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REVIEW ARTICLE

A Review on Solid Microneedles for Biomedical Applications

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Abstract
Microelectromechanical system (MEMS)-based microneedles are an innovative way of drug delivery that increases the permeability of the skin. It generates microscopic pores inside the skin that leads to the passive diffusion of drugs for dermal microcirculation to take place. This phenomenon helps toward efficient drug penetration. MEMS microneedles are small-sized needles usually in the micron to millimeter range, normally having a length to width of about 150–550 μm and 50–300 μm. respectively. Their tip diameter varies from 1 to 80 μm that can pierce through the epidermis layer directly to dermal tissues devoid of any pain. In this paper, a broad overview of solid microneedles for biomedical applications has been presented. The objective of this review is to collect the state of art main features related to solid microneedles. Particularly, the challenges related to solid microneedles, such as materials and methods used in the fabrication of microneedles, design and their performance, testing, safety concerns, commercialization issues, and applications, have been discussed. Microneedles can be characterized conferring to their fabrication procedure, structure, materials, general shape and size, the shape of the tip, microneedle array thickness, and applications. This comprehensive review on solid microneedles may provide significant useful information for scientists or researchers working on the design and development of solid microneedles for biomedical applications.

Keywords Drug delivery system · Biomedical · MEMS · Solid microneedles

Introduction

Microneedles are considered useful drug delivery devices because they provide painless and efficient drug delivery [1]. Microneedles can be used either way as a standalone system or as integrated with other devices forming the complicated microfluidic systems [2–4]. Even though the idea of microneedles was suggested in the 1970s, it wasn't established experimentally till the 1990s once the microelectronics industry delivered the required tools for microfabrication. The first studies of transdermal drug delivery were reported in 1998 [5]. After that, the development and use of microneedles for drug delivery and other pharmaceutical applications have increased rapidly.

Different materials like stainless steel, silicon, titanium, and polymers have been used so far to fabricate microneedles [6, 7]. Some of the microneedles are made with drugs, which means they have a needle shape but are delivered directly into the body and penetrate the skin easily. The microneedles are made in different sizes, shapes, and functions, but all are used as a substitute to former delivery methods like the conventional hypodermal needle or additional vaccination apparatuses [8–10]. Microneedle arrays or microneedles can be used as a separate device along with a measure of drug extraction, biological detection, or delivery system. Microneedles, due to their efficiency, can be integrated with biosensors, micropumps, microfluidic chips, and microelectronic devices. Microneedles have many advantages as they have improved the comfort of patients. Microneedles are harmless to be used in humans. Lately, microneedle technology has been proposed for increasing

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skin penetrability and particularly increase the transdermal delivery for macromolecules.

Correspondingly, several researchers have presented microneedles suitable for many biomedical applications, and they have become a broadly studied technique in this era for biomedicine [10–12]. But it still needs to have a brief overview of the latest apprises on the development of different microneedles for biomedical applications as these needles have limited obtainability for marketable use and remain at the study level. Few earlier reviews have been reported on microneedles. These different reviews provide brief information on microneedles and their applications. Donnelly et al. [13] presented a review article that provides facts about various MN types, fabrication approaches, and, prominently, inquiries of the medical safety of MN. Mahmood et al. [14] presented a broad review that focused on current and prospect progresses for microneedle technology containing the up-to-date microneedle design, tests, and schemes in microneedle development besides possible safety features collected from complete literature review relating to microneedle studies toward a date. Ahmed et al. [15] presented a brief review that summarizes the current substantiation for the custom of microneedle arrays as biosensors aimed at constant monitoring of glucose content of the interstitial fluid, concentrating on insertion mechanics, characteristics of microchannels, and protection profile. Florina et al. [16] reported a very substantial review in which delivery device, the central delivery approaches using the microneedles array, materials that are commonly used for fabrication procedure, geometrical, and profile considerations in addition to the present preclinical and clinical requests of the microneedle array. Quinn et al. [17] reported a fundamental and preliminary review that explains how microneedle arrays can upsurge the sum of compounds agreeable to transdermal delivery through piercing the skin's defensive barrier, the vein corneum, as well as constructing a path for drug infusion to the dermal nerve below. Kevin Ita [10] presented a review on hydrogel-forming microneedles, and special consideration is compensated to hydrogel-forming microneedles as they are new microneedles that do not comprise drugs however absorb interstitial fluid to custom constant conduits among dermal microcirculation as well as an involved patch-form reservoir. Numerous microneedles accepted through regulatory experts for experimental use are also studied. Chen et al. [18] presented a review on the perspective, as well as the experiments of applying microneedles, to provide nucleic acids aimed at gene therapy. It was also suggested that a grouping of microneedles and additional gene delivery methods may provide a path for the improved delivery method for gene rehabilitation. Marwah et al. [19] presented an introductory review that explains that new vigorous drug transport equipment is involved in increasing the transdermal infusion via the actual drug delivery method. Thakur et al. [20] presented a short overview of a variety of tests that are frequently encountered to attain well-organized optical drug levels inside fixed tissues of the eye. It also defines the difficulties met by means of conservative hypodermal needle-based optical vaccinations for frontal and subsequent section drug delivery. It argues research approved in the field of microneedles, up to date. Guojun Ma and Chengwei Wu et al. [21] presented a comprehensive review in which studies were introduced on the mechanical problems with respect to microneedles. All the above-discussed reviews present the facts and information about microneedles only and do not discuss any of its types solely. Here, the authors have given a complete review on solid microneedles that covers any recent development of solid microneedles in the field of medicine or drug delivery. Thus, it is the most comprehensive and simplified review that covers the up-to-date information of solid microneedles concerning the design and development, structure, parameters used for its performance, fabrication methods, materials used for fabrication, safety issues, and challenges, as well as applications.

Solid microneedles have been so far the most common and simplest method of microneedle devices because they are used for the maximum of the early work of microneedle delivery of drugs or vaccines [22]. Solid microneedles have no distribution or flow passages by themselves for drugs and are thus used for pretreatment of skin to generate transitory channels of micron sizes through stratum corneum over mechanically distorting epidermis preceding to drug supervision [23]. Then, drugs were inserted or applied in the form of square patches directly to the skin area penetrated by microneedles [24]. Wang et al. [25] reported a method in which a nanometer-scoped zinc-oxide pyramidal rod array was constructed to form a device in which tip, as well as a base diameter of 50×50-μm-long rods, were 60 nm and 150 nm, correspondingly [26]. Li et al. [26] reported a super short microneedle and studied how they can act as a safe and effective substitute in transdermal drug delivery of hydrophilic molecules. It was also studied that after these super short solid microneedles have been injected into a patient, no infection, e.g., *Staphylococcus aureus*, occurs, and the patient remains safe. Aoyagi et al. [27] proposed a new fabrication method for solid microneedle arrays using numerous tip angles prepared of a biodegradable polymer such as PLA. Their experimentation was confirmed by the simulation of finite element analysis. Coulman et al. [28] reported solid microneedles having a pyramidal shape and pointed/frustum tip to apprehend the performance of nanoparticle preparations inside the biological surroundings and their interface with the skin layers resulting in the disruption of the skin through an innovative delivery device, e.g., solid microneedle arrays. Oh et al. [29] proposed the study which recommends that a biocompatible PC solid microneedle might be an appropriate device for transdermal drug delivery scheme of

