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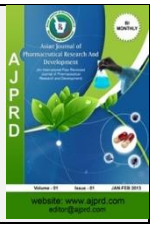

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Review Article

A Review of Microneedles – Elevation to TDDS Approach and Function in Management of Psoriasis

Saurabh Nandkisor Bodkhe*[1], R.H.Kale [2], K.R.Biyani [3]

[1]Department of Pharmacy, PRMS's Anuradha College of Pharmacy, Chikhali, Dist- Buldhana, (MS), India 443201
[2]Department of Pharmacy, PRMS's Anuradha College of Pharmacy, Chikhali, Dist- Buldhana, (MS), India 443201
[3]Department of Pharmacy, PRMS's Anuradha College of Pharmacy, Chikhali, Dist- Buldhana, (MS),India 443201

A B S T R A C T

Novel drug delivery system offers several advantages which could outweigh the benefits of other drug delivery system. The transdermal drug delivery system being one of them offers supremacy by by-passing the first pass metabolism which eventually helps in eradication of gastrointestinal irritation. The first patent for microneedles was field in 1970's, researchers on utilizing microneedles as a drug delivery system has progress significantly. This review aims to provide background on microneedles, clinical benefits and function of microneedles. The microneedle method is much more superior to those traditional transdermal delivery ways because of advantage such as invasive painless, convenience and improves patient compliance. Every type of microneedles has different advantages according to their unique properties and designs. We developed a dissolving microneedle (MN) patch made of hyaluronic acid (HA) with excellent water solubility, biocompatibility and mechanical properties. The traditional therapeutic method is diverse embracing topical drugs, systemic drugs, physical therapy etc. with the limitation of present drug, the demand for new delivery method for psoriasis is in the spotlight. The major drawback of the transdermal drug delivery system is the hindrance created via skin into the systemic circulation. Thus in order to overcome this hurdle a replacement to this type of novel drug delivery system. One of the best pharmaceutical dosage form for those patients. They cannot take medicaments orally. TDDS established itself as an integral part of NDDS.

Keyword: - Transdermal, Microneedles, Drug delivery, Hydrogel forming microneedles, Dissolving microneedles, Psoriasis, Sustained release

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***Address for Correspondence:**

Saurabh Nandkisor Bodkhe, Department of Pharmacy, PRMS's Anuradha College of Pharmacy, Chikhali, Dist- Buldhana, (MS), India 443201

1. INTRODUCTION

During the past few years, interest in the development of novel drug delivery systems for existing drug molecules has been renewed. The development of a novel delivery system for existing drug molecules not only improves the drug's performance in terms of efficacy and safety but also improves patient compliance and overall therapeutic benefit to a significant extent[1]. Transdermal Drug Delivery System are defined as self contained, discrete dosage forms which are also known as 'patches'[2].

The main objectives of transdermal drug delivery system is to deliver drugs into systemic circulation into the skin through skin at predetermined rate with minimal inter and intra patient variation[3]. Currently transdermal delivery is one of the most promising methods for drug application[4]. Transdermal drug delivery system includes the delivery of drugs via superficial lipophilic layer of the skin stratum corneum which is 10-15 micrometer thick. Stratum corneum obstructs the entry of antigens, bacteria; thus defining the skin barrier function which eventually suppress the percutaneous penetration. Henceforth, the utmost challenge include a search for an alternative way which would surpass the repercussion provided by the skin barrier

function of stratum corneum[5]. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliances and minimizes harmful side effect of a drug caused from temporary overdose and is convenience in transdermal delivery drugs that required only once weekly application[6]. A microneedle does not limit itself by improving only drug penetration. It has several other significant positive aspects[7]. The drug delivery is specially preferred for pediatric application[8]. The first transdermal system transderm scope was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel. Development of functional delivery system for new active pharmaceutical ingredients is a challenging task. Drug can be administered through most common routes like oral, parental, ophthalmic and transdermal route as well as less explored routes such as nasal, pulmonary and buccal[9] . Drug delivery (DD) has historically been pivotal in ensuring drugs can be administered in a manner that leads to therapeutic effect. Methods of DD, such as oral ingestion or hypodermic injection, are considered to be the most common forms of drug administration[10]. Each of them routes have specific merits and disadvantages. Oral drug delivery system offers advantages such as patient compliance large surface area with rich blood supply for absorption, low cost, ease in engineering of drug release in stomach, intestine etc. However limitations like drug degradation in the gastrointestinal tract, first pass metabolism, poor absorption, local irritation and variability in absorption (due to factors of pH, motility, food, mucous layer etc) are associated with these drug delivery system[11]. The parental route offers advantages like quick onset of action, accurate drug delivery and continuous drug delivery by infusion; its limitations include pain associated with the injections, expertise required to delivery the drug, risk of infection and difficulty in obtaining sustained drug delivery[12].

