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# 3d Printed Hollow Microneedles As A Potential Future Method For Treating Skin Wrinkles With Various Anti-Wrinkle Agents

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## ABSTRACT

Anti-wrinkle technology now in use is based on the fact that wrinkles are an inevitable consequence of aging owing to the destruction of scleroprotein fibers and considerable loss of collagen. Due to the stratum corneum's great resilience, conventional therapies like laser and Botulinum toxin have some disadvantages, such as adverse skin reactions, timeconsuming treatment methods, and ineffective anti-wrinkle product penetration. In light of this, the cosmetics industry has developed a number of products based on solid and dissolvable microneedles (MNs) combined with antiwrinkle formulations, taking advantage of the patient-compliant technology of MNs to treat skin wrinkles. However, the high molecular weight of the medicines limits the use of these MNs for medication delivery. Although a greater variety of active agents can be delivered by hollow MNs (HMNs), this is an area of antiwrinkle technology that has not received much attention. In this study, we address this gap by discussing the potential of bioinspired 3D printed HMNs in the treatment of wrinkles on the skin. We contrast anti-wrinkling treatment alternatives from the past and present, as well as the methods and difficulties associated with their production and marketing.

**Keywords :** antirinkle agents; hollow microneedles; skin wrinkles; 3D printing

## INTRODUCTION:

Wrinkles are caused by a number of inherent and external factors [3]. These variables play a major role and have the ability to change both dermal and epidermal structures [4]. Radiation, smoking, and environmental pollution are examples of extrinsic variables that might accelerate the aging process by changing the skin's oxidative stress, which has a detrimental impact on cellular processes. Internal wrinkle creation is also encouraged by factors including (i) diabetes mellitus, (ii) pathophysiological changes during menopause, (iii) metabolic disease in the elderly, and (iv) usage of certain medications like corticosteroids. For instance, glycation, an indirect cause of wrinkles on the skin, is brought on by diabetes mellitus. Dermal shrinkage, xerosis, and changes in skin texture are caused by a drop in estrogen levels after menopause. Our skin health is also greatly impacted by our bad lifestyle choices, such as sleep deprivation and diets deficient in antioxidants [3,5]. Photoaging, a form of extrinsic aging, involves premature changes to skin health due to continuous sun exposure. UV radiation acts as the central driver in this case [6,7]. Clinical features of both intrinsic and extrinsic skin aging mostly exist in a superimposed manner, however, they are completely distinct [8,9]. Usually, intrinsic aging is distinguished by increased fragility, xerosis, loss of underlying fat, fine wrinkles, and pruritus [4]. Contrastingly, extrinsic aging exhibits flimsy skin phototypes including skin dullness, fine and coarse wrinkles, less atrophy, roughness, mottled pigmentation, and telangiectasias [10]. In addition, a couple of more characteristics of extrinsic aging are leathery skin, deeper rhytid, and dyschromia [11,12]. Based on their anatomical features, wrinkles can be divided into four categories: atrophic, elastotic, expressional, and gravitational wrinkles. Crow's feet, often referred to as lateral canthal rhytids, are a prime example of skin wrinkles, and expressional wrinkles have distinct patterns [13]. Heredity also affects wrinkle variation. Although its direct impact on skin wrinkles has not yet been discovered, the MC1R gene has been reported to have an impact on photoaging and spots [1].

**Anti-Wrinkle Therapy Mediated by Microneedles :**

Because MNs are safe, painless, and non-invasive, they are frequently utilized in transdermal medication delivery. Their design is similar to the extremely thin needles that pierce the stratum corneum and travel into the dermal layers without damaging blood vessels or pain-sensing neurons . Additionally, MNs facilitate the drug's absorption in the ISF and make it easier for the ISF to diffuse painlessly through the skin . As a result, it is one of the painless dose forms that patients can administer on their own [20]. The stratum corneum (SC) route of administration is the biggest obstacle to transdermal medication distribution. SC is the skin's first line of defense that prevents medications from penetrating the skin. The micron-sized needle with a solid base size ranging from 25 to 2000 μm that can be easily inserted into the skin's stratum corneum is what allows the microneedle technique to outperform the SC [5,21]. This feature is regarded as one of the technique's main advantages [2]. Additionally, it can guarantee the direct transport of active molecules like antibodies, allergens, and other agents of therapeutic advantage to the skin, making it a technique of interest for transdermal immunotherapy [5,20]. In a recent case study, coated MN was utilized to control IgE in a mouse model through the skin, thereby reducing the symptoms of allergic rhinitis. To evaluate the safety and immunological response of allergen immunotherapy in comparison to subcutaneous immunotherapy (SCIT), two Phase I trials are in underway [5,13]. The microneedle product alszz targets a certain depth of skin, and an in vitro skin test shown that MNs may successfully pierce the layers of skin or epidermis. Additionally, themethod delivers the active medication molecules the active medication molecules to the skin with the least amount of invasiveness.

