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REVIEW ARTICLE

A Comprehensive Review on Microneedles

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Abstract: In recent years, a paradigm-shifting transdermal delivery technology has garnered significant attention for its efficacy in facilitating the dispersion of therapeutic and cosmeceutical agents across diverse applications, encompassing vaccines, pharmaceuticals, and biomolecules targeting cutaneous afflictions. Transdermal drug delivery (TDD) stands out for its manifold advantages, primarily characterized by its capability to sustain protracted drug release, thereby achieving optimal blood concentrations. Regrettably, the formidable stratum corneum (SC), an effective natural barrier, constrains TDD to specific drug types possessing requisite properties. To surmount this impediment and augment transdermal drug delivery, the innovative application of microneedles has been propounded. Microneedles, comprising micron-scale needles, offer a minimally invasive means to traverse the subcutaneous barrier, enabling the painless administration of a diverse spectrum of low molecular weight drugs, biotherapeutics, and vaccines. Notably, hollow microneedles find widespread clinical utilization for Influenza vaccination, while solid microneedle products have gained traction in cosmetic applications. Beyond dermatological contexts, microneedles have demonstrated adaptability for the delivery of bioactive substances not only into the skin but also into the ocular region and cellular environments. This comprehensive review provides a brief of this transformative technology at the intersection of biomedical science and transdermal therapeutics.

Keywords: Microneedles; Transdermal drug delivery; Vaccines; Biomolecules; Painless drug delivery

1. Introduction

Oral administration stands as a ubiquitous and conventional method for drug delivery, widely adopted for its ease of use. However, its efficacy is hampered in certain cases by the inherent limitations associated with poor drug absorption or enzymatic breakdown within the complex milieu of the liver or gastrointestinal system. The conventional recourse to this challenge has been hypodermic needle injections, a practice that has seen widespread adoption over the past century. Despite its historical prevalence, hypodermic needle injections pose multifaceted challenges. This includes the necessity for specialized training to administer injections accurately, the potential for pain and invasiveness, and the concomitant generation of sharp and biohazardous wastes, adding logistical complexities to their use [1,2]. Moreover, in the specific context of vaccine distribution, hypodermic needle injections into muscle tissue present additional drawbacks. The immune response elicited in muscle tissue is comparatively weaker than that attainable through skin-based delivery, complicating the effectiveness of vaccination strategies. In response to these challenges, transdermal drug delivery (TDD) emerges as a compelling and innovative alternative. TDD offers a range of advantages, including the circumvention of hepatic first-pass metabolism, thereby enhancing the bioavailability of drugs. Furthermore, TDD enables self-administration, representing a paradigm shift towards a non-invasive and painless mode of drug delivery [3]. It is within this context that this review article embarks on a comprehensive exploration of the pivotal role played by microneedles in revolutionizing drug delivery methodologies.

Microneedles, spanning a length range of 25 to 2000µm, represent a transformative technology that creates direct conduits for drug diffusion. This is achieved by physically penetrating the stratum corneum, the outermost layer of the skin, and generating micropores of dimensions larger than those requisite for macromolecular medications. Employing optimal size and design of these microneedles allows for precise control over drug delivery parameters, presenting a versatile platform for enhancing therapeutic outcomes. Hollow microneedles, when loaded with medications, enable direct injection into the circulatory system [4,5]. Moreover, microneedles facilitate both transdermal and non-transdermal medication delivery, eliminating injection pain and improving patient compliance. The intradermal route, characterized by conical, pyramidal, multidimensional, or micron-sized piercing protrusions, overcomes the limitations of traditional approaches. By temporarily opening channels in the skin's outer layer, microneedles facilitate the distribution of therapeutic chemicals that would otherwise be challenging via the transdermal route. Importantly, the painless nature of microneedle application enhances patient compliance, making it particularly advantageous for individuals with needle phobia (trypanophobia) [6,7]. The primary objective of this comprehensive review is to provide an in-depth analysis of microneedles, encompassing their types, materials, fabrication techniques, applications, and role in advancing drug delivery across various medical domains.

