WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 10, 381-402. Review Article ISSN 2277– 7105

A REVIEW: TRANSDERMAL DRUG DELIVERY SYSTEM

Siddhant Shelke*, Santosh Waghmare and Hemant Kamble

Loknete Shri Dadasaheb Pharate Patil College of Pharmacy, Mandavgoan Pharata, Tal-Shirur, Dist.-Pune. Maharashtra.

Article Received on
09 June 2021,

Revised on 29 June 2021,
Accepted on 19 July 2021

DOI: 10.20959/wjpr202110-21208

***Corresponding Author**
Siddhant Shelke
Loknete Shri Dadasaheb Pharate Patil College of Pharmacy, Mandavgoan Pharata, Tal- Shirur, Dist.-Pune. Maharashtra.

ABSTRACT

Transdermal drug delivery has been recognised as a non-invasive drug delivery option. Transdermal systems are designed to deliver medications to the systemic circulation in a controlled and continuous manner through the skin. The usage of penetration enhancers, which improve the stratum corneum's permeability. Permeation enhancers are defined as substances that are capable of promoting penetration of drugs into skin and transdermal therapeutic systems offers a more reliable mean of administering drug through the skin. This article provides an overview on structure of skin and barrier, penetration enhancer, formulation and evaluation.

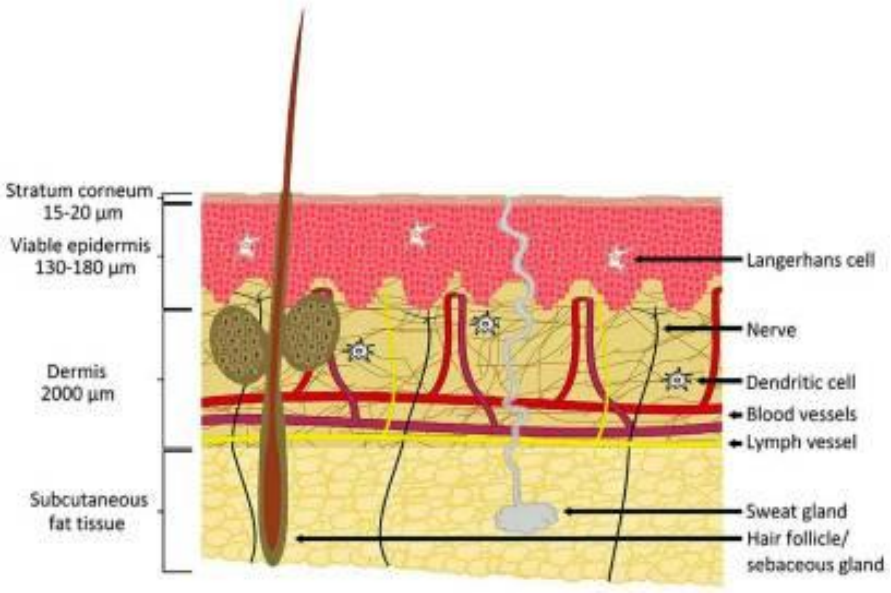
KEYWORDS: Transdermal drug delivery system, Skin, Penetration enhancers, Evaluation.

INTRODUCTION

The transdermal drug delivery system (TDDS), commonly known as "patches," is a dosage form that is designed to distribute a therapeutically effective amount of drug over the skin of a patient. The overall morphological, biophysical, and physiochemical aspects of the skin must be studied in order to transfer medicinal agents via the human skin for systemic action.[52] Transdermal delivery not only allows for controlled, consistent drug administration, but it also allows for continuous input of medications with short biological half-lives and prevents pulsed entry into systemic circulation, which can result in undesirable side effects. Transdermal drug delivery systems, controlled release systems, transmucosal drug delivery systems, and so on are examples of novel drug delivery methods.[53]

The stratum corneum, the outermost layer of the skin composed of keratin-rich cells embedded in numerous lipid bilayers, is the primary barrier to most transdermal medication

delivery. To circumvent the limited permeability of medications via the skin, a variety of techniques have been proposed. The use of penetration enhancers, which increase the permeability of the stratum corneum, is a popular method. These drugs partition into the stratum corneum and interact with its contents to cause a reversible increase in skin permeability.[54] Permeation enhancers are agents that impair the skin's capacity to form a barrier, making the skin more permeable and allowing medication molecules to pass through more quickly.



Skin structure

With a surface area of 1.7 m^2, skin is the most accessible and largest organ of the body, accounting for 16 percent of an average person's total body mass.[1,2,3] The skin's primary role is to protect the body from germs, ultraviolet (UV) radiation, chemicals, allergies, and water loss by acting as a barrier between the body and the external environment.[4]

The three main regions of the skin are

1. The epidermis, which contains the stratum corneum, is the outermost layer of the skin.
2. The dermis, the middle layer, and
3. The hypodermis is the innermost layer of the skin.[7,5,6]

Epidermis

The epidermis is the skin's outermost layer, having a thickness of around 0.8 mm on the palms of the hands and the soles of the feet.[4] The epidermal layers below the stratum corneum are made up of multi-layered regions of epithelial cells, and the viable epidermis is

often referred to as the epidermal layers.[16,4] The cellular content of the epidermis consists predominantly of keratinocytes (approximately 95% of cells), with other cells of the epidermal layers including melanocytes, Langerhans cells and merkel cells.[17] The stratum corneum is the epidermis' most superficial layer.[4,8,9] It is in direct contact with external environment, and its barrier properties may be attributed in part to its high density (1.4 g/cm^3 in the dry state) and low hydration (15–20%). The stratum corneum's cells are mostly made up of insoluble keratins (70 percent) and lipid (20 percent).[10] The presence of water in the stratum corneum is linked to the presence of keratin in the corneocytes.[4,11]

