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# A Comprehensive Review on Microneedles

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**ABSTRACT**

Drug release during the skin offer several compensations such in place of escaping of liver wort primary-go by absorption, protection of stable blood plasma meditation, protection, with observance more than verbal or Parenteral pathway. Though, the main task designed for transdermic transport remains that only a partial quantity of strong medications among best physicochemical property container inactively disperses then intercellular infuse during membrane barrier besides realize beneficial absorption by this direction. Important labours contain be prepared in the direction of the advance of approach to improve transdermic penetration of the medications. Amongst them, microneedles characterize single of the micro scale physical development techniques that significantly develop the range of drugs for transdermic and intradermal distribution. Microneedle characteristically measure 0.1–1 mm in distance. Now this assessment, micro needle material, manufacture route, description technique and application for trans-dermal deliverance are discuss. A selection of ingredients such by way of silicon, stainless steel, at the time polymers have been located used to manufacture solid, coated, hollow, or dissoluble micro needles. Their implication for transdermal medication distribution has remained deliberated widely. Though, readily available stay tasks with continuous distribution, efficiency, price-operative manufacture, and big-measure developed. This review discusses changed mode of categorization besides the gap in manufacturing skills connected with microneedle. These reviews too discuss their possible force on drug distribution, injection distribution, illness investigative, and cosmetic applications.

## INTRODUCTION:

Drugs contain be delivered in a range of pathway in the direction of recover the quality of physical condition and expand person life. Drug delivery system has seen severe improvement as of chew of healing foliage to capsule, pill, injectable and implantable devices [1]. In excess of the centuries, the healing effectiveness medication takes remained improved with targeting the contained complaint area a reduction its poisonous out come to fine cells [2]. Advanced adsorption and transportation of the drug remain able to be achieving to help difficult symptom for patients.

There remain changed ways used for remedy distribution interested in the human build, which consist of verbal, parenteral, inhalation, transdermic, etc. [3]. The verbal way is the oldest path so suitable for patients by suitable easiness of administration. For tall-period medication, the verbal routes have side effects since the situation impact essential body part such as the liver and kidneys. The parenteral routes introduce aquaphobic medications to the human body use intra-muscular, hypodermic, and intravenous pathway [4]. As per parenteral drug distribution is a fast distribution technique, it is measured the best selection of medication distribution in an emergency [5].

### Microneedle (MN) for Transdermal Drug Delivery:

MN knowledge is a type of energetic transdermic drug delivery then is planned in the direction of used as a substitution to the usual needle inoculations. The micro needle arrangement is use to enter the stratum corneum and distribute the medication by means of a simply aggressive act [6]. These ranges remain micro sized needles through a top range from 25 to 2000 μm [8]. Microneedles include be use for changed application such as drug and vaccine delivery, cosmetic, and illness diagnosis. Microneedle has several structural activities, shape, form, and ingredients the length of by means of different productive technique which is more illustrates in this assessment paper. Demonstrate several present profitable microneedle devices. Donnelly et al. claimed that 30% of the maximum present scholarly poetry in “transdermal delivery technology” accounting for microneedles study [9].


**Figure 1: Microneedle based drug delivery systems**

The MN drug delivery way is able to be impacted by exterior environment similar as skin structure, physio-chemical quality, with comprehensive situation [10]. These contain the comparative moisture and temperature in the surrounding area of the purpose part. To spare (inferior moisture) will delay the release of medications to the membrane coatings, though also high moisture (such as perspiration) can get into the way in the drug discharge kinetics suitable to additional water and attendance of next salts there by change the osmotic ascent designed for transdermic drug distribution. Additionally, an extra of sweat be able to stop the adhesion of the micro-needle patch to the skin more delay elution of medicines during the skin. Equally, too low or very high pH ranges approximately the skin area is able to consequence in lower penetrability of the drug interested in the stratus corneum and outside [11]. Unnecessary lipid films on the skin form a barricade layer to the stratus corneum and defeating this flake can support in transdermic adsorption [12]. Raise the skin temperature can increase penetration of medicines due to growth diffusivity and vasodilatation of skin vessel [13].

## HISTORY OF MICRONEEDLES

During 1905, Dr. Ernst Kromayer, a German dermatologist (skin doctor), preserved damaging, hyper active pigmentation, then other skin disorders by means of changed dimensions of power-driven dental burst (Dentist) [14]. The main part of poetry those discussions micro-needle usage be located in 1921 by Compartments anywhere she injected her needle hooked on the egg cell placing [15]. In the 1960s, transporting medicines by inoculation inside the stratum corneum activated in the direction of is a magnet for concentration [16]. After, the micro needle thought be located introduced in the 1970s [17]; though, this thought was non established experimentally up to the 1990s [18]. In 1979, the primary transdermic organization remained accepted used to distribute scopolamine (sedative, hypnotic drug) through put on a three days patch to remedy sign disorder [19]. In 1994, a sequence surgical procedure remained performed through Orient Reich anywhere he injected a try-bevelled hypodermal needle hooked on the skin to discharge rubbery components [20**].** This surgery targeted the coetaneous deficiencies placed below the skin which remained to blame designed for miserable scars and wrinkles. The primary micro-needle for transdermic distribution remained suggested in 1998 then be located made-up since silicon crackers finished particle engraving then photo lithography [20]. The study defined the usage of micro made-up micro needles designed for the reason of improve drug delivery crossways the membrane. These papers directed to wide-ranging investigate directed in the micro needle field. Different ingredients such as glass, ceramic, metallic, and polymer remained presented to manufacture micro needles. In 2004, a micro needle arrangement was used to penetrate holes interested in the skin for transdermic drug transfer [21], which led to some manufacture technique too material individual explore designed for the reason of TDD. Solid, coated, hollow, dissoluble, and hydro gel-creating MNs remain all dissimilar categories of MNs. additionally, a variety of manufacturing technique such as laser abstraction, photo lithography, micro-inoculation moulding, etc. This discovery led in the direction of the primary information of a dissoluble microneedle actuality used for TDD in 2005 [22]. According in the direction of clinical Trials Gov. Web site, towards date, 43 clinical trials contain be finished by means of microneedles, through the primary microneedle clinical testing finished in 2007 (accessed on 30 June 2021, 5 p.m.). Freshly, additive manufactured approaches to production MN moulds be located established to supply inferior-price solution for micro mould manufacturing [23,24]. Information viewing the usage of commercially presented 3D printer to manufacture the MN leading mould accessible a novel

phase in piece of equipment manufactures and potential for tradition constructed large-volume manufacturing of MNs [25, 26].

**TYPES OF MICRONEEDLES:**

**1. Solid Microneedle**

This type of microneedle assembly remains considered to enter the stratum corneum in direct in the direction of advance drug delivery to the dermis to progress the bioavailability also moving transportation crossways the skin [120,121]. In contrast to intra muscles deliverance, the compact microneedle is appropriate for distribution of inoculations in place of it takes long with owns a further forceful immune body reaction [122]. Compact micro needles remain simple to production; consume higher powered properties, and sharper directions following compare to hollow microneedles [123].