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2. Background

The idea of microneedles has changed over time, moving from the use of big needles to the contemporary designs. German dermatologist Dr. Ernst Kromayer used motor-powered dental burs in various sizes to treat skin conditions such as hyperpigmentation and scarring in 1905. Injection drug delivery into the stratum corneum started to get interest in the 1960s. The microneedle idea was then presented in the 1970s, but it wasn't until the 1990s that this idea was empirically proven. The first transdermal system was licenced in 1979 and was used to treat motion sickness by putting a three-day patch containing scopolamine [8]. 1994 saw Orentreich carried out a subcision procedure in which he punctured the skin with a tri-beveled hypodermic needle to liberate fibrous strands. The epidermal abnormalities under the skin's surface that caused wrinkles and depressed scars were the focus of this surgery. In 1998, the first transdermal microneedle was proposed and made from silicon wafers using photolithography and ion etching. The usage of microfabricated microneedles to improve medication delivery through the skin was discussed in the study. This work sparked a lot of research in the field of microneedles. First, use of a dissolvable microneedle for TDD appeared in 2005. As of now, 43 clinical trials have been completed with microneedles. The first microneedle clinical trial was finished in 2007 [9,10].

3. Advantages and disadvantages of using microneedles

The advantages of using microneedles include:

(1) The ability to administer large molecules;
(2) The painless administration of the active pharmaceutical ingredient;
(3) The avoidance of first-pass metabolism;
(4) Faster injection site healing compared to using a hypodermic needle;
(5) The absence of needle phobia; only punctures the needle [5].

The disadvantage of microneedles are:

(1) Precision in dosage administration might be diminished compared to the accuracy achieved with hypodermic needles.
(2) The device demands cautious handling to avoid particles rebounding from the skin's surface; improper orientation, not held vertically, may lead to dose leakage or uneven penetration into the skin.
(3) Variability in the thickness of the stratum corneum and other skin layers among individuals can influence the extent of particle penetration.
(4) External factors, such as skin moisture, may have an impact on deliver
(5) Repeated injections may cause the veins to collapse
(6) When the patch is removed, the microneedle tip may break off and stay in the skin [5].

4. Classification of microneedles

4.1 Solid Microneedles

Passive diffusion was performed by solid microneedles for medication delivery by making microchannels to improve skin permeability and then applying a patch filled with drugs on the channels. Solid microneedles made of polymer, metal, and silicon. Polymers can be used to create solid microneedles. Yadav et al. used the micromolding approach to create microneedles from biopolymer films that were taken from tilapia (*Oreochromiss* sp.) fish scales [2].

4.2 Hollow Microneedles

Hollow MN have been made utilizing ceramics, metal, silicon, and glass, integrating a hole on the needle tip with an empty cavity inside each needle. When compared to solid, coated, and dissolving MN arrays, the primary benefits of this kind of MN are its increased drug delivery capacity. They also show a high degree of rigidity as a result of the materials employed in their construction. Limitations include the observed clogging of needle tips' bores by skin tissue during insertion [11].

4.3 Coated Microneedles

A coated microneedle is made up of a solid film that contains the active ingredient and water-soluble inactive excipients, coated over a sharp, solid-core microneedle structure. The interstitial fluid that exists in the tissue is encountered by a drug-coated microneedle when it is put into the skin. The microneedle coating's water-soluble excipients are dissolved in contact with this watery solution, which in turn starts the coating's separation from the microneedle surface. The coating can separate in a matter of seconds to minutes, depending on how aqueously soluble the coating excipients are. Before microneedles are extracted from the skin, the coating just needs to separate from the surface of the needles; the residual material can dissolve completely over time [12,13].

