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Recent Advanced of Fabrication Techniques and Application of Micro-Needle

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ABSTRACT

Micro-needles are micron-scaled medical devices used to administer vaccines, drugs, and other therapeutic agents. Micro-needles typically measure 0.1–1 mm in length. A variety of materials such as silicon, ceramic, stainless steel and polymers have been used for fabrication. Micro-needles devices are compatible with the delivery of both Small and macromolecular therapeutics. Micro-needles (MNs) are currently being utilized to enhance transdermal delivery of small and large molecules. With the emergence of micro fabrication manufacturing technology over the past several decades, (MNs) have been developed by academic laboratories and pharmaceutical companies. Micro-needle has useful in application in diseases such as type 2 Diabetes, cancer treatment, Glaucoma, and also useful application in cosmetic, vaccine therapy. The present article provides an overview of micro-needle, fabrication technique, general properties, Material and methods of fabrication techniques, application and advantages and disadvantages of micro-needle drug delivery system. Micro-needles (MNs) are currently being utilized to enhance trans-dermal delivery of small and large molecules. With the emergence of micro fabrication manufacturing technology over the past several decades, have been developed by academic laboratories and pharmaceutical companies.

Keywords: Micro-Needle, Derma-roller, Hydro-gel Forming, Micro-Fabrication, Transdermal drug delivery system.

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INTRODUCTION:

The micro-needles (MNs) have been studied by various researchers for delivering drug through the trans-dermal route and for overcoming the limitations of the Conventional approaches [1]. Among transdermal drug delivery systems, micro-needles (MNs) are gaining attention for their cost-effective strategy and application with delivery at the deeper dermal layer in the management of Pain [2]. Currently, micro-needles products available in the Market, of which majority are dedicated for skin care and cosmetics include Derma-roller, micro-hyala, liteclear, ms-4, mf-8, c-8, and cit-8 [3]. Micro-needles (MNs) are currently being utilized to enhance trans-dermal delivery of small and large molecules. With the emergence of micro fabrication manufacturing technology over the past several decades, have been developed by academic laboratories and pharmaceutical companies [4]. The main process of drug delivery through the skin is passive diffusion, either by Intracellular route (the drug is dissolved in the lipidic matrix where the coenocytes are embedded) or by trans-cellular route [7]. The problem of poor drug transport can be addressed by development of micron-sized Needles, which deliver the drug painlessly across the stratum corneum [8]. However, the drug administered orally can Be extensively degraded in the liver or GI tract before reaching to systemic circulation (first-pass metabolism), issue of patient compliance where there is need for repeated dose administration and missed or erroneous multiple dosing increases the safety concerns [9]. While the needles are small, their ability to puncture the skin nevertheless renders them a potential sharps risk and their handling and disposal requires more than a modicum of caution [10]. Recent investigation on trans-dermal drug delivery systems is regarded as an effective method with magnificent patient acceptance for the management of pain. It is a non-invasive drug delivery system. As an alternative to invasive and painful hypodermic injections, a micro needle (MNs) drug delivery system is an attractive and effective method to provide painless self-administration of various drugs. The micro-channels created by piercing the skin using MNs may increase the permeability and absorption of the drugs [14]. Micro-needles (MNs) technology has been developed to provide patches with micron-sized projections (up to 1000 lm long) able to pierce the skin and overcome the SC barrier [47]. Micro needles with lengths ranging from 100–1500 µm can easily penetrate the stratum corneum, meaning that the number of drugs amenable for delivery using a micro-needle system is much higher [51]. MNs are arrays consisting of multiple micro-needles projections (ranging from 50-900 µm in height). Their micron scale allows them to successfully bypass the SC, without stimulating nociceptors (pain receptors) in the under lying epidermal/dermal tissue layer [52]. A particular advantage of MNs technology is that drug substances with high molecular weights and/or very water-soluble drugs can be efficiently delivered transdermally recently, there has been an increasing interest in investigating the influence of a variety of variables related to the use of micro-needles, in order to reach an optimum micro-needle design and, hence, improve MN-mediated trans-dermal drug delivery [53]. Polymeric micro-needle arrays have particular interest for the pharmaceutical industry, since they generally present good biocompatibility, degradability and mechanical properties. A reduced cost additionally, the disposal of these arrays does not generate any sharp waste, as they can be mechanically or chemically destroyed, or even dissolved by the interstitial fluid in the skin in the case of water-soluble polymers [54]. Transdermal drug delivery (TDD) systems deal with the movement of pharmaceutical compound through the skin to reach the systemic circulation for subsequent distribution in the human body. TDD systems consist of non-invasive and minimally invasive technologies for delivering drugs and vaccines across the skin [55].

