International Journal of Advances in Engineering and Management (IJAEM)
Volume 5, Issue 2 Feb. 2023, pp: 398-414 www.ijaem.net ISSN: 2395-5252

Use and Improvement of Microneedles in Diabetes Treatment

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Date of Submission: 03-02-2023 Date of Acceptance: 17-02-2023

ABSTRACT-The focus of this review is on the use of microneedles (MNs) as a newly developed medication delivery system for a successful treatment of diabetic patients. There are several restrictions on numerous distribution methods, including oral, subcutaneous, nasal, and other methods that hurt and have numerous unpleasant negative effects. Therefore, it has been determined that this drug delivery research has enormous promise for merging both the therapeutic and diagnostic components, thereby treating diabetes more effectively. The majority of glucose-sensing methods and traditional insulin treatments involve the transfer of physical objects through the skin.A drug delivery system based in Microneedles can do so in a minimally invasive or noninvasive way, which can be an added benefit for painless administration, simple handling, discrete, continuous delivery, and providing a controlled release method. Therefore, the review focuses on how this bioengineered system, like MNs, is now developing as a "smart" system that is specifically designed for autonomous diabetic therapy.(Zhang Y 2019)(Zaric BL 2019 January)

Key Words- Microneedles, Skin, Diabetes Mellitus,Transdermal Drug Delivery System

I. INTRODUCTION -

Skin is the largest organ in the body and covers the body's entire external surface. It is made up of three layers, the epidermis, dermis, and the hypodermis, all three of which vary significantly in their anatomy and function. The skin's structure is made up of an intricate network which serves as the body's initial barrier against pathogens, UV light, and chemicals, and mechanical injury. It also regulates temperature and the amount of water released into the environment. This article discusses the relevant anatomical structures of the skin's epidermal layer, its structure, function, embryology, vascular supply, innervation, surgical considerations, and clinical relevance.

A transdermal patch is an adhesive patch applied to the skin that contains medicine and is intended to be applied to the skin to deliver a particular amount of medication into the bloodstream. The fundamental drawback of transdermal delivery systems is that only drugs whose molecules are tiny enough to permeate the skin can be administered using this technique due to the skin's high effectiveness as a barrier.

Researchers have created microneedle transdermal patches (MNPs), which include an array of microneedles and can transport a wider variety of substances or molecules through the skin without the requirement to first micronize the medication, to get over the skin's restriction.

1.Anatomy of the skin—

Microscopically the skin is a multilayered organ composed of anatomically, many histological layer, but it is generally described in term of three tissue layers: the epidermis, The layer of the skin write below

1. Epidermis
2. Stratum basale-
3. Stratum spinosum-
4. Stratum granulosum–
5. Stratum lucidum–
6. Stratum corneum -.
7. Dermis
8. Hypodermis

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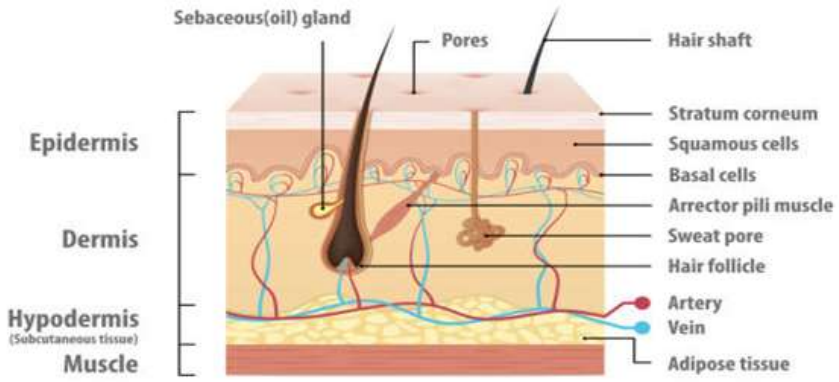

Fig 1- Structure Of Human Skin

II. DIABETES MELLITUS—

Diabeteswas first discovered in 1500BCE and has been recognized as a calamitous and lethal disease since then. The pathophysiology of diabetes is due to deficiency of insulin secretion, impaired insulin action, and both.(Diabetes. 2012)Diabetes can be classified into different types-

I. Type 1 diabetes mellitus (T1DM)-
II. Type 2 diabetes mellitus (T2DM),-
III. Gestational Diabetes Mellitus-
IV. Congenital Diabetes Mellitus

2.1Symptoms of Diabetes Mellitus-

Fig2 – Symptoms of Diabetes Mellitus

III. TRANSDERMAL DRUG DELIVERY SYSTEM-

Transdermal drug delivery is a method in which the drug is transported into the pores and skin layer for systemic distribution. Patch primarily based drug delivery gives unique and top-notch routes of administration for the hydrophobic capsules into the skin The skin's outer stratum cornea offers an impenetrable barrier for insulin drug delivery. To conquer this, micrometer-scale needles incorporate a unique technological method to decorate drug permeation across the skin layer, thereby permitting better insulin delivery, which would require infection for shipping. Transdermal drug transport is a gadget in which the unique, fixed and managed quantity of drug molecules is enclosed in a system to be introduced into the intact pores and skin floor at a predetermined rate into the systemic movement. Microneedles and thermal ablation are progressing via scientific trials for the delivery of macromolecules and vaccines, including insulin, parathyroid hormone and influenza vaccine.

