JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A DETAIL REVIEW ON TRANSDERMAL DRUG DELIVERY SYSTEM AND ITS APPLICATION

Sangramsing D. Deshmukh[1], Ketaki D. Gangavane[2], Sonia T. Sevlani[3], Juned Pinjari[4]

Student Of Pharmacy[1], Student of Pharmacy[2], Faculty of Pharmacy[3], Faculty of Pharmacy[3],Faculty of Pharmacy[4]

Department of Pharmacy

P.G. College of Pharmaceutical Science and Research, Nandurbar, Maharashtra, India

ABSTRACT:

Transdermal drug delivery systems (TDDS) are the topically applied "patches" designed to deliver a therapeutically effective quantum of a medicine across a case's skin at a controlled rate for the systemic action. TDDS has surfaced as a potential novel drug delivery system in the last 30 years. It is intended to improve the therapeutic efficacy and safety, maintain the steady state plasma level of drugs and overcome the significant drawbacks of the conventional oral dosage forms and parenteral preparations. It is ideally suited for the diseases that demand chronic treatment with frequent dosing. This review deals with a brief insight on the introduction, the formulation aspects, the physical and chemical enhancers explored or being explored to enhance the transdermal delivery of drugs across the stratum corneum, the evaluation parameters (physicochemical, in-vitro, in-vivo studies) and therapeutic applications of TDDS.

Keywords: First pass metabolism; Permeation enhancers; Stratum corneum; TDDS

INTRODUCTION:

The idea of delivering medicines through the skin is ancient, being used as early as the 16th century BC. Until recently, the use of transdermal patches for pharmaceuticals was limited. This was because few drugs have proven efficacy delivered through the skin.[36] Typically, heart drugs such as nitroglycerin and hormones such as estrogen. A transdermal drug delivery system (TDDS) is a "patch" that is applied topically to deliver a therapeutically effective dose of drug across a patient's skin at a controlled rate for systemic action. Designed. With the introduction of the first transdermal scopolamine patch in 1979, transdermal drug delivery has made an important contribution to medical practice over the past three decades, but it is still recognized as an important alternative to oral delivery and subcutaneous injection.[40] Is not ... A major obstacle to topical drug delivery is the slow rate of drug diffusion through the stratum corneum, the relatively impermeable outermost layer of the skin (Bouwstra et al., 2002).[7]Additionally, the intercellular lipid region, which serves as the main channel for lipophilic drugs, has a diffusion path length of roughly 500 mm, which is significantly longer than the stratum corneum's (20 mm) thickness (Gaur et al., 2009; Phillips et al., 1995).[15] Additionally, the intercellular lipid region, the main channel for lipophilic drugs, has a diffusion path length of around 500 mm, which is substantially longer than the stratum corneum's (20 mm) thickness (Gaur et al., 2009; Phillips et al., 1995).[15]

DEFINATION OF TDDS:

Transdermal drug delivery system is defined as, self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the system circulation.[1]

The first transdermal drug delivery (TDD) system, transderm-scop developed in 1980, contained the drug scopolamine for treatment of motion sickness. The transdermal device is a membrane-moderated system. The membrane in this system is a microporous polypropylene film. The drug is dissolved in a mixture of mineral oil and polyisobutylene to create the drug reservoir. Over a day, the study release is maintained.

ANATOMY OF SKIN:

The structure of human skin (fig. 1) can be categorized into four main layers:

- The epidermis.
- The viable epidermis.
- A non-viable epidermis (stratum corneum).
- The overlying dermis.
- The innermost subcutaneous fat layer (Hypodermis).

