Bioinspired 4D Transdermal Microneedles for the Advanced Drug Delivery: Current Status and Future Prospects

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

Department of Pharmacy
Brac University
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Declaration

It is hereby declared that

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2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
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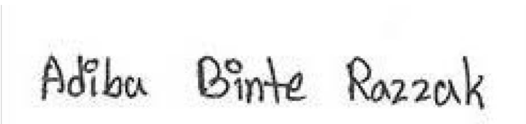

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Approval

The thesis titled "Bioinspired 4D Transdermal Microneedles for the Advanced Drug Delivery: Current Status And Future Prospects" submitted by Adiba Binte Razzak (17346047) of Spring, 2017 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons) on July, 2021.

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Ethics Statement

This project does not involve in any human or animal trial.

Abstract

Due to the invasive nature, the hypodermic needles cause pain and damage to the tissues. So, microneedles (MN) are a good alternative to hypodermic needles because of it's non-invasive, negligible pain and easy-to-administer nature. But, sometimes MN is associated with certain drawbacks such as the risk of being broken or bent and, the fragments can cause complications, low adhesiveness, less biocompatible. To overcome the limitations of previous MNs, microscopic structures with high tissue adhesion of living entities in nature give the inspiration to fabricate bioinspired MNs. For developing this type of complex shape-altering MNs, 4D printing technology and, smart materials are very important. 4D printed objects are programmed to change shapes along with time. These objects are made up of smart and responsive materials which evolve its shape, property, and functionality with time when it is exposed to the predetermined stimulus. So this review aims to study the alteration of different smart and bioinspired materials along with different stimuli, the use of 4D printing technology in the fabrication process of bioinspired MNs.

Keywords: Microneedle; Bioinspired; Smart materials; 4D printing; Shape alteration; Stimulus.

Dedication

Dedicated to my parents.

Acknowledgments

This is a collaborative research project under the joint supervision of Dr. Md Jasim Uddin, Associate Professor, and Easin Uddin Syed, Lecturer in the Department of Pharmacy, Brac University.

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List of Acronyms

MN	Microneedle
SLA	Stereolithography
SC	Stratum Corneum
LbL	Layer-by-Layer
TDs	Transdermal delivery systems
SCE	Shape Change Effect
SME	Shape Memory Effect
SM	Smart Material
SMC	Shape Memory Composite
SMCrs	Shape Memory Ceramics
SMA	Shape Memory Alloy
SMH	Shape Memory Hydrogel
SMP	Shape Memory Polymer
FEM	Finite Element Modeling
CAD	Computer Aided Design
AM	Additive Manufacturing
MAP	Mussel Adhesive Protein
SF	Silk Fibroin

MRDL	Magneto Rheological Drawing Lithography
SLS	Selective laser sintering
DLP	Digital Light Processing
FDM	Fused Deposition Modelling
RH	Rhinoceros
GH	Grasshopper
PVC	Polyvinyl Chloride
DCS	Dodecyl-modified Chitosan
PGLA	Poly Lactic co-Glycolic Acid
PD	Poly Dopamine
HA	Hydroxyapatite
PEGDA	Poly Ethylene Glycol Di-Acrylate
NS	Nano-Silver
LM	Liquid Metal

Chapter 1

Introduction

Microneedles (MNs) are micro-scale needle-like projections that are used for drug delivery and other applications as well. It has its distinctive miniature size which is less than 1 mm tall and is arranged in arrays that contain surface area ranging from a few square millimeters to several square centimeters (Plamadeala et al., 2020). MNs can be classified into four distinct groups based on their overall geometry and drug delivery mechanism such as- solid, coated, dissolving, and hollow MNs (Y. C. Kim et al., 2012). MNs would have some advantages over hypodermic needles due to their micro-scale size. Advantages include minimum pain, negligible invasiveness, and ease of operation. Besides, it has some chances of mechanical failures, which should be avoided in clinical applications (Ma & Wu, 2017).

Stereolithography (SLA) is the first prototyping technology which is known as 3D printing. It is first invented by Charles Hull in the early 20th century. The formal term of 3D printing is Additive manufacturing (AM) and the main technique of this technology is to print MNs by adding material layer by layer under computer control. In 2013, Professor Skylar Tibbits first coined the term '4D printing' at a conference held in MIT. He started the 4D printing concept by demonstrating how a fixed object can be transformed over time. Three dimensions are constituted length, width, and height and 3D printers build objects layer by layer along with those dimensions. On the other hand, the fourth dimension is time and 4D-printed objects are programmed to change shapes along with time. The materials of 4D-printed objects are smart materials, also called responsive materials which evolve its shape, property, and functionality with time when it is exposed to predetermined stimulus such as heat, water, light, pH. In several aspects, 4D printing technology has advantages over 3D printing technology. Furthermore, the exceptional properties such as high recoverable strains, low weight, tailor able properties, fast processing, and multiple activation methods, smart materials have gotten a lot of attention from the material research community. From synthesis to application, academic and industrial researchers have proposed, experimented, analyzed, and reported on various aspects of these materials (Melly et al., 2020). Another kind of smart materials are bioinspired materials, these are synthetic materials that are developed by imitating the natural or living matter in shape, characteristics, or features. These materials are sometimes recognized as intelligent materials, which give a reaction to environmental stimulation such as humidity, temperature, pressure, pH, and charged particles. These types of materials have been used in detectors, sensors, soft robots, pharmaceutical products, and artificial muscles. Smart device fabrication using three-dimensional (3D) printing techniques allow for complex designs and well-controlled fabrication processes. Thus, 3D printing of smart materials that can be greatly transformed over time is referred to as 4D printing (Falahati et al., 2020).

Moreover, the field of MN design has benefited greatly from biomimetic research. A lot of research is being done to figure out how various barbs or proboscis get inserted into the skin. MN design and development incorporated this expertise to develop a more advanced type of MNs. Furthermore, getting inspiration from the barbs, proboscis, stings of different biological species, bioinspired MNs can be fabricated. For developing this type of MNs, 4D printing technology plays an important role. Bioinspired MNs are capable of penetrating the outermost epidermal layers with greater accuracy without damaging nerve endings or penetrating deeper into the skin's blood vessels owing to their short dimensions, shallow penetration depths (Römgens et al., 2014), and varying its shapes according to the different alteration in the stimulus. Consequently, MNs are non-invasive and do not cause pain or bleeding (Gill et al., 2008). There are differences in size, resistance force against tissue between the bioinspired MN and the hypodermic needle. In addition, the drug delivery time and efficacy of the bioinspired MN can be managed more easily by altering various stimuli than other drug delivery systems.

Therefore, bioinspired MNs can be more effective than other traditional drug delivery systems for their distinctive small size and low inserting resistance force.

The purpose of this review article is to explore the bioinspired materials and microscopic needle-like structures that can be used to manufacture 4D MNs. Furthermore, the review gives an overview of 4D printing, smart materials, fabrication process, and clinical use along with its challenges.

1.1 History of 4D bioinspired microneedles

In the year 2012, W. K. Cho et al. along with his colleagues report that the North American porcupine quill microstructure also facilitates easy penetration of the tissue — even easier than a hypodermal needle of the same diameter. The author found that the barbs produced localized stress levels during insertion utilizing a combination of finite element modeling and experimentation on real porcupine quills, which allowed the quill to penetrate pig skin and chicken muscle mass with an extremely small force, reduced incidence, and damage compared to barbless control. The results have been repeated with synthetic polyurethane quills created through replication and manufactured also with hypodermic quill-mimetic needles. Cho et al. has also identified a different porcupine quill zone by suggesting a complex tissue adhesion mechanism, which contributed to easy penetration or resistance to removal. These new design concepts can now inspire transdermal products, which can penetrate the skin with even less force than conventional needles require, which is a key concern for products, such as MN arrays. Additionally, MN patches can remain in place credit goes to the clever combination of porcupine quills, which can easily penetrate and adhere strongly (Cho et al., 2012; Collier, 2013).

Moreover, the North American porcupine quill shows a distinctive geometrical structure that aids two different functions. Barbs on quills facilitate a secure insertion and strong adhesion to the tissue during the removal of the backward-facing barbs (Cho et al., 2012).

Then in 2013, a group of researchers had manufactured bioinspired swellable MN adhesives. They got inspiration from endoparasite *Pomphorhynchus laevis*. This parasite swells proboscis to adhere to the intestinal wall of the host. By imitating this mechanism they had developed MN array that has two phases. Mechanically, this MN interlocks with tissue via swellable tips and thus, it has increased in adhesion strength. The swellable tip is comprised of a poly (styrene)-block-poly-(acrylic acid) and, the non-swellable core is made up of polystyrene. These conical-shaped MNs have high adhesion strength and can penetrate tissue with the least insertion force and depth. Exceptionally, this bioinspired design containing MN provides complete soft tissue adhesion with minimal damage, less painful removal, low risk of infection, and optimum delivery of drugs (S. Y. Yang et al., 2013).

Another interesting example is Honeybee stingers which can easily penetrate the skin of animals with micro barbs to insert venom for self-protection. Based on this, in 2018, Zhipeng Chen and his group demonstrated a novel 3D-additive manufacturing method entitled magnetorheological drawing lithography (MRDL), to make bioinspired MNs that imitate stingers of honeybee very efficiently (Z. Chen, Lin, et al., 2018; Z. Chen, Ren, et al., 2018).

The parent MN was directly produced vertically with the help of an external magnetic field and tiled MNs were then made on the four sides of the parent MN. Hence, the micro-structured barbed MNs enable easy insertion of the skin and difficult removal compared with barbless MN. The bioinspired MN's extraction-penetration strength ratio was three times the barbless MN. The stress levels at the barbs help to decrease the force of insertion by reducing the frictional force while increasing the adhesive force via intersecting those barbs in tissue during removal. These findings can inspire the supplementary design of the barbed micro-tip base MN for tissue adherence, transdermal drug delivery, and so on (Wu et al., 2014; Chen, Lin, et al., 2018).

Inspired by the tissue-adherent microscopic features of parasite micro-hooks of parasites, barbed stingers of bees, and scaled quills of porcupines, in the year 2020, Rutgers researchers design a MN that, when inserted, is interlocked by tissues and enhanced their adhesion. They combined a micro 3D printing method with the 4D printing technique in order to create a micro-adhesive backward-facing barbed MN. The researchers have shown that tissue adhesion with their MN is 18 times stronger than with a barbless MN, using chicken muscle tissue as a model. According to their study, their developed MN is more stable and can be used in robust drug delivery (Han et al., 2020; Liu et al., 2020).

