



TRANSDERMAL DRUG DELIVERY SYSTEM: AN UPDATED REVIEW

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Article Received on 06/05/2023

Article Revised on 26/05/2023

Article Accepted on 16/06/2023

ABSTRACT

Transdermal administration has an advantage over injectable and oral methods because it increases patient compliance and avoids first-pass metabolism, respectively. Therapeutic agent delivery via topical means has various benefits over more intrusive and traditional medication delivery techniques like oral ingestion.^[24] Compared to other dosing methods, Predictable blood level profiles, controlled drug release into the patient, fewer systemic side effects, and occasionally higher efficacy are just a few advantages of transdermal medicine delivery. The primary goal of transdermal drug delivery systems is to deliver medications into the bloodstream through the skin at a predefined rate with little variation between and within individuals. This article gives a general review of the several types of transdermal patches, their preparation techniques, and their physicochemical methods of assessment.

KEYWORDS: TDDS, Transdermal patches, Diffusion process, Topical drug delivery system.

INTRODUCTION

Patches are medicine dosage forms designed to evenly distribute a patient's skin with a therapeutically effective amount of medication. To transport medications through the human skin for systemic effects, it is necessary to take into account all of the morphological, biophysical, and physicochemical characteristics of the skin. Because it improves patient compliance and avoids first pass metabolism, transdermal delivery has an advantage over injectable and oral routes.^[1] The first transdermal patch for treating motion sickness received FDA approval in 1979 after being developed in the 1970s.^[2] The main objective of transdermal drug administration is to transport drugs into systemic circulation into the epidermis through the skin at a predetermined rate with little patient variability.^[3,4]

Transdermal patches, adhesive patches, or skin patches are all used to gradually administer a regulated amount of medication through the skin. The rate at which a liquid medicine held in a reservoir inside a skin patch can pass through the skin and into the bloodstream is controlled by a particular membrane. For use in a skin patch, some medications need to be mixed with chemicals like alcohol that boost their capacity to permeate the skin. Many different pharmaceuticals are delivered by skin patches, including scopolamine for motion sickness, nicotine for quitting smoking, estrogen for menopause and to prevent osteoporosis after menopause, nitroglycerin for angina, lidocaine for shingles pain relief, and many others.^[5] the nicotine patch, which

distributes nicotine to aid in quitting smoking, was the most popular transdermal patch in the United States. The nicotine patch constantly reduces the smoker's desire for cigarettes by releasing throughout the course of sixteen hours, nicotine. To avoid motion sickness without the need to re-swallow pills, the scopolamine patch is worn behind the ear and releases the alkaloid for three days. The 72-hour action of the fentanyl patch results in long-lasting pain alleviation. Additionally, an estrogen-progestin contraceptive patch requires only once-weekly application, which is a relief for women who find it difficult to take one pill each day. Europe has approved the first commercially available vapour patch for quitting smoking. Using a rivastigmine patch, the first transdermal treatment for Alzheimer's condition was administered.^[6]

Principle of transdermal permeation^[7]

The skin was once thought to be an impermeable barrier that provided protection, but later studies showed that it could be used as a route for systemic delivery. Given that only a few hundredths of a millimetre of tissue separates the surface of the skin from the underlying capillary network, the skin is the most active and easily accessible organ in the body. Following are the many procedures involved in getting a medication from a patch into your bloodstream:

1. Drug diffusion from the drug reservoir to the rate-regulating membrane.
2. Drug diffusion through the stratum corneum from the rate-limiting membrane.

3. Infiltration through a live epidermis and stratum corneum sorption.
4. Drug absorption by the dermal papillary layer's capillary network.
5. Impact on the intended organ.

Advantages of Transdermal Drug Delivery System (TDDS)^[8-10]

The following are some benefits of transdermal distribution over other conventional delivery methods.

