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COMPREHENSIVE REVIEW: MICRONEEDLE PATCHES - A PAINLESS REVOLUTION IN TRANSDERMAL DRUG DELIVERY

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ABSTRACT

Microneedles are distributed into several types similar as solid microneedle, carpeted microneedle, concave microneedle, dissolvable microneedle, hydrogel microneedle, swellable microneedle, and pervious microneedle. Microneedles can be made of different accoutrements, and may vary in size and forms. They may also vary in design depending on composition, manufacturing process and area of operation. Silicon, polymers, coating accoutrements, biodegradable accoutrements, several crosslinking ways and biosensing bias are used to fabricate microneedles. The new drug delivery method based on Microneedle (MN) technology provides a painless way to administer medications through the skin while bypassing traditional drug administration methods. The skin microchannels created by MNs enable drug and vaccine and biomolecule delivery with minimal discomfort. The paper examines microneedle technology through its classification systems and production methods and current scientific developments. The paper includes experimental data and results and analysis and future research directions. The creation of microneedle patches will change how drugs are given with improving delivery effectiveness, treatment safety and patient compliance.

KEYWORDS: Microneedles, transdermal delivery, dissolving microneedles, fabrication techniques, drug delivery.

1. INTRODUCTION

Drug delivery systems are crucial for the safety, effectiveness, and success of pharmaceutical products. Traditional methods of drug administration, like oral, parenteral, and topical delivery, have been used in clinical settings for many years. However, these standard approaches have several limitations that can reduce treatment effectiveness. Oral drug delivery often suffers from low bioavailability due to first-pass metabolism, enzymatic breakdown, and varying absorption in the gastrointestinal tract. Parenteral administration offers quick therapeutic action but is invasive, painful, and requires trained healthcare professionals, which can lower patient compliance and increase the risk of infections. Topical drug delivery systems tend to be safer but are hindered by the skin's barrier properties.

Transdermal drug delivery systems have emerged as an alternative to address the challenges associated with these traditional methods. Transdermal systems provide benefits such as avoiding first-pass metabolism, controlled drug release, better bioavailability, and improved patient compliance. Despite these advantages, conventional transdermal patches can only be used with a limited number of drugs. The stratum corneum, the outer layer of the skin, creates a major barrier, making it hard for hydrophilic drugs, macromolecules, peptides, proteins, and vaccines to penetrate.

Microneedle technology has attracted significant attention as a creative and minimally invasive method to improve transdermal drug delivery. Microneedles are tiny needle-like structures, usually between 50 and 1500 micrometers long, designed to pierce the stratum corneum without triggering pain receptors or harming

blood vessels. These microstructures create temporary microchannels in the skin, which helps transport drugs efficiently into the epidermal and dermal layers while keeping the skin intact.

Microneedle-based drug delivery systems bring together the benefits of hypodermic injections and transdermal patches while reducing their drawbacks. They allow for painless administration, precise dosing, and enhanced patient acceptance. Based on their design, materials, and drug release methods, microneedles fall into categories such as solid, coated, dissolving, hollow, and hydrogel-forming microneedles. Each type is tailored for specific drugs and therapeutic uses, from small chemical compounds to biologics.

Recent improvements in microneedle manufacturing techniques, including micro-molding, laser micromachining, and additive manufacturing, have sped up their development for clinical use. Microneedle patches have demonstrated promising results in vaccinations, diabetes management, pain relief, skin conditions, and cosmetic uses. Their ability to provide controlled and sustained drug release enhances therapeutic outcomes and lowers systemic side effects.

In conclusion, microneedle technology marks a significant step forward in transdermal drug delivery systems. Ongoing research aimed at optimizing formulations, scaling up production, securing regulatory approval, and assessing clinical use is likely to increase their clinical value and commercial use, making microneedle-based delivery an important option in modern pharmaceutical treatment. Furthermore, microneedle systems facilitate self-administration, reduce medical waste, and improve treatment adherence in chronic illnesses requiring long-term care. Their compatibility with sensitive biomolecules and potential integration with diagnostic sensors further emphasize their future role in personalized medicine. As technology progresses, microneedle platforms are set to change drug delivery and patient-centered healthcare worldwide. These benefits position microneedles as a vital part of next-generation therapeutic systems.[1,2]

