ORIGINAL ARTICLE

Development and Evaluation of Transdermal Therapeutic System of Metoprolol Succinate using Acrylic Polymer

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Abstract

Aim: The main objective of the current investigation was to develop and evaluate the drug-in-adhesive patches of metoprolol succinate. **Materials and Methods:** Transdermal patches were formulated using various pressure sensitive adhesives such as Duro-Tak 387-2051, Duro-Tak 387-2052, Duro-Tak 87-2677, Duro-Tak 387-2051, and Duro-Tak 387-2052 alone and/or in combination. The patches were evaluated for different physical parameters with *in vitro* permeation and *ex vivo* permeation studies. Skin irritation studies are conducted using albino rats. **Results and Discussion:** Transdermal patch prepared with drug from formulation F_1 was very controlled. F_1 has selected for the further studies. Optimization was, therefore, effected by casting the patch at various drug concentrations, *viz*., 1%, 2%, 3% and 4% w/v and using permeation enhancer (*l*-menthol). The permeation of the drug from formulation F_1 was very controlled, and gradual enhancement of the drug permeation through the skin was noticed in comparison to other formulations. The formulation F_7 was made up of Duro-Tak 87-2677, although, released the drug very slowly but due to poor tackiness, this formulation was not further explored. **Conclusion:** The result obtained showed Duro-Tak formulations, with the exception of Duro-Tak 87- 2677, were able to deliver the drug for extended period of time without causing any skin toxicity. Overall, Duro-Tak formulations showed sufficient promise in the development of an efficient transdermal drug delivery system for the controlled drug delivery of Metoprolol Succinate.

Key words: Metoprolol succinate, pressure sensitive adhesive, rat skin, transdermal drug delivery system

INTRODUCTION

During the past few years, interest in the development of novel drug delivery systems for existing drug molecules has been renewed. A transdermal drug delivery (TDD) offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects, and sometimes, improved efficacy over other dosage forms. The main objective of TDD system (TDDS) is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intrapatient variation. In addition, because transdermal patches are user-friendly, convenient, painless, and offer multi-day dosing, it is generally accepted that they offer improved patient compliance.[1]

Hypertension is one of the main causes of heart disease and, in recent years, the age-adjusted hypertension and hypertensive disease death rates have been increasing. Consequently, the prevention and treatment of hypertension are of major social significance. At the present time, members of the class of drugs called beta-blockers are commonly used as the first-line treatment for elevated blood pressure. For achieving, these goals transdermal therapeutic patches of metoprolol succinate were prepared and evaluated. Transdermal administration can avoid or mitigate the metabolic processes associated with oral ingestion of medication.[1,2] Metoprolol succinate

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is subjected to hepatic first-pass metabolism following oral administration with a systemic bioavailability of 40-60%, also its dosing frequency is high indicating the need for alternative drug delivery modes. The preparation of TDDSs consists of three basic designs including reservoir, matrix, and drug in adhesive. Nevertheless, these devices could be grouped into two main categories: Reservoir-type and matrix-type devices. The transdermal devices of reservoir-type consist of a reservoir that contains active pharmaceutical ingredients (API). From the reservoir, the API diffuses through the controlling membrane into the absorption site. The main advantage of this type of device is that the rate of drug delivery is maintained practically constant for a long period of time. Nevertheless, these devices are usually bulky and delivery systems using a carrier solvent in a reservoir containment for the drug provide a steady flux of the drug across the membrane so long as undissolved drug remains in the reservoir.[2,3]