1. Bypassing intestinal, salivary, and hepatic first pass metabolism, medicines have a higher bioavailability and are more effective.
2. The capability of self-administration.
3. Terminating the patch by removing it from the skin's surface at any time during treatment might rapidly halt the input of active ingredients in the event of an emergency.
4. There is very little variance between and among patients because the biological and structural makeup of skin is nearly the same in all persons.
5. Steer clear of stomach-related compatibility issues.
6. Because it is simple to use, it helps patients comply and avoids the risks and discomfort of parenteral medication.
7. A steady and ideal blood concentration time profile is attained, minimizing negative consequences.
8. Extended medication release from a single application, extending the duration of an action.
9. Drugs having limited therapeutic windows and short biological half-lives are used.
10. Preventing medication plasma levels from fluctuating.
11. Potent medicines' plasma concentrations are kept constant.
12. It is simple to stop receiving therapy at any time.
13. The traditional multiple dose profile is eliminated, improving patient compliance.
14. Transdermal route is utilized as an alternative to administer the medication candidate when oral route is problematic, such as with vomiting and diarrhea.

Disadvantages of Transdermal Drug Delivery System (TDDS)^[11-15]

There is a potential of allergic responses caused by the medication, adhesive, or other excipients, such as itching, rashes, local edema at the application site for the patch, and the need to stop the therapy.

1. Transdermal delivery may not be cost-effective.
2. High drug levels cannot be achieved in the blood or plasma.
3. Because of the impermeability of skin, only highly potent API can be delivered by this route.
4. Drugs with large molecular sizes have trouble being absorbed.
5. Ionic medicines cause issues.
6. Administering big doses, or more than 10 mg per day, is challenging.
7. Very low or high partition coefficient drugs are unable to enter the systemic circulation.

8. Drugs needing high blood levels cannot be administered using this delivery method.
9. Due to their limited permeability, drugs with hydrophilic characteristics are less suited than those with lipophilic characteristics.
10. Only tiny amounts of lipophilic medication can be injected under the skin.
11. The skin's ability to act as a barrier varies from one spot to another on an individual, from person to person, and also with age.
12. Drugs cannot be administered in a pulsatile manner with this system.
13. Unfit for high medication dosage.
14. The type of patch and the surrounding conditions may affect adhesion.

Factors Influence Transdermal Drug Delivery System^[16, 17]

1) Physiochemical properties of drug

- a) Size of drug molecule and molecular weight
- b) Partition coefficient and solubility
- c) Drug concentration
- d) pH condition

2) Formulation characteristics

- a) Release rate of drug
- b) Ingredients of formulation
- c) Presence of permeation enhancer.

3) Physiological factors

- a) Skin hydration
- b) Temperature and pH
- c) Diffusion coefficient
- d) Drug concentration
- e) Partition coefficient
- f) Molecular size and shape

4) Biological factors

- a) Skin hydration
- b) Skin age
- c) Blood flow
- d) Regional skin site.
- e) Skin metabolism
- f) Species difference

Types of transdermal patches

Single layer drug in adhesive patches

A single layer of an adhesive polymer is utilized in Fig. 1 as a reservoir for the medication dispersion. Underneath the single layer lies an impervious backing laminate. The medication is released from the backing laminate layer that supports the drug reservoir after being deposited in and adhering to the single polymer layer.^[18] The transdermal product Day trana® is a single layer drug in adhesive transdermal patch containing methylphenidate.

Multiple layer drug in adhesive patches

Drug release is controlled over time in multilayer transdermal patches, which have an adhesive layer and a drug reservoir layer.^[19,20] Multilayer systems consist of a permanent backing laminate as well as a temporary protective layer. Drug administration can be sustained for up to seven days with multilayer patches, which are used

to administer hormone therapy, quit-smoking aids, and painkillers.

Vapor transdermal patches

The single layer of adhesive polymer that makes up vapour transdermal patches has the ability to release vapour.^[19,20] there are numerous vapour dermal patches on the market that are utilized for various uses. For instance, the transdermal nicotine vapour patch nicoderm CQ® contains essential oils that, when released, can aid in quitting smoking. In 2007, this product was released on the European market.

Membrane moderated transdermal reservoir patches

A transdermal patch with a drug reservoir, an impermeable metallic plastic laminate backing layer, and a porous polymeric membrane that regulates drug release over time is shown in Fig. 1. The membrane is constructed from polymeric components, such as ethylene vinyl acetate copolymer and hypoallergenic adhesive polymer. The drug's molecular dispersion in a polymer matrix component of the preparation regulates the amount of drug in the transdermal patch.^[20,21]

Micro reservoir transdermal patches

In micro reservoir transdermal patches, matrix dispersion and a drug reservoir are integrated.

