Review Article

Recent Advances in the Formulation of Transdermal System with Reference to the Polymers and Permeation Enhancers: A Review

Nishant Thakur*, Payal Mittal, Dr. Pradeep Goyal, Dr. Manish Goswami, Ritika Puri, Kritika Sharma
University Institute of Pharmaceutical Sciences, Chandigarh university, Gharuan, Mohali, India.
***Corresponding author's E-mail:** Nishant.thakur33@rediffmail.com

Received: 24-08-2017; **Revised:** 30-09-2017; **Accepted:** 16-10-2017.

ABSTRACT

A nation with a good social health is in the happiest situation and the pharmacist's role has widen from dispensing to innovating and formulating the drugs and nutraceuticals for today's needs. Challenges and needs in the 21st century have been changed. Now peoples are more concerned about their health and thus they are much concerned with drug products. Although it has boosted the healthcare segment but the role and responsibility on the pharmacist has increased. The administration of conventional oral dosage forms like tablets, capsules, liquids orals of drugs suffers a setback due to problem of gastro intestinal tract absorption, local irritation, dilution of drug strength , Liver first pass metabolism, degradation of drug by gastro intestinal tract enzymes, the protein binding of drug at an absorption surface and local toxicity. Transdermal medication delivers a steady infusion of the drug over prolonged period of time therefore avoiding adverse side effects and therapeutic failure frequently associated with intermittent dosing can also be avoided. Alternative route of administration for the patients who cannot tolerate oral dosage forms such as vomiting patient. Avoidance of first pass metabolism because it by passes the liver.

Keywords: Transdermal Patch, Permeation Enhancers, Skin, HPMC, Polymers, Devices.

INTRODUCTION

Today's pharmaceutical houses are engaged in production, design and development of new formulation which are more efficacious. Research is the mother of all the expertise including technology required to manufacture, simple as well as sophisticated remedies in the country. Although costing is the most important factor in this. The cost involved both in the terms of money and time in the development of a single new molecule has mandatory for pharmaceuticals companies to reconsider research focus. A drug can be delivered to its target area at a rate and concentration that both minimize side effects and maximize therapeutic effect, the drug will not be maximally beneficial to the patient and in the extreme, and an otherwise useful drug must be discarded. Current state of drug delivery approaches are humble steps in the direction of creating ZION on earth by attaining Zenith of health and cure for everyone. Last century had witnessed spectacular developments on the diverse kind of oral delivery systems. Nevertheless there is continuous need for developing delivery systems that can regulate drugs levels in a more efficacious, elegant and economic manner. In an attempt to reduce the cost of drug development process and advantageously reap the benefits of patient's regime, companies are now investing strategically in the development of controlled drug delivery system [CDDS]. Evolution of an existing drug molecule from a conventional form to CDDS can significantly improves its performance in terms of patient compliance, safety and efficacy. CDDS that can precisely control the release rate or target drugs to a specific body site have had an enormous impact on the healthcare system. In recent years the value of hydrophilic and hydrophobic polymers based drug delivery system as vehicles for controlled release delivery has been increasingly demonstrated as vehicle of numerous patents and research papers and their utilization new product in the market place. The use of biopolymeric devices to control the release of a variety of drugs has become important in the development of modified release dosage form.

The administration of conventional oral dosage forms like tablets, capsules, liquids orals of drugs suffers a setback due to problem of gastro intestinal tract absorption, local irritation, dilution of drug strength, Liver first pass metabolism, degradation of drug by gastro intestinal tract enzymes, the protein binding of drug at an absorption surface and local toxicity. All conventional dosage form except intravenous infusion, follow second-order kinetic.1 Dosage form releases drug initially at faster rate, leading to quick rise in blood level of drug and then falls exponentially until a further dose is administered. This results in peak and valleys pattern of drug concentration in blood and tissues.

Advantages of TDDS[2, 3]

- Transdermal medication delivers a steady infusion of the drug over prolonged period of time therefore avoiding adverse side effects and therapeutic failure frequently associated with intermittent dosing can also be avoided.
- Alternative route of administration for the patients who cannot tolerate oral dosage forms such as vomiting patient. Avoidance of first pass metabolism because it by passes the liver.

