Original Article
IASR Journal of Medical and Pharmaceutical Science
Website: https://ijmps.com/
ISSN (online): 2582-9343
Page No : 25-37

Current Trends And Recent Advances In Transdermal Drug Delivery

Navneet Kumar Verma[*1], Asheesh Kumar Singh[2], Prashant Singh[2], Ankur Yadav[1], Alok Dwivedi[3], Anamika Chauhan[3]

[1]Associate Professor, Buddha Institute of Pharmacy, GIDA, Gorakhpur Affiliated to Dr. APJ Abdul Kalam Technical University, Lucknow, UP, India
[2]Professor, Buddha Institute of Pharmacy, GIDA, Gorakhpur Affiliated to Dr. APJ Abdul Kalam Technical University, Lucknow, UP, India
[3]Students, Buddha Institute of Pharmacy, GIDA, Gorakhpur Affiliated to Dr. APJ Abdul Kalam Technical University, Lucknow, UP, India

ABSTRACT
It is one of the greatest pharmaceutical dose forms for individuals who are unable to take medications orally. Transdermal drug delivery systems (TDDS) have become an essential component of innovative drug delivery systems (NDDS). On The systemic impact is achieved through the use of transdermal patches, which distribute the medication through the dermis. TDDS is an expensive alternative to traditional formulation. It is also significant because of its distinct benefit. Some of the possible benefits of transdermal drug delivery include controlled absorption, more consistent plasma levels, increased bioavailability, decreased adverse effects, painless and uncomplicated application, and the flexibility of discontinuing drug administration by simply removing the patch from the skin. The creation of a controlled release transdermal dosage form is a time-consuming and labor-intensive operation.

Keywords: *TDDS, NDDS, Transdermal Patches, Drug polymer, Permeation enhancers.*

Corresponding Author
Navneet Kumar Verma
Associate Professor, Buddha Institute of Pharmacy, GIDA, Gorakhpur Affiliated to Dr. APJ Abdul Kalam Technical University, Lucknow, UP, India

INTRODUCTION
Recently, there has been a resurgence in interest in creating new methods for delivering current medicinal compounds.The creation of an innovative delivery mechanism for currently available drug molecules significantly increases patient compliance, overall therapeutic benefit, and the efficacy and safety of the treatment.[1] Novel delivery systems can effectively deliver drugs with improved bioavailability when properly designed and developed for a particular drug. For example, drugs that partially or completely degrade before reaching the site of action could be delivered with these novel concepts of timed or pulsatile release, or gastro-resistant delivery. [2] Drug compositions have improved during the past 20 years, as have new administration methods. We now understand more about how drugs move through tissues. The use of the skin as a channel for systemic drug delivery is relatively new, despite the fact that topical medicines or drug delivery systems have been utilised for generations to treat local skin problems.[3] The advantage of drug delivery by transdermal means is that it is comparatively painless. The benefits of using the skin as a medication entry point include the ease of access, the skin's large surface area, systemic access via underlying circulatory and lymphatic networks, and the noninvasiveness of drug delivery. When Ciba-Geigy released Transderm V (now sold as Transderm Scop) in 1981 to treat motion sickness, the term "transdermal delivery" was first used to describe the administration of medications through the skin for systemic effects. [4, 5] The transdermal patch has developed into a tested technology over the past 20 years that has a number of important clinical advantages over alternative dosing modalities. [6] It represents a fresh development in the field of controlled delivery systems and has broadened the scope of possible scientific advancements. Several significant benefits of transdermal medicine delivery over conventional oral and intravenous delivery methods are offered. Transdermally administered medications minimise the danger and inconvenience of intravenous therapy, typically offer a lower risk of overdose or underdose, permit simple discontinuation, and allow for both local and systemic therapeutic benefits. Transdermal medication delivery allows for a constant blood level profile, regulated drug release into the patient, less systemic side effects, and occasionally higher efficacy than conventional dose forms. [7,8] The most common method of medicine delivery is oral. Although it has several drawbacks including first pass metabolism, medication breakdown owing to enzymes in the digestive system, PH, etc. A unique drug delivery mechanism was designed to overcome these issues. In this transdermal delivery system, therapeutically effective amounts of medication are delivered across the skin when medicated adhesive patches are applied to the skin. Transdermal or medicated adhesive patches come in a variety of sizes and include multiple

ingredients. They penetrate skin barriers to transfer active compounds into systemic circulation once applied to intact skin. a patch with a large dose of medication within that is left on the skin for an extended period of time and diffuses into the bloodstream. Drugs can enter the skin through three different passageways: sweat ducts, sebaceous glands, and hair follicles. Transdermal medication delivery devices are used to treat a variety of skin conditions, as well as angina pectoris, pain, quitting smoking, and neurological illnesses like Parkinson's disease. [9,10]

One of the most effective and cutting-edge drug delivery systems for studies inpharmaceutical sciences is the transdermal method. By improving patient compliance and avoiding first pass metabolism, respectively, transdermal medication administration offers a competitive advantage over injectables and oral methods. Transdermal drug delivery allows for continuous infusion of medications with brief biological half-lives and eliminates pulsed entrance into the systemic circulation in addition to controlled, ongoing drug administration. The ability of a dermatological medicine to permeate the skin insufficiently to provide the intended therapeutic effect is crucial to the efficacy of its systemic drug delivery.In 1981, the first transdermal patch was given the go-ahead to treat motion sickness, nausea, and vomiting. Up until recently, the transdermal drug delivery business was primarily supported by passive patch technology, which depended on sample diffusion through the skin. Active patches, which allow the administration of molecules larger than 500 daltons and those with difficult physicochemical qualities, have a wide range of capabilities. As a result, active patches that carry proteins, vaccinations, and painkillers have been developed. Smaller patches with improved adherence are being produced through passive patch technology. The transdermal drug delivery system (TDDS) has made a name for itself as a crucial component of cutting-edge drug delivery systems. Transdermal medication delivery is thus described as self-contained, discrete dose forms that, when applied to undamaged skin, transfer the drug to the systemic circulation through the skin at a controlled rate. [11,12,13] It may comprise a transdermal drug delivery system, in which the rate of drug absorption improves and, ultimately, the rate of drug bioavailability increases. When using a transdermal drug delivery system, the medication is delivered to the mucous membrane and skin's outer surface. It is a new method of drug delivery or a targeted method of drug delivery with significant applications in the prevention of issues with presystemic metabolism or systemic circulation. This kind of drug delivery method has the ability to have both local and systemic effects. Preventing GI toxicity, gastric irritability, and GI mucosal injury is crucial. To keep skin healthy and prevent infections of the skin or mucous membranes, transdermal drug delivery systems are essential. These systems can include transdermal medications like ointments, creams, gels, and microemulsions as well as patches that are applied directly to the skin. [14-19] The first transdermal patch, a 3-day patch, was developed in the late 1970s to cure motion sickness. Since that time, the market for drug delivery via patches has been continuously growing. However, transdermal administration is severely constrained since the stratum corneum layer of the skin acts as a barrier, making it impossible for the majority of medications to penetrate the skin at therapeutic rates.[20,21] Drugs given in standard dosage forms frequently cause wide changes in plasma drug concentrations, which might result in unfavourable toxicity or ineffectiveness. The idea of a regulated drug delivery system or therapeutic system was developed as a result of these factors, as well as additional factors including recurrent dosing and unexpected absorption. A controlled drug delivery system is a dosage form that continually delivers one or more medications in a planned pattern for a set amount of time, either systemically or to a specific target organ. The main goals of controlled drug delivery are to increase patient compliance, ensure safety, and improve treatment efficacy. Less frequent dosage and improved plasma drug level management are used to achieve this. Transdermal therapy systems are self-contained discrete dosage forms that, when applied to healthy skin, transport the drug(s) to the systemic circulation through the skin at a controlled rate. [22,23] The first transdermal drug delivery (TDD) system, Transderm-Scop, was created in 1980 and contained the motion sickness medication Scopolamine. A membrane-moderated mechanism governs the transdermal device. This technique uses a microporous polypropylene film as the membrane. The medicine is dissolved in a mixture of mineral oil and polyisobutylene to create the drug reservoir. This study release will continue for three days. [24]To administer a specific amount of medication through the skin and into the bloodstream, a transdermal patch is employed. The FDA initially approved transdermal patch products in 1981.

Scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, and nicotine to help smokers quit are all currently available in transdermal administration systems. Transdermal delivery allows for continuous infusion of medications with short biological half-lives, eliminates pulsed entrance into the systemic circulation, and offers controlled, ongoing drug administration. Compared to conventional injection and oral procedures, TDDS has many benefits. It lessens the burden that taking medication orally frequently places on the liver and digestive system. It improves patient compliance and reduces dangerous pharmacological side effects brought on by transient overdose. It is practical, particularly for patches that only need to be applied once each week. Patient adherence to medication therapy is aided by the straightforward dose schedule. [25]

Transdermal patches' primary parts are:

• Polymer matrix:- which serves as the foundation of TDDS and regulates medication delivery. Polymers should not degrade when stored, exhibit no chemical reactivity, be nontoxic, and have low costs. Derivatives of cellulose, zein, gelatin, shellac, waxes, gums, etc. nitrile, acrylonitrile, neoprene, polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, and polyamide

• Drugs:- The transdermal route is a very alluring choice for medications with the proper physical chemistry and pharmacology. Drugs with a large first pass metabolism, a limited therapeutic window, or a short half life all benefit greatly from transdermal patches.such as nitroglycerine, fenatyl, etc.
• Permeation enhancers:-increase stratum corneum permeability to allow for higher therapeutic medication levels.
These come in three varieties: surface active substances, lipophilic solvents, and two component systems. Like DMSO
• Adhesive: Increase stratum corneum permeability to reach greater therapeutic doses ofmedication.
• Backing laminates ought to be flexible or low in modulus. vinyl, polyethylene, etc.
• Release liner – safeguards the patch while being stored. The liner is taken out before usage.
• Additional excipients, such as solvents and plasticizers. [26]
Routes for delivering drugs through human skin.

There are three ways drug molecules can enter the body.
1. Sweat glands
2. The hair follicles
3. Sebaceous ducts

Alternatively, straight across the stratum corneum.

The epidermis' uppermost layer, the stratum corneum, is made up of broad, flat, polyhedral, plate-like envelopes packed with keratin, which is created from dead cells that have moved up from the stratum granulosum. The majority of the dead, nuclear-free cells that make up this epidermal layer. These dead cells are continuously replaced by fresh cells from the stratum germinativum (basale) when they slough off on the surface in the thin, air-filled stratum disjunctum. The stratum corneum is made up of 10 to 15 layers of corneocytes, and its thickness ranges from 10 to 15 micrometres when it is dry to 40 micrometres when it is moist. It is primarily made up of keratin-rich corneocytes that are arranged in a multi-layered "brick and mortar" structure inside an intercellular matrix made up of long chain ceramides, free fatty acids, triglycerides, cholesterol, cholesterol sulphate, and sterol/wax esters. Keratinocytes in the middle to upper portion of the stratum granulosum release their lamellar contents into the intercellular space, resulting in the formation of the intercellular lipid matrix. The early stratum corneum layers reorganise to create wide intercellular lipid lamellae, which later join to form lipid bilayers. The behaviour of the lipid phase differs from that of other biological membranes as a result of the composition of the stratum corneum's lipids. Water is a crucial component of the stratum corneum, acting as a plasticizer to keep it from cracking and contributing to the production of a natural moisturising factor that keeps it supple. It is crucial to identify the main route of drug permeation within the stratum corneum in order to comprehend the physicochemical characteristics of the diffusing drug and vehicle influence across stratum corneum. A molecule travelling the transcellular route must first partition into and diffuse through the keratinocyte before continuing to the estimated 4–20 lipid lamellae that separate each keratinocyte in order to reach the next one. For the majority of medications, this process of partitioning into and diffusing across numerous hydrophilic and hydrophobic domains is undesirable. As a result, it is presently believed that the intercellular route is the main channel for the passage of the majority of medicines via the stratum corneum.

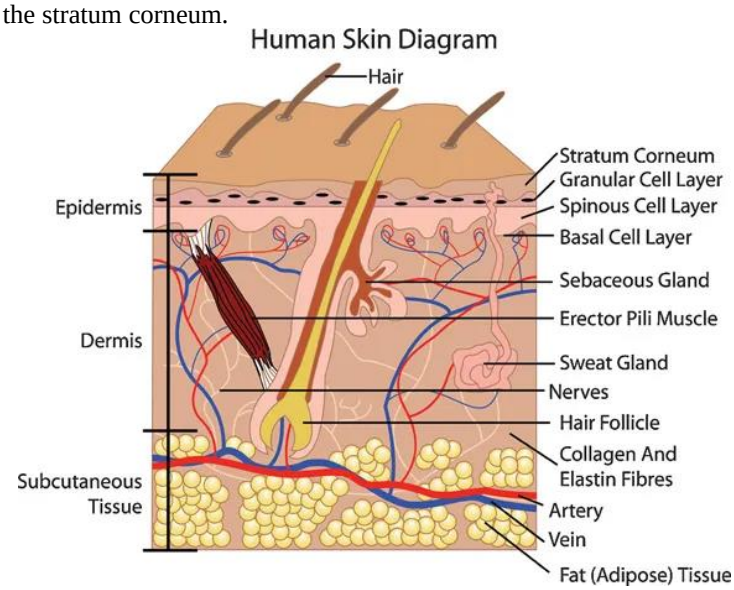

Fig. 1: Transverse skin slice illustrating points of penetration 1. directly across the stratum corneum; 2. via the sweat ducts; 3. via the hair follicles[26]

