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Nanomaterial and advance technologies in transdermal drug delivery

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Abstract

Transdermal drug delivery (TDD) is an alternative method of drug administration for drugs whose delivery by conventional oral, topical, intravenous, and intramuscular methods is of limited efficacy. Recent advances in TDD involve the use of nanoparticles (NPs), which exhibit a great potential to enhance drug permeation across the skin. NPs can also provide controlled release, the ability to deliver both hydrophilic and hydrophobic drugs and reduce side effects, and when used in a TDD method they are also non-invasive. Another developing technology for TDD employs skin patches containing microneedles. Microneedles represent a painless and minimally invasive method of TDD in which micron-sized pores are created in the epidermis to allow delivery of drugs to the blood vessels present in the dermal layer of the skin. New researches have focused on combining different TDD approaches to overcome previous constraints of drug delivery via conventional methods.

Keywords: Transdermal drug delivery, Nanoparticle, skin patch, microneedle, stratum corneum

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1. Introduction

Drug delivery to skin permits improved treatment through site-specific delivery, reduction of side effects, and is more readily accepted by the patients. In addition to treating skin diseases such as alopecia, dermatitis, psoriasis, acne vulgaris, vitiligo and skin cancer [1], the transdermal method may also be used for other diseases such as diabetes, osteoporosis, rheumatoid, Alzheimer and Parkinson's Disease. In transdermal methods of delivery, the drug traverses the skin layers and then enters the general blood circulation, subsequently reaching the target organ. To pass through the skin layers the main barrier is the superficial skin layer known as the stratum corneum (SC). This layer includes corneocytes or dead skin cells. These cells are located in multi-layered

lipids, which describe as a “bricks and mortar’’ model. Overcoming this barrier is the major challenge faced by researchers in formulating drugs and tools of drug delivery to the skin [1-3]. Among the different methods for drug delivery to the skin, nano-sized systems have attracted attention as drug carriers for TDD [4]. Also, skin patches, have enjoyed more commercial success as compared with ointment, creams and lotion.

2. The structural characteristic of skin

Skin is composed of three layers, namely the epidermis, dermis and hypodermis. The dermis layer contains blood vessels and has hydrophilic properties. The substances entering the blood circulation from the skin layers traverse the epidermis. The hydrophobic SC constitutes the most superficial layer of the epidermis. This layer has a typical thickness of 15 μm and is composed of 10 to 20 layers of corneocytes. The overlap between the corneocytes enhances the strength and stability of the SC. Corneocytes are interconnected by desmosomes ensuring better adhesion. The permeability of SC is 1000-fold lower than that of other membranes, which is attributed to its unique lipid content. Specifically, the lipids are ceramides, cholesterol, and fatty acids, which are arranged parallel to the skin surface. In SC lipids, the unusual length of the free fatty acid, the acyl chain in ceramides, as well as the relatively small polar head of the ceramide as compared with phospholipids create a more robust packaging. Strong cohesion due to the presence of hydrogen bonds between the ceramide molecules, causes the formation of more complicated multilayered planes. The water content of SC is 10 to 25%, corresponding to 8 rows of lipid bilayers. Corneocytes are filled with keratin. Unlike other cells, the hydrophobic and fibrous structure of corneocytes prevents loss of body water and invasion by foreign agents. Such a structure is not present in the fatty gland and hair follicles. The dermis layer can be directly reached from the hair follicle, but the number of hair follicles are not sufficient for TDD, since a sizable dose cannot be

transported. The use of hair follicles for drug delivery is, however reasonable if the object is to deliver the drug to the hair roots [2,3,5]. Fig. 1 schematically illustrates the skin structure and the SC layer.

3. Advantages of drug delivery via skin

The skin provides a large surface (1-2 m^2) for drug administration [6]. Transdermal administration reduces the depletion of the drug before entrance into the systemic circulation and prolongs the administration time. Skin is a suitable site for vaccination, because a variety of immune cells are located within the skin. Furthermore, many drugs are not suitable for oral administration due to their instability in the acidic environment of the stomach and enzymatic digestion and low oral efficiency associated with large molecules [5]. Patients mostly reject the injection method since the administration requires professional skill and requires frequent referrals to health centers. Furthermore, the probability of exposure to infection via a needle in this method and lack of controlled release are additional limitations associated with injection [7]. Nevertheless, in the transdermal method, gradual penetration of the drug allows sudden interruption of the treatment in the case of undesirable side effects, such as anaphylactic shock during vaccination. The capacity to reach the target via the shortest path is among the other advantages of TDD [5].

4. Methods of introducing substances through the skin

In order to introduce drugs into the systemic circulation or subcutaneous tissue, absorption and transportation have to occur across the SC, epidermis and deeper skin layers. The epidermis only serves as a barrier for the penetration of highly lipophilic compounds. Penetration through the skin appendages (sweat glands, hair follicles and fatty glands) is limited since they constitute a small area of the skin (approximately 0.1%). Specifically, ions, compounds with high molecular

weight, highly polar molecules (in the case of sweat glands) which do not readily interact with SC, are largely absorbed through the skin appendage. Penetration into the fatty gland is limited by the accumulation of the drug in the gland as well as the impediment to transport caused by the lipophilic medium of the gland. The hair follicle pathway presents a similar challenge. The route traversed by the hydrophilic molecules is intracellular, and the keratin fibrils assist their transport. On the other hand, the route adopted by lipophilic molecules is intercellular passing through the lipid matrix. The intracellular pathway represents a more challenging transport route compared with the intercellular, since the molecules must pass through the corneocytes, as well as the intercellular space between them, which involves both a hydrophilic and hydrophobic pathway. Fig 2 shows the different mechanisms of passing through the skin.

Therefore, the most suitable passage for transport of drugs is offered by the intercellular pathway, which requires disruption of the lipid plane structure. Consequently, most approaches towards the optimization of drug penetration into the skin focuses on influencing the solubility of the drug within the lipid environment of the SC or modifying the structure of this area [3,8].

Only 5% of drugs are suitable for administration through the skin [3]. These are drugs with small molecular weights (< 500 kD) and medium lipophilicity, that may penetrate the skin passively [9]. Protein or peptides serving as drugs have high molecular weight and are typically charged and therefore, cannot penetrate the SC [5]. The drug treatment is also a limiting factor in transdermal administration with the dose delivered restricted to a maximum value of 10 mg/day, and the absolute solubility should exceed 1 mg/ml [6]. Therefore, modifying the drug formulation to bypass this limitation is a new strategy for TDD.

