



Review

Revolutionizing drug delivery by bioinspired 4D transdermal microneedles: Advances and future horizons

Amisha S. Raikar^a, Deepak M. Kalaskar^b, Shilpa Bhilegaonkar^a, Sandesh N. Somnache^c, Mahdi Bodaghi^{d,*}

^a Department of Pharmaceutics, PES Rajaram and Tarabai Bandekar College of Pharmacy, Ponda, Goa 403601, India

^b Department of Bioengineering, UCL, Division of Surgery and Interventional Science, Royal National Orthopaedic Hospital, Rowland Hill Street, NW3 2PF London, UK

^c Department of Pharmaceutics, SSPM's VP College of Pharmacy, Madkhhol, Sawantwadi 416510, Maharashtra, India

^d Department of Engineering, School of Science and Technology, Nottingham Trent University, Nottingham NG11 8NS, UK

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ABSTRACT

Transdermal drug delivery holds great promise for enhancing therapeutic outcomes and patient compliance, and bioinspired 4D microneedles represent a cutting-edge approach in this field. This review provides a concise overview on the current progress and future prospects in the development of bioinspired 4D transdermal microneedles for drug delivery. Bioinspired 4D microneedles combine the principles of biomimicry and advanced materials science to create dynamic, responsive drug delivery systems. They are designed to overcome the limitations of conventional transdermal patches by offering enhanced control over drug release, improved patient comfort, and the ability to adapt to the dynamic properties of the skin. In this article, we discuss various fabrication techniques, materials, and designs that have been explored to create these innovative microneedles. This article explores various fabrication techniques, materials and designs of innovative microneedles. Current research in this field has demonstrated that bioinspired 4D microneedles enables precise and controlled drug administration for a wide range of therapeutic applications. These microneedles have shown potential in delivering both small molecule drugs and biologics, making them versatile tools in the pharmaceutical industry. Ongoing research efforts focus on improving biocompatibility, scalability, and commercial viability. The integration with smart technologies such as sensors and feedback control systems enable personalized and responsive delivery of drug. Bioinspired 4D transdermal microneedles represent a transformative approach to drug delivery. They offer precise, patient-friendly, and adaptable solutions for delivering a wide range of therapeutics. With continued research and development, Bioinspired 4D microneedles have the potential to revolutionize the way of drug administration, ultimately improving healthcare of the patient.

1. Introduction

Transdermal drug delivery systems (TDDS) represent a pivotal approach for administration of drugs into the body via topical route across dermal layer of skin thereby achieving systemic distribution without the need for invasive needle injections. This non-invasive method has gained substantial attention and research, positioning it as a prominent alternative over conventional routes of drug delivery. TDDS employs specialized patches that are applied topically, meticulously designed to facilitate the controlled, systemic release of drugs in therapeutically effective quantities [1]. Overcoming the primary challenge of drug diffusion through the outermost and relatively impermeable

layer of skin, the stratum corneum, has a focal point of innovation and exploration in this field. Various significance of TDDS over conventional drug delivery system are illustrated in Fig. 1.

Traditional methods of drug delivery such as oral or injectables have limitations related to drug degradation, variable effects, discomfort, and patient compliance [1]. They may not be effective for localized treatment and can lead to tolerance, dosing errors, and storage concerns. As a result, there is a need for alternative drug delivery methods that can enhance therapeutic effectiveness and patient experience.

Many biotherapeutics and vaccines are administered through hypodermic needles, offering a cost-effective, swift, and direct means of delivering various molecules into the body. But this method typically

* Corresponding author.

E-mail address: mahdi.bodaghi@ntu.ac.uk (M. Bodaghi).

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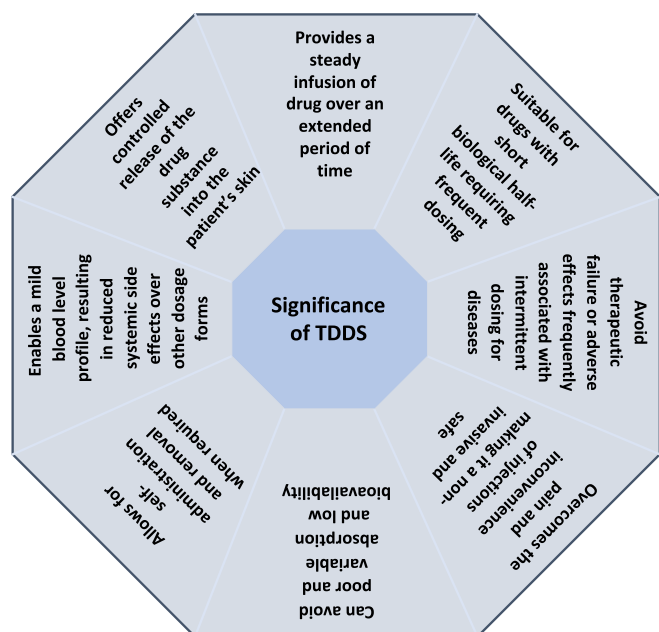


Fig. 1. Significance of transdermal drug delivery system in healthcare.

requires trained medical personnel for proper use and disposal, limiting patient self-administration [2]. Also, pain, needle-phobia, and concerns about bloodborne pathogen transmission are significant barriers to patient compliance. While oral delivery can address some of these issues, it is not suitable for all drugs as a result of assimilation and decomposition problems the gut and hepatic metabolism. Although different administration methods have been explored, none of them match the versatility of needle-based administration. Rather than completely avoiding the use of needles, some researchers, have proposed miniaturizing the needle to the micron scale. This approach can promote patient adherence to the therapy and also improve patient safety without compromising advantages of needle-based drug delivery systems. A microneedle, a device at the micron scale, must strike a balance between being adequately sized for delivering most medications or tiny particle formulations while also being compact enough to reduce discomfort, anxiety, and the necessity for extensive training. Microneedles [MN] allow precise localization of drug delivery within specific tissues, including the skin, the suprachoroidal space of the eye, and even within cell nuclei. Most of the research on microneedles has focused on transdermal drug and vaccine administration. Bioinspired 4D transdermal microneedles represent a groundbreaking innovation in the field of drug delivery and medical technology. Conventional methods such as moulding are challenging and expensive for crafting complex compositions. Recent advancements in 3D printing have enabled the fabrication of nanoscale MNs with intricate geometries. However, layer-by-layer printing has limitations, especially when mimicking natural designs. Adding supports or rotating the design can help but does not fully address the issue, especially with multiple materials. 4D printing goes beyond 3D printing by using smart materials responsive to various stimuli, such as physical, chemical, and biological cues [3]. These materials can change shape post-printing, such as bending, elongating, twisting, or corrugating, creating complex structures. For instance, MNs with backward-facing barbs inspired by honeybee stingers, a complex structure, can be made more feasible with 4D printing [4]. Arrays of MNs with initially undeformed barbs are printed and then exposed to ultraviolet light, causing them to bend and stabilize in their final shape [4]. This innovative approach can simplify complex MN fabrication compared to traditional 3D printing methods.

The concept of Bioinspired 4D transdermal microneedles is an inspiration from nature, drawing cues from biological structures and systems to create a more effective and patient-friendly approach to drug

delivery. The term “bioinspired” indicates that these microneedles are designed based on natural biological structures and processes. They aim to replicate the efficiency and effectiveness found in certain organisms and systems in the natural world. The “4D” aspect adds a dynamic dimension to these microneedles, signifying their ability to change and adapt over time. This adaptability is often driven by external stimuli, such as variations in temperature, pH levels, or the presence of specific substances [5]. These dynamic responses allow for precise and controlled drug delivery. Fig. 2 shows the merits of bioinspired 4D transdermal microneedles.

The current research in this field exploring optimal methods for manufacturing Microneedles (MNs) that provide strong adhesion to tissue with minimal damage. In this field, inspiration has been drawn from the adaptations seen in living organisms over the course of evolution. An intriguing example is found in endoparasite worms, specifically Acanthocephalans, which employ tissue penetration probes. Species like *Pomphorhynchus laevis* have developed an ingenious mechanism for firmly anchoring themselves to the gut wall of fish by elongating a bulb through a retractor located at the proboscis's base after penetrating the tissue [6]. To emulate this remarkable mechanism, team of researchers has been endeavouring to design MNs with dual-phase properties optimized for needle attachment and maximum tissue adhesion. They have harnessed the adaptable morphology of the worm proboscis and have successfully developed an advanced MN prototype with a swelling tip that promotes the interlocking of mechanical tissue [6]. The innovative design in question significantly reduces the pressure needed to penetrate tissue. It achieves this by using smooth conical needles that can be inserted into tissue without the need for the barb features present in other adhesive platforms based on microneedles (MNs). When these needles come into contact with the moisture in the tissue, the needle tips' cross-sectional area expands, creating a substantial pull-out force [5]. This force leads to localized tissue deformation and subsequent interlocking. This bioinspired adhesive, employing microneedles, has demonstrated outstanding adhesion to moist tissues such as skin and intestines, irrespective of variations in surface texture. This robust fixation can be established within dynamic tissues by undergoing several cycles of movement. The MNs with softer tips, characterized by a reduced modulus, enable removal without causing significant damage to the tissues, thanks to the increased pulling forces resulting from tissue enlargement. In addition to this, the ability of these swollen MNs to resist breakage during removal sets them apart from rigid MNs, which may fracture when extracted from the tissue [6].

2. History and evolution of microneedle technology in drug delivery

The history and evolution of microneedle technology in drug delivery is a story of innovation and progress. The earliest concepts of microneedles can be traced back to the 1920s. Early designs were primarily intended for skin perforation and laboratory use. However, they were not widely adopted in the medical field at the time. During a period of 1950s to 1960s, various microneedle technologies were developed, however they remained at experimental level [7]. Research into microneedles gained momentum after the emergence of Modern Microneedles in Late 20th Century from the period 1970s–1980s. Scientists began exploring the use of microneedles for drug delivery and transdermal applications. The goal was to develop a less invasive, pain-free method for administering medications [7,8]. One of the key breakthroughs came in 1998 when researchers at the Georgia Institute of Technology and Emory University introduced the concept of “microneedle arrays” for pharmaceutical delivery [9]. These arrays consisted of multiple microneedles that could be applied to the skin. Throughout the 2000s, researchers worldwide made significant strides in microneedle technology. They experimented with various designs, materials, and methods of microneedle fabrication. Biodegradable and dissolvable microneedles gained attention as they could release drugs painlessly and

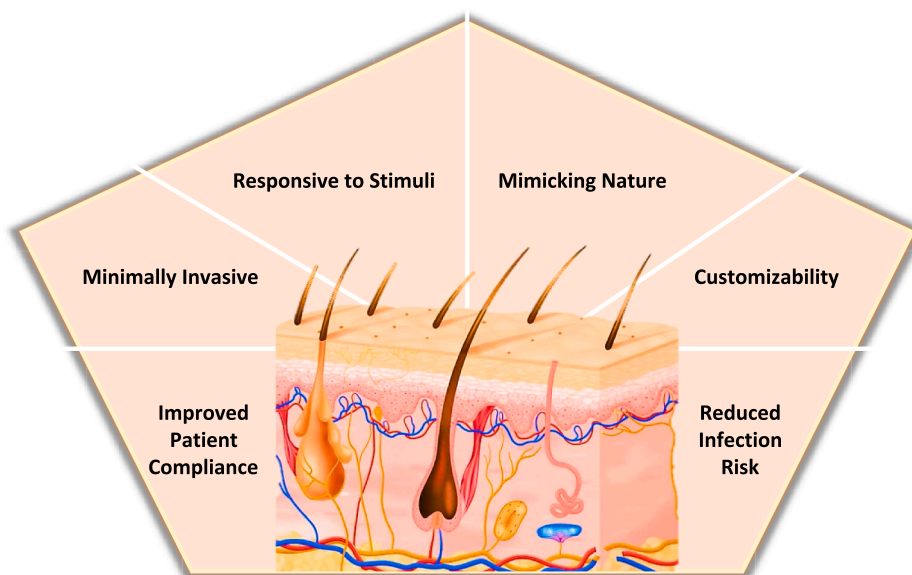


Fig. 2. Merits of bioinspired 4D transdermal microneedles.

dissolve after use. The U.S. Food and Drug Administration (FDA) approved the first microneedle-based product, a device for measuring glucose levels in the interstitial fluid, providing a strong validation for microneedle technology's safety and effectiveness [8]. In the mid-1990s, significant research into microneedles for drug delivery commenced through three simultaneous initiatives:

Becton Dickinson (BD): Becton Dickinson had a keen interest in enhancing hypodermic needles for parenteral injection, a substantial segment of their business [10]. They provided funding for research at the University of California in Berkeley and the University of Utah to investigate the potential of microfabrication technology in creating smaller needles that would yield better clinical and pharmacological results. Becton Dickinson concentrated on short hollow steel needles and solid microneedles with blunt tips, aiming to enhance skin permeability for topical vaccines. This endeavour ultimately resulted in the creation of marketable products like Soluvia® for intradermal vaccine injections.

Alza Corporation: Alza's fascination with microneedles traces its roots to the 1970s when they were actively involved in the advancement of iontophoresis for delivering drugs through the skin [11]. They delved into the integration of iontophoresis with sturdy metallic microneedles to improve drug administration. This innovative approach eventually led to the establishment of a fresh venture known as Zosano Pharma. Subsequently, this technology progressed to the stage of clinical trials, aimed at delivering drugs for the treatment of ailments such as osteoporosis.