4.4 Dissolving microneedles

Dissolving microneedles (DMs) are crafted from water-soluble components, including maltose, polyvinylpyrrolidone, chondroitin sulfate, dextran, hyaluronic acid, and albumin. When applied to the skin using a finger, these microneedles facilitate the absorption of medication molecules into the skin. Importantly, after use, they completely dissolve within the skin, eliminating any concerns about the presence of biohazardous sharp tips. This dissolution is attributed to the composition of DMs, which consist of biocompatible and water-soluble ingredients such as sugars and cellulose derivatives. Upon penetrating biological tissues, DMs often soften and dissolve, minimizing harm from the mechanical forces involved in application. Dissolving microneedles are therefore more beneficial than silicon and metal needles. Microneedles made of metal and silicon can break *in vivo* barriers to release the drug in the targeted sites [14,15].

4.5 Hydrogel-Forming microneedles

To produce hydrogel molds, substances like acrylamide, N-isopropylacrylamide, or methacrylated HA are initially introduced into the hydrogel to induce polymerization. The resulting fluid mixture is then injected into a microneedle (MN) mold, allowed to undergo curing, and subsequently the mold is removed and preserved through the process of drying. The objective of hydrogel gelation is to create a hydrophilic polymer network that possesses the capacity to absorb water and swell, features a porous structure to encapsulate active agents like drugs, maintains a solid state to minimize drug loss during transportation, and facilitates targeted drug delivery to specific anatomical locations or tissue types. This goal is achieved through various mechanisms, including the physical cross-linking of polymer chains, electrostatic interactions, and covalent chemical cross-linking [16]

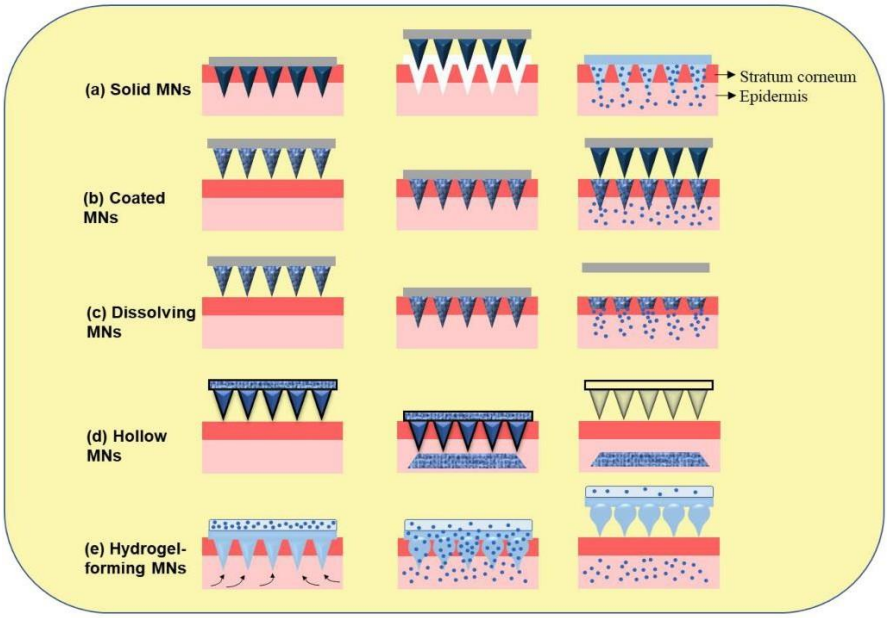

Figure 1 Different types of microneedles(**a**) Solid MNs; (**b**) coated MNs; (**c**) dissolving MNs; (**d**) hollow MNs; (**e**) hydrogel-forming MNs [20]

5. Materials used for Microneedles

5.1 Silicon

Silicon is preferred because of its well-established fabrication process, high tensile strength, Young's modulus to withstand insertion force, and biocompatibility. There are two primary categories of Si microneedles: in-plane and out-of- plane [17].

