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Transdermal insulin delivery via microneedle technology, patches, and pumps offers a promising alternative to traditional subcutaneous injections for diabetes management

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Abstract

Transdermal insulin delivery offers a promising alternative to traditional subcutaneous injections, providing a pain-free and self-administrable treatment option for diabetes management. Microneedle technology has emerged as a viable approach, leveraging tiny needle-like projections to bypass the stratum corneum and deliver insulin systemically. Various materials, including metal, silicon, ceramic, polymer, and silica glass, are being explored for microneedle fabrication. This review discusses the anatomy of skin, pathways of drug absorption, and advantages of transdermal drug delivery systems, including microneedle arrays, patches, and pumps. The potential of microneedles to replace subcutaneous insulin injections is highlighted, along with the importance of ensuring precise drug release and addressing challenges related to skin irritation, drug stability, and scalability.

Keyword: Transdermal insulin delivery; Microneedle technology; Patches; Pumps

1. Introduction

Diabetes comprises a group of metabolic disorders distinguished by significantly raised blood glucose levels (1). This results from either the loss of pancreatic β-cells in the Islets of Langerhans, leading to inadequate insulin production (type 1 diabetes – T1D), or from insulin resistance causing an inefficient insulin response (type 2 diabetes – T2D) (2). In recent decades, diabetes mellitus has developed globally as an epidemic and has become the fifth leading cause of mortality (3). Blood glucose (BG) levels, specifically hyperglycemia, in the body. Historically, subcutaneous insulin injection is employed for diabetes management (1). Diabetes mellitus (DM) is a chronic metabolic disorder characterized by high blood glucose levels due to impairments in insulin production, insulin action resistance, or a combination of both (4). Subsequently, various administration methods, such as pulmonary, nasal, transdermal, and oral routes, were studied. Pens, jet injectors, sharp needles, supersonic injectors, and infusion pumps have been developed to reduce discomfort and improve compliance with insulin regimes (3). The disruption of homeostatic control systems can result in persistently elevated blood glucose levels (5). The American Diabetes Association asserts that adequate glucose regulation (i.e., fasting glucose of less than 150 mg/dl or hemoglobin A1c of 7%) is crucial for averting subsequent problems in diabetes individuals (6). Type 2 diabetes mellitus (T2DM) constitutes the majority of cases, representing 85% to 95% worldwide; however, type 1 diabetes mellitus (T1DM) cases are rising significantly in certain areas of Europe and the USA, with an increase of 2–3% (7). The oral route is the most ancient method of administration, offering advantages of ease, cost-effectiveness, and lack of discomfort (8). Approximately 80% of patients with Type 2 Diabetes (9,10) expressed apprehension over needle discomfort, and 52% were reluctant to begin insulin treatment. Even today, a century after the discovery of injectable insulin in 1921, diabetic patients and healthcare professionals are seeking an alternative, individualized, pain-free, and self-administered dose form (2).

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Traditional methods of medication delivery, including oral and parenteral routes, frequently encounter constraints owing to the physicochemical characteristics of the drug. Oral administrations are linked to first-pass metabolism, which significantly diminishes the bioavailability of administered medicines (11).

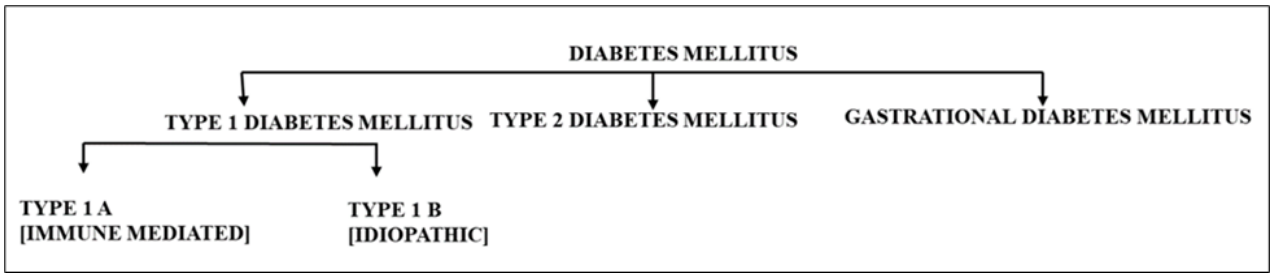

Figure 1 Classification of diabetes mellitus (12)