**2. Hollow Microneedle**

The hollow micro needle involves of an outline by empty/hollow centre/hollow in which medicine liquefied is vaccinated [54]. Associated in the direction of compact micro needle, the hollow micro needle may support a big dose of medicine solution [124]. A hollow microneedle similarly takes the capability to transport the drug interested in the workable skin or membrane which is appropriate designed for advanced molecular weight compound [125]. In addition, it controls the drug discharge complete occasion which kinds it appropriate meant for use through fluid vaccine preparations [126]. Different solid micro needles, if mainly eluted medicines created on the osmotic ascent, hollow micro needles be an energetic medication distribution organization making a channel used for medicine distribution interested in the derma built going proceeding a non-under pressure remedy basin. Individually solid preparation then production limitations of vacant micro needles are able to remain leverage towards permit tuneable discharge motion. Advanced concentrations drugs can outcome in disintegrated is charge medicine shapes, where atmosphere-burdened drugs be permitting a stable-condition drug discharge long lasting times to weeks dependent on the request determined [127].

### 3. Coated Microneedle

The coated micro needle is a compact-category MN covered with a medication elucidation. Characteristically, it transmits a reduced quantity of the drug dependent on the width of the covering stratum [128]. The achievement of distributing drug by a covered MN is subject to on the capacity to dependably cover an organized drug film against MNs [113]. A covered MN has the capacity to distribute proteins and DNA in a slightly aggressive method [129]. A benefit of a coated micro needle is quick transport of the medication a route for the membrane; though, the residue drug at the angle of the needle strength infects another patient [130]. To conclude, the outcomes of the distribution of the inoculation by means of coated MN are located comparable to injections by means of intra dermis and intramuscular routes [21].

### 4. Dissolving MN

The dissoluble MN primary appear in 2005 [21] with is a talented method base scheduled his description. These features contain simplifying the quick discharge of macro-molecules [91], in addition to a single-phase drugs function which spreads the comfort of medicine organization [131]. Due to development detected in put on dissoluble MNs subsequent "poke-and-release", this method is measured improved than additional methods [132]. The dissolvable MN nozzle is able to be burdened in a suitable means via a two-stage moulding technique [131]. Upon supplement of the dissoluble micro needle on the derm, the medicine-weight release and diffuse simply through disintegration by the syringe land fill [21]. Water soluble material is maximum suitable in the production by the dissoluble microneedle [133]. Similarly, the micro mould technique of production is for the maximum part suitable for the production of the dissoluble micro needle [125]. The formation and manufacture of a dissoluble MN arrangement involves industrial knowledge [21]. However, this category of MN needs whole supplement which is regularly not easy to achieve, and also experiences a suspension in dissolution [54].

## MATERIALS OF MICRONEEDLES

The primary explanation following the manufacture of MN, s is their capability to enter the skin without flouting or flexible. A number of influences, such as material, developed technique, and design, contain be measured in attacking the MN manufacture dare. A diversity of ingredients has remained used to manufacture dissimilar categories of MNs.

Samples of these ingredients are silicon, metals, ceramic, and polymer [28, 29, 30, 31, 32]. A mixture of dissimilar material categories has remained applied for bio-medical application in the extent of transport medications, tissue manufacturing, and bio-medical transplants [33, 34, 35, 36, 37, 38, 39, and 40].

### 4.1. Silicon

In 1990s, the primary MN remained made-up as of silicon material [43]. Silicon owns frequent advantages over additional ingredients, counting its characteristic flexibility, which permits for simple manufacture ability in conditions of necessary shape and size of microneedles. Silicon has been used to manufacture hard, gossipy, and covered micro needles [16]. On the previous indicator, around are limits related through by means of silicon such as time-consuming production [44], Advanced price [9], also the opportunity of causation breakages in the skin [45].

### 4.2. Metal

Metals be situated used in the making of micro needles as these include fine bio-compatibility then motorized character [46]. Metals consume advanced breakage hardiness [47] also produce potency standards. Associated to silicon, metals are strong and hard to breakdown [7]. The primary metal utilize in the production of a MN was stainless steel [48] follow through titanium. Contempt the capacity of metal MN to cut the membrane, the function of metallic MN power causes a hypersensitive response [6].

### 4.3. porcelaneous (Ceramic)

Due to their greater substance character besides density counteraction, Porcelaneous ingredient such as per alumina (argil) has been used to manufacture a MN [49]. Though, alumina has an inferior workable strength related to other constituents. Calcium sulphates dehydrate and calcium phosphate dehydrate are added type of porcelaneous ware applied in the production of micro needles [7]. A micro mould method is able used at construct a MN by means of Porcelaneous substance. Present method proposal climbed-active manufacture at small price [50]. An education directed by Bistro et al. presented those MNs made-upstarting alumina broken upon physical request towards the skin [51].

### 4.4. Polymer

Polymer's proposal a talented substance different in order to MN. They contain outstanding bio-compatibility, less toxic, and less price [52]. Though, the further more contain subordinate potency associated to silicon then metals [47]. Polymer is regularly working in the manufacture of dissoluble and hydro gel-making MN's array, hard, coated, and gossipy micro needle arrays [16]. Many categories by medications contain he apply to the skin with decomposable MNs [53]. Categories of polymers use on the manufacture of MNs comprised poly (methyl methacrylate) (PMMA), polylactic acid (PLA), poly (carbonate), polystyrene, and SU-8 photoresist [7].

**List of chemicals:**

**Table no.1: List of chemicals.**

| Sr. No. | Chemicals |
|---|---|
| **1.** | PLA |
| **2.** | Calcium phosphate |
| **3.** | Silicon |
| **4.** | PMMA |
| **5.** | Poly (methyl methacrylate) (PMMA) |
| **6.** | Poly lactic acid (PLA) |
| **7.** | Poly (carbonate) |
| **8.** | Polystyrene |
| **9.** | SU-8 photo resist |

## METHOD OF MANUFACTURING:

### 5.1. Laser Ablation

Laser removal includes the practice by an absorbed visual light ray in eliminate substance since a substratum to produce MN arrays. Lasers consume remained used to method different ingredients fluctuating as of abstruse and Nano-scale designed fora number of requests [54,55,56,57,58,59,60,61,62,63,64,65,66]. Different laser categories have been study meant for the production of MN collections. These consist of $CO_2$ [67, 68], UV excimer [69, 70], and fathom second laser apparatus [71]. The laser abstraction technique is considering an

actual and fast technique for MNs manufacture. The laser rays take to 10-100 Nano seconds to method the injury opinion in the substance sheet [52]. Laser possibly will too be use to shapes any metals. This technique is related with current effect at the cutting superficial that outcome in the modification of MN fabrication and mechanic property [72]. Present capacity led to unwanted properties in MNs such as crunch, or tiredness obstruction. However, the price of the optical maser is advanced linked to additional categories of equipment's [52]. The laser extirpation technique remains non suitable for wide range manufacture [72].

**Table 2: Different methods and polymers used**

| S. N. | Method | Polymer/Material | Use/Application | References |
|---|---|---|---|---|
| **1.** | Lithography and ceramic sintering micro moulding two photon polymerization (2PP) | α- aluminium (III) oxide (α-$Al_2O_3$), zirconia | Primarily deposition or etching. | [73, 85] |
| **2.** | Laser-ablation, micro moulding, | Nickel/iron | Skin resurfacing, cavity preparation, biopsies. | [89, 90] |
| **3.** | Laser cutting, laser ablation, etching, electroplating, electroplating, lithography | Stainless steel | Automotive, die, mould, tool, jewellery, and medical industries | [22,25,51,71,72,93] |
| **4.** | Photolithography | Amylopectin | To produce computer chips | [67] |
| **5.** | Atomized spraying process | Maltose, fructose | Formation of droplets | [80, 84] |

### 5.2. Lithography

The lithography method is used to shifting the main composition of the symmetrical shape against a surface of a substance [76,77,78,79,80,81,82,83]. Photo-lithography is primarily use for design transfer payable towards the issue extensive application in the zone of

microelectronics [84]. Further methods such as micro-electronic and micro-machining use lithography as the primary stage in manufacturing a MN [16]. Lithography needs specific technology of the photo resist [85]. This method donates to around 30–35% of charges for manufacturing combined routes [86]. Lithography owns the capability to produce product since an array of ingredients such as crystal, metal, ceramic objects, and plastic [87]. It similarly harvests accurate geometries and smooth perpendicular side walls [52]. Though, this method needs a highly developed facility (clean room) and comprehensive manufacture period [68].

