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BRIEF REVIEW ON TRANSDERMAL PATCHES: PRESENT & FUTURE PROSPECTIVE

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ABSTRACT

Transdermal drug delivery systems were introduced to address the issues with drug delivery, particularly via the oral route. A transdermal patch is an adhesive patch that is applied to the skin and contains medication that is intended to be absorbed through the skin and into the bloodstream. Bypassing the digestive system and the hepatic first-pass effect, transdermal patches deliver drugs directly into the circulatory system. The greatest challenge with transdermal drug delivery is the barrier nature of skin, which is provided by its outer layer, that is, the stratum corneum (SC). This barrier limits the number of drugs, which are capable of being administered via these routes. Pharmaceutical preparations known as transdermal patches come in a variety of sizes and contain one or more active ingredients that are circulated throughout the body. When used as a formulation method to improve drug administration through topical channels, TDDS technology is successfully capturing significant market value for biomedical applications in the pharmaceutical industry, which is growing significantly.The review provides insightful information about the transdermal patch, including its benefits and drawbacks,anatomy of skin in relation to TDDS ,mode of action, different types , basic factors that affect them , methods of evaluation, and modes of application and future prospective.

KEYWORDS: Transdermal drug delivery system, Circulatory system, Stratum corneum, Biomedical applications.

INTRODUCTION

The term "drug delivery system" (DDS) refers to a number of methods that can control the distribution and release of pharmaceuticals that have therapeutic effects. Allowing these methods could result in the desired outcomes for organs, tissues, and cells.[1,2] There are numerous drug administration techniques, including oral administration, transdermal administration, pulmonary inhalation, mucosal administration, topical administration, and parenteral administration, such as intravenous, intramuscular, subcutaneous, intradermal, intrathecal injections, etc.[3,4] Although the oral route is the most widely used path of drug delivery, it has certain drawbacks, including first-pass metabolism, drug degradation by the enzymes, pH, etc. in the gastrointestinal tract. A newer drug delivery approach was invented by Chien in 1992, Banker in 1990, and Guy in 1996 to deal with problems associated with the oral route. It was a transdermal delivery system or patch. Drugs can be safely and conveniently provided to children or the elderly via TDDS, a noninvasive administration approach that provides the patient the least amount of pain and load.[5,6] The term "transdermal drug delivery system" refers to pharmaceuticals that are topically applied and come in the form of patches that, when placed to the skin, allow the drug to be released through the skin at a predetermined and controlled rate. In order to optimize the therapeutic efficiency of the treatment and decrease adverse effects, transdermal patches deliver the drug via the skin in such a controlled and predefined manner. Transdermal drug delivery systems (TDDS) that carry the drug to the systemic circulation through the skin portal at a predetermined rate over an extended period of time can achieve controlled drug release.[7] TDDS, in contrast to commonly utilized direct administration routes that depend on needle-based injections, has emerged as one of the most extensively investigated techniques of noninvasive drug delivery into the body through the skin. The distribution of numerous therapeutic substances, particularly in the management of pain, hormone therapy, neurological disorders and the treatment of cardiovascular disorder such as angina pectoris, hypertension etc. has been significantly impacted by TDDS.[8,9] Transdermal patches preparations enable that drug levels should not decline below the minimum effective concentration or rise above the maximum effective concentration for an extended period of time.[10] The major barrier to skin penetration, which is primarily associated with the outermost stratum corneum layer of the epidermis, prevents the application of transdermal delivery to a wider range of drugs. According to the action's target site, there are two categories of skin

formulation. One of these two exhibits local effects in the skin while the other exhibits systemic action after absorption of drugs from the cutaneous vascular system.[11] For study in pharmaceutical sciences, the transdermal route has emerged as one of the most effective drug delivery systems. Because it improves patient compliance and avoids first pass metabolism, transdermal medication delivery has an advantage over injectables and oral methods. Transdermal drug delivery avoids entry into the systemic circulation and not only enables controlled release drug administration, but also permits continuous administration of drugs with shorter biological half-lives. The effectiveness of a dermatological medicine used for systemic drug delivery depends on its capacity to permeate skin insufficiently to provide the desired therapeutic effect.[12,13] Up until recently, the transdermal drug delivery market 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. This has made it possible to create active patches that carry proteins, vaccinations, and painkillers. Smaller patches with improved adherence are produced through passive patch technology. Transdermal drug delivery system (TDDS) has established itself as a crucial component of innovative drug delivery systems. Transdermal medication delivery is thus described as self-contained, discrete dosage forms that, when applied to undamaged skin; release the drug via the skin at a controlled rate to the systemic circulation.[13,14]

