Review Article

Transdermal Drug Delivery System: A Comprehensive Review

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ABSTRACT

Human societies have been applying cosmetic and therapeutic substances to the skin for thousands of years. A transdermal patch is an adhesive patch with medication applied to the skin that allows a prescribed dosage to enter the bloodstream through the skin. This frequently aids in the recovery of a damaged bodily part. A transdermal drug delivery system is a regulated medication applied to the skin that allows a certain amount of medication to enter the bloodstream through the skin. It is also noteworthy due to its intriguing advantages, which include reduced absorption, more consistent plasma levels, enhanced bioavailability, fewer adverse effects, and higher product quality and efficacy. With transdermal dosage forms, physicians may be able to provide their patients with more treatment options to increase their consideration. Transdermal drug delivery has an advantage over other forms of pharmaceutical delivery, including topical, intravenous, oral, and intramuscular.

Keywords: Transdermal drug delivery system, Epidermis, Systemic blood circulation.

INTRODUCTION

The medication Scopolamine was used to treat motion sickness in the first transdermal drug delivery (TDD) system, Transderm-Scop, which was created in 1980[1]. A membrane-moderated system is the transdermal device. This system uses a microporous polypropylene film as its membrane. The duration of this study release is three days[2]. Transdermal distribution is a desirable substitute for oral medication administration and is also on the verge of offering a substitute for hypodermic injections. There are several benefits to transdermal distribution over oral administration [3].

Transdermal drug delivery systems (TDDS) have emerged as a prominent method for noninvasive medication administration via the skin, compared to traditional needle-based injection techniques [4]. Transdermal Drug Delivery Systems (TDDS) have significantly influenced the administration of many therapeutic drugs, particularly in pain management, hormone therapy, and the treatment of cardiovascular and central nervous system disorders [5].

Since TDDS does not involve passage through the gastrointestinal tract, medications can be administered without interference from pH, enzymes, or intestinal flora, and there is no loss due to initial metabolism [6]. Most significantly, toddlers and the elderly can get medication safely and comfortably thanks to TDDS, a noninvasive administration technique that causes little discomfort or strain on patient [7]. There are numerous administration methods, including intravenous injection, mucosal administration, lung inhalation, oral administration, and transdermal administration, depending on the delivery method. The transdermal drug delivery system (TDDS) is one of the more appealing of these [8].

A transdermal medication delivery system is one that delivers drugs via the skin to achieve a systemic impact [9]. These dosage forms have a local therapeutic impact by delivering the medicine to the skin's reasonable epidermis and maybe dermal tissue [10]. Since many medications are now taken orally but aren't always as effective as intended, TDDS was developed in order to improve such characteristics[11].

Definition [12]

Transdermal patches, also known as skin patches, are medicated adhesive patches applied to the skin that allow a prescribed dosage of medication to enter the bloodstream through the skin.

Figure 1: Transdermal Patch [13]

Advantages of Transdermal Patches: [12, 14-20]

- Reduces dosing frequency.
- Topical patches are a non-invasive, painless method of delivering drugs straight into the body.
- Topical patches over extended periods of time for a regulated, consistent medicine distribution.
- Topical patches are reasonably priced.

- They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH, enzymatic activity and drug interactions with food, drink and other orally administered drugs.
- They are applicable to medications with a limited therapeutic window.
- It doesn't affect the stomach and intestinal fluids.
- Provides long-term control by maintaining steady and consistent blood levels.
- Decreased medication plasma concentration levels.
- Penetration can be enhanced through the skin using niosomes as drug carriers in transdermal drug delivery
- Use drug candidates with a low therapeutic index and a short half-life to minimize drug changes in plasma levels.

Disadvantages of Transdermal Patches:[14,21-24]

- The limitations of transdermal drug delivery are mainly associated with barrier function of skin, so it is limited to potent drug molecules.
- Chances to allergic reaction.
- High molecular drug level cannot attain therapeutic level.
- It is delivered to ionic drug.
- It requires significant lag time
- Transdermal drug delivery system cannot deliver ionic drugs
- It cannot achieve high drug levels in blood.
- It cannot develop for drugs of large molecular size
- It cannot deliver drugs in a pulsatile fashion.
- It cannot develop if drug or formulation causes irritation to skin.
- Possibility of local irritation at site of application.
- May cause allergic reaction.
- Sufficient aqueous and lipid solubility, a log P (octanol/ water) between 1 and 3 is required for permeating to transverse stratum corneum and underlying aqueous layer.

