Nigerian Journal of Technology (NIJOTECH)
Vol. 43, No. 2, June, 2024, pp.279 - 293
www.nijotech.com

Print ISSN: 0331-8443
Electronic ISSN: 2467-8821
https://doi.org/10.4314/njt.v43i2.11

POLYMERIC MICRONEEDLE ARRAYS FOR TRANSDERMAL RAPID DIAGNOSTIC TESTS AND DRUG DELIVERY: A REVIEW

AUTHORS:
I. V. Diwe[1,*], H. E. Mgbemere[2], O. A. Adeleye[3], and I. C. Ekpe[4]

AFFILIATIONS:
[1,3]Department of Biomedical Engineering, University of Lagos, Nigeria
[2]Department of Metallurgical and Materials Engineering, University of Lagos, Nigeria
[4]Department of Mechanical Engineering, Covenant University, Ota, Ogun State, Nigeria.

***CORRESPONDING AUTHOR:**
Email: ivdiwe@unilag.edu.ng

ARTICLE HISTORY:
Received: 12 October, 2023.
Revised: 08 April, 2024.
Accepted: 10 April, 2024.
Published: 12 June, 2024.

KEYWORDS:
Rapid Diagnostic Test, Microneedle, 3D-Printing, Biomarker, Drug delivery, Point of Care.

ARTICLE INCLUDES:
Peer review

DATA AVAILABILITY:
On request from author(s)

EDITORS:
Charles Chidozie Nnaji
Patrick Udemeobong Akpan

FUNDING:
None

Abstract

In recent times, the demand for innovative, insignificantly invasive diagnostic and therapeutic biomedical tools has reached enhanced attention. Rapid Diagnostic Tests (RDTs) for diagnosis, which are non-invasive, inexpensive, simple, and deliver results accurately in less than 20 minutes, have heightened the accessibility to parasite-based analysis globally. Microneedle (MN) arrays are a fast-developing and promising technology for drug delivery and extraction of Interstitial fluid (ISF) employed for numerous diagnostic and clinical therapies. This review gives a broad overview of the characteristics and history of Microneedles (MNs) patches together with their applications in drug delivery and transdermal rapid diagnostic purposes, classifications, and categories based on the design of fabrication from previous works of literature spanning the period 2018-2023. Utilizing PubMed, Scopus, Google Scholar, and Wiley online library search engines, an online search for scientific publications published between 2018 and 2023 was conducted using the keywords "microneedle patch" and "rapid diagnostic tests." 175 articles in all were found when the search terms were used. The acquired results were then narrowed to 64 citations in this review by applying the inclusion principle. Pictorial and tabular representations highlight the various features of Microneedle patches used in interstitial fluid testing and extraction that have been documented experimentally, including numerous applications of Microneedle patches, showing their dimensions, applications, fabrication methods, and findings made. Finally, research on bio-microneedles and bio-inspired MN are reviewed. The research findings indicate that dissolving microneedles has become increasingly popular since they have several benefits over other microneedles. It is among the most well-known microneedles, and since it degrades naturally, it is a superior option for diagnosis and long-term treatment.

1.0 INTRODUCTION

The lack of Point of Care (POC) diagnostic materials, requiring minimal skilled usage, for detecting parasitic diseases in endemic areas, has been a significant challenge towards effective, timely cure and elimination of some illnesses [1] It is more worrisome in paediatric populations in rural areas thus leading to an increase in avoidable mortality rates due to undiagnosed and inadequately treated ailments and diseases. Point-of-care diagnostics (POC) afford clinically significant productivity in a well-timed approach that allows a healthcare operative to make a clinical evaluation at the testing location. Their development has been supported by the World Health Organization (WHO) along with more international agencies for application in developing nations that lack adequate medical infrastructure [2]. Preferably,

HOW TO CITE:
Diwe, I. V., Mgbemere, H. E., Adeleye, O. A., and Ekpe, I. C. "Polymeric Microneedle Arrays for Transdermal Rapid Diagnostic Tests and Drug Delivery: A Review", *Nigerian Journal of Technology*, 2024; 43(2), pp. 279 – 293; *https://doi.org/10.4314/njt.v43i2.11*

the POC tools should be handy, fast, non-invasive, cost-effective, and not need the expertise of laboratory staff services and facilities [3].

Orthodox hypodermic needles have numerous drawbacks, which include consuming a lot of time during use, the mandatory professionally skilled workforce, and the danger of contamination spread through soiled needle pricks. Furthermore, nearly 10% of the population experience anxiety about sharp needles, and conventional needles application could cause aches, bruises, and blood loss, including pain at the location where it was used.

3D–Printed Microneedle (MN) made from biocompatible, biodegradable, and dissolvable polymeric materials for rapid diagnosis would greatly influence healthcare in many developing countries. MN patches can be described as an array of micron-sized protrusions, varying in dimensions from 25 µm to 2000 µm, manufactured on the surface of a backup foundation or array [4]. Microneedles have advanced into a predominantly appealing drug delivery method, transporting various curative molecules through the living membranes comprising the sclera, skin, and mucosal tissue [4]. Favorable pros obtainable by drug delivery and diagnosis using the microneedle technique include painless, injury-free skin, reduced risk of trypanophobia, no appointment with specialists, and stress-free self-use, including lack of hazard associated with blood-conveyed pathogens, which led to the consideration for substituting invasive usual procedure of needle injections. In addition to aiming at inexpensive technology and high-capacity production simplicity for convenient drug administration tools, this method helps to lessen the persistent serious concerns about biohazardous waste control [5].

At present, four methods of MNs are manufactured for delivering drugs percutaneously. These methods include solid, dissolving, coated, and hollow [4,6]. Amongst these four types, dissolving microneedles, made from several biocompatible water-soluble polymers, are the favored delivery technique for the reason that biohazardous pointed ends are not generated and do not dissolve while in contact with interstitial fluid following transdermal insertion. There has remained an intensified emphasis on applying microneedles to retrieve interstitial fluid and on producing diagnostic devices with microneedles having these characteristics. MN presents the prospect of a non-invasive checking/diagnosis procedure that can beat other orthodox needle-related inadequacies comprising the prerequisite for experienced usage and the danger of disease [4]. MNs- facilitated delivery of drug through the skin necessitates that the material possesses the adequate mechanical capability to pierce the transdermal wall, a biocompatible material, without causing any form of inflammation or additional immune responses following the application, the substance to be degraded as it discharges its contents and finally, the delivery outline of the medication should be gradual and consistent with delivering a continuous discharge for a long time interval [7].

2.0 MICRONEEDLES

2.1 Characteristics and History

Robert Chambers coined the term "microneedle" in 1921 when he and his colleagues used it to micro-investigate echinoderm eggs by inserting a needle into the nucleus [4]. Nonetheless, Gerstel and Place proposed MN-based medication delivery for the first time in 1976 [8]. In 1998, Henry and co. released the first notable microneedle assessments and proof-of-concept tests, demonstrating the usage of micro-fabricated silicon microneedles to increase calcine transport through human skin [4].

The microneedle (MN), an extraordinarily effective and multipurpose device, has previously drawn widespread scientific and industrial attention owing to outstanding characteristics comprising of a non-invasive penetration, inexpensive, exceptional therapeutic efficiency, and comparative safety [9, 8]. They are needle arrays with sub-millimeter needles that can non-invasively pierce the skin's surface layer to deliver medication into the body [10]. They come in a range of sizes; the needles' height (twenty-five to two thousand micrometers) ensures adequate piercing of the skin transdermally, whereas the base and tip diameter of 50-250 µm and 1-25 µm respectively, guarantees that nerves restricted in the dermis layer won’t be hurt during use [11]. Microneedles have sufficient length to pierce the skin yet are thin and short to prevent irritating dermal nerves and puncturing blood vessels. Because patients prefer painless microneedles over hypodermic needles for drug delivery, microneedle-based delivery could be a lucrative commercial invention, showing enhanced patient compliance, primarily for indications necessitating regular injections, for instance, insulin or hormone treatments [10]. This lack of pain, together with the ability of self-therapy, renders microneedle systems extremely patient-compliant [11].

Microneedles have become an exciting drug delivery method, having the capacity to transport a variety of curative and medicinal compounds across biological

membranes such as the skin, mucosal tissue, and sclera [4]. There has been heightened attention on using microneedles to retrieve interstitial fluid, including the production of diagnostic sensors that incorporate microneedles possessing this functionality. Transdermal observation of biomarkers is essential for obtaining time-sensitive clinical data and results for regular point-of-care (POC) health observations and supervision. Owing to their insignificantly invasive characteristics, microneedles may be helpful for transdermal sensing, including application in protracted wearable health monitoring gadgets.