Dermis

The dermis is around 2–3 mm thick and is made up of collagenous (70%) and elastin fibers, which provide the skin strength and flexibility.[2] The dermis contains blood arteries that supply nutrition to both the dermis and the epidermis. The dermis layer also contains nerves, macrophages, and lymphatic veins.[8]

Hypodermis

The hypodermis, also known as the subcutaneous layer, is the skin's lowest layer and is made up of a network of fat cells.[2] It is the layer that connects the skin to the body's underlying tissues, such as muscles and bone. As a result, the hypodermis' main roles are physical shock protection, heat insulation, and support and conductance of the skin's vascular and neurological signals.[12] Fat cells that reside in the hypodermis account for around half of the body's fat, with fibroblasts and macrophages making up the rest of the hypodermis' cells.[13]

Barrier to drug permeation: The stratum corneum

The dead cells of the stratum corneum, which hinder the inward and outward circulation of drug substances and have a high electrical resistance, are the principal barriers to absorption. The stratum corneum is a heterogeneous tissue made up of keratinized cells that have been flattened. The outer layers of these cells are less densely packed than the granular layer beneath them. As a result, the epidermal barrier becomes more impermeable in the lower region, raising the possibility that a second barrier, the stratum corneum, exists at this level. These horny cells have no nuclei and are therefore physiologically inactive.[14]

Penetration enhancers

Permeation enhancers are defined as substances that are capable of promoting penetration of drugs into skin and transdermal therapeutic systems offers a more reliable mean of administering drug through the skin.[15]

Properties of penetration enhancers[19]

1. They should be pharmacologically inactive in the body. In other words, it should not bind to receptor sites.
2. It should be nontoxic, irritant-free, and allergy-free.
3. The onset of effect must be quick, and the length of activity must be predictable and appropriate for the drug being taken.
4. When the enhancer is removed, the horny layer should quickly and completely regain its barrier properties.
5. When the barrier characteristics of the skin are eliminated, they should restore quickly and completely.
6. All medications and adjuvants to be formulated in topical treatments and devices should be chemically and physically compatible with the accelerant.
7. It should be a suitable solvent for drugs if it is liquid and will be utilised in large volume fractions.
8. It should spread evenly on the skin and have a pleasant "feel" to it.
9. It should be easy to make dermatological preparations, transdermal devices, and skin adhesives from it.

Advantages and Disadvantages of penetration enhancers[20]

Advantages

1. Using penetration enhancers, increase the drug's penetration rate to a level that is sufficient for therapeutic efficacy.
2. It is useful for facilitating the absorption of non-absorbable medicines through the skin.
3. It can promote transdermal absorption of topical preparation.
4. It determines the rate of penetration in a transdermal drug delivery system.
5. Terpenes in propylene glycol solution, such as limonene, are good penetration enhancers for cytotoxic drugs.
6. It also serves as a rate limiter.

Disadvantages

1. The effective concentration of a drug differs from one drug to the next.
2. The use of various penetration enhancers in varied concentrations is entirely prohibited.
3. The physicochemical properties of enhancers have an influence on the body's side effects.

Types of penetration enhancers[18]

1. Chemical enhancers

Mechanism of action

They act by three mechanisms

1. By disrupting the stratum corneum's lipid structure, which is highly organised.
2. By interaction with intercellular protein.
3. By improved drug or solvent partitioning into the stratum corneum.

Examples

1. Sulphoxides and similar chemicals-dimethyl sulphoxide (DMSO),dimethyl formamide(DMF), dimethyl acetamide(DMAC)
2. Azones
3. Pyrrolidones
4. Fattyacids–Lauric acid, Myristic acid and capric acid
5. oxizolidinones (4- decycloxazolidine-2-one)
6. Amine and Amides –Urea
7. Surfaceactiveagents–sodium lauryl sulphate, Benzalkonium chloride
8. cyclodextrins

2. Drug vehicle based

Mechanism

Interaction of enhancers with the stratum corneum and the development of a SAR for enhancers with the best properties and the least toxicity.

Example

Ion pairs and complex coacervates chemical potential adjustment.

3. Natural penetration enhancers

Mechanism

Mechanism for Terpenes It may increase one or more of following effects

1. Partition coefficient
2. Diffusion coefficient

3. Lipid Extraction
4. Drug Solubility
5. Macroscopic Barrier Perturbation
6. Molecular Orientation of Terpenes Molecule with Lipid Bilayer

Example

1. Terpens-Menthol, Linalool, Limonene, Carvacrol.
2. Essential oil-Basil oil, Neem oil, Eucalyptus, Chenopodium, Ylang- Ylang.

4. Physical enhancers

Mechanism

Physical separation, magnetic separation, and ultrasonic separation are all methods for improving penetration.

Examples

1. Iontophoresis
2. Sonophoresis
3. Phonophoresis
4. Magnetophoresis
5. Electroporation
6. Thermophoresis
7. Radiofrequency
8. Needleless injection
9. Hydration of stratum corneum
10. Stripping of stratum corneum

5. Biochemical approach

Mechanism

They act by modifying substances by converting it in to suitable form

Examples

1. Synthesis of bio-convertible prodrugs.
2. Co-administration of skin metabolite Inhibitors

6. Miscellaneous enhancers

Mechanism

Having Various Mechanism

Examples

1. Lipid synthesis inhibitors
2. Phospholipids
3. Clofibric acid
4. Dodecyl–N,N-Dimethyl

Table no. 1: Examples of penetration enhancers.