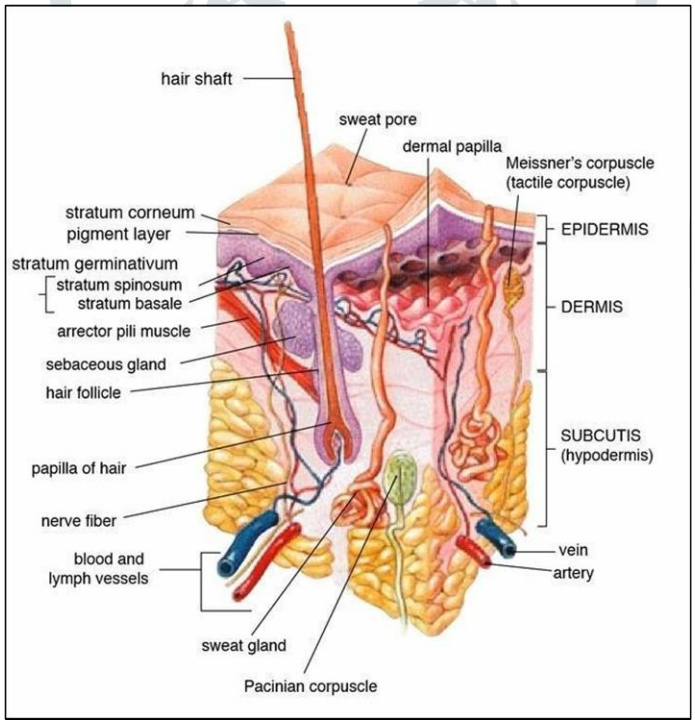

Fig: 1 Structure of skin

Functions of skin:

- Protecting the body against trauma.
- Controlling the body's temperature.
- Maintaining electrolyte and water balance.
- Recognizing unpleasant and pleasurable stimuli.
- Contributing to the production of vitamin D. The deficit may also be brought on by several disorders.

Advantages:

1. They can prevent problems with drug absorption in the gastrointestinal tract brought on by changes in gastrointestinal pH, enzyme activity, and drug interactions with food, drink, and other orally taken

medications.

2. In contrast to the limited controlled release from oral and intravenous routes, TDDS offers steady infusion of drug over a prolonged period of time, suitable for the drugs with short biological half-life requiring frequent dosing, increasing patient compliance and reducing inter- and intra-patient variability.
3. It is possible to avoid therapeutic failure or unfavorable consequences that are usually linked to intermittent dosage for chronic diseases.
4. Self-care and removal as necessary.
5. Oral dosing-related issues such stomach irritability, low bioavailability, deadly metabolite production from first pass metabolism, and poor and unpredictable absorption are avoided. Pain, inconvenience of injections can be overcome by this non- invasive and safe parenteral route of drug delivery.[36]
6. No first pass effect.
7. Suitable for drug candidates with a low therapeutic index and a short half-life.
8. Enhances patient compliance.[1]

Disadvantages:

1. Due to the skin's intrinsic impermeability, only reasonably potent medications are suitable for transdermal administration.
2. Contact dermatitis or skin irritation brought on by a drug's excipients.
3. The skin's barrier function varies with age, person, and from one site to another on the same person.
4. Drugs requiring high blood levels cannot be administered using the delivery system.
5. Transdermal delivery may not be cost-effective. The drug must have some desirable physic-chemical properties for penetration through stratum corneum.
6. Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability.[1]

Compositions of TDDS:

1. Polymer matrix.
2. Drug.
3. Permeation enhancers.
4. Pressure sensitive adhesives (PSAs).
5. Backing membrane.
6. Release liner.
7. Other excipients.

1. **Polymer matrix / Drug reservoir:**

The drug's release from the device is controlled by a polymer matrix that is created by dispersing the drug in a characteristic. Polymers used in TDDS should offer effective drug release throughout the device and be stable, compatible, and non-reactive with the medication and other system components. They should be simple to construct into the final product. Polymers must be nontoxic and non-antigenic to the host.[36]

The polymers used for TDDS can be classified as:

Natural polymers:

Hydroxypropyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (sodium CMC), cellulose acetate, methyl cellulose, ethyl cellulose, gelatin, chitosan, sodium carboxyethylguar, sodium alginate, polymerized rosin etc. [17]

Synthetic polymers:

Polyvinyl alcohol, polyethylene, polyethylene glycol, polyvinylpyrrolidone, eudragits, ethylene vinyl acetate copolymer, ethyl vinyl acetate, silicon rubber etc. [35]

2. Drug:

Drugs, having the following properties, are selected for TDDS:[36]

a.Physicochemical properties:

i. Low molecular weight (less than 500Daltons).
ii. Affinity for both hydrophilic and lipophilic phases.
iii. Low melting point (less than200°C).

b. Biological properties:

i. Extensive first pass metabolism.
ii. Narrow therapeutic window.
iii. Short biological half-life, requiring frequent dosing.
iv. Potent requiring few mg daily doses.
v. Should not induce cutaneous irritation and allergic response.

3. Permeation enhancers:

a.Chemical permeation enhancers:

By introducing amphiphilic molecules or by removing lipids, they disorganize the stratum corneum's highly organized intercellular lipid bilayers, reversibly lowering the barrier resistance and improving the permeability of the co-administered medications.[40] An ideal enhancer should function unidirectionally, be inert, non-toxic, non-allergenic, and non-irritating. It should also be compatible with the medications and excipients. Their potency seems to depend on the medication, the skin, and the concentration. A few examples of permeants include ethanol (the most popular permeation enhancer), essential oils or terpenes (cineole, carveol, menthone, citral, menthol, and limonene) [38], dimethyl sulfoxide, propylene glycol, Nmethyl-2-pyrrolidine, ethyl pyrrolidine, polyethylene glycol 400, isopropyl myristate, myristic acid, succinic. [38],

b. Physical permeation enhancers:

Iontophoresis uses a low-density electric current to improve and regulate medication entry via the skin. By applying high voltage pulses to the skin for a brief period of time, electroporation opens up fresh aqueous channels in the stratum corneum for drug diffusion.[19] The stratum corneum layers are removed using a single low-energy pulse from an erbium: yttrium- aluminum- garnet (Er:YAG) laser.[26] The stratum corneum is penetrated by ultrasound or microneedle application, opening tiny channels via which the medication can permeate.[25]

b. other permeation enhancers:

Ethanolic liposomes, niosomes, protransferosome gel, and prodrug approach are reported to promote permeability by boosting the drug's solubilization and partitioning into the skin.[19]

4. Pressure sensitive adhesives (PSAs):

When lightly pressed, PSAs firmly attach TDDS to the skin. They must be skin-friendly, non-irritating, and readily removed without leaving a trace or causing discomfort. They guarantee close contact between the skin's surface and the TDDS's drug-releasing area, which is essential for the medication's regulated release. PSAs made of silicone [30], polyacrylate, and polyisobutylene are all commercially accessible.

5. Membrane for backing:

The backing membrane's flexibility and strong tensile strength, together with its low water vapour transmission rates, help to hydrate the skin more effectively and increase its permeability. Backing membranes that are frequently utilized include polyvinyl alcohol and aluminumized plastic laminate (Alupoly foil).[35]

6. Release Liner:

The release liner is a barrier that protects the TDDS patch and is taken off before the patch is applied to the skin. Typically, it comprises of a silicon release coating layer on top of a base layer that may be either occlusive (such as polyethylene or polyvinyl chloride) or non-occlusive (such as paper cloth).[2]

7. **Additional excipients:**

To create the drug reservoir, a variety of solvents include water, ethanol, isopropylmyristate, isopropyl alcohol, and dichloromethane are either employed alone or in combination. In addition to the permeation enhancer, propylene glycol and ethanol are utilised as co-solvents (Magnusson et al., 1997; Ruland et al., 1994) [27] The transdermal patch's plasticity is provided by plasticizers like diethyl phthalate, dibutyl phthalate, glycerol, triethyl citrate, polyethylene glycol 400, eudralex, and propylene glycol.