Advantages

- An equivalent therapeutic effect can be obtained via transdermal drug input with a lower daily dose of the drug than is necessary, e.g. the drug is administered
- With these systems, self-administration is possible.
- Due to their physical presence, distinctive features, and identifying characteristics, they are quickly and easily recognized in crises (e.g., an unresponsive, unconscious, or comatose patient).
- They can be given to drugs that have a short therapeutic window.
- A reduction in dosage frequency due to the longer duration of action.
- Greater ease in administering the drug that would usually need to be dosed regularly.
- Enhanced bioavailability
- Prevent intra- and inter-patient variance, and improve therapeutic effectiveness.[15-17]
- Easy to discontinue the release of drug by removing the patch from the skin.
- Longer and predetermined duration of action
- The plasma drug concentration remains stable.
- The quantity of dosages is decreased, improving patient compliance.
- By minimizing problems with medications including decreased absorption, GI discomfort, and breakdown owing to hepatic first pass metabolism, many drugs' therapeutic efficacy is enhanced.[18,19]

Disadvantages

- Drugs with hydrophilic character cannot penetrate skin easily because of their low permeability hence their therapeutic efficacy will be reduced.
- Within the same individual, among individuals the barrier function of the skin varies from one region to another.
- Currently, only minute, lipophilic drugs can be given through the skin.
- Because the amount that can be supplied by a patch is limited, the drug's molecule needs to be strong.
- Inappropriate to be used with higher drug dosages.
- The type of patch and the environmental elements may have an impact on adhesion.
- Skin sensitivity and chances of allergic reactions at the site of application may possible.
- High blood level drugs cannot be given.[20,21]

Anatomy and physiology of skin

The skin is frequently described as the largest organ in the body; the average adult's skin has a surface area of roughly $2m^2$.The transdermal route of administration of medication could take the place of the oral route due to the ease with which some medications can pass via the skin barrier and into the bloodstream.But only those medications that exhibit the proper physicochemical and pharmacokinetic characteristics that enable their efficient distribution through the skin are commercialized as transdermal drug products.[22] When a transdermal patch is placed on a person's skin, it may keep the medication or active ingredient here without allowing it to be absorbed, such as in the case of cosmetics and antiseptics, or it might permit the medicine to pass through the skin into the dermis and epidermis, which are its deeper layers. Diadermal or endodermal are additional names for these formulations.Formulations. Possessing the third desirable quality is to be systemic drug absorption.[23] Skin is one of the most readily accessible organs of the human body.[24]

There are two kinds of human skin; one that is hair-less such as soles of foot and palms of hand, and the other kind which bears hair and sebaceous glands such as arms and face.[25]

The skin is divided histologically into the epidermis, the dermis, and the hypodermis; which collectively forms a cover against external agent and loss of water from the body. One of the human body's organs that is easiest to access is the skin, Human skin has two types: one without hair, like the palms of the hands and the soles of the feet and the other with hair. Another type that has sebaceous glands and hair, like face and arms. Histological, the epidermis, the dermis and the

hypodermis, which together make up a protection from external agents and water loss from the body.

Epidermis

The epidermis is made up of both viable and non-viable layers. The stratum corneum is referred to as the non-viable epidermis, whereas the layer below it is referred to as the viable epidermis. The cells in this layer are linked together by tonofibrils14, and the viable epidermis is composed of several sublayers of epidermis that are collectively 50-100 m thick. The dermis and subcutaneous fat layer are necessary for blood vessels and nerve fibers to reach the epidermis3.Keratinocytes, which account for 95% of all epidermis cells, are the primary epidermal cells. These cells move upward from the epidermal basement membrane towards the skin's surface, forming a number of distinct layers along the way. The many stages of keratin maturation are what create the distinct layers of the epidermis.[25] The epidermis has the Following sublayers:

Stratum basale (basal cell layer)

It is the epidermis's deepest sublayer and is made up entirely of basal cells. This sublayer produces keratinocytes. The border of the Dermis is formed by the stratum basale.8% of the water in the epidermis is stored there. Aging causes the stratum basale to thin down and lose its capacity to hold water. This Layer also contains melanocytes.[25]