Transdermal drug delivery involves the transport of drug across the skin optimal physiochemical properties are required in drug candidates for delivery via transdermal patches can be divided into two categories-reservoir based and matrix based according to their physical structure .Transdermal drug delivery offers advantages like patient compliance, avoidance of first pass metabolism large surface area of skin over which to deliver the drug , quick termination of dosing, etc[13] . However, only a few drug products with optimum characteristics have been successfully marketed to deliver a drug through the skin. This is due to the resistance to drug transport offered by the stratum corneum. The problem of poor drug transport can be addressed by development of microneedles, which deliver the drug painlessly across the stratum corneum[14] . In targeted drug delivery system the drug are designed to be active only on the target area of the body like cancerous tissue and by sustained release formation drug is release over a period of time in a controlled manner from a formulation. The system has to be designed in such way that it must overcome the host's defense mechanisms and circulate to intended site of action[15]. The motivation behind the development of transdermal delivery is the lack of control over drug delivery in existing method. Effective vaccination through skin can be achieved by increasing skin permeability to the vaccine [16].

CONVENTIONAL MODE OF DRUG DELIVERY:-

The delivery of drugs plays a vital part in medicine and paramedical field. Normally, drug delivery system can be referred to as various ways, methods, and approaches for delivering the particular drug at proper site of action in order to obtain the highest amount of desired therapeutic effect[17]. Normally, conventional modes of delivery include oral route, usage of carrier injections, or using novel approaches like transdermal drug delivery system of drug. With growing need for painless and less infectious prone way of drug delivery, microneedles are prone to fit the void for satisfying the requirement [18].

2. MICRONEEDLES :-

Microneedles can be define as solid or hollow cannula with an approximate length of 50-900 micrometer and an external diameter of not more than 300 micrometer[19] . Microneedles can be fabricated with in a patch for transdermal drug delivery. Patches containing microneedles have been evaluated in the delivery of drugs, biopharmaceuticals, vaccine etc. A quick response can be observed due to disruption of stratum corneum by microneedles . With passing time, different materials, such as dextrin, stainless steel, ceramic and maltose were utilized for preparing the microneedles[20]. Although microneedles were first proposed in 1976, the technology needed to make needled of micron dimensions was not widely available until 2000s[21]. Using d low cost mass production tools of the microelectronic industry, needles have been fabricated out of silicon, metals and other materials[22]. Microneedles have been designed to penetrate through the epidermis upto a depth of 70-200 micrometer. Microneedles are thin and short and do not penetrate the dermis layer with its nerves, hence painless application is possible[23].

Table: 1 Salient features of microneedles

Salient Features of microneedles drug delivery technology
• Rapid onset of action
• Possible self administration
• Painless drug delivery system
• Improved patient compliance
• Efficacy and safety comparable to approved injectable products
• Good stability
• Valuable source of intellectual property
• Cost effective

Microneedles are more capable of enhancing the transport of drugs across the skills as compared with other transdermal delivery method. Microneedles can also improved the stability of loaded biotherapeutic and potentially decreases side effects associated to systemic administration. Currently, application of microneedles expanded beyond their representative biomedical application comprising disease long term disease, immunobiological administration and cosmetic field. In addition to small molecules drugs, microneedles can also be used to deliver a large amount of macromolecules in controllable manner, such as insulin, growth hormones, receptor agonist, proteins and peptides[26]. Varieties of microneedle products have been developed to treat scaring and wrinkles, enable skin rejuvenation and improves skin appearance. Scientists put down efforts using technology for proper optimization and geometrical measurements required for achieving accurate insertion in the skin of human which was major goal with respect to microneedle[24].

