



ISSN: 2277- 7695

TPI 2015; 4(1): 37-43

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www.thepharmajournal.com

Received: 10-01-2015

Accepted: 09-02-2015

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A review on transdermal drug delivery system

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Abstract

Transdermal drug delivery systems are topically administered medicaments. Transdermal patches are pharmaceutical preparation of varying sizes, containing, one or more active ingredient, intended to be applied to the unbroken skin in order to deliver the active ingredient to the systemic circulation after passing through the skin barriers, and it avoid first pass effect. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. The present investigation was aimed to formulate transdermal films incorporating herbal drug components. Hence turning to safe, effective and time-tested Ayurvedic herbal drug formulation would be a preferable option. With this view transdermal films incorporating herbal drug components. Overall, it was observed that the well-known ayurvedic drugs have been found to be effective through modern pharmaceutical formulation techniques.

Keywords: transdermal drug delivery system, herbal patches, marketed Transdermal Patches, types of patches.

1. Introduction

Nowadays about 74% of drugs are taken orally and are found not to be as valuable as most wanted. To advance such characters transdermal drug delivery system was emerged. With the creation of current time of pharmaceutical dosage forms, transdermal drug delivery system (TDDS) recognized itself as an important part of novel drug delivery systems. Transdermal dosage forms, still a costly alternative to conventional formulations, are becoming popular because of their exclusive advantages. Improved bioavailability, Controlled absorption, extra uniform plasma levels, painless and reduced side effects easy application and flexibility of terminating drug administration by simply removing the patch to the skin are some of the potential advantages of transdermal drug delivery [1].

Oral Conventional dosage forms like tablets and capsules are most widely used drug delivery system but both dosage forms face problem of gastric drug/enzyme instability first pass metabolism. Oral route has many further problems like unpleasant taste, odour and color. Numerous additional problems are arising during taking pills; hence problems are being faced during treatment. Sometimes Patients become non-compliant. TDDS patches drugs are used by continuous release so they show their effect for exact duration and Transdermal patch is non-irritating and noninvasive technique. It is attractive alternative techniques over conservative techniques for systemic administration of drug [2]. Transdermal drug delivery systems (TDDS) are dosage forms designed to deliver a therapeutically effective dose of drug across a patient's skin [3-4]. Conventional systems of medication which require multi dose therapy have numerous problems and complications such as poor bioavailability due to hepatic first pass metabolism. This is removed by TDDS. For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin [5]. Transdermal drug delivery systems (TDDS) are defined as self-contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation. The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs [6]. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects Thus various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc Emerged [7].

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2. Advantages of Transdermal Drug Delivery ^[8-13]

1. TDDS is a drug delivery system in which a device usually known as patch is adhered on the skin surface to deliver the drug into the systemic circulation through the skin at predefined concentration for therapeutic effects, which avoids additional limitations due to other dosage forms.
2. It offers constant permeation of drugs through the skin giving constant serum drug level, the goal of therapy.
3. It can be used as an alternate to oral drug delivery system for those patients, who find difficulty in taking drugs through oral route.
4. It can be used as an alternative for nauseated or unconscious patients.
5. Patients having gastrointestinal problems can be given drugs through TDDS as there will be no direct contact between drug and stomach.
6. Like intravenous infusion, it also gives constant plasma level.
8. If toxicity develops from TDDS, patch can be removed easily.
9. It is very convenience as application of drug is very easy.
10. It eliminates first pass mechanism.
11. It reduces systemic drug interactions.
12. It offers long duration of action.
13. Self administration can be done.

3. Disadvantages of Transdermal Drug Delivery System ^[14]

1. Many hydrophilic drugs cannot pass or very slowly permeates the skin. This will affect the therapeutic efficacy of the drug.
2. Many problems like itching, edema, erythema etc. may be seen due to patches.
3. The barrier function of the skin may change from person to person, or with ages or with different sites on same person.
4. There may be some possibility of irritation at the site of drug administration.
5. Uneconomic system of drug delivery.
6. It is not use in acute condition, only used in chronic conditions
7. TDDS is not compatible with ionic drugs.
8. Dumping of dose may occur.
9. Drugs having affinity for both lipophilic and hydrophilic phases are used.
10. High drug level in blood cannot be attained.

