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Recent Development In Diabetes Therapy With Transdermal Patch

Kiran C. Mahajan[1], Akanksha S. Hande[2], Ganesh Y. Dama[3] , Akanksha H. Shingote[4], Dipti B. Thorat[5], Arti R. Dambe[6]

[1,2,4] Department of Pharmaceutics, (Savitribai Phule Pune University) SGMSPM's Sharadchandra Pawar College of Pharmacy, Dumbarwadi (Otur), Tal- Junnar, Dist- Pune,410504

[3,5]Department of Pharmacognosy, (Savitribai Phule Pune University) SGMSPM's Sharadchandra Pawar College of Pharmacy, Dumbarwadi (Otur), Tal- Junnar, Dist- Pune,410504

[6]Department of Pharmaceutical Quality assurance, (Savitribai Phule Pune University) SGMSPM's Sharadchandra Pawar College of Pharmacy, Dumbarwadi (Otur), Tal- Junnar, Dist- Pune,410504

Email: kirancmahajan@gmail.com

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ABSTRACT

Diabetes is a prevalent condition that affects people of all ages and is linked to either insufficient insulin production by the pancreas or loss of insulin. Diabetes is a long-term metabolic condition that has been acknowledged as a significant issue in primary healthcare practices since more than 1550 bc. Transdermal patches are developed and evaluated as part of the current effort. Physical parameters such as ph, stability study, thickness, weight change, folding endurance, drug content, and the percentage of moisture absorbed and lost were all assessed for the formulation. The formula was assessed for thickness, foreign particle, colour, odour, and visual appearance.

INTRODUCTION:

A collection of common endocrine disorders known as diabetes mellitus, or just diabetes, are typified by persistently elevated blood sugar levels. Diabetes results from either insufficient insulin production by the pancreas or from the cells of the body losing its ability to react to the hormone's effects. Typical symptoms include impaired vision, weight loss, thirst, and polyuria. The illness can cause a number of health issues, such as problems with the kidney, heart, eyes, and nerves, if treatment is not received. Every year, diabetes causes over 1.5 million fatalities due to inadequate or untreated treatment. To get a certain amount of medicine into the bloodstream through the skin, a transdermal fix is utilized. The FDA authorized the first transdermal patch products in 1981. There are currently transdermal administration systems for fentanyl for chronic pain, nitroglycerine and clonidine for cardiac diseases, scopolamine (hyoscine) for movement disorders, and nicotine to help people stop smoking. Transdermal distribution provides controlled, reliable sedate organization, as well as continuous administration of drugs with short organic half-lives and avoidance of beat entry into the systemic circulation. TDDS has many benefits over conventional verbal and infusion methods. The verbal course usually causes significant stress on the stomach and hepatic systems. It improves silent compliance and lessens the adverse effects of a medicine caused by a temporary overdose. It is particularly helpful for patches that must be applied, so to speak, once a week. Silent adherence to sedative therapy is encouraged by such a straightforward dosing schedule.

Although there are other types of diabetes, type 1 and type 2 are the most common. Insulin replacement therapy, or insulin injections, is the most widely used treatment for type 1, but

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antidiabetic drugs, such metformin and semaglutide, and lifestyle changes can be used to treat type 2. Some people develop gestational diabetes during pregnancy.

ladies, usually goes away soon after giving birth. Around 90% of all instances of diabetes are type 2, with a projected 537 million individuals globally having the disease as of 2021, making approximately 10.5% of the adult population. An estimated 783 million persons, or 1 in 8, are predicted to have diabetes by 2045, which represents a 46% more than the present numbers. The disease is becoming more and more common, especially in low- and middle-income countries. Diabetes is the sixth most common cause of mortality worldwide, and rates are comparable for men and women. The global expenditure on diabetes-related healthcare is an estimated US$760 billion a year.

Weight loss, thirst, and polyuria are the hallmark signs of untreated diabetes. A number of additional non-specific symptoms, such as exhaustion, impaired vision, and itching in the genitalia from a Candida infection, may also manifest. Approximately 50% of those impacted might also be asymptomatic. While type 2 has a more gradual development and individuals may go years without experiencing any symptoms, type 1 manifests suddenly after a pre-clinical phase.