Stratum spinosum (prickle cell layer)

The 10 to 20 layers that are located above the basal cell layer are referred to.Basal cells create these layers by flattening their structure somewhat during cell turnover.Because of their little spines on the exterior of their membrane, these cells are also known as prickle cells.This sublayer is between 50 and 150 m thick.[26]

Stratum granulosum (granular cell layer)

It has two to four granular cell layers. Measures of 3 mm make up this layer. The presence of cornification or Keratinocytes starts to turn into keratin. This technique involves the resolution of organelles like mitochondria and nuclei begins. Keratin fibers and other materials gradually fill the cells.lessen moisture content when compared to basal and prickle cells. Layers. When these cells divide, their form changes significantly to these actions.[26]

Stratum lucidum (clear layer)

It only appears on the soles and palms.During turnover, its cells flatten and compact closer together.[26]

Stratum corneum

The skin's barrier function is controlled by the stratum corneum; the topmost layer of the skin15.Non-viable epidermis is another name for it. The stratum corneum is composed of flattened, dead coenocytes that range in thickness from 10 to 15 micrometers, and it is encased in a lipid extracellular matrix. Epidermal keratinocytes undergo mortal differentiation to produce coenocytes, which increasingly significant renewal .It serves as a link between the body and the external environment.[27,28]

Dermis

The deeper epidermal tissues and dermis may be penetrated by a drug molecule once it has passed through the stratum corneum. It has a thickness of 1-2 mm and is primarily formed of fibrous tissues. The drug is absorbed into the systemic circulation from the dermis' abundant supply of blood capillaries.[29] From the dermis and subcutaneous layer, where they begin, sebaceous glands, sweat glands, and hair follicles emerge to the skin's surface. On each centimeter square of skin, it is known that there are 200–250 sweat glands and 10–70 hair follicles on average per person.[24]

Hypodermis

The third layer below the dermis is known in histology as the subcutis, or hypodermis. A substantial number of fat cells make up the elastic subcutis layer, which serves as a shock absorber for blood vessels and nerve terminals. This layer ranges from 4 to 9 mm in thickness on average. Nevertheless, the actual thickness varies from person to person and is also influenced by the area of the body.[26]

Drug penetration pathways

A drug molecule can penetrate the intact stratum corneum in one of three important ways: by skin appendages (shunt pathways), intercellular lipid domains, or a transcellular pathway. A specific drug is likely to enter the body by a combination of these pathways, with thephysicochemical characteristics of the molecule determining their respective contributions to the gross flux.[30]

The appendgeal route

A continuous passage directly over the stratum corneum barrier is provided by skin appendages. However, a variety of factors limit their ability to impact drug uptake. Hair follicles and sweat ducts only occupy a small portion of the skin's surface (usually 0.1%), which reduces the area that can be directly contacted by the applied medicinal formulation.[30]

Transcellular pathway

Drugs that penetrate the skin transcellularly pass via corneocytes on their way in. Highly hydrated keratin-containing corneocytes offer an aqueous environment through which hydrophilic medicines can pass. A variety of partitioning and diffusion processes are necessary for the transcellular route of drug diffusion.[30]

Intracellular route

The medication diffuses across the continuous lipid matrix in the intercellular route. This path is a major challenge for two reasons. In contrast to the relatively direct course of the transcellular route, the inter-digitating nature of the corneocytes produces a complex

track for intercellular drug absorption, evoking the "bricks and mortar" image of the stratum corneum, In the intercellular domain, bilayers with different structures alternate. As a result, amedication must continuously diffuse through aqueous and lipid domains and successively partition into each. It is commonly recognized that this pathway is the most typical way for minute, uncharged particles to penetrate skin.[30]

Types of transdermal drug delivery system

Single-layer drug-in-adhesive system

In this type of patch the adhesive layer of this system contains the drug. The adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but it is also responsible for the releasing the drug. The adhesive layer is surrounded by a temporary liner and a backing. The medication is also present in this system's sticky layer. The adhesive layer in this kind of patch not only keeps the various layers together and attaches the entire system to the skin, but it also controls the drug's release. There is a backer and a temporary liner around the adhesive layer.[31]

