PROSPECTS
IN PHARMACEUTICAL SCIENCES

Prospects in Pharmaceutical Sciences, 24(2), 131–148
https://prospects.wum.edu.pl/

Review Article

MICRONEEDLES IN BREAST CANCER: REVOLUTIONIZING DIAGNOSIS AND TREATMENT HORIZONS

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Received: 13.07.2025 / Revised: 04.11.2025 /Accepted: 07.12.2025 / Published in final version: 25.06.2026

ABSTRACT

Breast cancer (BC) is a prevalent and life-threatening disease that demands effective diagnostic and therapeutic solutions. Despite advancements in treatments such as chemotherapy, current approaches often involve invasive techniques that may cause significant patient discomfort and side effects. Microneedles offer a promising alternative for both BC diagnosis and treatment, providing minimally invasive sampling and targeted drug delivery. Microneedles bypass the gastrointestinal and metabolic barriers associated with traditional drug administration, allowing direct delivery of therapeutic agents to BC tissues while minimizing systemic toxicity. There are various microneedles types: solid, coated, dissolving, hollow, and hydrogel-forming. Microneedles exhibit unique mechanisms for delivering drugs and detecting BC biomarkers. Advances in microneedles materials and fabrication methods, including polymers, ceramics, metals, and biocompatible substances, enhance microneedles efficiency and safety. Microneedles have also been applied in BC immunotherapy, chemotherapy, and photothermal and photodynamic therapies, demonstrating high efficacy in tumour reduction, survival improvement, and reduced side effects in preclinical models. While microneedles show substantial potential, challenges such as variability in skin penetration, mechanical strength, and clinical scalability must be addressed. Continued research and clinical trials are essential to optimize microneedle technology for future BC management, potentially revolutionizing non-invasive cancer care. An extensive literature review has been carried out on microneedles for BC diagnosis and treatment horizons using ScienceDirect, PubMed and Google Scholar from 2009 to 2025.

KEYWORDS: micromolding, lithography, chemotherapy, immunotherapy, geometry.

1. Introduction

Cancer is one of the leading causes of death worldwide [1]. As per GLOBOCAN 2022, breast cancer (BC) has surpassed lung cancer to become one of the most prevalent types of cancer. Globally, in 2022, 2.3 million women were diagnosed with BC, out of which 0.67 million women died [2]. BC accounts for about 31% of all cancer diagnoses and is characterized by several subtypes [1]. BC subtypes are categorized into four groups: Luminal A, Luminal B, human epidermal growth factor receptor 2 (HER-2) positive, and triple-negative breast cancer (TNBC) [3]. It is also classified by stages, ranging from Stage 0 to Stage IV, as illustrated in Fig. 1. BC patients continue to have high rates of morbidity and death despite the extensive amount of research on the detection and management of the disease. The pathophysiology of BC involves the transformation of normal breast cells into malignant cells. This often results from genetic mutations, hormonal changes, and environmental factors [4]. The detailed mechanism of BC pathophysiology is explained in Fig. 2.

The standard of care for advanced BC is chemotherapy which is frequently combined with additional medical procedures, including radiotherapy, surgery, and hyperthermia [5, 6]. The most common ways to administer chemotherapy drugs are orally or by intravenous (I.V.) infusion. Despite being more convenient, oral administration has some drawbacks, such as inadequate absorption through the intestinal membrane and the enzymatic degradation of the drug in the gastrointestinal system [6, 7]. Oral drug administration often results in fluctuating drug levels. This is due to rapid absorption and elimination, which leads to peaks and troughs in plasma concentration. This lack of control over pharmacokinetics can contribute to subtherapeutic effects or toxicity. Furthermore, oral drugs cannot be easily targeted to specific tissues, which reduces efficacy and increases systemic side effects, especially in the case of anticancer agents [8]. These challenges lead to decreased bioavailability and rapid drug elimination.

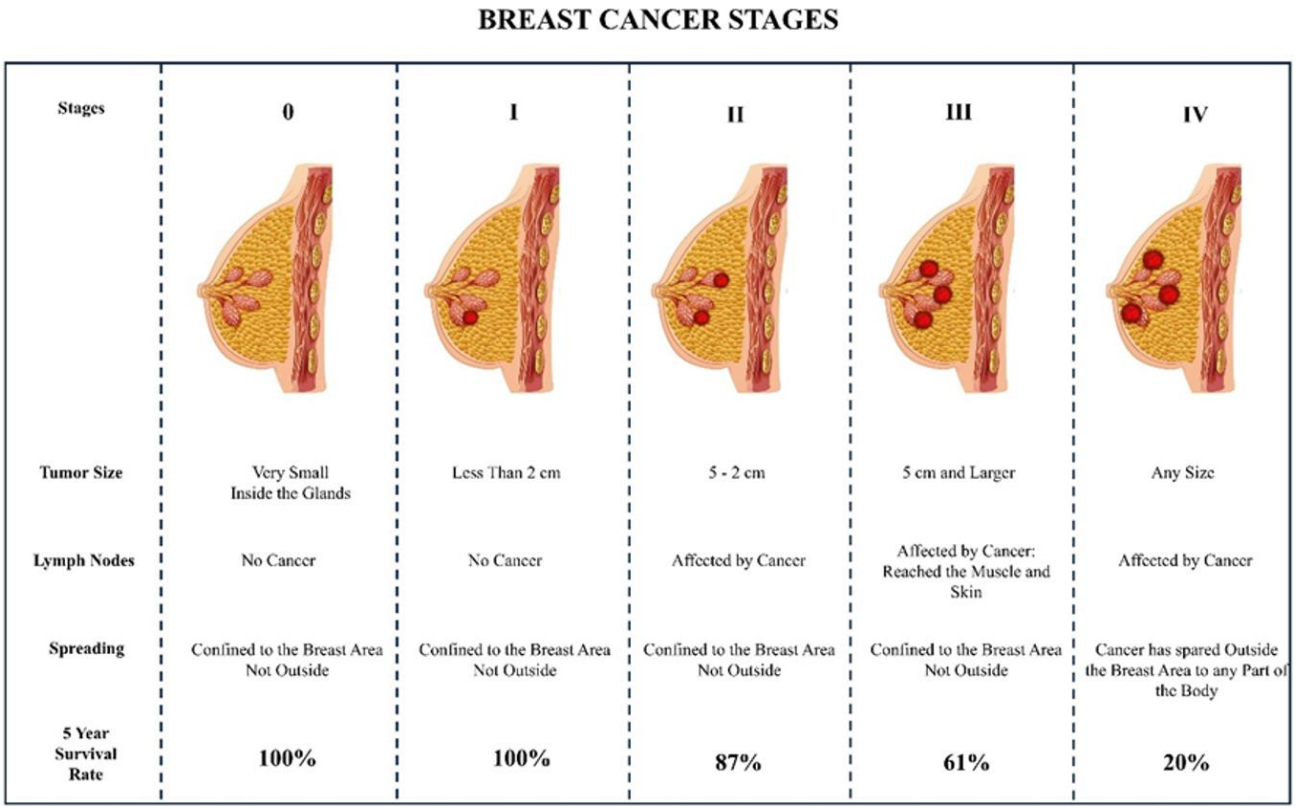

Fig. 1. Schematic diagram depicting stages of breast cancer.

