Research Article

# Design and Development of Transdermal Drug Delivery for Anti-Hypertensive Drug Using Different Polymeric System

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**ABSTRACT**
Atenolol is a selective $\beta_1$ receptor antagonist, a drug belonging to the group of beta blockers (sometimes written β-blockers), a class of drugs used primarily in cardiovascular diseases. Introduced in 1976, atenolol was developed as a replacement for propranolol in the treatment of hypertension. The purpose of this research was to develop a matrix-type transdermal therapeutic system containing drug Atenolol with different polymeric systems by the solvent evaporation technique using 20 % w/w of di butyl phthalate to the polymer weight, as plasticizer which can deliver the drug up to 24 hours in a controlled manner. The matrix-type transdermal patches were prepared using different polymers like Cellulose Acetate Butyrate (CAB), Cellulose Acetate Phthalate (CAP), Poly Methyl Methacrylate (PMM) and their combinations. Dichloromethane as a solvent system was selected for the preparation of patch of Atenolol and di butyl Phthalate (DBP) as plasticizer. The diffusion study was carried out using K-C type diffusion cell for 30 hours which showed drug release up to 25 hours in a sustained and controlled manner.

**Keywords:** Transdermal patches, Permeation enhancer, *In-vitro* permeation study, Atenolol.

## INTRODUCTION

Transdermal delivery of drugs is a novel drug delivery system and this system breaks many barriers in drug therapy like need of assistance, intermediate dosing and uncomfortable administration[1].The transdermal route of administration is recognized as one of the potential route for local and systemic delivery of drugs, it also provides a controlled release of medicament into patients[2].Transdermal delivery has many advantages over conventional modes of drug administration, it avoids hepatic first pass metabolism, potentially decreases side effects and improves patient compliance[3]. Atenolol is a β-blocker without membrane stabilizing or intrinsic sympathomimetic activity, which has been used for the treatment of hypertension[4]. The drug is also frequently indicated in the prophylactic treatment of migraine. Administration of conventional tablets of atenolol has been reported to exhibit fluctuations in the plasma drug levels, resulting either in manifestation of side effects such as diarrhea, ischemic colitis and mesenteric arterial thrombosis[5,6] or reduction in drug concentration at the receptor site. To overcome these adverse effects in the GI tract while sustaining the therapeutic efficacy of atenolol, an alternative drug delivery method might be useful[7]. Transdermal drug deli-very (TDD) method has been selected as it provides controlled release of the drug, and produces a steady blood-level profile[8] leading to reduced systemic side effects and, sometimes, improved efficacy over other dosage forms[9]. In addition, it confers several advantages over more traditional administration and leads to improved patient compliance. Consequently, the transdermal therapeutic system is of particular clinical significance for the prevention and long-term treatment of chronic diseases like hypertension. The aim of the present study was to investigate atenolol transport from a transdermal patch system and to determine whether therapeutically relevant delivery rates could be achieved under these conditions. After an initial investigation of formulation parameters their effect on atenolol transport across porcine ear skin, rat skin and snake sheded skin was also investigated by *in-vitro* method. The sustained activity was due to the controlled release of drug into the systemic

circulation following transdermal administration.

## EXPERIMENTAL

### Materials and Methods

Atenolol was gift from Zydus Cadila Pvt Ltd. (India). Cellulose Acetate Phthalate (CAP), di butyl Phthalate (DBP), Cellulose Acetate Butyrate (CAB), Poly Methyl Methacrylate (PMMA) were purchased from Hi media Chemicals Ltd. (India). All other chemicals used for this study were of analytical grade. Double-distilled water was used throughout the study.

### Drug–excipient interaction study

The pure drug, Atenolol and a mixture of it with the polymers, CAP, CAB and PMMA were mixed separately with IR grade KBr in the ratio of 100:1 and correspond-ing pellets were prepared by applying pressure in a hydraulic press. The pellets were scanned over a wave number range of 4000-400 $cm^{-1}$ in Shimadzu Japan, FTIR instrument. The spectra obtained for Atenolol, polymers, and physical mixtures of atenolol with polymers were compared.

### Formulation of Drug Free Patches

Polymers of single or in combination are accurately weighed and dissolve in respective solvent and then castled on a glass surface containing ring. The films were allowed to dry overnight at room temperature. Then the films were separated and noticed for film formations.

