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REVIEW OF TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

The oral route is the most common route of drug delivery, but the administration of drugs through the oral routeshows a few disadvantages, like first-passmetabolism, drug degradation in the gastrointestinal tract due to enzymes and pH of the stomach, GI irritation, low bioavailability, etc. To overcome this problems, the Transdermal Drug Delivery System (TDDS) was developed. Transdermal Drug Delivery Systems, also known as “Patches” are the painless way of systemically administering therapeutically active medication by placing a drug formulation on intact and healthy skin. Skin is an effective medium through which absorption of the drug takes place and entersin the blood stream overthe period of time. Different types of transdermal drug delivery systemsare developed, which demonstrate different release kinetics. This review article provides a detailed study of TDDS advantages, disadvantages, drug permeation pathways, types of transdermal drug delivery systems and their components, factors affecting the formulation of TDDS, and their evaluation parameters. The review also contains future prospects for transdermal drug delivery systems.

KEYWORDS: Drug Penetration, Matrix, Reservoir, Polymer, Pressure Sensitive Adhesive, Pro-Liposomes.

INTRODUCTION

The transdermal drug delivery system, also known as patches is a painless way of systemically administering therapeutically active medications by placing a drug formulation on intact and healthy skin.[1,2] The oral route is a more liked route of drug delivery, but it has a few disadvantages, including first-pass metabolism, drug degradation in the gastrointestinal

tract due to enzymes and pH of the stomach, GI irritation, low bioavailability, etc. To vanish these problems, a Novel Drug Delivery System was discovered by Chien in 1992, Banker in 1990, and Guy in 1996.It is a transdermal drug delivery system.[3] The skin is the largest and most accessible organ of the human body, so the delivery of the drug through the skin has been effective as well as a challenging area for research.[4] Among the newest drugs in pharmaceuticals, the most common transdermal system present on the market is mainly based on semi-permeable membranes, which arecalled as patches.[5] Transdermal patches were developed during the 1970s, and in 1979, the first FDA approval of Scopolamine was developed for the treatment of motion sickness. Thesecond patch approved in 1981 wasof nitroglycerine.[6,7] Now a day's numbers of patches are available on the market for transdermal use.

Table 1: The Drug Approved By FDA For TDDS.[7,8,9,10,11]

Sr.No.	Approvedyear	Drugproducts	Indication
1.	1979	Scopolamine	Motion sickness
2.	1982	Nitroglycerine	Angina pectoris
3.	1984	Clonidine	Hypertension
4.	1986	Estradiol	Menopausal symptoms
5.	1990	Fentanyl	Chronic pain
6.	1991	Nicotine	Smoking cessation
7.	1993	Testosterone	Testosterone deficiency
8.	1995	Lidocaine	Local analgesic
9.	1999	Lidocaine	Post hepatic pain
10.	2001	Ethinyl estradiol	Contraceptive
11.	2003	Oxybutynin	Overactive bladder
12.	2006	Fentanyl	Acute postoperative pain
13.	2007	Rotigotine	Parkinson's disease
14.	2008	Granisetron	Chemo induced emesis
15.	2010	Buprenorphine	Chronic pain
16	2022	Donepezil	Alzheimer's disease

ADVANTAGES AND DISADVANTAGES OF TDDS

1. Advantages[1]

1. Avoids first-pass metabolism and enzymatic disruption by GIT.
2. In a transdermal medication, there is the possibility of self-administration.
3. Topical patches have a constant drug release in the bloodstream.
4. Less painful method of drug delivery.
5. In comparison to oral methods, transdermal patches offer fewer negative effects.
6. Avoids GIT incompatibility of drugs.

7. Dose and therapeutic effects are advanced.
8. TDDS is a durable treatment.
9. Better patient's compliance.
10. Avoiding frequent dose administration.

2. Disadvantages[12]

1. Some patients develop contact dermatitis at the site of application from one or more of the system components then stop the use.
2. No use of ionic drugs.
3. May cause allergic reactions.
4. A molecular weight of drug molecules less than 500daltons is essential.
5. Transdermal therapy is suitable for certain potent drugs only.
6. Transdermal therapy is not carried out for ionic drugs.

