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MICRONEEDLE AS A NEW DRUG DELIVERY SYSTEM: AN OVERVIEW

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Abstract

Target drug delivery system always need new and advanced technique to deliver drug more precisely. Microneedle technology has been developed as an advanced technique for penetration of large molecular weight hydrophilic compound. Rapid onset of action and painless drug delivery system are the most important advantages of this delivery system .The rationale behind microneedle-based drug delivery is that such technology will reduce the need for hypodermic injection and since the needles are short ,they do not reach the nerve rich regions of the lower part of the skin. By employing batch-fabrication techniques from the microelectronics industry, small-scale microneedles can be mass-produced with high precision and reproducibility in a cost-effective manner.

Keywords: Target drug delivery system, Microneedle, hydrophilic compound, Transdermal patches.

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Introduction

Microneedle technology has been developed as a new drug delivery system for penetration of large molecular weight and/or hydrophilic compounds. Micron scale needles assembled on transdermal patches have been proposed as a hybrid between hypodermic needles and transdermal patches to overcome the individual limitations of both the injections as well as patches.

Salient features of microneedle drug delivery technology [1]

- Rapid onset of action
- Painless drug delivery system
- Possible self administration
- Efficacy and safety comparable to approve dinjectable products
- Improved patient compliance
- Good stability
- Cost effective
- Valuable source of intellectual property

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Hollow microneedles

It involves injecting the drug through the needle with a hollow bore. This approach is more reminiscent of an injection than a patch.

Few Basic Requirements of Microneedles [2]

Suited to the purpose:

That microneedle should work in *in vivo* environmentsis rather obvious, but nevertheless needs to be emphasized. There has been a tendency, particularly in the micro fabrication community, to use specialized fabrication techniques to make microneedles without demonstrating basic feasibility.

Batch compatible:

As a minimally invasive medical device, microneedles for drug delivery will need to be disposable, single-use, devices to gain acceptance in medical practice. Competing with standard

needles and syringes at minute costs microneedles need to be produced in cost-effective manner..

Biocompatible:
Microneedles are designed to be inserted into human tissue and as such they need to be compatible with the local environment, both in terms of toxicity and intended function. The duration of contact with the tissue range from minutes to days at the most (insulin infusion-sets are typically changed every third day).

Rationale behind microneedle based delivery

- The rationale behind microneedle-based drug delivery is that such technology will reduce the need for hypodermic injections, which can be painful and usually need to be administered by a trained professional.
- Combining the microneedle technology with more established transdermal delivery mechanisms may help overcome some of the shortcomings of the conventional transdermal drug delivery. For example, while the transdermal administration has been employed in indications ranging from pain management to hormone replacement, to date the approach has been limited to the delivery of drugs that can readily pass through the skin.
- Since the needles are short, they do not reach the nerve-rich regions of the lower parts of the skin. As a consequence, the stimulus caused by microneedle insertion into the skin is weak and perceived as painless. Thus a painless intradermal delivery is an important aspect of microneedle technology
- By employing batch-fabrication techniques from the microelectronics industry, small-scale microneedles can be mass-produced with highprecision and reproducibility in a cost-effective manner.
- By combining microneedles with a patch-like structure, a system can be realized which essentially has all the favorable properties of a traditional transdermal patch ,i.e. continuous release, ease-of-use, unobtrusiveness and painlessness. Unlike the standard patch, a microneedle-based patch enables delivery of virtually any macromolecular drug (including insulin and vaccine). Such a patch would not only offer a discreet and patient-friendly drug administration system, but also an efficient and possibly safe way to administer drugs with minimum involvement from health-care professionals.
- A number of Fortune 500 companies, as well as start-ups, are actively developing microneedle technology for transdermal drug delivery. Most of them work with solid, non-hollow, needles.