Georgia Institute of Technology: Georgia Tech's collaborative initiatives, spearheaded by Mark Prausnitz's proficiency in transdermal drug delivery and Mark Allen's mastery in microfabrication, resulted in the publication of the inaugural scientific article on microneedle-based drug delivery. Subsequently, Georgia Tech has remained actively engaged in ongoing research in the field of microneedles [12].

The end of the 20th century and the beginning of the 21st century, other companies and academic institutions began researching microneedles. But during the early stages of microneedle development, many designs and methods were primarily used for the progression of microfabrication research rather than drug delivery. Academic involvement in microneedle research was relatively limited until later on [8]. As the 2000s progressed, commercial microneedle development continued to grow, while there was a deceleration in academic microfabrication endeavours, academic research in drug delivery experienced substantial growth and expansion. The interdisciplinary gap between

microfabrication and drug delivery was eventually bridged, leading to the current state of the field. Currently, a multitude of functional microneedle systems can be found in different industry and academic laboratories. Several applications have been successfully exhibited in controlled laboratory settings and animal studies, with a few advancing to human trial stages. This presents the field with an opportunity for further translation into clinical applications and the incorporation of microneedle products into medical practice. The 2010s marked a period of increased research and development into microneedle technology. Researchers explored a wide range of applications, including vaccine delivery, hormonal contraception, pain management, and treatment of various medical conditions [7].

In 2012, Cho and his colleagues made a significant discovery regarding North American porcupine quills [13]. They found that the microstructure of these quills allowed for easier tissue penetration than hypodermic needles of the same diameter. The research made use of both finite element modeling and actual quill experiments. These experiments demonstrated that the quills could easily penetrate pig skin and chicken muscle with minimal force, resulting in less damage compared to quills without barbs. These findings were reaffirmed when synthetic polyurethane quills were tested. Cho et al. put forth an innovative theory regarding tissue adhesion mechanisms that either facilitated ease of penetration or hindered removal. This innovative design has implications for the development of transdermal products that require less force for skin penetration, such as microneedle (MN) arrays. In 2013, another group of researchers drew inspiration from the endoparasite *Pomphorhynchus laevis*, which expands its proboscis to affix itself to the host's intestinal lining [6]. This led to the development of MN arrays with two phases: mechanically interlocking with tissue via swellable tips, resulting in increased adhesion strength. These MNs featured a poly(styrene)-block-poly (acrylic acid) structure featuring a swollen tip and a non-expanding polystyrene core. The conical-shaped microneedles (MNs) displayed notable characteristics, including robust adhesion strength, reduced tissue penetration force, and shallower insertion depth. This bioinspired design provided effective adhesion to soft tissue with minimal damage, less painful removal, reduced infection risk, and optimized drug delivery. In 2018, Zhipeng Chen and his team drew inspiration from honeybee stingers, known for their micro barbs used in venom delivery [14]. They introduced a novel 3D additive manufacturing technique called magnetorheological drawing lithography (MRDL) to efficiently produce MNs that closely resembled

honeybee stingers. These barbed MNs, crafted with the aid of an external magnetic field, exhibited easier insertion but posed more challenges during removal compared to barbless MNs. The strength ratio between extraction and penetration was tripled that of barbless MNs, and the stress at the barbs reduced insertion force while enhancing adhesive force during removal, offering potential applications in tissue adherence and transdermal drug delivery. In 2020, Rutgers researchers leveraged micro 3D printing and 4D printing techniques to develop a micro-adhesive backward-facing barbed MN that exhibited 18 times stronger tissue adhesion compared to barbless MNs [15]. The combination of these printing technologies allowed for the creation of a more stable MN suitable for robust drug delivery. Traditional hypodermic needles deliver medication quickly but may not be ideal for long-term use. Microneedles are a less painful alternative but can sometimes detach, requiring reapplication. To address these issues, the 4D printed MN array was developed, emulating the efficiency of natural barbed needles for enhanced adherence. Researchers could customize the degree of barb curvature to optimize adhesion.

There have been significant advancements in the materials used to make microneedles in recent years (2020s and beyond). This includes biocompatible and biodegradable materials, as well as innovations in microneedle design. Microneedles have been combined with sensor technology to allow for real-time monitoring of biomarkers, such as glucose levels, and drug release. These smart microneedles have the potential to revolutionize healthcare monitoring and drug delivery [7]. Several microneedle-based drug delivery products and devices have entered clinical trials or gained commercial approval. These developments indicate a growing acceptance of this technology in the healthcare industry.

3. Microneedles

The fabrication of bioinspired 4D transdermal microneedles relies on a range of materials to create innovative and adaptable devices. These materials are carefully selected for their biocompatibility, mechanical properties, and responsiveness to stimuli.

Single small needles have been painstakingly crafted for research objectives for many decades. As early as the 1970s, the concept of economical microneedle arrays for medication delivery had been envisioned. The real breakthrough came in the 1990s, the microelectronics industry contributed the essential microfabrication tools required to create microneedles suitable for pharmaceutical applications [8].

The initial microneedles, given their roots in microelectronics

technology, were predominantly made from silicon. Since then, microneedles have been crafted from a wide range of materials, including metal, polymers, glass, and ceramics, and they come in various shapes and sizes, tailored to specific applications. Most methods for fabricating microneedles draw from conventional microfabrication techniques, involving processes like photolithography, silicon patterning, laser ablation, electrodeposition of metal, electrolytic polishing, and micro-structure moulding [16]. Microneedles can be categorized into four primary types as depicted in Fig. 3.

3.1. Solid microneedles

Solid microneedles serve as a method for skin preparation, creating microchannels within the skin to facilitate drug transport. These fine microneedles pierce or gently abrade the skin, generating channels through which medications can be administered. These channels allow for localized skin effects or systemic drug delivery through the skin's capillaries [17]. To administer drugs, a drug formulation can be applied to the skin's surface over these microchannels, either using a drug-loaded patch, following the conventional approach in transdermal drug delivery, or through the utilization of semi-solid topical formulations such as ointments, creams, gels, or lotions, commonly employed in various dermatological treatments. The fabrication of solid microneedles primarily revolves around ensuring adequate mechanical strength through the careful choice of microneedle materials and geometrical designs. The insertion force required for microneedles to penetrate tissue is minimized by optimizing the sharpness of their tips. Solid microneedles have been created using a diverse array of materials as depicted in Fig. 4.

Silicon: Short silicon microneedles are produced via a silicon dry-etching procedure, involving reactive ion etching with a chromium mask, along with isotropic etching carried out in an inductively coupled plasma etcher. Anisotropic wet etching of crystalline silicon has also been employed [17]. These techniques ensure that solid microneedles possess the necessary mechanical robustness.

Metal: Metal microneedles are crafted using techniques such as three-dimensional laser ablation, laser cutting, wet etching, and metal electroplating. Rows of solid metal microneedles are directly manufactured, while two-dimensional arrays of microneedles are created by cutting microneedles into stainless steel and titanium metal sheets, subsequently bending them at a 90° angle [18]. Two-dimensional metal microneedles can also be prepared through the process of electroplating or electroless-plating of metal onto microneedle molds.

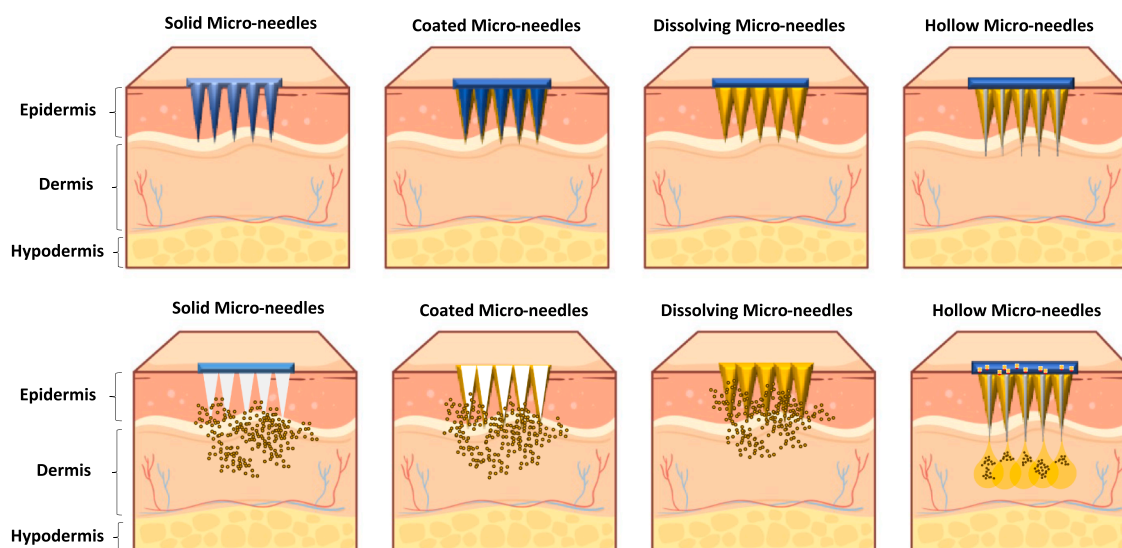


Fig. 3. Illustration depicting different types of microneedles based on the mechanism of drug release.

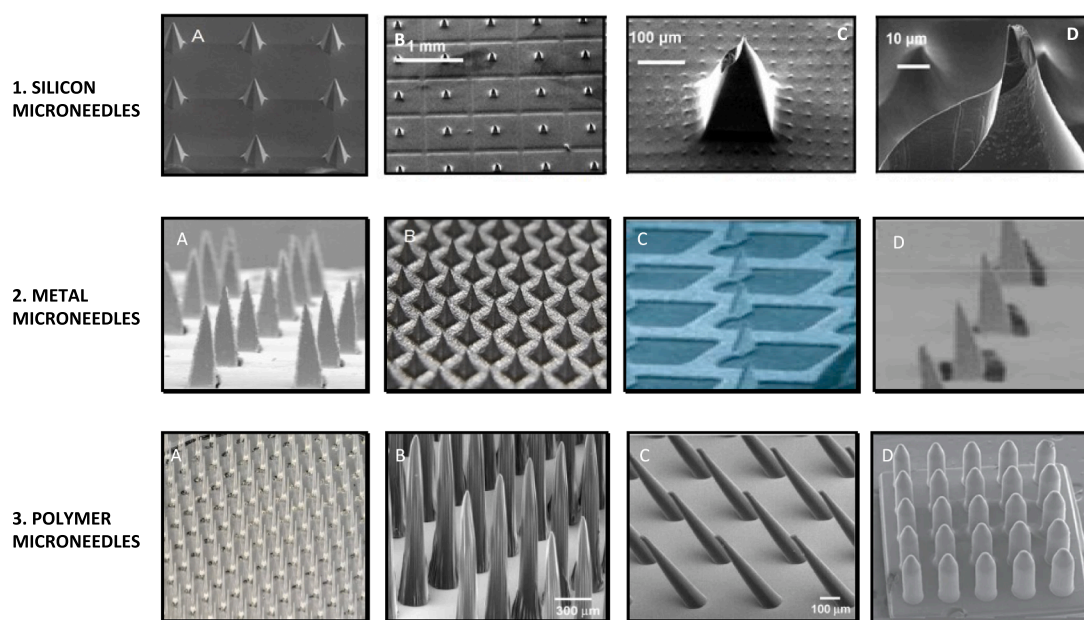


Fig. 4. Solid microneedles manufactured using different types of materials. 1: Silicon microneedles, 2: Metal Microneedles, 3: Polymer microneedles. Needs copyright.

Polymer: Polymer microneedles are generated through photolithography, employing optically curable polymers. The UV-curable polymer SU-8 is widely utilized for this purpose [18]. Polymer microneedles often serve as master structures for replication through molding.

Ceramic: Ceramic microneedles are manufactured through ceramic micromolding and sintering. Solid ceramic microneedles are crafted by micromolding an alumina slurry with the use of a PDMS microneedle mold, followed by ceramic sintering [19].

Microneedle Rollers: Certain microneedles are created on a cylindrical surface and applied to the skin using roller devices. These microneedle rollers are commercially available and find applications in cosmetic treatments, such as promoting skin rejuvenation and collagen induction, as well as enhancing skin permeability for drug delivery [20]. The manufacturing process of solid microneedles differs according to the material and shape of the microneedles. These microneedles have played a crucial role in improving the delivery of drugs through the skin.

3.2. Coated microneedles

Solid microneedles serve a dual purpose, not only as skin-piercing structures but also as carriers for the delivery of drugs into the skin or other tissues. This approach involves coating microneedles with a drug in a suitable formulation that can adhere to the microneedles and dissolve upon insertion into the tissue, delivering the drug rapidly.

Methods for Coating Microneedles: Various techniques have been applied to coat microneedles, with many of them involving the immersion or spraying of microneedles using an aqueous solution. Typically, this solution comprises a drug, vaccine, or another active substance, along with additives aimed at enhancing stability. The coating process can entail submerging the microneedles into a bath filled with the coating solution, placing them into separate microwells containing the solution, or spreading a thin layer of the solution onto a roller's surface. Layer-by-layer coating methods have been employed to coat microneedles with DNA or protein molecules [21]. This process involves alternatively immersing microneedles into solutions containing oppositely charged substances.

