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Review Article

Microneedles: Recent Convenience Therapeutic in the Future

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ABSTRACT

Even though first-pass metabolism impact and gastrointestinal irritation can be avoided, as well as enhanced patient compliance, barely any number of APIs, or active pharmaceutical ingredients, can be delivered by transdermal drug delivery systems (DDS) delivered in line with the more intriguing possibility for efficient medical treatment is microneedles (MNs). Transdermal medication administration enters the barrier-protecting skin painlessly and painlessly. Since the 1990s, when the initial MNs were established, this area of study has been constantly changing. As a result, new manufacturing techniques are presented for both MNs and MN molds, enabling the manufacture of MNs for the delivery of drugs and vaccines as well as for diagnostic and monitoring applications at a low cost. This review's main goal is to provide a concise overview of MN properties, material makeup, and the development of MN-based systems for use in industry.

Introduction

Since ancient times, different chemical substances have been applied to the skin for medicinal purposes, skin protection, and cosmetic purposes[1]. A mixture of water, lead (II) oxide, and olive oil was used by the ancient Greeks to make a balm that had occlusive and astringent properties, respectively[2]. Before Bourget's demonstration that topical salicylic acid therapy may effectively cure acute rheumatoid arthritis in 1893, the skin was thought to be an impervious membrane[3]. Beginning in the early 20th century, lipophilic substances were found to increase skin permeability[4]. Using Wolf's tape stripping method, Blank concluded that the stratum corneum (SC) reflects the main barrier for the diffusion and permeability of pharmaceutical active ingredients (APIs)[5]. Before 1954, when it was demonstrated whether two percent nitroglycerin ointment could manage angina pectoris, skin as a medication delivery channel to the systemic circulation had neither been economically nor scientifically used[6]. As a result, this ointment became the initial advertisement formulation created for the transdermal administration of API through the bloodstream[7].

1. History of microneedles

Microneedle conceptions have developed over time, moving from the usage of big needles to the new contemporary design[8]. German dermatologist Dr. Ernst Kromayer cured scarring, hyperpigmentation, and other skin conditions using various motor-powered dental burs in 1905[9]. In 1921, Chambers published the first piece of writing mentioning the usage of microneedles, in which he implanted the needle into the egg's nucleus[10]. Drug injection into the stratum corneum started to gain attention in the 1960s[11]. The microneedle idea was then presented in the 1970s, but it wasn't until the 1990s that this idea was actually tested[12]. Scopolamine was initially delivered using a transdermal approach in 1979 when a three-day patch was used to cure motion illness[13]. In order to release fibrous strands during a subcision procedure, Orent Reich used a tri-beveled hypodermic needle in 1994. The epidermal abnormalities that caused depressed scars and wrinkles were operated on since they were located beneath the skin[14]. Ion etching and photolithography were used to create the first microneedle for transdermal distribution, which was proposed in 1998. The study discussed using specially made microneedles to improve drug absorption via the skin[15]. A large-scale study in the field of microneedles was initiated by this paper. A variety of materials, including glass, ceramic, metal, and polymers, were used to create microneedles[16]. Transdermal drug delivery was first attempted in 2004 using a microneedle array to create punctures in the dermis. It prompted the exploration of

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different fabrication techniques and materials for TDD[17]. MNs can be classified as solid, coated, hollow, soluble, or hydrogel-forming. Different production techniques, such as photolithography, micro-injection moulding, laser ablation, etc. Due to these developments, the first accounts of the use of a dissolvable microneedle for TDD appeared in 2005[18]. The first clinical trial employing microneedles was finished in 2007, and 43 clinical trials have since been completed using them, according to the clinicalTrials.gov website (accessed on June 30, 2021, at 5 p.m.). In order to provide low-cost options for the production of micro-moulds, additive production technologies to create MN moulds have recently been developed. Studies demonstrating the production of the MN master mould using commonly available 3D printers heralded a new era in device fabrication and opened up prospects for large-scale, custom MN production[19].

2. Advantages of microneedles

As a result of the medications being supplied through this approach bypassing important human organs like the liver, an MN is thought to be one of the greatest methods for transdermal drug administration[20]. Additionally, by offering a pain-free experience, it removes the suffering connected with Intravenous injection. It is therefore regarded as the greatest option for those who have a fear of needles (trypanophobia)[21]. The application of transdermal drugs using microneedles can be used by anyone without the need for special training. The chance of spreading an illness inside the body is also decreased. Any medicinal drug molecules are blocked from entering the skin or dermis layer by the stratum corneum, which serves as a barrier. In order to administer the medication painlessly into the epidermis or upper dermis layer, a microneedle can penetrate the stratum corneum barrier[22]. Additionally, the MN array is both long enough to reach the nerve terminals and short enough to avoid damaging the dermis. As a result, the procedure is safe and can permeate the stratum corneum. In comparison to conventional hypodermic needles, microneedle delivery systems may offer better medication and vaccination administration. Microneedles are much less intrusive and have diameters that are intended to prevent irritating the patient's nerves[23]. The reduced pain associated with microneedle permeation has been shown in human skin permeation experiments, and the effect has been evaluated using the visual analogue scale (VAS), demonstrating an approximately 90% reduction in pain for a microneedle penetrating 480 m, compared to a conventional hypodermic needle which penetrates several millimetres into the skin. A 700 m microneedle caused slightly more discomfort, but even one that was over 1 mm in length reduced pain by more than 60%[24].

3. Disadvantages of microneedles

There are drawbacks to using a microneedle for transdermal drug administration, including a longer application process, the necessity for many patches in one location, a demand for a certain level of mechanical strength, and the need for a material that is effective for transdermal drug delivery[25]. According to Rzhevskiy et al. The dosage parameters may be affected, and there may be unfavourable side effects as a result of the difficulties in obtaining substantial pharmacokinetic data via the MN patch method. According to Bariya et al., MN depth design should also be significantly taken into account when analysing the variations in the stratum corneum and other skin layer thicknesses across a range of patient groups[26]. The MN device must be introduced orthogonally to the skin's surface in order for the drug delivery and penetration kinetics to work effectively[27]. The medicine dose might escape, or needles inserted at irregular angles might have difficulty penetrating the skin. Additionally, the use of microneedles repeatedly may leave scarring on the skin's surface[28]. Additionally, the geometries and conformation of needle formations may have some disadvantages that reduce their effectiveness. For hollow MNs, for instance, their delivery kinetics and penetrability may be impacted by the compressed tissue that occasionally occurs in specific skin types. However, there are some inherent problems with deploying TDD technologies in general that are not unique to MNs. These consist include skin rashes, redness, pain, swelling, infection at the application site, etc[29].

4. Classification of types of microneedles

Solid, coated, hollow, or dissolvable microneedles have been created using a variety of materials, including sugar, polymers, silicon, and stainless steel (Figure 1). According to Table 1, each type of microneedle has distinct qualities, benefits, uses, and types of materials[30].

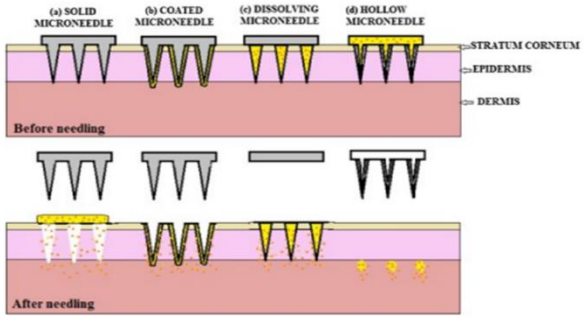

Fig 1. Different kinds of microneedles: (a) Pre-treatment with the skin is done using solid microneedles that are utilized in a poke with patch method. (b) Coated microneedles apply a coating of the medication solution to the needle surface using the coat-and-poke method. (c) Biodegradable polymers are used in the construction of dissolving microneedles. (d) Hollow microneedles that are packed with the medication solution inject the medication into the dermis[31].

4.1. Hollow microneedles

In order to inject or store medication fluid, the hollow microneedle has a hollow, empty core or chamber (Figure 2). The hollow microneedle is able to hold a larger dose or quantity of medication solution in comparison to the solid microneedle. The viability of the epidermis or dermis, which is suitable to use high molecular weight drugs, can also be used by a hollow microneedle to administer the medicine. It is appropriate to be utilised in liquid vaccine formulations since it also regulates the medication release over time[32].

Unlike solid microneedles, which largely elute pharmaceuticals depending upon osmosis gradients, hollowed microneedles are an active drug delivery method, establishing a conduit for drug diffusion through the skin's dermis depending on a non-pressurized drug reservoir. To provide tunable release kinetics, hollow microneedles' production parameters as well as the material composition can be used. Higher concentrations of pharmaceuticals may provide burst-release drug characteristics, whereas matrix-loaded drugs may allow for a constant state of drug release extending days to weeks, based on the application goal. Hollow microneedles can be created to allow for the control of the flow rate and

pressure, similar to hypodermic needles. Rapid release, gradual infusion, or time-dependent delivery rates can be achieved by controlling process variables such as the microneedle dimension ratio (with a height-to-base width ratio). The hollow microneedle has been used to administer a number of vaccines and inoculations with success over the years. The hollow microneedle has been used to administer a number of vaccines and inoculations with success over the years. However, due to the hollow microneedle's relative weakness and the need for special consideration in both needle design and insertion technique, it has garnered less attention than the solid microneedle. Additionally, there are technical issues with the hollow microneedle that include leakage and blockage during the injection procedure[33].

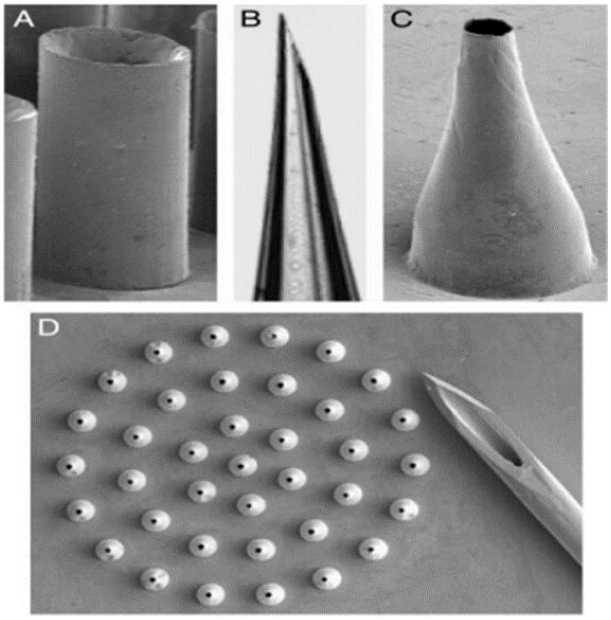

Fig 2. Glass, metal, and silicon hollow microneedles observed by optical and scanning electron microscopy. (A) A 100-needle array of straight-walled metal microneedles made by electrodeposition onto a 200-m-tall polymer mould. (B) A glass microneedle with a tapered, bevelled tip created with a standard micropipette puller (900 m length indicated). (C) Tapered, metal microneedle (500 m tall) electrodeposited onto a polymeric mould from a 37-needle array. (D) A 26-gauge hypodermic needle is displayed next to an array of tapered metal microneedles that are 500 micrometres tall[34].

