TRANSDERMAL DRUG DELIVERY SYSTEM: AN OVERVIEW

Umesh pawar , Poonam bagul , dr. Gajanan sanap

Late Bhagirathi yashwantrao pathrikar college of pharmacy

Abstract

Transdermal drug delivery systems (TDDS) have gained increasing importance in the field of pharmaceuticals due to their potential to provide controlled and sustained release of drugs with improved patient compliance and reduced side effects. This review offers a comprehensive exploration of TDDS, covering the principles, components, and formulation strategies involved in their development. We delve into the intricacies of skin anatomy and physiology as they relate to drug permeation, highlighting the critical factors influencing successful transdermal drug delivery. Additionally, we discuss the role of permeation enhancers, novel materials, and emerging technologies in optimizing TDDS performance. The review also underscores the significance of mathematical modeling and computational simulations in TDDS design and optimization. Furthermore, we examine the challenges and breakthroughs in delivering macromolecules and biologics via transdermal routes, along with emerging applications such as personalized medicine. Case studies and examples provide real-world insights, and we conclude by discussing future research directions and the evolving landscape of transdermal drug delivery. This review aims to serve as a valuable resource for researchers, clinicians, and pharmaceutical scientists, offering a comprehensive overview of the field and insights into its promising future.

Keywords : *Transdermal drug delivery system , skin , patches*

Introduction[1-10] :

TDDS is a painless method of applying a drug formulation to intact, healthy skin in order to systemically distribute medication. Without building up in the dermal layer, the medication passes through the stratum corneum before entering the deeper layers of the epidermis and dermis. Once the medicine penetrates the dermal layer, it becomes available for systemic absorption. It can be used to get around the phobia of injections by providing a non-invasive substitute for parenteral techniques. There are numerous options for transdermal absorption and implantation due to the skin's incredibly huge surface area and ease of access. In addition, the pharmacokinetic profiles of medications exhibit greater consistency and fewer peaks, hence decreasing the likelihood of serious adverse events. It is suitable for patients who are unconscious or vomiting and can improve patient compliance by reducing dose frequencies

Transdermal patch : An adhesive patch that has been medicated and applied to the skin to administer a specified dosage of medication via the skin is called a transdermal patch or skin patch. and into the circulation [11]

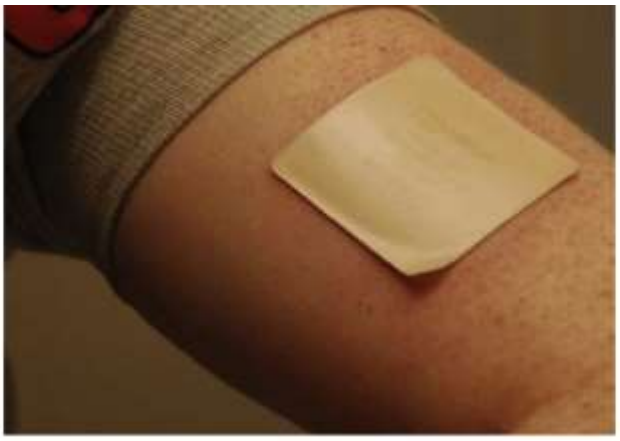

Figure 1 : Transdermal Patch

Advantages and Disadvantages

Advantages[12-13] :

- Dose frequency can be reduced.
- Increased bioavailability may result in a decrease in drug concentration.
- The liver's first pass metabolism can be circumvented.
- They can avoid problems with gastrointestinal medicine absorption brought on by enzyme activity, stomach pH, and drug interactions with food, beverages, and other oral medications.
- Lower drug side effects and decreased drug plasma concentration levels. They are non-invasive, so they avoid the inconvenience of parenteral therapy.
- Because they provided prolonged therapy with a single application, they increased compliance in comparison to earlier dosage forms that necessitated more frequent dose administration.
- The quick termination of medication therapy can be achieved by removing the application from the skin's surface.
- Self-administration is possible with these systems
- It reduces systemic drug interactions
- It offers longer duration of action

Disadvantages[14-15] :

- Transdermal delivery is appropriate only for strong medications.

- Some patients may experience skin irritation at the application site.
- This system is uneconomic
- Dosage dumping may result from the medication binding to the skin.
- It can only be used for chronic conditions, not acute ones, as long-term medication therapy is necessary for chronic conditions like diabetes, hypertension, and angina.
- Cutaneous metabolism can impact a medication's therapeutic efficacy; ionic medications are not appropriate for transdermal therapy.
- Fit for medications with smaller molecular weights, meaning fewer than 500 Daltons.

Care taken while applying transdermal patch

It is important to thoroughly clean the affected area of skin before to applying a patch. The patch shouldn't be cut since doing so ruins the drug delivery system. Make certain that the previous Before applying a new patch, the old one is deleted from the website. repair. It is important to use caution when applying or Taking off the patch because whoever is applying itcan take in the medication from the patch. The repair ought to be correctly applied to the administration site

First generation transdermal delivery system

The majority of transdermal patches that have been used in clinical settings to date are products of the first generation of transdermal delivery systems. notable developments in patch technology and public approval, have made it possible for the significant rise of first-Transdermal patches of the latest generation are being sold. But this spike will subside as medications containing The qualities that make such systems suitable are exhausted. First-delivery candidates for generation must be low-molecular weight, effective at low dosages, and lipophilic. Their transdermal delivery should typically be greater appealing compared to oral administration because to poor oral The requirement or preference for fewer frequent dosage, consistent administration patterns, or additional elements.

Second generation transdermal drug delivery system

The next generation of transdermal delivery technologies understands that increasing skin permeability is necessary to increase the range of transdermal medications. The perfect booster ought to (i) enhance skin permeability by temporarily interfering with structure of the stratum corneum, (ii) offer an additional driving power for skin absorption and (iii) prevent damage to living, deeper tissues. Still, improvement techniques created in this generation, include iontophoresis, traditional chemical enhancers, and non-avitational ultrasonography, have had difficulties with the strike a balance between increasing delivery across layer corneum, shielding more deeply situated tissues from injury. Thus, this subsequent generation of delivery systems has mostly improved clinical practice by enhancing the delivery of tiny molecules for localized, cosmetic, dermatological, and occasionally systemic applications, but hasn't had much of an effect on macromolecule delivery. [16,17,18]

Anatomy and physiology of skin

Three separate but interdependent tissues make up human skin: The cellular, vascular, and stratified layer known as the "epidermis" beneath the connective tissue's dermis, The hypodermis. [figure 2]

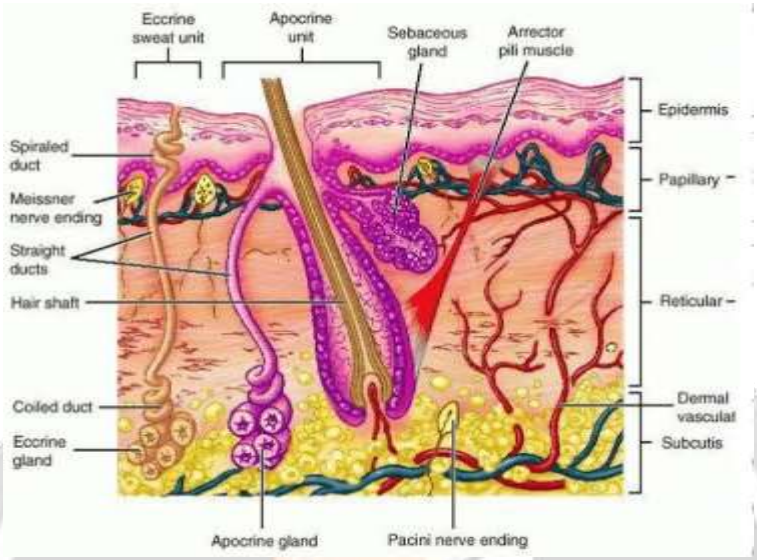

Figure 2 : structure of human skin [19]

