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THE OVERVIEW OF RECENT ADVANCEMENT IN MICRONEEDLE TECHNOLOGY FOR TRANSDERMAL DRUG DELIVERY SYSTEM

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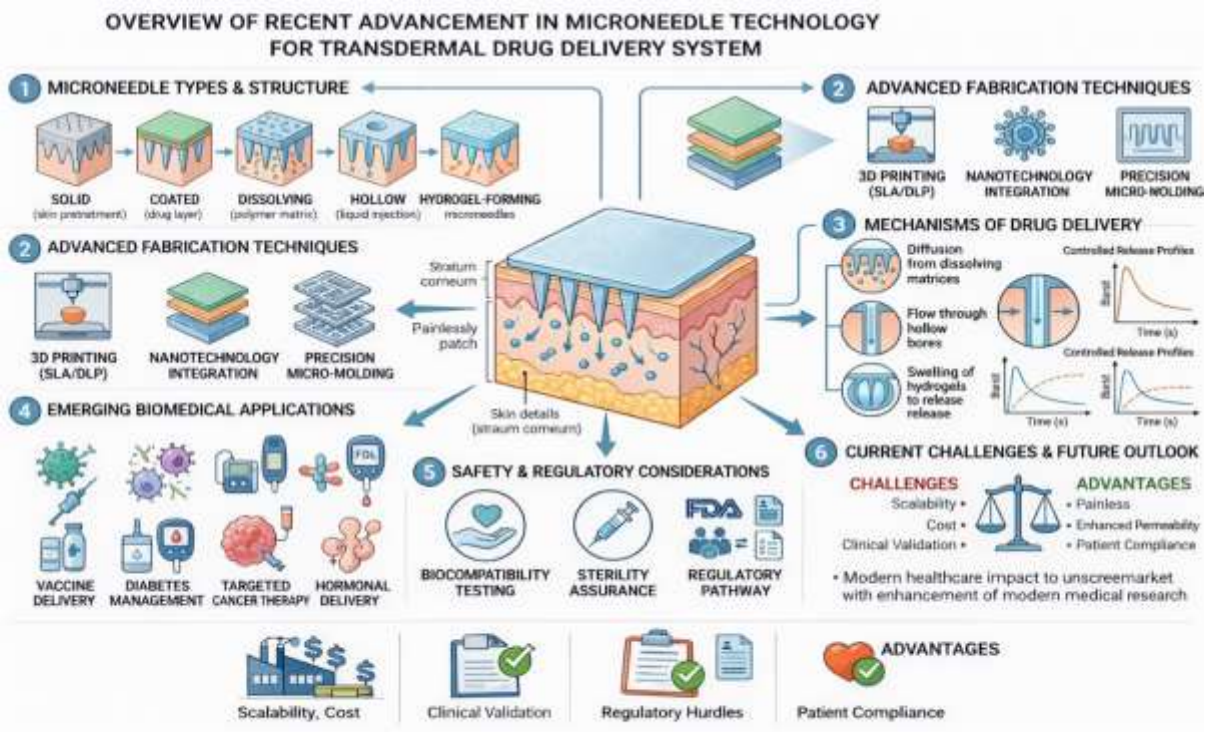
ABSTRACT

Microneedles (MN) has become an essential topic as a sophisticated technology in transdermal drug delivery to overcome the restriction of the traditional methods of drug delivery like oral and injectable methods. This review provides a review of the recent developments that have taken place in microneedles such as their design, methods of fabrication, drug delivery mechanisms, and various biomedical uses. Microneedles have the ability to enter the stratum corneum without inflicting pain or causing considerable tissue damage, therefore, increasing the drug permeability and compliance of the patients. The various types of microneedles are talked about in terms of their structure and functionality and include solid, coated, dissolving, hollow, and hydrogel-forming microneedles. New developments in the field of materials science and microfabrication technologies including 3D printing and nanotechnology have enhanced drug loading capacity, mechanical strength, and release control. Moreover, microneedles have been demonstrated to have more promising applications in the fields of vaccine delivery, management of diabetes and targeted cancer treatment. Safety considerations such as biocompatibility, sterility and regulations are also highlighted in the review. Although significant benefits are evident, such issues as scalability, costs, and clinical validation remain. In sum, the microneedle technology has the potential to provide an efficient, patient-friendly, platform of drug delivery in the contemporary healthcare.

Keywords: Microneedles, Transdermal drug delivery, Controlled drug release, Biocompatibility, Microfabrication

