WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 11, 1945-1958. Review Article ISSN 2277–7105

AN OVERVIEW: TRANSDERMAL PATCH FOR TOPICAL DRUG DELIVERY SYSTEM FOR ANTIFUNGAL EFFECT

Rajat Rohilla*, Anshu and Jiyaulhak

Research Scholar, Department of Pharmaceutics, IIMT College of Medical Science, IIMT University, Ganga Nagar, Meerut, Uttar Pradesh-250001.

Article Received on
18 April 2024,

Revised on 08 May 2024,
Accepted on 28 May 2024

DOI: 10.20959/wjpr202411-32692

***Corresponding Author**
Rajat Rohilla
Research Scholar, Department of Pharmaceutics, IIMT College of Medical Science, IIMT University, Ganga Nagar, Meerut, Uttar Pradesh-250001.

ABSTRACT

Transdermal drug delivery system was 1st introduced more than 20 years ago. This system is type of traditional drug delivery system in which drug under goes to the systemic circulation through the protective barrier i.e. skin. Skin is a major target and barrier for topical and transdermal drug delivery, but the low diffusion rate across the stratum corneum is a major hindrance. Various methods have been conducted to improve drug permeation rate temporarily via skin, such as by help of elastic vesicles or skin enhancers. Vesicular systems like ethosomes, are controversial methods for transdermal drug delivery due to their higher penetration rate through the skin due to their ethanolic content. Nanosuspension are colloidal dispersion of nanosized drug particle stabilized by surfactant particle of nanosuspension is less than 1mm to 200-600mm.

KEYWORDS: Anti-fungal, Topical route, Transdermal patch, Skin.

INTRODUCTION

Topical drug delivery system involves administering drugs through the skin for systemic distribution. This method offers several advantages, such as avoiding the gastrointestinal tract and providing controlled release, leading to improved patient compliance and reduced side effects. It is a non-invasive method and it allow the drug substance to enter the systemic circulation and provide desirable therapeutic effect.

Transdermal drug delivery systems (TDDS), commonly referred to as "patches," are medication dosage forms that deliver a regulated distribution of an amount of medication

across a patient's skin that is therapeutically effective. Due to its distinctive benefits, such as longer therapeutic efficacy, avoidance of first-pass metabolism, and simple therapy termination, TDDS has attracted intentional consideration for either local or systemic drug administration. Rate-controlling membranes, drugs, penetration enhancers, adhesives, backing laminates, release liners, etc. These are the core elements of TDDS. TDDS is divided into reservoir, matrix, and micro reservoir systems based on their architectural differences.[1] People have applied substances to the skin for medicinal purposes for thousands of years, and in the modern period, numerous topical formulations have been created to address regional medical issues.[2] It provides several benefits, including a longer therapeutic impact, fewer side effects, increased bioavailability, better patient compliance, and simple medication therapy cessation. The appendageal, transcellular, and intercellular pathways are the three main ways that drugs enter the body. When giving medication by this route, it is important to consider the following aspects: skin age, condition, physicochemical characteristics, and environmental conditions.[3] The phrase "transdermal delivery system" broadly refers to any medicine formulation applied topically to release the active component into the bloodstream. Transdermal therapy systems have been created to offer controlled and continuous drug administration to the systemic circulation through the skin.[4]

Human skin serves as a crucial barrier against endogenous substances like water and xenobiotic materials like chemicals and drugs, acting as the first line of defences in the human body. Skin consists of three primary layers are Epidermis, Dermis and Hypodermis (Figure 1).

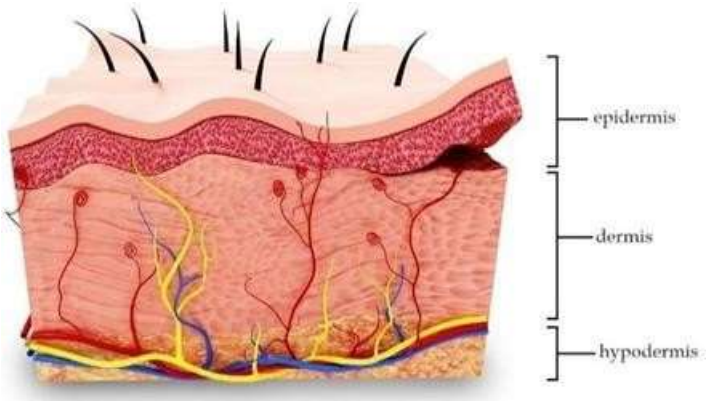


Fig. 1: Layers of skin.

