WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 1, 615-629. Review Article ISSN 2277– 7105

MICRONEEDLES: AN EMERGING TRANSDERMAL DRUG DELIVERY SYSTEM

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Article Received on
08 November 2020,
Revised on 29 Nov 2020,
Accepted on 20 Dec. 2020
DOI: 10.20959/wjpr20211-19482

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ABSTRACT

One of the thrust areas in drug delivery research is transdermal drug delivery systems (TDDS) due to their characteristic advantages over oral and parenteral drug delivery systems. Microneedles are fabricated using a microelectromechanical system employing silicon, metals, polymers or polysaccharides. Microneedles deliver the drug into the epidermis without disruption of nerve endings. Solid coated microneedles can be used to pierce the superficial skin layer followed by delivery of the drug. Advances in microneedle research led to development of dissolvable/degradable and hollow microneedles to deliver drugs at a higher dose and to engineer drug release. Iontophoresis, sonophoresis and electrophoresis can be used to modify drug delivery when used in concern with hollow microneedles. Microneedles can be used to deliver macromolecules such as insulin, growth hormones, immunobiologicals, proteins and peptides. Microneedle-based drug delivery system can be explored as a potential tool for the delivery of a variety of macromolecules that are not effectively delivered by conventional transdermal techniques.

KEYWORDS: Microneedles, macromolecules delivery, transdermal way.

INTRODUCTION

Development of functional delivery systems for new active pharmaceutical ingredients is a challenging task. Drug can be administered through most common routes like the oral, parenteral, ophthalmic and transdermal route, as well as less explored routes such as nasal, pulmonary and buccal. Each of these routes has specific merits and disadvantages. Oral drug delivery systems offer advantages such as patient compliance, large surface area with rich

blood supply for absorption, low cost, ease in engineering of drug release in stomach/ intestine, etc. However, limitations, like drug degradation in the gastrointestinal tract, first-pass metabolism, poor absorption, local irritation and variability in absorption (due to factors like pH, motility, food, mucus layer, etc.), are associated with these drug delivery systems. The parenteral route offers advantages like quick onset of action, accurate drug delivery and continuous drug delivery by infusion; its limitations include pain associated with the injections, expertise required to deliver the drug, risk of infection and difficulty in obtaining sustained drug delivery. Transdermal drug delivery involves the transport of drug across the skin. Optimal physiochemical properties are required in drug candidates for delivery via transdermal patches. Traditional transdermal patches can be divided into two categories – reservoir-based and matrix-based – according to their physical structure. Transdermal drug delivery offers advantages like patient compliance, avoidance of firstpass metabolism, large surface area of skin over which to deliver the drug, quick termination of dosing, etc. However, only a few drug products with optimum characteristics have been successfully marketed to deliver a drug through the skin. This is due to the resistance to drug transport offered by the stratum corneum. The problem of poor drug transport can be addressed by development of micron-sized needles, which deliver the drug painlessly across the stratum corneum.

Microneedles can be defined as solid or hollow cannula with an approximate length of 50–900 mm and an external diameter of not more than 300 mm. Microneedles can be fabricated within a patch for transdermal drug delivery. Patches containing microneedles have been evaluated in the delivery of drugs, biopharmaceuticals, vaccines, etc. A quick response can be observed due to disruption of stratum corneum by microneedles. Using the low-cost massproduction tools of the microelectronics industry, needles have been fabricated out of silicon, metals and other materials. Microneedles have been designed to penetrate through the epidermis up to a depth of 70–200 mm. Microneedles are thin and short and do not penetrate the dermis layer with its nerves; hence painless application is possible. Microneedles are more capable of enhancing the transport of drug across the skin as compared with other transdermal delivery methods.

Dissolving microneedle patches (MNs) have been proposed as a novel approach to increase skin permeability and may offer an ideal platform for i.d delivery. MNs are minimally invasive devices that consist of a series of microscopic projections attached to a base support.