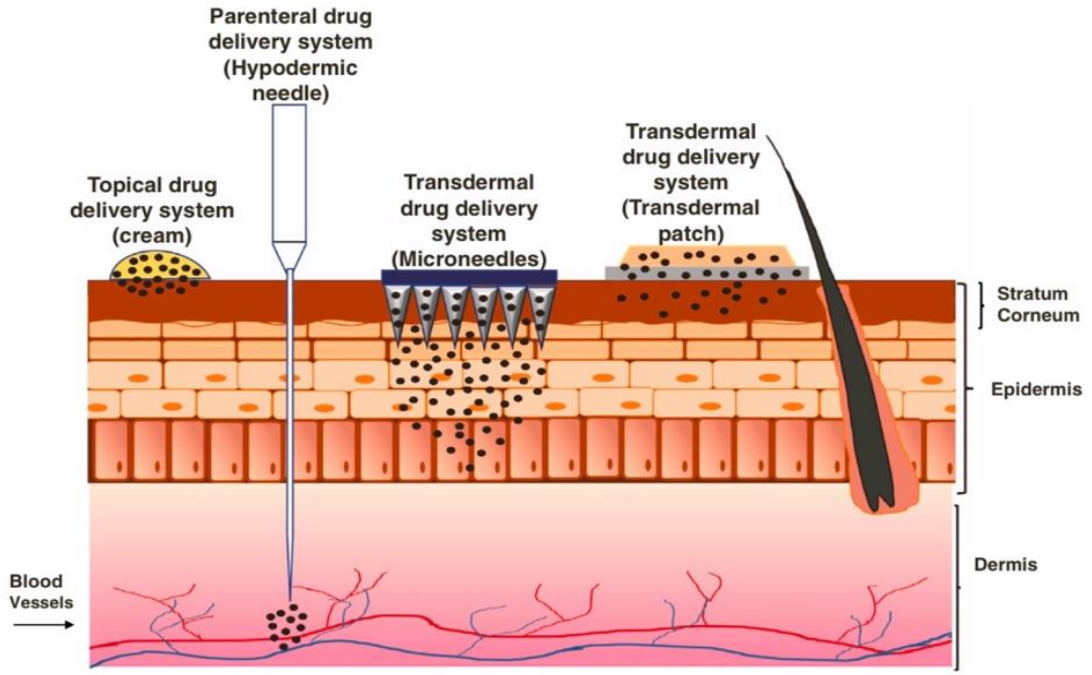

Fig 1: Schematic representation of comparison of topical, parenteral, and transdermal drug delivery systems utilized in the management of pain.

Detailed Drug Release Mechanisms from Different Microneedle Types

Solid Microneedles: The "Poke and Patch" Approach

The "poke and patch" method enables solid microneedles to operate through two distinct stages. The structures make temporary holes in the stratum corneum but they do not carry any drug substances. The microneedles enter the skin at depths between 50-900 μm to break down the barrier before being extracted for drug application to the prepared skin area. The skin microchannels stay accessible for drug penetration during multiple hours after the procedure. The method delivers drugs immediately while protecting unstable medications from degradation during storage.[3-4]

Coated Microneedles: Surface-Based Delivery

The "coat and poke" method of coated microneedles uses drug coating on solid microneedle structures through dip-coating or spray-coating or gas-jet drying processes. The skin penetration of coated microneedles leads to fast drug release from the coating material which dissolves within 2-10 minutes to deliver the drug payload into the dermal tissue. Research on clotrimazole-loaded microneedles showed that drug formulations dissolved in

the coating produced superior antifungal effects than formulations with suspended drugs which proves that drug solubility affects coating performance. The main drawback of coated microneedles exists in their limited drug capacity which reaches 0.1-1 mg per array thus making them appropriate for delivering potent medications in small amounts.[5-7]

Dissolving Microneedles: Integrated Drug-Polymer Systems

Dissolving microneedles are among the most promising designs in clinical settings. They work on a "poke and release" principle, where both the needle structure and the drug dissolve fully in the skin. These microneedles are manufactured from biodegradable plastics like polyvinyl alcohol (PVA), hyaluronic acid (HA), polyvinylpyrrolidone (PVP), and polylactic-co-glycolic acid (PLGA).[8-9]

The dissolution speed is managed through careful choices of polymers and the density of crosslinking. For example, a study on microneedles loaded with ginsenoside Rk3 and metformin showed ultra-long release lasting up to 10 days from a single administration. This was achieved using polydopamine-coated coordination-induced self-assembled nanomedicines. The quickly dissolving tips were made from PVA and PVP, while the backing layer provided structural support and additional therapeutic functions such as moisture retention and free radical scavenging.[10]

