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A BRIEF OVERVIEW ON MICRONEEDLES

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Abstract:

Transdermal drug delivery carried out a promising carrier in the transport of drugs to get direct access across the skin deep into the systemic circulation. Transdermal drug delivery has a number of advantages including improved patient compliance, sustained release, avoidance of gastric irritation, as well as elimination of pre-systemic first-pass effect. It gives attraction to many researchers due to various biomedical advantages. Due to the limitation of oral drug delivery system and the pain related with the use of needles in case of injections, drug delivery research has tremendously oriented towards the transdermal route. The objective of the present review is to focus on newly innovations in transdermal drug delivery systems which can create a platform for the research and development of pharmaceutical drug dosage form for efficient transdermal delivery. In this review, we tell about different types of microneedles are described and their methods of fabrication. Microneedles can be fabricated in different forms like hollow, solid, and dissolving. There are also hydrogel-forming microneedles. In relation to hydrogel-forming microneedles, special attention, these are innovative microneedles which does not contain drugs but imbibe interstitial fluid to form continuous conduits between dermal microcirculation and an attached patch-type reservoir. Regulatory authorities approved several microneedles for clinical uses are also examined. The last part of this review discusses concerns and challenges regarding microneedles use.

Key words: *transdermal drug delivery, microneedles, patient compliance, avoid first pass effect.*

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INTRODUCTION:

Drug delivery via transdermal route across the skin provides the most convenient route for various clinical implications deep into the systemic circulation and it developed for controlled drug delivery. Transdermal drug delivery system represents a system which delivers the drug (therapeutically active amount of drug) effectively across the human skin. These are generally describing as the devices, which holds drug molecules of defined surface area that delivers the predetermined amount of drug to the intact skin surface at a predetermined rate. These systems have been designed to deliver the drug through the skin to the systemic circulation. It is defined as a self-contained, innovative delivery system which is considered to deliver the drug upon application into the skin, at controlled rate to the systemic circulation. Hypodermic needles generally used in clinical practice to deliver medications across the skin into the bloodstream. Injections with hypodermic needles are important from a clinical standpoint, but painful. They may induce hypersensitivity; bruising, discomfort and bleeding at the site of administration, and in some cases are associated with risks of contamination. There are other concerns linked to their use including accidental needle stick injury and the necessity to train medical staff regarding the proper use of needles. The difficulty in crossing the skin is caused by its anatomical peculiarities. The skin is the largest organ in the body. It is about 1.5 m^2 in adults and provides protection for internal organs and also protects the human body against ingress of toxic chemicals and egress of water. Despite the large surface area of the skin, it is challenging for compounds including drugs and vaccines to cross the skin in therapeutically relevant amounts. The outer most layer of the skin i.e. stratum corneum plays role of major barrier in the skin. The stratum corneum is 10–15 μm thick with 15–20 corneocyte layers. It is made up of corneocytes embedded in an intercellular lipid matrix. In human stratum corneum, the main lipid classes are free fatty acids, ceramides and cholesterol which form two lamellar phases. These include the short periodicity phase and the long periodicity phase with repeat distances of approximately 6 and 13 nm, respectively. Below the stratum corneum is the viable epidermis, which is a cellular, avascular tissue measuring 50–100 μm thick. The viable epidermis consists mainly of keratinocytes and approximately 40% protein, 40% water and 15%–20% lipids. The undulating epidermal–dermal junction consists of papilla that project into the dermis. Cells in the basal layer of the epidermis form the most important structural and functional connection to the dermis below. The stratum corneum and viable epidermis together form the full epidermis. There is a basement membrane at the base of the epidermis and the existence of tight junctions in the viable epidermis has been recently documented. Base membrane and tight junctions may both offer resistance to the transport of molecules across the epidermis. Below epidermis layer is the reticular dermis, made up of thick collagen bundles and coarse elastic fibers. The dermis contains blood vessels, lymphatics and nerves, as well as the various skin appendages. Below the reticular dermis lies the hypodermis (subcutaneous fat tissue), which may have a thickness of up to several millimetres (Ryan F. Donnelly *et al*., 2010).

