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Microneedle: A useful tool for drug delivery system

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Abstract
Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. It includes various approaches, formulations, technologies and systems for transporting a pharmaceutical compound in body as needed to safely achieve its desired therapeutic effect Microneedles are three-dimensional (3D) microstructures with micro-scale length (usually <1000 µm) that can pierce the stratum corneum and generate transient micro-channels through which external molecules can passively diffuse into the skin. Microneedles could be designed in a manner that the penetration depth is superficial enough to not touch nerve receptors in the lower reticular dermis, this result in a painless drug administration. It is promising that this microneedle-based transdermal delivery approach will offer a self-management, patient-friendly, and efficient administration route for drug delivery. This system has increased its application to many fields like oligonucleotides delivery, vaccine delivery, insulin delivery, and even in cosmetics.

Keywords: Microneedle, drug delivery, transdermal, solid, hollow and dissolvable microneedle

Introduction
Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. It includes various approaches, formulations, technologies and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. Drug delivery is often approached via a drug's chemical formulation, but it may also involve medical devices or drug-device combination products (Samira *et al.*, 2019) [31].

Drug delivery technologies generally aimed to modify drug release profile or absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance. Hypodermic needles and topical creams are most commonly used when it comes to delivery of the drug through the skin. Needles are less accepted by patients due to pain associated with them and topical creams show less bioavailability. Skin serves as the major barrier for delivering drug through the topical route. Skin is made up of three main layers- the outermost stratum corneum, middle epidermis and the thickest of all, dermis. The stratum corneum layer behaves like a major barrier as it allows only certain molecules like lipophilic and low molecular weight drugs to pass through it. The relatively less permeability of the layer presents many problems in designing topical formulation. Various topical or transdermal delivery systems have been investigated for improving drug permeation through the skin like nanocarrier loaded topical creams, transdermal patches, and microneedles. A new form of delivery system called the microneedles helps to enhance the delivery of the drug through this route and overcoming the various problems associated with the conventional formulations (Wang and Von, 2011) [36].

Microneedles are three-dimensional (3D) microstructures with micro-scale length (usually <1000 µm) that can pierce the stratum corneum and generate transient micro-channels through which external molecules can passively diffuse into the skin. Microneedles could be designed in a manner that the penetration depth is superficial enough to not touch nerve receptors in the lower reticular dermis, this result in a painless drug administration. It is promising that this microneedle-based transdermal delivery approach will offer a self-management, patient-friendly, and efficient administration route for drug delivery (Donnelly *et al*., 2010) [10]. The primary principle involves disruption of the skin layer, thus creating micron size pathways that lead the drug directly to the epidermis or upper dermis region from where the drug can directly go into the systemic circulation without facing the barrier (Waghule *et al*., 2019) [37]. Microneedles are microscopic applicators used to deliver vaccines or other drugs through transdermal application; these are constructed through various methods usually involving photolithographic process or micro molding (Park *et al.,* 2005) [28].

History

Microneedles were first mentioned in 1998 in transdermal drug delivery demonstrating that microneedles could penetrate human skin that was published in a paper. Subsequent research into microneedle drug delivery has explored the medical and cosmetic applications of this technology and used for the vaccination, delivery of insulin and other pharmaceuticals. In dermatology, microneedles were used for scarring treatment with skin rollers and the major goal of any microneedle design is to penetrate the outermost layer of the skin the stratum corneum (10-15µm) (Jeong *et al.,* 2017) [14].

General Properties of Microneedles

Microneedles are made from a variety of material ranging from silicon, titanium, stainless steel, and polymers. Some microneedles are made of a drug to be delivered to the body but are shaped into a needle so they will penetrate the skin and ranges in size, shape, and function but are all used as an alternative to other delivery methods like the conventional hypodermic needle or other injection apparatus (Davis *et al.,* 2018) [12].

To ensure efficient drug delivery effect, microneedle chips are particularly designed to remain in a specific location; to maintain fluid communication with the tissues beneath the subcutaneous layer for an extended period of time. This is to remain conducive even when the skin is contoured and deformable. Earlier microneedle patches were made on a rigid and planar substrate made from silicon, stainless steel, or nickel was unable to effectively attach tightly onto the skin surface. Flexible microneedle patches have been developed to integrate polymer-based microneedles on a flexible substrate to be more pliable to the skin. Since fabricating tapered shape is not a standard process in the conventional MEMS (micro electromechanical system) technology, fabricating tapered microneedles using MEMS technology is the most critical part in a flexible microneedle patch (Kim *et al.,* 2012) [16].