**General Mehods of 3D Printing :**

Making (virtual) models of the items that will be produced is the first step in 3D printing. A 3D scanner or modeling tool is used to create the design in a CAD file. Three-dimensional designs are commonly transferred to the Standard Triangulation Lan- guage (STL) file format, which depicts a 3D model's external surface. The exteriors will then be divided into distinct printable layers by the 3D printing software, which will then transmit the digital instructions to the printer layer by layer. After printing, the generated products could go through additional dehydration, annealing, polishing, or other post-processing steps [5,21]. The various stages of Microneedle-Mediated Anti-Wrinkle Therapy are as follows: MNs' safe, painless, and non-invasive medication administration makes them popular in transdermal drug delivery.

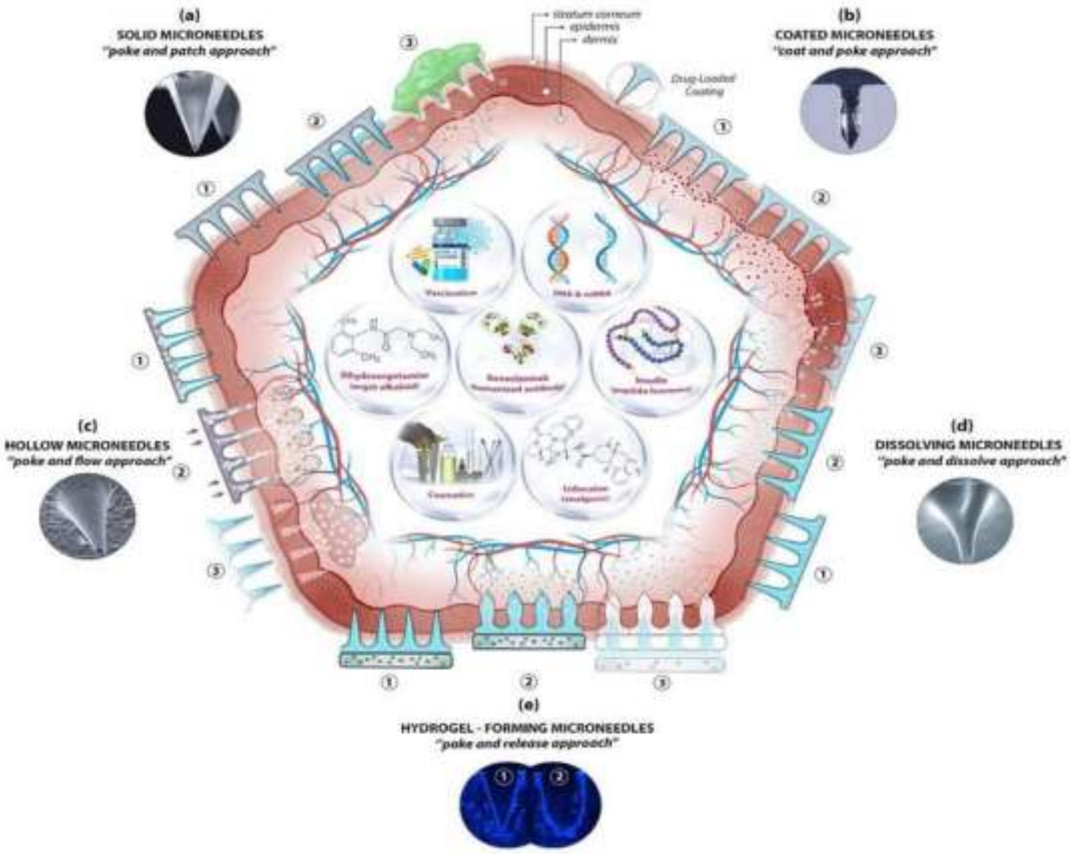


**Figure 3. Drug delivery via different types of MNs: (a) solid MNs, (b) coated MNs, (c) hollow MNs, (d) dissolving MNs, and (e) hydrogel-forming MNs. The step-by-step process of each delivery approach is numbered from 1 to 3**

**Types Of Micro Needles :**

1. **Solid Microneedles**

Solid microneedles can be used to make tiny holes in the skin that facilitate the easy delivery of molecules and medicinal substances. The purpose of this kind of microneedle construction is to promote drug delivery to the dermis by penetrating the stratum corneum, which will increase the drug's bioavailability and kinetic transport through the skin [. Hashmi et al. created the first microneedle arrays documented in the literature for intracellular administration in vitro by etching them into a silicon wafer [6,13].

Solid microneedles are easier to make and have better mechanical qualities than hollow microneedles [64, 65]. By creating pores in the skin, solid microneedles are mostly employed for pre-treatment [66–68]. When a medicine patch is applied, the needles' sharp ends pierce the skin, forming micron-sized channels that allow the medication to directly penetrate the layers of skin [6,22].

2 **Hollow Microneedles**

Because larger doses can fill the empty area inside the needle, hollow microneedles can hold a high dose of the drug dispersion or solution. High molecular weight substances like proteins and vaccines are the main applications for them . In contrast to solid microneedles, hollow microneedles are active drug delivery systems that use a non-pressurized drug reservoir to create a conduit for the effective diffusion of medications into the dermal layer . It is possible to modify the flow, pressure, and drug release rate of hollow microneedles [5,20].

A quick release, a steady infusion, or a time-varying delivery rate can all be achieved by adjusting the microneedle aspect ratio [1]. In order to attain a flow rate of 0.93 µL $s^{-1}$ at a pressure difference of 2 KPa, Mishra et al. created hollow microneedles that were aligned on the silicon substrate with a length of 500–600 µm and an outer diameter of 100 µm [3]. One drawback of hollow microneedles is that they can clog and leak during the injection process. In terms of needle design and insertion techniques, they too demand special attention and are comparatively weaker [7,14].