2.1 History of Microneedles:-

Microneedles were first conceptualized for drug delivery many decades ago, but only became the subject of significant research starting in the mid- 1990's. Hypodermic needles are common medical devices that draw or inject gas or liquid with a procedure piercing the skin. They are one of the most used devices worldwide with application in subcutaneous injection, intramuscular injection, intravenous injection, vein blood collection and various types of puncture procedure. Their use is generally associated with pain or discomfort. Howeven **the** limited absorption capacity of the SC and the size and other properties of drug molecules has meant that the application of many drugs through the alternative method of the traditional TDDS such as transdermal patches is restricted. The dosages of drugs may need to be increased to achieved a more satisfactory concentration of local skin or smarter methods, such as using microneedles, may be required. Gerstel and Martin from Alza corporation first raised the concept of " microneedles" in 1976 as a way of conquering the pain issue in drug administration[25]. The major goal of any microneedle design to penetrate the outer most layer of skin the stratum corneum. In dermatology microneedles are used for scarring treatment with skin rollers. The researchers have studied microneedle delivery of insulin, vaccines, anti-inflammatories and other pharmaceuticals. The use of MNP becomes more prominent with an increasing amount of research into smart devices.

2.2 Mechanism of Microneedles:-

Microneedles comprise two parts: invasive and supporting components. The invasive components is an array formed by hundred of needles with length from 25 to 2000 micron [24]. The supporting part is a base plate that offers an appropriate uniform mechanical support for the shape needle tips to enable them to pierce through the SC(Fig.1). These two part can be fabricated from the same kind of material or fabricated using separate raw material before they are tightly bonded with each other. The most important purposes of an MNP is to create a micron sized channel on the skin layer and to work as a delivery system. MNP function is influenced by MNP design and required sufficient hardness, suitable mechanical strength and sufficient toughness. Signs of failure of an MNP are needle tips that bend, deflect or fracture. These demand make choosing applicable materials and types of MNP critical.

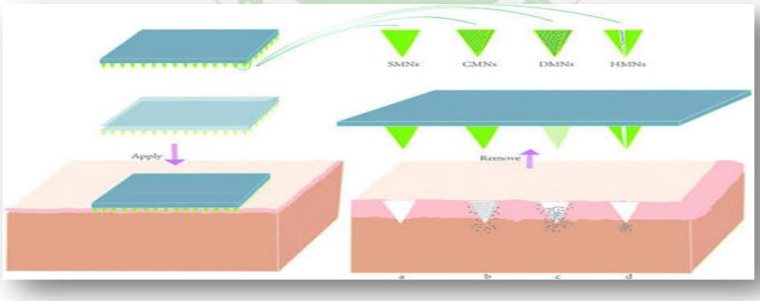

Figure: 1 **(a)** SMNs left pore in the skin. **(b)** CMNs deliver compounds from the outer coated layer containing compounds., **(c)** DMNs needle tip dissolve and release compounds.**(d)** HMNs deliver compounds through the hollow hole in the needle.

2.3 Materials used to constitute Microneedles:-

Selection of the material for the constitution of the microneedles should be based on criteria such as gentle fabrication without damage to sensitive biomolecules, sufficient mechanical strength for insertion into skin and control or rapid drug release as per the requirement. Microneedles have been produced using glass, silicons and metals. The use of polymers to constitute has also been explored solid Microneedles have been produced using plastic or biodegradable polymers. Metallic microneedles are expensive and non biodegradable and brittle. Polymers Microneedles overcomes the limitation of silicon and metal Microneedles and may provide advantages like low cost, mechanical strength and safety in case of accidental breakage of needle in skin.

