RESEARCH ARTICLE

Formulation and evaluation of transdermal patches of papaverine hydrochloride

Samip S Shah, Joshi Rahul[1], Prabhu Prabhakar[1]

Department of Pharmaceutical Technology, Pioneer Pharmacy Degree College, Vadodara, India, [1]Department of Pharmaceutics, N.G.S.M. Institute of Pharmaceutical Sciences, Mangalore, India

Transdermal patches of papaverine hydrochloride were prepared by the solvent casting method using ethyl cellulose: PVP, PVA: PVP and Eudragit RL-100: Eudragit RS-100 using different ratios. The physicochemical parameters such as flexibility, thickness, smoothness, weight variation, moisture content, hardness and tensile strength were evaluated for the prepared patches. The formulation exhibited flexibility, uniform thickness and weight, smoothness, good drug content (92 to 96%), and little moisture content. The *in vitro* diffusion studies were carried out using modified Keshery-Chein cell using cellophane as the diffusion membrane and the formulation followed the Higuchi diffusion mechanism. The formulation containing PVA: PVP as polymers showed faster release rate (hydrophilic polymers) compared to Eudragit RL-100: Eudragit RS-100 (hydrophobic polymers) or combination of hydrophilic and hydrophobic polymers (ethyl cellulose and PVP). The stability studies indicated that all the patches maintained good physicochemical properties and drug content after storing the patches in different storage conditions. Compatibility studies indicated that there was no interaction between the drug and polymers. *In vivo* studies showed that papaverine hydrochloride helps in decreasing the effect of isoproterenol-induced myocardial necrosis. Hence, the aim of the present study was to prepare the sustained release formulation (Transdermal patches) of the drug using different blend of polymers. The formulated patches containing the hydroplilic polymers showed best release rate of drug.

Key words: *Eudragit RL-100, eudragit RS-100, in vivo study, papaverine hydrochloride, transdermal patch*

INTRODUCTION

A recent approach to drug delivery is to deliver the drug into systemic circulation at predetermined rate using skin as a site of application. A transdermal drug delivery is a formulation or device that maintains the blood concentration of the drug within the therapeutic window ensuring that drug levels neither fall below the minimum effective concentration nor exceed the minimum toxic dose. Transdermal drug delivery promises many advantages over oral and/or intravenous administration, such as better control of blood levels, a reduced incidence of systemic toxicity, avoids hepatic first-pass metabolism and improves patient compliance. An ideal drug to be formulated as transdermal drug delivery should possess several physico-chemical prerequisites, such as short half- life, small molecular size, low dose, etc.[1] However, the highly organized structure of stratum corneum forms an effective barrier to the permeation of drugs, which must be modified if poorly penetrating drugs are to be administered. The use of chemical penetration enhancers would significantly increase the number of drug molecules suitable for transdermal delivery.[2]

Papaverine is an alkaloid present in opium. It belongs to the group of medicines called vasodilator. It has direct relaxant action on smooth muscle, which is attributed in part to its ability to inhibit phosphodiesterases. It has been given in the management of cerebral, peripheral, and coronary disorders. The biological half life of papaverine HCl by oral route is reported to be between 1 and 2 h. It shows less solubility in intestine pH. Papaverine is rapidly absorbed orally and undergoes extensive first pass metabolism in the gut wall and liver; moreover, the bioavailability of papaverine HCl is about 30% when administered orally. Hence, in order to avoid its extensive first pass metabolism, to improve its therapeutic efficacy by improving bioavailability, patient compliance and as well as to reduce the frequency of dosing and side effects, the transdermal drug delivery approach was considered to be better suitable for papaverine hydrochloride.[3]

The objective of the present work was to formulate and evaluate the papaverine hydrochloride the

Address for correspondence:
Mr. Samip S Shah, Pioneer Pharmacy Degree College, Vadodara, India. E-mail: samipshah2008@yahoo.com

DOI: 10.4103/0973-8398.63974

form of matrix diffusion controlled TDDS for *in vitro* release, *ex vivo* permeation, and mechanical properties. This is because there is no sustained release formulation available and the oral tablet undergoes extensive first pass metabolism.