Epidermis is act as a protective outer most layer or shield to the internal tissues of the body from the external environment. It has multiple layers, including- *Stratum Corneum* (The

outermost layer of the epidermis, composed of dead corneocytes filled with keratin, provides skin strength and waterproofing), *Stratum Lucidum* (This layer, found in specific body parts like palms and feet, consists of clear, flattened cells densely packed with keratin), *Stratum Granulosum* (The epidermis layer, containing keratin granules and proteins, aids in keratinization, a process where epidermal cells become filled with keratin and die, forming the protective skin barrier).

Dermis, the middle layer of the skin that placed between epidermis and hypodermis. It is composed of various tissues that provide mechanical support, elasticity, and nourishment. It contains collagen and elastic fibers, which provide strength and support to the skin, while allowing it to stretch and return to its normal shape. These fibers are crucial for maintaining the skin's firmness and flexibility. The dermis, a vital part of the skin, contains blood vessels that supply oxygen and nutrients to skin cells, regulating body temperature and giving skin its pinkish hue. It also contains sensory receptors like Meissner's and Pacinian corpuscles, which detect touch, pressure, and vibration, transmitting these signals to the brain.

Hypodermis the hypodermis, also known as subcutaneous tissue or subcutis, is the innermost layer of the skin, composed of adipose and connective tissue, and serves as a cushioning layer that insulates the body. Some of the main functions of hypodermis like- Insulation, Energy storage, Protection.

Transdermal therapeutic drug delivery system

This method has also been utilized to administer a variety of medications, including hydrophilic and hydrophobic substances.[5] Drugs may be effectively made available throughout the body with TDDS. Transdermal patches are cutting-edge drug delivery methods that are applied to the skin to provide a systemic effect. The use of the TDDS system has various clinical advantages over alternative methods.[12]

It offers reliable medication release, maintains a stable blood level profile, which might lessen systemic side effects, is practical, user-friendly, and helps to increase patient acceptance. Drugs that are continuously absorbed over an extended period don't need to be dosed as frequently, which improves patient compliance.[6] To improve the transdermal delivery and dermal absorption of drugs, a variety of strategies have been used. These include increasing the effective concentration of the drug in the vehicle, improving the partitioning between the formulations, using chemical penetration enhancers, and using various physical

enhancement techniques. The use of carrier systems such as liposomes, nanoparticles, and microparticles has also been investigated.[7,8]

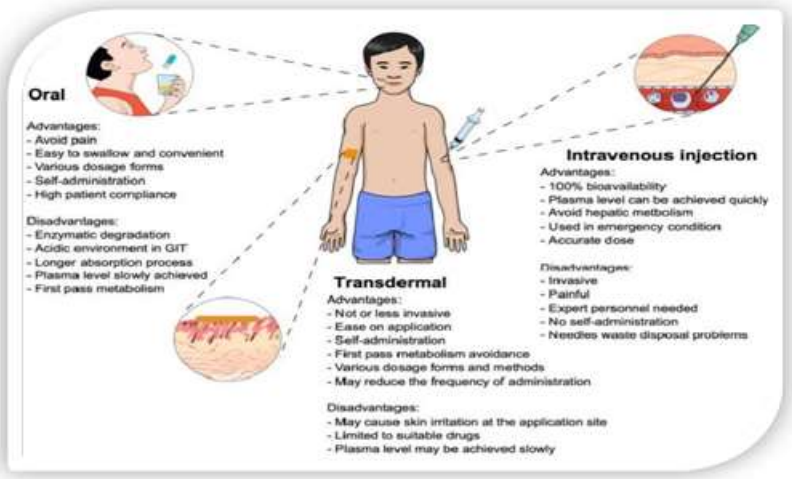
Nanomaterials offer substitutes for common transdermal medication delivery methods, including patches, gels, sprays, and lotions, but it's important to comprehend how such methods work.[9] Cutaneous formulation keeps drug levels within the therapeutic range for an extended length of time, making sure they don't drop below the minimum effective concentration or rise above the maximum effective concentration.[10]

Advantages of transdermal therapeutic system[14,15,16]

- Preventing a drug's first-pass metabolism
- Transdermal drugs provide a consistent infusion of a medicament over a long period
- The streamlined drug schedule improves patient compliance, lowers side effects, and reduces both intra and inter-patient variability.
- No disruption of the digestive and gastrointestinal fluids
- Keeps blood levels consistent, constant, and under control for a longer period.
- They can prevent problems with gastrointestinal medicine absorption.
- They can take the place of oral medicine administration when it is not appropriate.
- Limited side effects and a localized effect.
- Enhancing medication bioavailability and decreasing dosage frequency.
- Keeping medication delivery profiles constant
- Characteristics that are similar to those of intravenous infusion.