3. Anatomy and Physiology of Skin

Human skin consists of three distinct layers

- Epidermis
- Dermis
- Hypodermis

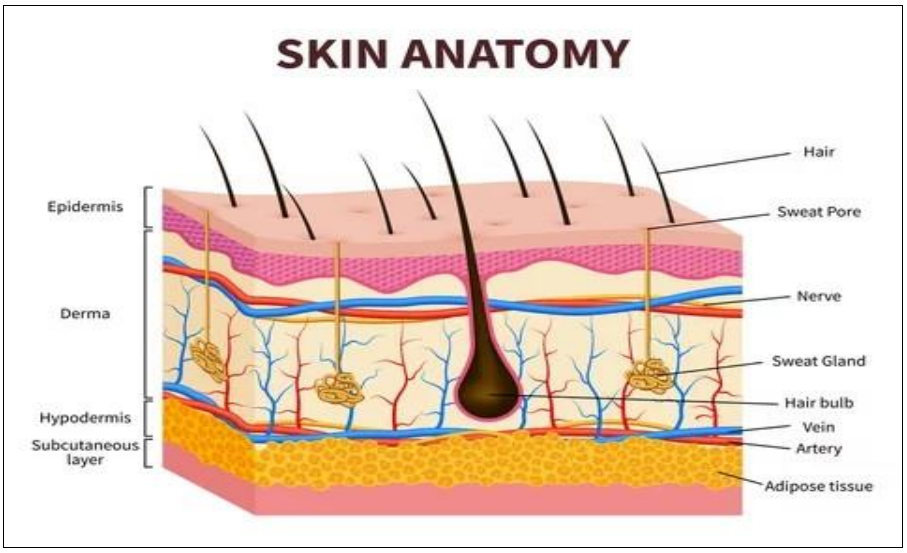

Figure 1: Skin Anatomy and Physiology.

The human body's outer layer of skin spans an estimated area of around 2 square meters. It plays a vital role in our overall health as it receives approximately one-third of the total circulating blood in the body. In simpler terms, our skin serves as a large canvas that interacts

with a significant portion of our blood supply, facilitating important functions and maintaining the well-being of our body as a whole.[13]

3.1. Epidermis

It is the peripheral hard and thin surface of the skin, as shown in Figure No.1. Mainly, the cells present in the epidermis are Keratinocytes; these cells form cells in the inner layer of skin, known as basal layer. It is a barrier like– structure, and they are composed of dead cells, which are the outermost part of the epidermis. This layer acts as obstacle; many drugs are not able to penetrated through the stratum corneumbut lipotropic drugs can easily penetrate as compared to hydrophilic drugs.[14]

3.2. Dermis

Dermis is 3 - 5mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerve tissue. The cutaneous blood supply plays a vital role in the regulation of body temperature. Additionally, it also provides nutrients and oxygen to the skin, eliminating toxins and waste products. The capillaries reach up to0.2mm of skin surface and provide sink conditions for most of the molecules penetrating through the skin barrier. The blood providation thus keeps the dermal concentration of a permeant very low, and the resulting concentration difference across the epidermis provides the essential concentration gradient for transdermal permeation.[15]

3.3. Hypodermis

The hypodermisor subcutaneous fat tissue holds up the dermis and epidermis. It is described as a fat storage area. This layer helps to regulate temperature, provides nutritional support, and spontaneous protection. It carries the principal blood vessels and nerves to the skin and may contain sensory pressure organs. For transdermal drug delivery, the drug has to penetrateall the three layers and arriving in systemic circulation.[15]

4. Drug Permeation Pathway throughtheSkin[12]

Transdermal absorption involves the passive diffusion of drug material through the skin. Amoleculemay use two distinct diffusionalroutesto successfully penetrate normal, intact skin.

4.1. Appendagial route

4.2. Epidermal route –a) Trans-cellular

b) Para-cellular

4.1. Appendagial route: The appendagial route comprises transport via sweat glands and hair follicles with their associated sebaceous glands. These routes found a way to penetrate through the stratum corneum and are thus known as "shunt" routes. This route is considered tobe of minor significance because of its fairly small area, roughly0.1 of the total skin area.

4.2. Epidermal route

a) Trans-cellular: Pathway means transport of drug molecules across the epithelial cellularmembrane. These include unresisting transport of small molecules, active transport of ionic and polarcompounds, and endocytosis and trans-cytosis of macromolecules.

b) Para-cellular: The para-cellular pathway means the transport of molecules around or between the cells. Tight junctions or analogous situations live between the cells. The top pathway taken by a permeant is determined substantially by the partitioncoefficient. Hydrophilic drugs tend to primarily enter the intracellular regions, while lipophilic drugs cross the stratum corneum via the intercellular pathway.

5. Types of Transdermal Drug Delivery Systems

5.1. Single-layer drug- in–adhesive: The adhesive layer in this type of system also containsthe drug. In this system of patches, the adhesive layer not only serves to adhere the number of layers together, along with the whole system, to the skin but is also responsible for the release of the drug. The adhesive layer is bounded by a temporary liner and a backing membrane.[12]

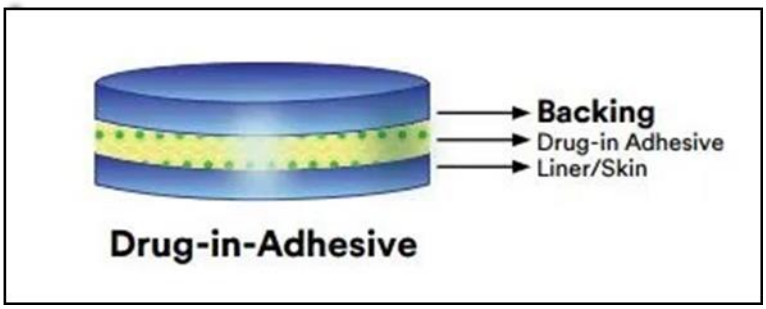

Figure 2: Single Layer Drug In Adhesive.