TRANSDERMAL ROUTE AND DRUG DELIVERY PROSPECTS:

Skin:

The largest organ:

With a surface area of over 2 square meters and a blood circulation rate of roughly one-third, skin is the biggest organ in the human body [26, 27]. With a thickness of only a few millimetres (2.97–0.28 mm), it is one of the body's most accessible organs and serves to isolate the external environment from the underlying blood circulation network. acts as a defense against attacks by microbes, chemicals, and physical forces maintains body temperature by acting as a thermostat[15]

Anatomy of Skin:

The skin is commonly categorized into three primary layers:[16]

(a) The outermost layer, known as the epidermis.

(b) The middle layer, referred to as the dermis; and

(c) The innermost layer, called the hypodermis.

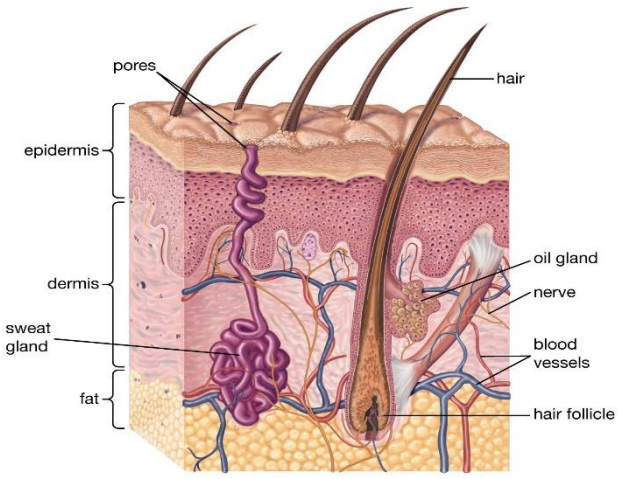

Figure 2: Structure of skin [27]

The 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 of the cells and the number of cell layers [14]. After emerging from red bone marrow, a Langerhans cell travels to the epidermis, where it makes up a small percentage of epidermis cells [11]. The dead cells of the stratum corneum, also known as the horny layer, the living or viable cells of the Malpighian layer (viable epidermis), and Markel cells are the smallest of the epidermal cells [26]. The epidermis layer, the primary layer of skin, is made up of living cells and is 150–200 mm thick [27].

It is made of five layers according to a degree of cell keratinizate on:

- Stratum corneum (SC, horny layer),
- Stratum lucidum (clear layer),
- Stratum granulosum (granular layer),
- Stratum spinosum (spinous or prickle layer)
- Stratum germinativum (basal layer)[27]

Stratum corneum:

This is the skin's outermost layer, sometimes referred to as the horny layer [26]. It is the rate-limiting barrier that prevents chemicals from moving both inward and outside. The components of the horny layer play a crucial role in determining its barrier nature: On a dry weight basis, there are 75–80% proteins, 5–15% lipids, and 5–10% ondansetron

material [26]. It varies in thickness over our body, with the soles of our feet and palms around 0.8 mm thick [27]. Tough proteins (70 percent keratin) and a small amount of fat (20 percent lipid) make up the stratum corneum. These proteins are linked to the water in this layer [28].

The Dermis:

The dermis, which is thicker than the epidermis and measures 3 to 5 mm, is situated beneath it The skin's appendages and sensory receptors are located in the dermis, which also supplies nutrition to the epidermis. One vital role of the cutaneous blood supply is to regulate body temperature. Along with eliminating waste and impurities, it also gives skin oxygen and nourishment [14]. As a result, the blood supply keeps the permeant's dermal concentration extremely low, creating the concentration gradient across the epidermis required for transdermal penetration [31].

It contains, such as:

1. Blood vessels
2. Hair follicles
3. Sweat glands
4. Sebaceous glands
5. Nerve endings
6. Collagen and elastin fibers [16]

This layer provides little resistance for most medications that dissolve in water, which facilitates the medications' passage through. However, this layer may make it more difficult for a medication to pass through if it is greasy, like some lotions or creams [32].