### Formulation of Drug Incorporated Transdermal Patches [12-14]

Accurately weighed quantities of polymer individually and /or in combination were dissolved in required quantity of solvents namely dichloromethane in which drug and polymer have been dissolved. The solution was mixed with magnetic stirrer to get homogeneous consistency. This was casted on a glass surface containing ring, it was covered by funnel to control evaporation of solvent and allowed to dry at room temperature over night. The films were separated and the backing membrane used was aluminum foil and the formulations were stored in desiccators. The composition of patches prepared using atenolol is given in Table 1.

### Physico chemical evaluation of the prepared films

### Thickness and weight variation

The thickness of the patch at three different points was determined using thickness gauge and the patches were then weighed individually using digital balance to determine the weight of each patch taken out from the casted film. The patches were subjected to weight variation by individually weighing ten randomly selected patches. Such determinations were carried out for each formulation [15].

### Folding Endurance[16]

It was determined by repeatedly folding a small strip of films at the same place till it broke. The number of times, the films could be folded at the same place without breaking gave the value of folding endurance.

### Percentage Moisture Loss

Accurately weighed films of each formulation were kept in desiccators and exposed to an atmosphere of 98% relative humidity (containing anhydrous calcium chloride) at room temperature and weighed after 3 days[17]. The test was carried out in triplicate. The percentage of moisture loss was calculated as the difference between initial and final weight with respect to initial weight.

### Percent Moisture Absorption[17]

The percent moisture absorption test was carried out to check the physical stability and integrity of the films at high humid conditions. In the present study the moisture absorption capacities of the films were determined in the following manner. The films were placed in desiccators containing saturated solution of aluminum chloride, keeping the humidity inside the desiccators at 79.5% RH. After 3 days the films were taken and weighed the percentage moisture absorption of three films was found.

$$\%\ Moisture\ Absorption = \frac{Final\ Weight - Initial\ Weight}{Initial\ Weight} \times 100$$

### Percent Moisture Loss[18]

This test was also carried to check the integrity of films at dry condition. Three films of 5 square centimeter area was cut out and weighed accurately and kept in a desiccators containing fused anhydrous calcium chloride. After 72 hours the films were removed and weighed. Average percentage moisture losses of three films were found out.

$$\%\ Moisture\ Loss = \frac{Initial\ Weight - Final\ Weight}{Initial\ Weight} \times 100$$

### Thickness[19]

Thicknesses of the films were measured at six different points using a screw gauge and

average thicknesses of three films were found out.

**Drug content** [20]

A film of 1 square centimeter area was cut and dissolved in phosphate buffer pH 7.4. After adding suitable reagent and dilution, optical density was found out at 229.2nm. Average drug content of three transdermal films were determined.

**Folding Endurance**[21]

It was determined by repeatedly folding a small strip of films at the same place till it broke. The number of times, the films could be folded at the same place without breaking gave the value of folding endurance.

**Weight Uniformity**[22]

Each film was weighed individually and average weight of three films was found.

**In vitro drug release studies**

The *in-vitro* release studies were carried out by using Keshary- chein apparatus. The receptor compartment was maintained at 37±1°C by means of a water bath, circulator, and a jacket surrounding the cell. The cells were filled with freshly prepared phosphate buffer pH 7.4. The solution in the receptor compartment was continuously stirred at 60 rpm by means of Teflon coated magnetic stirrer, in order to avoid diffusion layer effects. The Commercial Semi-permeable membrane were mounted between the donor and receptor compartment and secured in place by means of a clamp. The patch was placed on one side of the semi-permeable membrane[23]. Aliquots of 1ml were removed from the receptor compartment by means of a syringe and replaced immediately with the same volume of buffer solution kept at 37± 1°C. Test samples were taken from the medium at predetermined time intervals over a period of 24 hours and the samples were analyzed for atenolol content by UV spectrophotometer at 229 nm.[25]. The diffusion kinetics of the atenolol was analyzed by graphical method for zero order,