Upon application to the skin surface, MNs create microscopic holes in the skin, bypassing the SC, and subsequently delivering their payload into viable skin. MNs are typically fabricated such that they are long enough to bypass the SC, yet are short enough to avoid stimulation of dermal nerves. As such, they provide a painless, minimally invasive method of delivery that is well accepted by human subjects. MNs are advantageous for vaccination; due to direct targeting of skin APC, they are dose sparing, and offer improved protection, while concurrently reducing the requirement for usage by trained personnel. Further to this, MNs provide a more simplified supply chain due to their ease of storage, distribution and disposal due to avoidance generation of sharps wastes.

ADVANTAGES

The advantages of microneedles are:

1. Large molecules can be administered.
2. Painless administration of the active pharmaceutical ingredient.
3. First-pass metabolism is avoided.
4. Faster healing at injection site than with a hypodermic needle.
5. No fear of needle.
6. Ease of administration.
7. Decreased microbial penetration as compared with a hypodermic needle, the microneedle punctures only the epidermis.
8. Specific skin area can be targeted for desired drug delivery.
9. Enhanced drug efficacy may result in dose reduction.
10. Good tolerability without long-term oedema or erythema.
11. Rapid drug delivery can be achieved by coupling the microneedles with an electrically controlled micropump.
12. The rate of drug delivery can be controlled more effectively by this system as compared with drug delivery via the stratum corneum.
13. Good reproducibility
14. Good stability and enhanced drug efficacy may result in dose reduction

DISADVANTAGES

1. Dosage accuracy may be less than with hypodermic needles
2. Careful use of the device may be needed to avoid particles ‘bouncing off’ the skin surface; if the device is not held vertically, the dose may escape or can penetrate the skin

to differing degrees,

3. The thickness of the stratum corneum and other skin layers varies between individuals and so penetration depth of particles could vary too
4. The external environment, like hydration of the skin, could affect delivery
5. Repetitive injection may collapse the veins
6. The tip of the microneedle may break off and remain within the skin on removal of the patch

MECHANISM OF ACTION

The mechanism of action depends on the type of microneedle design. The general mechanism of delivery via microneedles is based on mechanical disruption of the skin and application of the drug or vaccine within the epidermis, from where it can more readily reach its targeted site of action. The drug is entrapped within the microneedles, which when inserted into the skin and releases the drug into the layers of skin which are highly vascularized. In some cases the needles dissolve within minutes, releasing the entrapped drug at the intended site of delivery from where they reach the target site.

MATERIAL CONSTITUTON FOR MICRONEEDLES

Microneedles can be broadly divided into three categories: solid, degradable/dissolvable and hollow. Selection of the material for constitution of the microneedle should be based on criteria such as gentle fabrication without damage to sensitive biomolecules, sufficient mechanical strength for insertion into skin and controlled or rapid drug release as per the requirement. Microneedles have been produced using glass, silicon and metals.

Tab (1): Materials used for construction of microneedles.

Materialof construction	Example	Type of microneedles produced
1. Metal	Nickel-iron, titanium, stainless steel	Hollow/solid/coated
2. Silicon	Silicon dioxide	
3. Glass	----	Solid/hollow
4. Bio-degradable polymers	Polylactic acid, polyglycolic acid, (PLGA), Polylactide-co-glycolic acid polycarbonate16, Polyvinylpyrrolidone (PVP)	Hollow Solid
5. Non-bio degradable polymers	Polyvinyl acetate (PVA) 18, Alginic acid 18, Gantrez AN-	Solid

	139, a copolymer of methylvinylether and maleic anhydride (PMVE/MA) 18,	
6. Polysaccharides	Carbopol 971 P-NF 18, Polyetherimide carboxymethylcellulose, Amylopectin, Maltose, Dextran, Galactose, Chondroitin Sulfate, Thermoplastic starch	Solid/dissolving

DRUG DELIVERY METHODS

A number of delivery strategies have been employed to use the microneedles for transdermal drug delivery. These include

- Poke and patch
- Coat and poke
- Poke and release
- Poke and flow

Poke and patch

It involves piercing an array of solid microneedles into the skin followed by application of the drug patch at the treated site. Transport of drug across skin can occur by diffusion or possibly by iontophoresis if an electric field is applied. This technique was also tried to extract the interstitial fluid to measure the glucose level by non-invasive method.