Dimension of micro-needles:

The epidermis is up to 1500 µm thick so the needle length of up to 1500 µm is sufficient to release the drug into the epidermis. Mostly they are 150–1500 microns long, 50-250 microns wide, and have 1–25 microns tip thickness. Micro-needles tips be cylindrical, triangular, pointed, pentagonal, octagonal and are available in many more shapes [44].

Dimension of Micro-needle:

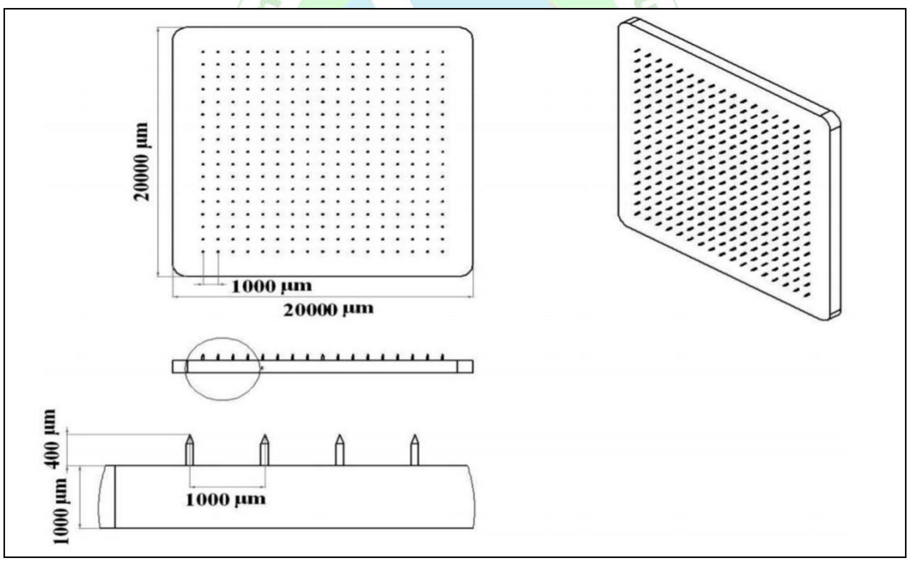

Figure 1: Dimension of Micro-needles.

Types of Micro-needle drug delivery system:

There are five basic types of micro-needles:

1. Micro-needles used for skin pre treatment rather than direct drug delivery,
2. Drug-coated micro-needles,
3. Polymer micro-needles that contain the drug and release it when they dissolve, and
4. Hollow micro-needles for liquid delivery into the skin
5. Hydro-gel forming micro-needles (MNs) are an array of sub millimeter sized needles (50-900 µm), minimally invasive means that bypass the stratum corneum (sc) and enables the transport of therapeutics into the epidermis [6].