To make the reservoir, the medication is uniformly spread over a lipophilic polymer after being suspended in an aqueous solution of a hydrophilic polymer.

During dispersion, a large shear mechanical force is applied, which results in the formation of hundreds of tiny, impractical spheres. By adhering to a zero order rate of kinetic drug release, the drug release profile keeps the drug level in the plasma constant.

Crosslinking polymeric agents are widely used since the medicine dispersion needs to be thermodynamically stable.^[20, 22]

Matrix system drug in adhesive

The drug reservoir is created to distribute the drug on an adhesive polymer using single layer or multilayer transdermal patches, as shown in Fig. 1. By melting the sticky polymeric components or casting the drug-polymer matrix in solvent onto an impermeable backing layer.^[24] There are many commercial transdermal patches of this type on the market; for instance, the Climara® patch contains 100 micrograms of estradiol for one-day application and the NicoDerm® CQ patch contains nicotine to support quitting smoking for up to 10 weeks.

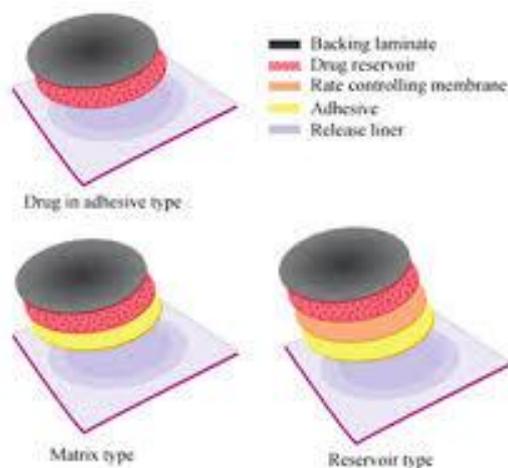


Fig. 1: Diagram of various types of transdermal patches.

Matrix System – Matrix Dispersion

A hydrophilic or lipophilic polymer matrix serves as the reservoir in a matrix transdermal patch, and the drug is uniformly dispersed in the matrix by placing the drug-polymer matrix over a plate with an impermeable laminate backing.^[23] A continuous medication flow through undamaged skin is provided by commercial

matrix dispersion patches like Nitro-Dur®, which comprises nitroglycerin and minitran.

Miscellaneous transdermal patches

Transdermal patches with adhesive tapes, transdermal gel, transdermal spray, iontophoretic delivery, and phonophoresis delivery are other FDA-approved transdermal matrix delivery methods.

Table I: FDA approved Transdermal delivery systems.

Drug	Product name	Transdermal delivery system
Flurandrenolide	Cordran® Tape	Transdermal tape
Testosterone	AndroGel®	Transdermal gel
Estradiol	Evamist®	Transdermal spray

Fentanyl HCl	IONSYS®	Iontophoretic patch
Insulin	Vyteris insulin patch®	Iontophoretic patch
Hydrocortisone	Tegaderm Patch	Electrophotophoresis

Preparation of transdermal patches

Transdermal medication delivery patches can be made in a variety of ways.

Mercury substrate method

The appropriate amount of medication is dissolved in a preset amount of polymer solution combined with a plasticizer in this approach. The aforesaid solution should be agitated for a short period of time to generate a homogeneous dispersion before being poured into a glass ring that is put over the mercury surface in a glass petri dish. By putting an inverted funnel above the petri dish, the rate of solvent evaporation can be managed. The dried films must be kept in a desiccator.^[25,26]

Circular teflon mould method

In an organic solvent, polymer solutions in various ratios are utilized. The calculated amount of medication is dissolved in half of the same organic solvent. A plasticizer was added to the drug polymer solution. The entire mixture should be mixed before being poured into a round Teflon Mould.