Microneedles can be broadly divided into 4 categories:-

1. Solid MN
2. Hollow MN
3. Drug Coated MN
4. Dissolvable/Degradable
5. MN

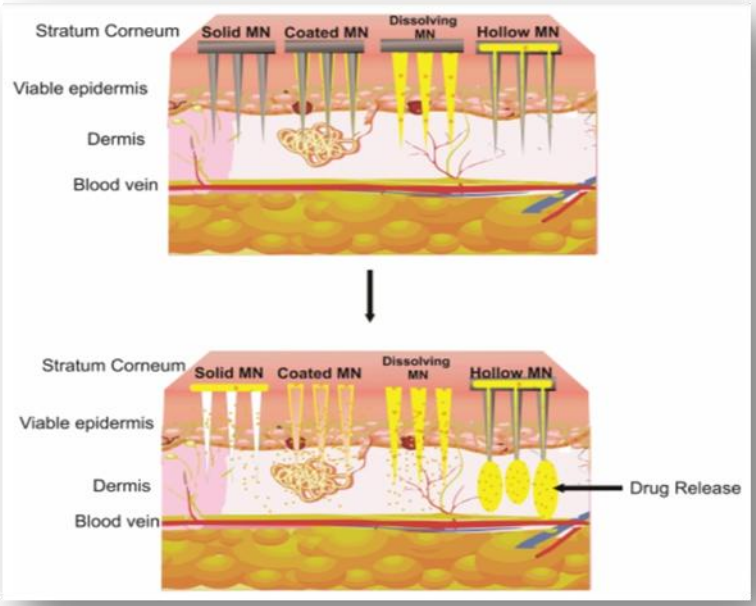

Figure: 2. Mechanism of delivery of drugs by four types of Microneedles solid, coated, dissolving and hollow.

1. **Solid MN:-** Solid MNs are more robust than hollow MNs and have stronger mechanical strength[26]. These Microneedles use the passive diffusion path. In this microneedle the microchannel in the skin are first created by inserting the microneedles, followed by allowing the drugs formulation to pass over the generated microchannels. Solid silicon microneedles proved to be the most prominent approach because of their sufficient biocompatibility. Solid Microneedles are already used by dermatologists in collagen induction therapy, a method which uses repeated puncturing of the skin with Microneedles. Solid Microneedles can be designed as skin pretreatment for producing large pores to deliver drugs. The shapes and tips of Microneedles are largely determined by the needle geometry device upon the basis of stimulating software. The first reported case of solid MNs in literature was in the study of gene therapy. However, Henry et al;(1998) was the first to demonstrate the feasibility of delivering drugs transdermally[27], fabricated solid metal MNs by cutting metal sheets with an infrared laser There have been several types of polymer MNs that have been created to overcome the non-biocompatibile and non-biodegradable properties of metal and silicon MNs. Mikszta *et al* reported a meaningful attempt at topical gene transfer. In this study devices known as microenhancer arrays (MEASs) were used, microfabricated with silicon projections that function as SMNs to achieve penetration of the skin barrier. MEA geometry was characterized by projections heights ranging from 50 to 200 microns and the interval between each projection was twice the height. Martanto and Co-workers fabricated SMNs with stainless steel finally fabricating arrays with 7 rows of 15 needles each, giving a total of 105 needles. Each needle had a tappering tip 1000 microns in length.
2. **Hollow MN:-** These microneedles are the one which allows the passage of the drug through the hollow bore channel present in the needle. The needle is inserted into the skin and the drug is allowed to pass through the bore which diffuses into the systemic circulation. Hollow microneedle are similar to solid microneedle in material. They contain reservoirs that deliver the drug directly into the site. Since the delivery of drug is dependent on the flow rate of the microneedle. They have an added advantage as they can permit the administration of larger drug dose compared to solid MNs .It is made up of various materials such as silicon metals, Glass, Polymers[27]. The structure and mechanical principles of HMNs are similar to those of hypodermic needles with a channel, the center of the needles tubes are hollow and there are holes at the needle tips.These needles were fabricated using a micropipette puller and bevelar with a tip radius of 60 micrometer.The depth of insertion into the skin is about 500-800 micrometer[28]. Hollow MNs are still considered to be mechanically weaker involving complicated manufacturing process and more complex to used than solid MNs as solid MNs are considered to be more robust[25].

