

A novel approach towards drug delivery systems: Microneedles

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ABSTRACT

Demand for a painless method of delivering macromolecular compounds is on the rise. However, large-molecule drugs typically cannot be administered in the oral tablet form patients and doctors prefer. In addition to the molecular weight being too high to enter the bloodstream from tablet ingestion, the body's digestion process would dilute the drug potency to a level of inefficacy. Microneedles are long and robust enough to penetrate across the barrier, but short enough to prevent nerve stimulation which projections of solid silicon or hollow drug-filled metal needle which are fabricated in several shapes and sizes

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KEYWORDS

Microneedles,
solid silicon,
metal needle.

INTRODUCTION

When oral administration of drugs is not feasible due to poor drug absorption or enzymatic degradation in the gastrointestinal tract or liver, injection using a painful hypodermic needle is the most common alternative. An approach that is more appealing to patients, and offers the possibility of controlled release over time, is drug delivery across the skin using a patch (transdermally)^[1,2]. Transdermal delivery is severely limited by the inability of the large majority of drugs to cross skin at therapeutic rates due to the great barrier imposed by skin's outer stratum corneum layer.

A novel approach which involves creating larger transport pathways of microns dimensions (size) using arrays of microscopic needles. These pathways are bigger than molecular dimensions and, therefore, should readily permit transport of macromolecules, as well as possibly supramolecular complexes and micro-particles. Despite their very large size relative to drug dimensions,

on a clinical length scale they remain small

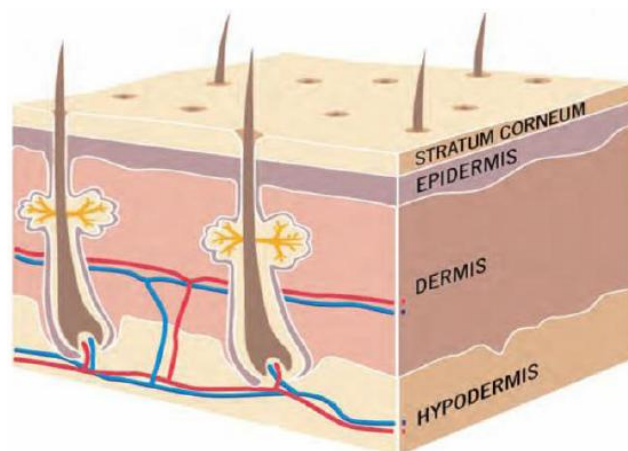


Figure 1 : Structure of skin

To increase skin permeability, a number of different approaches has been studied, ranging from chemical/lipid enhancers^[3,4] to electric fields employing iontophoresis and electroporation^[5,6] to pressure waves generated by ultrasound or photoacoustic effects^[7,8]

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All the mechanisms are different; these methods share the common goal to disrupt stratum corneum structure in order to create big enough space for molecules to pass through.

The size of disruptions generated by each of these methods is believed to be of nanometres dimensions (size/space), which are sufficient enough to allow the transport of small drugs and, macromolecules, but probably should be small so that enough to prevent causing damage of clinical significance. Despite their very large size relative to drug dimensions, on a clinical length scale they remain small. Although it is suggested that safety studies need to be performed because it is stated that micron-scale holes in the skin are likely to be safe, given that they are smaller than holes made by hypodermic needles or minor skin abrasions encountered in daily life^[9].

The Microneedles concept was proposed in the 1970s^[10], it was not demonstrated experimentally until the 1990s when the microelectronics industry provided the micro fabrication tools needed to make such small structures. Since the first studies of transdermal drug delivery in 1998^[11], there has been rapidly increasing interest in the field, with most activity in the micro fabrication community to develop novel needle fabrication technologies and the drug delivery industry to develop microneedles for pharmaceutical applications.

MICRONEEDLE DRUG DELIVERY SYSTEMS

Microneedles can range from 100 to 1000 μm in length, with a tip diameter of 15 μm to 400 μm in diameter at the base. They can be solid or hollow, and configured in NxN arrays as required.