## 6. MN Mechanical Characterizations

Throughout the micro needle composition stage, it is essential to deliberate the power-driven property of the Micro needles as these remain exposed to a well-becoming power for epidural anaesthesia addition. To achieve this, the MNs requirement to have necessary potency in direction to avoid dis appointment in the MN collection [89]. Luton et al. claimed to around be no only examination that can reproduce and study the machine-driven assets of syringe and the supplement of the micro needle in vivo [90]. Subsequently, a variety of motorised trials must be applied to the MN for classification. Many categories of power-driven trial on MNs contain axial strength, crosswise strength, dishonourable shield crack, and addition power. Furthermore, numerous surveys contain he perform to learning the connection among mechanical classification and MN production limitations [91].

### 6.1. Axial Force

In the axial force analysis is the maximum mutual then she involves by apply force to the commands of the syringe in a straight up way then toward the base of the MN collection [92]. This power-driven experiment is significant and attends to control the collapse strength of the needles. Expressive the collapse strength quantity of the needles is the most excellent respected in sequence or called the protection fact subsequently it gives an estimated series (expectancy) of needle supplement strength [88].

Various axial force studies contain be achieved to find out the let-down strength of MNs by means of dissimilar apparatus also count technique. Davis et al. calculated the abortiveness (miscarriage) (ScopeTest1, Endure TEC, Minnetonka, MN, USA) from calculate the strength and dislocation information [93]. More-over, Demir et al. considered the breakage strength by means of a common testing apparatus (Instron® Model 5969, Instron, and Nor-wood, MA,

USA). More-over, Khanna et al. studied (well- read) the axial damage test with a density weight compartment (LCFA-500gF detecting capability, Omega Co., Nor-walk, CT, USA) and power-driven actuator (Z600 sequence Thorlabs power-driven Actuators, Morganville, New Jersey, USA) [94]. Donnelly et al. applied a density power-driven trial by use a TA-XT2 quality Analise (Still Microsystem, Haslem ere, UK) among the support of a light microscope (GXMGE-5 digital microscope, Workshop Investigation Ltd., Devon, UK) [95]. Park and Parasnath calculated the collapse investigation with a dislocation-strength trial location (Model 921A, TRICOR method, and Elgin, IL, USA) [96].

### 6.2. Transverse Force

The transverse force analysis includes the purpose of an energy equivalent to the MN base plate by means of the y-axis. The disorder of the membrane shallow might main to crossways flexible of the MN, besides therefore the dimension of the crossway's breakage strength is vital. Further-more, beside through the axial strength, the crosswise strength finalizes the large image of the MN's power-driven belongings and therefore expects MN deflexion behaviour through addition [27]. The control of this examination is that the metallic investigation takes towards remain physically associated through a definite distance of the MN.

Different education remained achieved by Park et al. to quantity the crosswise strength by means of a strength–displacement position and an optical microscope [97]. The MN remained usual vertical on a metal plate with vertical loading by a PDMS construction. The transverse force was established up until the MNs stayed cracked consequently ultimate that movement growths linearly through a MN distance. Demir et al. verified the crosswise strength of the MN by means of a micro mechanical sample (Instron® Model 5969; Instron, Norwood, MA, USA) [27].

### 6.3. Insertion Test

The insertion test is further vital then dissimilar after the axial strength as the axial force ensures non give a correct dimension as the supplement trial. Besides, dissimilar skin topics were embattled in this trial which contain pigs, rats, mice and humans. Single benefit of by means of a MN is the capacity to weight the medicine and transport to the skin. Contempt consuming more than a few power-driven trials fake the breakage strength of the needle, it is vital to authorize the consequences by a real skin.

## APPLICATIONS OF MICRONEEDLES

MNs have involved wide-ranging attention by investigators, researchers, then industry participants. Some educations take established the possible and capacity to direct MN in changed grounds. These comprise medicine distribution, vaccine distribution, illness investigative, and greasepaints usage.

### 7.1. Drug Delivery

The primary request of micro needles used for medication distribution remained by means of a hard silicon MN in 1998 [20]. A dissoluble micro needle (MN) patch was used to distribute human development hormone for transdermal distribution to hairless mouse membrane [98]. Dissoluble caffeine burdened micro needle covering be present eligible to controller the heaviness of overweight rats also effort by means of a challenging-overweightness treat plan [99]. A coating MN covering remained used to distribute pink-orange thyrocalcitonin [100]. A compact microneedle was used to transport a protein antigen (albumen) hooked on hairless guinea pig membrane [101]. Compact silicon and metal MNs be situated use for the transport of calcian [102], BSA, and then insulin. Further-more, MNs consume stayed utilization for transdermic saturation used for some medications such as Ibuprofen, Ketoprofen, and Paracetamol [103]. Further medications administrated via micro needles comprise L-Ascorbic acid, Riboflavin, Aspirin, Docetaxel, Pilocarpine, Lidocaine, Hydrochloride, Ketoprofen, and Glycerol [104]. Contempt the circumstance that maximum educations utilization microneedle array for remedy transfer into rats, pigs, humans' skin, around be situated further studies which effectively established microneedle inoculation into chicken thigh [105], and brain tissue [106].

### 7.2. Vaccine Delivery

A dissoluble microneedle is a general category of MN utilised for vaccine distribution determinations. The dissoluble MNs remained use to exchange subcutaneous injections and needles that were characteristically used to administered serums. Dissimilar additional categories of MN, the dissoluble MNs are bio-compatible, healthy, mountable, and do not produce bio hazardous worthless [107]. Dissoluble MNs be situated applied to distribute vaccine for Malaria, Diphtheria [108], Influenza [109], Hepatitis B [110], H.I.V. [111], and Polio [112].

Furthermore, though dissoluble MNs are maximum commonly used for vaccines distribution, covered MNs selections consume similarly be located effectively used for immunization determinations [16]. An education used easy, secure, and acquiescent immunization technique to recover the pig's immune systems are strengthened by the administration of the BCG vaccine using a multilayer micro needle MN. Additional research successfully programmed the DNA vaccine with the disease protein of the hepatitis C virus, covered on micro needle [114]. The microneedle be situated effectually informed for exact Cytotoxic T Lymphocytes (CTLs) in rats. Furthermore, a coated microneedle passed flu infection antigen for immunization request in rats [115].

Gossipy micro needles must be located used to distribute splenic fever recombinant protecting antigen serum to a rabbit in its place of even injection [116]. A gossipy micro needle was estimated for immunization in contradiction of inscription in a mouse model [117]. An experimental test showed in persons by means of hollow micro needle through influenza immunization displayed parallel outcomes by the protected organization when connected to Intra-Muscular (IM) injection [118].