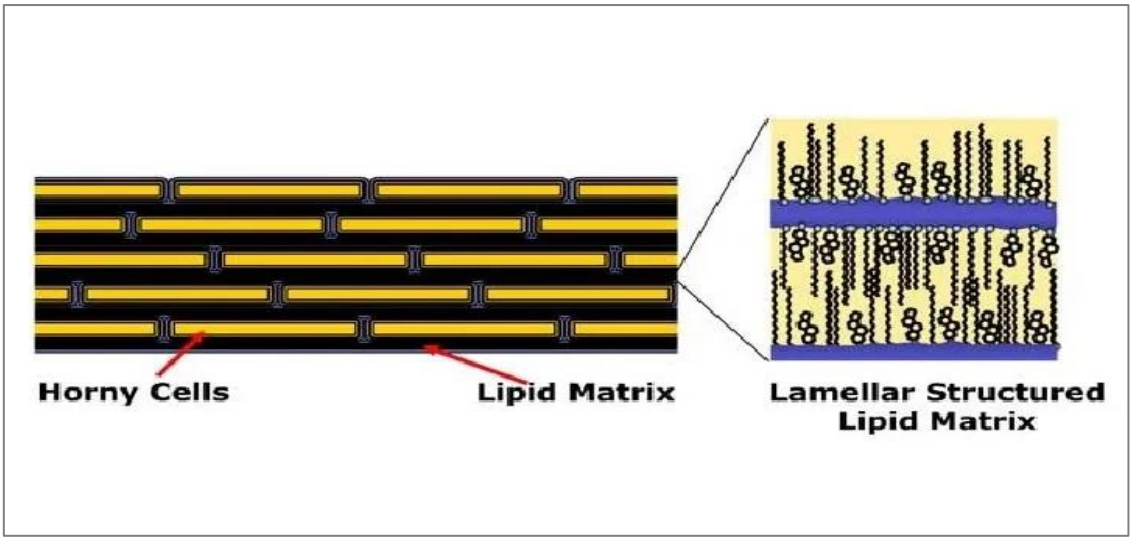

Fig. 2: The stratum corneum's schematic structure as depicted by the brick-and-mortar model [27]

Advantages

1. It is a practical approach that just needs to be applied once every week. Patient adherence to pharmacological therapy can be helped by such a straightforward dose schedule.
2. To accommodate patients who are unable to tolerate oral dosage forms, transdermal medication delivery can be employed as an alternative mode of administration.
3. Patients who are queasy or asleep benefit greatly from it.
4. Since transdermal distribution avoids direct effects on the stomach and intestine, medications that induce gastrointestinal discomfort may be suitable candidates.
5. Drugs that are broken down by the digestive system's enzymes and acids may also make good targets.
6. Transdermal administration can prevent first pass metabolism, another restriction on oral medication delivery.
7. Transdermal drug delivery is a great option for medications that need relatively constant plasma levels. [27]

Disadvantages

1. The potential for local irritation where the application was made.
2. The medication, the adhesive, or other excipients in the formulation of the patch can all result in erythema, itching, and local edoema.
3. Might result in allergic responses.
4. A molecular weight of 500 Da or less is required.
5. Adequate aqueous and lipid solubility is necessary for permeate to cross SC and the underlying aqueous layers. This requires a log P (octanol/water) between 1 and 3.

Techniques to Improve Transdermal Drug Delivery

Following techniques can improve skin penetration:

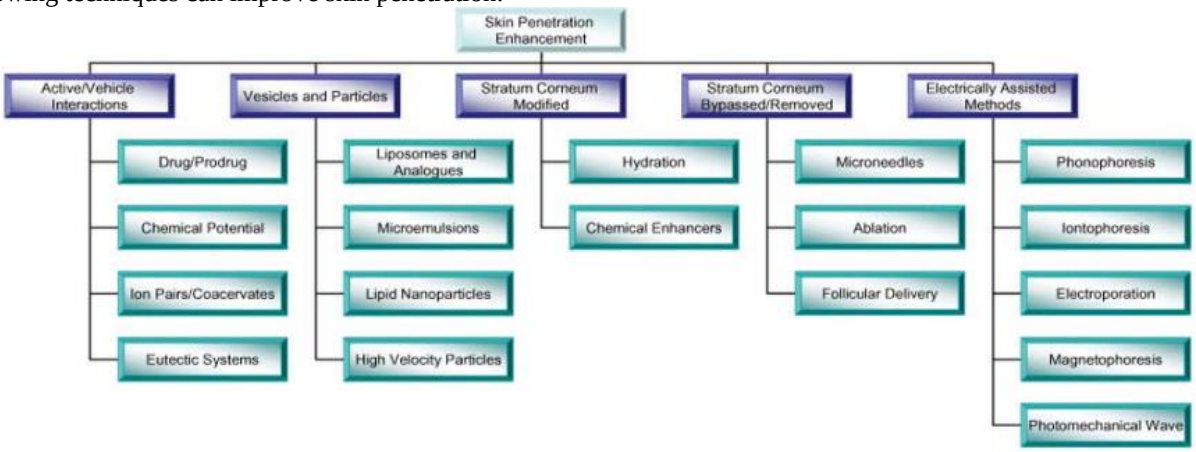

Fig 3. Various techniques to improve skin penetration [28]

1. **Drug/prodrug:-**Using a prodrug has improved the dermal and transdermal distribution of medications with poor partition coefficients. The prodrug design entails the addition of a promoiety to improve the parent drug's solubility and distribution in the stratum corneum as well as its partition coefficient. Esterases maximise solubility in the aqueous epidermis by hydrolyzing the parent medication once they reach the viable epidermis. For instance, utilising the S6-acyloxymethyl and 9-dialkylaminomethyl promoters, the intrinsically low permeability of the highly polar 6-mercaptopurine was raised up to 240 times. Increased skin permeability of non-steroidal anti-inflammatory medicines, such as naltrexone, nalbuphine, buprenorphine, alpha-blockers, and other pharmaceuticals, has also been explored using the prodrug strategy. [27,28]

2. **Eutectic system:-**An eutectic system is an amalgamation of chemical elements or compounds that has a single chemical composition that solidifies at a lower temperature than any other composition. Regular solution theory states that a substance, including skin lipids, is more soluble in a given solvent the lower its melting point. A drug delivery system's melting point can be decreased. Effective local anaesthesia is provided by EMLA cream, a formulation made up of a eutectic blend of lignocaine and prilocaine that is put underneath an occlusive film for pain-free venepuncture and other procedures.[27,28]

3. **Liposomes and vehicles:-**Drug-encapsulating liposomes are colloidal particles generated as concentric bimolecular layers. There are numerous instances of cosmetic goods with vesicles encasing the active components. These consist of humectants like urea and glycerol, agents for unscreening and tanning, enzymes, etc. Although many other potential constituents have been examined, the most typical composition is phosphatidylcholine from soy or egg yolk. [28] The addition of cholesterol to the mix tends to stabilise the structure, producing more stiff liposomes. Uncertainty surrounds the mechanism of increased medication absorption into the stratum corneum. It's possible that the liposomes either partially or completely penetrate the stratum corneum before interacting with the skin lipids to release their medicine, or that just a small portion of the liposomes really enter the stratum corneum.