4.2. Solid microneedles

The stratum corneum is intended to be penetrated by this kind of microneedle structure in order to improve drug administration to the dermis and, consequently, its bioavailability and kinetic transport across the skin. The solid microneedle has a longer lifespan and a stronger immune response than intramuscular administration, making it better suited for the delivery of vaccines. As compared to hollow microneedles, solid microneedles are simpler to produce, have better mechanical qualities, and have sharper points[35]. In addition, a variety of materials, including silicon, metals, and polymers, can be used to create the solid microneedle (Figure 3).

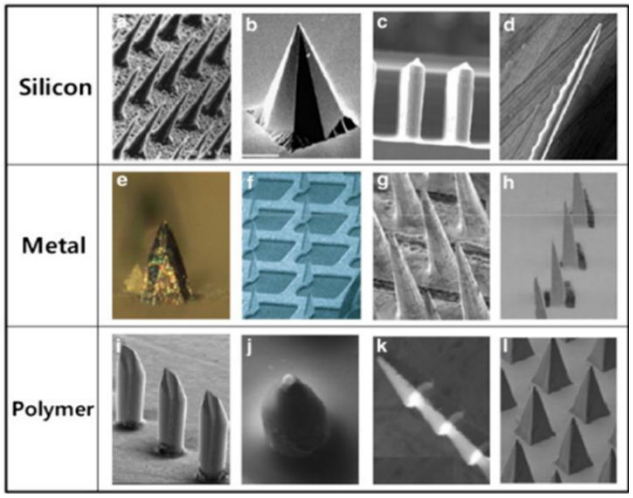

Fig 3. Solid microneedles composed of silicon, metals, and polymers (a–d) (e–h) (i–l) [34].

4.3. Dissolving microneedles

Based on its features, the dissolvable MN, which initially surfaced in 2005, is a promising method. One-step medication application, which promotes simplicity of drug administration, and promotes the quick release of macromolecules are two of these qualities[35]. Due to improvements in the "poke-and-release" dissolvable MN application, this strategy is thought to be superior to other approaches. Using a two-step casting technique, the dissolvable MN needle may be loaded quickly (Figure 4). When the dissolvable MN is inserted into the skin, the needle tip dissolves, allowing the medication load to freely release and spread. The manufacturing process for dissolvable MN is best suited for materials that are water-soluble[35]. The fabrication method best suited for creating the dissolvable MN is the micro-mould technique[34]. Technical know-how is necessary for the creation for a dissolvable MN array. But this kind of MN needs to be completely inserted, which is frequently challenging to do, and it also experiences a delay in disintegration.

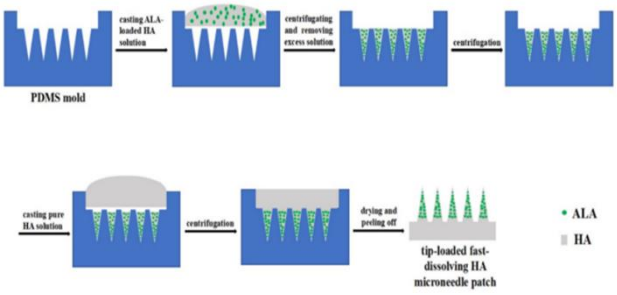

Fig 4. The tip-loaded, quickly disintegrating HA MN patch manufacturing process is shown schematically[36].

4.4. Coated microneedles

The coated microneedle (Figure 5) is a solid-type MN that has been coated in a medication solution. Regardless of the degree of thickness of the coatings layer, it usually contains less of the medicine. The capacity to consistently apply a regulated drug layer to MNs is essential for the efficacy of medication delivery employing coated MNs[37]. Proteins and DNA can be delivered with the least amount of invasiveness using a coated MN. Rapid drug delivery to the skin is a benefit of coated MNs, but the leftover

medication at the needle's tip could spread the infection to other patients. Last but not least, the outcomes of vaccine delivery utilising coated MN were comparable to vaccinations delivered by intradermal and intramuscular methods[38].

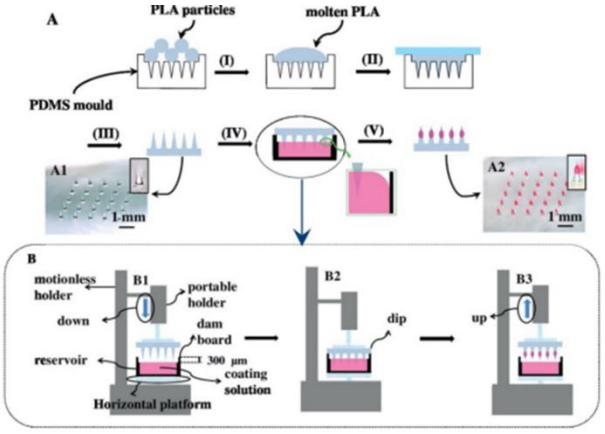

Fig 5. Construction of the coated polymer MNs: (A) A schematic illustration of the construction procedure. The process for creating the coated polymer MNs included (I) covering the polydimethylsiloxane (PDMS) cavities' surfaces with heated and melted PLA, (II) filling the mould cavities with melted PLA, (III) pressing down on the melted PLA and allowing it to cool to room temperature, (IV) dipping PLA MNs in the coating solution, and (V) drying the coated polymer MNs. The 650 m long PLA MNs are depicted in picture (A1). A picture of the 650 mm long MNs coated in formulation III can be found in the image (A2). The adjustable equipment that can be raised and lowered is shown schematically in the image (B). The PLA MNs is seen in image (B2) dipped in the coating solution, and in image (B3) the portable holder is shown emerging from the reservoir[39].

Table 1. Overview: Microneedle Types

MN Type	Characteristics	Advantages	Disadvantages	Application	Material	References
Solid	Creates channels in the skin to allow drugs reach the lower skin layer, Adequate mechanical strength, Sharper tip	Allows more drugs to pass into the skin Easy to manufacture	Damage to the skin and microincisions need to be closed to avoid infections	Drug delivery Cosmetics	Silicon Metal Polymer	
Hollow	Empty shape to be filled with the drug, Ability to control drug release over time	Handles a large dose/ amount of drug solution	Weak needles Require intensive care in terms of needle design and insertion method Might cause leakage and clogging	Disease diagnosis	Silicon	
Coated	Carries less amount of the drug due to the design. Ability to deliver the proteins and DNA in a minimally invasive manner	Deliver the drug quickly to the skin	Prone to infection	Drug delivery Vaccine delivery	Silicon	
Dissolving	Facilitates rapid release of macromolecules	Ease of administration for patients with one-step application	Requires technical expertise to manufacture Takes time to dissolve	Drug delivery Cosmetic Vaccine delivery	polymer	

5. The efficiency of the drug in microneedle

It is crucial to look into how MNs affect these issues because the ultimate purpose of employing MNs is to deliver medications to the skin effectively and painlessly[40]. For solid MNs, it was discovered that MNs with flat tips are superior to those with sharp points for improving skin permeability because increasing the amount of time a substance is held in the skin can also make it more permeable. Additionally[41], increasing the pressing pressure will make the skin more permeable, the improvement in skin permeability was better the longer the MNs were[42]. They hypothesized that this was due to the SC becoming more hydrated as a result of the longer MNs' ability to infiltrate the dermal tissue beneath the SC and permeate it. Until a particular MN length threshold was achieved[43], it was also discovered that longer MNs could improve skin permeability, they explain these phenomena as being caused by the dehydration and compaction of the skin, and they also discovered that an increase in the number of MNs in an array result in a pattern that is comparable to an increase in MN length. However, if the MN density is too high, a "bed of nails effect" may prevent individual MN from disrupting the SC barrier[44]. The MN geometry, but not the insertion speed, impacts the shape and depth of the conduits, hence the MN geometry plays an essential role in the effectiveness of drug administration, it was noted that an MN array with lower needle density and longer needle length may be used to create a better effect[45]. Furthermore, it was found that longer MNs could enhance skin permeability up to a specific MN length threshold[46]. This phenomenon, according to their explanation, is brought on by the skin becoming dry and compacted.