4.1. Modification of drug formulation enabling passage through the SC

Chemical penetration enhancers (CPE) are a class of chemicals which disrupt the lipid bilayer creating nanometer-sized defect within the SC layer. CPEs are mostly amphiphilic molecules which comprise three primary groups of substances, namely H-bond acceptor solvent, pure fatty acid and alcohols and surfactants with large polar groups. The mechanism enabling enhanced penetration involves the breaking of the hydrogen bonds between ceramides. Penetrating the packaging of the lipids, fluidizing the lipid bilayer, thereby reducing the resistance of the skin barrier. The presence of water in the drug formulation enhances penetration into the cell, since amino acid existing inside the corneocytes causes swelling of the cell and in turn, increase the water content of the intercellular space, leading to disruption of lipid plane. However, the use of CPEs may cause challenges such as burning of the skin, sensitization and other side effects [3].

4.2. Modification of the drug formulation using nano-carriers.

The use of lipophilic nanoparticles for drug delivery such as liposome and its derivative, liquid crystal (LC), solid lipid nanoparticle (SLN), and nanoemulsion, have a wide application in health and cosmetic industries is suitable for TDD. The nanoparticles are employed in the forms of gels, creams, lotion, and solutions. The mechanism of action employed by these systems involves disrupting the SC, breaking the tight junctions, perturbing the cell membrane structure, and thereby facilitating drug penetration. Protection of drugs against decomposition by the microbial flora of the skin, application over the wide area of the skin, low cost, specific cell targeting, and controlled release are among the advantages of this method [10,11]. The following nano-formulations have been proposed for transdermal drug delivery.

4.2.1 Liposome and its derivative

Liposome and its derivatives are capable of carrying hydrophilic drugs inside the aqueous phase as well as lipophilic drugs within the membrane bilayer of the liposome. Cationic liposomes

exhibit a higher penetration due to their interaction with the negative charge present on the surface of the skin cells. If small peptides are functionalized on the surface of the liposome, they may serve to increase cellular absorption and penetration into the skin layers. In order to enhance the capacity of liposomes for penetration, edge activators can be added. Edge activators are essentially individual chain surfactants that increase the elasticity, fluidity, and deformability of liposomes, thereby allowing liposomes to be squeezed through the intercellular space and diffuse through the skin layers. A transferosome is a liposome derivative that contains an edge activator [1]. Another method to increase the penetration of liposomes involves adding absorption enhancers such as ethanol or terpenes [12]. Ethanol increase the liposome membrane fluidity, which reduces the density of the lipid multilayer of the cell membrane. As a result, ethanol increases absorption through the skin. A liposome containing ethanol is known as an ethosome [13]. If stabilizing amphiphilic materials such as non-ionic, single-chain surfactant and cholesterol are incorporated in the liposome structure, in addition to increased penetration, the chemical stability of liposome is also enhanced. This type of liposome is known as a noisome. Noisomes have a high potential to be formulated as a cream or ointment due to their capacity for easy storage and manipulation [1]. Noisomes containing bile salt are known as bilosome. Bilosmes increase absorption via the skin and may be administered orally, since they can tolerate digestive enzyme as well as bile salt [14]. If a combination of soy phosphatidylcholine, lysophosphatidylcholine (LPC), terpene and ethanol is employed, a liposome known as invasome is formed. Lysophosphatidylcholine serves as an edge activator, whereas ethanol functions as an absorption enhancer and terpene penetration by perturbing the lipid packaging of the SC [15]. By combining phospholipid, tween 80, and ethanol using the film hydration technique, an NP called a flexosome is formed [16]. Among the limitation associated with the use of flexible liposomes, sensitization of the skin to ethanol and surfactant,

accumulation in hair follicles and fatty glands and their obstruction can be problematic for some patients [10]. Resveratrol-phospholipid complex (Phytosome®) contains plant compounds such as resveratrol, which has poor oral bioavailability. When presented as a part of the phospholipid complex, resveratrol has the same efficiency as topical administration; this effect is a result of the enhanced solubility and permeability [17].

4.2.2 Lipid-based nanocarrier

Another widely employed nanocarrier for TDD is the SLN which, belongs to the nanostructure lipid carriers (NLCs). Hence SLN holds great promise for reaching the goal of controlled and site-specific drug delivery and hence attracted wide attention of researchers. These NPs have the potential for drug delivery commercialization and may also find application in cosmetic and health industries. Surfactant and alcohol may also be employed to increase the absorption and stability of SLN [1,18]. Nanoemulsions are another type of suitable drug delivery system formed by combining two immiscible liquids such as water and oil. The surfactant can also be used in nanoemulsions to improve their stability by reducing the surface tension between phases through physical repulsion. Nanoemulsions have an optimum suitable size permitting their passage through hair follicles and fatty glands, and do not cause skin irritation. Nanoemulsions may be employed to carry drugs such as minoxidil intended to increase hair growth or prevent hair loss [1,11].

4.2.3 Liquid crystals

Liquid crystals (LCs) that enhance TDD consist of organic salt composed of an asymmetric cation and an organic or inorganic anion and are usually in liquid form at room temperature. LCs are usually intended to carry drugs with poor solubility, improving thermal stability, which in-turn improves the active pharmaceutical ingredient (API) effects. LCs also possess antimicrobial activity. LCs are essentially nanostructures that increase skin penetration directly. Cationic

surfactants present in LCs are capable of interaction with keratin fibrils in corneocytes, thereby perturbing the cell lipid matrix. The limitations of LCs include lack of feasibility of long term storage, sensitivity to temperature changes, pH, and deformation [19]. Furthermore, silk fibroin nanoparticles composed of a crystalline region with many hydrophobic amino acids and an amorphous region with many hydrophilic amino acids were useful as a carrier for transdermal administration of drugs because of the balance between hydrophilicity and hydrophobicity [4]. Lyotropic liquid crystals (LLCs) or lipid-based liquid nanocrystals exhibit high potential for TDD, given their highly ordered structure and thermodynamic stability. Multidrug loading with high entrapment efficiency and controlled release are among some of the advantages of LLC systems [20]. LLCs are categorized into three phases, namely lamellar, hexagonal, micellar cubic phases. The structure of these phases is modified by the introduction of surfactants such as non-toxic and biodegradable lipids. The surfactant increases the solubility of the drugs and allows accumulation of the drugs, given its structural similarity to the SC. LLCs have a higher capacity for hydration compared with emulsions. The presence of intra-lamellar water in the LC phase acts as a reservoir and causes continuous hydration of skin, thereby enhancing skin penetration [19]. Cubosomes represent one of the LCs forms, which include continuous cubic and reverse hexagonal phases. The most common cubosome is the monoglyceride/water system. Cubosomes may entrap a wide variety of molecules, including hydrophilic, amphiphilic, and lipophilic molecules. Besides, they provide good protection against harsh environmental conditions and permit controlled release.

4.2.4 Solid-in-oil dispersion

Another nanosystem for TDD is solid-in-oil (S/O) dispersions, which have been offered as a new method for delivering active ingredients through the skin. S/O dispersion is an oil-based dispersion which consists of hydrophilic molecules in solid powder form, which is obtained by elimination of water and cyclohexane from water in oil (W/O) emulsion through lyophilization.