Advantages of transdermal drug delivery:

- Improved patient compliance
- Avoids first pass hepatic metabolism in comparison to oral drug delivery systems.
- This system reduces the adverse effects regards with the drug caused due to overdose
- It is a convenient route and comprises of simple dosing, especially in case of transdermal patches that require only once in a week application which helps in patient adherence to drug therapy.
- It avoids gastrointestinal irritation, gastrointestinal absorption, enzymatic related deactivation and reduces fluctuations in plasma drug profile.
- It enhances the bioavailability as well as high concentrations of drugs delivered via this route can be localized at the site of action, thereby reducing the systemic drug levels.
- Drug delivery through transdermal route is an attractive method to transport drug or biological compounds due its advantage in reducing the pain and inconvenient intravenous injections.

Disadvantages of transdermal drug delivery system:

- local irritation, erythema, itching, and local oedema may be produced by the drug or other excipients at the site of application especially in the patch formulation.
- Limited permeability across through the skin may limit the delivery of number of drugs.

Characteristics of microneedles:

Microneedles are recently developed systems for drug delivery which is similar or likely to traditional needles but the difference is these are fabricated on the micron scale and the size ranges from 1-100 microns in length and 1 micron in diameter. These are defined as micro-scale needles, arranged on a transdermal patch. Microneedles are currently being

utilized to enhance transdermal delivery of small and large molecules. Transdermal microneedles create micron sized pores in the skin to enhance delivery of the drug across the skin. When microneedles are fabricated in arrays on a backing that can be applied to the skin like a bandage, the device is called a microneedles patch. Microneedles can be divided into four categories like hollow, solid, coated and polymer. Hollow microneedles are like regular hypodermic needles but shorter in length. A liquid formulation of the drug is infused through bores in the microneedles. Solid microneedles are used to create holes in the skin. Subsequently a patch is then applied. Coated microneedles are microneedles coated with the drug while polymer microneedles are made by polymers that can be dissolving, non-dissolving or hydrogel-forming (Gaurav Tiwari *et al.*, 2010).

The characteristics of micro needles include ruggedness, microneedles developed must be capable of insertion deep into the skin without breaking. They should be manufactured by taking optimum size and if they are too long, upper portion of micro needles may not have enough rigidity and could undergo breakage before penetration. Microneedles generally used in controlled drug released, they should deliver the controlled amount of drug at a definite and predetermined rate. The micro needles should be able to penetrate the drug to the required depth in the tissues of the body. Generally, the dimensions of micro needles can vary depending on the types of microneedles. Typical microneedles geometries may range from 150-1500 microns in length, 50-250 microns in base width, and 1-25 microns in tip diameter. The tips of microneedles are of different shapes like triangular, rounded or arrow shaped.

Most of microneedles make by materials includes glass, silicone (of brittle nature), metals such as stainless steel, solid or coat of gold over nickel, palladium, cobalt and platinum and biodegradable polymers.

Effective characteristics in case of ideal microneedles, designing of microneedles can be such so as to minimize the pain. Various studies revealed that specific micro needles of about a couple hundred microns length were reported to be painless. It was reported by various authors that l3-times increment in needle length (i.e., 500-1500 microns) increases the pain by 7 times (i.e., 5-35% caused by hypodermic needle). If the length remains constant, an increase in number of microneedles (i.e., 620 micron long) 10-fold from 5- 50 also increases the pain by 3 folds.

FABRICATION OF MICRONEEDLES:

Microneedles can be fabricated employing micro-electromechanical systems (MEMS). The basic process can be divided in to three parts: deposition, patterning and etching. Deposition specially referred to the formation of thin films with a thickness anywhere between a few nanometres to about 100 micrometres. Patterning is the transfer of a pattern into the film. Lithography is used to transfer a pattern into a photosensitive material by selective exposure to a radiation source such as light. This process can involve photolithography, ion beam lithography, electron beam lithography. Diamond patterning is also a good option for lithography. Etching is a process of using strong acid or mordant to cut into the unprotected parts of a material's surface to makes a design in it and can be divided into two categories: wet etching or dry etching. The selection of any of the above-mentioned methods largely depends on the material of construction and the type of microneedles. Microneedles fabricated in different forms like as hollow, solid, and dissolving given below.