### 7.3. Disease Diagnosis

Disease diagnosis too beneficial efficiency may be observed by means of some recognized bio-assays that illustration body solutions to measure and screening health situations. The current procedures induce pain, require focused methods, handmade apparatus, and qualified therapeutic employees [119]. However, microneedle technology proposals bio-assays solution with trouble-free knowledge and modest application [119].

## CONCLUSION:

The position of overcoming the outer layer blockade is essential towards effective MN-intermediary transdermic and intra dermic transfer. Present document summarizes micro needles technology in the Transdermic medication transport time. Wide-ranging educations and **i**nvestigate make sure be located directed in the production of micro needles due to its advantage. Many micro needle design categories, material, and manufacture approaches have been established in this document.

For the transportation of minor and significant molecules, a variety of M and organisations with various delivery methods have been formed and are being used. Recent studies

presented their temporal distractions of the skin microchannel lifespan enhances transdermal distribution effectiveness of small molecular pharmaceuticals station gents and Sardar creations impacts as highlight in this protracted evolution. macromolecules that are distributed intradermally and trans dermally, as well as helpful peptide and protein vaccinations, are developed jointly with a communication to Minnesota and a plan for dealing with them. Intradermic and transdermic distribution of macromolecules counting beneficial peptide and protein, vaccine, and synergetic outcome of joint development in accumulation to MN dealing be located prepared. Furthermore, MN power-driven trials and their description are discovered in the poetry.

Finally, this article explores the production gap for Minnesota. Although some new transdermic products have been intermediated by MNs, these have not yet entered the occupied realm of life. Through the advancement of MN-mediated developments, it gradually becomes clear that there is a gap in allowing for cost-effective manufacturing for large-scale MN production.

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**REFERENCES:**

1. Ranade V.V., Hollinger M.A., Cannon J.B. *Drug Delivery Systems.* CRC Press; Boca Raton, FL, USA: 2003.
2. Tiwari G., Tiwari R., Banerjee S., Bhatti L., Pandey S., Pandey P., Srivastava B. Drug delivery systems: An updated review. *Int. J. Pharm. Investing.* 2012; 2:2–11. Doi: 10.4103/2230-973X.96920.
3. Hassan B.A.R. Overview on Drug Delivery System. *Pharm. Anal. Acta.* 2012; 3:4172.
4. Robbie G., Wu T., Chiou W.L. Poor and unusually prolonged oral absorption of amphotericin B in rats. *Pharm. Res.* 1999; 16:455–458. Doi: 10.1023/A:1011961322883.
5. Date A.A., Nagarsenker M. Parenteral microemulsions: An overview. *Int. J. Pharm.* 2008; 355:19–30. doi: 10.1016/j.ijpharm.2008.01.004.
6. Donnelly A.D.W.R.F., Singh T.R.R., Morrow D.I.J. *Microneedle-Mediated Transdermal and Intradermal Drug Delivery.* John Wiley & Sons; Hoboken, NJ, USA: 2012.
7. Singh T., Mcmillan H., Mooney K., Alkilani A., Donnelly R. Microneedles for drug delivery and monitoring. *Microfluid.Devices Biomed. Appl.* 2013:185–230. doi: 10.1533/9780857097040.2.185.
8. Donnelly R.F., Singh T.R.R., Larrañeta E., McCrudde M.T.C. *Microneedles for Drug and Vaccine Delivery and Patient Monitoring.* John Wiley and Sons, Incorporated; Hoboken, NJ, USA: 2018.
9. Barry B.W. Novel mechanisms and devices to enable successful transdermal drug delivery. *Eur. J. Pharm. Sci.* 2001; 14:101–114. doi: 10.1016/S0928-0987(01)00167-1.
10. Ghosh P., Brogden N.K., Stinchcomb A.L. Effect of Formulation pH on Transport of Naltrexone Species and Pore Closure in Microneedle-Enhanced Transdermal Drug Delivery. *Mol. Pharm.* 2013; 10:2331–2339. doi: 10.1021/mp3007083.
11. Naik A., Kalia Y., Guy R. Transdermal drug delivery: Overcoming the skin's barrier function. *Pharm. Sci. Technol. Today.* 2000; 3:318–326. doi: 10.1016/S1461-5347(00)00295-9.
12. Arora A., Prausnitz M.R., Mitragotri S. Micro-scale devices for transdermal drug delivery. *Int. J. Pharm.* 2008; 364:227–236. doi: 10.1016/j.ijpharm.2008.08.032.
13. Walsh L. Microneedling: A versatile and popular treatment option. *J. Aesthetic Nurs.* 2019; 8:280–284. doi: 10.12968/joan.2019.8.6.280.
14. Chambers R. Microdissection studies, III. some problems in the maturation and fertilization of the echinoderm egg. *Biol. Bull.* 1921; 41:318–350. doi: 10.2307/1536756.