5.2 Ceramics

Compared to most polymers, biocompatible ceramics are more mechanically strong and have superior temperature and moisture stability. In order to improve molecular penetration, the ceramics' surface can also interact electrostatically with biomolecules. Dual-replicated PDMS production moulds and ceramic micromolding technology are typically used in the preparation of ceramic microneedles. The ceramic micromolding technology entails uniform mould filling and drying steps, during which the solvent evaporates and forms a raw tape, resulting in microstructure defects[18].

5.3 Silica glass

Glass can be utilized to create a variety of shapes on a tiny scale. Although silica glass is brittle by nature, it is biologically inert. More

elasticity can be found in borosilicate glass, which is composed of silica and boron trioxide. They take longer to complete because they are primarily made by hand. Currently, glass MNs are only utilized in experiments and are not used commercially [19].

5.4 Polymers

In order to support the polymer microneedles and prevent brittle breakage during skin insertion, microneedles composed of polymers typically have great toughness. Drugs can be encased in these dissolvable microneedles because some polymers, such as chitosan and poly-glycolic acid (PGA), poly-lactide-co-glycolide acid (PLGA), poly-L-lactic acid (PLA), and water-soluble polymer, are biodegradable. Drugs will be released upon skin insertion when these dissolvable microneedles break down or dissolve. Biodegradable polymeric microneedles are seen to be the most promising materials because of their low toxicity, biodegradability, biocompatibility, strength against breaking, and affordability. They also cause nearly no severe adverse effects. The primary materials utilized to create this type of microneedle include polystyrene, poly (methyl methacrylate), poly (carbonate), poly (vinylpyrrolidone (PVP)), and poly (vinyl alcohol (PVA) [20].

5.5 Metal

The outstanding mechanical and physical qualities, low breaking point, great biocompatibility, and inexpensive cost of metal materials make them ideal for use as the structural building blocks of microneedles. It is possible to employ metal microneedles for solid-state, coated, hollow, and other types of microneedles. Aluminum, Ni, titanium, and stainless steel are among the metal microneedles. The non-degradable and rigid nature of the metal microneedles is a drawback [21].

6. Fabrication techniques

The most common methods are laser ablation, micro-molding, additive manufacturing, injection molding, chemical isotropic etching, surface/bulk micromachining, and lithography-electroforming-replication.

6.1 Laser Ablation

In order to produce MN arrays, laser ablation uses a concentrated optical light beam to remove material from a substrate. For a variety of purposes, lasers have been utilized to treat materials at the micro- and nano scale. Different kinds of lasers have been investigated for the production of MN arrays. CO2, UV excimer, and femtosecond laser machine are a few of these. The laser ablation technique is thought to be a quick and efficient way to create MNs. It takes the laser beam between 10 and 100 nanoseconds to get close to the material sheet's burn point. Any metal could be shaped with a laser as well. The MN structure and mechanical properties are altered by this process due to heat impacts at the cutting surface [22].

6.2 Lithography

The lithography technique is used to transfer the master pattern of the geometric shapes onto a surface of a substrate. Photolithography is the most widely used type of lithography. This procedure is based on the observation that some materials, including metals, become opaque when subjected to UV light (λ = 193-236 nm), while glass remains clear. An opaque template called an optic mask is made during this operation in order to construct the required pattern in a wafer. The mask, made of a flat glass or quartz plate, only permits light to flow in a specific pattern. The silicon substrate is first heated to around 900 °C with steam or humidified oxygen to form an oxide layer. It is then rotated and covered with an organic polymer known as photoresist material, which is UV-sensitive. UV light and heat between 75 and 100°C eliminate the solvent [23].