**RESULTS AND DISCUSSION**

In the present work efforts have been made to prepare transdermal patches of atenolol by using different polymers individually and /or in combination such as cellulose acetate butyrate, cellulose Acetate phthalate and poly Methyl Methacrylate. The plasticizer used was di butyl phthalate. The physicochemical compatibility of the drugs and the polymer was established through FTIR studies which show no interactions. From the IR spectra (figure 1-3) it is observed that there were no changes in the main peaks in IR spectra of pure drug, drug and polymer, which shows there were no physical interactions due to some bands formation between drug, solvent and polymer Since there are no interactions between drug, solvent and polymer the patches were evaluated for In-Vitro skin permeability studies. FTIR spectra analysis of Atenolol showed that the principle peaks are observed at wave number 3357.79, 2964.94, 1638.30, 1515.81, 1242.91 $cm^{-1}$ in ( fig-1) confirming the purity of the drug. In the FTIR spectra of the physical mixture of the drug and polymer (fig-3) major peaks of Atenolol were observed at wave numbers 3357.79, 2964.94, 1638.30, 1515.81, 1242.91 $cm^{-1}$ however some additional peaks were observed due to additives in the formulation. Thus there was no probable interaction observed between drug and polymeric system. The prepared formulations were subjected to various physicochemical characteristics such as percent moisture absorption, percent moisture loss, drug content, thickness, folding endurance and weight uniformity. The results are shown in Table 2 The release characteristic of the formulation was studied by in-vitro dissolution test.

The formulation F5 (CAB**:** PMMA (1:1)) has shown lowest percent moisture absorption and percent moisture loss than other formulations. This might be because of the low water permeability of cellulose acetate butyrate polymer. It is also observed that F1 (CAB) has shown highest percent moisture absorption and percent moisture loss which might be due to high permeability of Cellulose acetate butyrate to water.

The thickness of the films varied from 0.21 to 0.23mm. The minimum standard deviation values assumed that the process used for preparing the drug delivery system is capable of giving reproducible results. This fact is further confirmed by drug content and weight uniformity studied. In order to evaluate the flexibility the film were subjected to folding endurance studies. The values in the range of 340to 367 were observed in all batches. This revealed that the prepared films were having capability to with stand the mechanical pressure along with good flexibility.

***In-vitro* Dissolution Studies**

*In-vitro* dissolution studies were carried out in phosphate buffer pH 7.4 for 30 hours. In order to find out the order of release and the mechanism, which was predominately influences, the drug release from the

membrane, the in-vitro dissolution data was subjected to graphical treatment that is: Percentage drug release Vs Time. The slope value and the degree of linearity of the above graphical treatment were considered as important statistical parameters to interpret the in-vitro profile of all formulations. From the graph of in – vitro drug release it is clearly observed that all the six formulations (F1-F6) showed the release of drug up to the period of 25 hours (fig:4-9) in a controlled manner. This indicates that the Cellulose based polymers either alone or in combination can be used to deliver the drug in a controlled manner for desired period of time.

## CONCLUSION

Atenolol is a multiple-action cardiovascular drug that is currently approved in many countries for the treatment of hypertension. Administration of these agents via dermal route can bypass various disadvantages caused when administered orally and may maintain relatively consistent plasma levels for long-term therapy. The present study is an attempt to develop transdermal drug delivery system for Atenolol Patches containing 30 % Atenolol with different polymer and Dibutyl Phthalate (DBP) as plasticizers has shown better permeability coefficient.

Hence, Atenolol transdermal Patches formulated using Plasticizer showed better flux enhancement. Transdermal patches consisting of the Cellulose Acetate Butyrate (CAB) Cellulose Acetate Phthalate (CAP), Poly Methyl Methacrylate (PMMA) drug reservoir with plasticizer demonstrated sustained and controlled release of the drug during *in vitro* permeation studies. As an extension of this work pharmacokinetic studies, in-vivo studies on higher animals and controlled clinical studies on human beings can be carried out in future.