2. Anatomy of Skin and Pathways of Drug Absorption

In order to comprehend the processes underlying medication absorption via the skin, we must first outline the complex structure of the skin and the several routes involved in drug uptake. The human skin, covering roughly 1.5 - 2.0 m^2, is the body's biggest organ and is essential for safeguarding against external environmental factors (13). The epidermis, the outermost layer of human skin, has an estimated thickness of 50–100 µm (14). The epidermis comprises keratinocytes, melanocytes, Langerhans cells, and Merkel cells. Keratinocytes are the primary cellular components of the epidermis, comprising more than 80% of the total epidermal cell population. Keratinocytes may be categorized into five layers based on their development stage: stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum (SC), arranged from innermost to outermost (13). The stratum corneum functions as the primary barrier against foreign substances (15). It consists of 15–30 layers of corneocyte cells, with an overall thickness of 10–20 µm. The primary constituents of the stratum corneum (SC) are keratin proteins sourced from deceased keratinocyte cells in the underlying layers and lipids (13).

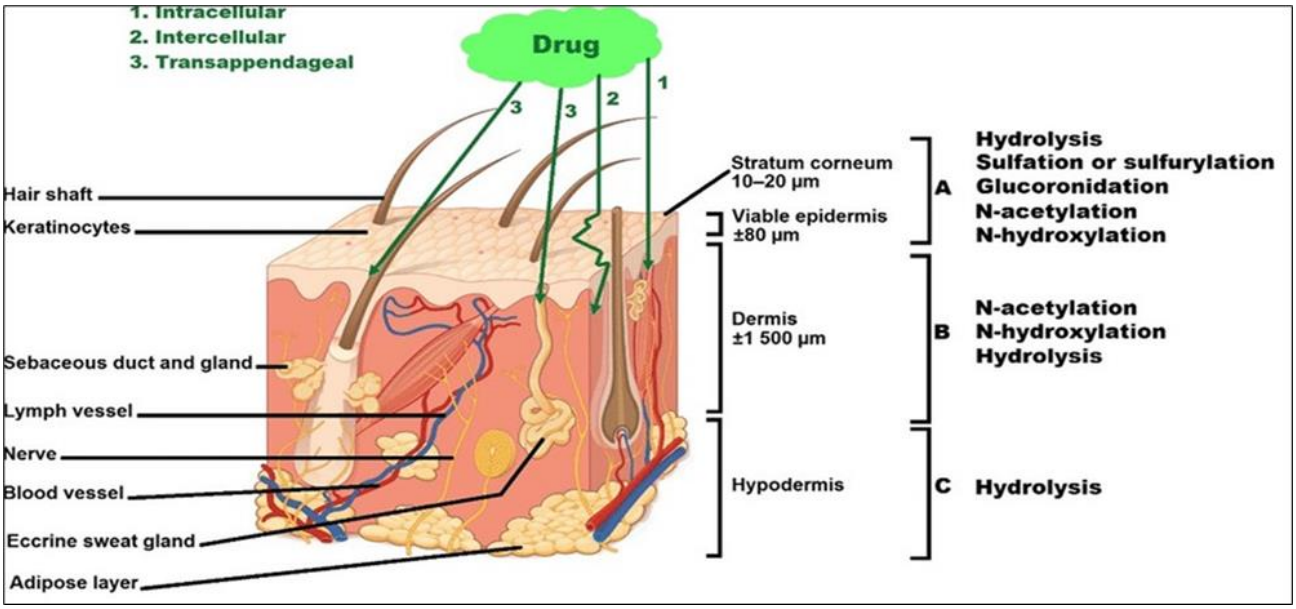

Figure 2 Schematic representation of the anatomy of the skin and pathways of drug administration (16)