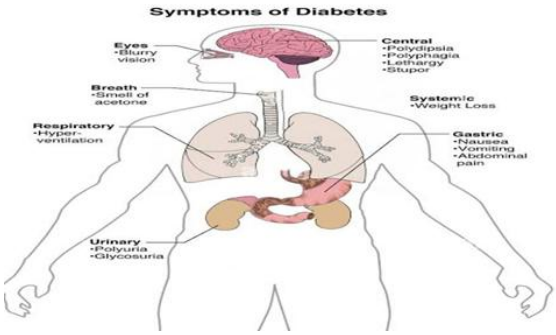

Figure 1: Patient suffering from diabetes

8.5% of persons over the age of 18 had diabetes in 2014. Diabetes was the direct cause of 1.5 million fatalities in 2019, with 48% of all diabetes-related deaths occurring in people under 70. Diabetes and elevated blood sugar levels contributed to an additional 460 000 renal disease deaths. Approximately 20% of cardiovascular fatalities are caused by hyperglycemia. Age-standardized death rates from diabetes increased by 3% between 2000 and 2019. The death rate from diabetes rose by 13% in lower-middle-income nations. In contrast, the likelihood of dying between the ages of 30 and 70 from any of the four major non communicable diseases—diabetes, cancer, chronic respiratory conditions, or cardiovascular diseases—decreased by 22% worldwide between 2000 and 2019.

Diabetes types

Type 1:

Form 1 diabetes is the most prevalent form diagnosed in the world, accounting for 5–10% of cases. people under the age of 20, however as the disease frequently manifests in maturity, the previous term "juvenile-onset diabetes" is no longer used. The illness can be further categorized as immune-mediated or idiopathic (cause unknown) and is typified by the death of the pancreatic islets' beta cells that produce insulin, resulting in a severe insulin shortage. Most cases are immune-mediated, including an autoimmune assault mediated by T cells. results in beta cell death and insulin insufficiency. Due to extremely low insulin and a compromised ability to counteract hypoglycemia, patients frequently have erratic and unpredictable blood sugar levels.

Type 2:

Insulin resistance, which can coexist with comparatively decreased insulin production, is a hallmark of type 2 diabetes. It is thought that the bodily tissues' poor sensitivity to insulin to engage the insulin receptor. The precise flaws remain unknown, though. Cases of diabetes mellitus brought on by a known defect are categorized differently. 95% of cases of diabetes are type 2, making it the most prevalent form of the disease. Before fulfilling the requirements for type 2 diabetes, many individuals with the disease exhibit signs of prediabetes, which includes reduced glucose tolerance and/or impaired fasting glucose. Lifestyle modifications or drugs that increase insulin sensitivity or lower the liver's synthesis of glucose can halt or even reverse the progression of prediabetes to overt type 2 diabetes.

Skin:

The skin covers the entire body thanks to the membranes lining its orifices, which also shield the underlying structures from damage and microbial invasion.

1. It contains somatic (temperature, touch, and pain) nerve endings.
2. It plays a part in regulating body temperature.

Structure of the skin

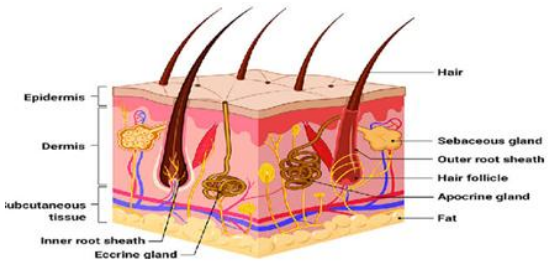

Fig. No. 2: Structure of skin.

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Among the many essential functions of the skin are:
1. Protection from physical, biological, or chemical threats
2. Prevents excessive water loss from the body
3. plays a vital role in thermoregulation.
4. An epidermal enzyme has the ability to denature drugs.

Transdermal Drug Delivery System:-
When applied to intact skin, transdermal drug delivery systems (TDDS) are discrete, self-contained dosage forms that enable the medication or drugs to be given to the systemic circulation at a regulated rate through the epidermis. Transdermal drug delivery is a practical method of administering potent, low-molecular-weight medications that are either extremely susceptible to the severe conditions of the gastrointestinal tract or highly susceptible to first-pass hepatic metabolism.

Fig. No. 3: Transdermal patch.

Transdermal drug delivery systems are patches that are applied topically and distribute drugs at a controlled, predetermined rate to provide systemic effects. A transdermal drug delivery system provides a another way to provide medication, which can possess a passive or active design. These technologies have made it possible to give medications over the skin barrier.

