Design and Evaluation of Matrix Diffusion Controlled Transdermal Patches of Dexibuprofen

S. Lakshmana Prabu[1]*

T.N.K. SuriyaPrakash[2]

S. Thiyagarajan[1]

M. Amritha[1]

R. Manibharathi[1]

N. Priyadharsini[1]

[1]Dept. of Pharm. Technology, Anna University of Technology, Tiruchirappalli – 620 024
[2]Dept of Pharmaceutics, Periyar College of Pharmaceutical Sciences, Trichy – 620 021

**Corresponding author:*
Tel.: +91-9750550965
E-mail address: slaxmanvel@gmail.com

KEY WORDS: Keywords

ABSTRACT

Objective: The present investigation was to prepare dexibuprofen matrix transdermal patches to produce the systemic and sustained effect for the treatment of inflammation associated pain.

Materials and Methods: Transdermal patch formulations were prepared by solvent evaporation technique. The prepared formulations were evaluated for its physicochemical properties like film thickness, weight variation, moisture content, water absorption studies, drug content uniformity, invitro and skin irritation studies.

Results and Discussion: The drug delivery of the formulations was analyzed using the paddle over disc method in phosphate buffer pH 7.4 medium and compared the release profile. From the release results formulation F3 showed a maximum amount of drug release. To improve the release rate of the drug, formulation F3 was made with various ratios of ethanol as penetration enhancers into the polymer matrix solution. Dexibuprofen patch containing ethyl cellulose: polyvinyl pyrrolidone in the ratio 1:3 with 1 ml of ethanol [F11] showed maximum amount of drug release. In in-vitro skin permeation studies, the mean cumulative amount of drug permeated per 1.5cm2 of the film from formulation F11 after 24 hours was found to be 305 mcg. The results of skin irritation studies show no signs of erythema when compared to that of the control. The absence of edema indicates that the polymeric patches are compatible with the skin.

Conclusion: The present study showed that the matrix transdermal patches of dexibuprofen containing ethyl cellulose: polyvinyl pyrrolidone in the ratio 1:3 with 1 ml of

ethanol exhibited better drug permeation and showed the desired objectives of transdermal drug delivery systems such as extended release and reduced frequency of administration may serve as a better system for transdermal delivery without causing skin irritation and, hence, can increase patient compliance for the treatment of inflammatory pain.

INTRODUCTION

New drug delivery systems are essential for the delivery of novel, genetically engineered pharmaceuticals to their site of action without incurring significant immunogenicity or biological inactivation. Apart from the advantages, the pharmaceutical companies recognize the possibility of repeating successful drugs by applying the concept and techniques of controlled drug delivery systems coupled with the increased expenses in bring new formulation to the market. Among the various formulations, the most often utilized formulations are Trans Drug Delivery systems (TDDS). The delivery of drug through the skin has long been a promising concept because of the ease of access, large surface area, vast exposure to the circulatory and lymphatic networks, and noninvasive nature of the treatment.[1-3] Transdermal drug delivery uses the skin as an alternative route for the delivery of systematically acting drugs. The skin is our largest organ, which covers a total surface area of approximately 1.8 m^2 and forms a fascinating and unique interface between the outside world and us.[4]

Such a system offers a variety of significant clinical benefits over other systems such as tablets and injections, the main advantage of transdermal delivery of hydrophilic drugs versus oral delivery lies in the molecular nature of the gastrointestinal tract (GIT).5-6 It provides controlled release of the drug and produces a steady blood level profile, leading to reduced systemic side effects and some times improved efficacy over other dosage forms.[7-8] The success of transdermal patches lies in their commercialization.[9-10]

Transdermal patches control the delivery of drugs at controlled rates by employing an appropriate combination of hydrophilic and lipophilic polymers.[11-15] In addition, the transdermal dosage form is user friendly, convenient, painless, and offers multi day dosing. It generally leads to improved patient compliance, protects the active compound from gastric enzymes, elimination of gastrointestinal irritation resulting from some drugs, avoiding first-pass metabolism and gastrointestinal degradation, sustaining drug delivery, maintaining a constant and prolonged drug level in plasma, reduced dosing frequency, minimizing inter- and intra- patient variability, and simple to interrupt or terminate the therapy if any adverse or undesired effects occur or treatment when necessary.[16-18]