- Simplified regimen leads to improved patient compliance and reduced inter and intrapatient variability.
- Self administration is possible and they are non invasive, avoiding the inconvenience of parenteral therapy.
- Drug input can be terminated at any point of time by removing the transdermal patch.
- They are easily and rapidly identified in emergencies (for example, unresponsive, unconscious or comatose patient) because of their physical presence, features and identifying markings.

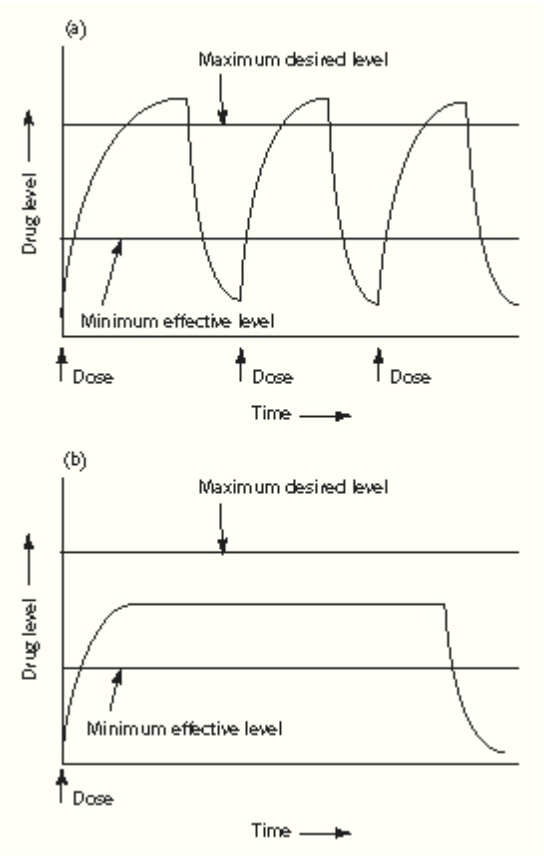

Fig: 01-Time course of various modes of administration

Disadvantages: 2, 3

- Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability.[4]
- Some patients develop contact dermatitis at the site of application from one or more of
- the system components, necessitating discontinuation.
- The delivery system cannot be used for drugs requiring high blood levels[4].
- The use of transdermal delivery may be uneconomical.

Recent Advances in Transdermal Patch Formulations

Patel JK and Jani RK (2016)[5] formulated and evaluated the biopharmaceutical behaviors of the matrix patch containing Diltiazem hydrochloride (DH) with an attempt of use of natural oils as permeation enhancers for transdermal applications. Transdermal patch prepared using 32 full factorial designs by solvent evaporation technique by incorporating propylene glycol as plasticizer and ethanol as solvent. Fourier transform infrared spectroscopy (FTIR) had employed to study drug and excipients incompatibility that showed the absence of any type of chemical interaction. Prepared patches evaluated for physico chemical parameters such as tensile strength, percent elongation, folding endurance, flatness, thickness, hardness, weight variation, percentage moisture loss and uptake, *ex-vivo* permeation study, *in-vivo* skin irritation study and stability study. The physicochemical and *ex-vivo* permeation studies indicated that patch containing HPMC K15M and psyllium in the ratio of 2:1 was better compare to all nine batches of factorial designs. Tensile strength, percent elongation and folding endurance found to be 4.48 kg/mm2, 21.84±0.335 and 384±3.21 respectively, which showed good mechanical property of prepared patch. Penetration enhancing capacity of natural oils (pumpkin seed oil, jojoba oil, tea tree oil, cumin oil, and linseed oil) was determined by performing *ex-vivo* study using wistar-rat skin. A maximum steady-state skin permeation flux of 239 µg/cm2/h achieved in the batch A2 which containing 20%w/w of pumpkin seed oil. The results of highest flux revealed that compare to all essential oils pumpkin seed oil enhance the permeation of drug through the skin.

