



e-ISSN: 2319-8753 | p-ISSN: 2347-6710

IJIRSET

International Journal of Innovative Research in
SCIENCE | ENGINEERING | TECHNOLOGY



INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH

IN SCIENCE | ENGINEERING | TECHNOLOGY

Volume 11, Issue 4, April 2022

ISSN INTERNATIONAL
STANDARD
SERIAL
NUMBER
INDIA

Impact Factor: 8.118



9940 572 462



6381 907 438



ijirset@gmail.com



www.ijirset.com

Microneedles: Uses in Insulin Dependent Diabetes Mellitus through Transdermal Drug Delivery

Prashant Jadhav* ¹, Ambadas Rote ², Meha Nakrani ³, Saurav Patil ⁴

P.G. Student, Department of Pharmaceutical Quality Assurance, MGVS College of Pharmacy Panchavati, Nashik, India¹

ABSTRACT: This review article focuses on the use of microneedles for effective treatment in insulin dependent diabetes mellitus. There are many limitations in oral, subcutaneous, nasal and other modes of delivery causing pain and have many other side effects. Insulin medication is currently effective in the treatment of type 1 diabetes. Poor absorption and enzymatic degradation in the gastrointestinal tract and liver of insulin therefore the most preferred route is subcutaneous. However, this route has poor patient compliance due to causing pain and also risk of infection and inflammation. Microneedle based drug delivery system added advantages towards the pain free administration and easy handling. Providing continuous and controlled release system. This article also focuses on recent emerging process in microneedles utilization for the transdermal delivery of insulin.

KEYWORDS: Microneedles, insulin, transdermal drug delivery, skin, diabetes mellitus.

I. INTRODUCTION

Diabetes is the biggest leading lethal disease in the world. Insulin is the most effective medicine to control blood glucose levels in type I diabetic patients. Over the past decades, the incidence of diabetes has been doubled, the diabetes are responsible for many adverse complications. Globally, as per the estimation in 2014, around 42.2 cr. are affected by diabetes as compared to 10.8 cr. in the year 1980. Since 1980, 4.7%–8.5% rise of diabetic patients among adult population has been observed, which is considered to be doubled globally [1,2].

The subcutaneous route is the preferred insulin administration method due to the poor absorption or enzymatic degradation of insulin in the gastrointestinal tract and liver. Insulin is given by subcutaneous needle injection, which is inconvenient and painful leads to poor patient compliance. During the past few years, the effort has been put into developing novel and more comfortable routes of insulin administration. However, degradation of insulin by proteolytic enzymes and acidic pH and the low penetration of insulin into the blood stream is due to the bioavailability of oral insulin is low. For inhalation therapy, the first FDA approved pulmonary delivered version of insulin, was withdrawn from the market due to high cost, device design, side effects and unknown health risks. A rapid-acting inhalable insulin by Mann-Kind, got the FDA approval in 2013. However, there are initial concerns that long-term exposure of the lungs to insulin could cause lung cancer, and it was not recommended for people with asthma and chronic obstructive pulmonary disease. Therefore, a more comfortable and effective method of administration of insulin is transdermal delivery. It also improved patient compliance and easy self-administration. It also avoids drug degradation within the gastrointestinal tract and active drug loss due to first pass hepatic metabolism. However, the outermost stratum corneum (SC) of the skin is an effective barrier against the entry of foreign drugs. The molecular weight of the drug molecule is important for permeation as it indicates if it can passively pass through the SC. It is applicable only for molecules that are traditionally smaller than 500 Da. Insulin, which has a molecular weight of 5.8 k Da, cannot pass through skin. Microneedles (MNs) is to be a promising alternative to overcome the barrier of the SC. MNs are the devices composed of needle-like structures with diameters in the size of microns. MNs create microscopic holes for drugs to pass through deeper layers of the skin to the micro-capillary bed for systemic absorption. Anatomy of the skin shown in fig 1 [7,9,11].

