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Biomedical Applications for Microneedles

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ABSTRACT: The microneedle was developed in 1976 as a drug delivery method that was painless and minimally invasive. With continuous mechanical progressions, microneedles now come in different shapes (cone and pyramid) and structures (strong, drug-covered, empty, dissolvable, and hydrogel-based). This survey dives into the biomedical uses of microneedles, starting with a short prologue to their orders and assembling processes, stressing the benefits and creation techniques for various sorts. Ensuing segments give an outline of microneedle applications in biomedical treatment, covering drug conveyance frameworks, illness diagnostics, wound fix, and disease treatment. The review comes to a close by discussing safety concerns and microneedle prospects for the future.

I. INTRODUCTION:

The distress related with conventional infusions hampers patient adherence, while oral organization is helpful however restricted by the first-pass impact. Microneedles offer an original arrangement by truly infiltrating the skin's external layer, making channels for productive medication dissemination. These microneedles, going from 25 to 2000 µm, can be utilized for transdermal and non-transdermal medication conveyance without harming brain tissue. In transdermal applications, microneedles make injections less painful and allow for continuous drug administration, which is especially helpful for insulin-dependent diabetics. Non-transdermal purposes incorporate buccal mucosa and uncovered tissues like eyeballs and vascular tissue. The improvement of microneedles traces all the way back to 1976, building up momentum in 1998 for transdermal medication conveyance. A flood in research, with 3407 articles beginning around 2000, mirrors the developing interest in microneedles, principally in biomedical fields like malignant growth treatment, skin sickness therapy, diabetes the executives, blood glucose identification, and immunizations. This survey centers around microneedle order, producing, biomedical applications, and addresses possible entanglements. Optimizing fabrication techniques and addressing limitations in subsequent studies are the keys to the promising future of microneedle administration.

The Manufacture of Microneedles :

Microneedles, made out of silicon, metals, and polymers, present different manufacture difficulties. Silicon, while handily molded, is inclined to break and requests a spotless climate, prompting high assembling costs. Metals, however less exorbitant, produce squander and biohazardous materials. Polymers, with high consistency and crack opposition, are biocompatible and reasonable for practical large scale manufacturing. Normal materials incorporate carboxymethyl cellulose (CMC), PVA, polyvinylpyrrolidone (PVP), poly(lactic-co-glycolic corrosive) (PLGA), hyaluronic corrosive (HA), and methacrylated hyaluronic corrosive (MeHA). Scientists have effectively integrated drugs like rapamycin into PVP microneedles, featuring amazing biocompatibility. Also, MeHAmicroneedles showed controlled debasement and improved cell movement in contrast with controls.

This outline principally centers around polymer-based assembling techniques, like drawing lithography and micromolding. Drawing lithography includes extending polymer on a substrate, framing microneedles through boosts like intensity, electric fields, attractive fields, or radial power. Shape helpedtechniques use intensity or bright (UV) light for crosslinking. Three-layered (3D) printing, including virtual plan with computer aided design programming and resulting creation utilizing a 3D printer, offers high-throughput creation with accuracy and reproducibility.

Drawing lithography is a process that uses the glass transition of a viscous polymer to create a 3D microstructure for manufacturing. It involves vertically stretching biodegradable poly(lactic-co-glycolic acid) (PLGA) through thermal drawing, adjusting the shape by varying temperature and fracture speed. Magnetorheological lithography creates a flexible microneedle arrayfrom curable

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magnetorheological fluid on a flexible substrate. Micromolding requires a mold with specific specifications, using techniques like UV light exposure, casting, and coating. Careful consideration of solution viscosity is crucial to avoid issues like bubble formation or overly thin microneedles. Three-dimensional printing offers high accuracy, flexibility, and fewer manufacturing steps, with techniques like 3D projection inkjet, fused deposition molding, stereolithography, and laser-assisted bioprinting.

Applications:

Since 1976, microneedles have been extensively researched in biomedicine, with applications in transdermal drug delivery, treating medical conditions like acne, diabetes, and tumors. They are also used in biosensors for extracting and analyzing interstitial fluid and blood, contributing to skin melanoma screening. This review focuses on microneedle applications in skin wound therapy, diabetes treatment, vaccines, and sensors, analyzing 978 articles published since 2011. The research output has shown a steady increase in recent years, showcasing the increasing interest in these applications.

Acne repair: Acne, a common skin condition, involves heightened collagenase during local skin inflammation, resulting in collagen loss and atrophic scars. Diverse treatments such as laser therapy and adjustable microneedle tips are employed to induce controlled micro-injuries, triggering growth factors and collagen production for skin repair. Camirand and Doucet pioneered microneedle use for acne scars, and innovations like Zhang et al.'s poly(ionic liquid)-MN patch with salicylic acid effectively inhibit inflammatory factors. Novel approaches, like DL-MN patches and microneedles loaded with substances such as black phosphorus quantum dots, show promise in wound healing. Microneedles also serve as delivery methods for various substances, addressing conditions like acne, diabetes, and tumors. Moreover, microneedle-based biosensors are emerging for diagnostics.