MATERIALS AND METHODS

Materials

Papaverine hydrochloride was obtained as a gift sample from Biological E. Ltd, Hyderabad. Polvinyl alcohol (hot) was purchased from CDH Laboratory reagent, Mumbai, Polvinyl pyrolidone from Ozone International, Mumbai, Eudragit RL-100 and Eudragit RS-100 from Degussa India Pvt. Ltd., Mumbai, Propylene glycol from Nav Niketan Pharmaceuticals, Mumbai, Dimethy sulfoxide from Ranbaxy Fine Chemicals Ltd. All other chemicals and reagents used were of analytical reagent grade.

Formulation of transdermal patches

In the present study, matrix type transdermal patches of papaverine HCl were prepared by the molding technique. A flat square-shaped, aluminum foil-coated glass molds having surface area of 25 cm^2 were fabricated for casting the patches [Figure 1].

Preparation of casting solutions

For ethyl cellulose and PVP (F1 and F2)

The casting solutions were prepared by dissolving weighed quantities [Table 1] of polymers in chloroform. The drug was dissolved in chloroform and added to the above polymer solution along with propylene glycol, as plasticizer, thoroughly mixed to form a homogeneous mixture. The volume was made up to 10 ml with chloroform. Entrapped air bubbles were removed by applying vacuum.

For PVA and PVP polymers (F3 and F4)

The casting solutions were prepared by dissolving weighed quantities [Table 2] of polymers in water by heating in water bath. The drug was dissolved in distilled water and added to the above polymer solution along with propylene glycol, as plasticizer, thoroughly mixed to form a homogeneous mixture. The volume was made up to 10 ml with water. Entrapped air bubbles were removed by applying vacuum.

For eudragit RL-100 and eudragit RL-100 (F5 and F6)

The casting solutions were prepared by dissolving weighed quantities [Table 3] of polymers in ethanol:acetone (6:4). The drug was dissolved in chloroform and added to the above polymer solution along with propylene glycol, as plasticizer, thoroughly mixed to form a homogeneous mixture. The volume was made up to 10 ml with ethanol. Entrapped air bubbles were removed by applying vacuum.

Preparation of transdermal patches

The casting solution (10 ml) was poured into glass moulds and dried at room temperature for 24 h for solvent evaporation.

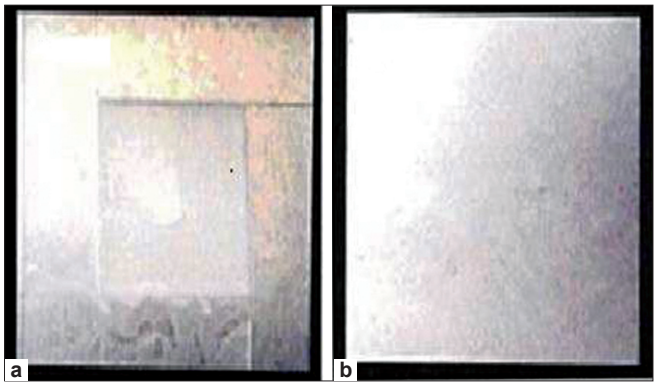

Figure 1: Formulation of transdermal patch: (a) casting solution in glass mould; (b) prepared transdermal film

Table 1: Formulation of EC and PVP combination

Code	Polymer ratio EC/PVP	Ethyl cellulose (mg)	Polyvinyl pyrrolidone (mg)	Papaverine HCl (mg)	Propylene glycol (ml)	DMSO (ml)	Chloroform upto (ml)
F1	4:1	400	100	350	0.1	0.1	10
F2	3:2	300	200	350	0.1	0.1	10

Table 2: Formulation of PVA and PVP combination

Code	Polymer ratio PVA/PVP	Polyvinyl alcohol (mg)	Polyvinyl pyrrolidone (mg)	Papaverine HCl (mg)	Propylene glycol (ml)	DMSO (ml)	Water upto (ml)
F3	2:1	333	167	350	0.1	0.1	10
F4	1:1	250	250	350	0.1	0.1	10

Table 3: Formulation of Eudragit RL-100 and RS-100 Combination

Code	Polymer ratio eudragit RL/RS 100	Eudragit RL-100 (mg)	Eudragit RS-100 (mg)	Papaverine HCl (mg)	Propylene glycol (ml)	DMSO (ml)	Ethanol: acetone upto (ml)
F5	1:1	125	125	350	0.1	0.1	10
F6	2:3	100	250	350	0.1	0.1	10

The patches were removed by peeling and cut into square dimension of 3 cm × 3 cm (9 cm^2). These patches were kept in desiccator for 2 days for further drying and wrapped in aluminum foil, packed in self-sealing covers. Transdermal patches were prepared with different polymer ratio, plasticizer concentration and permeation enhancers [Tables 1-3].