Graphical Abstract



INTRODUCTION

Drug delivery systems (DDS) are developed procedures to provide therapeutic agents in a desired pharmacological effect. Traditional routes are oral, intravenous, pulmonary, and nasal routes, each of which has its peculiar merits and drawbacks. DDS seek to maximize drug release, bioavailability, and the therapeutic adherence of a patient through controlling drug release and targeting a specific tissue. In the contemporary DDS, nanotechnology, liposomes, and polymeric carriers are being used to increase the effect of therapy. As an example, pulmonary and nasal systems are increasing popularity as a result of the fast absorption and non-invasive application [1]. DDS has to be designed that takes into consideration the drug properties, disease pathology, and patient needs [2]. New inventions in the DDS have led to more advanced technologies such as TDDS and the microneedles which correct inadequacy of the traditional ones [3]. Traditional drug delivery channels including oral and intravenous administration have a major challenge. The bioavailability of oral delivery is usually poor because of first-pass metabolism and gastrointestinal tract degradation [4]. I.V. methods though effective are invasive and result in systemic toxicity and patient discomfort. In addition, the high dose schedules cause low adherence to medications, particularly in chronic diseases [5]. These restrictions have led to the development of alternative systems that can offer control release, target delivery and enhanced safety [6]. To overcome these obstacles new methods such as TDDS and microneedles are being developed to avoid the first-pass metabolism as well as reduce systemic side effects. TDDS are self administrated dosage forms which are used to deliver an intact skin dose into the systemic circulation. They provide controlled release, enhanced bioavailability and circumventing of first-pass metabolism [7]. TDDS normally involve the use of patches which deliver drugs at a prolonged period, making patients more compliant [8]. Stratum corneum is the main barrier, and to enhance the drug flux, there is need of permeation enhancers or new technologies [9]. TDDS come in handy especially with drugs that demand constant plasma concentrations like hormones and cardiovascular agents. They are non-invasive and therefore can be used as an alternative to injections, which is more pain and infection-free. Irrespective of their promise, TDDS experience some difficulties because the skin has some barriers. The techniques of enhancement are needed to enhance drug permeation. Surfactants and solvents are examples of chemical agents that break lipid structures in stratum corneum [10]. Physical techniques including iontophoresis, sonophoresis, and microneedles make pathways of the drug molecules [11]. Several bio-enhancers such as peptides and lipids are also being investigated to be used in the delivery of macromolecules [12]. These methods have increased the use of TDDS to a broader spectrum of drugs, such as proteins and vaccines, which have a history of being problematic with skin penetration. Microneedles are micron sized instruments that can painlessly penetrate stratum corneum to deliver drugs to the masses with efficiency. They may be solid, coated, dissolving or hollow, all of which perform different functions [13]. As they do not pass through nerve ends, microneedles bypass the ionizing barrier of the skin, making them an almost painless intervention and user-friendly [14]. The latest developments are biodegradable microneedles and combination with nanotechnology to get controlled release [15]. They find use in vaccines, insulin, and cancer therapeutics as an alternative to traditional injections, and are revolutionary. Microneedle technology is capable of changing TDDS and, in this regard, allows delivery of a variety of drugs, including biologics and vaccines. The goals are to enhance patient compliance, decrease systemic toxicity and attain controlled release [16]. The microneedles also seek to increase the therapeutic uses it has to dermatology, oncology, and immunization programs [17]. Their mass vaccination and customized medicine are appropriate due to their scalability and adaptability. The directions in the future are the incorporation of micro needles into smart systems to provide real time monitoring and feedback [18].

SKIN ANATOMY AND BARRIER FUNCTION

The skin is a complicated organ that is used as the primary barrier of the body. It consists of three major layers where the epidermis, the dermis and the hypodermis are located. The outer layer, which is the epidermis, consists mainly of the keratinocytes and offers a protective barrier against the attacks of the environment including UV radiations, pathogens, and even chemicals [19]. The dermis is below it and it is filled with collagen, fibers of elastin, blood vessels and sensory nerves that give help in the elasticity, thermoregulation, and tactile sensation. The lowest part is the hypodermis that is enriched with adipose tissue, a cushion and source of energy [20]. The thickness of the skin differs among body parts, and this affects drug permeation; this is because palms and soles of the foot are thicker than the eyelids. These layers collectively keep the homeostasis, control water balance, and resist mechanical injury, so, in addition to being a protective barrier, skin is a dynamic organ, which is necessary to survive [21]. The stratum corneum is the most topical part of the epidermis and is essential in the support of the barrier property of the skin. It consists of corneocytes (dead cells filled with keratin) in a lipid matrix, which is commonly referred to as the brick and mortar model [22]. It is a structure that helps to avoid water wasting and to avoid microbial invasion as well as toxins and mechanical stress. Ceramides, cholesterol, and fatty acids are lipids that give structural integrity and the moisturizing factors in the corneocytes are naturally found to keep the skin hydrated [23]. Even though the stratum corneum has a protective effect, it is a significant obstacle to transdermal drug delivery because it limits the migration of hydrophilic and large molecules. The selective permeability of it permits the passage of only lipophilic, small drugs. Therefore, the stratum corneum is needed to survive, but is the main barrier that TDDS will have to surmount to be effective therapeutically [24]. The biological, physicochemical, and formulation factors affect the permeation of the drug through the skin. Biological factors like age, skin thickness, hydration, and site of anatomy, e.g., a hydrated skin or younger skin is more likely to be permeable [25]. The capacity of drugs to permeate through stratum corneum is influenced by physicochemical characteristics like molecular weight, lipophilicity, and partition coefficient. In most cases, molecules with a molecular weight less than 500 Da that are moderately lipophilic permeate better. Factors associated with the formulation, such as drug concentration, pH, presence of permeation enhancers are also vital [26]. Permeability can further be changed due to external conditions like temperature, occlusion and mechanical stress. It is essential to understand these factors to develop effective TDDS because they determine the effectiveness of the drug absorption and treatment outcome. The optimization of these variables enables the researchers to increase the number of drugs that could be delivered through transdermal delivery and therefore, TDDS is more dynamic and clinically applicable [27]. Passive systems of transdermal drug delivery only utilise the process of diffusion through stratum corneum and this is highly limiting to application. Small, low-dose and lipophilic drugs are the only type of drugs that can successfully penetrate without any enhancement methods [28]. The stratum corneum is very difficult to the molecules of hydrophilic nature, peptides, proteins, and vaccines. Furthermore, skin thickness, hydration and location between individuals may cause differences in drug absorption, thereby decreasing the predictability of therapy [29]. Passive TDDS also have a problem with giving drugs which have to act fast or produce high systemic concentrations. Such constraints restrict passive TDDS to a small range of drugs like nicotine and other hormones. To address these limitations, such sophisticated enhancement approaches as microneedles, iontophoresis, and chemical enhancers are under development and are extending TDDS to biologics and macromolecules, transforming drug delivery approaches [30]. All these ideas are demonstrated together in Figure 1, which emphasizes the skin structure, barrier properties, factors of permeation, and innovative methods of enhancing transdermal drug delivery.