Additionally, they found that a pattern is produced when the number of MNs in an array increase, which is similar to what happens when the length of an MN increases[47]. Individual MN may not be able to breach the SC barrier, though, if the MN density is too high. Up to a certain MN length threshold, it was discovered that longer MNs could improve skin permeability[48]. Their justification is that the skin being dry and compressed causes these phenomena. Furthermore, they discovered that a pattern is generated when the number of MNs in an array increase, which is comparable to what happens when an MN's length increases. Nevertheless, if the MN density is too great, individual MN might not be able to cross the SC barrier[49]. The flow rate rises roughly linearly with rising driving pressure, supporting this prediction, which has been empirically proven, on the other hand, solely explains the link between the geometry parameters of hollow MN and the intrinsic flow resistance without taking into account the presence of 15 skin. It is true that the skin and other elements have an impact on the flow rate of hollow MN[50]. The increased flow resistance that the skin tissues offer causes a significant reduction in flow rate when compared to an MN without skin. discovered that removing or vibrating the MNs can considerably enhance the flow rate. They explain this by speculating that either tissue coring may have caused the dermal tissue to be penetrated into the needle bore or that the dense dermal tissue surrounding the needle tip may have impeded blood flow[51]. It was found that the MN tip's skin's compaction likely squeezes out the majority of the water and greatly diminish its skin's ability to transmit flow. Skin compaction can be relieved and flow conductivity increased by retracting MN. Additionally, it was discovered that a bevel tip aids in weakening the compaction of tissue beneath the needle tip, allowing for an increase in infusion flow rate when utilizing a bevel tip. In stark contrast to those in solid MN, these observed behaviors. Additionally, it was discovered that the MN tip opening size had no discernible impact on infusion flow rate. This is further supported by the fact that, in comparison to the resistance provided by the MN conduit itself, the dense dermal tissue underneath the tip has a major role in the resistance to flow. Hyaluronidase, an enzyme that breaks down hyaluronic acid in the skin's extracellular matrix, can be co-injected with medication formulations to decrease fluid flow resistance in addition to enhancing MN design and delivery methods. A revolutionary hollow blood-collecting MN design was recently proposed[52]. The conduit diameter near the tip is greater than the conduit diameter inside the body section. According to a numerical study, this design gives the MN a mix of high mechanical for high-volume blood, strength, high extraction effectiveness, and low clogging issue collection. Last but not least, it should be noted that the flow rate often rises with deeper insertion, however, injection depth may not have an impact on intradermal immunogenicity One of the most significant benefits of MN is the lack of pain; nevertheless, there are few research on this subject, making it difficult to compare MN versus hypodermic injection[53]. According to our understanding, are the ones who have studied MN insertion pain first. According to experiments, a 26-gauge hypodermic needle causes far more pain than an array of 400 silicon MNs pressed into a human forearm[54]. The MN length had the biggest impact on pain, with a 3-fold increase in MN length leading to a 7-fold increase in pain, according to more in-depth research. MN implantation shorter than 400 m is painless, according to further investigations[55]. Additionally, it was discovered that the quantity of MNs also had an impact on pain, with a 10-fold increase in MNs causing an increase in discomfort of a little over 2-fold. The MN tip angle, thickness, and width have less impact on pain compared to the MN length. Pain in hollow MNs is influenced by the flow of 16 liquid medication solutions in addition to the geometrical size of the MN[56]. According to Gupta et al., higher pressure and MN retraction both make the pain worse, but lower flow rates and the addition of hyaluronidase to the injection reduce pain. additional research was done on the discomfort produced by hollow MNs when delivering various liquid medications at various transportation rates[57]. They discovered that MNs are frequently linked to painlessness. Taking into account these data, we don't think discomfort poses a significant issue for MN designs. The literatures examined in the aforementioned segments make it clear that the optimization of MN involves striking a balance between a number of various elements[58]. This is undoubtedly a difficult task. Fortunately, several bio-microneedles exist in nature that have superior integrated features. Studying and learning from them may provide us with some ideas for enhancing the MN design. We shall evaluate a few bio-microneedle experiments in the section that follows[59].

6. Factors affecting delivery efficiency

solely on the shafts of microneedles are coatings deposited. Any medicine coated over the array of microneedle is sometimes far of microneedle since only microneedle shafts reach the skin shafts cannot be delivered and makes the delivery procedure ineffective. It is possible to calculate the base area of the microneedle array's contribution to the inefficiency[60]. For instance, a 4 4 mm patch with 3364 microneedles makes up the conventional microneedle patch formulated to utilize into gas jet-assisted drying coatings with a 110 mm length and a 25 mm base diameter, each microneedle is small. Even if the shape of these microneedles is not conical, an approximation of the calculation assumes it to be so. In this case, the total surface area of the microneedles is therefore estimated to be around 14.6 mm2, plus an exterior zone over distance through them is estimated to be around 14.3 mm2. Due to the drug coating a core membrane as regards microneedle array, approximately 50% of the drug, if coated uniformly on the patch, would be squandered. The microneedle patch's base substrate should therefore remain uncoated in order to attain improved distribution efficiency[61].

A thick coating of substance on the microneedles. According to observations, as the amount of coated material increases, the delivery efficiency then declines beyond a particular threshold it was discovered that the amount of radiolabeled ovalbumin coated on the microneedles affected the effectiveness of delivery in hairless guinea pig skin[62]. When a high dose (25 mg) was coated, a delivery efficiency of 27% was seen; however, when a low dose (5 mg) was coated on the same patch, a delivery efficiency of 50% was seen. The study also discovered that, despite an increase in the amount of 5-aminolaevulinic acid on a microneedle patch from 206-350 to 458-680 mg/patch, the delivery efficiency had decreased across the dosing range, from around 90% to 60%. observed a threshold effect that was similar. When they coated tramadol onto microneedles, they observed that the ensuing distribution efficiencies were similar and measured at 73% and 72%, translating into delivery of 139 and 185 mg tramadol, respectively, at 20% or 30% (w/v) of tramadol in the coating solution. To the contrary, when the tramadol mass in the coating solution was raised to 50% (w/v), Nevertheless, despite the coatings containing a larger mass of tramadol, distribution efficiency decreased to 26% and a much smaller mass of tramadol was delivered (78 mg). When microneedles were inserted into the corneas of sedated rabbits, a similar result was seen[63]. While the amount of bevacizumab coated on microneedles increased from 1.1 to 7.6 mg, it was observed that the delivery efficiency decreased from approximately 52% to 44%. The duration of coated microneedles' tissue residence.

Additionally, it has been noted that if the coated amount is constant but the patch's use period is prolonged, the delivery effectiveness will rise. In a study by Peters et al. (2012), when a patch coated with 100 mg of erythropoietin was applied to skin for 15 minutes, a delivery efficiency of 75% was attained. This efficiency increased to 90% when the patch was applied for two hours. Similar results were seen when Zhang et al. (2012a) coated lidocaine on microneedles in a different investigation. As the wear time grew from 1 to 4 minutes, the distribution efficiency for a lesser dose (about 90 mg/array) increased from 53% to 71%. After a wear period of 1 minute, a substantially lower delivery efficiency was seen at a larger dose (around 225 mg/array), which increased to 28% with a wear time of 4 minutes[64]. When compared to the low dose group, it was still noticeably lower. One explanation for these phenomena is that a bigger quantity of material may not dissolve right away in the tissue's limited local interstitial fluid if it is supplied into the skin utilizing coatings. Because of this, if the microneedles are taken out while there is still material at the deposition site that has not yet been dissolved, the microneedle can only remove a small portion of it, which results in decreased delivery efficiency. The substance dissolves in the local tissue fluid and fades away from the delivery site, however, if the microneedle is allowed to remain in the skin[65].

Other aspects, The active molecule's hydrophobicity can also have an impact on delivery effectiveness. In one investigation, using low, medium, and high water-soluble peptides resulted in considerably variable delivery efficiencies of roughly 46%, 59%, and 90%, respectively, although all other parameters were held constant. The position of insertion can also affect how efficiently a delivery is made. For instance, Ma et al. (2014) found that when ovalbumin-coated microneedles were used, a delivery effectiveness of 64% was attained in the rabbit lip, compared to a much greater delivery efficiency of 91% when the patch was placed in the tongue. When opposed to the tongue, the lip has a smaller flat region where a microneedle patch can be inserted, which could have decreased delivery effectiveness[66].

7. The material used in the fabrication of microneedles

MNs have been created using a variety of materials, including metals, glass, zeolite, sugars silicon, and polymers. As research progresses, fabrication complexity decreases and the mechanical strength, geometrical forms, and needle sharpness all improve[67]. MNs Depending on the material used in their construction, MNs can be categorized as either biodegradable or non-biodegradable. The prototype material and its % usage in MN fabrication are given in Table 2.

Table 2. Materials used for fabrication of microneedles

Materials utilized for Microneedles	Materials utilized for publication in percent
Polymer	68
Ceramic	3
Glass	5
Metal	14
Silicon	10

The initial material used for MN manufacturing was silicon. Due to their exact 3D architectures and widespread application in target medication administration, silicon MNs were specifically manufactured for this purpose. However, because the needle is so brittle, there is a significant chance of it shattering as it is being inserted into the skin. The proportion of MNs was made public in a number of materials. Various keywords' hits were analyzed to calculate percentages[68].

1. Metal material.

Stainless steel was the original metal used in the construction of MN arrays. Metal MNs are created by either physically forcing the smallest stainless steel hypodermic needles through a support material with a preset thickness or by laser cutting metal sheets into MN shapes and twisting them out of the plane. This type of MNs avoids brittleness and is more suited than silicon because it is non-biodegradable. Nickel, titanium, palladium, and stainless steel are often utilized metals in the construction of MNs. Laser micromachining, laser ablation, and photochemical etching are among of the different fabrication techniques utilized for metal MNs[69]. Author Gill et al. created the stainless-steel MN by designing it on Auto CAD for the appropriate form and array orientation, cutting it out using a laser, then manually bending it at a 90-degree angle from the sheet. Choi et al. created titanium MNs using the alternate technique, lithographic masking. They produced a row of five in one plane MN and then underwent wet etching. The presence of atenolol analyzed the result at the receptor site by LC-MS, and the stainless-steel MN array has a greater transcutaneous flux than the other materials. A comparative study was conducted to determine the in vitro transdermal penetration of atenolol in the porcine ear skin by the stainless-steel, silicon MN array, or gold—titanium MN roller. Within the transdermal medication administration system, metal material's hardness and mechanical qualities are benefits[70].

1. Polymer

In comparison to metals and inorganic materials, polymers are the most promising material for the manufacture of MNs. MNs that are solid, coated, and hollow have all been created using the polymeric material. The polymers have viscoelasticity to increase resistance against shear-induced breaking and are less costly, biocompatible, and biocompatible[71]. The polymers are one of the popular materials used in the creation of MNs due to their compatibility and biodegradability. The majority of MNs that dissolve and generate hydrogels are made of polymers, whereas medication delivery is done via the poke-and-release method. There aren't many polymers that are employed to make solid coated or hollow MNs. Drugs and polymers are typically coated on MNs using the dip coating, inkjet printing, and spray drying methods. Due to polymer degradation-based drug release, high drug encapsulation can be accomplished in the event of dissolving needles. Due of their gradual disintegration over time, biodegradable polymers can be used to produce sustained release. Polyvinyl alcohol (PVA), hyaluronic acids (HA), polyvinyl pyrrolidone (PVP), poly-L-lactic acid (PLA), poly caprolactone, (PCL) Polylactide-co-glycosides acid (PLGA), polycaprolactone (PCL), poly-glycolic acid (PGA), carboxymethyl cellulose (CMC), sodium alginate, chitosan, fibroin, and others are among the polymers used to make MNs[72].

