crosslinking allows for greater swelling, which facilitates faster drug release. The swelling kinetics also influence the drug release rate, allowing hydrogel MNs to be tailored for both fast-acting and sustained-release DDS. Furthermore, the swelling of hydrogel MNs affects their interaction with the skin after insertion. While reducing tissue injury, the expanding MNs aid in the delivery of medicinal substances into deeper layers of the skin. Additionally, the swelling behavior contributes to patient comfort by enabling smooth insertion and gradual drug release, reducing the potential for irritation or discomfort during the treatment period [48].

15. Mechanisms Of Drug Delivery in Hydrogel MNs

Therapeutic agent distribution via MNs depends on a number of processes that allow for regulated release and efficient drug penetration. Skin penetration is one of the main processes. Drugs can flow through the stratum corneum's microchannels created by hydrogel MNs when they are placed to the skin. The hydrophilic aspect of the hydrogel improves insertion by absorbing moisture from the skin and facilitating smoother entry, while the sharpness of the MNs reduces irritation [49]. Additionally, this guarantees the MNs' ability to absorb interstitial fluid and retain their integrity upon insertion, both of which improve drug solubility. In order to increase their surface area and allow for the controlled release of encapsulated medications, the hydrogel MNs expand after insertion as they absorb interstitial fluid from the skin. As a result of this swelling, the hydrogel's water content gradient affects the drug's diffusion rate, causing molecules to migrate from high concentration regions

inside the MNs to lower concentrations in the surrounding skin tissue [30]. Hydrogel MNs are perfect for treatments that need steady medication levels, such insulin administration for diabetes or pain management, because of their swelling characteristic, which permits continuous drug release and guarantees that the drug is supplied gradually over an extended period of time. By altering the hydrogel's degree of crosslinking, the release rate may be regulated; more crosslinking slows down the process, while lower crosslinking accelerates drug release [50].

The delivery method also involves electrostatic interactions and osmotic pressure. The transfer of medications from the MNs into the skin is aided by the osmotic gradient produced when the hydrogel absorbs water from the skin. In some cases, drugs can be loaded into the MNs via electrostatic interactions, where charged drug molecules are attracted to the opposite charge on the hydrogel, facilitating efficient loading and release. Biodegradation and dissolution mechanisms also contribute to drug delivery, particularly in dissolvable MNs that break down in response to the skin's moisture [50]. This allows for in situ drug release, eliminating the need for MN removal. Biodegradable polymers like gelatin and hyaluronic acid enable the MNs to degrade over time, releasing their payload in a manner that can be tailored for slow or rapid drug release depending on the therapeutic need [51].

The encapsulation of drugs within the hydrogel matrix is another crucial aspect. Various techniques, such as solvent evaporation, coacervation, and crosslinking, are used to encapsulate drugs, ensuring they are protected from degradation before delivery. Hydrophilic drugs, such as proteins, peptides, and biologics, are particularly well-suited for encapsulation in hydrogel MNs due to the material's water-loving properties. This makes hydrogel MNs ideal for delivering biologics that are otherwise challenging to administer via traditional injections. Hydrogel MNs also offer both passive and active targeting mechanisms [51]. Passive targeting ensures that the drug is delivered directly to the local tissue, such as for local pain relief or topical treatments, while future advancements may enable active targeting through functionalized MNs. This would involve loading drugs with targeting moieties like antibodies or peptides to guide the drug to specific cells or tissues, enhancing the therapeutic effect and reducing systemic side effects. These combined mechanisms make hydrogel MNs a highly efficient and versatile platform for controlled, localized, and sustained drug delivery [52].