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**Table 1: Composition of Transdermal Patches of Atenolol**

| Formulation Code | Polymer | Plasticizer (20%) | Drug 30% wt of polymer | Solvent |
|---|---|---|---|---|
| F1 | CAB | DBP | Atenolol | DCM |
| F2 | CAP | DBP | Atenolol | DCM |
| F3 | PMM | DBP | Atenolol | DCM |
| F4 | CAB:CAP | DBP | Atenolol | DCM |
| F5 | CAB:PMM | DBP | Atenolol | DCM |
| F6 | CAP:PMM | DBP | Atenolol | DCM |

**Table 2: Physicochemical Evaluation data of Atenolol Transdermal Patches**

| Formulation code | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| % Moisture Absorption +SD | 8.64+0.047 | 6.44+0.023 | 7.027+0.039 | 5.35+0.032 | 4.26+0.015 | 7.08+0.024 |
| % Moisture Loss, +SD | 10.17+0.04 | 8.15+0.12 | 9.76+0.26 | 7.34+0.34 | 5.13+0.07 | 9.65+0.19 |
| Thickness (mm) +SD | 0.23+0.02 | 0.22+0.01 | 0.21+0.02 | 0.22+0.02 | 0.23+0.04 | 0.22+0.02 |
| Weight Variation (mg) | 302.4±0.21 | 289.4±0.14 | 293.4±0.07 | 299.4±0.11 | 321.4±0.30 | 308.4±0.19 |
| Folding Endurance +SD | 340+0.6 | 345+0.4 | 357+0.7 | 360+0.2 | 364+0.4 | 363+0.3 |
| % Drug Content +SD | 96.6+0.3 | 97.0+0.4 | 96.4+0.3 | 98.5+0.3 | 95.8+0.3 | 99.1+0.4 |