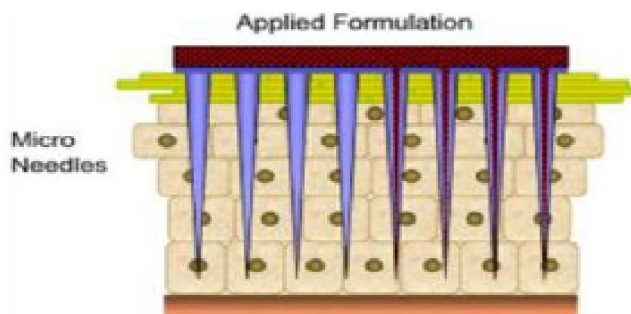


Figure 2 : Microneedle

The stratum corneum layer of skin is approximately 15-20 μm in thickness. Microneedle drug delivery systems

are designed to penetrate the stratum corneum to facilitate delivery of both small- and large-molecule drugs. Upon entering the skin, the compounds can rapidly diffuse through deeper tissue before absorbing into underlying capillaries. Since microneedles don't impinge on the nerve fibers and blood vessels in the dermal layer, they don't cause the anxiety, pain or bleeding associated with IVs or syringe injections that can adversely affect compliance among patients requiring frequent injections.

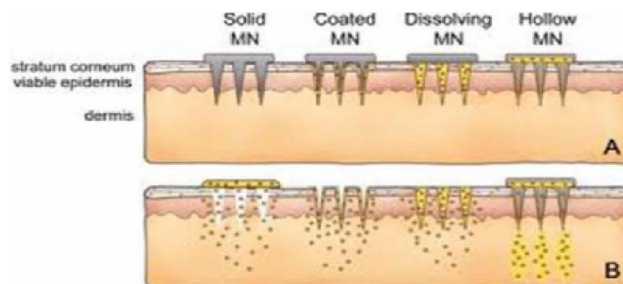


Figure 3 : Applied formulation

Microneedle drug delivery systems feature microneedles that can painlessly penetrate the uppermost layer of the skin called the stratum corneum. Capillaries and blood vessels then absorb the macromolecular drug for distribution throughout the body. The objective of microneedle drug delivery is to administer medicines or vaccines to the epidermis and dermis. However the thin top layer of skin, the stratum corneum, provides a significant and difficult barrier for the medicines to overcome. Large-molecule drugs can't successfully bypass the protective layer of packed, dead skin cells without help. An innovative, active method of drug delivery is required. The use of microneedles in drug-delivery systems is presently under review by the Food and Drug Administration (FDA). Once approved, microneedle drug delivery systems could potentially combine the effectiveness of delivery associated with syringe injections with the comfort and convenience of a less invasive delivery method.

The technology shows promise in allowing for:

- 1 Less pain, as the needles that are micro in scale do not penetrate past the epidermis
- 2 Simple medication administration, possibly by patients themselves, which enhances patient comfort, compliance and quality of life
- 3 Enhanced drug efficacy, resulting in reduced drug usage
- 4 Enhanced treatment safety, simplicity, and cost ef-

fectiveness

5 Less bio-hazardous sharp medical waste

In addition to administering medication, possible microneedle applications include vaccines, such as flu shots, and potentially interstitial fluid sampling for blood glucose monitoring.

PREPARATION OF MICRONEEDLES

Micro molding microneedles^[12]

Pharmaceutical and manufacturing companies are investing millions of dollars to design and develop effective methods of bypassing the top layer of skin as well as the supporting manufacturing machinery and technology to enhance drug delivery.

There are several competing solutions for manufacturing microneedles under development in the marketplace, such as laser etching and deposition modeling. Micro moulding allows for accurate and easy-to-manufacture devices that are scalable for small- to large-volume production. It also opens the door for small, complex, and innovative geometries e.g., microneedles could be cone or wedges shaped, have varied surfaces and feature within the flat sides, or incorporate unique tip geometries.

Types of microneedle

Microneedle drug delivery systems may include either solid, hollow, Semi Hollow and Dissolved microneedles. Microneedle materials can range from metals to ceramics, or engineered plastics. Solid microneedles are typically coated with powder forms of drugs for absorption into the dermis. Hollow microneedles, in contrast, are capable of delivering liquid drug formulations.