Ganju Kuldeep and Ganju Eisha (2015)[6] studied the effect of gearaniol, linalool and nerol (0.5% in each formulation) on the permeation of the curcumin from the goat skin and it was concluded that geraniol is the best among all the three oils and facillate the diffusion through the skin membrane. Amit Kumar, Geeta Aggarwal et al(2014)[7]formulated and evaluated delivery system of transdermal drug with a view of developing and preparing a losartan potassium releasing system utilizing natural oils as permeation enhancers for transdermal applications. Matrix systems were prepared with PVP and ethyl cellulose (EC) polymers by incorporating dibutyl phthalate as plasticizer and chloroform as solvent. The physicochemical and in vitro drug release studies indicated that formulation containing PVP and EC in the ratio of 3:2 was better than other combination of polymers. Penetration enhancing potential of vegetable oils (jojoba oil, sunflower oil, sesame oil) and volatile oils (clove oil, peppermint oil, eucalyptus oil) was determined by incorporating oils in different concentration in optimized transdermal patch and in vitro permeation of losartan potassium across goat skin was studied. Maximum transdermal flux of 0.29 mg/cm2/h was obtained with formulation containing 10 % jojoba oil (vegetable oil) as permeation enhancer while in case of volatile oil maximum transdermal flux of 0.27 mg/cm2/h

was obtained with 10% peppermint oil as permeation enhancer respectively. The results of permeation fluxes supported the data for prolongation of drug release characteristics of formulated transdermal films. Satish Kumar Gupta et al(2014)[8] studied the permeation of the 5 flurouracil with eucalyptus and found that it was enhancing the permeation of drug through the skin barriers and eucalyptus was compared with chenopodium oil, and anise oil. Drug permeated maximum with eucalyptus oil. Bijay Kumar Sahoo, Amiya Kanta Mishra (2013)[9] formulated Diclofenac with different ratios of hydrophilic (hydroxyl propyl methyl cellulose) and hydrophobic (ethyl cellulose) polymeric systems by the solvent evaporation technique and by using Glycerol as plasticizer. Different concentrations of oleic acid and isopropyl myristate were used as the permeation enhancer. Transdermal films were physically evaluated with regard to thickness, weight variation, drug content, flatness, tensile strength, folding endurance, percentage of moisture content and water vapour transmission rate. All prepared formulations indicated good physical stability. *In-vitro* permeation studies of formulations were performed by using Franz diffusion cells. Formulation prepared with hydrophilic polymer containing permeation enhancer showed best *in-vitro* skin permeation through rat skin (Wistar albino rat) as compared to all other formulations. John Lincy and coworkers (2013)[10] evaluated the transdermal patches of the amlodipine prepared with EC as polymer and found that with increase in the concentration of the polymer the cumulative release of the drug decreased and formulation with 1% ethyl cellulose showed maximum release of 80% within 8 hrs while the formulations with 1.5% ethyl cellulose release over the extended period of 24 hrs. Kunal N Patel, Hetal K Patel (2012)[11]and coworkers studied *In vitro* release of diclofenac acid from various matrix systems using Franz diffusion cell using human cadaver skin. The diffusion medium used during *in vitro* release study was phosphate buffer saline solution pH 7.4. Labraslo, oleic acid and triacetin were used as the permeation enhancers and triacetin showed maximum drug permeation among all the formulations. Also it was concluded that the drug crystallization also decreases the drug release from the the formulation. V.N.L. Sirisha et al (2012)[12] prepared the transdermal patches of the propranolol hydrochloride with various concentration