4. **Solid lipid nanoparticles (SLN) :-** have lately been researched as carriers for improved skin absorption of glucocorticoids, triptolide, vitamins A and E, and sunscreens. It is believed that the main reason for their improved skin penetration is an increase in skin hydration brought on by the occlusive film that has formed on the skin surface. [29]

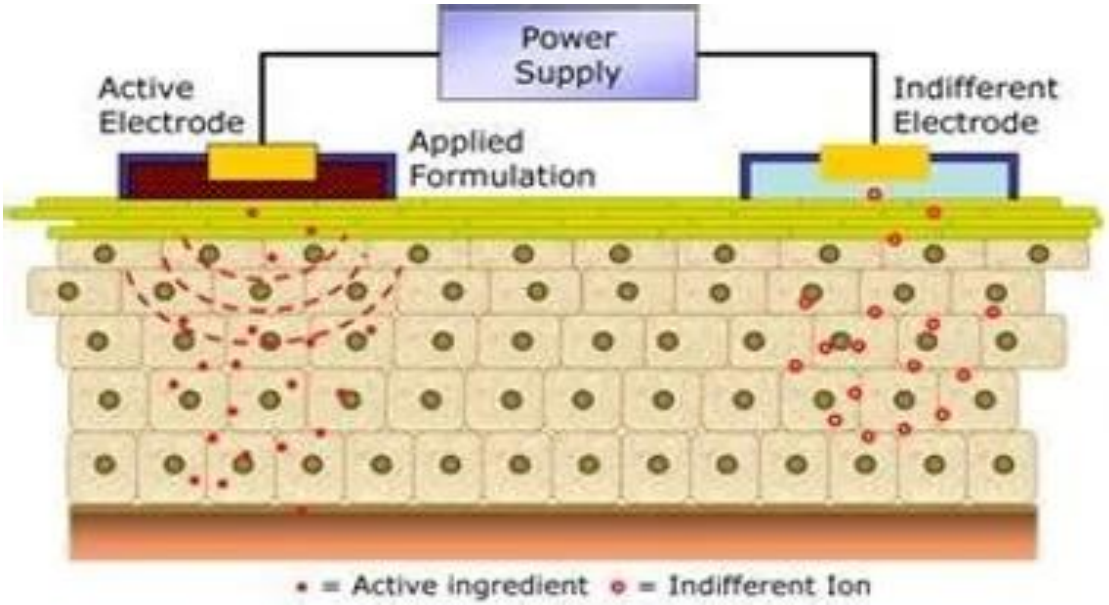

Fig. 4: Iontophoresis's fundamental idea [30]

5. **Iontophoresis:-** In this procedure, a topical medicinal substance is penetrated by a low-level electric current that is either delivered directly to the skin or indirectly through a dosage form. The electrode type, current intensity, and pH of the system are factors in the design of an ionophoretic skin delivery system. As a result of this methodology, increased drug penetration can be attributed to one or more of the following mechanisms: When it comes to charged solutes, electrorepulsion, electro-osmosis, and electro-perturbation all work in different ways. [30]

6. **Electroporation:-** It is the process of applying high voltage pulses to the skin in an effort to stimulate the development of temporary pores. Most typically, high voltages (100 V) and brief treatment times (milliseconds) are

used. Small molecules, proteins, peptides, and oligonucleotides, as well as biopharmaceuticals with molecular weights larger than 7kDA, have all been successfully improved in their skin permeability using this approach. [30]

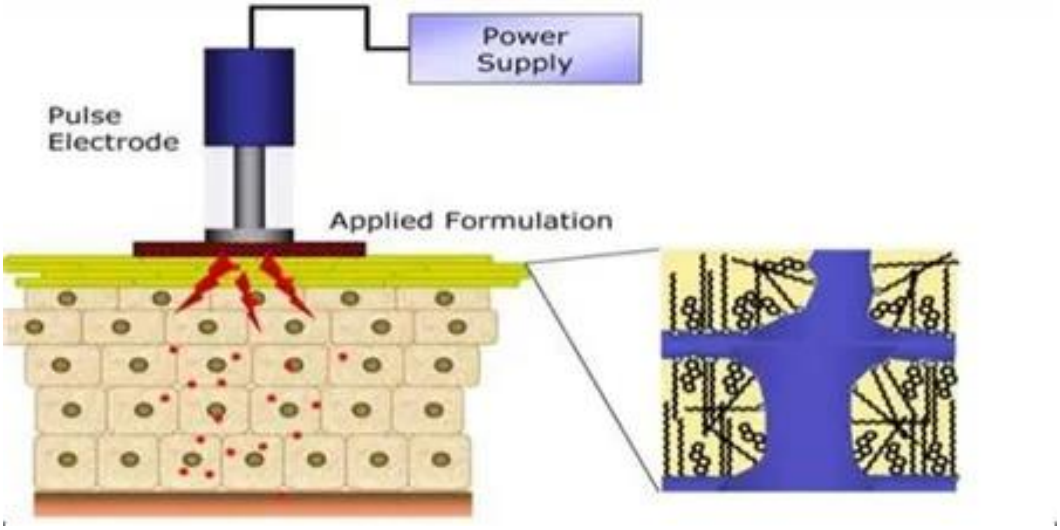

Fig. 5: The fundamental idea of electroporation [30]

7. **Ultrasound (sonophoresis and phonophoresis):-** Using ultrasonic energy to increase transdermal transport of solutes either simultaneously or through pretreatment is the goal of this approach. It increases skin permeability by applying low frequency ultrasound (55 kHz) for an average of 15 seconds. [31]

8. **Laser radiation and photomechanical waves:-**Lasers are often used to treat skin disorders like acne and to rejuvenate the face. This procedure includes applying a laser to the skin in a direct and regulated manner. This eliminates the stratum corneum while barely affecting the underlying epidermis. [32]

9. Radio frequency: This includes exposing skin to high-frequency alternating current, which causes the membrane to develop heat-induced microchannels. The quantity and depth of the device-created microchannels regulate the rate of drug distribution. Treatment time is under one second.

10. Magnetophoresis: This technique uses a magnetic field as an external driving force to speed up a diamagnetic solute's diffusion over the skin. Additionally, skin exposure to a magnetic field might result in structural changes that increase permeability. [33]

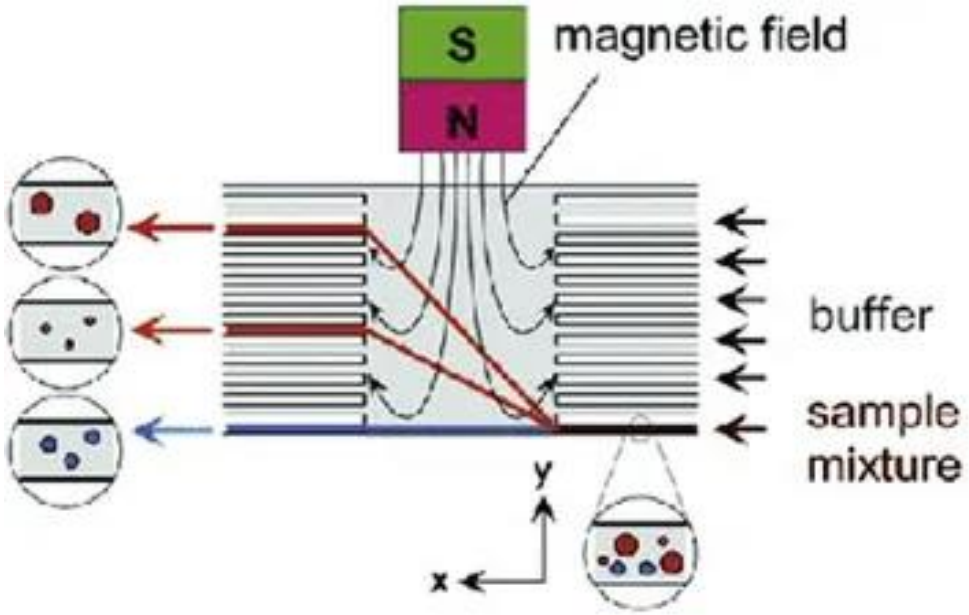

Fig. 6: Magnetophoresis procedure [33]

11. **Microneedle-based devices:-** This technique constituted the basis for the first ever patents for medication delivery for percutaneous administration. These 50–110 micrometre long microneedles will reach the SC and epidermis to administer the medication.