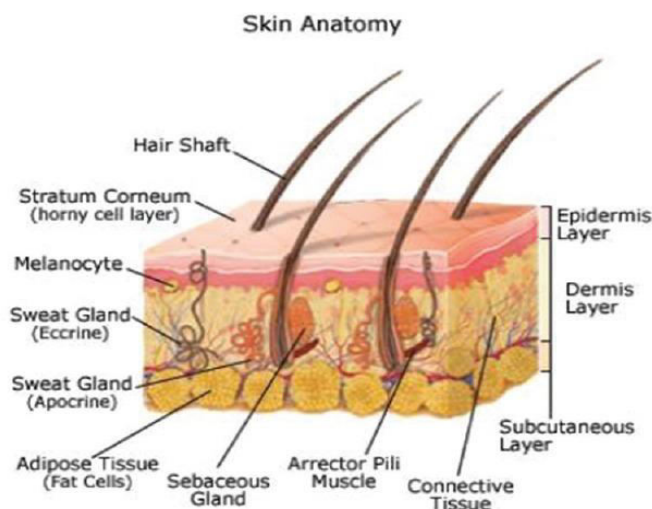


FIG 1

II. TYPES OF MICRONEDDLES

This review highlights 5 main types that is solid, coated, dissolving, hollow, and hydrogel-forming MNs.

1.Solid microneedles

Solid MN development is an approach termed as “poke with patch” which having a 2 steps. In the 1st step, solid MN arrays are applied to the skin, which creates a miniature microchannel on the stratum corneum into which the drugs can be easily transported inside the body. The mini microchannel increases the permeability of the stratum corneum through passive diffusion method. “coat and poke” which applied in the use of solid MNs array coated with macromolecules (drug or vaccine). The formulation which is coated on the MN After that the application of MN on to the stratum corneum. The formulation is deposite on the SC. The coated MN is beneficial for delivering macromolecules such as protein, nucleic acid, and vaccines into the skin. The use of coated MNs may be option for vaccination purposes or for the delivery of potent drugs, but this is suitable for delivering small amounts of active molecules not large amount of active molecule[1,2]. ” poke and patch” approach with solid microneedle arrays is shown in fig 2[6] and coat and poke” approach Shown in fig 3[6].

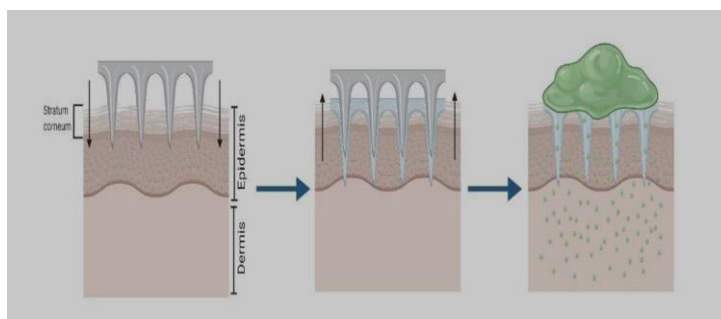
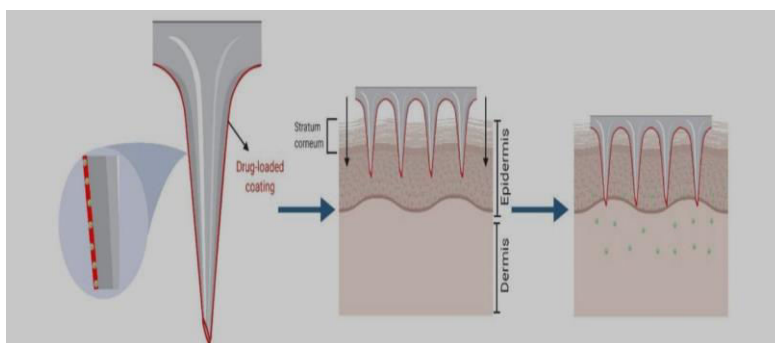
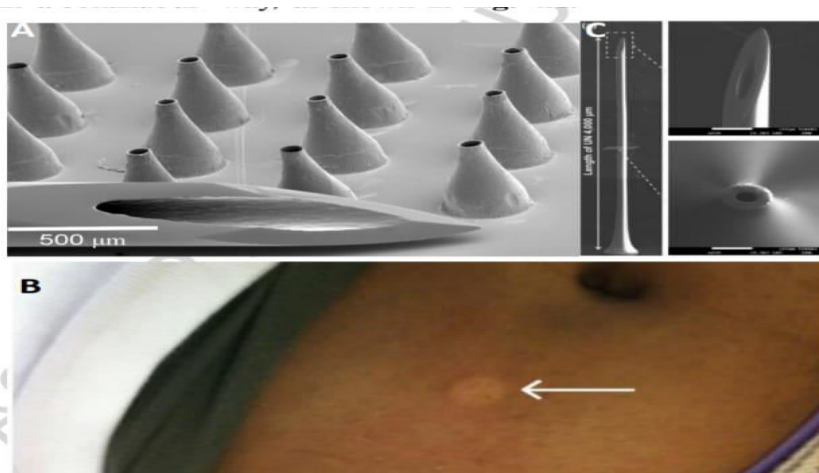


Fig 2 - schematic representation of ” poke and patch” approach with solid microneedle arrays^[6].