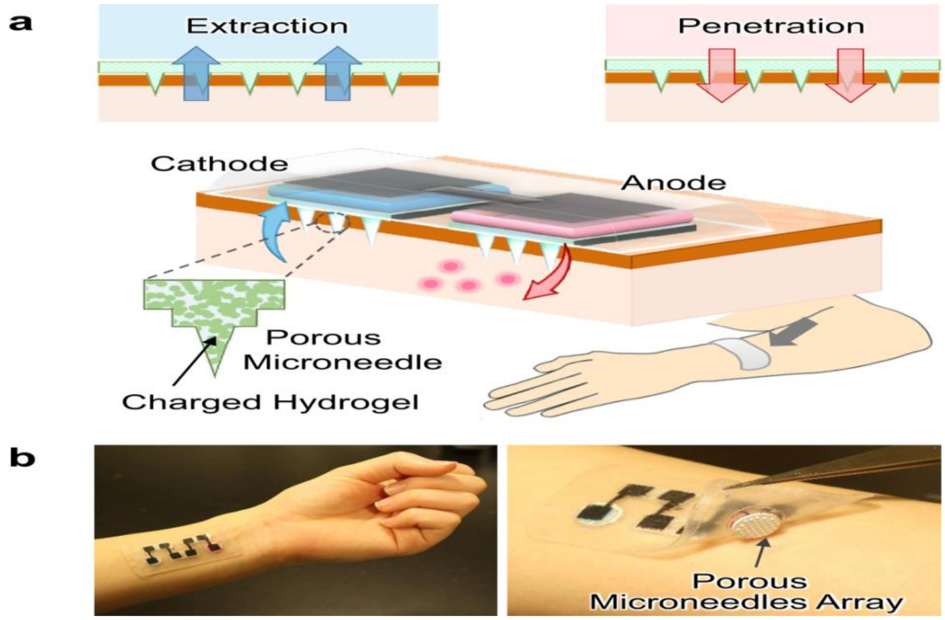

Figure: 2 Transdermal electro-osmotic flow generated by a porous micro-needle array patch.

1. Micro-needle:

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. micro-needle scan be prepare by coating with the drug and then inserted into the skin [12]. MNs delivers drugs via passive diffusion by creating micro channels to increase skin permeability followed by the application of a drug-loaded patch on the channels. From a safety perspective, it is desirable for the micro-channels to close soon after needle removal to prevent permeation of undesired toxic substances or infection by pathogenic micro-organisms [45].