4. Formulation Design

A transdermal therapeutic system is essentially a multi laminate structure that is composed of following constituents:

1. Drug;
2. Polymer matrix;
3. Penetration enhancers;
4. Adhesives;
5. Backing membrane;
6. Release linear.

5. Transdermal Patch: ^[15-18]

A transdermal patch is defined as adhesive medicated patch that is placed on to the above skin to deliver an exact dose of

drug through the skin into the bloodstream with a predetermined rate of release to reach in the body. Today the most common transdermal system present in the market mainly based on semi permeable membranes which were called as patches. Transdermal drug delivery systems (TDDS), also known as “Transdermal patches” or “Skin patches” are dosage forms designed to deliver a therapeutically effective amount of drug across a patient’s skin and in the bloodstream.



6. Main Ingredients Used For the Preparation of Transdermal Drug Delivery System ^[19-20]

Liners- It provides the protection of patches during storage and the liner should be removed previous touse.

Adhesive- It served to adhere the components of the patch together along with adhering the patch to skin.

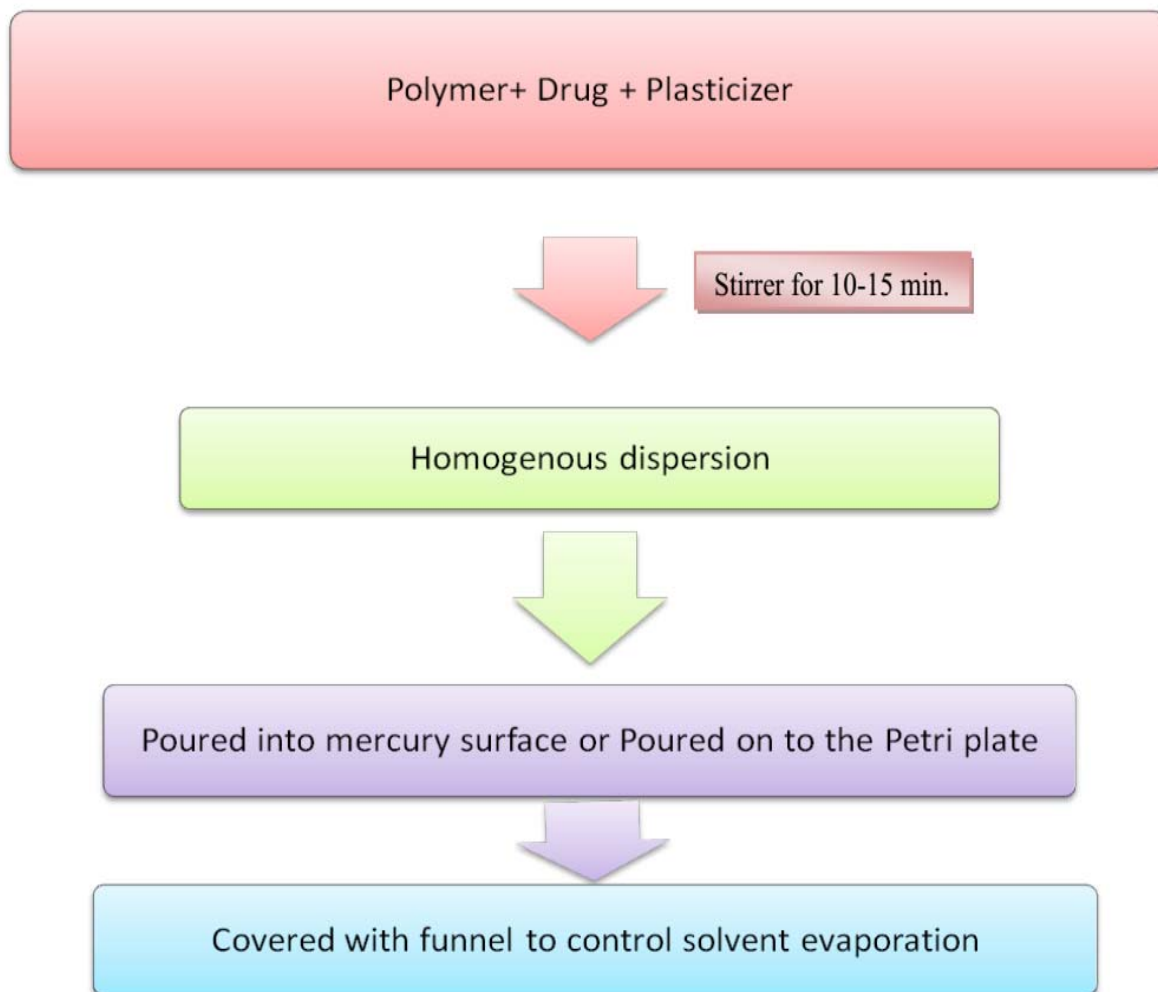
Membrane- Its controls the drug releases from the multi-layer patches. It’s also known as the permeation enhancer.