hydrophilic molecules through the potential applications toward macromolecules, e.g., proteins as well as peptides. Ding et al. [30] fabricated solid microneedle arrays having custom transitory conduits and improve the transportation of vaccine molecules transversely through the skin barrier and without any kind of pain. It was also examined in mice how the immune reactions are after applying TCI by means of two typical antigens, diphtheria-toxoid and respiratory tract infection vaccines. Han et al. [31] presented a new method for fabrication aimed at groove-inserted solid microneedle arrays of a biocompatible polymer as well as the immunization features to ovalbumin transported into mice through the solid microneedle arrays via the skin, and the results proved that it was a compatible way of drug delivery by keeping in mind the dimensions and shapes of microneedle arrays. Chandra Sekhar Kolli and Ajay K. Banga [22] demonstrated maltose solid microneedles characterized and exposed to construct microchannels in the skin that were also categorized and presented to increase the transdermal drug delivery of NH. Jin et al. [32] proposed a unique fabrication approach for an economical microneedle patch prepared by biocompatible polymer, besides efficient confirmations for fabricated solid microneedle patches over animal models, and no side effects were found such as infection or allergic reactions on the application of solid microneedle patches. Kim et al. [33] proposed the investigational factors and mechanical pathways through which deactivated infection vaccine can lose action, besides develop as well as measures upgraded solid microneedle coating preparations that defend the antigen from inactivity. Afterwards, coating microneedles have used a typical vaccine preparation, the constancy of respiratory tract infection vaccine was condensed to just 2%, as calculated by hemagglutination activity. Park et al. [34] reported polymer solid microneedle rollers having a conical shape and discussed that compared to injecting microneedles on a smooth patch, the consecutive inclusion of solid microneedles on a roller row by row require less inclusion strength in the full thickness of swinish skin. Generally, polymer solid microneedle rollers, made from simulated polymer films, provide an unpretentious way to upsurge skin penetrability for drug delivery purposes. Gomaa et al. [35] investigated the issue that by compelling transepidermal water loss depths of dermatome human skin models succeeding the inclusion of solid polymer microneedles. Inclusions triggered an initial severe drop in barricade function tracked by a slow imperfect recovery – an example constant with microneedle generation of microchannels which consequently contract, owing to the skin's elasticity. Donnelly et al. [36] reported the very first kind of polymeric microneedles that have been engaged for delivering a perfect lipophilic dye, Nile red, into the expunged pigskin. Prominently, the one-step delivery approach is used for the limited delivery of exceedingly hydrophobic agents that overwhelm several disadvantages of existing delivery approaches. Romgens et al. [37] proposed a study that presented that sharp solid microneedles are important to insert microneedles in a well-organized manner to a preferred depth. Zhang et al. [38] studied the permeation as well as the delivery of poly(lactic-co-glycolic acid) (PLGA) nanoparticles in human skin cured with solid microneedles. Fluorescent PLGA nanoparticles were arranged to show the transdermal transference procedure of nanoparticles. The studied results proposed that solid microneedles could increase the intradermal distribution of the PLGA nanoparticles. Julia et al. [39] studied the effect of solid microneedles on the transdermal delivery of particular antiepileptic drugs, and it was tested on pigskin to demonstrate the consequence of solid microneedle rollers. Hoang et al. [40] studied the effect of solid microneedles on transdermal delivery of amantadine hydrochloride as well as pramipexole di-hydrochloride through a pig ear skin in vitro and statistical analysis was also conceded. Mj Uddin et al. [41] proposed an innovative inkjet printing technology for coating solid microneedle arrays of metal material using three anticancer agents including 5-fluorouracil, cisplatin, as well as curcumin, for transdermal delivery. Witting et al. [42] highlighted precisely the protein balance throughout storage and also demonstrated that discriminatory intraepidermal installation of proteins or peptides via solid microneedles is a practical approach. The solid microneedle array pierces the strong barrier of the stratum corneum, causing the active molecules to diffuse through the arranged channels. When the microneedles array is removed, the drug formulation is customarily applied onto the pretreated area of the skin. The pores are formed in the skin which helps the variety of molecules to transport through gaps of closely damaged skin as well as reach the epidermis and dermis [43]. Different researchers have been working on solid microneedles using different materials for their fabrication and making them useful for human skin or other treatments. Solid microneedles made of metals are an attractive setup for having painless drug delivery. Though, fabrication procedures for metal microneedles are complex and require a large setup. An accessible building of metallic microneedle arrays by means of thermoplastic representation of metallic glasses has been reported. Microneedles with tuneable lengths as well as tips are created through monitoring the rheology and splintering of metallic glasses. And when these solid metallic glass microneedles are taken for in vitro insertion tests, they give an excellent piercing of porcine skin [44]. The first-time usage of TA.XTplus Texture Analyser toward characterization of spurt force in pigskin for drug delivery tests has been reported. With this force, the pigskin can easily be ruptured as demonstrated in their experiments and results [40]. It is reported that the sharper-tipped solid silicon microneedles having a higher aspect ratio have been fabricated. Tetramethylammonium hydroxide etching techniques have been

improved and used for the fabrication of stretched and pointed microneedles. The fabricated solid microneedles are considered to be appropriate for applications of drug delivery [45]. The safety measures of solid polymer microneedles for humans offered at different applications have been proposed. Also it was taken into account the diverse application locations of vaccination, cosmetology, and insulin delivery tangled through microneedles method, reasons persuading user receiving of microneedles comprising the length, density, and the proportions of microneedle patches by putting on diverse microneedle patches on the forearm, forehead, and abdomen skins of human participants [46]. It is reported that patch pretreatment of solid polymer microneedle improves the penetration of drug particles in the skin [46]. The solid microneedles are also made up of biodegradable polymers and biocompatible polymers for transdermal drug delivery. Polymer microneedles have the benefits of being easily fabricated, cost-efficient, and can be mass-produced, besides precise drug release by means of the water solubility and deprivation properties of polymers. Polymer microneedles, by using various physical and chemical properties of polymers, offer a promising method for drug delivery [47]. Solid microneedles are used for skin pretreatment as they have increased skin permeability. Solid microneedles are used in cosmetic surgery and other skin treatments due to their good skin permeability [48]. An innovative method for manufacturing solid polymer microneedles utilizing laser-ablated molds in a shot molding procedure has been reported. Research has been successfully conducted to create cone-shaped microholes through low tip areas in a device steel pattern, utilizing a femtosecond laser through a cross-hatching approach. Lastly, the achieved mold was made to be used in an injection molding procedure for replicating the polypropylene microneedles [49]. Verbaan et al. [50] described the enhanced piercing method of microneedle patches in dermatome human skin by an influence enclosure method. A detailed review of solid microneedles is presented in Table 1 below.(see Table 2)