12. **Skin Abrasion:-** In the abrasion procedure, the top layers of the skin are directly removed or damaged. These devices are based on methods doctors use to treat acne, scars, hyperpigmentation, and other skin imperfections through superficial skin resurfacing.

13. **No-needle Injection:-** Transdermal delivery is accomplished by propelling the liquid or solid particles through the outer layers of the skin at supersonic speeds utilising an appropriate energy source. The method includes pushing pressurised gas (helium) through the nozzle; the ensuing drug particles entrained inside the jet flow are then said to travel at a sufficient velocity for skin penetration.
This approach steers clear of risks, discomfort, and fear. [34]

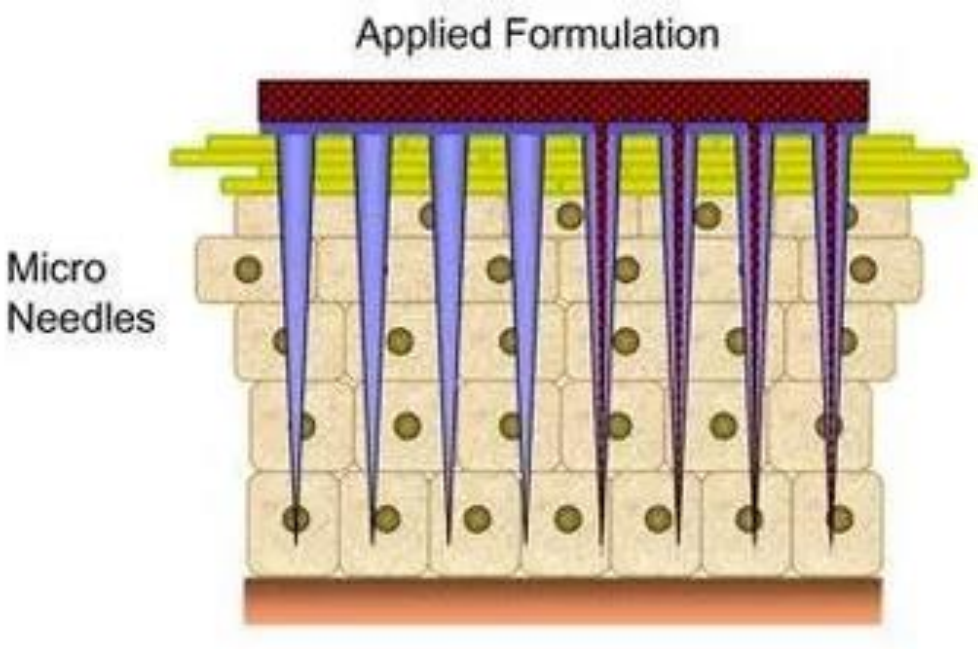

Fig.7; The Fundamental Layout of Microneedle Delivery Systems [34]

TRANSDERMAL DELIVERY SYSTEM DESIGN

Any transdermal delivery system's fundamental components include the drug dissolved or distributed in an inert polymer matrix, which acts as support and a platform for drug release.

The patch system's two primary designs, which determine the nature of drug release and patch behaviour, are as follows:

1) Matrix or Monolithic: The drug is bound to the inert polymer matrix, which regulates the drug's release from the device.

2) Reservoir or Membrane: Drug release is not regulated by the polymer matrix. The rate limiting barrier for drug release from the device is now provided by a rate-controlling membrane that is present between the drug matrix and the sticky layer. [35]

GENERAL CLINICAL THOUGHTS RELATED TO TDDS USE

The patient should be informed of the general rules listed below. For the skin to regain its natural permeability and to prevent skin irritation, rotating the application site is crucial. [36]

- To clean, dry skin that is largely hair-free and not oily, inflammatory, irritated, or cracked skin, TDDS should be applied. Drug penetration time might be accelerated by moist or wet skin.
- Skin that is too oily can make patches less adherent. If there is hair at the location, it should be carefully clipped; it should not be wet shaved or removed with a depilatory product, since these actions could disrupt stratum corneum and influence the pace and depth of drug absorption.
- At the application location, skin lotion usage should be avoided because it can change the drug's partition coefficient and have an impact on skin moisture.
- Patient shouldn't physically manipulate TDDS because doing so compromises the system's integrity.

- Remove the protective backing gently without letting your fingers touch it. For approximately 10 seconds, the TDDS should be firmly placed on the skin spot with the heel of the hand.
- A TDDS should be installed in a location where movement or clothes won't cause it to be removed. When bathing, swimming, or taking a shower, TDDS should be left on.
- A TDDS should be worn for the whole time recommended by the product's instructions, after which it should be removed and replaced with a new system.
- After using a TDDS, the patient or carer should wash their hands. During system handling, the patient shouldn't touch their mouth or rub their eyes.
- The patient should seek reevaluation if they show signs of sensitivity or intolerance to a TDDS or if excessive skin irritation occurs.
- To prevent re-use, a used TDDS should be folded in half with the adhesive layer together after removal. The used patch was disposed of in a way that was safe for kids and dogs.
- Transdermal patch usage To prevent skin irritation, it's crucial to utilise a fresh application site each day. The recommended rotation is:

Upper right arm, upper right chest, upper left arm, and then repeat from day one on days two through four.

CIRCUMSTANCES FOR THE USE OF TRANSDERMAL PATCHES

- When a patient needs an alternative form of drug delivery because they have terrible side effects (including constipation) and are unable to take oral medications due to dysphagia.
- Where effective management may be able to better control the discomfort. Patients with cognitive impairment or those who are unable to self-medicate with their analgesics for other reasons may find this helpful. [37,38]

CIRCUMSTANCES WHERE TRANSDERMAL PATCHES SHOULD NOT BE USED

(1) A treatment for acute pain is necessary, transdermal patches are not appropriate.
(2) When a quick dose titration is necessary.
(3) When the required amount is 30 mg or less per 24 hours. [37,38]

Drug Excipient Interaction Studies:

Transdermal Patch Evaluation Test

To create a stable product, the medicine and excipients must be compatible, and it is essential to look for any potential physical and chemical interactions. Thermal analysis, FT-IR, UV, and chromatographic techniques are frequently used in interaction studies to compare the physiochemical characteristics of the materials, such as assay, melting endotherms, distinctive wave numbers, and absorption maxima, etc. [39]

Drug Content

A given patch area needs to be dissolved in a predetermined volume of a suitable solvent. Following the solution's filtering through a filter medium, the drug content must be determined using the appropriate technology (UV or HPLC). Each value is the average over three samples. [40-42]

Weight Uniformity

Prior to testing, the produced patches must be dried at 60°C for 4 hours. A predetermined patch area must be divided into various patches and weighed using a digital balance. From the individual weights, the average weight and standard deviation values must be determined. [42,43]

Patch Thickness

To confirm the prepared patch's thickness, the thickness of the drug-loaded patch is measured at several spots using a digital micrometre to calculate its average thickness and standard deviation. [43-46]

Test for flatness

From each film, three longitudinal strips should be cut, one from the centre, one from the left side, and one from the right side. Each strip's length was measured, and the difference in length due to non-uniformity in flatness was calculated using the percent constriction formula, where 0% constriction is equal to 100% flatness. [37]

Percentage Moisture Uptake

To maintain 84% RH, the weighted films must be stored in desiccators at room temperature for 24 hours with saturated potassium chloride solution. The films must be reweighed after 24 hours to calculate the percentage moisture uptake using the formulas below. [46,47]

[Final weight-Initial weight/Initial weight] / 100 is the formula for percentage moisture uptake.