Subcutaneous tissue (Hypodermis): -

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis[14]. Sedate is required for transdermal drug delivery. penetrate all three of these layers and enter the underlying flow, but if topical medicine delivery occurs, just entering via the stratum corneum is essential, and then keeping the medication in the skin layers is desired [33].

TYPES OF TRANSDERMAL PATCH: [12,14,34,20,35]

1. Single-layer Drug-in-Adhesive
2. Multi-layer Drug-in-Adhesive
3. Reservoir
4. Matrix
5. Vapour Patch
6. Microreservoir system

1. Single-layer Drug-in-Adhesive:

The adhesive layer of this system contains drug [12]. However, the adhesive layer is also responsible for the drug's release to the epidermis, in addition to adhering the numerous layers together [14]. The adhesive layer in this kind of patch is in charge of both releasing the medication and holding the several layers and the complete system to the skin. A backing and a temporary liner encircle the adhesive.

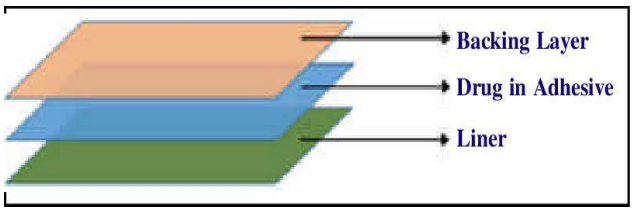

Figure 3: Single-layer Drug-in-Adhesive [12]

2. Multi-layer Drug-in-Adhesive: [12]

The multi-layer drug-in adhesive patch resembles the single-layer method in that both adhesive layers facilitate drug release. The multi-layer system is distinct in that it includes an additional layer of drug-in-adhesive, often partitioned by a membrane, but this is not universally applicable. This patch has a temporary liner layer and a permanent backing.

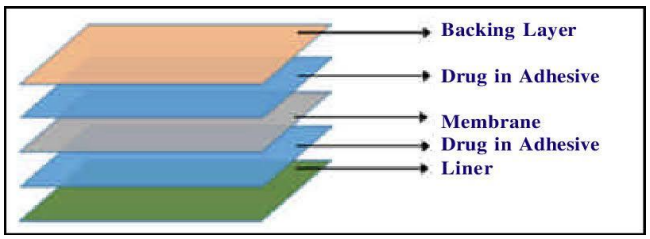

Figure 4: Multi-layer Drug-in-Adhesive [12]

3. Reservoir:

This system embeds the drug reservoir between a rate-controlling membrane an impermeable backing layer [14]. Only the rate-controlling membrane, which may be microporous or nonporous, allows the medicine to be released. The drug may be in the form of gel, suspension, solution, or dispersion within a solid polymer matrix within the drug reservoir compartment. It is possible to use hypoallergenic adhesive polymer as a drug-compatible outer surface polymeric membrane [14].

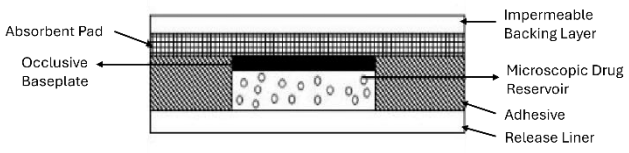

Figure 5: Reservoir [36]

4. Matrix:

i. Drug-in-adhesive system:

This kind of drug reservoir is created by spreading the drug after it has been dispersed in an adhesive polymer. Formulated adhesive polymer on an impermeable backing layer by solvent casting or melting (for hot-melt adhesives). For protection, unmediated sticky polymer films are put on top of the reservoir [34].

ii. Matrix-dispersion system:

This kind of medication is uniformly distributed within a matrix of hydrophilic or lipophilic polymers. In a compartment made of a drug-impermeable backing layer, this drug-containing polymer disc is fixed to an occlusive base plate. To create a strip of adhesive rim, the adhesive is placed around the outside of the drug reservoir rather than on its face [34].