Microneedle devices are composed of micron-size needles that can be organized in single structure or arranged in small arrays to mediate the localized delivery of therapeutic molecule. These micro-projections are generally of around 50 to 250 µm in width and few micrometers to 1500 µm in length. In general, the microneedles application aims to create a transport pathway for the delivery of therapeutic molecules, bypassing the external barriers that limit the therapeutics penetration in the target tissue. Microneedles devices are compatible with the delivery of both small and Macro-molecular therapeutics such as small drugs (e.g. doxorubicin), proteins (e.g. ovalbumin), genetic materials (e.g. pDNA and siRNA), or even nanomedicines. Additionally, the microneedles are highly versatile and are regarded as less painful, damaging, and safer to use, when compared to conventional needles.

Types of Microneedles

1. Solid microneedle

1. Hollow microneedle
2. Coated or layered microneedle
3. Dissolvable microneedle

2. Solid microneedle

Solid microneedles are mostly used for pre-treating the skin by forming pores. Pointed tips of the needles penetrate into the skin; create channels of micron size, through which the drug directly enters the skin layers on the application of a drug patch, thus increasing the permeation. The drug is taken up by the capillaries to show a systemic effect. It can be used for a local effect also; solid microneedles are being already used by dermatologists in collagen induction therapy. These microneedles deliver drug through passive diffusion, improve bioavailability and mechanical strength. Solid microneedle made-up of stainless steel enhances delivery of captopril and metoprolol tartrate (Lee *et al.,* 2012).

3. Hollow microneedle

Hollow microneedles have an empty space inside which is filled with the drug dispersion or solution. They have holes at the tips. On inserting into the skin, the drug is directly deposited into the epidermis or the upper dermis layer. Mostly it is used for high molecular weight compounds such as proteins, vaccines, and oligonucleotides, these microneedles are capable of administering a large dose of the drug as more amount of drug can be accommodated into the empty space inside the needle and allow faster application of the vaccine as well as higher bioavailability and antigen utilization, resulting in higher chances of lymphatic uptake of antigens. The great advantage of using hollow microneedle is controlled drug release; this type of microneedle can deliver successfully a variety of vaccines, including vaccines against influenza, anthrax and Japanese encephalitis with safe and efficacious profiles (Ita, 2015) [13].

4. Coated or layered microneedle

Coated microneedles are usually designed from polymers or metals just like solid microneedles. In this method the drug is applied directly to the microneedle array instead of being applied through other patches or applicators. Coated microneedles are often covered in other surfactants or thickening agents to assure that the drug is delivered properly (Park *et al.,* 2005) [28]. The development of polymer microneedles has focused on providing sufficient mechanical strength through different materials, including poly lactic acid (PLA), poly methyl methacrylate [PMMA] and maltose (Kolli and Banga, 2008) [17]. These polymer microneedles are normally patterned with the unconventional process due to their tapered 3D structures. These microneedles are able to inject very less amount of vaccine into the skin in an automated manner thus overcoming the drawbacks of the hypodermic needle (Han *et al.,* 2004) [11].

5. Dissolvable microneedle

Dissolving microneedles are fabricated with biodegradable polymers by encapsulating the drug into the polymer. After inserting microneedle in the skin, dissolution takes place which releases the drug. The application involves only a single step as the microneedle is not to be removed out after insertion as in other cases. The polymer gets degraded inside the skin and controls the drug release. The bio-acceptability and dissolution of the polymer inside the skin make it one of the best choices for long-term therapy with improved patient compliance (Ita, 2015) [13].

In a more recent adaptation of the microneedle design, dissolvable microneedles encapsulate the drug in a nontoxic polymer which dissolves once inside the skin. This polymer would allow the drug to be delivered into the skin and could be broken down once inside the body. Pharmaceutical companies and researchers have begun to study and implement polymers such as Fibroin, a silk-based protein that can be molded into structures like microneedles and dissolved once in the body (Bos and Meinardi, 2000) [5].