The group of researchers applied micro-3D pressing technology to create an efficient long-term needle system for drug delivery. Everyone knows the conventional hypodermic needle, and some patients may be feared by those needles. In just a few seconds, the hypodermic needle delivers a whole dose of medicines. But if someone had to provide the medication for a longer amount of time, it is frightening to think of having constant hypodermic needles, and this has led to the development of 'microneedles.' However, there is a problem, sometimes these MNs don't adhere properly, although they are pain-free. They tend to fall off and have to be applied again to the patient. If the medicines are critical, this may not be efficient and also harmful. By considering these problems, 4D printed MN array was produced by researchers from Rutgers and the University of Pisa utilizing advanced microprinting technology (Han et al., 2020). Specifically, with the assistance of Boston Micro Fabrication, the researchers have used the PμSL method. This method allows small-scale 3D printing with resolutions of 0.002mm (*Boston Micro Fabrication - Micro-Precision 3D Printers - PμSL Technology : BMF Boston Micro Fabrication*, n.d.).

The researchers have directed their attention to nature to understand how the best can be done, as there are numerous natural examples. The researchers found that natural barbed needles provide 70x more adhesion, and this is precisely what was needed. They created a needle system with barbed rows, as seen in Figure 1. Researchers have developed ways to apply different levels of barb curvature by changing the 3D printing post-processing processes. It might firmly curl the barbs inward, give less adhesion or almost completely stick out, ensuring maximum adherence (Han et al., 2020).

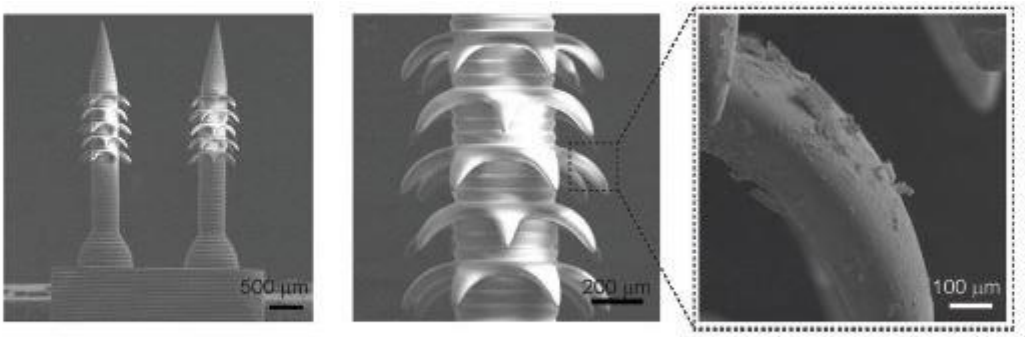


Figure 1: SEM images of 4D printed microneedle. (SEM= scanning electron microscope) (Han et al., 2020).

1.2 Considerations of transdermal drug delivery through skin

Human skin has a total area of the surface of 1.5 to 2.0 m^2. The skin provides a promising route for drug delivery because of this, as well as the fact that it is the most accessible organ (Desai et al., 2010). Additional advantages include the convenience of use, improved patient acceptance, continuous and regulated drug delivery, the ability to administer drugs both locally (dermal) and systemically (transdermal), the avoidance of adverse systemic effects, and the avoidance of GI tract problems and hepatic first-pass metabolism (Brown et al., 2006; Javadzadeh & Azharshekoufeh Bahari, 2017). Furthermore, skin drug delivery is not easy: despite being only around 15µm thick, the stratum corneum (SC) serves as an obstacle of the skin for drug penetration. The epidermis (50–100 µm thickness) and dermis (300–3000 µm thickness) of healthy human skin are divided by the basement membrane (Figure 2). The SC is made up of keratin-rich cells embedded in lipid bilayers and a 10–15 µm thick matrix containing the outer layer (Bouwstra et al., 2003). 25% cholesterol and 50% ceramides and other free fatty acids make up the lipid matrix. Nerve receptors, a large vascular network, and lymphatic vessels are all found in the dermis. This layer also contains sebaceous glands, hair follicles, and sweat glands. The hypodermis, often known as the subcutaneous layer, is a fibrous connective tissue layer that lies under the dermis (Kanikkannan et al., 2012).

Three sequential steps are followed to reach the desired therapeutic response of the dosage formulations in the transdermal drug delivery system-

1. In the first step the drug is released from the dosage form.
2. Then the drug is penetrated through the skin barrier SC
3. In the final step the desired therapeutic outcome is produced

Moreover, therapeutic agents can pass through the epidermis and into the systemic circulation through the embedded capillaries in the dermis in transdermal delivery systems (TDs) (Bouwstra et al., 2003; Javadzadeh & Azharshekoufeh Bahari, 2017; Uchechi et al., 2014).

1.2.1 Drug Penetration routes

Drugs can also be penetrated through the intercellular lipid path, the transcellular route, and appendage routes including hair follicles and sweat glands. The structure of the skin is illustrated in Figure 2 (Javadzadeh & Azharshekoufeh Bahari, 2017).

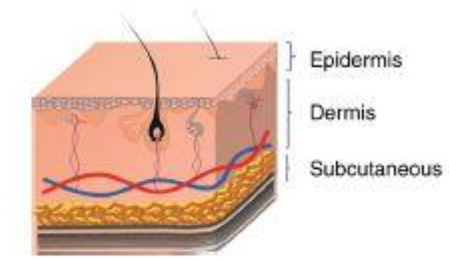


Figure 2: Schematic drawing of the structure of the skin (Javadzadeh & Azharshekoufeh Bahari, 2017).

1.2.1.1 Transcellular Route

This route is through the corneocyte. Since the corneocyte cell membrane (cornified envelope) is extremely impermeable, the transcellular route is assumed to be of little importance;

however, this fact is still debatable (Brown et al., 2006; Javadzadeh & Azharshekoufeh Bahari, 2017).

1.2.1.2 Intercellular Lipid Route

The keratinocytes occupy the intercellular spaces of this route and pass through the lipid matrix. Fluid lipids play an important role in the transepidermal diffusion of amphiphilic and lipidic molecules in order to achieve insertion and migration via intercellular lipid in this area. Polar molecules may use the free space between a lamella and a corneocyte outer membrane.

1.2.1.3 Skin Appendages

Transdermal drug delivery can be obtained through skin appendages, such as sweat or sebaceous glands as well as hair follicles. Previous research indicated that this path could be overlooked because of the negligible contribution of the skin surface. Recent studies, on the other hand, have shown that this route is a viable option (Hadgraft & Guy, 2002; Lademann et al., 2008). Additionally, nanoparticles have been described to be effective to serve as either potent drug carriers via the follicle or blockers on the follicles to prevent substances from penetrating in topical applications. As a result, the diffusional pathways, and the trans-appendageal route tends to be a very useful pathway in skin permeation (Neubert, 2011; Uchechi et al., 2014).

Drug accumulation in the skin prior to release into blood vessels allows a normal mechanism for continuous drug delivery during transdermal permeation. Even with its many benefits, transdermal drug delivery is restricted to a small number of molecules with specific physicochemical properties. For transdermal delivery, molecules should have a weight of less than 500 Da and a log P of 2–3. Transdermal permeation is hindered by the stratum corneum. As a result, several technologies have been developed to disrupt the stratum corneum and increase skin permeability. Sonophoresis, electroporation, magnetophoresis, lasermicroporation and, iontophoresis are some of these methods. These approaches have a lot of limitations in terms of suitability and cost. To overcome the issues associated with transdermal delivery, traditional drug delivery methods such as intradermal injections are now being used. Intradermal injections, on the other hand, have drawbacks such as needle infections, phobia, and the need for specialized personnel, both of which raise the cost of delivery. The drawbacks of the conventional medication types are resolved by MN drug delivery. The technology has been tested to deliver a variety of macromolecules, and micro/nanoparticles in addition to small molecules (Nagarkar et al., 2020).

1.3 Additive manufacturing process

The additive manufacturing process (AM) or 3D printing enables the production of structures that do not have complex geometry using conventional processes. 3D printing has advanced over the last years towards the fabrication of functional components that are available in a number of applications. 3D printing generally produces pieces with limited functionality, which limits their end-use (Lemu, 2019). 4D printing can also be done with 'regular' materials, along with smart materials (SM). Due to the specified stresses caused by the chemical reactions and adhesive diffusion among the printable layers during the printing process, these materials might transform their structure over time. Intelligent materials require changes in the environment such as moisture and heat, which can adversely affect several applications (Nagarkar et al., 2020; Ryan et al., 2021). Up to now, the majority of reports on the implementation of SLA, FDM, and DIW technologies are focused on 4D printing. Multi-material printing, embedded printing, and the filler-materials alignment employing magnetic fields and particulates have been carried out in the recent advancement of AM technologies (Kuang et al., 2019). In combination with adaptable materials, 4D printing could be realized as a suitable alternative for the manufacturing processes of the next generation. However, with the continuous progress made in both AM technology and the material these notions could soon be realized in the near future, several studies emphasized the focus on evidence of concepts and possible future applications (Ryan et al., 2021).

1.3.1 Categories of Additive Manufacturing

There are over 50 different additive manufacturing technologies. The American Society for Testing and Materials (ISO/ASTM 52900:2015) has categorized the technology. Generally, there are seven categories of AM technology process - binder jetting, sheet lamination, powder bed fusion, vat photo-polymerization, energy deposition, material jetting, and material extrusion (Kuang et al., 2019).

1. Binder jetting: In this technique, a binding agent is selectively deposited onto powdered material in a liquid state. The binding agent and building materials are deposited in varying layers through the head of the printer and the powder spreader helps to develop the product. The materials are fused without the use of heat in this process. The materials used in this process include metal, polymers, and ceramics. (Leary, 2019) .

2. Sheet lamination: Selective Deposition Lamination, Ultrasonic Additive Manufacturing, and Laminated Object Manufacturing can be grouped under the sheet lamination technology. In these technologies, sheets of material are stacked and laminated to build 3D products. This is done by using either ultrasonic welding or adhesives. After the development of the object, unwanted areas of the whole part are removed layer by layer. (Leary, 2019; Salmi, 2021).