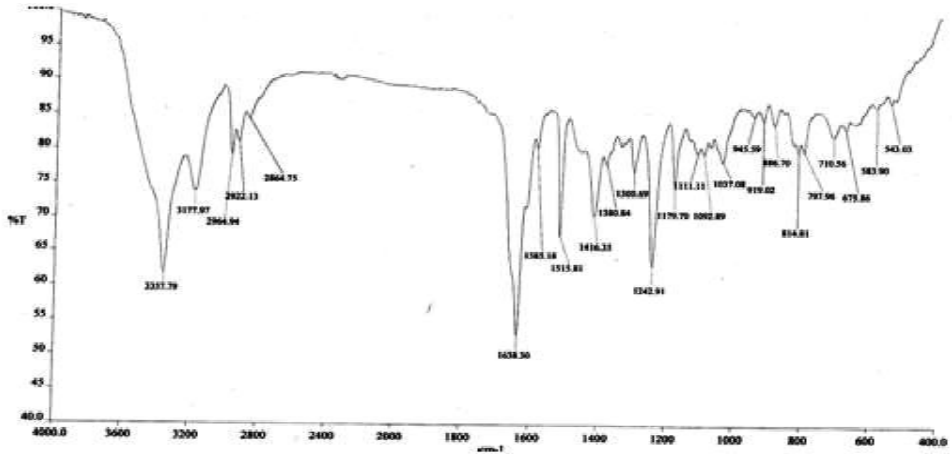

Fig. 1: IR Spectrum of drug

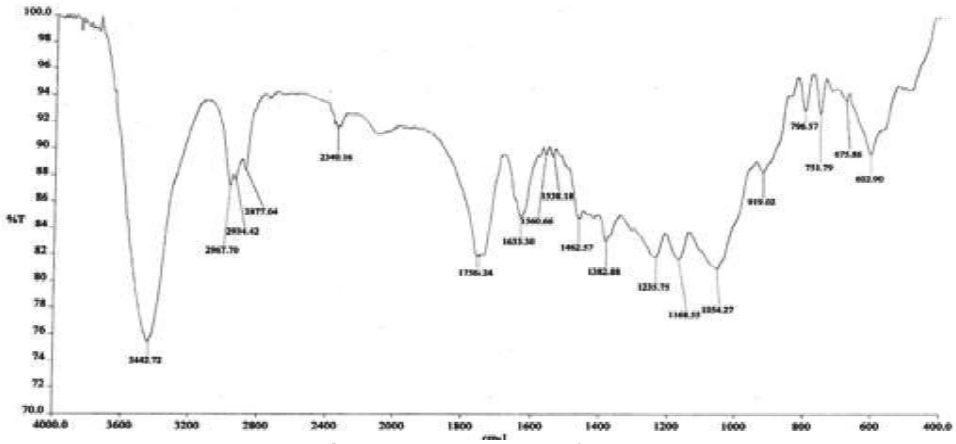

Fig. 2: IR Spectrum of CAP

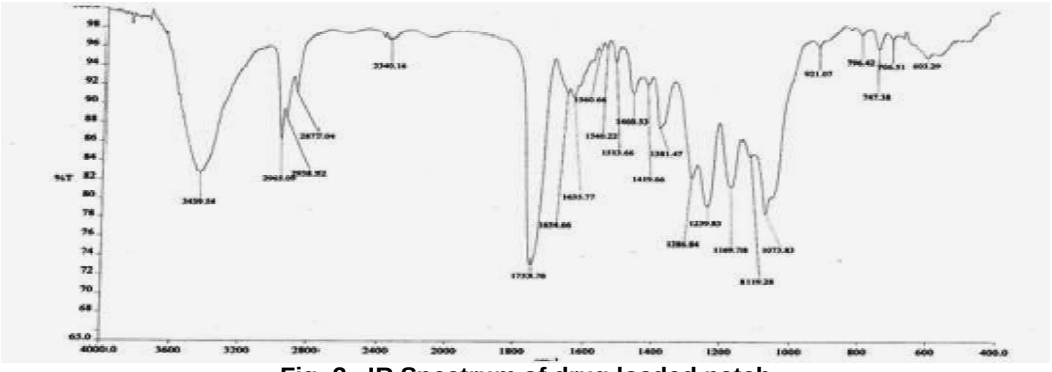

Fig. 3: IR Spectrum of drug loaded patch

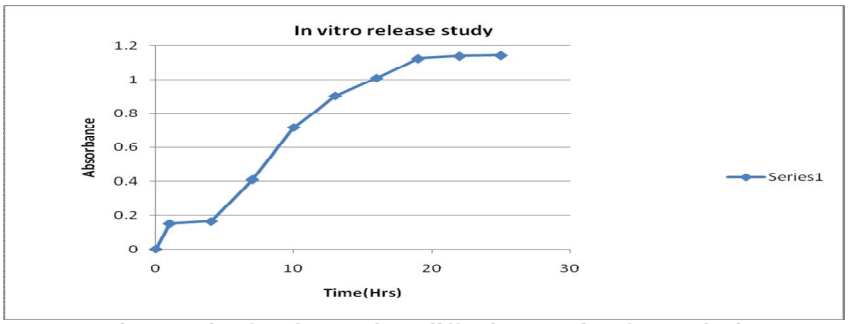


**Fig. 4: Plot for the In vitro diffusion study of CAB (F1)**

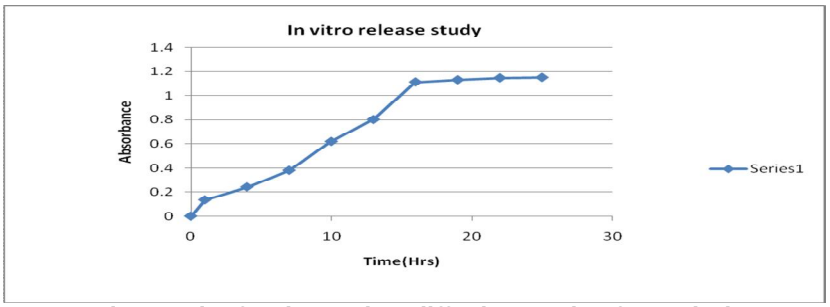


**Fig. 5: Plot for the In vitro diffusion study of CAP (F2)**

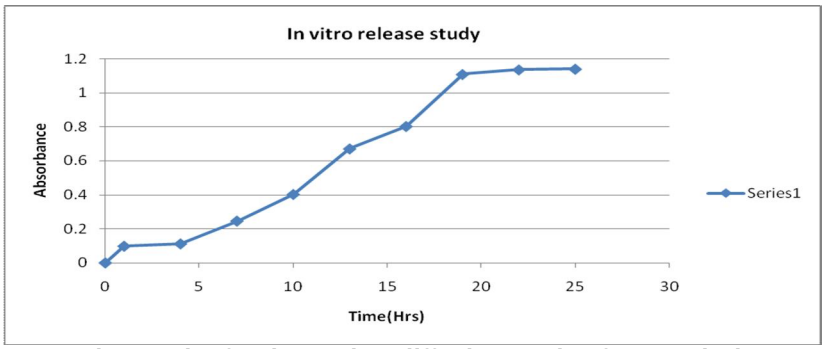


**Fig. 6: Plot for the In vitro diffusion study of PMMA (F3)**

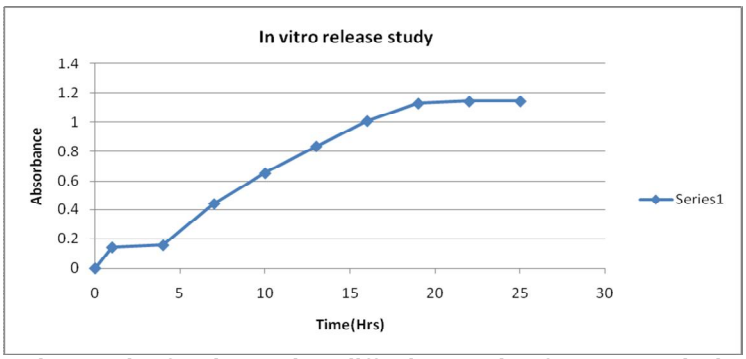


**Fig. 7: Plot for the In vitro diffusion study of CAB:CAP (F4)**

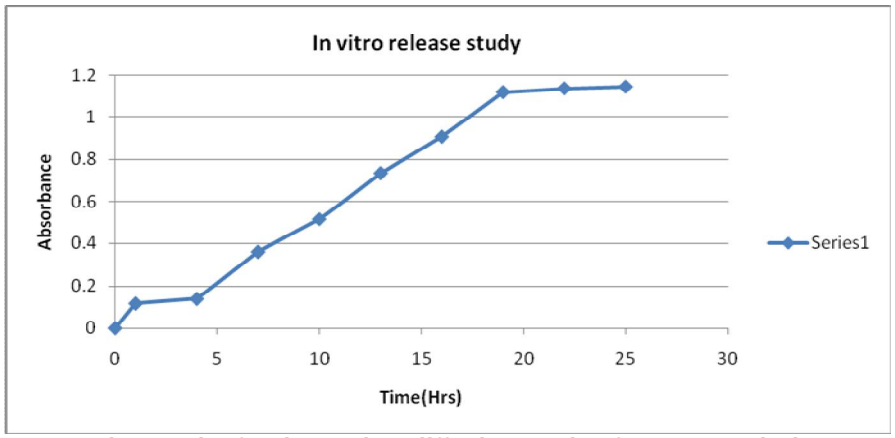


**Fig. 8: Plot for the In vitro diffusion study of CAB:PMM (F5)**

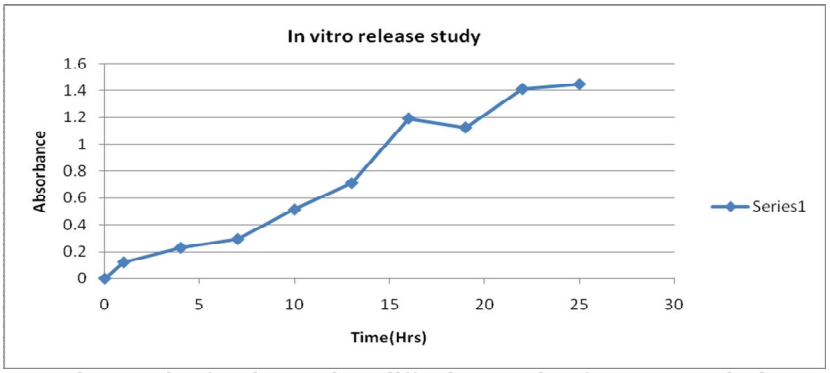


**Fig. 9: Plot for the In vitro diffusion study of CAP:PMM (F6)**

## REFERENCES


1. Misra AN. Controlled and Novel Drug Delivery. In: NK Jain (Eds.), Transdermal Drug Delivery New Delhi, India: CBS Publisher and Distributor. 1997;100-101.
2. Hoffman BB. Catecholamines, sympathomimetics drugs, and adrenergic receptor antagonists. In: Hardman JG, Limbird LE, eds. Goodman & Gilman's the Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw Hill; 2001.
3. Cho CW and Shin SC. Enhanced transdermal delivery of atenolol from the ethylene-vinyl acetate matrix In-ternational journal of Pharmaceutics. 2004;287:67.
4. Sastry SV, Reddy IK and Khan MA. Atenolol gastrointestinal therapeutic system: optimization of formulation va-riables using response surface methodology. Journal of Control Release. 1997;45:121-130.