Classification of Microneedles

There are four types of microneedles, i.e., solid microneedles, coated microneedles, hollow microneedles, and dissolving microneedles. (Fig. 1) Each type has pros and cons depending on its delivery methods and their functionalities [51]. Each type is explained below concerning its design, fabrication techniques, materials used for its fabrication, and applications. Solid microneedles deliver drugs to the body in two parts; firstly, the microneedle array is applied to the patient's skin to make microscopic bores, which are much deeper, to easily penetrate the skin's outermost layer, and secondly, the transdermal patch is used for the application of the drug. Solid microneedles are now used by dermatologists in skin treatment or collagen stimulation therapy [52]. Hollow microneedles are comparable to solid microneedles in terms of materials used. They have reservoirs through which drug is delivered directly into the body. Meanwhile, the drug delivery is reliant on the flow rate of the microneedle; therefore, this microneedle array has a possibility of becoming clogged through extreme swelling or faulty design. Hollow microneedles have the disadvantage of increasing the possibility of clipping under the pressure of, and consequently inadequate to deliver drugs []. Coated microneedles are commonly made from metals or polymers just like solid microneedles. Instead of being applied from any applicators or patches, the drug is transferred directly to the human body through microneedles or microneedle arrays; therefore, they have been named coated microneedles [53]. To make sure that the required dose of a drug is properly delivered to the body, these microneedles are often enclosed in other thickening agents or surfactants. Most of the chemicals used on coated microneedles are named irritants. When these microneedle arrays are applied, and there is a risk of local inflammation to the body where applied, then these arrays can be removed directly without any harm to the patient [54]. In the latest adaptation of microneedle designs, dissolvable microneedles have drugs encapsulated in a harmless polymer that formerly dissolves inside the skin [2].

Drug Administration on Insertion of Microneedles

The drug is inserted into the skin via different types of microneedles in the form of a patch that is placed on the body of a human, and then the transportation of the drug takes place as described below in Fig. 2. Also, when a drug is delivered properly, the microneedles are removed without giving any pain to the patient, and it is a very effective or easy process.

Design and Geometry of Solid Microneedles

To decide the performance and mechanical behavior of microneedles, it is very important to understand the design and geometry, which includes the shape of microneedles, their tip radius, length, aspect ratio, base width, and diameter, etc. So, it is very important to wisely select a correct material as well as an accurate methodology for the fabrication of ideal microneedles that are biocompatible, involuntarily strong to penetrate skin layers, proficient in loading miscellaneous active drug materials, and measured or continued drug delivery [7]. Wang et al. [63] carried an exceptional review on the characteristic of diverse polymer materials and approaches engaged in fabricating and getting

Table 1 Review of solid microneedles

References	Material used	Microneedle structure	Microneedle shapes	Dimension	Patch size	Analysis type	Testing	Fabrication methods	Applications
Kolli and Banga[22]	Maltose	Solid	Tetrahedron/ sharp tip	L = 450–500 µm D = 5–6 µm	27×27	Drug transportation	Mouse skin	Micro-molding	Transdermal drug delivery
Wei-Ze et al.[26]	Silicon	Solid	Super-short flat tips	L = 70–80 µm	10×10	Drug transportation	Rat skin	Wet etching technology	Transdermal drug delivery
Aoyagi et al.[27]	PLA	Solid	Straight/harpoon shape	L = 400 µm	Not reported	Structural	Artificial silicone rubber skin	Etching/injection molding	Drug delivery
Coulman et al. [28]	Silicon	Solid	Pyramidal shape/ pointed tip	L = 280 µm D = 200 µm	16 needles	Diffusion of nanoparticles	Human epidermal membrane	Wet etching	Transdermal/ intradermal drug delivery
Oh et al.[29]	Polycarbonate or plastic	Solid	Sharp edge tip	L = 500 µm	Not reported	Hydrophilic molecule transportation	Mouse skin	Molding/hot embossing	To improve skin permeability for hydrophilic molecules
Ding et al.[30]	Stainless steel	Solid/hollow/out-of-plane	Tangentially cut tip	L = 245, 300–900 µm D = 200 µm	4×4 9×9	Drug transportation	Mouse skin	Surface micromachining/etching	Dermal diphtheria/ influenza vaccination
Han et al.[31]	PLLA	Solid	Sharp 3D tip	L = 880 µm Wb = 710 µm	Not reported	Protein transportation analysis	Mouse skin	Lithography/ Ni electroplating/PDMS replication/hot embossing	Intradermal immunization
Jin et al.[32]	PMMA/PC	Solid	Quadrangular/ pyramidal	L = 200–1500 mm	Not reported	Drug transportation	Mouse skin and serum	DXRL/hot embossing	Transdermal drug delivery
Kim et al. [33]	Steel	Solid	Sharp tip	L = 750 µm Wb = 150 µm	5 needles	Drug transportation/statistical analysis	Mouse skin	Infrared laser	Vaccine delivery
Park et al.[34]	PLA	Solid	Canonical/square base	L = 600 µm Wb = 250 µm	10×10	Diffusion of trypan blue	Human/porcine cadaver skin	UV lithography	Transdermal drug delivery
Gomaa et al.[35]	Polymer	Solid	Square tip	L = 100 µm, 400 µm, 600 µm	18×18	Effect of skin permeability with microneedle density	Human skin	Laser micromachining	Drug delivery
Donnelly et al. [36]	Polymeric	Solid	Canonical	Not reported	Not reported	Statistical	Porcine skin	Molding process	Intradermal delivery
Römgens et al. [37]	PDMS	Solid	Sharp tip	L = 3.3 mm D = 15–37 µm	Not reported	Statistical analysis	Human skin	Micropipette puller	Drug delivery
Zhang et al.[38]	Silicon	Solid	Star shape	L = 200 µm	10×10	PLGA nanoparticle distribution	Human skin	RIE/thin film deposition photolithography	Transdermal drug delivery

Table 1 (continued)