A. Hollow microneedles:

Hollow microneedles contain a hollow bore in the centre of the needle. Hollow microneedles can be fabricated from a commercially available 30-gauge hypodermic needles. Pressure, and thereby flow rate, can be changed in hollow microneedles for a rapid bolus injection, a slow infusion or a varied delivery rate. Hollow microneedles can also be used to administer a larger dose of drug solution. When inserted into the skin, the hollow bore present by passes the stratum corneum layer of the skin and produces a direct channel into the other lower layers of the epidermis. The 4 × 4 pattern of holes was drilled in a polyether ether ketone mold (diameter 9 mm). Then, the needles were placed through the holes at a predetermined length of 300, 550, 700 and 900 μm. Subsequently, the needles were cut and glued at the back of the mold. A manual applicator was also designed for the microneedles array. These microneedles are mainly employed to inject the drug solutions directly into the skin. These are very expensive to prepare and require expensive micro fabrication techniques. These micro needles contain hollow bore which offers possibility of transporting drugs through the interior of well-defined needles by diffusion or for more rapid rates of delivery by pressure driven flow. Silicon microneedles are justified or described by their mechanical properties and their biocompatibility potential. However, inconveniences such as high production costs or fragility have spurred researchers to look for other options. Hollow silicon microneedles were fabricated by using isotropic etching followed by anisotropic

etching to obtain a tapered tip. Silicon microneedles of 300 µm in height, with 130 µm outer diameter and 110 µm inner diameter at the tip followed by 80 µm inner diameter and 160 µm outer diameter at the base were fabricated using this technique. In order to improve the biocompatibility of microneedles, the fabricated microneedles were coated with titanium (500 nm) by sputtering technique followed by gold coating using electroplating. Hollow microneedles can fabricate using other system like micro-electro-mechanical systems technologies such as laser micromachining, deep reactive ion etching, integrated lithographic molding technique, and wet chemical etching and X-ray photolithography. Admin Pen® microneedles have also been fabricated. These are hollow stainless-steel microneedles of varying lengths from 600 to 1500 µm, which can be connected to a syringe and used to deliver liquid formulations. Admin Stamp® devices contain Admin Patch® microneedle arrays attached to an applicator with six stainless steel screws. They can also be used to porate the skin without any liquid. When used in this way, they are like solid microneedles because they first create the holes before a drug solution is applied. Hollow microneedles can deposit a compound directly into the viable epidermis or the dermis avoiding the stratum corneum. This is especially useful for the delivery of high molecular weight compounds such as proteins, oligonucleotides and vaccines. Transdermal delivery of insulin continues to represent a significant scientific challenge. Cheung *et al.* used 1100 and 1400 µm long stainless-steel microneedles to deliver insulin across porcine skin.

B. Solid Microneedles:

Solid microneedles carried out passive diffusion for drug deliver by creating microchannels 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 microchannels to close soon after needle removal to prevent permeation of undesired toxic substances or infection by pathogenic microorganisms. Henry *et al.* used a deep reactive ion etching process to fabricate silicon microneedles and a chromium masking material was first deposited onto silicon wafers and patterned into dots which had a diameter approximately equal to the base of the desired microneedles. The wafers were then loaded into a reactive ion etcher and subjected to plasma etching. The regions protected by the metal mask remained 10 to form the microneedles. Vinay kumar *et al.* fabricated an array of rectangular cup shaped silicon microneedles. These microneedles have the potential for reduced drug leakage resulting in improvement of drug delivery efficiency and the possibility of introducing multiple drugs. The fabricated solid microneedles with rectangular cup shaped tip are 200 µm in height. The cup shaped tips have dimensions of 60 × 60 µm (length × breadth) with a depth of 60 µm. The cups are filled with drug using a novel drop coating system. Solid microneedles fabricated from silicon, metal and polymer.

Solid microneedles can be fabricated from polymers. Olatunji *et al.* prepared microneedles from biopolymer films extracted from fish scales of tilapia (*Oreochromiss* sp.) using micromolding technique. The microneedles were successfully inserted into porcine skin and were shown to dissolve gradually at 0, 60, 120 and 180 s after insertion. The microneedles contained methylene blue as model drug and successfully pierced porcine skin (Nahid Tabassumm *et al.*, 2011).