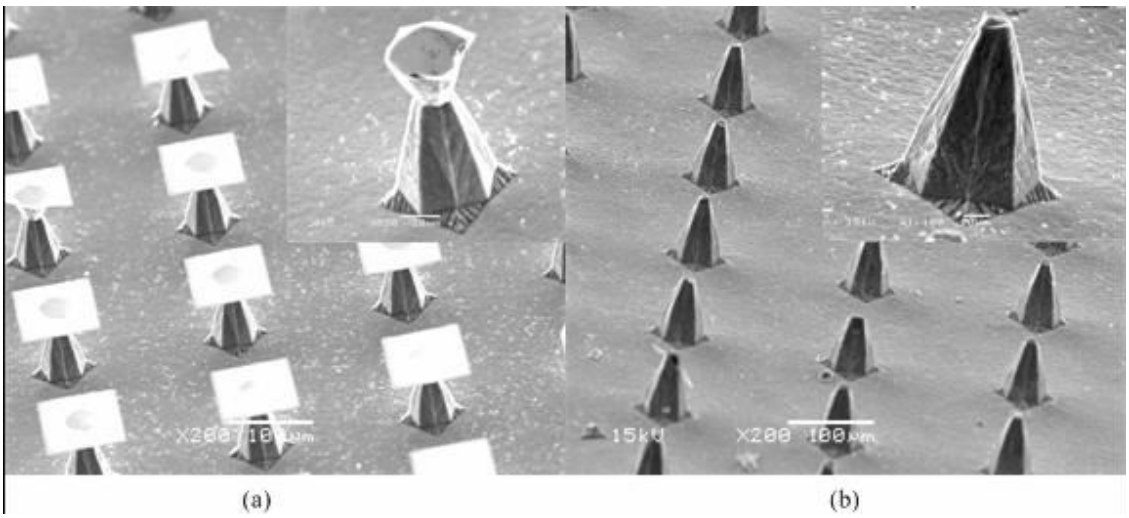


Fig. No. 01: SEM micrograph of microneedle array fabricated in KOH wet etching process. shows the microneedle fabricated in KOH wet etching process using a square mask. The mask size is 80 µm in length with 150 µm center-to-center distance. The wet etching results highly depend on the crystal plane of silicon. The etching results highly depended on crystal planes as shown in Fig. 1 (a), which shows the microneedle shapes during the KOH etching process. With increased etching time, the top part of the microneedle was etched away, as shown in Fig. 1b.[from ref 2]

Fabrication by Ion Sputtering deposition

Kazuyoshi Tisuchiya et al.[3] fabricated microneedle by thin film deposition process using RF magnetron sputtering method. Titanium and titanium alloys were deposited onto very thin copper wire with diameter ranging from 25 to 50 microns. This wire was rotated at 3-5 rpm by a rotor in sputtering chamber. Sputtering time required to obtain a microneedle with outer diameter 15 microns was about 4 hours with power input of 300 W. The sputtering time is adjusted to control the thickness of titanium layer. After titanium alloy and titanium respectively deposited and annealed the copper at the core is removed by wet etching process. Titanium is used as it is biocompatible.