Reservoir system

In this System the drug reservoir is kept in between backing layer and a rate controlling membrane and drug releases through microporous rate controlled membrane. Drug can be in the form of a solution, suspension, or gel or dispersed in a solid polymer matrix in the reservoir compartment. The reservoir transdermal system has a separate drug layer in contrast to the single-layer and multi-layer drug-in adhesive systems. The adhesive layer serves as a physical barrier between the drug layer and a liquid compartment carrying a drug solution or suspension. The backing layer is also located behind this patch. The rate of release in this kind of system is zero order.[32]

Matrix system

A semisolid matrix system that incorporates a drug solution or suspension is the drug layer of the Matrix system. This patch's drug layer is partially covered by such an adhesive layer that surrounds it. This system is of two types.

Drug-in-adhesive system: For the formation of drug reservoir, the drug dispersed in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in the case of hot-melt adhesives) on to an impervious backing layer.

Matrix-dispersion system: In this system the drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. And this containing polymer along with drug is fixed onto an occlusive base plate in a compartment fabricated from a drug- impermeable backing layer. In this system the adhesive is spread along the circumference instead of applying on the face of drug reservoir to form a strip of adhesive rim.[31,32]

Micro-reservoir system

This system is a combination of reservoir and matrix-dispersion systems. In which drug is suspended in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unleachable, microscopic spheres of drug reservoirs.[33]

Vapour patch

The adhesive layer in this kind of patch is used to release vapour in addition to adhering the several layers together. The vapour patches, which are brand-new to the market, disperse essential oils for up to 6 hours. The vapour patches, which are mostly employed in cases of nasal decongestant, release essential oils. Another type of vapour patch available on the market is a controller vapour patch that improves good sleep.[33]

Basic components of transdermal patch

Polymeric matrix

It is made by dispersing the drug in a synthetic polymer base, whether in a liquid or solid state. It should be chemically and biologically compatible with the medicine as well as other system components like penetration enhancers. The drug's release from the device is regulated by the polymer. A polymer needs to fulfill the following requirements.

(a) The polymer's molecular weight and chemical activity should be such that the individual drug diffuses and is released through it efficiently.
(b) The polymer must to be stable.
(c) It shouldn't be toxic
(d) it should be simple to manufacture
(e) it shouldn't be expensive
(f) both the polymer and the product of its degradation shouldn't be harmful to the host.
(g) It contains significant concentrations of the active agent.

Types of polymer

Natural polymers - Cellulose derivative, gelatin, waxes, proteins, gum, shellac, natural rubber, starch, chitosan etc.

Synthetic Elastomers - Hydrin rubber, silicone rubber, nitrile, acrylonitrile, neoprene, butyl rubber etc.

Synthetic polymers – Polyvinylalcohol, polyvinyl chloride, polyethylene, polypropylene, polyamiode, polyurea, epoxy, polyvinylpyrrolidone etc.[34]

Drug

The following are some excellent drug characteristics and some factors to take into account while manufacturing transdermal patches:

- Drug's first pass metabolism need to be greater.
- Drugs with a low therapeutic window.
- Drugs with a shorter half-life.
- Drugs that requires repeated dosing.

- Molecular weight of the drug should be less than 1000 Dalton
- Low-dose substances with a low melting point (less than 200^0C)
- Drugs that is compatible with both hydrophilic and lipophilic phases.
- Drugs that have no adverse effects on the skin can be formulated as transdermal patches.[35]

Permeation enhancers

The primary skin barrier limiting drug permeability is the stratum corneum. in order to maximize the amount of permeant passing this barrier, there has been a huge effort to investigate and develop new approaches. Innovative methods focus on modifying the interaction between the drug and the drug vehicle to improve partitioning into the stratum corneum or altering the structure of the stratum corneum to minimize its resistance to drug diffusion on to enhance partitioning into the stratum corneum or modifying the structure of the stratum corneum to make it less resistance to drug diffusion.

Ideal permeation enhancer characteristics

- They ought to be non-allergic, non-toxic, and non-irritating.
- They shouldn't exhibit any pharmacological action; therefore they should also not bind to receptor sites.
- They should have appropriate skin sensation and appropriate appearance.[36]

Backing laminates

It aids to protect the patch from the outside environment. They must be resistant to chemicals.