3. Transdermal Drug Delivery System

Transdermal drug delivery (TDD) refers to the administration of drugs via the skin, generally for systemic effects. It is now well acknowledged in the practice of medicine. The FDA has approved more than twenty transdermal medications so far. These medications have benefits like controlled and prolonged drug delivery, simple elimination, self-administration, and avoiding hepatic metabolism and gastrointestinal issues (17,18,19,20). Transdermal drug delivery has many benefits, including controlled and prolonged drug release at a steady rate, easy cessation of drug

administration by removing the device, self-application, and most importantly, the ability for the drug to avoid hepatic first-pass metabolism and gastrointestinal incompatibility (17, 21,22,23). Transdermal drug delivery systems (TDDS), generally referred to as patches, offer an alternate approach for the administration of drugs via the skin. These systems are engineered to effectively provide therapeutic amounts of drug into the circulation, reaching adequate concentrations for disease therapy and prevention (24,25).

3.1. Advantages of TDDS

- TDDS is minimally invasive and painless, permitting patients to administer themselves, hence enhancing convenience and cost-effectiveness (24,26).
- Traditionally, drug-loaded patches were the first generation of transdermal drug delivery devices, employing natural adhesive substances to enhance drug permeation through the layer of skin (24,27).
- Reduces gastrointestinal adverse effects (17)
- Can be readily withdrawn in the event of toxicity (17)
- Shows resemblances to intravenous infusions (17, 28)
- Facilitates self-governance (17, 29)
- Facilitates the penetration of both lipophilic and hydrophilic medication (17)

3.2. Disadvantages of Transdermal Drug Delivery Systems (TDDS):

- For transdermal administration, a medicament must possess specific physicochemical properties that facilitate its penetration through the stratum corneum. When the required amount of medication for therapy exceeds 10 mg per day, efficient transdermal delivery becomes challenging (24,30).
- Transdermal administration may result in relatively limited medication absorption into the circulation due to variations in skin barrier function, influenced by factors such as the specific skin location and the age of the individual (24,31,32).
- Difficulties emerge when dealing particulars that reveal low solubility, limited stability, a short half-life, and susceptibility to oxidation and hydrolysis. This leads to the excessive costs of production (24,33).
- A major risk exists with a medication adhering to the skin, which may result in a sudden release of a substantial quantity of the drug into the body (17,34).
- Some individuals may have skin irritation at the site of application of the medication (17,35).
- Applicable solely to substances with a molecular weight below 500 Daltons (17,36).

4. Methods of Transdermal Insulin Delivery

- **Microneedle:** Microneedle arrays (MNA) are widely acknowledged as a viable method for attaining systemic therapeutic effects via the transdermal delivery of medicines (37). The microneedles are invisible to the naked eye, measuring less than one millimeter in height (38). Individuals choose microneedle administration over traditional needle injections, such as vaccinations, due to its ease of use and versatility. Microneedles are tiny, ranging from 25 to 2000 μm in length, 50 to 250 μm in width, and 1 to 25 μm in tip circumference. They are organized in an array with a face area of 2000 mm^2 (2). This method has been found useful for delivering substantial mixtures. Furthermore, its objective is to avert individuals from experiencing pain-related difficulties throughout the injection admission process. Hypodermic needles (38,39). In the microneedles transdermal administration method, substances are directly introduced into the human body via capillaries to bypass first-pass metabolism and avoid gastrointestinal degradation (8,40,41).