Advantages and Dis advantages of transdermal drug delivery system(Patel RP, Formulation and evaluation consideration of transdermal drug delivery system 2011)(HP. 1989)

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Advantages	Disadvantages
1. It's an alternatives way of drug administration .	1. The drug can't be administered which molecular weight is < 500 dalton
2. It's improves patients compliances.	2. Rapid-action drugs cannot be administered by this process.
3. It's can be a shelf- administration	3. Anionic drug can't be delivered by this process
4. It's can be stable the blood levels.	4. The cost is high , so that poor people can't afford this
5. It's has no interaction with gastrointestinal fluid.	5. Only small lipophilic drugs can be delivered currently through the skin
6. It's reduce the side effect of drug administration.	6. Skin irritation and hypersensitivity reactions may occur The barrier functions of the skin change from one site to another on the same person, from person to person and with age

3.1 First generation -transdermal drug delivery system-

The first generation of transdermal delivery systems is responsible for most of the transdermal patches that have thus far been in clinical use. Significant advances in patch technology, and public acceptance, have enabled the recent surge in first-generation transdermal patches reaching the market. However, this surge will taper off as drugs with suitable properties for such systems are depleted. First-generation delivery candidates must be low-molecular weight, lipophilic and efficacious at low doses. Usually, their transdermal delivery should be more attractive than oral delivery due to low oral bioavailability, the need or desire for less frequent dosing or steady delivery profiles, or other factors.

The barrier created by the stratum corneum, the skin's thinnest layer, which is 10 to 20 m thick, is the main constraint for first-generation transdermal administration methods. The viable epidermis, which is avascular and has a thickness of 50 to 100 m, is located underneath this layer. The dermis, which is just below the dermal-epidermal junction and is 1-2 mm thick, is much deeper. It has a rich capillary bed for systemic medication absorption. A closer look at the stratum corneum barrier reveals a brick-and-mortar structure, with the nonliving corneocytes as the mortar and the mixture of lipids as the intercellular glue.

Drugs are normally transported across the stratum corneum via diffusion through the intercellular lipids in a tortuous course that loops around corneocytes, with hydrophilic molecules passing through the lipid head group areas and lipophilic molecules passing through the lipid tails. Because of the structural and solubility requirements for solution and diffusion inside stratum corneum lipid bilayers, this transport mechanism is severely restricted.

Instead of using a transdermal patch, a metered liquid spray, gel, or other topical formulation is applied to the skin. Upon evaporation or absorption, this formulation can propel tiny lipophilic medicines into the stratum corneum, which then acts as a drug reservoir for hours-long release into the viable epidermis(Morgan 1998).For example, testosterone gels have been in use for several years and a transdermal spray has been recently approved for estradiol delivery.

3.2 Second generation of Transdermal Drug delivery system-

The second generation of transdermal delivery systems acknowledges the necessity of improving skin permeability in order to broaden the application of transdermal medications. The ideal enhancer should: i) boost skin permeability by reversibly altering stratum corneum structure; (ii) offer an additional driving force for delivery into the skin; and (iii) avoid harming deeper, living tissues. The balance between attaining greater distribution across the stratum corneum and safeguarding deeper tissues from harm has proven difficult for enhancement methods created in this generation, such as traditional chemical enhancers, iontophoresis, and non-cavitational ultrasound. Because of this, the second generation of delivery technologies has improved small molecule distribution for localized, dermatological, cosmetic,

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and certain systemic uses, but has had little clinically significant impact on the delivery of macromolecules.(Guy 2003)(Prausnitz 2004)(Bronaugh 2005)(Miller 2005)

3.3 Third generation of Transdermal Drug delivery system-

The stratum corneum is the intended target of the third generation of transdermal delivery systems, which is expected to have a significant impact on medication delivery. While still sparing deeper tissues, this targeting enables a stronger rupture of the stratum corneum barrier and hence more effective transdermal distribution. In human clinical trials, it has been demonstrated that new chemical enhancers, electroporation, cavitational ultrasound, and more recently micro needles, thermal ablation, and microdermabrasion can transfer macromolecules, such as therapeutic proteins and vaccinations, across the skin. The development of methods to localize effects to the stratum corneum and the understanding that the safety provided by localization should make these more aggressive treatments medically acceptable were two factors that helped to make these advancements possible.(Arora 30August 2008)

IV. BASIC COMPONENT OF TRANSDERMAL DRUG DELIVERY SYSTEM-

I. Polymer matrix/drug reservoir
II. Membrane
III. Drug
IV. Permeation enhancers
V. Pressure-sensitive adhesives (PSA)
VI. Backing laminates
VII. Release liner
VIII. Other excipients like plasticizers and solvents

Polymer matrix/ drug reservoir-

Polymers are the backbone of TDDS, which manipulate the launch of the drug from the device. Polymers utilized in TDDS ought to have biocompatibility and chemical compatibility with the drug and other additives of the machine, such as penetration enhancers and PSAs .Additionally, they need to provide regular and effective delivery of a drug at some point of the product's meant shelf-life, and ought to be safe. The most applied polymers on skin belong to various classes, for example to cellulose derivatives, chitosan, carrageenan, poly-acrylates, poly-vinyl alcohol, poly-vinyl pyrolidone and silicones. They are gelatin agents, matrices in patches and wound dressings, anti-nucleate and penetration enhancers. [5] [6]

The criteria of the polymer which are used in TDDS-

I. Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.
II. The polymer should be stable, nonreactive with the drug, easily manufactured and fabricated into the desired product, and should be inexpensive.