Table 1: Types of Microneedles Used in Transdermal Drug Delivery Systems.[7-10]

Type of Microneedle	Material Used	Mechanism of Drug Delivery	Advantages	Limitations
Solid Microneedles	Silicon, metal, polymer	Used to pre-treat the skin by creating microchannels; drug is applied afterward as a patch or cream.	Simple design, reusable molds, stable	Two-step process, limited control over dose
Coated Microneedles	Metal, silicon, polymer	Drug is coated on the surface of microneedles and dissolves rapidly after insertion into the skin.	Rapid drug release, single-step delivery	Limited drug loading, uneven coating possible
Dissolving Microneedles	Biodegradable polymers (e.g., PVP, PVA, CMC, PLGA)	Microneedles dissolve after insertion, releasing the drug into the skin.	No sharp waste, safe and biocompatible	Fragile structure, limited for large molecules
Hollow Microneedles	Silicon, glass, metal	Work like miniature hypodermic needles; drug solution is injected through the hollow bore.	Controlled drug infusion, suitable for liquids	Complex fabrication, risk of clogging
Hydrogel-Forming Microneedles	Cross-linked hydrogels (e.g., PVA, PEG)	Swell upon skin insertion, forming a gel that controls drug release from a reservoir.	Long-term release, reusable patch design	Slower onset, limited for large-volume drugs

Recent innovations include tip-loaded bubble-soluble microneedles. In this design, the drug concentration is focused at the needle tip instead of being spread throughout the entire structure .This approach raises drug use rates above 90% by stopping drug diffusion to the substrate backing. Bubbles formed during production create controlled porosity, improving drug release.[11]

Hollow Microneedles: Direct Infusion Technology

Hollow microneedles operate on a "poke and flow" mechanism. They work similarly to regular hypodermic needles, but on a microscopic scale. These structures have internal channels that allow direct fluid injection into the dermal layers.[12]

Bernoulli's equation and Hagen-Poiseuille law control fluid flow through hollow microneedles, and fluid viscosity, applied pressure, and needle shape all affect flow rates.[13]

When the lumen diameter is between 40 and 100 µm, laminar flow with Reynolds numbers of roughly 3.9 is feasible. Hollow microneedles are suitable for circumstances requiring higher doses or continuous infusion because they can deliver larger drug volumes than other types.[14-15]

Blood backflow, possible clogging by skin tissue, and more intricate manufacturing requirements are obstacles, though.[16]

Hydrogel-Forming Microneedles: Swelling-Based Sustained Delivery

Hydrogel-forming microneedles operate on a special swelling mechanism. The polymer matrix takes in interstitial fluid from the skin, forming continuous channels for two-way transport .After insertion, these microneedles can lead to swell by 185 to 300% of their original volume within few minutes. They keep their shape while enabling sustained drug release.[17-18]

Hydrogel microneedles produce three phases of drug release: an initial burst release, which is usually 20-30% in the first hour; diffusion-controlled release; and in the case of biodegradable materials, degradation-controlled release. The backing layer generally provides a reservoir function for the drug, with formulations encompassing DCTs or hydrogel patches that provide continuous therapeutic levels of drug for extended periods.[19]

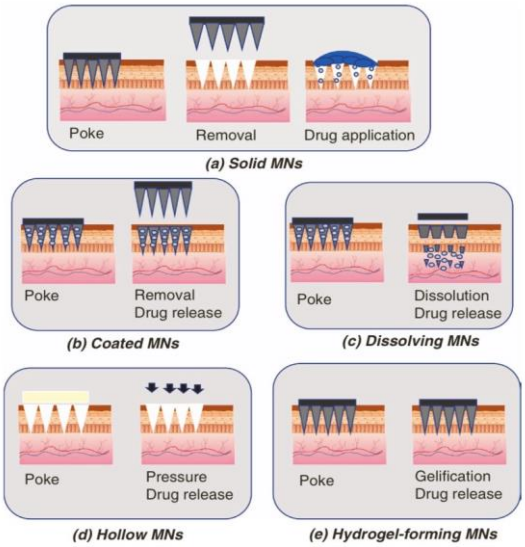

Fig. 2: Mechanisms of drug delivery used by different types of microneedles: (a) Solid MNs (Poke and patch); (b) Coated MNs (Coat and Poke); (c) Dissolving MNs (Poke and dissolve); (d) Hollow MNs (Poke and flow); (e) Hydrogel-forming MNs (Poke and release).