Penetration capabilities, drug loading volume, and delivery speeds are all determined by the size and form of microneedles. However, existing technologies require comprehensive optimization to control geometry [10]. Pattern limits, for instance, insufficiently obtainable aspect ratios, have often been created as a result of technological constraints of fabrication techniques, and 3D-Printing, which is an additive manufacturing of microneedle arrays, has recently been examined [10]. Additive manufacturing facilitates practically unrestricted manipulation over microneedle design. Figure 1 shows a pictorial representation of a microneedle patch.

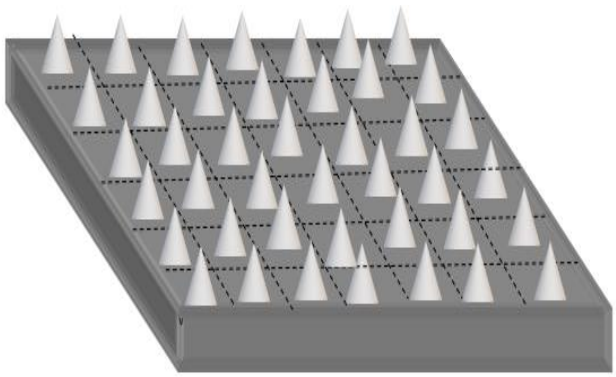

Figure 1: A pictorial representation of a microneedle patch [62]

In comparison with the MNs manufactured previously, for instance, metallic microneedles, those produced with polymers can eradicate the sharp biohazardous wastes, avoid detrimental effects on medication stability, and make it simple to modify drug loading [12]. Advances in biomedical and materials engineering support the growth of customized therapy through developing technology that speeds the detection of diseases, including its treatment utilizing the "point-of-care" method [1]. Subsequently, microneedles provide encouraging answers for the delivery of drugs transdermally, including diagnosis owning to the negligibly invasive nature of these microneedles [10, 13]. There are four major types of microneedles, which are frequently constructed of metal, polysaccharides, and polymeric materials [13].

3.0 ADDITIVE MANUFACTURING (AM)

Additive manufacturing is another name for 3D printing, which has materialized as a resourceful technology platform for computer-assisted design (CAD) and speedy manufacturing [14]. AM permits the fabrication of custom-made parts from metals, ceramics, and polymers without moulds or machining characteristics for usual formative and subtractive production and fabrication. Design constraints, such as limiting possible aspect ratios, are typically imposed as a result of fabrication technology limits [10]. MNs have recently been researched to collect or gain access to the interstitial fluid for subsequent monitoring and detection of some particular biomarkers [15]. When these two theories are combined in closed-loop devices, they have the potential to provide automated and less invasive illness detection, monitoring, and cure [16].

3.1 Design and Optimization of 3D-Printed MN and other Microneedle Fabrication Methods

Numerous researchers have worked on designing and optimizing 3D-printed MN and other Microneedle fabrication methods [1, 3]. Fused deposition modeling (FDM) was used to establish a new microfabrication approach for MNs employing polylactic acid, a Food and Drug Administration-approved, renewable, biodegradable thermoplastic material [17]. They could use natural degradability to overcome a critical issue with fused deposition modelling 3D printing, namely the low resolution of 3D printers, which was handled by dramatically increasing the feature size of the produced objects by developing a post-production chemical etching technique. As a result, they could get access to tip sizes as tiny as 1 µm. Leone et al., conducted research to show that the Polydimethylsiloxane (PDMS) mold design is a significant factor in the assembly of dissolving Microneedles and that the elevated antigen substance in Hyaluronic (HA)-based dissolving MN with the sharpness and capacity to penetrate the dermis unaffected [18]. They also showed that dissolving MN may be created using a 1:1 (w/w) ovalbumin: hyaluronan ratio without generating aggregates and that the dissolution rate of dissolving MN in the skin may be reduced with very high antigen loading.

Subsequent innovations have been made by [19] who tactically linked 3D laser lithography and micro-moulding with suitable materials. They created a

method for producing dissolving microneedle arrays possessing undercut MNs, which may be loaded at the tip using a range of bio-cargos. These microneedle arrays meet the geometry, including piercing tips with clean points and the mechanical necessities for successful and efficient skin-piercing while delivering drugs. Camovic et al., produced 3D-printed microneedles and investigated their capacity to coat various medication formulations [20]. They demonstrated that 3D printing combined with an etching phase after fabrication resulted in perfectly sized and designed microneedles. Due to its simplicity of use and capacity to deliver a consistent load across the microneedle arrays, Dip coating has been demonstrated to be the optimum coating technique for 3D-printed microneedles.

A straightforward and customizable microneedle mold fabrication procedure utilizing an affordable desktop Stereolithography (SLA) 3D printer, which did not need complicated and costly manufacturing facilities or microfabrication know-how when compared with the usual microneedle fabrication techniques was developed by [21]. This was achieved by a double-step "Print and Fill" mold production method, which resulted in sharp needles with a high aspect ratio that could enter the tissue. In a single step, a fabrication process for hollow microneedles with microfluidic layouts was created by Yeung *et al.*, [1]. They used stereo lithography and pushed technology to its limits. As a result, print resolutions are lower than the half-width maximum laser spot size resolution, thus allowing them to produce intricate designs at a lower cost and with faster print speeds. Their concept was implemented in a microfluidic-enabled microneedle that performed a hydrodynamic combination, including a single device that combines transdermal medication administration and both.

Biocompatible microneedle arrays that can permeate the skin's outer layers and disseminate a model therapeutic substance have been developed thanks to a unique technique of chemical etching that increases the characteristic dimensional resolution of Fused Deposition Model printed materials [17]. Using an MJP Pro 2500 3D printer, separate 3D-printed microneedle holders were created, and the interstitial fluid extraction efficacy in hairless rats was compared [3]. This was accomplished by modifying design elements, including throat thickness, tip curve, and throat diameter, that impact the skin-holder interface. They demonstrated that the MN holder's design factors influence ISF extraction and that concave tip fabrication is the best method for collecting interstitial fluid from animals.

4.0 CLASSIFICATION OF MICRONEEDLES (MNs)

The many varieties of MNs developed and investigated for various functions include hollow, solid, coated, hydrogel-forming, and dissolving microneedle arrays. Microneedles should possess a suitable blend of mechanical strength, hardness, and toughness to penetrate the skin and not undergo fracture and buckling failure. Moreover, the microneedle dimension should be as small as possible to guarantee pain-free and negligible invasiveness. Additionally, the drug delivery effectiveness ought to be fully well-thought-out during microneedle design [8]. Microneedles are extensively employed in biomedical diagnosis and therapy, as shown in Figure 2.

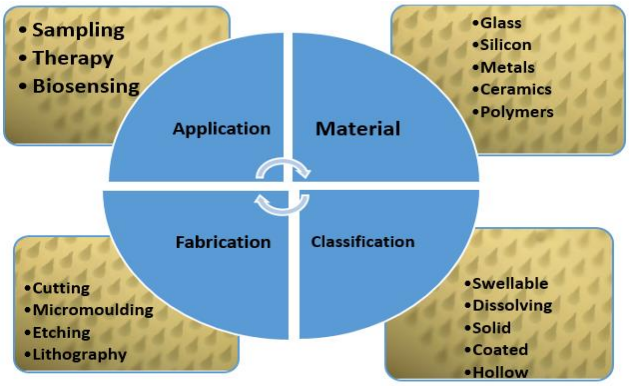

Figure 2: Categories of Microneedles by design, material, classification, and application

4.1 Solid Microneedles

Solid microneedles distribute pharmaceuticals by creating micro-channels in the skin's layers, allowing medications to penetrate deeper into the skin. This sort of microneedle array may be used to transport compounds with high molecular weight [22]. Using solid microneedles, the chosen drug might be simply supplied via microchannel cavities generated using solid microneedle patches [22]. It is possible to coat solid microneedles with the drug before being implanted into the skin and gradually disintegrating. Following that, the microneedles are detached from the dermis. However, additional factors influence the effectiveness of this transdermal administration. The chemical substance's molecular weight, partition coefficient, melting point, and permeability coefficient affect how much medicine enters the SC [23].

