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Review Article

A Review on Transdermal Drug Delivery System; Design, Evaluation, and Approach towards Painless Drug Delivery

Muhammad Shahid Latif, Asif Nawaz*, Muhammad Khursheed Alam Shah, Asif Iqbal

Advanced Drug Delivery Laboratory, Gomal Centre of Pharmaceutical Sciences, Faculty of Pharmacy, Gomal University, Dera Ismail Khan, 29050, Pakistan.
*Correspondence: asifnawaz676@gmail.com

Abstract

Transdermal drug delivery systems were developed to overcome the difficulties associated with oral drug delivery. Transdermal patches deliver medications into the bloodstream through an adhesive patch affixed to the skin. This treatment may benefit damaged areas of the body. Unlike oral, topical, intramuscular, and intravenous drug delivery methods, transdermal drug delivery enables controlled drug release into the body. A transdermal delivery system increases patient compliance and avoids first-pass metabolism, which makes it superior to injectable and oral delivery methods. Drugs with short biological half-lives are also continuously administered via transdermal delivery, avoiding pulsed entry into systemic circulation that may cause undesirable side effects. Body heat is used to melt thin layers of medication embedded in the adhesives through the transdermal patch's porous membrane. As a barrier against foreign invaders, the skin serves as a protective layer. A medication with a molecular weight of less than 500 Da can penetrate the stratum corneum through the outermost layer of the skin. Because the skin is a highly effective barrier, transdermal delivery systems can only deliver medications with molecules small enough to penetrate it. As a result, only medications with small molecules can be delivered this way. In recent years, transdermal patches have become available for various pharmaceutical products. This review article discussed transdermal patches, including matrix patches, reservoir patches, membrane patches, micro reservoir patches, and adhesive patches containing drugs. These dosage forms have also been evaluated using various methods. In this article, we also explored the already significant impact this field has made on the administration of many pharmaceutical products, discussed limitations of the current technology, and deliberated over methods under exploration to overcome these limitations and address the challenges ahead.

Keywords: Transdermal patches, micro-reservoir patches, drug-in-adhesive patches, reservoir patches, transdermal drug delivery, matrix patches.

1. Introduction

Skin-based drug delivery has been proven effective and efficient. The stratum corneum, epidermis, and dermis are the three layers of human skin. In the dermis, nerves, blood vessels, connective tissues, sebaceous glands, sweat glands, and hair follicles are located. Differentiation constantly occurs in the epidermis (Hmingthansanga et al. 2022). Skin's stratum corneum, the outermost lipophilic layer, is a major barrier to percutaneous penetration. There are embedded corneocytes and a lipid-rich matrix in the stratum corneum (Nesovic, Shakya, and Gill 2022). The stratum corneum is comprised of 10 μm to 15 μm. The transdermal administration of hydrophilic, hydrophobic, and macromolecule drugs is currently widespread (Mdanda et al. 2021). Drug delivery by transdermal means is an effective, painless, and self-administered method (Shravanth et al. 2021). By using transdermal drug delivery, patients experience no pain and require

less medication to achieve peak plasma concentrations than by using parenteral or oral routes (Ng and Gupta 2020). Drugs with a shorter half-life are ideal for transdermal administration (Jasti, Abraham, and Ghosh 2021). Transdermal patches bypass the stomach and liver and boost patient compliance (Patel et al. 2018).

Transdermal patches bypass 1st pass effect and are considered to be a safe route of drug administration for patients with hepatic impairment (Ramadon et al. 2022). To overcome the stratum corneum barrier, several technologies have been developed over the past three decades. Among these, electroporation (Zaid Alkilani, McCrudden, and Donnelly 2015), iontophoresis (Wang et al. 2022), microneedles (Ye et al. 2018), sonophoresis (Huang et al. 2015), magnetophoresis (Benson et al. 2019) and the use of chemical penetration enhancers (Kapoor et al. 2018). A transdermal patch can be formulated with a wide variety of medications and can alter the pharmacokinetic profile of the drugs. Only a few molecules can cross the stratum corneum because of its brick-and-mortar nature (Choudhury et al. 2017). The active pharmaceutical ingredients used in transdermal patches, most of which have been introduced into clinical practice, are predominantly lipophilic and do not exceed 500 Da in molecular weight (Wang et al. 2022).

2. Human Skin

The skin is the largest organ by surface area in the human body, covering about 2 m^2 and making up about 15 percent of the body's weight (Manevski et al. 2015). Human skin is comprised of 2mm thickness on average (Mendoza-Garcia et al. 2015). Human skin is thickest at the sole, palm, and interscapular regions and thinnest in the other regions of the body, i.e., the penis and eyelids. The pH of the skin surface is about 5.

There are three main layers to the skin.

a. Epidermis

The epidermis is composed of squamous epithelial tissues containing high keratin (Zhang 2018). In the epidermis, there are no blood vessels or nutritional sources. The epidermis is composed of two basic layers: the viable and the nonviable.

b. Dermis

The dermis lies underneath the stratum basale of the epidermis and is the second main layer of skin. The dermis, with a thickness of 1 mm to 4 mm, is thicker than the epidermal layer of the skin. A well-developed system of blood circulation and nervous system is attached to this hydrophilic layer of the skin, similar to that of the viable inner epidermis (Knöbel, O'Toole, and Smith 2015). Additionally, it contains mucopolysaccharides that entrap collagen fibers and elastin proteins, causing the dermis to be thicker and bulkier than the epidermis. In addition to having immune cells, the dermis also exhibits flexibility and strength in the skin.

Surface papillary layers and deeper reticular layers make up the epidermis. There are blood vessels, lymphatics, and nerve endings in the papillary layer. The papillae are finger-like projections of the epidermis surrounded by rete ridges. Communication occurs through these projections (Deo and Deshmukh 2018). The reticular layer lies beneath the papillary layer and contains fibroblasts, mast cells, elastic fibers, and reticular fibers. This skin layer comprises sebaceous glands and sweat glands and is embedded with reticular fibers and elastic fibers. Dermis also regulates temperature, pressure, and pain, providing mechanical support and elasticity (Foster et al. 2017).

c. Hypodermis

The innermost layer of the skin is the hypodermis, and its function is to connect body organs to the skin. The hypodermis contains hair follicles of smooth muscles and loose structures of connective tissues. The hypodermis serves as an insulator and plays an important role in the process of thermoregulation by preventing excessive heat loss from the body and cold environments (Gilaberte et al. 2016).