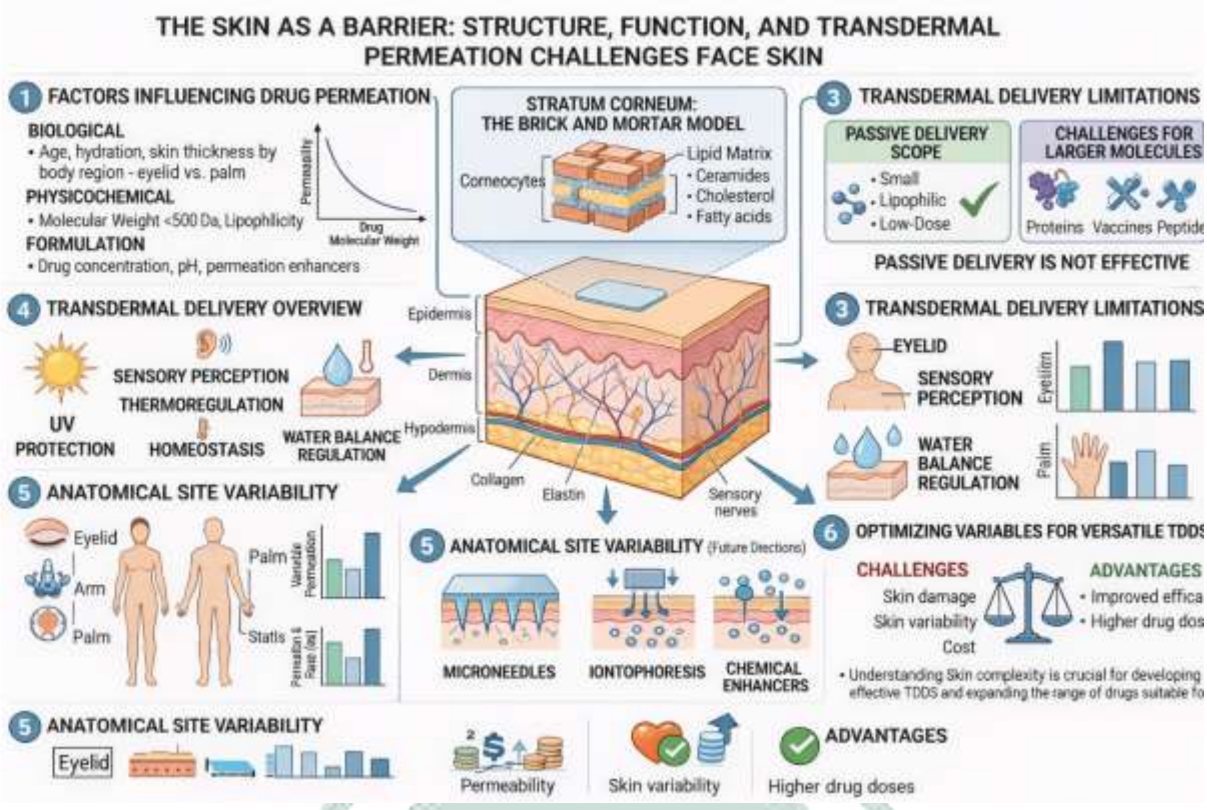


Figure No.: -1 The diagram shows the structure of the skin barrier. It shows the different elements which determine how substances pass through the skin. The diagram displays the obstacles that restrict drug delivery. The diagram shows advanced methods which use microneedles to improve drug delivery systems.

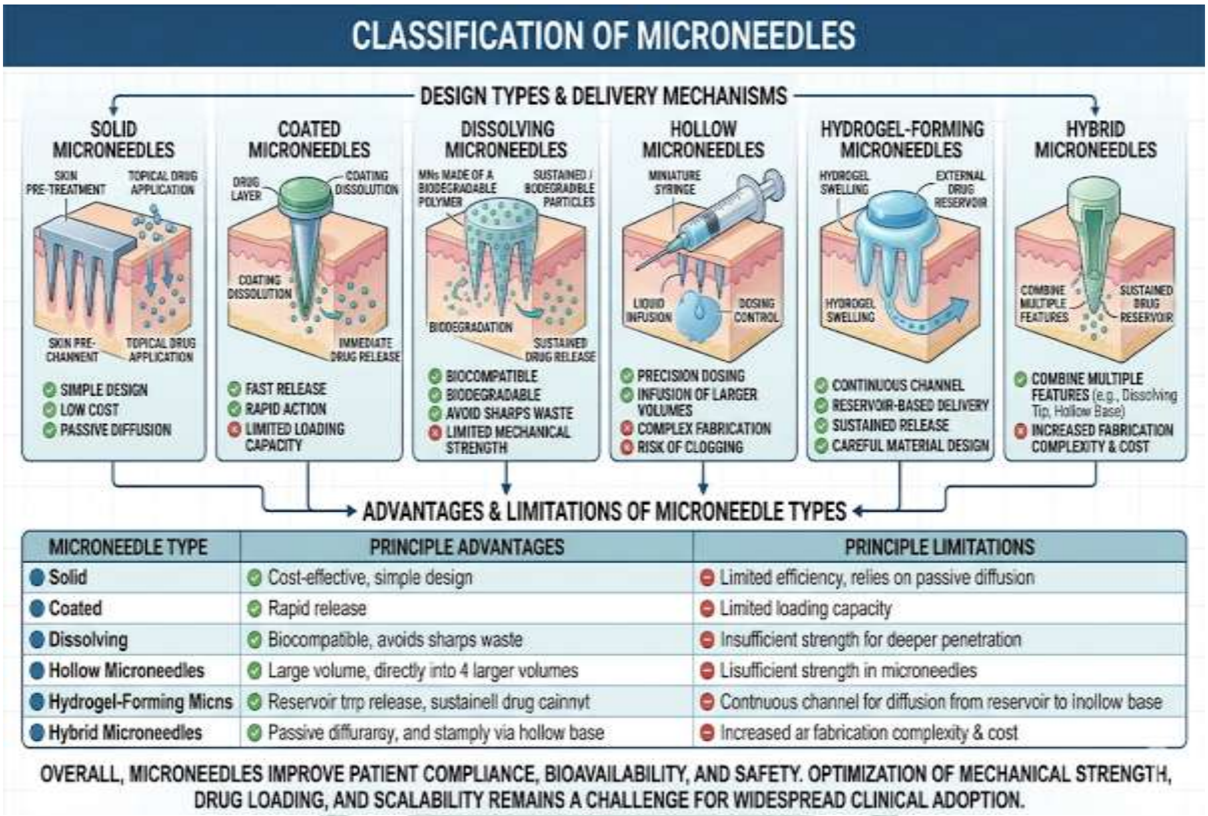
MICRONEEDLE TECHNOLOGY: CONCEPT AND MECHANISM