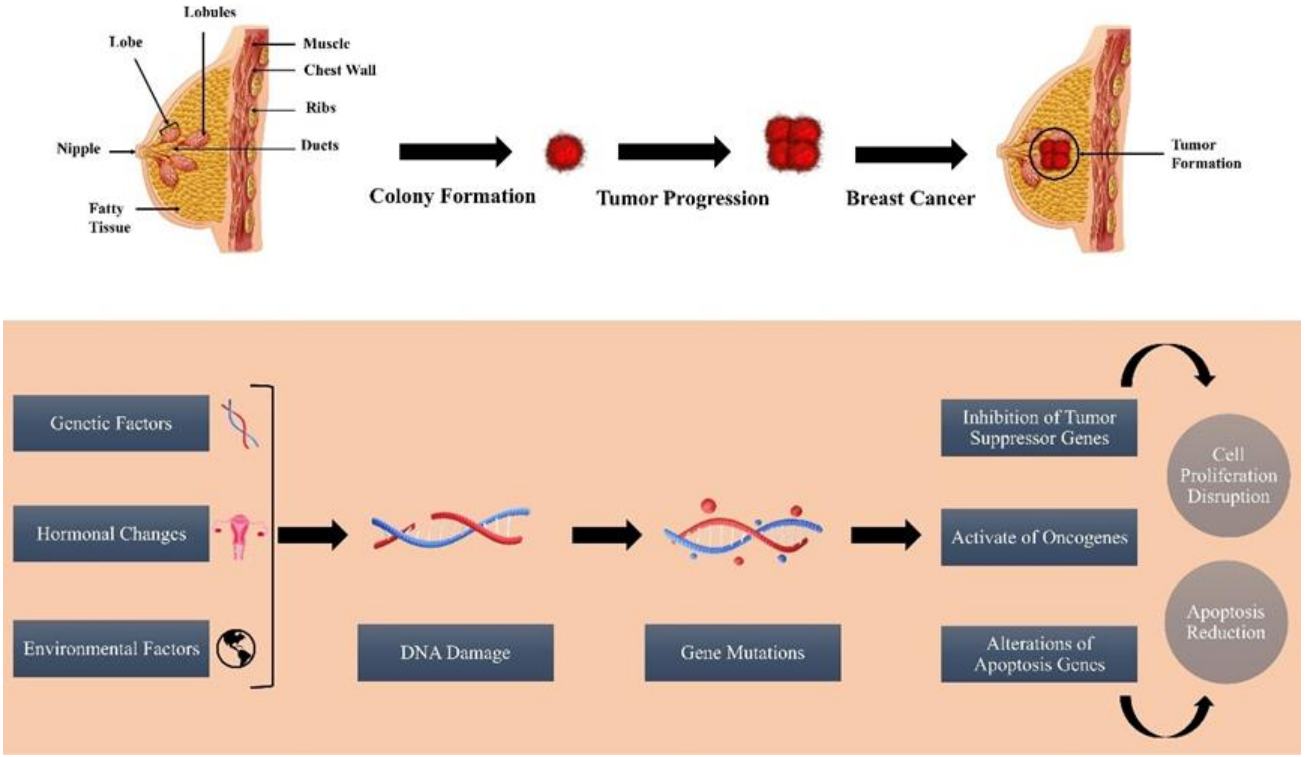

Fig. 2. Schematic diagram illustrating the pathophysiology of breast cancer.

Due to these limitations, I.V. infusion has become more popular among medical professionals. It enables the administration and maintenance of a high drug concentration in plasma, preventing gastrointestinal problems and improving therapeutic efficacy [9]. Nevertheless, it has limitations, such as discomfort in the administration of injections and environmental issues related to the disposal of used needles. Furthermore, the physical and emotional health of patients is further impacted by the intrusive sampling procedure used for the initial diagnosis and continuing surveillance of BC.

Transdermal delivery is a non-invasive substitute for I.V. and oral administration [10]. It is an efficient method of administering therapeutic substances that are impacted by first-pass metabolism or that cannot withstand the conditions of the gastrointestinal tract [11]. The outermost layer of the skin restricts the passage of medications with a molecular weight below 600 Da [12]. As a result, several chemical and physical techniques have been researched to break down the stratum corneum (SC) barrier and increase the penetration of therapeutic substances. Thus, to overcome the aforementioned limitations, scientists have developed microneedle arrays that allow for the advantages of topical transdermal patches and hypodermic needles while also detecting cancer by identifying markers [13]. Microneedles offer significant advantages, as they make it possible to administer targeted medication directly into the tumour and repeatedly detect tumour biomarkers to monitor the disease throughout therapy [14]. Microneedles minimize pain during tumour diagnosis and injection. They enable the co-delivery of multiple drugs. They also allow for precise control of drug levels inside the breast tissue. This minimizes the negative effects of oral or systemic drug administration on adjacent tissues [15, 16]. The present review highlights the innovations in microneedle technology for treating BC and contemplates its potential to circumvent the drawbacks of conventional drug delivery methods, thereby enhancing targeted therapeutic efficacy and enabling biomarker-based diagnostics, which ultimately leads to increased patient compliance. An extensive literature review has been carried out on microneedles for BC diagnosis and treatment horizons using ScienceDirect, PubMed, and Google Scholar from 2009 to 2025. This review also emphasizes on the advancements of microneedle technology for BC treatment and focuses on their potential to overcome the limitations of conventional drug delivery methods to enhance localized therapeutic efficacy and enable biomarker-based diagnostics to improve patient compliance and quality of life.

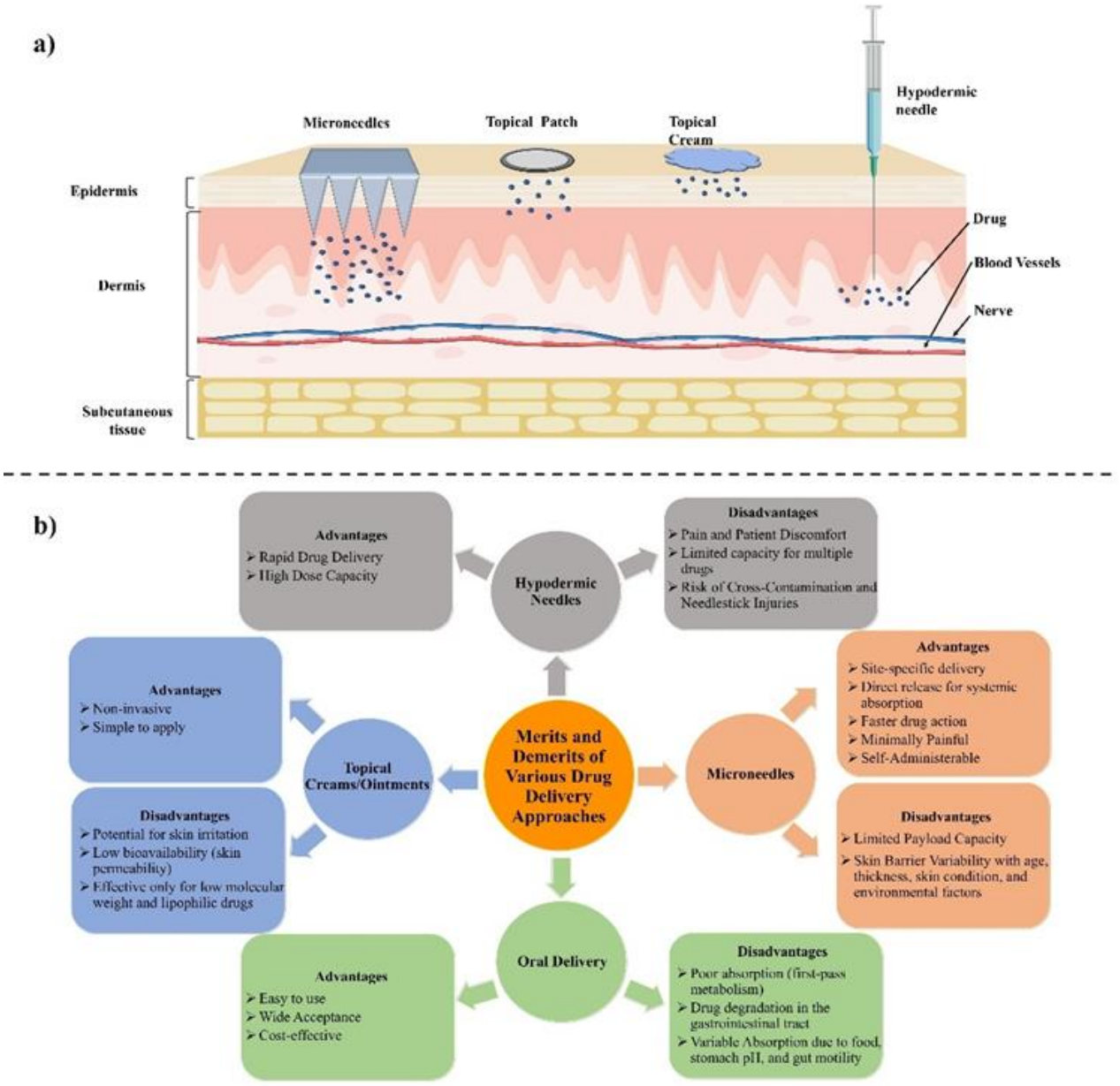

Fig. 3. (a) Comparison of topical, transdermal (microneedle) and parenteral drug delivery systems, (b) merits and demerits of oral, topical, hypodermic, and microneedle delivery approaches.