C. Dissolving Microneedles:

Dissolving microneedles have a number of advantages. These include the one-step application process which is convenient for patients. Dissolving microneedles are fabricated on the basis of the “poke and release” principle. They are made from polysaccharides or other polymers. These microneedles release encapsulated drug into the skin following application and dissolution. Micromoulding is the preferred fabrication method for making dissolving microneedles. Certain drugs and vaccines are thermolabile so moulds are often filled with solutions of drugs and excipients and then dried under mild conditions. The fabrication process involves pouring the polymer solution into female molds, filling the microcavities of the mould under vacuum or pressure, drying under ambient conditions, centrifugation or pressure. Master structures for microneedles supporting arrays, and pressing tools were created by Chen *et al.* using proprietary electro-discharge-machining technology. Each master structure consisted of 64 (8 × 8) microstructures. Polydimethylsiloxane (PDMS) molds were created as exact inverse-replicates of the master structures. To prevent adhesion to PDMS molds, all master structures were sputter-coated with platinum. PDMS molds were fabricated by pouring PDMS solution over the master structure and allowing the polymer to cure overnight at room temperature. The cured PDMS molds were then peeled from the master structures and used to make the chitosan microneedles, polylactic acid supporting arrays, and polycaprolactone pressing tools (Pablo Serrano-Castaneda *et al.*, 2018).

D. Coated Microneedles:
Coated microneedles refer to microneedles which have coating with the drug-containing dispersion. A plethora of techniques has been used in the literature to prepare coated microneedles. An approach using electrohydrodynamic atomization principles in the preparation of smart microneedles coatings was reported in the literature. Stainless steel (600–900 μm in height) microneedles were coupled to a ground electrode (in the electrohydrodynamic atomization coating set-up) with the deposition distance and collecting methodology varied for an ethanol: methanol (50:0) vehicle system. The authors used this technique to prepare nano- and micrometer-scaled pharmaceutical coatings. Fluorescein dye (serving as potential drug, sensory materials or disease state markers) and polyvinylpyrrolidone, (polymer matrix system) formed the remaining components of the coating formulation. Based on these excipients and by varying the coating process, particles (100 nm to 3 μm) and fibres (400 nm to 1 μm) were deposited directly on microneedles in controlled and selectable fashion.

E. Hydrogel-Forming Microneedles:
The first two microneedle-based products, just recently marketed, Soluvia® and Micronjet®, are based on metal and silicon, respectively. However, the current trend in microneedle-based research has recognized biocompatibility problems associated with the use of silicon and the potential for inappropriate re-use of silicon or metal microneedles, which remain fully intact after removal from a patient's skin. This has led to a multiplicity of technologies aimed at overcoming this shortcoming. In this regard, recent effort has focused on microneedles formulated from aqueous polymer gels. One of these approaches involves the use of hydrogel-forming microneedles. One of the differences and advantages in comparison with regular dissolving polymer microneedles is that by using this drug delivery system, delivered doses of drugs and biomolecules are no longer limited to what can be loaded into the needles themselves.

Donnelly *et al*. prepared hydrogel-forming microneedles from "super-swelling" polymeric compositions. These are microneedle arrays, prepared under ambient conditions, which contain no drug themselves. Instead, they rapidly imbibe skin interstitial fluid upon insertion to form continuous conduits between the dermal microcirculation and an attached patch-type drug reservoir. Such microneedles act initially as a tool to penetrate the stratum corneum barrier. Upon swelling, they become a rate controlling membrane. Fluid uptake range in one hour was 0.9–2.7 μL which is of the same order of magnitude as the rates of interstitial fluid uptake for hollow microneedles and microdialysis. Other advantages of hydrogel-forming microneedles are that they can be fabricated in a wide range of patch sizes and geometries, can be easily sterilized, resist hole closure while in place and are removed completely intact from the skin (Karmen Cheung *et al.*, 2016).

EVALUATION PARAMETERS
In vitro evaluation of microneedles is accomplished by using various mediums like agarose gel and methanol to insert the microneedles. In vitro tests are used to determine the characteristics of new test device or compound. The main key objectives of the in vitro testing of microneedles involves optimization of the microneedles, finding out the penetration force and bending force, evaluation of strength of microneedles, determination of the dissolution rate of coating material and the estimation of the efficiency of drug delivery. Various methods employed for conducting in vitro studies are as follows:

***In vitro* Testing of microneedles:**

A) Method 1:
In vitro methods tested the delivery efficacy of the microneedles. In this test, the microneedles are integrated with Para dimethyl siloxane biochip and black ink is injected by the microneedles into the petri dish, contains methanol widely used. The right triangular microneedles with 8.5 and 15 tip taper angles and isosceles triangular microneedles with 9.5 and 30 tip taper angles have been used for this purpose.