Moisture Loss

Each of the manufactured films needs to be weighed before being stored at 40°C in a desiccator with calcium chloride. The films must be reweighed after 24 hours in order to calculate the percentage of moisture loss using the formula below. [48] % Moisture loss is calculated as [Initial wt - Final wt/ Final wt] x 100.

Studies on the Water Vapour Transmission Rate (WVTR)

Equal-diameter glass vials were utilised as transmission cells. These transmission cells were given a thorough cleaning before being dried for a while in an oven at 100 oC. The cells were filled with approximately 1g of anhydrous calcium chloride, and the corresponding polymer film was fixed over the brim. To maintain a relative humidity of 84%, the cell were precisely weighed and stored in a closed desiccator filled with saturated potassium chloride solution. After preservation, the cells were removed and weighed. The following formulas [48,49] were used to calculate the amount of water vapour transferred.

Final weight minus initial weight divided by time and area equals the water vapour transmission rate.
It is measured in terms of the grammes of moisture gained each hour per square foot.

Swellability

The 3.14 cm2 patches were weighed, placed in a petri dish with 10 ml of double-distilled water, and left to soak. At predetermined intervals, the patch's weight increased until a consistent weight was noticed. [50]

The formula used to determine the swelling level (S) was S (%) = Wt - Wo /Wo 100.
Where Wo is the weight of the patch at time zero, Wt is the weight of the patch at time t, and S is the percent swelling.

Folding Endurance

A strip of a particular area must be cut uniformly and folded repeatedly at the same spot until it breaks.
The folding endurance of a film was measured by counting how many times it could be folded in the same spot without breaking. [51]

Polariscope analysis

The purpose of this test is to use a Polariscope to study the drug crystals from the patch. To determine if the drug is present in the patch in crystalline form or amorphous form, a certain surface area of the object must be preserved on the object slide and examined for drug crystals.[52]

Test for Percentage Elongation Break

To ascertain the percentage elongation break, note the length shortly before the break point. The percentage elongation can be calculated using the following formula. [53]

Elongation % is equal to 100 [L1-L2 / L2]. where L1 represents the overall length of each strip and L2 represents its beginning length.

Tensile Strengt

A universal strength testing machine was used to assess the film's tensile strength. The device had a 1 g sensitivity. There were two load cell grips in it.

The upper one is adjustable, while the lower one is fixed. Between these cell grips, a test film (4 x 1 cm2) is placed, and force is gradually increased until the film breaks. [54] The dial reading in kilogrammes is directly converted to the tensile strength of the film. The following is how tensile strength is stated.

Tensile strength is calculated as Tensile load at break / Cross sectional area.

Probe Tack Test

In this test, an adhesive is brought into contact with a clean probe tip with a specified level of surface roughness to see if a bond may be established. The probe is then mechanically broken during removal. Tack is measured as the force needed to remove the probe from the adhesive at a set rate and is stated in grams[53]

Skin Irritation Study

Healthy rabbits (weighing between 1.2 and 1.5 kg on average) can be used for investigating skin sensitization and irritation. It is necessary to clean the dorsal surface (50 cm2) of the rabbit, remove any hair from the clean region by shaving, and clean the surface with rectified spirit before applying the appropriate formulations to the skin. After 24 hours, the patch must be removed, and the skin must then be examined and divided into 5 grades based on the severity of the skin injury. [43]

Studies on the drug release in vitro

You can evaluate the drug release from the produced patches using the paddle over disc method (USP equipment V). A glass plate must be covered with dry films of defined thickness that have been cut into a specific form, weighed, and fastened with an adhesive. The device was then brought to an equilibrium temperature of 32 0.5 °C before the glass plate was submerged in 500 cc of the dissolving liquid or phosphate buffer (pH 7.4). The paddle was then turned on at a speed of 50 rpm while being placed 2.5 cm away from the glass plate. At suitable intervals up to 24 hours, samples (5 ml aliquots) can be taken out and analysed using a UV spectrophotometer or high performance liquid chromatography (HPLC). The experiment must be carried out three times, and the mean value may be computed. [55]

Studies on in vitro skin permeation

Diffusion cells can be used to conduct an in vitro permeation investigation. Male Wistar rats weighing 200–250 g have full thickness abdomen skin. The dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, and equilibrated for an hour in diffusion medium or phosphate buffer pH 7.4 before starting the experiment. Hair from the abdominal region is to be carefully removed using an electric clipper.

Diffusion medium is added to the diffusion cell, which is then put on a magnetic stirrer with a tiny magnetic bead to ensure that the diffusant is distributed evenly. A thermostatically controlled heater was used to keep the cell's temperature at 32 +/- 0.5°C. The isolated rat skin piece needs to be put in the diffusion cell between the compartments with the donor compartment's epidermis facing up. At regular intervals, a sample volume of a specific volume is to be taken out of the receptor compartment, and an equal volume of fresh medium is to be replaced. Samples must be filtered using a filtering media before being examined using high performance liquid chromatography (HPLC) or spectrophotometry. [56-65]

The permeability coefficients were obtained by dividing the flux by the initial drug load (mg cm -2), and flux can be calculated directly as the slope of the curve between steady-state values of the amount of drug penetrated (mg cm -2) vs. time in hours.

In-vivo studies

In-vivo assessments are the most accurate representations of a drug's effectiveness. In-vivo research can completely examine the variables that cannot be considered during in-vitro experiments. The following methods can be used for TDDS in-vivo evaluation:

Animal studies

Human participants

Model animals

The most often utilised animal species for testing transdermal drug delivery systems include the mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, and guinea pig.

Personae models

After applying the patch to human volunteers, the transdermal device's final stage of development entails gathering pharmacokinetic and pharmacodynamic data. Clinical studies have been carried out to evaluate the effectiveness, risks, side effects, patient compliance, etc.