Fig 3 - schematic representation of “coat and poke” approach^[6].

2. Hollow microneedles

Hollow MNs having a hollow needles through which the drug is delivered. Hollow MN, is made of varying materials such as silicon, metal, hollow glass, polymers, and ceramic. In this approach microneedles play a similar role to hypodermic needles, through which drug formulations are administered after skin perforation. Due to their micrometric size, their manufacturing process is very difficult and expensive, The manufacturing process requiring significant technological resources. The hollow MN which is extensively used in insulin delivery [1,2]. poke and flow is shown in fig 4 [6].

Fig 4 -schematic representation of poke and flow approach^[6]

3. Hydrogel-forming microneedles

Hydrogel-forming MN which contain a swelling material with a drug reservoir. Both the swelling material and drug reservoir in the hydrogel-forming MN array diffuse the drug by absorbing the interstitial fluid (ISF) through the swollen micro projections. Hydrogel-forming MN arrays are made by synthetic polymers. Macromolecules and micromolecules are distributed through hydrogel-forming MN. This technology will provide better glycemic control and management. The advantage of parenteral route is that it bypasses the body physical barrier and degradation and directly enters into the bloodstream. The length and dimension of MN is having such that it reaches the capillary and layer of the stratum corneum to deliver the drug into the circulation. This technology will provide great opportunity in the field of subcutaneous drug delivery as it has a pain-free manner of drug delivery approach [1,2,3]. Poke and release approach for hydrogel-forming microneedles is shown in fig 5 [6].

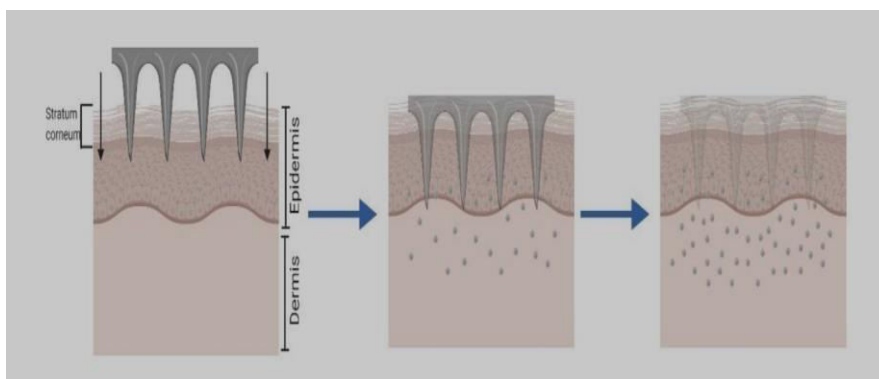


Fig 5 - schematic representation of "poke and release" approach for hydrogel forming microneedles^[6].

4. dissolving microneedles

Dissolving MNs are made of a soluble and biodegradable matrix that includes the active substance. After insertion of MNs needle matrix dissolves into the skin and the drug is delivered. Micro-molding techniques are used to produce dissolving MNs. Commonly, the dissolving MNs are made up of sugars, carbohydrates, or synthetic polymers which can be used in the delivery of insulin, low-molecular-weight heparin, ovalbumin, adenovirus vector, vaccine antigens, photosensitizers, and precursors. Dissolving MN is more effective in better delivery of the drug into the skin [1,3]. Various microneedles employed for transdermal insulin delivery are shown in fig 6[6].