Fabrication of Micro needle array with biodegradable tips

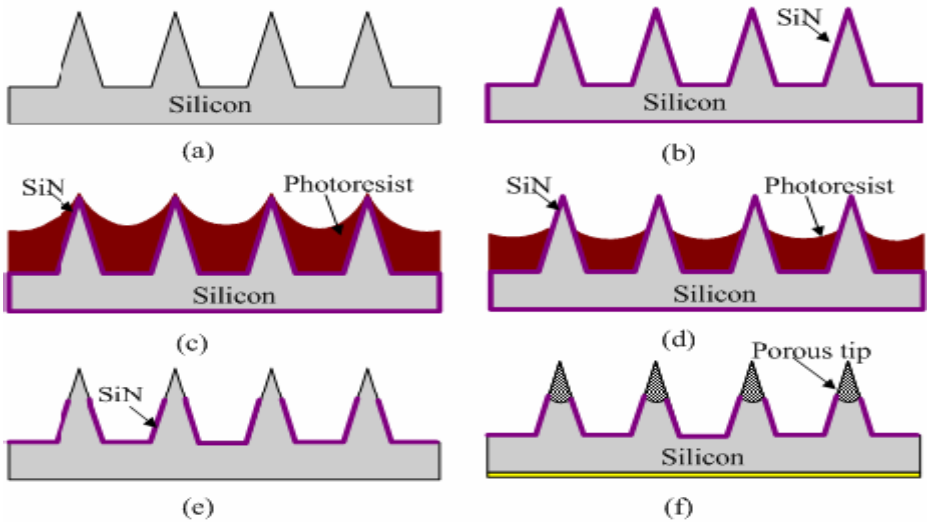


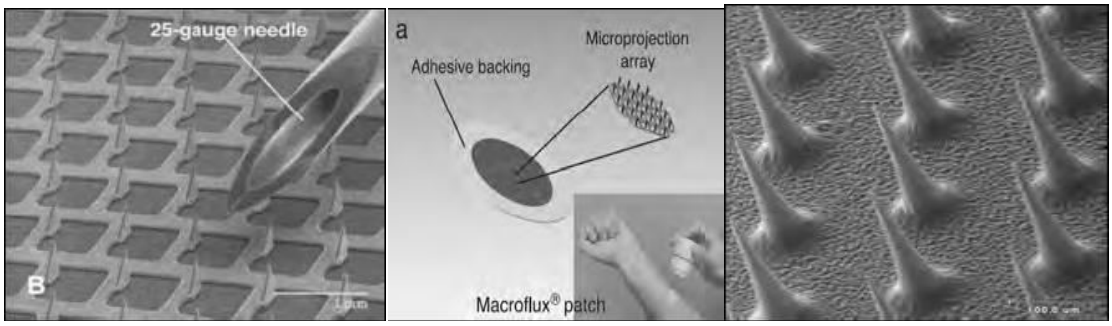
Fig. No. 02: Fabrication schedule of microneedle array with porous tips

A process has been developed to fabricate microneedles with macroporous tips. [4]Themacroporous silicon is marked as a biodegradable material [5]. Therefore, it has attractive potential application in biological area. Moreover, the porous structure provides an alternated method for drug loading. Fig. 2 (a) illustrates the overall process for porous tips fabrication. Firstly, a silicon nitride layer was deposited onto the fabricated microneedle surface (Fig. 2(b)). Secondly, a thick photo resist was coated to the structural substrate (Fig. 2(c)); and the sample was baked at temperature higher than the photo resist transition temperature to reflow the photo resist from the top of needle. Following the top photo resist etched in RIE with O2 gas (Fig. 2(d)), the top part and backside silicon nitride layer was removed in RIE using $CF4/O_2$ gases (Fig. 2(e)). Finally, a thin gold layer was deposited on the backside of sample. An electrochemical etching process was carried out to generate the porous tip using HF based electrolyte, resulting in the microneedles with porous tips (Fig. 2(f)). Fig. 3 shows the fabricated micro needles with porous tip. It is clear to see the porous structure is formed on the exposed tip part. The porous tip may serve as a tool to load drugs.

Development of microneedle arrays

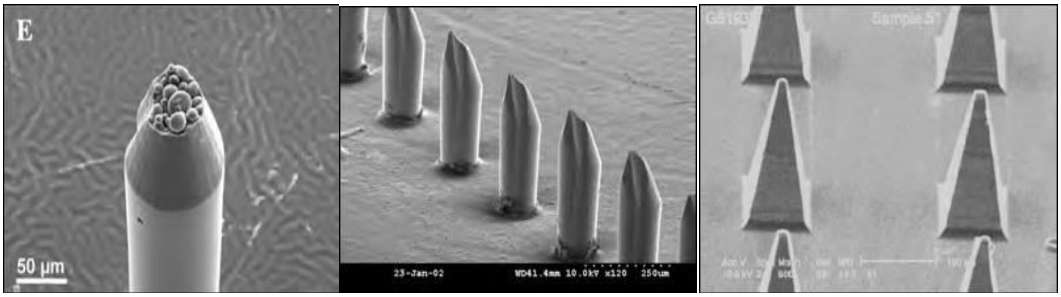
Solid Microneedle Arrays

The real interest of microneedles for transdermal drug delivery applications began in 1998. Henry et al. demonstrated four orders of magnitude increase in permeability for calcein and BSA (bovine serum albumin) through human epidermis *in vitro* after



(a) (b) (c)

Fig. No. 03: (a)The first out-of-plane microneedles for transdermal drug delivery applications. The solid silicon needles are 150 _m long and made of silicon. (b) Array of 330 _m long microneedles made from a titanium foil. Scale bar: 1 mm. (c)Illustration of the array mounted on an adhesive backing. The inset shows how the patch is applied to the skin with an impact applicator [2]