The "poke and patch" method is a solid MN procedure in which micropores are generated in the skin after removing the microneedle array. The perforated area is then smeared with an approved medication formulation [24]. The use of this method is restricted

since it necessitates a double-step procedure, which causes practical concerns among the users [24]. Solid MNs are regularly manufactured using silicon, polymers like polyvinylpyrrolidone, and metals like titanium and stainless steel [8].

4.2 Coated Microneedles

Coated microneedle arrays are coated with a drug-delivery mechanism and are used to deliver molecules of high molecular weight quickly through the dermis [9, 4, 24]. When the drug is implanted inside the skin, it is quickly discharged from the coating and to the skin. Nonetheless, the limited surface area of microneedle constructions restricts the number of drugs that can be successfully coated on top of them, which is a critical stumbling block to achieving a meaningful drug delivery profile. Other issues to be concerned with are the consistency, homogeneity, repeatability, and strength of the MN coating ingredients. Additionally, efforts should be adopted to ensure that no significant harmful medication leakage from the microneedle surface occurs throughout the coating procedure, particularly before skin insertion.

Dip-coating is the most straightforward approach for microneedle-coating microarrays and involves immersing them in a drug-containing dispersion before removal. After the liquid dispersion dries, a thin medicinal component coating remains on the microneedle's surface. The time-consuming drying process is a fundamental constraint on the dip-coating procedure, especially when dealing with rounded microneedles because the dispersion can slide away from the surface of the microneedle before drying. As a result, the film that holds the therapeutic substance is applied unevenly. A gas-jet drying method was devised to avoid this problem. This procedure involves suspending a therapeutic ingredient in a mixture and then transferring it to the gas phase using a gas-jet applicator [23]. Uniform synchronized drug-loading microneedles can be created using a customizable apparatus that may be raised and lowered.

The coated MN was a successful attempt to pierce swine cadaver skin and give medications to subcutaneous regions, according to skin penetration investigations. Subsequently, drug loading and release effectiveness were thoroughly contained by altering the MN height and modifying the viscosity of the coating solution 3D printed microneedles were developed by [20]. They looked at how well 3D-printed microneedles could coat various medication formulations. They demonstrated that combining 3D printing and etching after the fabrication may result in precisely sized and designed microneedles. Due to its simplicity and capacity to provide a constant load across the microneedles, Dip coating is the best for 3D-printed microneedles.

4.3 Hollow Microneedles

Metals, Silicon, ceramics, glass, and polymers are just a few of the materials that can be used to create hollow microneedles [8]. Antigens, proteins, and oligonucleotides are among the high molecular-weight molecules that are commonly used [24]. Hollow microneedles enable for constant infusion of more considerable quantities of pharmacological than coated or solid microneedles, which only deliver minute and defined quantities of medications [4]. This technique distributes molecules through the dermis by applying pressure, diffusion, or electrically driven flow [24]. Microneedle length is negatively correlated with medication flow rate and directly correlated with microneedle inner diameter, according to comprehensive research [4]. Adjusting infusion factors can enhance the rate of flow. As a result, regulated drug distribution can be achieved [4]. However, the risk of tissue clogging the needle bore opening during skin insertion may reduce the effectiveness of hollow microneedles [24].

Nevertheless, thanks to an ingenious model that sets the bore- opening a little asymmetrical instead of at the farthest point, this concern has been alleviated [4]. This approach reduces needle clogging while simultaneously increasing the area of drug delivery to tissue and keeping the tip sharp. Nevertheless, hollow microneedles regularly stand the possibility of fracture due to inadequate mechanical strength [9]. Hollow microneedles are also helpful for blood extraction, with a particular focus on the poking and flow conveyance processes. They retrieved twenty milliliters of mouse blood *in vivo* by puncturing the skin without breaking it, signifying that they might be employed in blood research systems for diagnostics [22].

4.4 Dissolving Microneedles

These types of MNs are often made from a biodegradable polymer in which the medicine is enclosed. Dissolution of the medication occurs as soon as these are placed on the skin, followed by drug release [12, 22]. The microneedle dissolves after being applied to the skin, releasing the encapsulated drug in the dermis. Dissolving MNs are fabricated using a range of substances, including polysaccharides and some polymers. They are created on the "poke and release" theory [23 - 24]. Polymers required to formulate dissolving microneedles are crucial in

influencing the integrated drug's delivery kinetics. The accompanying therapeutic period has been described to differ extensively, varying between hours to days. It is generally reliant on the dissolution kinetics of the chosen polymer and the dispensation time of microneedles [24].

Furthermore, monitoring drug administration can be achieved by tweaking the polymeric ingredients of the N array or changing the construction procedure Dissolving microneedles have grown in popularity as a result of their several advantages over other MN varieties [23]. It is one of the most well-known MNs, and because it is biodegradable, it is a better choice for long-term therapy. Patient compliance improves as a result of bio-suitability. Despite the apparent benefits, the construction and development of dissolving microneedle arrays are fraught with difficulties. In some cases, drug loading and design procedures can affect the mechanical strength and solidity of microneedles, including the encapsulated drug or macromolecule.

Courtenay et al., investigated the dispersion of a model protein antigen ovalbumin (OVA) using innovative hydrogel-forming and dissolving microneedles (OVA) [25]. They provided relative information about both types of microneedles in reference to in-vitro and in-vivo properties and immunogenicity, respectively. A dissolving microneedle array aimed at Inactivated Polio Vaccine (IPV) vaccination was invented by Kolluru et al., [26]. Preparation and process optimization assessments were performed during MN patch manufacturing to discover an excipient arrangement and drying setting that reduced IPV activity loss. The microneedle patch was easy to use and didn't leave any sharps behind. It also had better thermostability than traditional liquid IPV over extended storage at higher temperatures.

Researchers demonstrated that the PDMS mould design is a significant determinant in the assembly of dissolving Microneedles. That high antigen content in HA-based dissolving microneedles does not affect the sharpness or piercing capabilities [18]. They also demonstrated that dissolving microneedles could be made using a 1:1 (w/w) ovalbumin: hyaluronan without forming aggregates and that their breakdown rate in the skin may be reduced with very high antigen loading. Dissolving Microneedles based on DOX, DEC, and ABZOX-loaded Solid Lipid Nanoparticles were successfully created for treating Lymphatic Filariasis [27]. *In-vivo* analyses showed that compared to traditional oral administration, this combination technique increased the relative bioavailability of the three medications under study in plasma and lymph nodes, decreasing the pharmaceutical biodistribution in the kidney, liver, and spleen. 3D-laser lithography and micro-molding with suitable materials were tactically linked [19]. They used a technique to create dissolving microneedle arrays with undercut microneedles that could be loaded with various bio cargos at the tip.

Artemether and lumefantrine were encapsulated in dissolvable MN patches for sustained usage, which increased artemether and lumefantrine penetration for therapeutic use in the malaria parasite [28]. Lumefantrine-nanoparticles produced utilizing chitosan-mediated gelation exhibited a coordinated - release of 79.15 ± 2.45% for lumefantrine when the time exceeded 24 hours with sustained stability for 6 months. Systematic modelling was done and verified for predicting the administration of sumatriptan succinate using dissolving MNs, including its penetration into the outer dermis [29]. Material balance equations were also developed to show molecular transit and then assimilation into the general circulation. Solid drug particles were encapsulated in water-soluble microneedles with a pyramid pattern made of polyvinylpyrrolidone. According to the group's simulations, increasing the pitch width resulted in speedier drug delivery.

4.5 Hydrogel-Forming MNs

Many new technologies have recently been developed to address the biocompatibility issues and the risk of incorrect re-use related to silicon or metal microneedles. One of these strategies highlights the utilization of microneedles that produce hydrogels [4]. High-sell-up polymers are used in this innovative form of MN. Polymers in this production process may absorb more water through their 3-D structural network. Due to the body fluid, the polymers swell when these microneedles are put into the tissue. This eventually causes the creation of channels, which allow medication distribution from the reservoir into the microcirculation. The polymer's swelling property is a rate-controlling membrane [24, 4]. Furthermore, their unique ability to absorb interstitial fluids can be used to extract essential chemicals from the skin for further investigation [4]. This approach is projected to be tremendously valuable for defenseless patients, for instance, neonates and the aged populace. It can be recommended because the distribution profile of a hydrogel-based microneedle instrument may be adjusted depending on the needs of various pharmaceuticals with varied healing interfaces. Hydrogel-based microneedles are encouraging, and additional research ought to be done to increase the

spectrum of substances used to create them and include drugs supplied for treating chronic conditions.