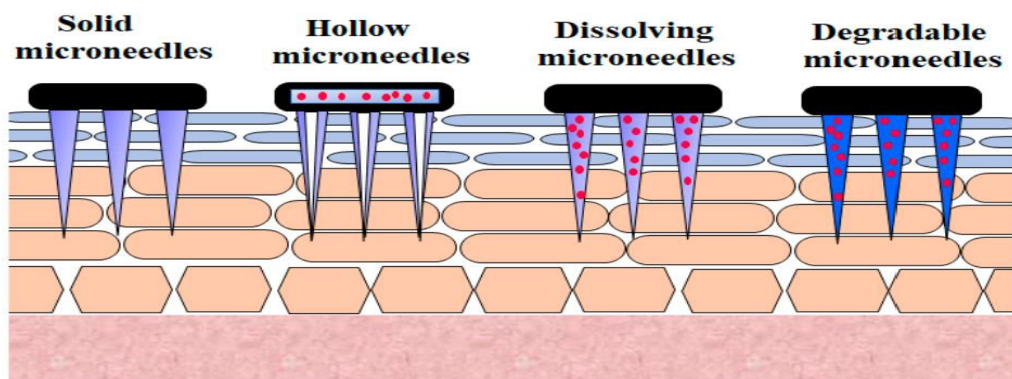


Fig 6 - various microneedles employed for transdermal insulin delivery

III. MICRONEEDLE ARRAY

As a drug delivery device, the concept for the use of MN was proposed in the 1970s. However, the first serious discussions of MN emerged in the 1990s, when Henry et al. demonstrated the use of silicon MN to successfully deliver a fluorescent dye and calcein across human skin. Since then, there has been rapidly increasing interest in the field to develop novel needle fabrication technologies and the drug delivery industry to develop MNs for pharmaceutical applications. MN arrays consist of a plurality of micron-sized projections with the length ranging from 25 μm to 2000 μm . The stratum corneum makes up the top 20 μm of the epidermal layer and provides much of the barrier to drug transport. The viable epidermis with a thickness of 130-180 μm is located below the stratum corneum. The nerve endings in the skin are a few microns below. Thus, MNs are used to pierce the upper layer of the skin in a non-invasive and painless way to increase skin permeability. By now, numbers of types of MNs composed of different materials have been used for the transdermal drug delivery. The first produced MNs for drug delivery were made from silicon wafers, which were much sharper than other materials. Silicon Microneedles production is expensive and the fragile MNs (silicon) may break and also remain in the skin. More recently, other MN production materials have been introduced for the generation of cheaper and biocompatible MNs, including metal, polymers and glass MNs. MN is crucial for efficient transdermal drug delivery. Various different shapes of microneedles have been developed from cylindrical, rectangular, pyramidal, conical, octagonal, to quadrangular, with different needle lengths and widths. Many factors that affect the drug permeability and also the insertion behavior. For example, the inherent designs of the MN

patches, such as the MN geometry (length, shape) and the number of needles, are important as they directly affect the drug permeability. Therefore, the drug release rate can be controlled by modulating the MN geometry or changing the drug formulations[3,10].

IV. SAFETY AND PERMEATION

MNs are made from a large number of different materials, such as silicon, glass, metal and polymers, and differ in length and in shape. The MN design parameters are critical as they can affect the drug permeability and safety. For example, the design of MNs can affect the level of pain felt and increasing MN length and number have been directly correlated to pain. Bal et al. investigated safety and barrier disruption following application of MN arrays varying in length and shape on the ventral forearms of 18 human volunteers. Redness values and trans-epidermal water loss (TEWL) were used to evaluate the safety (skin irritation and pain sensation) and barrier disruption. Results showed that TEWL and redness values after treatment with solid MN arrays of 400 μm were significantly increased compared to 200 μm . The MN insertion force is also a crucial factor in the enhancement of permeation. An increased insertion force increase the amount of insulin permeated, while using insufficient force may reduce or prevent the amount of insulin passing through the skin. For decreasing patient discomfort Several MN application devices have been developed. And also leading to a more effective depth controlled penetration of MN into the skin. A high MN density may be less efficient in piercing the skin because they can cause a 'bed of nails' effect[3,4,9].

V. CHALLENGES

MNs should be reliable and strong enough for repeated penetration and extended use. The degree of biocompatibility also plays an important role for its continuous use. Silicon is found to be excellent for MN fabrication, its degree of biocompatibility may vary. Biodegradable polymer-based MN should be explored. Some researchers believe that the continuous delivery of insulin via the auxiliary pump system requires maintaining more amount of insulin where as in the case of MNs it can be maintained through less volume or amount of insulin. Controlled injections of insulin over an extended period of time might deliver shot more frequently; thus, insulin concentration can be maintained[1].