Coat and poke

In this approach needles are first coated with the drug and then inserted into the skin for drug release by dissolution. The entire drug to be delivered is coated on the needle itself. Dip and scrape approach is a variation of this approach, where microneedles are first dipped into a drug solution and then scraped across the skin surface to leave behind the drug within the micro abrasions created by the needles. A limited amount of drug could be coated over the microneedles (only about 1 mg) and extensive optimization was required for uniform coating in this ‘coat and poke’ approach.

Poke and release

It involves release of encapsulated drug into the skin from the microneedles made from polymers and polysaccharides that either slowly dissolves or degrades after administration. Advantage of the ‘poke and release’ approach was that the drug release could be modulated

as per the requirement using a variety of available polymers and polysaccharides.

Poke and flow

In this approach first the skin is pierced (external pressure) and then the drug is allowed to flow through hollow microneedles from the reservoir in the patch.

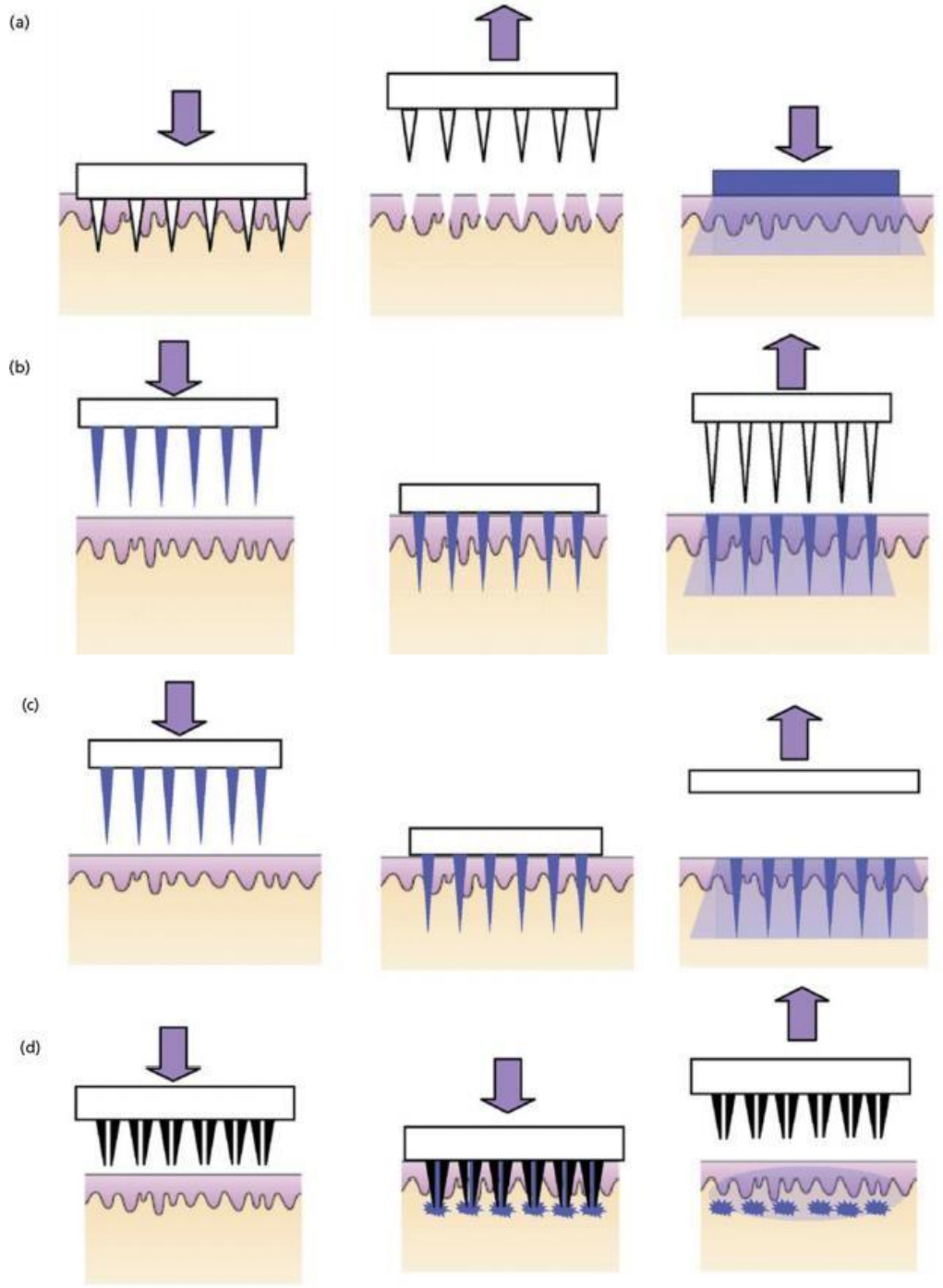

Fig 1: a-Poke and patch using solid microneedles, b-coat and poke using coated solid microneedles, c- poke and release using polymeric microneedles, d-poke and flow using hollow microneedles.

TYPES OF MICRONEEDLES

Classification for microneedles usually used in literature is based on the fabrication process: in-plane or out-of-plane microneedles. Another useful point of distinction is whether the microneedles are solid, hollow, coated or dissolving. The following sections will give an overview of these microneedles.

Solid microneedles

Solid micro needles are defined as the arrays of projections that are employed for creating holes in stratum corneum and are applied before the application of a drug and then removed afterwards. These can essentially create micron scale holes in the skin, through which drug molecules can easily enter. These needles are inserted into the skin for specified time period. The micro channels developed by the insertion of micro needles promote the drug transport in to the viable epidermis.

Hollow microneedles

Hollow microneedles contain a hollow bore in the center of the needle. When inserted into the skin, the hollow bore present bypasses the stratum corneum layer of the skin and produces a direct channel into the other lower layers of the epidermis. These microneedles are mainly employed to inject the drug solutions directly into the skin, to carry the drug into the body by diffusion. Similar to hypodermic injection, hollow microneedles enable pressure- driven flow of a liquid formulation. Pressure, and thereby flow rate, can be modulated for a rapid bolus injection, a slow infusion or a time-varying delivery rate. The apparent advantage of this is that a considerably larger amount of drug can be delivered for a given time, thus opening for applications where relatively large amounts are needed to obtain a therapeutic effect.