References	Material used	Microneedle structure	Microneedle shapes	Dimension	Patch size	Analysis type	Testing	Fabrication methods	Applications
Nguyen et al.[39]	Tiagabine hydrochloride	Solid	Not reported	L = 500 µm W = 192 µm	Not reported	Statistical analysis	Pigskin	Electric dermatome/digimatic micrometer	Transdermal drug delivery
Ita et al.[10]	Stainless steel	Solid	Not reported	L = 500 µm W = 192 µm	Not reported	Statistical analysis	Porcine skin	Mass spectrometry	Transdermal drug delivery
Uddin et al.[41]	PLA	Solid	Canonical	L = 700 µm D = 50 µm W = 200 µm	50 (single row)	HPLC analysis	Porcine skin	Laser cutting/electropolishing	Anticancer agent delivery
Witting et al.[42]	Proteins	Solid	Not reported	L = 300 µm	Not reported	Statistical analysis	Pigskin/human skin	Dip coating method/deposition method	Transdermal drug delivery
Hu et al.[44]	Metallic glass	Solid/hollow	Conical/parabolic/bevel	L = 1 mm D = 50 µm	50 needles	Drug transportation	Porcine skin	Thermomechanical processing	Transdermal drug delivery
Manoj et al. [201]	Silicon	Solid	Sharp tips	L = 158 µm Wb = 110.2 µm Tip D = 0.40 µm	7 × 7	Drug transportation	Not reported	Photolithography/micromachining	Transdermal drug delivery
Zhao et al. [202]	PLA	Solid	Sharp tips	L = 400–1000 µm Wb = 300 µm	10 × 10	Vaccination/drug transportation	Human skin	Laser-based molding	Cosmetology/drug delivery
Li et al. [48]	PLA	Solid	Not reported	L = 600–800 µm	10 × 10	Statistical analysis	Porcine cadaver skin	Laser/thermal micromolding	Drug delivery
Evens et al. [49]	PLA	Solid	Cone shape	L = 500 µm D = 80 µm	Not reported	Statistical analysis	Human skin	Laser ablation	Transdermal drug delivery
Jeong et al. [203]	PLA	Solid	Sharp tips	L = 500 µm Db = 200 µm D = 25 µm	Not reported	Drug transportation	Not reported	Micromolding technique	Transdermal drug delivery
Bodhale et al. [65]	Polymer	Solid	Side shallow sharp tip	L = 300 µm D = 300 µm	25 × 25	Structural/fluidic	Not reported	Hot embossing/UV excimer laser (proposed)	Drug delivery

*Notations: *L*, Length of needle; *Wb*, base width; *Db*, base diameter; *D*, diameter of microneedles

Table 2 Classification, advantages, disadvantages, and drug delivery methods

Microneedle classification	Materials	Advantages	Disadvantages	Drug-delivery methods	References
Solid	Silicon Polysilicon Silicon dioxide Silicon nitride PGA	Different materials can be used to fabricate solid microneedles	Solid microneedle break under the skin on insertion. The surface area accessible for drug concentration is limited	Generate microchannels in the skin where a drug is inserted	Ma et al. [55]; Li et al. [56]; Ullah et al. [57]
Hollow	PDMS PMMA Glass GaAs	Higher drug load can be inserted	It is required to use strong materials for fabrication to endure flow pressure	Pressure compelled flow through microneedles	Li et al. [58]; Kim et al. [6]; He et al. [59]
Dissolving	Titanium Ti-alloy Tungsten Tungsten-alloy	Easy built-up	Biodegradable/decomposable materials can only be used	Dissolves in the skin to relieve drug load	Lee et al. [60]; Kolli et al. [22]
Coated	Stainless steel Silver Gold Copper	Used for strong drugs demanding low doses	Related with drug loss even though manufacturing and temperature restrictions	Coating drug-load releases	Chen et al. [61]; Chen et al. [62]

ideal microneedles. The most important feature is that the geometry of microneedles simplifies the smooth insertion of needles into the skin. This is essential as human skin is robust and flexible in nature, and thus it tends to prevent the insertion of microneedles or may lead to the breaking of microneedles. This is usually seen with microneedles that are fabricated with weak materials having rounded tips. For that reason, the geometry of microneedles is subtle and critical for effective drug delivery.

Different shapes of microneedles that were established include rectangular with a sharp edge, conical, and pointed, etc., with variable widths and lengths. Figure 3 shows the design and geometry of solid microneedles. For example, Lee et al. reported solid polymer microneedles having pyramidal shapes without good mechanical strength vis-a-vis the conical molded microneedles by way of the pyramidal ones are related with an advanced cross-sectional area at a similar base width [60]. Moreover, Chen et al. reported that greater insertion depths were attained using chitosan microneedles having a 5-μm-tip radius [64]. Likewise, the microneedles having a sharp tip are vivacious for insertion because they have a higher potential to pierce with a small force, and vice versa is correct for microneedles with large diameter tips [65, 66].

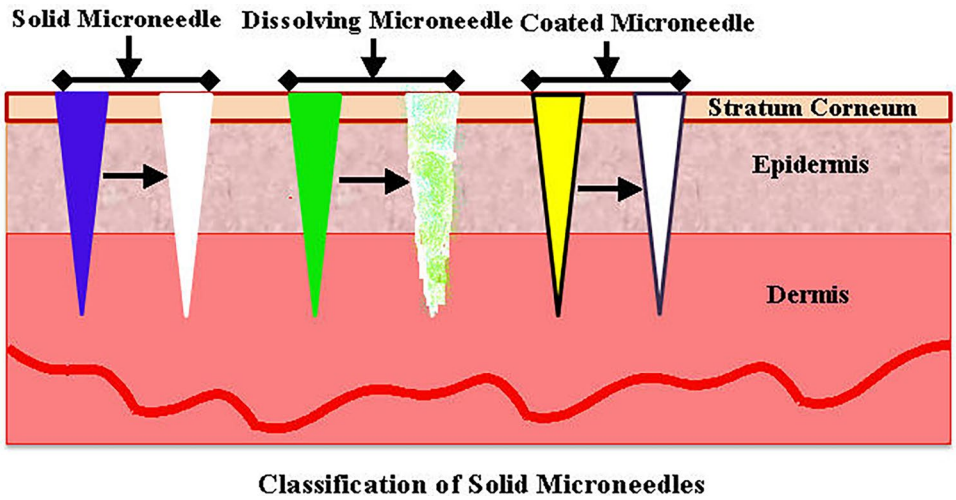

Fig. 1 Microneedle insertion on the skin and drug administration

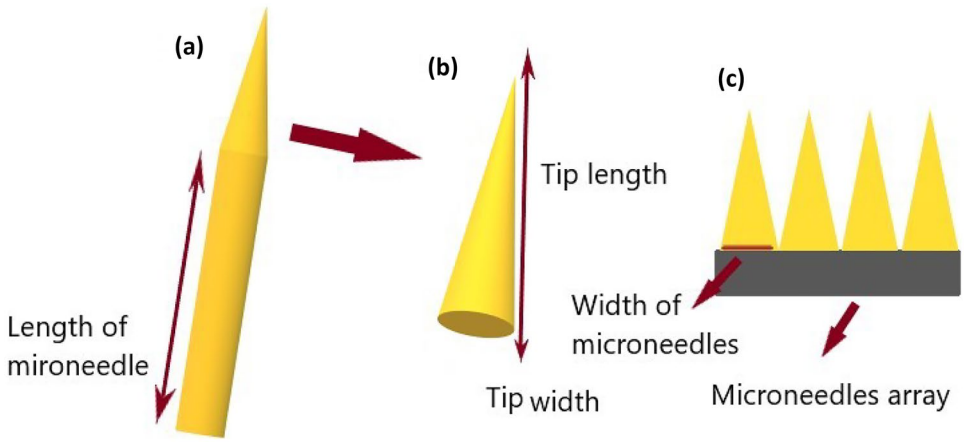

Fig. 2 **a** Geometry and design of solid microneedle, **b** tip view, and **c** microneedle array