The resulting dispersion is complexed with drug-surfactant in another oil-based carrier. The oil-based carrier whose diameter is less than 500 nm enhances the skin penetration capacity. Isopropyl myristate (IPM) is a common choice for the construction of the S/O, since it is capable of interacting with the lipids existing within the SC and is deemed to be biologically safe. The mechanism of its action for delivering of hydrophilic drugs involves separation of the hydrophobic surfactant from the drug such that only the hydrophilic molecules may pass through the epidermis and dermis layers. S/O is used in cancer immunotherapy administered through the skin by functionalizing the tumor antigen on the NP surface. The tumor antigen is entrapped by the dendritic cells within the skin, and this is followed by stimulation of T-lymphocytes possessing antitumor activity. This may serve as a viable method to generate cancer vaccines [5].

4.2.5 Hydrogel polymers

The use of hydrogel polymers has a particular significance in TDD. Besides control of drug delivery, hydrogels help retain skin moisture. Hydrogels consist of a network of hydrophilic polymers with a high capacity to absorb water. Poloxamer 407, is a temperature-sensitive hydrogel which is sol form at low temperature and in gel form at the normal body temperature and is maintained as a self-assembled micelle. Hydrophilic drugs may be incorporated in the micelle structure [21]. By adding other polymers such as carboxy-methyl-cellulose (CMC) to poloxamer 407 its properties such as adhesion surface morphology and porosity can be improved [22]. Another hydrogel for TDD is the poly (N-isopropylacrylamide-co-vinyl-2-pyrrolidinone) which is crumpled through stimulation by light releasing the drugs [23]. Gelatin methacryloyl (GelMA), as an NP, has the capacity for controlled drug release. This hydrogel has a swelling property in aqueous media, enabling it to retain moisture. GelMA penetrates the SC by perturbing the lipid packaging [24]. Hydrogels are useful for treating skin wounds, since their high adhesion and capacity to withstand surface motion permit their application to the dynamic surface of the skin.

In order to dress skin wounds, Polyvinyl alcohol (PVA), poly hydroxyalkyl methacrylate (PHAM), alginate biopolymer, collagen, and chitosan are commonly employed. Alginate polymers have long been used to treat skin wounds. This polymer allows the controllable delivery of drug agents for wound repair [25]. Nano-chitosan is useful in drug delivery due to their capacity for controlled drug release, high skin penetration, and bio-adhesion [26].

4.2.6 Dendrimers

Dendrimers can serve as permeability as well as solubility enhancers by facilitating the transport of lipophilic drugs through the skin. Cationic dendrimers can transport drug molecules across the negatively charged skin surface at physiological pH. For example, free peptidic dendrimer acts as a CPE through disruption of skin structure [27]. Polymeric dendrimers such as polyamidoamine (PAMAM), on the other hand, create nanoscale holes in the skin membrane by interacting with the phospholipids opening the skin barrier over time by extracting lipids from the SC. Dendrimers cause minimal skin irritation and have been reported to improve the skin deposition and permeation of several drugs, including indomethacin, ketoprofen and diflunisal, diclofenac sodium, 5-fluorouracil, 8-methoxy psoralene, tamsulosin, riboflavin and dithranol [28].

4.2.7 Metallic NPs

Metallic Au NPs can interact with skin lipids, thereby modifying the SC structure by inducing transient and reversible openings. Smaller metallic NPs can penetrate deep layers of skin. Generally, the charge and shape associated with the Au NPs impact their ability to permeate through skin. For example, positively-charged Au NPs in the form of rods exhibit deeper penetration into the skin layers as compared with negatively-charged spherical NPs. Coating the metallic NPs with polymers such as polyethylene glycol (PEG) and peptides can further improve the deposition as well as penetration of the drug into subcutaneous adipose tissue. Superparamagnetic iron-oxide nanoparticles (SPIONs) have been utilized for the transdermal

administration of drug treatment of tumors. In particular, the anticancer drug Epirubicin (EPI) demonstrated a strong inhibitory effect on the proliferation of the WM266 tumor cells when delivered as conjugated SPIONs. *In vivo* transdermal investigations have indicated that the nanoparticles may penetrate deep into the skin under the influence of an external magnetic driving field. Assisted by the magnetic field, the SPION transdermal vector has been shown to bypass the SC via follicular pathways. Therefore, magnetic field-assisted SPIONs exhibit great potential for transdermal therapy of the skin cancer [27]. A list of recently-used NPs for TDD is given in Table 1.

4.3. Challenges of nanocarrier-based TDD

Despite the benefits provided by the application of nanocarriers in TDD, there are serious challenges posed by this method for drug delivery to skin. One of the disadvantages associated with nanocarrier-based TDD is the accumulation of the lipid-based NPs in hair follicle canals and fatty glands, which restricts translocation to the viable epidermis, thereby limiting continuous drug delivery. Other challenges posed by NPs relate to the potential toxicity of some NPs, skin sensitivity and inflammation, restriction on the kind and the amount of loadable drug, and preservation issues [10,27,29]. Metallic NPs such as ZnO, TiO_2, Ag, SiO_2, Fe_3O_4, Au, and Cu are increasingly used in dermatology and cosmetology. Not only can these NPs pass through the SC of healthy skin but also hair follicles and sebaceous glands. However, they exhibit toxicity owing to efficient penetration, poor elimination, and tissue accumulation. In fact, their toxicity is a serious safety concern, given their capacity to increase skin exposure, which can lead to systemic absorption. The toxic effects produced by metallic NPs upon skin infiltration are included as oxidative stress, inducement of cell apoptosis, mitochondrial dysfunction, and damage to the cytomembrane and DNA. However, given the limited drug bioavailability associated with NP-

based transdermal delivery, this method is appropriate for the formulation of drugs requiring low doses. To increase the dose, the application of the drug to a larger surface of the skin is required, which can lead to patient dissatisfaction and increased costs. Also the relatively high cost and limitations associated with scale-up in manufacturing have limited the widespread application of NPs in TDD as compared with other viable methods [30,31].

4.4. Microsponge for TDD

A viable alternative for TDD, which may overcome some of the disadvantages associated with nano- and micro-formulations, is offered by a new drug delivery vehicle known as microsponge. In particular, microsponges alleviate skin irritation, allergic reaction, as well as greasiness of the skin, which tends to reduce patient compliance. Microsponges are spherical particles ranging in size from 5 to 300 μm which tend to form clusters of smaller spheres. These vehicles are capable of efficient delivery of the drug at a relatively smaller dose. Other advantages attributed to microsponges include enhancement of drug stability, modification of the drug release profile for controlled delivery as well as minimization of side effects by decreasing transdermal invasion of the skin by the active ingredient. Microsponge drug delivery systems are also reported to increase drug retention on the skin surface and within the epidermis. Further, given the ability of microsponges to absorb an amount of oil above four times their weight without drying, the patient's irritability resulting from topical application of the formulation can be significantly reduced. Microsponges are also known to be non-allergenic and non-mutagenic and tend to be more stable than micro and nano-formulations over a wider range of pH without requiring preservatives. A variety of polymers have been employed to develop microsponges, including poly hydroxyethyl methacrylate (PHEMA), ethylcellulose, acrylic polymers, Eudragit RS 100, and polystyrene [32].