1.1. Barriers to effective drug delivery through the skin

The human skin functions as a "wall" that inhibits foreign substances from penetrating the skin and interfering with the natural metabolism of the body [17]. As a result, the ideal temperature, humidity, and other conditions are provided for internal organs via the skin. It was believed that the skin acts as an impenetrable barrier to outside substances as various studies have demonstrated [18]. Numerous investigations have, however, demonstrated that skin is not impenetrable. Rather than being only a barrier, the skin is better understood and represented as a multi-layered, multifunctional structure [19]. The main barrier to absorbing medications is the stratum corneum (SC), which is the outermost layer. The layer beneath the SC is the epidermis, while the innermost layer is known as the dermis. Before reaching the blood vessels and bloodstream, the drug must pass through the epidermis and SC. Hair follicles, sweat ducts, and the SC are three well-recognized routes for passive drug diffusion. The drug must be suitably lipophilic with a Log P value between 1 and 3 and have a molecular weight of less than 600 Da to obtain a greater diffusion coefficient in this method [20]. However, because of their low delivery abilities, the convenience and practicality of medication distribution remain severely constrained. Therefore, it is extremely desirable to develop novel delivery devices that can effectively penetrate the outer layer of skin for transdermal drug administration and treatment.

1.2. Microneedles vs. hypodermic needles/oral/topical drug delivery systems

When choosing a drug delivery method, factors such as physical strength, patient treatment, circumstances, injection efficiency, and available facilities must be considered, as each method has unique benefits and drawbacks (Fig. 3a and 3b). Hypodermic needles are the preferred method of administering medication because of their high rate of drug delivery (>75%); however, they are restricted by injection-related discomfort, limited capacity for multiple therapeutics, and decreased drug durability [21]. Oral delivery is often unsuitable for cancer drugs due to poor absorption and degradation from first-pass metabolism, while topical creams and ointments, though non-invasive, suffer from low bioavailability and limitations imposed by skin permeability. Microneedles provide a targeted and minimally invasive route for drug delivery, offering benefits such as improved systemic absorption, faster onset of action, and reduced patient discomfort compared to hypodermic needles or oral routes. They also bypass gastrointestinal degradation and first-pass metabolism. However, limitations exist, including challenges in fabrication precision, potential dose variability, risk of mechanical failure, and issues such as microneedle blockage or incomplete skin penetration [22, 23]. Overall, microneedles provide a more effective and targeted approach, with approximately 75% effectiveness in drug delivery compared to traditional methods [24].

2. Classification of Microneedles

There are five main types of microneedles [25]. Each type of microneedle array has a different mechanism of action after application on the skin. Table 1 highlights the differences between various types of microneedles: solid, coated, dissolving, hollow, and hydrogel-forming (Fig. 4), outlining their benefits, drawbacks, effectiveness, and release mechanisms [26]. This detailed comparison is intended for a better understanding of the distinct features and performance of each microneedle type, aiding in the selection of the most suitable option for various drug delivery needs.

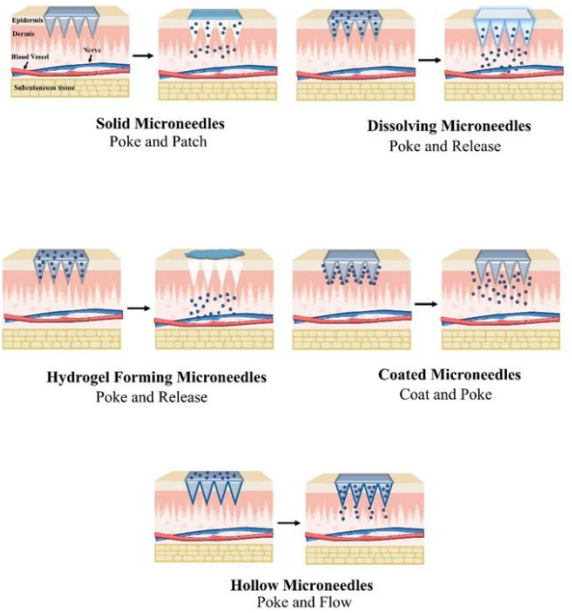

Fig. 4. Schematic diagram depicting common designs of microneedle-based drug delivery systems: solid microneedles, dissolving microneedles, hydrogel-forming microneedles, coated microneedles, and hollow microneedles.

2.1. Solid microneedles

Solid microneedles are fabricated from a single material with microscale fine tips and are free from excipients or drugs [28]. When a microneedle patch is applied, the sharp needle tips puncture the skin and form microscopic channels that allow the drug placed on the treatment area to be delivered directly into the skin layers, enhancing drug absorption [29]. This mechanism is often referred to as "poke and patch," where the microneedles are removed after creating channels, followed by the application of a conventional drug-loaded patch.

2.2. Dissolving microneedles

Dissolving microneedles are produced using biodegradable materials that contain the therapeutic agent and have adequate mechanical strength to pierce the skin. Dissolving microneedles employ a "poke and release" mechanism. They pierce the skin and then dissolve upon exposure to body fluids; thus, they do not produce any sharp waste [30].

2.3. Hydrogel-forming microneedles

Hydrogel-forming microneedles employ a "poke and release" mechanism and have the ability to "superswell" upon application. The drug is uniformly distributed in the entire microneedle (base, backing layer, and tip) and is gradually released when the microneedles are placed on the skin [31].

Table 1. Comparison of microneedles types.[27]

Type	Advantage	Disadvantage	Microneedles Efficacy	Release method
Solid	Simpler manufacturing Higher drug loading capacity	Potential for infections due to reuse May lead to skin damage	The drug loading is minimal and the delivery exhibits poor efficacy	Poke and patch
Coated	High precision, targeted delivery as the drug is coated on the needle Can be engineered for controlled release through coating composition	Dose Limitations Poor Biocompatibility Peeling during insertion	The drug loading is moderate and the delivery is of moderate efficacy.	Coat and poke
Dissolving	Drug incorporated within the microneedle structure, dissolves after application Eliminates the need for needle disposal, reducing biohazard risks Controlled release based on dissolution rate	Poor mechanical strength Dose limitations Physical stability	The drug loading is high and the drug delivery is highly effective.	Poke and release
Hollow	A substantial quantity of drugs can be loaded and delivered, and it is also suitable for tissue sampling.	Prone to leakage and clogging Low strength	The drug loading is high and delivery is high efficacy	Poke and Flow
Hydrogel forming	Size and shape have flexibility Reasonable drug loading	Limited mechanical strength May deform or swell	Moderate, depends on hydrogel properties	Poke and release

2.4. Coated microneedles

Coated microneedles employ a "coat and poke" mechanism, where a water-soluble matrix is applied to the surface of the solid needle. This coating must create a stable layer that adheres during both storage and skin insertion to ensure rapid release of the therapeutic agent upon penetration [32].

2.5. Hollow microneedles

Hollow microneedles resemble hypodermic needles in that they have reservoirs connected to inner channels to inject the medication directly into the skin [33]. The delivery is achieved through the "poke and flow" mechanism, allowing the controlled and continuous infusion of liquid formulations.

Among these, dissolving microneedles have gained significant attention in recent years due to their superior clinical applicability. Dissolving microneedles are fabricated using biodegradable polymers that safely dissolve within the skin after administration, thereby eliminating the need for sharp waste disposal. They offer a minimally invasive, pain-free, and patient-friendly route for the delivery of a wide range of therapeutics, including small molecules, peptides, and nanoparticles. Additionally, these microneedles enable controlled and sustained drug release, which is particularly beneficial in chronic or targeted therapies. Based on these attributes, dissolving microneedles are considered the most effective and practical option for modern medical applications, especially in transdermal drug delivery and cancer therapy [34-36].

