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Transdermal Delivery System for the Treatment of Diabetes Mellitus: An Overview

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ABSTRACT

Insulin therapy is essential for controlling the blood glucose level for patients with type 1 diabetes and advanced type 2 diabetes. Conventionally, insulin is administered via a subcutaneous route, it may be associated with pain, decreased adherence, needle phobia. Several attempts have been done to improve patient compliance, increase delivery adherence, reduce side effects, and to enhance the pharmaceutical performance of insulin delivery. Transdermal delivery is an effective, attractive, and non-invasive method. Therefore, the present review was aimed to focus on different transdermal delivery techniques, their respective advantages, limitation, and approaches for transdermal insulin delivery.

1. INTRODUCTION

Diabetes mellitus is a group of metabolic disorders characterized by increased production of glucose by the liver and decreased clearance of glucose into fat and muscle resulting in abnormal accumulation of glucose in the blood. Diabetes is usually caused by the failure of insulin secretion (type 1 diabetes) or defective responsiveness of the body to insulin (type 2 diabetes). Insulin is the first choice to treat type 1 diabetes & insulin can be administered by injections and insulin pump.

Individuals with diabetes mellitus may progress to life-threatening problems, including stroke, loss of vision, cardiovascular complication, or even death if the hyperglycemic condition is untreated. Among two types of DM, type 2 diabetes mellitus is more common than type 1 diabetes mellitus which occurs only in 5-10% of the population.[1] Approximately 425 million adults suffer from diabetes mellitus according to the 2018 report from the International Diabetes Federation. According to the World Health Organization's (WHO) latest statistics, DM had risen from 4.7% in 1980 to 8.5% in 2014 and the WHO projects that DM will be in the seventh place in the palette of the leading causes of death worldwide in 2030 since DM is one of the leading causes of heart and stroke, blindness, kidney failure, and lower limb amputation. Exogenous administration of insulin is essential in the management of both (type 1 and type 2) diabetes. Typically, patients with diabetes are instructed to self-inject insulin subcutaneously several times per day, which requires both training and self-management with frequent dose adjustments by patients based on glucose monitoring. Due to frequent injections, there is risk of infection, local tissue necrosis, and nerve damage. To address these limitations, several delivery methods have been investigated as needle-free alternatives for daily insulin therapy including oral, pulmonary, nasal and transdermal.[2,3]

2. Anatomy of the skin

The skin covers a surface area of approximately 2 sq.m. of the human body.[4] It serves as a permeability barrier against the absorption of various chemical and biological agents by transdermally. The human skin consists of mainly three layers.[5]

1. Epidermis

2. Dermis

3. Hypodermis

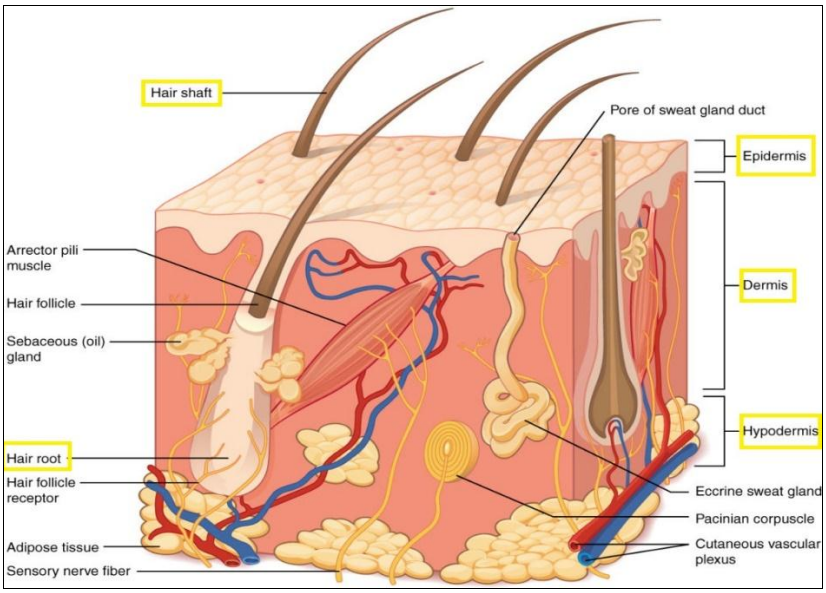

Figure No. 1: Shows Transverse section of human skin [10]

Epidermis

The epidermis is a self-renewing, stratified squamous epithelium covering the entire outer surface of the body. Epidermis mainly composed of two parts: the living or viable cells of the malpighian layer (viable epidermis) and the dead cells of the stratum corneum commonly known as the horny layer. The viable epidermis is divided into four distinct layers such as Stratum lucidum, Stratum granulosum, Stratum spinosum, and Stratum basale. Stratum corneum is the outermost layer of skin also called a horny layer. Stratum corneum is a barrier that restricts the inward and outward movement of chemical substances.[6,7]