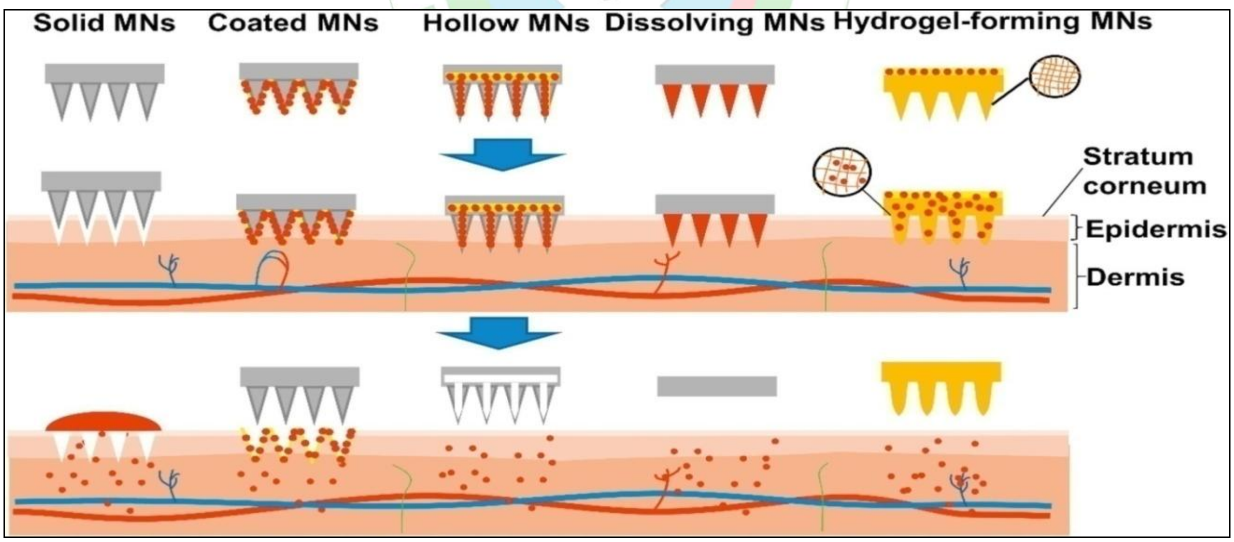

Figure 3: Types of Micro-needle Drug Delivery System

2. Coated Micro-needle:

Coated micro-needle drug solution is coated on the needle surface, minimally invasive; drug loading capacity depends on coating layer thickness and the needle size [13]. Coated micro-needles consist of micro-needles that have been coated with a drug solution or dispersion. There are various methods to produce coated micro-needles, including dip coating, in which the micro needles are "dipped" into the coating solution. Spray coating can also be used to coat the needle [42].

3. Hollow Micro-needles

Hollow micro-needles are designed with micro fluidic channels that disrupt the upper layers of the skin upon application creating micro-conduits to deliver liquid medications or extract biological fluids [11]. Hollow needles could eventually be used with drug patches and timed pumps to deliver drugs at specific times hollow micro-needles could also be used to remove fluid from the body for analysis such as blood glucose measurements and to then supply micro liter volumes of insulin or other drug as required [50].

4. Dissolved Micro-needle

Dissolving micro needles manufactured from safe materials, such as biodegradable polymers and natural polymers, can control the release of drugs or vaccine embedded in the polymer. That is, dissolving micro-needles controlling the release of encapsulated pharmaceutical agents are painless and safe in the application of disease diagnostics and treatment. Dissolving micro-needles were fabricated by micro-molding methodology at the room temperature [23].

5. Hydro-Gel Forming

Hydro-gel forming micro-needles is an array of sub millimeter-sized needles (50-900µm), minimally invasive means that bypass the stratum corneum and enables the transport of therapeutics into the epidermis [6]. Hydrogel-forming MNs arrays were prepared using laser-engineered silicone micro moulds manufactured, as described previously. The MNs arrays were comprised of 121 needles (11 × 11) having a needle height of 600 µm, base width of 300 µm and a base interspacing of 150 µm. The needles were conical shaped and each array had an approximate base area of 0.5 cm20 [28].

Fabrication Technique:

These techniques are used in isolation or combination to create implantable biomedical devices. Typically micro fabricated implants are developed in silicon or similar materials, due to ease of manufacturing. After proof of concept has been shown, the implant can then be modified to be cast in additional materials through techniques such as micro-molding [19]. Micro-molding is the most common fabrication technique for MNs. In this technique, negative elastomeric poly-di-methyl-siloxane (PDMS) molds are used for polymer casting to prepare MNs [47].

General Properties

In general, the micro-needles application aims to create a transport pathway for the delivery of therapeutic molecules, by passing the external barriers that limit the therapeutics penetration in the target tissue. Further, the micro-needles devices are compatible with the delivery of both small and macro molecular therapeutics such as small drugs (e.g. Doxorubicin), proteins (e.g. ovalbumin), genetic materials (e.g. Pdna and Sirna), or even nano medicines [20].

Material and Methods:

Silicon:

Silicon is an excellent material for micro-machining due to its crystalline nature which allows preferential etching to achieve very precise geometries, and to the use of long-established batch fabrication techniques developed by the semi conductor industry [13]. Micro-needle fabrication is based on the double sided etching of silicon wafers, and extends the single-sided process used for etching (hollow silicon micro-needles, fabricated using combined wet and dry etching techniques, for trans-dermal delivery and diagnostics [25].

Metal:

Stainless steel, titanium, palladium, nickel, platinum, alloys, and gold are the most often utilized metals in the manufacture of micro-needles. Metals are used to create , Hollow, and coated micro-needles as well as their basis [22]. Metals are also used for the fabrication of MNs, because some metals have outstanding mechanical strength and biocompatibility while noble metals usually work as sensitive components in a sensor. Some nano-structured metal materials can present catalytic activity. However, because of its sharp tip and strength, the used metal-based MNs must be carefully treated before being discarded as biohazardous waste [46].