1.1. Biodegradable

Natural and manmade polymers are combined to create the polymeric biodegradable MNs, which enhance drug delivery with a sustained or prolonged release at the desired site. The main synthetic materials used to make MNs are polycarbonate , polylactic acid (PLA) polyglycolic acid (PGA), and their copolymers , polystyrene (PS), polycaprolactone (PCL), and (poly(lactic-co-glycolic acid) (PLGA) , while natural biodegradable polymers like silk, chitin, and chitosan dissolve or degrade in the body through a metabolic process without causing any harmful hyaluronic acid, amylopectin, hydroxypropyl cellulose, dextrin, , carboxymethyl cellulose, alginate, and chondroitin are some more examples of naturally occurring

polysaccharides that degrade naturally. These substances have been utilized as biodegradable MNs[73]. The manufacture of MNs utilizing biodegradable polymers using a molding process is a unique strategy that enables reliable and affordable mass production. For the production of biodegradable MNs, polycaprolactone (PCL), polyglycolic acid (PGA) and their copolymers polylactide-co-glycol ide acid (PLGA), and poly-L-lactic acid (PLA) are employed because they are biocompatible, mechanically durable, economical, and resorbable. When pushed into the skin, biodegradable MNs eventually fracture, raising further security issues as it breaks down and travels into the skin[74]. The negative consequences of biodegradable polymers are often mild. The medication may be placed inside MNs and then injected into the dermal layer; as the polymer dissolves or degrades concurrently, the medication is delivered into the skin. This process does not result in any biological hazards, such as waste from sharp objects. Due to the low melting temperature at which this polymer material may be processed, micro-molding is the method of choice because of the polymer's potential for application in the production of MNs. The disadvantage of polymers is that they typically buckle catastrophically when injected or sampled during blood collection. In order to create an arrowhead with a sharp tip and a metal shaft as the basis. synthesized the biodegradable polymer MN. This production of intellectual property necessitates intricate procedures and additional expense. Because they are highly efficient, affordable, and secure, certain carbohydrates are a great source of natural materials for the production of MNs. Carbohydrates have a high degree of biocompatibility, are less poisonous, and result in strong products. Because they exhibit biocompatibility, are less expensive, and have sufficient mechanical strength for insertion into the skin, carbohydrates are a promising source of biodegradable polymers. This comprises several sugars utilized in the manufacture of MN, such as mannitol, trehalose, galactose maltose, and sucrose[75].

1.2. Nonbiodegradable.

The process of creating the non-biodegradable polymers typically involves live creatures in one manner or another. They have been identified as belonging to the xenobiotic class and were created artificially; hence, they are chemicals rather than natural polymers. There are several examples of xenobiotics that can be biodegraded, therefore not all xenobiotics are non-biodegradable[76]. The most abundant natural polymer, lignin, dissolves by specific microorganisms at a relatively slow rate, therefore we cannot declare that all-natural polymers are biodegradable. The Polyhistor is a biopolymer produced by fermentation of a recombinant E. coli bacterial strain and can yield significant amounts. Additionally, there are more advanced techniques such as in vitro enzymatic production, which involves immobilizing the lipase enzyme of Candida Antarctica in the presence of epsilon-caprolactone and 11-mercaptoundecanoic acid[77]. Because these polymers cannot be made from straightforward organic carbon components (lipids, carbohydrates), as well as from inorganic sources (Sulphur, sulfates), the poly thioesters are not biodegradable. Instead, they must be made from precursor substrates. The chemical synthesis of poly thioesters was first described in 1951; however, more recent research has shown that the yield of these compounds is low and not saleable for commercialization due to the scarcity of precursor substrates and the rarity of their occurrence in natural settings other than carbon sources[39]. Extracellular enzymes, or those found at the cell surface, are responsible for the breakdown of poly thioesters. Because of the polymer's high molecular weight and water-insolubility, the breakdown of poly thioesters is constrained, which lowers the entry of this method and does not result in enzymatic breakdown; the polymer enters a cell or the periplasm (cell surface)[78]. Hexadecane, which is broken down by several microorganisms, has a lower molecular weight than polyolefin, which is an example of a non-degradable polymer (polyethylene). Polyphenols and poly isoprenoids are poor biodegradable, water-insoluble polymers that break down slowly. Lignin is a type of cellulose that is widely used, although only specific fungi like white-rot fungus or others can break down sporopollenin. Natural rubbers (cis-1,4-isoprene) derived from the Hevea Brasiliense's rubber tree are examples of poly isoprenoids, and only Gram-positive bacteria are capable of degrading them[79].

1.3. Natural polymer.

Although they are more resilient than silicon and metals, polymers have a lower tensile strength. Proteins, polysaccharides, synthetic and semi-synthetic polymers, as well as many other naturally occurring polymers, are all utilized in the creation of MNs. These polymers are primarily employed to create solid, soluble MNs and coat the additional substance. As a highly efficient, affordable, and secure natural resource, carbohydrates make good MN building blocks. Carbohydrates make products with considerable strength and have a significant amount of biocompatibility and less toxicity. Carbohydrates can be shaped into ideal MNs that are inexpensive and biodegradable utilizing the master plate approach. They can be molded into active ingredient-carbohydrate mixes after being combined with active substances; upon implantation, the drug-carbohydrate mixture dissolves into the skin[80]. It is possible to create MNs using a variety of sugars, including galactose, maltose, sucrose, mannitol, and trehalose. The FDA-approved excipient in the parenteral preparation, maltose, is mostly utilized to prepare an MN array. The author Gouhua et al. does an in vitro investigation on the transdermal administration of monoclonal antibodies utilizing maltose MN on a human IgG protein model. Following the removal of the methylene blue by the maltose MN, the cryosection MN was pierced into the skin. Human IgG is delivered at a higher rate as the MN's length and arrays expand. The other ingredients, such as starch and gelatin, can also be employed because they dissolve into the skin within five minutes of injection[81]. The rat model was utilized to study the hypoglycemic effects of MNs, and it demonstrated that subcutaneous injections had an equal effect. The derivatives of collagen such as zein, silk gelatin, zein, and gelatin are the materials utilized to create protein-based MNs, and it is thought that these materials will carry high molecular weight protein-based medications and vaccines more effectively and more steadily into these MNs[71]. These proteins are increasingly being used for fabrication since they are often affordable and simple to create utilizing micro-molding[82].

2. Natural polysaccharide for Microneedles

Because of their biocompatibility, biodegradability, affordability, availability, simplicity of manufacture, and sustained distribution, polysaccharides are primarily employed in transdermal drug delivery. They come from living things that are found in nature, including plants, animals, microbes, and others[83]. They consist of biopolymers such as chitosan, dextran, and hyaluronic acid, among others:

(1) MNs based on chitin and chitosan:
(2) MNs Starch-based
(3) MNs based on cellulose: (4)
(4) MN based on chondroitin sulfate and
(5) MNs based on hyaluronic acid.

2.1. MNs based on chitin and chitosan

D- and N-acetyl-D-glucosamine units can be found in the -(1,4) linkage.

The molecular weight of this polymer, which ranges between 300 and 1000 kDa, makes it insoluble in water. By combining it with PLGA, this bottleneck can be removed because the reduced molecular weight corresponds to weak mechanical strength. However, chitosan naturally possesses antibacterial and wound-healing capabilities[84]. These MNs for the delivery of doxorubicin and Ausmus nanorods were created by combining micro-molding and electro-spraying methods. When the temperature was raised by 12 C while being exposed to near-infrared irradiation, it was found that Dox@MicroN patches had good photothermal capacity. These MNs, however, have gotten through a tumor-impersonating agarose gel and support layer-dependent drug release. However, the thiol group's addition increased the mechanical performance, and as a result, thiolate MNs have good mechanical strength and sharpness. Mei-Chin Chen et al. investigated MN made of chitosan and filled with bovine serum albumin for transdermal application. The produced MN demonstrated an eight-day in vitro drug release rate of 95% and a 300 m penetration depth[85].

2.2. MNs Starch-based.

A versatile biomaterial, starch has been investigated for use in a number of biomedical applications. It gives brittleness and can be used for many current issues. Numerous studies on starch-based MNs have been published, including one by Yujie Zhang et al. who created dissolving glucose-responsive, insulin-releasing MN patches for diabetes. The mechanical strength of MNs was enhanced by starch. The production of MN-loaded losartan using a starch and gelatin mixture was investigated as a proof-of-concept for transdermal applications[86].

2.3. MNs based on cellulose

A natural biomaterial known as cellulose can be derived from a variety of sources, including wood, cotton, bacteria, and algae. A beta (1,4) connection of glucose monomers is present. The use of cellulose in biomedicine has been reported. In cosmetics, cellulose nitrate is used to make films. It has been patented to use cellulose-based MNs into cancer management[87]. Additionally, researchers at Carnegie Mellon University and the University of Pittsburgh looked into the possibility of using (CMC) carboxymethyl cellulose MNs to incorporate various immune-stimulating and chemotherapy drugs for skin cancer. These MNs hold patents for both the delivery of anti-cancer drugs and genes. For transdermal medication delivery, Yong-Hun Park et al. showed the manufacture of cellulose-based MNs utilizing replica molding and laser writing. The produced MNs showed a three-fold increase in permeability, and as a result, it was thought to be an effective fabrication procedure even for cosmetic applications. For dermo-cosmetic applications, (BC) bacterial nano cellulose MNs and soluble hyaluronic acid (HA) have been employed. It was shown that combining HA and BC gives MNs the right amount of mechanical strength while BC encourages the regulated release of medication molecules. In vivo, investigations have validated this MN's safety profile[88].

2.4. MNs based on chondroitin sulfate.

It is a polysaccharide substance that is naturally occurring and is utilized as sodium chondroitin sulfate. It is utilized in the creation of dissolving MNs since it possesses some prospective qualities including high hydrophilicity and biodegradability. The body's extracellular matrix and cartilage both include it as an essential component. Desmopressin and rhGH-loaded sodium chondroitin sulfate and dextran MNs were created by Fukushima et al., who also found that the concentration varied depending on the amount of the compounds added. An MN array was also created by Poirier et al. utilizing CS and hydroxyethyl starch. Hepatitis B surface antigen and QS-21 saponin, which functions as an adjuvant, were placed onto the prepared MN array. According to stability analysis, antigenicity was still present at 37 after six months, and a 10% reduction was seen at 50 C[89].