Polymer used in Transdermal drug delivery system [5] [6]

Natural polymer – Cellulose derivatives, zein, gelatin, waxes, proteins and their derivatives, natural rubber, starch, chitosan, etc.

Synthetic elastomer –Poly-butadiene, Hydrine rubber, Polysiloxane , Silicone rubber, Nitrile, Acrylonitrile,

Butyl rubber, Styrene–butadiene rubber, Neoprene, etc.

Synthetic polymer-polyvinylchloride, polyethylene, polypropylene, Polyacrylate, Poly-urea, polyvinyl pyrrolidone, Polymethylmetha-crylate, epoxy, Ethylcellulose, Hydroxy propyl cellulose(HPC), polyamide, etc.

Membrane-

A membrane may be sealed to the backing to form a pocket to enclose the drug- containing matrix to form a pocket to enclose the drug-containing matrix or used as a single layer in the patch construction. The backing membrane serves as the back bone of patch. The backing membrane used as a polysterene, Silicone rubber, ethylene vinyl acetate and aluminized polyethylene [7] [8]

Drug-

For successfully developing a TDDS, the drug should be chosen with great care. Transdermal patches offer many advantages that undergo extensive first –pass metabolism, drugs with narrow therapeutic range [23] [24]There are some example of drugs that are suitable for TDDS Nicardipine Hydrochloride, Captopril, Atenolol, Metoprololtartarate, Clonidine, Propranolol Hydrochloride E.T.C

Permeation Enhancer-

One long- standing approach for improving TDD uses penetration enhancers, which increase the permeability of the SC so as to attain higher therapeutic levels of the drug candidate. Penetration enhancers interact with structural component of the Subcutaneous thus modifying the

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barrier function leading to increase permeability. [25] .Three pathways are suggested for drug penetration through the skin: Polar, Nonpolar, and Polar/Nonpolar. The Enhancers act by altering one of these pathways. Different permeation enhancers are used such as-

I. Sulphoxide(DMSO)
II. Azones (Lauracapran)
III. Fatty acid(Oleic Acid)
IV. Alcohol(Methanol)
V. Pyrollidone

Chemical and physical methods of augmentation are the two main types of techniques used to alter the barrier qualities of the Sub cutaneous to improve drug penetration (and absorption) through the skin.

Pressure Sensitive Adhesive (PSAs)-PSAs are the material that adheres to a substrate, in this case, skin by application of light force and leaves no residue when removed. They form interatomic and intermolecular attractive forces at the interfaces, provided that intimate contact is formed. Widely used PSA polymers in TDDS are poly-isobutylene-based adhesive, acrylics and silicone-based PSAs, Hydrocarbon resin E.T.C. The PSA can be located around the edge of the TDDS and compatible with the drug and excipients as their presence can modify the mechanical characteristics of the PSA and the drug delivery rate. [9] [10]

Backing laminates-The backing membrane must be impermeable to drug and permeation enhancers. The backing membrane serves as the purpose of holding the entire system together and at the same time, it protects the drug reservoir from exposure to the atmosphere, which could result in the breakage or loss of the drug by volatilization. The most comfortable backing will be one that exhibit lowest modules or high moisture, good oxygen transmission rate. Example of backing materials are vinyl, Polyethylene, polyester films, Aluminum and polyolefin films [11]

Release liner- During storage, the patch is covered by a protective liner that is removed and discared before the application of the patch to the skin because the liner is in intimate contact with TDDS patch, and the liner should be chemically inert. Teflon, silicon are used as release liner [12] [13]

Plasticizer- and Solvent-
Various solvents such as chloroform, methanol, acetone, isopropanol are used to prepare drug reservoirs. In addition plasticizers such as di butyl phthalate, and tri-ethyl citrate are added to provide plasticity to the transdermal patch

V. TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEM—

(Sudam KR, A Comprehensive Review on Transdermal drug delivery systems 2016)

1) Drug in adhesive patch

The single- layer drug in- adhesive patch-

In the single layer drug in the adhesive path, there is a single layer of adhesive in the patch. The adhesive layer of this patch also contain drug. Adhesive layer of this patch is not only serves to adhere to the various layer together but it also responsible for the release of the drug from patches

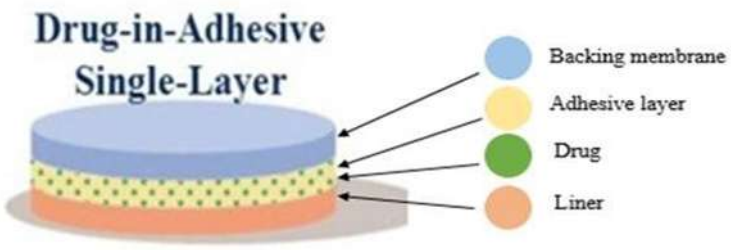

Fig3- Drug –in- Adhesive Single Layer

The multilayer drug in the adhesive patch-

The multi-layer drug in the adhesive patch is work as like as Single layer patch as a drug delivery. In the patch two adhesive layer are also responsible for the drug delivery. The two layer are usually are separated by a membrane. This patch also has a permanent backing and release liner.