6.3 Three Dimensional (3D) Printing Technology

The integration of three-dimensional printing into the manufacturing of microneedles has been achieved through the application of photopolymerization. Shin et al. detail the utilization of DLP-based 3D printing to fabricate microneedles through photo-crosslinking in a low-concentration aqueous solution, combining riboflavin and silk fibroin to produce a flexible microneedle. In a separate study, Seng et al. employed DLP to construct a dual-function microneedle array on curved surfaces, addressing both drug delivery and finger splinting. This approach capitalizes on the advantageous properties of microneedles, such as low drug load, coupled with the high flexibility afforded by 3D printing. The resulting microneedles exhibit significantly increased skin penetration of medication, with the microneedles demonstrating double the strength of an average thumb before breaking. Furthermore, the non-contact inkjet printing technique, containing minute amounts of proteins and nucleic acids, offers a versatile method for on-demand delivery of biological materials. This process enhances the uniformity, stability, and reproducibility of microneedle coatings [24].

6.4 Micro-molding

The fabrication of dissolving microneedles often involves the micromolding technique. In this process, the microneedle (MN) mold is filled either with molten polymer, which is then allowed to solidify, or with a concentrated polymer solution that undergoes drying. To introduce the drug-loaded polymer solution into micropores, a common practice is to cast it onto the polydimethylsiloxane (PDMS) surface of the female microneedle mold. Enhancements to this process are achieved through techniques such as vacuumizing and centrifugation. Typically, the polymer dispersion is poured into the microcavities of the female molds and subsequently subjected to pressure or vacuum, dried in ambient conditions, or centrifuged under pressure. The

construction of a polydimethylsiloxane (PDMS) micromold commonly involves the utilization of a master structure [25]

7. Applications of Microneedles

Skin serves as a useful barrier and a vehicle for the delivery of bioactive substances. As a result, it works effectively in molecular diagnostics and therapy. In order to improve drug penetration and transportation, microneedles (MNs) were typically created for the purpose of treating diseases. Currently, there is a push to apply microneedles in various domains, such as immunobiological administration, illness diagnosis, and cosmetic applications [26].

7.1 Diabetes

Microneedles are suggested as a drug delivery system allowing the introduction of drugs, therapeutic proteins, and insulin into the skin with minimal invasiveness. In a study conducted by Zhang et al., the efficacy of solid microneedles, measuring 150 mm in length, was explored to improve transdermal peptide delivery. The application of microneedles substantially increased the permeation of peptides through the skin, and the rates of permeation were found to be contingent on the molecular weights of the peptides. The researchers concluded that solid microneedles demonstrate effectiveness in augmenting the delivery of peptides through the skin. Hypoglycemia effect was observed in rats given insulin-loaded microneedles and an insulin subcutaneous injection, according to pharmacodynamic and pharmacokinetic data. After being encapsulated and released from microneedles, insulin exhibits pharmacological activity, as evidenced by its bioavailability of around 92%. Although insulin should normally be stored between 4 and 8 degrees Celsius, storage stability was shown to be greater than 90% of the insulin even after a month of storage at 25 or 37 degrees. These findings confirmed the high potential for transdermal delivery of various biomolecules using biomolecule encapsulation in microneedles. Additional research with insulin-releasing microneedles demonstrated their efficaciousness in insulin delivery for the management of diabetes [25].

7.2 Cosmetics

The cosmetics industry has somewhat already used microneedle technologies. Dissolvable microneedles were created to deliver cosmetic ingredients to the skin or promote skin regeneration, however this is still an unexplored field of study. Hyaluronic acid, a naturally occurring substance found in connective tissue, is one of the most often utilized materials. It is an excellent fit for the role it plays in the creation of microneedles intended for intradermal distribution and cosmetic uses.Use of HA microneedles in cosmetology and medication delivery, as well as what happens to them when severe ailments are treated via dermal and transdermal routes of administration [24].