Dissolving microneedles

Dissolving microneedles completely dissolve in the skin and thus leave no bio hazardous waste behind after use. These microneedles typically constitute of water-soluble materials such as polymers and sugars that are safe and inert and will dissolve in the skin after insertion. While dissolving microneedles can be used as a skin pretreatment to increase permeability, drugs are often encapsulated inside the microneedle for release into the skin.

Coated microneedles

Coated microneedles are solid microneedles that act as vehicles to carry and deposit drug within the skin or other tissue. This includes coating microneedles with a drug in a

formulation suitable for coating and subsequent dissolution. In this way, the desired dose of the drug is delivered into tissue quickly upon insertion of the microneedles. The drug dose that can be administered this way is limited to the amount that can be coated onto the tip and shaft of the microneedles, which is typically less than 1 mg for small microneedle arrays.

Hydrogel-forming microneedles

Hydrogel-forming microneedles are the latest development in microneedle technology. These are arrays of microneedles made up of a swelling material with a drug reservoir attached to the baseplate of the array. After insertion into the skin, the array absorbs interstitial fluid and swells to form continuous conduits between the dermal microcirculation and an attached patch-type drug reservoir leading to the diffusion of the drug into the skin. Such microneedles act initially as a tool to penetrate the stratum corneum barrier. Upon swelling, they become a rate controlling membrane. These microneedle arrays are produced mainly using synthetic polymers such as an aqueous polymer gel that can be easily cross- linked by chemical or physical methods. These materials, once swollen, should maintain structural integrity and be reasonably robust during handling. Although hydrogel-forming microneedles are made from polymers, there are distinct differences between these microneedles and the regular dissolving polymer microneedles. Advantages of hydrogel- forming microneedles are that they can be fabricated in a wide range of patch sizes and geometries, can be easily sterilized, resist hole closure while in place and are removed completely intact from the skin.