The rate of solvent vaporization was also regulated by placing an inverted glass funnel on a Teflon Mould. For 24 hours, the solvent is allowed to evaporate. The dried films must be kept in a desiccator.^[27,28]

Glass substrate method

After allowing the polymeric solutions to expand, the desired amount of plasticizer and drug solution is added and mixed for 10 minutes. It is then set aside for a short period of time to allow any trapped air to escape before being poured into a clean and dry anumbra petriplate. By inverting a glass funnel over the petriplate, the rate of solvent evaporation can be regulated. After drying overnight, the dried films are removed and stored in a desiccator.^[29,30]

By Using IPM Membranes Method

This method involves dispersing the medicine over a period of 12 hours in a magnetic stirrer in a solution of water and propylene glycol containing carbomer 940 polymers. Triethanolamine is to be added in order to neutralize the dispersion and make it viscous. If the drug's solubility in aqueous solution is particularly poor, buffer pH 7.4 can be employed to create solution gel. Incorporating the produced gel into the IPM membrane.^[31,32]

Using EVAC Membrane Method

The target transdermal treatment system can be made using carbopol reservoir gel, polyethylene (PE), and ethylene vinyl acetate copolymer (EVAC) membranes as rate control membranes. When the drug is not soluble in water, gel is created using propylene glycol. Propylene

glycol is used to make gel when the medication is not soluble in water. Propylene glycol is used to dissolve the drug, which is then combined with carbopol resin and neutralised with a 5% w/w sodium hydroxide solution.

On top of the medication (in gel form), a backing layer sheet is applied, covering the designated region. A rate-regulating membrane will be placed over the gel to produce a leak-proof device, and the edges will be heated to seal.^[31, 32]

Aluminium backed adhesive film method

If the loading dose is larger than 10 mg, transdermal drug delivery systems may result in unstable matrices. It is ok to use adhesive film with an Aluminium backing. Chloroform is the preferred solvent for its manufacture because it is soluble in the majority of medications and adhesives. Chloroform is used to dissolve the medicine, and then adhesive material is added and dissolved in the drug solution. Aluminium foil is used to line a specially constructed Aluminium former, and closely fitted cork blocks are used to blank off the ends.^[30,33]

Asymmetric TPX Membrane Method

A heat sealable polyester film (type 1009, 3m) with a backing membrane concave of 1 cm in diameter can be utilized to create a prototype patch. A poly (4-methyl-1-pentene) asymmetric membrane made of TPX is used to cover the concave membrane, and an adhesive is used to seal it.^[20]

Circumstances for the Use of Transdermal Patches

When a patient needs an alternative form of drug delivery because they have terrible side effects (including constipation) and are unable to take oral medications due to dysphagia.

Where effective management could help with pain control. For patients with cognitive impairment or those who are unable to self-medicate with their analgesics for other reasons, this could be helpful.^[5,20]

Circumstances Where Transdermal Patches Should Not Be Used

Transdermal patches should not be used when:

- 1) Acute pain must be treated.
- 2) When a quick dose titration is necessary.
- 3) Where the dosage needed is 30 mg/24 hours or less.^[5,20]

Transdermal Patch Testing and Evaluation Drug excipients interaction studies

To create a stable product, the medicine and excipients must be compatible, and it is essential to look for any potential physical and chemical interactions. By contrasting their physiochemical properties, such as

assay, melting endotherms, distinctive wave numbers, and absorption maxima, etc., interaction investigations are frequently conducted utilizing thermal analysis, FT-IR studies, UV, and chromatographic techniques.^[20]

Drug content

The patch must have a specific portion of the patch dissolve in a specific volume of an appropriate solvent. Following the solution's filtering through a filter medium, the drug content must be determined using the appropriate technology (UV or HPLC). Every value is the average over three samples.^[34,35]

Weight uniformity

Before testing, the produced patches must be dried at 60°C for 4 hours. A predetermined patch area must be divided into various patches and weighed using a digital balance. From the individual weights, the average weight and standard deviation values should be computed.^[35,36]

Thickness of the patch

Using a digital micrometer, the thickness of the drug-loaded patch is measured at several sites in order to calculate the average thickness and standard deviation for the patch's thickness.^[36,37]

Flatness test

Each film must have three longitudinal strips cut off it, each at a different location, such as the Centre, the left, and the right. Each strip's length was measured, and any variations in length due to non-uniform flatness were quantified by calculating the percent constriction—0% constriction being equal to 100% flatness.^[38]