Epidermis

The thickness of the multilayered epidermis varies from 0.8 mm on the palms and soles to 0.06 mm on the eyelids, depending on the size and number of cell layers in the epidermis. Corneum stratum. This is the skin's outermost layer, sometimes known as the horny layer. When completely hydrated, it swells to several times its dry thickness of about 10 mm. It is made up of 10 to 25 layers of corneocytes, which are dead, keratinized cells. Although flexible, it is not very permeable. The main obstacle to drug penetration is the stratum corneum. It is possible to model the architecture of the horny layer as a wall-like structure. The keratinized cells in this model serve as protein "bricks" encased in lipid "mortar."There are several bilayers made up of the lipids. The lipid fraction contains enough amphiphilic material to sustain a bilayer form, including cholesterol and polar free fatty acids. The stratum corneum is covered by viable epidermis, which ranges in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. It is made up of several layers that go inward, including the stratum lucidum, stratum granulosum, stratum spinosum, and the stratum basal. The epidermis in the basal layer is continuously renewed by cell mitosis, which makes up for the loss of dead horney cells from the skin's surface. The cells generated by the basal layer migrate outward, changing in morphology and histology as they undergo keratinization to form the stratum corneum's outermost layer..

Dermis

The dermis is a layer that is 3 to 5 mm thick and is made up of a connective tissue matrix that includes nerves, lymph vessels, and blood vessels. The skin's blood supply plays a crucial role in controlling body temperature. Along with eliminating waste and toxins, it also gives the skin nutrition and oxygen. The majority of molecules that penetrate the skin barrier find a sink condition in capillaries, which extend to within 0.2 mm of the skin's surface. Because of this, the blood supply maintains a very low dermal concentration of a permeate, and the concentration gradient that results across the epidermis is crucial for transdermal permeation.

Hypodermis

The dermis and epidermis are supported by the hypodermis, or subcutaneous fat tissue. It acts as a place to store fat. This layer offers mechanical protection, nutritional support, and temperature regulation assistance. Principal blood vessels, nerves, and possibly sensory pressure organs are carried to the skin by it. In order for a drug to be delivered transdermally, it must pass through all three of these layers and enter the bloodstream; however, for topical drug delivery, only the stratum corneum must pass through before the drug is retained in the skin layers. [20]

Drug penetration through skin [21]

One of the most important factors in cutaneous reactions to drugs, xenobiotics, and other chemicals is drug penetration through the skin. One of the hardest parts of accurately determining percutaneous absorption is the size of the compartments. A semisolid dosage form, like an ointment, gel, or cream, is typically applied topically to a thickness of less than 10 m. The viable epidermis, dermis, and, to a lesser extent, the systemic compartment function as a major sink for ingested poisons, diluting them to levels undetectable by all but the most sensitive techniques. The stratum corneum is likewise approximately 10 m thick. Therefore, sampling time-dependent changes in a compound's concentration in different compartments is technically challenging. Drugs can pass through the skin in a variety of ways.

- A] Via hair follicular penetration;
- B] Via transcorneal penetration;
- C] Via intracellular route;
- D] Via transcellular route.

- **Basic components of transdermal drug delivery system [22,23,24]**

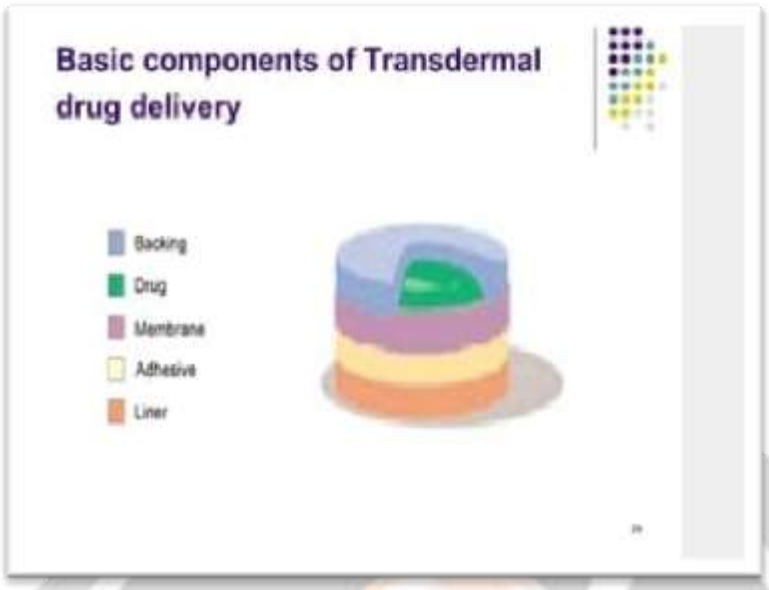

Figure 3 : basic components of TDDS

The components of transdermal device include :

- Polymer matrix
- Drug
- Permeation enhancer
- Other excipients

Polymer matrix : The drug's release from the device is regulated by the polymer. To be used in a transdermal system, a polymer needs to meet the following requirements. The following polymers could be helpful for transdermal devices:

Natural polymer	Synthetic elastomers	Synthetic polymers
• Cellulose derivative • Zein • gelatin • waxes • Proteins • gums • natural rubber • starch	• Polybutadiene • hydrin rubber • polysiloxane • silicone rubber • nitrile • acrylonitrile • butyl rubber • styrenebutadiene • neoprene etc .	• Polyethylene • polypropylene • polyacrylate • polyamide • polyvinylpyrrolidone • polymethyl methacrylate • epoxy • polyurea etc.

Drug

The drug must be carefully chosen in order to develop a transdermal drug delivery system that works. Some of the desired characteristics of a medication for transdermal delivery are listed below.

Physicochemical properties

- The medication's molecular weight should be less than about 1000 Daltons.
- The medication needs to be affinities for both hydrophilic and lipophilic phases. Severe partitioning properties are incompatible with effective transdermal drug delivery.
- The medication's melting point ought to be low.

Biological properties

- The medication ought to be strong, with a recommended daily dosage of a few milligrams.
- The medication should have a short half-life (t1/2).
- The medication must not cause allergic reactions or cutaneous irritation.
- Medications that undergo GI tract degradation or are rendered inactive by the hepatic first-pass effect are good candidates for transdermal administration.
- Transdermal delivery's nearly zero-order release profile prevents tolerance to the medication from developing.
- Medicines that must be applied topically or that have negative effects on tissues other than the intended target can also be prepared for transdermal delivery..

Permeation enhancers

Agents that can transfer the sorption of medications from drug delivery systems onto the skin are known as penetration enhancers or promoters. They are substances without any inherent medicinal qualities.