16. Integration With Advanced DDS

MNs offer an innovative approach in drug delivery, particularly when integrated with advanced DDS. By combining the unique properties of hydrogels with modern drug delivery technologies, hydrogel MNs enhance therapeutic outcomes and improve patient experiences. One significant advancement is the use of biodegradable MNs, which degrade in the skin after drug delivery, eliminating the need for needle removal [53]. These biodegradable MNs, typically made from natural polymers like gelatin, hyaluronic acid, or poly(lactic-co-glycolic acid) (PLGA), degrade over time into non-toxic by-products, ensuring biocompatibility and reducing post-treatment waste. Their combination with hydrogel's inherent swelling behavior enables sustained, controlled drug release. For example, a hydrogel MN made from gelatin or PLGA can slowly degrade and release drugs like vaccines, peptides, or tiny molecules for an extended length of time, reducing the requirement for recurrent dosage and enhancing patient adherence [54].

In addition to biodegradability, stimuli-responsive hydrogels—also known as smart hydrogels—offer another layer of precision in drug delivery. When exposed to external stimuli like pH, temperature, light, or electric fields, these materials alter their chemical or physical characteristics. pH-responsive hydrogels, for instance, swell or shrink in response to changes in pH and can be used to release drugs when MNs come into contact with the acidic or basic environments of the skin or specific target tissues. Temperature-responsive hydrogels undergo phase transitions at specific temperatures, facilitating on-demand drug release when applied to slightly warmer skin or when heat is applied. Light-responsive hydrogels change their structure when exposed to particular wavelengths of light, allowing for localized drug release at precise skin sites. Lastly, electric-field-responsive hydrogels alter their swelling behavior or drug release characteristics when subjected to an electric current, which could enable targeted drug delivery to specific tissues or organs [55].

Hydrogel MNs can also be integrated with nanoparticles and nanocarriers, such as liposomes, micelles, or dendrimers, to further enhance drug delivery. These nanoparticles can encapsulate hydrophobic drugs that may otherwise not dissolve in the hydrogel matrix, expanding the range of therapeutic agents that can be delivered. A hydrogel

MN embedded with nanoparticles, for example, could simultaneously deliver hydrophilic and hydrophobic drugs, offering more comprehensive treatment options [56]. Additionally, hydrogel MNs are being explored for gene therapy, enabling efficient delivery of plasmid DNA, RNA, or CRISPR components. The biocompatible nature of hydrogels ensures the integrity of the genetic material during encapsulation and release, making them a promising platform for gene therapies targeting skin disorders or localized cancers. Furthermore, the integration of hydrogel MNs with MEMS technology allows for smart, real-time monitoring and controlled drug delivery. These MEMS systems can sense physiological changes, such as alterations in skin temperature or blood pH, and adjust drug release accordingly, making hydrogel MNs even more adaptable for personalized treatment regimens. This integration with advanced DDS holds great promise for revolutionizing patient care by providing more efficient, targeted, and controlled therapies [57].

Table 02: Hydrogel MN in Disease Treatment

S. No.	Application Area	Description	Benefits	Examples	References
1.	**Vaccine Delivery**	Hydrogel MNs are used for painless and efficient vaccine administration, including those for influenza, COVID-19, and other infectious diseases.	Non-invasive delivery, reducing pain and improving patient compliance. Controlled release for enhanced immune response.	Influenza, COVID-19, and HPV vaccines.	[58], [59]
2.	**Chronic Disease Management**	Utilized to continuously release insulin or other therapeutic substances in the treatment of long-term conditions like diabetes.	Continuous, controlled drug delivery for stable therapeutic levels. Minimizes needle-related discomfort and enhances self-administration.	Insulin delivery for diabetes, hormone replacement therapies.	[60], [61]
3.	**Cancer Treatment**	By delivering chemotherapeutic medications or tailored treatments straight to cancer cells, hydrogel MNs can lessen the negative consequences of systemic drug exposure.	Delivery to tumors that is localized and focused, limiting harm to healthy tissues and lowering systemic adverse effects.	Chemotherapy, targeted gene therapies for cancer.	[62], [63]
4.	**Wound Healing and Tissue Regeneration**	used to encourage tissue regeneration and wound healing by the controlled release of growth	Enhanced healing with minimal scarring, controlled	Wound healing, burn treatment, chronic ulcer management.	[64], [65], [66]