Drug- Drug reservoir is direct contact with release liner.

Backing- protects the patches from outer environment.

7. Method of Preparing Transdermal Patches: ^[21-23]

Method of preparation of TDDS was summarized by modifying the earlier reported methods. The patches were prepared by solvent casting method. The polymer (for example PVP/HPMC) was taken in a beaker with aminimum quantity of the solvent. Then 2/3rd of the solvent was mixed with the other polymers (for example PVA) and was added firstly with stirring at lower rpm and later at a higher speed. The plasticizer was added and homogeneously mixed and the drug was included with enduring agitation and the volume was made up. The films were cast onto a suitably designed and fabricated glass mould and then dried in oven at 40 °C. The films were removed by using sharp blade by inserting along the edges of the film. The dried films were wrapped in butter paper and stored in a closed container away from light and in cool place.






8. Types of Transdermal Patch ^[24]

1. Single-layer Drug -in-Adhesive

The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

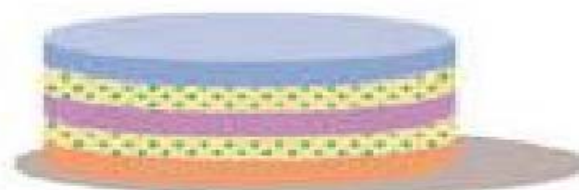


-  Backing
-  Drug-in-Adhesive
-  Liner

2. Multi-layer Drug-in-Adhesive

The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. The multi-layer system is

different however that it adds another layer of drug-in - adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing.



-  Backing
-  Drug-in-Adhesive
-  Membrane
-  Drug-in-Adhesive
-  Liner

3. Reservoir

Unlike the Single-layer and Multi-layer Drug-inadhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system the rate of release is zero order.



- Backing
- Drug
- Membrane
- Adhesive
- Liner



- Backing
- Adhesive
- Drug
- Liner

4. Matrix

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it.

5. Vapour Patch

In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapours patches release essential oils and are used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market.