3. **Drug Coated MN:-** Just like solid microneedles, coated microneedles are usually designed from polymer or metals. In this method the drug is applied directly to the microneedles array instead of being applied through other patches or applicators. Coated microneedles often covered in other surfactants or thickening agents to assure that the drugs is delivered properly. Some of chemicals used on coated microneedles are known

irritants. While there is a risk of local inflammation to the area where the array was, the array can be removed immediately with no harm to the patient. Jae-Ho *et al*;(2008) used polycarbonate MN arrays and investigated the permeation of calcein across excised rat skin in Franz-cell apparatus. These type include coating of the drug on the solid microneedle before inserting it into the skin[29]. The coated microneedle is inserted into the skin where the drug gets dispensed into the systemic circulation.This system is utilized to deliver complex and macro molecules including deoxyribonucleic acid, drug like desmopressin, parathyroid hormone and vaccines[29], Peptides[30], Proteins. CMN were confirmed as versatile device, due to extensive scope of coated drug. Coated microneedle is specifically used in diabetes insipidus, haemophilia A, whilebrand's disease and certain trauma induced disease[29].

4. **Dissolvable/Degradable MN:-** DMN manufactured from safe materials, such as biodegradable polymer and natural polymer, it can control the release of drugs or vaccine embedded in the polymer. The speed of drug release is decided by speed at which the polymer material dissolves. DMN system composes of polyvinyl pyrrolidone (PVP) and trehalose to encapsulated active pharmaceuticals peptides within the microneedles. The needle or the coating on the needle dissolve itself to release drug[31]. Use of DMNs loaded with 5-ALA, a widely used prodrug in photodynamic therapy, results in high activity and achieved greater inhibition of tumors at low dose with shorter application time than conventional method. These are prepared by lithographic approach or two-layered approach in which two plates are used, the push and pull movement is enforced on to the two plates placed parallel to each other. Recently, he prepared sinomenin loaded dissolving microneedles using a specialized fabrication technique using biocompatible polymers. This polymer would allow the drug to be delivered into the skin and could be broken down once inside the body.Unlike the typical high-temperature molding or methods which are unsuitable for mass production of dissolving polymeric MNs[32], proposed photo-polymerization of liquid monomer, vinyl pyrrolidone. Researchers have begun to study and implement polymers such as fibroin, a silk based protein that can be moulded into structure like microneedles and dissslolved once in body.

3. ADVANCES IN DRUG DELIVERY BY MICRONEEDLES:-

Application of physical method such as electroporation, sonophoresis and iontophoresis have been explored in conjunction with microneedles to provide enhanced drug delivery and better control of delivery of drug across the skin.

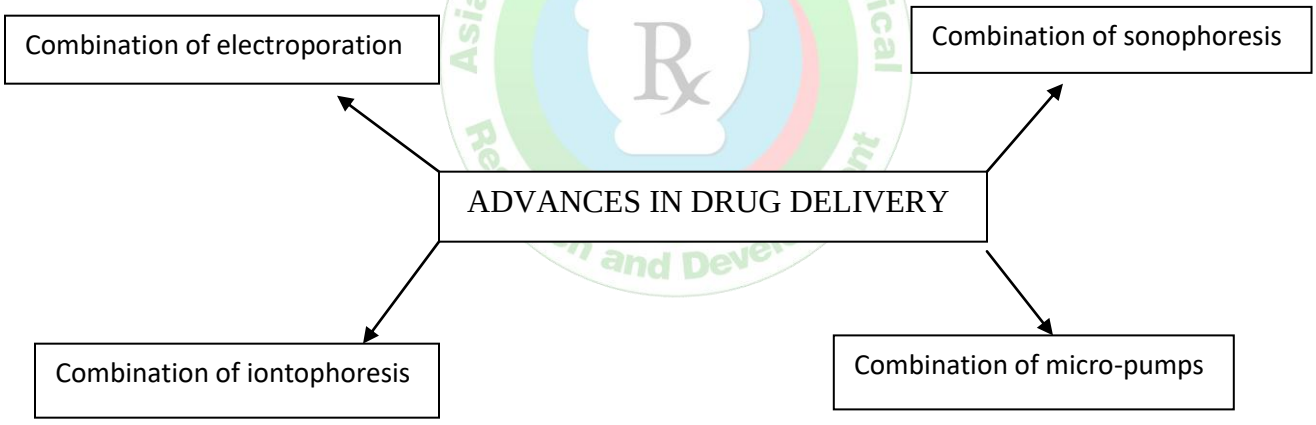

Figure: 3 Advances in drug delivery by microneedle

Combination of electroporation & microneedles:- Electroporation cause localized perturbation by forming aqueous pathways in the lipid bilayer of the skin using high voltage short duration current. A trans-membrane potential upto 1 KV for 10 microns to 500 microns was used for invitro electroporation of stratum coeneum[33]. Electroporation can be used in concert with chemotherapy for effective tumour treatment. Wilke *et al.* designed a silicon microneedle electron array with integrated temperature and fluidic system for drug delivery specially to tumour cell[34].