Forces Used During Penetration

In solid microneedles, pharmaceutical materials are coated to deliver the drugs into the patient's body. In the course of penetration, several forces, e.g., bending, lateral, buckling, axial, and resistive are usually experienced by microneedles. Therefore, it is very important to have perfectly designed microneedles that tolerate all these forces without any deflection because these forces can cause breakage of microneedles at the time of penetration. The force, which at the time of insertion becomes more dominant on the microneedle's tip, is axial [67]. The axial force is compressive, plus it points toward the buckling of microneedles. On the insertion of microneedles into the skin, another force called resistive force is applied by the skin. Hereafter, to penetrate the microneedle, the applied force must be larger than the resistive force. Also, uneven skin surface, as well as human inaccuracy in the course of needle penetration, may cause bending. As a result, it is essential to understand the geometry of microneedles and the material's mechanical properties concerning getting the perfect design of microneedles as well as the estimation of failure caused by microneedles [65, 68, 69]. The buckling force acted on microneedles in skin penetration is given as follows:

$$F_{\text{Buckling}} = \frac{\pi^2 EI}{L^2} \tag{1}$$

[70, 71]where E is Young's modulus, I is the moment of inertia, and L is the microneedle's length.

The bending force that the microneedle can bear without breakage is given as follows:

$$F_{\text{Bending}} = \frac{\sigma_y I}{cL} \tag{2}$$

[70]where c is the distance from the vertical axis to the outer edge of the skin.

The axial force that the microneedle can bear without breakage is given as follows:

$$F_{\text{Axial}} = \sigma_y A \tag{3}$$

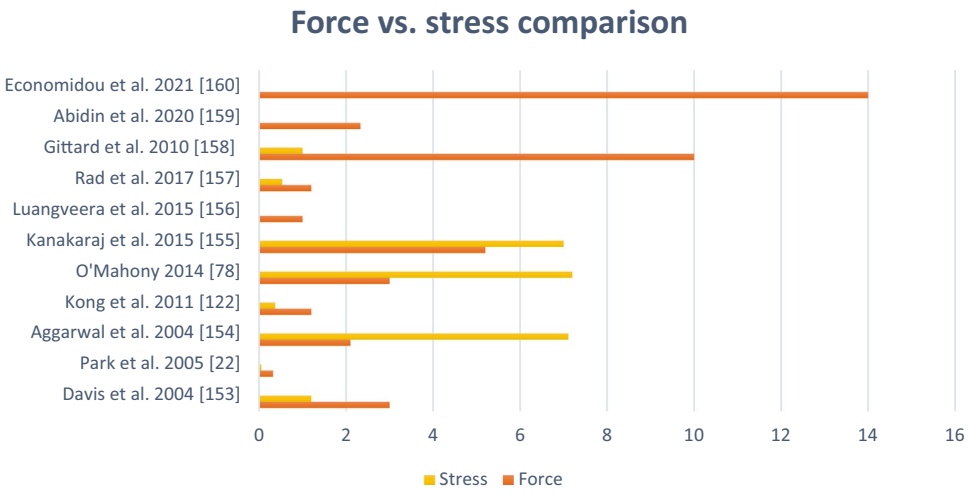

Fig. 3 Strength of materials w.r.t tensile strength and Young's modulus

[11, 70]where σ_y represents yield strength of a material or tip area.

Also, the resistive force which the skin applied when penetration takes place is given as follows:

$$F_{\text{Resistive}} = P_{\text{pierce}} A \tag{4}$$

[70]where P_{pierce} is the pressure needed to penetrate the solid microneedle in to the skin [72–77]. Afterward, the skin is penetrated by microneedles; the only force acting on microneedles is the frictional force that resulted from the tissues' and needles' interaction [74, 78].

Materials Used in the Fabrication of Solid Microneedles and Their Issues

For the design and fabrication of microneedles, it is very important to select appropriate materials for any particular application. Materials used for the fabrication of microneedles can be classified into two groups:

- Degradable
- Nondegradable

Degradable materials include materials like metals, glass, silicon, and ceramics, whereas degradable materials consist of polysaccharides as well as biodegradable polymers.

So far, scientists have fabricated the following:

- silicon microneedles [5, 79, 80]
- glass microneedles [23, 81–83]
- ceramic microneedles [84, 85]
- metal microneedles [86–89]
- hydrogel microneedles [90, 91]
- polymer microneedles [2, 47, 92–97]
- sugar microneedles [98–100] etc.

Numerous researchers have used silicon for the fabrication of microneedles but Si is a brittle material and is dangerous to health [26, 101–112]. Metal microneedles have the adequate mechanical strength to pierce the skin; however, they also have the disadvantage of generating probable biological wastes [2, 9] [113]. Many polymers have a history of biocompatibility. They display tremendous mechanical and chemical properties which are appropriate for the fabrication of microneedles. Different polymers have been reported for the fabrication of microneedles which include polyglycolide (PGA), poly(l-lactic acid) (PLLA), polydimethylsiloxane (PDMS), polycarbonate (PC), poly(methyl methacrylate) (PMMA), etc. The fabrication of microneedles using polymeric materials has been reported by numerous researchers. However, many polymers are so soft that during the insertion process, they cause buckling failure. Several other materials for the fabrication of microneedles have also been reported, e.g., glass, alloy, metal, silver, copper, and gold. Glass microneedles having hollow oval tips have been fabricated for intradermal delivery utilizing the micropipette pulling method, but they can also break easily inside the skin on the application of the drug. [70, 80, 93, 114115–117].

Fabrication Techniques: Their Advantages and Disadvantages

Different fabrication techniques have been used to fabricate microneedles which include the following:

Photolithography [118]

This process is commonly used for the fabrication of polymer microneedles, and this process, unlike other techniques, involves simple steps and less time. The tips of microneedles fabricated by photolithography are blunt and sharper as compared to others. However, it also has some limits, i.e., expensive masks, polymers must be photosensitive, and harsh processing conditions, therefore cannot be used in biological models.

Chemical Etching [119]

This fabrication method is highly selected by researchers as they are inexpensive and damage-free due to their pure chemical nature. But, it also has some disadvantages, i.e., reduced process control, temperature sensitivity, reduced particle control, and high costs for biochemical disposal.

Deep Reactive Ion Etching [120]

This method is used for the high-volume fabrication of microneedles and is commonly known as the Bosch process, but it has the disadvantage that it takes a long time because each phase lasts for several seconds.

Hot Embossing [121]

The hot embossing technique might assist in the development of greatly accurate and extremely effective fabrication of microneedles. It has the disadvantage of difficulty in demolding, substantial enduring thermal stress owing to varying coefficients of thermal expansion among the mold and polymer materials.

Laser Ablation [122]

In this technique, light pulses are used for giving the prominence of the desired shape of microneedles on a metal plate,

thus creating solid-metal microneedle arrays. However, owing to their high-intensity pulses of laser, the creation of plasma ions, as well as electrons, is not appropriate for the fabrication of required designs or structures.