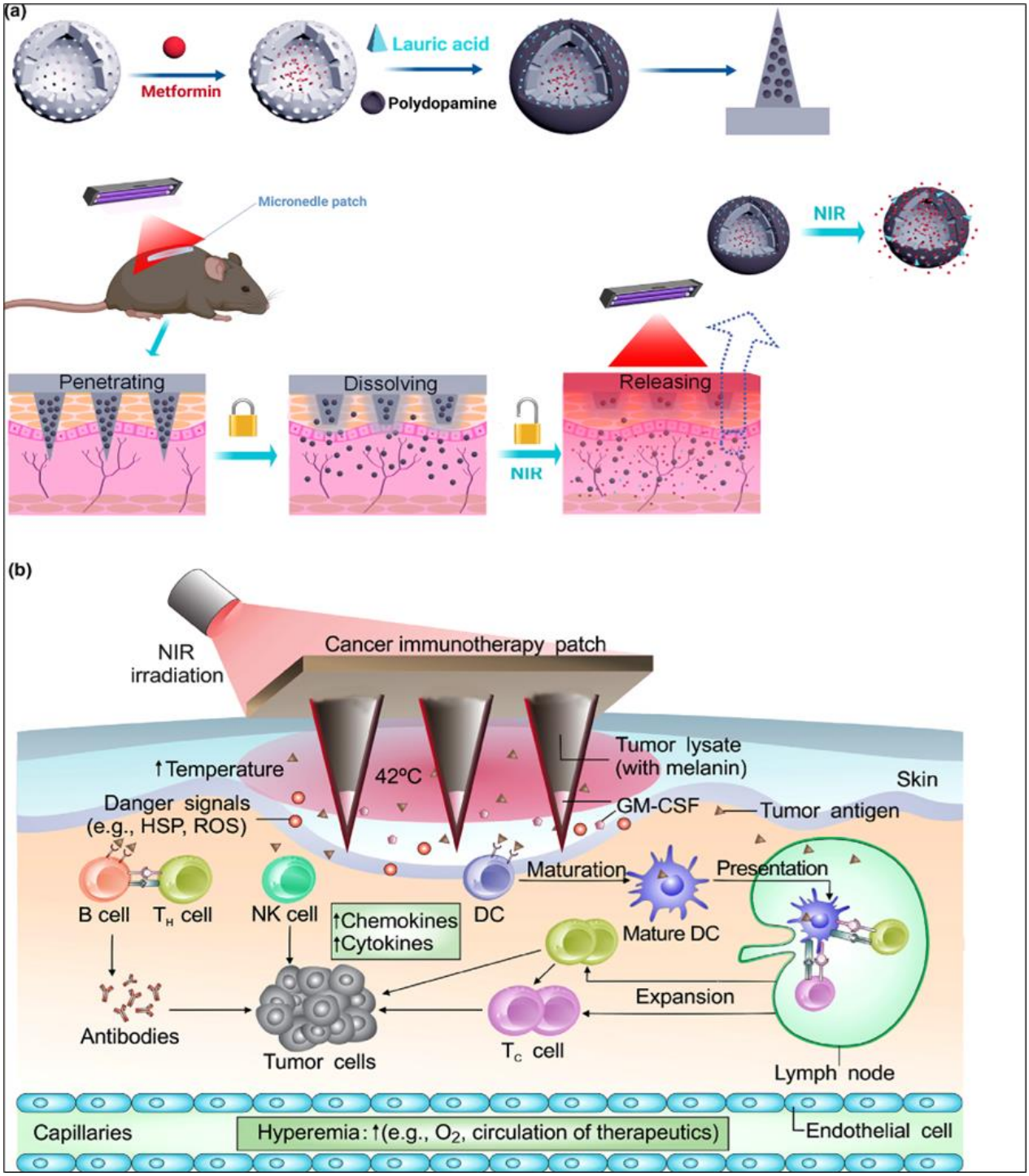

Figure 3 (a) Schematic of the preparation of metformin-loaded hollow mesoporous SiO2 (met/HMSN) and decoration of polydopamine (PDA) and lauric acid (LA) on the nanoparticles. Near-infrared (NIR)-responsive release of the loaded metformin on diabetic rats by the transdermal delivery is illustrated. Reproduced with modification from. (b) Illustration of melanin-mediated cancer immunotherapy through a transdermal MN vaccine patch. The presence of melanin, the natural-occurring pigment in the whole tumor lysate, leads to the local release of heat via controllable near-infrared light emission. HSP: heat shock protein; ROS: reactive oxygen species; GM-CSF: granulocyte–macrophage colony-stimulating factor; NK cell: natural killer cell; DC: dendritic cell. Reprinted with permission from microneedles (MNs) are promising to replace subcutaneous insulin injection in the treatment of type I diabetes (11)