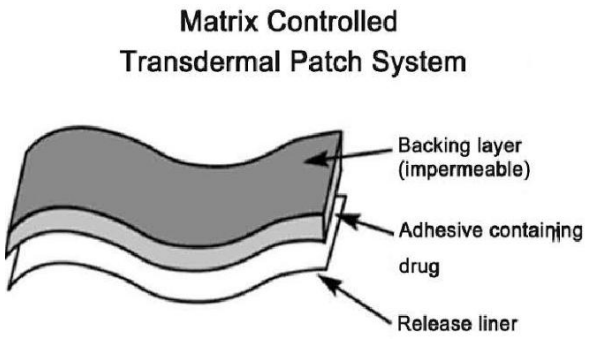

Figure 6: Matrix [37]

5. Vapour Patch:

The adhesive layer in this kind of patch releases vapour in addition to holding the different layers together. The essential oils are released by the recently released vapour patches for a maximum of six hours. Mostly utilised for decongestion, the vapour patches release essential oils. Other controller vapour patches that enhance sleep quality are available on the market [34].

6. Microreservoir system:

This kind of drug delivery device combines matrix-dispersion and reservoir technologies. Thousands of inaccessible, microscopic spheres of drug reservoirs are created by first suspending the drug in an aqueous solution of a water-soluble polymer and then uniformly spreading the solution in a lipophilic polymer. Using cross-linking agents to instantly cross-link the polymer in situ stabilizes this thermodynamically unstable dispersion [34].

BASIC COMPONENETS OF TRANSDERMAL DRUG DELIVERY SYSTEMS:

The components of Transdermal devices include [38, 39]

1. Polymer matrix
2. Drug
3. Permeation enhancers
4. Other excipient

1. Polymer Matrix:

The polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in a Transdermal system. Possible useful polymers for Transdermal devices are:

Table 1: Showing different types of polymers [20]

Natural polymer	Synthetic elastomer	Synthetic polymer
Cellulose derivatives, Zein, Gelatin, Waxes, Proteins, Gums, Natural rubber, Starch.	Polybutadiene, Hydrin rubber, polysiloxane, silicone rubber, Nitrile, Acrylonitrile, Butylrubber, Neoprene, Styrenebutadiene etc.	Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyvinylpyrrolidone, Polymethyl methacrylate, Epoxy, Polyurea, etc.

2. Drug: [44]

The transdermal route is highly advantageous for drugs with suitable pharmacology and physical chemistry. Transdermal patches are particularly beneficial for drugs susceptible to extensive first-pass metabolism, those with narrow therapeutic windows, or drugs with short half-lives causing non-compliance due to frequent dosing. Recent approvals for transdermal delivery include drugs like rivastigmine for Alzheimer's and Parkinson's dementia, rotigotine for Parkinson's, methylphenidate for attention deficit hyperactivity disorder, and selegiline for depression.

The following are some of the desirable properties of a drug for Transdermal delivery.

Physicochemical Properties:

- The drug should have a molecular weight less than approximately 1000 Daltons.
- The drug should have affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.
- The drug should have a low melting point.

Biological Properties:

- The drug should be potent with a daily dose of the order of a few mg/day
- The half-life (t1/2) of the drug should be short.
- The drug must not induce a cutaneous irritation or allergic response.
- Drugs, which degrade in the GI tract or are inactivated by hepatic first-pass effect, are suitable candidates for Transdermal delivery 40.

3. Permeation Enhancers

By changing the skin's function as a barrier to the flow of a desired penetrant, these substances increase skin permeability. Conveniently, these fall into the following primary categories:

a. Solvents [40]

These substances enhance penetration, either by fluidizing lipids or by snatching up the polar route.

b. Surfactants

These substances are thought to improve the transport of hydrophilic medicines via the polar pathway. The length of the hydrocarbon chain and the polar head group determine a surfactant's capacity to change penetration

c. Various substances

These consist of calcium thioglycolate, N, N-dimethyl-m-toluamide, urea, a moisturising and keratolytic agent, and anticholinergic substances.

4. Other excipient

a. Adhesives: [2]

The adherence of transdermal devices to the skin has thus far been accomplished using a pressure-sensitive adhesive. The pressure-sensitive adhesive may be applied to the front or back of the device, extending peripherally.

- Both adhesive systems must meet the following criteria:
- They should neither irritate or sensitize the skin, nor disrupt the natural skin flora.