Methotrexate delivery for the treatment of psoriasis was tested in one study. Hydrogel-forming microneedles loaded with nanoparticles provided sustained release for more than a week. This maintained effective therapeutic levels and reduced treatment frequency from daily administration to once every three days. The encapsulation in nanoparticles enhanced stability and provided controlled release and also prevent drug degradation prematurely.[20]

Fabrication materials

Since the semiconductor industry is where microfabrication technology initially emerged, base wafers consisting of silicon, plastic, or glass are commonly used. Many materials, including polymers, silicon, glass, paper, and biological materials can be employed for biological applications as discussed in table 2.

FDA-approved microneedle products and clinical trials: regulatory environment and approval processes.[21]

Table 2: Materials appropriate for microfabrication in biological applications.

SR	Material Type	Examples	Key Properties	Applications
1	**Silicon-based materials**	Silicon (Si), Silicon dioxide (SiO_2), Silicon nitride (Si_3N_4)	High mechanical strength, well-established microfabrication methods, good thermal stability	Microelectromechanical systems (MEMS), biosensors, lab-on-a-chip devices
2	**Polymers**	PDMS (Polydimethylsiloxane), PMMA (Polymethyl methacrylate), SU-8, PEG	Flexible, transparent, biocompatible, easy to mold or cast	Microfluidic chips, cell culture platforms, soft lithography
	Glass	Borosilicate glass, Fused silica	Chemically inert, transparent, thermally stable, biocompatible	Optical detection systems, microfluidic devices, biosensors
	Metals	Gold (Au), Platinum (Pt), Titanium (Ti), Aluminum(Al)	High electrical and thermal conductivity, biocompatible (for some metals)	Electrodes, conductive layers, biosensing elements
	Paper-based materials	Cellulose paper, nitrocellulose	Low-cost, biodegradable, capillary-driven fluid flow	Paper-based microfluidics, point-of-care diagnostics
	Biological materials	Gelatin, Collagen, Chitosan, Alginate	Biocompatible, biodegradable, support for cell growth	Tissue engineering scaffolds, biosensors, bio-MEMS

Products based on microneedles are classified as combination devices by the FDA

As a result, it requires very thorough sterility, stability, safety, and performance testing. Generally, the regulatory pathway includes preclinical studies followed by Phase I-III clinical trials that demonstrate safety and effectiveness. To date, several microneedle products have completed this process to reach the market.[22]

Commercial Microneedle Products

The commercial market for microneedles has grown significantly. It now spans cosmetic, therapeutic, and diagnostic applications. A number of products have been

successfully launched following thorough clinical validation, though specifics of some FDA approvals are still confidential.

Cosmetic Applications: The safety and efficacy of microneedle patches for skin brightening were established in a randomized, split-face clinical study involving thirty-four Korean women. After four and eight weeks, the study's measurements of skin brightness and melanin levels showed notable improvements. There were no negative side effects and participants saw moderate cosmetic results.[23]

Diabetes Management: Clinical efforts for glucose-responsive insulin delivery systems have shown promise. In vivo studies in rats indicated that microneedle patches maintained therapeutic insulin levels for 5 days. This duration is considerably longer compared to 48 hours of observation following oral administration. Dissolving microneedles reached their peak of 511.00 ± 277.24 ng/mL at 4 hours compared to hydrogel-forming microneedles, which reached a peak of 328.30 ± 98.04 ng/mL at 24 h.[24]

Pain Management: Pramipexole was investigated for Parkinson's disease treatment by transdermal delivery. The drug was successfully delivered by the microneedle systems, maintaining plasma levels that may reduce dosing frequency and enhance patient compliance.[24]

Vaccine Delivery: Studies have demonstrated that microneedle vaccine delivery techniques improve the immune response while lowering dosage. This suggests that a smaller dose of the vaccine may be needed to attain the same or greater level of effectiveness.[25]

Rheumatoid Arthritis: Rheumatoid Arthritis: Dissolved microneedles loaded with methotrexate showed definite advantages over traditional methods in clinical trials. According to animal tests, the patches provided a sustained release of the drug for seven days and significantly decreased inflammatory markers like TNF-α and IL-1β. They also showed greater tissue-sparing properties than methotrexate cream at the same dosage.[26]

Standards and Regulatory Difficulties: Microneedle product are constantly evolving, with new guidelines being.