3. **Coated Microneedles**

A solid film containing the active chemical and water-soluble inactive excipients is coated onto a sharp, solid-core microneedle structure to form a coated microneedle [5]. Proteins and DNA can be delivered minimally invasively using a coated microneedle [6]. The quick delivery of the medication to the skin is one benefit of a coated microneedle; nevertheless, the leftover medication at the needle's tip may infect additional patients . The mechanical properties of a solid microneedle are unaffected when a different drug is coated on its surface, in contrast to the dissolvable microneedle, whose mechanical properties can change when the encapsulated drug fraction is changed or when a different drug is dispersed in its matrix [15].

4. **Dissolving Microneedles**

Biodegradable polymers are used to make dissolving microneedles [6]. They are made to contain the pharmacological agents and regulate their release as the polymers break down and dissolve in the skin. Unlike other types of microneedles, this one does not require removal once inserted. It is one of the greatest options for long-term therapy with better patient compliance due to its bio-acceptability Pharmaceutics 2022, 14, 2693 8 of 30 and the polymer's dissolution inside the skin [9]. The best materials for producing dissolvable microneedles are those that dissolve in water.

Furthermore, one of the best methods for creating dissolvable microneedles is the micro-molding process. The process of micro-molding is either filling the microneedle mold with melted polymer and letting it solidify, or filling it with a concentrated polymer solution and drying. Dissolvable microneedles present a number of difficulties, including the possibility of a delay in disintegration and the impossibility of full insertion [2,6].

5. **Hydrogel-Forming Microneedles**

Aqueous polymer gels or swelling materials are typically used to create hydrogel-forming microneedles. When this kind of microneedle is put to the skin, it absorbs the interstitial fluid and expands, creating pathways between the medication patch and the capillary circulation. These microneedles act as a rate-controlling membrane when they are applied and swell. It is simple to sterilize and remove hydrogel-forming microneedles from the skin [9–11]. Crosslinked polymers can also be used to create hydrogel-forming microneedles. When utilized in transdermal drug administration, hydrogel-forming microneedles enhance penetration and bioavailability [8].

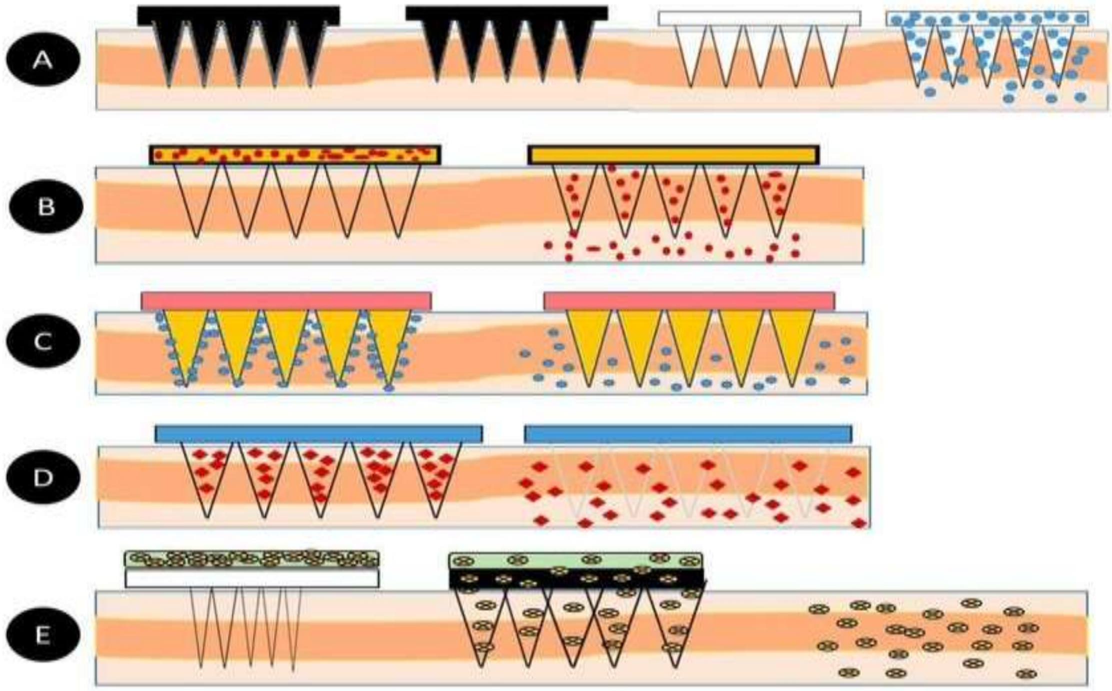


**Figure no.2 :- (A)—Solid microneedles; (B)—Hollow microneedles; (C)—Coated microneedles; (D)—Dissolving microneedles; (E)—Hydrogel-forming microneedles**