These systems are designed to be minimally invasive and painless, allowing them to bypass the outermost layer of the skin (stratum corneum). This overcomes the disadvantages of subcutaneous injections and other methods of transdermal delivery, such as chemical enhancers, nano and microparticles, or physical treatments. Microneedle arrays

(MNA) are devices that consist of tiny needle-like projections capable of puncturing the outermost layer of the skin, known as the stratum corneum. These projections create channels that allow the passage of large molecules (>500 Da), proteins, and nanoparticles through the skin (37). Currently, solid microneedles are widely used in medical cosmetology, and extensive data suggest that their use does not significantly alter the appearance or barrier function of the skin, nor does it increase the risk of infection. When it comes to insulin microneedles, insufficient release of insulin will not achieve the desired therapeutic effect, while excessive release can lead to hypoglycemia. Therefore, ensuring the precise release of drugs is crucial for safety (42).

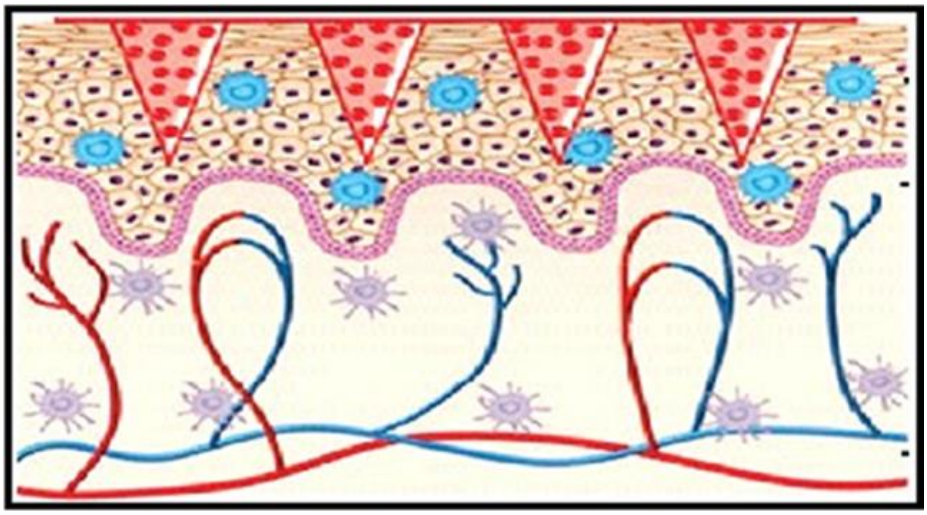

Figure 4 The schematic representation of the microneedles (8)