Ceramic:

Due to their superior chemical properties and compression resistance, ceramic materials such as alumina have been used to fabricate MNs. However, alumina possesses a lower tensile strength compared to other materials. Calcium sulfate dihydrate and calcium phosphate dihydrate are additional types of ceramics utilized in the fabrication of MNs a micro-mold technique can be used to fabricate a MNs using ceramic material [21]. Ceramic material opens the possibility to produce as as well porous MNs, which can be easily loaded with liquid for drug delivery or diagnostic sampling. Although micro-molding of ceramic mechanical structures is broadly discussed in the literature as a low cost process [49].

Carbohydrates:

MNs can be prepared easily by molding hot melts/slurries of carbohydrate materials using silicon or metal MNs as master templates. Carbohydrates are good alternatives to the previously described materials, as they are cheap and, additionally, safe for the human health [28]. Carbohydrates, such as sugars, hyaluronic acid, cellulose, and chemically modified methacrylate hyaluronic acid, carboxyl-methylcellulose, are utilized alone, in a blend, or as a composite. They are similar to the extracellular matrix and are simply recognized and accepted by the human body [30].

Polymer Micro-needles:

Polymer materials are currently receiving more interest because of biocompatibility, superior mechanical properties, low material cost, and biodegradability. Different types of polymer have been used to manufacture polymer micro-needles in this category of process, including dissolving versions for drug delivery [33]. Polymers exhibit all forms of bloating or swelling and degradability, and further more responsively to stimuli of physical and biological elements. MNs which are derived from these polymers can control the physiochemical and pharmacokinetic principles of drug-related molecules, as well as skin performance, in a variety of biomedical applications [35].

Material used for fabrication techniques:

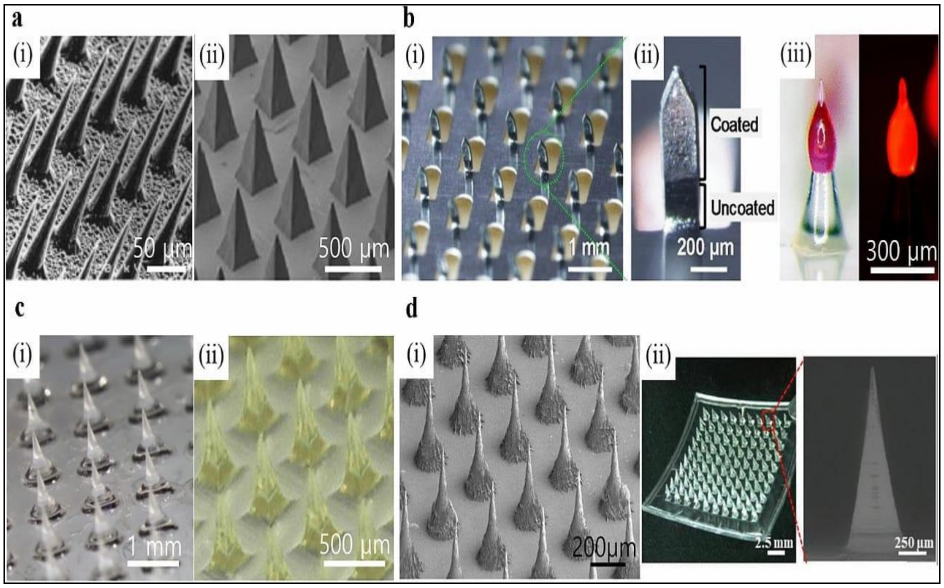

Figure: 4 a) Silicon micro-needles, b) coated micro-needles, c) dissolving micro-needles, d) hydro-gel micro-needles.

Methods of fabrication techniques:

Table: 1 Fabrications Methods of Micro-needle.