Disadvantages of transdermal therapeutic system[17]

- Several drugs, particularly those with hydrophilic properties that penetrate the skin too slowly, may not be effective at therapeutic levels.
- Erythema, itching, and localized edema may be brought on by the medication, the adhesive, or any excipients in the patch formulation.
- The skin's barrier function varies with age, from one location to another for the same individual, and also from person to person.
- Ionic medicines cannot be delivered via TDDS.
- High drug levels cannot be achieved via TDDS in the blood or plasma.
- It is impossible to build TDDS for medications with enormous molecular weights.
- Pulsatile drug delivery is not possible with TDDS
- A medicine or formulation cannot be used to create TDDS if it irritates the skin.



Method of preparation

1. **The asymmetric TPX membrane method:** Heat-sealable polyester paper (type 1009, 3 m) with a concave of 1 cm diameter will be employed as the backing membrane to create a prototype patch. An asymmetric TPX poly-(4-methyl-1- pentene) membrane is used to cover a concave membrane, which is subsequently attached using an adhesive.[23]

2. **Circular Teflon molding method:** Solutions with different ratios of polymers are utilized in an organic solvent. Half as much of the same organic solvent is used to dissolve the calculated amount of medication. The second half of the organic solventis used to dissolve enhancers at various concentrations before they are applied. The plasticizer di-N-butyl phthalate is included in the drug-polymer solution. The entire mixture is agitated for 12 hours before being placed in a Teflon mold. In a laminar flow hood model with a speed of 0.5 m/s, the molds are put on a flat surface and covered with an inverted funnel to control solvent vaporization. For 24 hours, the solvent is allowed to evaporate. Before evaluation, the dried films are kept for a further 24 hours at 250.5°C in a desiccator containing silica gel to remove aging effects.[24]

3. **Mercury substrate method:** The technique involves dissolving the medication and plasticizer in a polymer solution. Pour the solution into a levelled mercury surface, cover with an inverted glass vial, and agitate for 10 to 15 minutes to create a homogeneous dispersion for managing the evaporation of solvent.[25]

4. **IPM membrane method:** This approach involves mixing the medicine with water and propylene glycol to dissolve it, then stirring the mixture for 12 hours in a magnetic

stirrer. Triethanolamine is to be added in order 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. The gel that has been created will be integrated into the IPM membrane.[26]

5. **EVAC membrane method:** 1% Carbopol reservoir gel, polyethylene (PE), and ethylene vinyl acetate copolymer (EVAC) membranes can be employed as rate control membranes to prepare the target transdermal treatment system. Propylene glycol is used to make gel when the medication is not soluble in water. Propylene glycol is used to dissolve the drug, Carbopol resin is then added to the mixture, and the mixture is then neutralized using 5% sodium hydroxide solution. The medication is applied to a backing layer sheet that covers the designated region and is in the form of a gel. To create a leak-proof device, a rate-controlling membrane is placed over the gel, and the edges are heated to seal them.[27]

6. **Aluminium backed adhesive film method:** In the loading dose is larger than 10 mg, transdermal drug delivery systems may result in unstable matrices. The method of using adhesive film with aluminium backing is appropriate. Chloroform is the preferred solvent for its manufacture because it is soluble in the majority of medications and adhesives. The medicine is dissolved in chloroform, and then adhesive material is added and dissolved in the drug solution. Aluminium foil linesa custom-made aluminium former, which has its ends blanked off with tightly-fitting cork blocks.[28]

Transdermal bioavailability-affacting factors[31,32]

Physical-chemical variables

1. **Skin hydration:** The permeability of skin rises dramatically when it comes into touch with water. The most crucial aspect in promoting skin permeability is hydration. Therefore,humectant usage occurs during transdermal administration.

2. **Temperature and Ph:** With temperature change, drug permeability increases, with a drop-in temperature, the diffusion coefficient falls. Depending on the pH and pKa or pKb values, weak acids and bases separate. The amount of medication in skin is based on the percentage of unionized drug. Thus, a significant factor impacting medication penetration is temperature, along with pH.