**Fabrication of 3D Printed HMNs :**

Production of 3D Printed HMNs Rhodamine B, fluorescein iso-thiocyanate, and methylene blue were employed through the device in a study by Yeung et al. that demonstrated the use of a 3D printed microneedle with a hollow design. The fine-tipped syringe-shaped microneedle underwent a full assessment examination. These compounds were thought to have emission peaks, a diffusion profile, and a weight comparable to model pharmacological chemicals [1,14]. Because of the fluorescence that the particles produced, the study gave insight into the depth and analysis of fluorescence. It also showed that molecules that reduce wrinkles, such as antioxidants, anti-UV agents, antiinflammatory agents, etc., can be optimized through 3D printed hollow therapy to improve skin hydration (like hyaluronic acid) and elasticity (like retinoids). The drug's dosage and intervals can be controlled via 3D printed HMN treatment. This makes it possible to significantly reduce medication toxicity over a particular area of the skin. This also makes it possible to alter the medication's effectiveness because only the necessary dosage is permitted. This technique permits a higher potency since it offers a more permeable reaction to produce a drug-induced response. With all these benefits, skin regeneration can be guaranteed by minimizing the negative effects of hyaluronic acids, vitamin A/E, different hormones, and retinoids [7,14].

| MICRONEEDLE TYPE | FABRICATION TECHNIQUES |
| --- | --- |
| **1. Solid Microneedles**<br>Metal microneedles<br><br>Silicon microneedles<br><br>Polymer microneedles<br><br>Ceramic microneedles | • Wet etching<br>• Electroplating<br>• Laser cutting<br><br>• 3D Laser ablation<br>• Silicon dry etching<br>• Isotropic etching<br><br>• Sintering lithography<br>• Micro-molding<br><br>• Microfabrication<br>• Deep X-ray lithography<br>• Wet chemical etching<br>• Deep reactive ion-etching of silicoe |
| **2. Coated microneedles** | • Dipping or spraying microneedles with an aqueous solution of increased viscosity to retain formulations during drying<br>• Layer-by-layer coating techniques<br>• Dipping the microneedles into a coating solution, which is a microwell containing the drug solution |
| **3. Dissolvable microneedles** | • Micro-molding |
| **4. Hydrogel-forming microneedles** | • Micro-molding<br>• Drawing lithography<br>• Injection molding |
| **5. Hollow microneedles** | • Microfabrication |

| | |
|---|---|
| | • Deep X-ray lithography<br>• Wet chemical etching<br>• Deep reactive ion-etching of silicon<br>• Laser micromachining |

**Table No. 1 : MICRONEEDLE TYPE And Fabrication Techniques**

**Hollow Microneedles :**

Hollow MN have been created utilizing ceramics, metal, silicon, and glass, , as previously noted, a bore on the needle tip and an empty hollow inside each needle. Therefore, it is possible to inject medication solutions in microvolumes into the skin Higher drug delivery capacity compared to solid, coated, and dissolving MN arrays and the ability to deliver chemicals, proteins, vaccines, and oligonucleotides into the skin are the primary benefits of this type of MN[6]. They also have a high stiffness because of the materials utilized to make them [4]. Limitations include the possibility of skin tissue obstructing the bore of needle tips during insertion. Retracting the MN array and/or positioning the bore on the side of MN, however, can prevent this problem [4,8]. Additionally, the creation of hollow MN arrays requires precise manufacturing processes including lithography, etching, microelectromechanical systems (MEMS), and, more recently, 3D printing. These processes are discussed in the section that follows.

**Preparation Of Mns :**

The primary motivation behind the creation of MNs is their exceptional ability to penetrate the skin without breaking or flexing , offering a minimally invasive drug delivery technique [4,8]. To overcome the production challenges related to MNs, a number of factors, including as material selection, manufacturing processes, and design complexities, have been carefully taken into account. Simple, low-cost, and reasonably priced supplies are required to prepare MNs for pre-clinical [2].

**Properties Of Mns :**

With many crucial characteristics and attributes that define their utility for transdermal drug delivery and vaccination, MN technology seems promising [11,20]. The ability of MNs to penetrate the skin is largely dependent on their mechanical strength and structural design. The MNs' ability to sustain the stresses needed in skin penetration without breaking is ensured by their mechanical strength . Drug delivery, also known as drug release kinetics, is an important characteristic [21].

**Techniques Involved in 3D Printed HMNs :**

It has been demonstrated that utilizing 3D laser cutting or laser ablation, metal may be electroplated or electroless plated onto positive or negative MN molds to produce HMNs [14]. Additionally, by drilling trenches in dissolvable molds to create lumens in the microneedle structures, laser micromachining has been used to create MNs (400–800 m in length). Conical wire and metal or polymeric sheets can be cut with an infrared laser to create HMNs. HMNs with the required shape, geometry, and dimensions can be created using computer-aided design (CAD) software. The needle is bent perpendicular to the base plane after being laser-cut to the required profile. Any leftover debris is then removed by soaking it in hot water. MN are then electropolished, cleaned, and dried with compressed air to reduce their thickness and sharpen their points. Both single rows of MN with a range of forms and two-dimensional arrays of metallic MN can be produced using this method [5–8]. A team of researchers successfully created metallic HMN with tapered walls by using an excimer laser to drill holes of the necessary geometry into polyimide or polyethylene terephthalate polymer sheets (without the need for master polymeric molds). Tapered holes had to be bored all the way through in order to electroplate metallic HMNs with tapered walls [9, 10].