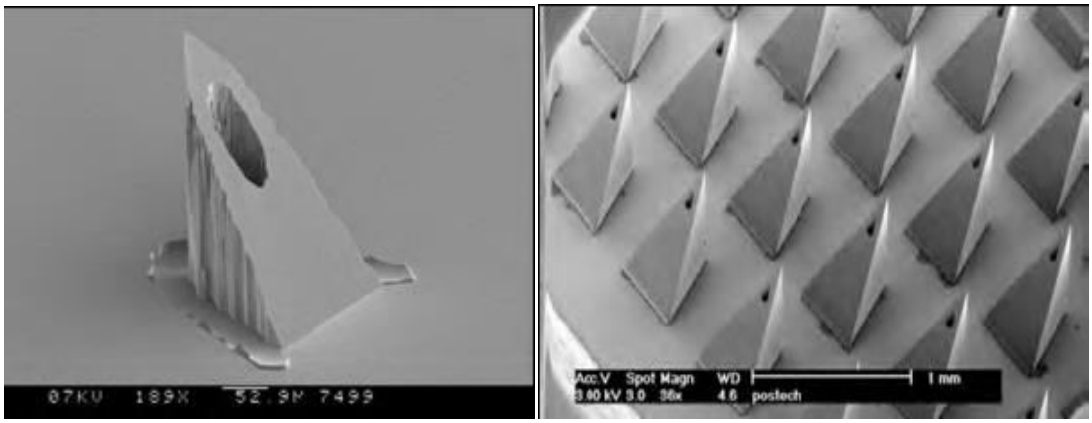
(a) (b) (c)

Fig. No. 04: [2](a) 3M'sMicrostructured Transdermal System (MTS). 250 _m long molded polymer needles. (b) Beveled PLGA microneedles inserted through human epidermal tissue in vitro. The needles are approximately 400 _m long. (c) Drug incorporated microneedle. The picture shows a cut off tip of a PLGA micro needle incorporating PLA micro particles encapsulating calcein.

Another multinational company working with microneedle arrays is 3M. The company's Microstructured Transdermal System (MTS) consists of an array featuring 250 m long pyramidal-shaped polymer microneedles (fig 4a) and is being tested for vaccine delivery [6]. The company holds more than 20 unique microneedle related patents including designs, fabrication methods, and various insertion tools. In 2002, Park et al. introduced biodegradable polymer microneedles [7].

Hollow Microneedle Arrays

In contrast to solid microneedles, hollow needles offer the possibility of active injection of the drug into the tissue. 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. Additionally, pressure-driven delivery adds the possibility to precisely steer the flow rate and to obtain a more controlled delivery. In 2000, Stoeber and Liepmann presented another type of hollow silicon microneedles [8, 9]. The fabrication of these 200 _m long needles starts by etching the needle bores from the backside of the silicon wafer using DRIE. The needle structures are then etched from the front side of the wafer by isotropic dry etching (figure 5).In a later study, the needles were tested by delivery of methyl nicotinate (a vasodilating agent) into human subjects [10]. Microneedle chips featuring a few needles were mounted on a standard 1 ml syringe and pressed against the subject's volar forearm while injecting. It was estimated that approximately 1 _l (0.1 M concentration) was injected during the 30 s administration period. Pharmacodynamical results showed a significant increase in blood flux after delivery through pointed microneedles (figure5a) while the increase for flat-tipped microneedles (figure 5b) was not statistically significant. However, the onset was significantly faster for both needle types as compared to the topical-delivery control.



(a) (b)

Fig. No. 05: [12](a) 350 _m long silicon microneedle by Gardeniers et al., etched by combining DRIE and wet etching. (b) Microneedles made in PMMA by Moon and Lee, using LIGA techniques.

After nearly a decade of microneedle research, a few trends can be noted. First, as the field has become more mature, more relevant and more adequate experimental evaluations are being performed, including *in vivo* trials. Second, the lengths of the needles are longer. Third, the material choice is more diverse and polymer needles are gaining more ground. To achieve skin penetration, some groups make use of an impact applicator or a special insertion device. While hollow microneedles have become more frequent in recent years, several groups actively work and develop delivery techniques for solid microneedles.

Applications of microneedle technology

Microneedle technology has been developed as a technique for delivery of high molecular mass and water soluble compounds through the skin (Table 1). The first ever study of transdermal drug delivery by microarray technology was conducted by Henry *et al* [11] who demonstrated an increase in the permeability of skin to a model compound calcein using microarray technology. In a follow up study, Mc-Allister *et al* [12] found a change in the permeability of cadaver skin to insulin, latex nanoparticles and bovine serum albumin after treatment with microneedles, and unleashed the mechanism of transport as simple diffusion.