Dermis

The dermis is the layer of skin just beneath the epidermis which is 3 to 5 mm thick layer and is composed of connective tissues, which contains blood vessels, lymph vessels, and nerves.[8]

Hypodermis

The hypodermis or subcutaneous tissue supports the dermis and epidermis. It serves as a storage area for fat. Hypodermis layer helps to regulate temperature, provides nutritional support and mechanical protection.[9]

3. Transdermal drug delivery system

Transdermal drug delivery systems (TDDS) are also known as "Transdermal patches" or "Skin patches". These are dosage forms designed to deliver a therapeutically exact and effective amount of drug across a patient's skin and in the bloodstream. For effective Transdermal drug delivery systems, the drugs should be easily able to penetrate the skin and easily reach the target site. The transdermal drug delivery system increases patient compliance. A transdermal delivery strategy that transports the insulin across the skin barrier represents the effective and minimally invasive method for insulin delivery.[10] The Altea Therapeutics PassPort™ System was the first product that provides a non-invasive, controllable, and efficient way to deliver insulin via a patch on the skin. It consists of an applicator and a reservoir patch.[11,12]

3.1. Advantages of transdermal drug delivery system [10,13,14,15,16]

1) The transdermal drug delivery system avoids the first-pass effect.

2) Increases bioavailability.

3) Reduces dosing frequency.

4) Self-administration is possible with the transdermal delivery system.

5) The transdermal delivery system does not interfere with gastric and intestinal fluids.

6) The transdermal system is an alternative route of administration to accommodate patients who cannot tolerate oral dosage forms.

7) The transdermal drug delivery system is suitable for patients who are nauseated or unconscious.

8) Drugs with consistent plasma levels are very good candidates for transdermal drug delivery.

9) It maintains stable or constant and controlled blood levels for a longer period.

10) The daily dose of the drug required is lower than that of the other conventional therapies.

11) Drug therapy may be terminated by the removal of a patch from the surface of the skin.

3.2. Disadvantages of Transdermal drug delivery system

1) Some patients develop contact dermatitis at the site of application of the patch from one or more of the system components.

2) Higher cost compared to the oral formulation.

3) Not suitable for the ionic drug.

4) It may cause allergic reactions.

5) The barrier function of the skin changes from one site to another site of the same person, from person to person and with age.

6) The molecular weight of less than 500 Da is essential.

7) Sufficient lipid and aqueous solubility, a log P (octanol/water) between 1 and 3 are required for permeation through the skin.

8) Only potent drugs are suitable candidates for transdermal delivery.

9) It cannot deliver the drug from the dosage form in a pulsatile fashion.

3.3. Other limitations of the transdermal drug delivery system.[15]

1) The difficulty for adhesion of patch to the skin.

2) The drug undergoes degradation in the skin.

3.4. Ideal Characteristics of the drug for transdermal drug delivery system[15,16,17,18]

Sr. No.	Parameters	Properties
1.	Molecular weight	<500 Daltons
2.	Dose	Less than 20 mg/day
3.	Half-life	10 or less(hr)
4.	Partition coefficient	Log P(1-4)
5.	Skin permeability coefficient	$>0.5*10^{-3}$ 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

3.5. Conditions in which Transdermal patches are used

A transdermal patch is used when:

1) When the patient is unable to take oral medicine and has intolerable side effects (including constipation).

2) When patients are nauseated or unconscious.

3) It can be used in combination with other enhancement strategies to produce synergistic effects for treatment.

4. Types of Transdermal Drug delivery systems[10]

There are four types of transdermal patches:

(I) The single-layer drug in–adhesive patch

In the single-layer drug in the adhesive patch, there is a single layer of adhesive in the patch. The adhesive layer of this patch also contains the drug. In this type of patch, the adhesive layer not only serves to adhere to the various layer together but is also responsible for the release of the drug from the patch. The adhesive layer is surrounded by a temporary liner and a backing membrane.

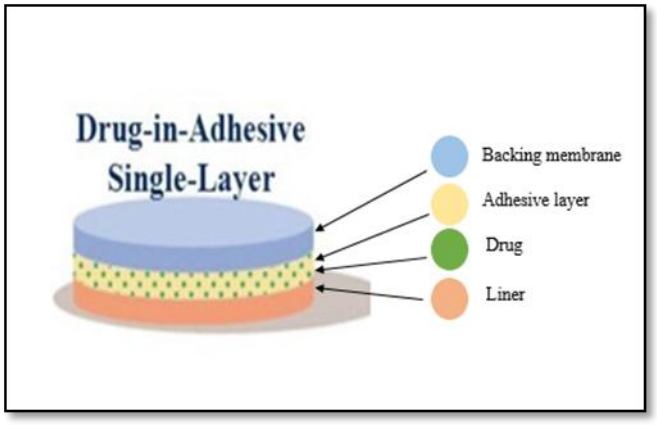

Figure No. 2: Single layer drug in the adhesive patch[10]

(II) The multi-layer drug in the adhesive patch

The multi-layer drug in the adhesive is similar to the single-layer drug in the adhesive system in that both adhesive layers are also responsible for the release of the drug. But it is different however that the other layer of the drug in–adhesive, usually separated by a membrane. This patch also has a permanent backing and release liner.