The flux, of drugs across the skin can be written as: $J = D X dc/dx$

where C is the concentration of the diffusing species, x is the spatial coordinate, and D is the diffusion coefficient, which depends on the size, shape, and flexibility of the diffusing molecule as well as the membrane resistance. Even though there are a lot of different boundary conditions and membrane heterogeneities in the solution for J, the above equation contains the fundamental ideas of flux enhancement. The diffusion coefficient is correlated with the size, shape, and energy needed to create a hole for diffusion, and the concentration

gradient has a thermodynamic origin. Therefore, improving flux across membranes comes down to the following factors:

- Thermodynamics (lattice energies, distribution coefficients).
- The form and size of molecules.lowering the energy needed to create a membrane-wide molecular hole.
- It is hypothesized that penetration enhancers will impact one or more of the layers to improve skin penetration. The potential of many different substances to increase stratum corneum permeability has been studied..

These conveniently classified under the following main headings:

solvents

these compounds increase penetration possibly by

- swelling the polar pathways in the skin ,
- fludization of lipids ,

Examples include laurocapram (Azone), pyrrolidones-2-pyrrolidone, alkyl homologs of methyl sulfoxide, dimethyl acetamide, and dimethyl formamide, water alcohols (methanol and ethanol), propylene glycol, glycerol, silicone fluids, and isopropyl palmitate.

Surfactant

It is suggested that these substances improve the transport of hydrophilic drugs along polar pathways.A surfactant's capacity to modify penetration depends on its head group and hydrocarbon chain length. Since these substances irritate the skin, it is necessary to strike a balance between irritation and penetration enhancement. Anionic surfactants have a strong ability to permeate and interact with skin. These surfactants have the ability to cause significant changes once they are absorbed by the skin. According to reports, cationic surfactants cause more irritation than anionic surfactants, and their ability to improve skin penetration has not received much research. The nonionic surfactant class is the most extensively researched and has long been acknowledged as having the lowest potential for causing irritation among the three main classes of surfactants.

Examples of commonly used surfactants are:

Anionic Surfactants : Dioctyl sulphosuccinate, decodecylmethyl sulfoxide, sodium lauryl sulfate, etc.

Nonionic Surfactants : Pluronic F68, F127, etc.

Bile Salts : Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

Miscellaneous Chemicals : Among them are the hydrating and keratolytic agent urea; calcium thioglycolate; N, N-dimethyl-m-toluamide; and anticholinergic agents.Although some possible permeation enhancers have recently been reported, there is little information on their efficacy at this time. Eucalyptol, di-o-methyl-beta-cyclodextrin, and soy-based casein are a few of these.

Other excipients

Adhesives ; Up until now, pressure-sensitive adhesive has been used to adhere transdermal devices to the skin. The pressure-sensitive adhesive may be applied to the device's face or its back, with its edges extending peripherally.

The following requirements should be met by both adhesive systems:

- Must not alter the natural skin flora or irritate or sensitize the skin.
- During the dosing interval, the skin should adhere firmly and should not be disturbed by activities like exercising or bathing.
- Should be easily removed.
- Should not leave an unwashable residue on the skin.
- Should make both macroscopic and microscopic excellent (intimate) contact with the skin.

Backing membrane : Because they are flexible, backing membranes accept printing, offer a strong bond to the drug reservoir, and keep the drug from escaping the dosage form through the top. For example, metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminum foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminum foil disc), etc., are examples of impermeable materials that shield products from the skin while they are being used.

Release Liner : Release liner stops contamination and drug loss during storage by preventing migration of the drug into the adhesive layer. As a result, it is thought of as a component of the main packing material as opposed to the drug's dosage form. The release liner consists of two layers: an occlusive (polyethylene, polyvinyl chloride) or non-occlusive (paper fabric) base layer, and a silicon or Teflon release coating layer. Metalized laminate and polyester foil are additional materials used in the production of TDDS release liners.

Types of transdermal patches

- Single-layer drug-in-adhesive.
- Multi-layer drug-in-adhesive.
- Reservoir.
- Matrix.
- Vapour patch**.**

Single-layer drug-in-adhesive : The fact that the medication is integrated directly into the skin-contacting glue sets it apart. This transdermal system design uses an adhesive that serves as both the foundation for the formulation and a means of skin attachment, keeping the medication and all excipients contained in a single backing film. The rate at which the drug diffuses through the skin affects the medication release rate of this kind of system[25,26].

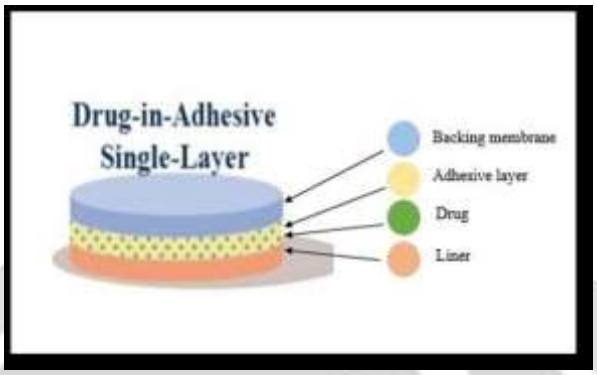

Figure 4 : Single-layer drug-in-adhesive

Multi-layer drug-in-adhesive : Since the medication is mixed right into the adhesive, it is comparable to the Single-layer Drug-in-Adhesive. The term "multi-layer" describes the insertion of multiple drug-in-adhesive layers or a membrane between two distinct drug-in-adhesive layers that are positioned beneath a single backing film.[25, 26]

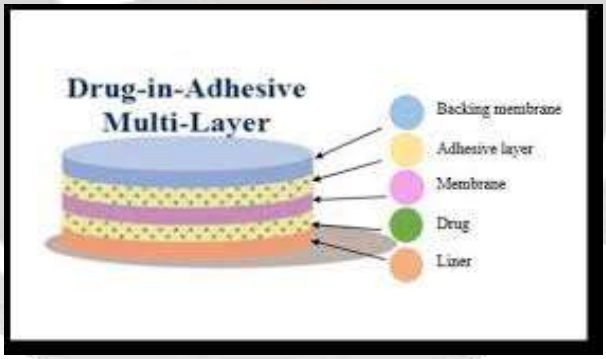

Figure 5 : Multi-layer drug-in-adhesive

Drug-reservoir-in -adhesive : It is distinguished by the presence of a liquid compartment with a drug solution or suspension that is kept apart from the release liner by an adhesive and semi-permeable membrane. The adhesive component of the product that is in charge of skin attachment can be included in either a concentric design surrounding the membrane or a continuous layer between the membrane and the release liner.[25, 26]

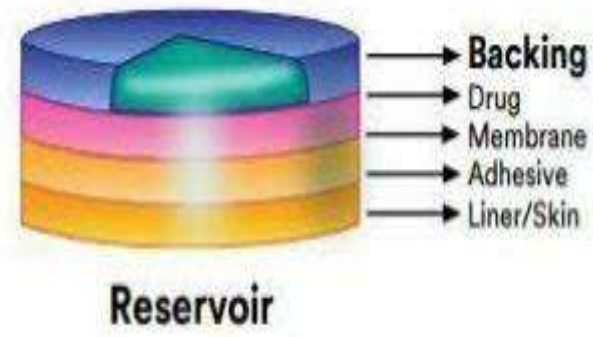

Figure 6 : reservoir patch

Drug Matrix-in-Adhesive : It is distinguished by the presence of a semisolid matrix that is in direct contact with the release liner and contains a drug solution or suspension. The skin-adhering component is integrated into an overlay and surrounds the semisolid matrix in a concentric pattern.[25, 26]

