ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 7, Issue 1, 2014

ISSN - 0974-2441

Research Article

COMPARISON OF AMLODIPINE TRANSDERMAL PATCHES USING HYDROXYPROPYLMETHYLCELLULOSE AND CHITOSAN

LINCY JOHN *[1] AND ARUN KUMAR[2]

[1]Department of pharmaceutics,KMCH college of pharmacy . DR MGR University, Coimbatore-641048,Tamilnadu, [2] Department of pharmaceutics,KMCH college of pharmacy . DR MGR University, Coimbatore-641048,Tamilnadu. Email: lincy.bikaner@gmail.com

Received: 17 October 2013, Revised and Accepted: 11 November 2013

ABSTRACT

Objective: The aim of our study was to design and evaluate Amlodipine transdermal patches & compare these patches using polymers such as hydroxypropylmethylcellulose and chitosan.

Methods: Amlodipine were prepared by solvent casting method by using polymers like hydroxypropylmethylcellulose and chitosan in different proportions(1%, 1.5%, 2% and 2.5%). Plasticizers used were propylene glycol and dibutylpthlate.The transdermal patches were evaluated for their physicochemical properties like folding endurance, thickness, percentage moisture loss, percentage moisture absorption, drug content and water vapour transmission rate.

Result: The diffusion studies were performed by using franz diffusion cell.Formulation H7(2% HPMC) and C7(2% CS) with DBP as plasticizer showed a maximum release of 99% in 24 hours

Conclusion: Out of these two formulations the use of chitosan in a transdermal patches seems to be attractive due to its biocompatibility and biodegradability as well as opportunities to modify the charge density and molecular chain length of the chitosan in the membrane without changing its status as a natural biopolymer. Thus the knowledge on the use of chitosan to control drug release in transdermal delivery systems might be applicable to other transdermal drug delivery system as well.

Keywords: Transdermal, hydroxypropylmethylcellulose, Chitosan, Amlodipine

INTRODUCTION

Delivering medicine to the general circulation through the skin is seen as a desirable alternative to taking it by mouth or by oral route. Patients often forget to take their medicine and also they get tired of swallowing pills. Additionally bypassing the gastrointestinal tract would obviate the GI irritation that frequently occurs & avoid partial first pass inactivation by the liver. Further, steady absorption of drug over hours or days is usually preferable to blood level spikes and troughs produced by oral dosage forms. [1]

These advantages are offered by the currently marketed transdermal products. Transdermal drug delivery is defined as self-contained, discrete dosage forms which when applied to intact skin deliver the drug through the skin at controlled rate to the systemic circulation. The transdermal patches uses a polymer membrane to control the rate at which the drug contained in the reservoir within the patch can pass through the skin and into the blood stream. Today most of the drug are taken orally but, they are found not to be as effective as desired, So to improve such character TDDS was emerged. Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery system. These are dosage forms which involves drug transport to viable epidermal and or dermal tissue of the skin for local therapeutic effect while a very major fraction of the drug is transported into systemic blood circulation. Currently TDDS is one of the most promising methods for drug application. Transdermal drug delivery provides a leading edge over injectables and oral route by increasing patient compliances and avoiding first pass metabolism respectively.TDDS not only provides a controlled, constant administration of drug, but also allows continuous input of drug with short biological half life and eliminates pulsed entry into systemic circulation which often causes undesirable side effect. [2]

Over the last two decades more than 35 transdermal patches have been approved, generating sales of $3.2 billion in 2002 to $4.5 billion in 2008. More recently such dosage forms have been developed and or modified in order to enhance the driving force of diffusion (thermodynamic activity) and or increase the permeability of skin. These approaches include permeability enhancer,prodrug, liposome and other vesicles.[3]

Transdermal drug delivery provides a leading edge over injectables and oral route by increasing patient compliances and avoiding first pass metabolism respectively. TDDS not only provides a controlled, constant administration of drug, but also allows continuous input of drug with short biological half life and eliminates pulsed entry into systemic circulation which often causes undesirable side effect.[4,5]