5.2. Multi-layer drug in adhesive

The multi-layer drug in adhesive is analogous to the single-layer system in that both adhesive layer are also responsible for the release of the drug. But it is different however in that it adds another layer of drug-in-adhesive, generally separated by a membrane. This patch also has a short-term liner of drug-layer and enduring backing.[12]

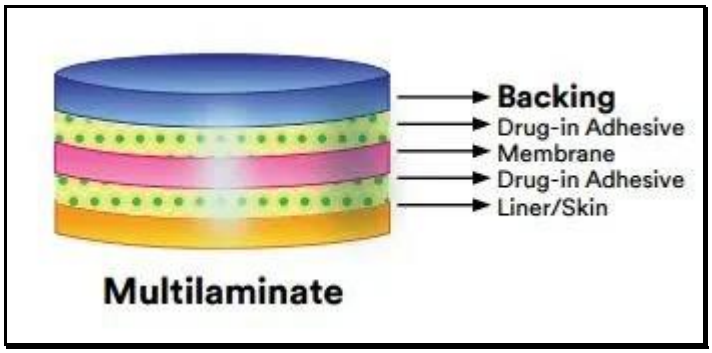

Figure 3: Multi-Layer Drug In Adhesive.

5.3. Drug reservoir-in-adhesive

This transdermal system contains a distinct drug layer. The drug layer is a liquid compartment adheringto a drug solution or suspension, separated by backing layer. In this reservoir system, the rate of release is zero order.[12]

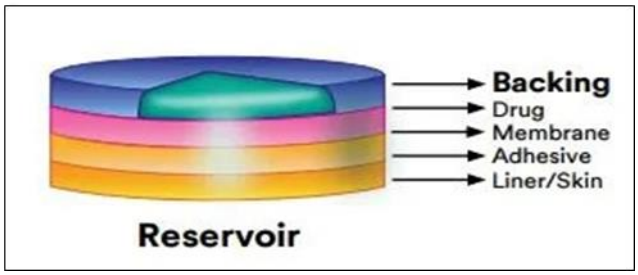

Figure 4: Drug Reservoir In Adhesive.

5.4. Drug matrix-in-adhesive

This matrix system has a drug layer of semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch bounded by a the drug layer, which partly overlies it.[12]

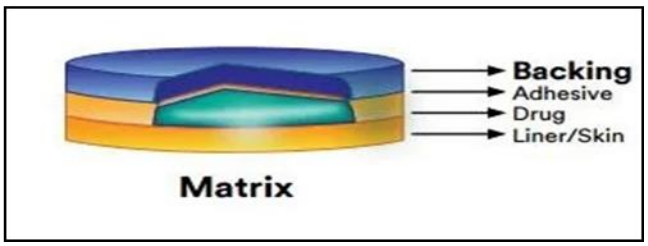

Figure 5: Drug Matrix In Adhesive.

6. Components of the Transdermal Drug Delivery System:

1. Polymer matrix
2. Drug reservoir

3. Permeation enhancers
4. Pressure-sensitive adhesive
5. Backing laminate
6. Other excipients

6.1. Polymer matrix

The Polymer prevents the unnecessary release of the drug from the device. Desirable useful polymers for transdermal devices are as follows[16]

Table 2: Polymers Used In Polymer Matrix.

Natural Polymers	Synthetic Elastomers	Synthetic Polymers
Cellulose derivatives, zein, gelatin, waxes, Proteins and their derivatives, Natural rubber, starch, Chitosan	Polybutadiene, hydrin rubber, nitrile, Acrylonitrile, butyl rubber, Styrene-butadiene rubber Neoprene	Polyvinyl alcohol, polyethylene, polypropylene, polyaactrylate, polyurea, Polyvinyl pyrrolidone, Polyamide.

6.2. Drug reservoir: Drug solution in direct contact the with release liner.

Physicochemical properties

a. The drug's have molecular weight upto 1000 Dalton.
b. The drug having lipophilicand hydrophilic phases.
c. A drug must have a low melting point.[13]

Biological properties

a. The drug should be potent with a regular dose in the order of the few mg/day.
b. The half of the drug must be short-live.
c. Tolerance to the drug should not develop under the near-extensive release profile of transdermal patches.
d. The allergic response should not be produced by the drug.[13]

6.3. Permeation enhancers

Permeation enhancers are used to enhancethe transformation of the stratum corneum by altering the lipid layer and proteinsand can be as follows.[14]

Solvents: Includes the swallowing of protein and lipid layers, which results in increased permeability. Example: Methanol, ethanol, dimethyl sulfoxide etc.

Surfactants: Surfactants are used to enhance polar pathways. Example: Non-ionic: Pluronic F68, Pluronic F127, Anionic: Sodium laurylsulfate, Dioctyl sulphosuccinate.