Microneedles are projections of the micron size, usually between 50 and 900 2 m in length, and are intended to enter the stratum corneum but not past the nerve terminals or blood vessels. This renders them painless and less invasive as compared to traditional hypodermic needles [31]. The principle of operation is the formation of microchannels in the skin and use them to circumvent the stratum corneum barrier properties of the skin [32]. Microneedles may be made out of metals, silicon, biodegradable polymers and can be categorized as solid, coated, dissolving and hollow with each mechanism having a unique drug release process [33]. Microneedles can be used as an alternative delivery method due to their ability to facilitate controlled and directed delivery, thereby enhancing bioavailability and patient compliance, thus, making microneedles a promising alternative to transdermal drug delivery systems. Microchannels formed in stratum corneum are the major mechanism of microneedles. These are channels usually 50100 m wide that serve as pathways through which drug molecules diffuse into the deeper layers of skin [34]. Micro needles, unlike hypodermic needles, do not produce a lot of pain or bleeding since they do not excite the dermal nerves and capillaries [35]. The formation of microchannels enhances the skin permeability several folds, and hydrophilic molecules, peptides, proteins, and even vaccines that would otherwise be blocked by the stratum corneum can be delivered [36]. These microchannels are short lived and the skin barrier function is reinstated in a few hours, thus reducing the risk of infection. This is the key to the effectiveness of microneedle-based TDDS. After the formation of the microchannels, the drugs can be carried into the skin by diffusion, convection, or direct deposition. Pre-applied drugs are applied to the skin following the channels creation in solid microneedles, whereas drugs are pumped onto the surface in coated microneedles [37]. Micro needles are dissolved in bio degradable polymers that hold drugs that are released after the microneedles dissolve in the skin [38]. Liquid formulations may be injected into the dermis via hollow microneedles, which resemble miniature syringes [39]. These routes have the capacity to transport a broad variety of molecules such as small drugs, proteins, DNA and vaccines. The flexibility of the transport pathways mediated by the microneedles renders them appropriate in both systemic and localized therapy. The microneedle technology has a number of benefits over the traditional drug delivery procedures. First, it is painless because microneedles do not penetrate the skin to stimulate pain receptors, but the skin is only penetrated in the very superficial layers [40]. Second, microneedles enhance bioavailability through overcoming the stratum corneum barrier permitting delivery of hydrophilic and macromolecular drugs that might otherwise be poorly absorbed [41].

Third, they pass through first-pass metabolism so that they are not degraded in the gastrointestinal tract and liver, raising systemic drug levels [33]. Also, microneedles are less harmful than hypodermic needles, patients are more compliant, and they can be self-administered. Such benefits have also resulted in microneedles being specifically useful in chronic therapy, vaccination, and biologic drug delivery, making them a disruptive technology in TDDS [42].

CLASSIFICATION OF MICRONEEDLES

There are a few types of microneedles depending on the design and method of drug delivery. Pre-treatment of the skin is done with solid microneedles by opening microchannels, which are then followed by the application of drug formulations topically. Micro-needles are coated with drugs over the surface, which dissolves quickly once inserted, and releases instantly [43]. Microneedles are dissolved using biodegradable polymers that entrap drugs into its matrix which are released as the microneedles dissolve in the skin. Hollow Microneedles HMNs are miniature syringes that infuse liquid formulations directly into the dermis [44]. Micro needles which mimic hydrogel will enlarge when in contact with the interstitial fluid to form a continuous channel through which the drug will diffuse. Lastly, hybrid microneedles are a combination of various types e.g. dissolving tips with hollow bases which optimize delivery. All the types are designed to achieve certain therapeutic uses, with vaccines to biologics, and offer a flexible platform in delivery of drugs through the skin [45]. The level of drug loading and release is different according to type of the microneedles. Microchannels in solid microneedles are created and then the drug is applied using passive diffusion. Microinjectors are used as coated needles where the drugs are deposited on the surface of the needles, to be released upon insertion [46]. Dissolving microneedles entrap drugs in biodegradable polymers to allow continuous delivery due to the breakdown of the microneedles. Direct Infusion of liquid formulations into the dermis Hollow microneedles can be used to deliver accurate dosage and timing [47]. Microneedles that form hydrogel are used as carriers, which expand creating continuous channels through which drugs may diffuse into a reservoir attached. As part of the combination of different mechanisms, hybrid microneedles utilize rapid release off coated surfaces and then sustained release off cores dissolving. These various applications allow the delivery of small molecules, peptides, proteins, and vaccines and therefore microneedles can now be tailored to meet a whole host of therapeutic applications [48]. All types of microneedles have their own peculiarities of benefits and drawbacks. Simple and inexpensive, solid microneedles depend on passive diffusion to achieve efficiency [49]. Micro-needles that are coated are fast in release, but have a low drug-loading capacity. Micro needles that are dissolved in solution are biocompatible and do not produce sharps waste, however, the mechanical properties are not as strong as required to penetrate deep [50]. Hollow microneedles enable more simple dosing and infusion of larger volumes and are more complex to produce and clog. Micro needle-forming hydrogel allows sustained release and reservoir-based delivery but must have particular attention to material design to allow swelling but not rupture. Hybrid microneedles are a combination of multiple types, with the effects of improved fabrication complexity and cost [32]. The general message is that microneedles are better than traditional injections in terms of patient compliance, bioavailability, and safety, although optimization of mechanical strength, drug loading, and scalability still presents a challenge to clinical implementation on a mass scale [43]. Figure 2 also demonstrates the detailed classification, drug delivery mechanism and the benefit and drawbacks of the various types of microneedles.