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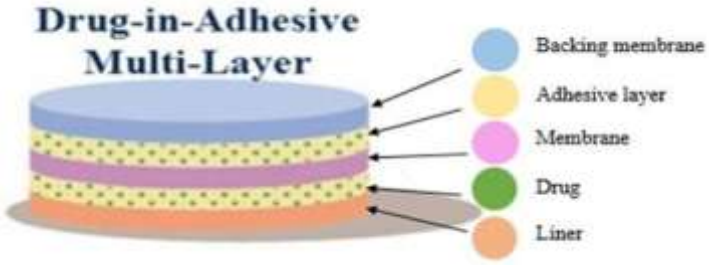


Fig 4- Drug-in – Adhesive Multi -Layer

2) **Reservoir patch-**

Reservoir transdermal system has a separate drug layer than the adhesive layer. The drug layer in the reservoir patch is a liquid compartment containing a drug solution or suspension which is separated by the backing layer.The drug reservoir is formed by first suspending the drug in an aqueous solution of water-soluble polymer after which dispersing the answer homogenously in a lipophilic polymer to form hundreds of unreachable, microscopic spheres of drug reservoirs.The thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ.(Yamagishi 2009,July)

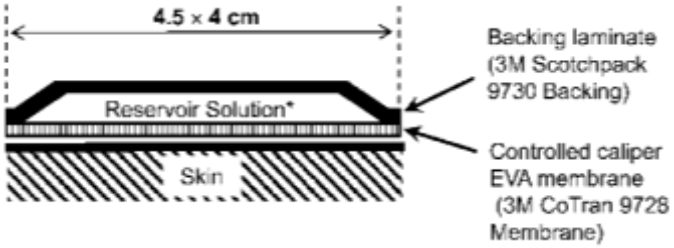
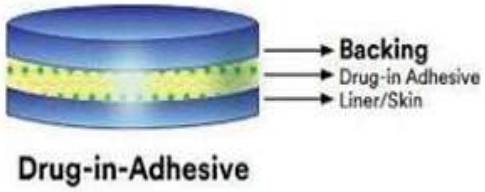


Fig 5- Reservoir Patch

3) Matrix TypeTransdermal Patch-

Drug- in- adhesive System-

In this type, the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting on an impervious backing layer. In this case unmediated adhesive polymer layer are applied for protective purpose (Robert 2020 ,February)



Matrix- Dispersion system-

The drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix.This drug-containing polymer disk is then fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing layer. It is spread along the circumstances to form a strip of adhesive rim.(Alptekin June 2022)

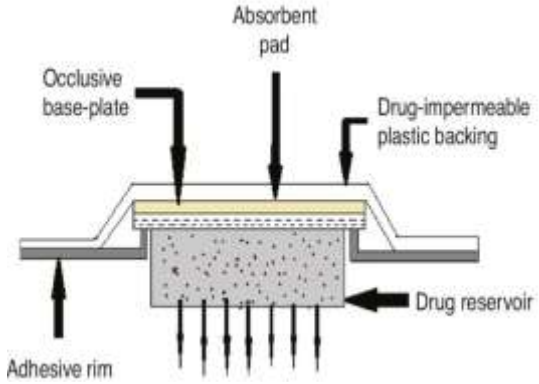


Fig6- Matrix-Dispersion System

4)Vapor patch -

In a vapor patch, the adhesive layer now not simplest serves to stick the diverse layers together but also to launch vapor. Vapor patches release essential oils for up to 6 hours and are especially used for decongestion. Other vapor patches on the market improve satisfactory of sleep or aid in smoking cessation.

Ideal characteristics of the drug for transdermal drug delivery system(Rastogi V 2014 Aug 23)(K. M. Arunachalam A 2010 Oct 1)(Naik A,

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Transdermal drug delivery: overcoming the skin's barrier function. 2000 Sep 1)

Sl no	Parameter	Properties
1	Molecular weight	<500 Dalton
2	Dose	Less than 20mg/day
3	Half-life	10 or less(hr)
4	Partition co efficient	Log P (1-4)
5	Skin permeability co-efficient	0.5×10^{-3} cm/h
6	Oral bioavailability	Low
7	Melting point	<200°C
8	Therapeutic index	Low
9	lipophilicity	10<ko/W< 1000
10	Ph	5-9

Various Types Of Transdermal Delivery system Used to Treat Diabetes

Methods	Advantages	Disadvantages
Chemical enhancers	High Effectiveness in combination with small molecules	Poor Effectiveness in combination with macromolecules and hydrophilic molecules 2) Inability to locate the effect on the Stratum corneum(SC)
Microsystems and nano-systems	Possibility to localized the effects and drug release in the first layer of the skin	Large size can hinder the penetration of the system into the skin
Pro-drugs	Improve chemical stability avoiding skin reaction	Large size can hinder the penetration of the system into the skin
Iontophoresis	1. Rapidly responsive molecular transport 2. Control of transport magnitude	1.Devices are expensive 2.Not applicable for long period of time due to the polarization of the skin 3.Inability to locate the effect on the SC 4.Skin Reactions(irritation, Inflammation)
Electroporation	1. Rapidly responsive molecular transport 2. Control of transport magnitude	1.Devices are expensive 2.Inability to located the effect on the SC
Sono-phoresis	1. Rapidly responsive molecular transport 2. Control of transport magnitude 3. Good effectiveness in combination with hydrophilic drugs and medium large molecular weight	1.Devices are expensive 2.Poor ranges of molecules administered safely
Thermal methods	Possibility to diffuse large-size, molecules	Inability to locate the effect on the SC
Jet Injectors	1. Delivery of solid particles or liquids	1.Not applicable for long period of time