3. **Diffusion coefficient:** Drug diffusion coefficient affects drug penetration. The features of the drug, the diffusion medium, and their interactions determine the drug's diffusion coefficient at a constant temperature.

4. **Drug concentration:** The flux is inversely correlated with the gradient of concentration across the barrier, and the gradient will be bigger if the drug concentration is higher across thebarrier.

5. **Partition coefficient:** For effective action, the ideal partition coefficient (K) is needed. High K drugs are not yet ready to leave the lipid layer of skin. Additionally, low-K medicines won't permeate the body.

6. **Molecular Size and Shape:** Drug absorption and molecular weight are unfavourably associated; tiny molecules enter more quickly than large ones.

Biological factors

i. **Skin condition:** Acids, alkalis, and several solvents, including methanol and chloroform, harm skin cells and encourage penetration. Skin problems change depending on the patient's state of illness. Although the skin is a better barrier when it is intact, the aforementioned factors affect penetration

ii. **Skin age:** Younger skin is more porous than older skin. Children have more sensitive skin when it comes to toxin absorption. Consequently, one of the factors influencing medication penetration in TDDS isskin age.

iii. **Blood flow:** Transdermal absorption may be influenced by changes in peripheral circulation.

iv. **Regional skin site:** Site differences include differences in appendage density, stratum corneum type, and skin thickness. All of these variables have a big impact on penetration.

v. **Skin metabolism:** Steroids, hormones, chemical carcinogens, and some medicines are all processed by the skin. Therefore, skin metabolism determines how well a medicine penetratesthe skin.

vi. **Species differences:** The penetration is affected by the thickness, density, and keratinizationof the skin, which differ from species to species.

Types of transdermal patch[21]

1. **Single layer drug in adhesive:** In this form, the medicine is included in the sticky

layer. The release of the medicine into the skin is accomplished by the adhesive layer, which also acts to cling several layers together. There is a backer and a temporary liner around the adhesive layer.

2. **Multi-layer drug in adhesive:** This type is comparable to the single layer but includes an immediate drug-release layer in addition to the adhesive layer, which makes it different from other layers that have a controlled release.
3. **A vapour patch:** The adhesive layer in this kind of patch serves as an exchange, which is frequently utilized to release essential oils in decongestion, in addition to holding the other layers together.
4. **A reservoir system:** In this technique, a membrane that controls the flow rate and an impervious backing layer are sandwiched together to form the drug reservoir. Only through the membrane that regulates the release rate does the medication release. The medication can be in a solution, suspension, or gel, or dispersed in a solid polymer matrix in the drug reservoir compartment.

Table 1: Materials used in the formulation of Transdermal Patch.

S. No.	Chemical required
1.	Itraconazole
2.	Polyvinyl pyrrolidone
3.	Cellulose derivatives
4.	PEG 400%
5.	Methanol
6.	HPMC
7.	Organoleptic agents

Evaluation of prepared itraconazole nanosupnsionloadedtransdermal patch

- **Scanning electron microscopy (SEM)**

Under a scanning electron microscope, the manufactured, optimized transdermal patch with itraconazole nanoparticles was examined for morphology. Double-sided adhesive tape was used to fix the sample to the slab surface, and various magnifications of scanning electron photomicrographs were taken.

- **Particle Size and Poly dispersibility index**

The particle size analyzer Photon Correlation Spectroscopy (PCS) Delsa Nano C (Beckman Coulter Counter, USA) was employed to determine particle size and polydispersibility index. For the measurements, samples were suitably diluted with the aqueous phase of the formulation. Polystyrene cuvettes were used to store the samples, and observations and were

carried out at a fixed angle of 165°.

- **Drug content**

In 100 ml of Phosphate Buffered Saline (PBS) 7.4 buffer, 50 mg of drug-equivalent nanoparticles were distributed, and the mixture was agitated for two hours. Samples were appropriately diluted before being examined at 265 nm in a UV spectrophotometer.

- **Entrapment efficiency**

Itraconazole-loaded nanoparticles' free drug concentration in the aqueous phase was assessed. The created suspension of nanoparticles was centrifuged for 45 minutes at 10,000 rpm in a high-speed cooling centrifuge.

- **Thickness**

Using a micrometer, the resultant films' thickness was determined. Five different spots on each film have been utilized to measure its thickness, and the mean values were determined.