FABRICATION OF TDDS:

The glass substrate casting-solvent evaporation technique is primarily used to create TDDS in the form of a matrix diffusion-controlled film with a predetermined amount of medication per unit area (sq. cm). Here, the polymer and plasticizer or adhesive solution is mixed with the medication and permeation enhancer solution. The mixture is then cast or poured into a glass ring on a mercury substrate or a foil cup with a backing membrane, where it is allowed to dry for 24 hours at ambient temperature or for 6 hours in a hot air oven at 400C. By flipping a funnel over the substrate, it is possible to regulate the pace of evaporation.[17] A thin, homogeneous layer of adhesive is formed on the dried film by pouring adhesive solution onto it and allowing the solvent to evaporate.[29]

CHARACTERIZATION OF TDDS:

TDDS can be characterized in terms of following parameters:

a.Evaluation of adhesion:

Adhesion of transdermal patch is evaluated for peel adhesion, tack properties (thumb tack test, rolling ball tack test, quick stick or peel tack test, probe tack test) and shear strength properties.[28]

b. Patch thickness:

Thickness of patches is measured by using a micrometer screw gauge and average thickness and standard deviation are calculated.[46]

c. Weight variation:

Each patch is weighed individually and average weight and standard deviation are calculated.[21]

d. Folding endurance:

The number of times a patch can be folded manually at the same place till it breaks gives the folding endurance.[10]

e. Mechanical properties:

The mechanical property is determined using plastic tensile test with Instron Instrument.[46]

f. Moisture content:

Accurately weighed patches of specific area are kept in a dessicator using activated silica and reweighed individually until a constant weight is obtained. Percentage of moisture content is calculated based on the change in the weight with respect to the initial weight.[46]

g.Moisture uptake:

Dry patches are exposed to higher relative humidity conditions and weight is taken periodically until a constant weight is obtained. The moisture uptake is calculated in terms of the percentage increase in weight of patch over its initial weight.[46]

h. Interaction study:

Any interaction among drug, polymer, excipients and stratum corneum is analyzed by Fourier Transform Infrared Spectroscopy (FTIR) or Differential Scanning Colorimetry (DSC).[4]

i. Stability test:

TDDS is analyzed for drug content, specific decomposition rate, color, consistency etc. [33]

j. Drug content and uniformity:

Patches of specific area are cut and weighed accurately. Drug is extracted in a suitable solvent and analyzed by ultraviolet- visible spectroscopy (uv-vis spectroscopy) or High-Performance Liquid Chromatography (HPLC).[17]

k. In vitro drug release studies:

The paddle over disc method (USP apparatus V) is used to assess the release of the drug from the prepared patches. Dry films of definite shape are weighed, and fixed over a glass plate with an adhesive. The glass plate is then placed in a 500 mL of phosphate buffer pH 7.4 as the dissolution medium and the apparatus is equilibrated to 37±2°C. The paddle is operated at a speed of 50 rpm. Samples (5ml aliquots) are withdrawn at appropriate time intervals and analyzed by spectrophotometry orspectrofluorimetry.[4][46]

l. In vitro skin permeation studies:

Various diffusion cells such as Kehsary chain diffusion cell, Franz diffusion cell, modified Franz diffusion cell (vertical type), cylindrical diffusion cell etc. are used for the in vitro skin permeation studies.[17] Skin of human cadaver, rat, mouse, guinea pig or pig can be excised from the abdominal or dorsal region and the whole, delipidated or stripped form of definite area and thickness is mounted between the compartments of the diffusion cell with the stratum corneum facing into the donor compartment.[16] The receptor compartment is filled with definite volume of phosphate buffer pH 7.4 and stirred by magnetic stirrer at a constant speed. Samples of definite volume are withdrawn from the receptor compartment at regular intervals and an equal volume of fresh medium is replaced. Samples are filtered and analyzed by radioimmunoassay, spectrophotometry or HPLC.[27]

m. In vivo evaluation:

The in vivo studies explore the pharmacokinetic and pharmacodynamic parameters which cannot be taken into account during the in vitro studies. In vivo evaluation of TDDS can be carried out using the animal models or healthy human volunteers. The most common animal species used are mouse, rat, dog and guinea pig.[26] However, animal models are not very good predictive models for human because the penetration in the animals is higher than that in the human. Rhesus monkey is one of the most reliable models for in vivo evaluation but the ethical consideration limits its use.[28] Healthy human volunteers can be used for reliable results.[30][4] The parameters studied are plasma concentration by Gas Liquid Chromatography (GLC), in vivo absorption study, in vivo delivery and deposition by confocal laser scanning microscopy, in vivo permeation by Gas Chromatography- Mass Spectrometry (GC-MS), ultra-structure of skin by Transmission Electron Microscopy (TEM) and various pharmacodynamic studies.[31]

n. Skin Irritation study:

Skin irritation or sensitization testing is performed on the hairless dorsal skin of healthy rats or rabbits. The patch is applied over the skin for 24 hours and removed and the skin is observed and classified into 4 grades (none, mild, moderate and severe) on the basis of the severity of erythema/edema and compared with that of the standard irritant, 0.8% formalin.[35][29]

o. Histological examination:

It is carried out to access the anatomical changes caused by the enhancers.[13]

p. Localized superficial infection:

Bacteria, fungi may proliferate under the occlusive dressing due to favorable conditions like increased temperature, hydration etc. It can be tested by the quantitative bacteriological cultures of the skin site before and after application of the transdermal patches.[28]

STAGES IN DRUG DELIVERY IN A TRANSDERMAL PATCH:

Following are the stages in drug delivery in a transdermal patch:[1]

1. Release of medicament from thevehicle.
2. Penetration through the skinbarriers.

3. Activation of the pharmacologicalresponse.

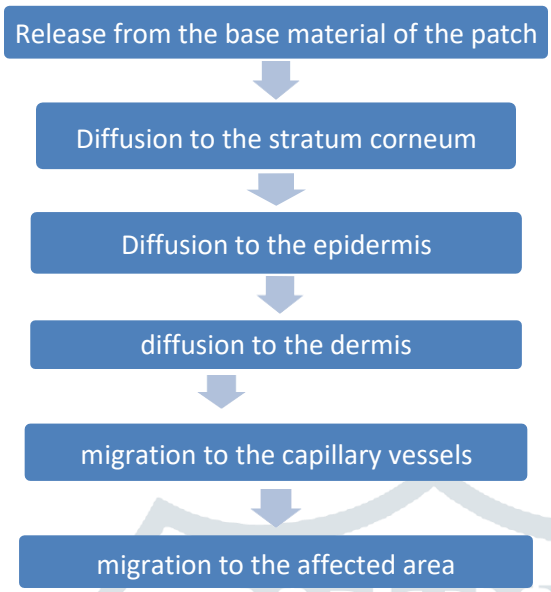

Fig : Mechanical of Transdermal Permeation

THERAPEUTIC APPLICATIONS:

i. Hisetal, used in the treatment of multiple sclerosis may be formulated in TDDS using oleic acid as permeation enhancer to achieve sufficient drug delivery.[45]

ii. Diclofenac sodium, celecoxib used as Non- Steroidal Anti-Inflammatory Drugs (NSAIDs), formulated in TDDS may overcome the gastric lesions associated with oral dosing.[43]

iii. Drugs used for long term dosing in the chronic diseases like captopril, verapamil, terbutaline sulphate, pinacidil, propranolol which have a short biological half-life, considerable first pass metabolism may be formulated as TDDS to achieve prolonged steady state plasma concentration.[21]

iv. Hydrophilic polymers like polyvinylpyrrolidone may provide faster drug release whereas hydrophobic polymers like ethyl cellulose can provide prolonged drug delivery.[10]

v. Gel formulation with lipid disperse system of betahistine has potential for the development of an efficient controlled release transdermal system.[31]

vi. Enhancer and co-solvent may synergistically enhance the delivery of peptides like thyrotropin releasing hormone across the human skin.[27]