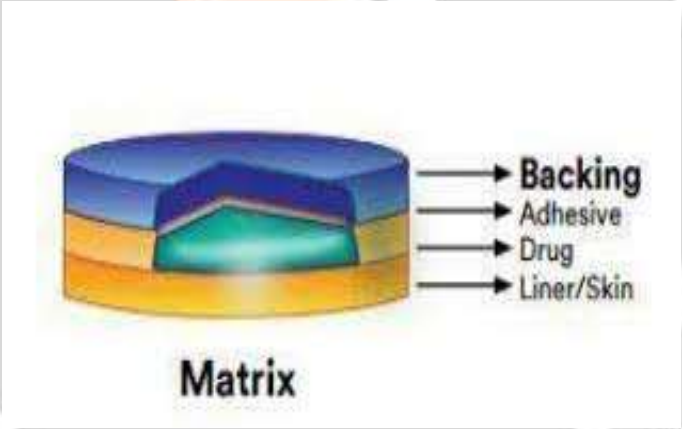

Figure 7 : matrix patch

Vapour Patch : This kind of patch uses an adhesive layer that releases vapour in addition to holding the different layers together. The newest products on the market are vapour patches, which release essential oils for as long as six hours. Vapour patches, which have the potential to release essential oils for up to six hours, are a relatively recent addition to the market. Essential oils are released by the vapour patches, which are primarily used to treat cases of congestion. As an alternative, controller vapour patches are available that improve the quality of sleep. Additionally, vapour patches that reduce the number of cigarettes a person smokes each month are available on the market. Month can also be found in the market. [27]

Various methods for preparation of transdermal drug delivery system:

Asymmetric TPX membrane method:

A heat-sealable polyester film (type 1009, 3m) with a 1cm diameter concave can be used as the backing membrane to create a prototype patch. The drug sample is injected into the concave membrane, sealed with an adhesive, and covered with an asymmetric TPX {poly (4-methyl-1-pentene)} membrane.[29]

Asymmetric TPX membrane preparation

The dry/wet inversion method is used to create these. To create a polymer solution, TPX is dissolved in a combination of nonsolvent additives and a solvent (cyclohexane) at 60°C. Using a garden knife, the polymer solution is cast to a predetermined thickness on a glass plate after being maintained at 40°C for 24 hours. Following a 30-second evaporation of the casting film at 50°C, the glass plate must be submerged right away in a coagulation bath with a temperature maintained at 25°C. The membrane can be removed after 10 minutes of immersion and allowed to air dry for 12 hours at 50°C in a circulation oven.[28]

Circular teflon mould method:

An organic solvent is used to dissolve solutions that contain polymers in different ratios. Half as much of the same organic solvent is used to dissolve the calculated amount of drug. The other half of the organic solvent is used to dissolve enhancers at varying concentrations before adding them. The drug polymer solution is plasticized with the addition of di-N-butylphthalate. After 12 hours of stirring, the entire mixture should be poured into a circular Teflon mold. To regulate solvent vaporization in a laminar flow hood model with an air speed of 1/2 m/sec, the molds are set on a level surface and covered with an inverted funnel. For twenty-four hours, the solvent is left to evaporate. To prevent aging effects, the dried films must be stored for a further 24 hours at 25±0.5 °C in a desiccator that contains silica gel before evaluation. These kinds of movies have to be reviewed within a week of production.[29]

Mercury substrate method:

This method dissolves the medication in a polymer solution with the plasticizer. To create a uniform dispersion, stir the aforementioned solution for ten to fifteen minutes before pouring it onto a leveled mercury surface. To regulate the evaporation of the solvent, an inverted funnel is placed over the solution.[29]

By using "IPM membranes" method:

Using a magnetic stirrer, the drug is dissolved in a solution of water and propylene glycol that contains carbomer 940 polymer, and the mixture is then shaken for a duration of 12 hours. Triethanolamine is to be added to the dispersion in order to neutralize it and make it viscous. If the drug's solubility in aqueous solution is extremely low, solution gel can be created using buffer pH 7.4. The IPM membrane will incorporate the gel that has formed.[28]

By using "EVAC membranes" method:

Rate control membranes such as polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membranes, and 1% carbopol reservoir gel can be utilized to prepare the target transdermal therapeutic system. Gel is made with propylene glycol if the medication is not soluble in water. Propylene glycol is used to dissolve the drug. Carbopol resin is then added to the mixture and neutralized with a 5% w/w sodium hydroxide solution. The medication (in gel form) is applied to a backing layer sheet that covers the designated area. To create a leak-proof device, a rate-regulating membrane will be placed over the gel and the edges will be heated to seal.[28]

Aluminium backed adhesive film method:

If the loading dose for a transdermal drug delivery system is more than 10 mg, unstable matrices may be produced. Since the majority of medications and adhesives are soluble in chloroform, the aluminum-backed adhesive film method is a good one for preparing the same. Adhesive material is added to the drug solution and dissolved after the drug is dissolved in chloroform. Aluminum foil is used to line a custom-made aluminum former, and cork blocks that fit tightly are used to blank off the ends.[28, 29]

Preparation of TDDS by using proliposomes:

The film deposition technique is used in the carrier method to prepare the proliposomes. Lecithin and the previously mentioned reference medication in a 1:2 ratio can be utilized as an ideal combination. In order to prepare the proliposomes, 5 mg of mannitol powder is placed in a 100 ml round-bottom flask and kept at a temperature between 60 and 70 °C. The flask is then rotated at 80 to 90 rpm and the mannitol is dried under vacuum for 30 minutes. The water bath's temperature is changed to between 20 and 30 °C after drying. A suitable mixture of organic solvent is used to dissolve the drug and lecithin After the organic solution has finished drying, another aliquot of 0.5 ml of the solution should be added. One aliquot of the organic solution is added to the round-bottomed flask containing mannitol at 37 °C.

Following the final loading, the proliposome-containing flask is attached to a lyophilizer. The drug-loaded mannitol powders (proliposomes) are then left in desiccators for the entire night before being sieved through a 100 mesh screen. After being gathered, the powder is put into a glass bottle and kept at freezing temperature until it is characterized.[29]

By using free film method:

Casting on a mercury surface creates a free film of cellulose acetate. Chloroform is utilized to prepare a 2% w/w polymer solution. At a concentration of 40% w/w of polymer weight, plasticizers are added. A glass ring set over the mercury surface in a glass petri dish was filled with five milliliters of the polymer solution. Over the petridish, an inverted funnel is used to regulate the solvent's rate of evaporation. After the solvent has completely evaporated, the mercury surface is examined to detect the formation of a film. Before being used, the dry film will be removed and kept in desiccators between the wax paper sheets. The volume of the polymer solution can be adjusted to create free films with varying thicknesses.[29]

Desirable features for transdermal patches: [30]

- Composition relatively invariant in use.
- System size reasonable.
- Defined site for application.
- Application technique highly reproducible.
- Delivery is zero order.
- Delivery is efficient.