5. Physical methods for circumventing the skin barrier

Passing the skin barrier by physical means is performed by electroporation, sonophoresis, iontophoresis, microdermal abrasion, and microneedles. Electroporation uses high voltage pulses of a short duration to break down SC lipids enabling diffusion of drugs into deep nanometric pores. The sonophoresis method employs ultrasound waves to breakdown lipids allowing skin penetration. Iontophoresis employs electric or magnetic fields to stimulate drug diffusion through the SC and subcutaneous skin layers. Electric currents can be used for delivering charged lipophilic molecules. Microdermal abrasion involves removing superficial skin layers [6]. Although these methods are effective, they tend to be costly, require dedicated equipment and professional expertise for their application, often causing long term damage to the skin, and hence patients do not readily accept these.

Microneedles (MNs) provide the best means of physical penetration through the skin barrier. The MNs pass through the SC, delivering the drug to the dermis layer and blood vessels. MNs do not penetrate deeply into the skin and therefore, do not cause pain and bleeding. Skin patches containing MNs have been recognized as the most effective type of patches and have gained widespread commercial acceptance [33]. As shown in fig 3, MNs can deliver drug molecules from skin layers.

When MNs are used to deliver the vaccine, a notable reduction in the presence of immune cells is observed in the area where the skin patches is applied, indicating the migration of the immune cells toward the lymph nodes to induce an immune response [34]. Other advantages of MNs include the capacity to deliver large molecules, the quality of being painless, easy

administration, reduction of exposure to microbial agents compared with regular injection and fast delivery of the drug [7]. Recently skin patches for the treatment of several diseases, including hypertension, chronic pain, smoking cessation, testosterone deficiency, osteoporosis, and others, have been manufactured [35]. Currently, the development of high-performance MNs have addressed the limitations of the material used in the older implementations. Metallic and silicon-based MNs may be partially retained by the skin, causing sensitivity, erythema, inflammation, change of color, and other side effects [36]. To address this issue, biodegradable materials such as poly lactic-co-glycolic acid (PLGA), polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), silk hydrogel and cellulose are recommended for use as excipient materials in the drug formulations. Biodegradable polymers, on the other hand, decompose within the skin and do not produce the adverse effects associated with metallic and silicon-based MNs [6]. The other disadvantage of such MNs, particularly the hollow variety, is their vulnerability to breakage within the skin. Adding nanomaterials to soluble polymers improves the mechanical properties of the patch without affecting the dissolving rate in the skin. Nanomaterials such as layered double hydroxide (LDH) and may also be added to a polymer to enhance the flexibility of the MNs and improve the efficiency of drug delivery [34]. Also, MNs eliminate the requirement of toxic solvents necessary for carrying lipophilic drugs. Notably, the use of dissolving microneedles (DMNs) permits the release of the drug from the polymeric matrix upon dissolution of the DMNs polymer. This method circumvents the requirement of solving lipophilic drugs in the toxic solvent [8]. Table 2 introduces the variety of MNs employed over recent years.

5.1.Benefits of NPs application in MNs

Incorporation of nanoparticles in MNs endows these delivery vehicles with uniquely favorable characteristics, most of which will be provided in this section.

5.1.1 Improvement of the mechanical strength of polymeric MNs

NPs have been shown to improve mechanical strength as a filler agent in the polymeric matrix of an MN. Specifically, the inclusion of sodium montmorillonite (Na^+ MMT) clay as a filler in the PVA matrix enhances the mechanical strength and thermal stability of the resulting PVA/PVP/Na^+ MMT composite. Strong hydrogen bonding between PVA and Na^+ MMT is believed to be responsible for these enhanced physical characteristics [37]. Besides, synthesis of chitosan as a matrix for graphene assembled in porous carbon (GAPC) produces a biocompatible, non-toxic, and biodegradable DMN patch exhibiting favorable mechanical and electrical properties [38]. It has been demonstrated that the introduction of DNA into the DMN leads to an increase in the Young modulus of the modified structure as compared with that of the standard DMNs. Moreover, the presence of DNA enhances the water solubility of the DMN owing to the hydrophilicity contributed by the sugar-phosphate backbone of DNA [39]. The poor mechanical strength of swelling or hydrogel-based MNs can be improved by incorporating novel nanomaterials into hydrogels serving as versatile TDD platforms. In particular, silver and gold NPs, carbon nanotubes (CNTs), graphene, reduced graphene oxide (rGO), and graphite have been introduced into hydrogel matrices to modify their mechanical, and thermal properties [40].

5.1.2 Capacity for controlled release

A number of NPs, not only serve to improve the mechanical characteristics of MNs, but also function as an encapsulating or intercalating agent enabling controlled release of drugs. We have explored the use of gallic-acid-loaded MMT composites for controlled release by utilizing the sensitivity to the amount released at different pH values [41]. Alternatively, the functionalization of chitosan using GAPC enables drug release in a controlled manner, while maintaining the facile dose [38]. DMNs incorporating the anticancer drug doxorubicin (DOX) intercalated in salmon DNA have also been reported. The special binding properties of DOX,

namely steric preference in the major and minor grooves, and electrostatic interactions associated with the phosphate backbone collectively lead to the controlled release of DOX from DNA following the dissolution of DMN in the blood [39]. Furthermore, PLGA nanocarriers permit controlled drug release from periods spanning a few days up to several months, depending on their molecular weight and ratio of lactide: glycolide chains. Specifically, the PLGA NPs prepared with PVA/ PVP gels form useful composites for the transdermal delivery of drugs[42]. In addition to controlled release, NPs can be utilized to effect the smart release of drugs. Deployment of transdermal biosensors on the skin surface can enhance the transdermal delivery of the drug in response to the concentration of the sensed species. Notably, smart insulin DMN patches embedding glucose oxidase (GOx) encapsulated within polymeric NPs basically implement a biosensing system capable of secreting insulin in response to the glucose concentration [43]. In another method, the swelling characteristic of hydrogel-based MNs in the presence of interstitial fluid has been employed to form continuous and unlockable conduits for drug delivery from the site of storage within the patch to the dermis layer. For example, hydrogel polymer prepared from 2-hydroxyethyl methacrylate (HEMA) and ethylene glycol dimethacrylate (EGDMA) incorporating ibuprofen has been utilized as a model drug. This hydrogel polymer was loaded with up to 5% (w/w) ibuprofen conjugated to the light-responsive 3,5-dimethoxybenzoin, which permits the controlled release of ibuprofen from the hydrogel matrix [44].