Percent moisture uptake: The weighed films must be stored in desiccators with saturated potassium chloride solutions at room temperature for 24 hours in order to maintain 84% relative humidity. The films must be reweighed after 24 hours to calculate the percentage moisture uptake using the procedure below.^[37,39]

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

Moisture loss

Each of the created films needs to be weighed before being stored at 40°C in a desiccator with calcium chloride. The films must be reweighed after 24 hours to calculate the percentage of moisture loss using the procedure below.^[40]

% Moisture Loss = [Initial wt – Final wt/ Final wt] × 100

Water Vapor Transmission Rate (WVTR) Studies

As transmission cells, glass vials with the same diameter were employed. These transmission cells were properly cleaned before being dried in an oven for a while at 100 °C. In each cell, 1g of anhydrous calcium chloride was added, and the corresponding polymer film was glued over the brim. The cell were precisely weighed and stored at 84% relative humidity in a closed desiccator with saturated potassium chloride solution. The cells

were removed from storage and weighed. The following formula was used to determine how much water vapour was transported.^[29,40]

Water Vapor Transmission Rate = Final Weight –Initial Weight/ Time X Area

It is expressed as the number of grams of moisture gained/hr /cm.sq.

Swellability

The 3.14 cm² patches were weighed, placed in a petri dish with 10 ml of double-distilled water, and left to drink. At predetermined time intervals, the patch's weight increased until a steady weight was noticed.

The degree of swelling (S) was calculated using the formula,

$S (\%) = W_t - W_o / W_o \times 100$

Where S is percent swelling

W_t is the weight of patch at time t and

W_o is the weight of patch at time zero.

Folding endurance

It is necessary to cut a strip of a particular region uniformly and fold it repeatedly until it breaks. The quantity of folds that the film could withstand at the same location without breaking determined its folding endurance.^[41]

Percentage elongation break test

By noting the length shortly before the break point, the percentage elongation break is to be calculated. The formula below can be used to calculate the % elongation.^[42]

Elongation percentage = $[L_1 - L_2 / L_2] \times 100$ Where, L₁ is the final length of each strip and L₂ is the initial length of each strip.

Tensile strength

Using a universal strength testing machine, the tensile strength of the film was determined. The device had a 1 g sensitivity. There were two load cell grips in it. The upper one is adjustable, while the lower one is fixed. Between these cell grips, a test film the size of (4 1 cm²) is attached, and force is gradually increased until the film breaks.^[33] The dial reading in kilograms is directly converted to the tensile strength of the film. The following is how tensile strength is stated.

Tensile strength = Tensile load at break / Cross section area

Skin irritation study

Healthy rabbits (weighing an average of 1.2 to 1.5 kg) can be used for assessing skin sensitivity and irritation. Cleaning the rabbit's dorsal surface (50 cm²), trimming off any hair, cleaning the area with rectified spirit, and applying the appropriate formulas to the skin are all necessary steps. After 24 hours, the patch must be removed, and the skin must then be examined and graded

into one of five categories based on the degree of the skin injury.^[36]

In-vitro drug release studies

For measuring the drug release from the produced patches, the paddle over disc method (USP apparatus V) can be used. Dry films that have a given thickness must be cut into precise shapes, weighed, and adhered to a glass plate with an adhesive. The apparatus was then adjusted to 32.0 ± 0.5 °C and the glass plate was submerged in 500 cc of the dissolution medium (phosphate buffer, pH 7.4). Then, with the paddle rotating at a speed of 50 rpm, it was positioned 2.5 cm away from the glass plate. Samples (5 ml aliquots) can be taken out at convenient intervals for up to 24 hours and then analyzed by UV or High performance liquid chromatography (HPLC). The experiment must be carried out in duplicate three times so that the mean value can be determined.^[43]