3. Materials used in microneedles

The choice of materials used to fabricate microneedles is directly related to the purpose for which they are designed. The material influences qualities like permeability, strength, and flexibility. This, in turn, influences the efficacy of therapeutic approaches. The materials utilized can affect the fabrication procedures. FDA-approved materials including metals, glass, ceramics, silicon, polysaccharides, and polymers are frequently used in the manufacturing of microneedles [37]. Microneedle arrays were originally composed of silicon, but major improvements in microneedles production have been accomplished since then because of developments in polymer chemistry and microengineering [38]. These advancements have encouraged creative ideas in microfabrication and microelectronic technologies.

3.1. Silicon microneedles

Silicon materials exhibit an anisotropic crystalline structure that offers diverse capabilities in transdermal drug delivery and biomedical applications, due to their properties varying depending on the direction of measurement within the crystal lattice [39]. The first material to be reported to be utilized in the production of microneedles was silicon. The needles can be made in a range of sizes and forms because of the flexibility, precision, physical properties, and accuracy of the crystal structure of silicon. It is utilized to fabricate coated, hollow, and solid microneedles. MicronJet® is a silicon microneedle device manufactured by NanoPass Technologies Ltd that enables painless intradermal drug delivery by targeting the dermis and enhances clinical response while lowering dose in comparison with standard injections [40]. The brittleness of silicon poses safety concerns, as it risks needle fracture during skin insertion. Porous silicon is a potential solution. It is biodegradable. It undergoes hydrolysis in living organisms at a pH of about 7.5. This addresses the problem of crystalline silicon [41]. Silicon microneedles are typically fabricated using dry and wet etching methods. Wet etching allows for either isotropic or anisotropic etching by immersing a single-crystal silicon disk in various chemical etchants. Isotropic etching employs a corrosive HNA solution of hydrofluoric, nitric, and acetic acids to produce a uniform etch rate in all

directions, while anisotropic etching, utilizing solutions such as EDP (organic wet chemical etchant), hydrazine-based solutions, or, more commonly, potassium hydroxide, results in variable etching rates depending on the crystal plane. On the other hand, dry etching offers enhanced control over microneedles density, design, and geometry, overcoming the limitations of wet etching by producing faceted pyramid-shaped microprotrusions through selective exposure of crystal surfaces [42]. A novel manufacturing process, Glass Cover on Silicon (GCoS) technology, has emerged for fabricating thin microneedles intended for deep brain drug delivery, combining the advantages of silicon microneedles with innovative approaches to penetrate the blood-brain barrier effectively [43].

3.2. Polymer microneedles

Polymers are widely used to fabricate dissolvable, solid, or hydrogel-forming microneedles due to their mechanical strength, low toxicity, biodegradability, tissue compatibility, and affordability. Commonly used materials include polylactic acid (PLA), polyglycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA), polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), and hyaluronic acid (HA) [44]. Micromolding is a preferred fabrication method for polymeric microneedles. This is because it is cost-effective, repeatable, and scalable [45]. This involves pouring a polymer solution or melt into precision molds, typically made of silicone or metal, designed to ensure uniform microneedle dimensions. Once solidified through cooling or solvent evaporation, the microneedles are removed from the mold. This method is scalable and enables the incorporation of drugs into the polymer matrix for controlled release. Other key fabrication techniques include lithography, etching, and master structure replication, which ensure precise and consistent microneedle shapes. Laser-based micromolding and photolithography processes are also employed. Photolithography involves spin-coating a photosensitive polymer (photoresist) onto a substrate, followed by UV light exposure through a mask or projection stepper. Depending on the resist type (positive or negative), the exposed areas become either more soluble or less soluble in a developing solution, enabling precise pattern formation for microneedle arrays [46]. An innovative approach, droplet-air blowing (DAB), creates dissolving microneedles with minimal drug loss. In this method, direct air-blowing shapes and solidifies polymer droplets into microneedles, offering a cutting-edge solution for efficient drug delivery [47]. These advanced techniques collectively enable the mass production of polymeric microneedles with consistent size, shape, and functionality, making them ideal for applications such as drug delivery, vaccination, and therapeutics.

3.3. Ceramic microneedles

Ceramic microneedles are fabricated from materials such as zirconia, alumina, and calcium sulfate dihydrate and offer enhanced mechanical strength and resistance to temperature and humidity compared to most polymeric microneedles [48]. Among the materials used, alumina is preferred due to its chemical resistance and stability in forming stable oxides [49]. The primary fabrication techniques for these ceramic microneedles include micromolding and sintering. Micromolding involves pouring an alumina slurry into a microneedles mold made of PDMS (polydimethylsiloxane) and then hardening it, while sintering involves heating ceramic powders to form a solid structure [50, 51]. Additionally, the two-photon polymerization method has been employed to create microneedles using Ormocer®, an organically modified ceramic. This method involves selectively polymerizing photosensitive resins within precisely defined regions using ultrashort laser pulses from a near-infrared femtosecond laser source. At the focus point of the laser, two photons are simultaneously absorbed, leading to electrical excitation and a non-linear high-energy distribution that breaks the chemical bonds of the photoinitiator. Once the energy exceeds a certain threshold, the polymerization begins, allowing for precise control over the geometry of three-dimensional structures [52]. These methods allow for durable, high-performance microneedles suitable for drug delivery, cancer treatment, and vaccinations, providing an effective and localized solution for medical applications.

3.4. Metal microneedles

Microneedles are made of metals such as titanium, stainless steel, nickel, and palladium because of their durability and biological safety [53]. The robustness of metals, in contrast to silicon microneedles, guards against needle breakage during skin insertion. Metal materials are utilized to produce solid, hollow, or coated microneedles [54]. The most popular techniques for creating metal microneedles are photochemical etching, metal electroplating, laser ablation, and laser cutting. Using a laser, a thick metal sheet is carved into the shape of a 2D microneedle, which is then twisted at a right angle, creating a 3D microneedle. In addition, by forming inverse molds, the metal sheet is formed into a three-dimensional form using the laser ablation method. This happens when heat and energy from the laser are absorbed by the substrate, leading to its evaporation or sublimation [53,55,56]. Another approach uses solvent casting to apply a conductive polymer composite layer to a mold that has a series of vertical pillars. The metal electroplating technique, which yields hollow metallic microneedles, utilizes the conductive polymer layer as a base layer.

3.5. Glass microneedles

Glass-based microneedles offer advantages like chemical inertness, affordability, transparency, and a high Young's modulus, allowing safe skin penetration without breaking [57]. Their low cost and simple fabrication make them appealing for medical applications. However, brittleness remains a concern, and their chemical inertness limits compatibility with most manufacturing techniques. The conventional micropipette pulling method, still predominantly used, is labor-intensive and restricts production to single needles, making it unsuitable for complex structures or high-throughput manufacturing. Despite these challenges, glass-based microneedles continue to attract interest for their unique properties and potential in healthcare applications, particularly where chemical stability and precision are crucial [58].

3.6. Carbohydrate microneedles

Microneedles can be manufactured using carbohydrates such as xylitol, chitosan, sucrose, maltose, trehalose, galactose, raffinose, mannitol, dextran, sugars, and various

polysaccharides [59]. Numerous carbohydrates are naturally occurring and have long been utilized in healthcare. Micromolding and drawing lithography are common methods used in the manufacturing of microneedles based on carbohydrates. Carbohydrate materials are commonly used to produce dissolving microneedles for drug delivery applications. They are also safe for human health and inexpensive. However, they have several disadvantages as well, such as the need for high processing temperatures and mechanical failure after buckling [60].