Sr. no.	Drug	Active ingredient	Reference
1.	Acyclovir	Dimethylsulfoxide	[21]
2.	Bupranolol (BPL)	(BPL) 2-Pyrrolidone, 1-methyl-2- pyrrolidone, partially methylated β-cyclodextrin (PMβCD)	[22]
3.	Acyclovir	Dimethylsulfoxide	[23]
4.	Piroxicam	Saturated (lauric acid), monounsaturated (oleic acid) and polyunsaturated (linoleic and linolenic acids)	[24]
5.	5-Fluorouracil, tamoxifen	Oleic acid (OA), ethanol, propylene glycol (PG)	[25]
6.	5-Fluorouracil (5- FU) & Oestradiol (OE)	1,8-Cineole & Limonene	[26]
7.	Lorazepam	Surfactants (sodium lauryl sulfate (SLS), cetyltrimethylammonium bromide (CTAB), benzalkonium chloride or Tween 80	[27]
8.	Piroxicam	Polyoxyethylene-2-oleyl ether	[28]
9.	Piroxicam	Polyoxyethylene-23-lauryl ether, Polyoxyethylene-2- oleyl ether, polyoxyethylene2-stearyl ether	[29]
10.	5-Fluorouracil (5- FU)	Azone (AZ), lauryl alcohol (LA), and isopropyl myristate (IPM)	[30]
11.	Piroxicam (PX)	β-cyclodextrin	[31]
12.	Indomethacin, Diclofanac & Piroxicam	Cardamom oil	[32]
13.	Haloperidol	Vitamins (ascorbic acid), Surfactants (cetrimide, polysorbate 20), Sulfoxides (dimethyl sulfoxide), Glycols (polyethylene glycol 400, propylene glycol) and Amides (urea)	[33]
14.	17b-Estradiol (E2)	Glycerylmonolaurate (LAU), l-menthol (MEN), sodium caprate (CAP)	[34]
15.	Cyclosporin A (CysA)	Ethanol, ethyl oleate, transcutol, isopropyl myristate, ethanol, labrasol, propylene glycol, lauroglycol FCC	[35]
16.	Ligustrazine Hydrochloride (LH)	D-limonene, L-limonene, and α-terpinene	[36]

Transdermal drug delivery system basic components

1. The drug.
2. Polymer matrix.
3. Permeation enhancers.
4. Adhesive.
5. Backing layer.
6. Release linear.
7. Other excipients such as plasticizers and solvent

The drug

Properties[37]

1. The drug's molecular weight should be less than 500 daltons.
2. The drug's affinity for both lipophilic and hydrophilic phases should be high.
3. The drug's melting point should be low.
4. The medicine should be effective with a daily dose of a few milligrames.
5. The drug's half-life (t1/2) should be short.
6. The drug must not cause skin irritation or an adverse reaction.
7. Drugs that breakdown in the gastrointestinal tract and are inactivated by the hepatic first-pass effect are good candidates for transdermal administration.
8. Tolerance to the drug must not develop due to transdermal delivery's near zero-order release profile.
9. Drugs that must be administered for an extended length of time or that have side effects in non-target tissues can be prepared for transdermal delivery.

Polymer matrix or matrices[38]

The polymer regulates the drug release from the device. For a polymer to be utilised in transdermal patches, it must meet the following requirements.

i. The polymer's weight and chemical activity should be such that the specific drug Molecular diffuses and is released appropriately through it.
ii. The polymer should be long-lasting.
iii. The polymer must not be harmful.
iv. The polymer should be simple to produce.
v. The polymer should be low-cost.

vi. The polymer, as well as its degradation products, must not be poisonous or unfavorable to the host.

Polymer used in transdermal drug delivery system[39]

The backbone of TDDS is polymers, which regulate the drug's release from the device. The drug can be dispersed in a liquid or solid state synthetic polymer basis to create a polymer matrix. Furthermore, they must distribute a medicine consistently and effectively throughout the product's stated shelf life and must be safe.

- **Natural polymers:** For example, cellulose derivatives, gelatin, shellac, waxes, gums, and chitosan.
- **Synthetic elastomers:** For example, polybutadiene, polyisobutylene, silicon, nitrile, acrylonitrile, neoprene, and butyl rubber.
- **Synthetic polymers:** For example, polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, and polyvinyl pyrrolidone.

Penetration enhancers[40]

By modifying the barrier characteristics of the stratum corneum, penetration enhancers aid drug absorption. Non-toxic, non-allergic, pharmacologically inert, tasteless, affordable, and compatible with drug and excipients are all requirements for a penetration enhancer. Intercellular lipid interactions can increase skin permeability by disrupting cellular structure and thereby increasing skin permeability.

Other excipients[41]

Adhesives

All transdermal devices are attached to the skin with a pressure sensitive adhesive that can be placed on the device's face or in the rear and extends peripherally. Both adhesive systems must meet the following requirements:

1. It should aggressively attach to the skin and be easily removed.
2. Shouldn't leave a sticky residue on the skin that can't be washed off.
3. Skin should not be irritated or sensitised., for example, Silicones, and polyisobutylene.

Backing membrane

Backing membranes are flexible and offer a good binding to the drug reservoir, as well as preventing the drug from escaping through the top of the dosage form and allowing printing.