6.4. Pressure-Sensitive Adhesive

A pressure-sensitive adhesive (PSA) is a substance that enables a strong and lasting bond between thetransdermal system and the skin's surface. APSA should adhere firmly with minimal finger pressure. It should also be tacky, providing strong adhesion. Furthermore, it should be easy to remove from a smooth surface without leaving any residue. Some commonly used adhesives in this context are polyacrylates, polyisobutylene, and silicone-based adhesives.

6.5. Backing laminate

When designing the baking layer, the following points should be considered:-

1. Should be flexible.
2. It has a low water vapor transmission rate so as to promote skin hydration and thus greater skin permeability.
3. While applying it to the body surface, it should be compatible with the transdermal system as long as remains in use.
4. It should be chemical resistance.
5. Tensile strength must be strong.
6. Not cause irritation.[3]

Examples: polyethylene film, polyester film, polyolefin film, aluminum-vapor-coated layer.

7. Factors affecting on transdermal bioavailability

Three major factors affecting the transdermal bioavailability of the drug through the transdermal route.

7.1. Physicochemical factors

Skin hydration: When exposed to water, the skin's permeability greatly increases. Adequate hydration plays a crucial role in enhancing skin permeation. Consequently, humectants are employed in transdermal delivery.[18]

Temperature and pH: The drug permeability experiences a ten-fold increase due to temperature fluctuations. As the temperature decreases, the diffusion coefficient decreases as well. Weak acids and weak bases dissociate based on the pH and pKa values. The

concentration of the drug in the skin depends on the proportion of the unionized drug. Consequently, drug penetration is significantly influenced by both temperature and pH.[18]

Diffusion coefficient: The ability of a drug to permeate tissues is influenced by the diffusion coefficient of the drug. When the temperature remains constant, the diffusion coefficient is determined by various factors, such as the characteristics of the drug itself, the properties of the surrounding medium through which it diffuses, and the potential interactions occurring between the drug and the medium. In simpler terms, the penetration of a drug is affected by the way it interacts with the environment it diffuses through, along with the inherent properties of the drug itself.[18]

Drug concentration: The flow rate is directly related to the difference in concentration between the two sides of the barrier, and this difference will be greater if there is a higher concentration of the drug across the barrier.[18]

Molecular sizeand shape: Drug absorption is inversely proportional to molecular weight; small molecules penetrate faster than large ones.[18]

7.2. Biological factors[18,19]

Skin condition: The unbroken skin functions as a protective barrier, but a variety of substances, such as acids and alkalis, can still pass through the skin cells and enter the body. Additionally, certain solvents have the ability to disrupt the intricate and compact structure of the outermost layer of skin, known as the horny layer. Solvents like methanol and chloroform can remove the lipid portion of this layer, creating artificial pathways through which drug molecules can effortlessly travel.

Skin age: It has been observed that the skin of adults and young individuals is more easily penetrated than that of older individuals, although the difference is not significant. Children are more susceptible to toxic effects due to their larger surface area relative to body weight. As a result, powerful steroids, boric acid, and hexachlorophene have caused severe adverse reactions.

Skin metabolism: Skin metabolism plays vital role in the metabolism of steroids, hormones, chemical carcinogens, and some drugs. So skin metabolism regulates the efficacy of drugs permeated through the skin.

Regional skin site: Thickness of skin, composition of the outermost layer of the stratum corneumand density of appendages (hair follicle and sweat gland) varies from site to site. These factors significantly affecting the penetration of drug molecules.

Blood supply: Changes in peripheral circulation can significantly affect on which substance are absorbs through the skin.

Species difference: The skin thickness, density of appendages, and keratinization of skin vary from species to species, which affects the penetration.

7.3. Environmental factors[18, 20]

Sunlight: Sunlight has the ability to cause thinning of the walls of blood vessels, resulting in bruising even with minor trauma in areas exposed to the sun. Additionally, one of the prominent effects of sunlight on the skin is the occurrence of pigmentation changes, with freckles being the most notable manifestation.

Cold season: Often results in itchy, dry skin. Skin s act by increasing oil production to compensate for the weather dryeffects. Good moisture will help ease symptoms of dry skin. Also, drinking lots of water can keep your skin hydrated and looking radiant.

Air pollution: Dust can block pores and increase the amount of bacteria on the face and skin surface, leading to acne or pimples. This affects drug delivery through the skin. Invisible chemical pollutants in the air can interfere with the skin's natural defense system, breaking down the skin's natural oils that normally trap moisture in the skin and keep it supple.

Effect of heat on transdermal patch: Heat causes high absorption of drugs injected through the skin. Patients should be advised to avoid exposing the patch application area to external heat sources such as hot water bags or hot water bottles. Even a high body temperature can increase the amount of drug applied to the skin. In this case, the patch must be removed immediately. Transdermal drug patches are kept in their original packaging and stored in a cool, dry place until ready for use.