Mechanism of action

The temporary mechanical disruption of the skin and the placement of the drug or vaccine within the epidermis, where it can more readily reach its site of action. Temporary mechanical disruption of the skin. The biomolecules form of drug is encapsulated within the microneedles, which are then inserted into the skin and drug is released into the bloodstream from a patch. The needles dissolve within minutes, releasing the trapped cargo at the intended delivery site. There is no need to be removed and no dangerous or bio-hazard-

ous substance is left behind on the skin, as the needles

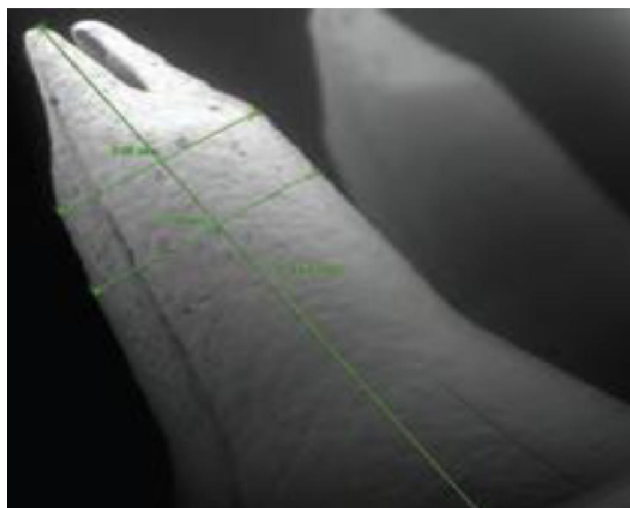


Figure 4 (a) : Hollow microneedle

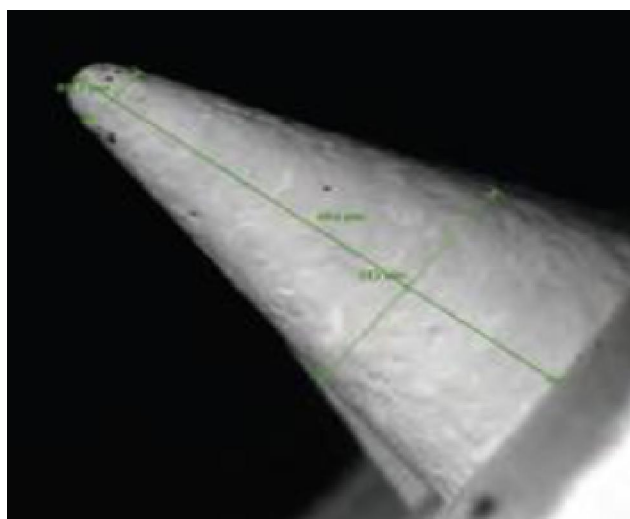


Figure 4 (b) : Solid microneedle

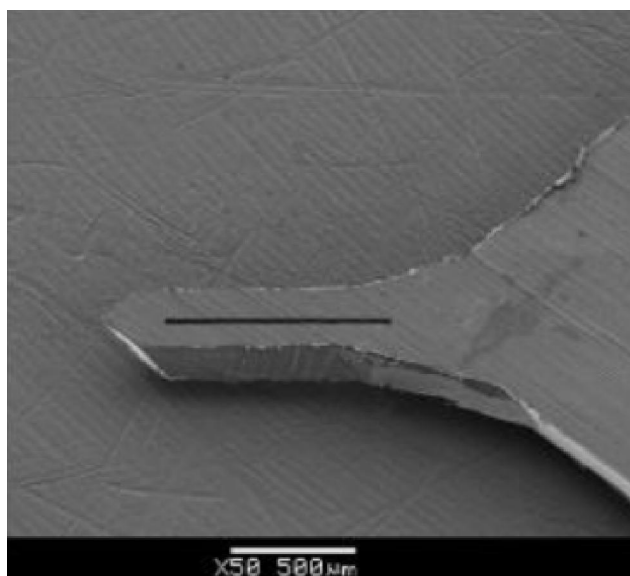


Figure 4 (c) : Semi hollow microneedle

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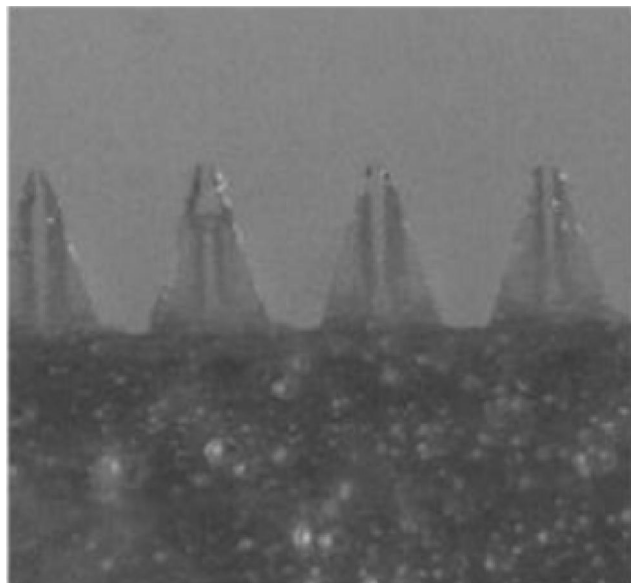


Figure 4 (d) : Dissolve microneedle

are made of a biodegradable substance.

A small area of patch is covered by hundreds of microneedles that pierce only the *stratum corneum*, thus allowing the drug to by pass this important barrier (Figure 5). The tiny needles are constructed in arrays to deliver sufficient amount of drug to the patient for the desired therapeutic response^[13].

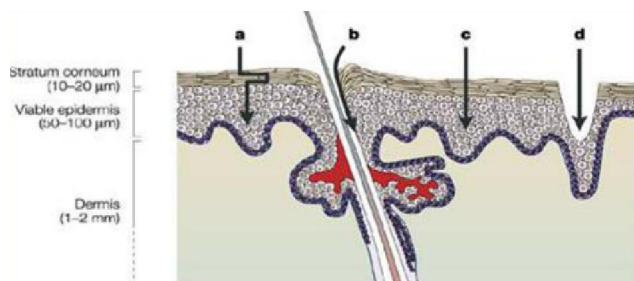


Figure 5 : Mechanism of action

VARIOUS TECHNIQUES INVOLVED IN MICRONEEDLE DRUG DELIVERY SYSTEM^[14,15]

1. Poke with patch approach
2. Coat and poke approach
3. Biodegradable microneedles
4. Hollow microneedles
5. Dip and scrape

Poke with patch approach

This technique involves piercing an array of solid microneedles into the skin followed by application of the drug patch at the treated site. These results in trans-

port of drug across skin can occur by diffusion or possibly by iontophoresis if an electric field is applied.

Coat and poke 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. Biodegradable microneedles It involves encapsulating the drug within the biodegradable, polymeric microneedles, followed by the insertion into the skin for a controlled drug release.