They won't permit components to permeate through the patches. They are the ideal combination of elastic, flexible, and tensile strength. It ought to have a slow transition rate for water vapour. The backing material should be heat stable if a drug is incorporated into a liquid (or) gel in the formulation to enable fluid-tight packing of the drug reservoir (form-fill seal process).E.g. vinyl, poly ethylene and poly ester film.[37]

Release linear

It is taken off when the patch is placed on the skin. It ought to be inert chemically. It is comprised of two layers a release coating layer and a base layer. The bottom layer may be occlusive (E.g. poly ethylene, poly vinyl chloride).The metalized laminate and polyester foil are also utilized as release liners.[36]

Plasticizer

They are intended to give transdermal patches flexibility. Additionally, it is chemically inert and compatible with all other chemicals in the mixture. PEG, PG, tri-ethyl citrate, and di-butyl phthalate are a few examples. Some plasticizers, like propylene glycol, also serve as permeability enhancers.[37]

Solvents

Chloroform, methanol, acetone, isopropanol and dichloromethane

Mechanism of action of transdermal patch

The application of the transdermal patch and the flow of the active drug constituent from the patch to the circulatory system via skin occur through various methods.

Iontophoresis

Over the electrode in contact with the formulation, iontophoresis delivers a few milliamperes of current to a small area of skin, allowing for easier delivery of drug through the barrier. Pilocarpine is mainly administered to produce sweating as part of a cystic fibrosis diagnostic test. A promising strategy for quick onset of anesthesia is the delivery of lidocaine by Iontophoresis.[38] Iontophoresis, which has been found to enhance skin penetration and increase the release rate of various drugs with poor absorption/permeation profiles, encourages the passage of ions through the membrane under the influence of a small externally applied potential difference (less than 0.5mA/cm2). By employing an electrochemical potential gradient, this technique has been used to transport drugs in vivo, whether they're ionic or nonionic.[39] Iontophoresis' effectiveness is influenced by the drug's polarity, valency, and mobility as well as the type of electrical cycle used and the formulation in which the drug is present. Similar to most other drug delivery methods, iontophoresis depends on current, which makes drug absorption less dependent on biological factors.[40]

Electroporation

A technique for applying rapid, high-voltage electrical pulses to the skin is called electroporation. The permeability of the skin for drug diffusion is raised by 4 orders of magnitude after electroporation. Electrical pulses are thought to form transient aqueous pores in the stratum corneum, through which drugs are delivered. By employing closely spaced electrodes to restrict the electric field within the nerve-free stratum corneum, it is risk-free and easy to administer electrical pulses without experiencing any pain.[38] This technique involves applying high-voltage electric pulses to the skin for brief periods of time (ms), resulting in the creation of tiny pores in the SC that increase permeability and facilitate drug diffusion.[41,42]

Sonophoresis

Transdermal drug administration may be enhanced by the desired range of ultrasound frequencies produced by an ultrasound device.[43] Because it enhances drug circulation by establishing an aqueous channel in the disturbed bilayer by cavitations, low-frequency ultrasound is more effective In order to create an aqueous route through which the drug can be administered, the drug in question is combined with a specialized coupler,

like a gel or cream, that couples ultrasonic waves to the skin and disrupts the skin layers.[44]

Application of ultrasound

It has been demonstrated that using ultrasound, especially low frequency ultrasound, can improve the transdermal delivery of many medications, including macromolecules. It's also referred to as sonophoresis. Katz et al. reported on the topical administration of EMLA cream using low-frequency Sonophoresis.[38]

Photomechanical waves

The SC can be penetrated by photodynamic waves that are directed at the skin, allowing the medication to enter via the momentarily formed channel.[45] Low radiation exposure of around 5-7 J/cm2 is used to increase the depth to 50–400 m for successful transmission. The incident wave induces limited ablation.[46]

Thermal ablation

Using targeted heat to selectively disturb the stratum corneum's structure through thermal ablation, also known as thermophoresis, offers the potential for improved drug delivery through the skin's newly formed micro channels.[47] A high temperature above 100°C is necessary to remove the stratum corneum through thermal ablation, which causes keratin to heat up and vaporise.

Methods of transdermal patch

Asymmetric TPX membrane method

Step 1: The polymer's molecular weight and chemical activity should be such that the individual drug diffuses and is released through it efficiently. The polymer's molecular weight and chemical activity should be such that the individual drug diffuses and is released through it efficiently.