Conditions in which patches are used:[31,32,33]

- When a patient requests an alternate drug delivery method due to dysphagia, which prevents them from taking oral medication, and when they experience intolerable side effects, such as constipation.
- Where appropriate administration could lead to better pain control. Patients with cognitive impairment or those unable to use their analgesia as a self-medication for other reasons may find this helpful.
- It can create synergistic effects when combined with other enhancement strategies.

Conditions in which patches are not used:[31,32,33,34]

- Cure for acute pain is required.
- Where rapid dose titration is required.
- Where requirement of dose is equal to or less than 30 mg/24 hrs.

Factors affecting transdermal permeation[35-41]

Biological factor:

Skin conditions:

Although the intact skin serves as a barrier, numerous substances such as acids and alkali can pass through the skin's barrier cells and open the intricate, dense horny layer structure. Lipid fraction is removed by solvents like methanol and chloroform, creating artificial shunts that allow drug molecules to move freely through.

Skin age:

Although there isn't a noticeable difference, it is observed that the skin of adults and children is more permeable than that of older people.Children's larger surface area per unit body weight causes toxic effects.As a result, strong steroids, boric acid, and hexachlorophene have caused serious adverse effects.

Blood Supply:

Transdermal absorption may be impacted by modifications to peripheral circulation.

Regional skin site:

Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect significantly penetration.

Skin metabolism:

Chemokines, hormones, steroids, and certain medications are all metabolized by the skin. Therefore, the effectiveness of a drug absorbed through the skin is determined by skin metabolism**.**

Species differences:

The penetration is influenced by the thickness, keratinization, and density of the skin, all of which differ among species.

Physicochemical factors:

Skin hydration:

Skin becomes much more permeable when it comes into contact with water. The most crucial element boosting skin penetration is hydration. Humectants are therefore used in transdermal delivery..

Temperature and pH:

The medication permeates the environment ten times more when the temperature changes. With a drop in temperature, the diffusion coefficient falls. The dissociation of weak bases and acids is contingent upon the pH and pKa or pKb values. The amount of unionized drug in the skin determines the drug concentration. As a result, two critical variables influencing drug penetration are pH and temperature**.**

Diffusion coefficient:

Drug penetration is based on the drug's diffusion coefficient. The properties of the drug, the diffusion medium, and their interactions all affect the drug's diffusion coefficient at constant temperature.

Drug concentration:

The gradient of concentration across the barrier determines the flux, and a higher concentration gradient indicates a higher drug concentration across the barrier.

Partition coefficient:

Good action requires the optimal partition coefficient (K). High K drugs are not yet ready to be removed from the ipid area of the skin. Furthermore, medications with low K won't permeate.

Molecular size and shape:

Molecular weight and drug absorption are inversely correlated; small molecules absorb more quickly than large ones.

Environmental factors:

Sunlight:

Sunlight causes the blood vessel walls to thin, which can result in bruises in areas exposed to the sun with only minor trauma. Additionally, pigmentation: Solar lentigo, or freckles, are the most obvious pigment changes brought on by the sun.

Cold Season:

frequently cause dry, itchy skin. In response, skin produces more oil to counteract the drying effects of the weather.An effective moisturizer can help reduce the signs and symptoms of dry skin. Additionally, consuming a lot of water helps maintain hydrated, glowing skin..

Air Pollution:

Acne and spots can result from dust clogging pores and increasing bacteria on the face and skin's surface. Drug delivery through the skin is impacted by this. Airborne invisible chemical pollutants can disrupt the skin's natural defense mechanism by dissolving the natural oils that the skin naturally produces to retain moisture and suppleness.

Effect of Heat on Transdermal patch:[42]

High absorption of transdermal medications caused by heat. The patient should be instructed not to expose the patch application site to outside heat sources, such as hot water bottles or heated water bags. The amount of medication administered transdermally may even rise with elevated body temperature. In this instance, the patch needs to be taken off right away. Until they are needed, transdermal medication patches should be kept in their original packaging and in a cool, dry environment**.**

Evaluation parameters:

1. Interaction studies:[43,44]

Excipients are essential parts of practically every dosage form used in medicine. The drug's compatibility with the excipients determines the stability of a formulation, among other things. It is essential to identify any potential physical or chemical interactions between the drug and the excipients as they may impact the drug's stability and bioavailability. Only then can a stable product be produced. Compatibility studies are crucial to the development of new formulations if the excipients have never been used in formulations with the active ingredient. Thermal analysis, FT-IR, UV, and chromatographic techniques are frequently used in interaction studies. These techniques compare the physicochemical characteristics of the materials, including assay, melting endotherms, characteristic wave numbers, absorption maxima, etc.

2. Thickness of the patch:[45]

To guarantee the thickness of the prepared patch, the thickness of the drug-loaded patch is measured at various points using a digital micrometer, which also calculates the average thickness and standard deviation for the same.

3. Weight uniformity:[45]

Before testing, the prepared patches must dry for four hours at 60°C. A predetermined patch area needs to be divided into several sections, then weighed using a digital balance. The individual weights must be used to compute the average weight and standard deviation values.

4. Folding endurance:[45]

It is necessary to cut a strip of a certain area uniformly and fold it at the same spot repeatedly until it breaks. The value of folding endurance was determined by counting how many times the film could be folded in the same direction without breaking.

5. Percentage Moisture content:[45]

The prepared films must be weighed individually and stored for 24 hours at room temperature in a desiccator filled with fused calcium chloride. The films must be reweighed after 24 hours in order to calculate the moisture content percentage using the formula below. Moisture content percentage is calculated as [original weight - final weight / final weight] × 100.

6. Percentage Moisture uptake:[45]

To maintain 84% relative humidity, the weighed films must be stored in a desiccator with a saturated potassium chloride solution for 24 hours at room temperature. The films must be reweighed after 24 hours in order to calculate the percentage of moisture absorption using the formula below.

Percentage moisture uptake = [Final weight- Initial weight/ initial weight] ×100.

7. Water vapour permeability (WVP) evaluation:[46]

The foam dressing method can be used to determine the water vapour permeability of an air forced oven that is replaced with a natural air circulation oven. This formula can be used to find the WVP.

WVP = W/A.

where A is the surface area of the exposure samples expressed in m2, W is the amount of vapour permeated through the patch expressed in gm/24 hours, and WVP is expressed in gm/m2 per 24 hours.

8. Drug content:[46]

A predetermined patch area needs to dissolve in a predetermined volume of an appropriate solvent. After that, the mixture must be filtered through a filter medium before the drug's content is examined using the appropriate technique (UV or HPLC). The average of three separate samples is represented by each value.

9. Uniformity of dosage unit test:[47]

To fully extract the drug from the patch, chop up a precisely weighed portion of the patch, transfer it to a volumetric flask of a specified capacity, dissolve it in an appropriate solvent, sonicate the mixture, and add more medication as needed. After letting the resultant solution settle for about an hour, the supernatant was appropriately diluted with the right kind of solvent to

achieve the required concentration. A 0.2□m membrane filter was used to filter the solution. It was then analyzed using an appropriate analytical technique (UV or HPLC), and the drug content of each piece was calculated.

