Microneedle Array Patches: Characterization and in -vitro Evaluation

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Abstract

Patches in transdermal drug delivery system (TDDS) have been used to overcome the hypodermic needles drawback. However, these patches also have absorption limitation for hydrophilic drugs and macromolecule like peptides and DNA. Therefore, micronized projections which have the ability for skin penetration named as microneedles were developed. Microneedle array patches can penetrate the stratum corenum to form conduits in the epidermis for drug delivery, avoiding nerve fibers and blood vessels contact to minimize pain sensation and bleeding. There are types of microneedles such as solid, coated, hollow, dissolving and hydrogel microneedles with different methods of microfabrication.

Keyword: Microneedle Array, Transdermal delivery, Penetration enhancement techniques, Microneedles application.

Introduction

Transdermal drug delivery system (TDDS) is delivery of a therapeutic agent through the skin for systemic effect. When compared to oral administration it has many advantages like avoiding the 1st pass effect of the liver (1). When it is compared with hypodermic needles, it has no pain and in addition it provides the advantages of no risk of transmitting disease that produced by the reusable of needle especially in developing countries (2). Transdermal drug delivery system is generally considered as a self-administering noninvasive sustained release drug delivery system. Human skin consists of three layers: epidermis, dermis and the subcutaneous fatty layer. Epidermis represents the outer layer of skin and it is a 100-150 μm in thickness and the stratum corneum which is the upper layer of epidermis exhibiting a formidable barrier towards transdermal delivery due to its composition that prevents foreign substances from entering and water to exit from human skin. Transdermal drug delivery system is also an alternative way for solving the issues of enzymatic degradation of drugs, or poorly absorption after oral administration. However, it shows some restrictions regarding the inability of large and hydrophilic molecules to penetrate through the skin (3,4). Therefore, several penetration enhancement strategies were used to facilitate drug delivery through the skin including passive and active penetration.

Factors affecting transdermal permeation physicochemical properties of drug (5-7)

1. The drug molecular weight must be less than 500Da.
2. The drug melting point must below 200 °C
3. Partition coefficient: If the drug having high partition coefficient, it is not readily leaving the skin lipid part. While, drug with low partition coefficient is not able to permeate. So that, the optimum partition coefficient is necessary for better action, log P (1-3).
4. Aqueous solubility, ideally the aqueous solubility of the drug should be equal or greater than 1 mg/mL.
5. The effective daily dose of the drug should be in the range of 10-40 mg/day .

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Biological properties of drug (8, 9)
1. Must not produce irritation or allergic effect.
2. Has short half-life.
3. Potent with low dose.
4. The drug which is inactivated by hepatic enzyme or degraded by GIT fluid is good candidate for transdermal delivery.

Active physical penetration enhancement techniques Iontophoresis
To increase the topical drug permeability to the skin, the electrical current used in which the same charge of electrode as the therapeutic agent is placed on the site of application while the opposite electrode is placed on the counter side of the body. The electrode presents over the drug will repel and force the therapeutic agent into the skin (10).

Heat
Many studies indicated that the change in temperature around 5°C was sufficient to produce changing in cell membrane permeability. In addition, it produces changes in transdermal patch physicochemical properties. Sweating lead to increase hydration and improving permeation of drug through the skin (11).

Sonophoresis
This method includes using of ultrasonic energy at low frequencies rather than high frequencies so that, skin penetration of the active ingredient will increase (12).

Magnetophoresis
It includes a magnetic field application as a driving force which leads to altering skin structure which results in an increase in drug penetration into the skin (13).

Radiofrequency
It involves the formation of microchannel in the cell membrane by using heat followed by skin exposure to high frequency 100KHZ of an alternating current. The drug delivery rate depends on the deepness and a number of microchannels formed which in turn influenced by the microelectrode used throughout the process (14).

Electroporation
The mechanism of drug penetration is by formation of transient pores by electrical pulses (pulses of very high voltage 50-100 volts) resulting in macromolecules passage from extracellular to intracellular Region. Thus, drug penetration is done by two processes which are diffusion and Electrophoresis. Many large macromolecules were delivered by electroporation like Vaccines, insulin and oligonucleotides.