When formulating coatings for microneedles, it is imperative to consider various crucial factors. This includes the need for controlled wetting, where the coating solution should uniformly spread across the

microneedle substrate to achieve an even coating [21]. To enhance wetting and coating thickness, increasing the solution's viscosity and reducing the contact angle, often with the addition of surfactants, proves effective [22]. The coating formulation should be water-soluble to allow efficient coating in an aqueous medium and to ensure the rapid and complete dissolution of the coating within the skin, which also presents an aqueous environment. The dried coating should possess the necessary mechanical strength to remain securely attached to the microneedle during its insertion into the skin. The safety and compatibility are vital aspects, necessitating that excipients and solvents in the coating solution are safe for human use and do not compromise the integrity of the coated drugs. The coating process should seamlessly align with established industrial pharmaceutical manufacturing procedures.

For the facilitation of microneedle coating, a diverse array of surfactants and thickening agents have found application. These encompass surfactants such as Lutrol F-68 NF, Tween 20, Poloxamer 188, and Quil-A, along with thickening agents like carboxymethylcellulose sodium salt (CMC), methylcellulose, hyaluronic acid, and more [22]. Stabilizers like trehalose, sucrose, glucose, inulin, and dextrans have been incorporated to mitigate potential damage to bioactive drugs during the coating and drying processes [23]. Coating techniques and formulations have demonstrated versatility and adaptability, accommodating a broad spectrum of compounds, ranging from small molecules and macromolecules to vaccines and even DNA.

3.3. Dissolving microneedles

Dissolving microneedles present an innovative approach to drug delivery, offering a unique advantage by completely dissolving in the skin after use, thus eliminating the risk of medical needle waste. Commonly, these microneedles consist of biocompatible and non-reactive water-soluble materials, like a range of polymers and sugars, which are specifically engineered to dissolve when inserted into the skin [24]. The encapsulation of drugs within these microneedles allows for controlled drug release into the skin.

Methods for Fabricating Dissolving Microneedles: Dissolving microneedles have primarily been fabricated through micromolding techniques that involve [25]:

- Solvent Casting:** Micromolds are filled with a solution containing water and the chosen polymer or sugar material. After filling, the solution is allowed to desiccate, occasionally assisted by vacuum and centrifugal power.
- Polymer Melt Solidification:** In this method, a polymer melt is injected into the mold cavities and made to congeal. This approach is also utilized for some rapidly dissolving microneedles.
- In-situ Polymerization:** Liquid monomers are introduced into the mold and then polymerized, often under ultraviolet radiation.
- Drawing Techniques:** A liquid formulation is drawn up to create tapered microneedle structures that solidify in place.

Other innovative methods include ultrasonic welding to form biodegradable polymer microneedles and controlled, stepwise drawing techniques to create multi-needle arrays.

Formulations and Designs for Dissolving Microneedles: Formulating and designing dissolving microneedles involves considerations such as:

- 1. Encapsulation of Heat-Sensitive Compounds:** Heat-sensitive substances, such as proteins and antigens, are enclosed in a manner that preserves their functionality without causing harm [26]. For example, they can be cast into hydrophilic polymers at room temperature or under vacuum conditions.

- 2. Encapsulation Location:** In some cases, drugs are encapsulated solely in the microneedle tips, which can be achieved through the use of multi-layered microneedles, particle-based molding methods, or by incorporating an air pocket at the microneedles base during the manufacturing process.

- 3. Dissolving Time:** The time required for dissolving microneedles to fully dissolve in the skin may vary, and efforts have been made to shorten this duration. Specialized designs like arrowhead microneedles detach from the shaft within seconds and persist within the skin for subsequent dissolution [27].

- 4. Biodegradable Polymeric Microneedles:** These are designed to remain in the skin for more extended periods, sometimes several days, to provide controlled-release delivery over weeks or months.

3.4. Hollow microneedles

Hollow microneedles are a significant advancement in drug delivery, providing a well-defined conduit for delivering liquid formulations into the skin or other tissues. Similar to traditional hypodermic injections, these microneedles enable the controlled flow of liquid drugs, offering versatility in drug delivery methods. Various methods have been employed to create hollow microneedles, which include:

Microelectromechanical Systems (MEMS) Techniques: These methods encompass laser micromachining, silicon deep reactive ion etching, integrated lithographic molding, deep X-ray photolithography, and wet chemical etching in the fabrication of hollow microneedles [28]. These techniques are employed to create precise hollow structures within microneedles.

Polymer, Metal, and Glass: Traditional fabrication methods have been adapted for materials such as glass, polymer, and metal. Conventional drawn glass micropipette methods are employed to craft hollow glass microneedles, whereas hollow metal microneedles are constructed by assembling hypodermic needles [29]. Polymer microneedles are created through drilling and milling processes, and more advanced techniques, such as digital micromirror stereolithography, are utilized to manufacture hollow polymer microneedles.

Indirect Methods: Certain designs require the use of multiple substrates with different properties to serve as sacrificial layers to create the hollow structures. Hollow metal microneedle arrays, for instance, are made through a multi-step process involving backside exposure, electroplating, and etching of the sacrificial layers.

Hollow microneedles, designed for the delivery of liquid substances, have seen the development of diverse actuation methods. These

encompass the common practice of using a syringe in conjunction with hollow microneedles for liquid injection, closely resembling traditional hypodermic needle injections. There are instances where hollow microneedles are equipped with integrated actuators, offering precise control over liquid flow. Various actuation techniques, including CO₂ gas pressure, springs, piezoelectric micropumps, linear servo motors, syringe pumps, and micro-gear pumps, have been implemented to facilitate this process [30]. Hollow microneedles come in two primary designs: single microneedles and arrays of multiple microneedles. Array-based designs are favored for delivering liquid formulations over larger skin areas quickly and with higher bioavailability [31]. But they may pose challenges if one of the microneedles has a leak, affecting the uniformity of fluid flow. Apart from drug delivery, hollow microneedles have been used for fluid extraction from the body, such as interstitial fluid or blood sampling. Hollow microneedles represent a significant innovation in medical and drug delivery technologies, offering precise and versatile methods for delivering drugs and extracting fluids from the body.

4. Role of shape-memory materials and other Shape-memory materials and other advanced advanced materials in microneedle

materials contribute significantly in the development of microneedles, contributing to their effectiveness and versatility in drug delivery and other healthcare applications. Shape-memory materials possess a remarkable property, as they can return to a pre-defined shape or configuration when exposed to specific stimuli, such as changes in temperature or pH. In the field of microneedle development, these materials offer numerous advantages. They enable dynamic deployment, allowing microneedles to transform into a sharp, pointed state for effective skin penetration and then revert to their original shape for safe removal after drug delivery [32]. This dynamic feature significantly diminishes the pain and discomfort associated with microneedle application. Microneedles crafted from shape-memory materials can be designed for self-application, automatically inserting themselves into the skin upon reaching body temperature [33]. This eliminates the need for external pressure or specialized applicators, enhancing user-friendliness. These materials enable adaptive drug delivery, allowing microneedles to alter their shape in response to environmental conditions or physiological factors, thereby releasing medication precisely when and where it is most required, thereby improving the precision and effectiveness of drug administration. The shape-memory materials can be engineered to minimize waste, exemplified by microneedles that fully retract after use, leaving no sharp waste behind [32]. This not only reduces the risk of needlestick injuries but also mitigates the need for disposal.

In the field of microneedle development, an array of advanced materials goes beyond shape-memory materials to elevate their performance and capabilities. An example encompasses biodegradable polymers like polylactic acid (PLA) and polyglycolic acid (PGA), which enable the creation of microneedles that can be safely absorbed by the body post-drug delivery, obviating the need for needle removal and diminishing the risk of infection, especially in prolonged applications [34]. Smart materials, such as pH or temperature-responsive hydrogels, are harnessed to craft adaptable microneedles capable of responding to their environment, initiating drug release, and catering to patient requirements. Some microneedles are constructed from or coated with biological materials like proteins or peptides, serving for targeted drug delivery or the dispensation of biologically active compounds, rendering them apt for specific therapeutic purposes. Metal alloys, including stainless steel or titanium, are employed in manufacturing robust and durable microneedles, making them ideal for repetitive usage scenarios such as continuous glucose monitoring or pain management [33]. The integration of nanomaterials, such as nanoparticles or nanotubes, augments microneedles by enhancing drug loading and controlled release,

leveraging their substantial surface area for drug encapsulation, which proves particularly advantageous for potent medications [35]. Cancer nanotherapeutics has experienced exponential growth in research and development since the early 2000s, with increasing excitement about the potential of nanoparticle technologies to revolutionize oncology drug development. Lessons from first-generation nanomedicines like DOXIL® and Abraxane® have paved the way for targeted and non-targeted nanoparticles like BIND-014 and MM-398. These advancements aim to enhance drug efficacy and tolerability, particularly in the context of personalized medicine's growing importance in cancer therapy [36].

Gold nanoparticles (AuNPs) have emerged as versatile drug delivery vehicles due to their unique physicochemical properties and low toxicity, offering superior performance compared to organic nanocarriers. By leveraging the unique properties of AuNPs, such as their tunable size and facile surface modification, microneedles can be designed to efficiently deliver drugs, vaccines, or other bioactive molecules, potentially improving therapeutic outcomes and patient compliance [37].

4.1. Drug loading and release mechanisms

Drug loading into bioinspired microneedles is a critical step in their development, ensuring efficient and controlled drug delivery. Several methods are employed for loading drugs into these microneedles:

Dip Coating: In dip coating, microneedles are immersed in a drug solution or suspension, allowing the drug to permeate the microneedle structures. After the coating process, the drug-laden microneedles are allowed to dry, leaving a drug layer on the microneedle surface [38]. This method is relatively simple and suitable for certain drugs and coatings.

Lyophilization (Freeze-Drying): Lyophilization is used for heat-sensitive drugs. The drug solution is frozen and then subjected to a freeze-drying process to remove water, leaving drug-loaded microneedles [39]. This method preserves the drug's stability and is especially useful for biologics.

Molding and Casting: Some microneedles are fabricated with drug-loaded polymers or materials. These microneedles are designed to release the drug as they dissolve or erode in the skin [40]. The drug is dispersed within the microneedle material during the casting process.

Coating and Spray Coating: Microneedles can be coated with drug-containing solutions using techniques like spray coating. These methods are precise and can achieve uniform drug loading on the microneedle surfaces [40]. The coating can be further modified for controlled release.

Inkjet Printing: Inkjet printing technology allows for precise drug deposition onto microneedles. It enables the creation of patterns or layers of drugs on microneedle surfaces, ensuring controlled release [41].

Controlled drug release plays a pivotal role in the realm of bioinspired microneedles, ensuring precision and efficiency in drug delivery. Several mechanisms are commonly employed to achieve this control. Some microneedles are meticulously designed to dissolve or erode once inserted into the skin. As these microneedles gradually disintegrate, the drugs they contain are released steadily into the surrounding tissue, and the pace of this dissolution or erosion can be regulated through the choice of materials. In diffusion-controlled release, drugs navigate through the microneedle material and subsequently diffuse into the adjacent skin tissue [26]. The rate of this diffusion hinges on various factors, including drug properties, material porosity, and skin attributes. Alternatively, specific microneedles incorporate drug-laden hydrogels that exhibit swelling and hydration in response to skin fluids. This swelling action compels the drug to release from the microneedles into the surrounding tissue, and the rate of release can be influenced by the hydrogel's distinct properties. Responsive materials, such as temperature-sensitive polymers or pH-responsive hydrogels, are employed to achieve on-demand or

triggered drug release [26]. These materials respond to environmental or physiological changes, ensuring that drug release occurs only when specific conditions are met.

Stimuli-responsive materials, encompassing temperature-sensitive polymers and pH-responsive hydrogels, wield a significant influence on microneedle-based drug release profiles. These materials empower precise control over drug release by reacting to specific triggers [32]. For instance, temperature-responsive materials initiate drug release upon exposure to body heat, ensuring that drug delivery occurs exclusively at the targeted site [33]. Conversely, pH-responsive materials adapt their properties in response to pH variations, making them ideal for applications where pH-dependent drug release is crucial, such as within the gastrointestinal tract. Some microneedles can be tailored to respond to external stimuli, including light or electrical signals, offering a pathway to finely tune and control drug release profiles, thereby ushering in novel possibilities for customized drug delivery strategies [32].

5. Bioinspired microneedle design

Bioinspired microneedle design represents a fascinating concept in the field of microneedle technology. This approach draws inspiration from the natural world, mimicking structures, functions, and designs found in biological organisms to create innovative and efficient microneedles as can be seen in Table 1. In particular, bioinspired microneedles often replicate the microstructures and functional properties of natural organisms as shown in Fig. 5. These microneedles may imitate the painless skin penetration and blood-feeding mechanisms of mosquitoes, resulting in microneedles that can puncture the skin with greater efficiency and less discomfort.

Rear-fanged snakes employ a clever venom delivery system with open grooves on their fangs. This system allows them to inject venom swiftly into their prey's tissue without putting excessive pressure on their Duvernoy's gland during venom delivery [42]. In contrast, front-fanged snakes with hollow-tube fangs must exert high pressure on the venom gland to inject venom into their prey's tissue, resulting in high surface energy requirements.

Drawing inspiration from the mono-grooved fangs of rear-fanged snakes, known for their rapid capillary force-driven delivery mechanism, scientists conceptualized and manufactured a microneedle (BMN) patch. This pioneering platform incorporated numerous exposed grooves on the needle's surface, enabling the transdermal administration of diverse liquid medications and vaccines with the simple application of thumb pressure, eliminating the necessity for intricate pumping systems. A variety of BMN patches with tri-, tetra-, penta-, and hexa-open-grooved designs, inspired by snake-fang architectures, were produced using photolithography [51]. These designs varied in needle height, with hexa-grooved BMNs being the tallest and achieving the maximum penetration depth into mouse skin. The penta-grooved version was chosen for *in vivo* studies due to concerns that the hexa-grooved version's shorter grooves might hinder effective liquid delivery into the skin.