Basic components of transdermal drug delivery systems:
Drug:- Having the right pharmacokinetic and physicochemical properties is the most important requirement for TDDS. Transdermal patches are particularly useful for medications having a narrow therapeutic window, a high first pass metabolism, or short half-lives that cause non-compliance with numerous dosages. For example, drugs that have recently been approved as TDDS include rotigotine for Parkinson's disease, rivastigmine for Alzheimer's and Parkinson's dementia, selegiline for depression, and methylphenidate for attention deficit hyperactivity disorder. Transdermal administration is an extremely attractive option for drugs with the proper pharmacology and physical chemistry. For drugs like nitroglycerine, fenatyl, and others with a short half-life, a narrow therapeutic window, or significant first pass metabolism, transdermal patches are highly advantageous.

Permeation enhancer :- Proteins and lipids, which are structural components of the stratum corneum, interact with drug penetration enhancers to raise the stratum corneum's permeability and enable the medication to reach higher therapeutic levels. The partial leaching of the epidermal lipids by the chemical enhancers appears to be the origin of the improvement in skin conditions for wetting, trans epidermal, and trans follicular penetration. This promotes the absorption of drugs that are soluble in oil. The enhanced transdermal penetration of water-soluble drugs may be due to the solution and miscibility properties of enhancers. Using various enhancers, pharmaceutical researchers have put a lot of effort into developing transdermal penetration testing for various medicine moisturizers. For instance, DMSO.

Pressure Sensitive Adhesive:- A PSA should be aggressive and constantly active, provide a strong holding force, and attach with pressure from the fingers to maintain the patch's close contact with the skin's surface. For instance, polyacrylates, polyisobutylene, and adhesives based on silicon. Selecting an adhesive involves a variety of factors, including the patch design and medication formulation. PSA should be consistent with biology and physicochemistry and should not alter the release of medications. The PSA can be positioned on the device's back, extending peripherally, as in the matrix system, or on the device's face, as in the resorvior system.

Backing laminates:- The primary function of the backing laminate is to provide support. The backing layer should be chemically robust and compatible with the excipients because prolonged contact between the two may cause additives to seep out or excipients, medications, or penetration enhancers to permeate through the layer. They should transfer moisture vapor slowly. They must have the proper amounts of elasticity, flexibility, and tensile strength. Examples of backing materials include a heat-seal layer, a polyethylene, polyester, polyvinyl chloride, and aluminum vapor-coated layer.

Release liner:- A release liner is regarded as a part of the primary packing material rather than the dosage form that is used to give the medication since it is employed in storage to prevent contamination and the loss of medication that has moved into the adhesive layer. The release liner is

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composed of either an occlusive layer, like polyethylene or polyvinyl chloride, or a base layer, like paper cloth. A silicon or teflon release coating layer comes after the base layer. The TDDS release liner is also made of polyester foil and metallized laminate.

Additional excipients, such as solvents and plasticisers

Advantages:-

1. This process is simple to follow and only requires one application per week. Patients may find it easier to stick to their drug regimen with a simple dosing plan like this.
2. As an alternative mode of administration, transdermal medicine delivery may be advantageous for patients who are incapable of taking oral dose forms.
3. It greatly aids persons who are unconscious or feeling nausea.
4. Drugs that are broken down by the enzymes and acids in the gastrointestinal tract may also be good targets.
5. Another limitation on the delivery of oral medications is first pass metabolism, which is circumvented via transdermal injection.

Disadvantages:-

1. Local pain may occur at the application site.
2. The medication, the patch's adhesive, or additional excipients may result in erythema, irritation, and local oedema.
3. Has the capacity to cause allergic responses.
4. The molecular weight must be less than 500 Da.
5. Sufficient lipid and aqueous solubility; to penetrate the SC and underlying aqueous layers, the permeate needs to have a log P (octanol/water) of 1 to 3.

Principles of Transdermal permeation:-

Until more recent studies revealed that the skin could be employed as a medium for systemic distribution, it was thought that the skin was an impervious barrier of protection. The skin is the most accessible and intensive organ in the body because the capillary network beneath it and the skin's surface are barely a millimeter apart. The following are some of the numerous steps that go into moving a medication from the patch into the bloodstream:

1. Drug diffusion from the drug reservoir to the membrane that controls the rate.
2. Drug diffusion into the stratum corneum from the membrane that restricts the rate.
3. The stratum corneum's sorption and penetration into viable epidermis.
4. The drug is absorbed by the dermal papillary layer's capillary network.
5. Effect on the targeted organ

Factors Affecting Permeability:

Physiological Factors:-

1. Skin stratum corneum layer
2. anatomical location of application on the body
3. skin health and disease
4. patient age
5. skin metabolism
6. skin irritation and sensitisation

Formulation Factors:-

1. physical chemistry of transportation
2. vehicles and membranes utilised;
3. Use of penetration enhancers
4. Method of Application
5. Use of Device

Physiochemical Properties of enhancer

1. It is necessary to have a partition coefficient of 1 or greater.
2. pH value should be moderate because variations in pH that modify the ratio of charged and uncharged species and their transdermal permeability can impact the flux of ionisable medicines.
3. When the concentration of the penetrant is higher than its solubility, the excess solid medication acts as a resorbent and aids in sustaining a steady drug concentration over an extended period of time.