of the eudragit by mercury substrate method using di butyl phthalate as the plasticizer. From the diffusion data it was concluded that the drug followed the zero order of the drug release from the matrix. Gajanan Darwhekar et al (2011), [13] prepared transdermal drug delivery system of Clopidogrel bisulphate using the polymers HPMC, EC and PVP, using polyethylene glycol as a plasticizer by solvent casting technique having 37mg drug per patch.. The selection of polymer combinations produced clear, smooth, uniform, substantive, flexible and desired thickness film for the transdermal drug delivery systems of Clopidogrel bisulphate. The prepared formulation were evaluated for different Physico-chemical characteristics such as Thickness, Folding endurance, Drug Content, Percent moisture absorption, Percentage moisture loss and Weight uniformity. It was revealed in the studies that with increase in the concentration of the PVP and Ethyl cellulose moisture content of the patch also increased. Formulation coded with F2 having ethyl cellulose and HPMC without PVP showed the maximum release of the drug in the 24 hrs, Jamakandi and co-workers (2009)[14] used different polymeric grades of hydroxypropyl methyl cellulose (6cps, 15cps and K4M) for the development of transdermal drug delivery system of Nicorandil, an antiaginal drug. Matrix patch were evaluated for their physiochemical characterization followed by in vitro evaluation. Among the six different HPMC formulations, transdermal patch with 6 cps and 6 %w/v DMSO as permeability enhancer showed maximum release. Janardhanan Bagyalakshmi and co-workers (2008)[15] developed membrane moderated transdermal systems of Ampicillin sodium and to evaluate them with respect to various in vitro and in vivo parameters. The membrane type transdermal systems were prepared using a drug with various antinucleant polymers like hydroxyl propyl methylcellulose (HPMC), Methyl cellulose (MC), Cellulose acetate phthalate, chitosan, sodium alginate (SA) and sodium carboxy methyl cellulose in an ethanol: pH 4.7 buffers by the solvent evaporation technique with HPMC as the rate controlling membrane for all the system. The release and permeation of the drug from the SA patch was found to be the maximum. The in vivo study of SA patch exhibited a peak plasma concentration of 126µg/mL at tmax 4 hours. Murthy T.E.G.K. and co-workers (2008)[16] studied the influence of hydrophilic polymers on the permeability of Carvidiol from cellulose acetate films. The dried films were evaluated for appearance, thickness and drug release characteristic. In vitro permeation studies were carried out with Franz-diffusion cell. The drug release followed zero order kinetics and controlled by diffusion mechanism. Wahid and co-workers (2008)[17] chemically modified chitosan using acetaldehyde and propionaldehyde to form Schiff"s bases. Drug free polymeric film of chitosan, chemically modified chitosan and chitosan/hydroxyl propyl methylcellulose blend were prepared and evaluated for various physiochemical characters. All the films were evaluated for bursting strength, swelling index, moisture uptake, thickness uniformity, drug content uniformity, tensile strength, percent elongation at break, flatness, water vapor transmission rate and in vitro drug permeation study. Shaila Lewis and co–workers (2007)[18] characterized plasma concentration time profiles for nicotine after single application of nicotine transdermal system to the upper fore arm of healthy smokers. A 12cm^2 system was applied for 24h. Plasma nicotine concentration achieved a mean Cmax value of 14.5ng/ml. the result indicated that the system has potential usefulness in smoking cessation. The pharmacokinetic profile of marketed patch system was compared with the developed system. Significant difference was observed in the pharmacokinetic parameters. Shahi S. R. and co-