3. Powder bed fusion: Powder bed fusion is one of the first industrial AM technologies. In this process, powdered materials are melted and then, combined to form a solid structure using an electron beam or laser. Powder bed fusion processes also include selective laser sintering (SLS), which requires partial melting of the particles (Beitz et al., 2019).

4. Vat photo-polymerization: This method employs a process known as Photopolymerization, it involves selectively exposing radiation curable resins or photopolymers to UV (ultraviolet) light in order to produce 3D structures. When these materials are exposed to air, chemical reactions cause them to solidify. Stereolithography (SLA), Digital Light Processing (DLP), and Continuous Digital Light Processing are the three main forms of this classification (Aznarte Garcia et al., 2018; Wilts et al., 2019).

5. Energy deposition: This technology uses controlled thermal energy for melting and combining materials to produce 3D structures. This process is similar to welding processes, nevertheless, they are more precisely detailed. Laser or electron beams are typically used to control thermal energy (dos Santos Paes et al., 2021).

6. Material jetting: In this AM technique, the droplets of the materials are selectively deposited layer by layer to produce the 3D product which is very similar to conventional inkjet printers. Then, UV light cures a layer until it is completed. Two popular types of material jetting printers are drop-on-demand and nanoparticle jetting (Srivastava et al., 2019).

7. Material extrusion: Material extrusion technology had developed in the 1980s under the name Fused Deposition Modelling (FDM). A heated nozzle produces a continuous thermoplastic filament and deposits the filament layer by layer on the platform to develop the product in this AM technique (Oskolkov et al., 2021).

1.3.2 Advantages

The most significant advantage of 4D printing is that items larger than printers can be printed in a single piece due to computational folding. Objects that are too large to fit into a printer can be compressed for 3D printing into their secondary form because 4D printed objects can shrink, change shape and, unfold. The use of possible applied materials is another benefit of

4D printing technology. 4D printing is currently recognized by researchers worldwide in changing materials (Ryan et al., 2021; Johnson & Procopio, 2019).

So far, multi-material shape polymer experiments have been performed. Materials can remember their form and transform configurations actively over time in response to environmental stimuli. This shape memory polymer is very important for the health industry and looks like customized forms. For example, we can make release medicine devices that change shape (Kokkinis et al., 2015; Kuang et al., 2019).

1.3.3 Limitations

During the current stage of the development of additive technology in the manufacturing of functional parts such as mechanic behavior, finishing of surfaces, geometric precision, and production rate barriers, some central limitations are studied and documented based on previous research. Micro-needle size and shape determine the capacity for penetration, drug loading, and release rate, but substantial improvement with existing methods is needed to manage geometric features. Due to technical limits in manufacturing technologies, design constraints such as limited available aspect ratios are often implemented. In addition, expensive equipment and complex processes required to result in long lead times (around months) and a high barrier to MN penetration (Lemu, 2019; Johnson & Procopio, 2019)

1.4 Concept of bioinspired microneedles

Researchers have been looking for an ideal method for manufacturing MNs with complete adhesion and minimum damage to the tissue. For this, they have received inspiration from living organisms, which have modified throughout evolution. Endoparastic worms referred to as spiny head worms use tissue penetration probes. Species like *Pomphorhynchus laevis* secure a strong anchorage to the fish intestinal wall by extending a bulb through a retractor at the bottom of the proboscis after penetration. A group of researchers has been trying to design

MNs that have two phases with optimal properties for needle attachment and maximum adhesion with tissue. For producing this kind of MN, they had used the adaptable morphology of the worm proboscis.

They demonstrated a technologically advanced MN with a swelling tip that facilitates the interconnection of the mechanical tissue (Figure 3). This prototype reduces the pressure required to penetrate tissue because smooth conic needles in a dry state can be placed into the tissue without incorporating barb features linked to other proposed MN-based adhesive platforms. In contact with the water content of the tissue, the cross-sectional area of the needle tip swells and provides a significant pull-out force that leads to localized deformation of the tissues and subsequent interlocking. The bioinspired MN adhesive showed high adhesion levels to wet tissues like skin and intestines irrespective of the surface texture differences. In the course of multiple movement cycles, the strong fixation can also be made in dynamic tissues. The soft tips MN (i.e. reduced modulus) enable removal without substantially affecting the tissues, due to an increase in pulling forces by swelling within the tissue. In addition, the swelling of modules prevents the breakage of the swollen MNs, contrary to rigid MNs that may break during removal from the tissue. Moreover, the achievement of significant soft tissue adhesive levels presents significant challenges, particularly when tissues are moist (S. Y. Yang et al., 2013).

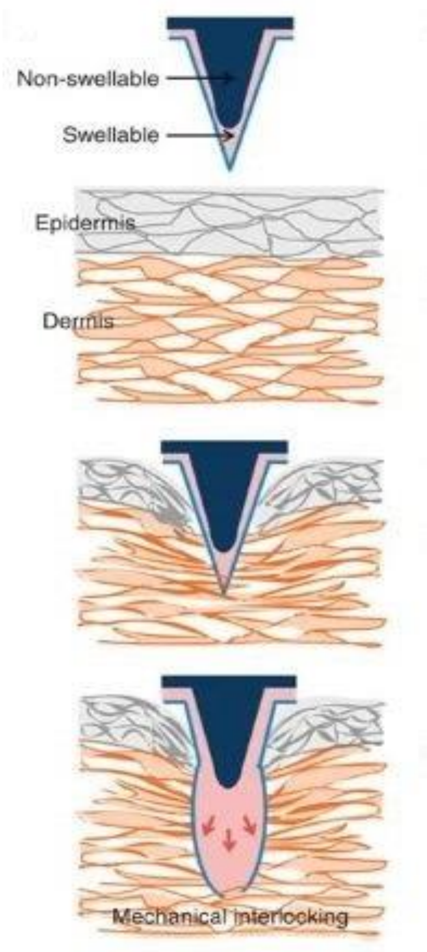


Figure 3: Illustration showing mechanical interlocking of a water-responsive shape-changeable microneedle following penetration into a tissue(S. Y. Yang et al., 2013).

Ideally, an appropriate approach to overcome the limits of the existing adhesives should prevent unwanted chemical reactions, deliver maximum tissue adhesion, make it easy to use quickly, properly placed on the target site, easily degradable or removable, negligible damage of the tissue, lower infection risk and have an effective therapeutic capability while maintaining multiples resilience.

Chapter 2

Methodology

In my quest to gather as much relevant and niche information regarding Bioinspired 4D microneedle I thoroughly read through various journals, research papers, and review articles from official sites and research databases. Renowned and reliable databases such as PubMed, Scopus, Academic Search, and Web of Science helped me find and bind the useful information of bioinspired 4D microneedle within the parameters of this research paper. I have used appropriate key terms to collect relevant articles, such as microneedle, bioinspired, 4D printing, smart materials, bioinspired materials, microneedle fabrication process, and so on. Since this is a fair novice topic, the number of articles is minimal, to say the least. Depending on the title and keywords, almost 200 articles have been screened. Then, around 160 articles were meticulously read, analyzed and relevant information was collected to write this review paper. I have used Mendeley software for proper and just referencing to be respectful with the work or the original authors. Finally for illustrating the diagrams I have used lucid chart, an online website, and also adobe illustrator.

Chapter 3

4D printing

Before exploring the details of 4D printing, it's required to first understand the fundamentals of additive manufacturing techniques to gain a thorough understanding of their functionality. Furthermore, profound knowledge on the subject is essential for their safe usage and to design as well as develop bioinspired MNs. In order to process the final prototype, almost every type of input feed is divided into powder and liquid-based feed categories. The method that is based on powder feed involves either melting or sintering for the final densification of the ultimate compaction of the preferred output design. In the aforementioned process, excess powder feedstock is obtained and recycled for subsequent steps. An attempt to produce topnotch output starts with 3D design modeling and simulation in software, which is then cut into two-dimensional prototypes of the original. The next step is to monitor an input program to the printer so that it can scan the feed material and restore it, resulting in a 3D printed usable product (Figure 4) (Rastogi & Kandasubramanian, 2019).

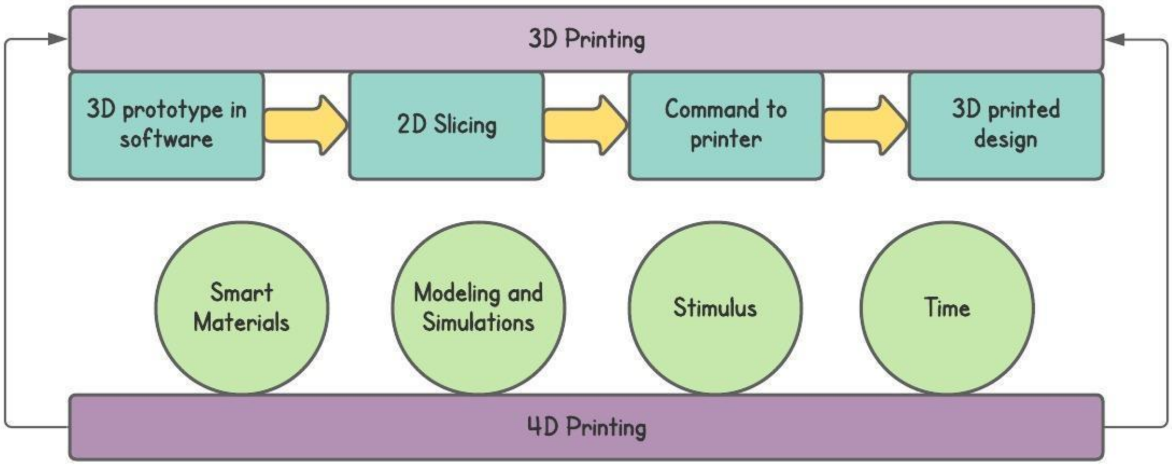


Figure 4: The flow of 3D and 4D printing. The 3D printing process begins with the design of the prototype, followed by slicing and commanding the printer for product manufacturing process and addition of smart materials, modeling, simulation, stimulus over time will produce 4D printed product.

Therefore, Smart materials can be stimulated over time with stimulation in a modeled and simulated design with 4D printing. The 4D printing technology facilitates the evolution of shape or function with the time of the printed product by using different materials under different stimuli. The elements, stimulus, and the categories of methods involved in 4D printing are shown (Figure 5). Additive manufacturing methods that are used - Direct-ink-writing (DIW), fused filament fabrication, (FFF), stereolithography (SLA), digital light procession (DLP), selective laser sintering (SLS), inkjet printing.