The researchers conducted live experiments to explore the transdermal delivery of liquid drugs using these multi-grooved BMN patches, loaded with a combination of rhodamine and human serum albumin (HSA) [52]. The outcomes revealed that the rhodamine-HSA combination was swiftly introduced into the skin of mice just 15 s after the microneedles were inserted. The snake-fang-inspired BMN patches enabled extended drug release. Examination of the drug's spread into the skin indicated that the fluorescence intensity of rhodamine-HSA remained consistent both before and after patch removal. Following the removal of the BMN patch, the intensity of rhodamine-HSA gradually declined, signifying a sustained diffusion of the conjugated compound into the mouse's skin.

An alternative design of bio-inspired microneedles (BMNs) drew inspiration from the serrated microstructure found on the forelegs of praying mantises. These serrated structures grant praying mantises

Table 1
Different sources of Bioinspiration for formulation of Biomimetic Microneedles.

Source of Bioinspiration	Biomimicked Organ/Tissue	Significant Milestones and Contrasts with Traditional MNs	Refs.
Snake Fang	Fangs	The grooved configuration of the snake fang-inspired biomimetic microneedle (BMN) patches facilitated swift cargo delivery. When a single dose of both influenza virus and ovalbumin antigen was administered via the multi-grooved BMN patches, it elicited strong and effective protective immune responses in mice.	[42]
Mantis Forelegs	Forelegs	The microstructures inspired by the mantis foreleg demonstrated strong adherence to the skin, maintaining their attachment even when subjected to external forces. This feature effectively addressed the shortcomings commonly associated with conventional microneedles, specifically their tendency to dislodge from the skin during movement. Notably, the glucocorticoid-loaded serrated biomimetic microneedles (BMNs) displayed improved effectiveness in treating psoriasis induced by imiquimod in mice.	[43]
Mussels and Octopuses	Mussels— adhesive protein of mussel byssi Octopuses— suction cups	The biomimetic microneedles (BMNs) inspired by mussels and octopuses demonstrated a remarkable load-bearing capacity, supporting objects weighing 60 g, which is over 240 times their own mass. These BMNs adhered to porcine skin even when subjected to lifting, bending, or exposure to water through spraying or immersion. The application of glucocorticoid-loaded suction-cup BMNs played a beneficial role in the healing of cartilage lesions, reducing inflammatory cell infiltration, and mitigating fibrosis in a knee osteoarthritis model.	[44]
Honeybee Stinger	Stinger	The backward-facing barb-inspired biomimetic microneedles (BMNs) exhibited a pull-out force that was 18 times greater than that of barless microneedles (MNs). Furthermore, the maximum pull-out force demonstrated an increase with the greater number of barbs and the augmentation of barb rows.	[45]
Limpets Tooth	Tooth	The composite biomimetic microneedles (BMNs) utilizing a 2.5 % aIO-based material punctured artificial skin without experiencing	[46]

Table 1 (continued)

Source of Bioinspiration	Biomimicked Organ/Tissue	Significant Milestones and Contrasts with Traditional MNs	Refs.
European True Bugs	External scent efferent systems	any buckling, which stood in contrast to the behavior of pure polymer microneedles (MNs) that tended to buckle during insertion. This underscores the BMNs' ability to overcome the mechanical limitations typically associated with conventional MNs. The mouse studies indicated that there were no observable behavioural changes indicative of pain following the application of BMN patches.	[47]
Flower Petal Surface	Petal surface	The drug or vaccine loaded at the base of the biomimetic microneedles (BMNs) was efficiently directed toward the MN tip in a unidirectional manner by the oriented microarrays. This innovative design exhibits significant potential for precise and controlled drug delivery.	[48]
Endoparasites	Swollen proboscis	A surface-enhanced Raman scattering (SERS) biosensor was created in the shape of nanoflower-like biomimetic microneedles (BMNs) for transdermal sensing. Gold (Au) was effectively deposited on the hyaluronic acid (HA)-coated BMNs, endowing them with a substantial surface area that promotes the generation of a pronounced SERS effect. Utilizing a shape-change-mediated mechanically interlocking mechanism, biomimetic microneedles (BMNs) demonstrated a versatile adhesion to soft tissues, forming mechanical interlocks with the tissues while causing minimal damage. This approach enabled the straightforward encapsulation of a model drug, mimicking the behavior observed in endoparasites.	[49]
Mosquito Proboscis	Proboscis	The biomimetic microneedles (BMNs) punctured artificial skin without undergoing buckling. The essential factor for reducing resistance force during needle insertion was the alternating vibratory motion of the two halves. The BMNs demonstrated the ability to collect human whole blood using capillary force, facilitating blood glucose measurement.	[49]

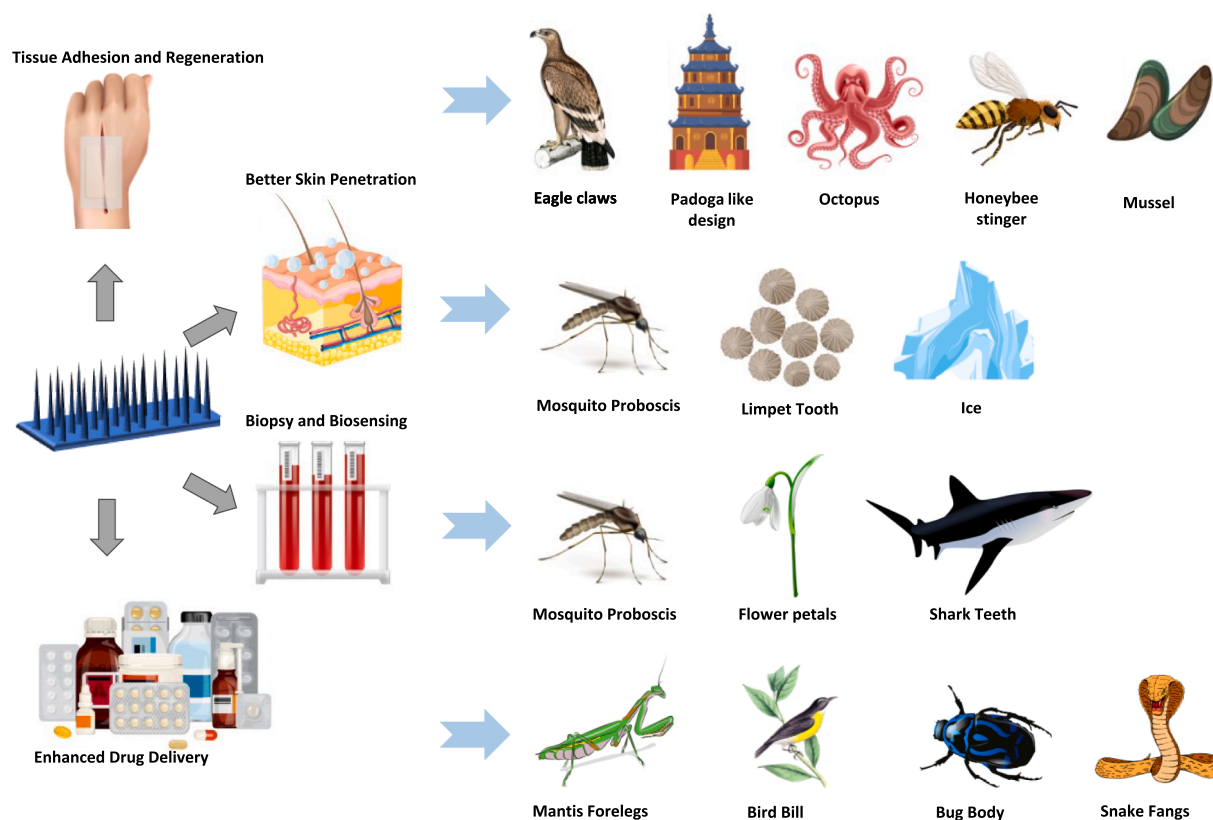


Fig. 5. An illustration depicting different living organisms and the specific biological functions harnessed in the development BMN patches for a wide range of medical uses.

exceptional grasping and holding abilities. Researchers utilized a ferrofluid-based molding technique to create a novel serration-like clamping MN array. This approach facilitated the efficient and cost-effective fabrication of micro hole arrays with varying sizes and angles toward the midline, ensuring strong adhesion of the BMNs to the skin, even under external forces [43]. The improved adhesive features of these notched clamping biomimetic microneedles (BMNs) were validated through their application at various inclinations on the sides of rats. These BMNs securely clung to the skin even as the rodents engaged in constant movements. To evaluate their drug release potential, scientists inserted BMNs coated with a combination of indocyanine green (ICG) and Alexa Fluor 594 into fresh porcine skin. Following BMN removal, distinct fluorescence was evident at the insertion sites, and three hours after application, the depth of ICG penetration had tripled compared to the initial post-insertion depth. In a separate investigation, glucocorticoids were enclosed within the serrated BMNs, resulting in a notable improvement in the delivery and assimilation of glucocorticoids [43]. This accelerated the management of contact dermatitis in mice. This inventive design, inspired by the microstructure of praying mantis forelegs, offers a solution to the challenges encountered with typical microneedles, which often detach from the skin due to external forces or movement.

Drawing inspiration from the endoparasite *Pomphorhynchus laevis*, which securely attaches itself to its host's intestinal wall via its proboscis, scientists pioneered the development of biphasic BMN patches. These patches achieve a mechanical interlock with soft tissues through their expandable microneedle tips, resulting in self-adhering soft tissue BMN patches that cause minimal tissue damage and reduce the risk of infection [50]. These patches enable sustained drug release. The optimization of their adhesive performance involved fine-tuning the swelling capacity of the outer needle layer and the needle's shape, with bullet-shaped expandable BMNs proving superior in terms of adhesion compared to cone-shaped counterparts. Specifically, swellable BMNs

with a 60 % tip height demonstrated the highest adhesion strength. In a different scenario, an in vivo study involving insulin-loaded BMNs showcased a gradual reduction in blood glucose levels, all without any noticeable clinical signs of inflammation or irritation at the insertion site [50].

Conventional methods for loading drugs or vaccines onto microneedle patches, such as spraying or dipping, exhibit low drug loading efficiency. The nature provides valuable inspiration for enhancing drug transport systems. Some insects possess droplet-shaped and open-capillary structures that efficiently transport defensive fluids, protecting them from predators. These insects utilize gland channels and microstructures to passively transport a variety of liquids. Taking inspiration from European true bugs (Heteroptera), scientists engineered pyramid-shaped BMNs adorned with miniature conical microstructures on their lateral surfaces [47]. Employing two-photon polymerization lithography, these BMNs were crafted to replicate the bugs' secretory systems. In experiments involving ex vivo human skin, methylene blue staining and optical coherence tomography validated the successful insertion of six out of nine marks, with incomplete insertion attributed to skin irregularities and elasticity. Importantly, these BMNs could be cleanly removed from the skin. When loaded with a drug or vaccine at the BMNs' base, the oriented microstructures orchestrated the movement of the liquid-containing cargo toward the needle tip as the solvent evaporated. This ingenious architecture facilitated unidirectional transport of drugs or vaccines to the needle tip, providing a novel approach for the development of advanced drug delivery systems through BMN patches.

Nature-inspired designs have paved the way for innovative approaches in creating micropores in the skin and enhancing drug or gel coatings. An example includes cactus-spine-like microneedles that effectively produce microholes in the skin, promoting extended drug delivery. The gecko-foot inspired BMNs have demonstrated their capability to load a high capacity of coated gel [53]. These cutting-edge BMN

designs harness inspiration from the natural world to propel advancements in drug delivery technology.

Effective tissue adhesion stands as a pivotal attribute for endeavours related to prolonged drug delivery or detection. Despite the usefulness of microneedle (MN) patches for painless and noninvasive drug delivery, the conventional MNs' limited adhesion and antimicrobial features have imposed constraints on their clinical applicability. Recent advancements in MN technology have sought to address these limitations. In a recent study, researchers drew inspiration from mussels and octopuses to develop innovative BMN. Mussels employ covalent and noncovalent chemical interactions between an adhesive protein derived from their byssi and the substrate to adhere to surfaces [54–56]. Octopuses, on the other hand, utilize their suction cups and inner dome-like protuberances to securely attach themselves to both wet and dry surfaces. These natural adhesive mechanisms served as inspiration for the BMN design.

The BMNs were created using a polydopamine hydrogel as the foundation for the microneedles, featuring a series of concave chambers around each microneedle that resembled suction cups. Polymyxin, an antimicrobial agent, was integrated into both the hydrogel tips and the polydopamine base to confer antimicrobial properties against common bacteria like *Escherichia coli* [57]. These BMNs could bear the weight of objects as heavy as 60 g, which was more than 240 times their own weight. These BMNs demonstrated strong adhesion to porcine skin, even when subjected to lifting, bending, or immersion in water.

In a significant application, BMNs equipped with suction cups and loaded with glucocorticoids were tested in a knee osteoarthritis model. Compared to the use of unloaded suction cup-bearing MNs, knee joints treated with drug-loaded BMNs exhibited less severe lesions, reduced inflammation, decreased joint swelling, and improved flexibility. Examination of stained tissue sections verified that the MNs with drug-loaded suction cups played a significant role in the recovery of cartilage lesions. They resulted in diminished infiltration of inflammatory cells, reduced fibrosis, and suppressed the formation of cell clusters [6]. This innovative BMN design, inspired by nature's adhesive principles, holds promise for advanced drug delivery and tissue treatment applications.