3. Transdermal Patches

Drugs are delivered to the bloodstream via transdermal patches, which are placed over the skin (Tanwar and Sachdeva 2016). The FDA approved transdermal patches in 1981 (Ghulaxe and Verma 2015). Scopolamine was delivered as controlled systemic absorption, and nitroglycerin was delivered as controlled systemic absorption to prevent motion sickness and angina pectoris (Bathe and Kapoor 2015).

More than 25 transdermal products have been developed over the last two decades. These products had a value of $ 3.2 billion in 2002 and were expected to reach $ 4.5 billion in 2008 (Shen and Burgess 2015). A total of $ 7.22 billion was generated from the transdermal skin patch market in 2021. As of 2027, transdermal patches are expected to reach a value of $9.57 billion on the global market (Ramesh et al. 2021). Recent developments in certain dosage forms have been aimed at improving Induces drug diffusion by enhancing skin permeability and thermodynamic activity. Among these approaches are supersaturated systems, penetration enhancers, liposomal vesicles, and pro-drugs (Williams 2021). Nicotine patches, which release nicotine to help people quit smoking, were the most popular transdermal patches in the United States last year (Adams and Hudmon 2018). In addition to delivering nicotine over sixteen hours, the nicotine patch also suppresses the desire to smoke cigarettes continuously (Prochaska and Benowitz 2016). For three days, scopolamine patches release alkaloids into the body, preventing motion sickness without having to swallow tablets.

In addition to preventing motion sickness, the scopolamine patch releases alkaloids for three days, so there is no need to swallow tablets continuously. The motion sickness was prevented with the use of a scopolamine transdermal patch. The patch releases alkaloids for a time interval of three days (Leung and Hon 2019). In addition to providing long-lasting pain relief, the fentanyl patch has exhibited a 72-hour acting time. It's a blessing for women who find taking a pill every day onerous to use an estrogen-progestin patch once a week (Galzote et al. 2017).

European governments approved commercially available vapor patches for smoking cessation in 2007 (Zhu et al. 2017). The rivastigmine patch was the first transdermal treatment for Alzheimer's disease (Nguyen et al. 2021). The transdermal patch facilitates the delivery of drugs across the skin simply and effectively. Through transdermal patches, drugs are delivered at a controlled rate, keeping blood concentrations constant (Malaiya et al. 2018). Due to the skin barrier nature, transdermal patches can only deliver molecules of smaller particle size, resulting in only molecules with smaller particle sizes (Uchechi, Ogbonna, and Attama 2014).

4. Components of Transdermal Patches

4.1. Polymers Matrixes

Drug release from transdermal patches is facilitated by polymers used in their formulation. Throughout the shelf life of the patch, the polymers should deliver the drugs effectively and consistently. Transdermal patches must be prepared using polymers that are physically and chemically compatible with the components and drug used in the formulation (Al Hanbali et al. 2019).

In the formulation of transdermal patches, the following types of polymers are commonly used.

a) ***Natural Polymers:*** e.g., Gums, natural chitosan, gelatin, shellac, and different derivatives of cellulose.

b) ***Synthetic Elastomers:*** e.g., acrylonitrile, silicon rubber, butyl rubber, polybutadiene, hydrin rubber, neoprene, and butyl rubber.

c) ***Synthetic Polymers:*** e.g., polyurea, polyacrylate, polyamide, polyvinylchloride, polyvinylpyrrolidone, polymethylmethacrylate, polyvinylalcohol, and polyethylene.

4.2. Drugs

To develop a successful transdermal patch, drug selection is crucial. Several factors should be considered when formulating transdermal patches, as shown in Tables 1 and 2.

Table 1. Properties of drugs used in transdermal drug application (Wang et al. 2022).

S.No	Parameter	Properties
1	Dose	Should be low in weight (less than 20 mg/day)
2	Half-life	10 / less (h)
3	Molecular weight	<400da
4	Skin permeation coefficient	<0.5 × 10-3 cm/h
5	Skin Reaction	Non-irritating Non-sensitizing
6	Oral bioavailability	Low

4.3. Permeation Enhancers

Transdermal patches using penetration enhancers enable the patients to achieve therapeutic levels of drug plasma concentrations by increasing the stratum corneum's permeability and enhancing the stratum corneum's permeability. Permeation enhancers help drug permeate the skin by disrupting the highly ordered structure of stratum corneum lipid, interacting with intercellular protein, or improving the drug's partition into stratum corneum. Permeation enhancers enhance drug permeability by altering the stratum corneum's structure (Kováčik, Kopečná, and Vávrová 2020).

There are three types of penetration enhancers:

a) Solvents

The solvent in transdermal patches facilitates penetration by fluidizing lipids and altering stratum corneum structure, e.g., dimethyl formamide, propylene glycol, silicone fluids, isopropyl palmitate, methanol, ethanol, and laurocapram (Azone) (Gupta et al. 2012).

b) Surfactants

The effect of surfactants on the transport of hydrophilic drugs is to enhance the transport of polar pathways. Changes and penetration functions are determined by hydrocarbon chains and polar head groups. In addition, ions and surfactants can alter surface properties, including sodium lauryl sulfate, pluronic f127, pluronic f68, dioctyl sulphosuccinate, sodium ms taurocholate, sodium deoxycholate, and Decodecylmethyl sulphoxide, etc. (Shaker et al. 2019).

c) Chemicals

Transdermal patches are formulated with calcium thioglycolate agents, keratolytics, hydration agents, N-dimethyl-m-toluamide, as well as anticholinergic agents and urea (Al Hanbali et al. 2019).

d) Properties of permeation enhancers used in the formulation of transdermal patches

- Transdermal patches should be prepared with permeation enhancers that are cosmetically acceptable
- Transdermal patches should not contain permeation enhancers that bind to receptors.
- It is important that the permeation enhancers used in transdermal patches are non-allergic, non-toxic, and non-irritating (Marwah et al. 2016).