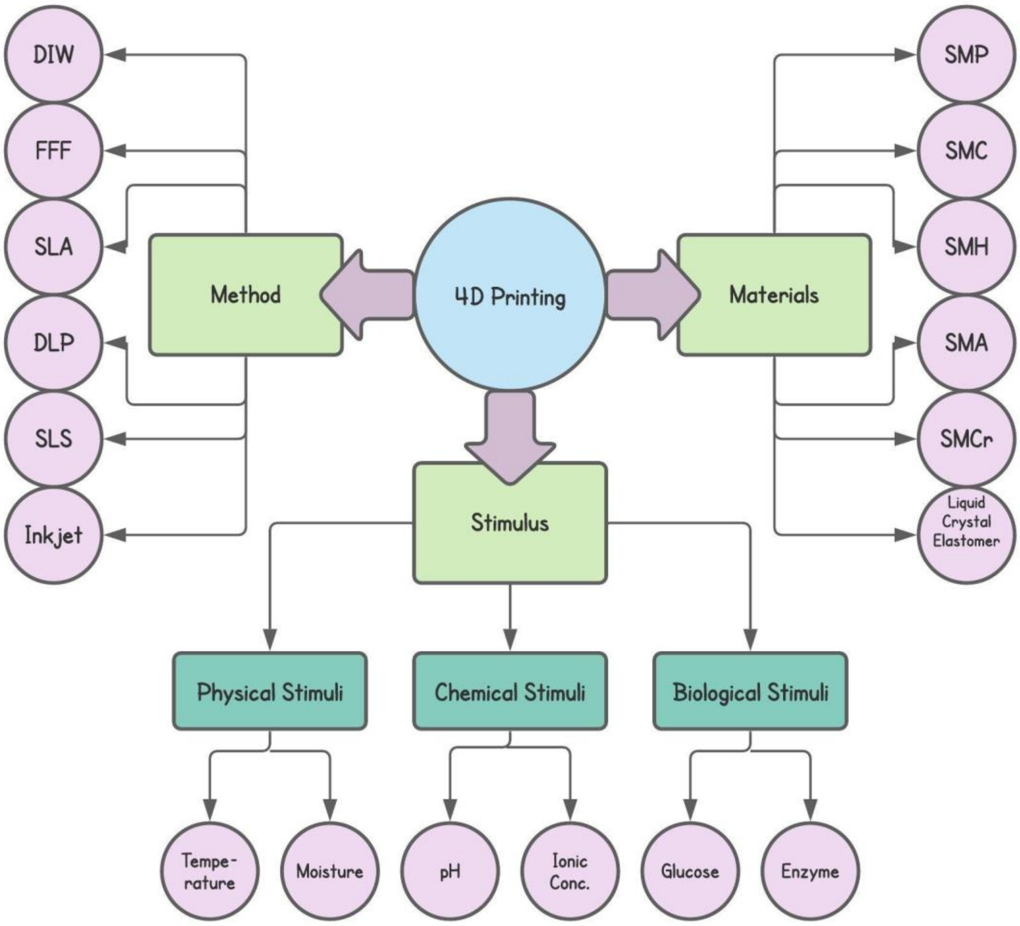


Figure 5: Method, stimulus, and materials of 4D Printing. *1) 3D printing technology: DIW, FFF, SLA, DLP, SLS, inkjet, and. 2) The stimulus for 4D printing: Physical stimulus (temperature, moisture), Chemical stimulus (pH, ionic concentration), Biological stimulus (glucose, enzyme). 3) Material systems for 4D printing: SMP, SMC, SMH, SMA, SMCr, Liquid Crystal Elastomer. [DIW=Direct-ink-writing, FFF= fused filament fabrication, SLA= Stereolithography, DLP= Digital light procession, SLS= Selective laser sintering, SMP=Shape memory polymer, SMC= Shape memory composite, SMH= Shape memory hydrogel, SMA= Shape memory alloy, SMCr= Shape memory ceramics]*

3.1 Shape and transition effect

Throughout processing, the accumulated strain energy is released for a material's characteristic functional transition. These materials' response after the triggering of a stimulus has been removed, is essential to the visibility of the transition or functional change (Rastogi & Kandasubramanian, 2019). When the triggering element, — for example, stimuli, is withdrawn, the material shifts to its primary form, resulting in the Shape Change Effect (SCE). Differently put, the material adapts to the adjustable shape whereas recognizing the route and preparing for the next stimulus to trigger the route, resulting in the Shape Memory Effect (SME). In addition, transitions adhere to a transient pattern before the next stimulus triggers an entire transformation cycle (Momeni et al., 2017).

3.2 Materials used in Smart Memory Effect

Smart or stimuli-responsive materials (SM) are the most common useful group of materials. Owing to the fact of their ability to recognize the structure programmed to them using stimuli such as heat, solvent, and others. This phenomenon is known as the shape memory effect. When these materials are integrated with a 3D printing method, they produce a scope of 4D printing, which transformed the design over time and prompted thorough research aimed at ultimate applications (Li & Loh, 2017). Ceramics (SMCrs), Alloys (SMA), Shape Memory Hydrogels (SMH), Polymers (SMPs) and, Composites (SMC), are classes of materials (Figure 6) that possess shape memory properties (Rastogi & Kandasubramanian, 2019).

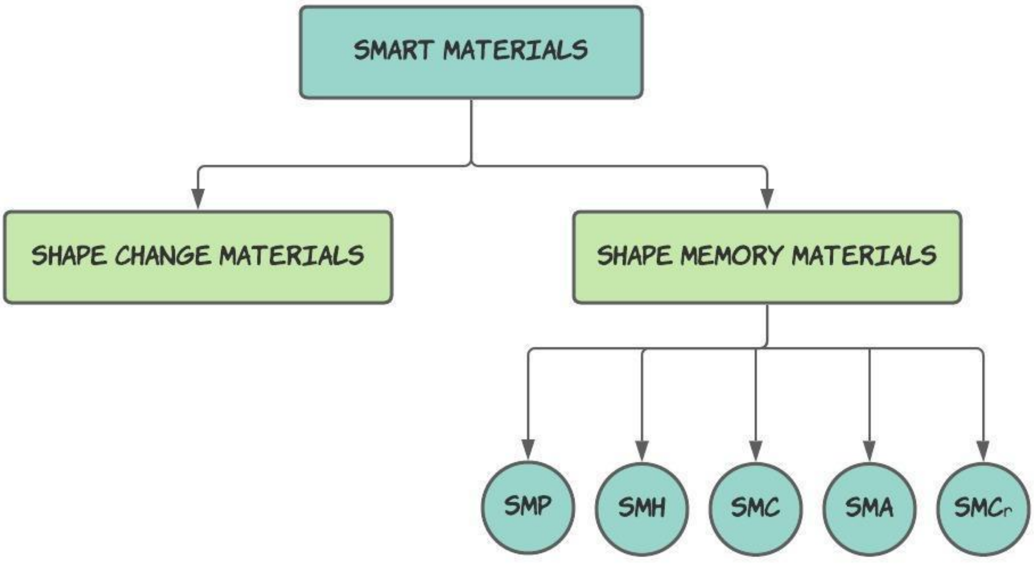


Figure 6: Classification of smart materials. [SMP=Shape memory polymer, SMH= Shape memory hydrogel, SMC= Shape memory composite, SMA= Shape memory alloy, SMCr= Shape memory ceramics]

Smart Memory Ceramics (SMCrs): High energy generation, high energy damping, high-temperature usage, and light weight are some of the properties of SMCrs. When few strain cycles are applied, some brittle materials go through a martensitic transformation and break at low strains. Christopher A. Schuh from Massachusetts Institute of Technology, Zehui Du, and C.L. Gan from Nanyang Technological University demonstrates that a fine-scale structure with few crystal grains can overcome such failure in normally brittle martensitic ceramics. During the mechanical deformation, such oligo-crystalline structures suppress internal mismatch stresses and thus resulting in shape memory ceramics that can withstand a large number of superelastic cycles (Lai et al., 2013).

Shape Memory Alloys (SMA): Nitinol, a SMA made of Nikel and Titanium, can be heated back to its original shape or configuration after being plastically deformed during the low-temperature martensitic process (Kelly et al., 2017). MN fabrication studies are presented using a multiple-pulse laser micro-hole drilling technique to drill an axial hole into a thin nitinol (Nickel-titanium alloy) wire with a diameter of 150 m. Nitinol was considered because of its outstanding super-elasticity and biocompatibility, which reduces the chance of breakage. This MN could be used to extract a small amount of blood for glucose monitoring (Tu & Reeves, 2019).

Shape Memory Hydrogels (SMH): The SMH has incredibly fast shape memory and temperature response. This hydrogel shape shift can be controlled by altering the recovery temperature, and the desired shape can be achieved in phases. Furthermore, the hydrogel remains stable in water without swelling. These outstanding characteristics will accelerate the SMH into a new era of success in biomedical technology (S. Yang et al., 2020).

A temperature-responsive strong hydrogel, such as Elastin-based thermo responsive SMH (Zhang et al., 2020), was manufactured without any chemical reactions using a soaking process.

Without any chemical cross-linkers, the hydrogel was generated by hydrogen bonding between gelatin and tannic acid alongside the triple helix of gelatin chains. Moreover, some recent examples of SMH are- cellulose nanocrystal mediated fast self-healing SMH (Xiao et al., 2021), double Network SMH.(J. Chen et al., 2021), photo-responsive SMH (Li et al., 2020), gelatin-based and salt-induced SMH (Löwenberg et al., 2020), multi-Responsive Lanthanide-Based SMH (Q. Zhou et al., 2020).

Smart Memory Polymers (SMPs): SMPs are dual-shape materials that belong to the ‘actively moving polymer' category. They have the ability to consciously transform from one form to another. The initial shape is a transitional shape obtained by mechanical deformation followed by fixation of that deformation. This phase also influences the transition of the alteration of shape, which leads to the final shape, which is the permanent shape. Besides, heat or light has been used as the stimulus in SMPs (Behl & Lendlein, 2007).

