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Recent Advance in Microneedle as a Drug Delivery System

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ABSTRACT:

The most widely used methods for transdermal administration of the drugs are hypodermic needles, topical creams, and transdermal patches. The effect of most of the therapeutic agents is limited due to the stratum corneum layer of the skin, which serves as a barrier for the molecules and thus only a few molecules are able to reach the site of action. 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. 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. This review describes the various potential and applications of the microneedles. The various types of microneedles can be fabricated like solid, dissolving, hydrogel, coated and hollow microneedles. Fabrication method selected depends on the type and material of the microneedle. This system has increased its application to many fields like oligo nucleotide 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.

KEY WORDS: Transdermal Drug delivery, Microneedle, Solid microneedle, Hydrogel micro needle.

INTRODUCTION

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. The microneedles (MNs) have been studied by various researchers for delivering drug through the transdermal route and for overcoming the limitations of the conventional approaches. Microneedle device consists of needles of micron size, which are arranged on a small patch. Considering the problems of the hypodermic needle and the transdermal patch, microneedle drug delivery system was developed and is thought to be the hybrid of both. The major problem associated with transdermal technology is that many of the drugs are not able to cross the skin at the required rate necessary for the therapeutic action¹⁻³. Researchers have developed a refined technology using microneedles, which allow hydrophilic high molecular weight compounds to enter the stratum corneum. Administration of drugs using the

microneedle device allows the drug molecules to cross the stratum corneum layer, thus allowing more drug molecules to enter the skin. The characteristic features of this technology are the faster onset of action, better patient compliance, self-administration, improved permeability and efficacy. In addition to improved therapeutic advantages, microneedles give highly accurate reproducible results with minimum inter-subject variability in bioavailability. Though it has many advantages it also possesses some limitations. There is the possibility of skin irritation or allergy to sensitive skin. Since the needle size is very small and thinner as compared to the thickness of hair, breaking of microneedle tips may take place which if remained inside the skin, can cause problems. These limitations are very rare and can be overcome with advanced material selection for microneedles. The main objective of developing this technology is to create larger transport pathway of micron size which is larger than molecular dimensions and smaller than holes by hypodermic needles, to disrupt the stratum corneum to allow large molecules to pass through thus increasing the permeability. Conventional methods like electric methods-iontophoresis and electro poration, chemical/ lipid enhancers create pores of nanosize which improve the permeability up to some extent but fail for large molecules. A comparative discussion is compiled for various transdermal drug delivery systems in Table. The drug delivery by various transdermal systems is presented in Fig. 1. The topical cream spreads only on the skin surface. It has been reported that only 10–20% of total drug loaded in cream is being permeated through the skin. In case of a transdermal patch, the drug has to pass the stratum corneum barrier thus it also shows less bioavailability. Addition of permeation enhancer in the transdermal patch can improve the drug permeation but up to a very limited extent. The hypodermic needle goes deep into the dermis where pain receptors are present. Thus it can deliver 90–100% of the loaded drug but it is very painful which results in poor patient compliance. Microneedle patch bypasses the stratum corneum barrier and delivers the drug directly into the epidermis or upper dermis layer which delivers 100% of the loaded drug without pain^{3,4}.

BENEFITS⁵⁻⁷

- Large molecules can be administered.
- Painless administration of the active pharmaceutical ingredient.
- First-pass metabolism is avoided, faster healing at injection site than with a hypodermic needle.
- No fear of needle, ease of administration.

- Decreased microbial penetration as compared with a hypodermic needle, the Specific skin area can be targeted for desired drug delivery.
- Enhanced drug efficacy may result in dose reduction, good tolerability without long-term oedema or erythema.
- Rapid drug delivery can be achieved by coupling the microneedles with an electrically controlled micropump.
- The rate of drug delivery can be controlled more effectively by this system as compared with drug delivery via the stratum corneum.

CLASSIFICATION⁸⁻¹⁰

Different types of microneedles fabricated and investigated for their application in drug delivery are solid, coated, dissolving, hollow, and hydrogel microneedles. Different types of microneedles with their unique properties are displayed in Fig. Each type of microneedle has its own way of delivering the drug into the epidermis. Some are used just to create pores in stratum corneum, some are precoated with the drug solution on their surface, some are dissolvable and some are prefilled with the drug solution.