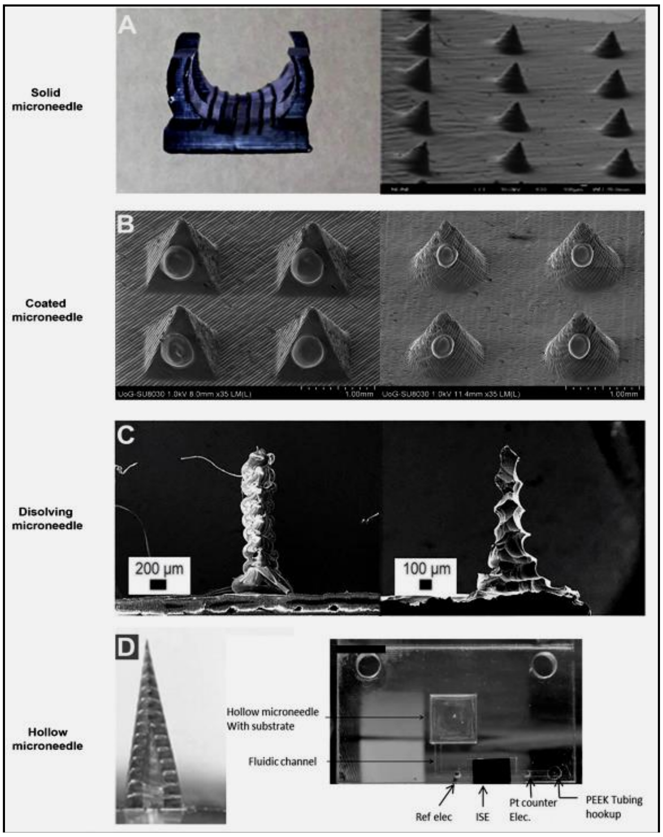

Fig 1: Types of microneedles (a) solid microneedle (b) coated microneedle (c) dissolving microneedle (d) hollow microneedle

Applications of Microneedle

(A) Disease diagnosis

Microneedles can be used for diagnosis of diseases Hollow puncture the skin into the epidermis to withdraw serum inhibitory factor (SIF) by capillary force or using vacuum. The extracted SIF metabolites can be applied to diagnose several diseases like cancer, atherosclerosis, thrombosis, cardiovascular disorders and diabetes. Recently, the microneedle-based enzyme electrode was functionalized with multi-layer reagents to monitor ethanol in SIF, Pt and Ag wires were used as electrode through the aperture of hollow microneedle immobilizing alcohol oxidase, followed by the biocatalytic reaction (Mohan *et al.*, 2017) [26].

(B) Disease treatment

i. Transdermal delivery of drugs

Transdermal drug diffusion across the skin is faced with great challenge due to thus strong barrier, the intact stratum corneum. Transdermal delivery possesses many overwhelming advantages as compared to intramuscular-injection, subcutaneous injection and intradermal injection Therefore, microneedle is considered as an effective and painless device that is easy to use for patients, holding tremendous promise for delivering macromolecules in transdermal drug delivery field (Sanjay *et al.*, 2018) [32].

ii. Microneedle associated anticancer therapy

Cancer affects many people every year in the world and cancer treatment faces lots of challenges.

(a) Microneedles have been investigated for various anticancer drugs delivery. Self-degradable microneedles were investigated for melanoma treatment by delivering anti-PD-1 (aPD1) in a sustained manner. Anti-PD-1(Programmed cell death-1 inhibitor) and glucose oxidase loaded pH-sensitive dextran nanoparticles were delivered through microneedle (Wang *et al.*, 2016) [35].

(b) A topical cream containing 5-fluorouracil is used to treat basal cell carcinoma. The permeability of 5-fluorouracil was enhanced up to 4.5 times when the cream was applied on the skin treated with solid microneedles. Significant inhibition of tumor growth further confirmed improved efficacy using microneedles (Kumar *et al.*, 2014) [19].