10. Polariscope examination:[47]

This test will be carried out using a polariscope to look at the drug crystals from the patch. To determine whether the drug is present in the patch in an amorphous or crystalline form, a particular surface area of the piece must be kept on the object slide and examined for drug crystals..

11. Shear Adhesion test:[47]

The purpose of this test is to determine an adhesive polymer's cohesive strength. The molecular weight, degree of crosslinking, polymer composition, type, and quantity of tackifier added can all have an impact. A stainless steel plate is covered with adhesive-coated tape, and to cause the tape to pull in a direction parallel to the plate, a predetermined weight is suspended from it. The time it takes to remove the tape from the plate is used to calculate shear adhesion strength. The shear strength increases with the length of time required for removal.

12. Peel Adhesion test:[47]

Peel adhesion is the term used in this test to describe the force needed to remove an adhesive coating from a test substrate. The variables that affected the peel adhesion properties were the adhesive polymer's molecular weight and the kind and quantity of additives. A single piece of tape is applied to a backing membrane or stainless steel plate. It is then pulled away from the substrate at a 180-degree angle, and the force needed to remove the tape is calculated.

13. Thumb tack test:[47]

It is a qualitative test used to determine the adhesive's tack properties. All that is needed to detect the relative tack property of the adhesive is pressing the thumb down on it.

14. Flatness test:[48]

It is necessary to cut three longitudinal strips—one from the center, one from the left, and one from the right—from each film at different portions. Each strip's length was measured, and the percentage of constriction—0% constriction being equal to 100% flatness—was used to calculate the length variation resulting from non-uniformity in flatness.

15. Percentage Elongation break test:[49]

The length immediately preceding the break point should be noted in order to calculate the percentage elongation break. This can be done using the formula below.

Proportion of elongation = L1-L2 / L2.100

where L2 is each strip's starting length and L1 is each strip's final length.

16. Rolling ball tack test:[50]

This test quantifies a polymer's talk-related softness. A 7/16-inch-diameter stainless steel ball is released onto an inclined track in this test, causing it to roll down and come into contact with an adhesive that faces upward and horizontally. The tack measurement, measured in inches, is derived from the distance the ball travels along the adhesive.

17. Quick Stick (peel-tack) test:[50]

In this test, the tape is pulled at a speed of 12 inches per minute and 90 degrees Celsius away from the substrate. Tactic value, which is measured and recorded as the peel force needed to break the bond between adhesive and substrate, is given in ounces or grams per inch width..

18. Probe Tack test:[50]

This test involves touching the adhesive with the tip of a clean probe that has a predetermined surface roughness to see if a bond forms between the probe and the adhesive. It breaks mechanically when the probe is removed later. Tack is the unit of measurement for the force needed to remove the probe from the adhesive at a set rate. It is expressed in grams.

19. In vitro drug release studies:[43]

The drug release from the prepared patches can be evaluated using the paddle over disc method (USP apparatus V). Dry films with a known thickness need to be weighed, cut into a specific shape, and adhered to a glass plate using an adhesive. After equilibrating the apparatus to 32±0.5°C, the glass plate was submerged in 500 ml of the phosphate buffer (pH 7.4) or dissolution medium. Next, the paddle was moved at a speed of 50 revolutions per minute and positioned 2.5 centimeters away from the glass plate. Samples (5-ml aliquots) can be taken out at predetermined intervals for up to 24 hours, and UV spectrophotometer or HPLC analysis can be performed. The experiment is to be performed in triplicate and the mean value can be calculated.

20. In vitro skin permeation studies:[43]

A diffusion cell can be used to conduct an in vitro permeation study. Completely developed abdominal skin in male Wistar rats weighing 200–250 grams. The dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels before

the experiment was started. It was then equilibrated for an hour in dissolution medium or phosphate buffer ph 7.4 and placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The abdominal region's hair should be carefully removed using an electric clipper. The thermostatically controlled heater was utilized to maintain the temperature of the cell at 32 ± 0.5°C. With the epidermis facing upward into the donor compartment, the isolated rat skin piece is to be mounted between the diffusion cell's compartments. At regular intervals, a specific volume of sample must be taken out of the receptor compartment and replaced with an equal volume of fresh medium. Samples must pass through a filtering medium before being subjected to HPLC or spectrophotometric analysis. The direct measurement of flux is the slope of the curve connecting the steady-state values of the drug penetration rate (mg cm-2) vs. Permeability coefficients and time in hours were calculated by dividing the flux by the starting drug load (mg cm-2).

21. Skin Irritation study:[47]

Testing for skin sensitivity and irritation can be done on healthy rabbits weighing between 1.2 and 1.5 kg on average. The rabbit's dorsal surface (50 cm2) needs to be cleaned. The hair should be shaved off of the clean surface, and rectified spirit can be used to clean the surface before representative formulations are applied to the skin. After 24 hours, the patch is to be taken off, and the skin is to be examined, with the severity of the skin injury being divided into 5 grades**.**

22. Stability studies:[43]

In accordance with the ICH guidelines, stability studies must be carried out by keeping the TDDS samples for six months at 40±0.5°C and 75±5% relative humidity. The samples were taken out at0,30,60,90, and 180 days, and their drug content was appropriately analyzed**.**

Applications of TDDS

- The nicotine patch, which releases nicotine in controlled doses to aid in quitting tobacco use, is the most popular transdermal patch in the United States. Europe approved the first vapour patch to quit smoking that was sold commercially in 2007..
- Two opioid patches, fentanyl CII (marketed as Duragesic) and buprenorphine CIII (marketed as Butrans), are frequently prescribed to treat severe pain continuously.
- Hormonal patches:
  - Two opioid patches are commonly prescribed to continuously treat severe pain: buprenorphine CIII (marketed as Butrans) and fentanyl CII (marketed as Duragesic).
  - Contraceptive patches (marketed as Ortho Evra or Evra) and
  - Testosterone CIII patches for both men (Androderm) and women (Intrinsa).
- Instead of sublingual tablets, nitroglycerin patches are occasionally prescribed for the treatment of angina.
- Transdermal scopolamine is commonly used as a treatment for motion sickness.
- Clonidine, an antihypertensive medication, is offered as a transdermal patch.
- In March 2006, the transdermal form of the MAOI selegiline, called Emsam, was approved for use as the first transdermal delivery agent for an antidepressant in the United States.
- Daytrana, the first methylphenidate transdermal delivery system for the treatment of attention deficit hyperactivity disorder (ADHD), was approved by the FDA in April 2006.[51]
- Secuado, a transdermal form of the atypical antipsychotic asenapine, was approved by the FDA in October 2019.[52]
- It is also possible to apply vitamin B12 via a transdermal patch. Vitamin B12 in the highly stable form of cyanocobalamin is suitable for transdermal patching.53]

- Another way to administer 5-hydroxytryptophan (5-HTP) is with a transdermal patch, which was introduced in the UK at the beginning of 2014.[54]
- Rivastigmine, an Alzheimer's treatment medication, was released in patch form in 2007 under the brand name Exelon.[55]
- In December 2019, Robert S. Langer and colleagues invented and filed for patent on a method that would allow medical data to be subcutaneously stored by using transdermal patches to mark individuals with invisible ink. The benefit to "developing nations"—where a lack of infrastructure equates to a lack of medical records—was touted. "Quantum dot dye that is delivered along with a vaccine" is the method employed by the technology.[56]
- caffeine patches, which are intended to absorb caffeine through the skin