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	2. Possibility to control department where the drug is deposited 3. Useful for vaccination	2.Possibility of contamination of the devices with interstitial fluids

Novel approaches as Microneedles for transdermal drug delivery In Diabetes Management-

Micro-needles a new approach-

Tiny micro needles via the stratumcornea layer are created by the medical micro needles devices, where these found to be of various brands and variants.. University of Marburg Germany, investigated and found that MN approach enhances the skin penetration for both lipophilic and hydrophilic compound. These MN can be of various types such as hollow, solid, coated, dissolving or hydrogel forming of which some have regulatory approval.

Solid micro needles-

The arrays of projections used to puncture the stratum corneum and then removed later are known as solid micro needles. These might effectively turn the skin into a porous surface with micron-sized holes that drug molecules could easily pass through.(S. V. Kumar SL 2012) For a predetermined amount of time, these needles are placed into the skin. Drug delivery into the living epidermis is facilitated by the microchannels created by the insertion of microneedles.(Morrow DIJ, Innovative strategies for enhancing topical and transdermal drug delivery, 2007)

Coated micro needles –

Solid microneedles that have been coated serve as delivery systems for drugs that are to be injected into the skin or other tissues. Included in this is dosing microneedles with a medication in a formulation appropriate for coating and later dissolution. As a result, upon insertion of the microneedles, the medicine is swiftly given in the desired dose into tissue. The maximum amount of medication that can be coated onto the microneedles' tip and shaft in this manner is typically less than 1 mg for small microneedle arrays.(P. M. Gill HS 2007)

Dissolvingmicro needles

Dissolving microneedles, as opposed to coated microneedles, totally dissolve in the skin after use and don't produce any bio hazardous waste. Usually made of harmless, water-soluble substances like polymers and sugars, these micro needles disintegrate in the skin after implantation. Drugs are frequently contained inside the micro needle for release into the skin, despite the fact that dissolving them can be utilized as a skin pretreatment to enhance permeability.(K. P. Kumar V 2011)

Hollow micro needles

The center of hollow microneedles is a hollow bore. A direct passage into the other lower layers of the epidermis is created when the hollow bore in the device is introduced into the skin, bypassing the stratum corneum layer of the skin. Most often, these microneedles are used to inject medicinal solutions directly into the skin so that the drugs can diffuse into the body.(Morrow DIJ, Innovative strategies for enhancing topical and transdermal drug delivery, 2007) Hollow microneedles allow a liquid formulation to flow under pressure, much like a hypodermic injection. (Vandervoort J 2008)For a quick bolus injection, a gradual infusion, or a time-varying delivery rate, pressure and therefore flow rate can be controlled.This has the apparent benefit of allowing for the delivery of a significantly higher dosage of medication over a given period of time, which opens up applications where relatively high dosages are required to produce a therapeutic effect(Suner S 2005). The liquid formulation may make it easier to use currently available injectable formulations for microneedle delivery, but it loses the chance to use solid microneedle delivery techniques to administer dry-state drug formulations without reconstitution to enhance drug stability and the patient-friendliness of a patch-based delivery method. Additionally, hollow microneedles are employed to draw fluid from the body for examination.

Hydrogel forming micro-needle-

Microneedle technology has recently advanced to include hydrogel-forming microneedles. A drug reservoir is linked to the baseplate of these arrays of microneedles, which are constructed of a substance that swells. (S. T. Donnelly RF 2013)(Larrañeta E 2015)Following implantation into the skin, the array absorbs interstitial fluid and swells to create continuous conduits between the dermal microcirculation and an attached patch-type drug reservoir, resulting in the diffusion of the medication into the skin.(S. T. Donnelly RF 2012)(M. M.-S.-Z. Donnelly RF

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2014) The stratum corneum barrier is first penetrated by using such microneedles as a tool. They inflate and turn into a membrane that regulates speed. The majority of these microneedle arrays are made from synthetic polymers, primarily an aqueous polymer gel that is easily cross-linked via chemical or physical techniques.The utilization of hydrogel-forming microneedle arrays for minimally invasive drug substance and glucose extraction and quantification from the skin in vitro and in vivo serves as a powerful example of the promise for hydrogel-forming microneedles inminimally invasive patient monitoring and diagnostics.(Caffarel-Salvador E, Hydrogel-forming microneedle arrays allow detection of drugs and glucose in vivo: potential for use in diagnosis and therapeutic drug monitoring, 2015)