4. Fabrication of microneedles

Microneedles of varying diameters, numbers, and shapes have been made using a variety of processes, each intended for the delivery of a particular medicinal substance. The three main methods of microneedles fabrication are additive, subtractive, and formative (Fig. 5) [61]. In subtractive manufacturing, the material is removed from a bulk substrate to fabricate the required microneedle shape. Examples of these processes include laser cutting, micromachining, and photolithography. Formative manufacturing techniques mainly include micromolding, sintering, and drawing lithography, in which material is poured into already prepared molds, and the resulting microneedles are removed once they have solidified. This simple, multi-step method works well for mass manufacturing and is frequently used to make ceramic- or polymer-based microneedles. Additive manufacturing, also known as 3D printing, includes techniques such as electroplating, stereolithography, two-photon polymerization, and fused deposition modeling. Because complex tooling and molds are not required, these methods provide several benefits, such as simplified setup and cost savings [62, 63]. The fabrication methods and their details are summarized in Table 2.

Table 2. Overview of microneedles fabrication methods: processes, materials, applications, and advantages/disadvantages.

Fabrication Method	Process	Materials	Applications	Advantages	Disadvantages	Ref
Micromolding	Cast material into a microneedles mold and solidify	Polymers, ceramics, metals	Drug delivery, cosmetics	Cost-effective, scalable, suitable for mass production	Limited to mold design, complex mold fabrication	[64, 65]
Photolithography	UV light exposure through mask to etch microneedles	Silicon, photoresist	Microelectronics, biomedical sensors	High precision, can create intricate designs	Expensive, time-consuming, limited to 2D patterns	[66, 67]
Electroplating	Electrochemical deposition of metals in a mold	Metals (e.g., gold, nickel)	Drug delivery, diagnostics	Produces strong, durable microneedles	Requires conductive substrates, limited to metal needles	[68, 69]
3D Printing	Additive manufacturing of microneedles layer by layer	Polymers, composites	Customizable drug delivery systems	High customization, rapid prototyping	Material limitations, lower resolution than lithography	[70, 71]
Laser Cutting/Ablation	Precision laser cuts or ablates material to form microneedles	Polymers, silicon, metals	Transdermal drug delivery, diagnostics	Precise control over shape and size	High equipment cost, limited to certain materials	[63, 72]
Micromachining	Mechanical etching, drilling, or milling at micro-scale	Silicon, metals, ceramics	Medical devices, sensors	Applicable to a wide range of materials	Low throughput, difficult for large-scale production	[73, 74]
Sintering	Compacted material particles are fused at high temperatures	Ceramics (e.g., alumina, zirconia), metals	Drug delivery, implants	Strong, high-temperature-resistant microneedles	Requires high temperatures, long processing time	[75, 76]
Drawing Lithography	Polymer solution drawn into needle shapes, then solidified	Polymers	Cosmetic treatments, drug delivery	Simple process, no complex equipment needed	Limited to polymer-based microneedles, low durability	[77, 78]

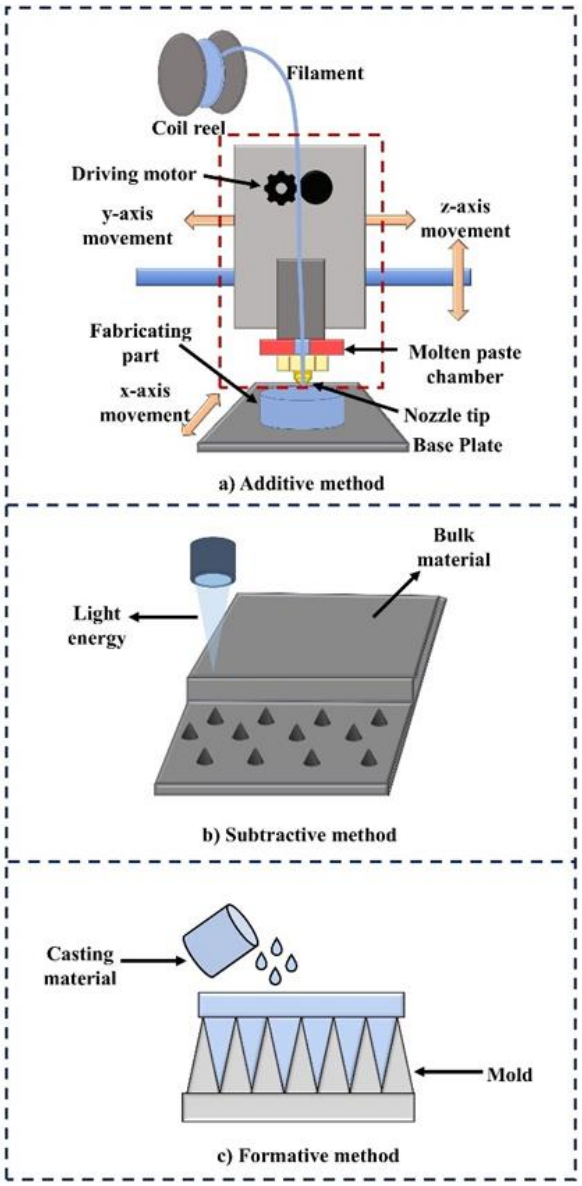

Fig. 5. Schematic illustration of the fabrication methods of microneedles a) additive method b) subtractive method and c) formative method.

5. Geometry of microneedles

Microneedles are tiny needles that are usually 25—2500 µm long, 20—250 µm wide, and have a tip diameter of 1—25 µm [79]. According to the desired use, they can be set up as a single needle, rows of needles, or patches with arrays of needles. It is important to consider certain parameters that influence the mechanical characteristics of microneedles while developing them for biomedical applications. Important factors to consider include the size of microneedles, structure, material choice, manufacturing processes, payload, force application strategies, sterilizing procedures, and stability during storage [80].

The ability of microneedles to achieve the desired target depth depends on their configurable parameters, including the length of the needle, base, and tip diameter (Fig. 6). These characteristics are crucial for tissue penetration. Most significantly, needle length must be properly chosen for efficient drug administration or sampling. For the microneedles to efficiently deliver medication to the epidermal layers and the dermis of the skin, respectively, they have to penetrate deeper than 20 µm and 150 µm. Longer microneedles have a higher chance of stimulating pain receptors. This is because nerves are found in the deeper layers of the dermis [81]. For skin sampling, a depth of 50 µm to 150 µm is sufficient to collect interstitial fluid (ISF), while a much greater depth of 1000 to 1500 µm is necessary for blood collection [82].

However, it is essential to understand that factors such as body mass index, age, gender, anatomical position, ethnicity, and skin type all affect skin thickness [83]. The thickness of the skin varies significantly across different anatomical locations; for example, the skin on the forearm or breast is thinner compared to the back or soles of the feet. This local variation influences microneedle insertion depth, drug delivery efficiency, and even pain perception. Wei, et al. demonstrated that skin thickness varies significantly across anatomical sites and correlates with body mass, affecting how deeply microneedles can penetrate and whether they reach the intended skin layers. Thicker skin needs longer microneedles for insertion. Thinner skin penetrates easily, potentially increasing the risk of over-insertion and systemic exposure. Microneedle design must be tailored to the application site. This ensures safe and effective delivery [84]. For deeper penetration, increasing the distance between needles leads to a rise in the insertion force for each needle [80]. To reduce the risk of microneedles breakage, a smaller tip diameter and a high aspect ratio are preferred. In human ex vivo skin, smaller needle tip sizes (5 µm) allow for more seamless piercing, whereas bigger tips result in more abrupt penetration. To achieve accurate and precise insertion of microneedles to the required depth in the skin, a tip radius of less than 15 µm is needed [85, 86]. Penetration depth is also influenced by the shape of the needle base. For instance, compared to hexagonal-based microneedles of the same length and spacing, microneedles shaped like triangles and squares penetrate deeper. This discrepancy results from hexagonal bases' reduced ability to pierce the SC [87].

Microneedles geometry also impacts their mechanical strength. To prevent unintended mechanical failures, microneedles strength must exceed the insertion force. A higher aspect ratio implies less stiffness in the needle. For example, an increase in the aspect ratio of the microneedles from 2:1 to 3:1 resulted in a reduction in stiffness from 7500 N/m to 1620 N/m [88]. Furthermore, there is an inverse relationship between the aspect ratio and the force required to bend the microneedles [89].