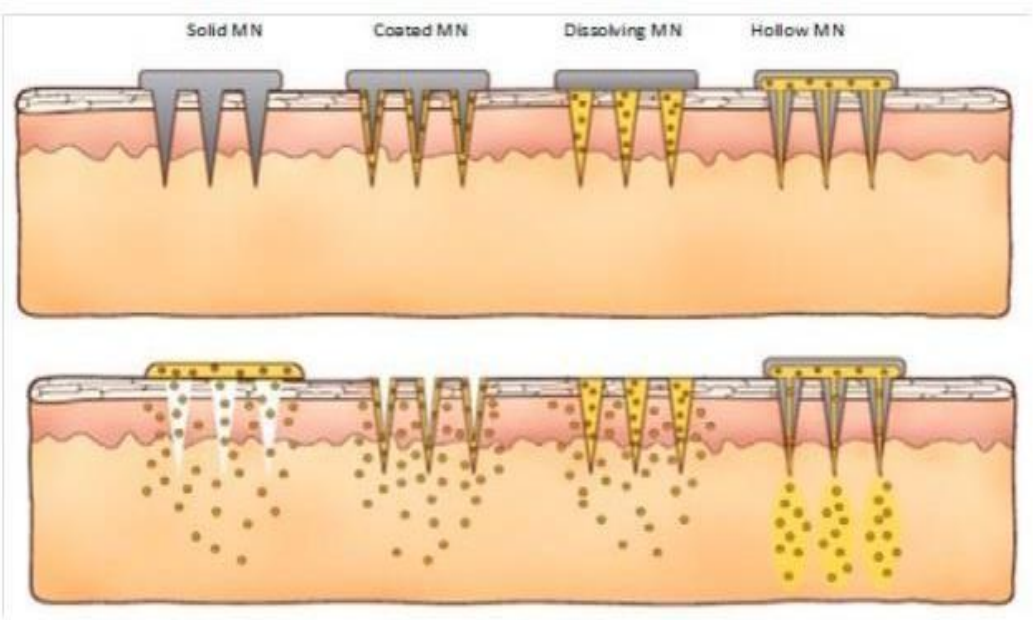

Fig. 2: Types of microneedles.

EVALUATION OF MICRONEEDLES

Margin of safety

Margin of safety is defined the ratio between the force required for piercing the stratum corneum and the force at which microneedles broke. If the ratio is <1 then microneedle array can be used in biomedical application. Margin of safety for silicon microneedles checked using computerized apparatus. For compressive failure force measurement, Enduratec station was used in which microneedles were placed between punch and load cell. An appropriate margin of safety was found for sample silicon microneedle arrays.

Measurement of fracture force

The force required for mechanical fracture of a microneedle was tested by Davis et al., employing an axial load test station that drove the microneedle against a flat block of aluminium at a rate of 0.01 mm/s until a preset displacement of 500 mm was reached. Microneedles were attached to the testing surface using adhesive tape around the base of the needle. Microneedle fracture was observed through an attached microscope to evaluate the mode of failure. The force and displacement data were used to quantitatively determine the fracture force.

Functional capacity test

Wang et al. evaluated the functional capacity of microfluidic lumens using a custom fluidic test setup. The test setup consisted of a syringe pump system with a dye-filled syringe, a polymer tube and microneedle array. This syringe pump system was used to examine the formation of the microneedle lumens by allowing dye to flow from the syringe to the microneedle orifice. Microscopic inspection of the microneedle tips and the base plate during the microfluidic characterization can be used to detect cracks in the base plate and passage continuity.

Measurement of insertion force into human skin

A displacement–force test station was used by Shawgo et al. to measure theforce applied to a needle, needle position and skin resistance during the sequence of the needle's translation, deflection of tissue around the needle and insertion into the skin of human subjects. A drop in electrical resistance of the skin was used to identify needle penetration since visual observation of needle insertion was extremely difficult. The electrical resistance of skin's outermost layer, the stratum corneum, is much greater than deeper tissues, therefore the resistance of the skin drops dramatically as soon as a needle penetrates.