- **Tensile strength**

Using a tensiometer, the patch's tensile strength was determined. There are two load cell grips in it. The upper one could be moved, but the lower one was fixed. Between these cell grips, 2 x 2 cm2 film strips were fastened, and force was gradually applied until the film snapped. The dial reading in kilograms was used todetermine the tensile strength.

- **Folding endurance**

This test was run to determine how brittle the prepared films were. The films were folded repeatedly in the same spot until they completely broke down. The number of folds necessary to rupture the films was calculated.

- **Moisture uptake**

The films were placed in a silica gel-filled desiccator for 24 hours, after which they were weighted (Wi) using a Schimatzu digital balance. The films were then moved toa different desiccator with saturated sodium chloride solution (relative humidity 75%) at 25° until a consistent weight was achieved. The patches were removed after equilibrium was reached and weighed (Wf). The following equation was used to determine moisture uptake capacity:

- **Moisture content**

The patch compositions were weighed (Wi) and kept at 25° in a desiccator with silica gel until they showed a constant weight (Wd). The following equation was used to determine the moisture content:

Were

Wd = weight of dried polymers =weight after swelling

- **In vitro dissolution Studies and Release kinetics**

Using a U.S.P. dissolution test instrument (Paddle over disc type method) heated to 37°C and stirred at a rate of 50 rpm, the drug release was calculated. The investigation was conducted in sink condition. With the aid of cyanoacrylate adhesive, each film was secured to a glass slide such that the medicine could only be released from the upper face. The slide was submerged in a 900 ml solution of phosphate buffer with a pH of 7.4. Up to 24 hours, 5 ml aliquots of the sample were taken out using a graduated pipette at intervals of one hour and replaced with an equivalent volume of phosphate buffer. The sample was spectrophotometrically examined at a wavelength of 261 nm, and the total amount of medication released during different time periods was computed. Three duplicates of each sample were tested.

Table no. 2: Effective transdermal delivery of Therapeutic active via novel vesicular carriers.

Drug	Therapeutic Indication	Vesicular Carrier	Inference
Celecoxib	Inflammation	Transferosomes	Therapeutically effective delivery for thetreatment of rheumatoid arthritis.
Itraconazole	Fungal infection	Liposomes	Enhanced transdermal permeation for theeffective treatment of topical infection.
Nystatin	Fungal infection	Transfersomes	Higher drug accumulation in the skin.
Ceramide	Skin care (moisturizer)	Liposomes	Enhanced permeation of ceramides *via* liposomes.
Cinnamic acid	Cancer	Transfersomes	Enhanced transdermal delivery of cinnamic acid and these vehicles penetrate the skin in the complete form.
Lidocaine Hydrochloride	Pain and itching	Liposomes	Effective drug release. Safe, non-toxic, canpenetrate the skin effectively.

Curcumin	Cancer	Transfersomes	Higher permeation of drug from transfersomalgel.
Cisplatin	Cancer	Transfersomes	Better drug penetration.
Felodipine	Hypertension	Transfersomes	358.42% relative bioavailability of felodipine versus oral administration, supported by the outcomes of confocal laser scanning microscopicstudies that suggested rapid drug permeation.
Indomethacin	Rheumatoid arthritis	Liposomes	Enhanced transdermal delivery for the treatmentof rheumatoid arthritis.
Diclofenac	Inflammation	Elastic Liposomes	Better efficacy observed in elastic liposomes incontrast to conventional carriers.
Clotrimazole	Fungal infection	Elastic Liposomes	Sustained release and higher skin permeationwith enhanced anti-fungal activity.
Clonazepam	Depression	Liposomes	Improved skin permeability.
Propranolol Hydrochloride	Hypertension	Elastic Liposomes	Efficient in improvising drug delivery in contrastto rigid vesicular carriers.

DISCUSSION AND CONCLUSION

New possibilities and challenges are emerging in the development of advanced therapies thanks to nanosuspension carriers. Nanosuspension, flexible and deformable vesicles, are promising vehicles for drug delivery. Their ease of preparation, safety, and effectiveness make them attractive candidates. Transdermal patch can be tailored to enhance the skin penetration of drugs. Compared to liposomes or hydroalcoholic solutions, patch have proven to be more successful in delivering drugs to the skin. It is evident that transdermal patch offer superior skin penetration compared to liposomes. Transdermal patch can significantly overcome the epidermal barrier, which has been the primary obstacle in transdermal drug delivery systems. Using nanosuspension as drug carriers offers benefits in treating skin diseases. enhance Transdermal patch the penetration of drugs through the skin and enable delivery to deeper layers, improving the effectiveness of treatments.