Microporation
This achieved by using sharp micron sized projection applied on the skin that improves skin penetration called microneedles (15).

Microneedles
They consist of different shape micro projection arrays ranging from 10 to 1800µm in length which are connected to the base that support each. Microneedles can be fabricated from different techniques such as etching, lithographic and molding using different materials such as plastic, ceramic, silicon and polymers. Following microneedles application, the skin is punctured to produce transient aqueous micro-channels which facilitate the transport of drug molecules. These micro-channel having a diameter larger than macromolecules which allow the transport of hydrophilic and supermolecule substances (19,20).

Advantages of microneedle array patches
The following are the advantages of microneedle array patches (21)
1. Minimally invasive, painless technique because they penetrate the skin superficial layer where the nerve receptor density is low.
2. They can provide an accurate complex drug release enhancement of the biological stability of drug and the local delivery can be achieved by drug storing in micro volume that can be controlled precisely.
3. Rapid healing at the site of injection.
4. Because the microneedles puncture only the epidermis so that the microbial penetration is low when compared with hypodermic needle.
5. Increasing patients’ compliance because the elimination of the fear from administration of needle.

Disadvantages of microneedles array patches
The following are the disadvantages of microneedle array patches (23-24)
1. Irritation of skin may occur due to sensitive or allergic skin
2. They have small and thin needle than hair diameter, so that the tips of microneedle could be broken and left under the skin.
3. Less dosage accuracy when compared with hypodermic needle.
4. There is a variation of stratum corenum thickness between individual, so that the depth of particles penetrations could vary too.

Types of microneedles
Solid microneedles
They made from metal, silica or polymers with sharp tips. They act by creating micro sized pores in skin which facilitate the direct travel of drug molecules within skin. This approach of drug delivery is called poke and patch (25).

Poke and patch approach
This approach consists of two steps (26):
1. Insertion of solid microneedles into the skin, the skin pierced and microchannels are created for drug transport.
2. The application of the patch (drug formulation) to microneedle pre-treated skin area for diffusion through the created channels. The rate of drug delivery depends on size of pores created and on concentration of drug in the formulation.

**Coat and poke approach**

Coat approach depends on drug diffusion that coat microneedle after its dissolution. After the microneedle insertion to the skin, the drug locally diffuses and distribute to the body circulation. The layer thickness that covering microneedle is considered the main limitation for the rate of drug delivery (27).

**Hallow microneedles**

Hallow microneedles consist of hallow lumen and solid microneedle which have the ability to increase loading of large molecules of drug and its drug delivery depend on pressure driven convection transport. The method by which the drug is delivered to the skin is called poke and flow, by which the drug delivery occurs after needle injection. Then, it flows throughout the lumen. In this approach, the fabricated hole inside the solid microneedle center allows the molecules of drug for reaching the skin inner layer (28).

**Dissolving Microneedles**

Water-soluble substances are used in dissolving microneedle fabrication like PVP, PVA, maltose, sodium hyaluronate and dextran (29). The substances used are water-soluble, biocompatible and completely dissolved in skin, so that protect both patient and health care by no formation of any stabbing edge after their use. Poke and release approach is considering the method of delivery of drug from dissolving microneedles (30). Figure 1 shows the type of microneedles drug delivery (31).

**Hydrogel forming microneedles**

This new developed microneedle type in which a super swelling polymer is used for microneedle creation. These polymers have the ability taking up water in large quantity in to their three dimensions’ network and swell when contact with skin interstitial fluid, resulting in channel creation between drug patch and blood vessels (32).

![Figure 1 Microneedle Drug Delivery: (a) ‘poke and patch’ (b) ‘coat and poke’ (c) ‘poke and release’ (d) ‘poke and flow’ (31).](image)

**Techniques used in microfabrication**

**Micromolding based fabrication**

This technique is used for lab scale work which depends on duplicate the master structure by using the mold. The wieldy using substance is poly dimethyl siloxane (PDMS) which provides both master mold’s reproducibility and plasticity. In addition, the mold can be reused for another fabrication process after its cleaning (33). Following that, the microneedles are produced by pouring the blend of polymer and drug manually with the use of vacuum or centrifuge to fill any microcavities, and then drying of the solution in the mold using moderate temperature (34).