Evaluation of transdermal patches

Physicochemical parameters

Physical appearance

All the transdermal patches were visually inspected for color, flexibility, homogeneity and smoothness.

Film thickness

The thickness of the patches was measured at five different places on a single patch of each formulation using a screw gauge and the mean values were calculated.[4]

Weight variation

A set of three patches from each batch having a diameter of 1 cm^2 were weighed on a digital balance and the mean values were calculated. The tests were performed on films which were dried at 60°C for 4 h prior to testing.[4,5]

Drug content uniformity

The patch (1 cm^2) was transferred into a graduated flask containing 100 ml of phosphate buffer pH 6.8. The flask was shaken for 4 h in a mechanical shaker. Then the solution was filtered and after suitable dilutions with phosphate buffer pH 6.8 the absorbance was measured at 249 nm using the placebo patch solution as blank and the drug content was calculated.[4,5]

Folding endurance

A strip of 2 cm × 2 cm (4 cm^2) was subjected to folding endurance by folding the patch at the same place repeatedly several times until a visible crack was observed and the values were reported.[6]

Elongation and tensile strength

This mechanical property was evaluated using Instron universal testing instrument (model F. 4026), Instron Ltd, Japan, NITK, surathkal) with a 5 kg load cell [Figure 2]. Film strips in special dimension and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the strips were pulled by the top clamps at a rate of 100 mm/min; the force and elongation were measured when the film broke. Results from film samples, which broke at and not between the clamps, were not included in the calculations. Measurements were run in triplicate for each film. Two mechanical properties, namely tensile strength and percentage elongation, were computed for the evaluation of the film. Tensile strength is computed from the following equation[7]:

Figure 2: Instron universal testing instrument (Model F. 4026)

$$\text{Tensile strength} = \frac{\text{Force at break}}{\text{Initial cross sectional area of the sample } (mm^2)}$$

Percentage elongation can be obtained by following equation:

$$\%\ \text{Elongation at break} = \frac{\text{Increase in length} \times 100}{\text{Original length}}$$

Hardness

To determine the hardness of the patches, an apparatus was designed in our laboratory [Figure 3]. It consists of a wooden stand of 11 cm height and top area of 16 cm × 16 cm. A small pan was fixed horizontally to one end of the 2 mm thick iron rod whose other end is reduced to a sharp point. A hole of 0.2 cm was made at the center of tip area of wooden stand, which was supported on the pan rod. An electric circuit was developed through a 3 vt battery in such a way that the bulb glows only when the circuit is completed through the contact of a metal plate and sharp end of the rod. The film was placed between the metal plate and sharp end of the rod. The weights were gradually added at an interval of 10 sec for the stabilization of the force till the bulb glowed. The final weight was considered as a measure of hardness.[8]

Moisture absorption

Films (1 cm^2) of each formulation were accurately weighed and exposed to ambient atmospheric conditions of temperature (avg. temp 34°C) and humidity (75%) for 3 days.

Figure 3: Hardness testing apparatus

After 3 days, the films were again weighed and % moisture absorption was calculated. Average % moisture absorption of each film was calculated.[9]

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

In vitro drug release studies

In vitro drug release profiles were carried out by using modified Keshery-Chein diffusion cell with the cellophane membrane. The cellophane membrane was soaked in 100 ml of phosphate buffer of pH 7.4 and then cut into pieces of 7 cm^2 area. It was mounted on the diffusion cell and equilibrated with receptor fluid for 15 min and used for the drug release studies. The cell consists of two compartments, the donor and the receptor compartments. The donor compartment was in contact with ambient conditions of the atmosphere. The receptor compartment was in contact with a solution in the receptor compartment (phosphate buffer pH 6.8.) and the contents were stirred by a rod-shaped magnetic bead driven by a magnetic stirrer. One patch of 1 cm^2 was placed in the donor compartment of the diffusion cell. The receptor fluid (5 ml) was withdrawn at predetermined time intervals and replaced immediately with same volume of phosphate buffer pH 6.8. The samples were analyzed for drug content at 249 nm using UV-visible spectrophotometer after suitable dilution with phosphate buffer pH 6.8.[5]

Kinetic study

To know the mechanism of drug release from these formulations, the data were treated according to first-order (log percentage of drug to be released vs time), Higuchi's (percentage of drug released vs square root of time), and zero-order (percentage of drug released vs time) patterns.