workers (2007)[19]studied the effect of various penetration enhancers such as Isopropyl Myristate (IPM), Dimethyl sulphoxide (DMSO), Benzyl alcohol, Menthol oil, oleic acid, Eucalyptus oil to increase the permeability of Ketorolac Tromethamine. The efficiency of the enhancers to improve the topical delivery of Ketorolac Tromethamine was sequenced in the order of DMSO> Eucalyptus > isopropyl myristate > menthol > oleic acid > benzyl alcohol. Vanja and co–workers (2006)[20]computed solubility of methotrexate using Fedor method. Permeability studied was carried out using artificial membranes such as cellophane and dialysis membrane and biological membrane such as rat skin and egg shell membrane. Flux and permeability coefficient determination showed that dialysis membrane and egg shell membrane exhibited similar barrier properties as that of rat skin when compared with cellophane. Saxena and co-workers (2006)[21] prepared Transdermal patches of metaclopramide hydrochloride using polyvinylalcohol and polyvinylpyrolidone. The physiochemical parameters like thickness, drug content, weight variation, moisture content, and moisture uptake and drug penetration studies were evaluated for the patch. The in vitro drug penetration studies showed that burst release of the drug in initial hours and thereafter the drug was released slowly up to 12 hr. The stability studies indicated that all the patches maintained good physical appearance and drug content for 6 month at 40°C and 75% RH. Bharkatiya and co-workers (2006)[22] prepared transdermal films of Nimesulide using four different polymers using solvent casting technique. Dibutylphthalate was used as plasticizer. In vitro permeation profile of formulation containing drug reservoir with HPMC: PVP showed highest permeation. The release of drug from all formulations followed the diffusion controlled Higuchi model and zero order release kinetics. Sadhna Gupta and co-workers (2005)[23] formulated and evaluated metaprolol tartarate transdermal drug delivery system using Eudragit RL and Hydroxypropyl methylcellulose. This transdermal drug delivery system was characterized for their thickness, tensile strength and drug content. They were characterized for in vitro release kinetics and drug skin permeation studies. The system comprising of Eudragit RL: Hydroxypropylmethylcellulose in 40:60 ratio exhibited drug skin permeation 87.5µg/h/cm2. The transdermal drug delivery system exhibited better and constant drug plasma profile for 24h as compared to oral administration. Ramesh Panchangula and co–workers (2005)[24]developed transdermal reservoir patch of naloxone and evaluated for *in vivo* studies, stability studies and irritancy potential. Propylene glycol and oleic acid have been used as penetration enhancers and showed developed transdermal system of naloxone is efficacious, stable and safe upon single and multiple dose application. Schurad B. and co-workers (2005)[25] investigated the transdermal in vitro permeation behavior of the Proterguride using hairless mouse skin as a model membrane. Drug in adhesive matrix formulations based on different types of pressure sensitive adhesives (Eudragit® E 100 and Gelva®7883 as acrylates, Oppanol® B 15 SFN as polyisobutylene, and BioPSA® 7-4202 as silicone) with a drug load of 3% by weight were prepared. It was found that Gelva®-based patches show good physical stability, good skin adhesion, and moderate flux values and, thus, can be evaluated as a basis for a suitable formulation for the transdermal administration of Proterguride. Kanikkannan N. and co-workers (2004)[26] prepared monolithic drug-in-adhesive type transdermal patches of melatonin containing penetration enhancers such as fatty alcohols, fatty acids, and terpenes. The addition of enhancers in the patch increased the permeation of melatonin through hairless rat skin. The flux values of patches containing octanol, nonanoic acid, and myristic acid were higher than the control patch (no enhancer), but the differences were not statistically significant ($P > 0.05$). Decanol, myristyl alcohol, and undecanoic acid at 5% concentrations showed significantly higher flux values through hairless rat skin (enhancement ratios 1.7, 1.5, and 1.6 for decanol, myristyl alcohol, and undecanoic acid, respectively) ($P < 0.05$). Menthol and limonene at 5% w/w showed maximum permeation of melatonin among all enhancers studied (enhancement ratios was 2.1 and 2.0 for menthol and limonene, respectively) ($P < 0.001$). Amir Mehdizadeh and co-workers (2004)[27] designed to evaluate different matrix, drug-in-adhesive and reservoir formulation of Fentanyl transdermal patches. He has designed drug-in-adhesive patches by designing full factorial design. The results showed that the release kinetics obeyed the square root of time or Higuchi model, indicating the diffusion controlled release mechanism. It was found that the amount of fentanyl needed for each 10cm2 three days drug-in-adhesive should be 3.3mg. The respective amount for reservoir and matrix patches were 2.5 and 5mg. it was concluded that acrylic pressure sensitive adhesive showed the best adhesion and release properties. Murthy S N and co-workers (2004)[28] prepared formulation containing 5mg/patch salbutamol sulfate (SS), providing an input rate of 100µg/h of SS and subjected for pharmacokinetic and pharmacodynamic evaluation in moderately asthmatic patients. A linear correlation was observed between cumulative amount of drug diffused in vitro and cumulative AUC of serum concentration time curve. A steady state serum concentration of 2.87 ± 0.1 ng/ml was attained after an initial lag period of 4.67 ± 1.03 hr. Y. S. R. Krishnaiah and co-workers (2004)[29] investigated the effect of limonene on the *in vitro* permeation of nimodipine across the excised rat abdominal skin from a 2% w/w hydroxypropyl methyl cellulose (HPMC) gel drug reservoir system. The HPMC gel formulations containing 1.5% w/w of nimodipine and selected concentrations of limonene (0% w/w to 8% w/w) were prepared, and subjected to *in vitro* permeation of the drug through excised rat abdominal epidermis. The flux of nimodipine across rat epidermis was markedly increased by the addition of limonene to the HPMC gels. A maximum flux of nimodipine was observed (203 ± 0.6 µg/cm^2·h) with an enhancement ratio