Sr. No.	Methods of fabrications	Types of micro-needles produced
1.	Laser Cutting	Metallic
2.	Laser Ablation	Metallic
3.	Vapour deposition	Silicon
4.	Dry Etching	Silicon Hollow Type
5.	Wet Etching	Silicon , Metallic,
6.	Micro-molding And Melt Casting	Dissolvable / Hydro-gel Forming, Ceramic.
7.	Micro-stereo lithography	Silicon, metallic.
8.	Metal electroplating	metallic, Hollow type
9.	Photolithography	Dissolvable/hydro-gel forming, hollow type.
10.	Dipping	Coated type.
11.	Continuous liquid interface production (CLIP)	Coated type

Mechanism of Action:

The mechanism of action depends on the type of micro-needle design. The drug is entrapped within the micro-needles, which when inserted into the skin and releases the drug into the layers of skin which are highly vascular zed. 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 [25]. micro-needles can either be pressed onto the skin or scraped on the skin for creating microscopic holes, thereby increasing skin permeability by up to four orders of magnitude. This coating can dissolve within 1 min after insertion into skin, after which the micro-needles can be withdrawn and discarde [41].

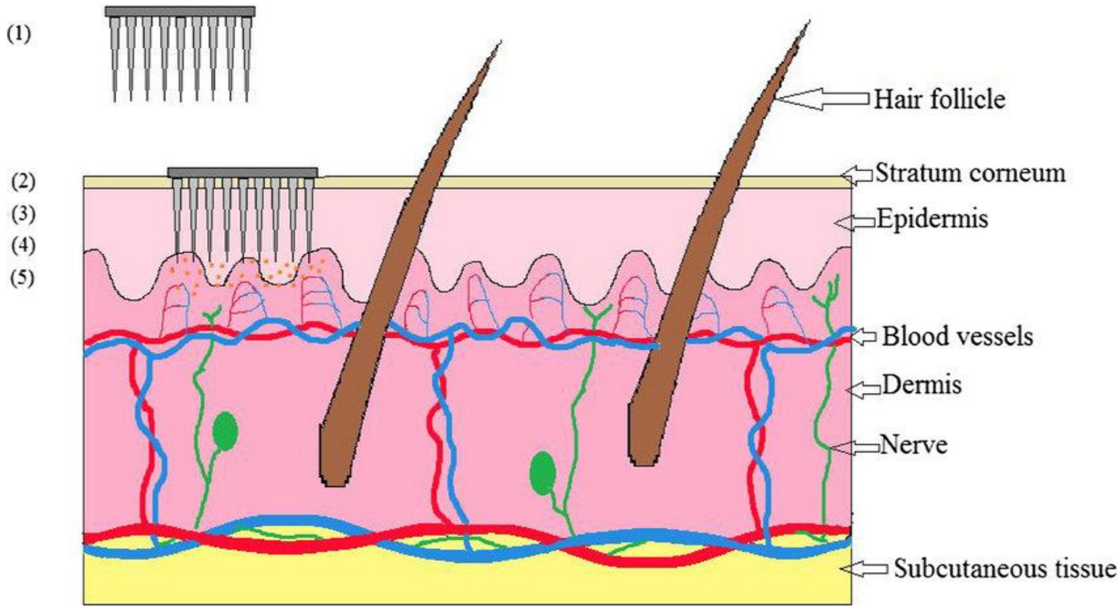

Figure: 5 Mechanism of drug delivery by micro-needle device: (1) Micro-needle device with drug solution; (2) Device inserted into the skin; (3) Temporary mechanical disruption of the skin; (4) Releasing the drug in the epidermis; (5) Transport of drug to the site of action.

MNs have been proposed as a mechanism for adjuvant hair re-growth in alopecia. The efficacy of MN in both androgentic alopecia (AGA) and has been highlighted over the last 5 years Derma roller treatment combined with 5% minoxidil lotion was administered to half of the participants, with 80% showing moderately or greatly increased hair re-growth per the investigators [27]. Generally, MNs patches or substrates possess similar basic design elements such as an ordered array of MNs ranging from a few to a few hundred in number. MNs are prepared from various materials and manufactured in a plethora of shapes and sizes [43].