The matrix-type transdermal devices generally comprise a nonpermeable backing liner, a polymeric adhesive matrix in which the active drug or drugs are dissolved or dispersed and a release liner. They have a total surface area that is the same as that of the active surface. One disadvantage of the matrix type device is that for some active substances, it is difficult to maintain a constant dose for an extended period of time. In general, in this type of device, the delivery rate diminishes with time as a consequence of the decreasing concentration of the API in the matrix. However, the major challenge in fabricating both matrix and micro reservoir type TDDS is the adhereness of the patch to the skin which seems to be an important parameter for maintaining the concentration gradient from the patch into the systemic circulation. In addition to the usual requirements of functional adhesive properties, adhesives for TDD applications must have good biocompatibility with the skin, chemical compatibility with the drug, various components of the formulation, and provide consistent, effective delivery of the drug. The innovative design of using drug in an adhesive delivery system using pressure sensitive adhesives (PSAs) in TDD is a significant tool for eliminating adhesive challenges. The primary function of PSA is to help in adhesion of patch to skin, but more importantly it acts as a matrix for the drug and other excipients. Hence, apart from adhesion of the patch, PSA also affects other critical quality attributes of the TDDS such as drug delivery, flux through skin and physical and chemical stability of the finished product. This research discusses the uses of various grades of Duro-Tak, acrylic polymer, in fabrication, and controlling the drug release from the Transdermal system.

Drug-in-adhesive patches of metoprolol succinate were formulated using various PSAs Duro-Tak 387-2051, Duro-Tak 387-2052, Duro-Tak 87-2677 alone and in a combination of Duro-Tak 387-2051, and Duro-Tak 387-2052. The patches were evaluated for various physicochemical parameters, drug excipient interaction studies, *in vitro* skin permeation studies, effect of penteration enhancer on the drug release, evaluation of adhesive quality, and skin irritation studies.

MATERIALS AND METHODS

Materials

Metoprolol Succinate and Duro-Tak 387-2051, Duro-Tak 387-2052, and Duro-Tak 87- 2677 were obtained from Aarti Drugs, India and Henkel Limited, U.K., respectively. Double-distilled water was used throughout the study. All chemicals and reagents used were of analytical grade.

Drug excipient interaction study

While designing any drug delivery system, it is imperative to give consideration to the compatibility of drug and polymer used within the system. Therefore, it is necessary to confirm that drug is not interacting with the polymer under experimental conditions and shelf life. In this study, the drug-polymer interaction studies were conducted for the pure drug and the physical mixture of drug-polymer by ATR analysis.

Formulation of transdermal patches

Transdermal films containing metoprolol succinate were prepared by solvent evaporation technique as describe by Shingade *et al*.[4] Initially, seven formulations were formulated using different polymers, combination of polymers and concentration of metoprolol succinate. The detailed compositions of the patches are given in Table 1. The formulation of transdermal patches comprises the preparation of backing membrane, casting solution, and finally the casting of drug matrix on the backing membrane.

Preparation of backing membrane

The backing membrane was prepared with an aqueous solution of a 6% w/v poly (vinyl alcohol). A weighed amount of poly (vinyl alcohol) was added to a requisite volume of warm, glass-distilled water and a homogeneous solution was made by constant stirring and intermittent heating at 60°C for a few seconds. Care was taken during stirring to prevent the formation of any bubbles during the preparation of this solution. The homogeneous solution was then spread on a sheet of aluminum foil and kept for 24 h. The poly (vinyl alcohol) laminated aluminum foil was then used as a backing membrane.

Preparation of casting solution

The casting solutions were prepared by dissolving appropriate polymers in a suitable vehicle (methanol) using a magnetic stirrer and a small magnetic bead. The mixture was stirred continuously in such a manner that evaporation

Table 1: Composition of transdermal patches

Formulation code	Polymers	Drug in methanol (% w/v)
F_1	Duro-Tak 387-2051	5
F_2	Duro-Tak 387-2052	5
F_3	Duro-Tak 387-2051: Duro-Tak 387-2052=(50:50)	5
F_4	Duro-Tak 387-2051: Duro-Tak 387-2052=(80:20)	5
F_5	Duro-Tak 387-2051	2.5
F_6	Duro-Tak 387-2052	2.5
F_7	Duro-Tak™ 87-2677	2.5

was minimum. The drug was added previously to the vehicle (methanol) and dissolved by continuous stirring.