Dexibuprofen is chemically (2S)-2-[4-(2-ethylpropyl)phenyl] propanoic acid, and used as an NSAID for management of pain and inflammation associated with osteoarthritis, other musculoskeletal disorders, and symptomatic treatment of mild to moderate pain and inflammation including dysmenorrhoea and dental pain having biological half life of 1.8 -3.5 hr. The recommended dosage is 600-900 mg per day at 2-3 divided doses. Due to short biological half-life and frequent administration of dexibuprofen make it a potential candidate for sustained release preparations.

The aim of the present investigation was to prepare dexibuprofen matrix transdermal systems to produce the systemic and sustained effect for the treatment of inflammation associated pain.

EXPERIMENTAL

Materials

Dexibuprofen was obtained as gift sample from Shasun Chemicals and Drugs Pvt. Ltd., Pondicherry; Eudragit RL was procured from M/s. Rohm Pharma, West Germany; ethyl cellulose and polyvinyl pyrrolidone were obtained from Loba Chemie Pct. Ltd., Mumbai; polyvinyl alcohol, sodium chloride, ammonium hydrogen phosphate, sodium hydroxide, potassium dihydrogen phosphate, and dichloromethane from M/s.

Table 1. *Composition of Transdermal Patches*

Formulation code	Drug (mg)	Polymer (mg)			Plasticizer Dibutylpthalate (w/w)	Solvent Chloroform (ml)
		Ethyl Cellulose	Eudragit RL	PVP		
F1	50	250	-	250	30%	5
F2	50	166.66	-	333.34	30%	5
F3	50	125	-	375	30%	5
F4	50	333.34	-	166.66	30%	5
F5	50	375	-	125	30%	5
F6	50	-	250	250	30%	5
F7	50	-	166.66	333.34	30%	5
F8	50	-	125	375	30%	5
F9	50	-	333.34	166.66	30%	5
F10	50	-	375	125	30%	5

S.D. Fine Chemicals Ltd, India. Membrane for the permeability studies was the dorsal section of full thickness skin from Wistar rats weighing around 200 – 250 g, whose hair had been previously removed with an electronic clipper. Stratum corneum was prepared from the full thickness skin.

Methods

Preparation of film and Preparation of backing membrane

PVA film was used as backing membrane, prepared by pouring 10 ml of 3%w/v (in water) PVA solution onto a glass petri dish and dried at 40°C for 24 hours.

Polymer Matrix SolutionPreparation

The composition of various patche formulations are provided in Table 1. The patches of the respective compositions were devised using polymers along with the drug. Chloroform was used as solvent for the film, and the polymers were weighed accurately and dissolved in corresponding solvents. To this polymer solution various ratio's of plasticizer was added and mixed well. The calculated amount of the drug was added to the polymer solution and mixed using a cyclomixer. The uniform dispersion was poured on the PVA backing membrane and dried at 40°C for 24 hr. Controlled solvent evaporation was achieved by placing an inverted funnel over the petri dish. The dry films were removed and kept in desiccators until used.

Drug Compatibility Studies

The drug and the excipients must be compatible with one another to produce a product that is stable, efficacious, attractive, safe, and easy to administer. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. Excipients are integral components of almost all pharmaceutical dosage forms. Unexpected stability problems usually lead to increase in time and cost of drug development. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. FT-IR and UV19 are used to investigate any physicochemical interactions between drug and excipients used in the formulation.

Physicochemical Properties of the Films

The films were evaluated for the following physicochemical properties.

Film Thickness

The thickness of the patches was determined using screw gauge (Omega, India), recording a mean of six determinations.

Weight Variation

Six films from each batch were weighed individually and the average weight was calculated.