In-vitro skin permeation studies

Using a diffusion cell, one can do an in vitro permeation research. Male Wistar rats weighing 200–250 g, with the entire thickness of their abdomen skin. The dermal side of the skin was carefully cleaned with distilled water to remove any adhering tissues or blood vessels, and equilibrated for an hour in diffusion medium or phosphate buffer pH 7.4 before beginning the experiment. Hair from the abdominal region is to be carefully removed using an electric clipper. Diffusion medium is added to the diffusion cell, which is then put on a magnetic stirrer with a tiny magnetic bead to ensure that the diffusion is distributed evenly. A thermostatically controlled heater was used to keep the cell's temperature at 32 ± 0.5°C. The isolated rat skin piece needs to be put in the diffusion cell between the compartments with the donor compartment's epidermis facing up. At regular intervals, a sample volume of a specific volume is to be taken out of the receptor compartment, and an equal volume of fresh medium is to be replaced. Samples must be filtered through a filtering media before being analyzed using high performance liquid chromatography (HPLC) or spectrophotometry.^[44,45]

The permeability coefficients were calculated by dividing the flux by the initial drug load (mg cm⁻²). Flux is calculated as the slope of the curve between the steady-state values of the amount of drug penetrated (mg cm⁻²) vs. time in hours.

In-vivo studies: In-vivo assessments are the most accurate representations of a drug's effectiveness. In-vivo research can completely examine the variables that cannot be considered during in-vitro experiments.

The following methods can be used for TDDS in-vivo evaluation:

Animal models
Human volunteers

Human models: After applying the patch to human volunteers, the transdermal device's last development stage entails gathering pharmacokinetic and pharmacodynamics data. Clinical studies have been carried out to evaluate the effectiveness, risks, side effects, patient compliance, etc. of a treatment.

Stability Studies: In accordance with the ICH recommendations, stability studies must be carried out by holding TDDS samples at 40.0 ± 0.5 °C and 75% RH for six months. At 0, 30, 60, 90, and 180 days, the samples were taken out and properly analyzed for drug content.^[36,46]

Limitations for TDDS Selection

This technique cannot be used to give all medications; the drug must possess some beneficial Physico-Chemical characteristics.^[1]

Not appropriate for medications that need high plasma levels.

Not suited for medications that cause contact dermatitis and skin rashes.

Drugs having a high molecular weight are not appropriate.

Not appropriate for medications that are metabolized as they pass through the skin.

Since the skin is a very effective barrier to drug penetration, a substantial variety of medications cannot be administered by the transdermal route. Only a low dose may be used for administration.

The skin's ability to act as a barrier varies from one spot to another within a single individual, between individuals, and with age.

CONCLUSION

Regular doses of various medications can be administered painlessly, conveniently, and possibly effectively using transdermal drug delivery. Better medication absorption, wide selection of medicines available Low cheap and simple to use with little issues and negative effects. Therapeutic agent distribution topically has several advantages over traditional oral and invasive medication delivery strategies. Transdermal drug delivery offers a number of significant benefits, including the restriction of hepatic first-pass metabolism, improvement of therapeutic effectiveness, and preservation of a constant plasma level of the drug. This article offers crucial details on the formulation and assessment of transdermal medication delivery systems.

REFERENCES

1. Jain NK. Advances in controlled and novel drug delivery, CBS Publishers and distributors, New Delhi, 2001; 1: 108-110.
2. Mali AD. An updated review on transdermal drug delivery systems. *Skin*, 2015; 8(9).
3. Tanwar H, Sachdeva R. Transdermal drug delivery system: A review. *International journal of pharmaceutical sciences and research*, 2016; 1, 7(6): 2274.