B) Method 2:
In this method, the diluted form of Rhodamine B dye is injected through the microneedles into the 1% agarose gel to evaluate the penetration and flow of the solution after penetrating into the 1% agarose gel.

C) Method 3:
Inserting microneedles into the porcine cadaver skin and pig cadaver skin for 10 s to 20 s and 5 minutes respectively are evaluated by this method. This method is used to test the delivery efficacy, dissolution rate of the coated material, which is coated on the microneedle tip, coated with vitamin B, calcein or sulfurhodamine.

***In vivo* Testing of microneedles:**
To conduct the *in vivo* preclinical study, generally mice, rabbits, guinea pigs, mouse and monkey etc are used. The main motive of the *in vivo* testing is the

determination of safety as well toxicity of the tested compound. The key objectives behind *in vivo* testing of the microneedles includes to perform skin toxicity test, determination of penetration force in different skin, mechanical stability, bending breakage force, to perform various non-clinical safety study and pharmacological study, determination of various parameters like immunogenicity, genotoxicity, skin sensitization and allerginisation, study, developmental toxicity, acute and chronic dermal toxicity, carcinogenicity.

A) Method 1:
This *in vivo* method involves testing of microneedles by pricking the microneedles into vein of the tail of hairless mice. It is used for the determination of the penetration force of the microneedles into the skin.

B) Method 2:
This method of *in vivo* testing of the microneedles, Rhodamine B is injected into tail of laboratory mouse-tail and anaesthetized for the determination of penetration force and bending breakage force.

C) Method 3:
This method has been performed for the evaluation of vaccine delivery via microneedles. Ovalbumin is used in this method, as a model protein antigen and administered into hairless guinea pig by using solid metal microneedles at the rate of 20 µg ovalbumin in 5s up to 80 µg.

D) Method 4:
In this method rabbits have been used to evaluate the vaccine delivery. The anthrax vaccine containing recombinant protective antigen (rPA) of Bacillus anthracis has been administered in the rabbits via solid and hollow microneedles.

APPLICATIONS OF MICRONEEDLES:
Microneedles have been explored for different applications and are extended to many fields. Owing to benefit of piercing in a minimally invasive manner, apart from being an alternative to conventional hypodermic therapy, they have also been employed for ocular, systemic and intracellular delivery. Microneedles can be used to deliver high molecular weight compounds like proteins and peptides, immune biologicals like vaccines, antibodies etc. bioactive agents or bio macromolecules like insulin, heparin, albumin, growth hormones. Microneedles have also gained prominent attention in the field of cosmetics and various cosmeceuticals have been used for the treatment of acne, pigmentation, scars and wrinkles as well as for skin toning (Jiawei Zhao *et al.*, 2018).

A. Immuno biologicals:
Attributing to the drawbacks of conventional vaccination procedure of needle phobia and the pain associated with insertion of needle into the skin, recent studies have focused on development of needle-free vaccination like liquid jet injectors, powder injectors, thermal ablation and microneedles for the administration of immune biologicals via the subcutaneous, intramuscular or intradermal route for prevention of infectious diseases. Microneedles have an edge over the other methods due to lack of pain, self-administration and quick delivery of vaccine. Making use of the microneedles allows vaccines to cross the stratum corneum and stimulate a clinical response. In case of dissolving microneedles, controlled and complete penetration is an important parameter to be considered. These are capable of delivering a small dose, less than several milligrams, of peptides, proteins, vaccines, hormones and organic compounds. Numerous studies have been performed and reported on vaccine delivery using microneedles including human IgG, tetanus toxoid, DNA vaccine, influenza vaccine, hepatitis B vaccine, human papilloma virus vaccine, west nile virus vaccine, chikungunya virus vaccine, herpes simplex virus vaccine, Bacillus Calmette Guerin vaccine, ovalbumin, live attenuated chimeric JE vaccine (Chimeri Vax)-JE/flavivirus vaccine, diphtheria, malaria, combination and recombinant protein vaccines for anthrax, botulism, plague and staphylococcal toxic shock (Devender Sharma *et al.*, 2018).