Applications of Transdermal Patches

- The highest selling transdermal patch in the United States is the nicotine patch, which releases nicotine in controlled doses to help with cessation of tobacco smoking.
- Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl (marketed as Duragesic) and Buprenorphine (marketed as BuTrans).
- Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as post-menopausal osteoporosis. Other transdermal patches for hormone delivery include the contraceptive patch (marketed as Ortho Evra or Evra).
- Nitroglycerin patches are sometimes prescribed for the treatment of angina ectoris.
- The anti-hypertensive drug Clonidine is available in transdermal patch form.
- Transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant.[6]

The objective of this research work was to develop a transdermal system which can produce a constant and prolonged release of the drug, to evaluate the effect of HPMC and Chitosan on the fabrication of the patch and drug release from the patch, to evaluate the effect of plasticizers on the physico-chemical properties of the patch and on drug permeation across the membrane.

MATERIALS AND METHODS

Material

Amlodipine was kindly supplied as gift samples by Microlabs Pharmaceuticals, Bangalore, India. Polymer and plasticizers used were purchased by SD fine chemicals, India. The Drug analysis was performed using UV Spectroscopy. In addition, an electronic balance (Shimadzu AX200), magnetic stirrer (REMI model Mumbai), a sonicator (Spectra Lab, model UCB 40), a hot air oven (Labhosp) and a Franz diffusion cell (self fabrication) were used in this study.

Methodology

Formulation of transdermal drug delivery system

TDDS was developed using solvent evaporation method. In this polymer is dissolved in particular solvent and then the specified quantity of drug as well as plasticizers were added and was air dried for 24 hrs in petridish with help of inverted funnel for controlled evaporation. A total of 8 formulations were made in as shown in table 1. [7,8,9]

Table1: It Shows The Various Compositions Of Amlodipine Transdermal Patches Containing HPMC And Chitosan Patches

Drug	Polymers	Plasticizers	Polymer Percentage(%)
Amlodipine	HPMC CHITOSAN	DBP PG	1 1.5 2 2.5

(HPMC =hydroxypropyl methyllcellulose ; PG = Propyleneglycol ; DBP = Dibutylphthlate)

Preparation of Amlodipine patches

Drug loaded matrix type transdermal films of Amlodipine were prepared by solvent evaporation method. The polymers HPMC were dissolved in methanol & Chitosan were dissolved in lactic acid with help of magnetic stirrer followed by the addition of drug into each polymeric solution and then the plasticizers were incorporated with continuous stirring and the volume was made up. The resultant solutions were casted onto the petridish and an inverted funnel was placed. After 24 hours the films were removed by using sharp knife by inserting along the edge of the films and stored for further studies.[10]

Evaluation of transdermal patches

Physical appearance

All the prepared patches were visually inspected for color,clarity, flexibility and smoothness.[11]

Thickness uniformity

The thickness of the formulated film was measured at 3 different points using a calliper and average thickness was calculated.[12]

Folding endurance[13]

The folding endurance was measured manually for the prepared films. A strip of film 1cm^2 was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking or cracking gives the value of folding endurance.[13]

Percentage moisture absorption

The films were weighed accurately and placed in a desiccators containing 100 ml of saturated solution of potassium chloride after 3 days, the films were taken out and weighed. The percentage moisture absorption was calculated using the formula. [14]

$$\% \text{ moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage moisture loss[15]

The films were weighed accurately and placed in a desiccators containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed. The percentage moisture loss was calculated using the formula given below.[15]

$$\% \text{ moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Water vapour transmission rate