Recently, numerous research studies have been done on the use of hydrogels for the production of microneedle patches applied in drug delivery and interstitial fluid extraction purposes [30]. Founded on Digital light processing with great precision, 3D-printed Multi-Operational Hydrogel Microneedles were produced [30]. The length of each layer's exposure significantly impacted stiffness and precision, and the printing parameters were changed to achieve a balance of precision and stiffness. Point-of-care testing using Hydrogel Microneedle was also developed using skin interstitial fluid [31]. Point-of-Care hydrogel microneedle was created using Chitosan and Polyvinyl alcohol established on interstitial fluid. Poly Vinyl Alcohol/ Chitosan hydrogel stiffened microneedles once they were dry due to phase transition property, allowing for easier skin penetration. Following that, the hydrogel's porosity microstructure allowed for good interstitial fluid extraction. Polyvinyl Alcohol's thermal breakdown feature made it simple to rapidly and effectively retrieve targeted biomarkers on the microneedle for future diagnostic purposes.

Using interstitial fluid from the skin, hydrogel-coated MN patches were created for non-invasive Testing and Detection of particular Circulating Nucleic Acids [32]. They made microneedles covered in a hybrid material of alginate-peptide nucleic acid for testing, segregation, and detection of sequence-specific nucleic acid biomarkers in skin interstitial fluid. Microliters of Skin Interstitial Fluid Extraction in Minutes using Osmosis-Powered Hydrogel Microneedles was invented by Zheng and co. [33] Osmolytes (maltose) and hydrogel (i.e., methacrylate hyaluronic acid) were used to make the microneedle patch. The osmolytes dissolved in the matrix during extraction, providing osmotic pressure that accelerated interstitial fluid diffusion through the hydrogel matrix and onto the skin. Thanks to the extracted ISF, in-vivo quantification of indicators, such as glucose, or medications, such as insulin, was possible. The system's integration with electronic glucose sensors allowed for direct and quick analysis of the extracted glucose.

By combining two model medications routinely employed in children (caffeine and lidocaine hydrochloride), polymeric-dissolving MNs and hydrogel-forming MNs were created [34]. *In-vitro* and in vivo investigations were used to look into the efficacy of these microneedles for paediatric dosage. In both investigations, polymeric microneedles significantly improved the skin penetrability of typical medicinal compounds. *In-vitro*, a hydrogel-forming microneedle resulted in a 6.1-fold rise in caffeine release, whereas a dissolving microneedle led to a 3.3-fold rise in lidocaine HCl distribution. Figure 3 shows the different classifications of microneedle patches and how they behave during drug delivery.

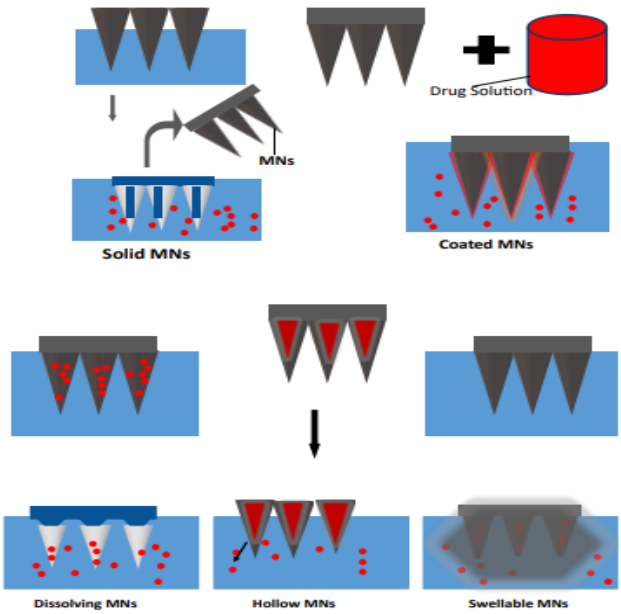

Figure 3: Classifications of microneedle patches for drug delivery purposes [63].

5.0 INTEGRATED SENSING AND QUANTIFICATION FOR SWELLING POLYMERIC MICRONEEDLES

Several recent publications have defined swell-able hydrogel microneedles with analyte-receptive components that permit recognition or quantification with only minor subsequent treatment of the array [32, 35]. The first illustration described swelling microneedles made of polyethylene glycol diacrylate, photonic crystals, and colloidal silica crystals with a structural color that can be adjusted depending on their size and placement. The barcodes were functionalized with antibodies for specific biomarkers found in interstitial fluids and integrated into the microneedle formation, allowing biomarkers to be picked up when the microneedles were drawn out of the interstitial fluid [35]. The physical color of the photonic crystal barcode can be used to confirm the biomarker's features.

Quantifying can be done using a sandwich test, which involves putting a fluorophore-functionalized antibody on the microneedles and then withdrawing them from the skin. For glucose detection, a polyethylene glycol-diacrylate-centered swelling

microneedle patch with colloidal crystal-based discovery was used; nevertheless, the microneedle portion prone to swelling was still only a surface layer and not the complete microneedle structure [36]. Microneedle patches functionalized for biomarker detention offer several advantages, including flexibility: their design permits the extraction and recognition of any protein biomarker present in the interstitial fluid by just coating the microneedle exterior with the appropriate antibody.

6.0 USES OF MICRONEEDLES

6.1 Delivery of Drug and Vaccination

In transdermal medication delivery, the microneedle is regarded as a valuable and minimally invasive tool that patients can utilize efficiently, with massive potential for releasing macromolecules [9, 22]. Novel vaccine tools utilizing microneedles pose an effective and painless approach for delivering antigens into the skin that, someday, could unravel some difficulties in the traditional vaccination. Vaccination programmes use cold chain storage, produce vaccine waste, including hazardous waste, and need skilled personnel. These issues lead to sizeable expenses for immunization programs. Vaccine advancement programs aim to lessen the price of each dose of the vaccine, and personally dispensed administration does not necessitate skilled staff. MN dermal vaccines prevent these difficulties. Furthermore, the stabilization of a vaccine and the troubles accompanying reconstitution in a liquid solution for dispensation are taken care of [8]. When vaccines are administered through microneedles, they are discovered to be more efficient than conventional needles [24]. It leads to patients preferring safe, efficient, and effective vaccination. While intramuscular or dermal routes are unpleasant, they reach beyond the skin's immune system, delivering vaccinations to locations without a high concentration of antigen-exhibiting cells [4].

Conversely, microneedles distribute medications through an increased network of antigen-presentation cells in the epidermis and dermis. This has boosted their acceptance as a viable vaccination delivery method. Due to decreased pain scores during skin penetration with a microneedle and its self-administering nature, which negates the need for medical assistance, MN insulin delivery enhances patient compliance. Clinically acceptable doses of minimum strength, drugs with a high dose, for instance, ibuprofen sodium, as well as delivery of protein and peptide have all been achieved using microneedle patches that produce a hydrogel [4]. Figure 4 shows a schematic representation of triggered drug release by a stimuli-responsive microneedle-array patch.

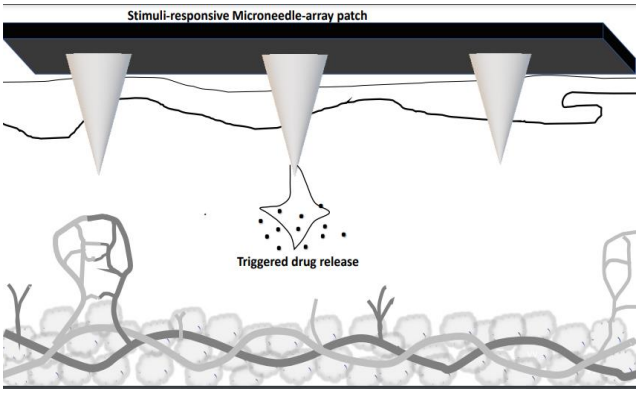

Figure 4: Schematic representation of triggered drug release by a stimuli-responsive microneedle-array patch [64]

6.2 Diagnostics

It is difficult to make the right therapy exclusive of a suitable diagnosis. This is fundamental and vital for the realization of therapy; hence, the utilization of microneedles has assisted in this area. Hollow microneedles can be joined with additional technologies. Biosensors with microfluidic chips, for example, could be used to create less intrusive blood analysis techniques for diagnostics. Alternatively, they can be utilized for the electrochemical discovery of drugs *in vivo* [8]. Microneedles hold possible applications in numerous blood examination or sensor systems in POC diagnostics [8]. The benefit that the microneedles pose in the diagnosis is the ability to pierce deeper layers of the skin, permitting the checking of bio-signals with superior consistency and thereby decreasing the obstructions with other substances. Hydrogel-forming microneedle patches are another method for interstitial fluid extraction. Depending on the cross-linking degree of the polymer, they collect interstitial fluid after becoming attached to the skin and grow larger.