- Should adhere tightly to the skin during the dosage time, being undisturbed by activities such as bathing or exercise.

b. Backing Membrane: [2]

Backing membranes are flexible and offer a good bind to the drug reservoir, preventing the drug from exiting the dosage form through the top, and allowing printing. It is impermeable and protects the product while it is on the skin, such as a metallic plastic laminate, a plastic backing with an absorbent pad and an occlusive base plate (aluminum foil), or an adhesive foam pad (flexible polyurethane) with an occlusive base plate.

c. Release Liner: [41]

During storage, the release liner prevents the medicine from migrating into the adhesive layer and becoming contaminated. As a result, it is regarded as part of the principal packing material rather than a component of the dosage form used to administer the medicine. The release liner consists of a base layer that can be nonocclusive (paper fabric) or occlusive (polyethylene and polyvinyl chloride) and a release coating layer comprised of silicon or teflon. Other materials utilized for TDDS release liners include polyester foil and metallized laminate.

TECHNOLOGIES FOR DEVELOPING TRANSDERMAL DRUG DELIVERY SYSTEMS: [42,43,14]

Several technologies have been successfully developed to manage the rate of medication release and skin permeability. These technologies can be divided as four fundamental techniques.

1. Polymer membrane permeation-controlled TDD Systems:

TDD Systems with Polymer Membrane Permeation Control In this device, the drug reservoir is sandwiched between a drug-impermeable metallic plastic laminate and a rate-regulating polymeric membrane. The drug molecules can only be released through the rate-controlled polymeric membrane [42]. The rate-controlling membrane can be microporous or nonporous polymeric membrane, such as ethylene-vinyl acetate copolymer, with drug permeability. A thin layer of drug-compatible, hypoallergenic pressure-sensitive adhesive polymer, such as silicone adhesive, may be placed to the external surface of the polymeric membrane to create close contact between the TDD system and the skin surface [43].

2. Polymer matrix Diffusion-Controlled TDD Systems:

By uniformly dispersing the drug particles in a hydrophilic or lipophilic polymer matrix, this method creates a drug reservoir. The resulting medicated polymer is then moulded into medicated discs with a predetermined surface area and regulated thickness. A compartment made of a drug-impermeable plastic backing is then used to place the drug reservoir with polymer disc onto an occlusive base plate. This approach creates an adhesive rim around the medicated disc by applying the adhesive polymer around the patch's perimeter [42].

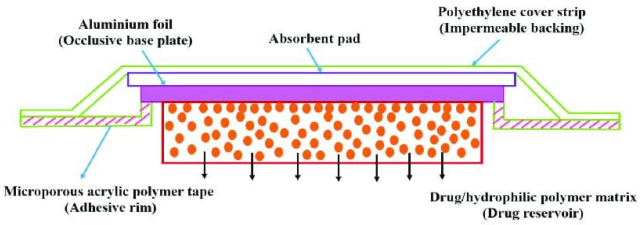

Figure 7: Nitro-Dur Transdermal System [45]

3. Drug Reservoir Gradient-Controlled TDD Systems:

To solve the non-zero-order drug release profiles, polymer matrix drug dispersion-type TDD system can be adjusted to have the drug loading level altered in an incremental way, generating a gradient of drug reservoir along the diffusional channel across the multilaminate adhesive layer[2]

4. Microreservoir Dissolution-Controlled TDD Systems:

This type of delivery method is a mix of reservoir and matrix dispersion systems. In this method, the drug reservoir is formed by first suspending the drug solids in an aqueous solution of a water-miscible drug solubilizer, such as polyethylene glycol, and then homogeneously dispersing the drug suspension, with controlled aqueous solubility, in a lipophilic polymer using high shear mechanical force to form thousands of unleachable, microscopic drug reservoirs. This thermodynamically unstable dispersion is promptly stabilized by crosslinking the polymer chain in situ, resulting in a medicated polymer disc with a constant surface area and thickness[2].

VARIOUS METHODS FOR PREPARATION OF TRANSDERMAL DRUG DELIVERY SYSTEM:

1. Asymmetric TPX membrane method: [46]

A prototype patch for this heat sealable polyester film (type 1009, 3m) with a 1cm diameter concave will be utilized as the backing membrane. Drug samples are dispensed into the concave membrane, covered by a TPX {poly(4-methyl-1-pentene)} asymmetric membrane, and sealed with an adhesive.