Davis et al. used a modified LIGA approach to micromold polyethylene terephthalate using an ultraviolet laser. Selective etching was used to remove 16 metal MN (500 nm long and 75 nm in diameter at the tip) from the polymeric molds after a nickel coating was electrodeposited onto a sputter-deposited seed layer. These MN were demonstrated to be strong enough to pierce biological tissue without breaking after mechanical tests [11]. The materials and manufacturing method frequently utilized in HMN fabrication are compiled .

One possible way to introduce various therapeutic chemicals into the skin is using transdermal microneedle patches. MNs must pierce the stratum corneum of human skin without ripping or bending in order to serve as a substitute for traditional hypodermic needles. This ensures that the substance is released at the designated time and place [1,9]. As a result, MN patches' ability to pierce the skin enough is crucial. Even though the work seems straightforward, proper MN insertion depends on a variety of criteria, including needle length, shape, thickness and tip radii, base diameter, needle saturation, and MN material [10,11].

To get the ideal level of MN penetration required for efficient medication administration or precise site targeting, these parameters may be changed. As a result, altering the MN design, geometry, and manufacturing material can have an impact on the needles' ability to pierce the skin and withstand the skin's natural elasticity, all of which can be modified on an individual basis to improve drug delivery [12]. Furthermore, a number of crucial MN design elements have a significant impact on the active agent's therapeutic efficacy. The MNs' strength, rate of release, and drug loading capacity are all influenced by the fabrication's composition . Every factor that determines the efficacy depends critically on the height of the needles [1].

The targeted region, cells, and drug loading capacity are all determined by the patch area [3,5]. However, these methods of producing MNs using a variety of pricey components might occasionally be more expensive, particularly for metal MN arrays for big batch production or to make additional MNs like solid, coated, or dissolvable MN [16]. On the other hand, new techniques can be used to HMN to increase its cost-effectiveness [9,7]. To overcome the current difficulties, researchers propose a high-fidelity replication method with a high potential for large yields. The tips of conventionally produced hypodermic needles are employed to form a metal HMN array template, which serves as the foundation for an elastic polydimethylsiloxane stamp (PDMS).

It then uses the PDMS stamp to recreate the hollow structure of the needle arrays, resulting in the low-cost and largescale manufacture of HMN arrays composed of different materials [14,17]. The needle size, density, height, and area of the conventionally made hypodermic needle arrays can be easily adjusted thanks to this building method. Because the replicating processes demonstrated excellent consistency throughout the replicated HMN arrays, concurrency was feasible. Because of the polymer material and replication process, each microneedle array is anticipated to cost less than 20 cents, making them extremely inexpensive and potentially mass-producible [22] .

**Hollow microneedles: Benefits for drug delivery :**

By providing a less intrusive and more accurate manner than conventional techniques like injections or oral medication, hollow microneedles (HMNs) are transforming drug delivery. They provide an almost painless experience by penetrating the skin's barrier without activating deeper nerve endings. This has several advantages, particularly for people who are afraid of needles or who need regular shots, like kids.[8].

**Here's a closer look at the advantages of HMNs for drug delivery:**

1. **Painless and minimally invasive**

   HMNs are made to be incredibly tiny; their length usually ranges from tens to hundreds of microns. This makes the administration mostly painless by enabling them to pass through the stratum corneum, the skin's outermost layer, without getting to the deeper layers that contain nerve endings [21,22].

2. **Precise and controlled drug delivery**

   Liquid medicine formulations can be directly and carefully delivered into the desired skin layers (dermis or epidermis) thanks to the hollow structure of HMNs. Compared to techniques like dissolving or coated microneedles, where drug concentrations may be restricted, this is a big advantage. Using integrated systems such as microfluidic devices or external applicators, HMNs allow for exact control over the dosage and delivery rate.For example, HMNs have shown the potential :- Insulin delivery , Vaccine delivery , Targeted therapies [14].

3. **Versatile and adaptable**

   HMNs can be used to transport large proteins, small molecules, and even formulations based on nanoparticles. Furthermore, their design can be modified for a number of applications, such as ocular or buccal delivery. Advances in manufacturing techniques like 3D printing, which allow for patient-specific designs and even the integration of features like real-time monitoring, further improve this customization [13,21].

**3D printing microneedles: challenges and limitations :**

A viable method for creating microneedles (MNs) for a range of biomedical uses is 3D printing, which has the benefit of customized designs and perhaps economical production. [5,15].

**Material Selection And Optimization :**

1. **Biocompatibility And Mechanical Strength :**

:Trade-off : For materials to be used safely in the body, they must be biocompatible (non-toxic, non-immunogenic) and have enough mechanical strength to pierce the skin without breaking. Since many biocompatible polymers used in high-resolution printing methods (such as stereolithography (SLA) or two-photon polymerization (2PP)) can be brittle, strikingthe ideal balance is extremely difficult [20]
Printability: Materials that can be precisely formed and cured are necessary for high-resolution processes, which may restrict the selection of materials [6].

Degradation and Stability: Optimizing material degradation profiles and guaranteeing stability during storage are essential for efficient drug delivery for dissolvable or biodegradable MNs.[15].

Restricted Material Options: While some 3D printing methods are linked to high-resolution printing, they only offer a small range of materials that can be used, such as CLIP, SLA, or 2PP. [5].