5.1.3 Improvement of treatment outcomes

Transdermal administration along with photothermal therapy (PTT) and chemotherapy, can improve cancer treatment outcomes. In particular, the anticancer drug, DOX, can be integrated within gold nanocages in a hyaluronic acid MN array for synergistic treatment of superficial tumors. Dissolvable PVA/PVP supporting patches incorporating photothermal NPs and an antitumor drug has been shown to eliminate 4T1 tumors over one week without tumor recurrence.

Therefore, nanocarrier-based combinational therapeutics exhibit the potential to serve as a potent alternative to long-term cancer polytherapy [45]. Fabrication of MNs incorporating DOX and indocyanine green (ICG) has also been reported by employing mesoporous silica nanoparticles (MSNs) to improve the stability of ICG, thereby enhancing PTT efficacy *in vivo* [46].

5.1.4 Effective vaccination

The utilization of nanomicelles in vaccination with DMNs has been shown to lead to a ten-fold increase in the production of antibodies. Ovalbumin (OVA)- loaded nanomicelles, in particular, show higher absorption and colonization in antigen-presenting cells (APC) within the lymph nodes as compared with those loaded with OVA alone [47]. An approach to enhance the potency of DNA vaccines involves delivering DNA into the immunogenic layers of the skin, accommodating a wealth of APCs. DNA complexed with cationic lipids, polymers, and peptides is known to improve transfection efficiency through condensation of DNA into the range of size associated with nanoparticle to enhance cell uptake. A complex of DNA with cationic peptide, RALA, complexed with DNA and incorporated in DMNs fabricated from PVA, exhibited a 10-fold increase in transfection efficiency compared with the corresponding complexes released from PVA/PVP matrices [48]. In addition, the introduction of NPs into DMNs for vaccination has been demonstrated to improve immunogenicity through enhancement of antigen delivery and sustained release [49]. Antigen-adjuvant formulations incorporated into NPs has been suggested as a means of improving immunogenicity with NPs facilitating uptake and presentation by dendritic cells (DCs). To this end, a model vaccine combining OVA with platycodin (PD), a saponin adjuvant has been evaluated. Specifically, the PD/OVA was encapsulated in a liposome and then incorporated into DMNs. An investigation conducted at the Institute of Cancer Research has demonstrated that mice treated with OVA-PD-Lipos-DMNs exhibit a significantly-enhanced immune response [50]. Another advantage offered by incorporating NPs into the DMNs for

vaccination is the entail of enhancing the retention of vaccine compounds within the lymphatic tissue. The size and charge of NPs are known to exert a significant effect on uptake and retention of lymphatic tissues. Rhodamine employed as a model tracer can be employed to monitor the retention of antigen compounds in lymphatic tissue. In one study, following DMN application, rhodamine was detected in the livers, kidneys, spleens, and superficial parotid lymph nodes of the mice [51]. Another strategy serving to increase the retention of vaccine compounds in the lymphatic nodes entails the manipulation of vaccine solubility using NPs. Since most vaccine components are poorly soluble in water, amphiphilic polymers incorporated into nanomicelle form can be integrated into the DMN's highly soluble structure to compensate for the poorly soluble nature of the vaccine [52].

Hollow MNs have been employed for the delivery of the influenza vaccine. In human trials, hollow MNs for influenza vaccination have been demonstrated to require lower doses in comparison with intramuscular immunization. Notably, tetanus antigen toxoid encapsulated in chitosan-based particles has been recently delivered through 3 hollow MNs 600 μm in height and via a roller composed of 540 solid MNs with heights of 500 μm. Results showed *in vitro* controlled release of the antigen from the NP and adequate *in vitro* cellular uptake and skin penetration. Furthermore, immunization of mice using both technologies indicates that hollow MNs have superior performance for the delivery of antigen-loaded NPs [49].

5.2. Challenges posed by microneedles

While MN-based administration has been successfully utilized to deliver some drugs, various challenges must be overcome before this approach can gain widespread market acceptance. Generally, numerous supporting studies have to be conducted before securing clinical approval. Furthermore, the MN technology suffers from many disadvantages, including inducement of

contact dermatitis and the associated redness and irritation, limitation of the loadable amount of drug, and the inherent challenge posed by transporting large hydrophilic compounds through the skin. A material with adequate mechanical strength and capable of generating sufficient insertion force has to be selected for the fabrication of MNs. One of the chief objectives is to increase drug permeation without causing pain. Patient compliance is adversely affected if poking the skin with a needle before the application of the patch is required. In addition, a chance of infection will not be negligible, if the skin pores do not close following the implementation of the MN [53]. The fabrication process of DMNs also presents particular challenges including the length of time required for fabrication, which may exceed 24 hours, loss of drug activity, aesthetics during storage or processing, and difficulty in the regulation of drug loading into the MNs [54]. The development of new technologies for TDD is time-consuming and costly, requiring high-tech equipment typically found only in dedicated laboratories to allow processing of complicated steps. MNs may also be fabricated based on microelectromechanical systems (MEMS) technology. Basic processing steps in MEMS technology include reactive ion etching, laser cutting, and photolithography implemented to achieve the desired size and spacing between MNs within the patch [55]. This technology forms the basis of microfabrication of all types of MNs. As illustrated in Fig 4, solid and coated types of MNs are fabricated based on lithography and etching processes. These processes are also employed in the manufacture of hydrogel and dissolving MNs by micro molding. In the micro molding technique, first a positive metallic master mold is fabricated, and then the negative polydimethylsiloxane (PDMS) mold is produced using the positive master mold. The negative mold, in turn, is employed to produce the polymeric or hydrogel MN. Hollow MNs can also be built using the MEMS technology; however, the fabrication process is considerably more complicated [45].

6. Advanced combinational therapy:

Combining the use of MNs with other methods such as iontophoresis, sonophoresis, electroporation, vibratory actuation and micro-pumping will lead to significant progress in the manufacture of skin patches. Applying these methods to skin patches allows the control of the amount of drug released, regulation of drug consumption through turning the control device on and off as well as mode change of the injection force [7].