2. Asymmetric TPX membrane preparation: [47]

The preparation of asymmetric TPX membranes involves the dry/wet inversion process. This process begins with the dissolution of TPX in a mixture of cyclohexane solvent and nonsolvent additives at a temperature of 60°C, resulting in a polymer solution. The polymer solution is then maintained at a temperature of 40°C for a period of 24 hours. Following this, the solution is cast onto a glass plate to a predetermined thickness using a gardener knife. The casting film is subsequently evaporated at a temperature of 50°C for a duration of 30 seconds. Immediately after evaporation, the glass plate is immersed in a coagulation bath maintained at a temperature of 25°C. After 10 minutes of immersion, the membrane is removed and subjected to air drying in a circulation oven at a temperature of 50°C for a period of 12 hours.

3. Circular teflon mould method: [48, 49]

In an organic solvent, solutions with different ratios of polymers are employed. Half the amount of the same organic solvent is used to dissolve the calculated amount of medication. The remaining half of the organic solvent is used to dissolve enhancers at varying concentrations, which are then added. A plasticizer called di-n-butyl phthalate is added to drug polymer solutions. After 12 hours of stirring, the entire mixture should be placed into a circular teflon mould. The moulds are placed on a leveled surface and covered with an inverted funnel to control solvent vaporization in a laminar flow hood model with speed of air 1/2 m /sec. The solvent is allowed to evaporate for 24 h. Before evaluation, the dried films are to be stored for another 24 h at 25±0.5 °C in a desiccator containing silica gel before to eliminate aging effects. These types of films are to be evaluated within one week of their preparation.

4. Mercury substrate method: [50]

This method involves dissolving the medication in a polymer solution with plasticizer, stirring the mixture for 10 to 15 minutes to create a uniform dispersion, and then pouring the mixture onto a leveled mercury surface. To regulate solvent evaporation, the solution is covered with an inverted funnel.

5. By using “IPM membranes” method: [51]

Using a magnetic stirrer, the medication is dissolved in a solution of water and propylene glycol that contains the carbomer 940 polymer and stirred for 12 hours. Triethanolamine is to be added to neutralize the dispersion and make it viscous. If the drug's solubility in aqueous solution is extremely low, solution gel can be generated using buffer pH 7.4. The IPM membrane will integrate the gel that has been created.

6. By using “EVAC membranes” method: [52]

Polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes, and 1% Carbopol reservoir gel can all be utilized as rate control membranes to produce the intended transdermal therapeutic system. Gel is made with propylene glycol if the medication is insoluble in water. The medication is dissolved in propylene glycol, and then Carbopol resin is added. A 5% w/w sodium hydroxide solution is used to neutralize the mixture. The medication (in gel form) is applied to the designated region on a backing layer sheet. To create a leak-proof device, a rate-controlling membrane will be positioned over the gel and the edges will be heated to seal.

7. Aluminium backed adhesive film method: [53]

Transdermal drug delivery systems can be unstable if the dose exceeds 10mg. A reliable method for preparing these systems involves using an aluminum-backed adhesive film. Chloroform is the preferred solvent, as it can dissolve most drugs and adhesives. To prepare the system, the drug is first dissolved in chloroform, and then the adhesive material is added and dissolved. A custom-made aluminum former, lined with aluminum foil and sealed with cork blocks. Once cast, the solvent is allowed to evaporate, leaving a thin film. This film is then removed from the aluminium former, cut into desired shapes and sizes, and used as transdermal patches.

8. Preparation of TDDS by using Proliposomes: [54, 55]

The preparation of Transdermal Drug Delivery Systems (TDDS) using proliposomes involves a carrier method with film deposition technique. An optimized ratio of drug to lecithin, 0.1:2.0, is utilized. To initiate preparation, 5mg of mannitol powder is placed in a 100ml round-bottom flask, which is then heated to 60-70°C and rotated at 80-90 rpm. The mannitol is dried under vacuum for 30 minutes. Following drying, the temperature is adjusted to 20-30°C. A solution of drug and lecithin in an organic solvent mixture is then introduced into the flask in two 0.5ml aliquots, with complete drying occurring between additions. The resulting proliposome-containing flask is subsequently attached to a lyophilizer. The drug-loaded mannitol powders, or proliposomes, are stored overnight in a desiccator and then sieved through a 100 mesh screen. Finally, the gathered powder is stored in a glass bottle at freezing temperatures prior to characterization.