Efficacy Standards: To demonstrate that treatments are as effective as or more effective than those that are currently on the market, closely monitored clinical trials must be conducted.

Quality Control: This focuses on developing manufacturing standards to ensure consistent microneedle shape, uniform drug loading, and sterility.[27]

Manufacturing Techniques and Scalability Analysis

Typical fabrication techniques consist of: The most popular technique for creating polymeric microneedles is micromolding technology. It entails centrifugation, drying, and removal after casting polymer solutions into exact molds .This method can achieve high-volume production with great consistency; however, it usually requires a significant initial investment in equipment.[28]

Laser Micromachining: The laser techniques apply focused beams for material removal from substrates to build microneedles with high precision, as mentioned by ref. This process offers maskless fabrication and rapid prototyping. However, the scaling up of this process is limited due to its sequential processing nature, according to ref.[29]

Microelectromechanical Systems

The method for making MEMS uses semiconductor processes. These include photolithography, deep reactive ion etching, and wet and dry etching to create silicon or metal microneedles. Despite its ability to control dimensions with sub-micron accuracy, MEMS is not widely used due to its high cost and complexity.[30-31]

New Developments in Manufacturing: Additive Manufacturing/3D Printing: These techniques have changed how we produce microneedles.

They allow for fast and customized fabrication without the need for costly molds. Many of the following techniques show particular promise.

Continuous Liquid Interface Production (CLIP): This technique can create single-step formation of microneedle arrays in less than 10 minutes per patch. This is enabled by the oxygen-inhibited photopolymerization to produce sharp tips down to 5 μm resolution. CLIP technology is far more precise in comparison to conventional methods of 3D printing.[32]

Stereolithography: The development of low-cost desktop SLA printers has led to the fabrication of microneedle master molds utilizing a "Print & Fill" method. This two-step process prints high-aspect-ratio needles in basins and subsequently backfills and cures to reveal sub-millimeter microneedles. Studies have achieved tip radii of 20-40 μm, smaller than the specified printer resolution of 50 μm.

DLP: The DLP (Digital Light Processing) printing technique uses digital micromirror devices to project light patterns, which allows for rapid curing of entire layers of microneedles simultaneously. Custom MATLAB code controls the grayscale of the individual micromirrors to enhance needle tip sharpness and precision, yielding tip radii of about 15 μm in 30 minutes per patch. Electrospinning and Bioprinting represent novel techniques creating complex structures with added functionalities.[33]

Scalability Challenges and Solutions

Manufacturing Output: The achievement of large-scale productions (>1 million patches/day) can only be ensured by the focus on cycle times and the ability to process in parallel. Of the technologies investigated, injection molding and hot embossing have the most promise for high throughput, with cycle times less than 60 s per array.[34-35]

Quality Assurance: Maintaining consistent dimensions, strength, and drug loading of micronees in large batches has to be ensured with adequate quality control systems. Machine vision-based automated inspection and statistical process control will help in spotting defects and ensuring standards.

Advanced Biosensing and Diagnostic Uses

Biosensor Platforms Integrated into Microneedles

A new generation of platforms for therapeutic monitoring and minimally invasive diagnostics has been created by combining the microneedle concept with biosensing technologies. These devices combine the analytical accuracy of electrochemical, optical, or acoustic sensors with the skin-penetrating potential of microneedles.[36]

Systems for Monitoring Blood Sugar:-One of the most advantageous uses of microneedle-based biosensors is continuous glucose monitoring. These systems make it possible to sample interstitial fluid and monitor blood glucose in real time. With a time delay of roughly 5 to 15 minutes, this closely resembles blood glucose. Enzyme-based electrochemical sensors that embed glucose oxidase or glucose dehydrogenase in hydrogel-forming microneedles have been a recent development in this field. When in use, these microneedles absorb interstitial.[37]

In use, such microneedles soak up interstitial fluid, which brings glucose into contact with an enzyme for a catalytic reaction. The electrical signal resulting from this reaction is proportional to the glucose level, hence enabling continuous monitoring over long periods.[38]

Glucose responsive microneedle patches take this a step further by the integration of sensing with drug delivery. Such smart systems employ glucose oxidase to catalyze glucose oxidation to gluconic acid, which lowers the local pH. This pH change triggers the release of insulin from pH-sensitive vesicles or nanoparticles within the microneedle. This presents a closed loop system in mimicry of pancreatic function.[39]

Biomarker Detection for Disease Diagnosis

Microneedle biosensors detect a wide range of biomarkers crucial for diagnosing and monitoring diseases.