MICRONEEDLE TYPE	PRINCIPLE ADVANTAGES	PRINCIPLE LIMITATIONS
Solid	Cost-effective, simple design	Limited efficiency, relies on passive diffusion
Coated	Rapid release	Limited loading capacity
Dissolving	Biocompatible, avoids sharps waste	Insufficient strength for deeper penetration
Hollow Microneedles	Large volume, directly into 4 larger volumes	Lisufficient strength in microneedles
Hydrogel-Forming Micns	Reservoir trp release, sustainell drug cainnvt	Contnuous channel for diffusion from reservoir to inollow base
Hybrid Microneedles	Passive diffurarsy, and stamply via hollow base	Increased ar fabrication complexity & cost

OVERALL, MICRONEEDLES IMPROVE PATIENT COMPLIANCE, BIOAVAILABILITY, AND SAFETY. OPTIMIZATION OF MECHANICAL STRENGTH, DRUG LOADING, AND SCALABILITY REMAINS A CHALLENGE FOR WIDESPREAD CLINICAL ADOPTION.

Figure No.: -2 Microneedles classification outlining various design types, drug delivery methods, and their pros and cons.

MATERIALS AND FABRICATION TECHNIQUES

Silicon is still at the forefront of microelectronics owing to its semiconductive nature and the suitability with ICs [51]. Conductive pathways, interconnects, and electrodes are commonly used in microfabrication using metals like copper, aluminium and gold [52]. Polymers (PDMS and PMMA) are flexible, biocompatible and easy to process, thus useful in biomedical devices [53]. Carbohydrates are also less traditional and are also investigated as biodegradable and bio-inspired materials, also providing a sustainable option in drug delivery and tissue engineering [54]. These materials create a rich arsenal of tools that can be used in electronics and biomedicine. They are also chosen based on mechanical strength, conductivity, biocompatibility, and scalability, to provide a specific device solution. Micromolding allows microstructures to be replicated with high accuracy with elastomers such as PDMS, which is commonly used in microfluidics [55]. Photolithography is the best semiconductor patterning technique to date, with a resolution capability of nanoscale in the area of UV light exposure on photoresists [56]. The laser-based techniques, laser ablation, and micromachining, offer direct-write functions in rapid prototyping, and material removal [57]. In the meantime, additive manufacturing is being introduced in 3D printing where the geometries are complex and multi-material integration is possible [58]. Both methods have trade-offs, photolithography is precise but expensive, micromolding can be scaled, but limited by materials, lasers can be used in many applications, but consume energy, and 3D printing is flexible, but its throughput is slower. The combination of them creates a complementary set in the fabrication of modern devices. With high surface area, electrospinning is applicable in tissue scaffold, drug delivery, and filtration applications [59]. It gives the option of adjusting fiber diameter and porosity, which opens variable mechanical and biological characteristics. However, another technology that transforms nanoscale fabrication is known as two-photon polymerization (2PP) that allows actual nanoscale 3D structuring down to the diffraction limit [60]. This method is especially useful in photonic gadgets, biomedical implantation and micro-optics. Recent developments on laser nanoprinting combine 2PP with stereolithography and can be used in micro-robotics and sensors [61]. Both methods are a transition to nanoscale accuracy and bio integration, and a complement to the conventional fabrication technologies with a previously unseen resolution and functionality [62].