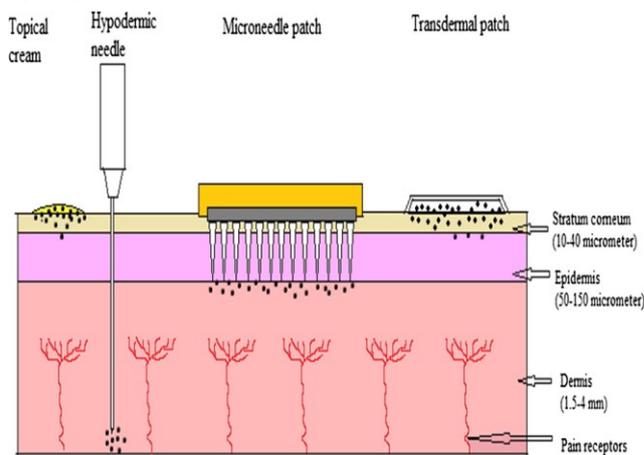


Figure 1. Comparison of topical cream, hypodermic needle, microneedle patch and transdermal patch

METHOD OF MICRONEEDLE⁹⁻¹⁵

Solid microneedles⁹

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 deliver the drug with passive diffusion to skin layers fabricated solid silicon long and tapered microneedles using tetramethyl ammonium hydroxide

etching process. Microneedles with an average height of 158 μm and base width of 110.5 μm were successfully fabricated. Later he also fabricated the gold-coated solid silicon microneedles with the dimension of 250 μm in height, the base width of 52.8 μm , the aspect ratio of 4.73, tip angle and diameter of 24.5° and 45 μm . The results demonstrated improved bioavailability and mechanical strength. studied polylactic acid microneedles and found that biodegradable polymer solid microneedles have sufficient mechanical strength to pierce the stratum corneum and can enhance the absorption of the drug. The microneedles having 800 μm depth and density of 256 MNS per cm^2 was found to enhance the drug permeation. Stainless steel microneedles are also studied by various researchers. Enhanced delivery of captopril and metoprolol tartrate was studied after application of stainless-steel MN arrays.

Coated microneedles¹⁰

The microneedles are surrounded with the drug solution or drug dispersion layer. Subsequent dissolution of drug from the layer takes place and the drug is delivered quickly. The amount of drug that can be loaded depends on the thickness of the coating layer and the size of the needle which is usually very less. Baek et al loaded lidocaine on poly L-lactide (PLLA) microneedle arrays. The loaded lidocaine released rapidly in phosphate buffer saline and was found to be stable for 3 weeks. Coated microneedle also explored for delivery of multiple agents through same formulation. Li et al coated each microneedle with different formulations and drugs thus allowing co-delivery of multiple agents with different properties. These delivered water soluble and water insoluble dyes simultaneously. Chen and co-workers coated PLA microneedles with sulforhodamine B and found the drug delivery efficiency to be approximately 90%. The in vitro studies in mice confirmed the continuous drug delivery.

Dissolving microneedles^{12, 13}

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. Effective needle drug distribution is an important factor which faces problems while developing dissolving microneedles. Hence, polymer-

drug mixing is a critical step in such fabrication. Chen and his group developed tip dissolving microneedles which showed rapid and efficient drug delivery without skin irritation. Dissolving microneedles take time to dissolve and complete insertion is difficult. developed rapidly separating microneedles mounted on solid microneedles which gave sufficient mechanical strength to the microneedles and approx. 90% delivery efficiency was observed in 30. Wang et al introduced the addition of bubbles to the dissolving microneedles to prevent drug diffusion in the entire microneedles. These were found to achieve about 80% of drug delivery efficiency in 20 s. Separable arrowhead microneedles were developed. Sharp polymer tips encapsulated with the drug were mounted on blunt metal shafts which separate or dissolve on insertion in the skin within a few seconds. These modifications in dissolving microneedles showed that possibilities of the rapid drug delivery with controlled release kinetics