Biocompatibility of UV-curable Resins: Because leftover monomers and photoinitiators can be cytotoxic, ensuring the biocompatibility of UV-curable resins necessitates careful post-processing to eliminate any unreacted components.[8]

**2. Mechanical strength and durability :**

**Skin Penetration**: MNs must be strong enough to endure the stratum corneum penetration stresses without breaking or bending. Inaccurate biosensing or insufficient drug administration might result from mechanical malfunctions. **Sharpness vs. Strength:** It might be difficult to strike the perfect balance between enough strength to avoid breaking at the microscale and sharp tips for simple penetration.

**Printed structures' brittleness**: Because of the intrinsic characteristics of photopolymer resins, high-resolution methods frequently produce brittle structures.
**Durability for Extended Use**: MNs must withstand deterioration while retaining performance for applications that call for frequent insertions or extended exposure to biological conditions (such as continuous monitoring).
**Material Properties and Design characteristics**: Material composition and geometric characteristics (thickness, length, diameter) have a direct impact on mechanical properties.

**Effect of Drug Loading**: The mechanical characteristics of the microneedle construction may be impacted by the drug loading.

**3. Scalability And Manufacturing Cost :**

**poor Throughput**: Large-scale production is hampered by the poor throughput and high prices of high-resolution techniques like SLA and 2PP.

**Costs of Equipment and Materials**: These methods require specialized equipment and materials, which raises manufacturing costs. Quality Consistency: Safety and effectiveness depend on maintaining consistent quality over big batches.

**Absence of Standardized Manufacturing**: A lot of procedures are still done by hand and are not appropriate for largescale manufacturing.

**Diversity in Designs and Applications**: The range of MNA designs necessitates the creation of specific tools and procedures.

**Long Drying Times**: Scalability is hampered by the lengthy drying times needed for some MN kinds, including as dissolvable ones.

**Limited Contract Manufacturing Options**: Production challenges are exacerbated by a lack of contract manufacturers with the requisite skills.
**Material Costs**: Economic viability may be impacted by the price of biocompatible resins and polymers made for applications.
**Manufacturing Cost:** Adoption of high-resolution printers may be hampered by the initial outlay.

**Manufacturing Speed**: High-volume production may be constrained by the speed of 3D printing. The comparative efficacy of various anti-wrinkle medicines when administered via hollow microneedles (MNs) presents a potential method.

**Anti-Wrinkle Agents Delivered via Microneedles :**

- **Retinoids :**

Mechanism: Retinoids, which are vitamin A derivatives like tretinoin, improve skin tone, fade age spots, and increase the development of collagen and new blood vessels. Delivery through MNs: According to studies, MNs can increase retinoids' penetration, which may increase how well they reduce wrinkles. Limitations: The broad usage of retinoids has been restricted due to their instability in topical formulations and potential for dryness and irritation. By enabling direct distribution and maybe permitting lower dosages, MNs may aid in overcoming some of these restrictions [20,22].

- **Peptides :**

  Mechanism: Bioactive peptides, such as arginine/lysine polypeptide, palmitoyl tripeptide-5, and acetyl octapeptide-3 (AHP-8), can increase the production of collagen and elastin, lessen muscle contractions, and strengthen the skin's resistance to external stimuli. Delivery via MNs: It has been demonstrated that MNs, especially dissolving MNs consisting of hyaluronic acid (HA), can successfully transfer peptides like AHP-8 into the skin, improving skin hydration, reducing wrinkles, and increasing dermal density and thickness. Effectiveness: Research indicates that MN patches containing bioactive peptides and other compounds can reduce wrinkles and fine lines by 25.8%, improve skin hydration by 15.4%, and increase skin thickness and density by 12.9% and 14.2%, respectively [11,16].

- **Hyaluronic acid :**

  Mechanism: A significant part of the extracellular matrix, hyaluronic acid (HA) has a high capacity to bind water and contributes to the hydration, suppleness, and viscosity of skin. Delivery through MNs: In order to properly transfer itself and other active chemicals into the skin, HA is frequently utilized as the basic material for dissolving MNs. HA-based MNs have a volumizing impact and improve skin moisture. HA that is crosslinked (CLHA): MN patches have also included CLHA, which is frequently utilized in dermal fillers. According to studies, CLHA-based MNs may provide long-lasting wrinkle reduction when paired with additional substances as AHP-8 and EGF [5,9].

- **Growth factors :**

  Mechanism: Growth factors, such as Epidermal Growth Factor (EGF), are essential for wound healing and skin renewal because they promote cell proliferation, differentiation, and tissue regeneration. Delivery with MNs: EGF administered by MNs has demonstrated encouraging outcomes in terms of enhanced skin and wrinkle reduction. Effectiveness: Research indicates that MN patches containing EGF may significantly reduce wrinkles and boost the moisture content of the skin.

- **Plant-based extracts :**

  Mechanism: By neutralizing free radicals, lowering inflammation, and perhaps influencing collagen formation, antioxidants and anti-inflammatory chemicals found in many plant extracts can prevent skin aging.