DESIGN PARAMETERS AND OPTIMIZATION

Microneedle geometry has a primary role in penetration efficiency and comfort in the patient. The ideal lengths are between 300900 1 mm, which is enough to penetrate the stratum corneum without causing pain receptors [63]. Conical, pyramidal, and bevelled ends are some of the shapes, which influence the ease of insertion and consistency in drug delivery [64]. Density needs to be matched between coverage and mechanical strength because excessively high density can result in tearing of the skin, whereas excessively low density will decrease the drug load. Research indicates that hollow microneedles having a length of 500 µm and a tip diameter of 20 µm offer efficient delivery with little harm [65]. Dimensions can be controlled with precision using manufacturing methods such as those of micromilling and lithography, thus can be reproducible and scalable. Therefore, optimization of geometry is necessary to create a balance between efficacy, safety and manufacturability. Robustness of the needles is provided by mechanical strength so that microneedles can penetrate without fracturing [66]. The compression tests show that the polymeric microneedles should resist the forces of over 0.1 N per needle so that the needles can be inserted reliably. Such materials as silicon, stainless steel, biocompatible polymers, etc., are considered to have fracture resistance [67]. The force required to insert is determined by the sharpness of the tip and the elasticity of the skin; the sharper the tip, the less force is needed but the more the tip can be easily broken. Commercial microneedles may be subjected to mechanical integrity tests in order to be regulated. Research indicates that the direct relationship between mechanical strength and patient safety is based on the fact that broken needles may lead to irritation or incomplete administration of drugs [68]. To maximize the insertion force, the balance between sharpness, material toughness and array design is required to produce painless but effective penetration. Microneedles make it possible to load drugs and release them in a controlled manner. Micro needles made of polymers such as PVA or hyaluronic acid can be dissolved and put drugs in the matrix [69]. The rate of release is dependent on the rate of the dissolution of the material, the solubility of the drug, and the geometry of the microneedle. The dual-drug delivery systems have been achieved in order to experience sequential release to improve therapeutic outcomes. Micro needle Hydrogel-based microneedles allow sustained release when the needles swell in the interstitial fluid to extend the availability of the drug [70]. Research points out that in order to optimize drug loading, payload size needs to be matched with mechanical strength because increased loading can lead to structural integrity loss. Current development of programmable microneedles has made customized profiles of the release, enhancing patient adherence and treatment accuracy [71]. The most important thing in the design of the microneedles is safety. Regulatory requirements focus on the sterility, biocompatibility, and mechanical integrity in order to avoid the infection or tissue damage. The risks comprise skin irritation, allergic reactions and partial delivery of the drug in the event that needles become broken. It mandates that clinical safety procedures involve an appropriate patient evaluation, device cleanliness, and monitoring of their post-application [72]. FDA recommendations emphasize the necessity of standard testing so that the performance of the devices should be similar. Research indicates that the success of microneedles is safer than hypodermic needles, providing the least invasive method with reduced pain and trauma [73]. Nonetheless, contraindications, including the usage in patients with skin conditions or damaged immunity, have to be optimized. Safety: Safety is ensured through vigorous testing, meeting of regulations and educating patients [74].

EVALUATION AND CHARACTERIZATION

Biomaterials need to be mechanically tested in order to ascertain their strength, elasticity and durability. Such methods as tensile, compressive and fatigue tests are commonly used to determine the performance under physiological loads. As an example, tensile test can assess the modulo of Young and ultimate tensile strength whereas fatigue test imitates the cyclic stresses in vivo. These tests guarantee the biomaterials to be subjected to mechanical requirements in implants or scaffolds [75]. Such evaluations are guided by ASTM standards so that there is reproducibility and comparability. Nanoparticles, polymers are also incorporated in smart biomaterials, which exhibit different mechanical behavior depending on the composition, thus, the significance of biomechanical analysis [76]. This testing is not only a validation of safety but also it helps in informing design improvements in the biomedical applications. My in vitro and in vivo studies will be important to determine the biocompatibility and functionality of biomaterials. In vitro tests, including cell adhesion and cytotoxicity assays, give the initial information on the cellular reactions [77]. Such studies are used to determine possible inflammatory or toxic effects prior to animal testing. In vivo research, which is done on animal models, analyses tissue integration, degradation and immune responses [78]. An example is the use of biodegradable polymers such as magnesium alloys that have indicated positive outlook in regeneration of bones [79]. Collectively, these methods are used in bridging laboratory discoveries to clinical relevance, whereby biomaterials are safe and are effective in human use. Scanning electron microscopy (SEM) and optical microscopy are the types of imaging methods that cannot be denied to characterize biomaterial surfaces. SEM offers images with high resolution on surface morphology, that is, porosity, roughness, and microstructural variations [80]. These parameters affect the cell adhesion and tissue integration. Microscopy is also used in visualizing the interactions of biomaterial and cells, and it will give an insight in to the biocompatibility [81]. The biomaterial-bio interface layers can be studied using advanced SEM applications, which are important in the success of implants [82]. These imaging methods are useful as supplementary to mechanical and biological testing allowing complete assessment of biomaterials. The permeation and drug release analyses test biomaterials, which are utilized in controlled drug delivery systems. These researches quantify release dynamics, diffusion rate, and bioavailability of therapeutic agents incorporated in biomaterials [83]. To illustrate, hydrogels and polymeric nanoparticles are studied in sustained release profiles, which guarantee the effectiveness of constant therapeutic impact [84]. The permeation analysis of different types of biological membrane is used to determine the efficiency of drug transport, which is important in cases of oral or transdermal delivery systems. These evaluations together give biomaterials a safe, predictable and effective release of drugs in clinical use [85]. Altogether, such full assessment and characterization methods guarantee the safety, functionality, and clinical usefulness of biomaterials, as explained in detail in Figure 3.