4.4. Adhesives

Patches prepared by transdermal application require adhesives. Transdermal patches are attached to the skin surface by adhesives. Before using adhesives in transdermal patches formulations, the following criteria must be taken into consideration:

i. The attachment and removal of the transdermal patch must be done aggressively.
ii. It is imperative that the prepared patch does not leave un−washable residue on the surface of the skin
iii. There should be no potential for skin irritation after applying transdermal patch formulation.

iv. Transdermal patches should be prepared with an adhesive that offers biocompatibility with excipients and drugs
v. In terms of drug permeation, adhesives have no effect on the permeation of drugs across the stratum corneum (Musazzi et al. 2020).

Table 2. Various factors influencing transdermal application (Wang et al. 2022).

	Physicochemical	Pharmacokinetic	Biological
1	Solubility	Half life	Skin toxxicites
2	Crystallinity	Volume of Distribution	Site of application
3	Molecular weight	Total Body Clearance	Allergic reaction
4	Polarity	Therapeutic plasma concentration	Skin metabolism
5	Melting point	Bioavailability factor	

4.5. Backing Laminate

Insoluble backing membranes offer strong bonds between drug reservoirs and insoluble substances. Physical or chemical incompatibility should not be present in the backing membrane. Adhesive foam pads, metallic plastic laminates, etc., prevent early drug release on the skin surface (Bathe and Kapoor 2015).

4.6. Release Liner

An inert material made up of silicon and Teflon makes up the release liner of a transdermal patch. For the preparation of transdermal patches, release liners are usually permeable penetration enhancers composed of drugs and water (Kanabar, Patel, and Doshi 2015).

4.7. Plasticizers and Solvents Used in the Preparation of Transdermal Patches

To prepare transdermal patches safely, all materials must be physically and chemically compatible with any plasticizers or solvents used in their development. There are several solvents used in the preparation of transdermal patches, including isopropanol, dichloromethane, acetone, chloroform, ethanol, and methanol. The plasticizers used in the formulation of transdermal patches include triethyl citrate, dibutyl pthalate, polyethylene glycol, PEG-400, and propylene glycol (Quaroni et al. 2018).

5. Types of Transdermal Patches

5.1. Single Layer Drug In Adhesive

Drugs are applied as a single layer on the surface of the skin, and the layer adheres to the skin (Al Hanbali et al. 2019). A transdermal patch consists of three layers: a baking membrane, a drug in the adhesive layer, and a liner layer.

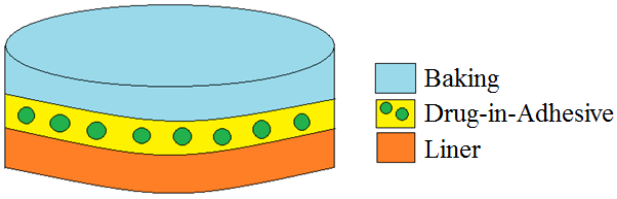

Figure 1. Single layer Drug in Adhesive System.

5.2. Multi-Layer Drug In Adhesive

The drug is released from the system when applied to the skin via transdermal patches, usually consisting of two layers (but not always). These transdermal patches have a permanent backing membrane and a temporary liner layer. A transdermal patch consists of a baking layer, an adhesive layer, a membrane, an adhesive layer, and a liner membrane, respectively (Lee et al. 2020).

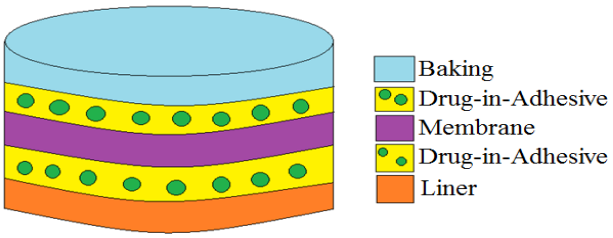

Figure 2. Multi-layer Drug in Adhesive System.

5.3. Reservoir

The system consists of a polymeric membrane attached to a laminated backing material and is surrounded by molded compartment. Diffusion processes across rate-controlling membranes will lead to drug release from transdermal patches. In such a case, the drug is released at a zero-order rate (Kim et al. 2015).

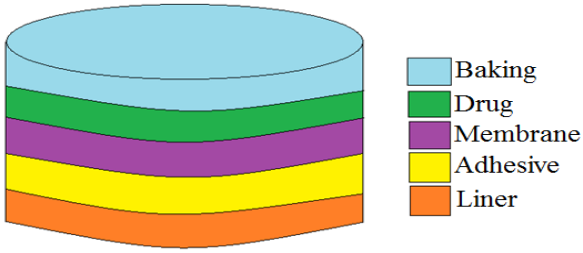

Figure 3. Reservoir System

5.4. Matrix

The transdermal patches that are prepared by using this method are known as monolithic patches. Drug-containing suspensions and solutions are used in monolithic patches. An adhesive layer surrounds a drug layer in matrix patches (Mali 2015).

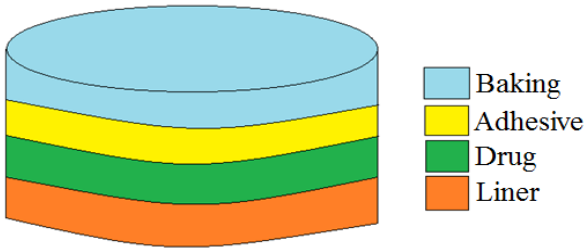

Figure 4. Matrix System

5.5. Vapour Patch

The adhesion property of transdermal patches can be achieved with the addition of adhesive material in the formulation. Decongestions are also carried out with this layer in order to release essential oils. Sleep quality can be improved, and cigarette cessation therapies can be achieved using these patches (Al Hanbali et al. 2019).

6. Preparation Methods of Transdermal Patches

6.1. Asymmetric TPX Membrane

Dry or wet inversions can be used to formulate patches with asymmetric TPX membranes. TPX is added to the non-solvent and solvent at 60 degrees Celsius to prepare the polymer solution. In order to determine the thickness of the film, the solution of polymer is placed at 40°C for 24 hours, and then the solution of polymer is cast onto a glass plate (plate of glass) and allowed to evaporate for 30 seconds at 50°C. During coagulation, a glass plate is immersed at 25°C in a coagulation bath. After the immersion process, the membrane can be removed and allowed to air dry for 12 hours at 50°C (Halder et al. 2021).