4. Rani S, Saroha K, Syan N, Mathur P. Transdermal patches a successful tool in transdermal drug delivery system. *Plegia Res. Lib*, 2011; 2(5): 17-29.
5. Shah S, Shah D. Transdermal drug delivery technology revisited: recent advances. *Pharmainfo. Net*, 2008; 6(5): 3-8.
6. Azim AA, El-Ashmoony M, Swealem AM, Shoukry RA. Transdermal films containing tizanidine: in vitro and in vivo evaluation. *Journal of drug delivery science and technology*, 2014; 1, 24(1): 92-9.
7. Aggarwal G, Dhawan S. Development, fabrication and evaluation of transdermal drug delivery system- A review. *Pharmainfo. Net*, 2009; 7(5): 1-28.
8. Arunachalam A, Karthikeyan, Vinay Kumar D, Prathap M, Sethuraman S, Ashutosh Kumar S and Manidipa S. Transdermal Drug Delivery System: A review. *Current Pharma Research*, 2010; 1(1): 70-81. 3.
9. Patel Divyesh, Patel Nirav, Parmar Meghal, Kaur Navpreet. Transdermal delivery System: An overview. *International Journal of Biopharmaceutical & Toxicological Research*, 2011; 1(1): 61-80.
10. Tyagi RK, Chandra A, Singh D and Rahman MdA. Transdermal Drug Delivery System (TDDS): an overview. *International Journal of Pharmaceutical Sciences and Research*, 2011; 2(6): 1379-1388.
11. Latheeshjlal L, P Phanitejaswini, Y Soujanya, U Swapna, V Sarika, G Moulika. *Int. J. Pharm. Res.*, 2011; 3(4): 2140-2148.
12. Paudel KS, Milewski M, Swadley CL, Brogden NK, Ghosh P, Stinchcomb AL. *Ther. Delivery*, 2010; 1: 109-131.
13. Hayat S, Nawaz R. *World J. Pharm. Pharm. Sci.*, 2014; 3(12): 124-137.
14. Murugan KB, Kumar PP. *World J. Pharm. Pharm. Sci.*, 2014; 3(8): 277-292.
15. Patel H, Dr. Patel U, Bhimani B, Daslaniya D, Patel G. *Int. J. Pharm. Res. Bio-Sci.*, 2012; 1(3): 42-65.
16. Jhawar VC, Saini V, Kamboj S, Maggon N. *Int. J. Pharm. Sci. Rev. & Res.*, 2013; 20(1): 47-56.
17. Latheeshjlal L, P Phanitejaswini, Y Soujanya, U Swapna, V Sarika, G Moulika. *Int. J. Pharm. Res.*, 2011; 3(4): 2140-2148.
18. M. Imani, F. Lahooti-Fard, S. M. Taghizadeh and M Takrousta, Effect of adhesive layer thickness and drug loading on estradiol crystallization in a transdermal drug delivery system, *AAPS Pharm. Sci. Tech.*, 2010; 11: 1268-1275; <https://doi.org/10.1208/s12249-010-9494-9>
19. S. Dhiman, T. G. Singh and A. K. Rehni, Transdermal patches: A recent approach to new drug delivery system, *Int. J. Pharm. Pharm. Sci.*, 2011; 3: 26-34. 25.
20. S. Rani, K. Saroha, N. Syan and P. Mathur, Transdermal patches a successful tool in transdermal drug delivery system: An overview, *Der Pharm. Sinica*, 2011; 2: 17-29.
21. B. Berner and V. A. John, Pharmacokinetic characterization of transdermal delivery system, *J. Clin. Pharmacol.*, 1994; 26: 121-134.
22. C. L. Stevenson, J. T. Jr. Santini and R. Langer, Reservoir-based drug delivery systems utilizing microtechnology, *Adv. Drug Deliv. Rev.*, 2012; 64: 1590-1602. <https://doi.org/10.1016/j.addr.2012.02.005>
23. S. Cherukuri, U. R. Batchu, K. Mandava, V. Cherukuri, K. R. Ganapuram, Formulation and evaluation of transdermal drug delivery of topiramate, *Int. J. Pharm. Investig.*, 2017; 7: 10-17. https://doi.org/10.4103/jphi.JPHI_35_16
24. P. J. Hughes, M. K. Freeman and T. M. Wensel, Appropriate use of transdermal drug delivery systems, *J. Nurs. Edu. Pract.*, 2013; 3: 129-138.
25. Mohamed Aqil, Yasmin Sultana and Asgar Ali, Matrix Type Transdermal Drug Delivery Systems of Metoprolol Tartrate, *Invitro Characterization*, *Acta Pharm.*, 2003; 53: 119-12.
26. Sridevi S, Chary M.G, Krishna D.R, Prakash V, Diwan, Pharmacodynamic Evaluation of Transdermal Drug Delivery System of Glibenclamide in Rats, *Indian Journal of Pharmacology*, 2000; 32: 309-312.
27. Sharma Teja, Rawal Gaurav, Transdermal Therapeutic Systems, An overview, *International Journal of Pharmaceutical & Biological Archives*, 2011; 2(6): 1581-1587.
28. Wiechers J, Use of Chemical Penetration Enhancers in Transdermal Drug Delivery-Possibilities and Difficulties, *Acta Pharm.*, 1992; 4: 123.
29. Manvi F.V, Dandagi P.M, Gadad A.P, Mastiholimat V.S and Jagdeesh T, Formulation of Transdermal Drug Delivery System of Ketotifen Fumarate, *IJPS*, 2003; 65(3): 239-243.
30. Parthasarathy G, Bhaskar reddy K and Prasanth V.V, Formulation and Characterization of Transdermal Patches of Naproxen with various polymers, *International Journal of Comprehensive Pharmacy*, 2011; 6(07): 1-3.
31. Shalu Rani, Kamal Saroha, Navneet Syan, Transdermal Patches a successful tool in Transdermal Drug Delivery System: An overview, *Der Pharmacia Sinica*, 2011; 2(5): 17-29.
32. Azhar Ahmed, Nirmal Karki, Rita Charde, Manoj Charde, Bhushan Gandhare, Transdermal Drug Delivery Systems, An overview, *International Journal of Biomedical and Advance Research*, 2011; 02(01): 38-56.
33. Kavitha K and More Mangesh Rajendra, Design and Evaluation of Transdermal Films of Lornoxicam, *IJPBS*, 2011; 2(2): 54-62.
34. Prabhu Prabhakara, Marina Koland, Preparation and Evaluation of Transdermal Patches of Papaverine Hydrochloride, *International Journal of Research Pharmaceutical Sciences*, 2010; 1(3): 259-266.
35. Mutalik, N, Udupa, Glibenclamide Transdermal Patches, Physicochemical, Pharmacodynamic and