vii. Prazosin Hydrochloride in membrane controlled TDDS may deliver the drug enough to maintain the minimum effective concentration and can avoid hypotension associated with high initial oral dosing.[42]

viii. TDDS of indomethacin in polyvinylpyrrolidone polymer (acting as antinucleating agent) may provide better anti-inflammatory activity and lower ulcer indices compared to oral administration.[44]

ix. Diclofenac sodium, existing in anionic form at skin pH may be formulated as ion-pairs with oppositely charged enhancers to enhance the transdermal delivery compared to non-ion paired forms.[43]

x. Iontophoresis may increase the permeation rate of hydrophilic atenolol to a greater extent than permeation enhancer and overcome incomplete absorption in the gastrointestinal (GI)tract.[6]

xi. Nimesulide in sodium alginate transdermal gel may provide better analgesic and anti- inflammatory activity and avoid the adverse effects associated with long term treatment with high oral dosing.[33]

xii. Terbutaline sulphate, being diamagnetic, may be incorporated in the magnetic TDDS to experience driving force to escape from the applied magnetic field and enhance diffusion across the skin.[29]

xiii. Bupropion Hydrochloride, an antidepressant drug may be converted to free base to increase the lipophilicity and transdermal delivery and avoid the release of fatal metabolites associated with oral dosing.[16]

xiv. Zidovudine, an anti-Human Immuno Deficiency Virus (anti-HIV) drug, formulated in TDDS may overcome toxic effects associated with frequent higher oral dose.[41]

CONCLUSION:

TDDS has gained realistic eventuality as the coming generation medicine delivery system for the dragged, controlled release of both hydrophobic and hydrophilic medicines, efficiently addressing the low oral bioavailability and vexation of injection. Unborn exploration will be aimed at better transdermal device design with lesser understanding of the different mechanisms of natural relation with saturation enhancers and perfecting the flux for a wide variety of motes especially macromolecules and vaccines using cost effective, new physical improvement ways along with being chemical enhancers.

REFERENCES:

1. Book of Novel drug delivery system by N.K. Jain ,1 january2017.
2. Aqil, M., Ali, A., Sultana, Y., Dubey, K., Najmi, A. K., Pillai, K.K., 2006. In vivo characterization of monolithic
3. matrix type transdermal drug delivery systems of pinacidil monohydrate: A technical note. AAPS Pharm Sci Tech, 7(1), Article6.
4. Bagyalakshmi, J., Vamsikrisna, R.P., Manavalan, R., Ravi, T.K., Manna, P.K., 2007. Formulation development and in vitro and in vivo evaluation of membrane moderated transdermal systems of ampicillin sodium in ethanol: pH4. 7buffersolventsystem.AAPSPharmSciTech,8(1): Article7.
5. Barichello, J.M., Yamakawa, N., Kisyuku, M., Handa, H., Shibata, T., Ishida, T., et al., 2008. Combined effect of liposomalization and addition of glycerol on the transdermal delivery of isosorbide 5-nitrate inrat skin. Int J Pharm, 357,199–205.
6. Bhaskaran, S., Shre Harsha, N., 2000. Effect of permeation enhancer and iontophoresis on permeation of atenolol from transdermal gels. Indian Journal of Pharmaceutical Sciences, 6, 424- 426.
7. Bouwstra, J.A., Honeywell-Nguyen, P.L., 2002. Skin structure and mode of action of vesicles. AdvancedDrug Delivery Reviews, 54(1): S41–S55.
8. Calpena, A.C., Lauroba, J., Suriol, M., Obach, R, Domenech J. Effect of d-limonene on the transdermal.
9. Dubey V, Mishra D, Nahar M, Jain V, Jain NK. Enhanced transdermal delivery of an anti-HIV agent via ethanolic liposomes. Nanomedicine permeation of nifedipine and domperidone. Int J Pharm. 1994; 103: 179-186 Chakkapan S, Gandhi K, Thomas S, Katkam RR, Puri CP,Shrivastava
   R. Studies in transdermal drug delivery systems for estradiol. Indian Journal of Pharmaceutical Sciences. 1994; 56(4): 121-125.
10. Dey BK, Nath LK, Mohanti B, Bhowmik BB. Development and evaluation of propranolol hydrochloride patches by using hydrophilic and hydrophobic polymer. Indian Journal of Pharmaceutical Education and Research. 2007; 41 (4):388-393.
11. Dimas DA, Dallas PP, Rekkas DM, Choulis NH. Effect of several factors on the mechanical properties of pressure- sensitive adhesives used in transdermal therapeutic systems. AAPS PharmSciTech. 2000; 1(2): Article16.
12. : Nanotechnology, Biology, and Medicine. 2010; 6:590–596