		factors, anti-inflammatory medications, or antibacterial substances.	release of drugs to improve tissue repair, and reduced risk of infection.		
5.	**Pain Management**	Delivery of analgesic drugs or local anesthetics directly into the tissue for localized pain relief, such as in post-surgical or chronic pain management.	Reduced pain during and after application, minimal systemic drug exposure, and targeted pain relief.	Post-operative pain management, chronic pain treatment.	[67]
6.	**Dermatological Treatments**	For skin-related diseases such as acne, psoriasis, and eczema, hydrogel MNs can deliver corticosteroids, antibiotics, or biologics directly to the skin.	Localized treatment with reduced systemic side effects, better drug penetration for more effective outcomes.	Treatment of acne, psoriasis, eczema, and skin infections.	[68], [69]
7.	**Gene Therapy**	Used for the delivery of nucleic acids such as plasmid DNA or RNA directly to targeted cells for gene therapy, reducing systemic exposure and improving efficacy.	Provides efficient and localized gene delivery, minimizing immune responses and side effects.	Gene therapies for skin disorders, localized cancers, or genetic diseases.	[70]
8.	**Vaccination in Needle-phobic Patients**	Ideal for individuals with a fear of needles, hydrogel MNs offer a painless alternative to traditional needle-based vaccination.	Non-invasive, pain-free administration, making vaccinations more accessible for needle-phobic individuals.	Vaccinations for children, elderly, and needle-phobic individuals.	[71], [72], [73]
9.	**Cosmetic and Aesthetic Applications**	For cosmetic applications like skin rejuvenation and anti-aging, hydrogel MNs can deliver hydrating agents, collagen boosters, and other aesthetic treatments.	Non-invasive, pain-free treatment, improving skin appearance by delivering active ingredients directly to the dermis.	Anti-aging treatments, collagen boosting, skin hydration.	[74]

Table 05: Advantages and Challenges

S. No.	Aspect	Advantages	Challenges	References
1.	**Minimally Invasive**	i) Hydrogel MNs only penetrate the outermost layers of the skin, reducing pain and discomfort ii) Non-invasive nature allows for easy, at-home administration without medical supervision.	a) Incomplete skin penetration may reduce drug delivery efficiency for deeper targets. b) The depth of penetration must be optimized for different skin types, which could complicate product development.	[75], [76]
2.	**Patient Compliance**	i) Non-invasive, which improves patient compliance, especially for needle-phobic individuals and children. ii) Reduced need for frequent visits to healthcare providers.	a) Some patients may still feel discomfort during the application process, especially with certain materials. b) Patient education on proper self-administration is required for effective use, especially for complex applications.	[77]
3.	**Controlled Release**	i) Provides sustained, controlled drug release over time, reducing the frequency of administration. ii) Enables a consistent therapeutic effect, reducing peaks and troughs associated with conventional drug delivery methods.	a) Complex release mechanisms may require extensive optimization and testing for each drug. b) The stability of the drug and hydrogel under various environmental conditions needs thorough testing.	[78], [79]
4.	**Targeted Delivery**	i) Allows for localized delivery, minimizing systemic exposure and associated side effects. ii) Can deliver drugs directly to the skin for conditions like psoriasis, acne, or skin cancer.	a) Targeting specific tissues or organs with MNs may be challenging, especially in deeper or complex anatomical sites. b) Ensuring precise drug delivery in varying skin types may require tailored designs and formulations.	[80], [81], [82]
5.	**Biocompatibility**	i) Hydrogel materials are often biocompatible and biodegradable, reducing the risk of adverse reactions. ii) Reduced risk of inflammation and scarring compared to traditional injections.	a) Degradation rates of hydrogels must be carefully controlled to avoid premature drug release or inadequate stability. b) The long-term impact of biodegradable	[83], [84]