For example, Metallic plastic, is an impermeable substance that protects the product while it is being used on the skin. For example, cellulose derivatives and polypropylene silicon.

Linear

During storage, keep the patch safe. Before using, the linear is removed.

Types of transdermal patches[42,43]

Single layer drug-in-adhesive

The drug is also contained in the adhesive layer of this system. The adhesive layer of this kind of patch not only serves to adhere the numerous layers together, as well as the entire system to the skin, but it also serves to release the drug. To the outer side of adhesive layer there is lining of temporary liner and a backing.

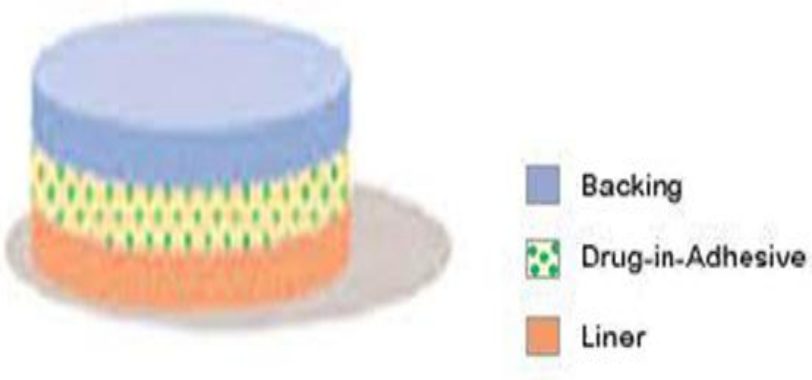


Fig. Single layer drug-in-adhesive.

Multi-layer Drug-in-adhesive

In the same way that both adhesive layers are responsible for drug release, it's identical to the single layer system. The multilayer system, on the other hand, adds a second layer of drug-in adhesive material, usually separated by a membrane (but not in all cases). A temporary liner layer and a permanent backing surround this patch.

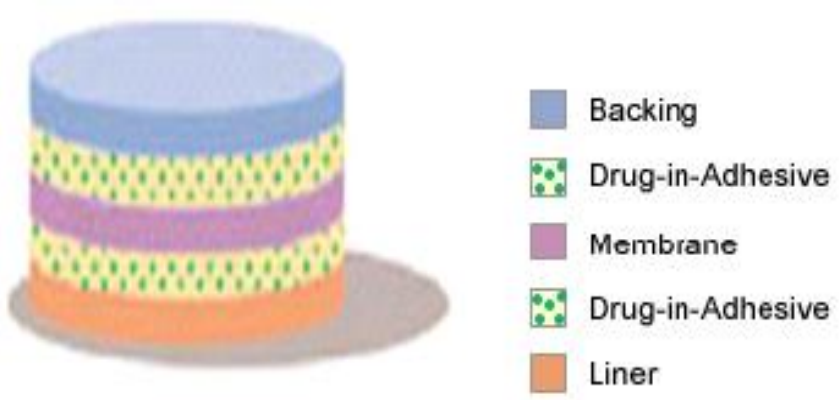


Fig. Multi-layer Drug-in-adhesive.

Rservoir system

The drug reservoir is placed between an impermeable backing layer and a rate-controlling membrane in this system. The drug can be released through a rate-controlling membrane that is either microporous or nonporous. The drug can be in the form of a solution, suspension, gel, or dispersed in a solid polymer matrix in the drug reservoir compartment.

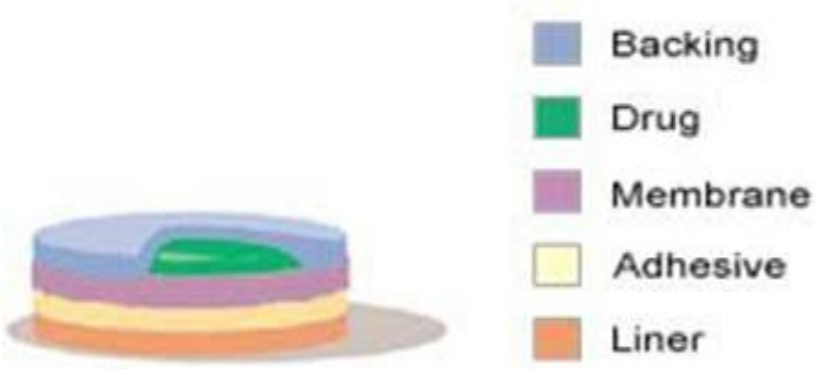


Fig. Reservoir system.

Micro reservoir system

The drug delivery system in this case is a hybrid of a reservoir and a matrix system. The drug reservoir is created by suspending the drug in an aqueous solution of a water-soluble polymer and then homogeneously dispersing the solution in a lipophilic polymer to produce thousands of inaccessible, microscopic drug reservoir spheres. This thermodynamically unstable dispersion is quickly stabilised by applying crosslinking agents to crosslink the polymer in situ.

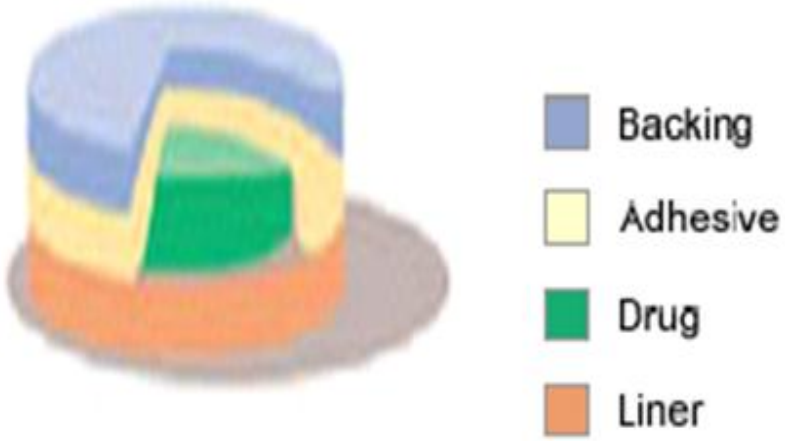


Fig. Matrix system.