Hollow microneedles

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

Dip and scrape

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. The arrays were dipped into a solution of drug and scraped multiple times across the skin of mice in vivo to create micro abrasions. Unlike microneedles used previously, this study used blunt-tipped microneedles measuring 50– 200 μm in length over a 1 cm^2 area.

ADVANTAGES OF MICRONEEDLES

The major advantages of microneedles over traditional needles are as follows:

1. When inserted into the skin it does bypass the stratum corneum. Which Conventional needles pass this layer of skin and may effectively transmit the drug but results in infection and pain. As for microneedles they can be fabricated to be long enough to penetrate the stratum corneum, but short enough not to puncture nerve endings. Thus reduces the chances of pain, infection, or injury^[16].
2. Fabricating these needles on a silicon substrate because of their small size, thousands of needles can be fabricated on single unit. This leads to high accuracy, good reproducibility, and a moderate fabrication cost.
3. Hollow like hypodermic needle; solid— increase permeability by poking holes in skin, rub drug over area, or coat needles with drug

4. Arrays of hollow needles could be used to continuously carry drugs into the body using simple diffusion or a pump system.
5. Hollow microneedles could be used to remove fluid from the body for analysis – such as blood glucose measurements – and to then supply micro litre volumes of insulin or other drug as required^[17]
6. Immunization programs in developing countries, or mass vaccination or administration of antidotes in bioterrorism incidents, could be applied with minimal medical training.
7. Very small microneedles could provide highly targeted drug administration to individual cells.
8. These are capable of very accurate dosing, complex release patterns, local delivery and biological drug stability enhancement by storing in a micro volume that can be precisely controlled.