Wound healing and regenerative medicine are essential in medical science. Proper wound closure, especially around internal organs, is crucial to prevent air and fluid leakage and facilitate effective healing. Researchers have found inspiration in various natural mechanisms to develop innovative hydrogel-based bio-inspired microneedle (BMN) patches [58,59].

One such BMN patch, inspired by endoparasites, consists of a biphasic structure comprising a nonswellable silk fibroin-based core and a swellable MAP-based shell [58]. This structure offers both surface adhesion and needle stiffness, making them suitable for human skin insertion. BMN patches significantly improved wound appearance and healing in external wound closure studies. For internal wound healing, these patches efficiently sealed wounds, arresting hemorrhage and reducing tissue damage. These BMN patches have the potential for transdermal drug delivery, as demonstrated using FITC-dextran. This implies that they have the potential to serve dual purposes in wound healing and drug delivery. The adhesive qualities of BMNs can also be harnessed for tissue immobilization and swift hemostasis [60].

Researchers designed a BMN patch inspired by the eagle's claw to grasp and tighten the skin adjacent to linear wounds, preventing wound dehiscence. This BMN patch promoted wound healing through electrical stimulation, resulting in faster healing times and reduced wound width compared to controls. Histological analysis showed a higher epidermal thickness and increased collagen presence, indicative of enhanced wound healing [61–63].

Taking inspiration from honeybees' stingers, a BMN patch with backward-facing curved barbs was created to enhance tissue adhesion, presenting superior adhesion compared to barbless microneedles [64,65]. This innovation opens opportunities for applications in tissue engineering, transdermal drug delivery, and biosensing.

Researchers mimicked the structural design of shark's teeth for BMNs, incorporating microfluidic channels and photonic crystals. These multifunctional BMNs allowed for biomarker analysis within wound areas, improved biochemical sensitivity, and controlled drug release [66]. Flexible electro-circuits within the BMNs enabled motion sensing, making them valuable for wound site management. In vivo studies showed higher wound recovery rates with these multifunctional BMNs.

Needle biopsy is crucial for obtaining tissue samples for analysis in medical diagnosis. Precision needle biopsy is often challenged by issues like tissue deformation and displacement during insertion, especially when targeting tumors [67]. Researchers found inspiration in the mosquito's proboscis, which efficiently collects blood with minimal resistance and pain, for developing painless bio-inspired microneedles (BMNs) for biopsy sampling. These BMNs mimic the mosquito's proboscis, featuring a robust three-piece structure that can collect blood effectively at high rates using capillary force [68]. When tested, the mosquito-inspired BMNs reduced local tissue deformation and global tissue displacement, making them a promising tool for precision biopsy.

The design of the Bioinspired microneedles intricately mimics the fine patterns of ice crystals, ensuring precise penetration into the skin with minimal discomfort and tissue damage—an ideal feature for medical applications. Taking inspiration from the tiered structures of pagodas, the microneedles gain stability against external forces, contributing to their overall robustness and durability, essential for withstanding the challenges of skin penetration and medical procedures. Drawing on the flexibility of octopus tentacles, the microneedles effortlessly navigate skin contours, promoting a natural interaction that reduces the risk of tissue damage and enhances their adaptability for various skin types and applications. Additionally, by incorporating characteristics reminiscent of bird bills, the microneedles achieve heightened precision and control during skin penetration, adapted for specific functions and promising advancements in targeted medication delivery or sample extraction.

In the field of biosensing, there is a growing need for noninvasive and easy methods to detect interstitial fluid biomarkers that reflect an organism's physiological function. Blood collection methods, such as venous withdrawal and finger pricking, are still commonly used but have limitations. BMN patches have the potential to extract interstitial fluid biomarkers without contacting capillaries or nerve fibers, offering a minimally invasive approach for collecting samples for analysis [69,70]. For example, a nanoflower-inspired BMN sensor was developed for intradermal biosensing. This sensor, based on surface-enhanced Raman spectroscopy (SERS), exhibited high sensitivity and signal uniformity [71]. Gold nano-islands deposited on the petal-like structure of the BMNs created "hot spots" for SERS, making it a promising tool for identifying molecules and detecting biomarkers in interstitial fluid.

6. Materials and fabrication techniques

6.1. 4D Printing

Before delving into the intricacies of 4D printing [72,73], it is crucial to establish a foundational understanding of additive manufacturing techniques to comprehend their operations thoroughly. This knowledge is pivotal for their safe application and for designing and developing bioinspired Microneedles (MNs). To produce the final prototype, various input materials are typically categorized into two main groups: powder-based and liquid-based feeds.

In the powder-based approach, these materials undergo processes such as melting or sintering to achieve the desired compaction and densification for the final output design. This method also ensures that any surplus powder feedstock can be reclaimed and reused in subsequent steps of the process. The journey to creating high-quality output commences with a 3D design model and simulation within specialized software. This model is then translated into two-dimensional prototypes of the original design [74]. Subsequently, an input program is fed into

the printer, allowing it to scan the feed material and transform it into a three-dimensional, printed, and usable product.

Smart materials, when subjected to stimulation in a modelled and simulated design, can evolve over time through the concept of 4D printing. This technology enables a step-by-step alteration of shape or functionality in the printed object by utilizing diverse materials that respond to different stimuli. A range of additive manufacturing techniques are utilized in this process, including Direct-ink-writing (DIW), fused filament fabrication (FFF), stereolithography (SLA), digital light processing (DLP), selective laser sintering (SLS), and inkjet printing [75] as shown in Fig. 6.

6.2. Shape and transition effect

During the processing of these materials, the accumulated strain energy is gradually released, leading to the characteristic functional transition of the material. The way these materials respond after the stimulus that triggered the transition is removed is crucial for observing the transition or functional change, as outlined in Rastogi and Kandabramanian's work from 2019 [76].

When the initiating element, such as a stimulus, is withdrawn, the material reverts to its original form, resulting in what is known as the Shape Change Effect (SCE). In simpler terms, the material adjusts to its adaptable shape while retaining the knowledge of the transformation pathway, preparing for the next stimulus that will initiate the process anew, which is referred to as the Shape Memory Effect (SME) [77]. Moreover, these transitions follow a temporary pattern before the subsequent stimulus triggers a complete transformation cycle, as discussed in Momeni *et al.*'s research in 2017 [3].

6.3. Shape-memory materials

Stimuli-responsive or smart materials (SM) represent a highly valuable group of materials due to their capacity to respond to programmed structures through stimuli like heat, solvents, and other triggers. This remarkable behaviour is commonly referred to as the shape memory effect. When integrated into 3D printing processes, these materials give

rise to the concept of 4D printing, which introduces dynamic design changes over time, prompting extensive research into various potential applications, as discussed in the work by Li and Loh in 2017 [78]. Several classes of materials possess shape memory properties, including Ceramics (SMCRs), Alloys (SMA), Shape Memory Hydrogels (SMH), Polymers (SMPs), and Composites (SMC) [77].

Smart Memory Ceramics (SMCRs): These ceramics offer properties such as high energy generation, efficient energy damping, the ability to withstand high temperatures, and lightweight characteristics. Certain fragile materials can experience a martensitic transformation and break under low strains when exposed to a few cycles of strain. Studies conducted by experts like Christopher A. Schuh from the Massachusetts Institute of Technology and Zehui Du, and C.L. Gan from Nanyang Technological University have revealed that the presence of a fine-scale structure with a limited number of crystal grains can mitigate such brittleness in martensitic ceramics [79]. These oligo-crystalline structures effectively alleviate internal mismatch stresses during mechanical deformation, resulting in shape memory ceramics capable of withstanding numerous super-elastic cycles, as demonstrated by the work of Lai *et al.* in 2013 [79].

Shape Memory Alloys (SMA): Notable among SMAs is Nitinol, composed of Nickel and Titanium. It can return to its original shape or configuration after being plastically deformed during the low-temperature martensitic process. This alloy has been employed in the manufacturing of Microneedles, for instance, using a multiple-pulse laser micro-hole drilling technique, which drills an axial hole into a thin Nitinol wire [80]. Nitinol's outstanding super-elasticity and biocompatibility make it a suitable choice for applications such as extracting small blood samples for glucose monitoring.

Shape Memory Hydrogels (SMH): These materials exhibit rapid shape memory and temperature response capabilities. The transformation of SMH can be controlled by adjusting the recovery temperature, allowing for shape changes in stages. Importantly, these hydrogels remain stable in water without significant swelling, making them highly promising for advancements in biomedical technology. Various types of SMH have been developed, including temperature-responsive hydrogels and those utilizing hydrogen bonding for their formation, as well as

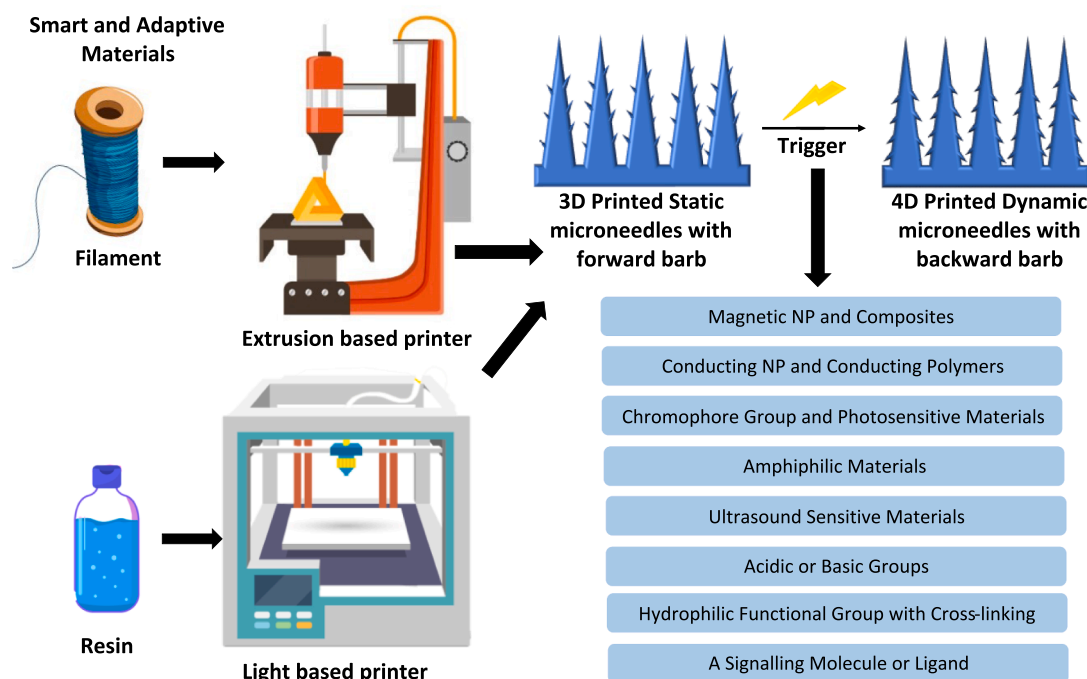


Fig. 6. Depiction of general concept of 4D printing along with simulative materials.

other innovative approaches [81].

Smart Memory Polymers (SMPs): SMPs belong to the class of dual-shape materials, commonly known as “actively responsive polymers.” They exhibit the remarkable capability to intentionally shift from one configuration to another. This transformation initiates with a temporary shape achieved through mechanical alteration, which is subsequently retained. Subsequently, the application of heat or light serves as the stimulus for the SMPs, influencing the transformation of shape from transitional to a final, permanent shape. This fascinating behavior has been explored in depth in works such as Behl and Lendlein’s research from 2007 [82].

Bioresponsive polymers, exemplified by poly(disulfide)s with dynamic and reversible disulfide bonds, are highly sought-after for their degradability and responsiveness to stimuli like reductants, light, heat, and mechanical force, making them ideal for on-demand drug delivery [83].

6.4. Nature and mechanism of the stimulus

Various stimuli can impact bioinspired 4D Microneedles (MNs), including thermal, magnetic fields, current and voltage, light, hydro, and pH stimuli, as outlined in Rastogi and Kandasubramanian’s research from 2019 [77]. The mechanisms behind these stimuli are described below and shown in the Fig. 7:

1. Thermal Stimulus: stressed structures through the exchange of thermal energy. This process governs crosslinking, which can take on a physical nature in thermoplastics and a chemical one in thermosets. It also orchestrates transition points that stabilize and restore a material’s shape. Entropy plays a crucial role in the regulation of Shape Memory Materials (SMM), predominantly observed in materials like Shape Memory Polymers (SMPs) and Shape Memory Ceramics (SMCs). The

transition temperature, influenced by the interplay between rigid and soft domains, acts as the pivotal factor for shape-shifting in polymers and composites [84].

2. pH Stimulus: The pH-responsive stimulus mechanism is linked to the swelling process in polymers or hydrogels driven by the diffusion of water, which can be modulated by pH levels. Materials display either shrinking or swelling behaviours in acidic or basic environments, depending on their specific sensitivity.

3. Magnetic Field Stimulus: The reaction to a magnetic field stimulus is achieved by incorporating magnetic particles into a matrix. These particles can respond to magnetic fields and serve as magnetothermal sources, instigating transformations when influenced by a magnetic field stimulus. When the material contains oriented polarized particles responsive to a magnetic field, the material’s structure can be manipulated magnetically. Magneto-thermal sources can indirectly induce heating to facilitate these transformations [85].