Combination of sonophoresis & microneedles:- Sonophoresis uses ultra sound for enhancing transportation of drugs by forming cavitation and change in the lipid arrangement of the stratum corneum. Drug permeation can be controlled by controlling the frequency of the ultra sound. As the sound frequency increases from 20 KHz to ≈ 1MHz, skin perturbation increases 1000 fold[33]. Chen et al; found that an increase in the rate and extent of delivery of calcein (623 Da) and bovin serum albumin (66.430 kDa) could be achieved by using the combination of sonophoresis and microneedles[35].

Combination of iontophoresis and microneedles:- In iontophoresis a small electrical current is used for transportation of drugs across the stratum corneum of the skin. The main advantage of using iontophoresis along with microneedles is to control delivery of drug by controlling the current. The current may be turn on an off by the

patient, and can deliver small drug molecules and biomolecules having a molecular weight upto a few thousand Daltons[36]. Chen *et al;* studied the administration of insulin unilamellar nanovesicles through microneedles along with iontophoresis[35]. Lin *et al*. investigated the delivery of antisense oligonucleotides (ODN) by using Macroflux microprojection patch technology. Macroflux patch technology was found capable of delivering a therapeutically relevant amount of ODN into an through an skin[37].

Combination of micro-pumps and microneedles:- Micro-pumps, when associated with microneedles, provide precise delivery of drug. Pumps control flow rate and pressure for delivery of concentrated drug solution as per specifications. Zahn *et al*. prepared an integrated system, with micro-valves and micro-pumps, which was capable of controlling fluid withdrawal for medical analysis and delivering the drug in response to metabolites levels[38].

APPLICATIONS OF MICRONEEDLES AND PSORIASIS:-

Microneedles for insulin delivery:- Many research studies were carried out for insulin found that insulin delivered through microneedle drug delivery was appropriate and it produced proper biological effect and maintained the blood glucose level. The first approach for insulin delivery was done by using 10-IU standardized insulin lispro which showed good absorption rate[39-40].

Microneedles for glucose monitoring:- Microneedle are used indirectly for glucose monitoring. Previously, devices namely, 'Cygnus glucowatch' were used more for monitoring glucose levels in the body . Commercially available glucose monitoring device is Kumetrix which is made up of silicon microneedle[41].

Microneedle for transdermal protin delivery:- Miconeedle mask devices have been prepared using continuous liquid interface production technique coated on polyeyhylene glycol base for appropriate delivery of protein like serum, albumin and ovalbumin. The successful delivery has been noted in studied carried out on mice for 72 hours in which sustained retention was observed[42].

Microneedle for acne scar treatment (Dermaroller):- For acne scar treatment, microneedle are used. The area with acne scar is treated with anesthetic agent and the Dermaroller is used and allowed to move in vertical and horizontal direction. The saline pads are used for treating the bleeding which could be controlled. The process takes 20 minutes for getting completed. Also, home care derma rollers are used for delivering anti- ageing products[43].

Microneedles for vaccine delivery:- The increase in awareness among people regarding vaccination has led scientists to find new approaches for the delivery of vaccine. Various technique and devices like "mantoux" or "soluvia microinjection system" can be used to perform this process. According to studies, mantoux technique is difficult to perform as it required professional person, whereas soluvia technique is commonly used and that too for the delivery of influenza vaccines, such as trivalent or quadrivalent or influenza type A or B[44].

Table: 2 List of marketed products used in specific treatment.