15. Larraneta E., Lutton R.E.M., Woolfson A.D., Donnelly R.F. *Microneedle Arrays as Transdermal and Intradermal Drug Delivery Systems: Materials Science, Manufacture and Commercial Development.* Volume 104. Elsevier; Amsterdam, The Netherlands: 2016. pp. 1–32.
16. Gerstel M.S., Place V.A. Drug Delivery Device. US3964482A. *U.S. Patent.* 1976 Jun 22;
17. Reed M., Lye W.-K. Microsystems for Drug and Gene Delivery. *Proc. IEEE.* 2004; 92:56–75. doi: 10.1109/JPROC.2003.820542.
18. Orentreich D.S., Orentreich N. Subcutaneous Incisionless (Subcision) Surgery for the Correction of Depressed Scars and Wrinkles. *Dermatol. Surg.* 1995; 21:543–549. doi: 10.1111/j.1524-4725. 1995.tb00259. x.
19. Henry S., McAllister D.V., Allen M.G., Prausnitz M.R. MicrofabricatedMicroneedles: A Novel Approach to Transdermal Drug Delivery. *J. Pharm. Sci.* 1998; 87:922–925. doi: 10.1021/js980042+.
20. Prausnitz M.R. Microneedles for transdermal drug delivery. *Adv. Drug Deliv. Rev.* 2004; 56:581–587. doi: 10.1016/j.addr.2003.10.023.
21. Dang N., Liu T.Y., Prow T.W. *Micro and Nanotechnology in Vaccine Development.* William Andrew Publishing; Norwich, NY, USA: 2017. Nano-and Microtechnology in Skin Delivery of Vaccines
22. Johnson A.R., Procopio A.T. Low-cost additive manufacturing of microneedle masters. *3D Print. Med.* 2019; 5:2. doi: 10.1186/s41205-019-0039-x.
23. Chen Z., Lin Y., Lee W., Ren L., Liu B., Liang L., Wang Z., Jiang L. Additive Manufacturing of Honeybee-Inspired Microneedle for Easy Skin Insertion and Difficult Removal. *ACS Appl. Mater. Interfaces.* 2018; 10:29338–29346. doi: 10.1021/acsami.8b09563.
24. Caudill C.L., Perry J.L., Tian S., Luft J.C., DeSimone J.M. Spatially controlled coating of continuous liquid interface production microneedles for transdermal protein delivery. *J. Control. Release.* 2018; 284:122–132. doi: 10.1016/j.jconrel.2018.05.042.
25. Krieger K.J., Bertollo N., Dangol M., Sheridan J.T., Lowery M.M., O'Cearbhaill E.D. Simple and customizable method for fabrication of high-aspect ratio microneedlemolds using low-cost 3D printing. *Microsyst.Nanoeng.* 2019; 5:42. doi: 10.1038/s41378-019-0088-8.
26. Zhao X., Li X., Zhang P., Du J., Wang Y. Tip-loaded fast-dissolving microneedle patches for photodynamic therapy of subcutaneous tumor. *J. Control. Release.* 2018; 286:201–209. doi: 10.1016/j.jconrel.2018.07.038.
27. Desai S., Bidanda B., Bártolo P.J. Emerging Trends in the Applications of Metallic and Ceramic Biomaterials. In: Bártolo P.J., Bidanda B., editors. *Bio-Materials and Prototyping Applications in Medicine.* Springer International Publishing; Cham, Switzerland: 2021. pp. 1–17.
28. Desai S., Shankar M.R. *Bio-Materials and Prototyping Applications in Medicine.* Springer International Publishing; Cham, Switzerland: 2021. Emerging Trends in Polymers, Composites, and Nano Biomaterial Applications; pp. 19–34
29. Li W., Ruff B., Yin J., Venkatasubramanian R., Mast D., Sowani A., Krishnaswamy A., Shanov V., Alvarez N., Malik R., et al. *Nanotube Superfiber Materials: Changing Engineering Design.* Elsevier Inc.; Amsterdam, The Netherlands: 2013. Tiny Medicine; pp. 713–747.
30. Desai S., Shankar M.R. *Bio-Materials and Prototyping Applications in Medicine.* Springer US; New York, NY, USA: 2008. Polymers, composites and nano biomaterials: Current and future developments; pp. 15–26.
31. Desai S., Bidanda B., Bártolo P. *Bio-Materials and Prototyping Applications in Medicine.* Springer US; New York, NY, USA: 2008. Metallic and ceramic biomaterials: Current and future developments; pp. 1–14.
32. Perkins J., Desai S., Wagner W., Hong Y. *IIE Annual Conference. Proceedings.* Institute of Industrial Engineers-Publisher; Norcross, GA, USA: 2011. Biomanufacturing: Direct-writing of controlled release coatings for cardiovascular (Stents) applications; pp. 1–6.
33. Marquetti I., Desai S. Orientation effects on the nanoscale adsorption behaviour of bone morphogenetic protein-2 on hydrophilic silicon dioxide. *RSC Adv.* 2019; 9:906–916. doi: 10.1039/C8RA09165J.
34. Desai S., Harrison B. *Printed Biomaterials.* Springer; New York, NY, USA: 2010. Direct-Writing of Biomedia for Drug Delivery and Tissue Regeneration; pp. 71–89.
35. Perkins J., Xu Z., Smith C., Roy A., Kumta P.N., Waterman J., Conklin D., Desai S. Direct Writing of Polymeric Coatings on Magnesium Alloy for Tracheal Stent Applications. *Ann. Biomed. Eng.* 2014; 43:1158–1165. doi: 10.1007/s10439-014-1169-3.
36. Perkins J.L., Desai S., Harrison B., Sankar J. Understanding Release Kinetics of Calcium Alginate Microcapsules Using Drop on Demand Inkjet Printing; Proceedings of the ASME 2009 International Mechanical Engineering Congress and Exposition, Lake Buena Vista; FL, USA. 13–19 November 2009;
37. Desai S., Sankar J., Moore A., Harrison B. Biomanufacturing of microcapsules for drug delivery and tissue engineering applications; Proceedings of the 2008 Industrial Engineering Research Conference; Vancouver, BC, Canada. 17–21 May 2008; pp. 507–513.
38. Desai S., Moore A., Harrison B., Sankar J. Understanding Microdroplet Formations for Biomedical Applications; Proceedings of the ASME 2008 International Mechanical Engineering Congress and Exposition; Boston, MA, USA. 31 October–6 November 2008;

39. Desai S., Richardson A., Lee S.J. Bioprinting of FITC conjugated bovine serum albumin towards stem cell differentiation; Proceedings of the 2010 Industrial Engineering Research Conference; Cancun, Mexico. 6−9 June 2010.
40. ParupelliS.k., Aljohani A., Khanal S., Bhattarai N., Desai S. Direct Jet Printing and Characterization of Calcium Alginate Microcapsules for Biomedical Applications; Proceedings of the 2019 IISE Annual Conference; Orlando, FL, USA. 18–21 May 2019.
41. Cahill E.M., O' Cearbhaill E.D. Toward Bio functional Microneedles for Stimulus Responsive Dru Delivery. *Bioconjugate Chem.* 2015; 26:1289–1296. doi: 10.1021/acs.bioconjchem.5b00211.
42. Sharma D. Microneedles: An Approach in Transdermal Drug Delivery: A Review. *PharmaTutor.* 2018; 6:7–15. doi: 10.29161/PT. v6.i1.2018.7.
43. Badilescu S., Packirisamy M. *BioMEMS: Science and Engineering Perspectives.* CRC Press; Boca Raton, FL, USA: 2016.
44. O'Mahony C. Structural characterization and in-vivo reliability evaluation of silicon microneedles. *Biomed.Microdevices.* 2014; 16:333–343. doi: 10.1007/s10544-014-9836-6.
45. Niinomi M., Nakai M. Titanium-Based Biomaterials for Preventing Stress Shielding between Implant Devices and Bone. *Int. J. Biomater.* 2011; 2011:836587. doi: 10.1155/2011/836587.
46. Monteiro-Riviere N.A. *Toxicology of the Skin.* CRC Press; New York, NY, USA: 2010.
47. Verbaan F., Bal S., Berg D.-J.V.D., Groenink W., Verpoorten H., Lüttge R., Bouwstra J. Assembled microneedle arrays enhance the transport of compounds varying over a large range of molecular weight across human dermatomed skin. *J. Control. Release.* 2007; 117:238–245. doi: 10.1016/j.jconrel.2006.11.009.
48. Pignatello R. *Biomaterials: Applications for Nanomedicine.* BoD–Books on Demand; Norderstedt, Germany: 2011.
49. Indermun S., Luttge R., Choonara Y., Kumar P., du Toit L., Modi G., Pillay V. Current advances in the fabrication of microneedles for transdermal delivery. *J. Control. Release.* 2014; 185:130–138. doi: 10.1016/j.jconrel.2014.04.052.
50. Bystrova S., Luttge R. Micromolding for ceramic microneedle arrays. *Microelectron. Eng.* 2011; 88:1681–1684. doi: 10.1016/j.mee.2010.12.067.
51. Jeggy C. *Micro-Injection Moulding: From Process to Modelling.* Presses Univ. de Louvain; Louvain-la-Neuve, Belgium: 2004.
52. Yuan W., Hong X., Wu Z., Chen L., Liu Z., Wu F., Wei L.L. Dissolving and biodegradable microneedle technologies for transdermal sustained delivery of drug and vaccine. *Drug Des. Dev. Ther.* 2013; 7:945–952. doi: 10.2147/DDDT.S44401.
53. Adarkwa E., Desai S. Scalable Droplet Based Manufacturing Using In-Flight Laser Evaporation. *J. Nanoeng. Nanomanuf.* 2016; 6:87–92. doi: 10.1166/jnan.2016.1265.
54. Yang M., Xu Z., Desai S., Kumar D., Sankar J. Fabrication of Micro Single Chamber Solid Oxide Fuel Cell Using Photolithography and Pulsed Laser Deposition. *J. Fuel Cell Sci. Technol.* 2015; 12:021004. doi: 10.1115/1.4029094.
55. Desai S., Esho T., Kaware R. Experimental investigation of controlled microdroplet evaporation toward scalable micro/nanomanufacturing. *IIE Trans.* 2012; 44:155–162. doi: 10.1080/0740817X.2011.593610.
56. Desai S. Methods and Apparatus for Manufacturing Micro- and/or Nano-Scale Features. US20130314472A1. *U.S. Patents.* 2013 Nov 28;
57. Esho T., Desai S. Laser based microdroplet evaporation towards scalable micro and nano manufacturing; Proceedings of the 2012 Industrial and Systems Engineering Research Conference; Orlando, FL, USA. 19–23 May 2012; pp. 1750–1757.
58. Parupelli S.K., Desai S. Understanding Hybrid Additive Manufacturing of Functional Devices. *Am. J. Eng. Appl. Sci.* 2017; 10:264–271. doi: 10.3844/ajeassp.2017.264.271.
59. McKenzie J., Desai S. Investigating Sintering Mechanisms for Additive Manufacturing of Conductive Traces. *Am. J. Eng. Appl. Sci.* 2018; 11:652–662. doi: 10.3844/ajeassp.2018.652.662.
60. Esho T., Desai S., Craps M. Direct writing of enriched single walled carbon nanotubes towards thin film transistors (TFTs); Proceedings of the 2011 Industrial Engineering Research Conference; Reno, NV, USA. 21–25 May 2011.
61. Desai S., De P., Gomes F. Design for Nano/Micro Manufacturing: A Holistic Approach Towards Achieving Manufacturing Excellence. *J. UdyogPragati.* 2015; 39:18–25.
62. Desai S., Craps M., Esho T. Direct writing of nanomaterials for flexible thin-film transistors (fTFTs) *Int. J. Adv. Manuf. Technol.* 2012;64:537–543. doi: 10.1007/s00170-012-4425-4.
63. Ahmed M., El-Naggar M.E., Aldalbahi A., El-Newehy M.H., Menazea A. Methylene blue degradation under visible light of metallic nanoparticles scattered into graphene oxide using laser ablation technique in aqueous solutions. *J. Mol. Liq.* 2020; 315:113794. doi: 10.1016/j.molliq.2020.113794.