Glass vials of 5ml capacity were washed thoroughly and dried to a constant weight in an oven. About 1gm of fused calcium chloride was taken in the vials and the polymer films were fixed over the brim with the help of adhesive tape. Then the vials were weighed and stored in a humidity chamber of 70-80% RH condition for a period of 24 hr. The vials were removed and weighed after 24 hrs to note down the weight gain and transmission rate was found out.[16]

$$\text{Transmission rate} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Time} \times \text{Area}} \times 100$$

Drug content

6.1544 cm^2 area of the small films was cut and was dissolved in sufficient quantity of methanol. The volume was made up to 100ml. The absorbance of the diluted solution was measured at 238nm and the drug content in the film was calculated.[17]

In- vitro drug diffusion studies

In- vitro diffusion studies were performed by using Franz diffusion cell with a receptor compartment capacity of 20 ml. The synthetic cellophane membrane was mounted between donor and receptor compartment of the diffusion cell. The formulated patches were cut into size of 1.4 cm radius and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm. The sample of 2ml were withdrawn at time intervals of 30 min, 1 hr, 1.30 hr, 2 hr,3 hr, 4 hr , 5 hr ,6hr, 7hr, 8hr and 24 hr and analyzed for drug content spectrophotomerically at 238 nm.[18,19,20]

RESULT AND DISCUSSION

Calculation of total drug loading

The formulation of the patch was made in such a way that each small circular patch of 1.4cm radius (which is the radius of the franz diffusion cell) contains 5mg of the drug. The total amount of drug to be loaded in the patch was calculated by measuring the total area of the petri dish in which the patch will be casted. The calculation was done as follows;

Area of the small circular patch = 6.1544 cm^2

Desired drug content in the small patch = 5mg

Area of the petri dish = 67.89 cm^2

Total amount of drug to be loaded = 67.89 x 5 / 6.1544 = 55mg

Hence 55mg of the drug was added in each formulation in order to get 5mg per small circular patch.

Preparation of transdermal patches

As per the methodology transdermal patches using HPMC and chitosan were prepared by using solvent casting method. The polymers were dissolved in particular solvent followed by the addition of drug into the polymeric solution. Plasticizers were then added to the drug- polymer solution and was casted on petridish. It was covered by funnel to control evaporation of solvent and allowed to dry at room temperature over night. All the formulations showed a smooth and desirable consistency.

Evaluation Of Prepared Transdermal Patches

Folding endurance

In general, folding endurance of all the films was found to be satisfactory indicating good strength and elasticity. Folding endurance of HPMC and chitosan was found to be in the range of 289-300 and 300-311 respectively as shown in table 2 and table 3. Folding endurance was found to increase with the polymer content. The influence of plasticizers on the folding endurance was clearly demonstrated in this study. Dibutyl phthalate showed more endurance than propylene glycol and irrespective of the polymers used in the formulations.

Thickness

Thickness of HPMC & chitosan were evaluated with the use of a vernier caliper and was found to be in the range of 0.21-0.28 mm and 0.22-0.27mm respectively as shown in table 2 & 3. The thickness was found to be uniform with respect to each formulations and there was an increase of thickness with increase in the percentage of polymer(1%, 1.5%, 2% and 2.5%). The plasticizer type or content does not have any influence on the thickness of the patches.

Percentage moisture loss

Percentage moisture loss for HPMC & chitosan containing patches was found in the range of 3.44 – 22.22% and 2.44 – 15.38% respectively (Table 2 & 3) . Percentage moisture loss of prepared HPMC & chitosan patches was found to decrease with increase in the percentage of the polymer(1%,1.5%,2% and 2.5%) irrespective of the plasticizers (DBP & PG) used, which may be due to the hydrophilic character of both the polymers.

Percentage moisture absorption

Percentage moisture absorption for HPMC and chitosan was found in the range of 5.21 – 20.34% and 2.56 – 23.38% respectively as shown in table 2 & 3. The percentage moisture absorption was found to be increased with increase in the polymer content (1%,1.5%,2%,2.5%) irrespective of plasticizers (DBP &PG) used. This may be due to the hydrophilic character of polymers which readily absorbs water.