Product name	Purpose	Reference
Kumetrix[R]	Glucose monitoring	(Koschinsky, 2001)
Soluvia[R]	Vaccine delivery	(Wiwanitki, 2014)
Micronjet[R]	Vaccine delivery	(Levin *et al;* 2014)
Dermaroller[R]	Scars,wrinkles treatment	(Nair and Arora, 2014)
Nicotinell[R]	Nicotine patches for treating addition	(Moffatt *et al;* 2017)

Microneedle for cosmetic purpose (Dermaabrasion):- Microneedle are used for decreasing the scars, wrinkles, etc from the skin. This is achieved by puncturing the skin multiple times through microneedle, earlier which was done through hypodermic needle. The pores, created through microneedles resulted in the increase of collagen growth and breaking or disruption of old collagen which caused damaged to the skin. The needles can be adjusted according to the depth, skin layer in which one wants the insertion .

4.1 PSORIASIS:- Psoriasis is a polygenic inflammatory chronic disorders diseases of the skin. It is immune-mediated and relapse is common[45]. Psoriasis reportedly affects approximately 2% of the worlds population[48]. negatively influencing the life quality of patients. The immune system is involved in psoriasis development and the key pathogenic factor including but not limited to TNF-α, IL-17A, IL-23 as its been widely acknowledge. Psoriasis lesions typically feature erythema, scales, red papules and thicken skin. Itching, desquamation and visible plaques are the most common symptoms and signs of psoriasis and may have a serious impact on the quality of life; that there is no cure for psoriasis so far is regrettable. Systemic therapy is often associated with side effect[46]. It is been reported that 74% of drugs delivery orally are not as effective s desired[47]. In the systemic therapy, the first line drugs in the treatment of psoriasis include methotrexate (MTX), cyclosporine A (CyA) and retinoic acid[48]. These drugs are effective but bring about harmful side effects such as hepatotoxicity, impaired renal function and hypertension. The high cost of biologics is an obstacle to extensive promotion. MNP strategies for psoriasis are of particular focus here.

Table: 3. Application of microneedle in treatment for psoriasis.

Delivered compounds	Matrix material
MTX	Soluble maltose
MTX	Poly lactic-co-glycolic (PLGA)
CyA	Hydroxypropyl cellulc

Anti-TNF-α Ab	Sodium carboxymethcellulose
Anti-TNF-α Ab	Sodium carboxymethcellulose
Calcipotriol ointment	Hyaluronic acid, (HA)

Researchers have developed MNPs to improve the MTX treatment efficacy for psoriasis and reduced the side effects caused by microneedles. Ajay K. Banga and teammates works have reported that when MTX is applied under MNP-pretreated skin, the delivery of MTX is more effective than with control methods. In 2008, their team developed a MNP fabricated by soluble maltose, consisting of 56 needles with a height of 500 micrometer[49]. In vivo, the MNP completely dissolve within 10 min with a reduction in ear thickness and down regulation of the IL23/IL17 axis in the MTX-MNP group. (Fig 4.) This research, demonstrating a new method based on dissolving hyaluronic acid MNP to deliver MTX from the skin, showed a strengthened therapeutic effect in comparision with current method.

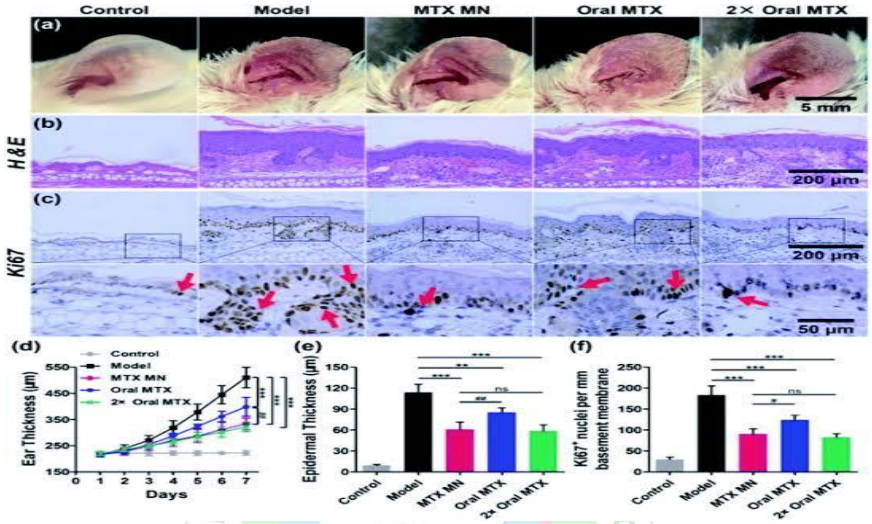

Figure: 4. Therapeutic effect of MTX loaded MNs (13.8 microgram),oral administration of same dose(13.8 microgram) and double dose (27.6 microgram) of MTX on IMU induce psoriasis like skin inflammation.