Surface Micromachining [123]

The surface micromachining technique offers a benefit that can be used on different materials as compared to substrates of a single crystal. This technique is extensively used by the researcher as it provides less loss of materials, better mechanical properties, and good dimensional control. However, it is expensive because higher steps of fabrication are involved, repetitive processes, and difficulty in implementing it for larger structures.

Atomized Spraying Method [124]

This method disables the problems related to limited volume for the mass production of dissolving microneedles through the required geometry as well as physical characteristics. Moreover, the difficulties related to liquid surface tension effects, as well as viscosity once filling the microneedle molds, can be reduced. However, it has issues of higher air emissions and the use of highly compressed air.

Micro-Molding [125]

In this method, microneedles are made by using molds and filled with liquids or chemicals. It has the advantages of being comparatively simple and is a cost-effective microneedle production.

Every fabrication method has its benefits and limits as described briefly. For silicon microneedle fabrication, lithography and deep reactive ion etching methods are commonly used. The key phenomenon in the growth of microneedles is etching and deposition [126–128]. Laser ablation and hot embossing methods are favorable fabrication methods for polymeric microneedles. However, electrochemical etching is the most effective and is an economic way for fabricating microneedles of silver, gold, copper, other metals, etc. [129–132].

Testing and Evaluation

After the successful fabrication and designing of microneedles till 2005, the researchers switched their interests and started exploring the methods for testing fabricated microneedles.

For microneedle testing, different skins from animals and vegetables besides humans have been used until now:

- potato skin [133],
- chicken skin [134],
- mouse skin [13, 32, 124, 135],
- beef liver [92],
- cadaver skin [34, 115],
- pigskin [136, 137],
- chicken leg, and
- human skin [29, 138–142] have been used.

Also, microneedles are coated using a solid-state influenza vaccine to increase the efficiency of the vaccine and then tested on the skin of mice [143]. A short closely pointed microinjection array has been established to understand the result of stress rate on the accuracy of permeation into animal skin [144]. Reference [145] has examined that influenza disease-like elements coated on microneedle arrays can produce stimulatory consequences on Langerhans cells in the skin of a human. The extremely short microneedle has been fabricated by Si wet-etching technology as well as tested for transdermal drug delivery into human skin [26]. The detachable-tipped microneedles have been presented and verified for simple delivery of drugs and vaccines into human remains skin [146]. A nominally intrusive structure has been established employing a microneedle conductor array to transport macromolecular medicines to the subterranean skin nerves and tested on tonsured mouse skin [138]. Solid-silicon microneedle patches have been consumed using altered lengths and geometry to pierce the human epidermis [147, 148]. Microneedle array rollers have been established and tried on human and pigskin to rise skin penetrability and for cosmetic surgery [149]. Microneedles have also been used for delivering PLGA nanoparticles in the skin of humans [38]. Solid-based polymer microneedles have been established to examine the transepidermal water loss depths of dermatome human skin [35]. The effectiveness of transdermal delivery of insulin has been examined by means of microneedle rollers on rats which are diabetic [150]. The influenza vaccine having viral particles has been studied and tested by means of microneedle patches on bone marrow cells and lungs of mice [151]. Thus, many researchers have tested their fabricated needles to make sure their quality is good and they are safe to use for biomedical applications.

Safety Concerns

Solid microneedles are being used for harmless and effective drug delivery and for vaccines through generating flexible microchannels in the skin [152].

Microneedles are insignificantly invasive drug delivery structures that have been considered or deliberated for safety.

Safety concerns are primarily associated with any kind of infection risk. Other factors to study include user suitability as well as environmental issues.

- Pain
- Bleeding
- Skin irritation
- Remaining vaccine left in structure and on the surface of the skin

On experience using hypodermic needles, the contaminated needles can cause the greatest risk of infection. Therefore, single-use adequately clean microneedles that are sterilized would cause a little risk of infection. Though, the skin is continually in connection with environmental entities and becomes voluntarily colonized through definite microbial species. Any hole in the skin can give entry to microorganisms that might cause confined or total infection. Microneedle arrays comprising hundreds as well as thousands of microneedles might consequently be problematic. Though, the threat of infection is linked to a large number of factors including.

- the number of breaches as well as their sizes,
- the penetration of breaches,
- the number of microbes entering the skin as well as their nature, and
- the discrete vulnerability of the patient.

In clinical practice, it looks improbable that any trivial injuries caused by the usage of microneedles would result in substantial safety concerns. Certainly, the skin barrier is regularly breached in the course of communal experiences of slight abrasion, e.g., shaving; nonetheless, infection hardly occurs [153, 154].

Even though pain is not a safety concern per capita; it, however, has an emotional impact on patient reception and safety perception. Initial studies about sharp-tipped microneedles revealed that they are considered normal as painless in human subjects [51, 155].

Also, the epidermis is lacking vasculature, and the utmost shallow capillary bed is situated in the upper dermis near the junction of the dermal-epidermal. As a consequence, microneedles piercing the skin deeper than nearly 100 μm might rupture capillaries. Regardless of this expectation, many animal and human studies have not witnessed bleeding after treatment with microneedles [156, 157].

Also, no skin irritation occurs in any of the studies when insertion of drug or vaccination is done by using microneedles. However, some more sensitive skins can have some redness or tenderness; otherwise, there is no such proof found [24, 158].

The insinuations of having vaccine residual left on microneedles or on the skin surface rest on the particulars of the vaccines and their preparation. In any situation, minimalizing the residuals could be useful from a safety and conservational standpoint [154].

Jiang et al. [159] studied the existence of microchannels or infections after the inclusion of microneedles into the rabbit's cornea through a standard lamp. They identified that microchannels vanished in 3 h, and there was no sign of a provocative response. Thus, it proposes that microneedles can be considered appropriate for drug delivery to the eyes for the cure of ocular diseases. Damme et al. administered the influenza injection intradermally through microneedles as well as intramuscularly via conventional hypodermic needles. They considered that pain linked with the insertion of a needle was considerably less through microneedles. After the insertion of the microneedle, ephemeral reactions happening on the skin at the site where microneedles were applied were found to be endurable. They determined that efficient vaccination could be accomplished utilizing microneedles as compared to the conservative intramuscular distribution of influenza injection. Laurent et al. [160] proved a study in which protection, as well as the effectiveness of rabies vaccination, were administered via microneedles. They also found acceptability with effective vaccination via microneedles as compared to conservative vaccination. Gill et al. [161] deliberated the consequence of microneedle length as well as their number on pain. They described that pain increases with the increase in length of microneedles, while pain increases slightly when the number of microneedles increases. Thus, it was concluded that skin permeation should have an increase in the number of microneedles as compared to microneedle length to consider less pain. Bal et al. [162] and Kaushik et al. [51] considered the protection of microneedles and stated that drugs could be transported deprived of any adversarial reactions and pain via microneedles. Generally, it is concluded that microneedles are secure; nonetheless, few trials remain to be confronted for their commercialization and improvement as an effective transdermal drug delivery technology.