13. El-Laithy HM, Shoukry O, Mahran LG. Novel sugar esters proniosomes for transdermal delivery of vinpocetine: Preclinical and clinical studies. Eur J Pharm Biopharm. 2011; 77:43–55.

14. Ganem-Quintanar A, Lafforgue C, Falson-Rieg F, Buri P. Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss. Int J Pharm. 1997; 147: 165- 171.

15. Gaur PK, Mishra S, Purohit S, Dave K. Transdermal drug delivery system: A review. Asian Journal of Pharmaceutical and Clinical Research. 2009; 2 (1):14-20.

16. Gondaliya D, Pundarikakshudu K. Studies in formulation and pharmacotechnical evaluation of controlled release transdermal delivery system of bupropion. AAPS PharmSciTech. 2003; 4(1): Article3.

17. Hassan M. Dehghan GR, Parakh SR, Deshpande SG. Studies on polymeric systems for transdermal drugdelivery. Indian drugs. 1993; 30 (12):616-621.

18. Ho KY, Dodou K. Rheological studies on pressuresensitive silicone adhesives and drug-in- adhesivelayers as a means to characterise adhesive performance. Int J Pharm. 2007; 333:24-33.

19. Jadoul A, Preat V. Electrically enhanced transdermal delivery of domperidone. Int J Pharm. 1997;154:229-234.

20. Jain S, Sapre R, Tiwary AK, Jain NK. Proultraflexible lipid vesicles for effective transdermal delivery of levonorgestrel: development, characterization, and performance evaluation. AAPS PharmSciTech. 2005; 6(3): Article64.

21. Koteshwar KB, Udupa N, Kumar V. Design and evaluation of captopril transdermal preparations. IndianDrugs. 1992; 15(29):680-685.

22. Kulkarni RV, Hiremath D, Sagar P. Skin deep: Terpenes can enhance drug permeation. Delivery. 2007:39-42,53.

23. Kulkarni VH, Keshavayya J, Shastry CS, Kulkarni PV. Transdermal delivery of terbutaline sulphatethrough modified chitosan membrane. Indian Journal of Pharmaceutical Education. 2004; 38(4):189-190.

24. Langer R. Transdermal drug delivery: Past progress, current status and future prospects. Advanced DrugDelivery Reviews. 2004; 56:557-558.

25. Lanke SSS, Kolli CS, Strom JG, Banga AK. Enhanced transdermal delivery of low molecular weight heparin by barrier perturbation. Int J Pharm. 2009; 365:26–33.

26. Lee W, Pan T, Wang P, Zhuo R, Huang C, Fang J. Erbium:YAG laser enhances transdermal peptide delivery and skin vaccination. J Control Release. 2008; 128:200–208.

27. Magnusson BM, Runn P, Karlsson K, Koshinen LOD. Terpenes and ethanol enhance the trandermal permeation of the tripeptide thyrotropin releasing hormone in human epidermis. Int J Pharm. 1997; 157:113-121.

28. Mishra AN. Transdermal Drug Delivery. In: Jain NK, Editor. Controlled and Novel Drug Delivery. 1sted. New Dehli: CBS Publishers and Distributers; 1997. p.100-129.