Stability Studies

In accordance with the ICH recommendations, stability studies must be carried out by holding TDDS samples at 40 0.5 °C and 75 5% RH for six months. The samples were taken out and properly analysed for drug content at 0, 30, 60, 90, and 180 days. [43,66]

LIMITATIONS FOR TDDS SELECTION

Not all medications can be supplied by this route; the medication must possess a few favourable PhysicoChemical characteristics.[67]

- Not appropriate for medications that need high plasma levels.
- Not suited for medications that cause contact dermatitis and skin rashes.
- Drugs having a high molecular weight are not appropriate.
- Not appropriate for medications that are metabolised as they pass through the skin.
- Since the skin is a very effective barrier to drug penetration, a substantial variety of medications cannot be administered by the transdermal route. Only a small dose may be used for administration.
- The skin's ability to act as a barrier varies from one spot to another within a single individual, between individuals, and with age.

CONCLUSION

Transdermal drug delivery provides a painless, practical, and possibly effective technique to administer several drugs in regular doses. better medication absorption, wide selection of medicines available minimal difficulties, negative effects, low cost, and simplicity of use. Example Ten years prior, nitroglycerin for angina, clonidine for hypertension, scopolamine for motion sickness, and estradiol for oestrogen shortage were all administered to patients using patches, which were worn by more than a million people annually.

A medicinal product that is currently licenced for oral dosing can evade first pass metabolism by being delivered transdermally. The most popular method of transdermal medication administration uses skin patches. However, the somewhat impermeable thick outer stratum corneum layer places restrictions for transdermal technologies. Poor permeability is a challenge that researchers are working to tackle using physical and chemical methods.

REFERENCE

1. Garg, S, Kndarapu, R. and Kannan, V., Pharm. Tech., 2003, 27 (2), 74.
2. Jain, N.K., In; Advances in Controlled and Novel Drug Delivery, 1st Edn., CBS publishers and distributors, 2002, 428-37
3. Corrigan, O.I., Transdermal Drug Delivery Systems, Department of Pharmaceutics, Unviersity of Dublin, Ireland.
4. Electronic Rrange Book, Food and Drug Administration, www.fda.gov/cder/ob.
5. Ghosh, T.K. and Banga, A.K., Pharma. Tech., 1993, 75-78.
6. Ryan D.G. and Peterson, T.A., Drug Delivery Tech., 2003, 3(4): 46-51.
7. Soni, S. and Dixit, V.K., Indian Drugs, 1992, 29(11), 466-467.
8. Chong, S., Fung, H.L., In: Hadgraft, J., Guy, R.H., Eds., Transdermal Drug Delivery: Developmental Issues and Research Initiatives, Marcel Dekker, New York, 1989, 135 S.
9. Arti Kesarwani, Ajit Kumar Yadav, Sunil Singh,Hemendra Gautam, Haribansh N. Singh, Anamika Shvarma, Chitresh Yadav. A review – Theoretical aspects of Transdermal Drug Delivery System. Bulletin of Pharmaceutical Research, 3(2), 2013, 78-89.
10. Sampath Kumar KP, Debjit Bhowmik and Chiranjib B, R M Chandira. A review- Transdermal Drug Delivery System - A Novel Drug Delivery System and its market scope and opportunities. International Journal of Pharma and Bio Sciences, 2010, 1(2),1-21.
11. Jain NK. Advances in controlled and novel drug delivery, 1st Ed., CBS Publishers and distributors, New Delhi .2001; 108- 110.
12. Barry BW, William AC. In: Swarbrick J(ed)) Boylon JC.Encyclopedia of pharmaceutical technology vol-II, Marcel Dekker: Inc New York, 1995, 49-93.
13. Tanner T, Marks R.Delivering Drugs by the Transdermal Route: review and comment. Skin Research and Technology, 14, 2008, 249-260.
14. Saltzman W, Mark Torchilin, Vladimir P. Drug delivery systems, Access Science, McGraw-Hill Companies, 5(2), 2008, 125-136.
15. Flynn G L. Cutaneous and transdermal delivery: Processes and systems of delivery. In Modern Pharmaceutics, Banker, G.S and Rhodes, C.T, Eds. New York, NY: Marcel Dekker, Vol.2, 1996, 239-299.
16. Rastogi V, Yadav P. Transdermal drug delivery system: An overview. Asian Journal of Pharmaceutics, 6(3), 2012, 161- 170.
17. Soni S and Dixit V K. Transdermal delivery system. Indian Drugs, 29(11), 1992, 466-467.
18. Panchagnula R. Transdermal delivery of drugs. Indian Journals Pharmacology, 29(2), 1997, 140-56.
19. Vyas S P and Khar R K. Targeted and controlled Drug Delivery Novel carrier system, CBS Publishers and distributors, New Delhi, (2-Volume set), 1st Edition, 2002, 411- 447.
20. Marc B Brown, Matthew JT, Gary PM and Franklin KA. Transdermal drug delivery systems. Skin perturbation devices.1- 32.
21. Prausnitz MR. Microneedles for transdermal drug delivery. Advance Drug Delivery Reviews, 56, 2004, 581-587.
22. Panner Selvam R, Anoop Kumar Singh, Sivakumar T, Transdermal drug delivery systems for antihypertensive drugs - A review, IJPBR, 2010, 1(1), 1-8.
23. Kakkar A, P and Ajay Gupta, Gelatin Based Transdermal Therapeutic System, Indian Drugs, 1991, 29 (7), 308-315.
24. Chowdary K.P.R and Naidu R.A.S, Transdermal Drug Delivery, A Review of Current Status, Indian Drugs, 1995, 32(9), 414- 422.
25. Gaur PK, Mishra S, Purohit S, Dave K. Transdermal drug delivery system- A review. Asian Journal of Pharmaceutical and Clinical Research. 2009; 2:14-20.
26. Aggarwal G, Dhawan S. Development, Fabrication and Evaluation of Transdermal Drug Delivery System - A Review. Pharmainfo.net. 2009; 7(5).
27. Heather AE. Transdermal Drug Delivery: Penetration Enhancement Techniques. Current Drug Delivery. 2005; 2:23-33
28. Touitou E, Junginger H, Weiner ND, Nagai T, Mezei M. Liposomes as carriers for topical & transdermal delivery. Journal of Pharmaceutical Science. 1994; 83:1189-1203.