3.3 Nature and mechanism of the stimulus

The types of stimulus that can affect the bioinspired 4D MNs are-Thermal stimulus, Magnetic field stimulus, Current and voltage stimulus, Light stimulus, Hydro stimulus, pH stimulus (Rastogi & Kandasubramanian, 2019). The mechanism of these stimuli is discussed below-

<u>Thermal stimulus:</u> Low energy and stressed structures are balanced with the transfer of thermal energy in the thermal stimulation mechanism (Rossiter et al., 2014). Crosslinking (physical for thermoplastics and chemical for thermosets) and transition points for stabilization and re-attainment of a material form are entropically regulated by the Shape Memory materials (SMM), mostly in SMPs and SMCs. The pivot for shape-morphing in polymers and composites is the transition temperature which is controlled by rigid and soft domains. (Behl & Lendlein, 2007; Wong et al., 2014).

Magnetic field stimulus: Absorbed magnetic particles in a matrix that can respond to magnetic fields or acts as a magnetothermal source that drives transformation with magnetic field stimulus (Mu et al., 2018; Kim et al., 2018). Moreover, the structure of the product is magnetically stimulated when the material contains oriented polarized particles that respond to a magnetic field and also the magneto thermal source which functions with indirect heating (Kokkinis et al., 2015).

Current and voltage stimulus: The mechanism of current stimulus has two intermediate stages where in stage one anisotropic temperature generates due to Joule’s heating and, due to large temperature rise heat distribution along with bending occurs in stage two (Rastogi & Kandasubramanian, 2019).

Light stimulus: In the mechanism of light stimulus, it fixes and cleaves the crosslinks between the particles by UV illumination and by UV, NIR, or other sources depending on the presence of photo thermally-activated or photo-activated particles respectively (Lendlein & Shastri, 2010a). In the SMM, light-driven shape transfiguration occurs when photon energy interacts with innate functional groups, modifying the bond relationship and causing a tangible alteration in the material. This occurs when UV stimulates a material, causing physical and chemical crosslinks to form for temporary shape stabilization, and then UV relaxes the material by breaking the crosslinks by supplying the necessary energy to bond (Lendlein & Shastri, 2010b).

Hydro stimulus: The water stimulation mechanism involves the swelling and drying of water molecules, which causes a plasticizing effect in molecular chains, resulting in macroscopic transformation (Leng et al., 2011).

pH stimulus: The swelling process in polymers or hydrogels triggering through water is characterized by water diffusion, which can be further exemplified by pH. Thus, the pH stimulation mechanism involves the shrinking or swelling of materials in acidic or basic environments depending on the sensitivity of the materials (Z. Wang et al., 2015).

3.4 Modeling and simulation

Modeling is a modern approach that allows the user to design real-world applications in the simulated world in order to improve design parameters and corresponding complexity. 4D printing modeling saves both resources and cost by transforming the shape as well as eliminating the repetition while modeling the required product. The predefined application is an inverse strategy that helps to resolve the majority of the problems whereas the forward strategy is followed when the actual application is not known. Different types of software are used to model designs for 4D printing, such as FEM (Finite Element Modeling), ANSYS (Analysis System), COMSOL Multi-physics, Solid Works, CAD (Computer-Aided Design), ABAQUS, and so on (Momeni et al., 2017).

The material complexity enabled by additive manufacturing (AM) has made the production of smart materials (SMs) simpler than normal, giving credence to 4D printing (4DP). The design space around AM has grown even more as a result of this development. However, for designers to accept this design space, it is necessary to make SMs modeling and simulation easier, especially in conceptual design. Previously, efforts were firmly focused on developing a voxel-based modeling and simulation platform for SMEs, demonstrating the importance of material distributions in 4DP architecture (Sossou et al., 2019).

VoxSmart: A computational design tool was used to make Germain Sossou and Frederic Demoly's modeling strategy for SMs simulation tangible. Grasshopper (GH) is incorporated within the Rhinoceros (RH) to develop the system. RH is a CAD-specific simulation program that enables the development of various complex structures in a fast and efficient manner. GH is a script-free graphical algorithm editor that allows for the generation and, computation of any form virtually in the RH framework. A graphical algorithm is usually made up of a series of components that performs computation and are connected by wires that carry the data. The ability to develop plugins for specific tasks such as design, simulation, and even manufacturing control makes the GH computation engine practically upgradable. Researchers have developed a GH plugin to materialize SMs modeling and simulation framework because of the shape complexity allowed by RH and GH. Besides, the plugin of the voxsmart is written in the C programming language. Moreover, the components of voxsmart are divided into six categories: Material Edition, Voxel Edition, Stimulus Definition, Boundary Conditions Definition, Simulation, and Distribution Computation. Also, finding the right distribution to achieve a particular shape change for an application cannot be simple, particularly if one has limited knowledge of SMs and also the mismatched strains of materials can lead to dissimilarities. Automation will help to fix the problems in the design by having a starting point and thereby saving time on different versions. Therefore, this tool makes it much easier to define and simulate any material distribution on a voxel basis. As a result, the tool can simulate any heterogeneous object with material distribution, including SMs and traditional materials (Sossou et al., 2019).

Any multi-material printing AM machine, in general, can print any structure as long as the required materials are available in a form that the machine can operate. Many AM techniques, whether personalized or commercially accessible, can print multi-materials. It's worth noting the Poly-Jet process, which is capable of handling voxel-based material distribution (Bader et al., 2016; Vidimče et al., 2013).

CAD (Computer-Aided Design): It is possible to build an object model in the correct size and dimensions using CAD software. The CAD file is saved and uploaded to the 3D printer for processing after the object model is done. The object will then be developed utilizing the directions included in the CAD file by the 3d printing machine. Johnson et al. had printed dissolving MN structures in a 3D printing machine from a CAD file using the Continuous Liquid Interface Production (CLIP) method of AM (Johnson et al., 2016).

Several authors, for instance, have modeled light intensity distributions generated with Digital Light Processing (DLP) chips to improve the light intensity projected from each pixel to follow the target CAD file as closely as possible (Sun et al., 2005; C. Zhou & Chen, 2012). As a result, AM technology is a direct manufacturing method that can fabricate parts from CAD models without the need for part-specific tooling or fixtures (C. Zhou & Chen, 2012).

3.5 Different design parameters

It has been observed that improved control over MN design parameters such as sharpness, composition, height, aspect ratio (Park & Prausnitz, 2010), inter-needle spacing, (Kochhar et al., 2013), and MN shape can be obtained (L. Y. Chu et al., 2010). MN efficacy is considered to be influenced by these design parameters (Donnelly, Garland, et al., 2010; Donnelly, Raj Singh, et al., 2010). Due to the complex steps of current MN manufacturing methods (such as silicon etching, (Wilke et al., 2005) tilted UV (ultraviolet) photolithography, (J. W. Lee et al., 2008), and laser ablation associated with micro-molding), time is needed to develop a new design. Furthermore, many of these techniques have technical limitations that prevent the development of certain types of MNs (such as MNs composed of a tall, sharp, or high aspect ratio). As a result, MN height, aspect ratio, and spacing are often determined by manufacturing effectiveness rather than ideal design.

There is a relationship between MN design parameters and therapeutic efficacy. In this relationship (Table 1) MN design parameters affect the efficacy during transdermal drug delivery by affecting different determinants. Here is a list of MN design parameters in the left column, whereas the right column is a list of factors affecting the efficacy of MNs used for transdermal drug delivery. The list of parameters that affect the determinants are shown below (Johnson et al., 2016):

MN Design Parameters	Efficacy Determinants
Composition	Drug loading, strength, release rate
Height	Drug loading, strength, depth of penetration, release rate
Aspect Ratio	Drug loading, strength, depth of penetration, release rate
Patch Area	Drug loading, treated area, depth of penetration, cells targeted

Table 1: Relationship between MN design parameters and efficacy determinants

Chapter 4

Bioinspired 4D microneedles

4.1 Bioinspired materials

Smart materials (SM) are special types of materials having one or more properties that alter significantly as a result of their reaction to the environment. Smart materials' specific properties can be used to build multirole sensing, actuation, energy transfer, and structural elements for bioinspired systems. Smart materials' unique properties can be used to develop bioinspired materials (*Bioinspired Smart Materials and Systems - Smart Materials and Structures - IOPscience*, n.d.).

Studying from the natural world will aid in the development of advanced materials that imitate natural materials. Researcher Zhang suggested synthesizing and designing method of bioinspired hybrid materials by using the effects of super-hydrophilicity and super-hydrophobicity as examples: (1) choosing a feature in a biological structure as inspiration, (2) analyzing the transformation between macroscopic structure and multi-scale properties, (3) designing and synthesizing appropriate necessary molecules, and (4) constructing the overall design to achieve the desired feature (F. Zhang et al., 2018). Although the concept of creating hybrid materials appears straightforward in theory, it can be very tough to execute. Organic and inorganic components in natural materials need perfect arrangement at both the micro and nanoscales. Lithography, self-assembly, chemical vapor deposition, and other synthetic techniques have all been created to construct advanced materials that mimic the framework and function of natural organisms. So, getting inspiration from the naturally occurring materials, bioinspired hybrid materials can be produced (C. Zhang et al., 2016). Some of the examples of naturally occurring materials and bioinspired hybrid materials are explored below-

Naturally Occurring Materials: Some examples of naturally occurring materials, regarding the nanostructure, chemical configuration, and the essential mechanisms underlying their functions, properties, and mechanical activity are –

1. Nacre and Bone: Nacre and bone, for example, are natural hybrid materials with greater strength and durability than their individual components, which are mostly simple components with specific mechanical properties (Wegst et al., 2015). The laminated composite architecture of nacre and bone is identical, consisting of aligned ceramic platelets surrounded by a small fraction of polymer. Nacre's main strengthening and stiffening mechanisms, according to some sources, are regulated by its special hybrid architecture (C. Zhang et al., 2016). Thus, the engineered materials with exceptional strength and resilience are inspired by the classified structures of bone and nacre.

2. Petal Effect and gecko feet: Natural nanostructured surfaces with ultrahigh adhesion can be divided into two categories. The petal effect describes how certain plants can keep a water droplet from falling off their petals and retain it in a globular form (Feng et al., 2008). Animals such as gecko lizards can selectively adhere to a variety of items with molecularly

smoother or irregular surfaces, large or tiny, dry or wet. The adhesive strength of these animals will carry more than their own weight (Tian et al., 2012). As per recent research, the heavy adhesive force of gecko feet and petals was recently discovered to be related to their periodic arrays of hierarchical micro and nanostructures (Yeh et al., 2014). Hence, petals and gecko feet have periodic hierarchical nano and microstructures that can be used to create new synthetic adhesive materials (Geim et al., 2003).