64. Ismail A.M., El-Newehy M.H., El-Naggar M.E., Moydeen A.M., Menazea A.A. *Enhancement the Electrical Conductivity of the Synthesized Polyvinylidene Fluoride/Polyvinyl Chloride Composite Doped with Palladium Nanoparticles via Laser Ablation.* Volume 9. Elsevier; Amsterdam, The Netherlands: 2020. pp. 11178–11188.
65. Menazea A., El-Newehy M.H., Thamer B.M., El-Naggar M.E. Preparation of antibacterial film-based biopolymer embedded with vanadium oxide nanoparticles using one-pot laser ablation. *J. Mol. Struct.* 2021; 1225:129163. doi: 10.1016/j.molstruc.2020.129163.
66. Tu K.T., Chung C.K. Fabrication of biodegradable polymer microneedle array via $CO_2$ laser ablation; Proceedings of the 10th IEEE International Conference on Nano/Micro Engineered and Molecular Systems; Xi'an, China. 7–11 April 2015; pp. 494–497.
67. Nejad H.R., Sadeqi A., Kiaee G., Sonkusale S. Low-cost and cleanroom-free fabrication of microneedles. *Microsyst.Nanoeng.* 2018; 4:17073. doi: 10.1038/micronano.2017.73.
68. Aoyagi S., Izumi H., Isono Y., Fukuda M., Ogawa H. Laser fabrication of high aspect ratio thin holes on biodegradable polymer and its application to a microneedle. *Sensors Actuators A Phys.* 2007; 139:293–302. doi: 10.1016/j.sna.2006.11.022.
69. Chen Y.-T., Ma K.-J., Tseng A.A., Chen P.-H. Projection ablation of glass-based single and arrayed microstructures using excimer laser. *Opt. Laser Technol.* 2005; 37:271–280. doi: 10.1016/j.optlastec.2004.04.007.
70. Zheng H., Lam Y., Sundarraman C., Tran D. Influence of substrate cooling on femtosecond laser machined hole depth and diameter. *Appl. Phys. A.* 2007; 89:559–563. doi: 10.1007/s00339-007-4132-4.
71. Lutton R., Larrañeta E., Kearney M.-C., Boyd P., Woolfson A., Donnelly R.F. A novel scalable manufacturing process for the production of hydrogel-forming microneedle arrays. *Int. J. Pharm.* 2015; 494:417–429. doi: 10.1016/j.ijpharm.2015.08.049.
72. Zaied M., Miraoui I. *AIP Conference Proceedings.* American Institute of Physics; College Park, MD, USA: 2013. Analysis of heat affected zone obtained by $CO_2$ laser cutting of low carbon steel (S235)
73. Sato Y., Tsukamoto M., Nariyama T., Nakai K., Matsuoka F., Takahashi K., Masuno S., Ohkubo T., Nakano H. Analysis of laser ablation dynamics of CFRP in order to reduce heat affected zone; Proceedings of the SPIE Photonics West; San Francisco, CA, USA. 1–6 February 2014;
74. Brookhaven National Laboratory. *Ultrafast Nonlinear Optics.* Springer; Berlin/Heidelberg, Germany: 2013. Femtosecond Laser Micromachining.
75. Donnelly R.F., Raghu T., Singh R., Woolfson D. Microneedle-based drug delivery systems: Microfabrication, drug delivery, and safety. *Drug Deliv.* 2010; 17:187–207. doi: 10.3109/10717541003667798.
76. Gaikwad A., Desai S. Understanding Material Deformation in Nanoimprint of Gold using Molecular Dynamics Simulations. *Am. J. Eng. Appl. Sci.* 2018; 11:837–844. doi: 10.3844/ajeassp.2018.837.844.
77. Gaikwad A., Odujole J., Desai S. Atomistic investigation of process parameter variations on material deformation behavior in nanoimprintlithography of gold. *Precis. Eng.* 2020; 64:7–19. doi: 10.1016/j.precisioneng.2020.03.007.
78. Odujole J.I., Desai S. Molecular dynamics investigation of material deformation behavior of PMMA in nanoimprint lithography. *AIP Adv.* 2020; 10:095102. doi: 10.1063/5.0014458.
79. Odujole J., Desai S. Atomistic Investigation of Material Deformation Behavior of Polystyrene in Nanoimprint Lithography. *Surfaces.* 2020; 3:649–663. doi: 10.3390/surfaces3040043.
80. Gaikwad A., Clarke J. *Proceedings of the 2019 IISE Annual Conference.* National Science Foundation; Alexandria, VA, USA: 2019. Molecular Dynamics Study of the Quenching Effect on Direct Nanoimprint of Gold.
81. Odujole J., Desai S. Molecular Dynamics Simulation of Poly Acrylic Acid as a Resist Material for Thermal Nanoimprint Lithography Processes; Proceedings of the Industrial Engineers Research Conference 2020; New Orleans, LA, USA. 1 October 2020.
82. Gaikwad A., Desai S. Molecular Dynamics Investigation of the Deformation Mechanism of Gold with Variations in Mold Profiles during Nanoimprinting. *Materials.* 2021; 14:2548. doi: 10.3390/ma14102548
83. Madou M.J. *Fundamentals of Microfabrication: The Science of Miniaturization.* CRC Press; Boca Raton, FL, USA: 2002
84. Khuen H.W., Lay L.L., Schaper C. On control of resist film uniformity in the microlithography process. *IFAC Proc. Vol.* 2002; 35:19–24. doi: 10.3182/20020721-6-ES-1901.01154.
85. Plummer J.D., Deal M.D., Griffin P.B. *Silicon VLSI Technology: Fundamentals, Practice and Modeling.* Pearson Education; India: 2009.
86. Tran K.T., Nguyen T.D. Lithography-based methods to manufacture biomaterials at small scales. *J. Sci. Adv. Mater. Devices.* 2017; 2:1–14. doi: 10.1016/j.jsamd.2016.12.001.
87. Park J.-H., Allen M.G., Prausnitz M.R. Biodegradable polymer microneedles Fabrication, mechanics andtransdermal drug delivery. *J. Control. Release.* 2005; 104:51–66. doi: 10.1016/j.jconrel.2005.02.002.
88. Khanna P., Silva H., Bhansali S. Variation in microneedle geometry to increase shear strength. *Procedia Eng.* 2010; 5:977–980. doi: 10.1016/j.proeng.2010.09.272.