Water vapour transmission rate

Water vapour transmission rates for HPMC and chitosan was found in the range of 0.2981 – 0.4986gm/cm^2/hr and 0.3116 – 0.3658gm/cm^2/hr respectively as shown in table 2 & 3. Water vapour transmission rate results were found to be similar to the results obtained in moisture absorption studies.

Table 2: It Shows the Evaluation Parameter Of Prepared HPMC Patches

Formulations	Folding Endurance	Thickness (mm)	Percentage Moisture loss (%)	Percentage Moisture Absorption (%)	Water Vapour Transmission Rate (gm/cm^2/hr)
H1(1% HPMC & PG)	290	0.22	15.38	5.77	0.2981
H2(1.5%HPMC & PG)	293	0.24	13.33	12.05	0.4600
H3(2% HPMC & PG)	294	0.25	5.12	15.64	0.4742
H4(2.5%HPMC & PG)	296	0.26	3.44	20.34	0.4771
H5(1%HPMC & DBP)	294	0.23	12.52	6.61	0.3929
H6(1.5%HPMC&DBP)	296	0.25	9.81	8.63	0.4013
H7(2% HPMC & DBP)	298	0.27	9.65	15.12	0.4471
H8(2.5%HPMC&DBP)	300	0.28	5.88	21.21	0.4471

(HPMC =hydroxypropyl methyllcellulose ; PG = Propyleneglycol ; DBP = Dibutylphthlate)

Table3 : It Shows the Evaluation Parameter Of Prepared Chitosan Patches

Formulations	Folding Endurance	Thickness (mm)	Percentage Moisture loss (%)	Percentage Moisture Absorption (%)	Water Vapour Transmission Rate (gm/cm^2/hr)
C1(1% Chitosan & PG)	301	0.22	13.84	2.56	0.3321
C2(1.5%Chitosan & PG)	303	0.23	11.76	5.12	0.3421
C3(2% Chitosan & PG)	304	0.24	9.09	15.34	0.3658
C4(2.5%Chitosan & PG)	306	0.25	2.44	22.03	0.3658
C5(1%Chitosan & DBP)	308	0.23	15.38	6.61	0.3187
C6(1.5%Chitosan&DBP)	309	0.25	13.76	8.63	0.3252
C7(2% Chitosan & DBP)	311	0.26	8.95	15.12	0.3416
C8(2.5%Chitosan&DBP)	315	0.27	6.12	21.21	0.3541

(PG = PROPYLENE GLYCOL ; DBP = DIBUTYLPHTHLATE)

Drug content

Drug content in each small circular patches were analyzed spectrophotmetrically and It was observed that all the formulations showed a satisfactory drug content values ranging from 92 – 99% as given in table 4 which is in accordance with the standard values prescribed for drug content analysis.

Table 4: It Shows the Drug Content Of Prepared HPMC & Chitosan Patches

Formulation	Assay (%)	Formulation	Assay (%)
H1(1% HPMC & PG)	92.69	C1(1% Chitosan & PG)	97.53
H2(1.5%HPMC& PG)	95.83	C2(1.5%Chitosan& PG)	99.43
H3(2% HPMC & PG)	93.61	C3(2% Chitosan & PG)	98.72
H4(2.5%HPMC& PG)	99.06	C4(2.5%Chitosan& PG)	94.52
H5(1%HPMC & DBP)	95.13	C5(1%Chitosan& DBP)	96.53
H6(1.5%HPMC DBP)	98.14	C6(1.5%Chitosan&DBP)	99.59
H7(2%HPMC & DBP)	97.32	C7(2%Chitosan & DBP)	98.96
H8(2.5%HPMC&DBP)	96.74	C8(2.5%Chitosan&DBP)	99.91

(PG = PROPYLENE GLYCOL ; DBP = DIBUTYLPHTHLATE)