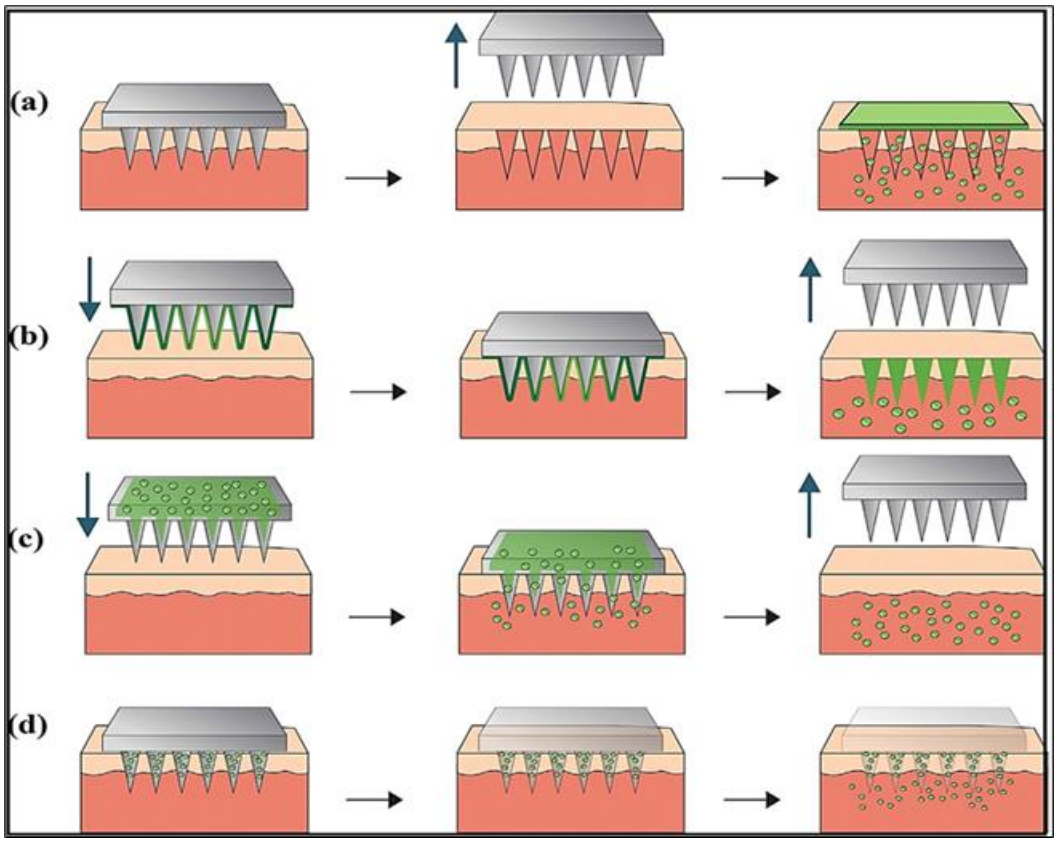

Figure 5 Categories of Microneedles: a) solid microneedles, b) coated microneedles, c) dissolving microneedles, d) hollow microneedles (8)

The categories of microneedles often utilized in drug delivery applications are solid, coated, dissolvable, hollow, and hydrogel microneedles. Solid microneedles are employed for medication administration. A pharmaceutical agent capable of passive diffusion across the dermal layers (43). The microneedle has superior solubility, facilitating fast dissolution and efficient insulin release. The basic substance expands without dissolving, functioning as a carrier for the insulin. As a therapeutic agent, upon dissolution of the needles, the basal component can perpetually release insulin via the microporous channel established by the microneedle. The utilization of dissolved microneedles can efficiently sustain the activity of proteins or peptides and avoid their denaturation. Insulin maintained at room temperature, in contrast to the traditional result-oriented solutions (42).

4.1. Adhesive transdermal patches and mechanical infusion pumps

Patch pumps can be categorized as either simple or fully featured devices, and as mechanical or electromechanical devices. However, these categories often intersect (44). The advancement of patch pumps has been propelled by the constraints of infusion setups. These pumps are engineered to be free of infusion sets, be tiny, lightweight, and adhere to the skin via an adhesive. Additional considerations include the expense and the scope of insurance coverage. Uninsured instances may suffer expenses ranging from $4,500 to $6,500 for an insulin pump and its associated reservoirs, based upon the brand. Research indicates that using microneedles for insulin patches is a more economical alternative to pump therapy (7). Diverse materials with unique qualities are utilized, alongside changes in needle length, diameter, and excipients, to investigate the variances and ascertain how these variations might provide optimum and favorable outcomes (12). The fundamental components of an insulin pump are an insulin reservoir, infusion set, and tubing. The insulin reservoir is present. The infusion set is connected to a catheter for the continuous administration of insulin to satisfy daily insulin requirements (45).