Drug Content

Films of a specified area were cut and weighed accurately. Pieces were taken into a 100 ml volumetric flask and 50 ml of phosphate buffer solution (pH 7.4) was added and kept in a shaker for 12 hours. A blank was performed by using a drug free film. The solution was filtered and samples were analyzed spectrophotometrically at 223 nm for drug content.

Moisture Content

The prepared patches were cut into 20 x 50 mm strips, weighed individually, and kept in a desiccators containing calcium chloride at 37°C for 24 hr. The films were reweighed individually until a constant weight was obtained. Percentage of moisture content was then calculated based on the change in the weight with respect to the initial weight of the film.

Water Absorption Studies

The water absorption capacities of various films were determined at 75% and 93% relative humidity (RH). Films were cut into 20 X 50 mm strips, weighed, kept in a desiccators at 40°C for 24 hr, removed, and exposed to RH conditions of 75% (containing saturated solution of sodium chloride) and 93% (containing saturated solution of ammonium hydrogen phosphate) in different desiccators at room temperature. Weight was taken periodically until a constant weight was obtained. The water absorption capacity of the films (in weight %) was calculated in terms of percentage increase in the weight of film over the initial weight of the strip.

In vitro Release Studies

The paddle over disc method (USP apparatus V) was employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness were cut into circular shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32 ± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5-mL aliquots) were withdrawn at appropriate time intervals up to 24 hr and analyzed for drug content at 223 nm using Shimadzu double beam UV-visible spectrophotometer (Shimadzu, Japan). The experiment was performed in triplicate and the mean value was calculated.

In vitro Permeation Studies

An in vitro permeation study was carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats weighing 200 to 250g was used. Hair from the abdominal region was carefully removed by using a electric clipper. The dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in pH 7.4 buffer before starting the experiment, and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece was mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volumes of 3 ml were removed from the receptor compartment at regular intervals, and an equal volume of fresh medium was added. Samples were filtered through Whatman filter paper No: 41 and analyzed spectrophotometrically at 223 nm. The study was performed for 24 hr, and amount of drug release was calculated.

Skin Irritation and Sensitization Testing

Skin irritation and sensitization testing were performed on healthy rabbits (average weight: 1.2 to 1.5 kg). The dorsal surface (50cm2) of the rabbit was cleaned, and the hair was removed by shaving after the skin was cleaned using rectified spirit and the representative formulations were applied over the skin. These were removed after 24 hr and the skin was examined for any untoward reaction.

RESULTS AND DISCUSSION

Table 2. *The Results of Thickness and Drug Content*

Formulation code	Weight variation (g)	Thickness (mm)	Drug content (mg)
F1	0.0729	0.20 ± 0.02	98.56 ± 0.20
F2	0.0792	0.21 ± 0.02	98.32 ± 0.26
F3	0.0707	0.20 ± 0.03	99.00 ± 0.10
F4	0.0756	0.22 ± 0.02	97.31 ± 0.21
F5	0.0730	0.21 ± 0.02	98.31 ± 0.31

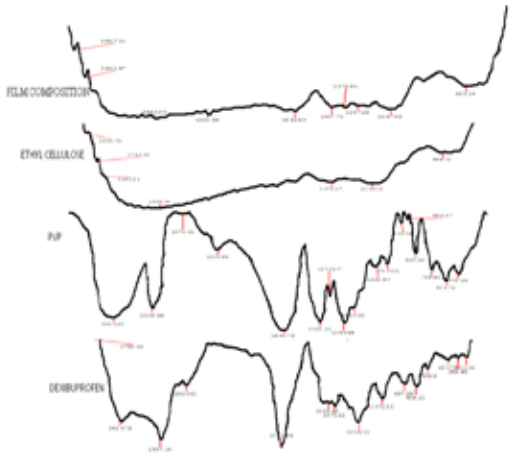
All the values are presented as Mean ± S.D.; n=3.