Applications:

Micro-needles are an attractive and useful transdermal drug delivery system (TDDS) for the Development of an alternative pharmaceutical preparation for the injection of drugs having poor permeability through the skin [15]. Human studies demonstrated that Micro-needles can be inserted painlessly into the skin. Although significant attention has been given to fabrication of both and hollow micro-needles, most drug delivery studies have employed just micro-needles used either to pierce holes in the skin as a pre treatment before application of a trans-dermal patch or coated with drug that dissolves off the needles upon insertion into the skin [17]. Micro-needle application can be used to enhance the delivery of drug-loaded solutions applied to the skin drug coated micro-needle arrays have the advantage of producing a single unit delivery system, incorporating the drug and delivery device (micro-needle array) in a single dosage form [18].

Type 2 Diabetic's mellitus:

Metformin hcl [1, 1-dimethyl biguanide Hydrochloride] is the most widely prescribed drug for treatment of individuals with type 2 diabetes mellitus. It is recommended, in combination with life style modification (diet, Weight control and physical activity), as a first line oral therapy [16].

Cancer Treatment:

Currently, although MNs are widely used in the treatment of tumors, the release efficiency of loaded drugs is often affected by the MN carrier matrix. Breast cancer, BCC or squamous cell carcinoma, head and neck carcinoma, human oral epidermis carcinoma, and melanoma are currently high incidences of SST. Taking melanoma as an example, surgical resection, chemotherapy, gene intervention, and locally targeted therapy are all effective treatments [34].

Vaccine therapy:

IM injections are commonly used for vaccine delivery because more blood vessels are distributed around the muscles than the skin. ID and SC injections are also often used for delivery of some vaccines, and small number of vaccines is administered via the oral route [36].

Glaucoma:

Glaucoma is characterized by genetic as well as biological risk factors. The treatment for glaucoma includes use of topical agents, different class of drugs are used in glaucoma like beta blocker, alpha adrenergic agonist, carbonic anhydrase, prostaglandin analogues, cholinergics, etc [37].

Cosmetics:

There are two main approaches for cosmetic applications of MNs:

(i) To stimulate the natural healing of the skin (which leads to reduction in skin scars, pigmentation, and wrinkles).

(ii) To enhance the delivery of cosmeceuticals into the skin by perforation of the epidermis. These two approaches often complement each other and can be applied in combination depending on the need [38].

Table: 2 List of Advantages, Disadvantages, and Method of delivery of various micro-needles in detail:

Sr. No.	Micro-needle classification	Advantages	Disadvantages
1.		Can be made from the range of materials	Micro-needle facture under skin Limited surface area available for the drug absorption.
2.	Hollow	High drug load can be injected	Must be fabricated with strong material to withstand flow pressure
3.	Dissolving	Easy manufacturing	Only biodegradable material can be sued
4.	Coated	Used for potent drugs required low doses	Associate with drug loose while manufacturing , temperature limitations
5.	Hydro-gel forming	No residual excipients in the skin after removal easy to manufacture reasonable drug loading control drug release profile.	Poor mechanical strength and physical stability ingressing body fluids.

DISCUSSION & CONCLUSION:

Micro-needles either in the form of patch or an array had been observed as a potential carrier for the delivery of numerous macromolecular drugs for the effective transdermal delivery. It was convenient, painless, and less invasive alternative to injection & it could be used a common method for administering large proteins and peptides, antibiotics, vaccines in low manufacturing cost. There was a need to investigate further skin pore closure after MNs application especially as it relates to the risk of infections. Micro-needles could be used for the delivery of vaccines, biologics, and small molecules through the skin and currently the suprachoroidal space and palatal mucosa; and in the diagnosis and monitoring of diseases; the commercialization of micro-needle systems will offer significant benefits to patients. Micro-needle drug delivery systems will increasesd the number of drugs available for use by patients who have difficulty swallowing oral medication or receiving daily injections and also the number of individuals who can be vaccinated.

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