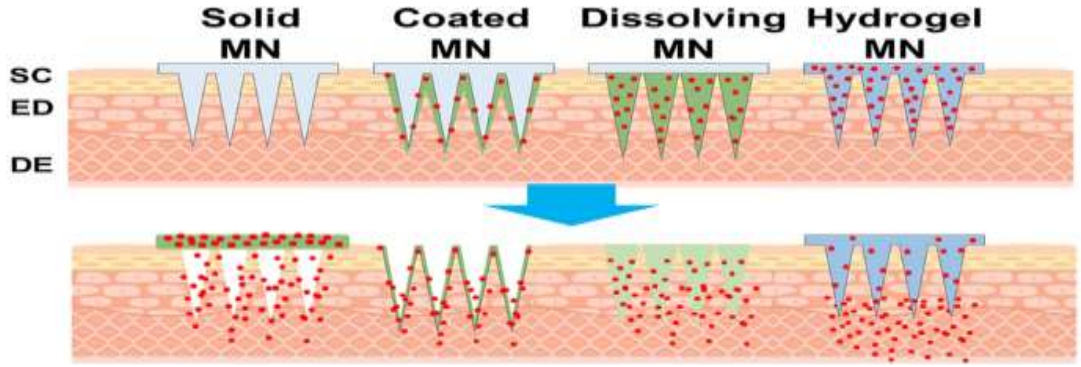

Fig 7 – Different types of Microneedles- Solid,Coated,Dissolving,and HydrogelMicroneedles

Materials used in construction of micro-needles

Material Of construction	Examples	Type of miconeedle Procedure	Merit	Demerits
Metal	Nickel-Iron(Arora A 2008), stainless steel(Chen H 2009)	Hollow/solid/coated	Good Mechanical strength	Non-Biodegradable expensive, brittle
Silicon	Silicon di oxide(Ashraf MW Tayyaba S 2010)	Solid/Hollow	Greater mechanical Strength	Expensive,brittle
Glass	----------	Hollow	High drug Loading capacity	Non-Biodegradable
Biodegradable polymer	Polylactic acid(Park JH 2005), polyvinylpyrrolidone(PVP)(Ji J 2005),polylactide-co- glycolic acid(PLGA), Polycarbonate(Jin CY 2009)	Solid	Good resistance, Biocompatible,	Thermal Instability
Non-biodegradable polymer	Polyvinyl acetate(PVA)(M. R. Donnelly RF 2011),Alginic acid, Carbopol 971 , polyethermide(You SK 2010)	Solid	Cost effective, Good resistance	Non-Biodegradable
Polysaccharide	Carboxylmethylcellulose(Lee JW 2008), Maltose(Li	Solid, Dissolving	Rapid drug delivery, Biodegrada	Hygroscopic Caramelization

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	G Badkar A 2009), Dextran, Galactose, Chondroitin Sulfate(Ito Y 2008)		ble	

Methodology of drug delivery by micro needles-
Few numbers of drug delivery mechanism are followed to transfer the drug from the microneedles These include-

I. Poke and patch
II. Coat and poke
III. Poke and release
IV. Poke and flow

Poke and Patch-

It entails inserting a variety of solid microneedles into the skin before applying the medication patch to the area being treated. If an electric field is produced, iontophoresis or diffusion may be used to transport drugs over skin. Using this procedure, interstitial fluid was also extracted to measure the glucose level non-invasively.(Prausnitz MR, Microneedles for transdermal drug delivery, 2004)(Wang PM 2005)

Coat and Patch-

In this method, needles are coated with the drug beforehand and then put into the skin to release it by disintegration. The needle itself has a coating that covers the entire medication to be administered. A variation of this strategy is called the "dip and scrape approach," in which tiny needles are first dipped in a medication solution and then scraped over the skin to leave behind the drug in the tiny abrasions they caused. . In this "coat and poke" method, only a little amount of medication could be coated over the microneedles (only around 1 mg), and substantial tuning was needed for uniform coating.(Bora P 2008)(Prausnitz MR, Microneedles for transdermal drug delivery 2004)

Poke and release-

After injection, microneedles made of polymers and polysaccharides progressively dissolve or degrade, releasing the medicine that has been encapsulated into the skin. The "poke and release" method had the advantage that the release of drugs could be regulated to meet the needs using a number of readily accessible polymers and polysaccharides.(K. P. Kumar V 2011)

Poke and flow-

In this method, the medicine is first allowed to pass via hollow microneedles from the reservoirs in the patch after the skin has been punctured (external pressure). By using the poke and flow approach, a significant amount of medication can be delivered. Furthermore, pressure-driven distribution increases the potential for precisely controlling the flow rate and achieving a more regulated delivery.(Milewski M 2010)To distribute medications either systemically or to a specific place, all of the aforementioned methods can be used (local action).

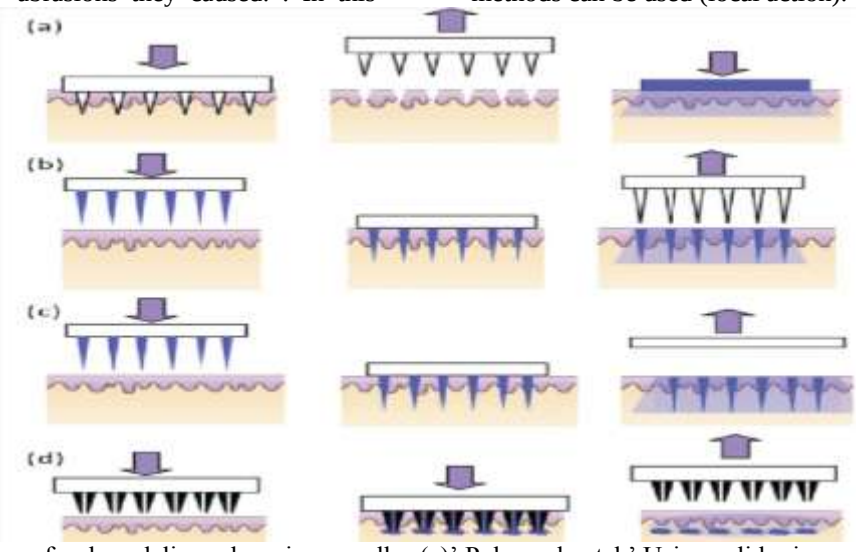

Fig 8- Methodology for drug delivery by micro needles (a)' Poke and patch' Using solid micro needles (b)' Coat and poak' using coated solid micro needles, (C)' Poke and Release" using polymeric micro needles (d) ' Poke and flow using hollow micro needles