29. Wissing SA, Muller RH. The influence of solid lipid nanoparticles on skin hydration & viscoelasticity-In vivo study. European Journal of Pharmaceutics and Biopharmaceutics. 2003; 56:67-72.
30. Guy RH, KaliaYN, Delgado-Charro MB, Merino V, Lopez A, Marro D. Iontophoresis: electro repulsion and electroosmosis. J control release. 2000; 64:129-132.
31. Mitragotri S, Blankschtein D, Langer R. Ultrasound mediated transdermal protein delivery. Science. 1995; 269:850-853.
32. Lee WR, Shen SC, Lai HH, Hu CH, Fang JY. Transdermal drug delivery enhanced and controlled by erbium:YAG laser. J controlled release. 2001; 75:155-166.
33. Treffel P, Panisset FF, Humbert P, Remoussenard O, Bechtel Y, Agache P. Effect of pressure on in vitro percutaneous absorption of caffeiene.Acta.Derm.Venereo.1993; 73:200- 202.
34. Brown MB, Traynor MJ, Martin GP, Akomeah FK. Drug Delivery Systems: Skin Perturbation Devices. Methods in Molecular Biology. 2008; 437:119-139.
35. Lyn Margetts, and Richard Sawyer, Transdermal Drug Delivery: Principles And opioid Therapy, Continuing Education in Anaesthesia, Critical Care & Pain, 2007,7(5),171-176.
36. Nikhil Sharma, Geta Agarwal, Rana A.C, A Review Transdermal Drug Delivery System a tool for Novel Drug Delivery System, IJDDR, 2011, 3 (3), 70.
37. Kamal Saroha, Bhavna Yadav, Benika Sharma, Transdermal Patch, A Discrete Dosage Form, International Journal of Current Pharma Research, 2011,3(3), 98-108.
38. Shah S, Transdermal Drug Delivery Technology Revisited, Recent Advances, Pharmainfo Net, 2008, 6(5),
39. Shalu Rani, Kamal Saroha, Navneet Syan, Pooja Mathur, Transdermal Patches A Successful Tool In Transdermal Drug Delivery System: An overview, Der Pharmacia Sinica, 2011, 2 (5), 17-29.
40. Prabhu Prabhakara, Marina Koland, Preparation and Evaluation of Transdermal Patches of Papaverine Hydrochloride, International Journal of Research Pharmaceutical Sciences, 2010,1(3), 259-266.
41. Kulkarni V.H, Keshavayya J, Transdermal Delivery of Terbutaline sulphate through modified Chitosan membrane, Indian Journal of Pharmaceutical Education, 2004, 38(4), 189- 190.
42. Mutalik, N, Udupa, Glibenclamide Transdermal Patches, Physicochemical, Pharmacodynamic and Pharmacokinetic Evaluations, Journal of Pharmaceutical Sciences, 2004, 93 (6), 1557-1594.
43. Pravin Gavali, Atul, Gaikwad, Radhika P.R, Sivakumar T, Design and Development of Hydroxypropyl Methylcellulose based polymeric film of Enalapril Maleate, International Journal Of Pharmtech Research, 2010, 2(1), 274-282.
44. Basavaraj K, Nanjwade, Kiran Suryadevara, Kella M.R and Sai Susmitha, Formulation and Evaluation of Transdermal Patches of Ondansetron Hydrochloride using various polymers in different ratios, Current Trends In Biotechnology and Pharmacy, 2010, 4 (4), 917-921.
45. Janos Bajdik, Geza Regdon JR, The effect of the solvent on the film-forming parameters of Hydroxypropyl-cellulose, International Journal of Pharmaceutics, 2005, 301, 192-198.
46. Koteshwar K.B, Udupa N and Vasantha Kumar, Design and Evaluation of Captopril Transdermal Preparations, Indian Drugs, 15 (29), 680-685.
47. Priyanka Arora, Biswajit Mukherjee, Design Development Physicochemical and in-vitro Evaluation of Transdermal Patches Containing Diclofenac Diethylammonium Salt, Journal of Pharmaceutical Sciences, 2002, 91(9), 2076-2089.
48. Sankar V, Velrajan G, Palaniappan R and Rajasekar S, Design and Evaluation of Nifedipine Transdermal Patches, Indian journal of Pharmaceutical, Sciences, 2003, 65(5), 510-515.
49. Manvi F.V, Dandagi P.M, Gadad A.P, Mastiholimat V.S and Jagdeesh T, Formulation of Transdermal Drug Delivery System of Ketotifen Fumarate, Indian journal of Pharmaceutical Sciences, 2003, 65(3), 239-243.
50. Bharkatiya M, Nema R.K, Bhatnagar M, Designing and Characterization of Drug free patches for Transdermal Application, IJPSDR 2010, 2(1), 35-39.
51. Yuveraj Singh Tanwar, Chetan Singh Chauhan, Anshu Sharma, Development and Evaluation of Carvidilol Transdermal Patches, Acta Pharm, 2007,57, 151–159.
52. Sharma Teja, Rawal Gaurav, Transdermal Therapeutic Systems, An overview, International Journal of Pharmaceutical & Biological Archives, 2011, 2(6),1581-1587.
53. Diveyesh Patel, Nirav Patel, Meghal Parmar, Transdermal Drug Delivery System, Review, International Journal of Biopharmaceutical and Toxicological Research,2011,1(1),61- 80.
54. Kavitha K and More Mangesh Rajendra, Design and Evaluation of Transdermal Films of Lornoxicam, IJPBS, 2011, 2(2), 54-62.
55. Deepak Gondaliya and Kilambi Pundarikakshudu, Studies in Formulation and Pharmacotechnical Evaluation of Controlled Release Transdermal Delivery System of Bupropion, AAPS Pharmscitech, 2003, 4 (1), 1-9.
56. Vamshi Vishnu Y, Chandrasekhar K, Ramesh G and Madhusudan Rao Y, Development of Mucoadhesive Patches for Buccal Administration of Carvedilol, Current Drug Delivery, 2007, 4, 27-39.
57. Amnon C, Sintov, Igor Krymberk, Vladimir Gavrilov and Rafael Gorodischer, Transdermal Delivery of Paracetamol for Paediatric use, effects of vehicle formulations on the percutaneous penetration, Journal of Pharmacy and Pharmacology, 2003, 55, 911-919.
58. Ayman el-kattan, Charles, S, Asbill and sam haidar, transdermal testing, practical aspects and methods, PSTT, 2000, 3(12), 426- 430.

59. Samir D, Roy and Elizabeth Manoukian, Transdermal Delivery of ketorolac Tromethamine, Permeation enhancement, Device Design, and Pharmacokinetics in Healthy Humans, Journal of Pharmaceutical Sciences, 1995, 84 (10), 1190-1199.
60. Rajeev Gokhale, Cynthia Schmidt, Lisa Alcorn, James Stolzenbach, Transdermal Drug Delivery Systems of Albuterol, In Vitro and In Vivo Studies, Journal of Pharmaceutical Sciences, 1992, 81(10), 996-999.
61. Deepak Gondaliya and Kilambi Pundarikakshudu, Studies in formulation and pharmacotechnical evaluation of Controlled Release Transdermal Delivery System of Bupropion, AAPS PharmSciTech, 2003, 4(1), 1-9.
62. Kumar,S,K, Jain,S,K, Pancholi,S,S, Agrawal,S, Saraf,D,K and Agrawal,G,P, Provesiculare Transdermal Drug Delivery System of Ethinylestradiol and Levonorgestrel for Contraception and Hormone Replacement Therapy, Indian journal of Pharm, Sci, 2003, 65(6), 620-627.
63. Sadhana P, Gupta and S,K, Jain, Effective and controlled Transdermal Delivery of Metoprolol Tartarate, Indian journal of Pharmaceutical Sciences, 2005, 67(3), 346-350.
64. Csoka, E, Csanyi, Eros,I, In-vitro and in- vivo Percutaneous absorption of topical dosage forms, case studies, International Journal of Pharmaceutics, 2005,291, 11-19.
65. P,mayorga, F, Puisieux, Couarraze,G, Formulation study of Transdermal delivery systems of primaquine, International journal of Pharmaceutics, 1996, 132, 71-79.
66. Mohamed Aqil, Yasmin Sultana Asgar Ali, Matrix Type Transdermal Drug Delivery Systems of Metoprolol Tartrate, In Vitro Characterization, Acta Pharm, 2003, 53,119–125.
67. Jain N. K, Controlled and Novel Drug Delivery, 1997, 100-115