Various Methods used to enhance the skin penetration:

1. **Eutectic system:-** According to standard solution theory, the lower a substance's melting point, the more soluble it is in a given solvent, including skin lipids. The melting point of a drug delivery device can be lowered. EMLA cream, a eutectic mixture of lignocaine and prilocaine applied under an occlusive film, provides effective local anesthesia for painless vein punctures and other procedures.

2. **Liposomes and vehicles:-** Liposomes are colloidal particles composed of concentric bimolecular layers that can encapsulate drugs. Several cosmetic products contain active ingredients that are encapsulated in vesicles. These consist of humectants such as urea and glycerol, enzymes, and unscreening and tanning agents. Because cholesterol tends to stabilize the structure, adding it to the mixture results in more rigid liposomes. How the stratum corneum absorbs medications more easily is unknown. The stratum corneum may be partially penetrated by the liposomes before they interact with the lipids in the skin to release their medicament, or only their

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constituents may pass through.

3. **Solid lipid Nanoparticles:-** Solid lipid nanoparticles (SLN) have recently been investigated by researchers as carriers for better skin delivery of sunscreens, vitamins A and E, triptolide, and glucocorticoids. Their greater skin penetration is thought to be mostly due to increased skin moisture caused by the occlusive film that forms on the skin's surface.

4. **Iontophoresis:-** An ionophoretic skin delivery system's design is influenced by a number of factors, including the electrode type, current intensity, and system pH. The enhanced drug penetration resulting from this approach could be attributed to one or more of the following mechanisms: Electro-perturbation for both charged and uncharged solutes, electro-osmosis for uncharged solutes, and electro-repulsion for charged solutes

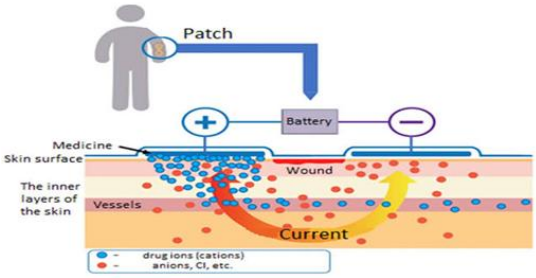

Fig no.4 : Iontophoresis

5. **Electroporation:-** It entails subjecting the skin to high-voltage pulses, which have been demonstrated to induce the formation of transient pores. High voltages (100 V) and milliseconds are the most often utilized treatment durations. The method has been effectively used to improve the permeability of the skin for biopharmaceuticals with molecular weights more than 7kDA. Proteins, peptides, oligonucleotides, and small molecules with different sizes and lipophilicity are examples of these molecules.

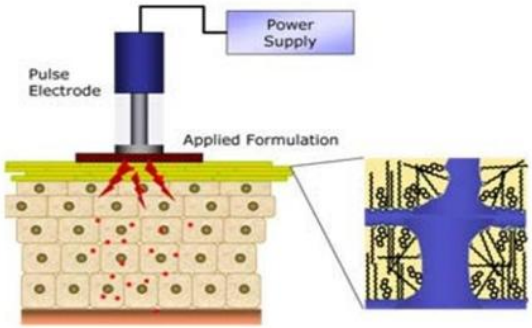

Fig no. 5: Electroporation

6. **Ultrasound (sonophoresis and phonophoresis):-** This technique enhances solute transdermal dispersion by using ultrasonic energy, either in conjunction with or as a pretreatment. It increases skin permeability by applying low frequency ultrasonography (55 kHz) for an average of 15 seconds.
7. **Skin Abrasion:-** The abrasion technique directly removes or disturbs the epidermis' outermost layers. The superficial skin resurfacing techniques used by dermatologists to treat scars, acne, hyperpigmentation, and other skin defects constitute the foundation of these devices.