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VI. APPLICATION IN DIABETES MANAGEMENT-

Worldwide, type I diabetes is a fairly prevalent chronic condition that can seldom be cured and has substantial secondary effects. The sole available treatment at this time is a long-term subcutaneous insulin injection to keep blood glucose levels stable. The patients' compliance with this therapy is, however, quite low. Long-term injections not only increase the danger of pain and infection, but they can also frequently result in hypoglycemia, which can be fatal. Microneedles (MNs) have the potential to replace subcutaneous insulin injections in the treatment of type I diabetes due to their advantages of being painless and minimally intrusive.These issues can be significantly resolved when an effective microneedle drug delivery system is created.As a protein, insulin is extremely easily denatured, hence microneedles must be sufficiently stable to guarantee drug action. The foundation for ensuring the security of microneedle self-administration is the controllability of drug release. Additionally, the components used to create microneedles must be biocompatible. Rapid and long-lasting medication release do not clash with one another. In contrast to controlled release microneedles with high drug loading, which can decrease the number of times a drug must be administered and extend its effective period, rapid drug release can assure the promptness of blood glucose management. This raises patient adherence and lowers the chance of infection. In order to successfully transition insulin-loaded microneedles into clinical or commercial, three factors are necessary.(Tuomi T 2014)(Ng LC 2020)(Guo X 2017)(Caucanas M 2011)(Lee G 2018)(Lee KJ 2020)

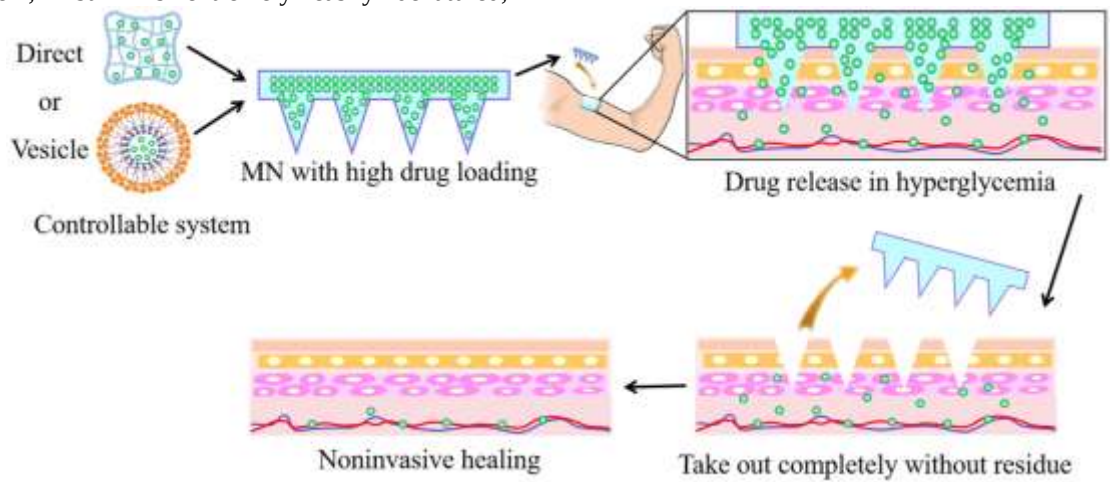

Fig 9 - Schematic presentation of Microneedle's Mode of action

4.1 Increase the proportion of insulin in the needle-

To systematically investigate the maximal drug loading of the soluble quick separating MNs, **Zhu et al.** combined polyvinyl alcohol (PVA) with sulfanilamide B as the model drug using mechanical stirring. The drug loading can exceed 900 ng per microneedle under the assumption of ensuring mechanical strength, drug delivery effectiveness, and other characteristics. Insulin's instability and non-water solubility will cause a modest reduction in drug loading, which may not even be enough to meet patients' daily needs. In order to create an implantable powder carrying microneedle (PCM) system, **Kim et al**. modified the drug loading technique and created a soluble microneedle shell utilizingcarboxymethyl cellulose (CMC) as the matrix material.