In diabetes: Diabetes, affecting over 425 million people globally, is typically managed through frequent insulin injections, presenting challenges like long-term complications, poor compliance, and the risk of insulin overdose. Addressing these issues is crucial, leading to a demand for a painless, noninvasive, and self-administered method with adaptable dosing. Microneedles, serving as a transdermal drug delivery system, provide a solution by avoiding gastrointestinal issues associated with oral delivery. Researchers, including Migdadi et al., have devised hydrogel-based microneedles for sustained metformin delivery, mitigating gastrointestinal side effects. Innovative devices like the glucose-responsive insulin patch by Yu et al. utilize microneedle arrays for painless administration and controlled insulin release triggered by enzymatic reactions in response to hyperglycemia. Ye et al. utilized microneedles for glucose-sensitive adjustments, regulating insulin secretion by pancreatic β-cells. Zeng et al. introduced minimally invasive GCC MNs for colorimetric glucose monitoring. While solid, dissolvable, and drug-coated microneedles have limitations, hollow microneedles have demonstrated effectiveness in delivering rapid insulin doses to type I diabetes patients. Lee et al. showcased microneedles' potential for steady blood glucose management, akin to traditional hypodermic needles, in both type II diabetes patients and healthy adults.

For cancer treatment: Microneedles loaded with nanoparticles offer a promising approach for the treatment of superficial tumors. Su and colleagues initially reported the use of microneedles loaded with pH-responsive tumor-targeted lipid-coated cisplatin nanoparticles. Building on this, they explored an innovative microneedle strategy for synergistic immuno-chemotherapy, combining antibodies against programmed cell death protein 1 with cisplatin-diammineplatinum-loaded nanoparticles (aPD-1/CDDP@NPs). Remarkably, these microneedles demonstrated increased response rates in mouse models of squamous-cell carcinoma, showcasing their potential efficacy in cancer treatment.

Similarly, Yang et al. introduced a strategic method employing microneedles for topical and targeted photothermal therapy (PTT). In this approach, indocyanine green encapsulated in chitosan nanoparticles was placed on the microneedle's tip. When coupled with Near Infrared (NIR) irradiation, this system effectively inhibited early melanoma growth by destroying a significant portion of tumor cells. Furthermore, when combined with chitosan microneedles loaded with antiprogrammed death-ligand 1 and indoleamine 2,3-dioxygenase inhibitor indoximod (aPD-L1/1-MT CSMNs), complete inhibition of tumor growth was achieved within a remarkably short period of 10 days. This underscores the potential of microneedles in offering targeted and effective therapies for cancer treatment.

Vaccine:Certain vaccines undergo processes like lyophilization, dilution, and multiple injections, leading to heightened costs, increased waste, and potential contamination during transport and storage. Microneedles provide a solution to these challenges by reducing costs, minimizing waste, and offering sustained administration, thereby promoting a stronger immune response. Sullivan Sean P and colleagues employed dissolvable microneedles for influenza vaccination in model mice, noting improvements in lung IgA titers, cellular immune responses, and antibody-secreting cells, leading to more effective virus clearance. McHugh et al. utilized dissolvable microneedles embedded with microparticles containing near-infrared quantum dots for rat identification.

Microneedles also find application in AIDS prevention and treatment, facilitating the delivery of vaccines and antiretroviral drugs due to their convenience and potential for eliciting higher antibody levels. Boopathy et al. designed microneedles incorporating the antigen ovalbumin (OVA) in regenerated silk fibroin protein with a dissolving PAA polymer backing. This design achieved significantly higher antibody titers compared to equivalent intradermal injections. In response to the COVID-19 pandemic, Kim et al. treated COVID-19 mice with a recombinant SARS-CoV-2 S1 vaccine using dissolvable microneedles, demonstrating a robust antigen-specific antibody response. Additionally, Niu et al. utilized hollow microneedles for transdermal administration of model antigen OVA and Toll-like receptor agonists, showing enhanced immune responses compared to conventional subcutaneous injection. This underscores the superior targeting and therapeutic effects of microneedles with nanoparticles for drug delivery compared to traditional vaccines.

Other applications:

Pain therapy involves the use of lidocaine, a local anesthetic, to manage procedural pain. Kathuria et al. developed a microneedle loaded with lidocaine to alleviate acute and chronic injection-related pain. Xie et al. used dissolvable microneedles containing anti-CGRP peptides to address chronic nerve pain from post-traumatic inflammation. Caffarel-Salvador et al. delivered human insulin and hGH to the buccal mucosa using dissolvable microneedles, significantly reducing pain. Ma et al. coated microneedles with doxorubicin (DOX) to prevent DOX leakage, resulting in fewer side effects compared to traditional injections.

Eye therapy uses microneedles for their minimally invasive nature and enhanced ocular bioavailability. Patel et al. used hollow microneedles to deliver particles loaded with sulforhodamine B into the suprachoroidal part of pig, rabbit, and human cadaver eyes. Roy et al. designed a PVA-PVP patch combining contact lenses and microneedles, loaded with pilocarpine hydrochloride. Comparison with a pilocarpine solution in removed human corneas revealed superior release and retention capabilities in microneedles compared to the solution form of pilocarpine.

II. CONCLUSIONS:

Over the past 40 years, various techniques and materials have been used to create microneedles for improved transdermal medication delivery. Materials have evolved from metals to silicon and polymers, and techniques like lithography, micromolds, and 3D printing have become more adaptable and effective. 3D printing, though cost-effective, is not widely used due to its complexity. Different types of microneedles are suitable for different medications and can also be used to distinguish biomarkers like blood glucose. Microneedles can be further developed to create a strong connection between drugs and the human body. However, successful microneedle patches in animal models should be tested in clinical preliminaries to ensure their effectiveness in humans.

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