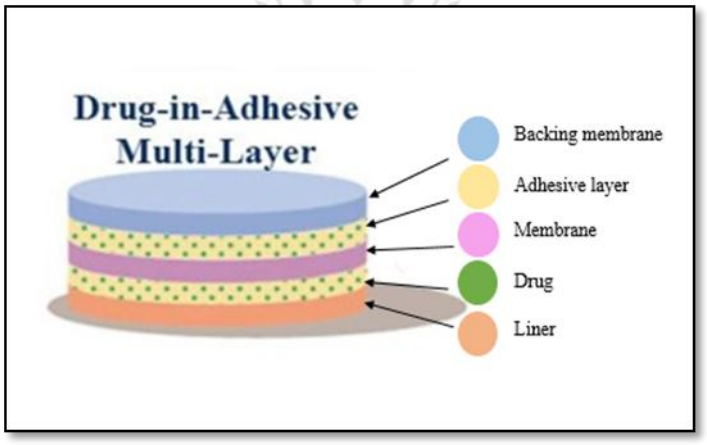

Figure No. 3: Multiple layer drug in the adhesive patch[10]

(III) 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. In this type of system, the rate of release is zero-order kinetic.

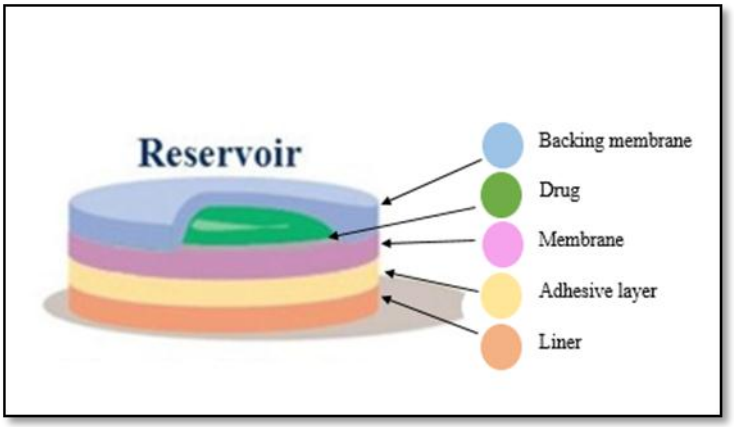

Figure No. 4: Reservior patch[10]

(IV) Matrix patch

The matrix patch containing a drug layer of a semisolid matrix containing a drug solution or suspension. Adhesive layer in the matrix patch surrounds the drug layer partially overlaying it.

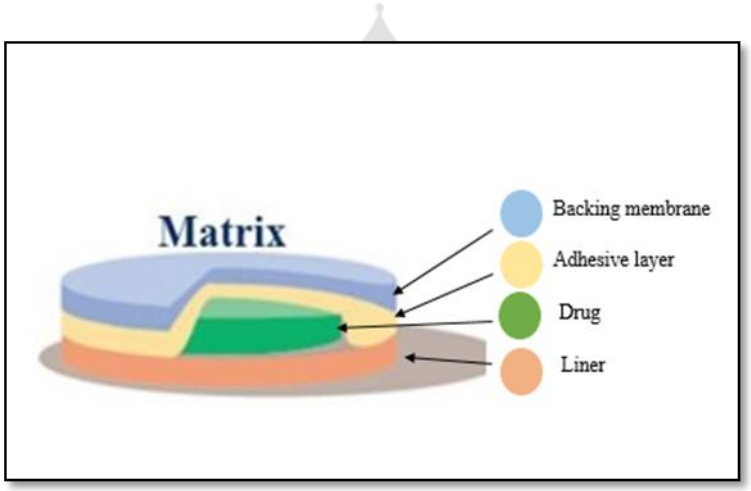

Figure No. 5: Matrix patch[10]

(V) Vapour patch

In this type of the patch, the adhesive layer not only serves to various layers adhere together but also responsible for releasing vapor from the patch.