Table No. 01: Applications of Microneedle technology

Type of drug	Example
Genetic material	Plasmid DNA, Oligonucleotides
Peptides	Insulin, Desmopressin
Vaccines	Japanese encephalitis, Anthrax, Hepatitis B

Oligonucleotide delivery

Lin and coworkers [13] extended the *in vitro* findings of microarray drug delivery to *in vivo* environment. Anoligonucleotide, 20-merpho-sphorothioated oligodeoxynucleotide was delivered across the skin of hairless guinea pig either alone or in combination with iontophoresis. Lin and coworkers used solid microneedles etched from stainless steel or titanium sheet prepared with the poke with patch approach. This delivery system increased the absorption of the molecules relative to the intact skin. Iontophoresis combined with microneedles was able to increase the transdermal flux by 100 fold compared to the ion tophoresis alone.

DNA vaccine delivery The cells of Langerhans present in the skin serve as the first level of immune defense of the body to the pathogensinva ding from the environment. These cells locate the antigens from the pathogens and present them to Tlymphocytes, which in turn stimulate the production of antibodies. Mikszta *et al* [14] reported the delivery of a DNA vaccine using microneedle technology prepared with the dip and scrape approach. The arrays were dipped into a solution of DNA and scrapped multiple times across the skin of mice *in vivo.* Expression of luciferase reporter gene was increased by2800 fold using micro enhancer arrays. In addition, microneedle delivery induced immune responses were stronger and less

variable compared to that induced by the hypodermic injections. Similar results were obtained by researchers at Beckett- Dickinson™ in an animal study for antibody response to Hep.B naked plasmid DNA vaccine. This approach has a potential to lower the doses and the number of boosters needed for immunization.

Desmopressin delivery

M. Cormier *et al* [15] (Alza Corporation, USA) examined the use of microneedles to deliver desmopressin, a potent peptide hormone used in the treatment of nocturnal enuresis in young children, as well as for the treatment of diabetes insipidus and haemophilia A. Microneedles were coated by an aqueous film coating of desmopressin acetate on titanium microneedles of length 200 µm, a maximal width of 170 µm and a thickness of 35 µm. Microneedle patch was inserted into the skin with the help of an impact applicator. A target dose of 20 µg of desmopressin was delivered to hairless guinea pig from 2 cm^2 microneedle array within 15 minutes. This study demonstrated that the transdermal delivery of desmopressin is safe and efficient alternative to the currently available routes of administration.

Insulin delivery

Insulin is one of the most challenging drug of all times for the drug delivery technologists. Martano *et* al [16], used microarrays for the delivery of insulin to diabetic hairless rats. Solid microneedles of stainless steel having 1mm length and tip width of 75µm were inserted into the rat skin and delivered insulin using poke with patch approach. Over a period of 4 hours, blood glucose level steadily decreased by as much as 80% with the decrease in glucose level being dependent on the insulin concentration.