6.2. Circular Teflon Mould

Polymers are dissolved in an organic solvent system to form the transdermal patches using circular Teflon molds. Dissolution of a specific amount of drug takes place in an organic solvent system. The drug-polymer solution is also added to the plasticizer solution and mixed thoroughly, then poured into a circular Teflon mold. By placing an inverted funnel on the Teflon mold, the rate of solvent vaporization can be controlled. A desiccator is used to preserve the patches after the solvent has evaporated for 24 hours (Mali 2015).

6.3. Mercury Substrate

Polymeric solutions are used to disperse plasticizers and drug gels. After 10 to 15 minutes of mixing, the polymer solution is poured on top of the mercury surface for homogeneous mixing. Solvent evaporation rates are controlled by inverted funnels.

6.4. IPM Membranes

A mixture of propylene glycol and water is used in making this type of patch. Triethanolamine is then added to neutralize the drug dispersion. In the case of the low solubility of the drug in water, a buffer solution pH 7.4 is added to obtain a gel solution. After the gel has been prepared, it will be poured into the membranes of the IPM system (Kharia, Gilhotra, and Singhai 2019).

6.5. Ethylene Vinyl Acetate Copolymer (EVAC) Membranes

The preparation of a targeted transdermal system uses polyethylene and ethylene vinyl acetate copolymer (EVAC) membranes as rate-regulating membranes. The drug is dissolved in propylene glycol when it cannot be dissolved in water. Upon formulation, carbopol resin will be added to the solution. A sodium hydroxide solution of 5% will neutralize this. An area is selected, and the drug is spread over the backing layer. The solvent evaporation rate is controlled with an inverted funnel (D'Amelia et al. 2016)

6.6. Proliposomes

Proliposomes are prepared by deposition techniques. 5 mg of mannitol powder was taken and kept at 60 °C to 70 °C and stirred at 80 rpm in a 100 ml round bottom flask. Afterward, the mannitol was vacuum-dried for 30 minutes. Drug and lecithin are dissolved in 0.5 ml of an organic solvent mixture. An aliquot of 0.5 ml of the product was added to the flask containing the proliposomes after they had been dried completely. The flask was finally connected to a lyophilizer. The proliposomes are dried overnight in a desiccator, then sieved through a mesh size of 100. A glass bottle is used to store proliposome powder, and it is frozen until needed (Dhiman, Sarvaiya, and Mohindroo 2022).

6.7. Free Film

Films made without cellulose acetate are prepared with mercury surfaces. Chloroform was used to prepare the polymer solution at 2% w/w. To make the polymeric solution, 40 w/w plasticizers was added to the solution. In a glass petri dish, a 0.5 ml portion of the polymeric solution was placed within a glass ring which was kept over the mercury surface. Inverted funnels were placed over Petri dishes to control solvent evaporation. The film formation is observed after the solvent has evaporated completely. A desiccator will be used to store and dry the dried film. Different volumes of polymeric solutions can be used to formulate free films of various thicknesses (Saravanakumar et al. 2015).

7. Evaluation Parameters for Transdermal Patches

7.1 Thickness of the Patch

A digital micrometer is used to measure the thickness of a drug-loaded patch and calculate an average thickness and standard deviation. Dial gauges, micrometers, and screw gauges are used to measure transdermal film thickness (Latif, Al-Harbi, et al. 2022).

7.2. Weight Uniformity

In order to test the patches, they must be dried for four hours at 60°C after they have been prepared. Digital balances are used to weigh a specific area of the patch. Transdermal patches should be averaged, and the standard deviation should be

calculated from the individual weights (Latif et al. 2021).

7.3. Folding Endurance

An area in the middle was cut, and a fold in the same spot was repeated until a crack or break appeared in the strip. In order to measure folding endurance, fold a film at the same place until a crack or break appears. This represents the folding strength for the prepared transdermal patches (Latif, Nawaz, et al. 2022).

7.4. Percentage Moisture Content

The films should be weighed and placed in a desiccator containing fused calcium chloride at room temperature for 24 hours (Ullah et al. 2021). You can determine the moisture content by weighing the films again after 24 hours:

% Moisture content = Initial weight – Final weight X 100

7.5. Content Uniformity Test

This procedure involves selecting ten patches and determining their drug content. In order to pass the test of content uniformity, nine out of ten patches must have 85% to 115% of the content. It will, however, be necessary to test an additional 20 patches if there are three patches that contain drug content between 75% and 125%. The transdermal patches meet this test based on the range of 85% to 115% for these 20 patches (Shivalingam 2021).

7.6. Moisture Uptake

Films are stored in desiccators at room temperature for 24 hours after they have been weighed. The weight of desiccators is maintained by exposing them to a saturated solution of potassium chloride until 84% relative humidity is reached (Singh and Bali 2016). The formula below can be used to calculate the moisture uptake percentage:

% moisture uptake = Final weight – Initial weight X 100 (Initial weight).

7.7. Drug Content

In order to dissolve a patch area, a suitable solvent must be added in a specified volume. In the next step, a filter medium is used to filter out the solution, and the drug contained in it is analyzed using the appropriate technique (UV or HPLC). Each value was calculated by averaging three samples (Bathe and Kapoor 2015).

7.8. Shear Adhesion Test

It is used to determine whether adhesive polymers are effective by testing their cohesive strength. In addition to molecular weight, crosslinking degree, polymer composition, and polymer type, adhesion can be influenced by a variety of factors. A stainless steel plate is coated with adhesive tape that pulls the tape parallel to it. Shear adhesion strength is measured by pulling off the tape. As a rule of thumb, stronger shears take longer to remove (Gennari et al. 2020).

7.9. Peel Adhesion Test

When an adhesive coating is peeled away from a test substrate, the force required to remove it is measured. Peel adhesion is influenced by polymer molecule weight and its type. A single tape is applied to stainless steel plates or backing membranes. As a final step, the tape is pulled away from the substrate at a 180-degree angle. After the tape has been removed, measure the force needed to remove it (Musazzi et al. 2020).

7.10. Water Vapor Transmission Studies (WVT)

In order to measure water vapor transmission, calcium chloride can be put in dried vials of equal diameter and weighed. The polymer films were pasted to the brim after applying silicon adhesive grease and allowed to be set for five minutes. Once the vials have been weighed, they are placed in a humidity chamber at 68 % RH. Every 1st, 2nd, and 3rd day for seven consecutive days, a weight increase was used to quantify moisture transmission through the patch. Sodium bromide and potassium chloride solutions containing 200 mL each were placed in vials in desiccators in another method. Humidity was measured inside tightly closed desiccators via a hygrometer. A desiccator was used to dry each vial after weighing it (Hussain et al. 2016).