DISADVANTAGES OF MICRONEEDLES

1. The needles made of silicon after removing if left under the skin may create problems
2. The needles are very small and much thinner compared to the diameter of hairs, so the microneedle tip may be broken off and left under the skin. This may lead to several problems
3. Skin irritation or allergy may result if the skin is sensitive
4. The designs of needle are very difficult to apply on skin, therefore proper application is needed
5. Self administration is difficult

APPLICATION OF MICRONEEDLE TECHNOLOGY

DNA vaccine delivery^[14,15]

The cells of Langerhans present in the skin serve as the first level of immune defence of the body to the pathogens invading from the environment. These cells locate the antigens from the pathogens and present them to T-lymphocytes, which in turn stimulate the production of antibodies. Mikszta *et al* 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 by 2800

fold using microenhancer 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 HepB naked plasmid DNA vaccine 3. This approach has a potential to lower the doses and the number of boosters needed for immunization.

Oligonucleotide delivery^[14,15]

Lin and co-workers extended the *in vitro* findings of microarray drug delivery to *in vivo* environment. An Oligonucleotide, 20-merphosphorothioated oligodeoxynucleotide was delivered across the skin of hairless guinea pig either alone or in combination with iontophoresis. Lin and co-workers 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 iontophoresis alone.

Desmopressin delivery^[14,15]

M. Cormier *et al* (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 cm² microneedle array within 15 minutes

Insulin delivery

Insulin is one of the most challenging drugs of all times for the drug delivery technologists. Martano *et al*¹⁰, used microarrays for the delivery of insulin to diabetic hairless rats. Solid microneedles of stainless steel having 1mm length and tip width of 75 µm were inserted into the rat skin and delivered insulin using poke with patch approach. Over a period of 4 hours, blood

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glucose level steadily decreased by as much as 80% with the decrease in glucose level being dependent on the insulin concentration.

Porphyryn precursor 5-Aminolevulinic acid (ALA) delivery

Photodynamic therapy of deep or nodular skin tumours is currently limited by the poor tissue penetration of the Porphyryn precursor 5-aminolevulinic acid (ALA). Ryan F. Donnelly and co workers have shown that, *in vivo* experiments using nude mice showed that microneedle puncture could reduce application time and ALA dose required to induce high levels of the photosensitiser protoporphyrin IX in skin. This clearly has implications for clinical practice, as shorter application times would mean improved patient and clinician convenience and also that more patients could be treated in the same session.

In vitro transdermal delivery of monoclonal antibody

In all the previously mentioned studies, purified human IgG was used as a model drug for large proteins in transdermal delivery, and later the feasibility of microneedle-mediated transdermal delivery was further investigated using a human monoclonal antibody IgG to demonstrate the applicability of this technique for delivery of macromolecules.

Cellular delivery^[25]

The delivery of membrane-impermeable molecules into cells is needed for a broad variety of applications in molecular and cell biology. Molecules of interest include peptides, proteins, Oligonucleotide, DNA, and a variety of other probes that alter or assay cell function. Currently available methods for introducing molecules into cells can be divided into four categories:

- Chemical (e.g. ATP, EDTA, DEAE dextran etc)
- Vehicles (e.g., Erythrocyte fusion or Vesicle fusion)
- Electrical (e.g., Electroporation)
- Mechanical (e.g. Microinjection, Hyposmotic shock, sonication, micro projectiles)

In many ways, microinjection is the gold standard method for loading cells. It can reproducibly deliver large number of macromolecules to most cell types with high cell viability and function^[18]. However, because this technique involves injecting cells at a time with individual glass micropipettes, it is extremely labour inten-

sive and is practical only when treating small number of cells (e.g. <100 cells). To make microinjection simpler and faster, it is suggested to perform microinjection simultaneously on thousands of cells or more, with arrays of densely spaced microneedles. With multiple needles arranged in a high-density array, many cells can be treated at one time, which overcomes the major limitation of microinjection.

Local tissue delivery^[25]

Conventional drug delivery often involves administering medication systemically, thereby treating the desired region of the body, but also exposing other parts of the body to the drug, which can have detrimental effects. Drug delivery targeted to a precise region in the body can reduce side effects, minimize the dose of a costly drug, or provide a means of delivery to a location that is difficult to treat^[19]. Two novel devices have been discussed that deliver drugs to specific regions of tissue inside the body. Micro fabricated neural probes have been used to deliver drugs into neural tissue of guinea pigs *in-vivo*^[20] while simultaneously monitoring and stimulating neuronal activity. Microprobes have also been inserted across vessel walls of normal and atherosclerotic rabbit arteries *in-vitro*^[21].