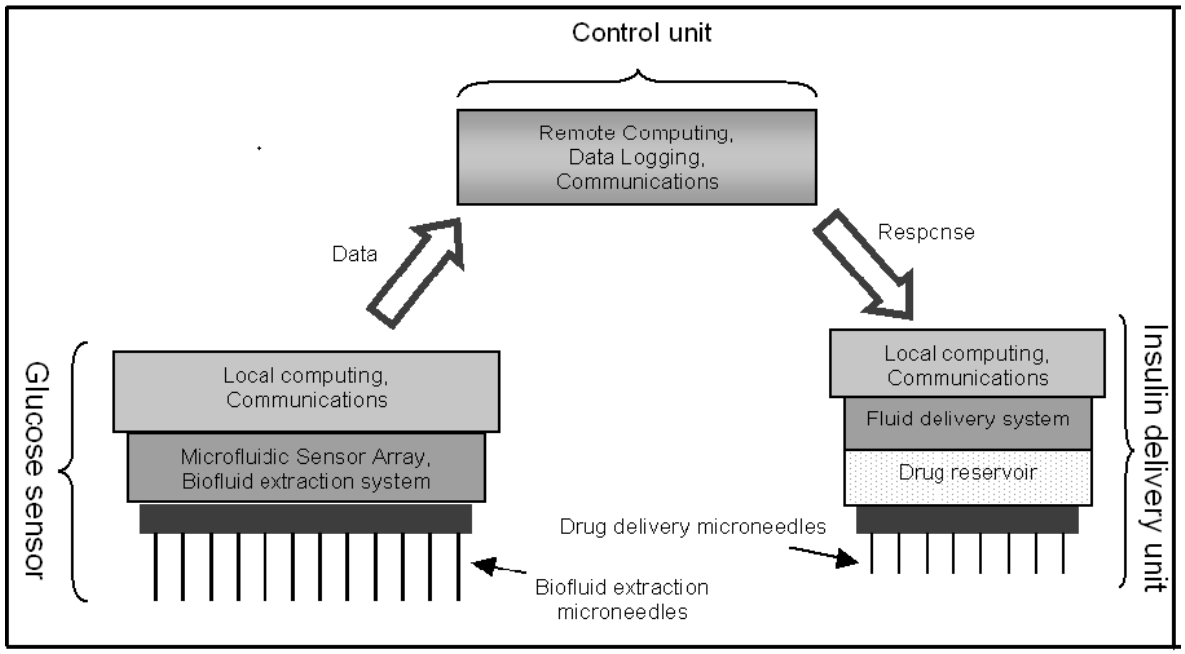


Fig. No. 06: Elements of the prototypical microneedle-based autonomous diabetes therapy system.

Currently autonomous insulin therapy systems that automatically monitor the glucose levels and intermittently inject the requisite amount of insulin at appropriate times are being developed using microneedle based transdermal drug delivery. As shown in the above figure.

Commercial Microneedle Technologies

Number of Micro needle based drug delivery devices and systems are being developed commercially. The table below provides an over view of these systems in market. Few important of these systems are explained in this section.

Table No. 02: Representative list of advanced microneedle based drug delivery technologies

Name of the technology	Manufacturer	Available drug products	Drug products in development
h-patch	Valeritas	Bolus insulin delivery system	-
Macroflux	Zosano Pharma	None	PTH patch, Vaccines, Proteins
Micro-Trans	Valeritas	None	Fluid sensing of glucose, hormones blood gases, Vaccines, Proteins
Microinfusor	BD	None	Vaccines, Macromolecules
Microstructured transdermal system	3M	None	Hydrophillic molecules, Macromolecules
Micropiles	Texmac-Nanodes	10% Lidocaine and Indomethacin	-
Microneedle Thrapy System	Clinical resolution lab	Microneedle Dermaroller	-

Macroflux®

Macroflux® technology is another novel transdermal drug delivery system that ALZA Corporation has developed to deliver biopharmaceutical drugs in a controlled reproducible manner that optimizes bioavailability and efficacy without significant discomfort for the patient. The system is now owned by Zosano Pharma and is being tested for PTH delivery and is in Phase 2 trials. The system incorporates a titanium microprojection array that creates superficial pathway through the skin barrier layer to allow transportation of therapeutic proteins and vaccines or access to the interstitial fluids for sampling. Macroflux® has an area of up to 8cm^{2}and contains as many as 300 microprojection per cm^2 with individual micro projection length being < 200µm. The maximal adhesive patch size is 10 cm^2. A coating process is used to apply drug to the tip of each microprojection in the array. When the patch is applied to the skin, the drug-coated microprojections penetrate through the skin barrier layer into the epidermis. The microcapillaries for systemic distribution absorb the drug. The rate of absorption is promoted by the high local drug concentration around the microprojections and the large surface area provided by the patch array.[17] Three types of Macroflux ® have been designed and tested in preclinical studies. They include,

• *Dry-Coated Macroflux* ® system for short duration administration that consists of a drug coated microprojection array adhered to a flexible polymeric adhesive backing.

• *D-TRANS® Macroflux® system* for short duration administration that consist of a microprojection array coupled with a drug reservoir.