Casting of drug matrix

For the formulation of films, about 10 ml of the casting solution was poured on the previously prepared backing membrane and spread with the help of glass rod and kept at a room temperature for 48 h. The rate of evaporation was controlled by inverting a funnel over the glass slide.[5,6] After drying, the patches were covered with release liner and cut into appropriate sizes, packed in aluminum foil and stored in a dessicator. The films were then used for the various physical-chemical evaluations.

Physico-chemical characterization of transdermal patches

Weight variation

Uniformity of weight was determined by weighing five matrices of each formulation. After each film unit was weighed individually on a digital balance, the average weight of film was taken as the weight of the film.

Thickness uniformity

The thickness of the films was determined by measuring the thickness at five sites on three films of each formulations using micrometer screw gauge and the average was calculated.[7]

Evaluation of adhesion (thumb tack test)

1 week after the preparation of the TDDSs, a thumb tack test was performed by lightly pressing a thumb on a patch for 5 s and then quickly removing it. By varying the pressure and time of contact, and considering the difficulty of pulling the thumb from the adhesive, it was possible to guess how easily, quickly and strongly the adhesive formed a bond with the skin. The test was performed blindly on various types of formulations to determine the proper formulation for further studies. The patches were applied on the forearm of 10 volunteers. After 24 h, the patches were removed to study the skin-adhesion capability and compatibilities of the formulations with the skin. Ultimate scoring of acceptability was based on result of a thumb tack test as well as skin adhesion, removal capacities, and the formulations' compatibilities with the skin.

Drug content uniformity

A circular patch of 1 cm diameter was cut and dissolved in sufficient quantity of phosphate buffer pH 6.0. The volume was made up to 10 ml. 1 ml was then withdrawn from this solution and diluted to 10 ml.The absorbance was then measured at 222 nm. From the absorbance and the dilution factor, the drug content in the film was calculated.[8,9]

Skin irritation studies

All animal experiments were carried out in accordance with the guidelines of CPCSEA, and the protocol was approved by the Institutional Animal Ethical Committee, college of Pharmacy, IFTM, Moradabad (837/ac/04/CPCSEA). The Skin irritation studies were carried out to investigate the potential for metoprolol succinate to cause irritation in the hairless rat skin. Each hairless rat (n = 3) received one adhesive device containing metoprolol succinate on the left side of the abdominal skin and an adhesive device containing only adhesive on the right side of the abdominal skin to differentiate irritation caused by the adhesive used or the metoprolol succinate itself. The devices remained on the hairless rats for 24 h, and fresh devices were re-applied to the same sites daily for 7 days. The abdominal skin of the hairless rats was evaluated for:[10,11]

F → Flushing of skin (redness)
P → Papules and wheals
E → Erythema and oedema.

In vitro release studies

The aim of *in vitro* experimentation in TDD was to understand or predict the delivery and permeation of a molecule from the skin surface into the body via the skin of a living animal. This was achieved using a Franz diffusion cell.[11]

Permeation cell

A Franz diffusion cell was used for *in vitro* permeation study of transdermal patches. The diffusion cell was fabricated from borosilicate glass and consisted of two compartments receptor and donor. The cell had an effective receptor volume

of 65 ml and having an inner diameter of 1 cm and a side arm for easy withdrawal of samples.

Preparation of rat abdomen skin

Male Wistar rats weighing 180-220 g (6-8 weeks old) will be anesthetized with urethane (20% w/w i.p.). After shaving their abdomen carefully, a full thickness skin will be excised from the shaved abdomen site. After removing the fat and subdermal tissues, it will be used for skin permeation studies. At the time of use, the epidermis was spread on the cell and allowed to equilibrate with receptor fluid for 15 min before commencing the experiment.