5. Composition of a transdermal patch

A transdermal therapeutic system is a multilaminate structure which is composed of the following constituents:

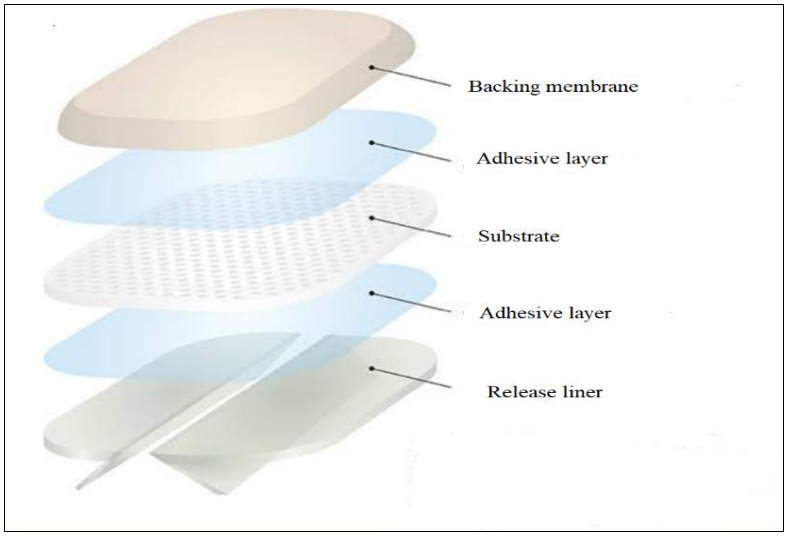

Figure No. 6: Composition of patch

A. Drug

The drug is an active ingredient that is incorporated in the patch.

B. Polymer matrix

Polymers are the backbone of the transdermal drug delivery system. Transdermal drug delivery system are fabricated as multi-layered polymeric laminates in which a drug reservoir or a drug-polymer matrix is sandwiched between the two polymeric layers, an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive, or rate controlled membrane.[19]

C. Penetration enhancers

These are the compounds that promote skin permeability by altering the skin structure as a barrier to the flux of the desired penetrant. Different penetration enhancers are used such as:

1. Sulphoxides

2. Azones

3. Pyrrolidones

4. Fatty acid

5. Alcohol

6. Surfactants[20]

D. Adhesives

Pressure-sensitive adhesives are used to achieve contact between the skin and transdermal patch. The adhesive should adhere with not more than applied finger pressure, be aggressively and permanently tacky, and exert a strong holding force. Additionally, it should be easily removable from the surface without leaving a residue on the skin.[14]

There are three types of adhesive used mainly.

1. Silicone type adhesive;

2. Polyisobutylene adhesive and;

3. Polyacrylate based adhesive.

E. Backing membrane

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 backing material used such as polyester, aluminized polyethylene terephthalate and siliconised polyethylene.

F. Release linear

The release liner is a packaging material that prevents the loss of the drug that has migrated into the adhesive layer during storage and protects the finished device against contamination. The material used for release liner is Polyesters foils and other metalized laminates.

6. Novel approaches for transdermal drug delivery system

6.1. Microemulsion gel

Shinde et al studied microemulsion gel formulation for the transdermal delivery of the Repaglinide for the enhancement of drug penetration and antidiabetic effect. The microemulsion system was prepared by mixing surfactant, co-surfactant, oil (8%), and water. In the microemulsion, xanthan gum was added to prepare microemulsion gel while repaglinide was loaded into it under ultrasonication. The rationale behind their study was based on the drug dissolution properties, it avoids the first-pass metabolism, controlled and sustained drug release properties of microemulsion using the transdermal route. This transdermal system demonstrated better glucose reducing property or hypoglycemic effect than other oral formulation. Malakar et al developed a transferosomal gel containing insulin for diabetic treatment. The gel was prepared by reverse-phase evaporation method for the treatment of diabetes mellitus which reduced the blood glucose level.

6.2. Transferosomal gel

Transferosomes is a novel, elastic or ultra deformable vesicular drug carrier system composed of phospholipid, surfactant, and water for enhanced transdermal delivery. Marwah et al presented transferosomal gel system which contains chemical enhancer such as “iodophor” to investigate its use in the permeation of the antidiabetic agent such as insulin into the skin. The transferosomes are prepared by using sodium cholate as a surfactant, soya lecithin as a phospholipid, and insulin as a drug by a conventional rotary evaporation sonication method. This study showed that 78% of insulin was successfully entrapped in the formulation with 2.5 I.U. of the drug and 25% of sodium cholate. The transpersonal gel system with a chemical enhancer iodophor has good potential to disrupt the epidermal layer of the skin to deliver insulin into the skin, thus achieving a higher bioavailability of the drug. Transferosomes are effective as phospholipids vesicles for transdermal drug delivery. Because transferosomes are self-optimized and ultra-flexible membrane properties, they can deliver the drug reproducibly either into or through the skin.[11]

6.3. Nanoparticle

Nanosized colloidal particles, such as micelles, solid lipid nanoparticles, niosomes, ethosomes, polymeric and inorganic nanoparticles have been developed as carriers to enhance the percutaneous absorption of therapeutic agents. Encapsulation of therapeutic agent into colloidal carrier not only enhances the permeability but also protect the drug from degradation.[21]

6.3.1. Ethosomes

Ethosomes mainly contain phospholipids, alcohol, and water. Compared to the liposomes, ethosomes are characterized by their high concentration of alcohol. Ethosomes are used for transdermal delivery of repaglinide (RPG) in the treatment of type II diabetes mellitus in rats.