Step 2: The drug is poured into a backing laminate made of a polyester film (1009, 3m) that may be heat sealed and has a concave of 4 cm in diameter.

Step 3: It is then covered with an asymmetric TPX [poly (4-methyl-1-pentene)] membrane before being sealed with glue.[48]

Circular teflon method

Simply mixing the polymers with organic solvents yields the polymer solution. Calculated drug dosage is dispersed (or dissolved) in half the volume of the same organic solvents that are used to make polymer solution. The enhancer is contained in the residual organic solvents. Then the Di-Nbutylpthalate is added to this combination as a plasticizer along with the drug solution, enhancer mixture, and polymer solution The above-mentioned mixture is stirred for 12 hours and then poured into a circular Teflon mould that has already been leveled. To control the vaporization of the solvent in a laminar flow, the funnel is placed over the mould in an anticlockwise direction (hood model). For 24 hours, the air is maintained at a speed of 0.5 m/s. The dry films are then kept in desiccators with silica gel at a temperature of 25+ 0.5^0C for a further 24 hours. Within one week of its formulation, such a type of film is assessed.[48]

Mercury substrate method

This approach simply involves dissolving the drug in a polymer solution that also includes plasticizer and other ingredients. After being agitated for 10 to 15 minutes, the solution combination becomes a uniform dispersion, which is then poured over a mercury surface that has been leveled. By laying a funnel over the surface inverted, you can regulate the speed of evaporation.[48]

By using IPM membrane method

With the use of a magnetic stirrer, the drug is agitated for 12 hours while being disseminated in a mixture of solve nts, including water and propylene glycol, which already includes carbomer 940 polymers. Triethanolamine is add ed to the combination above to produce a viscous solutio n (gel) that will be integrated onto the IPM membrane aft er being neutralized.[49]

By using EVAC membranes method

1% carbopol reservoir gel, polyethylene (PE), and ethylene vinyl acetate copolymer (EVAC) membrane are required as rate control membranes for the preparation of TDS. Use propylene glycol to prepare a gel if the drug is not soluble in water. Drug is dissolved in propylene glycol, carbopol resin is added to the above solution, and 5% w/w sodium hydroxide solution is used to neutralize the mixture. A sheet of backing layer covering the designated area is placed on top of the medicine (in gel form). The gel will be covered by a rate regulating membrane, and the edges will be heated to seal them, creating a leak-proof device.[49]

Preparation of TDDS by using proliposomes

Proliposomes are created utilizing the carrier approach and the film deposition process. The optimal drug to lecithin ratio, as determined by prior references, should be 0.1:2.0. To make proliosomes, place 5 mg of mannitol powder in a 100 ml round bottom flask. The flask is then rotated at 80–90 rpm while being kept at 60–70°c, and the mannitol is dried under vacuum for 30 minutes. The water bath's temperature is set to 20–30°C after drying.[50] Drug and lecithin are dissolved in a suitable organic solvent mixture, and then 0.5ml of the organic solution is added to the round-bottomed flask at 37°C. After the solution has dried completely, a second 0.5ml aliquot of the solution is then added. The flask containing the proliposomes is connected to a lyophilizer after the final loading, and the drug-loaded mannitol powders (proliposomes) are then left in the desiccator overnight before being sieved through a 100 mesh screen. A glass bottle is used to retain the gathered powder while keeping it frozen until characterization.[50]

By using free film method

In this procedure, cellulose-acetate-free film is initially created by casting it over a surface made of mercury. 2% weight-to-weight polymer solution is also made using chloroform. Plasticizers must be applied at a 40% weight-to-weight (w/w) concentration to polymers. The glass ring is then placed over the mercury surface in the glass petridish, and 5 ml of the polymer solution is then poured into it.[49] By putting an inverted funnel over the petridish, you can regulate how quickly the solvent evaporates. After the solvent has completely evaporated, the mercury surface is observed to detect the film formation. In a desiccator, the dry film will be separated and kept until use between wax paper sheets By using this method, we can create free films of various thicknesses by adjusting the volume of the polymer solution.[50]

Evaluation of transdermal patch

Physicochemical evaluation

Thickness of patch - Dimensions of the patch at various spots along the transdermal film, the thickness is measured using a micrometer, dial gauge, screw gauge, or travelling microscope.[51]