8. MATERIALS AND METHOD

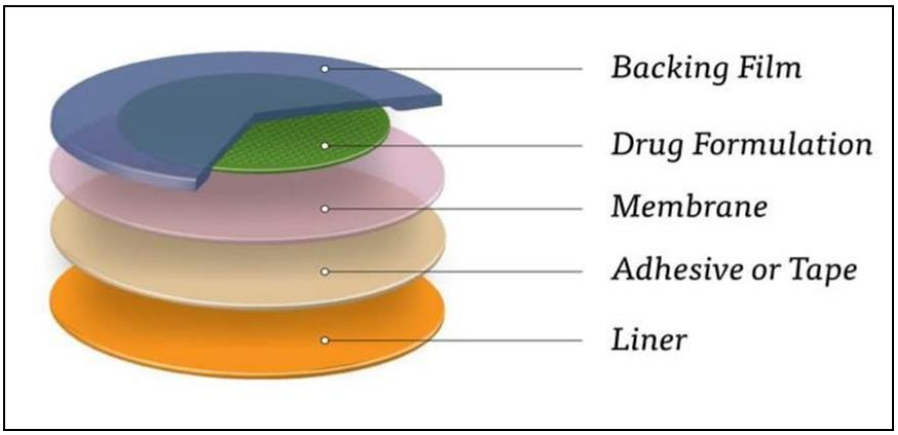

Figure 6: Different Layers of Transdermal Patches.

- **Liners:** Theygives protection to the patches during storage, and the liner must be removed prior to use. Example – poly ethylene, poly vinyl alcohol.
- **Adhesive:** It served to adhere the components of the patch together, along with adhering the patch to the skin. Example – polyacrylates.
- **Membrane**: It prevents the release of drugsfrom the multi-layer patches. It is also known as a permeation enhancer.
- **Drug:** The drug reservoirs have direct contact with the release liner.
- **Backing** membrane: It provides protection to the patch from the external environment.
- Example – polyethylene and polyester film.[21]

9. Various methods of preparation of TDDS[22]

1. Asymmetric TPX membrane method
2. Circular Teflon MouldMethod
3. Mercury substrate method
4. IMP membranes method
5. “EVAC membranes” method
6. Aluminum backed adhesive film method
7. Preparation of TDDS by using pro-liposomes
8. Free film method

9.1. Asymmetric TPX membrane method

A prototype patch can be made by utilizing a heat-sealable polyester film with a concave of 1cmindiameter as the backing membrane for an asymmetric TPX membrane. Asymmetric

TPX poly-(4-methyl-1-pentene) membrane is used to cover the concave membrane, which is then sealed with an adhesive.[22]

9.2. Circular TeflonMould Method

Using a circular Teflon mould, solutions with different ratios of polymers are dissolved in an o-rganic solvent. Half as much of the same organic solvent is used to dissolve the calculated amount of medication. The second half of the organic solvent is used to dissolve the enhancers at various concentrations before they are applied. The Plasticizer di-N-butyl phthalate is included in the drug polymer solution. The entire mixture must be agitated for 12 hours before being placed into a Teflon mould. In order to achieve solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s, the mould must be put on a flat surface and covered with an air-inverted funnel. For 24 hours, the solvent is allowed to evaporate. The dried films must be kept for an additional 24 hours at 25±0.5°C in a desiccators containing silica gel before evaluation to vanish aging effects. The types of films are to be evaluated within one week of their preparation.[23]

9.3. Mercury substrate method

In this technique, the drug is dissolved in a polymer solution together with a plasticizer. The aforementioned solution is then stirred for 10-15 minutes to create a uniform dispersion and poured onto a leveled mercury surface. An inverted funnel is used to regulate the evaporation of the solvent.[24]

9.4. Using the "IPM membranes" method

In this approach, the drug is dispersed in a mixture of water and propylene glycol that contains carbomer 940 polymer. The mixture is stirred for 12 hours using a magnetic stirrer. The dispersion is then neutralized and made viscous with additionof triethanolamine. If the drug has poor solubility in an aqueous solution, a buffer with a pH of 7.4 can be used to obtain a solution gel. The resulting gel will be incorporated into the IPM membrane.[25]

9.5. “EVAC membranes” method

In this system, medicine is dispersed in an admixture of water and propylene glycol containing carbomer-940 polymer and stirred for 12 hours in glamorous stirrer. The dissipation is annulled and made thicker by the addition of triethanolamine. Buffer pH7.4 can be used in order to gain a gel result if the medicine’s solubility in waterless result is veritably poor. The gel solution will be incorporated into the IPM membrane.[22]

9.6. Aluminium-backed adhesive film method

The transdermal medicine delivery system may produce unstable matrices if the lading cure is less than 10 mg. The aluminum-backed tenacious film system is a suitable bone. For medication of the same type, chloroform is choice of solvent because most of the medicines as well as glue are answerable in chloroform. The medicine is dissolved in chloroform and tenacious material will be added to the medicine result and dissolved. A custom-made Aluminum former is lined with Aluminum antipode and the ends blanked off with tightly fitting cork blocks.[26]