The number of various analytes, including biomarkers, can then be determined using the microneedle patch [4]. According to the researchers, a swellable microneedles array for Point-of-Care diagnostics and personalized healthcare checks was used to transport skin ISF comprising glucose and cholesterol [9]. Dissolving microneedles have been used to enhance the effectiveness of rheumatoid arthritis treatment by transdermal delivery of methotrexate [37]. Microneedles offer the possibility of a painless and non-invasive observation/diagnosis system and the ability to overcome the limitations of traditional needles, such as the requirement for professional use and the risk of contamination.

Samples obtained with MNs can be analyzed in the future, or a hybrid system combining a diagnostic system with microneedle manufacture can be used [4].

Bio-sensing with MNs opens up new options for bio-sensing analysis, allowing for the creation of simple, easy-to-use, minimally invasive procedures that require little preparation. In today's society, innovation can be awe-inspiring. There are currently just a few articles on using microneedles as a diagnostic device. There are various advantages to using microneedles as a diagnostic instrument, including fewer samples collected as assay material, increased efficiency, and faster reaction times [24]. Table 1 shows the geometrical features of MN arrays that have applications in bodily fluid sampling or extraction.

6.3 Cosmetic Field

Lately, cosmetics, together with microneedle therapy, have attained enormous growth. Cosmetic therapy is encouraging, as evidenced by the numerous cosmeceutical products generated. Cosmetic uses are usually split into two categories. One is to help the wounded skin's natural therapeutic process. Another goal is to promote cosmeceutical penetration through the skin. Less invasive microneedle delivery creates temporary holes to increase penetration, allowing wound repair to begin naturally [9].

Furthermore, by forming micro-channels without contacting the nerve, a microneedle may accurately distribute forceful cosmetic compounds into the skin, improving efficiency and safety. Microneedle patches have been used to accelerate diabetic wound healing using a double-layer drug-loaded MN patch incorporated with antibacterial and angiogenic drugs [38]. A microneedle patch encased in a curcumin-zinc framework has also been reported by researchers to promote hair growth [39]. A silk fibroin microneedle patch is a practical and minimally invasive method of obtaining scarless tissue. The biocompatible microneedles were found to dramatically reduce the scar elevation index in the rabbit ear hypertrophic scar model and boost ultimate tensile strength like normal skin by simply adjusting the microneedle size and density [40].

Table 2 reviews numerous applications of microneedle patches, showing their dimensions and fabrication methods.

Table 1: Features of microneedle patches used in interstitial fluid testing and extraction that have been documented experimentally

Aim	Microneedle Height (µm)	MN Base Diameter (µm)	Microneedle array	Quantity of ISF extracted or drug delivered	Reference
Growth hormone delivery	800	300	12 x 12 array	185 µg	[41]
Transdermal COVID-19 vaccine drug delivery	800	400	28 × 18 × 2 mm^3	22.35 ± 2.32 µg	[42]
Drug delivery for cutaneous wound healing	750	210	20 x 20 array	100 µL	[43]
Transdermal drug delivery of levosulpiride	575	200	10 x 10 array	25mg	[44]
Oral drug delivery of mucosal topical anesthesia	700	280	10 x 10 array	494 ± 5 µg per microneedle patch	[45]
Nano drug delivery for antipsoriatic treatment.	600	200	15 x 15 array	1 mg Methotrexate-Loaded Albumin Nanoparticles	[46]
Healing of Infected Wounds	650	750	12 x 12 array	-	[47]
ARV drug delivery	850	300	16 x 16 array	47.87 ± 16.33 µg and 1208.04 ± 417.9 µg	[48]
Contraceptive drug delivery	600	1.1 cm	112	0.28 ± 0.01 mg	[49]
Skin interstitial fluid (ISF) extraction	600	300	121	≈0.02mg	[50]
ISF extraction	1000 and 1500	-	16 and 32	Flat profile geometry: 0.028 ± 0.021 µL/min Concave: 0.053 ± 0.040 µL/min Convex: 0.020 ± 0.013 µL/min	[3]
Interstitial fluid collection	1000	1000	21	≈7.15mg	[51]
Skin ISF extraction	250, 450, and 650	200	5	0.46 ± 0.52µL	[34]
Dermal ISF extraction	1000, 1500, and 2000	-	5	4 µL in Humans and 12 µL in Rats	[52]
ISF extraction	900	280	100	Pig skin extraction = 0.079 microliters, Rat skin extraction = 0.0382 microliters.	[33]
Nucleic acid biomarkers from skin ISF	550	250	49	≈0.133 µL	[32]
ISF extraction	680	380	144	0.0250 ± 0.0042 mg	[53]

Dermal ISF extraction	750 and 650	100 µm by 70 µm and 50 µm by 150 µm.	5,9	8 to 97nL	[54]
Detection of skin ISF biomarkers	800	150	16	-	[35]
Skin ISF extraction	1266 ± 91 µm	500 ± 31 µm	100	0.0125 to 0.075 mg	[31]

Table 2: Review of numerous Applications of Microneedle Patches, Showing Their Dimensions and Fabrication Methods

MN type and Fabrication Technique	MN height (µm)	MN application	Biomarker extracted / Drug delivered	References
Self-powered enzyme-linked MN patch made of anode and cathode MN array	600 (11 x 11 array)	Scar-prevention healing of diabetic wounds	glucose oxidase and horse-radish peroxide delivery	[55]
Self-cross linkable and glucose-responsive polymer-based MN.	800 (10 x10 array)	On-demand Insulin delivery	Insulin delivery	[56]
Gelatin-methacryloyl (GelMA)/ Photoinitiator/ PVA separable dissolving MN patch	600	Drug delivery for Parkinson's disease treatment	L-DOPA drug delivery	[57]
Dissolving MN patch containing carboxymethylcellulose and methylcellulose	700 ~0.8 cm^2	Vaccine delivery	Inactivated rotavirus and polio vaccine	[58]
Porous microneedle patch with mesenchymal stem cells	600 (4mm x 4 mm)	Delivery of extracellular vesicles for spinal cord injury therapy	Extracellular vesicles	[59]
Programmable CRISPR-Cas9 MN	600 ± 50 µm. (12 x 12 array)	Real-time monitoring of universal cell-free DNA	Target DNA	[60]
SLA-built 3D-printed hollow MN with microfluidic structures.	900 µm (4 x 4 array)	Combinational medication therapy	Combinational Drug delivery	[1]
SLA- based 3D-printed cone MN	1 mm ht. (1mm×1mm) base	Transdermal Drug-delivery of insulin	Insulin	[13]
Dissolving Hydrogel forming MNs	550 µm 300 µm base width. (19 x19 needles)	Dissemination of a model protein, antigen ovalbumin.	Drug-delivery (Vaccination) of an antigen Ovalbumin (OVA).	[25]
Dissolving MN patch	650 µm (10 x 10 array)	Inactivated polio vaccine (IPV) immunization	Drug delivery of IPV vaccination.	[26]
Double-layered dissolving Microneedles using PVA and PVP.	500 µm	Drug delivery of anti-filariasis medications,	Intradermal delivery of anti-filariasis medicines for treating filariasis	[27]
Gelatin methacryloyl (GelMA) biodegradable polymeric MN	600 µm height, 300µm base (11 x 11 array)	For the continuous delivery of anti-cancer medications	Drug-delivery rate optimization of anticancer drug doxorubicin (DOX)	[7]
(3D) laser lithography, and micro-molding fabrication of dissolving MNs	750 µm height (250 x 250 µm) base area	Antigen (ovalbumin) and adjuvant are drug-delivered.	Drug delivery of multiple bio cargos.	[19]
Poly Vinyl Alcohol and PVP K-12 Polymers for MN loaded with drugs.	672 ± 0.99 µm.	Encapsulating artemether and lumefantrine in dissolvable microneedles	Therapeutic drug delivery of anti-malaria drugs.	[28]
Dissolving Microneedles	500 µm height, 300 µm base width	To forecast the delivery of sumatriptan succinate	Drug-delivery of Sumatriptan succinate	[29]
3D-Printed microneedles	0.1 mm height, 2 mm length, 0.6 mm breadth	Coating various drug preparations on 3D-printed microneedles	Drug -delivery	[20]
Stereolithography 3D-printing of hollow microneedles	Base width of 800 and heights of less than 1 mm. (10 x 10 array)	Hollow microneedles with microfluidic assemblies for drug delivery	Drug-delivery optimization	[1]
Fused Deposition Modelling (FDM) biocompatible MN	layer height: 0.2 mm.	Drug-delivery of therapeutic agent	Drug-delivery	[17]
Microneedle holders made in 3D using a MJP Pro 2500 3D printer	1000 µm versus 1500µm needle lengths	Optimization of microneedle design parameters for ISF extraction.	Design optimization of 3D printed MN	[3]
SLA dissolvable MN patches	750 µm long, with a 375 µm base diameter and an 80 µm hole diameter.	Microneedle-based transdermal patch for RDT of malaria parasite	malaria parasite diagnosis from ISF using PfHr2 protein biomarker	[61]
PVA/CS hydrogel microneedle patches	height and base length are 1266	Diagnostic purposes.	Glucose, chloride, lactate, and protein	[31]