WVT = W/ ST

W represents increased weight in the time interval of 24 hours, S represents exposed film (cm^2), and T represents time.

7.11. Rolling Ball Tack Test

This test compares the softness of polymers to tack. An inclined track releases a 7/16-inch steel ball, so it rolls down and contacts a horizontal adhesive facing upward. In addition to measuring the distance covered by the ball (inches), the adhesiveness properties were also measured (Zhao et al. 2016).

7.12. Quick Stick (Peel-Tack) Test

During this process, the tape is pulled apart from the substrate at a speed of 12 inches/minute at a 90-degree angle. When an adhesive bond is broken, the tack value is expressed in ounces or grams per inch width (Kharia, Gilhotra, and Singhai 2019)..

7.13. Probe Tack Test

A bond is formed between an adhesive and a probe having a defined surface roughness. The probe breaks when it is mechanically removed. In tack measurements, a fixed rate of retraction between a probe and adhesive is recorded in grams (Chen et al. 2022).

7.13. In Vitro Drug Release Studies

USP apparatus V is used to assess drug release from prepared patches. A glass plate must be used for cutting, weighing, and attaching dry films after they have been cut into definite shapes. The apparatus is equilibrated at 32 ± 0.5°C. Afterward, the glass plate is placed in a 500 mL paddle containing a pH 7.4 phosphate buffer solution. It is necessary to set the paddle at a distance of 2.5 cm from the plate at a speed of 50 rpm in order to operate it. At appropriate intervals, samples (5-mL aliquots) can be withdrawn for analysis by UV spectrophotometer or HPLC by UV spectrophotometer or HPLC. To calculate the mean value, the experiment must be performed in triplicate (Zhao et al. 2016).

7.14. In Vitro Skin Permeation Studies

An in vitro permeation study can be conducted with diffusion cells. Westar rats weighing 200 to 250 grams will be analyzed at full thickness. Electric clippers should be used to remove hair from the abdominal region. Distilled water is used to thoroughly clean the dermal side of the skin to remove adhering tissue or blood vessels. It is necessary to equilibrate the excised skin in dissolution media or phosphate buffer pH 7.4 prior to the experiment. The diffusant is evenly distributed over the skin once it has been equilibrated via a magnetic stirrer. At 32°C ± 0.5°C, the temperature of the cell is maintained by a thermostatically controlled heater. When the rat skin piece is mounted between compartments of the diffusion cell, its epidermis should face upward into the donor compartment. At regular intervals, a definite amount of sample medium will be collected from the receptor compartment. To maintain sink conditions, a fresh amount of medium will be replaced. After filtration, samples can be analyzed spectrophotometrically or by HPLC. Divide the flux by the initial drug load (mg cm^2) to calculate the permeability coefficient. Calculate the permeability coefficient from the slope between steady-state values (mg cm^2) and time (hours) (Cilurzo et al. 2018).

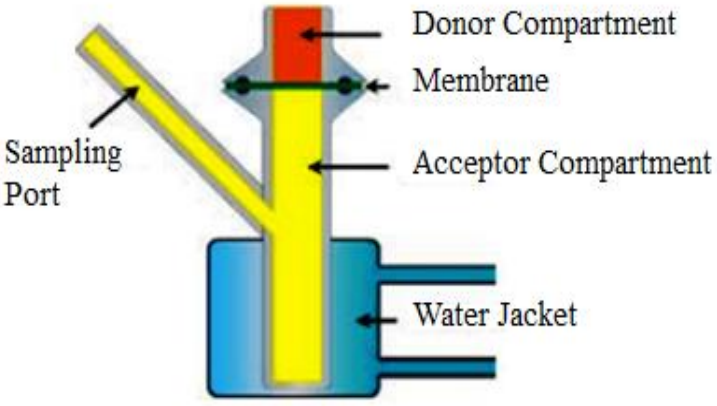

Figure 5. Franz Diffusion Cell.

7.15. In Vivo Studies

The only way to determine the effectiveness of drugs is to test them in vivo. Studying variables in vivo can provide insights into factors that cannot be considered in vitro. To evaluate transdermal

drug delivery *in vivo*, animal models can be used. Most transdermal drug delivery systems are evaluated using mice, rats, dogs, rabbits, and guinea pigs. Pharmacokinetic and pharmacodynamics data are collected after the patch has been applied to test animals (Singh and Bali 2016).

7.16. Skin Irritation Study

A healthy rabbit (weighing between 1.2 kg to 2.5 kg) can be used to test for skin irritations or sensitizations. To clean the rabbit's dorsal skin surface (50 cm^2), an electrical clipper is required. After that, apply spirit to clean the surface. The patch can be applied to the skin. Remove the patch after 24 hours. Based on the severity of the injury, the skin is graded into five grades (Iwata et al. 2020).

7.17. Stability Studies

In accordance with ICH recommendations, TDDS samples should be stored for 6 months at 40°C with 0.5°C and 75%) RH. In addition to removing samples at 0, 30, 60, 90 and 180 days, the samples are analyzed for the presence of drugs at each time point (Amodwala, Kumar, and Thakkar 2017).

8. Future Perspective

The next generation of formulations will involve liposomes, nanosomes, and microemulsions. It includes steroids, antifungals, antibacterials, methotrexate, interferon, and local anesthetics as potential delivery agents. A growth rate of 25% has been observed in recent years in the market for transdermal devices. With the development of novel devices and the increase in marketed topical drugs, this figure is expected to increase in the future. With further improvements in design, transdermal analgesic delivery will likely continue to gain popularity. In addition, efficacy and safety are being improved through research.

Changing the skin barrier or modifying drug molecules' energy could also increase drug flux across the skin. A variety of 'active' transdermal technologies have been investigated for drugs since iontophoresis patches have been successfully developed. An electroporation procedure involves applying short electrical pulses of high voltage to the skin in order to create aqueous pores. An ultrasonic wave is used in sonophoresis to disrupt the stratum corneum, and thermal energy (to enhance the skin's permeability and enhance the energy of drug molecules) is used to disrupt the stratum corneum. Using magnetic energy, magnetophoresis, it has been possible to increase drug flux across the skin.