Evaluation Parameter:

1. **Thickness of patch:-** The thickness of the drug-loaded patch is measured at multiple locations using a digital micrometre. The average thickness and standard deviation are computed to ensure the thickness of the generated patch. A moving microscope dial gauge, screw gauge, or micrometre is used to measure the thickness of the transdermal film at different points along the film.
2. **Weight Uniformity:-** The produced patches are dried at 60°C for four hours prior to testing. A digital balance must be used to weigh a specific patch area once it has been divided into multiple portions. The average weight and standard deviation data must be obtained using the individual weights.
3. **Folding endurance:-** A uniformly cut strip of a specific length must be folded repeatedly at the same location until it breaks. The number of times the film can be folded in the same location without breaking is known as folding endurance.
4. **Content Uniformity test:-** Ten patches are selected, and the content of each patch is determined. If nine out of 10 transdermal patches contain content between 85% and 115% of the recommended value, and one has content that is at least 75% to 125% of the specified value, then the patches pass the content uniformity test. However, if three of the patches have a drug level of 75% to 125%, another 20 patches are tested for drug content. If the range of these 20 patches falls between 85% and 115%, the transdermal patches pass the test.
5. **Drug Content:-** A certain volume of a patch must be dissolved in an appropriate solvent. After that, the solution must be filtered through a filter medium, and the drug content must be examined using the appropriate technology (either HPLC or UV). The average of three distinct samples is shown by each value.
6. **Rolling ball tack test:-** This test assesses the

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talk-related softness of a polymer. A 7/16-inch-diameter stainless steel ball is released onto an incline track for this test, where it travels downward and encounters horizontal, upward-facing adhesive. The distance the ball travels along the adhesive determines the tack, which is expressed in inches.

7. **Quick Stick test:-** In this test, the tape is pulled 12 inches per minute away from the substrate at 90 degrees Celsius. The tack value, expressed in grams or ounces per inch of width, is the amount of peel power required to break the adhesive-substrate bond.

Recent Advances in the field of Transdermal Patches:

1. **Pain Free-diabetic monitoring using transdermal patch:-** The original prototype patch, which measures about cm in size, is made of polymers and thin metallic sheets. The 5×5 sampling array is easily visible along with its metallic connectors. When the seal is broken, the interstitial fluid and the biomolecules it contains are accessible on the skin's surface. Using micro-heating elements incorporated into the patch's structural layer closest to the skin's surface, a high-temperature heat pulse can be applied locally, piercing the stratum corneum. During this ablation process, the skin's surface reaches temperatures of 130°C for 30 milliseconds. The temperature rapidly decreases from the skin's surface, and neither vital tissue nor nerve endings are affected. This operation is painless and bloodless, and it disrupts an area of the dead skin layer around the size of a hair follicle with a diameter of 40-50μm. This allows the interstitial fluid to interact with the electrode locations on the patch.

2. **Pain Relief:-** Pain relief is often aided by transdermal patch technology. The Duragesic patch is recognizable to most readers. Numerous others are now accessible. One of these is Lidoderm, a lidocaine patch used to treat post-herpetic neuralgia. The E-Trans fentanyl (Cl) patch is another significant advancement in pain management. This credit card-sized patch is an active delivery system that uses a self-contained battery to deliver potent fentanyl (Cl) pulses. The use of expensive, intricate, and nursing-care-intensive intravenous self-controlled analgesia systems is comparable to this.

Future Technologies and approaches:-

1. Traditional medicines and the extraction of intestinal fluid glucose from humans have both made use of thermal poration, which uses pulsed heat to form aqueous channels across the stratum corneum.These days, jet injectors are getting more attention, which is leading to better device design for controlled, needle-free drug solution administration into deeper tissue and across the skin.
2. This technique, which includes putting a tiny needle a few millimeters into the skin and using a micro-infusion pump contained in a big patch affixed to the skin to pump medication solution through the needle into the skin at regulated rates, has been used to give morphine to humans.
3. A number of ideas have been proposed during the past ten years to address the following combinations: chemicals and iontophoresis; chemicals and electroporation; chemicals and ultrasound; iontophoresis and ultrasound; electroporation and iontophoresis; and electroporation and ultrasound.

CONCLUSION:-

There has been significant advancement in the field of transdermal patches. Many researchers are interested in the Transdermal Drug Delivery System because of its many benefits.There are currently a lot of fresh studies being conducted to integrate more recent medications through this system. Additionally under investigation are a number of gadgets that aid in speeding up the drug's absorption and penetration. However, due to several drawbacks in the present, such as the inability to deliver large drug molecules, the inability to administer high doses, the lower drug absorption rate, skin irritation, and so forth. The Transdermal Drug Delivery System has had limited utility. Nowadays, however, its use is growing quickly due to the development of new medications and technologies that can be integrated through this system.

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