Applications of Microneedles

Today there are numerous and diverse applications of microneedles. In genetic engineering, cell biology, and molecular engineering, it is preferred to change a method to host peptides, oligonucleotides, proteins, DNA, as well as other inquiries into the cells to modify their functions. Therefore, solid microneedles can be applied to the cells for the distribution of molecules over impervious membranes. It has been verified that microfabricated needle patches could

be used to transport DNA into plants and mammalian cells, persuading cell alteration [12, 163, 164].

Another significant application of microneedle is in nominally invasive drug delivery. Due to the slight cross-sectional area of normally several-hundred square micrometers, any risk of damaging effects can be easily reduced. Also, the drug delivery can be restricted to a precise and confined tissue or area in the human body. Also, to study the neural events through some degree of trauma to the tissues, solid microneedles have been used. The short channel of solid microneedles offers another benefit in drug delivery. Microfabrication technology permits the needles to have channel lengths easily controllable at a microscopic scale. The needles can be premeditated to pierce just below the outer layer of skin which is called stratum corneum, and it has precise permeability. As the endings of nerves occur at the penetration of ~ 100 µm, therefore delivery at this position will ease pain, contamination, or wound. Furthermore, since there is a large number of capillaries present inside the skin layer, the drug will be freely immersed in the body, thus allowing quick treatment [165].

Microneedles can likewise be used to extract samples, hence finding substantial applications in the health monitoring field as well as performing biochemical analysis. For example, in patients having diabetes, microneedles are the finest way to check their glucose level and to manage multiple dosages of insulin. The usage of microneedles can make it practically a painless and considerably more pleasant experience for patients.

Microneedles also have applications in the electronics field as well as sensors. They have been used in scanning tunneling microscopes, Millipede data storage techniques, and atomic force microscopes, as probes for superficial modification and reporting. Microneedles have been functional in microdialysis where the microneedles are made penetrable only to trivial molecular weight combinations. This guards the sensors against advanced molecular weight composites, e.g., proteins assisting to maintain the operative viability of the medicinal monitors. Further applications comprise heads of printer and electrospray emitter control valve [66, 166–171].

Products Made with Different Types of Microneedles

Prospective of microneedles to change the worldwide transdermal market is emphasized in terms of the accomplishment rate of microneedle technologies in clinical trials getting to the worldwide market. Thus, the arrival of commercial microneedle products in the market is extremely estimated as they have the potential of representing the incredible impact on clinical medication in the nearby future. The summary of designed products using different types of microneedles is given in Table 3.

Commercialization Issues

It has been observed that there are numerous applications of solid microneedles, but only a small number of products have been marketed until now. For the delivery of drugs at both large and small scale, it is necessary to consider the efficiency and safety of microneedles while developing them. When metallic microneedles are inserted into the skin, there is a chance of some metallic traces to be retained under the skin which afterward causes irritation, swelling, erythema, discoloration, or further side effects. Repeated insertion of microneedles at the same spot may result in the above-mentioned problems. Application of microneedles at altered sites each time or deviation in skin depth in persons may result in deviation in bioavailability that needs to be measured while developing the microneedles. Nowadays, research is more fixated on the expansion of new technologies for the supervision of current molecules that are previously confirmed as safe, therefore reducing growth time and promising an increased success rate. That is why staff in the pharmaceutical industry struggle for the successful expansion of microneedles as transdermal drug delivery systems [185, 186].

Additionally, biohazardous piercing waste may be left behind after practice which needs to destruct carefully. Dissolving microneedles on the other hand are usually made of polysaccharides, which on insertion completely dissolve in the skin, leaving behind no harmful waste. Whole dissolution, correct insertion into the skin as well as filling of drugs comprehensively at the tip merely are the top challenges to be confronted during the development of dissolving microneedles. The usage of hollow microneedles is an alternative approach that gains the interest of researchers owing to its capacity to control a larger range of molecules. However, hollow microneedles do not hold enough strength, and this is their main issue that must be focused on [187, 188].

Other Challenges

There are several challenges related to microfluidic devices in the biomedical field which include fabrication issues, designing level issues, and packing level issues when considering these devices to be used in different practical applications. The more common and severe issues

Table 3 Summary of products manufactured using different microneedles

Product name	Manufacturer name	Description of microneedles	Commercial applications	References
Dermaroller®	DermaSpark, Canada	Metal-based microneedle arrays	Used for acne treatment, stretch mark removal, reduce hair loss. Capable of enhancing drug absorption	Ita et al. [10]
MicroHyala®	CosMED Pharmaceutical Co. Ltd., Japan	Dissolvable microneedle arrays	It comprises hyaluronic acid which is released into the skin for wrinkle treatment	Hirobe et al. [172]
VaxMat®	TheraJect Inc., USA	Dissolvable microneedle arrays	It is used for providing macromolecules, e.g., peptides, proteins, and drug vaccines	Lhernould et al. [173]
Micro-Trans®	Valeritas Inc., USA	Microneedle arrays	Delivery of drug inside the dermis deprived of drug size limitations, control, structure, or patient's skin appearances	Wilke et al. [110]; Bora et al. [174]
DrugMAT®	TheraJect Inc., USA	Dissolvable microneedle arrays	It transports drugs of hundred micrograms quickly through the stratum corneum in epidermal tissues	Caffarel et al. [175]; Halder et al. [176]
NANOJECT®	Debiotech, Switzerland	Microneedles patch device	Beneficial for intradermal as well as hypodermic drug delivery also for diagnostics of interstitial fluids	Joshi et al. [200]
Soluvia®	Becton Dickinson, USA	Hollow microneedles arrays	It is a pre-fillable microinjection scheme for precise intradermal drug transportation and injections	Donnelly et al. [177]
IDflu®/INTANZA®	Sanofi Pasteur, Lyon, France	Intradermal microneedle vaccinations	Pre-filled with influenza shot for vaccination of intradermal infection	Bragazzi et al. [178]
MicronJet®	NanoPass Technologies, Israel	Intradermal microneedle booster	Used via any normal syringe for painless drug delivery, protein, as well as vaccines	Levin et al. [179]
Macroflux®	Zosano Pharma Inc., USA	Metallic-based microneedle arrays	Transportation of peptides as well as vaccines	Garland et al. [180]
Microcore®	Corium International Inc., USA	Dissolvable based peptide microneedle arrays	Delivery of small and large molecules, e.g., peptides, proteins, plus vaccines	Jana et al. [181]
Dermapen®	Not reported	Microneedle patch-based device	Used for the treatment of numerous disorders of the skin, e.g., acne, stretch marks, as well as hair loss, and improve drug immersion	Ali et al. [182]; McCrudden et al. [183]
Micro-structured transdermal patch	3 M Corp., USA	Hollow microneedle patch	It transports liquid preparations over a series of viscidness	Davis et al. [184]

related to microneedles at fabrication and design levels are evading of clogging consequence, appropriate length, toughness, strength, piercing tip to evade pain, drug confrontation, less cost of fabrication, dependability, and biocompatibility. It is needed to adopt appropriate group fabrication techniques to decrease the budget for devices. The main consideration is the packaging of these microfluidic devices. Packaging should be vigorous and resilient to avoid any damage or infection caused by these microfluidic devices [10, 189]. Concurrently, the accidental drug discharge in storage from the reservoir should be stopped. A protective covering may be mandatory to protect such kinds of small-sized devices, e.g., sharp-tipped microneedles. Mostly, the microneedles stated in the literature have been suggested as stand-alone devices. The integration of microneedles is a prodigious challenge that confines the