Compatibility studies

In the present study, compatibility studies were carried out to assess any incompatibility between the drug and polymers. The IR studies were performed to check the compatibility with excipients. Spectra of the pure drug and the formulated patch were taken individually by the potassium bromide pellet method.[10]

Stability studies

The stability studies of the formulated transdermal patches were carried out on prepared films at different temperature and humidity: 25-30°C (60%RH) and 45-50°C (75%RH) over a period of 60 days. The patches were wrapped in aluminum foil and stored in a desiccator for stability study. The patches were characterized for drug content and other parameters at regular intervals (0, 15, 30, 45 and 60 days).[11]

Skin irritation studies

Patches were applied to the shaved skin on one side of the back of rabbit and secured using adhesive tape. On other back side of the rabbit, control patch (without drug) was secured in a similar way. The animal was observed for any sign of erythema or edema for a period of 48 h.[12]

Lamination of transdermal patch

The transdermal patch of 3 cm diameter was cut and placed on an aluminum foil of 3.5 cm diameter that serves as the backing membrane. A solution of propylene glycol was applied along the circumference of the aluminum foil and dried at room temperature for 10 h. The patch was covered with silicone-coated release liner.

***In vivo* studies (Effect of patch containing drug on isoproterenol induced myocardial necrosis)**

The *in vivo* experimental protocol was approved by the Institutional Animal Ethical Committee (KSHEMA/AEC/084/2008). The animals used for *in vivo* experiments were adult male Wistar rats (6-8 weeks old) weighing 150-200 g for this study. They were divided into two groups (n=4). One group received 8.5 mg/kg isoproterenol (s.c.) on two consecutive days. The other group was first pretreated with the test drug by applying the transdermal patch of 1 cm^2 (12.90 mg drug). After 6 h, they were injected with 8.5 mg/kg isoproterenol s.c. on two consecutive days. After 48 h of first isoproterenol administration, the rats were sacrificed and autopsied. The animal heart was removed after withdrawing the blood sample (0.5 ml, for lactate dehydrogenase enzyme estimation) from the retro orbital route and weighed, and frontal sections were embedded for histological examination.

RESULT AND DISCUSSION

All the patches prepared with different polymer concentration were found to be flexible, smooth, opaque, non-sticky and homogeneous in nature [Table 4]. This may

be due to the presence of plasticizer. Marginal difference in thickness was observed among each group indicated that more the amount of polymer higher the thickness values [Table 5]. All the six patches have showed good folding endurance, and [Table 4] indicated that the patches have good flexibility.

Water absorption studies revealed that as the concentration of PVP, PVA, Eudragit RS-100 (F2, F3, F6) increased the amount of water absorption also increased. Among the patches, F3 (PVA: PVP ratio 2:1) patch absorbed higher moisture content. This may be due to the hydrophilic nature of the PVA and PVP. The least percentage of moisture absorption was observed for F1 patch (EC: PVP) as compared to other patches because of hydrophobic nature of ethyl cellulose.

The effect of concentration of polymers was observed on the percentage elongation and tensile strength. It was found that as the concentration of PVP increased, the percentage elongation and tensile strength were also increased within the patches containing the combination of EC and PVP. Eudragit patches showed better tensile strength due to the nature of polymers. There was no significant difference in the drug content among the patches [Table 6] indicated content uniformity.