3. Lotus Effect: Plant leaves also have a unique water repellency or surface wettability. Water droplets are unable to adhere firmly to the surface of plants with repellant petals or leaves, allowing them to fall off. The "self-cleaning" or "lotus effect" refers to this property (L. Zhang et al., 2012). According to some research, the non-wetting property of cilium-like nanostructures is because of the micro-scale and nano-scale hierarchical roughness in their form. On the top, these structures are superimposed and unevenly spaced, and the papillae have a low surface energy epicuticular wax coating (Xu et al., 2012).

<u>Bioinspired Hybrid Materials:</u> For millions of years, nature has produced high-performance materials. Engineered material systems may benefit from those materials as a source of inspiration. Biomimetics has the ability to increase quality while reducing our environmental footprint by allowing for more feasible design and fabrication of advanced materials. Many synthetic strategies have been established in recent decades to produce different bioinspired hybrid materials (C. Zhang et al., 2016).

1. Structural Materials: For manufacturing synthetic hybrid materials, various technologies are applied. These materials can imitate similar principles of function of the microstructure of nacre and bone, as well as their remarkable mechanical properties. Two particular methods that have been successfully used for this purpose are ice templating and layer-by-layer (LbL) assembly. For manufacturing multilayer functional thin-film composites, LbL

assembly is a convenient and simple technique. The method involves ionic bonding for the deposition of multiple materials through simultaneous interactions (Finnemore et al., 2012; Sukhorukov et al., 1998). Besides, this process is effective for producing the layered structure of bioinspired hybrid materials because of the variety of available organic and inorganic materials, as well as the ability to monitor morphology and width at the nanoscale via parameters such as charge density, pH, concentration (Y. Wang et al., 2008).

In the course of the formation of sea ice, hexagonal ice platelets remove various impurities such as biological species, salt into the channels between ice crystals and thus, expand across horizontal crystallographic axes. By using this self-organizing theory, an ice templating method was developed for the development of several hybrid materials (Munch et al., 2008). Some of the hybrid composites are, multilayer nano-composite films (Tang et al., 2003), Highly cross-linked nano-composite structures (Podsiadlo et al., 2007), hybrid films (Bonderer et al., 2008), silicate/PMMA nano-composites, Al2O3/ PMMA composite (B. Y. Kim et al., 2015), high impact-resistant composites (Grunenfelder et al., 2014), Hydroxyapatite scaffolds (Deville et al., 2006), layered bulk materials (Bouville et al., 2014). These composites are made by LBL or by ice templating technique.

2. Adhesive Materials: Van der Waals adhesion system of gecko lizard has shed new light on adhesive techniques. Scientific interest has been growing in this newly discovered mechanism. Synthetic gecko hair has shown promising basic features such as high tensile strength, hydrophobicity high aspect ratio at nanometer and micrometer levels, high micro or nano-hair density, high nano-hair stiffness (Sitti & Fearing, 2003). For designing gecko feet-simulated solid-solid adhesives, several synthetic approaches are applied. Nano-molding is considered a commonly applied method to imitate polymer configuration. A Micro or nano-scaled template with a high aspect ratio is used for the molding. It combinedly functions with curable liquid polymers. To accomplish this, different

techniques have been developed to construct the templates such as, the usage of nanopore membrane, usage of atomic force microscopy to create an indentation on a wax surface, selective concealment of the curable liquid polymer that has been exposed to UV light. A variety of other polymers are also available such as polydimethylsiloxane (PDMS), polyvinyl siloxane, poly methyl methacrylate (PMMA), polyurethane, and thus different manufacturing techniques have been using these materials to mimic the adhesion property of gecko lizard (C. Zhang et al., 2016).

3. Super-hydrophobic Surface Materials: By integrating both surface chemistry and texture, several methods have been applied to manufacture super hydrophobic surfaces by getting inspiration from the lotus effect. For instance, Lau et al. produced poly tetra-fluoro-ethylene (PTFE) covered carbon nano tube (CNT) forests utilizing chemical vapor deposition (Lau et al., 2003). Besides, researcher Ajayaghosh and his team manufactured superhydrophobic coatings of CNT and oligon p-phenylenevinylene (OPV) on the surface of the metal, glass, or mica based on a self-assembly method (Guo et al., 2015; Lu et al., 2015; Yao et al., 2010).

Moreover, by enabling the special features, smart material technology helps us to respond to environmental changes. Multifunctional materials, which are a type of smart material. It can be enabled by electrical stimuli to alter its structure or properties. Carbon nanotubes, inorganic nanoparticles, conducting polymers, and other multifunctional materials have been available since the development of nanotechnology. Future multifunctional smart materials, on the other hand, should be compatible with our living environment. As a result, it is good for the environment to create smart materials that are sustainable in nature. Biopolymers are environmentally friendly, recycled materials (J. Kim, 2017).

4.2 Manufacturing of bioinspired materials

A good example of bioinspired material is the mussel adhesive protein (MAP) and along with silk fibroin (SF). MAP is used for manufacturing the shell and SF is used for manufacturing the core of the MN (Jeon et al., 2019).

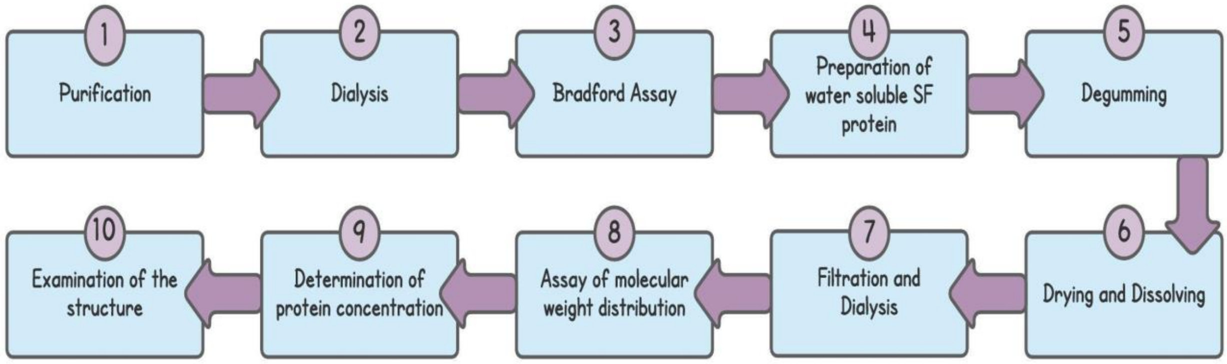


Figure 7: The steps of fabricating MAP and SF-based hydrogels, [MAP= Mussel Adhesive Protein, SF= Silk Fibroin]

The steps of fabricating MAP and SF-based hydrogels are shown in Figure 7 and discussed below-

1. Purification: Endotoxins, lipopolysaccharides, and impurities are removed and filtered in an E. coli expression system (Hwang et al., 2007) by following the established purification steps (Choi et al., 2014).
2. Dialysis: Dialysis of the purified protein solution is done by using distilled water (DW) and then the lyophilization of the solution is done.
3. Bradford assay: By following the Bradford assay (Bio-Rad), the concentration of the protein is determined. (Protein standard such as bovine serum albumin is used)
4. Preparation of water-soluble SF protein: To disrupt the intermolecular hydrogen bonds with minor modification, the dissolution method is used along with some natural salts.

5. Degumming: Degummed Silkworm cocoon (Uljin Silk) twice + Sodium oleate + Sodium carbonate liquefied in DW. Temperature: 100 °C; Time: 40 min. Then washing with DW (Kim et al., 2014)
6. Drying and Dissolving: Drying of degummed SF fibers is done at room temperature (RT). Then it is dissolved in a mixture of calcium chloride: DW: ethanol (a molar ratio of 1:8:2). Temperature: 100 °C; Time: 20 h.
7. Filtration and Dialysis: By using a Mira Cloth (Calbiochem) the solution is filtered. Then it is dialyzed with DW and then lyophilized.
8. Assay of molecular weight distribution: It is done by 12% (wt/vol) SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis)
9. Determination of protein concentration: The Bradford assay helps to determine the concentration of protein and BSA is used as a protein standard.
10. Examination of the structure: FT-IR (Fourier-transform infrared spectroscopy) is used to observe the structures of both regenerated and, degummed SFs. Between the transmission mode 4000 cm^{-1} to 400 cm^{-1}, the spectrum is collected (Jeon et al., 2019).

The fabrication of intelligent objects can be enabled based on the shape and functions of printed smart materials. To minimize space for storage and transportation, the stimulus-sensitive shape-changing function can be used (Kuang et al., 2019). The majority of 4D printing has so far focused on 3D-printed shape-shifting materials and structures. During or after printing, alteration of shape is accomplished by either using SMs directly or by mismatching the strain within a printed object (Rayate & Jain, 2018). It should be noted that Eigenstates have long been used in the smart material research area to build shape-changing structures (*Engineering Analysis of Smart Material Systems | Wiley*, n.d.).

4.2 Shape variety of bio-microneedles

Due to the fact that evolution happens in almost all organisms, many animals have different organs for performing various physical activities. Predation, protection, and reproduction are all functions of these creatures for which they use micro-structured barbs or parts of their body (Wu et al., 2014). The fascicle of the mosquito (Kong & Wu, 2009), the spine of the North American porcupine (Cho et al., 2012), and the stinger of the worker honeybee all bear some similarity to bio-MNs (Lenau et al., 2017). The backward-facing micro-structured barbs of these organisms have evolved, as seen in the table below - (Zhipeng Chen, Lin, et al., 2018a).