- Pharmacokinetic Evaluations, Journal of Pharmaceutical Sciences, 2004; 93(6): 1557-1594.
36. Pravin Gavali, Atul, Gaikwad, Radhika P.R, Sivakumar T, Design and Development of Hydroxypropyl Methylcellulose based polymeric film of Enalapril Maleate, International Journal Of Pharmtech Research, 2010; 2(1): 274-282.
 37. Koteswar K.B, Udupa N and Vasantha Kumar, Design and Evaluation of Captopril Transdermal Preparations, Indian Drugs, 15(29): 680-685.
 38. Kamal Saroha, Bhavna Yadav, Benika Sharma, Transdermal Patch, A Discrete Dosage Form, International Journal of Current Pharma Research, 2011; 3(3): 98-108.
 39. Priyanka Arora, Biswajit Mukherjee, Design Development Physicochemical and in-vitro Evaluation of Transdermal Patches Containing Diclofenac Diethylammonium Salt, Journal of Pharmaceutical Sciences, 2002; 91(9): 2076-2089.
 40. Sankar V, Velrajan G, Palaniappan R and Rajasekar S, Design and Evaluation of Nifedipine Transdermal Patches, Indian journal of Pharmaceutical, Sciences, 2003; 65(5): 510-515.
 41. Yuveraj Singh Tanwar, Chetan Singh Chauhan, Anshu Sharma, Development and Evaluation of Carvedilol Transdermal Patches, Acta Pharm, 2007; 57: 151-159.
 42. Diveyesh Patel, Nirav Patel, Meghal Parmar, Transdermal Drug Delivery System, Review, International Journal of Biopharmaceutical and Toxicological Research, 2011; 1(1): 61-80.
 43. Deepak Gondaliya and Kilambi Pundarikakshudu, Studies in Formulation and Pharmacotechnical Evaluation of Controlled Release Transdermal Delivery System of Bupropion, AAPS Pharmscitech, 2003; 4(1): 1-9.
 44. Vamshi Vishnu Y, Chandrasekhar K, Ramesh G and Madhusudan Rao Y, Development of Mucoadhesive Patches for Buccal Administration of Carvedilol, Current Drug Delivery, 2007; 4: 27-39.
 45. P,mayorga, F, Puisieux, Couarraze, G, Formulation study of Transdermal delivery systems of primaquine, International journal of Pharmaceutics, 1996; 132: 71-79.
 46. Mohamed Aqil, Yasmin Sultana Asgar Ali, Matrix Type Transdermal Drug Delivery Systems of Metoprolol Tartrate, In Vitro Characterization, Acta Pharm, 2003; 53: 119-125.