In vitro drug release study showed that from hydrophilic polymers (F3 and F4) the drug release was found to be faster compared to the combination of hydrophilic and hydrophobic polymers (F1 and F2) or only hydrophobic polymers (F5 and F6) used in the study [Figure 4]. Patches prepared with PVP and EC as polymers, found that more the amount of PVP better the drug release due to the hydrophilic nature of PVP. Significant changes in drug release were observed from patches containing more amount of PVA showed highest release (F3 compared to F4). This may be attributed to hydrophilic nature of the polymers which have more affinity for water resulting in increased thermodynamic activity of the drug in the film. Patches containing Eudragit RL-100 and Eudragit RS-100 (F5 and F6) showed slower release as the patches contains only hydrophobic polymers, which might have lead to slower release of drug from the patches. Further the drug release study (F2, F3, and F5) was when conducted for 40 h; it was observed that approximately 75-80% of drug was released. Hence, transdermal patches can be used for extended period of time. The release profile was correlated with the moisture absorption which further reflected by the nature of polymer.

Comparison of *in vitro* % drug release of formulations

Percentage drug release

Time (hours)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	9.68	11.21	13.46	11.71	8.72	7.34
4	12.54	14.49	17.23	14.47	11.88	9.79
6	15.42	17.96	20.85	18.48	14.75	12.14
8	18.16	20.8	24.98	22.62	17.38	15.54
10	21.18	24.3	29.24	26.29	20.36	17.46
12	23.98	28.27	32.76	30.31	23.95	21.2
16	29.63	32.88	40.29	35.42	29.41	26.5
24	36.52	38.24	49.83	42.33	34.35	31.11

From the above data, it can be concluded that the release characteristics may be restricted to only *in vitro* release study, as the *in vitro* release model mainly favors the hydrophilicity. However, when theses patches applied to the skin results may differ as the lipophilicity may play a major role for the drug transport system.

The release kinetics of the transdermal patches followed first order and Higuchi's diffusion kinetics [Table 7]. According to the first order, the release of drug is based on the concentration of the drug in the formulation. Further as per Higuchi release kinetics, the drug release follows diffusion mechanism. Percentage of drug released when plotted against square root of time, the plots showed high linearity. It indicated that release pattern followed Higuchi's diffusion mechanism which indicates that as the time increases, the diffusion path length also increases.

Stability studies showed that, there is no significant change in physical characteristics and drug content [Table 8]. Based

Table 4: Physicochemical properties of the prepared transdermal patches

Formulation code	Flexibility	Smoothness	Transparency	Stickiness	*Folding endurance	*Weight (mg) AM±SD
F1	Flexible	Smooth	Opaque	Non-sticky	170-210	29.002±0.054
F2	Flexible	Smooth	Opaque	Non-sticky	170-210	31.323±0.095
F3	Flexible	Smooth	Opaque	Non-sticky	170-210	31.541±0.064
F4	Flexible	Smooth	Opaque	Non-sticky	170-210	33.867±0.043
F5	Flexible	Smooth	Opaque	Non-sticky	200-250	26.812±0.057
F6	Flexible	Smooth	Opaque	Non-sticky	200-250	27.971±0.019

*Average of three determinations

Table 5: Physicochemical properties of the prepared transdermal patches

Formulation code	*Hardness (kg) AM±SD	*%Moisture absorption	*Thickness (mm) AM±SD	Width (mm) AM±SD	Initial length (mm)AM±SD	Final length (mm) AM±SD	Elongation (mm) AM±SD	%Elongation AM±SD	Weight required to break (kg) AM±SD	*Tensile strength (kg/mm) AM±SD
F1	0.326±0.024	2.91	0.320±.0021	5.0±0.0	10.0±0.0	17.810±1.201	7.810±1.254	78.10±11.12	0.455±0.0154	0.416±0.051
F2	0.306±0.012	3.14	0.328±0.016	5.0±0.0	10.0±0.0	18.24±1.364	8.240±1.00	82.40±10.31	0.479±0.0257	0.439±0.047
F3	0.386±0.021	5.26	0.321±0.028	5.0±0.0	10.0±0.0	18.97±1.642	8.97±1.23	89.70±12.41	0.593±0.0147	0.493±0.078
F4	0.419±0.018	5.17	0.332±0.023	5.0±0.0	10.0±0.0	17.95±1.387	8.57±1.520	85.70±11.85	0.638±0.0239	0.452±0.063
F5	0.396±0.028	3.20	0.249±0.071	5.0±0.0	10.0±0.0	18.66±1.652	9.17±1.845	91.20±12.34	0.691±0.0641	0.545±0.022
F6	0.418±0.031	3.50	0.260±0.062	5.0±0.0	10.0±0.0	18.16±10.00	9.07±1.164	90.70±11.94	0.652±0.0836	0.520±0.035