(c) Tamoxifen and gemcitabine can be delivered through microneedles for the treatment of breast cancer. This delivery provides localized delivery of these drugs which would help to reduce the side effects (Bhatnagar *et al.*, 2018) [4].

iii. Delivery of insulin in treatment of diabetes

(a) Insulin is a peptide hormone; the medication is used to lower the high blood sugar levels. Delivering insulin using microneedle was found to lower blood glucose levels more efficiently (Martano *et al.*, 2004) [23]. Delivery of insulin by fabricated solid microneedles reduce blood glucose levels to 29% of the initial level at 5 h which confirmed the improved permeability of insulin to the skin using microneedle in diabetic mice (Li *et al.*, 2017) [21].

(b) Microneedles integrated with pancreatic β-cell capsules which sense the blood glucose levels and secrete the insulin, but the patch was not found to function effectively thus, microneedle matrix containing synthetic glucose signal amplifiers (GSAs) was developed which was consist of nanovesicles containing glucose oxidase, α- amylase and glucoamylase enzymes. These amplifiers showed the secretion of insulin from the β-cells capsules (Ye *et al.*, 2016) [38].

iv. Microneedle for treatment of obesity

Fig 2: Application of microneedle in skin for cosmetic therapy

There are two different types of adipose tissues i.e. brown adipose tissue (BAT) and white adipose tissue (WAT). BAT plays a crucial role in producing heat thus increasing body energy expenditure. Whereas the WAT stores exceeded energy resulting in weight gain, it may further deteriorate the disease due to reactive oxygen species and free fatty acids. Caffeine extracted from tea or coffee was reported to possess anti-obesity activity without harmful effects for mankind. A HA-based (hyaluronic acid) dissolving microneedle loading caffeine can lead to the significant weight loss of high-fat diet-induced obese mice (Dangol *et al.*, 2017) [7].

v. Other diseases

Microneedle for drug delivery were also applied in the treatment of other diseases like Alzheimer's disease (AD), whose clinical symptoms are memory loss and language problems, is regarded as a chronic neuro-degenerative disorder. Donepezil hydrochloride (DPH) are considered as a safe drug having long half-life, which was approved by FDA for the effective treatment of AD. Transdermal delivery of 95% DPH in the tips was transported into porcine skin in 5 min. obviously, tip-loaded dissolving microneedles encapsulating DPH was more effective as compared with oral administration (Baron, 2006) [3].

Neuropathic pain resulting from nerve injury can be treated by anti-calcitonin gene related peptide (A-CGRP) which is able to selectively block CGRP receptors, thereby inhibiting CGRP signaling to relieve the pain. It is reported that the analgesic microneedle patches have an effective and simple alternative to relieve localized neuropathic pain by transdermally delivering the high specificity of A-CGRP as compared with clinical treatments.

Lidocaine is used to induce local anesthesia, administering lidocaine through microneedle causes less pain as compared to hypodermic injection and thus shows better patient compliance (Shan *et al*., 2017) [33].

vi. Immunobiological administration

Conventionally vaccines are generally administered by hypodermic, intramuscular or intradermal injections. However, conventional vaccination procedures have several shortcomings like needle phobia and the pain accompanying puncture of needle into the dermis.

vii Cosmetic application

Microneedle use in cosmetics is gaining importance; specially to improve the skin appearance and to treat skin blemishes and scars. An attempt to deliver some cosmetic active ingredients like ascorbic acid, eflornithine, retinyl retinoate was made using the microneedle approach. Melanin was incorporated into phosphatidylcholine liposomes (nanoliposomes) which showed increased solubility in lipids. Amount of pigment that reached deep near the hair structures was found to be more on application by an e-roller. Enhanced delivery of melanostatin, rigin and pal-KTTKS (Palmitoyl-pentapeptide) was also investigated through the use of microneedles (Mohammad *et al.*, 2014) [25].

Advantages of Microneedle

- **Drug delivery across skin's stratum corneum**

A primary goal in drug delivery to the skin is diffusion through the skin's outer layer of stratum corneum, which is 10–20 µm thick at typical administration sites such as arm and leg. Microneedles measuring hundreds of microns in length also effectively cross the stratum corneum in a minimally invasive manner compared to hypodermic injections (Kim *et al.*, 2012) [16].