Diffusion study

Effect of HPMC patches on drug release

The drug release rate among the HPMC patches was found to be decreased when concentration of HPMC was increased. This may be due to increased swelling of the polymer when concentration is increased which leads to increased viscosity of the medium and thus increases the mean diffusional path length of the drug molecule to get released into the diffusion medium. As shown in fig 1. & 2 the cumulative drug release was found to be around 90% for patches with 1 and 1.5% of HPMC and around 50-60% at 8 hours for patches with 2% and 2.5 % of HPMC . Since almost complete release was obtained with 1% and 1.5% HPMC within 8 hours they are not considered for further studies. Similarly patches with 2.5% HPMC could not provide a complete release at 24 hours and hence they were also not selected. Formulations H3 & H7 which have 2 % HPMC were found to be satisfactory as they produced a sustained as well as complete release for 24 hours. Among these 2 formulations, formulation H7 which contains DBP as plasticizers was chosen as the best formulation in comparison to H3, which contains PG as

plasticizers because H7 gave almost 100 % release at 24 hours whereas H3 give 91.72% release respectively.

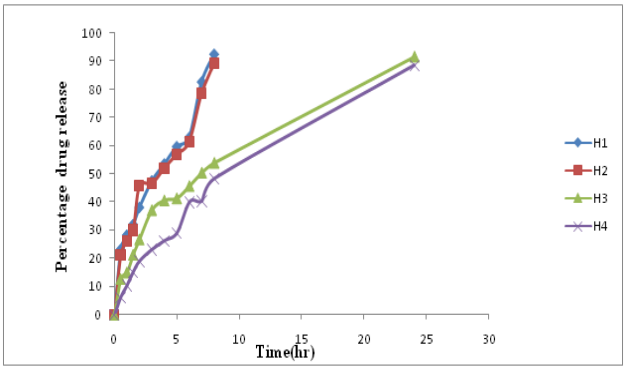

Figure 1: It Shows the Drug release of formulations H1, H2, H3 and H4

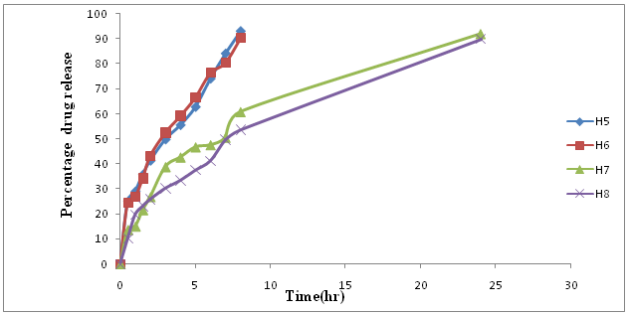

Figure 2: It Shows the drug release of formulations H5, H6, H7 and H8

Effect of Chitosan patches on drug release

Formuations C1, C2, C5 and C6 which contains 1 % and 1.5% chitosan gave a initial burst release of around 50% within the first 2 hours and the release was completed in less than 8 hours. Formulations C4 and C8 containing 2.5% chitosan gave a sustained release but they could not produce a complete release of the drug in 24 hours. The cumulative release from these formulation were found to be 88.52% and 89.58% respectively. Hence all the above formulations could not satisfy the reqirements for a sustained as well as complete release in 24 hours. As shown in figure 3 & 4 formulations C3 and C7 with 2% chitosan showed a satisfactory sustained effect and a complete release of about 95.23% and 99.78% at 24 hours respectively. Among these 2 formulations, formulation C7 with 2 % chitosan and DBP as plasticizers was chosen as best formulation as it showed a sustained and a complete release.