The use of transdermal patches may be beneficial for chronic pain as well as acute pain. A wider range of analgesics and improved delivery methods will make this delivery method more popular and applicable. Drug delivery systems using transdermal routes are currently among the most successful innovative research areas. This is due to approximately 40% of drug delivery candidates in clinical trials being topical or dermal.

Transdermal drug delivery systems (TDDS) offer a safe, fast, and convenient method of delivering systemic drugs. When medications are administered through the skin, they are maintained at a constant level in the blood plasma, cause fewer side effects, and are more bioavailable because they bypass the hepatic first-pass metabolism. Additionally, it helps patients comply with treatment regimens more effectively. It has been considered safe to administer drugs through the skin because it provides continuous drug release into systemic circulation.

9. Conclusions

It has been known that transdermal drug delivery systems have been safe and effective for delivering drugs since 1981. Transdermal patches have undergone several advancements. Researchers are highly interested in the Transdermal Drug Delivery System due to its many advantages. Numerous studies are being conducted today to incorporate the latest drugs into this system. As a result, clinicians may be able to provide their patients with more therapeutic options through

transdermal dosage forms. We have gained a deeper understanding of how chemicals interact with and influence the stratum corneum barrier through various biophysical techniques in recent years. Enhancers with optimal properties and minimal toxicity will be designed by examining how they interact with the stratum corneum and determining structure-activity relationships for minimizing toxicities.

Conflict of Interest

The authors declare no conflict of interest.

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Study Approval

The study was conducted according to the guidelines of the declaration of Helsinki and approved by the institutional Review Board/Ethics Committee of Gomal University.

Consent Forms

NA.

Authors Contribution

MSL conceptualized the study and wrote the final manuscript, MK & AS helped in the analysis and writing the first draft, AI did the literature search and analysis, and AN supervised the whole project and wrote the final manuscript.

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References

Adams, Alex J, and Karen Suchanek Hudmon. 2018. "Pharmacist prescriptive authority for smoking cessation medications in the United States." *Journal of the American Pharmacists Association* 58 (3):253-257.

Al Hanbali, Othman A, Haji Muhammad Shoaib Khan, Muhammad Sarfraz, Mosab Arafat, Shakeel Ijaz, and Abdul Hameed. 2019. "Transdermal patches: Design and current approaches to painless drug delivery." *Acta Pharmaceutica* 69 (2):197-215.

Amodwala, Sejal, Praveen Kumar, and Hetal P Thakkar. 2017. "Statistically optimized fast dissolving microneedle transdermal patch of meloxicam: A patient friendly approach to manage arthritis." *European Journal of Pharmaceutical Sciences* 104:114-123.

Bathe, Ritesh, and R Kapoor. 2015. "Transdermal drug delivery system: formulation, development and evaluation-An overview." *Drug Deliv* 6:7-12.

Benson, Heather AE, Jeffrey E Grice, Yousuf Mohammed, Sarika Namjoshi, and Michael S Roberts. 2019. "Topical and transdermal drug delivery: from simple potions to smart technologies." *Current drug delivery* 16 (5):444-460.

Chen, Hua, Xun Ma, Daiyue Xu, Guang Chen, and Langchong He. 2022. "Investigation of the tack force of poultices using the probe tack test." *Journal of Adhesion Science and Technology*:1-10.

Choudhury, Hira, Bapi Gorain, Manisha Pandey, Lipika Alok Chatterjee, Pinaki Sengupta, Arindam Das, Nagashekhara Molugulu, and Prashant Kesharwani. 2017. "Recent update on nanoemulgel as topical drug delivery system." *Journal of Pharmaceutical Sciences* 106 (7):1736-1751.

Cilurzo, Francesco, Umberto M Musazzi, Silvia Franzé, Guido Fedele, and Paola Minghetti. 2018. "Design of in vitro skin permeation studies according to the EMA guideline on quality of transdermal patches." *European Journal of Pharmaceutical Sciences* 125:86-92.

D'Amelia, Ronald P, Samantha Gentile, William F Nirode, and Ling Huang. 2016. "Quantitative analysis of copolymers and

blends of polyvinyl acetate (PVAc) using Fourier transform infrared spectroscopy (FTIR) and elemental analysis (EA)." *World J. Chem. Educ* 4 (2):25-31.

Deo, Priya Nimish, and Revati Deshmukh. 2018. "Pathophysiology of keratinization." *Journal of oral and maxillofacial pathology: JOMFP* 22 (1):86.

Dhiman, Neha, Jayrajsinh Sarvaiya, and Poorti Mohindroo. 2022. "A drift on liposomes to proliposomes: recent advances and promising approaches." *Journal of Liposome Research*:1-15.

Foster, Matthew W, William M Gwinn, Francine L Kelly, David M Brass, Ashlee M Valente, M Arthur Moseley, J Will Thompson, Daniel L Morgan, and Scott M Palmer. 2017. "Proteomic analysis of primary human airway epithelial cells exposed to the respiratory toxicant diacetyl." *Journal of proteome research* 16 (2):538-549.

Galzote, Rosanna M, Sally Rafie, Rachel Teal, and Sheila K Mody. 2017. "Transdermal delivery of combined hormonal contraception: a review of the current literature." *International journal of women's health* 9:315.

Gennari, Chiara Grazia Milena, Gaia Maria Giorgia Quaroni, Costantino Creton, Paola Minghetti, and Francesco Cilurzo. 2020. "SEBS block copolymers as novel materials to design transdermal patches." *International Journal of Pharmaceutics* 575:118975.

Ghulaxe, Chetan, and Rameshwar Verma. 2015. "A review on transdermal drug delivery system." *The Pharma Innovation* 4 (1, Part A):37.

Gilaberte, Y, Lucía Prieto-Torres, Ievgenia Pastushenko, and Á Juarranz. 2016. "Anatomy and Function of the Skin." In *Nanoscience in Dermatology*, 1-14. Elsevier.

Gupta, MM, Soumya Singh, Renu Jindal, and Savita Patidar. 2012. "Penetration enhancers: role in transdermal drug delivery system." *Pharmacie Globale* 3 (9):1.