of about 5.7 when limonene was incorporated in HPMC gel at a concentration of 4% w/w. The results suggest that limonene is useful for enhancing the skin permeability of nimodipine from transdermal therapeutic systems containing HPMC gel as a reservoir. Priyanka Arora and co-workers (2002)[30] deigned matrix type transdermal patches containing diclofenac diethylamine using different ratios of polyvinylpyrrolidone (PVP) and Eethylcellulose (EC) by solvent evaporation technique. All the prepared formulations were subjected to physical studies like moisture content, moisture uptake and flatness and in vitro release studies and in vivo skin permeation studies. In vitro permeation studies were performed across cadaver skin using a modified diffusion cell. They concluded that diclofenac diethylamine can be formulated into the transdermal matrices type patches to sustain its release characteristics and the polymer composition (PVP:EC, 1:2) was found to be the best choice for manufacturing transdermal patches of diclofenac diethylamine among the formulation studies. M. Aquil and co-workers (2002)[31] developed matrix type transdermal drug delivery system of Pinacidil monohydrate by film casting technique or mercury substrate method and skin penetration studies using Keshary Chien diffusion cell on albino rat skin. The cumulative % of drug release in 48h was found to be highest (92.18%) from formulation Eudragit RL100: PVP K-30 (6:4). Hong Zaho and co-workers (2002)[32] formulated matrix-type transdermal delivery systems of testosterone (TS) using three different pressure sensitive adhesives (PSA) The effect of PSA, skin permeation enhancers and solubilizers on the rat skin permeation rate of TS were systematically investigated. The highest skin permeation rate (4.14 µg/cm^2/hr) was achieved when 2% TS was loaded in DuroTak® 87-2516 together with 10% span 80 and 3% dodecylamine, the permeation enhancer. In vivo studied showed that the application of an experimental patch on rat abdominal skin resulted in a prompt and significantly higher plasma concentration of TS than that of a commercially product (Testoderm) designed to apply on scrotal skin. Michael H. and co–workers (2002)[33] studied the release of permeation enhancers from transdermal drug delivery system of drug-in-adhesive type using known enhancers from eight types of adhesive polymers. They showed that, enhancers released completely from the adhesive and the release rate depended on the types of adhesives. They also showed that acrylic adhesive and polyisobutylene adhesive showed slower drug release rate than silicon adhesive. Kim J.H. and co-workers (2002)[34] investigated the effect of various pressure sensitive adhesives (PSA) on the percutaneous absorption of physostigmine across hairless mouse skin. Physostigmine showed the highest permeability from silicone adhesive matrix.