Adverse events

- The FDA declared in 2005 that it was looking into reports of fatalities and other severe side effects associated with narcotic overdose in patients taking Duragesic, a transdermal patch containing fentanyl, for pain relief. Later, in June 2005, the Duragesic product label was revised to include safety information.[57]
- The Daytrana ADHD patch's makers, Shire and Noven Pharmaceuticals, announced a voluntary recall of multiple lots of the patch in 2007 because of issues releasing the patch from its protective release liner. No additional issues have been reported since then regarding the patch or its protective packaging. [58]
- In 2008, a manufacturing defect caused the gel containing the medication to leak out of its pouch too quickly, potentially leading to overdose and death. As a result, two manufacturers of the fentanyl patch, Sandoz and ALZA Pharmaceuticals, a division of large medical manufacturer Johnson & Johnson, issued a recall of their versions of the

patch. Since March 2009, Sandoz—now produced by ALZA—has discontinued the use of gel in its transdermal fentanyl patches. Rather, Sandoz-branded fentanyl patches, like those made by Mylan and Janssen, use a matrix/adhesive suspension, in which the drug is mixed with the adhesive rather than being kept in a separate pouch with a porous membrane. [59, 60]

- In 2009, transdermal drug patches with metallic backings were linked to a risk of burns during MRI scans, according to a public health advisory issued by the FDA. It is recommended that patients take off any medicated patches before having an MRI and replace them with fresh ones after the scan is finished.[61]
- An article published in the journal Europace in 2009 described cases of skin burns brought on by shock therapy from both internal and external cardioverter defibrillators (ICD) that involved transdermal patches containing metal (typically as a backing material). [62]
-

Conclusion

As a handy resource for research scientists working on transdermal drug delivery systems, this article offers insightful information about these systems and the specifics of the evaluation process. The information above demonstrates the great potential of TDDS, as it can be used to create promising deliverable drugs with both hydrophobic and hydrophilic active substances. More knowledge of the various biological interaction mechanisms and polymers are needed to optimize this drug delivery system. A feasible real-world use for TDDS as the upcoming generation of drug delivery systems

References :

1. Han, T.; Das, D.B. Potential of Combined Ultrasound and Microneedles for Enhanced Transdermal Drug Permeation: A Review. Eur. J. Pharm. Biopharm. 2015; 89:312-328. https://doi.org/10.1016/j.ejpb.2014.12.020

2. Schoellhammer, C.M.; Blankschtein, D.; Langer, R. Skin Permeabilization for Transdermal Drug Delivery: Recent Advances and Future Prospects. Expert Opin. Drug Deliv. 2014; 11:393-407. https://doi.org/10.1517/17425247.2014.875528

3. Donnelly, R.F.; Singh, T.R.R.; Morrow, D.I.; Woolfson, A.D. Microneedle-Mediated Transdermal and Intradermal Drug Delivery; Wiley: Hoboken, NJ, USA, 2012. https://doi.org/10.1002/9781119959687

4. Kretsos, K.; Kasting, G.B. A Geometrical Model of Dermal Capillary Clearance. Math. Biosci. 2007; 208:430-453. https://doi.org/10.1016/j.mbs.2006.10.012

5. Prausnitz, M.R.; Langer, R. Transdermal Drug Delivery. Nat. Biotechnol. 2008; 26:1261-1268. https://doi.org/10.1038/nbt.1504

6. Waghule T, Singhvi G, Dubey SK, Pandey MM, et al. Microneedles: A smart approach and increasing potential for transdermal drug delivery system. Biomed Pharmacother. 2019; 109:1249-1258. https://doi.org/10.1016/j.biopha.2018.10.078

7. Rai VK, Mishra N, Yadav KS, Yadav NP. Nanoemulsion as pharmaceutical carrier for dermal and transdermal drug delivery: Formulation development, stability issues, basic considerations and applications. J Controlled Release. 2018; 270:203-225. https://doi.org/10.1016/j.jconrel.2017.11.049

8. Kathe K, Kathpalia H. Film forming systems for topical and transdermal drug delivery. Asian J Pharm Sci. 2017; 12:487-497. https://doi.org/10.1016/j.ajps.2017.07.004

9. Kim H, Kim JT, Barua S, Yoo SY, et al. Seeking better topical delivery technologies of moisturizing agents for enhanced skin moisturization. Expert Opin Drug Delivery. 2018; 15:17-31. https://doi.org/10.1080/17425247.2017.1306054

10. Barua S, Lee DI, Kim H, Jo K, Yeo S, et al. Solid Lipid Nanoparticles of Serine Designed by Evaluating Affinity of Solid Lipids to Stratum Corneum for Enhanced Skin Hydration in Combination with Reed Root Extract. Bull Korean Chem Soc. 2018; 39:220- 226. https://doi.org/10.1002/bkcs.11371

11. Wiechers J. Use of Chemical Penetration Enhancers in Transdermal Drug Delivery-Possibilities and Difficulties. Acta Pharm. 1992: 4: 123.

12. Yamamoto T, Katakabe K, Akiyoshi K, Kan K and Asano T. Topical Application of Glibenclamide Lowers Blood Glucose Levels in Rats. Diabetes Res. Clin. Pract. 1990; 8: 19-22.

13. Rhaghuram Rk, Muttalik S, Reddy S. Once – Daily Sustained- Release Matrix Tablets of Nicorandil: Formulation and Invitro Evaluation. Aaps Pharm.Scitech. 2003; 4(4):480–488.

14. Shaila L, Pandey S, Udupa N. Design and Evaluation of Matrix Type Membrane Controlled Transdermal Drug Delivery System of Nicotin Suitable for Use in Smoking Cessation. Indian Journal of Pharmaceutical Sciences. 2006; 68:179-184.

15. Aarti N, Louk Armp, Russsel Op. Richard Hg. Mechanism of Oleic Acid Induced Skin Permeation Enhancement in Vivo in Humans. Jour. Control. Release. 1995; 37:299-306.

16. Baichwal Mr. Polymer Films as Drug Delivery Systems Advances in Drug Delivery Systems. Bombay, Msr Foundation; 1985; 136-147.

17. Vyas Sp, Khar Rk. Targetted and Controlled Drug Delivery Novel Carrier System. 1st Ed. Cbs Publishers and Distributors New Delhi. 2002; 411-447.

18. Singh J, Tripathi Kt, Sakia Tr. Effect of Penetration Enhancers on The in vitro Transport of Ephedrine Through Rate Skin and Human Epidermis From Matrix Based Transdermal Formulations. Drug Dev Ind Pharm. 1993; 19:1623-1628.

19. Rohit Tiwari, Manish Jaimini, Shailender Mohan, Sanjay Sharma. Transdermal Drug Delivery System: A Review. International Journal of Therapeutic Applications. 2013; 14:22-28.

20. Ghosh B, Preethi Gb, Mishra R, Parcha V. Transdermal Delivery of Ibuprofen ond Its Prodrugs by Passive Diffusion and Iontophoresis. Int J Pharm Pharm Sci. 2010; 2(1):79-85.