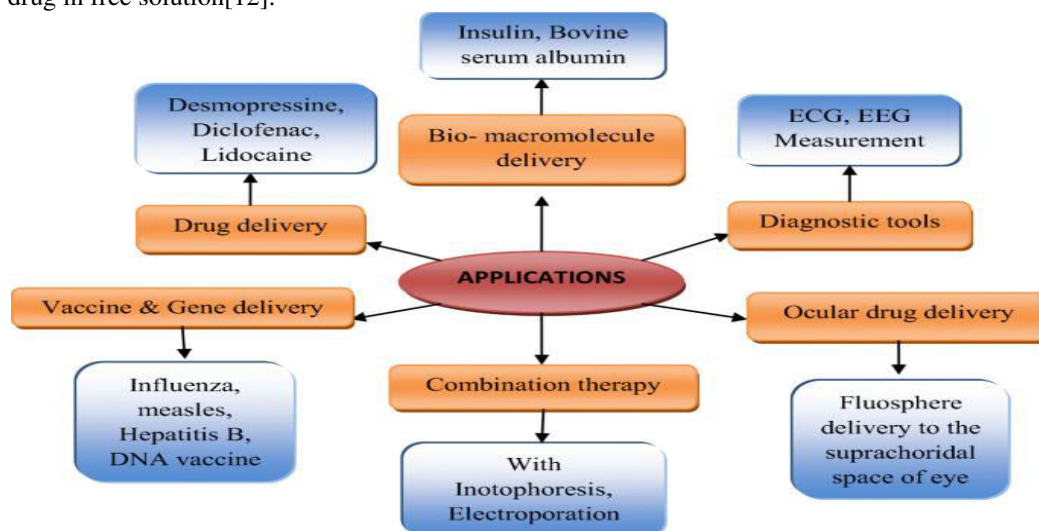
VI. PERSPECTIVES

Microneedles have been widely studied for transdermal delivery of insulin. In this review, describe the recent progress of MN technologies for insulin delivery, which provide a powerful new approach for transdermal insulin delivery. For example, silicon, the most commonly-employed MN material, has biocompatibility. Besides, solid MNs require a two-step administration process. For coated MNs, a drawback from this approach is the restricted amount of drug that can be coated. Furthermore, the heating step in the dissolving MN fabrication may give the pharmacological activity of insulin. The MNs with different geometries, lengths and geometries would impact the transdermal delivery efficiency of insulin. microneedle technologies have a bright future for transdermal delivery of insulin[3].

VII. APPLICATION

- The microneedles are developed for delivering biotherapeutics, biomacromolecules, like insulin, growth hormones, immunobiological, proteins, and peptides. Insulin having dissolvable microneedle of starch and gelatin and bovine serum albumin microneedles are some of the best examples[12].
- Vaccine delivery by the microneedle is meant to replace hypodermic needle for avoiding site specific pain. Kommareddy et al. investigated influenza subunit vaccine-coated microneedle patches for their immune responses with intramuscular injections in guinea pigs[12].
- A new investigation is carried out recently by Kim et al. reports that the recombinant coronavirus vaccine is delivering through the skin with the help of microneedle for treatment of COVID-19[12].
- For ocular drug delivery, the microneedle therapy is the best have been observed to be more effective than topical application[6,12].
- Microneedle has also been used for local anesthesia. In an investigation, Baek et al. suggested the use of microneedles pain-free and rapid local anesthesia. developed lidocaine coated microneedle that showed in vitro skin penetration and also enhanced delivery of the drug in a short duration, i.e. in 2 min[12].

- For pain management, meloxicam-loaded polymeric microneedles have also been developed using polydimethylsiloxane molds. The in vitro release studies showed near about 100% drug release in 60 min[12].
- Penetrating the biofilm and delivering antibiotics directly to regions of active growth a patch of microneedle is used for the treatment. They developed chloramphenicol (CAM)-bearing and gelatin sensitive gelatin nanoparticle (CAM @ GNP)-filled patches with self-dissolving microneedles and needle tips. Finally concluded that for the treatment of *Vibrio vulnificus*, biofilm microneedle treatment is more effective than the drug in free solution[12].

Fig 7 – applications of microneedles^[12]

➤ **List of ingredients used for the preparation of microneedle :**

- **Metals :** Silicon, Titanium, Stainless steel, Silicon Palladium.
- **Biodegradable polymers :** PLGA, PLA, PVP, Polyglycolic acid, Polycarbonate, Polyvinyl pyrrolidone.
- **Non-biodegradable polymers:** Alginic acid, Gantrez AN-139, Polyvinyl acetate, Polyvinyl alcohol (PVA), Carbopol 971P-NF, Polyetherimide.
- **Natural polymers:** Zein, Chitosan, Thermoplastic starch, Carboxymethyl cellulose, Amylopectine, Dextran, Galactose, Maltose, Chondroitin sulfate.