Drug in adhesive system:- The drug reservoir is created by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer on an impervious backing layer by solvent casting or melting (in the case of hot melt adhesive). For protection, unmediated adhesive polymer films are put on top of the reservoir.

Fig. Drug in adhesive system.

Matrix dispersion system:- The drug is dispersed uniformly in a hydrophilic or lipophilic polymer matrix in this type. In a compartment made from a drug impermeable backing layer, a drug-containing polymer disc is fixed to an occlusive base plate. Instead of applying adhesive to the face of the drug reservoir, a strip of adhesive rim is formed by spreading it around the circumference.

Evaluation parameters

1. Interaction studies[44,45]

Excipients are a necessary component of almost every pharmaceutical dosage form. The compatibility of the drug with the excipients, among other things, determines the stability of a formulation. To make a stable product, the drug and excipients must be compatible with one another, therefore any possible physical or chemical interaction must be detected, as it can alter the drug bioavailability and stability. Compatibility studies are important in the formulation development of new excipients that have never been utilised in formulations containing the active ingredient. By comparing their physicochemical properties such as assay, melting endotherms, characteristic wave numbers, absorption maxima, interaction studies, etc. are often carried out in Thermal analysis, FT-IR, UV, and chromatographic procedures.

2. Thickness of the patch[46]

Using a digital micrometer, the thickness of the drug-loaded patch is measured at several points and the average thickness and standard deviation are calculated to ensure the thickness of the created patch.

3. Weight uniformity[46]

Before testing, the prepared patches must be dried at 60°C for 4 hours. A defined patch area must be split into distinct sections and weighed in a digital balance. Individual weights will be used to establish the average weight and standard deviation.

4. Folding endurance[46]

A strip of a specified area must be cut uniformly and folded repeatedly at the same place until it breaks. The value of the folding endurance was determined by the number of times the film could be folded in the same place without breaking.

5. Percentage moisture content[46]

The prepared films must be weighed individually and maintained at room temperature for 24 hours in a desiccator containing fused calcium chloride. After 24 hours, reweigh the films and use the formula below to calculate the percentage moisture content.

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

6. Percentage moisture uptake[46]

To maintain a RH of 84 percent, the weighed films must be stored in a desiccator at room temperature for 24 hours in a saturated potassium chloride solution. After 24 hours, reweigh the films and use the formula below to calculate the percentage moisture uptake.

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

7. Water vapour permeability (WVP) evaluation[47]

The water vapour permeability can be determined using the foam dressing method, which uses a natural air circulation oven instead of an air forced oven. The WVP can be calculated using the following formula.

WVP=W/A

Where, WVP is expressed in gm/m^2 per 24hrs,

W represents the amount of vapour permeated through the patch in gm/24 hours, and A represents the surface area of the exposure samples in m^2.

8. Drug content[47]

A certain area of the patch must be dissolved in a precise volume of a suitable solvent. The solution is then filtered via a filter medium, and the drug content is determined using the appropriate method (UV or HPLC technique). Each value represents average of three different samples.

9. Uniformity of dosage unit test[48]

A accurately weighted portion of the patch should be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent, and sonicated for complete drug extraction from the patch, and made up to the mark with the same. After allowing the solution to settle for about an hour, the supernatant was diluted to the required concentration using a suitable solvent. The solution was filtered through a 0.2m membrane filter and then analysed using a suitable analytical technique (UV or HPLC) to determine the drug content per piece.

10. Polariscope examination[48]

The purpose of this test is to use a polariscope to examine at the drug crystals on the patch. To determine if the drug is present in crystalline or amorphous form in the patch, a certain surface area of the piece should be kept on the object slide and the drug crystals should be observed.

11. Shear adhesion test[48]

The purpose of this test is to determine the cohesive strength of an adhesive polymer. The molecular weight, degree of crosslinking, polymer composition, type, and amount of tackifier applied can all influence it. A specified weight is hung from an adhesive coated tape that is applied to a stainless steel plate, causing it to pull in a direction parallel to the plate. The time it takes to pull the tape off the plate is used to assess shear adhesion strength. The longer the time take for removal, greater is the shear strength.

12. Peel adhesion test[48]

Peel adhesion is the force required to remove an adhesive covering from a test substrate in this test. The peel adhesion capabilities were governed by the molecular weight of the adhesive polymer, as well as the type and amount of additives used. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180º angle, and the force required for tape removed is measured.

13. Thumb tack test[48]

It is a qualitative test used to determine the adhesive's tack property. The relative tack property is detected by simply pressing the thumb on the adhesive.

14. Flatness test[49]

Each film should have three longitudinal strips cut off it, one from the centre, other from the left side, and another another from the right side. Each strip's length was measured, and the difference in length due to non-uniformity in flatness was calculated using percent constriction, with 0 percent constriction equivalent to 100 percent flatness.