			hydrogel residues in the body needs to be evaluated.	
6.	**Ease of Fabrication**	i) Various fabrication methods (e.g., micromolding, 3D printing) allow for scalable, cost-effective production. ii) Mass production is feasible for uniform MN arrays.	a) The fabrication process for some MN designs may be time-consuming or costly, particularly for complex structures. b) Fabrication of highly intricate designs can lead to inconsistent quality control and defects in the final product.	[85]
7.	**Drug Loading Capacity**	i) Hydrogels can encapsulate and release a variety of drugs, including proteins, peptides, and biologics. ii) Can be tailored for specific types of drugs or therapeutic needs.	a) Drug loading efficiency may be limited depending on the hydrogel's swelling properties and the drug's solubility. b) The drug release profile can be influenced by the molecular weight and hydrophilicity of the drug.	[86]
8.	**Reduced Side Effects**	i) Direct delivery to the skin or target tissue minimizes systemic exposure, reducing side effects. ii) Higher local concentration at the site of action can lead to better therapeutic outcomes.	a) Hydrogel MNs may not be suitable for delivering all types of drugs (e.g., large molecules like antibodies). b) Over-penetration or improper application may cause skin irritation or damage.	[87], [88]
9.	**Customization**	i) High versatility in material selection and design, allowing customization for different applications. ii) Can be engineered to respond to specific stimuli such as pH, temperature, or light.	a) Design complexity can increase, requiring careful optimization of parameters like size, shape, and drug release profile. b) Manufacturing techniques must be adapted to produce precise and uniform structures for consistency in drug delivery	[89], [90]
10.	**Versatility**	i) Can be used for a range of applications, including vaccines, pain management,	a) Limited clinical data available for widespread use in certain therapeutic areas, particularly long-	[91]

		wound healing, and cosmetics. ii) Suitable for both topical and systemic therapies.	term treatment. b) Regulatory hurdles for novel DDS may slow the pace of adoption.	
11.	**Enhanced Patient Comfort**	Minimizes the risk of needle-stick injuries and associated infections.	Complex interactions between MN material and skin may sometimes lead to inconsistent drug absorption.	[92]
12.	**Improved Drug Stability**	Hydrogels can protect sensitive molecules like proteins, peptides, and vaccines from degradation.	Ensuring drug stability during the hydrogel's degradation process is a challenge, particularly for biologics.	[93], [94]
13.	**Non-Disruptive to Daily Life**	MNs are small and lightweight, making them less disruptive to daily activities compared to traditional injections.	Risk of MNs breaking or bending during application, leading to incomplete drug delivery or skin irritation.	[95]

16. Future Perspectives of Hydrogel MNs in Drug Delivery and Disease Treatment

The future of MNs promises to significantly transform drug delivery and disease treatment, offering a minimally invasive, efficient, and patient-friendly alternative to traditional methods like hypodermic injections. As advancements in material science, fabrication technologies, and DDS continue, hydrogel MNs are expected to expand into new therapeutic areas and overcome existing challenges to enhance their clinical application. A key area for future development is in material innovation [96]. Current materials, including polyvinyl alcohol (PVA), gelatin, hyaluronic acid, and chitosan, have shown promise, but researchers are increasingly exploring stimuli-responsive hydrogels. When exposed to external stimuli such as pH, temperature, or light, these materials can change their structure or behavior. With the exact control that such hydrogels would provide over medication release, therapies may be customized to meet the needs of each patient. For instance, local environmental factors at the illness site may induce medicine release, resulting in more effective therapies and fewer adverse effects [97].

Composite hydrogels, which blend natural and manmade polymers, are another fascinating field of study. These materials seek to combine the adjustable qualities of synthetic polymers with the biocompatibility and biodegradability of natural polymers. By enhancing mechanical strength, swelling behavior, and drug encapsulation capability, the combination makes hydrogel MNs more effective and suitable for a wider range of applications. 3D printing has enormous potential for the manufacture of hydrogel MNs in the future. Despite the drawbacks of current production techniques like micromolding and photolithography, 3D printing has the capacity to produce intricate, bespoke MN structures that may be adapted to certain drug delivery requirements [98]. The development of 3D printing technology will lower production costs, boost scalability, and make it possible to create highly customized MNs. In the future, hydrogel MNs' medication loading and release processes will likewise advance. The capacity of hydrogel MNs to transport a variety of medication types, including as proteins, peptides, and biologics like vaccines, is one of its key benefits. Nevertheless, maintaining regulated release and maximizing drug stability are constant difficulties. Multi-layered MNs that mix several drug release characteristics may be developed in the future to improve treatment results for chronic disorders and provide sustained delivery over time [99].