Figure 6 Adhesive transdermal patches (17,46)

5. Materials for microneedle manufacturing

- **Metal:** Metals have been utilized in the pharmaceutical area for numerous decades. Typical examples are stainless steel (e.g., hypodermic needles) and titanium (e.g., implants and prostheses) (47). Metallic components are extensively utilized in transdermal medication delivery systems because to their mechanical strength and endurance. Metallic materials can be utilized to manufacture durable microneedles (48), innovative microneedles (49), and hollow shaft microneedles (50). However, a drawback is that the risk of breakage of these microneedles within the dermis may raise safety issues, challenging the advancement of novel materials. Various metals employed in the fabrication of solid microneedles include stainless steel, gold, platinum, titanium, nickel, and iron (51).
- **Silicon:** The earliest microneedle was fabricated using silicon in the 1990s (47). Silicon possesses anisotropic properties and exhibits a crystalline structure. The properties are contingent upon the alignment within the crystalline structure, exhibiting varying elastic moduli (50 to 180 GPa) (52). Hollow beveled silicon microneedles have been developed; however, their fabrication typically depends significantly on wet chemical processes such as KOH or HF for the formation of the beveled surface, or plasma treatment of the bevel surface leads to an atypical needle morphology (53). microneedles were produced via boron work, employing double-sided polished silicon wafers, 300μm thick, with a thermally grown silicon dioxide substrate on both the front and back (Silicon Materials, Germany) (54). Its adaptable characteristics allow the production of needles in various sizes and configurations. Its unique physical features render it a versatile material. Silicon substrates may be fabricated with precision and are excellent for batch production. The expense of silicon and its labor-

intensive, intricate production process restrict its application in microneedles. Moreover, there are biocompatibility concerns, as silicon is brittle; fragments may fracture and remain embedded in the skin, potentially leading to health complications (51).