15. Percentage elongation break test[50]

The percentage elongation break is determined by measuring the length shortly before the break point and using the formula below to calculate the percentage elongation.

$$\text{Elongation percentage} = L1\text{-}L2/L2 \times 100$$

Where, L1 is the strip's final length and L2 is the strip's initial length of each strip.

16. Rolling ball tack test[51]

This test determines how soft a polymer is when it relates to talk. In this test, a 7/16-inch-diameter stainless steel ball is released on an inclined track and rolls down, coming into touch

with horizontal, upward-facing adhesive. The tack, which is measured in inches, is determined by the distance the ball travels along the adhesive.

17. Quick stick (peel-tack) test[51]

The tape is pulled away from the substrate at 90^{o}C at a speed of 12 inches per minute in this test. Tack value, which is given in ounces or grammes per inch width, is the peel force necessary to break the bond between adhesive and substrate.

18. Probe tack test[51]

The tip of a clean probe with a specific surface roughness is brought into contact with adhesive in this test, and a bond between the probe and the adhesive is produced. The probe is then mechanically broken when it is removed. Tack is the force necessary to pull the probe away from the adhesive at a constant rate. It is measured in grams.

19. In vitro drug release studies[44]

For assessing the release of the drug from the prepared patches, the paddle over disc method (USP apparatus V) can be used. Dry films of defined thickness will be cut into a specific shape, weighed, and adhered to a glass plate. After that, the glass plate was immersed in 500 mL of dissolving media or phosphate buffer (pH 7.4), and the apparatus was equilibrated at 32±0.5°C. The paddle was then placed 2.5 cm away from the glass plate and rotated at a speed of 50 rpm. Samples (5-mL aliquots) can be taken at intervals of up to 24 hours and examined using a UV spectrophotometer or HPLC. The experiment should be repeated three times so that the mean value can be calculated.

20. In vitro skin permeation studies[44]

A diffusion cell can be used to conduct an in vitro permeation research. Male Wistar rats weighing 200 to 250g have full thickness abdomen skin. Hair from the abdomen region should be gently removed with an electric clipper; the dermal side of the skin should be completely cleaned with distilled water to remove any adhering tissues or blood vessels, then equilibrated in dissolving medium or phosphate buffer pH 7.4 for an hour. Before starting the experiment, the diffusant was placed on a magnetic stirrer with a small magnetic needle to ensure even distribution. A thermostatically controlled heater was used to keep the cell temperature at 32± 0.5°C. The epidermis of the isolated rat skin piece should face upward into the donor compartment and be mounted between the compartments of the diffusion cell. At regular intervals, a sample volume of specified volume should be withdrawn from the

receptor compartment and replaced with an equal volume of fresh medium. Samples should be filtered using a filtering medium and analysed using spectrophotometry or HPLC. The slope of the curve between the steady-state values of the amount of drug permeated (mg cm^{-2}) vs. time in hours was used to calculate flux, and permeability coefficients were calculated by dividing the flux by the initial drug load (mg cm^{-2}).

21. Skin irritation study[48]

Healthy rabbits can be used to test for skin irritation and sensitization (average weight 1.2 to 1.5 kg). The rabbit's dorsal surface (50cm^2) should be cleaned, and hair should be removed from the clean dorsal surface by shaving. The surface should then be cleaned with rectified spirit, and representative formulations should be applied over the skin. After 24 hours, the patch should be removed, and the skin should be examined and graded into five grades based on the severity of the skin injury.

22. Stability studies[44]

The TDDS samples must be stored at 40.55°C and 75.5% RH for 6 months in order to undertake stability studies according to ICH guidelines. The samples were taken at 0, 30, 60, 90, and 180 days and analysed for drug content as needed.

CONCLUSION

Less absorption, more uniform plasma levels, improved bioavailability, decreased adverse effects, efficacy, and product quality are all advantages of using a transdermal drug delivery system for therapeutic therapy. When it comes to providing medication to small children and the elderly, transdermal distribution enhances and simplifies patient compliance. Penetration enhancers are used to increase the drug availability through intact skin. This article discusses the nature of the skin and its barrier, as well as penetration enhancers, formulation, and evaluation of transdermal patches. The transdermal medication delivery system has the potential to become one of the greatest innovative drug delivery systems in the future.

ACKNOWLEDGEMENT

The authors are grateful to the management of Loknete Shri Dadasaheb Pharate Patil College of Pharmacy, Mandavgoan Pharata, for providing the facilities and access to online resources needed to conduct the literature review. The author is also grateful to Dr.Amol Lokhande for his valuable guidance.