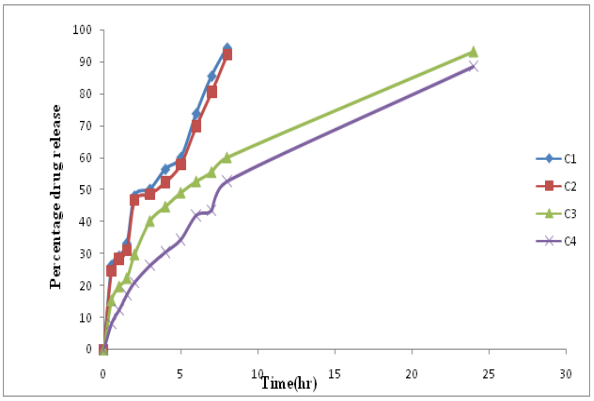

Figure 3: It Shows the Drug release of formulations C1, C2, C3 and C4

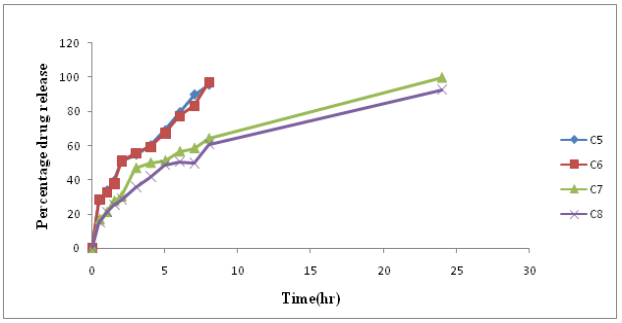

Figure 4: It Shows the Drug release of formulations C5, C6, C7 and C8

CONCLUSION

Delivery of drug into systemic circulation through skin has created lot of interest among pharmaceutical scientist during recent years. The transdermal system offers several advantages over oral dosage forms which include avoidance of hepatic first pass effect metabolism, decrease in frequency of administration, providing steady state plasma concentration and improves patient compliance etc. Hence in this study an attempt was made to deliver Amlodipine transdermally in order to provide a constant serum level of drug over the prolonged period of time. Polymers like HPMC and chitosan were selected for the study and were used at different concentrations. PG and DBP were incorporated as plasticizers in the formulations. On evaluation of various parameter it was found that the polymers produced a satisfactory results with respect to the physical characteristics of the film and the release characteristics across synthetic membrane. The release profile suggested that increase in polymer content led to decrease in release rate of the drug. Lower concentration of polymers gave an initial burst release of about 50% within 2 hours and as concentration were increased they were able to sustained the release for prolonged period but could not release the entire content in the prescribed time limit. Hence it was concluded that concentration of 2% for HPMC (H7) and Chitosan (C7) with DBP as plasticizers will be the most suitable one for the transdermal systems of Amlodipine as these showed a sustained and a complete release over a period of 24 hours. Among these two formulations chitosan containing patches were found to be most suitable one since it is a natural as well as biodegradable polymer. Further studies using various animal models can throw more light on the variability of the prepared transdermal systems.

ABBREVIATION

TDDS	Transdermal drug delivery system
HPMC	Hydroxyl propyl methyl cellulose
Avg	Average
Hrs	Hours
RPM	Revolution per minute
T	Time
PG	Propylene glycol
DBP	Dibutylphthlate

ACKNOWLEDGEMENT

With immense pleasure I express my deep gratitude to computer lab technicians and staffs of KMCH College of Pharmacy, and all those who helped directly and indirectly in every aspect of constructing this work.

REFERENCES

1. Bhowmik D, Chiranjib, Margret C, Jayakar B, Sampath K P. Recent Advances in Transdermal Drug Delivery System: International Journal of Pharmaceutical. Technology and Research. 2010; 2(1): 68-77.
2. Guru S, Biplab K, Nagarajan K, Sujit D, Vijaykumar. S, Dinesh.V. Effect of permeation enhancer on propanolol

hydrochloride formulated patches: International Journal Of pharmaceutical science. 2010 ; 2(2): 21- 31.

3. Gaur P, Mishra S, Purohit S, Dave K. Transdermal drug delivery system a review: Asian Journal of pharmaceutical. and Clinical. research. 2009 ; 2 (1): 14-19.