In iontophoresis, a relatively small electrical current enables the transport of drugs across the SC layer. The main advantage offered by iontophoresis in MN technology is to affect the controlled release of the drug by adjusting the value of the current. This method allows the delivery of small drug molecules with molecular weights up to a few thousand Daltons. For example, iontophoresis has been used for the delivery of insulin nanovesicles via MNs. In this case, the positive zeta-potential, as well as the small diameter of the nanovesicles, contribute to the enhancement of penetration by insulin. On the other hand, sonophoresis relies on ultrasound frequencies in the range of 20 kHz to 10 MHz to enhance drug transport by forming cavitation and rearrangement of lipids within the SC. Varying the ultrasound frequency allows control of drug permeation to effect controlled release. Specifically, as the sound frequency is increased, a significant increase in skin perturbation results. Improvement in the rate and amount of delivery have been reported for small biomolecules such as calcein as well as large proteins like bovine serum albumin using a combination of sonophoresis and MNs. Electroporation involves the introduction of localized skin perturbation resulting from the formation of aqueous pathways within the SC using high-voltage pulses of short duration. Typical amplitudes of up to 1 kV and pulse widths in the range of 10 ms to 500 ms have been used for *in vitro* electroporation of the SC

layer. Wider pulses width with higher voltage amplitudes is required to increase skin perturbation. This method has been employed to enhance the permeation of larger molecules with molecular weights in the several kilodalton (kDa) range. In this technique, the MN itself can serve as the electrode. Vibratory actuation is another technology used in combination with MNs allowing a significant reduction in the insertion force, thereby reducing the chance of MN fracture. The decline in the insertion force by vibratory actuation involves tissue damage through fluid cavitation as well as thermal damage resulting from frictional interaction. Combining vibratory actuation with the MN technology permits fabrication of metallic and polymeric MNs, which tend to exhibit low values of Young's Modulus. Application of Micro-pumps in association with MNs, enables controlled release of drugs. Notably, pumps control the flow rate and the pressure allowing delivery of concentrated drug solutions. Micro-pumps also provide the capability of withdrawing fluids for medical analysis in controlled amounts as well as delivering the drug in response to specific metabolite levels [7].

Recently nanoneedles have been employed to transport genetic materials and proteins into the cells. Nanoneedle made from silicon have been utilized for intracellular drug delivery. Nanoneedles passively perturb the plasma membrane allowing the drug to enter the intracellular space without destroying the cell structure. Nanoneedles can also be made from diamond, forming diamond-based nanoneedle patches, which may be used for drug delivery to the nucleus [34].

7. Current challenges and future perspectives

Some technologies have been advanced to modify and enhance the conventional MNs for TDD. MN-based technologies have transformed TDD into a flexible drug delivery method, in some cases allowing the administration of some hundreds of milligrams of proteins directly into the systemic circulation [56]. Combining the MN technology with several other technologies such

as iontophoresis, sonophoresis, vibratory actuation, and micro pumping has led to further increases in drug permeability through the skin and provided the means for controlled release of drugs. These enhancements to the underlying MN technology have revolutionized transdermal delivery leading to the development of smart TDD systems [53]. Despite the intensive ongoing research on TDD, a significant challenge is the further development of miniaturized portable and cost-effective enabling devices. [57].

In the field of vaccination, MNs have broadened the potential of TDD systems. While conventional jet injectors have been utilized in mass vaccinations, this approach does not effectively prevent transmission of pathogens, since the cost of disposable nozzles is prohibitive in developing countries. The MNs technology can potentially overcome this limitation; however, this requires a serious undertaking to establish more cost-effective MN technologies [58].

The requirements of storage and packaging impose one of the serious impediments to the commercialization of MNs. In addition to protection against breakage, the storage and packaging of MNs should provide safeguards against exposure to air and severe temperature and humidity changes. Our research involving polymeric MNs has revealed that these environmental changes may cause drug release before administration, which necessitates the development of impermeable MN packaging technologies [59].

While the TDD technology has been enhanced by the utilization of devices providing superior sensing capabilities and mechanical properties comparable with those of skin, unlike skin, smart TDD systems are not capable of collectively transforming the chemical and physical input signals into sensations. Advanced healthcare monitoring devices intended to provide personalized patient care are expected to improve health care standards significantly. By utilizing data analytics and machine learning, a smart device could assist diagnosis using specific health standards for

monitoring. Once a given index level goes beyond the safety range, the device can trigger an alarm based on the patient's routinely-collected data or even provide automatic feedback therapy. Monolithic integration of sensing, memory, and therapeutic modules within a smart TDD system offers the prospects of overcoming these challenges in the future [60].

8. Conclusions

Among the different strategies available for TDD, technologies based on NPs and MNs have attracted the most attention, and consequently, have undergone the most development. NPs such as flexible liposomes, including ethosomes, transferosomes, noisomes, bilosome, etc., exhibit suitable penetration into the skin, with the NPs crossing the skin layers by squeezing through intercellular spaces. Subsequently, nano-formulations, such as liquid crystals and solid-in-oil dispersion have been successfully employed for TDD. In addition, microsponges have been proposed as alternative means of TDD surpassing such limitations associated with nano- and microparticles, as oiliness, and greasiness. On the other hand, as an alternative to hypodermic injection, microneedle technology represents a safer and more patient-friendly drug delivery method. Microneedles, pass through the SC making micro-sized channels in the epidermis permitting the delivery of the drug to the dermis layer. In addition, nanoneedles as components of the future generation of drug delivery systems can deliver genes, proteins, and medicines to the intracellular space. Finally, the use of MNs in combination with other transdermal drug delivery devices can improve the efficacy of MNs by improving drug permeability through the skin as well as permitting controlled release.

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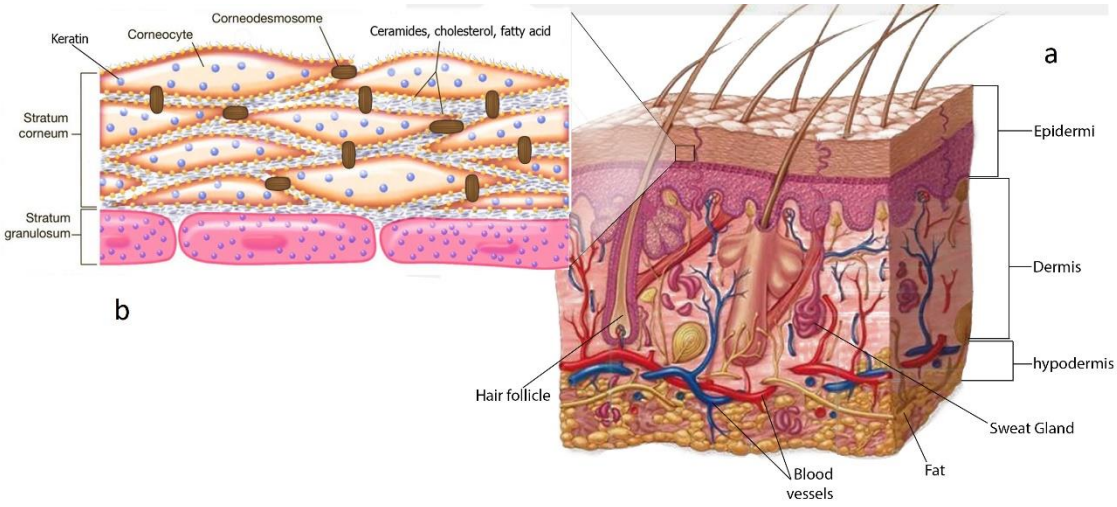


Figure. 1. Schematic illustration of a) the three layers of skin, b) stratum corneum.