9. By using free film method: [56]

Casting on the surface of mercury creates a free film of cellulose acetate. Chloroform should be used to create a 2% w/w polymer solution. A 40 % w/w concentration of polymer weight is required for the incorporation of plasticizers. A glass ring set over the mercury surface in a glass petri dish was filled with five millilitres of the polymer

solution. An inverted funnel is placed over the petri dish to regulate the solvent's rate of evaporation. After the solvent has completely evaporated, the mercury surface is examined to observe the film creation. Before being used, the dry film will be separated and kept in a desiccator between the wax paper sheets. Free films of different thickness can be prepared by changing the volume of the polymer solution.

ROUTES OF DRUG PENETRATION THROUGH SKIN:

There are two main routes by which drugs can penetrate the skin: through the skin's outer layer (transepidermal pathway) or through hair follicles, sweat glands, and other skin appendages (transappendageal pathway):

Drugs can penetrate the skin through two main pathways:

1. Transepidermal Pathway: [57]

This pathway involves drugs passing through the skin's outermost layer, the stratum corneum. There are two sub-routes:

- Intra-cellular Route: Water-soluble drugs can pass through specialized skin cells called corneocytes.

- Inter-cellular Route: Fat-soluble drugs can travel through the spaces between skin cells, passing through the skin's fatty layer.

2. Transappendageal Pathway:[58,59]

The Transappendageal Pathway allows drugs to penetrate the skin through tiny openings, specifically:

- Sweat glands

- Hair follicles

These small tunnels provide an alternative route for certain substances to pass through the skin.

Penetration Enhancers:

Substances used to increase the permeability of active chemicals, like medications, via the skin are known as penetration enhancers, permeation enhancers, or skin penetration enhancers. They work by momentarily altering the composition and characteristics of the stratum corneum, the outermost layer of the skin. This change increases the efficacy of topical treatments by facilitating improved absorption of the active substances into the bloodstream or deeper layers of the skin.

- Transdermal Patch [60, 61,62]

A transdermal patch is a device that sticks to the skin and delivers a controlled dose of medication into the bloodstream. This innovative design helps patients who struggle with swallowing tablets or receiving injections, as patches provide a convenient and prolonged release of medication. Unlike tablets, patches can remain effective for an extended period, reducing the need for frequent dosing. Transdermal patches are versatile and widely used in various medical treatments, including:

- Pain management

- Heart disease treatment

- Smoking cessation

- Motion sickness management

- Hormone replacement therapy

EVALUATION PARAMETERS:

1. Interaction studies: [63-65]

Excipients play a crucial role in pharmaceutical products, and their compatibility with the active drug is essential to ensure stability and effectiveness. To guarantee the quality of the final product, it's vital to identify any potential physical or chemical interactions between the drug and excipients, as these can impact the drug's bioavailability and stability. When new or untested excipients are used in a formulation, conducting compatibility studies is a critical step in the development process.

2. Thickness of the Patch: [66-69]

The depth of the drug-loaded patch is measured at various points using a digital micrometer to determine the average depth and standard deviation.

3. Weight Uniformity: [66, 68,70-72]

The prepared patches are dried at 60°C for 4 hours before evaluation. A specified area of the patch is cut into different parts and weighed using a digital scale. The average weight and standard deviation values are calculated from individual weights.

4. Folding Endurance: [66, 73-75]

This evaluation determines the patch's ability to withstand repeated folding. Folding Endurance is assessed by folding the film at the same point until it breaks. The number of folds the film withstands without breaking is considered its flexural strength value.

5. Percentage Moisture content: [66, 67]

Prepared films are individually weighed and stored in a desiccator with fused calcium chloride at room temperature for 24 hours. After 24 hours, the films are reweighed, and the percentage moisture content is calculated using the formula:

Percentage moisture content = [(Initial weight - Final weight) / Final weight] × 100.

Where:

- Initial Weight = Weight of the sample before drying

- Final Weight = Weight of the sample after drying.

6. Percentage Moisture Uptake: [66, 69,76,77]

To maintain 84% relative humidity, the weighed films must be stored in desiccators with saturated potassium chloride solution at room temperature for 24 hours. The films must be reweighed after a day to calculate the percentage

moisture uptake using the formula below. [Final weight-Initial weight/Initial weight] x 100 is the percentage of moisture uptake.