2.5. MNs based on hyaluronic acid.

HA has mucoadhesive characteristics and is a natural, important extracellular component of cartilage and matrix. In the form of nonsulfated glycosaminoglycan, it is widely distributed throughout the human body, including the dermis, synovial fluid, tooth pulp, and vitreous humor[90]. It is in water-soluble salt and has a negative charge form. It is described in a variety of lengths between 200 and 800 m[91]. The high-water solubility of HA MNs has numerous manufacturing advantages, including increased economic gains and high drug loading. 5-Aminolevulinic acid-loaded HA MNs were explored by Jinjin Zhu et al. for the effective pharmacodynamics therapy for the penetration of superficial tumors that demonstrated long-term stability and deep penetration. As part of immunochemotherapy, hyaluronic acid is utilized in combination with phototherapy and gene therapy[92]. For efficient distribution, p53 DNA and IR820 can be easily inserted into the HA MN patch. To cure melanoma and epidermal cancer, Ying Hao et al. created HA-based MNs[93]. MNs demonstrated a regulated release of the medication. To increase solubility and mechanical qualities while treating psoriasis, Hongyao et al. created HA-based MNs. The FDA-approved product is called Microhyala, and it dissolves in gastrointestinal fluid while being degraded by lysosomal enzymes. Saha et al. demonstrated the use of the HA MN array in the domains of medicine and cosmetics. Micro molding, photopolymerization, and drawing lithography are a few techniques utilized to create MNs[94].

2. Silicon

Silicon is frequently utilized to make solid and coated microneedles because it has sufficient mechanical strength for skin implantation; using deep reactive ion etching and photolithography[95], silicon microneedles with small, sharp points and lengths of 100 m or less can be precisely made However[96], the pricey method, expensive equipment, and slow manufacturing speed all must be considered When the silicon microneedle separates from the skin and pieces are left in the tissue, there may be safety issues Recently, silicon has replaced solid microneedles in reverse master moulds[97].

3.Glass.

micropipette puller or wet etching). It displays sufficient strength for skin implantation, making the tapered shape easier to process. Because the substance is stable at high temperatures and pressures and is biocompatible, sterilisation is simple. However, it is brittle and breaks readily. Specifically, if the microneedle's tip breaks and stays in the skin tissue, it may result in inflammation or granulomas.

3. Ceramic.

Studies have looked into the usage of ceramic materials in the creation of microneedles because they are biocompatible and have sufficient mechanical strength, like calcium sulfate, alumina, and calcium phosphate[98].

8. Characterization of MNS

The amount of water that remains in the polymeric MNs affects both mechanical strength and indentation resistance significantly[99]. Because of this, we now briefly examine how MNs are described. For instance, the mechanical characteristics of the soluble MNs can be altered by the addition of sucrose[100]. Additionally, compared to MN formulations without sucrose, sucrose/dissolvable MNs formulations release their sucrose more quickly after the addition of sucrose. Proteins require gentle manufacturing techniques because, in contrast to low-molecular-weight pharmaceuticals, they are sensitive to pH, temperature, and fabrication techniques[101].

Biomolecule activity

A free biomolecule has greater stability and sensitivity to temperature, humidity, and solvent storage than an encapsulated biomolecule does[102]. In contrast to organic molecules, proteins, antibodies, and viruses are particularly vulnerable to degradation. This is especially true if proteins are exposed to certain organic solvents, like dichloromethane, ethyl acetate, and dimethyl carbonate (DMC), which are used in the double emulsion method to produce PLGA microparticles[103]. The thermostability of MNs is highly intriguing because both liquid and commercially available lyophilized medications lose their activity after being preserved at room temperature. High temperatures, vacuum, or exposure to a UV source are frequently used in the manufacture of protein-loaded MNs, all of which may be detrimental to the protein's ability to function[104].A different method involves encapsulating the medications in a polymeric matrix, which has the benefit of delivering a greater dose of medication in a single phase. In fact, the encapsulation of proteins in micro/nanomaterials has already been researched utilizing a variety of techniques, including single/double emulsion, microfabrication, and electrospray. For example, protein solutions can be used to hydrate a mixture of lipids whereas lipid nanocarriers can be used to encapsulate proteins. In this way, therapeutic proteins like insulin or inactivated flu vaccinations can be encapsulated inside of microneedles[105]. In particular, the inactivated influenza virus vaccine was able to be enclosed by microneedles made of a biocompatible polymer. This, when injected under mice's skin, elicited a strong immune reaction and an effective immune response, offering full protection from influenza. In a different investigation, dextrin was used to make insulin-loaded microneedles that could deliver the hormone via the skin. This formulation was able to keep the active insulin intact even after a month of storage at temperatures between 80 and 40 °C[106]. According to additional research, utilizing MNs that dissolve and are composed of a starch/gelatin matrix improves the stability of insulin at room temperature or a little higher for at least a month. A recent approach for encapsulating BSA in MNs was devised by Yang et al. using photolithography and low UV light exposure. They examined the protein's primary, secondary, and tertiary structures to test its stability, and they found that the protein was completely stable under normal operating settings[107]. Additionally, embedding Human Growth Hormone (HGH) in dissolvable MNs enabled the maintenance of its full activity during encapsulation and the retention of the majority of HGH activity following storage for up to 15 months at normal temperature and humidity levels. In addition, immunoglobulin G-loaded microneedles made of hyaluronan produced positive outcomes (IgG). During the preparation procedure, protein stability was maintained by these MNs' capacity to quickly and effectively dissolve in the skin. The molecular, submicron, and micron-size levels of protein stability and aggregation were specifically examined. Additionally, other research focused on the stability of proteins in microneedle formulations, highlighting how proteins can be treated using this technique[108].

9. Sterilization and storage

Before MNs are commercialized, scaling up should take into account sterilization, packaging, and storage. Unlike conventional transdermal delivery platforms, MNs penetrate the skin's outermost layer of protection, the epidermis, and the dermis, which are typically sterile regions of the body[109]. MNs are therefore required to be free of any microorganisms that can lead to skin infections or other systemic diseases. Additionally, the bioburden needs to be under control to prevent stimulating the dermal and epidermal immune cell populations. Actually, according to certain studies that have been published, the capacity of microbes to pass through the skin holes caused by MN insertion appears to be negligible[110]. According to certain research, solid silicon MNs have a smaller effect on infections like Candida albicans and Pseudomonas aeruginosa than 21G hypodermic needles do on the ability of those organisms to cross cell membranes. Along with these findings, a different investigation by Wei-Ze et al. revealed that rats treated with solid silicon MNs did not develop Staphylococcus aureus septicemia. The MNs should always go through a thorough sterilizing procedure, though, as that is the best course of action. After the manufacture of MNs is complete, one of the options is to use gamma radiation. In accordance with several investigations on hydrogel MN arrays, endotoxin levels were below the FDA's (20 endotoxin units/device) limitations and no significant bioburden was found in any gamma-sterilized devices[111]. Utilizing substances with antibacterial properties, such as polymers functionalized with quaternary ammonium and chitosan and its derivatives, is another strategy that might be used. Regarding the health of the chosen materials, there are additional safety issues that need to be considered in this situation. A balance between antibacterial activity and cytotoxicity, as well as biocompatibility and safety, are required in the materials chosen in order to prevent the onset of local or systemic reactions. To prevent modifying the product and raising manufacturing costs, sterilizing techniques should be carefully chosen. Heat or microwave heating, for instance, could harm MNs or their cargo, and aseptic processing could be costly[112]. If sterilization were to be avoided, GMP production would be required. When it comes to storage, it is important to preserve the patches in a state free of humidity, such as in a desiccator, because MNs are extremely sensitive to temperature and mechanical stress. But long-term patches need stability studies, too. The mechanical strength of the microneedle patches is affected by environmental humidity, according to a study by Hiraishi et al. The mechanical failure force test revealed that the needle strength reduced with increasing humidity. A controlled environment can actually cause proteins to unfurl, aggregate, or degrade chemically, therefore wet circumstances are not ideal for maintaining protein stability. However, as was already said, MNs don't require a cold chain because keeping at low temperatures is increasingly being used to transfer medicines to underdeveloped nations without the requirement for specialized personnel, like as nurses and doctors[113].

10. Barriers in microneedles drug delivery system

Beginning as a straightforward, smaller alternative to hypodermic needles, microneedles (NDs) have developed into sophisticated micro-biomedical tools that can administer a variety of treatments[114]. To reach the deeper skin layers, pharmacological payloads (such as tiny molecules, proteins, DNA, etc.) must pass through the stratum corneum barrier. There is a great deal of interest in and quickly expanding research on "NDs" since this painless and secure method of drug delivery is one of the most promising platforms for administering medications and vaccines through the skin. A deeper comprehension of the biomechanical and drug-diffusional features

of skin is necessary for the design and development of NDs that can successfully complete clinical trials and meet pre-clinical characterization standards. Design and material decisions for NDs may be made for the best possible therapy with knowledge of these biophysical properties of the skin and how microneedles of different geometries interact with the skin. The majority of published review studies to date have mostly ignored skin biomechanics and drug permeation/diffusion qualities in favour of discussing the material composition, mechanical strength, and drug loading capacity of NDs. By emphasizing the skin biomechanics, in particular the mechanical characteristics of the skin during an NDs insertion event, the numerous analytical methodologies used to calculate skin layer thickness, and the drug diffusion kinetics following the application of NDs, we want to fill this gap in the field. In addition to shedding some light on the origins of some of the imbalances seen between preclinical and clinical research using NDs, we did so by addressing the skin biomechanics elements[115].

10.1. Skin layers thickness

However, it should be emphasized that there is variance based on anatomical position, individuals, diverse species, and disease types. Over the past few decades, there have been significant advancements in measuring the thickness of the various skin layers. By adjusting the length of their projections to a depth below that of the skin's nerve endings, which are located at a depth of around 1,000 m, NDs enable the delivery of therapeutic payloads without inflicting any discomfort. In order to properly construct the length and geometry of the ND projections, it is crucial to be able to precisely determine the skin layer thickness and the depth of various locations and anatomical features that the projections may affect[116]. The term "thickness" directly correlates to the number of cellular layers in the VE, and the "shrinkage effect," defined as the retractable qualities of excised skin due to the collagen and elastin fibers, plays a vital role when embedding the excised tissue in paraffin/formalin solution. Other non-invasive methods to measure the SC and VE thicknesses, including magnetic resonance imaging, pulsed terahertz radiation, ultrasonography, conductance and capacitance, and infrared (IR) spectroscopy, have been researched, but their resolution is insufficient to accurately measure SC thickness[117]. The concentration of water in each layer can be measured using optical coherence tomography (OCT) and confocal Raman spectroscopy (CRS), with CRS being found to be substantially more sensitive than OCT when monitoring a thinner SC site (15 m). In order to better understand how water and lipid-based formulations affect the hydration characteristics of the SC layer and the subsequent impact on SC thickness in human volunteers, Crowther et al. proved the value of CRS assessment of SC thickness. Because of the osmotic actions of the moisturizing components, lipophilic-based moisturizers enhanced SC thickness while hydrophilic moisturizers decreased it[118]. Using reflectance confocal microscopy (RCM), Berar esca et al. measured the human SC thickness at several anatomical places and found that it was thinner on the volar forearm than on the dorsal forearm and face. It is important to keep in mind that the type of analytical tool utilized determines the thickness of the skin layer. In addition, it is challenging to directly compare such data with experimentation techniques because of the skin's strain rate. According to data obtained in using a variety of measuring methods and skin sites, different species' skin layers differ in thickness[119]. Because of this, it's crucial to create and characterize NDs' penetration qualities using human skin or a suitable substitute with a skin layer that's identical to the skin. The use of suitable models will assist in choosing the right material to produce NDs and the perfect ND geometrical parameters (height, base diameter, intermeddle spacing, etc.) to ensure sufficient mechanical strength for successful penetration into the skin without inducing a pain response[120].