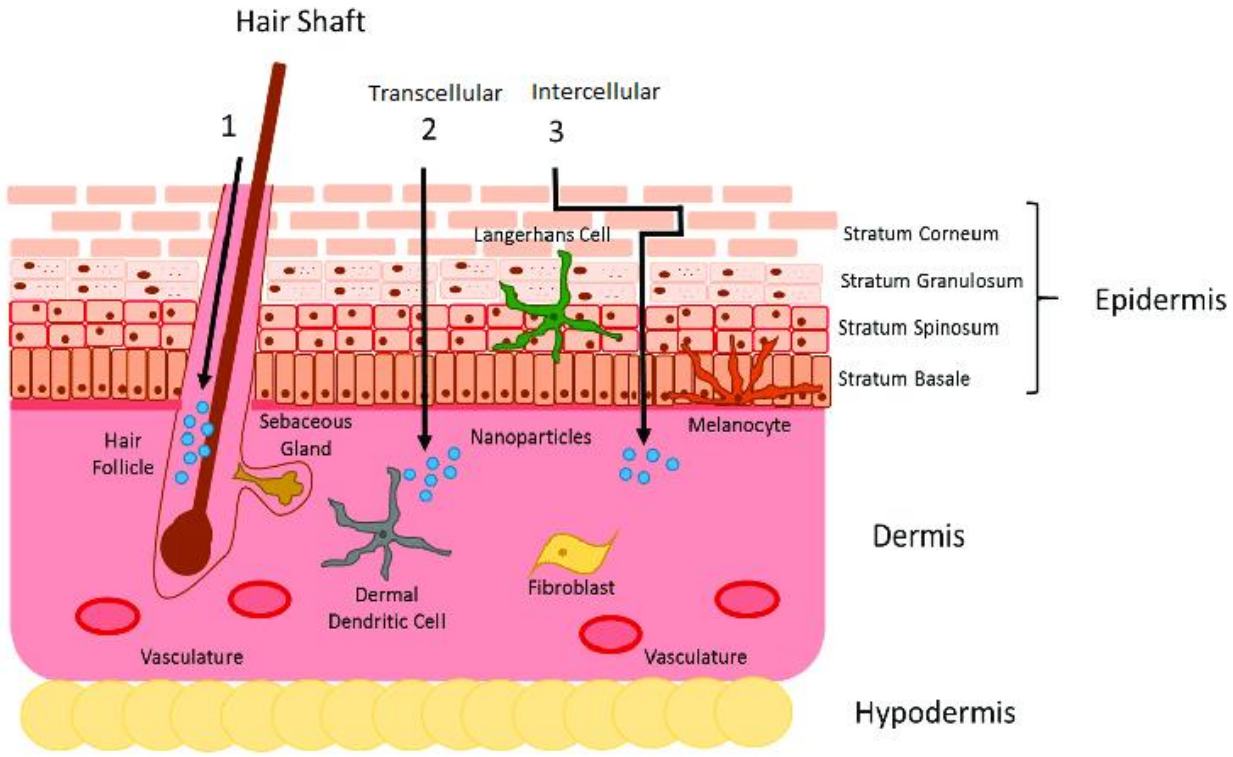


Fig2. Schematic of transporting route in the skin [61]

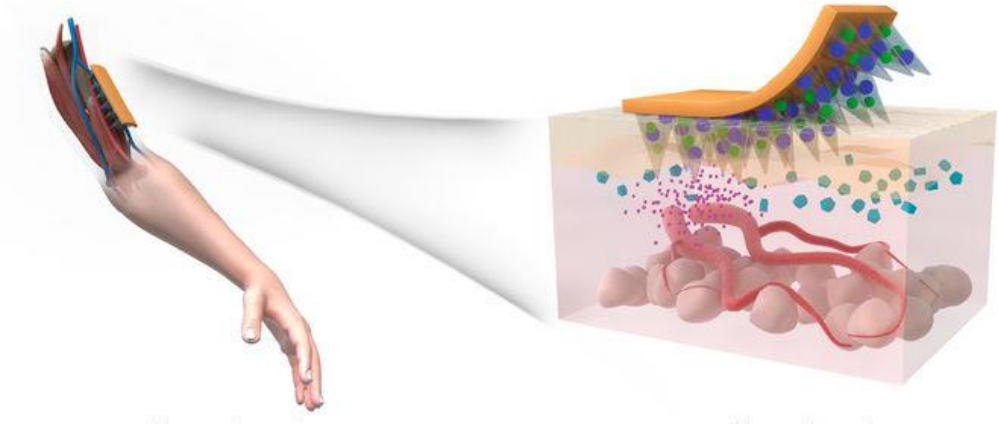


Fig3. Schematic illustration of microneedle device.[62]