Despite the solubility of insulin and its manufacturing loss, this PCMs has enough mechanical properties to provide the appropriate amount in a more concentrated form. These PCMs do have one drawback, which is that when the shell dissolves, a significant amount of unmodified insulin enters the body and contributes to hypoglycemia, which carries a danger. The above-mentioned glucose-responsive insulin nanoparticles can be inserted into the microneedle cavity after freeze-drying, allowing for safer and more regulated release under specific circumstances.(Zhu DD 2019)(Kim S 2020)

4.2 Controlled and rapid drug release of microneedles-

An intelligent insulin delivery device that can release insulin at elevated blood glucose concentrations and regulate blood glucose levels

International Journal of Advances in Engineering and Management (IJAEM)
Volume 5, Issue 2 Feb. 2023, pp: 398-414 www.ijaem.net ISSN: 2395-5252

within normal limits is being developed to reduce the danger of hypoglycemia brought on by massive insulin release during administration. In order to create glucose-dependent insulin release systems, glucose-binding protein (GBP)(Wang C 2017)(Yang R 2018), glucose oxidase (GOX)(Yu J 2015)(Xu B 2018), and phenylboronic acid (PBA) are frequently used as glucose-sensing components (Table 1). Con A is often based on its numerous binding sites and competitive interaction with glucose and dextranmatrix as the most frequently utilized GBP for insulin administration. However, because to its toxicity and instability in vivo, its clinical applicability is restricted. It is also unsuitable for response in microneedlesto create controlled release effect. Consequently, this chapter primarily introduces the use of GOX

4.3 Make use of the base to carry drug-

The microneedle's needles are very tiny and few in number, yet their bases have a huge capacity and a wide range of adjustability. The medication loading will be significantly boosted if the base can be utilized effectively. With silk fibroin as a base material**, Zhu et al**. created a composite insulin MN patch(Zhu M 2020). A microneedle has a needle with good solubility, which can dissolve quickly and facilitate the release of insulin.

In addition to carrying insulin as a pharmacological reserve, the base expands but does not disintegrate. The base portion can keep releasing insulin continuously through the microporous channel that the microneedles created even after they have been dissolved.The base could not directly contact the skin interstitial fluid, though, because the pores created by the microneedles will quickly constrict and vanish. This will make it difficult for insulin to fully enter the body and cause it to have a low bioavailability. But there's no doubt that this concept is incredibly interesting and merits additional investigation.

An almost flawless polymer MNarray patch was created by **Chen et al** using a hydrogel containing boronate that is partially pierced by biocompatible silk fibroin.(Chen S 2019)The microneedle has the potential to release insulin in both an acute and sustained manner while maintaining safety. To create the matrix of microneedles, they crosslinked phenylboronic acid derivatives (AmECFPBA), N-isopropyl acrylamide (NIPAAm), MBAAm (cross-linker), and SF. AmECFPBA stands out among the rest of them as a reversible glucose-responsive component that offers SF enough mechanical strength, great biocompatibility, and a programmable degradation rate. The fact that insulin can be replaced after depletion and that the back of the microneedle includes a "reservoir" filled with insulin solution contributes to its long-term effects. This might easily eliminate the requirement for daily or weekly insulin administration.

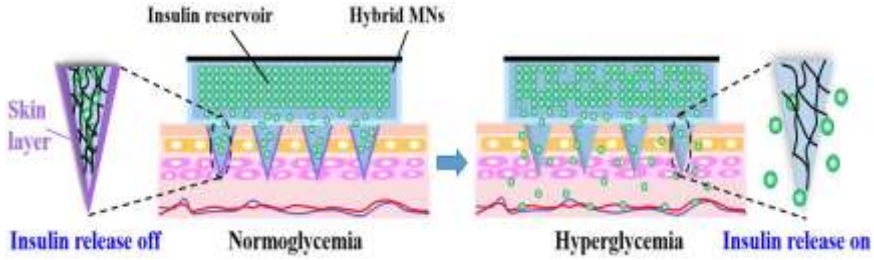

Fig10 - Schematic of "skin layer"controlled glucose-responsive insulin release from MN array controlled glucose-responsive insulin release from the MNarray patch

4.4Safety of Insulin Microneedles-

Solid microneedles are currently employed often in medical cosmetology, and a wealth of data shows that doing so neither significantly alters the skin's look or barrier function nor raises the risk of infection.(Serrano-Castaneda P 2018) Thus, proper usage of microneedles won't result in too many safety issues by itself; instead, issues with product quality, medication regulation, and microneedle composition will mostly be at play.For all kinds of insulin microneedles, too little insulin release will not achieve the therapeutic effect, and too much release will lead to hypoglycemia, so the precise release of drugs is the fundamental requirement to ensure safety.

DMNs are the majority of MNs that are used to load insulin in current studies. There is no disputing the superiority of these DMNs' release mechanism and therapeutic impact. DMNs, on the other hand, are typically manufactured from high-molecular-weight synthetic polymers, which could result in polymer deposition and subsequent consequences including tissue accumulation or erythema.(Quinn HL 2015) For MNs, for instance,

McCrudden et al.(McCrudden MTC 2014)discovered that around 5-10 mg of polymer deposited in the skin per square centimeter. In the ongoing hunt for biocompatible materials to create MNs, researchers put forth significant effort and contribution.

VII. CONCLUSION-

While not covering all pertinent studies, this article examines the current state of research on the use of microneedle-loaded insulin for the treatment of type 1 diabetes in recent year. A small number of typical studies are used as examples to show how certain conditions must be met before insulin microneedles can be used in clinical settings. Long-term, stability, safety, and the controlled and quick release of insulin are some of these factors. Additionally, the widespread manufacturing, sterilization, and storage of microneedles must be taken into account.Patients with type I diabetes will live far better lives if insulin microneedles are available. In order to advance the use of insulin MNs in patients and realize its immense promise, academics and industry must collaborate to address these problems.

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