• *E-TRANS® Macroflux* ®system for pulsatile oron demand delivery that include a microprojection array coupled with an electrotransport system.[18]Therapeutic peptides, proteins and vaccines such as desmopressin, human growth hormone(HGH), TH 9507 (a human growth hormone releasing factor analog), ovalbumin(45000 Daprotein) are in the developmental stage for transdermal delivery by Macroflux® [19]

Metered-Dose Transdermal Spray (MDTS)

Metered-dose transdermal spray (MDTSTM),originally developed at the Victorian College of Pharmacy [Monash University (Parkville Campus), Parkville, Victoria, Australia] and currently being commercialized by Acrux Limited[Melbourne, Victoria, Australia] has the

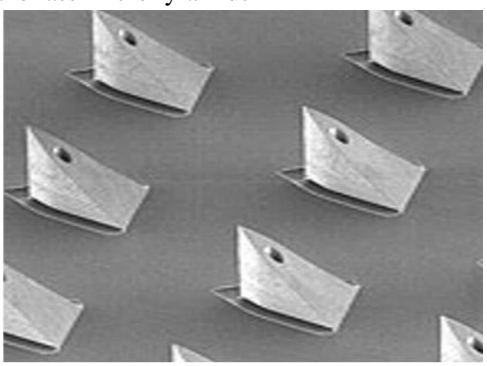
potential to expand the growth of TDD systems by broadening patient acceptance and pharmaceutical applications for enhanced TDD.MDTS relies on the combination of a newly identified GRAS (generally recognized as safe)chemical penetration enhancer (AcrossTM) and the accurate and precise topical dosing of avolatile: nonvolatile vehicle. This MDTS can be classified, as an enhanced, passive TDD system.[18] It is a topical solution made up of avolatile cum nonvolatile vehicle containing thedrug dissolved as a single-phase solution. Afinite metered - dose application of the formulation to intact skin results in subsequent evaporation of the volatile component of the vehicle, leaving the remaining nonvolatile penetration enhancer and drug to rapidly partition into the stratum corneum during the first minute after application, resulting in a stratum corneum reservoir of drug and enhancer.[20]Following a once daily application of the MDTS, a sustained and enhanced penetration of the drug across the skin can be achieved from thestratum corneum reservoir. Different types of penetration enhancers, such as ethanol and azone, are commonly used.[21] Clinical experience with estradiol-MDTS to post-menopausal women have shown increased higher plasma level of estradiol than the baseline value measured by radioimmunoassay. The MDTS has the following potential advantages:

1. Enhanced passive TDDS with little or no skin irritation primarily as a result of its non occlusive nature.
2. Improved cosmetic acceptability.
3. Dose flexibility. 4. Simplicity of manufacture.

NanoMAP Technology

NanoMAPs are polymer patches that are surface structured, with solid microneedles that are specifically designed to penetrate the stratum corneum. These provide a controlled, direct mechanism of delivery to the underlying tissue. The density of microneedles of each Nano MAP lies in the range of 100–1,000 per square centimetre, depending on the loading of the nanoparticles required. The length of the microneedles is between 100 and 250 μm, depending on the site of application, and their thickness and shape are optimized for penetration and loading. NanoMAPs can be designed for either short-term bolus delivery or sustained release. Drugs are incorporated into the NanoMAP polymer matrix, so that application to the skin results in a slow release of drugs from both diffusion and polymer dissolution.

NanoPass MicroPyramids



Micro Pyramids are manufactured by MEMS (Micro Electro Mechanical Systems) technology and are made of pure silicone crystals. MEMS technology has enabled the creation of elaborate miniature devices with unprecedented mechanical stability and structural precision. NanoPass MicroPyramid arrays are manufacture in industrial clean room, in a high-precision production process, with a very high yield. Based on its MicroPyramid technology, NanoPass currently develops hollow microneedles for intradermal injections and solid Microprojections for cosmetic enhancement.

Nanopass MicronJet

The MicronJet needle is a MicroPyramid-based device for direct intradermal delivery. Mounted on a standard syringe instead of a conventional needle, the MicronJet can be used to inject virtually any substance allowing controlled intradermal delivery. The MicronJet is ideal for intradermal administration of drugs, proteins and vaccines, and requires minimal performer expertise.

MTS Roller™

At the heart of Microneedle Therapy System (MTS) is patented MTS Roller™ – a unique 'Type I' FDA-approved supplemental medical tool that is ideal for non-surgical and non-ablative treatment of various skin conditions suchas aging (wrinkles, stretching), scarring (acne,surgical), and hype rpigmentation. Clinical studies have shown MTS (microneedle therapy system) to be more effective than ablative treatments like laser resurfacing, dermabrasion, and chemical peel and just as effective as non-ablative treatments like IPL, CO2 laser, and Fraxelin stimulating collagen and elastin production to thicken the skin thereby erasing wrinkles and soothing scars.

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