4. Jitendra B, Subhash P, Pathak A. Formulation and evaluation of matrix type transdermal system of Lisinopril dehydrate using permeation enhancers: Journal of pharmaceutical. research. 2008; 1(1): 16-21.

5. Hadgraft J, Guy R. H. Transdermal Drug Delivery.2nd ed. New York: Marcel Dekker, 35. p.14-16.

6. Jain.N.K, Controlled and novel drug delivery: Transdermal drug delivery system novel method .New Delhi: CBS publishers and distributors; 1997. P.428-430.

7. Hemangi .J, Jitendra S, Desai .B, Keyur.D. Design and evaluation of Amlodipine besilate transdermal patches containing film former: International Journal of pharmaceutical research and development . 2009; 7(001): 1-12.

8. Jadhav.R.T, Gattani S.G, Surana S.J. Formulation and evaluation of transdermal films of diclofenac sodium: International Journal of pharmaceutical Technology and research. 2009 ; 1(4): 1508-1511.

9. Pravin G, Atul.G, Radhika P.R, Sivakumar.T. Design and evaluation of hydroxypropyl methylcellulose(HPMC) based polymeric film of enalprilat maleate: International. Journal of pharmaceutical Technology and research. 2010 ; 2(1): 274-280.

10. Mangesh R, Design and evaluation of transdermal films of lornoxicam: International Journal of pharmaceutical. bioscience. 2011; 2(2): 54-60.

11. Sanap GS, Dama GY, Hande AS, Karpe SP, Nalawade SV, Kakade RS, et al., Preparation of transdermal monolithic systems of indapamide by solvent casting method and the use of vegetable oils as permeation enhancer: International Journal of Green Pharmacy. 2(2): 129-33.

12. Murthy TEGK, Kishore VS, Effect of casting solvent on permeability of antihypertensive drugs through ethyl cellulose films: Journal of pharmaceutical science. 2008; 67(2): 147-150.

13. .Murthy TEGK and Kishore VS, Effect of casting solvent and polymer on permeability of propranolol hydrochloride through membrane controlled transdermal drug delivery system: Indian Journal of Pharmaceutical Science. 2007; 69(5): 646-650.

14. Subramanian K, Sathyapriya LS, Jayaprakash S, Prabhu RS, Abirami A, Madhumitha B et al. An Approach to the formulation and evaluation of transdermal DDS of isoxsuprine HCl: International. Journal of. Pharmaceutical. Science and Technology. 2008; 1(1): 8 – 22.

15. Shinde AJ, Garala KC, More HN, Development and characterization of transdermal therapeutics system of tramadol hydrochloride: Asian Journal of Pharmaceutics. 2008 Mar; 2(4): 265-269.

16. Pandit V, Khanum A, Bhaskaran S, Banu V, Formulation and evaluation of transdermal films for the treatment of overactive bladder: International. Journal of Pharmaceutical Technology and Research. 2009; 1(3): 799-804.

17. Rao V, Mamatha T, Mukkanti K and Ramesh. Transdermal drug delivery system for atomoxetine hydrochloride- in vitro and ex vivo evaluation: Current. Trends in Biotechnology and Pharmacy. 2009; 3(2): 96 - 188.

18. Satturwar PM, Fulzele SV, Dorle AK, Evaluation of polymerized rosin for the formulation and development of transdermal drug delivery system: A Technical Note: Journal of membrane science. 2005; 6(4): 649 - 654.

19. R. K. Kar, S.Mohapatra, B.B.Barik .Design and Characterization of Controlled Release Matrix Tablets of Lamivudine: Asian Journal of Pharmaceutical and Clinical. Research. 2009; 2(2): 212-220.

20. Beny B, Abin A, Ramesh K, Rajarajan S.Design of transdermal patches of ketorolac tromethamine and its Invitro drug release studies. Journal of pharmaceutical research. 2009; 2(3): 357-362.