6.3.2. Solid lipid nanoparticle.[22]

Solid lipid nanoparticle is by nature a special form of nano-emulsions wherein the matrix material is a solid lipid (e.g. highly purified triglycerides, wax, etc.) instead of liquid lipid, i.e. oil. The reports showed decreased blood glucose levels by using transdermal patches loaded with M-SLN when compared with oral administration of Metformin (2mg) in both normal and diabetic rats.

6.4. Sweat based electrochemical patch

Lee et al designed and fabricated a disposable wearable multilayer patch that can monitor blood glucose level with a built-in sensor that works on non-invasive sweat based mechanism and also provide the feedback to a transdermal antidiabetic through Microneedles. This wearable patch-based device is claimed to achieve controlled drug release according to patients' sweat glucose levels. The device utilized a silicon patch to collect the sweat from the wearer. This multipoint enzyme-based glucose, temperature, and pH sensors were used in measuring the correlated blood glucose level according to the sweat collected, allowing for more accurate and sensitive glucose measurement.[23,24]

7. Approaches for enhanced transdermal drug delivery systems

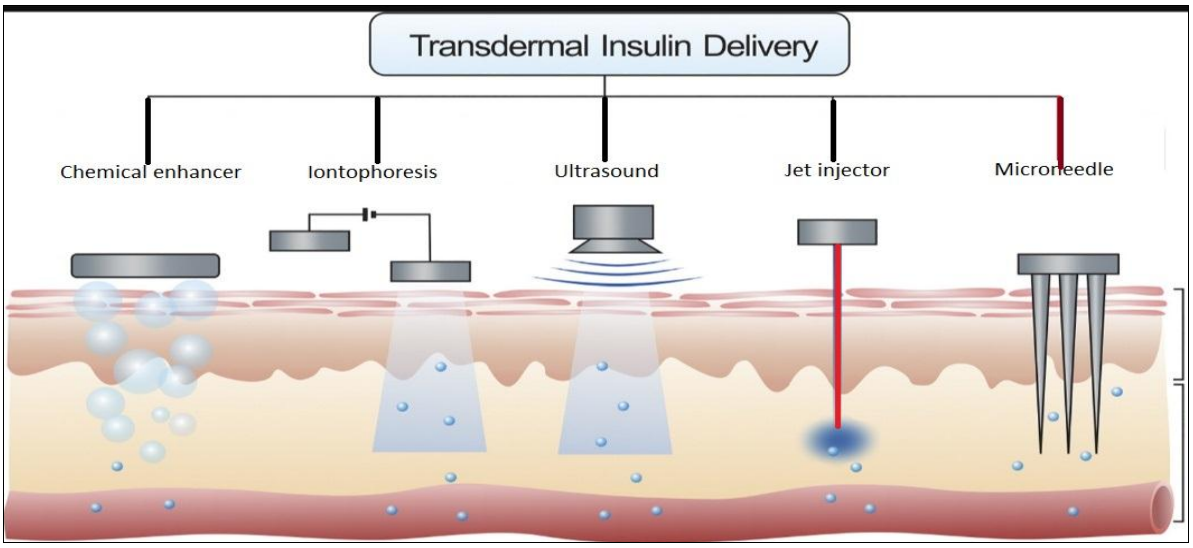

Figure No. 7: Transdermal delivery approaches

7.1. Iontophoresis

Iontophoresis method involves the application of electromotive force to drive or repel oppositely charged ions through the dermal layers of the skin into the area of the skin to be treated, either into the surrounding tissues for localized treatment or into the circulatory system for systemic treatment. Positively charged ions are driven into skin at the anode side while negatively charged ions are driven into skin at the cathode side. Dependent upon the net charge of the insulin particle, the associated electrical potential has been seemed to fabricate the pace of insulin move across over the skin.[11] Studies have shown increased skin permeation of drugs at anodic /cathodic side of electrodes regardless of predominant molecular ionic charge. Improved drug permeation as a result of iontophoresis technology can be attributed to either one or a combination of the different mechanisms such as electro-perturbation (for both charged and uncharged), Electro-repulsion (for charged solutes), electro-osmosis (for uncharged solutes). Jang et al. developed a patch containing insulin formulated in a gel for the iontophoretically driven transdermal delivery of insulin.[25,26]Pillai and Panchagnula investigated transdermal delivery of insulin from poloxamer gel. In this study, gels were considered the most appropriate delivery vehicle for iontophoresis, and insulin was used for diabetic treatment. An insulin gel formulation was prepared using poloxamer 407. Ex vivo and in vivo skin permeation studies were performed with chemical enhancer and/or iontophoresis using rat as the model animal. The poloxamer gel showed

physical as well as chemical stability during the storage period. Results of this ex-vivo studies show, using linoleic acid and menthone in combination with iontophoresis showed a synergistic insulin permeation enhancement.[27,28]