B. Bioactive macromolecules (Biopharmaceuticals):
Owing to the proteolytic degradation and hindered absorption, bioactive macromolecules such as insulin, heparin, and growth hormones are not administered orally. The majority of commercially available biopharmaceuticals are administered via the parenteral route and hence a suitable non-invasive route is desirable. Microneedle arrays have been found to enhance the transport across dermatomed human skin for both low and high molecular weight compounds and also that the length of the microneedles and the depth up to which the microneedles penetrated in the skin had no effect on the transport of either low or high molecular weight compounds. For rapid release as well as controlled release of molecules, an approach of preparing dissolving microneedles constituting water-soluble polysaccharides has been done. Studies performed and reported on administration of biopharmaceuticals

using microneedles include delivery of low molecular weight heparin, insulin, L-Carnitine, calcein and bovine serum albumin, desmopressin, recombinant human growth hormone and desmopressin, albumin, calcein, erythropoietin, oligonucleotides, porphyrin precursor 5-aminolevulinic acid (ALA), salmon calcitonin, daniplestim, leuprolide acetate, Para thyroid hormone, human growth hormone etc.

C. Drugs:

It is essential for a drug molecule to possess the necessary physicochemical properties to cross the skin barrier. Transport of a drug molecule through the skin and also the rate of transportation are governed by these physico-chemical properties like hydrophilic- lipophilic balance, solubility, molecular weight, etc. The challenges posed in transdermal drug delivery can be overcome by use of microneedles. Use of microneedles enhances the bioavailability of drugs and can exclude the need for penetration enhancers, which may induce irritation. Microneedles may also reduce the side effects and complications associated with systemic administration. Drugs administered via microneedles include L-Ascorbic acid, riboflavin, galanthamine, aspirin, docetaxel, pilocarpine, methotrexate, prochlorperazine edisylate, lidocaine hydrochloride, ropinirole hydrochloride, ketoprofen, naltrexone with diclofenac sodium, phenylephrine, naltrexone, mannitol, glycerol etc.

D. Phlebotomy:

Phlebotomy refers to the withdrawal of blood samples for analysis of specific blood constituents for diagnosis of a disease. Blood samples are generally collected from capillaries by pricking the skin or from veins using evacuated collection tube, depending on the volume of blood required for analysis. These methods are associated with disadvantages such as excessive bleeding, infection, scarring, fainting or feeling light-headed. People may hesitate to give blood due to fear of needles and the moderate pain associated with the procedure. In such case, painless blood sampling using microneedles can be a very good alternative to hypodermic needles. Microneedles situated at a distance of 500–2000 mm in the dermis layer beneath the skin can be used to obtain precise body fluids as well as blood samples from the capillaries. Apart from making the procedure painless, microneedles also reduce the blood sample requirements (up to 200 nanolitres). However, the most essential requirement is that the microneedle must penetrate to sufficient depth; hence care should be taken in the design, material selection and dimensions of the microneedle, to ensure penetration at low pressure without breakage. Painless hollow microneedle-based micro sampling can be used instead of traditional methods for glucose estimation in case of disease diabetes which requires frequent monitoring of blood for estimation of glucose concentration or disease severity. Microneedles can also be used for monitoring of therapeutic drug levels 88. A jagged-shaped, hollow in-plane silicon microneedle resembling the proboscis of a mosquito has been prepared for collection of blood for testing. Arrays of 350 m long, hollow, out-of-plane microneedles demonstrated in-situ analysis biological fluid extraction through capillary action (Eneko Larraneta *et al*., 2016).