Biomarkers of Cancer: Carcinoembryonic antigen (CEA) has been detected with the use of immunoassay-based microneedle sensors. Antibodies fixed on the surface of a microneedle specifically bind to CEA in interstitial fluid samples. Quantitative measurements from the electrochemical readout are suitable for cancer screening and monitoring treatment response.

Neurological Disorder Monitorin: Neurological Disorder Monitoring: Microneedle biosensors can measure drug levels and dopamine metabolite amounts in Parkinson's disease treatment. This approach enables personalized dosing according to each patient's individual needs.[40]

Therapeutic Drug Monitoring

A wearable microneedle-based array patch has been developed for continuous electrochemical monitoring and on-demand drug delivery of methotrexate. The system operates linearly from 25-400 μM, fitting within the therapeutic range for high-dose cancer treatment and providing excellent continuous operation over two days . Iontophoretic hollow microneedle arrays, having both anode and cathode electrodes, can concurrently perform transdermal on-demand drug delivery with real-time monitoring .This represents a significant step toward the development of closed-loop therapeutic systems in which drug administration varies dynamically according to the measured concentrations and biomarker response.[41]

Power Sources for Wearable Biosensors

Sustainable power generation is a prerequisite for the long-term operation of wearable biosensors. Examples of new solutions include.

Triboelectric nanogenerators, which convert the mechanical motion from body movement into electrical energy to provide intermittent power for sensors.

Systems based on piezoelectric materials, whose mechanical deformations are used to generate electric energy owing to an external mechanical action, as by walking or other activities.

- Biofuel Cells: The fuel used in these cells is glucose or lactate from the interstitial fluid and continuous power is generated while consuming the analytes of interest.

Integration of IoT and Artificial Intelligence

The incorporation of microneedle biosensors into AI and IoT technologies is a key component of their future. Complex patterns from biosensors can be interpreted by machine learning algorithms to improve treatment plans, anticipate the course of disease, and provide early warnings of unfavorable events. Cloud-based data storage increases access to advanced diagnostics in underserved or remote areas by enabling telemedicine consultations and tracking over time.[42]

Prospects for the Future and Upcoming Difficulties

Material Innovation

In the future, the development of microneedles would be done with biodegradable materials possessing enhanced mechanical properties. Further studies will be performed

on bio-inspired geometries, such as those taken from caterpillar spines, which have developed an optimal geometry through evolution. Drug release can be precisely controlled to meet the needs of each patient thanks to new polymers that contain elements sensitive to variations in pH, temperature, light, or a magnetic field.[43-44]

Applications of Personalized Medicine Additive manufacturing technologies make it possible to fabricate patient-specific microneedle designs that fit the anatomy, disease state, and drug absorption profiles of each individual. Optimizing microneedle size, drug loading, and release rates for better therapeutic results may be possible with digital platforms that combine patient data with computational modeling.[45-46]

Expansion to Non-Transdermal Applications While current research focuses on transdermal delivery, microneedles are also being adapted for new anatomical sites, including the oral mucosa, eye tissues, gastrointestinal tract, and cardiovascular applications. Each target tissue presents unique challenges that require specially designed microneedles and materials.[47]

Harmonization of regulatory requirements International collaboration on the development of uniform regulatory frameworks will promote market access and faster clinical translation.

Product development costs will be reduced and development cycles will be accelerated by standardizing testing parameters, quality standards, and regulatory approval procedures unique to microneedle devices.[48]

Sustainability of the Environment It is possible to create biodegradable microneedle materials that dissolve or break down into non-toxic byproducts. These energy-efficient, renewable resource-based, sustainable manufacturing techniques align with pharmaceutical manufacturing's larger sustainability objective.[49]

SUMMARY

Microneedle technology has evolved from its initial concept stage into a medical-ready platform which now includes multiple commercial products and active clinical studies. The different microneedle types including solid and coated and dissolving and hollow and hydrogel-forming provide unique drug release methods for various therapeutic applications. Multiple disease states show safety and effectiveness through clinical evidence which has led to FDA approval and market authorization for several products. The development of additive manufacturing techniques has reduced production expenses while enabling quick prototype creation but big-scale manufacturing remains difficult to achieve. The integration of biosensing technologies with microneedles creates new theranostic systems which unite diagnostic and therapeutic functions into single devices.

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