Systemic delivery^[25]

In recent years, biotechnology has produced a battery of sophisticated and potent drugs. However, methods to effectively deliver these drugs into the body have limitations^[22,23]. Oral delivery of the new protein based, DNA-based and other therapeutic compounds is generally not possible owing to drug degradation in the gastrointestinal tract/ or elimination by the liver. The usual alternative to oral delivery is via injection, either directly into the bloodstream or into tissues (e.g subcutaneous or intramuscular injection). Although injection effectively delivers drug in large quantities, it has significant limitations, such as pain and trauma caused by the needle, failure to provide convenient controlled or sustained release, and the need to expertise to perform an injection. To overcome these limitations microneedles have been designed in such a way that by decreasing the size of hypodermic needles, insertion pain and tissue trauma experienced by patients can be reduced. Also, the combination of these needles with micropumps and other devices can yield more sophisticated needles

that can potentially deliver drugs in a more controlled manner^[24].

RECENT ADVANCEMENT IN MICRONEEDLE DRUG DELIVERY SYSTEM

DNA vaccination in the skin using microneedles improves protection against influenza^[26]

DNA vaccination in the skin using microneedles improves protective immunity compared to conventional intramuscular (IM) injection of a plasmid DNA vaccine encoding the influenza hemagglutinin (HA). A reporter gene delivered to the skin using a solid microneedle patch coated with plasmid DNA. Vaccination at a low dose (3 µg HA DNA) using microneedles generated significantly stronger humoral immune responses and better protective responses post-challenge compared to IM vaccination at either low or high (10 µg HA DNA) dose. Vaccination using microneedles at a high (10 µg) dose further generated improved post-challenge protection, as measured by survival, recall antibody-secreting cell responses in

spleen and bone marrow, and interferon (IFN)-γ cytokine T-cell responses. DNA vaccination in the skin using microneedles induces higher humoral and cellular immune responses as well as improves protective immunity compared to conventional IM injection of HA DNA vaccine.

Microneedle skin therapy^[27]

Microneedle skin therapy is still in testing development, but it seems to show much promise. Microneedle therapy is a way to rejuvenate the skin without destroying the epidermis. It is similar to laser treatments but with less damage. Companies like the Clinical Resolution Lab utilize treatments using microrollers^[28]. Microneedles penetrate the epidermis and break away old collagen strands. The only disadvantage of this method is that it causes blood oozing, which laser treatments do not. It does the collagen strands that are destroyed create more collagen under the epidermis. This leads to youthful looking skin. However have advantages such as: increased collagen, non sun-sensitivity upon treatment, no breaking of the epidermis, lower cost, and ease of application.

TABLE 1 : List of the technology used with the manufacture and the drug products.

Sr. No.	Technology name	Manufacturer	Available drug products	Drug products in Development
1	Macroflux	Alza	None	PTH patch, Vaccines, Proteins
2	h-patch	Valeritas	Bolus insulin delivery	-
3	Microinfusor	BD	None	Vaccines, Macromolecules
4	Micro-Trans	Valeritas	None	Fluid sensing of glucose, hormones, blood gases, Vaccines, Proteins
5	Microstructured transdermal system	3M	None	Hydrophilic molecules, Macromolecules
6	Micropiles	Texmac-Nanodes	10% Lidocaine and Indomethacin	-
7	Micro Needle Therapy System	Clinical resolution lab	Microneedle Dermaroller	-

CONCLUSION

In this review, we suggest that Micro-technology based Transdermal Delivery System by using Microneedles is a Novel Approach for Drug delivery system. It is a convenient, painless, and less invasive alternative to injection & it can be used a common method for administering large proteins and peptides, antibiotics, vaccines in low manufacturing cost. This technology overcome the first pass metabolism effect and

offers the benefit of immediate cessation of drug administration in case of an adverse effect or overdose which is the major limitation of oral drug delivery system. There is also no molecular size limitation, no molecular electrical charge requirement, and no specific formulation pH constraint. In contrast to conventional TDSS, this can also be using for potent & less potent the drug, the more extended release the delivery system. The drug delivering ratio can be increased when use the longer needle because the surface area with drug sticking can be increased.

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