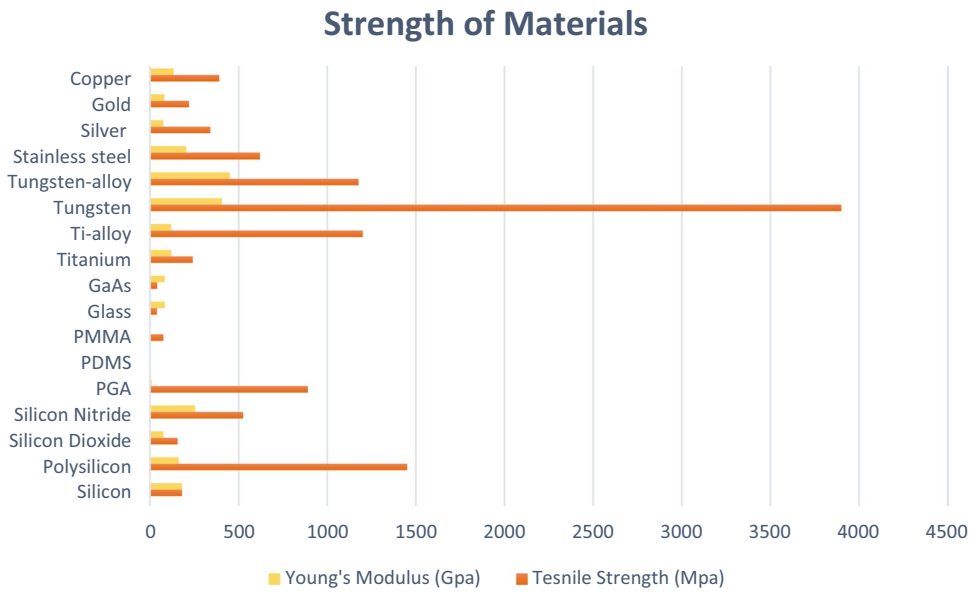

Fig. 4 Comparison between force and stress on microneedle insertion

usage of these microfluidic devices for biomedical applications. The final price of these delivery devices should be reasonable for the patients [190–192]. Nowadays, the trend is changing toward the usage of polymer materials (e.g., PDMS, PGA, PMMA) for the fabrication of microneedles to overawe most of the above-referred issues as these stated materials are biocompatible, inexpensive, and they show exceptional mechanical as well as chemical properties [193–195].

Discussion

Solid microneedles are therefore considered to be crucial components for biomedical systems. Material selection is an important concern in biomedical devices. Silicon has been extensively used as a material in microfluidic devices; however, polymer materials (e.g., PGA, PMMA, PDMS, PLLA, PC, and PLA) are exchanging Si owing to biocompatibility, ease of fabrication, low cost, as well as exceptional structural properties [196–198].

Solid microneedles having sharp tips are considered to be more useful for drug delivery/transport. The efficiency of drug delivery in recent years has also been explained through various researchers by microneedle testing on mice, pigs, chickens, and humans. Many researchers have described the structure, as well as breakage studies of microneedles, through applying force and stress to foresee the failure and twisting of microneedles [199]. The graphic illustration of force and stress comparison for microneedles is given below in Fig. 4.

The material selection is very important for the fabrication of microneedles, and how much strength they endure when applied to human skin or any animal body is also important. The strength of materials concerning their

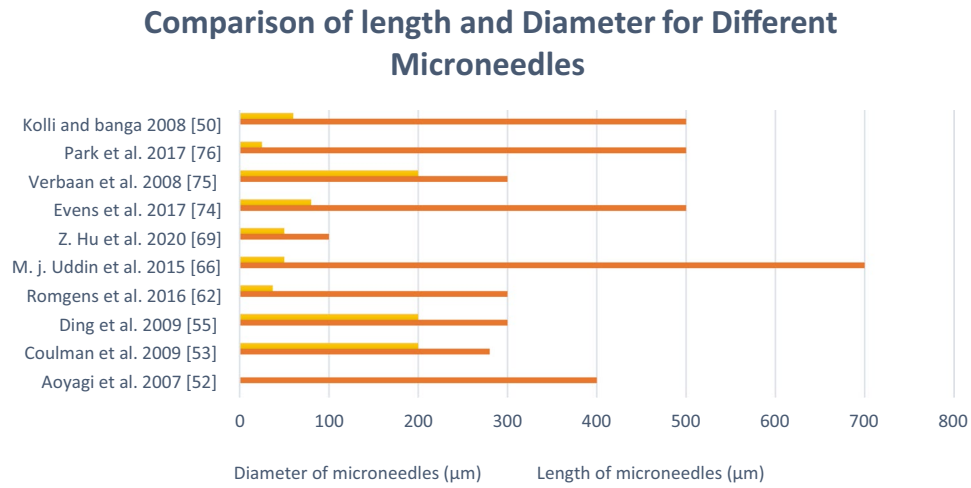

Fig. 5 Comparison between length and force for different microneedles

ultimate tensile strength and Young's modulus is given in the graph below:

The length and diameter of microneedles are also important parameters to be studied while developing microneedles and how they are useful in the insertion or application of microneedles. The graph for length and diameter comparison is given in Fig. 5 below.

Conclusion

Microneedles give many different benefits compared to the conventional needle/syringe as well as other delivery techniques that might also be harmless and effective. For instance, the patch-based setup of numerous microneedle designs would assist simple vaccine supervision and probably self-administration by patients. The minor size of microneedle structures should also ease storing and prompt distribution to dominant locations. Solid microneedles are considered to be a striking platform for drug delivery as they have a low cost of manufacturing, and they can play a significant role in the medicinal response to a virus pandemic. Solid microneedles can be easily fabricated and are stronger as compared to hollow and dissolving microneedles. Solid microneedles using diverse materials, such as glass, metals, silicon, and polymers, have been stated for biomedical applications; however, silicon has been typically used as a substrate among other materials in the fabrication of microfluidic devices. Silicon is brittle and each time involves some risks for health care. Biocompatibility is very essential for well-being, and the reason trend is shifting toward polymer materials. Most polymers, such as PDMS, PGA, PLA, and PMMA, are precisely appropriate for biomedical devices owing to their upright biocompatibility, low budget, easiness of fabrication, and exceptional chemical as well as mechanical properties. According to the given literature review, the authors determine that microneedles, their commercialization, and biomedical applications continue to be growing day by day and still need improvements and advancements.

Declarations

Conflict of Interest The authors declare no competing interests.

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