4. Current and Voltage Stimulus: The current stimulus mechanism consists of two intermediate stages. In the initial stage, Joule’s heating generates anisotropic temperature changes. The second stage involves a substantial temperature increase, which leads to heat distribution and subsequent bending. This overall process underlies the response to a current stimulus, as detailed in the research conducted by Rastogi and Kandasubramanian in 2019 [78].

5. Light Stimulus: Light stimulus mechanisms operate by establishing or breaking crosslinks between particles when exposed to specific types of light, such as UV illumination or NIR. The choice of light source depends on the presence of photo-thermally activated or photo-activated particles within the Shape Memory materials (SMM). In the case of UV-induced transformations, physical and chemical crosslinks are formed to temporarily stabilize the shape, while subsequent exposure to UV light leads to the relaxation of the material and the breaking

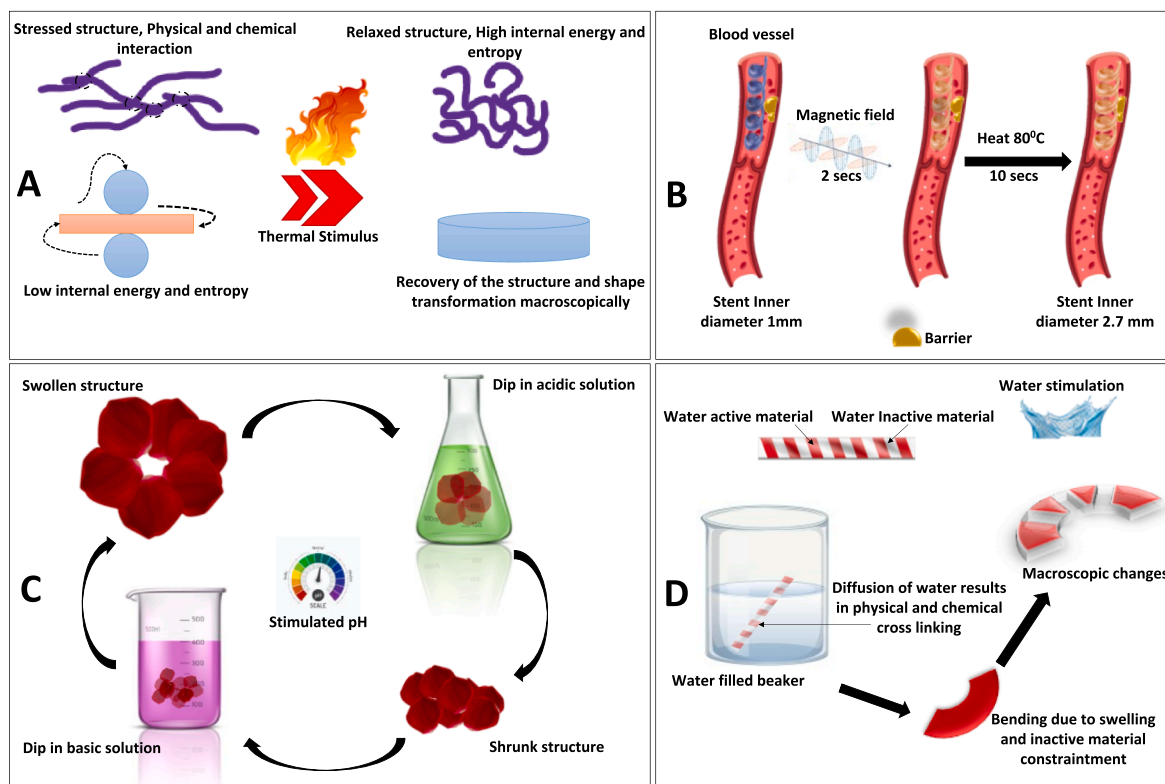


Fig. 7. Mechanism of Stimuli responsive Bioinspired 4-D microneedles. A) Illustrates the process of thermal stimulation wherein the low energy stressed structure is relaxed through application of thermal heat. B) The blood vessel stent, when activated within a magnetic field, restores blood flow by expanding, thereby overcoming barriers that restrict the flow in the blood vessel. C) Illustrate how materials respond to pH stimuli, contracting in acidic solutions and expanding in basic environments, and thereby leveraging their sensitivity for shape actuation. D) Depiction of the process of water stimulus, wherein swelling and drying occur through the diffusion of water, leading to a plasticizing effect in molecular chains and resulting in a macroscopic transformation.

of these crosslinks, facilitated by the energy supplied to form new bonds.

6. Hydro Stimulus: The water stimulus mechanism triggers macroscopic transformations by causing the swelling and drying of water molecules. This process exerts a plasticizing effect on the molecular chains within the material, ultimately leading to the observed changes in its properties.

7. pH Stimulus: The pH stimulus mechanism involves a swelling process in polymers or hydrogels initiated by the diffusion of water. Whether these materials will shrink or swell in response to pH stimulus depends on their sensitivity, as discussed in the research conducted by Z. Wang *et al.* in 2015 [86].

8. Photothermal Stimulus: The photothermal effect occurs when photothermal materials absorb light energy and convert it into heat, raising the temperature of materials. This effect is utilized in photothermal therapy to target and abate cancer cells. Near-infrared (NIR) light, particularly in the second region of NIR, is commonly used due to its noninvasive nature and deep tissue penetration. For instance, scaffolds coated with polydopamine (PDA) demonstrate a significant photothermal effect under NIR illumination, reaching temperatures conducive for therapeutic effects. Other applications include the control of release in multiunit implants and the development of shape-morphing constructs for tissue engineering, where materials responsive to NIR irradiation enable dynamic changes in shape and function [87].

7. Modeling and simulation in 4D printing

Modeling is a modern method that enables the development of practical applications within a simulated setting. In 4D printing, modeling is particularly valuable as it aids in refining design parameters and reducing complexity. It offers cost and resource savings by enabling the transformation of shapes and eliminating redundancy during product modeling. Two primary strategies are employed: the inverse strategy, which is utilized to address most issues when the intended application is known in advance, and the forward strategy, which is applied when the actual application is unclear. A range of software tools is utilized for creating models in 4D printing, including Finite Element Modeling (FEM) [88], ANSYS, COMSOL Multi-physics [89], Solid Works, Computer-Aided Design (CAD), ABAQUS [90], and more [91]. The integration of additive manufacturing (AM) has streamlined the fabrication of smart materials (SMs), playing a pivotal role in the evolution of 4D printing. This has expanded the design space around AM. To facilitate the modeling and simulation of SMs, especially in conceptual design, a voxel-based modeling and simulation platform for SMs has been developed. The VoxSmart tool, a computational design tool, plays a crucial role in this strategy. It integrates Grasshopper (GH) into Rhinoceros (RH) for system development. RH, a CAD-specific simulation program, facilitates the rapid and efficient creation of complex structures. In contrast, GH is a script-free graphical algorithm editor that facilitates the creation and calculation of a wide range of shapes within the RH framework [92]. The VoxSmart plugin, coded in the C programming language, encompasses six primary categories: Material Edition, Voxel Edition, Stimulus Definition, Boundary Conditions Definition, Simulation, and Distribution Computation. It streamlines the process of defining and simulating material distributions on a voxel basis, making it easier to model heterogeneous objects with material distributions, including both SMs and traditional materials. Various AM techniques, whether personalized or commercially available, can handle multi-material printing, with the Poly-Jet process being capable of managing voxel-based material distribution. Computer-Aided Design (CAD): CAD software is essential for building object models with the correct size and dimensions. The CAD file is then saved and uploaded to a 3D printer for processing. The 3D printer interprets the CAD file's instructions and manufactures the object accordingly [92]. Various AM technologies, such as Continuous Liquid Interface Production (CLIP), are used for 3D printing based on CAD models [93]. Researchers have even modeled light intensity distributions with technologies like Digital Light

Processing (DLP) to ensure that the light intensity closely follows the target CAD file during printing. This approach allows direct manufacturing of parts from CAD models without the need for specific tooling or fixtures.

8. Materials commonly used in the fabrication of bioinspired 4D transdermal

Bioinspired 4D microneedles are an exciting area of research that draws inspiration from nature to create innovative materials and structures. The utilization of smart materials is crucial in the fabrication of these microneedles, as these materials can undergo substantial property changes when exposed to environmental triggers. Smart materials have diverse applications in sensing, actuation, energy transfer, and structural components within bioinspired systems. When developing bioinspired materials, scientists draw inspiration from the natural world. For example, they seek to replicate the effects observed in specific biological structures that exhibit super-hydrophilicity and super-hydrophobicity. The process typically involves:

1. Choosing a feature from a biological structure as a source of inspiration.
2. Analysing the transformation between the macroscopic structure and multi-scale properties of the natural material.
3. Designing and synthesizing appropriate molecules to replicate these properties.
4. Constructing an overall design that achieves the desired feature.

While the concept of creating bioinspired hybrid materials is straightforward in theory, it can be challenging to execute in practice. Natural materials consist of organic and inorganic components that are perfectly arranged at both the micro and nanoscales. Various techniques, such as lithography, self-assembly, and chemical vapor deposition, have been developed to construct advanced materials that mimic the structure and function of natural organisms.

Bioinspired hybrid materials, drawing inspiration from natural wonders like nacre and bone with their remarkable composite structures, have given rise to synthetic materials known for their exceptional strength and durability as can be seen in Table 2. Natural adhesion mechanisms, including the petal effect and gecko feet, have spurred the development of synthetic adhesives boasting high adhesion properties [43]. The lotus effect, preventing water adhesion, has led to super-hydrophobic materials. These biomimetic materials aim to emulate nature's designs for diverse engineering applications, employing strategies like ice templating and layer-by-layer assembly, along with the replication of gecko-like adhesion and super hydrophobicity. Smart materials responsive to environmental changes and multifunctional materials manipulable by electrical stimuli are being pursued, with an eye on sustainability through biopolymer and recycled material usage.

9. Manufacturing of bioinspired materials

Producing bioinspired materials frequently entails complex procedures, with prominent illustrations such as Mussel Adhesive Protein (MAP) and Silk Fibroin (SF). The fabrication of MAP and SF-based hydrogels is as below [94]:

Purification: The initial step entails the removal of endotoxins, lipopolysaccharides, and impurities in an *E. coli* expression system, following established purification protocols.

Dialysis: Following purification, the protein solution is subjected to dialysis using distilled water (DW), and subsequently lyophilized to eliminate surplus water.

Protein Concentration Assessment (Bradford Assay): The protein concentration is determined using the Bradford assay (Bio-Rad) with a protein standard such as bovine serum albumin (BSA).

Preparation of Water-Soluble SF Protein: SF fibers are treated to

Table 2
Different types of Bioinspired hybrid material used in healthcare applications.

Bioinspired hybrid materials	Type of Bioinspiration	Description
Structural material	Bioinspired Composite Material (e.g., synthetic nacre)	A composite material that mimics the layered structure and high strength of natural nacre (mother of pearl)
	Biomimetic Hydrogel	A hydrogel that imitates the water-absorbing properties of natural tissues, such as cartilage or the intervertebral disc.
	Synthetic Bone Scaffold	A scaffold material designed to replicate the structure and mechanical properties of natural bone tissue for regenerative medicine applications.
	Artificial Coral Reef Material	Materials used to create artificial coral reefs, resembling the structure and texture of natural coral, providing a habitat for marine life.
Adhesive Material	Bioinspired Adhesive Material	Adhesives inspired by the adhesive properties of creatures like geckos, mussels, or barnacles.
	Geckel (Gecko-Inspired Adhesive)	An adhesive material that mimics the adhesive properties of gecko feet, using synthetic microstructures and van der Waals forces to stick to various surfaces.
	Mussel-Inspired Adhesive	Adhesives inspired by the adhesive proteins found in mussels, which create strong and durable underwater adhesion through a combination of proteins and metal ions.
	Barnacle Adhesive Mimic	Synthetic adhesives that replicate the adhesive properties of barnacles, allowing for effective adhesion to a variety of substrates in wet environments.
	Burdock-Burr-Inspired Adhesive	Adhesives inspired by the burrs of burdock plants, which use hooks and loops to attach to other surfaces, serving as the basis for Velcro-like materials.
Super-Hydrophobic Material	Spider Silk-Inspired Adhesive	Adhesives that replicate the stickiness of spider silk through the use of synthetic fibres and structures, often used in medical and industrial applications.
	Lotus-Leaf-Inspired Coatings	Coatings that mimic the surface properties of lotus leaves, which have micro- and nanostructures that repel water and prevent adhesion of contaminants.
	Butterfly Wing-Inspired Surfaces	Surfaces designed with microscopic structures similar to those found on butterfly wings, which create air pockets that reduce contact with water droplets.
	Shark Skin-Inspired Coatings	Coatings that replicate the texture of shark skin, with tiny scales that reduce water resistance, making them useful for applications like ship hulls and swimsuits.
	Cactus-Inspired Super-Hydrophobic Surfaces	Surfaces inspired by the texture of cactus spines, which trap air and prevent water from wetting the surface, suitable for self-cleaning materials.
	Salvinia Leaf-Inspired Materials	Materials inspired by the <i>Salvinia molesta</i> aquatic plant, which has super-hydrophobic properties to trap a layer of air underwater, reducing friction and enhancing buoyancy.

disrupt intermolecular hydrogen bonds. Degumming involves subjecting silkworm cocoon (Uljin Silk) to a process that includes sodium oleate and sodium carbonate liquefaction in DW at 100 °C for 40 min. It is then washed with DW.