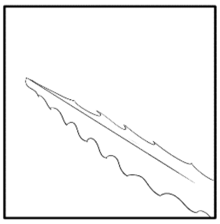
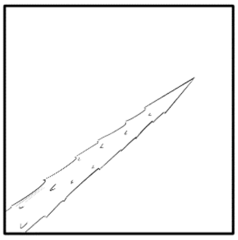
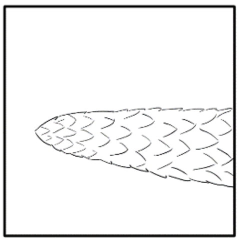
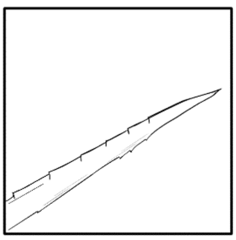
Bio-microneedles	Image	Geometry		Penetration force		Pull-out force
		Length	Diameter	Range	Average	
Fascicle of the mosquito (*Aedes asbopictus)*		1.5-2.5 mm	30 µm	6-38 µN	18 µN	NA
Spine of the caterpillar *(Paras Consocia)*		500-700 µm	30-50 µm	80-265 µN	173 µN	NA
Quill of the North American porcupine		Several centimeters	1.26 mm	-	0.043± 0.013 N	Average: 0.44± 0.06 N
Stinger of the worker honeybee		1.8 mm	90 µm	-	5.75 mN	Average: 113.5 mN

Table 2: Geometry of bio-microneedles and their penetration and pull-out force.

In addition to barbless MN, the bioinspired MN's micro-structured barbs allow for simple skin insertion and difficult removal. Bioinspired MNs had three times the extraction-penetration force ratio of barbless MNs. During the retraction, the amount of the stress at the barbs helps to reduce the insertion force of bioinspired MNs via interlocking them in the tissue and thus minimizes frictional force while increasing the strength of adhesiveness. Such findings may also prove useful for the development of new barbed MNs consist of micro-sized tips for tissue adhesion, bio-signal recording, transdermal drug delivery, and other applications (Zhipeng Chen, Lin, et al., 2018a).

4.3 Fabrication of bioinspired 4D microneedles

Based on the structure of the MNs and also the mechanism of the bioinspired model, the fabrication processes can vary. There are different type of methods for fabricating this special type of MN, among them two important methods are discussed below-

4.3.1 Magnetorheological drawing lithography (MRDL)

Replica molding can easily replicate bioinspired needles on a centimeter scale, but it is extremely challenging to manufacture advanced and complex bio-MNs on a micrometer scale. A group of scientists proposed a design of bioinspired needles for percutaneous procedures that are similar to honeybee stingers and this can be created by 3D printing (Sahlabadi & Hutapea, 2018). In PVC gel insertion tests, 21-35% decreased insertion force of the honeybee-inspired needles is observed. Whereas the insertion force of that MN decreased by 46% in bovine liver tissue insertion tests. So, the researcher group proposed a novel MRDL method to competently manufacture MN, molding-free MN array and, bioinspired MN in a study (Zhipeng Chen, Ren, et al., 2018). As a demonstration, researchers developed a bioinspired MN with barbs imitating the stinger of the honeybee. However, the manufacturing process, as well as the penetration-retraction performance of this MN, have yet to be studied and explored (Zhipeng Chen, Lin, et al., 2018b).

The manufacturing of bioinspired MNs utilizing the MRDL method is narrowed down into two stages (Chen, Lin, et al., 2018) that are shown in the figure below (Figure 8).

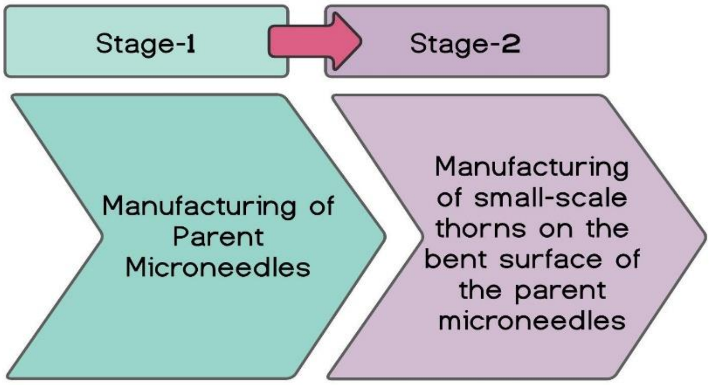


Figure 8: Stages of manufacturing bioinspired MNs in MRDL method, MRDL= Magnetorheological drawing lithography.

Following the earlier studies on the mechanical characteristics of honeybee stingers, researchers developed this MRDL method for manufacturing honeybee-inspired barbed MN. Therefore, this MRDL method is less complex as well as, less expensive (Zhipeng Chen, Ren, et al., 2018). It is capable of producing highly complicated microstructures that are difficult to achieve using lithography technology or traditional subtractive manufacturing. Further, with the help of the cohesive zone model the penetration-retraction mechanism will be evaluated via finite element analysis (FEA) (Zhipeng Chen, Lin, et al., 2018a). Moreover, a LED-based PμSL 3D printer is also capable of manufacturing micro-scale MNs. The optical system based on optical engineering principles, which comprises projection optics and illumination optics, was designed and implemented for this purpose (Behroodi et al., 2019).

4.3.2 Microstereolithography (PμSL) method

The major portion of MN was planned to be 400 μm in diameter, 4 mm in length, and 10° cone angle, as shown in Figure 9. Around the MN have been created three-angle barbs with a base width of 200 μm and a length of 450 μm. The micro stereolithography (PμSL) method was used for 3D MN array production (Figure 9).

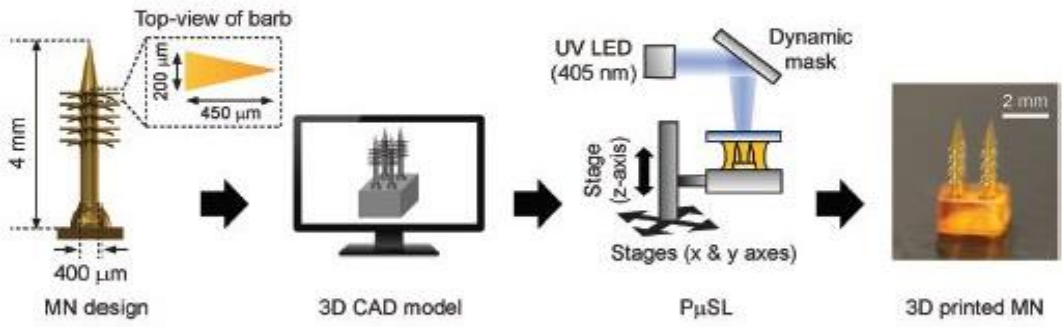


Figure 9: The stages of printing the bioinspired microneedle array using PμSL (Han et al., 2020)

Computational design software has been used to create the 3D model of the MN array (Paik et al., 2004). A series of cross-sectional photos were cut into a digitally designed 3D model. The digital picture was transferred to a DMD device (digital micromirror device) to provide a 405nm wavelength containing patterned light and then projected to the surface of the photo-curable precursor solution. Continuous image processing was conducted using a screen lens. Then that solution has been transformed into a solid layer under the projection light. In order to produce a 3D MN array, the method was repeated via the LbL process. Two other steps in the printing plane have been used in the step-and-repeat procedure for manufacturing a large area MN array. In addition, MN dimensions can be further scaled down when required with a microscale resolution provided by PμSL (Paik et al., 2004). Although the described MN can be manufactured using a wide range of photocurable polymers, researchers have been using PEGDA 250 as a monomer, phenyl bis (2, 4, 6-trimethyl benzoyl) phosphine oxide as a photoinitiator (PI), and Sudan I, all of which were verified biocompatible (Bagheri & Jin, 2019). For improved tissue adherence following insertion, the barbs on the MN must face the direction opposite to the MN tip. However, it is difficult to manufacture it in 3D printing because of this complex geometry. As a result of the LbL nature of the 3D printing is restricted for any section of the structure that is not supported by an earlier layer. In micro-sized 3D printing, it is not feasible to use support structures due to restricted capacity for 3D multi-material printing and limited disposable materials. Researchers have developed a 4D printing method to bend horizontally printed barbs in a backward face form in order to solve this manufacturing issue and create a backward-moving barb for increased adhesion for tissue (Figure 10). As the light is concentrated on the precursor solution surface, a photo-polymerization begins on the surface and steadily spreads to the solution. (Figure 10 (i, ii)) (Han et al., 2020).

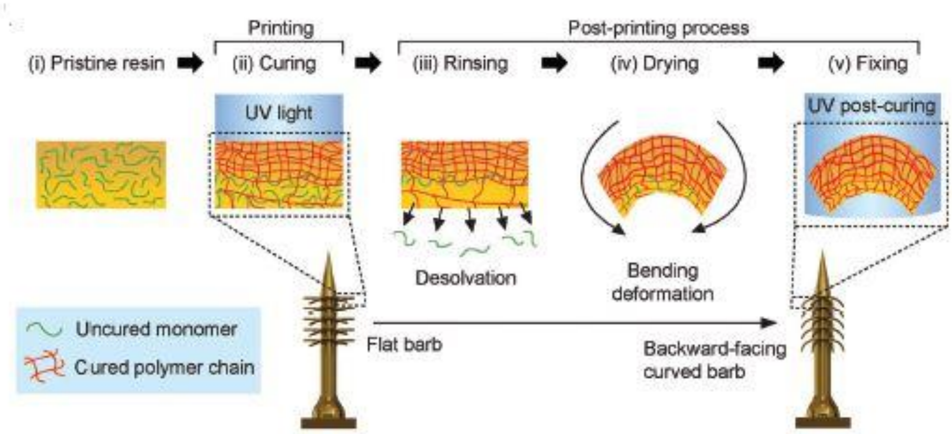


Figure 10: Schematic illustration of 4Dprinting approach to program deformation of horizontally printed barbs into a backward-facing shape (Han et al., 2020)

The intensity of light radiation decays when the light passes through the precursor solution, a gradient of cross-link density is generated within the layer with a high cross-link between the top part and the bottom part with a lower cross-linking density. Therefore, some monomers remain uncross-linked and partly connected underneath. The triangular barbs remain horizontal throughout 3D printing. The MN array is soaked in ethanol as it needs to be rinsed after printing. Then the untreated monomers spread out towards the lower part of the barbs, leaving behind from the structure via dissolving (Figure 10(iii)) (Urrios et al., 2016). The lower part of the barb shrinks after the MN array is dried. This causes the barb to bend downwards. (Figure 10(iv)). The bent form of the barbs is stabilized by a flood UV exposure (Figure 10(v)).