Halder, Sudip, Prodipta Chakraborty, Darshan Pradhan, and Arnab Bagchi. 2021. "Recent advancement in the method of transdermal drug delivery system: A review." *Journal of Applied Pharmaceutical Research* 9 (2):06-09.

Hmingthansanga, Victor, Nidhi Singh, Superna Banerjee, Sivakumar Manickam, Ravichandiran Velayutham, and Subramanian Natesan. 2022. "Improved Topical Drug Delivery: Role of Permeation Enhancers and Advanced Approaches." *Pharmaceutics* 14 (12):2818.

Huang, Bin, Wei-Jiang Dong, Gao-Yi Yang, Wei Wang, Cong-Hua Ji, and Fei-Ni Zhou. 2015. "Dendrimer-coupled sonophoresis-mediated transdermal drug-delivery system for diclofenac." *Drug design, development and therapy* 9:3867.

Hussain, Ismail, VB Narayanaswamy, Injamamul Haque, and Mohibul Hoque. 2016. "Design and Evaluation of Transdermal Patches Containing Risperidone." *Asian Journal of Research in Pharmaceutical Science* 6 (4):208-222.

Iwata, Nakao, Jun Ishigooka, Won-Hyoung Kim, Bo-Hyun Yoon, Shih-Ku Lin, Ahmad Hatim Sulaiman, Rowena Cosca, Lina Wang, Yury Suchkov, and Alexey Agarkov. 2020. "Efficacy and safety of blonanserin transdermal patch in patients with schizophrenia: a 6-week randomized, double-blind, placebo-controlled, multicenter study." *Schizophrenia research* 215:408-415.

Jasti, Bhaskara R, William Abraham, and Tapash K Ghosh. 2021. "Transdermal and Topical drug delivery systems." In *Theory and Practice of Contemporary Pharmaceutics*, 423-454. CRC Press.

Kanabar, Vishvesh B, Vipul P Patel, and Sumit M Doshi. 2015. "Formulation and evaluation of transdermal patch of Cefdinir with various polymers." *The Pharma Innovation* 4 (6, Part B):74.

Kapoor, Anupriya, Shashi Kiran Mishra, Dharmesh Kumar Verma, and Prashant Pandey. 2018. "Chemical penetration enhancers for transdermal drug delivery system." *Journal of Drug Delivery and Therapeutics* 8 (5-s):62-66.

Kharia, A, R Gilhotra, and AK Singhai. 2019. "Overview of Transdermal Medicated Patches with its research updates in preceding years." *Journal of Drug Delivery and Therapeutics* 9 (3-s):1094-1102.

Kim, Haneul, Hyeonjin Lee, Keum-Yong Seong, Eunsu Lee, Seung Yun Yang, and Jinhwan Yoon. 2015. "Visible light-triggered on-demand drug release from hybrid hydrogels and its application in transdermal patches." *Advanced healthcare materials* 4 (14):2071-2077.

Knöbel, Maria, Edel A O'Toole, and Frances JD Smith. 2015. "Keratins and skin disease." *Cell and tissue research* 360 (3):583-589.

Kováčik, Andrej, Monika Kopečná, and Kateřina Vávrová. 2020. "Permeation enhancers in transdermal drug delivery: Benefits and limitations." *Expert opinion on drug delivery* 17 (2):145-155.

Latif, Muhammad Shahid, Fatemah F Al-Harbi, Asif Nawaz, Sheikh Abdur Rashid, Arshad Farid, Mohammad Al Mohaini, Abdulkhaliq J Alsalman, Maitham A Al Hawaj, and Yousef N Alhashem. 2022. "Formulation and Evaluation of Hydrophilic Polymer Based Methotrexate Patches: In Vitro and In Vivo Characterization." *Polymers* 14 (7):1310.

Latif, Muhammad Shahid, Abul Kalam Azad, Asif Nawaz, Sheikh Abdur Rashid, Md Habibur Rahman, Suliman Y Al Omar, Simona G Bungau, Lotfi Aleya, and Mohamed M Abdel-Daim. 2021. "Ethyl Cellulose and Hydroxypropyl Methyl Cellulose Blended Methotrexate-Loaded Transdermal Patches: In Vitro and Ex Vivo." *Polymers* 13 (20):3455.

Latif, Muhammad Shahid, Asif Nawaz, Sheikh Abdur Rashid, Muhammad Akhlaq, Asif Iqbal, Muhammad Jamil Khan, Muhammad Shuaib Khan, Vuanghao Lim, and Mulham Alfatama. 2022. "Formulation of Polymers-Based Methotrexate Patches and Investigation of the Effect of Various Penetration Enhancers: In Vitro, Ex Vivo and In Vivo Characterization." *Polymers* 14 (11):2211.

Lee, Jihun, Hyoryong Lee, Su-hyun Kwon, and Sukho Park. 2020. "Active delivery of multi-layer drug-loaded microneedle patches using magnetically driven capsule." *Medical Engineering & Physics* 85:87-96.

Leung, Alexander Kc, and Kam Lun Hon. 2019. "Motion sickness: an overview." *Drugs in context* 8.

Malaiya, Mayank Kumar, Ashish Jain, Hurkat Pooja, Anki Jain, and Dharmendra Jain. 2018. "Controlled delivery of rivastigmine using transdermal patch for effective management of alzheimer's disease." *Journal of Drug Delivery Science and Technology* 45:408-414.

Mali, Audumbar Digambar. 2015. "An updated review on transdermal drug delivery systems." *skin* 8 (9).

Manevski, Nenad, Piet Swart, Kamal Kumar Balavenkatraman, Barbara Bertschi, Gian Camenisch, Olivier Kretz, Hilmar Schiller, Markus Walles, Barbara Ling, and Reto Wettstein. 2015. "Phase II metabolism in human skin: skin explants show full coverage for glucuronidation, sulfation, N-acetylation, catechol methylation, and glutathione conjugation." *Drug Metabolism and Disposition* 43 (1):126-139.

Marwah, Harneet, Tarun Garg, Amit K Goyal, and Goutam Rath. 2016. "Permeation enhancer strategies in transdermal drug delivery." *Drug delivery* 23 (2):564-578.

Mdanda, Sipho, Philemon Ubanako, Pierre PD Kondiah, Pradeep Kumar, and Yahya E Choonara. 2021. "Recent advances in microneedle platforms for transdermal drug delivery technologies." *Polymers* 13 (15):2405.