- **Targeted skin delivery**

Efficacy of drug can be altered by the alteration of skin access by different anatomy and physiology, for example, the drug administration through rich capillary bed in the superficial dermis and effective drainage of lymphatic fluids from skin give rapid access of drug to the systemic circulation (Arya and Prausnitz, 2016) [2].

- **Reduced expertise**

Microneedle reduces the expertise needed for the administration because they are simply pressed to the skin by hand or using a hand-held applicator. For example, people suffering from type 1 diabetes are trained to self-inject insulin because there is no other therapeutic option, but many types 2 diabetes is not put on GLP-1 receptor against drugs. Thus, the microneedles are advantageous where the administration of drug has to be done in many individuals (Mass vaccination) and trained health care professionals are less in number thus there would be cost savings associated with drug administration by lesser-trained personnel (Norman *et al.*, 2016).

- **Improved thermal stability**

Many drugs need constant refrigeration, including during transportation. This increases costs and complicates logistics, especially in developing countries where mechanisms to maintain refrigeration from manufacturer to patient (i.e., the "cold chain") are not always intact (Allen *et al*, 2016) [1].

- **Reduction or elimination of sharps waste**

Hypodermic injection of drugs generates bio-hazardous sharps waste such as used needles. It also poses a safety risk due to transmission of diseases by accidental or intentional reuse of needles. It also incurs additional costs and requires logistics for safe sharps disposal (Marinan *et al.*, 2015) [22].

- **Lack of pain and needle phobia**

Pain from injections can be an impediment to patient adherence with therapy because microneedles are small; they do not hurt and therefore are better accepted by patients. In addition, fear of hypodermic needles is widespread and can be a barrier to patients' accessing health care (John *et al.*, 2011) [15].

- **Low-cost manufacturing**

Microneedle can be expected to be competitive with injectable drugs in terms of manufacturing costs and are beneficial to physicians as well since they produce less hazardous waste than needles and are generally easier to use. Microneedles are also less expensive than needles as they require less material and the material used is cheaper than the materials in hypodermic needle thus, microneedles present a new opportunity for home and community-based healthcare (Hagarty *et al.*, 2018).

One of the benefits of microneedles is their lower rates of microbial invasion into delivery sites. Traditional injection methods can leave puncture wounds for up to 48 hours post-treatment. This leaves a large window of opportunity for harmful bacteria to enter into the skin. Microneedles only damage the skin to a depth of 10-15µm making it difficult for bacteria to enter the bloodstream, and giving the body a smaller wound to repair (Prausnitz *et al.*, 2005).

Disadvantages of Microneedle

- Hollow and coated microneedles can leak on to a person's skin either by damage of the microneedle or incorrect application by the physician. Thus, affect the efficacy of drug.
- Incorrectly applied arrays of microneedle could leave foreign material in the body so there is a lower risk of infection associated with microneedles.
- Arrays of microneedles are fragile thus have a chance of breaking off and remaining in the skin.
- Some of the material used to construct the microneedles, such as titanium, cannot be absorbed by the body and any fragments of the needles would cause irritation (Singh *et al.*, 2018).
- Skin allergy, redness, irritation and limited amount of drug can be loaded into the microneedle.
- Passing hydrophilic and large compounds through the skin by microneedle is a major challenge.
- Microneedles can be difficult to apply on the skin, the clinician must learn proper application technique.
- The needles are very small and much thinner than the diameter of hair, so the microneedle tips can be broken off and left under the skin.

Conclusion

Microneedles are a new form of delivery system which helps to enhance the delivery of the drug and overcoming the various problems associated with the conventional formulations. The primary principle involves disruption of the skin layer, thus creating micron size pathways that lead the drug directly to the epidermis or upper dermis region from where the drug can directly go into the systemic circulation without facing the barrier. Microneedle based delivery has the potential to overcome the problems associated with delivery of small hydrophilic molecules, macromolecules and biopharmaceuticals across biological barriers, particularly the sub-cut region. This method gives the potential of such agents as next generation therapeutics. This system has increased its application to many fields like oligonucleotides delivery, vaccine delivery, insulin delivery, and even in cosmetics. In recent years, many microneedle products are coming into the market. Although a lot of research needs to be done to overcome the various challenges before the microneedles can successfully launch into the market.