Advancement in the Bioadhesivity Evaluation of The Patch

Akthar Betul et al optimized the bioadhesivity of the biopolymer based transdermal films on the drug metaclopramide using the polymer sodium alginate. The prepared formulations were smooth and transparent. The adhesive properties of the sodium alginate based transdermal films of MTC and control formulation prepared in this study were assessed on a synthetic cellulose membrane (Visking Tubing 27/32, London, UK) using the TPA. The membrane was allowed to hydrate with phosphate buffer pH 7.4 at 37 °C prior to the experiments. The membrane was held on the lower platform of the instrument and the transdermal film was applied on it. The upper probe was immersed on the film surface, kept in contact for 120 s, and then it moved at a constant speed of 1 mm·s^{-1}.

Bio adhesion work (mJ/cm^2) = AUC1-2/πr^2

$\pi r2$ = Area of the transdermal formulation in contact with the skin

AUC1-2 = Area under the force-distance plot

The method used recorded the weight or force require to detach the film from the membrane and work done on the bioadhesion was calculated[35]. This simple experiment provided the mechanical basis for the evaluation of the bioadhesivity of the film applied on the skin although these parameters will not provide the exact value of the bioadhesion as there are other factors like temperature, force applied, area of skin on which patch is applied, backing membrane properties and surface area of the film will change the bioadhesivity of the film.

REFERENCES

1. Praveen Tyle, drug delivery device fundamental and biomedical application; Marcel dekker: New York, 1988, 386-419.
2. Controlled and novel drug delivery, N.K.Jain. barry b, 2002, Pp:100-129
3. Transdermal drug delivery, in edition: Aulton M.E, Pharmaceutics: the science of dosage form design, Churhcill Livingston. Pp: 499-533
4. Allen lv, Popvich NG, Ansel HC (2005). Ansel's pharmaceutical dosage forms and drug delivery systems, 8th edition,lippincott williams & wilkins pp 298-315.
5. Patel JK and Jani RK, enhancing effect of natural oils as permeation enhancer for transdermal delivery of diltiazem hydrochloride through wistar rat skin.Int. J. Pharm. Sci. Rev. Res., 36(1), january – february 2016; article no. 02, pages: 9-16.
6. Ganju Kuldeep, Ganju Eisha, To study the in vitro effect of some alcohol containing volatile oils as the skin penetration enhancers of curcumin, journal of harmonized research 4(1), 2015, 60-63
7. Amit Kumar, Geeta Aggarwal, Kashmir Singh and S. l. Harikumar comparison of vegetable and volatile oils as skin permeation enhancers fortransdermal delivery of losartan potassium scholars research library, der pharmacia lettre, 6 (1), 2014, 199-213