	± 91 and 500 ± 31 µm, respectively	concentrations are four common biomarkers.

7.0 CONCLUSION

Owing to its unique qualities, the microneedle patch is a very promising technique for transdermal drug delivery and ISF extraction. Using fast separable and durable approaches, MN patches can be further enhanced with desirable features like shorter application times, more effective drug delivery, and fewer administration frequencies. This article provides a quick overview of the many types of microneedle patches. These include a general summary of the properties and background of Microneedles (MNs) patches, their uses in drug delivery and transdermal rapid diagnostics; classifications and categories based on the fabrication design. Dissolving microneedles have gained popularity due to their numerous advantages over other microneedles, according to numerous research findings. It is one of the most popular microneedles and a better choice for diagnostic and long-term treatment because it degrades naturally, and its level of degradation can be controlled.

REFERENCES

[1] Yeung, C., Chen, S., King, B., Lin, H., King, K., Akhtar, F., Diaz, G., Wang, B., Zhu, J., Sun, W., and Khademhosseini, A. "A 3D-printed microfluidic-enabled hollow microneedle architecture for transdermal drug delivery", *Biomicrofluidics*, vol. 13, no. 6, 2019, doi: 10.1063/1.5127778.

[2] Malekjahani, A., Sindhwani, S., Syed, A. M., and Chan, W. C. W. "Engineering Steps for Mobile Point-of-Care Diagnostic Devices", *Acc. Chem. Res.*, vol. 52, no. 9, pp. 2406–2414, 2019, doi: 10.1021/acs.accounts.9b00200.

[3] Taylor, R. M., Maharjan, D., Moreu, F., and Baca, J. T. "Parametric study of 3D printed microneedle (MN) holders for interstitial fluid (ISF) extraction", *Microsyst. Technol.*, vol. 26, no. 6, pp. 2067–2073, 2020, doi: 10.1007/s00542-020-04758-0.

[4] Duarah, S., Sharma, M., and Wen, J. "Recent advances in microneedle-based drug delivery: Special emphasis on its use in paediatric population", *Eur. J. Pharm. Biopharm.*, vol. 136, no. November 2018, pp. 48–69, 2019, doi: 10.1016/j.ejpb.2019.01.005.

[5] Koyani, R. D. "Biopolymers for microneedle synthesis: from then to now", *Biomanufacturing Rev.*, vol. 4, no. 1, pp. 1–26, 2019, doi: 10.1007/s40898-019-0006-8.

[6] Choi, J. T., Park, S. J., and Park, J. H. "Microneedles containing cross-linked hyaluronic acid particulates for control of degradation and swelling behaviour after administration into skin", *J. Drug Target.*, vol. 26, no. 10, pp. 884–894, 2018, doi: 10.1080/1061186X.2018.1435664.

[7] Luo, Z., Sun, W., Fang, J., Lee, KJ., Li, S., Gu, Z., Dokmeci, M. R., and Khademhosseini, A. "Biodegradable Gelatin Methacryloyl Microneedles for Transdermal Drug Delivery", *Adv. Healthc. Mater.*, vol. 8, no. 3, pp. 1–9, 2019, doi: 10.1002/adhm.2018 01054.

[8] Serrano-Castañeda, P., Escobar-Chávez, J. J., Rodríguez-Cruz, I. M., Melgoza-Contreras, L. M., and Martínez-Hernández, J. "Microneedles as enhancer of drug absorption through the skin and applications in medicine and cosmetology", *J. Pharm. Pharm. Sci.*, vol. 21, no. 1, pp. 73–93, 2018, doi: 10.18433/jpps29610.

[9] Yang, J., Liu, X., Fu, Y., and Song, Y. "Recent advances of microneedles for biomedical applications: drug delivery and beyond", *Acta Pharm. Sin. B*, vol. 9, no. 3, pp. 469–483, 2019, doi: 10.1016/j.apsb.2019.03.007.

[10] Johnson, A. R., and Procopio, A. T. "Low cost additive manufacturing of microneedle masters", *3D Print. Med.*, vol. 5, no. 1, 2019, doi: 10.1186/s41205-019-0039-x.

[11] Economidou, S. N., Lamprou, D. A., and Douroumis, D. "3D printing applications for transdermal drug delivery", *Int. J. Pharm.*, vol. 544, no. 2, pp. 415–424, 2018, doi: 10.1016/j.ijpharm.2018.01.031.

[12] Ye, Y., Yu, J., Wen, D., Kahkoska, A. R., and Gu, Z. "Polymeric microneedles for transdermal protein delivery", *Adv. Drug Deliv. Rev.*, vol. 127, pp. 106–118, 2018, doi: 10.1016/j.addr.2018.01.015.

[13] Pere, C. P. P., Economidou, S. N., Lall, G., Ziraud, C., Boateng, J. S., Alexander, B. D., Lamprou, D. A., and Douroumis, D. "3D printed microneedles for insulin skin delivery," *Int. J. Pharm.*, vol. 544, no. 2, pp. 425–432, 2018, doi: 10.1016/j.ijpharm.2018.03.031.

[14] Ligon, S. C., Liska, R., Stampfl, J., Gurr, M., and Mülhaupt, R. "Polymers for 3D Printing and Customized Additive Manufacturing", *Chem. Rev.*, vol. 117, no. 15, pp. 10212–10290, 2017, doi: 10.1021/acs.chemrev.7b00074.

[15] Xue, P., Zhang, L., Xu, Z., Yan, J., Gu, Z., and Kang, Y. "Blood sampling using microneedles as a minimally invasive platform for biomedical diagnostics", *Appl. Mater. Today*, vol. 13, pp. 144–157, 2018, doi: 10.1016/j.apmt.2018.08.013.

[16] Pires, L. R., Vinayakumar, K. B., Turos, M., Miguel, V., and Gaspar, J. "A perspective on microneedle-based drug delivery and diagnostics in paediatrics", *J. Pers. Med.*, vol. 9, no. 4, 2019, doi: 10.3390/jpm9040049.

[17] Luzuriaga, M. A., Berry, D. R., Reagan, J. C., Smaldone, R. A., and Gassensmith, J. J. "Biodegradable 3D printed polymer microneedles for transdermal drug delivery", *Lab Chip*, vol. 18, no. 8, pp. 1223–1230, 2018, doi: 10.1039/c8lc00098k.

[18] Leone, M., Priestera, M. I., Romeijna, S., Reza Nejadnika, M., Mönkärea, J., O'Mahony, C., Jiskoota, W., Kerstena, G., and Bouwstra, J.A. "Hyaluronan-based dissolving microneedles with high antigen content for intradermal vaccination: Formulation, physicochemical characterizat-ion and immunogenicity assessment", *Eur. J. Pharm. Biopharm.*, vol. 134, no. September 2018, pp. 49–59, 2019, doi: 10.1016/j.ejpb.201 8.11.013.

[19] Balmert, S. C., Carey, C. D., Falo, G. D., Sethi, S. K., Erdos, G., Korkmaz, E., Falo Jr. L. D. "Dissolving undercut microneedle arrays for multicomponent cutaneous vaccination", *J. Control. Release*, vol. 317, no. July 2019, pp. 336–346, 2020, doi: 10.1016/j.jconrel.2019.11.023.