Hydrogel MNs have significant potential in vaccine delivery, offering a painless alternative to traditional injections, which could improve vaccination rates, especially in needle-phobic individuals. By enabling the delivery of vaccines and other biologics through the skin, hydrogel MNs could improve access to healthcare, especially in regions with limited resources. Despite these exciting advancements,

challenges remain. The uniformity and quality control of MNs during production need to be addressed to ensure consistent performance. Additionally, the stability of drugs during encapsulation and release, especially for biologics, requires further research. Finally, rigorous clinical testing and regulatory approval will be necessary to bring hydrogel MNs into mainstream healthcare [100].

Overall, the future of hydrogel MNs is promising, with significant potential to enhance drug delivery, improve patient outcomes, and expand the range of treatable diseases. As material science, fabrication technologies, and DDS continue to evolve, hydrogel MNs are poised to become a key tool in the advancement of minimally invasive therapies. By addressing current challenges and exploring new possibilities, hydrogel MNs have the potential to revolutionize the way we treat diseases and manage patient care [101].

Conclusion

Recent years have seen impressive developments in hydrogel MNs, fueled by improvements in drug delivery systems, manufacturing methods, and materials. The performance of MNs has been greatly improved by the addition of biocompatible hydrogels such polyvinyl alcohol (PVA), gelatin, hyaluronic acid, and chitosan, which makes them a practical solution for a variety of medical applications. These materials provide the necessary mechanical strength, biocompatibility, and biodegradability required for efficient drug delivery. Moreover, the exploration of stimuli-responsive hydrogels has expanded the potential for more personalized and controlled drug release, making it possible to target specific tissues or conditions. The use of composite materials, combining natural and synthetic polymers, further improves the functionality of hydrogel MNs, offering enhanced drug encapsulation capacity and greater mechanical stability. Hydrogel MNs have the potential to have a significant influence on healthcare worldwide. By offering a painless, minimally intrusive substitute for conventional drug administration techniques including oral medicines and hypodermic injections, hydrogel MNs offer a solution that can improve patient compliance, particularly in needle-phobic individuals and children. This technology has the capacity to enhance drug delivery for both small molecules and biologics, including vaccines, proteins, and peptides. In areas with limited access to healthcare, the ease of use and cost-effectiveness of hydrogel MNs could revolutionize the distribution of vaccines, enabling efficient immunization campaigns. Furthermore, by enabling regulated and prolonged drug release over time and eliminating the need for regular dosage, hydrogel MNs have the potential to revolutionize the treatment of chronic illnesses and enhancing therapeutic outcomes. While the progress made in hydrogel MN technology is promising, challenges remain. Issues such as ensuring the stability of drugs during encapsulation and release, achieving consistent fabrication quality, and meeting regulatory standards will need to be addressed. Continued interdisciplinary research, combining material science, engineering, pharmacology, and clinical expertise, is essential for overcoming these hurdles. Future advancements in hydrogel MN technology hold great promise in revolutionizing drug and vaccine delivery, ultimately improving patient outcomes and global healthcare accessibility. Hydrogel MNs have the potential to be a key component of contemporary medical therapies with more study and advancement.

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Author Contributions

B.P. conceptualized the review, wrote the manuscript, and reviewed the final draft. **P.S.J.** contributed to the literature review, provided valuable feedback, and edited the manuscript. Both authors approved the final version of the manuscript.

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The authors declare that there is no conflict of interest.

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