7.3 Anti−Wrinkle Therapy

Various cosmetic treatments utilizing microneedles have been implemented to address skin wrinkles. A significant focus has been directed toward the distribution of active ingredients, particularly in the non-cosmeceuticals domain, where dissolvable microneedles (DMNs) arrays have become a subject of extensive investigation for topical cosmetic applications. In the cosmetic sector, the development of DMNs aims to deliver active ingredients—such as retinyl retinoate, ascorbic acid, 4-n-butylresorcinol, and epidermal growth factor—through the skin in a minimally invasive manner, specifically targeting skin depigmentation and wrinkle reduction. Numerous formulations are undergoing testing, with some already accessible in the market, showcasing their potential for treating epidermal wrinkles. Furthermore, the efficacy of peptides and nucleoside-dependent microneedle delivery systems has been demonstrated in treating various skin disorders and enhancing overall skin texture [13].

7.4 Burn wound healing

Burn injuries rank among the most dangerous skin traumas and have a high death rate. Even after surviving a burn injury, people still require assistance to improve the creation of scars, which lowers their quality of life. Burn injuries can leave behind two types of scars: hypertrophic scars (HS) and keloid scars. These scars are quite common and typically result in contractures, neuropathic discomfort, and surface abnormalities. Medical needling is being utilized in clinics and the beauty business. It involves repeatedly puncturing burn scars with a roller fitted with metal microneedle arrays. The microneedles pierce the dermal blood vessels and penetrate the scar, causing dermal restructuring and collagen redeposition. The collagen scar will fracture and physiological collagen in a lattice structure increased, along with fibronectin and glycosaminoglycans, resulting in a more elastic and flat skin surface [12].

7.5 Obesity

It has been observed that caffeine from tea or coffee has anti-obesity properties without being detrimental to people. Dangol et al. discovered that high-fat diet-induced obese mice can significantly lose weight when given caffeine by HA-based dissolving microneedle loading. Furthermore, by increasing the effectiveness of caffeine's transdermal distribution, this study demonstrated that caffeine has exceptional therapeutic action against obesity. Furthermore, a novel approach utilizing HA-based microneedles that dissolve was achieved for the targeted management of obesity [17].

7.5 Cancer Treatment

Microneedles (MNs) find application in the treatment of breast cancer, skin carcinoma, and, notably, in the 3D printing of MNs for cancer treatment. The utilization of MNs proves advantageous in delivering anticancer medications, such as chemotherapy, as well

as chemicals for photodynamic treatment (PDT) and photothermal therapy (PTT), to skin tumor sites with increased efficacy and reduced invasiveness. Cryomicroneedles, specifically, have been employed to deliver ovalbumin-pulsed dendritic cells, resulting in enhanced antigen-specific immune responses and slower tumor growth compared to intravenous and subcutaneous injections in mice with subcutaneous melanoma tumors. The delivery of cells through cryomicroneedles ensures the maintenance of their viability and proliferative capacity, showcasing potential applications in various cell therapies [27].

Biocompatible cryomicroneedles present an avenue for facilitating minimally invasive cell administration in diverse cell therapies. Combining MN percutaneous delivery with cancer immunotherapy emerges as an attractive strategy to enhance the overall effectiveness of cancer treatment. Research by Duong et al. emphasizes the potential of soluble MNs for combining adjuvants and vaccinations, releasing them into skin tissues. In comparative studies, subcutaneous injection of MN-free nanocomposites resulted in a weaker antigen-specific antibody response than subepithelial implantation of the MNs combination. The soluble MN mixture exhibited an improvement in antibody memory compared to conventional immunization methods, pointing towards its potential in augmenting immune responses .

7.6 Biosensors

Microneedles are also utilized in sensors for two functions: sample and transfer biological fluids to biosensors, as well as acting as the active components of biosensors. Microneedle biosensors are superior to other continuous monitoring devices because of the following: Because of their small size, MNs are less invasive to the skin; (2) their replaceable capacity reduces biofouling effects; (3) they offer larger electrode surface areas for larger currents; and (4) despite being a less expensive device, MNs are accurate because they can measure glucose concentrations in dermal ISF, which is comparable to blood glucose levels. (5) After the microneedle sensor is removed, the wound it caused can heal in a day [14].