[20] Camović, M., Biščević, A., Brčić, I., Borčak, K., Bušatlić, S., Ćenanović, N., Dedović, A., Mulalić, A., Osmanlić, M., Sirbubalo, M., Tucak, A., and Vranić, E. "Coated 3d printed pla microneedles as transdermal drug delivery systems", 2020, doi: 10.1007/978-3-030-17971-7_109.

[21] Krieger, K. J., Bertollo, N., Dangol, M., Sheridan, J. T., Lowery, M. M., and O'Cearbhaill, E. D. "Simple and customizable method for fabrication of high-aspect ratio microneedle molds using low-cost 3D printing", *Microsystems Nanoeng.*, vol. 5, no. 1, 2019, doi: 10.1038/s41378-019-0088-8.

[22] He, X., Sun, J., Zhuang, J., Xu, H., Liu, Y., and Wu, D. "Microneedle System for Transdermal Drug and Vaccine Delivery: Devices, Safety, and Prospects", *Dose-Response*, vol. 17, no. 4, pp. 1–18, 2019, doi: 10.1177/1559325819878585.

[23] Lim, D. J., Vines, J. B., Park, H., and Lee, S. H. "Microneedles: A versatile strategy for transdermal delivery of biological molecules", *Int. J. Biol. Macromol.*, vol. 110, pp. 30–38, 2018, doi: 10.1016/j.ijbiomac.2017.12.027.

[24] Sharma, S., Hatware, K., Bhadane, P., Sindhikar, S., and Mishra, D. K. "Recent advances in microneedle composites for biomedical applications: Advanced drug delivery technologies", *Mater. Sci. Eng. C*, vol. 103, no. April, p. 109717, 2019, doi: 10.1016/j.msec.2019.05.002.

[25] Courtenay, A. J., Rodgers, A. M., McCrudden, M. T. C., McCarthy, H. O., and Donnelly, R. F. "Novel Hydrogel-Forming Microneedle Array for Intradermal Vaccination in Mice Using Ovalbumin as a Model Protein Antigen", *Mol. Pharm.*, vol. 16, no. 1, pp. 118–127, 2019, doi: 10.1021/acs.molpharmaceut.8 b00895.

[26] Kolluru, C., Gomaa, Y., and Prausnitz, M. R. "Development of a thermostable microneedle patch for polio vaccination", *Drug Deliv. Transl. Res.*, vol. 9, no. 1, pp. 192–203, 2019, doi: 10.1007/s13346-018-00608-9.

[27] Permana, A. D., Tekko, I. A., McCrudden, M. T., Anjani, Q. K., Ramadon, D., McCarthy, H. O., and Donnelly, R. F. "Solid lipid nanoparticle-based dissolving microneedles: A promising intradermal lymph targeting drug delivery system with potential for enhanced treatment of lymphatic filariasis", *J. Control. Release*, vol. 316, no. September, pp. 34–52, 2019, doi: 10.1016/j.jconrel.2019.10.004.

[28] Pawar, S., and Shende, P. "22 Factorial Design-Based Biocompatible Microneedle Arrays Containing Artemether Co-Loaded With Lumefantrine Nanoparticles for Transepidermal Delivery", *Biomed. Microdevices*, vol. 22, no. 1, pp. 1–15, 2020, doi: 10.1007/s10544-020-0476-8.

[29] Ronnander, P., Simon, L., and Koch, A. "Experimental and mathematical study of the transdermal delivery of sumatriptan succinate from polyvinylpyrrolidone-based microneedles", *Eur. J. Pharm. Biopharm.*, vol. 146, no. September 2019, pp. 32–40, 2020, doi: 10.1016/j.ejpb.2019.11.007.

[30] Yao, W., Li, D., Zhao, Y., Zhan, Z., Jin, G., Liang, H., and Yang, R. "3D Printed multifunctional hydrogel microneedles based on high-precision digital light processing", *Micromachines*, vol. 11, no. 1, 2020, doi: 10.3390/mi11010017.

[31] He, R., Niu, Y., Li, Z., Li, A., Yang, H., Xu, F., and Li, F. "A Hydrogel Microneedle Patch

for Point-of-Care Testing Based on Skin Interstitial Fluid", *Adv. Healthc. Mater.*, vol. 9, no. 4, pp. 1–11, 2020, doi: 10.1002/adhm.201901201.

[32] Al Sulaiman, D., Chang, J. Y., Bennett, N. R., Topouzi, H., Higgins, C. A., Irvine, D. J., and Ladame, S. "Hydrogel-Coated Microneedle Arrays for Minimally Invasive Sampling and Sensing of Specific Circulating Nucleic Acids from Skin Interstitial Fluid", *ACS Nano*, vol. 13, no. 8, pp. 9620–9628, 2019, doi: 10.1021/acsnano.9b04783.

[33] Zheng, M., Wang, Z., Chang, H., Wang, L., Chew, S. W., Lio, D. C., Cui, M., Liu, L., Tee, B. C., and Xu, C. "Osmosis-Powered Hydrogel Microneedles for Microliters of Skin Interstit-ial Fluid Extraction within Minutes", *Adv. Healthc. Mater.*, vol. 9, no. 10, pp. 1–11, 2020, doi: 10.1002/adhm.201901683.

[34] Samant, P. P., Niedzwiecki, M. M., Raviele, N., Tran, V., Mena-Lapaix, J., Walker, D. I., Felner, E. I., Jones, D. P., Miller, G. W., and Prausnitz, M. R. "Sampling interstitial fluid from human skin using a microneedle patch", *Sci. Transl. Med.*, vol. 12, no. 571, pp. 1–16, 2020, doi: 10.1126/SCITRANSLMED.AAW0285.

[35] Zhang, X., Chen, G., Bian, F., Cai, L., and Zhao, Y. "Encoded Microneedle Arrays for Detection of Skin Interstitial Fluid Biomark-ers", *Adv. Mater.*, vol. 31, no. 37, pp. 1–8, 2019, doi: 10.1002/adma.201902825.

[36] Zeng, Y., Wang, J., Wang, Z., Chen, G., Yu, J., Li, S., Li, Q., Li, H., Wen, D., and Gu, Z. "Colloidal crystal microneedle patch for glucose monitoring", *Nano Today*, vol. 35, p. 100984, 2020, doi: 10.1016/j.nantod.2020.100984.

[37] Zhao, W., Zheng, L., Yang, J., Ma, Z., Tao, X., and Wang, Q. "Dissolving microneedle patch-assisted transdermal delivery of methotrexate improve the therapeutic efficacy of rheumatoid arthritis", *Drug Deliv.*, vol. 30, no. 1, pp. 121–132, 2023, doi: 10.1080/10717544.2022.2157518.

[38] Gao, S., Zhang, W., Zhai, X., Zhao, X., Wang, J., Weng, J., Li, J., and Chen, X. "An antibacterial and proangiogenic double-layer drug-loaded microneedle patch for accelerating diabetic wound healing", *Biomater. Sci.*, vol. 11, no. 2, pp. 533–541, 2022, doi: 10.1039/d2bm01588a.

[39] Yang, Y., Wang, P., Gong, Y., Yu, Z., Gan, Y., Li, P., Liu, W., and Wang, X. "Curcumin-zinc framework encapsulated microneedle patch for promoting hair growth", *Theranostics*, vol. 13, no. 11, pp. 3675–3688, 2023, doi: 10.7150/thno.84118.

[40] Zhang, Q., ,Shi, L., He, H., Liu, X., Huang, Y., Xu, D., Yao, M., Zhang, N., Guo, Y., Lu, Y., and Li, H. "Down-Regulating Scar Formation by Microneedles Directly via a Mechanical Communication Pathway", *ACS Nano*, vol. 16, no. 7, pp. 10163–10178, 2022, doi: 10.1021/acsnano.1c11016.

[41] Yang, L., Liu, Q., Wang, X., Gao, N., Li, X., Chen, H., Mei, L., and Zeng, X. "Actively separated microneedle patch for sustained-release of growth hormone to treat growth hormone deficiency", *Acta Pharm. Sin. B*, vol. 13, no. 1, pp. 344–358, 2023, doi: 10.1016/j.apsb.2022.0 4.015.