* Average of three determinations

Table 6: Drug content of the prepared transdermal patches

Formulation code	*Amount in 1 cm² (mg)	Percentage drug content in 1 cm²
F1	12.92±0.0316	93.24±0.5127
F2	13.25±0.0358	95.40±0.5714
F3	12.90±0.0291	92.88±0.4015
F4	13.20±0.0471	95.04±0.7481
F5	12.90±0.0312	93.02±0.5104
F6	13.00±0.0425	93.60±0.7345

*Average of three determinations

Table 7: R^2 values of all the patches

Code	F1	F2	F3	F4	F5	F6
Zero order	0.9443	0.9071	0.9427	0.9244	0.9346	0.9472
First order	0.9724	0.9456	0.9816	0.9630	0.9615	0.9674
Higuchi model	0.9873	0.9928	0.9878	0.9901	0.9852	0.9755

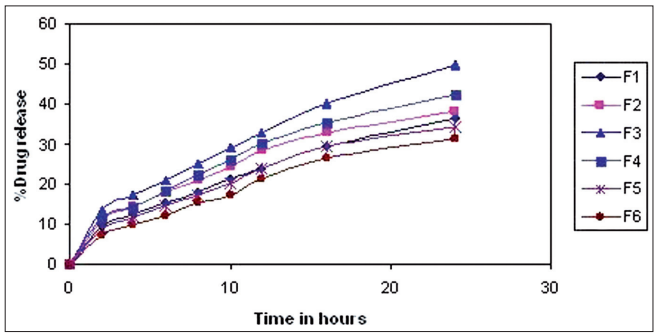

Figure 4: Comparison of *in vitro* % drug release of all formulations

on these results it was concluded that the formulated transdermal patches were found to be physically and chemically stable during the study period (60 days).

Results of the skin irritancy study revealed that neither blank patch nor patch containing papaverine hydrochloride caused any noticeable sign of erythema or edema on rabbit skin throughout the period of 48 h. Hence, the patches were found to be compatible with the skin.

Interaction between drug and formulation was studied using IR analysis. The IR spectrum revealed that there were no interaction between drug and excipients [Figure 5 a,b,c,d].

From the *in vivo* effect of drug on the isoproterenol-induced myocardial necrosis study, (slides of rat heart are shown in Figure 6), it was found that the LDH (lactate dehydrogenase) level increased marginally in rats treated with transdermal patch (604 U/L) compared to the group of animals which were not treated with transdermal patch (717 U/L) [Table 9]. The normal value for LDH is 450-500 U/L. Thus, the extent of damage was found to be minimal. Further, from the above figures it was found that there was a significant decrease in myocardial necrosis in rats applied with the transdermal patch

Table 8: Stability study of trandermal patches at various temperature and humidity

Formulation code	Initial % drug content	25-30°C (60% RH)			45-50°C (75% RH)		
		15 days	30 days	60 days	15 days	30 days	60 days
F1	93.24	93.22	93.18	93.11	93.20	93.15	93.09
F2	95.40	95.37	95.35	95.29	95.32	95.28	95.22
F3	92.88	92.70	92.65	92.58	92.68	92.61	92.55
F4	95.04	94.97	94.92	94.89	94.95	94.90	94.86
F5	93.02	92.99	92.95	92.91	92.98	92.94	92.88
F6	93.60	93.59	93.57	93.54	93.58	93.55	93.53