29. Murthy SN, Hamsa V, Bhaskaran S. Formulation and evaluation of transdermal films of terbutaline sulphate. Indian Journal of Pharmaceutical Sciences. 1995; 57 (5):207-209.

30. Murthy SN, Rani S, Hiremath R. Physical and chemical permeation enhancers in transdermal delivery of terbutaline sulphate. AAPS PharmSciTech. 2001; 2(1) Technical Note1.

31. Ogiso T, Iwaki M, Jing-ping Z, Tanino T, Noguchi A. Percutaneous absorption of betahistine through rat skin and pharmacokinetic analysis of the plasma concentration. Int J Pharm. 1994; 102: 141-149.

32. Ohara N, Takayama K, Machida Y, Nagai T. Combined effect of d-limonene and temperature on the skin permeation of ketoprofen. Int J Pharm. 1994; 105:31-38.

33. Pandey S, Praveen SH, Udupi N. Formulation and evaluation of nimesulide transdermal drug delivery systems. Indian Journal of Pharmaceutical Sciences. 2000; 62(5):376-379.

34. Panigrahi L, Pattnaik S, Ghosal SK. The effect of pH and organic ester penetration enhancers on skin permeation kinetics of terbutaline sulphate from pseudolatex-type transdermal delivery systems through mouse and human cadaver skins. AAPS PharmSciTech. 2005; 6(2): Article25.

35. Paranjothy KLK, Thampi PP. Development of transdermal patches of verapamil hydrochloride using sodium carboxymethyl guar as a monolithic polymeric matrix and their in vitro release studies. Indian Journal of Pharmaceutical Sciences. 1997; 59(2):49-54.

36. Patel DM, Kavitha K. Formulation and evaluation aspects of transdermal drug delivery system. International Journal of Pharmaceutical Sciences Review and Research. 2011; 6 (2):83-90.

37. Phillips CA, Michniak BB. Transdermal delivery of drugs with differing lipophilicities using Azone analogs as dermal permeation enhancers. J Pharm Sci, 1995; 84 (12):1427-1433.

38. Prabhakar B, Deshpande SG. Simultaneous estimation of ethinyl estradiol and levonorgestrel from transdermal patches by HPLC. Indian Journal of Pharmaceutical Sciences. 1999; 61(1):12-15.

39. Prasad R, Koul V, Anand S, Khar RK. Effect of DC/mDC iontophoresis and terpenes on transdermal permeation of methotrexate: In vitro study. Int J Pharm. 2007; 333:70-78.

40. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008; 26 (11):1261-1268.

41. Puglia C, Filosa R, Peduto A, Caprariis P, Rizza L, Bonina F, et al. Evaluation of alternative strategies to optimize ketorolac transdermal delivery. AAPS PharmSciTech. 2006; 7(3): Article64.

42. Rajendran D, Sivabalan M, Dhanaraj SA, Ponnusankar S, Dube R, Suresh B. Transdermal delivery of prazosin HCl with non- ionic surfactants. Indian Journal of Pharmaceutical Sciences. 1997; 150- 153.

43. Rana V, Rai P, Tiwary AK, Gupta S. Enhanced in vitropercutaneous permeation of diclofenac sodium with primary amine and pyrrolidone ion-pairs. Indian Drugs. 1999; 36(1):21-28.

44. Rao PR, Diwan PV. Formulation and evaluation of polymeric films of indomethacin for transdermal administration. Indian Journal of Pharmaceutical Sciences. 1998;169-171.

45. Ruland A, Kreuter J, Rytting JH. Transdermal delivery of tetra peptides hisetal (melanotropin (6- 9)). I. Effect of various penetration enhancers: in vitro study across hairless mouse skin. Int J Pharm. 1994;101:57-71.

46. Satturwar PM, Fulzele SV, Dorle AK. Evaluation of polymerized rosin for the formulation and development of transdermal drug delivery system: A technical note. AAPS PharmSciTech. 2005; 6(4): Article81.