7.2. Electroporation

Electroporation is another attractive technique for the electrically assisted transdermal delivery system).[29,30,31,32] In electroporation, a short electric pulse (milliseconds or microseconds) is applied to the skin for the transitory structural perturbation of the lipid bilayer membranes. It is usually known that 0.5 to 1.0 volt of transmembrane potential difference should be required for electroporation. It has been shown that electroporation can also induce the alteration of the stratum corneum lipid domain. The increase in skin permeability is caused by the generation of transient pores during electro-poration. The technology has been successfully used to enhance the skin permeability of molecules with different size and lipophilicity (i.e.small molecules, Proteins, Peptides, oligonucleotides).[10,27]

7.3. Sonophoresis

Ultrasound, especially in the frequencies between 20 to 100 KHz, has shown to significantly increase the permeability of skin which facilitates transdermal drug delivery of the insulin. Ultrasound produces cavitation leads to the formation of localized regions of high permeability. Short application of the ultrasound causes the permeation of the skin before the application of drugs or drug and ultrasound could be applied simultaneously to the skin. Some parameters including frequency, intensity, and application time, can be adjusted to achieve a safe reversible breach in the skin. The SonoPrep R device uses low-frequency ultrasound (55 kHz) for an average duration of 15 s to enhance the skin permeability of the skin. This battery-operated handheld device consists of a control unit, ultrasonic horn with a control panel, a disposable coupling medium cartridge, and a return electrode. The use of other small, lightweight novel ultrasound transducers to enhance the in vitro skin transport of insulin has also been reported by a range of workers.[27,33,34,29]

7.4. Laser radiation

In the laser radiation technique, exposure of the laser to the skin occurred by directly and controlled manner that results in the ablation of stratum corneum without significantly damaging the underlying epidermis. Pantec Biosolutions developed Laser skin microporation system. The P.L.E.A.S.E (Painless Laser Epidermal System) device uses a laser that emits light at 294 nm. It was found that laser treatment causes the formation of the cylindrical pore with the diameters ranging from150-200µm.[35]

7.5. Jet injector

Jet injector is velocity based device, either powder or liquid jet injections, employ a high-velocity jet with velocities ranging from 100 to 200 m/s to puncture or penetrate the skin and deliver drugs using a power source (compressed gas or spring) .[36,37] A jet injector is a needle-free device which is capable of delivering electronically controlled doses of medication or insulin which result in improved consistency of delivery and reduced pain for the patient.[37,38,39] Instead of solid syringes, the jet injector applies at a high-speed narrow stream containing the insulin to create a tiny hole for insulin transport through the skin. Insulin administration by the jet injectors leads to faster onset of action of plasma insulin. It contains compressed air or gas, either by a pressure hose from a large cylinder or a built-in gas cartridge or small cylinder. Although liquid jet injection technology is a needle-free route, the large volume high-pressure spray leads to some adverse reactions such as bruising, bleeding, and pain. To minimize the adverse reaction caused by jet injector, Mitragotri and coworkers designed a microjet injection device that only injects solution volumes within the nanolitre range.[40,2]

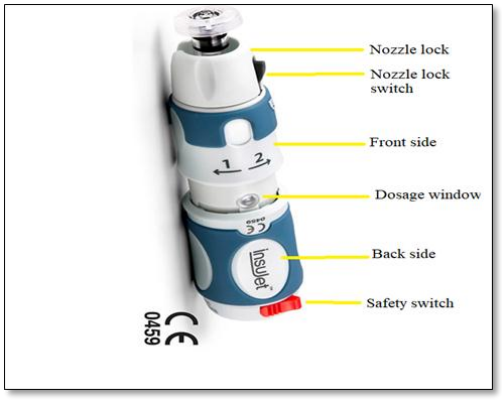

Figure No. 8: Jet injector

7.6. Microneedle [41,42,41,43]

MN devices consisting of the needles of the micron size, which are arranged on a small patch. The micro-scaled needles can disrupt the stratum corneum layer and reach the dermal and epidermal layer of the skin for drug release. The microneedle temporarily created the microchannel for the drug transport but quickly recover after removal of the microneedle to prevent the damage to the skin tissue.[19] Novel and minimally invasive approach, MN is capable of creating superficial pathways across the skin for the transport of small drugs, macromolecules, nanoparticles to achieve enhanced transdermal drug delivery [44]. The sharp tips of microneedle are short enough to limit contact with skin nerves, thus preventing pain sensation [45] and they are narrow enough to induce minimal trauma and reduce the opportunities for infections to develop the following insertion. This method combines the efficacy of conventional injection needles with the convenience of transdermal delivery system formulation such as the patch. Based on the mechanism of action and the type of material used for the microneedle, the MN device is classified into different types. Generally, solid microneedle is designed to pierce the skin to improve the drug transport, hollow microneedles are designed for injection of fluid drug formulation.[46,47]