In 2018, an open pilot trial in Korea that included 10 patients, assessed the enhanced role of hyaluronic acid based MNP as a topical therapy for psoriasis. After a topical application of calcipotrion ointment (Daivobet[R]) daily for atleast 4 weeks, resistant psoriasis plaques were selected to be the target sites of MNP[50]. The MNP remains on the surface of Daivobet[R] pretreated plaques overnight and clinical improvement was assessed at week 0 and week 1.

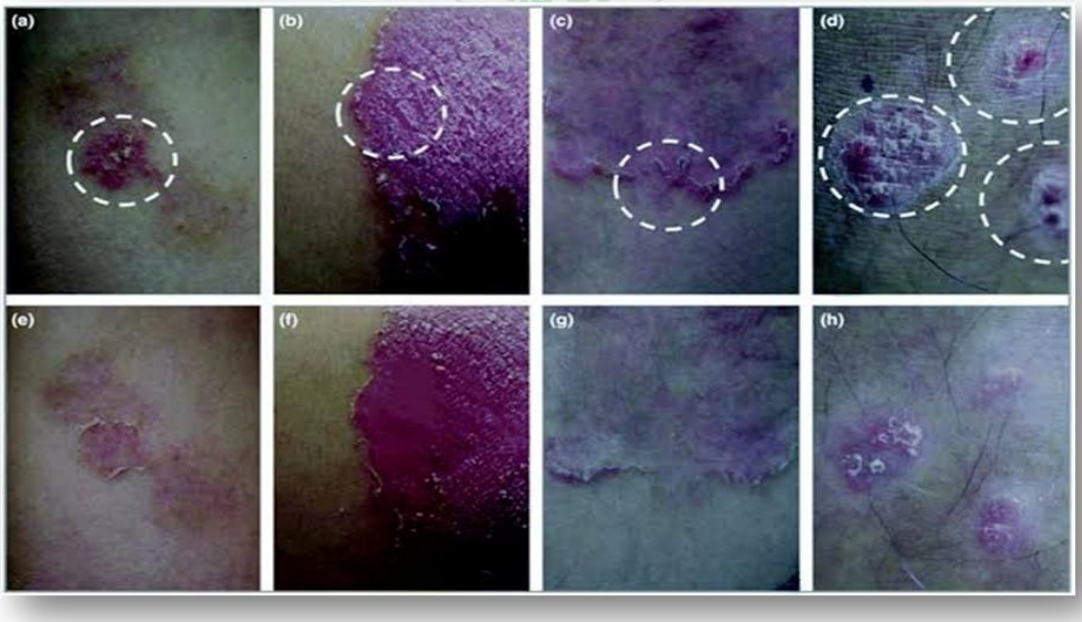

Figure: 5. Psoriasis plaques improves significantly after 1 week of microneedle patch application. The circle indicated by white dotted line is a plaque treated with a microneedle patch. The modified psoriasis area and severity index decrease from 7 to 1 in patient 1 (a and e), from 9 to 3 in patient 5 (b and f), from 5 to 0 in patient 6 (c and g) and from 6 to 2 in patient 9 (d and h). These 4 patients were very satisfied with the additional application of microneedle patch.

CONCLUSION:-

This review article included the basics of TDDS as well as microneedle drug delivery system. It can replace conventional method of drug delivery most probably the transdermal approach. The biggest advantage that is offers is the painless treatment, the biological treatment are an alternative to conventional trearment for moderate and severe psoriasis. Pharmacist have a potentially role important educational role to help support patients and improve disease outcomes.

AUTHOR CONTRIBUTION:-

The manuscript is conceptualized & data acquisition done by Saurabh Bodkhe .Critically reviewed the content & revised it.

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