Drug content analysis - A precisely measured portion of precisely prepared patches is dissolved in a suitable solvent in which the medicine is soluble, and the solution is then constantly agitated in a shaker incubator for 24 hours. After that, the solution is sonicated and filtered. The filtrate is then properly diluted and subjected to an analysis using appropriate methods, such as UV (or) HPL.[52]

Percentage moisture content - The prepared patches are weighed separately and maintained in desiccators with anhydrous calcium chloride at room temperature for 24 hours. The patches are weighed every so often after the first 24 hours until a steady weight is achieved. The following formulas are used to compute the % moisture loss. The formula for percentage moisture loss is (starting weight - final weight)/initial weight multiplied by 100.[53]

Uniformity of weight - The prepared patches were dried at 600°C for 4 hours before to the weight uniformity test. A predetermined patch area must be divided into several portions before being weighed on a digital scale. It is necessary to compute the average weight and standard deviation values from the individual weights.[52]

Folding endurance - The patch is evenly chopped in one location, folded repeatedly in the same spot, and then snapped. Prior to the patch being broken, the number of folding is recorded. The folding will gain durability as a result.[52]

Fatness - The surface of a transdermal patch should be smooth and not shrink over time. It can be examined using a flatness test. In this test, two strips are cut from the right and left sides, and one strip is cut from the center. It is measured how long each strip is. Percentage constriction is used to calculate the length variation. 100% flatness is shown if the percentage constriction is zero. (Initial length - Final length) / Initial length x 100 = % construction.[53]

In vitro evaluation

The in-vitro permeation analysis of developed transdermal patches was conducted using franz diffusion cells and cut rat abdominal skin. Between the donor and receptor compartments of the diffusion cell was the skin. A patch with a diameter of 2.2cm was applied in closeproximity to the skin's stratum corneum side, with aluminium foil used as a backing membrane on the top side. 54 A Teflon bead was inserted into the receptor compartment, which had 12 ml of ordinary saline in it. Using a magnetic stirrer, the cell contents were swirled, and a temperature of 37±5°C was maintained throughout the experiment. Over the course of 24 hours, 1ml samples were taken through the sampling port at various intervals, with an equal volume of phosphate buffer pH 7.4 being added at the same time. The samples were then subjected to a spectrophotometric analysis.[55]

In vivo evaluation

The most accurate representation of a drug's effectiveness is seen in in vivo evaluation studies. In vivo investigations can completely examine the variables that cannot be considered during in vitro experiments. TDDS can be evaluated in vivo using. Models using animals or Human volunteers the most popular animal species used to test transdermal drug delivery systems include the mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, and guinea pig. Gathering pharmacokinetic and pharmacodynamic data after applying the patch to human volunteers is the last step in the development of a transdermal device. Clinical trials have been carried out to evaluate the effectiveness, risks, side effects, patient compliance, etc.[56]

Factor effecting of transdermal patch

Physicochemical properties of permeant

Partition coefficient - It is necessary for effective action to have the ideal partition coefficient (K). Drugs with high K levels take a while to leave the lipid layer of the skin. Furthermore, low K drug concentrations won't permeate.

Diffusion coefficient - The drug's diffusion coefficient affects how well it is absorbed. The features of the drug, diffusion medium, and interactions between them all affect the drug's coefficient of diffusion at a constant temperature.

Drug concentration - The flow is inversely proportional to the concentration gradient across the barrier, and the gradient will be bigger if there is a higher drug concentration across the barrier.

Molecular size and shape - Small molecules infiltrate the body more quickly than large ones, and drug absorption is inversely correlated with molecular weight.

Skin hydration - Skin becomes substantially more permeable when in touch with water. The most crucial aspect in promoting skin permeability is hydration. Therefore, humectant usage occurs during transdermal administration.[57]

Physiological factor

Skin condition - Methanol and chloroform cause skin cell destruction and encourage penetration. The skin problems change depending on the patient's state of illness. Although the skin is a better barrier when it is intact, the aforementioned factors affect penetration.

Skin age - Younger skin is more porous than older skin. Children are more susceptible to toxin absorption through the skin. Age of the skin is therefore one of the elements affecting the drug's penetration in TDDS.

Blood flow - Transdermal absorption may be impacted by changes in peripheral circulation.