Chapter 5

Clinical application and challenges

5.1 Clinical application of bioinspired 4D microneedle

Microneedling improves scars, cellulite, and rhytides significantly clinically, with minimal side effects along with quick recovery. For the clinical outcomes, the cascade of the simulation of wound healing and controlled dermal wounding rises the production of collagen. (Alster & Graham, 2018). Moreover, several clinical trials are currently in progress to investigate the safety and effectiveness of MN-based systems (Bhatnagar et al., 2017). Multiple studies have shown that micro-needling is effective in the treatment of facial rhytides (H. J. Lee et al., 2014).

Over the last decade, micro-needling has been extensively researched, with several recent articles discussing therapeutic effectiveness, treatment details, histologic evaluations, and targeted therapy (Hou et al., 2017). Recently bioinspired 4D MN has added more bio-compatible and new aspects in the sector of clinical applications. Bioinspired MNs are being researched for various clinical uses. Different bioinspired MN along with their clinical uses are shown in the Table 3.

SL No.	Material	Inspiration	Structure	Trial demonstration model	Clinical use	Reference
1.	Dodecyl-modified chitosan (DCS)	–	Pagoda-like multilayer MN patch	In-vivo experiment on rabbit model. The model includes acute tissue injuries such as bleeding on the liver, spleen, and kidney.	-Tissue fixation -Fast hemostasis	(Zhang, Chen, Cai, et al., 2021)
2.	On the surface of poly lactic-co-glycolic acid (PLGA), Coated interlayer with poly dopamine (PD) Crystalized Hydroxyapatite (HA)	The process of bio-mineralization.	Nano-flower structure	Skin phantom model	-It has intradermal sensing applications. -It can sense chemical biomarkers in interstitial fluids of skin	(Linh et al., 2021)
3	Poly ethylene glycol di-acrylate (PEGDA), Nano-silver (NS) is used in coating and gelatin/sucrose film for en-capsulation	A green process to synthesis NS (In the presence of silk fibroin template the ionic state silver is crystalized)	–	In-vitro experiment in bacterial suspension	-It has good mechanical strength for skin penetration, -Also has antibacterial activity against Gram-positive and Gram-negative bacteria. -Exhibits minimally invasive strategy Potential for realizing a broad-spectrum antibacterial effect, -It is used to manage poly-microbial skin infection during clinical trials	(Linh et al., 2021)

SL No.	Material	Inspiration	Structure	Clinical trial demonstration	Clinical use	Reference
4.	Liquid metal (LM)	Claws of eagles	Claw-like clamping structure	Wounded SD rats.	-Wound-healing	(Zhang, Chen, Sun, et al., 2021)
5.	Polymer encapsulated Micro-bundles of aligned iron oxide nanoparticles (aIOs)	Limpet teeth	Hierarchical structure	Demonstrated in the skin for long term wearable drug delivery	-The morphology of MN can be optimized for painless drug delivery in clinical trials.	(Zhang, Chen, Sun, et al., 2021)
6.	MN base: poly-dopamine hydrogel and poly-dopamine Polymyxin is loaded into both the hydrogel tips and the poly-dopamine base,	The antibacterial strategy of Paenibacillus polymyxin and adhesion mechanisms of mussel byssi and octopus tentacles	Hierarchical MN with multifunctional adhesive and antibacterial abilities	Osteoarthritis rat model.	-Well fitted on the skin; - It has strong adhesion in dry, moist, and wet environments, -It can self-repair after being split into two parts. -It can resist common bacteria during usage and storage.	(Zhang et al., 2020)
7.	Photo-curable polymer	Micro-hooks of parasites, barbed honeybee singers, porcupine quills	Backward-facing curved MN	It was demonstrated on the skin and showed 18 times stronger tissue adhesion than that of barbless MN	-Improved tissue adhesion - Robust and more stable performance for drug delivery, -Used in the bio-fluid collection, and bio-sensing	(Han et al., 2020)

SL No.	Material	Inspiration	Structure	Clinical trial demonstration	Clinical use	Reference
8.	Propylene glycol methyl ether acetate	Spiny-headed parasitic worm	Barbed MN	Porcine small intestine tissue.	-It has the passive anchoring mechanism, with lower actuation and power requirements, -Used in minimally invasive GI resident devices.	(Liu et al., 2020)
9.	Synthetic polyurethane	Specialized hairs, or quills of North American porcupines	Backward-facing deployable barbed MN	–	-It is used as tissue adhesives or needles, trocars, and vascular tunnelers, -It can prevent collateral damage by minimizing the penetration force.	(Cho et al., 2012)
10.	Hydrogel-forming double-layered adhesive MN patch consisting of a swellable mussel adhesive protein (MAP)-based shell and a non-swellable silk fibroin (SF)-based core	Endoparasites that swell their proboscis	Swellable MN patch	In vivo experiment on a wet and dynamic external and internal tissue model	-Vascular and gastrointestinal wound healing -Transdermal drug delivery for pro-regenerative or anti-inflammatory agents to target tissues.	(Jeon et al., 2019a)

SL No.	Material	Inspiration	Structure	Clinical trial demonstration	Clinical use	Reference
11.	2-hydroxy-2-methyl-propiophenone rhodamine B budesonide, Ferrofluids	Serrated micro-structured forelegs of mantises	Serration-like clamping MN array	Imiquimod-induced psoriasis in mice	-Minimal invasion -Sustained glucocorticoids release during the treatment - Wearable transdermal drug delivery systems	(Zhang et al., 2019)
12.	_	Honeybee stinger	Micro-structured barbed MN	_	- Bio-signal recording, -Transdermal drug delivery, -Tissue adhesion.	(Zhipeng Chen, Lin, et al., 2018a) (Wu et al., 2014)
13.	Degradable cross-linked gel	Mimicking the complementary function of enzymes in peroxisomes to protect normal tissues from an oxidative stress injury.	Core-shell MN array patch	Mouse model, induced chemically by type 1 diabetes	-Smart insulin delivery -Gives rapid response, -Biocompatible, -Regulates the blood glucose level effectively	(Wang et al., 2018)
14.	_	Labium and fascicle bundle of mosquito	MN with a diameter of 60–140 µm & mechano-physical stimulus	_	-The application of mechano-physical stimuli allows MN to be deeply and easily inserted into the skin in a controlled way.	(Jonghun Kim et al., 2018b)

Table 3: List of bioinspired MNs along with the materials, structure, clinical demonstration, and clinical use.

5.2 Challenges

One of the major challenges is the contradictory results of some studies. Such as some of the current findings are insufficient to resolve some issues. Even among the current studies, several results are incongruent. According to one study, the penetration force of a needle increases as the pre-tension in the skin increases (Frick et al., 2001). On the other hand, another study discovered that the force needed to puncture preloaded skin is less than that required to puncture loose skin (Aoyagi et al., 2007; HINGSON, 1949). Stretching the skin to minimize the insertion force was also observed (Aoyagi et al., 2008). There are also several conflicting findings on the interaction between adding strength and speed, in addition to these conflicting findings. Brett et al. another researcher discovered that increasing needle speed reduces insertion power (Brett et al., 1997). However, when the needle's moving speed is increased from 1 to 10 mm/s, the insertion force remains unchanged (Frick et al., 2001). Some of this is due to the skin's complex properties (Chandrasekaran & Frazier, 2003). The key processing challenges in additive manufacturing are the development of void, anisotropic actions, machine design limitations, and layer-by-layer appearance (Ngo et al., 2018). Besides, for reducing environmental challenges, a healable and recyclable printing method can play an important role with the uninterrupted use of printing materials (Kuang et al., 2019).

Another challenge is the compromised drug loading capacity. The size and mechanical strength of the needles will limit the drug-loading capability, limiting this technique to the delivery of effective therapeutics. Another issue is the possible toxicity of the residual polymer matrix and material degradation (Zhongjian Chen et al., 2020).

A further challenging issue is, MNs are difficult to apply for long-term use and sometimes managing the delivery of drugs since they must stay attached to soft tissue for an extended period of time. It's because standard fabrication techniques for developing MN result in MNs with a smooth and simple side profile, which eventually leads to poor tissue adhesion (Han et al., 2020).

Chapter 6

Future prospects and conclusion

A group of researchers hypothesized that in the near future, hundreds of MNs will be linked by a network of leading channels made up of insect models. MN arrays could be easily filled with the essential drugs/vaccines without the need for complicated storage procedures and with minimal formulation waste (Plamadeala et al., 2020). Their prediction has become almost true which we can see from the examples of various MNs inspired by different insects or animal species. Bioinspired 4D MNs should be available in clinics shortly, owing to a breakthrough in MN fabrication on an industrial scale (Zhongjian Chen et al., 2020).

Moreover, there is still a lot of space for development, such as lowering the force needed for MN insertion and improving penetration depth precision (Jonghun Kim et al., 2018a). This platform, according to researchers, could be further established in the future for more flexible and dynamic drug delivery, bio-fluid collection, and bio-sensing (Han et al., 2020). 4D printing has a bright future ahead of it, with the ability to change the world in even more aspects, including biomedical and surgical procedures, as well as improved learning (Rastogi & Kandasubramanian, 2019).

For those who choose not to have surgery or have milder disease, bioinspired MN will provide a clinically meaningful alternative. MNs in combination with neuromodulators can be used to enhance clinical benefits and increase patient satisfaction (Alexiades, 2020). Furthermore, analyses of the chemical environment's effect can reveal new knowledge about how to control the chemistry of smart materials. This paves the way for material complexes to be widely used in science (Andersen et al., 2019). Thus, at the same period, the smart material structures, transformation mechanisms, 3D printing methods should be investigated to improve dimensional stability, load-bearing strength, and production speed in 4D printing designs (Yuan et al., 2021).

The 4D printing platform should be implemented properly in the future. A ferromagnetic 4DP platform will be designed based on the design in the research study. The samples fabricated with the platform will be tested, and the findings will be compared to the conventional 4DP platform fabrication process. It is indeed possible to look at cloud-based 4DP monitoring and control. Additionally, by encapsulating more software and 4DP models, more 4DP simulations can be run (Qinglei et al., 2020). 4D printing would be able to fulfill a large number of potential applications as emerging printing methods, structural design, smart materials, and modeling tools/software progress (Kuang et al., 2019)

It is anticipated that the advancement of micro/nano-manufacturing technology, as well as more comprehensive studies on the associated mechanic's problems relating to bioinspired MNs, would result in several new exciting inventions in medical, healthcare, and biological applications. Therefore, by overviewing the future possibilities we also can say that the future market economy of bioinspired MN is very promising.

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