8. Satish Kumar Gupta and S. Kumar, transdermal drug delivery enhancement by essential oils of eucalyptus globules,advances in biological research 8 (6), 249-250, 2014
9. Bijay Kumar Sahoo, Amiya Kanta Mishra, Formulation and evaluation of transdermal patches, of diclofenac, world journal of pharmacy and pharmaceutical science, volume 2, issue 6, 4965-4971.
10. Lincy John,Arun Kumar and Sandra Samuel, formulation and evaluation of amlodipine transdermal patch using ethyl cellulose , international research journal of pharmacy, 4(10), 2013, 85-88
11. Kunal N Patel, Hetal K Patel, Vishnu A Patel, Formulation and characterization of drug in adhesive transdermal patches of diclofenac acid , international journal of pharmacy and pharmaceutical sciences vol 4, issue 1, 2012, 297-299
12. V.N.L. Sirisha, P. Kirankumar, M.Chinnaeswaraiah, Formulation and evaluation of transdermal patches of propranolol hydrochloride, iosr journal of pharmacy ISSN: 2250-3013, volume 2 issue 5, sep-oct. 2012, pp.31-37 31
13. Gajanan Darwhekar, Dinesh Kumar Jain, Vinod Kumar Patidar,Formulation and evaluation of transdermal drug delivery system of clopidogrelbisulfate, asian journal of pharmacy and life science issn 2231 – 4423vol. 1 (3), july-sept, 2011, 269-278
14. Jamakandi V.G., Mulla J.S., Vinay B.L., Formulation, characterization and evaluation of matrix type transdermal patches of a model antihypertensive drug.asian j. Pharm., 1, 2009, 59-65.
15. Bagyalakshmi J., Vmshikrishna R. P., Formulation, development and in vitro and in vivo evaluation of membrane-moderated transdermal systems of ampicillin sodium in ethanol: ph 4.7 buffer solvent system, aaps pharm. Sci. Tech., 8(1), 2008, e50-e55.
16. Murthy T.E.G.K., Ramana R.V., Kishore B.M., Influence of polymers on the release of carvediol from transdermal films, indian drugs, 45(12), 2008, 970-974.
17. Wahid A., Sridhar B.K., Shiv Kumar S., Preparation and evaluation of transdermal delivery system of etoricoxib using modified chitosan, indian j. Pharm. Sci., 2008, 455-460.
18. Lewis S., Subramanyam G., Pandey S., Udupa N., Pharmacokinetic evaluation of a developed nicotine transdermal system, indian j. Pharm. Sci., 69(2), 2007, 309-312.
19. Shahi S. R., Somani V. G., Shamkuvar P. B., Kale M. A., Kataria M. V., Effect of enhancers on topical delivery of ketorolac tromethamine. Asian j.Pharmaceutics, 1, 2007, 184-186.
20. Vanja k., Shobha Rani R.H., Pre formulation studies of methotrexate for assessing its suitability for transdermal vesicular drug delivery system, int. J.Pharm. Excip., 7, 2006, 93-98.
21. Saxena M., Mutalik S., Reddy M.S., Formulation and evaluation of transdermal patches of metaclopramide hydrochloride, indian drugs, 43(9), 2006, 740-745.
22. Bharkatia M., Nema R. K., Designing and evaluation of transdermal patches of nimesulide, Asian j. Pharm. 1(1), 2006, 46-48.
23. Gupta S. P., Jain S. K., Effective and controlled transdermal delivery of metoprolol tartarate, Indian j. Pharm. Sci., 67(3), 2005, 346-350.
24. Panchangula R., Bokalial R., Sharma P., Khandavilli S., Transdermal delivery of naloxone: skin permeation, pharmacokinetic, irritancy and stability studies, int. J. Pharm, 293, 2005, 213-223.
25. Schurad B., Tack J., Lipp R., Evaluation of the transdermal permeation behavior of proterguride from drug in adhesive matrix patches through hairless mouse skin, drug. Dev. Ind. Pharm., 31(6), 2005, 505 – 513.
26. Kanikkannan N., Andega S., Burton S., Babu R. J., Singh M. , A formulation and in vitro evaluation of transdermal patches of melatonin, drug dev. Ind.Pharm, 30(2), 2004, 205 – 212
27. Mehdizadeh A., Toliate T., Rouini M. R., Design and in vitro evaluation of new drug-in-adhesive formulation of fentanyl transdermal patches, acta pharm., 54, 2004, 301-317.
28. Murthy S. N., Hiremath S. R., Clinical pharmacokinetic and pharmacodynamic evaluation of transdermal drug delivery systems of salbutamol sulfate, int. J pharm. Sci., 287, 2004, 47-53.
29. Krishnaiah Y.S.R., Bhaskar P., Satyanarayana V., *In vitro* percutaneous permeability enhancement of nimodipine by limonene across the excised rat abdominal skin, pharmazie, 59(12), 2004, 942-947.
30. Arora P., Mukherjee B., Design, Development, Physiochemical and in vitro and in vivo evaluation of transdermal patches containing diclofenac diethylammonium salt, j. Pharm. Sci., 91(9), 2002, 2076-2090.
31. Aquil M, Asgar A., Monolithic matrix type transdermal drug delivery systems of Pinacidil monohydrate: in vitro characterization, European j. Pharm.Biopharm., 54, 2002, 161-164.
32. Zaho H., Park D.W., Kim S.K., lee C.H., Kim D.D., The effects of pressuresensitive ashesives and solubilizers on the skin permeation of testosteone from matrix – type transdermal delivery system, drug dev. Ind. Pharm., 28(9), 2002, 1125-1131.
33. Qvist M.H, Ulla H., Kreilgaard B., Flemming M., Release of chemical permeation enhancers from drug-in-adhesive transdermal patches, int. J. Pharm, 231, 2002, 253-263.
34. Kim J.H., lee C.H., Choi H.K., Transdermal delivery of physostigmine: effects of enhancers and pressure sensitive adhesive, drug dev. Ind. Pharm., 28(7), 2002, 833-839.
35. Betül Aktar, Meryem Sedef Erdal, Olcay Sagirli, Sevgi Güngör and YildizÖzsoy optimization of biopolymer based transdermal films of metoclopramide as an alternative delivery approach, *polymers* 6, 2014, 1350-1365.

Source of Support: Nil, **Conflict of Interest:** None.