The intensity of interest in the potential biomedical application of transdermal controlled drug administration is demonstrated in increasing research activity in the development of various types of transdermal therapeutic systems. The transdermal therapeutic system is of particular clinical significance for the prevention and long term treatment of chronic diseases. Transdermal delivery is a successful controlled release technology in terms of the number of approved products, which are on the market.

Ten different compositions of patches containing varying proportions of ethyl cellulose, Eudragit RL, and polyvinyl pyrrolidone were prepared. The composition is shown in Table 1. The patches prepared with the combination of Eudragit RL with ethyl cellulose were not transparent ones, whereas the patches prepared with the combination of eudragit RL with polyvinyl pyrrolidone forms a transparent film. So the patches prepared with the combination of eudragit RL with polyvinyl pyrrolidone were taken into consideration for further studies.

Plasticizer is often incorporated in transdermal delivery system to give flexibility to the formulation, which improves the contact between the skin and patch, which leads to an increase of flexibility and permeability of the drug. In the present study, various ratios of plasticizer (based on the polymer weight) were added to the polymer solution ie, 5%, 10%, 15%, 20,% and 30%w/w. The result revealed that 30%w/w of plasticizer was found to be optimum for the formation of a flexible patch.

Figure 1. *IR Spectra of Drug and Physical Mixture*



Compatibility studies were carried out by FTIR and UV spectroscopy techniques. Infrared studies revealed that the dexibuprofen contains the chemical functional groups like the carboxyl group, alkyl group, methylene group, and methyl group The corresponding wave numbers were at 1,712, 2,957.19,1,419, and 1,372 respectively. These characteristic bands were present in all spectra. No new bands or shift in characteristic peaks appeared. IR spectra are shown in Figure 1. In UV technique, the UV spectrum of drug is super-imposable with the spectrum obtained with drug excipients mixtures and there is no change in the λmax 223 nm between the drug and drug excipients mixtures. From the FTIR and UV,

Table 3. *Results of Percentage Moisture Content and Percentage Moisture Uptake*

Formulation code	Percentage Moisture content	Percentage Moisture uptake
F1	95.56	96.01
F2	93.45	94.20
F3	93.00	97.03
F4	94.01	93.64
F5	93.50	95.78

results revealed that there is no interaction between the drug and the excipients used in the formulation.

The formulated films were characterized for various parameters such as weight variation, thickness, and drug content. These are essential parameters for the evaluation of the dosage form in order to achieve a formulation with uniformity and consistency within a batch. The results of thickness and drug content are shown in Table 2. The drug content analysis of the prepared formulations show that the processes used to prepare the patches in this investigation gives uniform drug content, minimum batch variability, and exhibit uniform thickness. The uniformity in drug content and thickness indicates that the polymeric solution of the drug is well dispersed. However little variation in weight and thickness were observed in different formulations, which may be due to the variation in polymeric content.

The percentage moisture content and water absorption capacity of the patches was calculated from the weight difference relative to final weight, the results are shown in Table 3.

An in vitro release study is a characterizing tool to predict the rate and extent to which the drug is released from the device. Dissolution of polymer from the matrices is an essential one for ensuring the sustained release of the drug substances. Typically, most products in the market employ one of the following three established apparatus mentioned in the USP to establish release specifications i.e. apparatus V (paddle over disk), apparatus VI (rotating cylinder and apparatus) and apparati VII (reciprocating disk). Paddle over disk method is one of the most convenient and often used to characterize drug release from a transdermal system. This method has been improved and simplified by making use of a watch glass patch Teflon mesh sandwich assembly, held together with clips immersed beneath in the USP apparatus II paddle equipment, and is equivalent to the apparatus V.