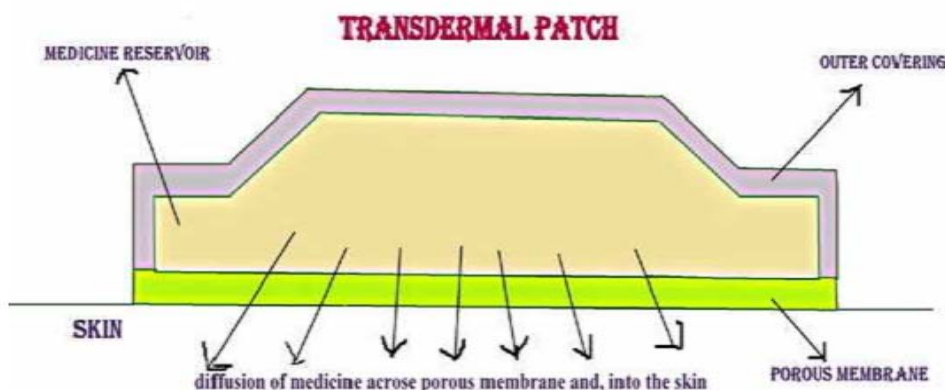
9. Drugs used in the Transdermal Patch

Brand Name	Drug	Manufacturer	Indications
Nicotine II ^R	Nicotine	Novartis	Pharmacological smoking cessation
Matifen ^R	Fentanyl	Nycomed	Pain relief patch
Ortho Evra TM	Norelgos tromin/Ethinyl Estradiol	ORTHO-McNEIL	Postmenstrual syndrome
NuPatch 100	Diclofen ac Diethyla mine	Zydus Cadila	Anti Inflammatory
Neupro ^R	Rigotine	UCB and Schwarz Pharma	early-stage idiopathic Parkinson's disease
Alora	Estradiol	TheraTech/Proctol and Gamble	Postmenstrual Syndrome
Estrader M	Estradiol	Alza/Norvatis	Postmenstrual Syndrome
Androde Rm	Testoster One	TheraTech/GlaxoS mithKline	Hypogonadism in males
Transderm Scop ^R	Scopola Mine	Alza/Norvatis	Motion Sickness
Nitrodur	Nitroglyc Erin	Key Pharmaceuticals	Angina Pectoris
Catapres TTS ^R	Clonidine	Alza/Boehinger Ing Elheim	Hypertension
Duragesic ^R	Fentanyl	Alza/Janssen Pharmaceutical	Moderate/severe Pain
Oxytrol ^R	Oxybutynin	Watson Pharma	Overactive Bladder
Neupro	Rotigotine	Schwarz Pharma	Parkinson's Disease ^[25]

10. Mechanism of Action of Transdermal Patches: ^[26]

The function of the transdermal patch and the flow of the active drug ingredient from the patch to the circulatory system via skin transpire through different methods. For a

systemically active drug to reach a target tissue, it has to take some physicochemical properties which make easy the sorption of the drug through the skin and enter the microcirculation.



11. Beneficial Use of Herbal Transdermal Therapy [27-31]

There are different patches, which are available to lose weight, quit smoking, help to relieve stress and even increase sexuality, insect repellent patches, detoxification, male energizer, better sleeping, postpone menopause etc

Slim herbal patch – slim patches are 100% prepared of natural herbs and processed to soft patch form with transdermal technology. It's smooth, soft and smells slightly herbal. It is the natural way to lose weight permanently. The weight loss patch eliminates hunger while burning fat. The body slowly absorbs these elements, resulting in a "boost" to the thyroid gland. This increases the metabolism and activates fat burning mechanisms. The thyroid controls your metabolism, which in turn burns fat and decreases appetite. List of ingredients used in herbal slim patch are. Fucusvesiculosus, Guarana, 5-HTTP, Zinc Pyruvate, Flax seedoil, Lecithin, L-Carnitine, Zinc Citrate.

Anti-rheumatic herbal patch- Rheumatic diseases affected mankind since ages and are one of the commonest inflammatory conditions in developing countries. The main ingredients used in Anti-rheumatic herbal patches are Boswellic acid and Curcumin. Ethano botanically *Boswellia serrata*, *Curcuma longa* and *Trichodesma indicum* were used for antirheumatic, antiinflammatory and in the treatment of different skindiseases. Waghulkar *et al.*, (2011) [30] developed the transdermal patches (films) for the antirheumatic activity by using chloroform extract of *Trichodesma indicum* and *Boswellia serrata*. Further research work also highlights on *Curcuma longa* that turmeric oil may be incorporated into the transdermal drug delivery system for their suitable and convenient use Vishwakarma *et al.*, (2012). [29] Studies have shown promising results; hence, there is a scope for further pharmacodynamic and pharmacokinetic evaluation.

Cholesterol herbal patch- TDDS is applicable to help lower Cholesterol, Triglycerides, LDL, Lp (a) lipoprotein, and raise HDL. Side effects like flushing due to high dosage Niacin are absent when applied through Transdermal Patches without any loss in potency or efficiency. Cholesterol patches work best when taken with nutritional supplement organic magnesium on a daily basis. Briefly, one can roughly equate one 50 mg Transdermal Patch to about a 500 mg Oral dose taken two to three times a day in actual effectiveness but without the discomfort associated with oral intake. The main ingredients used in herbal cholesterol patch are Vitamin B-Complex 5mg, Niacin 20 mg, Organic Vitamin C 20 mg, Commiphora Mukul 20 mg, Organic Chromium 100 mg.