7.7 Immunobiologicals

Combination vaccinations, such as "DPT," which guards against tetanus, pertussis, and diphtheria infections, are one approach for reducing down on the number of shots required. It is difficult to create such a formulation because the interactions between the vaccine's chemical, biological, and physical components could compromise its efficacy or safety. Researchers did not find any evidence of adverse effects on the biological activities of any component, nor of physical or chemical interaction.

By creating temporary channels, microneedles facilitate the vaccine molecule's transit through the epidermal barrier. Vaccines can penetrate the stratum corneum and trigger a therapeutic response by means of microneedles. When the influenza vaccination and cholera toxoid were given together using microneedles, there was a rise in haemagglutination inhibition (HI) and IgG subtype titres.Comparing the clinical reaction following intramuscular injection of the simple vaccination, it was significantly higher.

Compared to full inactivated or live attenuated vaccines, high purity subunit vaccinations are safer. The immunogenicity of vaccinations is reduced when they are used pure. Numerous investigations have been conducted to effectively immunize vaccine recipients using adjuvant and microneedle administration [11].

8. Drug delivery

Microneedles (MNs) have evolved through extensive research activities over recent decades, utilizing a diverse array of constituent materials, patterns, and shapes, ranging from metals and glass to polymers and hydrogels. The field has witnessed increased exploration, leading to various delivery methods. Initially proposed were four approaches: "poke and patch" involving solid MNs, "coat and poke" with coated MNs, "poke and flow" utilizing hollow MNs, and "poke and dissolve" featuring dissolving MNs. Subsequently, an additional method was developed. The early stages of microneedle research primarily employed solid microneedle arrays to puncture the skin and overcome the barrier effect posed by the stratum corneum. The treated skin surface was then covered with a medicated patch, and the needles were composed of silicon wafers. "Poke and patch" is the term for this strategy. This method was also attempted for non-invasively measuring the glucose level by extracting the interstitial fluid. A "poke and release" strategy was developed as a result of additional research. Polymers and polysaccharides that either slowly dissolved or broke down after delivery were used to make microneedles. The "poke and release" strategy has the benefit of allowing the drug's release to be adjusted based on need by utilizing a range of readily available polymers and polysaccharides. Hollow microneedles were developed as a result of the inability of dissolvable or degradable microneedles to administer large amounts of medicine in a manner similar to other physical ways. This method, called "poke and flow," involved puncturing the skin and allowing medication to seep through hollow microneedles into the skin from the patch's reservoir [21,22].

A coated microneedle is made up of a solid film that contains the active ingredient and water-soluble inactive excipients, coated over a sharp, solid-core microneedle structure. In addition to helping with the microneedle coating procedure, the water-soluble excipients hasten the film's separation from the microneedle surface. The interstitial fluid that exists in the tissue is encountered by a drug-coated microneedle when it is put into the skin. The microneedle coating's water- soluble excipients are dissolved in contact with this watery solution, which in turn starts the coating's separation from the microneedle surface. The separation of the coated excipients based on their aqueous solubility. The coating can be done in a matter of minutes or seconds. Before microneedles are extracted from the skin, the coating just needs to separate from the surface of the needles; the residual material can dissolve

completely over time. The coated payload of coated microneedles can be applied to different tissues in addition to skin [17,25]

9. Conclusion

Microneedles have emerged as a revolutionary technology, offering a precise and minimally invasive approach to administering drugs, therapeutic proteins, and vaccines. The versatility of microneedles extends from enhancing transdermal peptide delivery to addressing critical medical conditions like breast cancer and skin carcinoma. Notably, the advent of 3D-printed microneedles heralds a new era in personalized cancer therapy. In the cosmetic domain, dissolvable microneedles exhibit promise for targeted delivery of active ingredients, presenting a paradigm shift in addressing skin-related concerns. Furthermore, the integration of microneedles with immunotherapy holds significant potential for advancing the effectiveness of cancer treatment.

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