10.2. Biomechanics of skin and viscoelasticity

Invasion can be stopped by the skin's natural barriers quite effectively toxin and pathogen levels. Skin biomechanics and viscoelasticity are crucial components of that barrier; the SC layer, which is made up of dead keratinized cells, offers an elastic barrier above the strain-rate-dependent VE layer, followed by the dermis, which contains collagen, blood capillaries, and neurons[121]. The dermal-epidermal junction, an important thermal and mechanical unit of the skin tissue, connects the dermis to the epidermis by a basement membrane (basal membrane) which are shown in (Fig 6). As a result of mechanical signals (environmental stresses or deformation), fibroblast cells constantly produce both collagen and elastin fibers in the extracellular matrix (e.g., mechanoenzyme).[122] The highest papillary layer, which is undulating, and the bottom, thicker reticular layer is the two additional divisions of the dermis. These divisions are often distinguished by the varied cellular density, fiber distribution, vasculature, and neurons[123]. In the papillary dermis, where collagen fibers are less dense and more structured in space, the stress-strain relationship of the collagen is divided into three phases; the reticular dermis contains a dense distribution of collagen fibers, which become less dense in the deeper areas as it reaches the dermis; I pre-load: Skin tissues tend to be isotropic at low stresses, with the predominant response contribution coming from elastin and ground matrix, while collagen fibers are undulated and crimped; (ii) under load: With increasing mechanical load, collagen fibers gradually unfold and align, when more fibers un-crimp, the stiffness increases even further; (iii) post-load: the collagen fibers de-crimp after the mechanical load has subsided[124]. As a result, the extracellular matrix, collagen fibers, and elastin all contribute significantly to the body's reaction to stress and strain. The widespread consensus is that skin tissue is viscoelastic and anisotropic, meaning that it responds to external mechanical stimuli differently mechanically in the axial and circumferential directions. The skin tissue can be modeled as a fiber-reinforced material, where an exponential stress-strain relationship is established that is associated with the reinforcement of the tissue as well as the progressive alignment of the collagen and elastin fibers. Since the extracellular matrix fibers are the main mechanical components of the skin tissue[125]. The dermis, with its collagen and elastin in the matrix, gives skin strength and flexibility during puncture, with increased stiffness as the fibers straighten, while the hypodermis aids in tissue deformation during an ND's penetration event. It is obviously crucial to comprehend the skin biomechanics during a penetration event in order to rationally design NDs before to fabrication. This is especially true for figuring out the best NDs geometries, application techniques, and ways to produce reproducible NDs penetration. The effects of altering skin resistance to ND indentation by applying an external stimulus to the tissue were recently studied by Kim et al. A significant obstacle to generating reliable ND penetrations is the skin's innate viscoelasticity and uneven surface[126]. Depending on the height of the ND shaft, the skin can fold around the insertion point, piercing may be partial or not at all. For any given ND design, it is crucial to comprehend the force needed for repeatable skin penetration. In fact, it has been shown that the force used to apply ND has an impact on how deeply it penetrates the skin. Instead of depending on manual insertion of NDs, this study suggests the use of an appropriate applicator device to assure uniform ND penetration from patient to patient. However, the expense of producing such extra devices and patient compliance must also be taken into account[127].

To make sure they won't buckle after skin implantation, the mechanical characteristics of NDs (elastic modulus) must also be examined. The applied force to the ND tip must be greater than the skin resistive force, or about 0.03 MN, in order to overcome the skin's viscoelasticity. The critical buckling load of a single ND lowers with rising ND height, whereas the failure force—defined as the force at which a partial ND penetration occurs—increases with reduced ND shaft height[129].

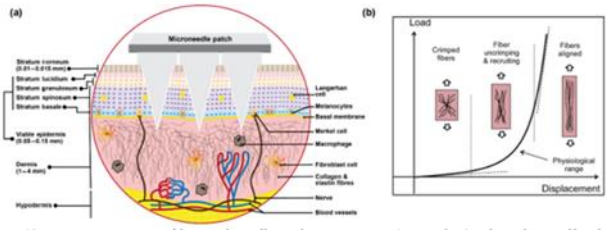

Fig 6. Diagram representation of various human skin layers[128]

Because of the larger ND capacity, raising the ND shaft height increases maximum cargo loading but also causes more pain. While increasing the number of NDs in an array can increase the amount of embedded cargo, it also makes skin piercing more difficult. The closure of the skin's micropores is another important factor because it affects how quickly drugs diffuse into the skin's interstitial fluid and microvasculature. A solid ND array's produced micropores were seen to be close to around 25% of their original diameter in the first 30 minutes, and then virtually completely after about 6 hours. It has been demonstrated that the skin's viscoelasticity and ND shape both affect how much medication is entrenched in the skin and how quickly it dissolves[130]. On conical NDs, reducing the ND aspect ratio (base diameter to height ratio) and ND tip radii decreased the skin insertion force while also drastically reducing the amount of medicine implanted in the skin. Similar results were observed for pyramidal NDs, however the amount of drug penetration through the skin was decreased by widening the intermeddle space between two neighboring NDs[131]. Additionally, increasing the drug's molecular radius and the amount it is loaded into the NDs matrix has resulted in faster breakdown, which increases the amount of drug that diffuses effectively through the skin. According to a recent study, conical NDs dissolve more quickly than conical heads on cylinders, rectangular pyramids, and hexagonal pyramids. To improve drug distribution into the skin, more needles must be inserted and the time it takes for them to dissolve must be shorter[132].

11. Microneedles applications

The main goal of the solid and hollow MNs, which were first used for drug delivery uses, was to improve skin permeability in comparison to ordinary hypodermic needles. For better intradermal drug administration, the MNs were coated or filled with drug formulations or solutions. MNs are currently the most innovative drug delivery method in a number of areas, including intracellular, intradermal, and ocular drug administration. Nevertheless, the transdermal route continues to be the primary use for MNs, particularly for vaccine-based delivery.

11.1. Drug Intradermal Delivery Using MNs Formulations

Because of the stratum corneum's toughness and barrier qualities, drug administration to the skin is difficult because it may involve local or systemic application[133]. The human stratum corneum, which is 10–15 m thick, nevertheless forbids the use of therapeutic doses of medications. Having a molecular mass of less than 400 Da and a greater log P, the Food and Drug Administration, or FDA, licenses more than 20 medications for use in transdermal patches[134]. Despite the skin's small micron sizes and difficult barrier, fresh MNs formulations were created to cross the stratum corneum and load the medicine into the dermal skin without inducing any discomfort or bleeding in the human host. MNs boosted the number of medications given through the dermis, taking low molecular weight, biomolecules, vaccines, proteins, and other substances into consideration[135].

11.2. Drugs with Low Molecular Weights (Small Molecules)

In comparison to larger molecules or biomolecules, which might easily permeate the skin, medications with low molecular weight or small molecules have higher skin diffusion coefficients[136]. This is done so that MNs can swiftly carry the tiny chemical to the skin. For enhanced HIV infection therapy and long-acting drug delivery, Rojekar et al. have created dissolving MNs containing etravirine and etravirine nanosuspension. With considerable drug deposition of 12.84 1.33% ex vivo in neonatal pig skin for 6 hours, they were able to illustrate the robust nature of MNs. Improved characteristics were seen in the in vivo pharmacokinetic investigations; the Cmax values for DMNs containing ETR powder and ETR NS were 158 10 ng/mL and 177 30 ng/mL, respectively. Additionally, it was discovered that the longer mean residence time (MRT) and enhanced t1/2, Tmax, and MRT compared to intravenous ETR solutions demonstrated the long-acting nature of etravirine delivery through DMNs[137]. To effectively treat radiation-induced damage, Lin Zhu et al. created estriol-loaded EMNs. Biocompatible polymer polyvinyl pyrrolidone K90 was utilized for the creation of EMNs. To create a casting, the medication is dissolved in methanol and combined with polymer gel into a mould to produce EMNs with a conical shape. The created EMNs are reliable and simple 200 m into the mouse skin. Most intriguingly, these EMNs disintegrate swiftly in 5 minutes, which might aid in the drug's rapid penetration of the skin. n. The source of 6.5 Gy radiation from a 60 Co ray was used to create a mouse model of an injury caused by ionizing radiation. Additionally, EMNs boosted the number of peripheral blood leukocytes in irradiated mice, protecting the hematopoietic system in the bone marrow and 80% increasing the survival rate of the irradiated mice. Alyaa et al. studied and created dissolving MNs utilizing poly(vinylpyrrolidone) (PVP) and hyaluronic acid (HA), which are biocompatible and biodegradable polymers, to deliver Amphotericin-B (AMP-B) intradermally to cure the fungus infection. It was discovered that, in comparison to the drug-free solution, both of the polymers utilized in the development process lessened AMP-B cytotoxicity. Furthermore, AMP-B-loaded dissolving MNs were found to have substantial antifungal activity in comparison to unloaded medicines[138]. Furthermore, MNs continue to use pharmaceuticals. For the first time, Ismaiel A. Tekko et al. created MNs array patches (MAP) with a greater Cabotegravir or micronized sodium salt loading of (3 mg/0.5 cm2). Skin penetration potential was strong for the MAP. The medication was immediately deposited in the skin once the tips disintegrated after 30 minutes. Additionally, both variants of the drug-loaded MAP deposition into the skin, establishing the depot, were studied in vivo using dermatokinetic methods in Sprague Dawley rats. Following a single application, both medication forms maintain therapeutic blood concentrations for a full month. Tenofovir alafenamide (TAF) loaded implantable and dissolving MAPs were created by Alejandro J. Paredes et al. to deliver or release the medication consistently[139]. The fully formed MNs are mechanically capable of penetrating the excised newborn porcine skin and depositing the medication in a depot form. The dialysis-based release research showed that both formulations of the medication release relatively quickly.