Another important consideration in the design of microneedles is their structures, which affect the processes for both drug administration and sampling. Solid, dissolving, hollow, coated, and hydrogel-forming microneedles are the five common microneedles forms that were initially intended for drug administration. Each of these structures has a unique method of drug delivery [90]. To improve their functionality and increase the range of uses for microneedles, creative designs have been created in addition to the conventional structures.

For instance, core-shell or double-layered microneedles offer controlled drug release kinetics, whereas multi-microchannel microneedles facilitate highly efficient and uniform transport of intracellular cargo. After application, bubble-containing microneedles can separate quickly, leaving the tips buried in tissues to release drugs for a longer period. Larger medication dosages are delivered to certain skin layers via candle flame-shaped microneedles, while porous microneedles improve deeper and more accurate gas administration or make it easier to load CAR T (chimeric antigen receptor T) cells for successful cell therapy. Additionally, by interacting with tissues, arrowhead-shaped microneedles promote adherence.

In addition to structural innovations, the drug-loading capacity and uptake potential of microneedles are critical factors in therapeutic success. Cao et al. developed hydrogel-forming microneedles that offer excellent biocompatibility, high drug-loading capacity, and tunable release properties. Their system facilitates sustained drug delivery through interstitial fluid uptake, forming continuous microchannels for efficient diffusion [91]. Zuo et al. formulated nanomaterial-integrated microneedles that enhanced drug stability and enabled precise, controlled release kinetics for therapeutic agents [92]. Sadeqi et al. designed porous microneedles capable of delivering solid drug formulations with improved loading and prolonged release, particularly suitable for analgesics and NSAIDs [93]. These advancements highlight the importance of optimizing microneedle architecture and composition to maximize drug loading and uptake potential in clinical applications.

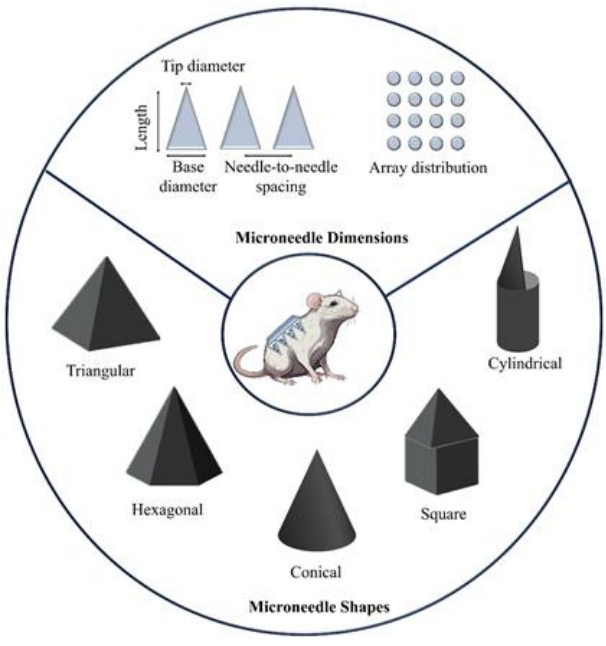

Fig. 6. Schematic diagram depicting geometry of microneedles.

6. Diagnosis of breast cancer by employing microneedles

Microneedles play a vital role in disease diagnosis and metabolic activity analysis due to their microinvasive nature and ability to collect tissue samples. They can be used to obtain small samples of breast tissue or ISF, which is advantageous because certain BC biomarkers are present in higher concentrations in ISF surrounding developing tumors compared to blood [94, 95]. This method addresses the challenges of traditional blood collection, which is often painful and prone to inaccuracies. By sampling ISF, microneedles offer a more precise and less invasive way to detect BC biomarkers, enhancing diagnostic accuracy and patient comfort while potentially improving early detection and prognosis.

However, the implementation of microneedles for diagnostics faces critical hurdles, particularly in ensuring the extraction of sufficient volumes of ISF (>5 μL) consistently and rapidly (>5 min). While fast extraction of ISF is attempted, the success of microneedle-based ISF extraction largely depends on the swelling capacity of the microneedle materials, their mechanical strength, and the insertion efficiency. Furthermore, maintaining the stability of collected biomarkers during and after the minimally invasive extraction process presents a crucial challenge that must be addressed for clinical research [96].

In this context, Huang et al. developed a GelMA-AA (gelatin methacrylate-acrylic acid) microneedles patch for minimally invasive ISF sampling in BC screening. The patch rapidly extracted 1.29 mg ISF in 60 seconds and detected cancer biomarkers (CA15-3, carcinoembryonic antigen) earlier than standard methods. It demonstrated rapid sampling, strong skin penetration, and excellent swelling for effective biomarker analysis [97]. Chen et al. developed a microneedles-based colorimetric method using nano-Ag MBL-film for early BC diagnosis, detecting tumors in 7 days. It enabled accurate differentiation between healthy and tumor-present individuals, demonstrated survival benefits after doxorubicin therapy, and showed clinical potential with Fe_3O_4Ag nanoparticles enhancing the system's efficacy for practical applications [98].

Dervisevic et al. developed an electrochemical immunosensor using gold-coated silicon microneedles (Au-Si-MNA) for HER-2 detection. It exhibited a linear response (10—250 ng/ml) with a 4.8 ng/ml detection limit in artificial ISF. From phantom gel mimicking skin layers, ErbB2 was extracted with a linear range of 50—250 ng/ml and a 25 ng/ml detection limit [99].

7. Treatment of breast cancer employing microneedles

Microneedles are frequently employed in medication or vaccine administration to treat BC [100]. Using microneedles to administer medications enables them to initially reach local tissue, compared to drugs entering the bloodstream, where they can be diluted and metabolized in the liver. Microneedles enhance drug efficacy by increasing its accumulation in the target tissue before distribution throughout the body [101].

7.1. Microneedles in breast cancer vaccines

Due to their specificity, stability, and speed of action, vaccination techniques aiming at treating BC are more successful in obtaining humoral and cellular responses [102]. In this regard, microneedles present a possible solution, since they can cover a greater vaccine injection area, administer vaccines without being rapidly eliminated by phagocytic systems, and shield vaccines from degradation brought on by changes in temperature or

environmental stress [103]. For example, Chablani et al. enhanced BC immune response in mice using microneedles loaded with a dried vaccine from murine BC T07 cells. This method increased IgG, IgG2a, and lymphocyte levels, reducing BC incidence fivefold. Microneedles proved four times more effective than oral vaccination with the same antigen dose [104].

7.2. Microneedles in breast cancer chemotherapy

When it comes to treating BC, chemotherapy is one of the primary choices [105]. Anti-cancer chemotherapeutic drugs face several challenges. These include severe side effects from systemic circulation. They also have insufficient tumor targeting and an inability to address metastatic spread, and significant non-specific toxicity [106]. Microneedles offer a unique potential for topical delivery of these drugs [107].

7.2.1. Targeted nanoparticle delivery

Targeted nanoparticle delivery highlights a sophisticated strategy for overcoming the systemic toxicity and poor targeting of conventional chemotherapy by integrating chemotherapeutic agents into nanoparticles and delivering them via microneedles. Illustrating this approach, Jha et al. developed dissolving microneedles for targeted cabazitaxel (CBT) delivery using HA-oleylamine and chitosan-oleic acid nanoparticles (125 nm) loaded with cetuximab. These 550 µm-height microneedles delivered 250 µg CBT, achieving fourfold higher ex vivo permeation and significantly reducing tumor volume while tripling survival in tumor-bearing rats compared to intravenous CBT [108]. Similarly, Sharma et al. developed dissolvable microneedles for targeted ribociclib (RB) delivery in HR+/HER2 metastatic breast cancer. The microneedles comprised polyvinyl alcohol, polyvinylpyrrolidone, and HA-integrated RB-loaded transfersomes. They enhance drug delivery, extending release up to six times, reducing toxicity, and maintaining therapeutic levels for 48 hours [100].