9.7. Preparation of TDDS by using pro-liposomes

Proliposomes are created using the carrier method, specifically the film deposition technique. According to a previous study, an optimized ratio of 0.1:2.0 is used for the drug and lecithin. The process begins by taking 5mg of mannitol powder in a 100ml round- bottom flask. This flask is then heated to a temperature of 60-70°C while being rotated at a speed of 80-90 rpm. The mannitol is dried the vacuum for 30 minutes. Once the drying is complete, the temperature of the water bath is adjusted to 20-30°C. The drug and lecithin are dissolved in a suitable organic solvent mixture. At a temperature of 37°C, a 0.5ml portion of the organic solution is added to the round-bottomed flask. After thorough drying, additional 0.5ml aliquots of the solution are added until the desired loading is achieved. After the final loading, the flask containing the proliposomes is connected to a lyophilizer. The drug-loaded mannitol powders (proliposomes) are then placed in a desiccator overnight and subsequently sieved through a 100-mesh sieve. The collected powder is finally transferred intoaglass bottle and stored atfreezingtemperature until further characterization.[27]

9.8. By using the free film method

By using the free film system, free film of cellulose acetate is prepared by casting on mercury. A polymer result of 2 % w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at 40%w/w of polymer weight. 5ml of the polymer solution mixture was poured into a glass ring, which was placed over the mercury surface ina glass petri dish. The evaporation rate of the solvents controlled by placing the funnel over the petri dish. The conformation of the film formation is noted by observing the mercury surface afterthe evaporation of the dissolvent. The dry film will be separated out and stored between the covers of wax paper in a desiccator until use. Free films of different consistencies can be prepared by changing the volume of the polymer solution mixture.[28]

10. Evaluation or Characterization of TDDS

Transdermal drug delivery systems have been developed to improve the clinical efficacy of the drug and patches toenhance patient compliance by delivering a smaller and longer release of the drug at a predetermined rate.

➢ Physical Appearance

All the formulated patches were visually audited for color, clarity, opacity, translucency, flexibility and smoothness.[23]

➢ Thickness of Patch

To determine the thickness of the formulated patches, various points on each patch were measured using digital micrometers, micrometer screw gauges, traveling microscopes, or vernier calipers. The measurements were taken at different points on each patch. By calculating the average thickness and standard deviation, we ensured accuracy in assessing the thickness of the formulated patches.[29]

➢ Weight Uniformity

Prior to conducting the weight uniformity test, the formulated patches were subjected to a drying process at a temperature of 60^0C for duration of 4 hours. To perform the test, a designated area of each patch was cut into different parts, and the individual parts were weighed using a digital balance. The average weight and standard deviation were then calculated from these individual weight measurements.[29]

➢ Folding Endurance

A specific area of the patch is cut uniformly and folded constantly at the same place until it breaks. The number of folds of patch is noted before the patch breaks. It'll give the folding abidance.[19]

➢ Percentage Moisture Loss

The formulated patches are weighed individually and kept in desiccators containing anhydrous calcium chloride at room temperature for 24 hours. After the 24 hours, the patches are weighed at a specific time interval until a constant weight is obtained. The percentage moisture loss is calculated by using the following formulas:[23]

Percentage moisture loss= (Initial wt- final wt)/(initial wt) X 100

- **Percentage Moisture Uptake**

Formulated patches are weighed individually and kept in desiccators containing saturated potassium chloride or ammonium chloride. The RH is maintained at 84%. After 24 hours, the patches are reweighed at specific time intervals untila constant weight is attained.[23]

Percentage moisture uptake = (final wt - initial wt)/(initial wt) X 100

- **Water Vapor Permeability Evaluation (WVP)[19]**

It is determined by natural air circulation. It can be estimatedby usingfollowing formulae:

WVP=W/A

WVP is expressed in g/m^2per 24 hours.

Where W = amount of vapor permeated through the patch (gm/24 hour)

A = surface area of exposure samples (m^2)

- **Drug Content Analysis**

The formulated patches are carefully weighed and added to a solvent that can dissolve the drug effectively. This mixture is then subjected to continuous shaking for a duration of 24 hours using a shaker incubator. Subsequently, the solution undergoes sonication to ensure proper mixing, followed by filtration to remove any impurities. The resulting filtrate is then analyzed using appropriate techniques such as UV spectrophotometry or high-performance liquid chromatography (HPLC), after the necessary dilution has been applied.[30]

- **Uniformity of Dosage Unit**

An accurately weighed portion of the formulated patches is cut into small pieces, which are transferred into a specific volume in a volumetric flask. Dissolve it in a suitable solvent and sonicate for complete extraction of the drug from the patch and volume make-up with solvent. The solution is allowed to settle down for an hour, and the supernatant liquid is collected and subjected to a proper dilution to give the desired concentration. It is filtered using 0.2µm membrane filter and analyzed using suitable analytical techniques like UV, HPLC, etc.[23]