**Master structure fabrication techniques lithography**

This method involves two-steps; drawing lithography and soft lithography as shown in Figure 2 (35). The melted polymer distributed over a plate, following formation of elongated pillars by the movement of the plate in upward movement. The viscosity of polymer increased due to cooling till the polymer reaching the glass transition temperature, further cooling lead to polymer solidification to a strength that piercing the skin. The advantage of this
method is low polymer wastage and rapid fabrication (36). While, soft lithography is done by polymer film coupling with micro cavity mold then passed through out a heated nip. After that, the filled mold put on a flexible plate and re-pass again throughout the heated nip (37).

**Laser-based fabrication**

This method uses a monochromatic, coherent wavelength with low angle of divergence. The beam of laser can focus on small spot diameter.

The amount of removed material depends on material type, intensity of length and laser light (38-39).

**Injection molding**

This is widely used in thermoplastic, thermostet molding and elastomer. It is expensive and complex method. In this method, a molten polymer is injected at high temperature and pressure in to a mold. After that, it is cooled to solidify (40).

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**Figure 2.** Manufacturing methods of microneedle array patch (35).

**Mechanism of drug delivery from microneedles**

Microneedle patch prepared by hundred microneedles arrangement in arrays form to supply a suitable drug quantity, thus producing a prerequisite therapy responses. After the stratum corneum punctured by microneedles, the drug directly delivered to epidermis or dermis upper layer and then absorbed to systemic circulation to produce its therapeutic activity (41-42).

**Materials used in microneedles fabrication**

**Metallic materials**

Due to its advantages of toughness and mechanical strength, they are widely used in transdermal drug delivery. Metallic materials are used for solid microneedle, hallow and coated microneedle creation. The delivery of a drug form these materials is affected by pore density, size and shape of microneedles (43).

**Inorganic materials**

Many inorganic materials such as glass, silicone and ceramic are used for microneedle fabrication. Inorganic materials can be used for solid microneedle, hallow and coated microneedles creation, but broken silicon and biocompatibility are the main factors affecting the inorganic microneedle application (44).

**Polymeric materials**

They are used for dissolving, solid, coated and hallow microneedles creation. Many polymeric materials are used for microneedle preparation such as hyaluronic acid, PVP, PVA, PGA (poly glycolic acid), PLGA (poly lactide–coglycolide acid). PVP and CMC are wieldy used in dissolving microneedle fabrication because they rapidly dissolve in skin (45).

**Microneedle application**

Due to the convenience associated with the use of microneedles including their invasiveness, pain-free administration and improvement of patients’ compliance in addition to their higher efficiency in drug delivery. Nowadays, microneedles can be used in diagnosis, cancer therapy, administration of anti-inflammatory/analgesic drugs, oligonucleotides delivery, Vaccine therapy and cosmetics (46).

**Diagnosis**

The microneedles can be inserted through the skin for biomarkers harvesting from interstitial fluid of skin’s blood vessel by capillary force. The interstitial fluid of skin is considered as biomarkers source for the diagnosis of diseases. Microneedles consist of crosslinked methacrylate hyaluronic acid were used for skin interstitial fluid extraction, in which the microneedle patch provided
the advantages of easy application, no pain and the ability of skin interstitial fluid extraction in short time. After that, the skin interstitial fluid removed by centrifugation from microneedle patch for analysis(47). For chronic health conditions monitoring, microneedle can be used. Mohan et al. developed sensor array of microneedles to alcohol monitoring. Alcoholism is considered the main causative factor for many diseases and traffic fatalities. Therefore, it is necessary for the development of a new method to monitor the consumption of alcohol blood testing is considered an accurate method for this task, but it is painful so that, microneedle arrays can be used for continuous monitoring of alcohol from skin interstitial fluid (48). Microneedles can be used indirectly in monitoring glucose level by using silicone microneedles that give a proper precision in which an appropriate penetration of needle helped for interstitial fluid extraction with minimum pain, commercial device for glucose monitoring is Kumertrix® that made from silicone microneedles (49). Birchall et al. developed a system containing therapeutic agents on the tip and the indicator substances is beyond its on microneedles, at the moment the drug delivered, the indicator give indication for the drug delivery successfully to the site of action (50).