Kick the nicotine habit naturally- The researchers have discovered a new way to combine the all-natural healing properties of a unique Variety of traditional herbal formulas to completely and naturally eliminate your body's need for nicotine. Detailed list of ingredients used in anti smoking patch are. Gotu Kola, Hops, Skullcap, Oat, Peppermint, Ginger, Gentian, Myrrh, Safflower, Eucalyptus, Licorice Root, Sarsaparilla Bayberry.

Anti-smoking patch- This patch is a novel termination support designed to help give up smoking safely and naturally, without putting more nicotine into the body. Its unique combine of ingredients, zero nicotine patches offers the greatest possible chance to finally drop the habit. They are applied to the skin, and put a dose of nicotine into the body.

Herbal body foot patches- These patches are based on molecular development analysis. Molecular alteration therapy has four major components.

1) **Heath Regulation** - To promote mental health and health restoration

2) **Increasing Oxygen intake-** to enhance metabolism

3) **Detoxification-** To remove waste and toxins from the body

4) **Balance Nutrition** - To supply the body with all essential nutrients According to Chinese medical, our human body has over 360 acupuncture points, with more than 60 acupuncture points found on the soles of the foot. When the blood circulates to the soles, the Foot Patch can absorb toxins released from the acupressure points. Circulation of blood and lymphatic fluids reach their furthest point in the soles of the feet before being return 'pumped' back up into the higher portions of the body. The body detox foot patch contains all natural ingredients, which are described as below: Bamboo Vinegar, Wood Vinegar, Tourmaline, and Eucalypt us.

Herbal plasters patches- Plaster Patches are warm, soft, flexible, Pain Relieving Patch. Previously applied, its ingredients are absorbed into the skin to stimulate blood circulation. It's provides speedy Temporary Pain Relief and comfort for hours. Plasters are specially used in chronic or prolonged Sore Muscles, Arthritis Pain, Painful Joints, Sprains, Backache, Bruises, Shoulder Pain, Arthraiga, Rheumatic Pain, Neuralgia, and Fracture Pain. There are main two type of plaster patches are Cool plaster patch and Mild hot plaster patch. Cool plaster patch provides Rapid, Soothing Pain Relief and Alleviates swelling, with a Cool Refreshing Feeling owing to its "Cool pack effect". Patches hold a High Moisture Content in a water-soluble Polymer Base, which enables the Deep Penetration of active ingredients in to the affected area, and provides Sustained Effects through the Continuous Release of its moisture. Caused by its Transdermal Therapeutic System, Plaster Patches can be used safely by the elderly and weak. Herbal Plasters Size 4" x 5.5" includes natural herbs like: Powdered Philodendron Bark, Capsicum Extract, Zanthoxylum Fruit, and Gardenia Fruit Methyl Salicylate.

Antidiabetic Activity - *Momordica charantia* Linn. Ethano medicinally is used as a medicine for diabetes therefore Bhujbal *et al* (2011) [28] reported that *M. charantia* used for the formulation of herbal transdermal patches for the treatment of diabetes. The transdermal route exhibited negligible skin irritation and in vivo results revealed that the patches successfully decrease the blood glucose level.

12. Applications of Transdermal Patches [32-34]

- The highest selling transdermal patch in the United States is the nicotine patch, which releases nicotine in controlled doses to help with cessation of tobacco smoking.
- Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl (marketed as Duragesic) and Buprenorphine (Marketed as BuTrans).
- Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as post-menopausal osteoporosis. Other transdermal patches for hormone delivery include the contraceptive patch (marketed as Ortho Evra or Evra).
- Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.