- **Percentage Elongation Break Test**

It is determined by calculating the length of the patch just before the break point.[23]

Percentage elongation = (final length-initial length)/initial lengthx100

➢ **Flatness**

A transdermal patch of drug must be possess a smooth surfacearea thatdoes not constrict with time. It can be studied by a flatness test. In this test, one strip is cut from the centre, and two strips are cuts from the right and left sides. The length of each strip is measured. The variation in length is measured by percentage constriction. If the percentage constriction is 0%, it indicates 100% flatness.[30]

% construction = (initial length -final length)/initial length x100

➢ **Thumb Tack Test**

It is one of the qualitative tests applied for the determination of the tack property of adhesives. Simplypress the thumb over the adhesive layer, and the relative tack property is determined.[23,31]

➢ **Rolling Ball Tack Test**

In this evaluation, the distance that a stainless steel ball travels along an upward-facing adhesive is measured. If the rolling is ball moving forward, it indicates the adhesive membrane is less tacky.[31]

➢ **Quick Stick (Peel Tack) Test**

It is used for the measurement of the peel force required to break the bond between the adhesive and the substrate by pulling the tape (adhesive layer) away from the substrate (stainless steel plate) at the speed of 12 inches per minute.[23]

➢ **Probe Tack Test**

The measurement of the force that is required to pull the probe away from the adhesive is lower at a fixed rate. It is expressed in grams.[16]

➢ **Peel Adhesion Properties**

The peel adhesion is known as the force required to remove the adhesive film from the substrates. The force required to pull a single-coated tape is measured in this test. The coat is must be applied to a substrate at 180^0C.[23]

➢ **Skin Irritation Test**

Skin permeation and sensitization testing involves the use of healthy rabbits. Theformulated patches are carefully applied on the skin of rabbits, specifically on the dorsal surface. Prior to attaching the patch, the hair is removed from the rabbits' skin. After duration of 24 hours, the

skin is meticulously observed and examined for any potential signs of irritation or adverse reactions.[16]

- **In-vitro Drug Release Studies**

The paddle over the slice system (USP outfitC) can be utilized for the assessment of the medicine release from the set patches. The dry film is cut to a specific size and the shape and it's counted directly, and the piece of cut patchesare fixedto a glass plate by using glue. Also, the plates are immersed in the 500ml of dissolution medium placed in the spherical vessel. The temperature is maintained at 30°-5°C, and the paddle was set at distance of 2.5cm from the glass plate at the bottom. RPM is fixed as 50. The samples are withdrawn at applicable time intervals up to 24 hours, and fresh medium is replaced during each slice. Also, the samples are analyzed by UV (HPLC) to determine the drug release.[23]

- **In-Vitro Drug Permeation Studies**

In-Vitro Drug Permeation Studies involve the use of a Franz diffusion cell. The experiment involves using abdominal skin from male Wistar rats with full thickness (weighing between 200-250 grams) as a semi-permeable membrane. To prepare the membrane, the abdominal skin is carefully isolated from the rat's abdomen and cleaned thoroughly. Any tissues and blood vessels present on the skin are removed. Next, the skin is equilibrated in a medium for 1 hour before the start of the experiments. It is then placed on a magnetic stirrer with a small magnetic needle to ensure uniform distribution of the diffusant. The temperature of the cell is maintained at 32°C ± 5°C using a thermostatically controlled heater. The isolated rat skin is then mounted between the donor and receptor compartments of the Franz diffusion cell, with the epidermis facing upward into the receptor compartment. A specified volume of medium is withdrawn from the receptor compartment and replaced with fresh medium at regular intervals. Finally, the samples collected from the receptor compartment are filtered and analyzed using UV or HPLC techniques to determine the permeation of the drug through the skin.[3]

- **Stability Studies:** It is carried out according to ICH guidelines. The prepared transdermal patches are stored at 40 + 0.5^{0}C and 75 + 5% RH for six months. The samples were withdrawn at 0, 30, 60, 90 and 180 days, and they were examined suitably for drug content.[16]

11. Application of TDDS[33,34,11]

1. The nicotine patch is highest-selling transdermal patch for the cessation of tobacco smoking. It was approved in 2007 as a vapor patch to reduce smoking.
2. Hormonal application:

- Oestrogenpatches are used to treat menopausal symptoms.
- Ortho Evra or Evra as a contraceptive patch.

3. Scopolamine patches areused for motion sickness.
4. For treatment of angina nitroglycerine patch is used.
5. Supplements of vitamin B12are also taken from the transdermal patch, i.e., Cynocobalaminepatch.
6. Caffeine patches are designed to deliver caffeine to the body through the skin.
7. In 2014, the United Kingdom 5-Hydoxytryptophan patchwas also launched.
8. The Exelon brand is used for treatment of Alzheimer's disease.