Cancer therapy
According to the world cancer report from world health organization (WHO), cancer in the world is considered the deadliest disease. It exceeds twenty million by 2025 (51). Human epidermal and breast cancer which belong to superficial cancer are considered the public health problem so that, many efforts made for superficial cancer therapy (52). Microneedles can be used for various delivering of anticancer therapy, for melanoma treatment, self-degradable microneedles were used for delivery anti-PD-1 (aPD1) with glucose oxide loaded pH sensitive dextran nanoparticles (53). The permeability of 5- fluorouracil topical cream that used in basal cell carcinoma will be increasing up to 4.5 times when the cream used on skin pretreated with solid microneedles (54). Bhatnagar et al. investigate the tamoxifen and gemcitabine chemotherapeutic agents through microneedles for breast cancer treatment (55). treatment subcutaneous cancer 5-aminolevulinic acid is coated to tips of sodium hyaluronate fast dissolving microneedles, this leading to maximizes the utilization of drug and reducing of drug residue (56).

Delivery of anti-inflammatory and analgesic drugs
Pain divided into acute and chronic according to its duration. Acute pain produced from tumor, infection trauma, metabolic and endocrine diseases. Chronic pain may last for three to six months without biological value apparent. Transdermal administration in pain relieving producing lower systemic side effects than oral administration of analgesics(57).

Microneedle array patches are regarded as one of more important technologies for pain management. Microneedles act by delivering peptide locally, anti-CGRP (calcitonin gene-related peptide) produces selective anti-hypersensitivity throughout peripheral CGRP receptor antagonism by microneedle dissolving in neuropathic pain area. In this study, the anti-CGRP peptide delivered directly to the painful area by dissolvable microneedles. Thus, reducing both systemic exposure and its side effects (58). In addition, a microneedle patch was used for lidocaine delivery for the management of acute and chronic pain. This microneedle patch was designed with high drug loading for lidocaine delivery into the skin to relieve acute and chronic pain (59). Baek et al. design microneedles tips coated with lidocaine that showed improvement in the drug delivery within 2 min so that provided pain free and faster local anesthesia (60). Polymeric microneedles loaded with meloxicam was prepared by using polydimethylsilicone molds, it was seen there is improvement in transdermal flux and the in-vitro permeation will increase about 2.58 times when compared to a free drug solution (61).

Oligonucleotides delivery
They are short RNA or DNA molecules, oligonucleotides delivery to intra site of action is very difficult, so that an attempt for using microneedles to deliver oligodeoxynucleotid by using solid microneedles made from titanium or stainless steel through using the poke with patch approach. It was found that more drug amount reaching to the action site as compared to the intact skin (62).

Vaccine therapy
Is a biological preparation of a weakened or a killed form of diseases causing microorganism. Vaccine therapy act by the immune system stimulation and providing the protection against the micro-organism encounter. In the delivery of DNA vaccine, the microneedles approach will be effective by better immunity responses than normal injection (63). There is attempt for developing microneedles patch to be use in influenza vaccine administration (64). Administration of rabies and anthrax vaccine also studies by using hallow microneedles, it was found a less dose of drug is required as compared to intramuscular injection (65).

Cosmetics
Microneedles used for skin blemishes, scars treatment and for skin appearance improvement. Marketed product used for scars and wrinkles treatment is Dermaroller (66). There is an attempt for deliver cosmetic ingredients such as retinyl retinote, eflornithine, ascorbic acid by using microneedles approach (67). Melanin pigment
incorporated into nanoliposome showed increasing the solubility in the lipids and it was found that the pigment amount reaching deeply near the hair structure will be more when applied by e-roller (68).

**Evaluation of microneedle array patches**

**Microneedle patch morphology**

Digital microscope is used to study the dimension and morphology of prepared patch including the length, width, height of patch and microneedle patch interspace. After that, it analyzed and the result compared with the master mold (69).