The TAF was quickly metabolized into tenofovir in the in vivo experiments on rats, and the metabolite was quickly removed from the blood plasma. In

order to improve HIV therapy and patient compliance, Maelosa Crudden et al. created Rilpivirine nanosuspension-loaded, dissolving MN array patches (MAPs). As depot formulations, MAPs were mechanically powerful enough to puncture the skin and deliver the medication for a protracted impact. The average plasma concentration in rats was found to be 431 ng/mL after seven days of in vivo pharmacokinetic tests, which is roughly 10 times higher compared with the trough concentration discovered following a single dosage in the prior clinical research. In order to co-formulate dexamethasone and the pro-drug dexamethasone sodium phosphate in the DMNs, Mingshan Li et al. created a unique method. That might have produced the desired instant result for long-term medication administration. The MN baseplate was made using a 3D printing process for the first time. The sturdy foundation plate from the 3D printing process offers the loaded or encapsulated medication tips great support. These innovative trilayer-based MNs have demonstrated the efficient administration of dexamethasone, a medication that may represent a novel and promising oral and injectable drug delivery strategy[140].

11.3. Biotherapeutic Large Molecules

After oral delivery, protein and peptides become exceedingly unstable and start to break down. Transdermal drug delivery could eliminate this problem, but doing so is tricky because of the complex skin barriers[141]. Delivery of proteins and peptides through MNs has the potential to be a great improvement over current transdermal patch. MNs have exceptional mechanical qualities that allow them to permeate the dermis and circumvent the penetration and permeation issues that plague traditional medication delivery. Additionally, it possesses high thermostable qualities, which may be useful for protein and peptide medication delivery. A synthetic version of the powerful peptide hormone vasopressin called desmopressin is used in therapy to make up for decreased vasopressin levels. This is used to treat diabetes insipidus, which leads to hemophilia A and child bedwetting. When compared to other traditional ways, the MNs formulation revealed to be a more effective and safe method of delivering desmopressin[142].

Gap-junction blocker GAP-26, created by Liu et al., uses polyethylene glycol diacrylate MNs to distribute peptides by a swelling action. The new MNs formulation has enhanced peptide penetration, which results in enhanced suppression of the keloid fibroblasts and the expression of collagen I. Many skin and dermal illnesses are treated with cyclosporin A, a high molecular weight, hydrophobic drug with a cyclic peptide. 600 m long and 250 m wide cyclosporine A-loaded dissolving MNs were created by a moulding method. The porcine skin was exposed to 10% w/w of Cyclosporin A for 60 minutes thanks to this artificial MNs formulation[143]. With a 34 6.5 g medication administration, almost 65% of MNs were disintegrated. The 51-amino-acid peptide hormone insulin regulates blood glucose levels. However, the patient's compliance may suffer due to the extraordinarily high pain that frequent subcutaneous injections cause. Despite this, transdermal insulin administration is a striking delivery strategy. MN-loaded insulin delivery via SC injections would help diabetic patients through self-administration and minimal pain. By increasing the insulin permeability through skin pre-treatment, the solid MNs made from a variety of materials, including polymer, silicon, and metal, effectively reduced blood glucose levels. When testing the effectiveness of insulin delivery in diabetic rats, Zhou et al. showed the usefulness of stainless steel MNs with various needle lengths. Within one hour of application, the results showed that the skin's permeability dramatically increased with a quickly falling glucose level[144]. Furthermore, it has been observed that the use of solid MNs in conjunction with iontophoresis could significantly enhance the intradermal administration of insulin. McAllister et al. showed that hollow MNs can carry the microliter solution to the skin; larger pressure, though, would cause a quicker drop in blood sugar levels. The hollow MNs-based intradermal insulin delivery led to a quicker onset of insulin, whether it was caused by passive diffusion, electricity, or pressure. MNs have been designed and optimized by Li et al. to evaluate the impact of insulin administration on mouse blood levels. Blood glucose levels were shown to drop to 29% of the initial level at 5 hours, which could attest to the enhanced insulin permeability achieved with MN-based medication delivery[145].

Ye and colleagues have investigated how MNs interact with pancreatic-cell capsules, which may sense blood glucose levels and produce insulin when needed[146].

The patch was discovered to be insufficiently effective. Synthetic glucose signal amplifiers filled with MNs were created. These MNs, which comprise - amylase, glucoamylase, and glucose oxidase, show that the capsules of -cells are secreting insulin. The t1/2 and Tmax were two and three times shorter in the clinical investigation of the parathyroid hormone (I-34) coated MNs than in the traditional injectable therapy. These investigations showed the MN's potential for hormonal drug delivery, pointing to the effectiveness and efficiency of MN formulations. These could also be changed using the right polymers for a long-lasting effect[147]. Additionally, it was revealed that iontophoresis combined with MNs may transport a variety of hormones. demonstrated MNs for insulin delivery which is shown in (Fig 7), (Fig 8).

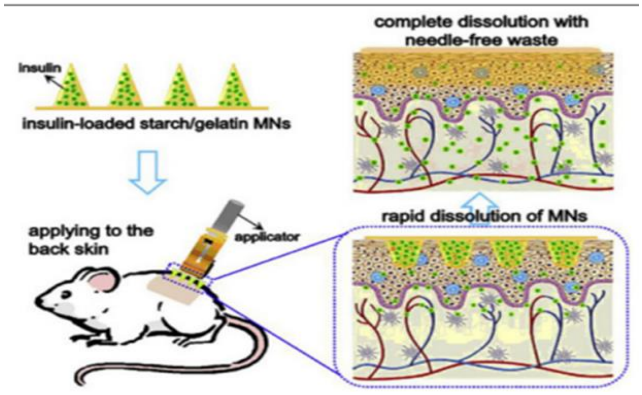

Fig 7. MNs for insulin delivery[147].

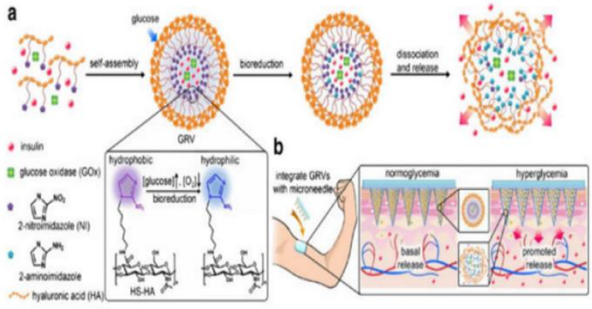

Fig 8. MNs for insulin delivery (a) GRVs made of HS-HA formation and function. (b) A schematic of the GRV-containing MN-array patch (smart insulin patch), which releases more insulin when blood sugar levels are elevated[147].

11.4. Other biomolecules

Short oligonucleotides, or smaller units than proteins, are what makeup DNA and RNA. Due to the difficulty in delivering oligonucleotides due to their characteristics, many delivery methods have been used. Using the MNs formulations method, the 20-mer phosphonothioates oligodeoxynucleotide was delivered. We employed the poke-with-patch method to distribute these oligonucleotides using solid MNs made of stainless steel. In comparison to unbroken skin, it was discovered that this method delivered more medicines[148].

11.5 Vaccine

A vaccination is a sophisticated biological formulation or preparation. It effectively provides disease-specific active acquired immunity. Vaccines are made of disease-causing bacteria that have been killed or rendered weaker, as well as their toxins or one of their surface proteins[149]. Vaccines may boost the immune response in the body and shield the patient from further illness or infection. An excellent and efficient choice was the MN-based intradermal vaccination medication delivery. Immune responses from the DNA-based vaccination were substantially better than those from conventional injections thanks to the MNs' delivery of it[150]. An attempt was made to create an MNs patch for the influenza vaccine. As opposed to intramuscular injections, hollow MNs allow the medicine to be delivered with less amount[102]. Hollow MNs have been investigated for the delivery of rabies and anthrax vaccines. To increase the effectiveness of the vaccine's intradermal administration, Ogai et al. created hollow MNs using biodegradable PLGA. It has been proven that administering a medication or vaccine to the upper dermis can boost immunity. The antibody titers were also discovered to be substantially higher than with conventional delivery. Figure 9 depicts dissolving MNs for enhanced cancer therapy that have been loaded with vaccinations and hydrophobic adjuvants[151]. Shown in (Fig 9).

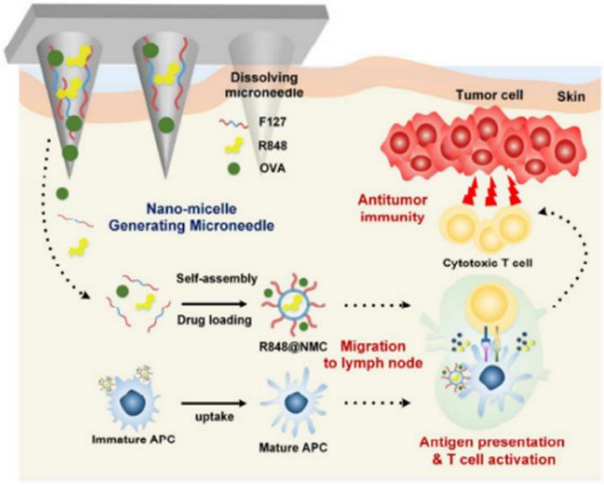

Fig 9. improving cancer therapy by dissolving MNs containing hydrophobic adjuvants and vaccinations[152].

11.6 Diagnosis

The main benefit of MNs over traditional blood collection procedures is the painless removal of biological fluids from the body. For the diagnosis of many diseases like diabetes, cancer, arthritis, and others, as well as for effective, prompt medical intervention, several biomarkers that are present in interstitial fluid beneath the skin may be helpful[153]. The value of MNs for disease diagnosis has been shown in numerous studies. Chang et al. described how MNs were used to capture interstitial fluid and analyze its compounds. Methacrylate hyaluronic acid-based MNs patch effectively retrieved skin interstitial fluid. Additional diagnostic uses for the collected fluid are also possible. MNs have been shown to be helpful in Mantoux tests for tuberculosis (TB), according to Jin and colleagues[154]. In TB skin testing, the MNs effectively distribute the pure protein derivative (PPD). Using MNs has advantages due to the controlled and exact delivery in the deep skin. According to El-Laboudi et al., the MNs array is effective in monitoring glucose, which makes it possible to diagnose diabetes and related illnesses[155]. MNs are used in pediatrics, according to Pires et al. Within a year after the child's birth, necessary vaccinations such as those for tetanus, diphtheria, and pertussis are administered[156]. The use of MNs enables effective kid immunization while reducing the pain and phobia linked to conventional needles. The MNs can be utilized to diagnose a variety of pediatric skin illnesses like psoriasis and other inflammatory problems in addition to immunization. Diagnosing various cancerous disorders is one of the main uses of MNs[157]. Utilizing nanocarriers, numerous anticancer vaccines and medications are given through MNs. This cancer diagnostic medicines' administration via MNs demonstrates enhanced biodistribution and effective diagnosis[158].