The in vitro release studies were carried out for the above patches by paddle over disk method. From the release results formulation F3 showed a maximum amount of

Table 4*. Composition of Various Film Formulations*

Ingredients in mg	D1	D2	D3	D4
Dexibuprofen	50mg	50mg	50mg	50mg
Ethyl cellulose	375mg	375mg	375mg	375mg
Polyvinyl pyrrollidone	125mg	125mg	125mg	125mg
Polyvinyl alcohol	3%w/v	3% w/v	3% w/v	3% w/v
Chloroform	4ml	4.25ml	4.5ml	4.75ml
Ethanol	1ml	0.75ml	0.5ml	0.25ml
Dibutylphthalate	30% w/w	30% w/w	30%w/w	30% w/w

***Table 5**. The Results of Thickness and Drug Content*

Formulation Code	Thickness (mm)	Drug content (%)	Weight Variation(g)
D1	0.21 ± 0.02	98.48 ± 0.17	0.0792
D2	0.21 ± 0.02	98.62 ± 0.30	0.0710
D3	0.21 ± 0.03	98.20 ± 0.20	0.0731
D4	0.20 ± 0.03	98.13 ± 0.28	0.0763

drug release (ie, 1,724 mcg) and a minimum with formulation F5 (ie, 1,102 mcg). The results are shown in Figure 2. These results indicate that the release of drug from the patch increases on increasing the concentration of polyvinyl pyrrolidone. This may be due to hydrophilic nature of polyvinyl pyrrolidone. In order to improve the release rate of the drug, formulation F3 was made with various ratios of ethanol as penetration enhancers into the polymer matrix solution. The composition of the formulation is shown in Table 4. The formulated films were characterized for various parameters such as weight variation, thickness and drug content and the results are shown in Table 5.

The percentage moisture content and water absorption capacity of the patches was calculated from the weight difference relative to final weight and the results are shown in Table 6. The in vitro release studies carried out for the above patches by paddle over disk method and the maximum drug release was observed with formulation F6 (ie, 1,847 mcg). The results are shown in Figure 6.

Drug release from the transdermal patches is controlled by the physiological and physicochemical properties of the biological membrane, type of delivery and chemical properties of drug.[20] The in vitro permeation studies are predictive of in vivo performance of a drug. Matrix or monolithic transdermal drug delivery devices are used when the rate of drug permeation through the stratum corneum is the rate-limiting step for the drug absorption.

Membranes from rats, mice, pigs, guinea pigs, snakes, rabbits, and humans as well as synthetic membranes have been used for these drug diffusion studies. Although human cadaver skin may be the first choice as a skin model for a study of a final product to be used in humans, it is not always easy to obtain, and rat skin is a commonly used substitute for permeation studies.[21-23]

The drug release from matrix system is rapid initially and falls as the matrix is depleted off the drug. Concentrations of drug in the matrix, chemical nature of matrix material, and device geometry are the rate controlling factors to release the drug from the transdermal therapeutic system. The cumulative amount of dexibuprofen permeated through the rat abdominal skin, into a receptor solution, as a function of time. It is shown in Figure 4. The mean cumulative amount of drug permeated per 1.5cm^2 of the film from formulation F11 after 24 hours was found to be 305 mcg. The results of skin irritation studies show no signs of erythema when compared to that of the control. The absence of edema indicates that the polymeric patches are compatible with the skin.

***Table 6.** Results of Moisture Content and Moisture Uptake*

Formulation code	Moisture content (%)	Moisture uptake (%)
D1	94.56	96.02
D2	93.86	95.97
D3	94.65	95.43
D4	92.75	93.84