89. Lutton R.E.M., Moore J., Larrañeta E., Ligett S., Woolfson A.D., Donnelly R.F. Microneedle characterisation: The need for universal acceptance criteria and GMP specifications when moving towards commercialisation. *Drug Deliv. Transl. Res.* 2015; 5:313–331. doi: 10.1007/s13346-015-0237-z.
90. Gittard S.D., Chen B., Xu H., Ovsianikov A., Chichkov B., Monteiro-Riviere N., Narayan R.J. The effects of geometry on skin penetration and failure of polymer microneedles. *J. Adhes. Sci. Technol.* 2013; 27:227–243. doi: 10.1080/01694243.2012.705101.
91. Donnelly R.F., Majithiya R., Singh R.R.T., Morrow D.I.J., Garland M.J., Demir Y.K., Migalska K., Ryan E., Gillen D., Scott C.J., et al. Design, Optimization and Characterisation of Polymeric Microneedle Arrays Prepared by a Novel Laser-Based Micromoulding Technique. *Pharm. Res.* 2011; 28:41–57. doi: 10.1007/s11095-010-0169-8.
92. Davis S.P., Landis B.J., Adams Z.H., Allen M.G., Prausnitz M.R. Insertion of microneedles into skin: Measurement and prediction of insertion force and needle fracture force. *J. Biomech.* 2004; 37:1155–1163. doi: 10.1016/j.jbiomech.2003.12.010.
93. Khanna P., Luongo K., Strom J.A., Bhansali S. Axial and shear fracture strength evaluation of silicon microneedles. *Microsyst. Technol.* 2010; 16:973–978. doi: 10.1007/s00542-010-1070-4.
94. Maelíosa R.F.D., McCrudden T.C., Alkilani A.Z., McCrudden C.M., McAlister E., McCarthy H.O., Woolfson A.D. Design and physicochemical characterisation of novel dissolvingpolymericmicroneedle arrays for transdermal delivery of high dose, low molecular weight drugs. *J. Control. Release.* 2014; 180:71–80.
95. Park J.-H., Prausnitz M.R. Analysis of mechanical failure of polymer microneedles by axial force. *J. Korean Phys. Soc.* 2010; 56:1223–1227. doi: 10.3938/jkps.56.1223.
96. Park J.-H., Yoon Y.-K., Choi S.-O., Prausnitz M.R., Allen M.G. Tapered Conical Polymer Microneedles Fabricated Using an Integrated Lens Technique for Transdermal Drug Delivery. *IEEE Trans. Biomed. Eng.* 2007; 54:903–913. doi: 10.1109/TBME.2006.889173.
97. Lee J.W., Choi S.-O., Felner E.I., Prausnitz M.R. Dissolving Microneedle Patch for Transdermal Delivery of Human Growth Hormone. *Small.* 2011; 7:531–539. doi: 10.1002/smll.201001091.
98. Dangol M., Kim S., Li C.G., Lahiji S.F., Jang M., Ma Y., Huh I., Jung H. Anti-obesity effect of a novel caffeine-loaded dissolving microneedlepatchin high-fat diet-induced obese C57BL:6J mice. *J. Control. Release.* 2017; 265:41–47. doi: 10.1016/j.jconrel.2017.03.400.
99. Tas C., Mansoor S., Kalluri H., Zarnitsyn V.G., Choi S.-O., Banga A.K., Prausnitz M.R. Delivery of salmon calcitonin using a microneedle patch. *Int. J. Pharm.* 2012; 423:257–263. doi: 10.1016/j.ijpharm.2011.11.046.
100. Matriano J.A., Cormier M., Johnson J., Young W.A., Buttery M., Nyam K., Daddona P.E. Macroflux® Microprojection Array Patch Technology: A New and Efficient Approach for Intracutaneous Immunization. *Pharm. Res.* 2002; 19:63–70. doi: 10.1023/A:1013607400040.
101. Donnelly R.F., Morrow D.I.J., McCarron P., Woolfson A.D., Morrissey A., Juzenas P., Juzeniene A., Iani V., McCarthy H., Moan J. Microneedle Arrays Permit Enhanced Intradermal Delivery of a Preformed Photosensitizer. *Photochem.Photobiol.* 2009; 85:195–204. doi: 10.1111/j.1751-1097.2008.00417. x.
102. Stahl J., Wohlert M., Kietzmann M. Microneedlepretreatment enhances the percutaneous permeation of hydrophilic compounds with high melting points. *BMC Pharmacol.Toxicol.* 2012; 13:5. doi: 10.1186/2050-6511-13-5.
103. Nayak S., Suryawanshi S., Bhaskar V. Microneedle Technology for Transdermal Drug Delivery: Applications and Combination with Other Enhancing Techniques. *J. Drug Deliv. Ther.* 2016; 6:65–83. doi: 10.22270/jddt. v6i5.1285.
104. Stoeber B., Liepmann D. Fluid injection through out-of-plane microneedles; Proceedings of the 1st Annual International IEEE-EMBS Special Topic Conference on Microtechnologies in Medicine and Biology. Proceedings; Lyon, France. 12–14 October 2000; pp. 224–228.
105. Chen J., Wise K.D., Hetke J.F., Bledsoe S.C. A multichannel neural probe for selective chemical delivery at the cellular level. *IEEE Trans. Biomed. Eng.* 1997; 44:760–769. doi: 10.1109/10.605435.
106. Marshall S., Sahm L.J., Moore A. The success of microneedle-mediated vaccine delivery into skin. *Hum. Vaccines Immunother.* 2016; 12:2975–2983. doi: 10.1080/21645515.2016.1171440.
107. Matsuo K., Hirobe S., Yokota Y., Ayabe Y., Seto M., Quan Y.S., Kamiyama F., Tougan T., Horii T., Mukai Y., et al. Transcutaneous immunization using a dissolving microneedle array protects against tetanus, diphtheria, malaria, and influenza. *J. Control. Release.* 2012; 160:495–501. doi: 10.1016/j.jconrel.2012.04.001.
108. Yang J., Liu X., Fu Y., Song Y. Recent advances of microneedles for biomedicalapplications- drug delivery and beyond.pdf. *Acta Pharm. Sin. B.* 2019; 9:469–483. doi: 10.1016/j.apsb.2019.03.007.
109. Poirier D., Renaud F., Dewar V., Strodiot L., Wauters F., Janimak J., Shimada T., Nomura T., Kabata K., Kuruma K., et al. Hepatitis B surface antigen incorporated in dissolvable microneedle array patch is antigenic and thermostable. *Biomaterials.* 2017; 145:256–265. doi: 10.1016/j.biomaterials.2017.08.038.
110. Pattani A., McKay P., Garland M.J., Curran R.M., Migalska K., Cassidy C.M., Malcolm K., Shattock R.J., McCarthy H., Donnelly R.F. Microneedle mediated intradermal delivery of adjuvanted recombinant HIV-1