Mendoza-Garcia, Jenifer, Anil Sebastian, Teresa Alonso-Rasgado, and Ardeshir Bayat. 2015. "Optimization of an ex vivo wound healing model in the adult human skin: Functional evaluation using photodynamic therapy." *Wound Repair and Regeneration* 23 (5):685-702.

Musazzi, Umberto M, Marco A Ortenzi, Chiara GM Gennari, Antonella Casiraghi, Paola Minghetti, and Francesco Cilurzo. 2020. "Design of pressure-sensitive adhesive suitable for the preparation of transdermal patches by hot-melt printing." *International Journal of Pharmaceutics* 586:119607.

Nesovic, Lazar D, Akhilesh Kumar Shakya, and Harvinder Singh Gill. 2022. "Treating Allergies Via Skin–Recent Advances in Cutaneous Allergen Immunotherapy." *Advanced Drug Delivery Reviews*:114458.

Ng, Li Ching, and Manish Gupta. 2020. "Transdermal drug delivery systems in diabetes management: A review." *Asian journal of pharmaceutical sciences* 15 (1):13-25.

Nguyen, Kevin, Heidi Hoffman, Binu Chakkamparambil, and George T Grossberg. 2021. "Evaluation of rivastigmine in Alzheimer's disease." *Neurodegenerative disease management* 11 (1):35-48.

Patel, Anuradha, Richa Solanki, Saumya Jain, Yuvraj Singh Dangi, and Naina Dubey. 2018. "Formulation, Development and Evaluation of Etoricoxib containing Transdermal patches in Arthritis management." *International Journal of Research and Analytical Reviews* 5:i242-i249.

Prochaska, Judith J, and Neal L Benowitz. 2016. "The past, present, and future of nicotine addiction therapy." *Annual review of medicine* 67:467.

Quaroni, Gaia MG, Chiara GM Gennari, Francesco Cilurzo, Guylaine Ducouret, Costantino Creton, and Paola Minghetti. 2018. "Tuning the rheological properties of an ammonium methacrylate copolymer for the design of adhesives suitable for transdermal patches." *European Journal of Pharmaceutical Sciences* 111:238-246.

Ramadon, Delly, Maeliosa TC McCrudden, Aaron J Courtenay, and Ryan F Donnelly. 2022. "Enhancement strategies for transdermal drug delivery systems: Current trends and applications." *Drug Delivery and Translational Research* 12 (4):758-791.

Ramesh, Gautam, Ali Zamat, Srujan Vadlamudi, Neiman Liu, and Praveen Akuthota. 2021. "Development and Testing of a Novel Universal Transdermal Drug Delivery Platform to Reduce Medication Nonadherence."

Saravanakumar, K, P Swapna, P Nagaveni, P Vani, and K Pujitha. 2015. "Transdermal drug delivery system: a review." *J Glob Trends Pharm Sci* 1:70-81.

Shaker, Dalia S, Rania AH Ishak, Amira Ghoneim, and Muaeid A Elhuoni. 2019. "Nanoemulsion: A review on mechanisms for the transdermal delivery of hydrophobic and hydrophilic drugs." *Scientia Pharmaceutica* 87 (3):17.

Shen, Jie, and Diane J Burgess. 2015. "In vitro–in vivo correlation for complex non-oral drug products: Where do we stand?" *Journal of controlled release* 219:644-651.

Shivalingam, Balasubramanian and Ramalingam 2021. 2021. "Formulation and evaluation of transdermal patches of pantoprazole sodium." *International Journal of Applied Pharmaceutics*:287-291.

Shravanth, SH, Riyaz Ali M Osmani, VP Anupama, Mohamed Rahamathulla, and HV Gangadharappa. 2021. "Microneedles-based drug delivery for the treatment of psoriasis." *Journal of Drug Delivery Science and Technology* 64:102668.

Singh, Amandeep, and Alka Bali. 2016. "Formulation and characterization of transdermal patches for controlled delivery of duloxetine hydrochloride." *Journal of Analytical Science and Technology* 7 (1):1-13.

Tanwar, Himanshi, and Ruchika Sachdeva. 2016. "Transdermal drug delivery system: A review." *International journal of pharmaceutical sciences and research* 7 (6):2274.

Uchechi, Okoro, John DN Ogbonna, and Anthony A Attama. 2014. "Nanoparticles for dermal and transdermal drug delivery." *Application of nanotechnology in drug delivery* 4:193-227.

Ullah, Wasi, Asif Nawaz, Muhammad Akhlaq, Kifayat Ullah Shah, Muhammad Shahid Latif, and Mulham Alfatama. 2021. "Transdermal delivery of gatifloxacin carboxymethyl cellulose-based patches: Preparation and characterization." *Journal of Drug Delivery Science and Technology* 66:102783.

Wang, Yu, Lijuan Zeng, Wenting Song, and Jianping Liu. 2022. "Influencing factors and drug application of iontophoresis in transdermal drug delivery: an overview of recent progress." *Drug Delivery and Translational Research* 12 (1):15-26.

Williams, Adrian. 2021. "Controlled Drug Delivery into and Through Skin." *Fundamentals of Drug Delivery*:507-534.

Ye, Yanqi, Jicheng Yu, Di Wen, Anna R Kahkoska, and Zhen Gu. 2018. "Polymeric microneedles for transdermal protein delivery." *Advanced drug delivery reviews* 127:106-118.

Zaid Alkilani, Ahlam, Maelíosa TC McCrudden, and Ryan F Donnelly. 2015. "Transdermal drug delivery: innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum." *Pharmaceutics* 7 (4):438-470.

Zhang, Ling-juan. 2018. "Keratins in skin epidermal development and diseases." In *Keratin*. IntechOpen.

Zhao, Chunyi, Peng Quan, Chao Liu, Qiaoyun Li, and Liang Fang. 2016. "Effect of isopropyl myristate on the viscoelasticity and drug release of a drug-in-adhesive transdermal patch containing blonanserin." *Acta pharmaceutica sinica B* 6 (6):623-628.

Zhu, Shu-Hong, Yue-Lin Zhuang, Shiushing Wong, Sharon E Cummins, and Gary J Tedeschi. 2017. "E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys." *bmj* 358.