Figure 2. *In vitro Release Profile of Formulations F1 to F5*

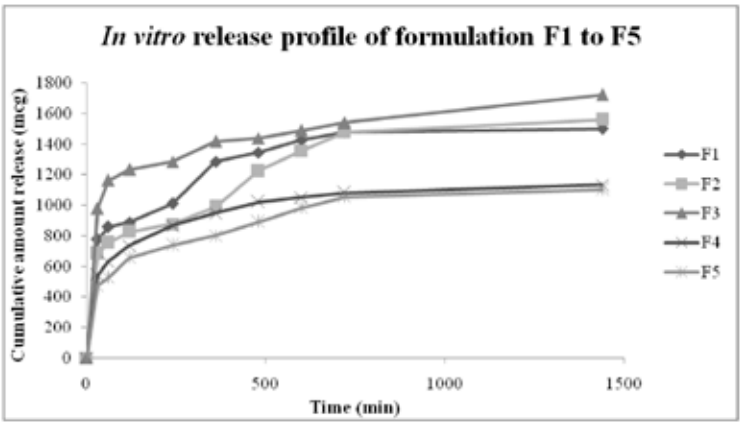


Figure 3. *In vitro Release Profile of Formulations F11 to F14*

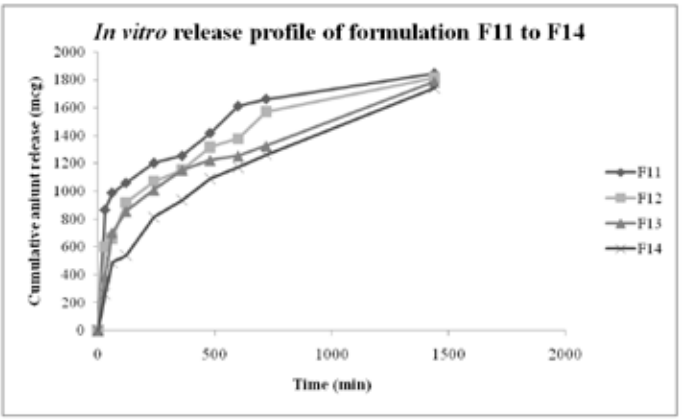
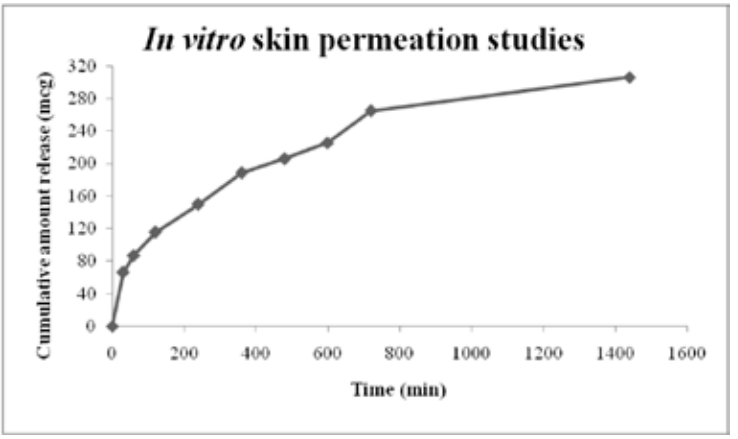


Figure 4. *In vitro Permeation Study of Formulation F11*



CONCLUSION

Dexibuprofen can be developed as a transdermal patch with ethyl cellulose and polyvinyl pyrrolidone as the rate-controlling membrane. The present study showed that matrix transdermal patches of dexibuprofen exhibited better drug permeation. The present study shows that dexibuprofen patch containing ethyl cellulose: polyvinyl pyrrolidone in the ratio 1:3 with 1 ml of ethanol showed the desired objectives of transdermal drug delivery systems, such as extended release and reduced frequency of administration may serve as a better system for transdermal delivery without causing skin irritation and hence can increase patient compliance. It also satisfies the requirements of modern drug delivery systems in delivering the drug in predetermined manner. A transdermal patch of dexibuprofen may offer a promising drug delivery tool for the treatment of inflammatory pain.