7.2.2. Novel delivery routes and fabrication

Novel delivery routes and fabrication explore innovative approaches beyond simple skin patch application, focusing on unique anatomical delivery routes and advanced manufacturing techniques. One such route is transpapillary delivery for direct delivery of chemotherapy to underlying cancerous tissue. Patil, et al. explored transpapillary breast cancer treatment using artesunate-loaded microneedles (1.2 mm height, 200 µm interspace). Layer-by-layer (LBL)-coated solid lipid nanoparticles (SLN, 319 nm) enhanced ex vivo drug release (84.75%) and inhibited MCF-7 BC cell proliferation by 7.92%, demonstrating the potential of microneedle-based transpapillary drug delivery [109].

Furthermore, microneedles can also be fabricated by 3D technology. For example, Alafnan et al. fabricated polyethylene glycol diacrylate (PEGDA) microneedles using Projection Micro-Stereo Lithography (PµSL). Coated with gemcitabine and sodium carboxymethyl cellulose, these microneedles released most of the drug within an hour. SEM analysis confirmed precise dimensions, while HPLC and drug permeation tests demonstrated effective in vitro skin penetration [110].

7.2.3. Dual drug and combination strategies

Microneedles facilitate the administration of dual chemotherapy agents for treating BC, a strategy critical for overcoming drug resistance and enhancing overall efficacy. In this context, Bhatnagar et al. developed dissolvable polymeric microneedles from polyvinylpyrrolidone and polyvinyl alcohol for dual delivery of doxorubicin HCl and docetaxel. With payloads of 533 µg and 227 µg, respectively, ex vivo tests confirmed effective skin insertion and drug permeation. In vivo, the microneedles achieved 100% survival and controlled tumour growth in BC mouse models [111].

7.2.4. Microneedles for natural compound and repurposed drug delivery

Microneedles can successfully deliver non-conventional cancer therapeutics, including natural plant compounds and repurposed established drugs, by significantly improving bioavailability and localized concentration. Recently, for instance, Gadag et al. developed resveratrol-loaded nanostructured lipid carriers (RVT-NLCs) for breast tissue targeting using hollow microneedles (AdminPatch® Array 1200). Resveratrol is a natural compound found in red wine, grapes, and peanuts that is currently investigated as a potential anticancer agent but is not approved for clinical cancer therapy. Optimized RVT-NLCs enhanced skin penetration, internalization, and anticancer efficacy in MDA-MB-231 cells. Preclinical rat studies showed superior breast tissue localization and improved pharmacokinetics (C_{max}, T_{max}, AUC0-inf) compared to oral resveratrol administration [112].

Similar studies have investigated the use of microneedles loaded with honokiol and zein protein, showing enhanced drug delivery and therapeutic efficacy for BC treatment. Honokiol is a natural plant-derived compound from Magnolia bark currently under investigation for its potential anticancer properties. Zein protein is used as a biodegradable polymer to fabricate the microneedles and achieve controlled drug release. Gao et al. developed maltose microneedles (500 µm length, 600 µm base), enhancing honokiol delivery threefold, and 27-fold with oleic acid. Breast skin showed maximum drug retention compared to mammary papillae. Honokiol exhibited anticancer effects by suppressing Ki-67 and reducing IL-6 levels, highlighting its potential for localized breast cancer therapy [113].

Bhatnagar et al. fabricated zein protein microneedles (36 microneedles per 1 cm2 area) loaded with gemcitabine and tamoxifen. Gemcitabine, with higher water solubility, showed greater release (1459 ± 74 µg) than tamoxifen (607 ± 21 µg). Studies revealed that the deposition of tamoxifen improved with coating, while the permeation of gemcitabine excelled when using the poke-and-patch method on pig skin [114].

Regarding repurposed drugs, Heikal, et al. developed atorvastatin-loaded pumpkisomes (ATV-PUMP) integrated into dissolving microneedles (ATV-PUMP@dMN) for localized breast cancer therapy. Atorvastatin is currently investigated for its potential anticancer effects through drug repurposing. Compared to free atorvastatin, ATV-PUMP achieved a significantly lower IC_{50} (2.82 µg/mL vs. 18.02 µg/mL), a 1.8-fold higher skin permeation than ATV-PUMP gel,

and a 4.2-fold greater tumour volume reduction. Tumor biomarkers were restored (PTEN: 2.3 ng/mg vs. 0.2 ng/mg in the positive control, VEGF reduced by 77% vs. positive control), and apoptosis indicators (Bax: 7.5-fold, caspase-3: 9-fold) were significantly upregulated [115].

7.3. Breast cancer treatment with microneedles-assisted photodynamic and photothermal therapies

Two promising approaches for treating BC are photodynamic therapy (PDT) and photothermal therapy (PTT). Both treatments use light, often delivered by a laser and absorbed by certain substances called chromophores in the tissue. PTT involves the transformation of light into heat, confined to the tumor site due to the spatial localization of both the chromophore and the laser. On the other hand, PDT uses light to activate and degrade a chemical molecule, producing free radicals that aid in a synergistic healing process. In addition to lowering medication side effects by permitting lower dosages, a combination of photothermal and photodynamic treatments with chemotherapy may also help avoid metastasis, which is often induced by chemotherapy or surgery.

Fu et al. developed a dissolvable microneedles patch (100 tips within 8 x 8 mm^2 area, with the base measuring 250 µm and a height of 800 µm), delivering cisplatin and IR820 for synergistic chemo-photodynamic BC treatment. The 4T1 live/dead test confirmed efficient tumor cell death, and in vivo studies in Balb/c mice demonstrated significant apoptosis and tumor regression, highlighting the patch's potential for effective BC therapy [116]. Similarly, Chen et al. developed a reproducible and minimally invasive system using near-infrared (NIR) light-activatable microneedles for superficial BC. Combining photothermal treatment with doxorubicin, a chemotherapy medication, allows the system to reduce toxicity and generate synergistic anticancer benefits. When triggered by near-infrared light, the microneedles can deliver heat and medicines locally, enabling precise control over drug release and thermal ablation. In one week, the medication completely eradicated the tumors in animal models, and there was no recurrence. The technology also offered a viable substitute for conventional cancer treatments by allowing for several treatments from a single dose and dramatically reducing systemic adverse effects including weight loss and organ damage [117].

7.4. Microneedles in breast cancer immunotherapy

Immunotherapy targets the immune system to treat BC as an alternative to treating the tumour directly. Immunotherapy was first presented as a means of introducing foreign antigens — also referred to as therapeutic vaccines — to stimulate the immune system. This vaccine approach hasn't been extensively replicated, though, and it still has to be improved upon and optimized. Two extremely promising new avenues for cancer immunotherapy treatment have recently surfaced. To boost the immune response of the body against tumors, the first method is introducing T cells that have been genetically modified to express chimeric antigen receptors (CARs). The second strategy uses antibodies to prevent the tumor microenvironment's suppressive effects through checkpoint inhibition, especially targeting molecules like programmed death-1 (PD-1) and cytotoxic T lymphocyte antigen-4 (CTLA-4).

Huang et al. developed a dissolvable microneedles patch co-delivering R848 and aPD-1 to modify the immunosuppressive microenvironment in TNBC. The patch enhanced drug accumulation, stimulated tumour-infiltrating dendritic cells (TIDCs), increased CD8+ T cells, and inhibited PD-1/PD-L1 checkpoints, significantly prolonging survival, reducing metastasis, and preventing tumor recurrence in 4T1 tumor-bearing mice [118].

7.5. Microneedles in breast cancer chemoimmunotherapy

Chemoimmunotherapy utilizing microneedles represents a cutting-edge approach that combines the site-specific delivery of chemotherapeutic agents and immune-modulating therapies to enhance therapeutic efficacy and minimize systemic side effects in cancer treatment, offering precise control over drug release and improved patient outcomes through localized treatment that utilizes both chemotherapy and immunotherapy mechanisms [119]. Wang et al. designed a dissolvable microneedles patch for targeted intradermal delivery of aPD-1 and albumin-bound paclitaxel nanoparticle (nab-PTX) in TNBC treatment. By increasing drug concentration at the tumor site, inducing immunogenic cell death, and inhibiting the PD-1 pathway, the patch enhanced T cell activation and infiltration, offering a synergistic and effective chemoimmunotherapy strategy with reduced side effects [120].