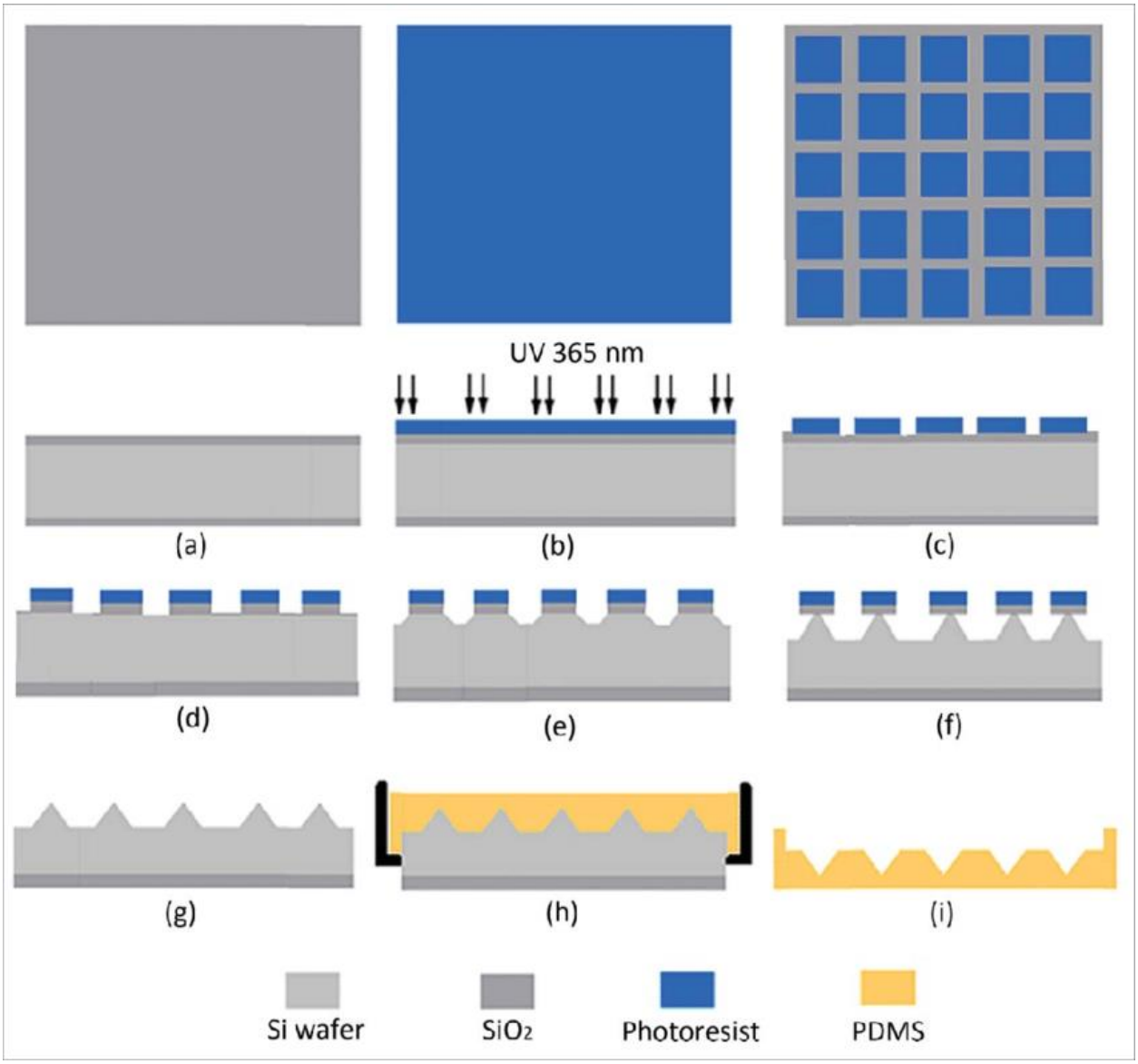


Fig4. MEMS technology for fabrication of silicon master mold and PDMS. Coating of photoactive layer (a) and (b), patterning and isotropic etching (c) and (d), anisotropic etching (e), (f) and (g), polymerization and molding (h) and (i) [63].

Table 1**:** NPs used for transdermal drug delivery

Diseases/drug	Transdermal nanocarrier	Benefits	References
Diabetes/glimepiride	Ethosome	Prevention of oral drug side effects, sustained release of the drug, avoid the hepatic first-pass metabolism.	[13]
Psoriasis/ Osthole	Transfersome and ethosome	Enhanced skin penetration, improve solubility, increased bioavailability	[64]
Hypertension/Olmesartan medoxomil	Nano-invasome	Increased drug half-life and patient compliance	[15]
OA and RA/Oxaprozin	Drug-cyclodextrin in liposome and NLC	Improve solubility and enhance penetration through the skin	[65]
Skin cancer/ Epirubicin	Superparamagnetic Iron-Oxide NPs	Providing pH-sensitive release, better penetration and accumulation in tumor, and reduce the adverse effect.	[66]
Hormonal disturbances in pre-and postmenopausal women/Progesterone	Liquid crystalline NP (LCNP)	Increased solubility and half-life of the drug, prevent from first-pass metabolism, decrease side effect and patient compliance	[21]
Atopic dermatitis/ Corticosteroids	Thermo-sensitive Poloxamer 407/Carboxymethyl cellulose sodium (P407/CMCs) composite hydrogel	Skin hydration, reduced side effect, enhance bio-adhesion, and surface morphology.	[22]
Schizophrenia/Risperidone	Nano soft lipid vesicle containing phospholipid, safranal and ethanol	Increase solubility, and bioavailability, avoiding its first-pass metabolism and produce stable plasma concentrations over a long period.	[12]

Rheumatic diseases/ Tenoxicam (TX)	Bilosome	Avoid unnecessary GI side effects associated with oral administration.	[14]
Rheumatism and neuralgia/ Paeonol	Transethosome	Increase solubility and bioavailability, decrease volatility	[67]
RA, psoriasis and cancer/Methotrexate (MTX)	NLC	Eliminate adverse effect of MTX	[68]
Skin diseases/ 8-methoxypsoraln (8-MOP)	Noisome	Eliminate gastrointestinal the adverse effects and a higher risk of severe complications, e.g., glaucoma or carcinogenesis	[69]
OA and RA/ Meloxicam	Flexosomes	Deeper skin penetration, improved therapeutic effect compared with oral administration in the rat paw	[16]
Dermatitis and eczema/ Triptolide	Nanoemulsion gels	The stable release of the drug, maintaining effective drug concentration.	[70]
Skin cancer/ Curcumin and 5-fluorouracil	Two copolymers: alginate coated aminated nanodextran (ALG@AND) and chitosan-coated folate decorated aminated -CD nanoparticles (CS@FA-g-ACD).	Elute the drugs in a sustained manner, and could also act as penetration enhancers.	[71]
RA, OA and ankylosing spondylitis/Aceclofenac	NLC	Improved skin penetration and dermatokinetic, increase the anti-inflammatory effect	[72]
RA/ Diflunisal (DIF)	Supramolecular nano-engineered lipidic carriers (SNLCs)	Decrease ear edema in mice and paw edema in the CFA model. The levels of TNF-α were reduced in synovial fluid and serum.	[73]
Hemorrhage and pain/ Dencichine	Ionic liquid – microemulsions	10-fold increased penetration compared with a drug solution, minor cell toxicity, and skin irritation, significant hemostatic activity	[74]
Hypertension/ Lacidipine	Niosomal gel	Skin permeation enhancement of 2.15 times as compared to control gel, higher antihypertensive activity	[75]
Hypertension/ Eprosartan mesylate	Nano-transferosome	Higher and deeper penetration into the skin compared with liposome	[76]
Hypertension/Amlodipine	NLC	Enhanced bioavailability of amlodipine in the Wistar rats	[77]

Gout/ Febuxostat	Niosomal gel	Improved solubility and stability of the drug	[78]
OSP/ Raloxifene hydrochloride	Nano-transferosome	Provide controlled release and improve bioavailability	[79]
5-fluorouracil	PAMAM dendrimer	Enhancing the skin permeation, increasing the skin partitioning of 5-fluorouracil	[80]

Table 2**:** Microneedles used for drug delivery

MNs materials	Drug	Diseases	Reference
Titanium	Parathyroid hormone (Forteo)	Osteoporosis	[81]
PVP	Insulin	Diabetes	[36]
CMC, PVA, PVP	Capsaicin	RA	[8]
solid silicon	cholesterol-modified housekeeping gene (Gapdh) siRNA	Alopecia, allergic skin diseases, hyperpigmentation, psoriasis, skin cancer, pachyonychia Congenital	[82]
PVA and PVP in the polymeric matrix	Memantine	AD	[83]
N-methyl 2-pyrrolidone or dimethyl sulfoxide	Diclofenac	Analgesic effect	[6]
PVP, PVA	Vitamin D3-PLGA	Vaccination goal	[42]