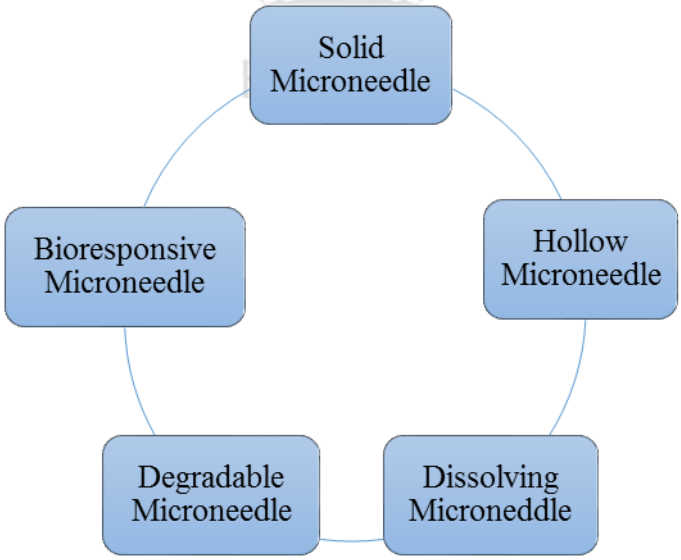

Figure No. 9: Types of microneedle

7.7.1. Solid microneedle

Solid microneedles are mostly used for pre-treating the skin by forming the pores. The MN-aided transdermal delivery by solid MN is also termed as the ‘‘poke with patch’’ approach .[48] Solid Microneedles contains the pointed tips of the needle that penetrate the skin, creates the micron size channel, through which the drug directly enter into the skin layers on the application of the patch, thus increasing penetration. Prausnitz and co-workers demonstrated MN for the hypoglycemic action of insulin in diabetic rats. An array of 105 microneedles was prepared by laser cut from stainless steel sheet, which is then inserted into the diabetic rats after this insulin solution was administered in contact of the skin for 4 hr. This solid metal Microneedles shows increased transdermal delivery of the insulin and decreases BGLs in vivo as much as 80 %.

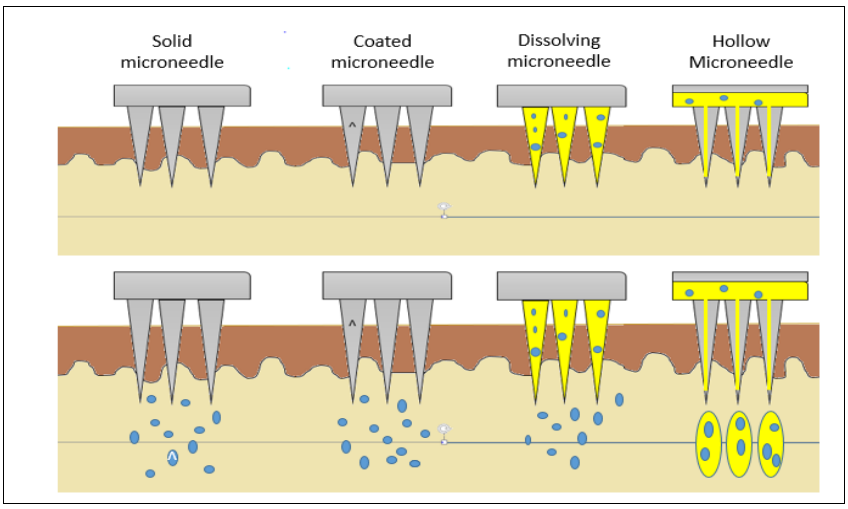

Figure No. 10: Microneedle assisted transdermal delivery system

7.7.2. Hollow Microneedle

Hollow Microneedles have a space inside the microneedle in which the drug solution or dispersion to be filled. Hollow microneedle can be designed to infuse milliliter quantities of fluid into the skin for transdermal delivery. To facilitate the delivery of the drug into the skin by the convection, hollow Microneedles are used to inject insulin or other solution. Prausnitz and co-workers injected insulin into the diabetic rat's skin through hollow glass microneedle by microinfusion, a 30 min microinfusion of insulin at 10 or 14 psi cause a steady decrease in blood glucose level over a 5 hr period.[49] Gupta et al. first examined the transdermal delivery

of insulin by the hollow metal microneedle for the treatment of the type 1 diabetes mellitus in adults.[50]