12. Currently Approved Trans-dermally Delivered Drugs

The TDD market has a considerable impact on the delivery of numerous drugs, primarily in the fields of pain management, hormonal applications, central nervous system disorders, cardiovascular diseases, and other applications, such as smoking cessation. The global transdermal drug delivery market is predicted to be quite large. Factors such as the prevalence of chronic diseases and technological improvements in transdermal drug delivery methods are leading this market forward. In 1979, the first transdermal patch for systemic delivery was approved in the United States (Transderm Scop; Novartis, Basel, Switzerland), a three-day patch that delivered scopolamine for the treatment of motion sickness. The most recent approved patch for severe pain is buprenorphine (Butrans; Purdue Pharma L.P., Stamford, CT, USA), approved by the FDA for the management of chronic pain that is non-responsive to other medications. In addition, several over-the-counter (OTC) products are also available, including nicotine, capsaicin, and menthol patches. In the year 2018, the first anti-histamine drug transdermal patch, Emedastine, Difumarate (Allesaga™ TAPE, Hisamitsu Pharmaceutical, Tosu, Japan), indicated to treat allergic rhinitis, was approved by the Japanese market system. It has a dose-dependent anti-histaminic action and a long-lasting effect that lasts up to 24 hours after administration. In the year of 2007, development of the first Parkinson's patch that contains rotigotine (Neupro™, UCB, Brussels, Belgium) was approved by the FDA as a once-daily patch that comes in four dose strengths: 2 mg, 4 mg, 6 mg, and 8 mg. Rivastigmine is currently FDA-approved for administration via a transdermal

patch (Exelon, Novartis) for the treatment of Alzheimer's disease; the patch overcomes gastrointestinal (GI) adverse effects associated with oral rivastigmine. Ortho Evra is an FDA-approved transdermal ethinyl estradiol and norelgestromin contraceptive patch. The application of patch is - once-a-week for three weeks (21 days), with one patch-free week included in the cycle. Apleek is a transdermal contraceptive patch containing 550 micrograms of ethinylestradiol and 2.10 mg of gestodene as active ingredients; its application is once a week for three weeks, followed by a seven-day patch-free period.[35]

13. Future Prospects for Transdermal Drug Delivery Systems

In recent times, there has been a significant focus on developing advanced transdermal delivery systems that utilize non- and minimally invasive technologies to improve drug delivery through the skin. These technologies include iontophoresis, microneedles, electroporation, and sonophoretic. Their aim is to enhance the delivery of drugs that traditionally face challenges in terms of low penetration flux and potency. However, the development of active patches utilizing these technologies has faced obstacles in terms of commercial success, technical issues, and customer acceptance. For example, the FDA-approved topical sonophoretic patch system called Iontocaine by Iomed was approved in 1995 but discontinued in 2005. Similarly, the ultrasound Sonoprep® and sonophoretic LidoSite® were approved in 2004 but discontinued in 2007 and 2008, respectively. Another instance is the i.d. powder injector called Zingo®, which was approved in 2008, withdrawn in the same year, and re-launched in September 2014. The only non-invasive glucose monitor approved by the FDA is the failed iontophoresis GlucoWatch Biographer®. One of the latest trends in drug delivery systems is the use of micro-needles, which have gained significant attention. They show promise in delivering antigens to the skin to induce antibody responses comparable to conventional intramuscular injections. Micro-needles have also been investigated for long-term treatment of opiate and alcohol dependence using naltrexone, an opioid antagonist. Additionally, a micro-needle patch coated with parathyroid hormonedeveloped by Zosano Pharma (formerly Macroflux® Alza Corporation) has demonstrated efficacy in Phase II clinical trials for the treatment of osteoporosis. In summary, the pharmaceutical industry is exploring various non- and minimally invasive technologies like iontophoresis, micro-needles, electroporation, and iontophoresis to improve drug delivery through the skin. However, despite initial successes and promising developments, several challenges have hampered the widespread commercialization of active patches utilizing these technologies. Nonetheless, ongoing research and development

continue to explore new avenues for effective and efficient drug delivery to overcome these obstacles.

Eventually, transdermal delivery systems, particularly transdermal patches, will be less commonly used in the pediatric population. A range of transdermal patches (i.e., about 10 medicines) have been used in children, and some have been specifically developed for pediatric use, as illustrated by the methylphenidate patch for the treatment of attention deficient hyperactivity complaints. Still, while transdermal delivery can be regarded as an accessible, non-invasive system of medicine delivery for term babies and aged children taking lower boluses than grown-ups, expression challenges remain for unseasonable babes with an immature skin barrier.[11]

CONCLUSION

Transdermal drug delivery offers a painless and convenient method of administering regular doses of various medications. It has the potential to effectively deliver a wide range of drugs, improving drug absorption while minimizing complications and side effects. Additionally, transdermal delivery is a cost-effective and user-friendly approach. Over the years, significant advancements have been made in the transdermal route of drug delivery, starting from its inception in 1981 up until the recent developments in 2022. This review article focuses on providing valuable information about transdermal drug delivery systems and the preparation of transdermal patches. It serves as a useful reference for researchers involved in the field of transdermal drug delivery systems.

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