CN54gp140 effectively primes mucosal boost inoculations. *J. Control. Release.* 2012; 162:529–537. doi: 10.1016/j.jconrel.2012.07.039.
111. Edens C., Dybdahl-Sissoko N.C., Weldon W.C., Oberste M.S., Prausnitz M.R. Inactivated polio vaccination using a microneedle patch is immunogenic in the rhesus macaque. *Vaccine.* 2015; 33:4683–4690. doi: 10.1016/j.vaccine.2015.01.089.
112. Hiraishi Y., Nandakumar S., Choi S.-O., Lee J.W., Kim Y.-C., Posey J.E., Sable S.B., Prausnitz M.R. Bacillus Calmette-Guérin vaccination using a microneedle patch. *Vaccine.* 2011; 29:2626–2636. doi: 10.1016/j.vaccine.2011.01.042.
113. Gill H.S., Söderholm J., Prausnitz M.R., Sällberg M. Cutaneous vaccination using microneedles coated with hepatitis C DNA vaccine. *Gene Ther.* 2010; 17:811–814. doi: 10.1038/gt.2010.22.
114. Zhu Q., Zarnitsyn V.G., Ye L., Wen Z., Gao Y., Pan L., Skountzou I., Gill H.S., Prausnitz M.R., Yang C., et al. Immunization by vaccine-coated microneedle arrays protects against lethal influenza virus challenge. *Proc. Natl. Acad. Sci. USA.* 2009; 106:7968–79739. doi: 10.1073/pnas.0812652106.
115. Mikszta J.A., Dekker J.P., Harvey N.G., Dean C.H., Brittingham J.M., Huang J., Sullivan V.J., Dyas B., Roy C., Ulrich R.G. Microneedle-Based Intradermal Delivery of the Anthrax Recombinant Protective Antigen Vaccine. *Infect. Immun.* 2006; 74:6806–6810. doi: 10.1128/IAI.01210-06.
116. Huang J., D'Souza A.J., Alarcon J.B., Mikszta J.A., Ford B.M., Ferreter M.S., Evans M., Stewart T., Amemiya K., Ulrich R.G., et al. Protective Immunity in Mice Achieved with Dry Powder Formulation and Alternative Delivery of Plague F1-V Vaccine. *Clin.VaccineImmunol.* 2009; 16:719–725. doi: 10.1128/CVI.00447-08.
117. Van Damme P., Oosterhuis-Kafeja F., van der Wielen M., Almagor Y., Sharon O., Levin Y. Safety and efficacy of a novel microneedle device for dose sparing intradermal influenza vaccination in healthy adults. *Vaccine.* 2009; 27:454–459. doi: 10.1016/j.vaccine.2008.10.077.
118. Zhu J., Zhou X., Libanori A., Sun W. Microneedle-based bioassays. *Nanoscale Adv.* 2020; 2:4295–4304. doi: 10.1039/D0NA00543F.
119. Chang H., Zheng M., Yu X., Then A., Seeni R.Z., Kang R., Tian J., Khanh D.P., Liu L., Chen P., et al. A SwellableMicroneedle Patch to Rapidly Extract Skin Interstitial Fluid for Timely Metabolic Analysis. *Adv. Mater.* 2017; 29:1–8. doi: 10.1002/adma.201702243.
120. Moo-Young M. *Comprehensive Biotechnology.* Elsevier; Amsterdam, The Netherlands: 2019.
121. Gupta J., Gill H.S., Andrews S.N., Prausnitz M.R. Kinetics of skin resealing after insertion of microneedles in human subjects. *J. Control. Release.* 2011; 154:148–155. doi: 10.1016/j.jconrel.2011.05.021.
122. Jacoby E., Jarrahian C., Hull H.F., Zehrung D. *Opportunities and Challenges in DeliveringinfluenzaVaccinebyMicroneedle Patch.* Elsevier; Amsterdam, The Netherlands: 2015. p. 20892.
123. Nair K.J. *Micro-Injection Moulded Microneedles for Drug Delivery.* University of Bradford; Bradford, UK: 2014.
124. Cheung K., Das D.B. Microneedles for drug delivery: Trends and progress. *Drug Deliv.* 2014; 23:2338–2354. doi: 10.3109/10717544.2014.986309.
125. Ita K. Transdermal Delivery of Drugs with Microneedles—Potential and Challenges. *Pharmaceutics.* 2015; 7:90–105. doi: 10.3390/pharmaceutics7030090.
126. Sanjay S.T., Dou M., Fu G., Xu F., Li X. Controlled Drug Delivery Using Microdevices Sharma. *Curr. Pharm. Biotechnol.* 2017; 25:1032–1057.
127. Donnelly R.F., Morrow D.I.J., McCrudden M.T.C., Alkilani A.Z., Vicente-Pérez E.M., O'Mahony C., González-Vázquez P., McCarron P., Woolfson A.D. Hydrogel-Forming and Dissolving Microneedles for Enhanced Delivery of Photosensitizers and Precursors. *Photochem. Photobiol.* 2014; 90:641–647. doi: 10.1111/php.12209.
128. Li J., Zeng M., Shan H., Tong C. Microneedle Patches as Drug and Vaccine Delivery Platform. *Curr. Med. Chem.* 2017; 24:2413–2422. doi: 10.2174/0929867324666170526124053.
129. Duong H.T.T., Kim N.W., Thambi T., Phan V.G., Lee M.S., Yin Y., Jeong J.H., Lee D.S. Microneedle arrays coated with charge reversal pH-sensitive copolymers improve antigen presenting cells-homing DNA vaccine delivery and immune responses. *J. Control. Release.* 2018; 269:225–234. doi: 10.1016/j.jconrel.2017.11.025.
130. Kwon K.M., Lim S.-M., Choi S., Kim D.-H., Jin H.-E., Jee G., Hong K.-J., Kim J.Y. Microneedles: Quick and easy delivery methods of vaccines. *Clin. Exp. Vaccine Res.* 2017; 6:156–159. doi: 10.7774/cevr.2017.6.2.156.
131. Rodgers A.M., Cordeiro A.S., Donnelly R.F. Technology update: Dissolvable microneedle patches for vaccine delivery. *Med. Devices.* 2019; 12:379–398. doi: 10.2147/MDER.S198220.
132. Guillot A.J., Cordeiro A.S., Donnelly R.F., Montesinos M.C., Garrigues T.M., Melero A. Microneedle-Based Delivery: An Overview of Current Applications and Trends. *Pharmaceutics.* 2020; 12:569. doi: 10.3390/pharmaceutics12060569.

133. González-Vázquez P., Larrañeta E., McCrudden M.T., Jarrahian C., Rein-Weston A., Quintanar-Solares M., Zehrung D., McCarthy H., Courtenay A.J., Donnelly R.F. Transdermal delivery of gentamicin using dissolving microneedle arrays for potential treatment of neonatal sepsis. *J. Control. Release.* 2017; 265:30–40. doi: 10.1016/j.jconrel.2017.07.032.