- The anti-hypertensive drug Clonidine is available in transdermal patch form.
- Transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant.
- Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD)

13. Regulatory Strategy for Investigational New Drug (IND) Application and New Drug Application Submissions for Tdds ^[35]

Standard irritation and sensitization studies should be performed with the patch itself in animals/humans. Negotiate the timing and implementation of the toxicology requirements. The dermatology division at FDA should review dermal aspects of the IND and new drug Application (NDA). Primary review should occur at the division that handles the indication under study. Dose ranging studies are required in Phase 2. Single Phase 3 study could be negotiated.

14. Future of Transdermal Therapy

Couple of year ago, the nicotine patch had revolutionized smoking cessation; patients were being treated with nitroglycerin for angina, clonidine for hypertension, scopolamine for motion sickness and estradiol for estrogen deficiency, all through patches. At that time, biotech medicinal was still being developed. During the past decade, the number of drugs formulated in the patches has hardly increased, and there has been little change in the composition of the patch systems. Modifications have been mostly limited to refinements of the materials used. The reason is the only a limited number of drugs fit the molecular weight, and potency requirements for transdermal absorption.

15. Conclusion

This review article concluded that, an older drug by formulating them in new dosage forms has generated enthusiasm among the pharmaceutical scientists to develop new dosage forms. In addition, new dosage forms are essential for other drugs in order to enhance their performance by reducing their dose, increasing absorption, delivering to the target site etc. The patented innovations in transdermal drug delivery arena aim at these goals. However, the ultimate test that an innovative technique should pass relates to its successful performance in vivo.

16. Reference

1. Ahmed A, Karki N, Charde R, Charde M, Ganghare B. Transdermal Drug Delivery System an Overview. *Int J Biomed Adv Res* 2011; 2:38-56.
2. Patel A, Visht S, Sharma PK. Transdermal Drug Delivery System: Next Generation Patches. *J Drug Discov Dev* 1, 43-65.
3. Kumar JA, Pullakandam N, Prabu SL, Gopal V. Transdermal drug delivery System: An overview. *Int J Pharma Sci Rev Res* 2010; 3(2):49-53.
4. Jain NK. *Advances in controlled and novel drug delivery*. 1st Ed. CBS Publishers and distributors, New Delhi, 2001, 108-110.
5. Shivaraj A, Selvam RP, Mani TT, Sivakumar T. Design and evaluation of transdermal drug delivery of ketotifen fumarate. *Int J Pharm Biomed Res* 2010; 1(2):42-47.
6. Selvam RP, Singh AK, Sivakumar T. Transdermal drug delivery systems for antihypertensive drugs - A review. *Int J Pharm Biomed Res* 2010; 1(1):1-8.
7. Hadgraft J, Guy R, In: *Transdermal Drug Delivery*, Vol. 35, Marcel Dekker, Inc: New York and Basel, 296.
8. Latheeshjhal L, Phanitejaswini P, Soujanya Y, Swapna U, Sarika V, Moulika G, *Transdermal Drug Delivery Systems: An Overview*, *Int J Pharm Tech Res* 2011; 3(4):2140-2148.
9. Chien YW, *Novel drug delivery systems, drugs and the Pharmaceutical sciences*, Vol.50, Marcel Dekkar, New York, 1992, 797.
10. Banker GS, Rhodes CT. *Modern pharmaceuticals*, third edition, New York, Marcel Dekkar Inc, 1990.
11. Guy RH. Current status and future prospects of transdermal drug delivery. *Pharm Res* 1996; 13:1765-1769.
12. Benson HAE. *Transdermal Drug Delivery: Penetration Enhancement Techniques*, *Current Drug Delivery* 2005; 2:23-33.
13. Guy RH, Hadgraft J, Bucks DA, *Transdermal drug delivery and cutaneous metabolism*, *Xonobiotica* 1987; 7:325-343.
14. Dass S, Dey SK. A novel approach towards transdermal drug delivery system: a precise review. *Indo American Journal of Pharm Research* 2013; 3(6):4680-96.
15. Gupta V, Yadav SK, Dwivedi AK, Gupta N. *Transdermal Drug Delivery: Post, Present, Future Trends*. *Int J Pharm Life Sci* 2011; 12:1096-1106.
16. Ravi S, Sharma PK, Bansal M. A Review: Transdermal Drug Delivery of Nicotine. *Int J Drug Dev Res* 2011; 3:01-08.
17. Patel D, Patel N, Parmar M, Kaur N. *Transdermal Drug Delivery System: Review*. *Int J Bio Pharm Toxicol Res* 2011; 1:61-80.
18. Sachan R, Bajpai M. *Transdermal Drug Delivery System: A Review*. *Int J Res Dev Pharm Life Sci* 2013; 3:748-765.
19. Kumar KPS, Bhowmik D, Chiranjib B, Chandira RM. *Transdermal Drug Delivery System- A Novel Drug Delivery System and Its Market Scope and Opportunities*. *Int J Pharma Bio Sci* 2010; 1:1-21.
20. Patil PM, Chaudhari PD, Patel JK, Kedar KA, Katolkar PP. Recent Trend in Challenges and Opportunities of Transdermal Drug Delivery System. *Int J Drug Dev Res* 2012; 4:39-50.
21. Shrivastava D. *Transdermal Approach of Antidiabetic Drug Glibenclamide: A Review*. *W J Pharm Pharma Sci* 2012; 1:532-544.
22. Sharma A. *Transdermal Approach of Antidiabetic Drug Glibenclamide: A Review*. *Int J Pharm Res Dev* 2012; 3:25-32.
23. Ghinaiya M. *Formulation and Evaluation of Transdermal Patch of an Antihypertensive Drug*. *Int J Pharm Sci* 2013; 4:3664-3682.
24. Patel D, Chaudhary SA, Parmar B, Bhura N. *Transdermal Drug Delivery System: A Review* 2012; 1:78-87.
25. Kumar KPS, Bhowmik D, Chiranjib B, Chandira RM. *Transdermal drug delivery system- A novel drug delivery system and its market scope and opportunities*. *Int J Pharma Bio Sci* 2010; 1(2):1-21.
26. Rasheed SH, Haribabu R, Mohiddin Md. K, Vineela J, Teja AR, Pathuri RK *et al*. *Transdermal Drug Delivery System. Simplified Medication Regimen- A Review*. *Res J Pharm Bio Chem Sci* 2011; 2:223-238.
27. Rathva SR, Patel NN, Shah V, Upaydhay UM. *Herbal Transdermal Patches: A Review*. *Int J Drug Discov Herb Res* 2012; 2:397-402.