5. Young-Chang Ah, Jin-Kyu Choi, Yang-Kyu Choi, Han-Moi Ki and Joon-Ho Bae. A novel transdermal patch incorpo-rating meloxicam: In vitro and in vivo characteriza-tion. International Journal of Pharmaceutics. 2010;385(1-2):12-19.
6. Modamio P, Lastra CF and Marino EL. A comparative in vitro study of percutaneous penetration of beta-blockers in human skin. International Journal of Pharmaceutics. 2000;194:249–259.
7. Ranade VV. Drug delivery systems. Transdermal drug delivery. Journal of Clinical Pharmacology. 1991;31:401–418.
8. Changshun Rena, Liang Fanga, Lei Ling, QiangWang, Sihai Liu, LiGang Zhao and Zhonggui He. Design and in vivo evaluation of an indapamide transdermal patch. International Journal of Pharmaceutics. 2009;370: 129–135.

9. Jagmohan. Organic Spectroscopy. Edn 2, Narosa Publi-cations, Inc., New Delhi, 2003:212-232.
10. Udupa. International Journal of Pharmaceutical Sciences, 1993:147-243.
11. Samanta MK, Wagh V D, Kavitha, Jagadeesh C, Pati and Suresh B. Transdermal drug delivery system of Haloperidol to overcome self induced extrapyramidal syndrome,International Journal of Pharmaceutical Sciences. 2002:328.
12. Kulkarni RV, Mutalik S and Hiremath D. Effect of plasticizers on the permeability and mechanical properties of Eudragit films for Transdermal applications, International Journal of Pharmaceutical Sciences, 2002;64 (1): 28 -31.
13. Mundada AS and Avari JG. Damar Batu as a novel matrix former for the transdermal drug delivery: in-vitro evaluation. Drug Development and Industrial Pharmacy 2009;35:1147–1154.