[42] Zheng, Y., Ye, R., Gong, X., Yang, J., Liu, B., Xu, Y., Nie, G., Xie, X., and Jiang, L. "Iontophoresis-driven microneedle patch for the active transdermal delivery of vaccine macromolecules", *Microsystems Nanoeng.*, vol. 9, no. 1, pp. 1–14, 2023, doi: 10.1038/s41378-023-00515-1.

[43] Yang, J., Wang, X., Wu, D., Yi, K., and Zhao, Y. "Yunnan Baiyao-loaded multifunctional microneedle patches for rapid hemostasis and cutaneous wound healing", *J. Nanobiotechnology*, vol. 21, no. 1, pp. 1–15, 2023, doi: 10.1186/s12951-023-01936-w.

[44] Habib, R., Azad, A. K., Akhlaq, M., Al-Joufi, F. A., Shahnaz, G., Mohamed, H. R., Naeem, M., Almalki, A. S., Asghar, J., Jalil, A., and Abdel-Daim, M. M. "Thiolated Chitosan Microneedle Patch of Levosulpiride from Enhancement Approach", 2022.

[45] Zhu, T., Yu, X., Yi, X., Guo, X., Li, L., Hao, Y., and Wang, W. "Lidocaine-Loaded Hyaluronic Acid Adhesive Microneedle Patch for Oral Mucosal Topical Anesthesia", *Pharmaceutics*, vol. 14, no. 4, pp. 1–15, 2022, doi: 10.3390/pharmaceutics14040686.

[46] Wang, H., Zhao, Z., Wu, C., Tong, X., Shi, Y., and Chen, S. "Microneedle Patch Delivery of Methotrexate-Loaded Albumin Nanoparticles to Immune Cells Achieves a Potent Antipsoriatic Effect", *Int. J. Nanomedicine*, vol. 17, no. August, pp. 3841–3851, 2022, doi: 10.2147/IJN.S371183.

[47] Li, S., Wang, X., Yan, Z., Wang, T., Chen, Z., Song, H., and Zheng, Y. "Microneedle Patches with Antimicrobial and Immunomodulating Proper-ties for Infected Wound Healing", *Adv. Sci.*, vol. 10, no. 22, pp. 1–12, 2023, doi: 10.1002/advs.202300576.

[48] Paredes, A. J., Volpe-Zanutto, F., Vora, L. K., Tekko, I. A., Permana, A. D., Picco, C. J., McCarthy, H. O., and Donnelly, R. F. "Systemic delivery of tenofovir alafenamide using dissolving and implantable microneedle patches", *Mater. Today Bio*, vol. 13, no. December 2021, p. 100217, 2022, doi: 10.1016/j.mtbio.2022.10 0217.

[49] Li, W., Chen, J. Y., Terry, R. N., Tang, J., Romanyuk, A., Schwendeman, S. P., and Prausnitz, M. R. "Core-shell microneedle patch for six-month controlled-release contraceptive delivery", *J. Control. Release*, vol. 347, pp. 489–499, 2022, doi: 10.1016/j.jconrel.2022.04 .051.

[50] Zhu, J., Zhou, X., Kim, H. J., Qu, M., Jiang, X., Lee, K., Ren, L., Wu, Q., Wang, C., Zhu, X., and Tebon, P. "Gelatin Methacryloyl Micronee-dle Patches for Minimally Invasive Extraction of Skin Interstitial Fluid", *Small*, vol. 16, no. 16, pp. 1–9, 2020, doi: 10.1002/smll.201905 910.

[51] Takeuchi, K., Takama, N., Kim, B., Sharma, K., Paul, O., and Ruther, P. "Microfluidic chip to interface porous microneedles for ISF collection", *Biomed. Microdevices*, vol. 21, no. 1, pp. 1–10, 2019, doi: 10.1007/s10544-019-0370-4.

[52] Miller, P. R., Taylor, R. M., Tran, B. Q., Boyd, G., Glaros, T., Chavez, V. H., Krishnakumar, R., Sinha, A., Poorey, K., Williams, K. P., and Branda, S. S. "Extraction and biomolecular analysis of dermal interstitial fluid collected with hollow microneedles", *Commun. Biol.*, vol. 1, no. 1, 2018, doi: 10.1038/s42003-018-0170-z.

[53] Chen, J., Wang, M., Ye, Y., Yang, Z., Ruan, Z., and Jin, N. "Fabrication of sponge-forming microneedle patch for rapidly sampling interstitial fluid for analysis", *Biomed. Microdevices*, vol. 21, no. 3, 2019, doi: 10.1007/s10544-019-0413-x.

[54] Kolluru, C., Gupta, R., Jiang, Q., Williams, M., Gholami Derami, H., Cao, S., Noel, R. K., Singamaneni, S., and Prausnitz, M. R. "Plasmonic Paper Microneedle Patch for On-Patch Detection of Molecules in Dermal Interstitial Fluid", *ACS Sensors*, vol. 4, no. 6, pp. 1569–1576, 2019, doi: 10.1021/acssensors.9b00258.

[55] Zhang, X., Wang, Z., Jiang, H., Zeng, H., An, N., Liu, B., Sun, L., and Fan, Z. "Self-powered enzyme-linked microneedle patch for scar-prevention healing of diabetic wounds", *Sci. Adv.*, vol. 9, no. 28, pp. 1–13, 2023, doi: 10.1126/sciadv.adh1415.

[56] Liu, J. F., GhavamiNejad, A., Lu, B., Mirzaie, S., Samarikhalaj, M., Giacca, A., and Wu, X. Y. "Smart' Matrix Microneedle Patch Made of Self-Crosslinkable and Multifunctional Polymers for Delivering Insulin On-Demand", *Adv. Sci.*, vol. 10, no. 30, pp. 1–10, 2023, doi: 10.1002/advs.202303665.

[57] Zhou, X., Li, B., Guo, M., Peng, W., Wang, D., Guo, Q., Wang, S., Ming, D., and Zheng. B. "Microneedle patch based on molecular motor as a spatio-temporal controll-able dosing strategy of L-DOPA for Parkinson's disease", *Chem. Eng. J.*, vol. 427, no. April 2021, 2022, doi: 10.1016/j.cej.202 1.131555.

[58] Moon, S. S., Richter-Roche, M., Resch, T. K., Wang, Y., Foytich, K. R., Wang, H., Mainou, B. A., Pewin, W., Lee, J., Henry, S., and McAllister, D. V. "Microneedle patch as a new platform to effectively deliver inactivated polio vaccine and inactivated rotavirus vaccine", *npj Vaccines*, vol. 7, no. 1, 2022, doi: 10.1038/s41541-022-00443-7.

[59] Fang, A., Wang, Y., Guan, N., Zuo, Y., Lin, L., Guo, B., Mo, A., Wu, Y., Lin, X., Cai, W., and Chen, X. "Porous microneedle patch with sustained delivery of extracellular vesicles mitigates severe spinal cord injury", *Nat. Commun.*, vol. 14, no. 1, pp. 1–17, 2023, doi: 10.1038/s41467-023-39745-2.

[60] Yang, B., Kong, J., and Fang, X. "Programmable CRISPR-Cas9 microneedle patch for long-term capture and real-time monitoring of universal cell-free DNA", *Nat. Commun.*, vol. 13, no. 1, pp. 1–16, 2022, doi: 10.1038/s41467-022-31740-3.

[61] Jiang, X., and Lillehoj, P. B. "Microneedle-based skin patch for blood-free rapid diagnostic testing", *Microsystems Nanoeng.*, vol. 6, no. 1, pp. 1–11, 2020, doi: 10.1038/s41378-020-00206-1.

[62] Connelly, D. "Microneedles: a new way to deliver vaccines", *Pharm. J.*, vol. 307, no. 7953, 2021, doi: 10.1211/PJ.2021.1.100134.

[63] Dugam, S., Tade, R., Dhole, R., and Nangare, S. "Emerging era of microneedle array for pharmaceutical and biomedical applications: recent advances and toxicological perspectives", *Futur. J. Pharm. Sci.*, vol. 7, no. 1, pp. 1–26, 2021, doi: 10.1186/s43094-020-00176-1.

[64] Makvandi, P., Jamaledin, R., Chen, G., Baghbantaraghdari, Z., Zare, E. N., Di Natale, C., Onesto, V., Vecchione, R., Lee, J., Tay, F.

R., and Netti, P. "Stimuli-responsive transdermal microneedle patches", *Mater. Today*, vol. 47, no. August, pp. 206–222, 2021, doi: 10.1016/j.mattod.2021.03.012.