NCT No.	Condition	Drug	Phase	Status
NCT00837512	Type1 DM	Insulin	2, 3	Completed
NCT00558649	Influenza, human	Fluvaccine(FLUARIX®)	NA	Completed
NCT02745392	Acute migraine	ZP Zolmitriptan P	2,3	Completed
NCT02837094	Type 1 diabetes	C19-A3 GNP	1	Active,not recruiting
NCT04053140 1	Healthy volunteers	Penicillin G	NA	Recruiting

Table no. 1 - status of clinical trials based on mn technique^[12].

Brand name	Manufacturer	Description	Application
Darmaroller®	Derma spark, Canada	Metallic microneedle array	treatment of acne, stretch mark and hair loss.
MicroHyal®	CosMED Pharmaceutical Co. Ltd., Japan	Dissolvable microneedle patch	to treat the skin wrinkle.
VaxMat®	TheraJect Inc., USA	Dissolvable microneedle patch	It used to delivery of proteins, peptides, and vaccines.
Micro-Trans®	Valeritas Inc., USA	Microneedle patch	It deliver the drug to the dermis.
Soluvia®	Becton Dickinson, USA	Hollow microneedle array	It is a prefilled microinjection system for tdds.
IDflu®/Intanza®	Sanofi Pasteur, Lyon, France	Intradermal microneedle injection	Prefilled with influenza vaccine.
Microcore®	Corium International Inc., USA	Dissolvable peptide microneedle patch	Delivered proteins, peptides, and vaccines.

Table no 2 - marketed microneedle-based transdermal products^[12].

REFERENCES

- [1] Bhaishali A., jana and ashish d. wadhavani. Microneedle-future prospect for efficient drug delivery in diabetes management. Indian journal of pharmacology 2019 jan ;51(1):4-10.
- [2] khanna p. strom JA, Malone JI, bhansali S. microneedles based automated therapy for diabetes mellitus. J Diabetes Sci Technol.2008;2:1122-9[PMC free article] [pubmed] [google Scholar]
- [3] Song xie, zinging le, zongqin yu. Mironeddles for transdermal delivery of insulin. Journal of Drug Delivery Science and Technology. 23-4-2015 doi: 10.1016/j.jddst.2015.04.008
- [4] Bal SM, Caussin J, Pavel S, Bouwstra JA. In vivo assessment of safety of micro-needle arrays in human skin. Eur. J. Pharm. Sci. 2008; 35: 193–202. [PubMed: 18657610].
- [5] Cheung K, Han T, Bhusan D. Effect of Force of Microneedle Insertion on the Permeability of Insulin in Skin. J. Diabetes Sci. Technol. 2014; 8: 444–452. [PubMed: 24876604].
- [6] Antoneo jose guillot, ana sara cordeiro, rayan f. Donnelly, Teresa m. garrigues. Microneedle-Based Delivery: An Overview of Current Applications and Trends. Pharmaceutics 2020;4-6[cross ref]
- [7] Banga AK. Microporation applications for enhancing drug delivery. Expert Opin.Drug Deliv. 2009; 6: 343–354. [PubMed: 19348604].
- [8] Silpi C, Manish B, Kumar TR. Microneedle-based automated therapy for diabetes mellitus. *IRJP*. 2011;2:72–8. [Google Scholar]
- [9] Jeong, H.-R Lee, H.-S Choi, I.-J Park, J.-H. Considerations in the Use of Microneedles: Pain, Convenience, Anxiety and Safety. J. Drug Target 2017, 25, 29–40. [CrossRef]
- [10] Bal,S.M,Caussin,et al. InVivo Assessment of Safety of Microneedle Arrays in Human Skin. Eur. J. Pharm. Sci. 2008, 35, 193–202. [CrossRef] [PubMed]
- [11] Ling M, Chen M. Dissolving polymer microneedle patches for rapid and efficient transdermal delivery of insulin to diabetic rats. Acta. Biomater. 2013; 9: 8952–8961. [PubMed: 23816646].
- [12] Jitu Halder,Sudhanshu Gupta, Rakhi Kumari, Ghanshyam Das Gupta,Vineet Kumar. Microneedle Array: Applications, Recent Advances, and Clinical Pertinence in Transdermal Drug Delivery.Journal of Pharmaceutical Innovation (2021) 16:558–565.Published 8 June 2020.<https://doi.org/10.1007/s12247-020-09460-2>.



ISSN INTERNATIONAL
STANDARD
SERIAL
NUMBER
INDIA



INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH

IN SCIENCE | ENGINEERING | TECHNOLOGY

 9940 572 462  6381 907 438  ijirset@gmail.com



www.ijirset.com

Scan to save the contact details