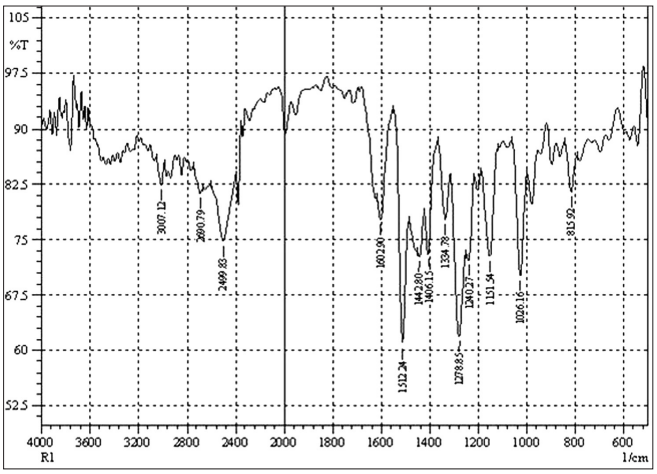

Figure 5a: IR spectra of papaverine hydrochloride

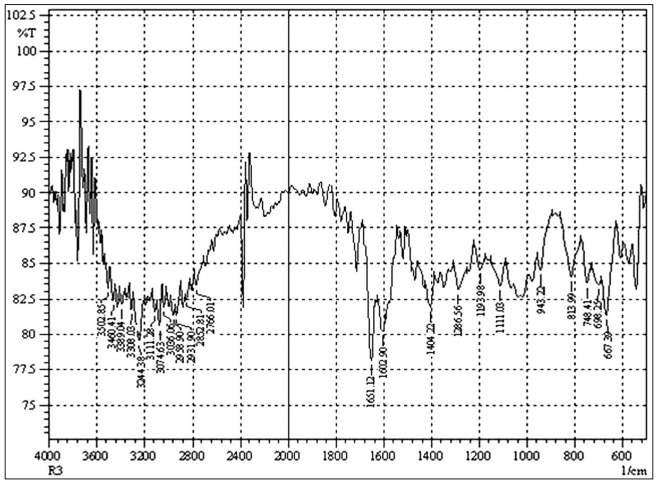

Figure 5b: IR spectra of F2 formulation

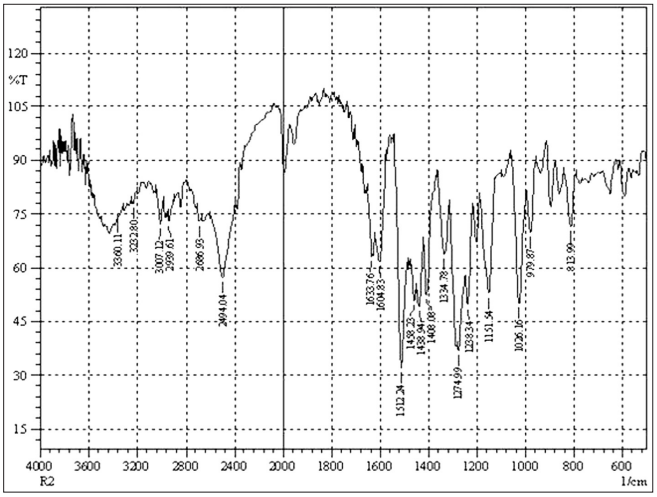

Figure 5c: IR spectra of F4 formulation

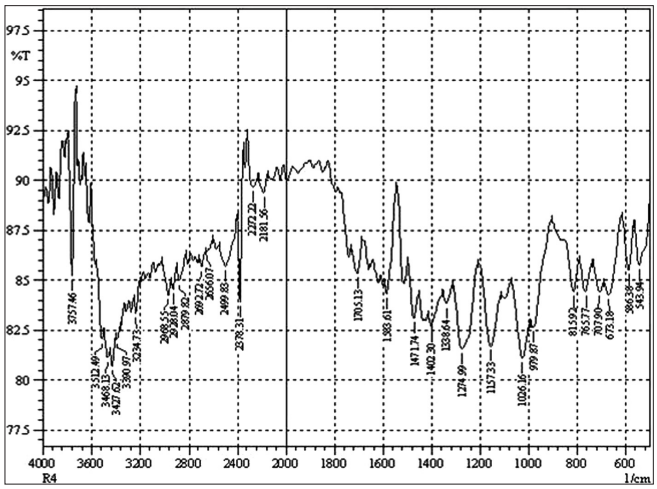

Figure 5d: IR spectra of F6 formulation

containing papaverine hydrochloride compared to the animal not treated with the transdermal patch. When the animal was not treated with drug containing transdermal patch, the myocardial necrosis was found to be severe [Figure 6a]. Hence, papaverine hydrochloride transdermal patches help in decreasing the effect of isoproterenol-induced myocardial necrosis. This suggests that drug absorption through the skin has taken place from the patches.