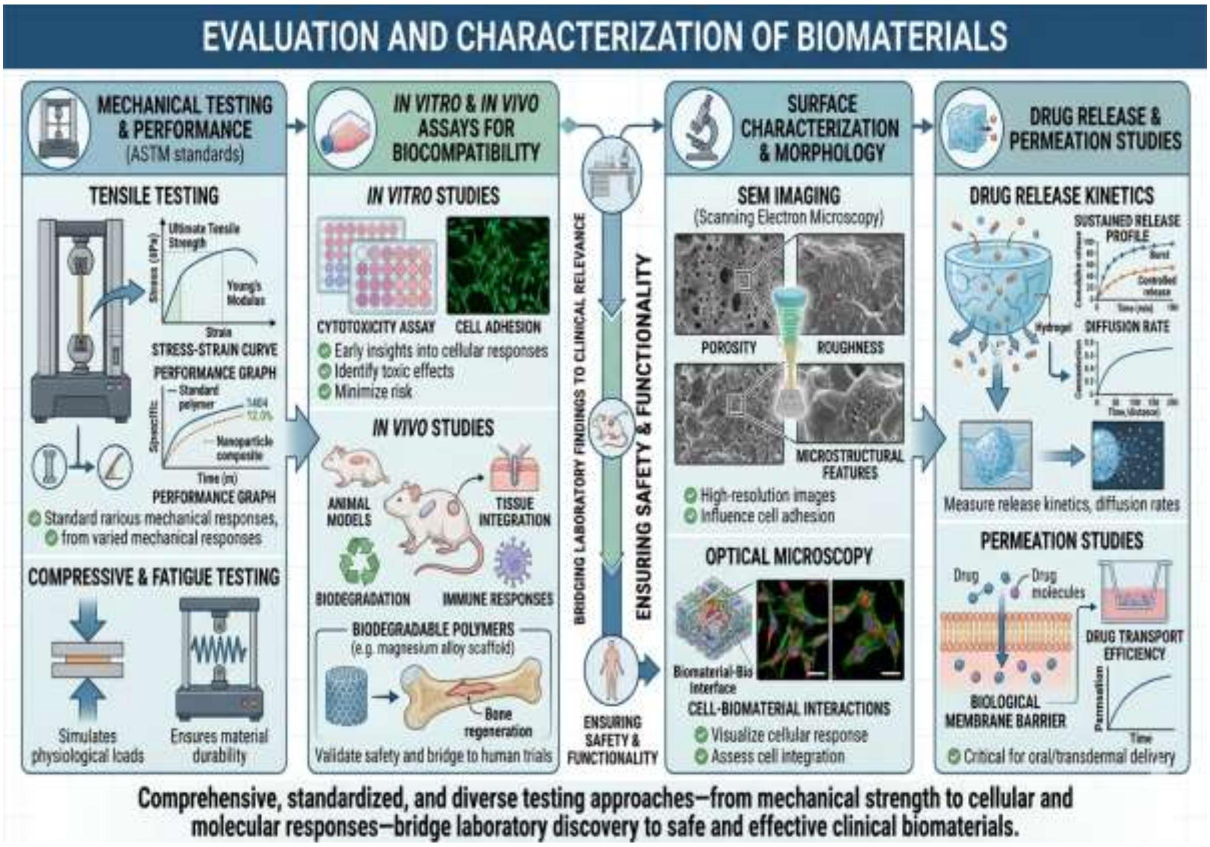


Figure No.: -3 The research evaluated and characterized biomaterials through mechanical tests and biocompatibility tests and surface morphology tests and drug release and permeation tests.

RECENT ADVANCEMENTS IN MICRONEEDLE TECHNOLOGY

Microneedle (MN) technology has progressed from its original transdermal system design to its current state, which uses intelligent systems that incorporate smart materials and nanotechnology and digital health technologies. The microneedles which respond to stimuli, enable doctors to release drugs in a precise manner through their ability to respond to both physiological and environmental stimuli [86]. Through 3D printing technology, it becomes possible to create microneedle designs which can be tailored to individual needs while still maintaining their ability to be produced consistently. The application of artificial intelligence to design optimization results in faster development processes which create personalized drug delivery systems for individual patients. The application of nanotechnology technologies enhances drug development, while the nanotechnology integration brings about benefits in drug stability and targeting and controlled release, which scientists use to develop new cancer and vaccine treatment methods [87]. The use of wearable biosensing microneedles facilitates continuous patient monitoring, while also providing therapy that uses feedback mechanisms for treatment control. The research results demonstrate how these technological advancements enable the creation of intelligent microneedle systems, which possess the ability to adapt their functions while performing multiple tasks, for use in future healthcare solutions [88]. The detailed data is summarized in the table 1.

Table No.: - 1: A summary of the latest advanced microneedle technologies, their working mechanisms, practical applications, advantages, and the challenges they bring.

Subtopic	Mechanism/Principle	Applications	Benefits	Challenges	Reference
Smart / Stimuli-Responsive Microneedles	Respond to pH, glucose, or temperature changes	Diabetes (insulin release), cancer therapy	Controlled drug release, reduced side effects	Complex fabrication, stability issues	[89]
Glucose-Responsive Microneedles	Release insulin when glucose levels rise	Diabetes management	Prevents hypoglycemia, patient-friendly	Calibration needed for accuracy	[90]
Temperature-Sensitive Microneedles	Hydrogel swelling at specific temperatures	Localized drug delivery	Site-specific release	Limited range of stimuli	[91]
3D-Printed Microneedles	Fabricated via stereolithography or two-photon polymerization	Vaccines, personalized medicine	Customizable, cost-effective	Material biocompatibility concerns	[92]
Biodegradable 3D-Printed Microneedles	Made from polymers like PLA or PCL	Vaccine delivery	Safe degradation, eco-friendly	Mechanical strength limitations	[93]
AI-Based Microneedle Design	Machine learning predicts strength & penetration	Personalized drug delivery	Faster prototyping, precision	Requires large datasets	[94]
Nanoparticle-Integrated Microneedles	Gold nanoparticles, nanocarriers embedded	Photothermal therapy, mRNA vaccines	Enhanced stability, deeper penetration	Risk of nanoparticle toxicity	[95]
Nanofiber-Coated Microneedles	Nanofiber layers improve drug loading	Cancer and gene therapy	High drug payload	Complex manufacturing	[96]
Wearable Biosensing Microneedles	Integrated sensors for glucose, lactate, cortisol	Chronic disease monitoring	Real-time data, painless	Sensor calibration, power supply	[97]
Wireless Microneedle Systems	Connect to smartphones/telemedicine platforms	Remote patient monitoring	Continuous feedback, telehealth	Data privacy, connectivity	[98]

APPLICATIONS OF MICRONEEDLES

Microneedles (MNs) have diverse applications in modern healthcare because they provide a minimally invasive method which enables effective transdermal drug delivery. The use of MNs for drug and vaccine delivery increases bioavailability while allowing patients to receive protein and peptide and vaccine injections without discomfort [99].