REFERENCES

1. Menon G.K. New Insights into Skin Structure: Scratching the Surface. Adv. Drug Delivery. Rev, 2002; 54: S3–S17. doi: 10.1016/S0169-409X(02)00121-7.
2. Liu X., Kruger P., Maibach H., Colditz P.B., Roberts M.S. Using Skin for Drug Delivery and Diagnosis in the Critically Ill. Adv. Drug Delivery. Rev, 2014; 77: 40–49. doi: 10.1016/j.addr.2014.10.004.
3. Williams A.C., Barry B.W. Penetration Enhancers. Adv. Drug Delivery. Rev, 2012; 64: 128–137. doi: 10.1016/j.addr.2012.09.032.
4. Benson H.A., Watkinson A.C. Topical and Transdermal Drug Delivery: Principles and Practice. Wiley; Hoboken, NJ, USA, 2012.
5. Gratieri T., Alberti I., Lapteva M., Kalia Y.N. Next Generation Intra-and Transdermal Therapeutic Systems: Using Non-and Minimally-Invasive Technologies to Increase Drug Delivery into and Across the Skin. Eur. J. Pharm. Sci, 2013; 50: 609–622. doi: 10.1016/j.ejps.2013.03.019.
6. Lambert P.H., Laurent P.E. Intradermal Vaccine Delivery: Will New Delivery Systems Transform Vaccine Administration? Vaccine, 2008; 26: 3197–3208. doi: 10.1016/j.vaccine.2008.03.095.
7. Schoellhammer C.M., Blankschtein D., Langer R. Skin Permeabilization for Transdermal Drug Delivery: Recent Advances and Future Prospects. Expert Opin. Drug Deliv, 2014; 11: 393–407. doi: 10.1517/17425247.2014.875528.
8. Domínguez-Delgado C.L., Rodríguez-Cruz I.M., López-Cervantes M., Escobar-Chávez J., Merino V. The Skin a Valuable Route for Administration of Drugs. Current Technologies to Increase the Transdermal Delivery of Drugs. Bentham Science; Sharjah, UAE, 2010; 1–22.
9. El Maghraby G., Barry B., Williams A. Liposomes and Skin: From Drug Delivery to Model Membranes. Eur. J. Pharm. Sci, 2008; 34: 203–222. doi: 10.1016/j.ejps.2008.05.002.
10. Walters K.A. Dermatological and Transdermal Formulations. CRC Press; Boca Raton, FL, USA, 2002.
11. Alexander A., Dwivedi S., Giri T.K., Saraf S., Saraf S., Tripathi D.K. Approaches for Breaking the Barriers of Drug Permeation through Transdermal Drug Delivery. J. Control. Release, 2012; 164: 26–40. doi: 10.1016/j.jconrel.2012.09.017.
12. Sherwood A., Bower J.K., McFetridge-Durdle J., Blumenthal J.A., Newby L.K., Hinderliter A.L. Age Moderates the Short-Term Effects of Transdermal 17β-Estradiol on

Endothelium-Dependent Vascular Function in Postmenopausal Women. Arterioscler. Thromb. Vasc. Biol, 2007; 27: 1782–1787. doi: 10.1161/ATVBAHA.107.145383.

13. McLennan D.N., Porter C.J., Charman S.A. Subcutaneous Drug Delivery and the Role of the Lymphatics. Drug Discovery. Today Technol, 2005; 2: 89–96. doi: 10.1016/j.ddtec.2005.05.006.
14. Ramteke KH, Dhole SN, Patil SV. Transdermal drug delivery system: a review. J Adv Scient Res, 2012; 3(1): 22-35.
15. Patil UK, Saraogi R. Natural products as potential drug permeation enhancer in transdermal drug delivery system. Archives Dermato Research, 2014; 306(5): 419-426.
16. Donnelly R.F., Singh T.R.R., Morrow D.I., Woolfson A.D. Microneedle-Mediated Transdermal and Intradermal Drug Delivery. Wiley; Hoboken, NJ, USA, 2012.
17. Suh H., Shin J., Kim Y. Microneedle Patches for Vaccine Delivery. Clin. Exp. Vaccine Res, 2014; 3: 42–49. doi: 10.7774/cevr.2014.3.1.42.
18. Saini S, Chauhan SB, Agrawal SS. Recent development in penetration enhancers and techniques in transdermal drug delivery system. J Adv Pharm Edu Res, 2014; 4(1): 31-40.
19. Jagannath SS, Manohar SD, Bhanudas SR. Chemical penetration enhancers-a review. World J Pharmacy Pharma Sciences, 2014; 3(2): 1068-1080.
20. Bavaskar K, Jain A, Patil M, Kalamkar R. The impact of penetration enhancers on transdermal drug delivery system: physical and chemical approach. Int J Phar Res Review, 2015; 4(7): 14-24.
21. Dey S, Mazumder B, Patel JR. Enhanced percutaneous permeability of acyclovir by DMSO from topical gel formulation. Int J Pharm Sci Drug Research, 2009; 1(1): 13-18.
22. Babu RJ, Pandit JK. Effect of penetration enhancers on the release and skin permeation of bupranolol from reservoir-type transdermal delivery systems. Int J Pharm, 2005; 288: 325-334.
23. Kumar B, Jain SK, Prajapati SK. Effect of penetration enhancer dmso on in-vitro skin permeation of acyclovir transdermal microemulsion formulation. Int J Drug Delivery, 2011; 3: 83-94.
24. Santoyo S, Ygartua P. Effect of skin pretreatment with fatty acids on percutaneous absorption and skin retention of piroxicam after its topical application. Euro J Pharm Biopharm, 2000; 50: 245-250.
25. Gao S, Singh J. Effect of oleic acid:ethanol and oleic acid:propylene glycol on the in vitro percutaneous absorption of 5-fluorouracil and tamoxifen and the macroscopic barrier property of porcine epidermis. Int J Pharm, 1998; 165: 45–55.