Regional skin sites - Site differences exist in appendage density, stratum corneum type, and skin thickness. These elements have a big impact on penetration.

Skin metabolism - Steroids, hormones, chemical carcinogens, and some medicines are all processed by the skin. Therefore, the efficacy of a medicine that has penetrated the skin is determined by skin metabolism.

Species differences - The thickness of the skin, the density of the appendages, and the keratinization of the skin differ from species to species, which has an impact on the penetration.[57]

Application of transdermal patch

Nicotine transdermal patches, which release nicotine in amounts that are carefully regulated to aid in quitting smoking. Additionally, doctors may advise using nitroglycerin patches to treat angina. There are additional transdermal patches for the hypertension medicine clonidine and the non-steroidal anti-inflammatory drug ketoprofen.The MAOI selegiline was the first transdermal delivery agent for an antidepressant in transdermal form.Attention Deficit Hyperactivity Disorder transdermal delivery system (ADHD).[58]

Future of transdermal drug delivery system

Liposomes, niosomes, and micro emulsion are upcoming developments in drug delivery systems. The purpose of this invention is to enhance the distribution of drugs with limited intrinsic solubility in the majority of excipients used in traditional formulations. Steroids, antifungal, antibacterial, interferon, methotrexate, and local anesthetics are just a few examples of the many potential medications that could be delivered. The market for transdermal patches has reportedly witnessed annual growth of at a rate of 25% and is expected to rise in the future. As new technologies are developed and the number of transdermal drugs that are marketed grows, this number will rise in the future. As there are more advancements in design, transdermal distribution of analgesics is probably going to gain prominence. Research is being done to improve effectiveness and safety to provide more precise drug delivery associated with longer duration of action and to enhance practical aspects such as the experience for the patch wearer. Other possible enhancements include enhanced transdermal technology, which uses mechanical energy to increase drug flux across the skin either by changing the skin barrier or boosting the energy of the drug molecules. Several 'active' transdermal technologies are being researched for various medications after the successful development of patches utilizing iontophoresis. These include sonophoresis, which employs low frequency ultrasonic energy to damage the stratum corneum, electroporation, which uses rapid, high voltage electrical pulses to temporarily open aqueous pores in the skin (uses heat to make the skin more permeable and to increase the energy of drug molecules). It has been explored how to boost medication permeability across the skin by using magnetic energy, or magnetophoresis. An underappreciated technique for managing both acute and chronic pain may be the transdermal patch. We assume that this technique of drug delivery will become more ubiquitous and applicable with enhanced delivery and a larger choice of analgesics. With over 40% of the drug delivery candidate items currently in clinical trials relevant to transdermal or dermal system, transdermal route of drug delivery system is currently the most successful novel research area in new drug delivery system when compared to oral treatment. The most convenient, safest, and alternative method of systemic delivery of drug is through the use of transdermal drug delivery systems (TDDS). Systemic drug administration through the skin has a number of benefits, along with ensuring a constant drug level in blood plasma, reducing side effects, improving bioavailability by avoiding hepatic first pass metabolism, and increasing patient compliance with regard to the drug regimen used for treatment. For continuous medication release into the systemic circulation, skin has recently been recognized as the safest route for drug administration.[59]

CONCLUSION

The development of TDDS technology is widely acknowledged as the conception of a mass delivery methodology, making it the preferred drug injection modality for transdermal delivery across the spectrum of skin types while avoiding first-pass metabolism and other sensitivities connected to various alternative drug administration routes. Drugs can be administered through the skin to the systemic circulation using a variety of devices and TDDSs. The majority of the time, TDDS is a reliable and secure method of delivering drugs, and once they get to the target region, they remain secure and

stable against biochemical changes. Drugs may be distributed uniformly at predetermined and controlled rates with TDDS since it is noninvasive, nonallergenic, and has a predetermined duration and dose delivery technique. The bioavailability of medications with low absorption is being improved by numerous new and outdated formulations through simple administration routes that enable big dosages to be given over an extended period of time. As a result, TDDS technology is expanding quickly in the pharmaceutical industry and has been successful in seizing significant market value for biomedical applications as a formulation system that can enhance drug administration through topical channels. However, despite extensive research over the past few decades, passive methods like chemical enhancers have only moderately increased the transdermal transport of small molecules, and they have only moderately increased the transport of macromolecules under potentially.

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