REFERENCE

1. Mishra, Brahmeshwar, and Gunjan Vasant Bonde. "Transdermal drug delivery." *Controlled DrugDelivery Systems*. CRC Press, 2020; 239-275.
2. Miller, M.A. & Pisani, E. The cost of unsafe injections. *Bull. World Health Organ,* 1999; 77: 808–811. CAS PubMed PubMed Central Google Scholar

3. Rastogi, Vaibhav, and Pragya Yadav. "Transdermal drug delivery system: An overview." *AsianJournal of Pharmaceutics (AJP)*, 2012; 6: 3.
4. Ranade, Vasant V. "Drug delivery systems. Transdermal drug delivery." *The Journal ofClinical Pharmacology*, 1991; 6, 31, 5: 401-418.
5. Agrawal SS, Munjal P. Permeation studies of atenolol and metoprolol tartrate from threedifferent polymer matrices for transdermal delivery. Indi J Pharm Sci, 2007; 69(4): 535.
6. Darwhekar G, Jain DK, Patidar VK. Formulation and evaluation of transdermal drug deliverysystem of clopidogrel bisulfate. Asian J Pharm Life Sci, 2011; 2231: 4423.
7. Cleary GW, Beskar E. Transdermal and transdermal like delivery system opportunities. BusinessBriefing: Pharm Tech, 2004; 1-4.
8. Smith EW, Maibach HI. Percutaceous penetration enhancement. Boca Raton, Taylor & FrancisGroup, 2006; 3-15.
9. Leong, Moong Yan, et al. "Recent Development of Nanomaterials for Transdermal DrugDelivery." *Biomedicines*, 2023; 11, 4: 1124.
10. Darwhekar G, Jain DK, Paditar VK. Formulation and Evaluation of Transdermal drug deliverysystem of Clopidogrel Bisulfate. Asi. J. Pharmacy Life Sci, 2011; 1(3): 269-278.
11. Kumar SR, Jain A, Nayak S. Development and Evaluation of Transdermal patches of Colchicine.Der Pharmacia Lettre, 2012; 4(1): 330-343.
12. Kurczewska, Drug Delivery. *Polymers*, 2022; *14*: 4189. https://cdn.shopify.com/s/files/1/2476/3692/files/Prostaglandins_form_in_response_to_the_drop_in_the_hormone_progesterone_1c0906f0-9167-448c-b74f-
13. Sharma N, Parashar B, Sharma S, Mahajan U. Blooming Pharma Industry with Transdermal Drug Delivery System. Indo Global J Pharm. Sci, 2012; 2(3): 262-278.
14. Keleb E, Sharma RK, Mosa EB, Aljahwi AZ. Transdermal Drug Delivery System-Design and Evaluation. Int. J. Adv. Pharm. Sci, 2010; 1: 201-211.
15. Arunachalam A, Karthikeyan M, Kumar VD, Prathap M, Sethuraman S, Ashutosh Kumar S, Manidipa S. Transdermal Drug Delivery System: A Review. Current Pharma Res, 2010; 1(1): 70- 81.
16. Latheeshjlal L, Phanitejaswini P, Soujanya Y, Swapna U, Sarika V, Moulika G. Transdermal drug delivery systems: an overview. Int. J. PharmTech Res, 2011; 3(4): 2140-8.
17. Jain NK. Advances in controlled and novel drug delivery. Delhi: CBS Publishers, 2001; 1: 426-48.