26. Moghimi HR, Williams AC, Barry BW. A lamellar martrix model for stratum corneum intercellular lipids III. Effects of terpene penetration enhancers on the release of 5-fluorouracil and oestradiol from the matrix. Int J Pharm, 1996; 145: 37-47.
27. Nokhodchi A, Shokri J, Dashbolaghi A, Zadeh DH, Ghafourian T, Jalali MB. The enhancement effect of surfactants on the penetration of lorazepam through rat skin. Int J Pharm, 2003; 250: 359-/369.
28. Shin SC, Cho CW, Oh IJ. Enhanced efficacy by percutaneous absorption of piroxicam from the poloxamer gel in rats. Int J Pharm, 2000; 193: 213-218.
29. Shin SC, Cho CW, Oh IJ. Effect of non-ionic surfactant as permeation enhancers towards piroxicam from the poloxamer gel through rat skins. Int J Pharm, 2001; 222: 199-203.
30. Singh BN, Singh RB, Singh J. Effects of ionization and penetration enhancers on the transdermal delivery of 5-fluorouracil through excised human stratum corneum. Int J Pharm, 2005; 298: 98–107.
31. Jug M, Lacan MB, Kwokal A, Cizmek BC. Influence of cyclodextrin complexation on piroxicam gel formulations. Acta Pharm, 2005; 55: 223–236.
32. Huang YB, Wu PC, Ko HM, Tsai YH. Cardamom oil as a skin permeation enhancer for indomethacin, piroxicam and diclofenac. Int J Pharm, 1995; 126: 111-117.
33. Vaddi HK, Wang LZ, Ho PC, Chan SY. Effect of some enhancers on the permeation of haloperidol through rat skin in vitro. Inte J Pharm, 2001; 212: 247-255.
34. Kitano M, Maitani Y, Takayama K, Nagai T. Buccal absorption through golden hamster cheek pouch in vitro and in vivo of 17b-estradiol from hydrogels containing three types of absorption enhancers. Int J Pharma, 1998; 174: 19-28.
35. Liu H, Li S, Wang Y, Yao H, Zhang Y. Effect of vehicles and enhancers on the topical delivery of cyclosporin A. Int J Pharm, 2006; 311: 182-186.
36. Zhang CF, Yang ZL, Luo JB. Effects of enantiomer and isomer permeation enhancers on transdermal delivery of ligustrazine hydrochloride. Pharma Development Technology, 2006; 11: 417-424.
37. Bhowmik D, Pusupoleti KR, Duraivel S, Kumar KS. Recent approaches in transdermal drug delivery system. Pharma Innov, 2013; 2: 99.
38. Srivastava S, Maurya A, Gupta P. A review article on transdermal drug delivery system. World J Pharm Pharm Sci, 2016; 5: 1702-25.
39. Tyagi S, Goyal K. Transdermal drug delivery system: Quality approaches and evaluation. Innov Int J Med Pharm Sci, 2017; 2: 15-21.

40. Kaur J, Kaur J, Jaiswal S, Gupta GD. Recent advances in topical drug delivery system. Pharm Res, 2016; 6: 6325-32.
41. Sahu CS, Sahu KK, Agrawal M, Tripathi D, Ajazuddin AA. An exhaustive review based on the formulation and evaluation methods behind the development of transdermal drug delivery systems. Res J Pharm Technol, 2017; 10: 1531.
42. Sharma N, Agarwal G, Rana A, Bhat ZA, Kumar D. A review: Transdermal drug delivery system: A tool for novel drug delivery system. Int J Drug Dev Res, 2011; 3: 70-84.
43. Rani S, Saroha K, Syan N, Mathur P. Transdermal patches a successful tool in transdermal drug delivery system: An overview. Der Pharm Sin, 2011; 2: 17-29.
44. Singh J, Tripathi K.T and SakiaT.R. Effect of penetration enhancers on the invitro transport of ephedrine through rate skin and human epidermis from matrix based Transdermal formulations. Drug Dev.Ind. Pharm, 1993; 19: 1623-1628.
45. Wade A, Weller P.J. Handbook of pharmaceutical Excipients. Washington, DC: American Pharmaceutical Publishing Association, 1994: 362- 366.
46. Rhaghuram reddy k, Muttalik S and Reddy S. Once – daily sustained- release matrix tablets of nicorandil: formulation and invitro evaluation. AAPS Pharm.Sci.Tech, 2003; 4: 4.
47. Shaila L, Pandey S and Udupa N. Design and evaluation of matrix type membrane controlled Transdermal drug delivery system of nicotin suitable for use in smoking cessation. Indian Journ. Pharm. Sci, 2006; 68: 179-184.
48. Aarti N, Louk A.R.M.P, Russsel.O.P and Richard H.G. Mechanism of oleic acid induced skin permeation enhancement in vivo in humans. Jour. control. Release, 1995; 37: 299-306.
49. Wade A and Weller P.J. Handbook of pharmaceutical Excipients. Washington, DC: American Pharmaceutical Publishing Association, 1994; 362-366.
50. Lec S.T, Yac S.H, Kim S.W and Berner B. One way membrane for Transdermal drug delivery systems / sy
51. Vyas S.P and Khar R.K. Targetted and controlled Drug Delivery Novel carrier system1st Ed., CBS Publishers and distributors, New Delhi, 2002; 411- 447. stem optimization. Int. J Pharm, 1991; 77: 231 - 237.
52. Prabhakar V, Shivendra A, Ritika S, Sharma S. Transdermal drug delivery system: review. Int Rese J Pharm, 2012; 3(5): 50-53.
53. Loyd V. Allen Jr, Nicholas G. Popovich, Howard C. Ansel. Pharmaceutical dosage forms and drug delivery systems, Wolter Kluwer Publishers, New Delhi, 2005; 8: 298-299.

54. Chein Y.W. Transdermal drug delivery and delivery system. In, Novel drug delivery system, Marcel Dekker, Inc., New york, 1992; 50: 301-381.
55. Willams A.C and barry B. W., "Penetration Enhancers," Adv. Drug Del. Rev, 2004; 56: 603-618.