**Comparative Effectiveness Via Hollow Microneedles :**

Compared to solid or dissolving MNs, hollow microneedles (HMNs) have the benefit of regulating the release rate of active agents and delivering bigger molecules. In contrast to other MN types, research on the relative efficacy of various anti-wrinkle medicines administered via HMNs is still very lacking [9] . The effectiveness of particular agents when administered by dissolving HA-based MNs is the main focus of current research, which demonstrates statistically significant benefits in skin hydration, wrinkle reduction, and enhanced dermal density and thickness with combinations such AHP-8 and EGF [14,17]. To compare the efficacy of various anti-wrinkle drugs administered by HMNs, more study is required to investigate alternative formulations and optimize delivery parameters for optimal benefits. Applications of aesthetic dermatology for skin renewal and the treatment of wrinkles and fine lines A range of procedures are available in aesthetic dermatology to treat deep wrinkles, fine lines, and general skin renewal. These therapies can include more sophisticated methods as well as less intrusive ones [16,19] .

**Role In Reducing Fine Lines And Deep Wrinkles :**

- **Botulinum toxin (Botox) injections**: Botox relaxes the muscles in the face that result in dynamic wrinkles, such as crow's feet, frown lines, and forehead lines. This lessens the appearance of wrinkles and helps to smooth out those that already exist.
- **Dermal Fillers**: According to Medical News Today, fillers, which are frequently composed of hyaluronic acid (HA), are injected to smooth out deeper creases and fine lines by adding volume and plumping up places where volume has been lost due to aging. They work especially well for static wrinkles, such marionette lines and nasolabial folds, which are present even when at rest.
- **Laser Skin Resurfacing:** In order to reduce wrinkles and improve the texture of the skin, this surgery uses lasers to remove the skin's outer layers and promote the creation of collagen. While non-ablative lasers are less intrusive and produce more modest outcomes for moderate wrinkles and fine lines, ablative lasers are more intense and appropriate for deeper wrinkles and scars.
- **Chemical Peels**: Applying chemical solutions to the skin reduces wrinkles and improves texture by exfoliating dead skin cells and encouraging the creation of new, smoother skin. The efficiency of the peel in treating various wrinkle levels depends on its depth.
- **Microneedling**: This process makes microscopic punctures in the skin to encourage the creation of collagen and elastin, which can improve the texture of the skin and minimize fine wrinkles.

**Comparison With Botox, Fillers, And Topical Creams :**

- **Botox vs. Fillers:** While fillers give volume to address static wrinkles and volume loss, Botox mainly targets dynamic wrinkles by relaxing muscles. For complete facial rejuvenation, many patients find that a combination of the two is beneficial. While filler results can last anywhere from six months to two years, depending on the type, Botox results usually last three to six months [17,21] .
- **Topical Creams**: Topical treatments that stimulate the formation of collagen and elastin, such as vitamin C serums, niacinamide, bakuchiol, and prescription-strength and over-the-counter retinoids, can improve the texture, pigmentation, and moisture of the skin while reducing fine lines and wrinkles. But compared to medical procedures like Botox, fillers, or laser treatments, their results are typically less dramatic, and they need to be used consistently over an extended period of time [9].
- **Other Treatments vs. Topical Creams:** When it comes to treating deeper wrinkles, scars, and pigmentation issues, procedures like laser skin resurfacing, chemical peels, and microneedling frequently provide more substantial and longlasting results than topical treatments alone. The decision is based on the patient's desired outcome and the seriousness of the issues [6].

**Important Considerations :**

Consultation with a dermatologist is crucial: A skilled and knowledgeable dermatologist can evaluate your skin type, problems, and objectives to suggest the safest course of action. Patient compliance, safety, and regulations for microneedle-based treatments

1**. Safety considerations :-**

- Risk of infection: If correct sanitation and sterilization procedures are not followed, microneedling causes microinjuries in the skin that increase susceptibility to infections.
- Skin damage: Unnecessary skin damage, such as keloids, hyperpigmentation, or hypopigmentation, can result from excessive pressure, poor technique, or inadequate aftercare.

- Allergic reactions: Topical anesthetics and other medications given during or after the surgery may cause allergic responses in patients.

- Contradictions: People with active acne, infections (such as herpes or impetigo), or specific skin diseases like eczema or rosacea should generally avoid microneedling.

**2. Regulatory aspects in cosmetic dermatology :-**

- Varying regulations: In cosmetic dermatology, different regions may have different regulations and classifications for microneedling devices (e.g., US, EU).

- Medical device vs. cosmetic product: The manufacturer's claims determine the classification. While devices used only for exfoliation or aesthetic enhancement may not be regulated as medical devices, those used to penetrate the skin and alter its structure or function are often.

- Pre-market authorization: Pre-market notice (510(k)) and proof of safety and efficacy to regulatory agencies may be necessary for medical device categorization.

- Labeling and instructions: Technical specifications, recommended treatment procedures, disposal and reprocessing guidelines, dangers, advantages, and post-operative care must all be included on the label.

**3. Patient comfort and acceptance :-**

- Minimally invasive: Compared to standard injections, microneedling is typically thought to be less intrusive, which may improve patient acceptability and comfort.

- Painlessness: According to studies, microneedling can be a somewhat painless operation if the right needle length and technique are used.

- Reduced tissue damage: Compared to certain alternative therapies, minimal and localized inflammatory responses are frequently seen following therapy, which helps to speed up healing.