Transepidermal water loss (TEWL)

DermaLab TEWL probe and Tewameter TM 210 probe were used by researchers during their investigation on microneedles. TEWL can be determined by employing a diffusion cell and intact animal skin. Probes were held in a clamp to prevent any interference above the application site and readings were taken over three minutes at various time intervals before and after application of microneedle array. The researchers concluded that there was an increase in skin permeability after the use of microneedle.

Penetration/diffusion test

In-vitro and ex-vivo test

In-vitro/ex-vivo tests are performed on isolated animal/ human dermatomed skin to study penetration or diffusion of drug from a dosage form to its site of application. These tests can also be used to compare the depth of penetration of the molecule.

In-vivo test

For a transdermal drug delivery system, it is practically impossible to predict the skin permeability of formulations using in-vitro experiments alone. Significantly different results might be observed while performing in-vivo study. Thus, along with in-vitro/ex-vivo testing, in-vivo tests should always be performed. If correlation is established between ex-vivo and in-vivo models, the drug development process could be made more economic and shorter.

Biological safety test

Extraction of chemicals from microneedles was done by immersing microneedles in physiological saline at 37°C for 72 h. The extract was then directly applied on shaved intact human skin for checking dermal irritation. Negative result of the test revealed the biological safety of the microneedles.

APPLICATIONS OF MICRONEEDLES

Microneedles have been explored for different applications and are extended to many fields. Owing to benefit of piercing in a minimally invasive manner, apart from being an alternative to conventional hypodermic therapy, they have also been employed for ocular, systemic and intracellular delivery. Microneedles can be used to deliver high molecular weight compounds like proteins and peptides, immunobiologicals like vaccines, antibodies etc. bioactive agents or bio macromolecules like insulin, heparin, albumin, growth hormones 43. Microneedles have also gained prominent attention in the field of cosmetics and various cosmeceuticals

have been used for the treatment of acne, pigmentation, scars and wrinkles as well as for skin toning. Microneedle delivery of gene is better than a microinjection technique because many cells can be treated at once.

Bioactive macromolecules

Owing to the proteolytic degradation and hindered absorption, bioactive macromolecules such as insulin, heparin, and growth hormones are not administered orally. The majority of commercially available biopharmaceuticals are administered via the parenteral route and hence a suitable non-invasive route is desirable. Microneedle arrays have been found to enhance the transport across dermatomed human skin for both low and high molecular weight compounds and also that the length of the microneedles and the depth up to which the microneedles penetrated in the skin had no effect on the transport of either low or high molecular weight compounds. For rapid release as well as controlled release of molecules, an approach of preparing dissolving microneedles constituting watersoluble polysaccharides has been done. Studies performed and reported on administration of biopharmaceuticals using microneedles include delivery of low molecular weight heparin, insulin, L-Carnitine, calcein and bovine serum albumin, desmopressin, recombinant human growth hormone and desmopressin, albumin, calcein, erythropoietin, oligonucleotides, porphyrin precursor 5-aminolevulinic acid (ALA), salmon calcitonin , daniplestim, leuprolide acetate, Para thyroid hormone, human growth hormone etc.

Immunobiologicals

Conventionally immunobiologicals are administered through a needle via the subcutaneous, intramuscular or intradermal route for prevention of infectious diseases. However the conventional vaccination procedure suffers from drawbacks like needle phobia and the pain associated with insertion of needle into the skin. Research has focused on development of needle-free vaccination like liquid jet injectors, powder injectors, thermal ablation and microneedles. Microneedles have an edge over the other methods due to lack of pain, self administration and quick delivery of vaccine.

Conventional liquid vaccines require cold conditions during transportation and tend to have a short shelf life. The stability of vaccines at high temperature as well as maintenance of antigenicity was reported by Hirschberg et al. in coated microneedles.

High purity subunit vaccines are safer than live attenuated or whole inactivated vaccines. The

use of pure vaccines results in decreased immunogenicity. Several studies have been carried out to achieve effective immunization of vaccines via microneedle delivery along with adjuvant.