7. Drug content: [23, 78,79]

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug contain with the suitable method (UV or HPLC technique). Each value represents an average of three different samples.

8. Uniformity of dosage unit test: [80]

An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2um membrane filter and analyzed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated.

9. Polariscope examination: [80]

This test is to be performed to study the drug crystals from patch using polariscope. A particular surface area of the piece is to be kept on the object slide and observe for the drugs crystals to identify whether the drug is present as crystalline form or amorphous form in the patch.

10. Shear Adhesion test: [80]

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

11. Peel Adhesion test: [22, 80]

Peel adhesion is the term used in this test to describe the force needed to remove an adhesive covering from a test substrate. The variables that influenced the peel adhesion qualities were the adhesive polymer's molecular weight and the kind and quantity of additives. The force needed to remove a single piece of tape is measured after it has been attached to a stainless-steel plate or any preferred backing membrane. The tape is then peeled from the substrate at a 180º angle.

12. Thumb tack test: [80, 81]

The force required to remove thumb from adhesive is a measure of tack.

13. Flatness Test: [82,83]

Each film should have three longitudinal strips cut out of it at different points, such as the centre, left, and right. 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 caused by non-uniformity in flatness.

14. Percentage Elongation Break Test: [85, 86]

To find the percentage elongation break, measure the length immediately preceding the break point. The formula below can be used to calculate the percentage elongation.

Elongation percentage = [L1-L2 / L2] × 100

Where, L1 is the final length of each strip and

L2 is the initial length of each strip.

15. Tack properties: [87]

It refers to the polymer's capacity to stick to a substrate with minimal contact pressure. Tack is influenced by the polymer's molecular weight, composition, and application of tackifying resins.

16. Probe Tack test: [70,86,88]

In this test, the adhesive is applied to the tip of a clean probe with a specified surface roughness, and the probe and adhesive are then allowed to bond. It is mechanically broken when the probe is subsequently removed. Tack, which is measured in grammes, is the force needed to remove the probe from the adhesive at a set rate.

17. In vitro drug release studies: [63,89,90,91]

The drug release from the produced patches can be evaluated using the paddle over disc method (USP equipment V). Dry films of a given thickness must be cut into precise shapes, weighed, and adhered to a glass plate. After that, the apparatus was equilibrated to 32± 0.5°C and the glass plate was submerged in 500 mL of the phosphate buffer or dissolving media (pH 7.4). After that, the paddle was positioned 2.5 cm away from the glass plate and ran at 50 rpm. 5-mL aliquots of samples can be taken out at suitable intervals for up to 24 hours and subjected to HPLC or UV spectrophotometer analysis. The mean value can be computed, and the experiment must be carried out in triplicate.

18. In vivo Studies: [63, 70,92]

Transdermal patches can be assessed in vivo for Drug performance is accurately depicted by in vivo evaluations. In Vivo investigations allow for a thorough exploration of the variables that are not possible to consider in vitro. Human volunteers or animal models can be used to evaluate TDDS in vivo.

19. Skin Irritation Study: [68]

Healthy rabbits (average weight 1.2 to 1.5 kg) can be used for skin irritation and sensitization tests. The rabbit's dorsal surface (50 cm2) should be cleaned. Hair should be shaved from the clean dorsal area, and the surface should be cleaned with rectified spirit and representative formulations applied to the skin. After a day, the patch

must be taken off, and the skin must be examined and categorized into five grades according to the extent of the skin damage. To ensure adequate skin absorption and penetration, the drug should typically be non-ionic and relatively lipophilic to effectively traverse the skin barrier [84].

CONCLUSION

This article provides an valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who are involved in TDDS. Transdermal drug delivery is a painless, convenient, and potentially effective way to deliver regular doses of many medications. Successful transdermal drug application requires numerous considerations. Bearing in mind that the basic functions of the skin are protection and containment, it would seem exceptionally difficult to target the skin for drug delivery. TDDS used for the used for drug therapy for less absorption, more uniform plasma levels, improved bioavailability, decrease side effect, efficacy and quality of the product. A patch has some simple components, which perform a vital role in the release of drug through the skin. Future prospective of TDDS would be focused on the controlled therapeutic use.

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