Dehydration and Reconstitution: Following the air-drying of degummed SF fibers at room temperature (RT), they are reconstituted by immersing them in a solution containing calcium chloride, distilled water (DW), and ethanol (with a molar ratio of 1:8:2). This reconstitution process involves heating at 100 °C for a period of 20 h.

Filtration and Dialysis: The SF solution is filtered using a Mira Cloth (Calbiochem) and then dialyzed with DW before lyophilization.

Molecular Weight Distribution Analysis: The determination of molecular weight distribution involves the utilization of 12 % (wt/vol) SDS-PAGE, an acronym for sodium dodecyl sulfate–polyacrylamide gel electrophoresis.

Protein Concentration Determination: Protein concentration is quantified using the Bradford assay, with BSA serving as a protein standard.

Structure Examination: Fourier-transform infrared spectroscopy (FT-IR) is employed to study the structures of both regenerated and degummed SFs. Spectra are collected between 4000 cm⁻¹ to 400 cm⁻¹.

Manufacturing intelligent objects often relies on the properties of printed smart materials. Stimulus-sensitive shape-changing features can be utilized to reduce storage and transportation space. The primary focus of 4D printing has predominantly revolved around the development of 3D-printed materials and structures capable of shape transformation. This transformation is typically initiated during or after the printing process, involving the utilization of smart materials (SMs) or the manipulation of strain within the printed object. Eigenstates played a significant role in the realm of smart material research, particularly in the creation of structures capable of undergoing shape changes.

9.1. Diversity in bio-microneedle shapes

Bio-microneedles exhibit a fascinating range of shapes, drawing inspiration from the diverse functions and evolutionary adaptations seen in various organisms depicted in Table 3. These natural adaptations serve purposes such as predation, protection, and reproduction. Certain organisms have micro-structured barbs or specialized body parts that resemble bio-microneedles, such as the mosquito fascicle, the North American porcupine spine, and the stinger of worker honeybees [95].

In contrast to barbless microneedles, bioinspired microneedles feature micro-structured barbs that facilitate easy skin insertion but challenging removal. Bioinspired microneedles exhibit a threefold increase in the extraction-penetration force ratio compared to barbless counterparts. The application of stress at the barbs during retraction plays a vital role in diminishing the insertion force of bioinspired microneedles by mechanically interlocking them within the tissue. This mechanism serves to reduce friction while simultaneously boosting adhesion strength. These discoveries offer exciting prospects for the advancement of novel barbed microneedles with micro-sized tips, making them well-suited for various tasks, including tissue adhesion, bio-signal recording, transdermal drug delivery, and a diverse array of applications.

9.2. Manufacturing bioinspired dynamic 4D microneedles

The fabrication of bioinspired 4D microneedles can be influenced by the structure of the microneedles and the mechanisms they are inspired by. Two essential methods for manufacturing these special microneedles are described below:

9.2.1. Magnetorheological Drawing lithography (MRDL)

Replica moulding has been successful in replicating bioinspired needles on a centimetre scale. But developing sophisticated and intricate bio-MNs at a micrometre level has proven to be extremely challenging.

Table 3
Diversity in the shape of Bioinspired Microneedles.

Bio-microstructure	Length Range	Diameter Range	Penetration Force Range	Average Penetration Force	Pull-out Force
Cluster of Mosquitoes (<i>Aedes aegypti</i>)	0.15–0.25 cm.	0.0030 cm	0.006–0.0038 N	0.0018 cm	NA
Caterpillar Spines (<i>Parasa consocia</i>)	0.05–0.07 cm.	0.003–0.005 cm	0.008–0.0265 N	0.0173 cm	NA
North American Porcupine Quill	Few inches	0.126 cm	–	4.3 cm	44.8 cm
Worker Honeybee Stinger	0.18 cm.	0.009 cm	–	57.5 cm	11.35 cm

Scientists have proposed designs for bioinspired needles resembling honeybee stingers, which can be created using 3D printing. These honeybee-inspired needles have shown a 21–35 % reduction in insertion force during PVC gel insertion tests and a 46 % decrease in insertion force during bovine liver tissue insertion tests [96]. To address the challenge of manufacturing such microneedles, a novel Magnetorheological Drawing Lithography (MRDL) method has been introduced, enabling the efficient production of moulding-free MN arrays and bioinspired MNs.

The MRDL method is less complex and less expensive than some alternative techniques. It can create exceptionally detailed microstructures that are challenging to attain using lithography technology or conventional subtractive manufacturing. Finite Element Analysis (FEA) is employed to evaluate the penetration-retraction mechanism using the cohesive zone model. A Light-Emitting Diode (LED)-based P μ SL 3D printer has been developed for manufacturing micro-scale MNs [97]. This printer utilizes optical engineering principles, incorporating projection optics and illumination optics.

9.2.2. Microstereolithography (P μ SL) method

Within the Microstereolithography (P μ SL) approach, the primary characteristics of the microneedles are commonly configured with a diameter of 400 μ m, a length of 4 mm, and a cone angle of 10°. Three-angle barbs are crafted, featuring a base width of 200 μ m and a length of 450 μ m, positioned around the microneedle. Computational design software is employed to generate a 3D representation of the microneedle array. Cross-sectional photos are generated from this digital model, which are then transferred to a Digital Micromirror Device (DMD) device. The DMD device provides patterned light with a 405 nm wavelength and projects it onto the surface of a photo-curable precursor solution [98]. The solution solidifies under the projection light, and the Layer-by-Layer (LbL) process is repeated to create a 3D MN array. The P μ SL method can be used to produce MNs with microscale resolution when necessary.

For the production of these microneedles, scientists have utilized photocurable polymers like PEGDA 250 as the monomer, phenyl bis (2, 4, 6-trimethyl benzoyl) phosphine oxide as the photoinitiator (PI), and Sudan I, all of which are biocompatible materials [99]. To improve tissue adhesion after insertion, it's essential for the barbs on the microneedles to face the opposite direction of the microneedle tip, adding complexity to the 3D printing process due to this specific geometry. Researchers have devised a 4D printing technique to flexibly transform horizontally printed barbs into a backward-facing configuration, thereby enhancing tissue adhesion. This method involves projecting light onto the precursor solution surface, triggering photopolymerization and establishing a gradient of cross-link density within the microneedle array. After the microneedle array dries, the lower section of the barb's contracts, causing the barbs to bend downwards, and their shape is fixed through flood UV exposure. Comparison between Magnetorheological Drawing Lithography (MRDL) and Microstereolithography (P μ SL) is illustrated in Table 4.

10. Applications in drug delivery

Microneedling has demonstrated significant clinical improvements in scars, cellulite, and wrinkles with minimal side effects and a speedy recovery. This is achieved by simulating the wound healing process and

Table 4
Comparison of Magnetorheological Drawing Lithography (MRDL) and Microstereolithography (P μ SL) for Fabricating Bioinspired 4D Microneedles.

Aspect	Magnetorheological Drawing Lithography (MRDL)	Microstereolithography (P μ SL) Method
Advantages	<ol style="list-style-type: none"> Efficient Production: Enables moulding-free microneedle (MN) arrays and bioinspired MNs. Exceptional Detailing: Creates exceptionally detailed microstructures, challenging to achieve with conventional methods. Cost-effectiveness: Less complex and less expensive compared to some alternative techniques, making it a cost-effective option. 	<ol style="list-style-type: none"> High Resolution: Offers high-resolution printing capabilities, allowing for microneedles with microscale precision when necessary. Customizable Design: Computational design software enables the generation of customized 3D representations, providing flexibility in design. Biocompatibility: Utilization of biocompatible materials ensures fabricated microneedles are suitable for biomedical applications.
Limitations	<ol style="list-style-type: none"> Limited Materials Compatibility: May have limited compatibility with certain materials, restricting the range of materials for bioinspired microneedle fabrication. Equipment Requirements: Requires specialized equipment like LED-based PμSL 3D printers, which may not be readily available or affordable for all facilities. Process Complexity: Involves multiple steps and requires expertise in finite element analysis and optical engineering, which may pose challenges for inexperienced users. 	<ol style="list-style-type: none"> Complexity in Geometric Design: Achieving specific geometric features, such as barbs positioned opposite to the microneedle tip, adds complexity to the printing process. Equipment Dependency: Relies on specialized equipment like Digital Micromirror Devices (DMD), which may not be universally accessible or affordable. Process Optimization Challenges: Optimizing the 4D printing technique for desired mechanical properties may require extensive experimentation and refinement.

controlled wounding of the skin, which boosts collagen production [100]. Ongoing clinical trials, as highlighted by Bhatnagar et al. in 2017, are exploring the safety and efficacy of microneedling-based systems [101].

In the past decade, extensive research has been conducted on microneedling, encompassing therapeutic effectiveness, treatment protocols, histological assessments, and targeted therapies. Recent developments in the field have introduced bioinspired 4D microneedles, bringing new dimensions to clinical applications. Bioinspired microneedles are currently under investigation for various clinical purposes such as the Dodecyl-modified chitosan (DCS) material has been used to create a Pagoda-like multilayer microneedle (MN) patch, as described in a study by Zhang, Chen, Cai, et al. in 2021 [102]. This MN patch was subjected to in-vivo experiments using a rabbit model. In these experiments, the rabbit model experienced acute tissue injuries that included bleeding in vital organs such as the liver, spleen, and kidney. The primary clinical objectives of this MN patch were to achieve tissue fixation and fast hemostasis. Tissue fixation involves securing and stabilizing the damaged tissue, which is critical in the management of traumatic injuries. Fast hemostasis, on the other hand, pertains to the rapid cessation of bleeding, a crucial aspect of wound care to prevent excessive blood

loss and promote healing. The Pagoda-like multilayer MN patch developed from Dodecyl-modified chitosan demonstrates its potential for addressing these clinical needs by offering a minimally invasive approach for tissue fixation and swift hemostasis.

In a study conducted by Linh et al. in 2021, a novel microneedle system was developed with a unique structure and application [103]. The microneedles were created using poly lactic-co-glycolic acid (PLGA) as the base material, with an interlayer coated with poly dopamine (PD). These microneedles further featured a distinctive Nano-flower structure. The innovation in this design was the incorporation of Crystallized Hydroxyapatite (HA), a process referred to as bio-mineralization. These microneedles were evaluated using a skin phantom model, which represents an artificial model of human skin. The significance of this microneedle system lies in its intradermal sensing applications. It was shown to have the capability to sense chemical biomarkers present in the interstitial fluids of the skin. This technology has the potential to revolutionize the field of intradermal sensing, offering a non-invasive method to detect and monitor chemical markers in the skin. Such applications could be invaluable in various medical and diagnostic contexts, potentially contributing to early disease detection and personalized healthcare.

In Linh et al.'s study in 2021, a microneedle system was developed using Poly ethylene glycol di-acrylate (PEGDA) as the base material. Nano-silver (NS) was utilized for coating, and the microneedles were further encapsulated in a gelatin/sucrose film. What sets this approach apart is the green synthesis process used to create the Nano-silver (NS). This green synthesis process involved the presence of a silk fibroin template, which facilitated the crystallization of ionic state silver. The microneedle system was then subjected to in-vitro experiments using a bacterial suspension to assess its performance. The microneedles demonstrated good mechanical strength, making them suitable for skin penetration. They also exhibited antibacterial activity against both Gram-positive and Gram-negative bacteria, which is essential for managing microbial skin infections. This microneedle system is designed with a minimally invasive strategy, potentially minimizing discomfort and skin damage during use. One of the notable applications of this technology is its potential to address a broad spectrum of bacterial infections. It can be employed in the management of polymicrobial skin infections, offering a promising solution for clinical use, particularly in cases where antibacterial interventions are required.

Zhang, Chen, Sun, et al. in 2021 [104], conducted a study wherein a microneedle system was developed using liquid metal (LM) and featured a claw-like clamping structure. This innovative design was tested on wounded SD rats to evaluate its effectiveness in wound healing. The claw-like clamping structure allows for secure attachment to the skin. The microneedles are designed to assist in wound closure and healing.

In a recent research study conducted by Zhang et al. in 2020, a microneedle (MN) system was developed with a base made of poly-dopamine hydrogel and poly-dopamine [105]. These microneedles were loaded with Polymyxin, an antibiotic. The design of these microneedles was inspired by the antibacterial strategy of *Paenibacillus* polymyxin and the adhesive mechanisms of mussel byssi and octopus tentacles. This resulted in a hierarchical microneedle structure with multifunctional adhesive and antibacterial capabilities. These microneedles were tested on an osteoarthritis rat model and demonstrated several key features. They were well-fitted on the skin and exhibited strong adhesion in dry, moist, and wet environments. They had the ability to self-repair after being split into two parts, making them highly durable. These microneedles also demonstrated resistance against common bacteria during usage and storage.

In a study by Han et al. in 2020, a microneedle (MN) system was developed using a photo-curable polymer. The design of these microneedles incorporated features inspired by the micro-hooks of parasites, barbed honeybee stingers, and porcupine quills, resulting in a unique backward-facing curved MN structure [106]. These microneedles were tested on the skin and demonstrated impressive results, showing 18

times stronger tissue adhesion compared to barbless MN. This enhanced tissue adhesion is a significant advantage, making them suitable for various applications. The technology offers improved tissue adhesion, which can be particularly beneficial for applications like drug delivery, where stable and reliable attachment to the skin is essential. These microneedles are robust and provide a more stable performance, making them a valuable tool for drug delivery, bio-fluid collection, and bio-sensing.