References

1. Allen EA, Vrdoljak A, Ferrara F, Temperton NJ, Crean AM, Moore AC. Induction of broad immunity by thermostabilised vaccines incorporated in dissolvable microneedles using novel fabrication methods. Journal of Control Release. 2016; 225(10):192-204.
2. Arya K, Dewitt M, Chiang YW, Prausnitz MR. Rabies vaccination in dogs using a dissolving microneedle patch. Journal of Control Release. 2016; 239:19-26.
3. Baron R. Mechanism of disease: neuropathic pain-a clinical perspective. Journal of Natural Clinical Practice Neurology. 2006; 2(2):95-108.
4. Bhatnagar S, Kumari P, Venuganti V, Pattarabhiran S. Zein microneedles for localized delivery of chemotherapeutic agents to treat breast cancer: drug loading, release behavior and skin permeation studies. Journals of Pharmaceutical Science and Technology. 2018; 19(4):1818-1826.
5. Bos JD, Meinardi MM. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. Journal of Experimental Dermatology. 2000; 9(3):165-9.
6. Chen F, Yan Q, Yu Y, Wu M. BCG vaccine powder-laden and dissolvable microneedle arrays for lesion free vaccination. Journal of Control Release. 2017; 255:36-44.
7. Dangol M, Kim S, Li C, Lahiji S, Jang M. Anti-obesity effect of a novel caffeine loaded dissolving microneedle patch in high fat diet induced obese C57BL/6J mice. Journal of Control Release. 2017; 265(2):41-47.
8. Davis SP, Landis BJ, Adams ZH, Prausnitz MR. Insertion of microneedle into skin: Measurement and prediction of insertion force and needle fracture force. Journal of Biomechanics. 2018; 37(2):1155-1163.
9. Dewar V, Poirier D, Renaud F, Strodiot L, Wauters F, Janimak J *et al*. Hepatitis B surface antigen incorporated in dissolvable microneedle array patch is antigenic and thermostable. Journal of Biomaterial. 2017; 145:256-265.
10. Donnelly RF, Singh R, Woolfson AD. Microneedle based drug delivery system: Microfabrication, drug delivery and safety. Journal of Drug Delivery. 2010; 17(1):187-207.
11. Han M, Lee W, Lee SK, Lee SS. 3D microfabrication with inclined/rotated UV lithography. Journal of Sensors and Actuators A: Physical, 2004; 111:14-20.
12. Hegarty C, McConville A, Davis J. Mini-Review: Assessing the Potential Impact of Microneedle Technologies on Home Healthcare Applications. Journal of Medicines. 2018; 5(2):50-51.
13. Ita K. Transdermal delivery of drugs with microneedles-potential and challenges. Journal of Pharmaceuticals and Research, 2015; 7(3):90-105.
14. Jeong HR, Lee HS, Choi IJ, Park JH. Considerations in the use of microneedles: pain, convenience, anxiety and safety. Journal of Drug Targeting. 2017; 25(1):29-40.
15. John DN, Birchall JC, Clemo R, Anstey A. Microneedles in clinical practice – an exploratory study into the opinions of healthcare professionals and the public. Journal of Pharmaceutical Research. 2011; 28(1):95-106.
16. Kim JY, Han MR, Shin SY, Park JH. Dissolving microneedles for transdermal delivery of Donepezil hydrochloride for treatment of Alzheimer’s disease. *European* Journal of Biopharmaceuticals. 2012; 105:148-155.
17. Kolli CS, Banga AK. Characterization of solid maltose microneedles and their use for transdermal delivery. Journal of Pharmaceutical Research. 2008; 25(1):104-113.
18. Koning RI, Nejdnik MR, Nasr M, Hathout R. Intradermal vaccination with hollow microneedles: a comparative study of various protein antigen and adjuvant encapsulated nanoparticles. Journal of Control Release. 2017; 266(1):109-118.
19. Kumar A, Naguib Y, CUI Z. The effect of microneedle on the skin permeability and antitumor activity of topical 5- fluorouracil. Journal of Acta Pharmaceutica Sinica B. 2014; 4(1):94-99.
20. Lee BY, Bartsch SM, Mvundura M, Jarrahian C, Zapf KM, Marinan K. An economic model assessing the value of microneedle patches delivery of the seasonal influenza vaccine. Journal of Vaccines and Immunology. 2015; 33(37):4727-4736.
21. LI Q, Zang N, Chen Z, Wang D, Guo D. A solid polymer microneedle patch pretreatment enhances the permeation