Hollow microneedles^{9,14}

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. Different types of microneedles (a) Solid microneedles use poke with patch approach, are used for pre-treatment of the skin; (b) Coated microneedles use coat and poke approach, a coating of drug solution is applied on the needle surface; (c) Dissolving microneedles are made of biodegradable polymers; (d) Hollow microneedles are filled with the drug solution and deposit the drug in the dermis or the upper dermis layer. Mostly it is used for high molecular weight compounds such as proteins, vaccines, and oligo nucleotides. The drug flow rate and release pressure can be adjusted if the drug is to be given by a rapid bolus injection. 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. Maintaining a constant flow rate is essential here. Increase in the microneedle bore can increase flow rate but lead to reduced strength and sharpness. Sometimes a metal coat is applied on the microneedle to increase the strength of the microneedle but this can make the needles sharp. developed hollow microneedles aligned on the silicon substrate having a length of 500–600 μm and 100 μm outer diameter. The flow rate of 0.93 $\mu\text{l s}^{-1}$ was achieved at 2 K Pa pressure difference. Maaden and co-workers fabricated fused silica hollow microneedles using hydrofluoric acid etching. These microneedles were able to inject very less amount of vaccine into the skin in an automated manner

thus overcoming the drawbacks of the hypodermic needle. Interestingly Suzuki and colleagues developed hollow microneedles which were mimicking the action of mosquitoes and the designed microneedles showed improved penetration in the skin.

Hydrogel-forming microneedles¹⁵

This type of microneedle is recently developed. Super-swelling polymers are used to make microneedles. The polymers constitute the hydrophilic structure which makes it capable of taking up a large amount of water into their three-dimensional polymeric network. These polymers swell when inserted into the skin due to the presence of the interstitial fluid. This leads to the formation of channels between the capillary circulation and the drug patch. Before needling, these microneedles are just used to disrupt the skin barrier. On swelling, they behave as a rate controlling membrane. They have flexibility in size and shape. Easy sterilization and intact removal from the skin are the unique properties of such microneedles. Migdadi et al studied hydrogel-forming microneedles to administer metformin transdermally so as to decrease the gastrointestinal side effects associated with the oral delivery.

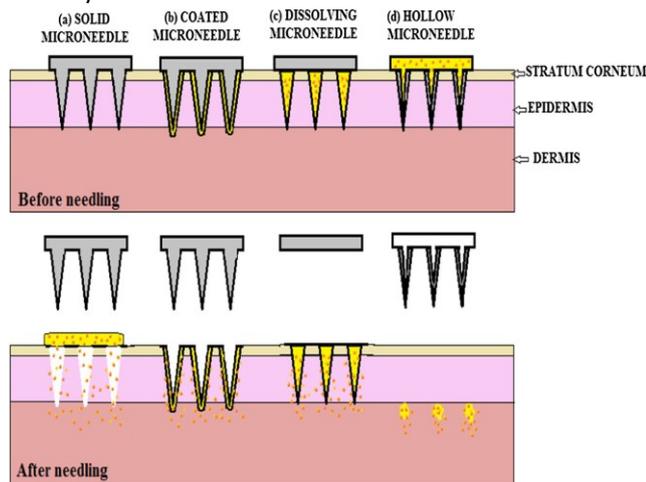


Fig. 2. Different types of microneedles

(a) Solid microneedles use poke with patch approach, are used for pre-treatment of the skin; (b) Coated microneedles use coat and poke approach, an coating of drug solution is applied on the needle surface; (c) Dissolving microneedles are made of biodegradable polymers; (d) Hollow microneedles are filled with the drug solution and deposit the drug in the dermis

Microneedle fabrication and properties

Silicon^{16,17}

The first microneedle was made from silicon in the. Silicon is anisotropic in nature and has a crystalline structure. Its properties depend on the alignment in the crystal lattice,

which shows different elastic moduli (50 to 180 GPa). Its flexible nature allows producing needles of different sizes and shapes. Its attractive physical properties make it a versatile material. Silicon substrates can be precisely manufactured and are capable of batch production. The cost of silicon and its time-consuming complex fabrication process limits its use in microneedle. In addition, there are some biocompatibility issues, as silicon is brittle, some part may break and remain in the skin thus causing some health issues.

Metal¹⁸

The main metals used are stainless-steel and titanium. Palladium, nickel, palladium-cobalt alloys are also used. They have good mechanical properties and good biocompatibility. Metals are strong enough to avoid breaking, thus more suitable as compared to silicon for microneedle production. The first metal used in the production of microneedle was stainless steel. Titanium is a good alternative to stainless steel.