21. Hans Schaefer, Thomas E. Redelmeier. Skin Penetration. Chapter 11; 2020:167-176. https://doi.org/10.1007/3-540-31301-X_11

22 . Jain N. K, Controlled and Novel Drug Delivery, 1997, 100-115.

23 . Swarnlata Sonl and Vinod K, Dixit, Transdermal Penetration Enhancers, Categorization, Indian Drugs, 1992, 29(11), 465-471.

24 . Tanu Bhargava, Current trends in NDDS with special reference to NSAIDS, International Journal of Pharma and Bio Sciences, 2011, 2, 92-114.

25 . Jain.N.K, Controlled and novel drug delivery, first edition, CBS publishers and distributors, New Delhi.1997.

26. Mathiowitz.Z. E, Chickering, Lehr.C.M, Bio adhesive drug delivery systems; fundamentals, novel approaches and development, Marcel Dekker, Inc. New York. Basel

27. Sharma N, Parashar B, Sharma S, Mahajan U. Blooming Pharma Industry with Transdermal Drug Delivery System. Indo Global J Pharm. Sci. 2012; 2(3): 262-278.

28. Kumar A, Pullankandam N, Prabhu SL, Gopal V. Transdermal drug delivery system: an overview. Int. J Pharm Sci. Review Res. 2010;3(2):49-54.

29. Rani S, Saroha K, Syan N, Mathur P. Transdermal patches a successful tool in transdermal drug delivery system. Plegia Res. Lib. 2011;2(5):17-29.

30. Yadav V. Transdermal drug delivery system: review. Int. J Pharm Sci. Res. 2012;3(2):376-382.

31. atel D, Chaudhary SA, Parmar B, Bhura N. Transdermal drug delivery system: a review. The Pharm Innovation. 2012;1(4):66-75.

32. Singh MC, Naik AS, Sawant SD. Transdermal drug delivery system with major emphasis on transdermal patches: a review. J Pharm Res. 2010;3(10):2537-2543.

33. Yadav B, Sharma B, Saroha K. Transdermal patches: a discrete dosage form. Int. J Current Pharm Res. 2011;3(3):98-108.

34. Patel D, Chaudhary A S, Parmar B. Transdermal drug delivery system: A review. The Pharm Innovation. 2012;1(4):66-75.

35. Kumar D, Sharma N, Rana AC, Agarwal G, Bhat ZA. A review: transdermal drug delivery system: a tools for novel drug delivery sestem. Int. J Drug Dev. Res. 2011;3(3):70-84.

36. Ramteke KH, Dhole SN, Patil SV. Transdermal drug delivery system: a review. J Advanced Sci. Res. 2012;3(1):22-35.

37. Yadav V. Transdermal drug delivery system: review. Int. J Pharm Sci. Res. 2012;3(2):376-382.

38. Dhiman S, Thakur GS, Rehni AK. Transdermal patches: a recent approach to new drug delivery system. Int. J Pharmacy Pharm Sci. 2011;3(5):26-34.

39. Sharma RK, Keleb E, Mosa EB, Aljahwi AAZ. Transdermal drug delivery system- design and evaluation. Int. J Advances Pharm Sci. 2010;1:201-211.

40. Sandhu P, Bilandi A, Kataria S, Middha A. Transdermal drug delivery system (patches), applications in present scenario. Int. J Res. Pharm Chem. 2011;1(4):1139-1151.

41. Singh MC, Naik AS, Sawant SD. Transdermal drug system with major emphasis on transdermal patches: a review. J Pharm Res. 2010;3(10):2537-2543.

42. Tom WC. Effects of heat on transdermal drug patches. 1st Ed.:1-2.

43. Singh J, Tripathi K.T and SakiaT.R. Effect of penetration enhancers on the invitro transport of ephedrine through rate skin and human epidermis from matrix based Transdermal formulations. Drug Dev.Ind. Pharm. 1993; 19: 1623-1628.

44. Wade A, Weller P.J. Handbook of pharmaceutical Excipients. Washington, DC: American Pharmaceutical Publishing Association; 1994: 362 -366.

45. Rhaghuram reddy k, Muttalik S and Reddy S. Once – daily sustained- release matrix tablets of nicorandil: formulation and invitro evaluation. AAPS Pharm.Sci.Tech. 2003;4:4.

46. Shaila L, Pandey S and Udupa N. Design and evaluation of matrix type membrane controlled Transdermal drug delivery system of nicotin suitable for use in smoking cessation. Indian Journ. Pharm. Sci. 2006;68: 179-184

47. Aarti N, Louk A.R.M.P, Russsel.O.P and Richard H.G. Mechanism of oleic acid induced skin permeation enhancement in vivo in humans. Jour. control. Release 1995; 37: 299-306.

48. Wade A and Weller P.J. Handbook of pharmaceutical Excipients. Washington, DC:

American Pharmaceutical Publishing Association 1994; 362-366.

49. Lec S.T, Yac S.H, Kim S.W and Berner B. One way membrane for Transdermal drug delivery systems / system optimization. Int. J Pharm. 1991; 77: 231 -237.

50. Vyas S.P and Khar R.K. Targetted and controlled Drug Delivery Novel carrier system1st Ed., CBS Publishers and distributors, New Delhi, 2002; 411-447.

51. Cabray, Matthew (2006-04-12). "Transdermal Patch Approved for Treatment Of ADHD". Retrieved 2010-09-28.

52. Carrithers, Brennan; El-Mallakh, Rif S (18 March 2020). "Transdermal Asenapine in Schizophrenia: A Systematic Review". Patient Preference and Adherence. 14: 1541–1551. doi:10.2147/PPA.S235104. PMC 7468370. PMID 32943849

53. Tirupati; et al. (2014-05-02). "Preparation and Evaluation of Transdermal Films of Verapamil" (PDF). S2CID 22480093. Archived from the original (PDF) on 2018-07-28. Retrieved 2018-07-28

54. Revolutionary' 24-hour slow release 5-HTP transdermal patch, launched in early 2014 in the United Kingdom". 5htppatch.co.uk. Retrieved 2014-06-18

55. Peck, Peggy (2007-07-10). "Medical News: FDA Approves Rivastigmine Patch for Alzheimer's Disease". Retrieved 2011-03-10.

56. Trafton, Anne (18 December 2019). "Storing medical information below the skin's surface". MIT News.

57. FDA ALERT (07/2005): Narcotic Overdose and Death". Food and Drug Administration. 2005-07-15. Archived from the original on 2007-02-20. Retrieved 2007-02-24

58. Megget, Katrina (2007-09-05). "ADHD Transdermal Patches Withdrawn". Retrieved 2010-09-28.

59. Silverman, Ed (2008-02-12). "J&J and Sandoz Recall Fentanyl Patches". Retrieved 2010-09-28.

60. As stated on the packaging and labels of Sandoz-branded Fentanyl Transdermal System products, revised March 2009.

61. "FDA Public Health Advisory: Risk of Burns during MRI Scans from Transdermal Drug Patches with Metallic Backings". Food and Drug Administration. Archived from the original on March 7, 2009. Retrieved March 9, 2009

62. Brown, MR: "Analgesic patches and defibrillators: a cautionary tale", Europace,2009 Nov;11(11):1552-3