7.7.3. Dissolving Microneedle

Dissolving microneedles are formulated with biodegradable polymers by encapsulating the drug into the matrix, and upon insertion into the skin, can fully dissolve and release the drug. The polymer present in the microneedle gets dissolved inside the skin and control the drug release. Chen and coworkers developed a dissolving microneedle patch that contains the starch and gelatin for transdermal insulin delivery.[51,52]Some researcher designed fully insertable Microneedles with the supporting structure which provides extended length for counteracting skin compressive deformation during administration. Insulin was first loaded on tips 600 μm tips of high Microneedles which are made up of poly-□-glutamic-acid, while the next layer of PVA/PVP which was filled in Microneedles molds to form the 600 μm high supporting structure. When these Microneedles are inserted into the skin, both the microneedle and supporting layer dissolved within a 4 min to fully release the drug load.[52] Kim et al. developed an alternative technique by applying droplet born air blowing to directly shape the polymer droplets to solidified the Microneedles. A decrease in glucose level in diabetic mice and increasing the bioavailability confirmed the efficacy of insulin delivery.[53]

7.7.3.1. Double layered, bullet-shaped microneedle with swellable tips patch

Seonge et al developed bullet-shaped, double-layered microneedle with swellable tips that are capable of loading the insulin for interlocking mediated adhesion to the skin tissue which prolonged insulin delivery. The interlocking adhesion was achieved by increasing the volume of swellable tips. Ex vivo tests are carried out, which showed that insulin loaded microneedle was equally distributed throughout the swellable layer. Hence, it is suggested that the double-layered bullet-shaped microneedle patches are a potential candidate for the delivery of insulin in diabetes treatment.[54,55]

7.7.4. Hydrogel-forming microneedle arrays

Donnelly et al described a new category of MN array which are prepared from hydrogel-forming matrices, consisting of cross-linked drug-free polymers. The mechanism of hydrogel-forming MN is by forming the hydrogel from the reservoir type of patch to the capillary circulation under the skin tissue because the skin interstitial fluid can be rapidly

taken up by inserted needle tips after application of the MN arrays into the skin.[56] Migadi et al. studied the hydrogel-forming microneedle for the administration of metformin for the treatment of diabetes by a transdermal route to decrease the gastrointestinal side effect of oral route.

8. Evaluation of transdermal patch

a) In-vitro study

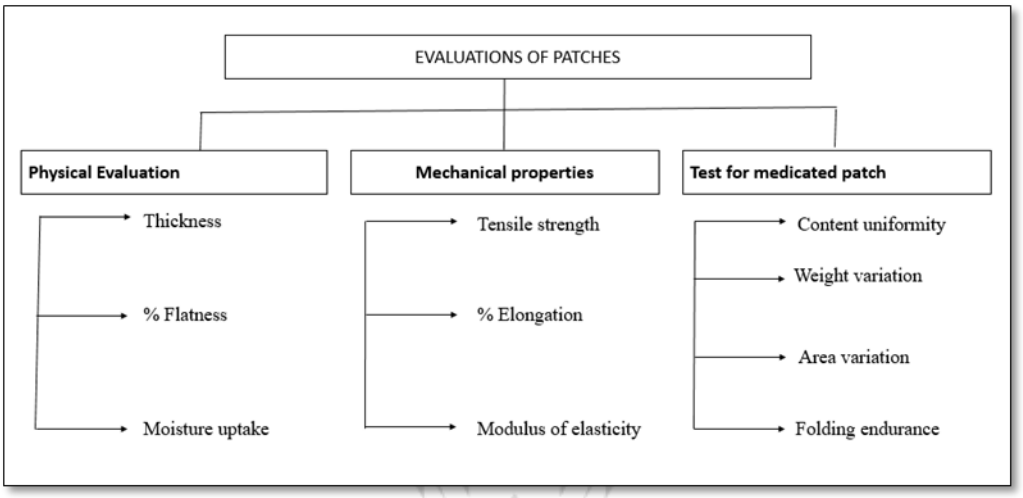

Figure No. 11: Evaluation of transdermal patch

b) In vitro drug release studies

c) Ex-vivo permeation study

d) Stability study

CONCLUSION

The topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods. Here, different technologies for improving the transdermal delivery of insulin for the treatment of diabetes mellitus have been reviewed. Unlike traditional needle injections, transdermal delivery demonstrates a non-invasive and patient-friendly method. Transdermal drug delivery systems represent a beneficial innovation for drug delivery, particularly in patients who cannot swallow or remember to take their medications.

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