8. Clinical trials of microneedles in cancer treatment

For optimal anticancer therapy, drugs need to accumulate in adequate amounts at the target site while minimizing adverse effects. The narrow therapeutic window is additionally complicated by patient discomfort, variations in disease progression, and resistance to treatment. Microneedles can manage medication administration and distribution, which makes their use in the BC treatment a promising option for the future. Overall, the development of microneedles has been greatly encouraged by both published and unreported clinical studies in the administration of medications and vaccines, especially in the area of cancer therapy. Despite this, there are currently limited clinical trials assessing the use of microneedles for cancer detection and treatment, particularly for BC, and the findings from these trials have not yet been released. Table 3 provides a detailed overview of ongoing and completed clinical trials, highlighting key aspects relevant to the use of microneedles in cancer treatment.

9. Challenges in Microneedles Technology

Microneedle technology has advanced quickly, but several challenges still stand in the way of its effective clinical application. These hurdles can be broadly categorized as technical, biological, and regulatory/ environmental.

9.1. Technical and fabrication challenges

Technical issues primarily revolve around ensuring physical reliability and manufacturing consistency. Microneedle performance depends on design factors such as shape, length, and tip size, which must be tailored for specific drugs and uses. A critical challenge is ensuring that the microneedle patches achieve suitable

Table 3. Clinical trials involving microneedles for cancer treatment: study details and phases.

Interventions/ Treatment	Conditions	Summary	Phase	Sample Size	Status	NCT Number
Dissolvable microneedle array	Cutaneous Squamous Cell Carcinoma Skin Cancers - Squamous Cell Carcinoma	The study evaluates microneedle-delivered doxorubicin for treating cutaneous squamous cell carcinoma, targeting tumor cells, and inducing immune responses	II	48	Recruiting	NCT05377905
Placebo, Tip-loaded, dissolvable microneedle array	Basal Cell Carcinoma	Part I examines microneedle array dissolution factors, and Part II tests the doxorubicin microneedle array in basal cell cancer patients at varying doses.	I/II	25	Active, not recruiting	NCT04928222
Tip-loaded dissolvable microneedle array	Basal Cell Carcinoma	The Phase I study tests dissolvable doxorubicin microneedle arrays for basal cell carcinoma, determining the maximum tolerated dose across placebo and 25 µg, 50 µg, 100 µg, and 200 µg groups with weekly applications.	I	13	Terminated	NCT03646188
Modi-1/Modi-1v vaccines administered intradermally using the MicronJet600™ microneedle device	TNBC Renal Cell Cancer High Grade Ovarian Serous Adenocarcinoma Squamous Cell Carcinoma of the Head and Neck	The Phase 1/2 study evaluates the safety and efficacy of Modi-1/Modi-1v vaccines in advanced cancers, administered via MicronJet600 microneedles	I/II	144	Recruiting	NCT05329532

*TNBC: Triple Negative Breast Cancer

skin penetration. This penetration is complicated by skin thickness variability across body areas and individuals.

Furthermore, mechanical strength and fracture resistance are essential, especially for polymeric microneedles used on flexible skin like the breast. Optimizing the composition and geometry of microneedles is required to balance mechanical strength with a high drug payload. Manufacturing precise microstructures remains challenging, with advanced 3D printing methods currently limited by the scarcity of biocompatible photoactive materials. Issues like microneedle blockage or incomplete skin penetration also remain a risk.

9.2. Biological and patient-related challenges

Biological challenges involve the complexity of the delivery site and patient safety. One major issue is that the thickness of human skin is greater compared to animal models, which complicates translating research findings. Skin elasticity, which varies by body area, age, gender, and health conditions, also affects microneedle penetration and drug delivery. In addition to penetration challenges, achieving adequate drug loading and ensuring controlled, reproducible release remains a critical hurdle for dosage accuracy. Potential dose variability and the risk of mechanical failure are concerns. Although rare, microbial contamination and skin sensitivities pose risks, often due to design flaws, though coated microneedles can mitigate these risks. The inherent properties of materials also present challenges. The degree of crosslinking, residual solvent, and polymer molecular weight can all affect the toxicity profile of biodegradable polymers like hyaluronic acid (HA) and polyvinyl alcohol (PVA). For instance, crosslinked HA forms may cause mild immune responses. Metallic microneedles, such as stainless steel, may emit trace amounts of nickel ions if not properly treated, potentially causing allergic reactions.

9.3. Regulatory and environmental challenges

For regulatory compliance and successful clinical translation, comprehensive toxicological evaluations are essential. These evaluations should align with ISO 10993 and OECD guidelines and include cytotoxicity, systemic toxicity, biodegradation, and environmental persistence to ensure patient safety and environmental compatibility. Beyond tissue safety, the environmental effects of disposing of microneedles must be considered. Biodegradable polymers like HA and PVA provide a more environmentally friendly option because they decompose into non-toxic byproducts, reducing ecological accumulation. Finally, microbiological control and safe post-use handling are crucial, particularly for reusable or multi-component devices, to address the risk of cross-contamination.

10. Concluding remarks

Advancements in microneedle technology offer promising breakthroughs in breast cancer (BC) diagnosis and treatment. These minimally invasive tools enable precise biomarker sampling and targeted drug delivery, enhancing patient comfort and compliance. Microneedles support therapies like chemotherapy, immunotherapy, and combination treatments such as photodynamic and photothermal therapies, delivering drugs directly to tumour sites while minimizing side effects. The use

of advanced materials like metals, ceramics, and polymers, along with fabrication methods such as 3D printing and micromolding, has improved microneedle strength, biocompatibility, and functionality. Clinical and preclinical studies show significant tumor reduction, improved survival rates, and enhanced drug targeting. Challenges like skin penetration variability, drug formulation standardization, and clinical scalability remain, presenting opportunities for future research. Optimizing microneedle systems could enable personalized medicine and integrated diagnostic-therapeutic platforms. The future of microneedles technology in BC is poised for transformation through integration with smart systems and advanced computational design:

(a) Smart microneedles integrated with biosensors: Future research will focus on developing smart microneedles systems integrated with micro-sensors and biosensors. These patches could not only deliver therapeutics but also simultaneously monitor critical BC biomarkers or physiological parameters directly within the interstitial fluid of the breast tissue. This integration will enable real-time feedback on treatment efficacy and disease progression, facilitating dynamic dosing adjustments.

(b) AI-driven design optimization of microneedles: Computational tools and Artificial Intelligence (AI) are set to revolutionize microneedles design and manufacturing. AI algorithms can rapidly process complex data sets regarding drug properties, polymer characteristics, and skin biomechanics. This capability will allow for the optimized selection of microneedles geometry, material composition, and array density to maximize skin penetration and drug payload while minimizing the risk of mechanical failure.

(c) Personalized microneedle-based drug delivery: The development of microneedles is moving toward personalized medicine. By considering individual patient factors such as skin thickness and tumour subtype, microneedles systems can be tailored. This personalization will involve microneedles loaded with customized drug cocktails or vaccines to match a patient's unique biological needs, offering a safer, more effective, and truly individualized approach to BC therapy. These advancements signify a paradigm shift in BC management, offering safer, more effective, and patient-friendly solutions.

Author contributions: Conceptualization, JN and MMP; design of the work JN, SC and MMP; data acquisition JN and SC; Writing - original draft preparation: JN and SC; Writing - review and editing: PV, GN and MMP; Supervision: GN and MMP; all authors contribute in manuscript drafting and approved the final version.

Funding: The authors are highly thankful to Gujarat State Biotechnology Mission (GSBTM), Gujarat, India for providing financial assistance in form of Major Research Project [GSBTM Project ID: 202425_23].

Acknowledgements: JN and MMP are thankful to the Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat, India for providing the necessary facilities to generate the manuscript that is a part of Doctor of Philosophy (Ph.D.) work of Mr. Jai Naik.

Conflicts of Interest: The authors declare no conflict of interest.

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