of drug molecules into the skin. Journal of Royal Society Chemistry Advances. 2017; 7(25):15408-15415.
22. Marinan K, Lee BY, Bartsch SM, Mvundura M, Jarrahian C. An economic model for assessing the value of microneedle patches delivery of the seasonal influenza vaccine. Journal of Vaccines and Immunology. 2015; 33(11):4727-4736.
23. Martano W, Davis S, Holiday N, Wang J, Gill M. Transdermal delivery of insulin using microneedles *in vivo*, Journal of Pharmaceutical Research. 2004; 21(6):947-952.
24. Mills LK, Littauer EQ, Brock N, Ramanyuk A. Stable incorporation of GM-CSF into dissolvable microneedle patch improves skin vaccination against influenza. Journal of Control Release. 2018; 276(3):1-16.
25. Mohammed YH, Yamada M, Benson HA, Raphael AP. Microneedle enhanced delivery of cosmeceutically relevant peptides in human skin, Journal of Public Library of Science. 2014; 9(7):101-956.
26. Mohan A, Windmiller J, Mishra R, Wang J. Continuous minimally invasive alcohol monitoring using microneedle sensor arrays. Journal of Biosensors and Bioelectronics. 2017; 91(5):574-579.
27. Norman JJ, Arya JM, Clain MA, Frew PM, Meltzer MI, Prausnitz MR. Microneedle patches: Usability and acceptability for self-vaccination against influenza. Journal of Vaccine and Immunology. 2014; 32:1856-62.
28. Park JH, Allen MG, Prausnitz MR. Biodegradable polymer microneedles: fabrication, mechanics and transdermal drug delivery. Journal of Controlled Release. 2005; 104(1):51-66.
29. Prausnitz MR, Kim JY, Park JH. Microneedles for drug and vaccine delivery. Journal of Advance Drug Delivery. 2008; 64(14):1547-1568.
30. Rojanarata T, Pamornpathomkul B, Niyomtham N, Ngawhirunpat T. Cationic niosomes for enhanced skin immunization of plasmid DNA-encoding ovalbumin via hollow microneedles. Journal of Pharmaceutical Science and Technology. 2018; 19(5):481-488.
31. Samira M, Hassan H, Saba R, Zahra A. Design and Synthesis of Gatekeeper Coated Dendritic Silica/Titania Mesoporous Nanoparticles with Sustained and Controlled Drug Release Properties for Targeted Synergetic Chemo-Sonodynamic Therapy. Journal of Science and Technology. 2019; 5(9):4405–4415.
32. Sanjay T, Zhou W, Dou M, Tavakoli H. Recent advances of controlled drug delivery using micro-fluidic platforms. Journal of Advance Drug Delivery. 2018; 128(5):3-28.
33. Shan H, Li J, Tong C. Microneedle patches as drug and vaccine delivery platform. Journal of Current Medical Chemistry, 2017; 24(22):2413-2422.
34. Singh R, Singh S, Lillard JW. Past, present and future technologies for oral delivery of therapeutic proteins. Journal of Pharmaceutical Science. 2018; 97:2497-2523.
35. Wang C, Ye Y, Hochu GM, Sadeghifar H. Enhanced cancer immunotherapy by microneedle patch assisted delivery of Anti- PD1 antibody. Journal of Nanoscience and Nanotechnology. 2016; 16(4):2334-2340.
36. Wang NX, Von HA. Affinity based drug delivery. Journal of Micro-molecular and Bioscience. 2011; 11(3):321-332.
37. Wanghule T, Gautam S, Dubey S, Pandey MM, Gupta G, Singh M. Microneedle: A smart approach and increasing potential for transdermal drug delivery system. Journal of Biomedicine and Pharmacotherapy. 2019; 109(2):1249-1258.
38. Ye Y, Wang C, Nguyen N, Walker G, Buse JB. Microneedles integrated with pancreatic cells and synthetic glucose- signal amplifiers for smart insulin delivery. Journal of Advance Materials. 2016; 28(16):3115-3121.