E. Diagnosis:

The use of microneedles can also be employed in the field of diagnosis. Hollow microneedles, along with quantum dots, help in medical diagnosis. Quantum dots are Nano scale crystals with a light-emitting property. The multiphoton microscopy method could rapidly diagnose cancers or other medical problems. Recent research focuses on the development of magnetic nanoparticles along with magnetic microneedle tips those safely collect biomarkers that indicate early-stage osteoarthritis in knees, hips and other joints. Work has been carried out on development of two sensing device based on hybrid microneedles array for diagnostic and therapeutic applications. Hybrid microneedles having a porous structure were prepared, which can include a variety of biological molecules, as bioprobes or drugs. The first device is an electrochemical sensor where microneedles contain enzymes in their matrix that interact with glucose. The redox reaction with glucose, mediated by ferrocene, creates a charge transfer resulting in a current proportional to the glucose concentration. The second device is a therapeutic tool with optically controlled release of drug. In this case the device includes a porous silicon membrane with a Bragg's mirror, whose reflection wavelength is related to the drug’s concentration in the microneedle. Microneedle sensors fabricated at the end of an endoscope using poly caprolactone (PCL) microneedles coated with poly (3, 4-ethylenedioxythiophene) (PEDOT), functionalized with hemin molecules on the surface were employed for both endomicroscopic imaging and biosensing of colon cancer by real-time electrical detection of nitric oxide. Microneedles have also been developed as sensors for hydrogen peroxide, lactate, dissolved oxygen and glutamate. Microneedles have been employed as bioelectrical interfaces, especially for neural recording and stimulation, as well as for electrocardiography (ECG) and electroencephalography (EEG) measurements (M. Ogundele *et al.,* 2017).

F. Cosmeceuticals:

Cosmeceutical industry has shown great interest in microneedle technology, the majority of cosmetic products are lending themselves to microneedle technology for non-surgical and non-ablative treatment of skin conditions such as ageing (wrinkles, lax skin), scarring (acne, surgical), photo damage, hyperpigmentation (age/brown spots) and hair loss (alopecia). The process facilitates and stimulates skin's natural repair without causing permanent epidermal damage. Microneedles can be used for cosmetic applications, mainly for treatment of skin blemishes and the delivery of active cosmetic ingredients. Marketed microneedles like Derma rollers® and stamps are available for treatment of skin problems as well as to improve looks. MTS Dermaroller® marketed by Clinical Resolution Laboratory is a cosmetic aid possessing needles that penetrate the skin up to a depth of 0.2–0.3 mm. It contains 200 very fine stainless-steel needles that pierce the epidermis, creating a micro-channel effect. Clinical studies from various countries have proven that therapeutic serum absorption is increased by as much as 1000 times when applied using the MTS Dermaroller. A hyaluronic acid based dissolving microneedle patch developed for the intradermal delivery of ascorbic acid and retinyl retinoate displayed improved skin appearance in terms of roughness and wrinkle appearance when tested in human volunteers. An enhancement in the local delivery of eflornithine (used to reduce facial hirsutism) was observed both in vitro and in vivo when the skin was exposed to microneedle pretreatment followed by local administration of an eflornithine cream. Microneedle technology can be used to treat different types of scars by dermabrasion. Dermabrasion involves piercing the skin multiple times with microneedles to induce collagen growth. A noticeable improvement was observed in the treatment of patients with dermal scars (striae distensae) using a disc microneedle therapy. However, similar to the treatment of acne, this treatment too is associated with limitations of skin bleeding and painful treatment. An aesthetic improvement in patients with acne scars was reported with a reduction in scar severity in all subjects when treated with Dermaroller®. Similar results were obtained for treatment of atrophic facial scars using Dermarollers®. An alternative approach to the use of Dermarollers® for the treatment of acne scars reported is the fractional radio frequency microneedle system. This system was introduced recently as a new device for facial rejuvenation. It involves creating radiofrequency-induced thermal zones. This causes damage to the reticular dermis followed by the dermal thickening. This system was clinically evaluated and the results suggested that this novel technique is efficacious for the treatment of acne scars, as it reduced the severity of the scars in more than 80% of volunteers (Nayak Smita *et al.*, 2016).

CONCLUSION:

Microneedles either in the form of patch or an array have been observed as a potential carrier for the effective transdermal delivery for the delivery of numerous macromolecular drugs.

Various research reports studied confirmed that microneedles are ought to be the prominent carriers for enhancing the permeation deep into the systemic circulation and providing a painless, effective and safe route for the drug delivery. In future microneedles plays important role in innovation and design of controlled drug delivery for various drugs. These painless systems are slowly gaining importance and would qualify to be one of the important devices for controlled drug release in future. Thus, it was concluded that, these systems represented it to be an efficient and superior carriers as compared to other needle based formulation for the transdermal delivery.

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