Diabetic patients can achieve better glycaemic control through insulin-loaded microneedles which deliver medication in a controlled manner that adapts to their needs. Microneedles (MNs) permit precise delivery of chemotherapy drugs which decreases harmful side effects while improving treatment results [100]. The dermatological field and the cosmetic industry use microneedles to treat acne and scars and wrinkles and skin rejuvenation because they stimulate collagen synthesis. Doctors use diagnostic microneedles to perform tiny fluid extractions from patients which allows them to observe biomarker changes and identify diseases while creating customized treatment plans [101]. The detailed classification of mechanisms, applications, benefits, and challenges is summarized in Table 2.

Table No.: -2 The study provides a summary of microneedle technology which includes its operational principles and different fields of application together with its advantages and the obstacles which must be overcome in therapeutic and cosmetic and diagnostic uses.

Subtopic	**Mechanism/Principle**	**Applications**	**Benefits**	**Challenges**	**Reference**
Drug Delivery	Microneedles pierce stratum corneum to deliver drugs	Pain management, antibiotics	Minimally invasive, rapid absorption	Limited payload capacity	[102]
Vaccine Delivery	Microneedles deposit antigens intradermally	Influenza, COVID-19 vaccines	Enhanced immune response, self-administration	Stability of vaccine formulations	[103]
Diabetes Management (Insulin)	Glucose-responsive microneedles release insulin	Type 1 & Type 2 diabetes	Prevents hypoglycemia, painless	Calibration for glucose sensitivity	[104]
Continuous Insulin Delivery	Hydrogel-based microneedles provide sustained release	Long-term diabetes therapy	Steady insulin levels	Risk of over-delivery	[105]
Cancer Therapy	Microneedles deliver chemotherapeutics locally	Skin cancers, melanoma	Targeted therapy, reduced systemic toxicity	Limited penetration depth	[106]
Immunotherapy	Microneedles deliver immune modulators	Tumor vaccines, checkpoint inhibitors	Localized immune activation	Complex dosing requirements	[107]
Dermatological Uses	Microneedles enhance transdermal absorption	Anti-aging, acne treatment	Improved cosmetic outcomes	Patient acceptance in cosmetics	[108]
Cosmetic Applications	Microneedles stimulate collagen production	Wrinkle reduction, skin rejuvenation	Non-surgical, minimal downtime	Requires repeated sessions	[109]
Diagnostic Applications	Microneedles extract interstitial fluid	Glucose, lactate, cortisol monitoring	Real-time biomarker detection	Sensor calibration issues	[110]
Wearable Diagnostics	Microneedles integrated with biosensors	Continuous health monitoring	Telemedicine-ready, painless	Data privacy, device cost	[111]

REGULATORY AND SAFETY CONSIDERATIONS

The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) offer elaborate regulatory frameworks of medical devices. The FDA guidance documents specify design, production, labelling, and testing requirements that are used to make sure of safety and effectiveness before approval to be put in the market [112]. EMA manages conformity check in the EU Medical Device Regulation (MDR) where CE marking is required following audits of quality systems and technical documentation [113]. Although the two focus on patient safety, they do not follow similar methods as FDA is largely dependent on premarket submissions and EMA requires compliance throughout the lifecycle and the use of notified bodies [114]. These frameworks require the manufacturers to negotiate access to the global market without compromising risk based decision-making process and strong quality systems. Toxicity testing is conducted to make sure the biomaterials to the device used do not cause adverse biological reactions in line with ISO 10993 standards [115]. The implantable and injectable products are sensitive, and sterility is extremely important because when these products are contaminated by microbes it may result in serious infections. Membrane filtration and the direct inoculation test are two tools of sterility testing that are commonly used in pharmaceutical and biotechnology [116]. In Good Manufacturing Practices (GMP) quality control (QC) incorporates sterility assurance with the monitoring of the environment, cleanroom validation and the control of contamination. Collectively, the toxicity analysis, sterility verification, and QC form the basis of the safety of biomedical fabrication, as they assure that the products are of high standard in relation to regulatory standards and safeguard the health of patients [117].

FUTURE PERSPECTIVES

It is believed that the microneedle technology will have a considerable positive impact on the transdermal drug delivery, with the innovations of smart and personalized systems. The next generation of stimuli-responsive microneedles will be created, which will be able to release drugs in response to physiological signals (glucose, pH, temperature, etc.) in order to provide a precise and controlled treatment. The wearable devices and biosensors will be integrated to enable real-time biomarkers monitoring and feedback-controlled drug delivery, which will enhance the management of chronic diseases. Increased delivery in biologics, such as proteins, vaccines and nucleic acids, will also provide further improvements in therapeutics. Recent fabrication processes such as 3D printing and nanotechnology will enhance flexibility in designs, scalability and cost-effectiveness. Nonetheless, it will have to overcome such problems as regulatory approval, mass production, and safety in the long term. All in all, it can be concluded that microneedles will become multifunctional, patient-friendly systems that combine diagnosis and treatment and serve a central role in healthcare in the future and individual medicine.

CONCLUSION

The microneedle is one such technology that has borne great progress in transdermal drug delivery systems through providing an alternative route that is less invasive, painless and effective than the traditional routes. It is very effective in breaking the barrier of the stratum corneum allowing the delivery of diverse therapeutic agents such as small molecules, proteins and vaccines to be delivered more effectively. A range of microneedles, including solid, coated, dissolving, hollow, and hydrogel-forming systems, gives the form of flexibility in drug delivery methods. The developments of the materials and fabricating methods have enhanced their performance, safety, and compliance with the patients. In spite of these advantages, there are the problems associated with the mass production, cost-efficiency, regulation acceptance, and safety at a long distance. More research and technological advancement is needed to overcome these shortcomings. Altogether, the potential of microneedles to change the method of drug delivery can be significant by enhancing the effect of therapy, decreasing side effects, and facilitating the creation of patient-centric and innovative medical tools.

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