Ceramic¹⁹

Alumina (Al₂O₃) is mainly used because of its chemical resistance. It forms a stable oxide because of the highly energetic ionic and covalent bonds between Al and O atoms. Other types of ceramics used are calcium sulfate dihydrate [Gypsum (CaSO₄ · 0.2H₂O)] and calcium phosphate dihydrate [Brushite (CaHPO₄ · 2H₂O)]. In recent years an organically modified ceramic called Ormocer[®] has been used. It is a three-dimensionally cross linked copolymer. A polymer with different properties can be produced by using different organic units during polymerization. Mainly they are produced using a micro moulding technique. Ceramic slurry is cast into a micro-mold. Micro moulding techniques are cheaper processes, and also have the potential for scale-up.

Silica glass^{9,11}

Varying geometries can be produced on small scale using glass. Silica glass is physiologically inert but brittle in nature. Borosilicate glass which is made up of silica and boron trioxide is more elastic. They are mostly fabricated manually, thus are less time efficient. Glass MNs are not used now commercially, but only for experimental purposes.

Carbohydrate¹⁵

Maltose is one of the most common sugars used. Other sugars, such as mannitol, trehalose, sucrose, xylitol and galactose, polysaccharides can also be used. Carbohydrate slurries are moulded by making use of silicon or metal templates. The drug-loaded carbohydrate mixture is casted into the moulds to get the microneedles. The time-based

dissolution of carbohydrate regulates the drug release inside the skin. Carbohydrates are cheap and safe for the human health but degradation at high temperatures makes the fabrication process difficult.

Polymer¹⁸

A wide variety of polymers including poly (methyl methacrylate)(PMMA) , polylactic acid (PLA), poly (lactico-glycolic acid)(PLGA), polyglycolic acid (PGA), poly (carbonate) ,cyclic-olefin copolymer, poly (vinylpyrrolidone) PVP), poly (vinylalcohol) (PVA), polystyrene (PS), poly (methyl vinyl ether-comaleicanhydride), SU-8 photoresist are reported for microneedles preparation. Mostly, dissolving or biodegradable and hydrogen forming microneedles arrays are made from these polymers. Microneedles fabricated with these polymers have less strength than other materials but are tougher than glass and ceramics.

CHARACTERIZATION OF MICRONEEDLE^{20-26,29}

Characterization of microneedle geometry

Scanning electron microscopy can be used to determine the base radius, tip radius and wall thickness of the microneedles. Interfacial area (i.e. the effective area of contact between the needle and the skin) can be calculated in two ways: (1) the annular surface area, A_a; at the needle tip $A_a = 2\pi r t$ (1)

and (2) the full cross-sectional area, A_f; at the needle tip $A_f = \pi r^2$ (2)

UTILIZATION OF MICRONEEDLE PRODUCT^{9,11,16,19,20,25,27-35}

SR.NO	PRODUCT NAME	COMPANY NAME	USE
1	Dermarolle	Dermaroller® Germany, White Lotus	Improve skin texture, treat scars and hyperpigmentation
2	C-8 (Cosmetic type)	The Dermaroller Series by Anastassakis K.	Used to enhance penetration of topical agents.
3	CIT-8 (Collagen Induction Therapy)	The Dermaroller Series by Anastassakis K.	Used in collagen induction and skin remodeling
4	MF-8 type	The Dermaroller Series by Anastassakis	Treat scars
5	MS-4	The Dermaroller Series by Anastassakis K.	Used on facial acne scars
6	MicroHyala	CosMed transdermal drug delivery	Wrinkle treatment
7	LiteClea	Nanomed skincare	Treats acne and skin blemishes
8	Soluvia	Sanofi Pasteur Europe	Influenza vaccination
9	h-patch	Valeritas	To deliver drugs in subcutaneous tissue (insulin)
10	Microstructured transdermal system	3M	To deliver biologics and other small molecules

Needle wall angle, α , is calculated as

$$\alpha = \tan^{-1}(r_b - r_t / h) \quad (3)$$

where r_t is the outer radius of the microneedle tip, r_b is the outer radius at the needle base, t is the wall thickness and h is the height.