- Self-administration potential: Particularly in situations when access to medical experts is restricted, the simplicity of usage, especially with microneedle patches, may boost patient compliance.

- Dosing consistency and biocompatibility: Certain microneedle types provide difficulties in guaranteeing accurate and reliable drug administration, and continuous investigation and assessment are necessary to determine the long-term biocompatibility of these materials.

- Addressing patient education: To control expectations and increase satisfaction, it is essential to inform patients about the treatment, anticipated outcomes, possible adverse effects, and appropriate aftercare [2,8,10].

**The future of microneedle technology lies in the integration :**

- **AI, Nanotechnology, and 4D Printing** : The development of microneedles has significant potential thanks to the convergence of AI, nanotechnology, and 4D printing.

- AI: Microneedle design optimization, drug release profile prediction, and therapy personalization based on patient data are all possible with AI algorithms.
- Nanotechnology: Targeted therapy, better drug delivery, and increased biocompatibility can all be achieved by incorporating nanomaterials into microneedles.
- 4D Printing: Microneedles that adjust to the skin's surroundings and release medications in a controlled way can be made via 4D printing, which prints materials that can change shape over time in reaction to stimul

**•. Hollow Microneedles for Anti-Aging** :- Hollow microneedles have great potential for anti-aging applications since they can contain greater drug quantities and enable continuous release. They have the ability to reduce wrinkles, increase skin suppleness, and encourage tissue regeneration by directly delivering anti-aging substances like growth factors or peptides into the skin [7].

**Future direction :**

The creation of microneedles from hydrogels is a recent discovery in microneedle technology. According to Joseph G. Turner et al., hydrogel-forming microneedles are a good choice for use in biocompatible monitoring or sensing devices because they can aid in the passive evacuation of interstitial fluid from the skin. Opportunities for selfadministered health care monitoring and therapy may arise with this sort of microneedle . Numerous transdermal applications have made extensive use of microneedles. These days, dissolvable microneedles are used to transport medications (and macromolecules) orally throughout the body [10–14], particularly in oral devices that target the gastrointestinal tract's organs.

The luminal unfolding microneedle injector, an ingestible capsule created by Alex Bramson et al., uses a set of unfolding arms to administer medications orally into the intestinal tissue [18,20]. The field of regenerative medicine has been developing quickly, and significant advancements in the study of microneedle use in this area should be anticipated. The ability of microneedles to load drugs and the repeatability of drug exposure for long-term drug release are anticipated to significantly increase in the near future. The performance characteristics and quality aspects of 3Dprinted microneedle arrays can be optimized by utilizing the power of artificial intelligence (AI), particularly machine learning (ML) and deep learning (DL).

A promising field that will further advance the integration of AI-based prediction of microneedle arrays for the development of advanced healthcare systems is the tuning of 3D-printing Pharmaceutics 2022, 14, 2693 22 of 30 parameters for optimizing the manufacturing of biomedical devices, particularly in the areas of quality assurance and defect detection in microneedle array features [14,16]. In order to forecast novel and more effective results for the production of microneedles, AI models have demonstrated feasibility in recognizing and matching the similarity metrics between the various microneedle designs [18,21]. Furthermore, ML has shown itself to be an effective method for modeling the workflow of 3D printing . According to the research by B. Muñiz Castro et al. [19,22], ML algorithms combined with ANN were able to estimate the drug release timings of various drug formulations using the existing data sets. The field of medicines and, more significantly, the improvement of microneedle array features can both benefit from these machine learning models. Another new possibility is the 4D printing of microneedles. D. Han et al. showed how backward-facing barbed microneedles with tips that had comparatively higher mechanical strength than barbless microneedle arrays were made using the 4D-printing technique [3]. This method produces microneedles with increased tissue adhesion, which greatly enhances their performance in soft tissue applications, controlled drug administration, wound healing, and biosensing. In the future, painful hypodermic needles may be replaced by 4D-printed microneedles. 3D-printed microneedles may be a viable option for the painless delivery of COVID-19 vaccinations [1,4–6]. Because of their large surface area, 3D-printed microneedles made using continuous liquid interface production (CLIP) were discovered to improve the surface coating of the model vaccine components in the field of public health. A noninvasive, self-administered immunization may benefit from the use of three-dimensional-printed microneedles [16].

**Conclusion:**

MNs show great promise in anti-wrinkle therapy by offering a systematic technique for the painless transdermal delivery of medications. Although the micron-sized nature of microneedle arrays makes it difficult to build them as desired, this innovative method has gained popularity for medication delivery. When it comes to creating intricate structures and customized medications, 3D printing is an efficient manufacturing technique. These days, this technology is being used to create microneedle patches that can increase the use of MN arrays in a variety of scientific fields, including cosmeceutics and pharmaceutics. However, the pharmaceutical industry is still reluctant to invest in its commercialization because of its effectiveness and appeal to scientists. There are now 13 microneedle-based products on the market for cosmetic and certain pharmaceutical (drug and vaccine delivery) applications. The market for MN-based goods is expected to develop at a compound annual growth rate of 7.1%. Overall, advancements in 3D printing technology may make it easier to fabricate MNs to effectively deliver antiwrinkle therapy in the future, along with increased understanding of various tactics and polymers.

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