14. Dandagi PM, Manvi FV, Gadad AP, Mastiholimath VS and Jagadeesh T. Formulation of Transdermal drug Delivery system of Ketotifen fumarate, International Journal of Pharmaceutical Sciences, 2003;6(3): 239-243.
15. Kusum Devi V, Saisivam S, Maria GR and Depti PU. Design and Evaluation of Matrix diffusion Controlled Trans-dermal patches of Verapamil Hydrochloride. Drug Development and Industrial Pharmacy. 2003;29: 495–503.
16. Lewis Sharila. International Journal of Pharmaceutical Sciences, 2006;68: 179-184.
17. Chowdary KPR and Naidu RAS, Preparation and Evaluation of cellulose acetate films as rate controlling membranes for Transdermal use, Indian Drugs. 29 (7):312-315.
18. Kakkar AP, Ajay Gupta. Gelatin based transdermal therapeutic system, Indian Drugs. 29(7): 308-311.
19. Dandagi PM, Manvi FV, Gadad AP, Mastiholimath VS and Jagadeesh T. Formulation of Transdermal drug Delivery system of Ketotifen fumarate, International Journal of Pharmaceutical Sciences. 2003;6(3): 239-243.
20. Udupa N, Koteshwar KB and Vasantha kumar. Formulation and Evaluation of Captopril Transdermal preparations, Indian Drugs, 29(15): 680-850.
21. Ji-Hui Zhao, Ji-Hua Fu and Shu-Ming Wang. A novel trans-dermal patch incorporating Isosorbide dinitrate with Bisoprolol: In vitro and In vivo characterization. In-ternational Journal of Pharmaceutics 2007;337: 88–101.
22. Yanli Gao and Jinying Liang. Double-layer weekly sustained release transdermal patch containing gestodene and ethinylestradiol. International Journal of Pharmaceu-tics. 2009;377:128–134.
23. Vlassios Andronis and Mounir S Mesiha. Design and evalu-ation of transdermal Chlorpheniramine maleate drug delivery system. Pharmaceutics Acta Helvetiae. 1995; 70:301-306.