28. Bhujbal SS, Hadawale SS, Kulkarni PA, Bidkar JS, Thatte VA, Providencia CA, Yeola RR. A Nobel Herbal Formulation in the Management of Diabetes. *Int J Pharm Invest* 2011; 1:222-226.
29. Vishwakarma AK, Maurya OP, Srivastava D. Formulation and Evaluation of Transdermal Patch Containing Turmeric Oil. *Int J Pharm Pharm Sci.* 2012; 4: 358-361.
30. Waghulkar VM, Udasi TA, SabooSS. Development of Transdermal Patches (Films) For the Anti-Rheumatic Activity of Chloroform Extract of *Trichodesma Indicum* and *Boswellia Serrata*. *Inventi Impact: Pharm Tech* 2011; 304-305.
31. Baskar V, Selvakumar K, Madhan R, Srinivasan G, Muralidharan M. Study on Improving Bioavailability Ratio of Anti-Inflammatory Compound From Ginger Through Nano Transdermal Delivery. *Asian J Pharm Clin Res* 2012; 5:241-246.
32. Jain NK. *Controlled and Novel Drug Delivery*. CBS Publishers and Distributors, New Delhi, 2002, 107.
33. Chien YW. *Novel drug delivery systems: Drugs and the Pharmaceutical Sciences*. Vol.50, Marcel Dekker, New York, 1992:797.
34. Jain NK. *Controlled and novel drug delivery*, 1st edition, CBS publishers and distributors, New Delhi, 1997.
35. Singhal P *et al.*, *Transdermal Drug Delivery System as a Tool for Novel Drug Delivery System*. *American Journal of PharmTech Research* 2012; 2(1):106-125.