Characterization methods

The drug can be loaded onto or into the microneedles either in suspension/dispersion form or encapsulated form (liposomes, nanoparticles, nanoliposomes). The drug can be coated with the polymer solution or can be applied as a patch. Various physicochemical characterizations including particle size, poly dispersity index, viscosity, and zeta potential can be evaluated for loaded drug depending on the type of formulation used in the microneedles . Drug release, adhesion, permeation tests are performed for a patch which is applied after pre-treatment. The size, internal structure, and crystallinity of the liposomes or nanocarriers can be performed using a dynamic light scattering, X-ray scattering, and transmission electron microscopy technique. Stability studies of drug dispersion and microneedles can be studied at a different temperature, pH and simulated in-vivo physiological conditions (cell line or tissues). Other tests like solubility studies, drug content, in-vitro release tests, and biocompatibility studies are also performed on designed microneedle.

11	Micro-Trans	Valeritas Inc., USA	It can deliver the drug into dermis without limitations of drug size, structure.
12	Nanoject	Debiotech, Switzerland	Useful for intradermal and hypodermic drug delivery and for interstitial fluid diagnostics.
13	Janisys	Janisys, Ireland	Actively delivers drugs from transdermal patches and multiple drugs.
14	BD Soluvia	Becton Dickinson, USA	prefillable microinjection system for accurate intradermal delivery of drugs and vaccines.
15	Onvax	Becton Dickinson, USA	It is a skin micro abrader having plastic microneedles for disruption of stratum corneum for the delivery of vaccines
16	MicronJet	NanoPass Inc., Israel	standard syringe for painless delivery of drugs, protein and vaccines approved for this delivery route
17	Macroflux	Zosano Pharma Inc., USA	Metallic microneedles for the delivery of peptides and vaccines
18	AdminPen	AdminMed, USA	Liquid pharmaceutical formulation or cosmetics can be conveniently injected in to the skin
19	NanoCar	NanoPass Inc., Israel	It is a small hand-held device for rejuvenation of skin and to boosts the cosmetic effect of topical applications
20	MTS-Rollers	Clinical Resolution Laboratory Inc., USA	It is used for transdermal delivery of cosmetics in deeper skin layers

EVALUTION OF MICRONEEDLE³⁶⁻⁴²

Dimensional evaluation³⁶⁻³⁷

Various methods are used to evaluate the needle geometry and to measure the tip radius, length, height of the microneedle. Most common methods are optical or electrical microscopy. Analysis of a 3D image gives a better picture of needle geometry and helps in quality control. Scanning Electron Microscope (SEM) and confocal laser microscope have been used for this purpose. SEM produces an image of a sample by making use of a focused beam of electrons which interact with the atoms in the sample while scanning and produce various signal which give information about sample surface topography and composition. Confocal laser microscope produces high-resolution images.

Mechanical properties or insertion forces³⁸⁻³⁹

A microneedle must be sharp and slender enough so that it can easily penetrate into the skin and also be strong enough so that it does not break when inside the skin. Mechanical tests which are performed on microneedles are given in Table Two important factors for a safe and efficient design of microneedles are the force at which the microneedle loses its structural integrity and the insertion force.

The ratio of these two forces is called as the 'safety factor'. The ratio is preferred to be as high as possible.

In-vitro skin permeation studies⁴⁰⁻⁴²

Diffusion cell apparatus is used to find the permeation of the drug through the skin. Pig ear skin is mostly used in the experiment which is mounted between the receptor and donor compartment. The cumulative permeation profiles of microneedle treated and untreated skin are compared.

In-vivo animal model studies⁴⁰

Hairless rats can be used for the study. A suitable technique to anesthetize the animal shall be used. One of the parameters considered is trans-epidermal water loss (TEWL) which is measured before and after microneedling. Delfin Vapometer is used to measure this parameter.

Functional capacity test⁴²

Evaluated the functional capacity of microfluidic devices using a custom fluidic test set up. The test set up 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.

CONCLUSION

Transdermal drug delivery system is an emerging area for systemic well as local delivery of macromolecules. The biggest drawback of TDDS is poor permeability through stratum corneum and it can be overcome by using microneedles. Hence, researchers focused their attention on development of different types of microneedles for delivery of macromolecules, immunobiologicals and drugs as well as to withdraw the tissue fluids. Physical approaches have also been combined with microneedles to enhance drug delivery through skin. In conclusion, microneedles have been tried by many scientists as a novel means to administer the molecules. Many patents have been filed to cover the invention and this reflects the scope of development of microneedle as a means to administer the problematic macromolecules. Improved therapeutic response can be obtained using microneedles.

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