**Weight variation**

Three patches are selected and weigh individually by using electrical balance to calculate the average weight value (70).

**Thickness uniformity**

This test is done by using digital venire caliper. Three patches are selected randomly to measure their thickness at five points to find the average point (71).

**Drug content uniformity**

The drug content can be measured by immersing the prepared microneedle patch in 100 mL phosphate buffer pH 7.4 for 30 min. After that, the resulted solution is filtered and analyzed for drug content (72).

**Folding test**

Folding test can be defined as the number of folds that obtained with no patch breaking, when the folding repeated at same place. This test is done in triplicate, to measure the mean value (73).

**pH measurement**

The patch is immersed in a glass container containing 10 mL of deionized water. The pH is recorded by placing the pH electrode in contact with patch surface for one minute for equilibrium (74).

**Percentage of moisture loss (PML)**

Three patches are weighed individually and placed in a desiccator containing anhydrous calcium chloride for three days at room temperature. After that, the patch is reweighed again to calculate the difference between the weights. Finally, the percentage of moisture loss is calculated according to the following equation: (75).

\[
PML = \left[\frac{W_0 - W_t}{W_0}\right] \times 100
\]

\(W_0=\) initial weight, \(W_t=\) final weight

**Percentage of moisture absorbed (PMA)**

Three patches are weighed individually and placed in a desiccator containing saturated solution of potassium sulphate for three days at room temperature. After that, the patch is reweighed again to calculate the difference between the weights, finally the percentage of moisture absorbed is calculated according to the following equation (76).

\[
\text{Percent Moisture Absorbed} = \left[\frac{W_0 - W_t}{W_0}\right] \times 100
\]

\(W_0=\) initial weight, \(W_t=\) final weight

**Measurement of axial needle fracture force**

The axial needle fracture force can be defined as the minimum force that applied parallel to microneedle axis which causes microneedles breakdown. This test measures using texture analyzer TA. XT apparatus. In this test, a microneedle patch is placed on affixed cylinder platform and the instrument programed to compress axially the microneedle patch. The maximum force that immediately apply before patch deflection is considered the axial needle fracture force and the sudden force drop recorded as a needle failure (77).

**In-vitro skin permeation study**

In vitro skin permeation study was done by using a Franz cell diffusion apparatus with an effective diffusion area and an appropriate receptor volume. Animal skin is placed between the donor and receptor in which the subcutaneous layer placed in the face of donor cell. The medium of receptor was stirred to produce regular drug distribution throughout the experiment, certain sample volume withdrawal from receptor fluid and replaced by equal volume at certain time interval. Finally, the profile of cumulative permeation for microneedle treated and untreated skin was compared (78).

**Histological study**

The microneedle patch efficiency for stratum corneum penetration is studied by using rat skin through applying microneedle patch on the skin for 1 min by using gentle thumb pressure, after that the skin immersed in 10% formalin solution and left for one day. Then the tissue imbedded with paraffin and by using of microtome, a thin section is cut and fixed on the slide and stain by haematoxylin and eosin pigment (79).

**In-vitro release study**

By using Franz cell diffusion, a microneedle patch is mounted between the donor and receptor compartment of diffusion cell. The receptor filled with certain volume of phosphate buffer pH 7.4 and the temperature adjusted at 32°C, the liquid of receptor is stirred by magnetic stirrer. Sample withdrawals at certain time interval and replaced with same volume of phosphate buffer pH7.4. After that, analyzed at certain wave length after a certain dilution, the test done in triplicates then take the mean value (80).

**Conclusion**

Drugs administration by microneedles array patch permit the drug molecules to cross the stratum corneum of skin layer. Microneedles array patch improve patient compliance, self-administration, providing rapid onset of action and increasing drug permeation. Also, there are some limitations of their uses like allergy to sensitive skin, skin irritation, redness and breaking of microneedles tips and if it remains within the skin may cause inflammation but these limitations are rare and can
overcome by the selection of advanced materials for microneedles fabrication. Microneedle and ultrasound combination are studied to further increasing drug permeability. Modification of conventional microneedles may be used to administer hundred milligrams protein to go directly to systemic circulation.

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