- **Ceramic:** Ceramic is a further material utilized in the production of Microneedles. They are mostly produced via a micromolding process, when ceramic slurry is cast into micromolds. Micromolding techniques are advantageous for developing device products as a cost-effective procedure, owing to the potential for technological oversaturation (47). Alumina (Al2O3) is extensively utilized owing to its remarkable chemical resistance (51, 47). The strong ionic and covalent bonds that hold the high energy levels between the oxygen (O) and aluminum (Al) atoms provide the conformation of a stable oxide. The newly utilized ceramics comprise calcium sulfate dihydrate, referred to as gypsum (CaSO4·2H2O), and calcium phosphate dihydrate, known as brushite (CaHPO4·2H2O) (51). Alumina (Al2O3) has been the principal ceramic material utilized for the production of Microneedle (47).
- **Polymer**: Polymeric materials offer potential as alternate options for MN production**,** as indicated by prior research (47). A diverse range of polymers, such as poly (methyl methacrylate) (PMMA), poly lactic acid (PLA), poly (lactic-co-glycolic acid) (PLGA), poly glycolic acid (PGA), poly (carbonate), cyclic-olefin copolymer, poly (vinylpyrrolidone) (PVP), poly(vinyl alcohol)(PVA), polystyrene(PS), poly (methyl vinyl ether-comaleic anhydride), and SU-8 photoresist, have been documented for the preparation of microneedles. Typically, these polymers are used to create dissolvable or biodegradable microneedle arrays that can generate hydrogels. Objects made from these polymers possess lower strength compared to other materials, but they exhibit greater toughness than glass and ceramics (51). Silicon is unsuitable for microneedles because of its brittleness and lack of biocompatibility. Polymers are favored for their economic efficiency, biocompatibility, biodegradability, cleanliness, and capacity to expand and dissolve. Biodegradable polymers are insoluble in water but become soluble upon contact to fluids via chemical reactions. Dissolution strategies encompass side-chain bonding groups, crosslinking agents, and water-insoluble polymers containing hydrated functional groups. These polymers possess elevated molecular weight and superior mechanical characteristics, rendering them appropriate for drug delivery systems (55).
- **Silica glass**: Glass can be used to create different shapes on a tiny scale. Silica glass is biologically inactive but prone to breaking due to its fragility (37). Borosilicate glass, composed of silica and boron trioxide, exhibits higher adaptability (52). Silica glass serves as a reserve for the forenamed materials. Glass micro reactors can be fleetly manufactured in several shapes and sizes for laboratory employments on a small scale (47). Silicon and silica glass exhibit similar fracture durability. The product of glass micro-needles isn't time-effective, as it's generally done manually. Glass MNs are presently employed solely for experimental purposes and aren't considered doable for marketable medicine delivery (47). They're primarily constructed by hand, making them less effective in terms of time. presently, glass MNs aren't employed for marketable applications, but rather simply for experimental purposes (52).
- **Challenges**: Insulin is a hormone that is seen as proliferative in certain conditions. No long-term research exists on the cytotoxicity and biocompatibility of insulin MNs administered via various routes. The dermal layer contains many antigen-presenting cells that could trigger immunological responses upon the intradermal administration of a foreign substance. Furthermore, recurrent MN insertion at the same target could provoke immune responses. Therefore, the long-term immunological safety must be evaluated. Sterility, endotoxin limitations, particulate matter, and water activity must be assessed for MNs to prevent clinical infections in patients (2). While MNs induced by external physical stimuli exhibit considerable robustness, they frequently need an external source. Portable devices for administering these external stimuli may be difficult to obtain or even prohibitively expensive for patients (11). MNs must be dependable and strong enough to endure repeated penetration and prolonged usage, as failure may result in improper dosage delivery. The level of biocompatibility is significantly influenced by its ongoing usage demands. Silicon has greater versatility for MN building; yet its biocompatibility differs in use relative to certain other metals. While silicon is recognized for its versatility in MN manufacturing, its level of biocompatibility may differ. The exploration of biodegradable polymer-based microneedles is needed. Certain researchers contend that the quantitative regulation and continuous administration of insulin through the auxiliary pump system necessitate a greater volume of insulin, but in the case of microneedles, it may be sustained with a reduced volume of insulin. In a conventional therapeutic regimen, the infrequent delivery of slow-acting insulin requires a prolonged duration for it to exhibit its effects in diabetes patients. Prolonged controlled injections may facilitate the more frequent administration of short-acting insulin, hence sustaining insulin concentration (56). Although TDDS offers several advantages, they encounter problems like the requirement for pharmaceuticals to exhibit physicochemical features, restricted applicability for high-dose medications, and elevated costs associated with complex formulations (24).

6. Conclusion

Transdermal drug delivery methods, such as microneedle technology, patches, and pumps, offer significant advantages over conventional oral medications. The microneedle technique is being utilized for several medications; however, it must overcome significant hurdles prior to commercial release. Several studies must be undertaken to achieve clinical approval. Several innovative microneedle designs are emerging, promising significant assistance in the future. These innovative systems reduce irritation and infection risks, enhance patient adherence, and facilitate regulated insulin release. Microneedles can deliver insulin systemically, bypassing the stratum corneum, and offer potential due to their biocompatibility, biodegradability, and cost-effectiveness. Despite challenges related to biocompatibility, sterility, and scalability, ongoing research and development are addressing these concerns. As transdermal insulin delivery advances, it holds promise for transforming diabetes treatment, improving quality of life, and alleviating the economic burden of diabetes on healthcare systems.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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