Liu et al. in 2020 and co-researchers developed a microneedle system using Propylene glycol methyl ether acetate. The design of these microneedles was inspired by the spiny-headed parasitic worm, resulting in a barbed microneedle (MN) structure [107]. These barbed microneedles were tested on porcine small intestine tissue and showcased a novel passive anchoring mechanism. This mechanism allows the microneedles to attach securely to the tissue with minimal actuation and power requirements. The unique feature of these microneedles makes them suitable for use in minimally invasive gastrointestinal (GI) resident devices. Their passive anchoring capability enhances their stability within the GI tract, which is especially important for applications requiring precise positioning and reduced interference. This innovation has the potential to advance the field of minimally invasive medical procedures, particularly within the realm of GI interventions. Jeon et al. conducted a study in 2019, in which they developed a microneedle (MN) patch with a hydrogel-forming double-layered adhesive structure. This MN patch consisted of two layers: a swellable outer shell based on mussel adhesive protein (MAP) and a non-swellable inner core made of silk fibroin (SF). The design of these microneedles was inspired by endoparasites that swell their proboscis, resulting in a swellable MN patch. This innovative patch was then tested in an in vivo experiment using a wet and dynamic external and internal tissue model. The primary applications of this technology include vascular and gastrointestinal wound healing. The swellable MN patch can effectively adhere to wet and dynamic tissue surfaces, making it suitable for wound closure and healing in these regions. It has the potential for transdermal drug delivery, particularly for pro-regenerative or anti-inflammatory agents targeting specific tissues.

Recent advancements in multi-material three-dimensional printing have revolutionized the production of shape-memory polymer (SMP)-based functional structures through four-dimensional (4D) printing. In a study by Ali et al., 2023, a novel design approach for 4D printing multimaterial composites, focusing on controlling the shape memory properties of smart polymers was designed. By utilizing bilayer laminates comprising SMP and flexible elastomers with adjustable thickness ratios, the self-bending behavior of the composite can be tailored. Finite element (FE) simulations are employed to comprehend the composite material processes and predict experimental outcomes accurately, reducing both costs and development time. The practical application of this approach is demonstrated through the creation of a soft robotic gripper capable of delicately manipulating fragile objects [108].

Zolfagharian et al. also conducted research on the recent proliferation of soft robots and actuators, leveraging three-dimensional (3D) bioprinting. They explored the use of stimuli-responsive polymers in these dynamic structures, enabling soft manipulations in delicate environments, with applications in biomedical and food sectors. The study focused on integrating topology optimization (TO) with 3D bioprinting to enhance the performance of soft actuators with electrolytic stimulation. The research demonstrated the effectiveness of multimaterial 3D bioprinting optimization in improving the rate of actuation and bending in soft actuators [109].

Hyperthermia and photothermal therapy are effective methods for inducing cell death in cancer treatments, typically achieved at tissue temperatures between 42 °C and 46 °C for 10 min. Hyperthermia, a form of thermal ablation, utilizes temperatures higher than the body's temperature to target and kill cancer cells. This can be induced through various stimuli, including light, magnetic fields, ultrasound, and electrical currents, with photothermal therapy specifically employing light-

induced hyperthermia. Notably, near-infrared (NIR) light, particularly in the NIR-I and NIR-II ranges, is preferred for its deep tissue penetration capabilities. In this context, 3D printing plays a crucial role in both producing personalized structures for hyperthermia procedures and fabricating implanted scaffolds capable of generating heat. These scaffolds, often composed of light-sensitive and magnetic-sensitive composites, can effectively kill cancer cells while supporting tissue regeneration. Additionally, advancements in 4D printing have further enhanced these structures, offering dynamic functions triggered by specific stimuli, thus expanding their potential applications in hyperthermia and photothermal therapies [87].

Patient compliance is a crucial aspect of healthcare, particularly in the context of medical device usage like microneedles. Microneedles offer a promising approach for drug delivery due to their ability to painlessly penetrate the skin's outer layers, potentially improving patient adherence to treatment regimens. Several studies have explored patient perceptions and experiences with microneedle use, some of which is listed in Table 5.

11. Challenge and future prospects

One of the prominent challenges in the field of microneedles (MNs) is the presence of contradictory results in various studies, which makes it difficult to establish conclusive findings. Some current research findings remain insufficient to resolve certain critical issues. Even among recent studies, there are discrepancies in results. Various studies have reported differing observations regarding factors influencing needle insertion force. For instance, skin moisture levels can significantly impact needle penetration force, with higher skin hydration reducing insertion force [119], whereas another researcher found that dry skin requires less force for needle penetration than well-moisturized skin. In another context, Jiang et al., 2014 revealed that the angle at which a needle approaches the skin's surface affects insertion force, with a shallower angle requiring less force than a steeper one [120]. Reed et al. (2012) discovered that needle diameter plays a role in insertion force, with

smaller-diameter needles demanding less force for penetration compared to larger-diameter ones [121]. Beyond these challenges, the fabrication of microneedles encounters several intricacies within the field of additive manufacturing. These intricacies encompass issues like void formation, anisotropic behaviours, machine design constraints, and the characteristic layer-by-layer structure of printed microneedles. The environmental concerns are emerging in the context of microneedle production. This has prompted the quest for printing methods that are sustainable and offer the ability to heal and recycle materials, thereby minimizing waste. These microneedles face a significant hurdle related to their drug-loading capacity. The physical attributes and mechanical properties of these microneedles can impose limitations on their effectiveness in carrying and delivering therapeutic substances. There is also a concern pertaining to the potential toxicity of the residual polymer matrix and material degradation. Overcoming the challenge of long-term drug delivery with microneedles is a critical endeavour, as it requires ensuring that microneedles maintain secure attachment to soft tissues. This aspect is complicated by the fact that conventional microneedle fabrication methods often yield needles with a smooth and uncomplicated side profile, resulting in suboptimal tissue adhesion. Effectively addressing these multifaceted issues is paramount to unlocking the full potential of microneedle technology in the field of medicine.

A hypothesis proposed by a group of researchers envisions a future where interconnected microneedles (MNs) draw inspiration from insect models, forming networks of leading channels. In this envisioned scenario, MN arrays could be effortlessly loaded with essential drugs and vaccines, streamlining storage and minimizing formulation waste. This vision appears increasingly feasible, as evidenced by the development of diverse MNs inspired by various insects and animal species. The emergence of bioinspired 4D MNs on an industrial scale suggests their impending integration into clinical settings. Self-assembly and self-folding techniques are emerging as promising avenues for fabricating intricate 3D and 4D structures. By capitalizing on the inherent properties of materials and precise manipulation of environmental conditions,

Table 5
Overview of Studies on Microneedle as a drug delivery system: Perspectives, Usability, and Patient Compliance.

References	Objective	Method	Results	Conclusion
[110]	Investigate perceptions of microneedle technology for vaccine and therapeutic delivery among public and healthcare professionals	Focus group discussions and questionnaire analysis	Identified benefits (reduced pain, tissue damage) and concerns (delayed onset, potential misuse)	Positive perception of microneedle technology, advocating continued translational research
[111]	Assess usability and acceptability of self-administered microneedle patches for influenza vaccination	Quantitative questionnaires	Increased intent to vaccinate (44 % to 65 %), preference for self-vaccination, no serious adverse events reported	Feasibility and potential to enhance vaccination rates with microneedle patches
[112]	Evaluate acceptability of administering influenza vaccine through microneedle patches compared to hypodermic needle injection	Randomized trial with 100 healthy adults	Positive experience reported by 98.6 % of participants receiving MNP vaccination, preference for MNP over injections or nasal spray	Well-accepted MNP delivery for influenza vaccine, indicating potential for future vaccination campaigns
[113]	Assess feasibility of microneedle patch application in human participants	Placebo patches with dissolving microneedles administered to 15 individuals	No pain or swelling reported, easily administered by hand, strong preference over conventional needle injections	High acceptance and preference for microneedle patches, supporting clinical translation
[114]	Explore perspectives on microneedle technology among healthcare professionals, lay public, and HIV patients	Mixed methods study with questionnaires and focus groups	Strong support for MN technology, positive attitudes towards MN for HIV treatment, concerns raised advocate for continued translational research	Positive perspectives on microneedle technology, highlighting potential for HIV treatment but advocating for further research
[115]	Investigate fluid mechanics and pain associated with microneedle injection into skin	Human subjects' study	Minimal to no pain reported with microneedle injection, weak dependence on infusion parameters	Microneedles offer simple, low-pain method for skin infusion
[116]	Provide overview of human studies with microneedles	Review of human studies	Positive results in various medical applications, including vaccine therapy and drug delivery	Validation of microneedle performance and safety in human subjects
[117]	Validate painless intradermal delivery via microneedle array for insulin administration	Study in diabetic rats	Minimal pain reported with intradermal insulin infusion, reduced plasma glucose with intradermal and subcutaneous infusion	Microneedle patch offers controllable, minimally painful insulin delivery
[118]	Evaluate microneedle performance and safety in human subjects	Review of human studies	Validation of preclinical findings, positive responses from patients and providers	Microneedles offer new approach to human medical applications, supported by patient and provider preferences

these methods enable the creation of dynamic constructs without the need for external manipulation. Self-assembly entails the spontaneous organization of materials into ordered structures, driven by molecular interactions and surface chemistry, while self-folding involves inducing shape changes in materials through programmed stress patterns or stimuli-responsive elements. Both methodologies are integral to 4D printing applications, as they yield structures capable of adapting and responding to environmental cues.

The field still harbours significant potential for further development, focusing on reducing the insertion force of MNs and enhancing precision in penetration depth. Researchers anticipate the evolution of this platform for more flexible and dynamic applications in drug delivery, bio-fluid collection, and bio-sensing. The promising future of 4D printing extends to various domains, encompassing biomedical and surgical procedures, as well as advancements in education. For individuals seeking non-surgical treatments or dealing with milder medical conditions, bioinspired MNs offer a clinically relevant alternative. When combined with neuromodulators, MNs have the potential to enhance clinical outcomes and increase patient satisfaction. Moreover, investigations into the effects of the chemical environment can provide valuable insights into controlling the chemistry of smart materials, paving the way for widespread use in scientific applications.

Biofabrication methodologies, such as bioprinting and cell-laden hydrogel printing, have made significant strides, facilitating the integration of living cells and biomolecules into both 3D- and 4D-printed structures. This capability holds utmost importance in fields like tissue engineering and regenerative medicine, where the interaction between fabricated materials and living cells is pivotal for successful outcomes. The advancements in biofabrication techniques have resulted in the development of increasingly biomimetic and functional tissue constructs, thereby enhancing their compatibility within the biological environment and fostering the healing process.

At the same time, it is essential to focus on investigating intelligent material architectures, transformation processes, and 3D printing techniques to improve dimensional reliability, load-carrying capacity, and production efficiency within 4D printing concepts. The successful implementation of the 4D printing platform in the future hinges on the development of a ferromagnetic 4D printing platform based on research findings. The platform's samples will be rigorously tested, and their performance will be compared with traditional 4D printing platform fabrication methods. The potential for cloud-based 4D printing monitoring and control is an exciting avenue to explore, along with the encapsulation of additional software and 4D printing models to enable more simulations. The integration of embedded sensors and actuators within 4D-printed constructs provides the capability for real-time monitoring and control of their responses to diverse stimuli, thereby facilitating the development of intelligent structures. Progress in fabrication methods enables the smooth incorporation of these components into printed constructs, thereby augmenting their overall functionality. For example, within tissue-engineered constructs, embedded sensors can continuously monitor cellular activities.

In a research study by Zolfagharian et al., 2020, advances the field of four-dimensional (4D) printing by introducing control-based techniques to develop adaptive 4D-printed systems with versatile applications in medicine, wearable electronics, agriculture, and microfluidics. By synergistically integrating 3D-printed sensors and machine learning-based controllers into 4D printing, these systems can dynamically adapt to environmental stimuli, mimicking nature's organic responses [122].

The utilization of machine learning and AI-driven design has become increasingly integral in refining and advancing fabrication processes, notably in the realm of 4D printing. These cutting-edge technologies possess the capability to forecast the behavior of materials and structures produced through 4D printing, aiding in the meticulous selection of materials, geometries, and fabrication parameters to attain desired functionalities. By integrating AI and machine learning into the design workflow, researchers can explore extensive design spaces, pinpoint

optimal solutions, and accurately predict material properties and performance outcomes. Consequently, this integration results in heightened efficiency and effectiveness in fabrication processes and the production of enhanced 4D-printed constructs. With ongoing advancements in AI and machine learning, their amalgamation with fabrication techniques is poised to elevate the capabilities of 4D printing technology, facilitating the creation of progressively intricate, functional, and adaptable materials and structures across diverse applications and industries. In a study by Zolfagharian et al. in 2022, polyelectrolyte hydrogels, characterized by highly polar polymer chains forming hydrophilic networks, are explored for their potential in three-dimensional (3D)-printed biomedical applications. Leveraging advancements in materials science and 3D printing, the study investigates the application of polyelectrolytes in 4D printing and soft robotics, aiming to harness their shape-changing properties in response to external stimuli for manufacturing specialized functional materials [123].

The future of printing is being influenced by innovative printing technologies, inventive structural designs, integration of intelligent materials and modeling tools/software continue to advance, 4D printing is poised to find applications in numerous fields. The future holds great promise, especially with the anticipated progress in micro/nano-manufacturing technology and comprehensive investigations into the mechanical aspects related to bioinspired MNs. This anticipates a plethora of exciting innovations in medical, healthcare, and biological applications.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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