18. Gilman AG. The pharmacological basis of therapeutics. New York: McGraw Hill, 1996.
19. Vyas SP, Khar RK. Controlled drug delivery concepts and advances. New Delhi: Vallabh Prakashan, 2002; 1: 411 -47.
20. Berner B, John VA. Pharmacokinetic characterization of Transdermal delivery system. J. Clin. Pharmaco, 1994; 26(2): 121-134.
https://www.tapecon.com//material-considerations-for-transdermal-patch-layers
23. Hadgraft J, Guy RH. Transdermal Drug Delivery: Developmental Issues and Research Initiatives. Marcel Dekker, Inc.: New York, 1989; 293-311.
24. Wiechers J. Use of chemical penetration enhancers in transdermal drug delivery-possibilities and difficulties. Acta Pharm. Nord, 1992; 4(2): 123.
25. Yamamoto T, Kataka Topical application of the hypoglycemic agent glibenclamide and changes in blood glucose, plasma insulin (IRI) levels and plasma concentration of glibenclamide in normal rats. Diabetes Res. Clin. Pract, 1990; 8(1): 19- 22. [DOI: 10.1016/0168-8227(90)90091-7
26. Al-Khamis KI, Davis SS, Had graft J. Micro viscosity and drug release from topical gel formulations. Pharm. Res, 1986; 3(4): 214-7. [DOI: 10.1023/A:1016386613239]
27. Anon. Transdermal delivery systems-general drug release standards. Pharmacopeial Forum, 1980; 14: 3860-5.
28. Mayorga P, Puisieux F, Couarraze G. Formulation study of a transdermal delivery system of primaquine. Int. J. pharm, 1996; 132(1-2): 71-9. [DOI: 10.1016/0378-5173(9 5)04348-9]
29. Deo MR, Sant VP, Parekh SR, Khopade AJ, Banakar UV. Proliposomes-based transdermal delivery of levonor gestrel. J. Biomater. Appl, 1997; 12(1): 77-88.
30. Crawford RR and Esmerian OK. Effect of plasticizers on some physical properties of cellulose acetate phthalate films. J. Pharm. Sci, 1971; 60(2): 312-4. [DOI: 10.1002/jps. 2600600238]
31. Shingade GM, Quazi A, Sabale PM, Grampurohit ND, Gadhave MV, Jadhav SL, Gaikwad DD. Review on: recent trend on transdermal drug delivery system. J. Drug Deliv. Ther, 2012; 2(1): 66- 75.
32. Sharma N, Agarwal G, Rana AC, Bhat ZA, Kumar D. A review: Transdermal drug delivery system: A tool for novel drug delivery system. Int. J. Drug Dev. Res, 2011; 3(3): 70-84.
33. Latheeshjlal L, Phanitejaswini P, Soujanya Y, Swapna U, Sarika V, Moulika G. Transdermal drug delivery systems: an overview. Int. J. PharmTech Res, 2011; 3(4):

2140-8.

34. Chudasama, Arpan, et al. "Investigation of microemulsion system for transdermal delivery of itraconazole." *Journal of advanced pharmaceutical technology & research*, 2011; 2, 1: 30.
35. Zheng, Wen-sheng, et al. "Preparation and quality assessment of itraconazole transfersomes." *International journal of pharmaceutics*, 2012; 436, 1-2: 291-298.
36. Wagh, Vijay D., and Onkar J. Deshmukh. "Itraconazole niosomes drug delivery system and its antimycotic activity against Candida albicans." *International Scholarly Research Notices*, 2012; 2012.
37. Zheng, Wen-sheng, et al. "Preparation and quality assessment of itraconazole transfersomes." *International journal of pharmaceutics*, 2012; 436, 1-2: 291-298.
38. Mohamed, MOHAMED SALAMA, et al. "Preparation and release characteristics of itraconazolepolymeric films for topical application." *Int. J. Pharm. Pharm. Sci*, 2013; 5: 167- 170.
39. Sampathi, S., et al. "Nano emulsion based hydrogels of Itraconazole for transdermal drug delivery.", 2015.
40. Choudhury, Hira, et al. "Recent update on nanoemulgel as topical drug delivery system." *Journal of pharmaceutical sciences*, 2017; 106, 7: 1736-1751.
41. Patel, tejas b., Tushar R. Patel, and B. N. Suhagia. "Preparation, characterization, and optimization of microemulsion for topical delivery of itraconazole." *Journal of drug delivery and therapeutics*, 2018; 8, 2: 136-145.
42. Goyal, Manoj Kumar, and Junaid Qureshi. "Formulation and evaluation of itraconazole niosomal gel for topical application." *Journal of Drug Delivery and Therapeutics*, 2019; 9, 4-s: 961-966.
43. Passos, Julia Sapienza, et al. "Development, skin targeting and antifungal efficacy of topical lipid nanoparticles containing itraconazole." *European Journal of Pharmaceutical Sciences*, 2020; 149: 105296.
44. Thakre, Durgesh, Swati Saxena, and Sarang Jain. "Development and Characterization of Transfersomes of Itraconazole for Effective Treatment of Fungal Disease." *Ajper*, 2021; 10, 1: 26-34.