REFERENCES

1. Daniels R, Knie U. Galenics of dermal products vehicles, properties and drug release. *J Dtsch Dermatol Ges* 2007; 5: 367-381
2. Grego C, Gabriele B, Andreas S, Dieter G, Amla P. The skin: a pathway for systemic treatment with patches and lipid-based agent carriers. *Adv Drug Del Rev* 1996; 18: 349-378.
3. Hadgraft J. Skin deep. *Eur J Pharm Biopharm* 2004; 58: 291–299.
4. Nguyen PLH, Bouwstra1 JA. Vesicles as a tool for transdermal and dermal delivery. *Drug disco today: Tech* 2005; 2: 67-74
5. Bagyalakshmi J, Vamsikrishna RP, Manavalan R, Ravi TK, Manna PK. Formulation Development and invitro and in vivo evaluation of membrane-moderated transdermal systems of ampicillin sodium in ethanol: pH 4.7 buffer solvent system, AAPS PharmSciTech 2007; 8: E1-E6.
6. Peng L, Nimni ME. Delivery of erythromycin to subcutaneous tissues in rats by means of a transphase delivery system. *J Pharm Pharmacol* 1999; 51: 1135-41.
7. Ramade V. Drug delivery systems: Transdermal drug delivery, *Clinical Pharmacol* 1991; 31(6): 401-408.
8. Modamio P, Lastra EL, Marino. A comparative in vitro study of percutaneous penetration of beta-blockers in human skin. *Int J Pharm* 2000; 194: 249-259.
9. Babu RJ, Pandit JK. Effect of penetration enhancers on the release and skin permeation of bupranolol from reservoir-type transdermal delivery systems. *Int J Pharm* 2005; 288: 325–334.
10. Guy RH. Current status and future prospects of transdermal drug delivery, *Pharm Res* 1996; 13: 1765–1769.
11. Mukherjee B, Mahapatra S, Gupta R, Patra B, Tiwari A, Arora P. A comparison between povidone-ethylcellulose and povidone-eudragit transdermal dexamethasone matrix patches based on invitro skin permeation. *Eur J Pharm Biopharm* 2005; 59: 475–483.
12. Keith AD. Polymeric matrix consideration for transdermal devices. *Drug Dev Ind Pharm* 1983; 9: 605–621.
13. Chien YW. Development of transdermal drug delivery system. *Drug Dev Ind Pharm* 1987; 13: 589–651.
14. Misra AN. Transdermal drug delivery in Controlled and Novel Drug Delivery (Ed. N.K. Jain) Varghese Publication, New Delhi, 1988, pp. 100–129.
15. Walters KA. Transdermal drug delivery: system design and composition in Encyclopedia of Pharmaceutial Technology (Ed. K. Swarbrick and J.C. Boylan), Marcel Dekker, New York, 1999, pp. 306–320.
16. Patel VM, Prajapati BG, Patel MM. Effect of Hydrophilic Polymers on Buccoadhesive Eudragit Patches of Propranolol Hydrochloride Using Factorial Design. AAPS PharmSciTech 2007; 8 (2): E1-E8.
17. Junginger HE, Hoogstraate JA, Verhoef JC. Recent advances in buccal drug delivery and absorption: invitro and in vivo studies. *J Con Rel* 1999; 62: 149-159.
18. NagaiT, Konishi R. Buccal/gingival drug delivery systems. *J Con Rel* 1987; 6: 353-360.
19. Balestrieri F, Magri AD, Magri AL, Marini D, Sacchini A. Application of differential scanning calorimetry to the study of drug excipient compatibility. *Thermo acta* 1996; 285: 337-345.
20. Rao PR, Ramakrishnan S, Diwan PV. Drug release kinetic from polymeric films containing propranolol hydrochloride for transdermal use. *Pharm Dev Techno* 2000; 15: 465-472.
21. Nair VB, Panchagnula R. The effect of pretreatment with terpenes on transdermal iontophoretic delivery of arginine vasopressin. *Farmaco* 2004; 59: 575-581.
22. Tokudome Y, Sugibayashi K. The synergic effects of various electrolytes and electroporation on the invitro skin permeation of calcein. . *J Con Rel* 2003; 92: 93-101.
23. Al-Saidan SM, Krishnaiah YSR, Chandrasekhar DV, Lalla JK, Rama B, Jayaram B, et al. Formulation of an HPMC gel drug reservoir system with ethanol-water as a solvent system and limonene as a penetration enhancer for enhancing invitro transdermal delivery of nicorandil. *Skin Pharmacol Physiol* 2004; 17: 310-320.