Drugs

Very few drug molecules possess the necessary physicochemical properties to cross the skin barrier and even if the drug can cross the barrier, drug delivery rate via the transdermal route is very low. Physico-chemical properties like hydrophilic-lipophilic balance, solubility, molecular weight, etc., govern the transport of a drug through the skin and also the rate of transportation. These challenges can be overcome by use of microneedles. Highly hydrophilic drug formulations like PEGylated naltrexone or hydrophobic formulations of drugs like ketoprofen, show a many-fold increase in area under the curve (AUC) and maximum drug concentration (Cmax) as compared with conventional cream or gel formulations. The need for penetration enhancers, which may induce irritation, can be eliminated by the use of microneedles.

Phlebotomy

Phlebotomy is the withdrawal of blood for diagnostic purpose. Painless hollow microneedle-based micro sampling can be used instead of traditional methods for glucose estimation. Microneedles can be used to obtain precise body fluids as well as blood samples from the capillaries, which are situated at a distance of 500–2000 mm in the dermis layer beneath the skin. This method has many advantages like reduction in blood sample requirements (up to 200 nanolitres) while making the procedure painless. The microneedle must penetrate to sufficient depth, hence care should be taken in the design, material selection and dimensions of the microneedle, to ensure penetration at low pressure without breakage.

Diagnosis

Hollow microneedles can be used to withdraw fluid from tissue or blood which can be subsequently analysed to check the status of diseases like cancer, diabetes and many more. Hollow microneedles, along with quantum dots, help in medical diagnosis.

ADVANCES OF MICRONEEDLES IN COMBINATION WITH OTHER TECHNIQUES

Microneedles in combination with Electroporation

Electroporation involves application of high voltage short-duration (milliseconds) current

(generally 50– 1000 V/cm) causing a transitory, localized perturbation of lipid bilayer inducing structural rearrangements of the cell membrane due to the electric fields that are produced during current application. The aqueous pores formed as a result act as the aqueous pathways and provide a local driving force that facilitates the transport of molecules across the stratum corneum. A trans-membrane potential up to 1 kV for 10 ms to 500 ms was used for in-vitro electroporation of stratum corneum. Although this process is useful for delivering large hydrophilic drug species like small molecules, proteins, peptides and oligonucleotides, including biopharmaceuticals with molecular weights greater than 7 kilo Daltons, electroporation was also used for permeation enhancement of larger molecules having molecular weight up to several kilo Daltons.

Microneedles in combination with Microparticles and Nanoparticles

The versatility of microparticles and nanoparticles for the effective and targeted release of different therapeutic agents to different anatomical regions makes them a good candidate as drug carriers or vehicles for topical and transdermal drug delivery for enhanced drug permeation. These carriers can be constituted of biodegradable polymers or lipid materials. Penetration of nanoparticles through human skin depends on the nanoparticle size and shape, material properties etc. Nanospheres or nanocapsules of different sizes can be obtained by varying the materials employed and the method of preparation. A dramatic increase in cellular uptake can be achieved by reducing the size of nanoparticles. Combining microneedles with these nanoparticulate systems may significantly enhance the transdermal drug delivery wherein microchannels created by the microneedles may prove to be large enough to deliver drug-loaded nanostructures into the skin.

Microneedles in combination with Micro pumps

Conjunction of microneedles with micro pumps provide precise delivery of drug as the pumps control the flow rate and pressure for delivery of concentrated drug solution as required. This combination was employed in preparing an integrated system, with micro valves and micro-pumps, which was capable of controlling fluid withdrawal for medical analysis and delivering the drug in response to metabolites levels.

Pocketed and Grooved Microneedles

Modification of the microneedle surface can be employed for targeted drug delivery to a specific depth in the skin and for loading greater amount of drug onto the microneedle. This can be achieved by applying the protective coat or second drug coat on the same

microneedles after filling the first part in the pockets. Such microneedles are known as pocketed microneedles. These can also be obtained by fabricating microneedles with one or more holes cut through the center. Also grooved microneedles that capable of loading greater amount of drug onto the microneedle can be employed for enhanced drug delivery.

ACKNOWLEDGEMENT

I am thankful to Ezhuthachan College of Pharmaceutical Sciences providing all the necessary facilities like internet, books available in the college library to do work. All the authors have no conflict of internet.

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