CONCLUSION

Propylene glycol was used as plasticizer at a conc. of 1% v/v for all patches which exhibited good flexibility, tensile strength, hardness and handling property. Based on the physicochemical parameters and *in vitro* release studies, formulation F3 and F4 were considered as the best formulations. The *in vivo* study showed that papaverine

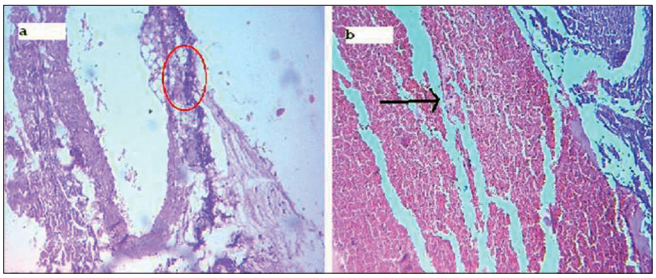

Figure 6: (a) Slide of rat heart injected with isoproterenol without patch; (b) with transdermal patch containing drug

Table 9: Effect of drug on isoproterenol induced myocardial necrosis

Sample	LDH	
Rat	Test	604 U/L
	Control	717 U/L

hydrochloride helps in decreasing the effect of isoproterenol on myocardial necrosis. Based on the encouraging results, the papaverine hydrochloride transdermal patch can be used as a controlled drug delivery system and frequency of administration can be minimized. Though the efforts were made for the development of papaverine hydrochloride transdermal patch, long-term pharmacokinetic and pharmacodynamic studies are needed to undertake the establishment of the usefulness of these patches. Further, these findings may help the industry to scale up for commercial production. Transdermal dosage form of papaverine hydrochloride may provide clinicians an opportunity to offer more therapeutic options to their patients to optimize their care.

ACKNOWLEDGEMENT

I especially thanks to Biological E. Ltd, Hyderabad to provide drug sample. I also especially thanks to Mr. Prabhakar Prabhu, Asst. Prof., N.G.S.M. Institute of Pharmaceutical Sciences, Mangalore (Karnataka) to guide for research work.

REFERENCES

1. Chein YW. Novel drug delivery systems. Vol. 50. New York: Marcel Dekker, Inc.; 1992. p. 301.
2. Kanikannan N, Andega S, Burton S, Babu RJ, Singh M. Formulation and *in vitro* evaluation of transdermal patches of melatonin. Drug Dev Ind Pharm 2004;30:205-12.
3. Goodman and Gillman's The Pharmacological Basis of Therapeutics. 10th ed. New York: Medical Publishing Division; 2001. p. 448-9.
4. Gattani SG, Gaud RS, Chaturvedi SC. Formulation and evaluation of transdermal films of chlorpheniramine maleate. Indian Drugs 2007;44:27-33.
5. Rao RP, Divan PV. Influence of casting solvent on permeability of ethyl cellulose free films for transdermal use. East Pharma 1997;40: 135-7.
6. Kusum DV, Saisivam S, Maria GR, Deepti PU. Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. Drug Devel Indust Pharm 2003;29:495-503.
7. Kulkarni R, Doddayya H, Marihal SC, Patil CC, Habbu PV. Comparative evaluation of polymeric films for transdermal application. East Pharma 2000;93:109-11.
8. Das MK, Bhattacharya A, Ghosal SK. Transdermal delivery of trazodone hydrochloride from acrylic films prepared from aqueous latex. Indian J Pharm Sci 2006;68:41-6.
9. Gannu R, Vishnu YV, Kishan V, Rao YM. development of nitrendipine transdermal patches: *In vitro* and *ex vivo* characterization. Curr Drug Deliv 2007;4:69-76.
10. Pandit V, Khanum A, Bhaskaran S, Banu V. Formulation and evaluation of transdermal films for the treatment of overactive bladder. Int J Pharm Tech Res 2009;1:799-804.
11. Sankar V, Johnson DB, Sivanad V, Ravichadran V, Raghuram S. Design and evaluation of nifedipine transdermal patches. Indian J Pharm Sci 2003;65:510-5.
12. Vogel GH, Vogel WH, editors. Drug discovery and evaluation: Pharmacological assays New York: Springer Verlag Berlin Heidelburg; 1997. p. 192.

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