11.7. Biosensing

MNs are remarkably effective at biosensing a variety of biomarkers and metabolites. MNs are more practical than ordinary hypodermic needles for collecting biofluid[159]. Biosensing has enhanced as a result of recent developments in MNs.MN-based biosensors have been proven by Strambini et al. to detect glycemia in interstitial fluid. Electrochemical biosensors are a recent development in MN's biosensing technology[160]. MNs with innovative geometrical arrangements have an advantage in biosensing. After conducting their research, Zho et al. concluded that the MNs made from silk, polyols, and glucose oxidase may be employed for electrochemical biosensing technology to measure glucose levels[161]. Second-generation MN-based biosensors that detect lactate have been developed, according to Bollela and colleagues[162]. In order to facilitate lactate oxidase's transport of electrons, the gold MNs had been modified with nanocarbon. This allowed for effective lactate sensing[163]. Biosensing also typically makes use of MNs made of polymers. Polymeric needle-based MNs are useful for biosensing a variety of endogenous chemicals, according to numerous researchers from around the world. MNs made from poly (ethylene glycol) diacrylate have been used successfully in biosensing applications, as proven by Calio et al[164].

Fig 10. MNs gadgets that are offered for sale (A) Transdermal Microstructure Syst (B) BD (C), (D), and (E) Micro infuser, Microfluxr, and MTS Roller h-patch by Vaaleritas (F) Micro trans (G) (H) MicronJet DebioJectTM (I) Intanza®[167]

The electrodes needed for the biosensing of lactic acid and glucose were made using the produced polymeric MNs. Biosensing additionally makes use of a number of MNs with carbon bases[165]. For the biosensing of hydrogen peroxide, Jin et al. showed the value of hybrid MNs made of decreased graphene oxide and platinum nanoparticles[166]. all types of biosensors are shown in (Fig 10).

11.8. Therapy of Cancer

Through effective anticancer medication delivery, MNs technology opens up a new vista in cancer therapy[168]. Through MN-based devices, numerous chemotherapeutic drugs, genes, and proteins can be effectively supplied. The effectiveness of MN's technique for the management of epidermoid cancer therapy was established by Hao et al. The researchers created the PEGylated gold nanorod that responds to near-infrared light, and Dissolvable Hyaluronic Acid MNs with Doxorubicin were effective in treating epidermoid carcinoma locally and also had anticancer activity[169]. Gamb and Coworkers also provided evidence of the value of MNs in the treatment of breast cancer. One of the effective anticancer drugs employed for the treatment of breast cancer is resveratrol, however, its bioavailability is low. Researchers created Resveratrol nanostructured lipid carriers and administered them using MNs arrays to get over this restriction. At the tumor location, the medication administration via MNs enhanced penetration and bioavailability. MNs have been used to treat skin cancer, as shown by Hao et al. In order to treat human epidermoid carcinoma and melanoma, researchers created near-infrared sensitive 5-indocyanine green and fluorouracil-containing monomethoxypoly (ethylene glycol)-polycaprolactone nanoparticles. For effective cancer chemo-photothermal therapy, Moreira et al. showed that doxorubicin and AuMSS nanorods may be delivered by polyvinyl alcohol/chitosan layer-by-layer MNs. MN's major uses in transport proteins for cancer immunotherapy were also revealed by Lan and colleagues[170]. They created an MNs patch with tumor-targeted lipid nanoparticles loaded with PD-1 and cisplatin thanks to effective immunotherapy and precise drug delivery. Biodegradable hyaluronic acid MNs (HAMN) with antibodies for the therapy of skin cancer were shown in (Figure 11).

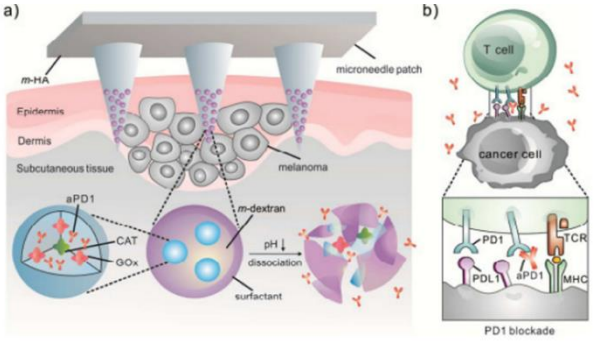

Fig 11. Skin cancer treatment using biodegradable hyaluronic acid MNs (HAMN) with antibodies. Schematic of the aPD1 supplied by an MN patch containing NPs that have been physiologically self-dissociated. (b) The blocking of PD-1 by aPD1, which causes the immune system to become active and kill skin cancer cells[171].

11.9. Ocular Drug Delivery

The benefit of MNs over intravitreal injection is that they bypass the ocular barrier having the least amount of invasion. Several research showed how MNs could be used for ocular medication delivery[172]. Hollow MNs were used by Patel et al. to successfully distribute micro- and nanoparticle solutions in the suprachoroidal area of the eyes of pigs, rabbits, and humans (ex vivo). The results of optimizing th dimension and procedure parameters showed that a needle with a length of 800-1000 m and a pressure of 250–300 kPa could deliver drugs effectively. Jiang et al.'s research also supported the use of MN's technique for ocular medication delivery. The intrascleral and intracorneal delivery of medication, protein, and DNA were evaluated using the coated solid MNs[173]. There was minimal intrusion and successful drug transport in the ocular system.

12.List of Marketed Microneedles

Table 3. Marketed formulations based on microneedles as a transdermal delivery system

Market product	Description	Manufacturer
AdminPen™	Microneedle array-based pen-injector device	AdminMed
AdminPatch™	Microneedle array	AdminMed
Macroflux®	Microneedle array	Macroflux®
Microcore®	Dissolvable peptide microneedle patch	Corium
Microjet®	Intradermal microneedle injection system	NanoPass

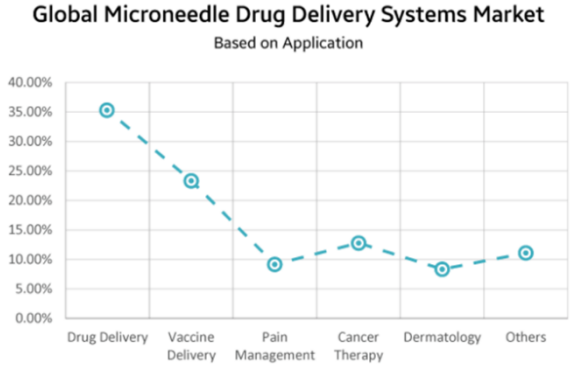

Fig 12. Global Microneedle Drug Delivery Systems Market Based Application[174].

13. Conclusion

The key to effective MN mediate transdermal and intradermal administration is breaking through the stratum corneum barrier. In the era of transdermal medication delivery, MN's technique is outlined in this study. Due to the benefits of MN manufacturing, extensive study has been done in this area. This document provides examples of different MN categories, materials, and production processes. For the administration of tiny or large molecules, a range of MN platforms with unique delivery mechanisms has been created during the last few decades. Recent studies revealed that transdermal transport of tiny molecular medicines, salt forms, excipients, and other formulated elements is enhanced by a brief interruption of the skin microchannel lifespan, as noted in this in-depth study. We provided an overview of the intradermal and transdermal distribution of macromolecules, including therapeutic peptides and proteins, vaccinations, and the synergistic effects of combination enhancement in addition to MN treatment. The literature also explores MN mechanical tests and their characterization. Last but not least, this work highlights the research deficit in MN fabrication. Despite the fact that MNs

are already used to mediate a number of new transdermal products, these products still have not fully matured. There is a gap in the ability to enable cost-effective manufacturing for MNs to be produced in large quantities, and this gap is becoming more and more obvious as our awareness of MN-mediated increases. For the last 15 years, researchers working in this field have placed a high priority on the creation of Minnesota-based products and their regulation due to the trend towards increasing transdermal delivery of bigger peptides, proteins, and vaccine compounds as well as conventional molecules. A variety of commercial MN goods are eagerly awaited around the world in the future, MN could have a significant effect on clinical therapy.

Future of Microneedles

Platforms for transdermal medication delivery based on nanotechnology have recently regained popularity. in order to find a means to administer a variety of nanotherapeutics intradermally and maintain the release of the therapeutic levels with just a small amount of skin contact one MN application only. To address both clinical demands and patient adherence, it is now imperative to swiftly address this unmet patient need. According to the World Economic Form's list of "10 Emerging Technologies 2020," MN technology ranks first. Overall, the clinical translation of MN technology is still in its early stages. The first zolmitriptan-containing MN product, QtryptaTM 1978, was created by Zosano Pharma Corp. and is anticipated to be released in the upcoming year. The US FDA has now finished its initial thorough assessment of this Minnesota product's NDA, and the business is now attempting to allay FDA worries about inconsistent medication plasma levels during clinical trials from various production batches. As a result, MN drug delivery systems should be developed that are straightforward, scalable, and user-friendly. The most difficult chronic and life-threatening diseases, including HIV/AIDS, cancer, diabetes, cardiovascular disorders, etc., could be treated with this innovative MN-assisted medication once it is introduced to the market. Currently, most long-acting MN methods are geared toward PK and PD optimization in preclinical settings. MNs are capable of delivering both hydrophobic and hydrophilic, big and tiny compounds for long-acting release, but to support this, more preclinical investigations need to be finished. In order to close the gap between patient encounters and test results, hospitals, industry, non-profits, and academia must work effectively together. The "Microarray Patches-Centre of Excellence" has been developed by PATH, an international, non-profit global health organization, to integrate all stakeholders under one roof and speed up the regulatory and clinical testing processes as well as the scale-up of MN manufacture. Finally, health and regulatory authorities should create and enforce definitions (MN as a pharmaceutical product or device), guidelines, and regulations for the MN medication delivery platform. There will be a need for additional investigational new drug (IND) type studies that concentrate on in vivo efficacy and long-term toxicity. We anticipate that more preclinical research (and possibly clinical research) will be conducted over the coming years, and we anticipate the publication of further promising findings to support MN's adaptability as a top platform for long-acting drug delivery. This could be the crucial step that the field has to take in order to advance and fully realize the potential of this unique medication delivery platform.

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