Procedure

A Franz diffusion cell was used for evaluating drug release profiles across excised rat abdomen skin. The receptor compartment was filled with 65 ml of phosphate buffer pH 6.0 stirred by the use of the Teflon coated bead on a magnetic stirrer. The above skin was mounted on the diffusion cell, and the transdermal patch was placed over the skin. The whole assembly was kept on the magnetic stirrer and the temperature was maintained at 37 ± 1°C with the water jacket.[12] The withdrawal port was covered with the glass cork. Measures were taken to prevent air entrapment and also proper filling of the cell to mesh the position of the horizontal membrane. The upper portion of the cell is the donor compartment which was open at the top to maintain the exposure of the system to the ambient conditions. The amount of drug permeated into the receptor solution was determined by removing samples (1 ml) at hourly intervals. The withdrawn volume was replaced with an equal volume of fresh buffer solution. The drug permeated was determined by analyzing the samples at 222 nm. The results of *in vitro* release study are represented by cumulative percent drug release versus time. The data were linearly regressed and statistical parameters related to it were derived.[13]

Selection of the formulations for further studies

The screening of patch formulations was based on cumulative percent drug release and constantness of percent drug diffuse per hour. The optimized formulation from above all is F_1.

The following studies were performed on F_1:

1. Effect of drug concentration on skin permeation of metoprolol succinate.
2. Effect of permeation enhancer (*l*-menthol) on skin permeation of metoprolol succinate.

Effect of drug concentration on skin permeation of metoprolol succinate

The modification of formulation F_1 containing Duro-Tak 387-2051 was effected by casting the patch with varying concentration of metoprolol succinate, *viz*., 1%, 2%, 3% and 4%. They are designated as F_8, F_9, F_{10} and F_{11}, respectively. The detailed composition was given in Table 2.

Effect of permeation enhancer (l-menthol) on skin permeation of metoprolol succinate

The modification of formulation F_1 containing Duro-Tak 387-2051 was affected by casting the patch using permeation enhancer (*l*-menthol). They are designated as F_{12}, F_{13} and F_{14}. The detailed composition was given in Table 2.

The modified preparation was then again characterized for uniformity in thickness, weight variation, drug content, but no significant changes were observed.

RESULTS AND DISCUSSION

Drug-excipient interaction

It was studied at the very outset before the beginning of the development of formulations. Various methods such as differential scanning calorimetry, infrared (IR) spectra, attenuated total reflection (ATR) spectra, and thin-layer chromatography are used frequently to study the drug-excipient interaction. The ATR spectrum can accurately clarify drug-excipient interactions at the various functional groups between the drug and excipient molecules. Compatibility evaluation was carried out to ascertain any kind of interaction of the drug with the adhesive used in the preparation of transdermal patch. The ATR spectra of adhesive alone and mixture of drug and adhesive were shown in Figures 1 and 2. From the spectra, it was clear that the pure drug shows a characteristic peak at 1383.2 cm^{-1} which is due to C-H deformation of dimethyl group and a peak at 1240.8/cm is indicative of C-O str in a secondary alcohol. On the other hand, the ATR spectra of transdermal adhesives and drug correspond to the spectrum of their mixtures with the exception of a mixture containing transdermal adhesive Duro-Tak 87-2677 (especially at 5% level), which showed marginal interaction with drug which corresponds to the

Table 2: Composition of transdermal patches with permeation enhancer

F.C.	Polymers	Drug in methanol (% w/v)	Permeation enhancer (*l*-menthol) (% w/v)
F_8	Duro-Tak 387-2051	1	-
F_9	Duro-Tak 387-2051	2	-
F_{10}	Duro-Tak 387-2051	3	-
F_{11}	Duro-Tak 387-2051	4	-
F_{12}	Duro-Tak 387-2051	5	2
F_{13}	Duro-Tak 387-2051	5	4
F_{14}	Duro-Tak 387-2051	5	6

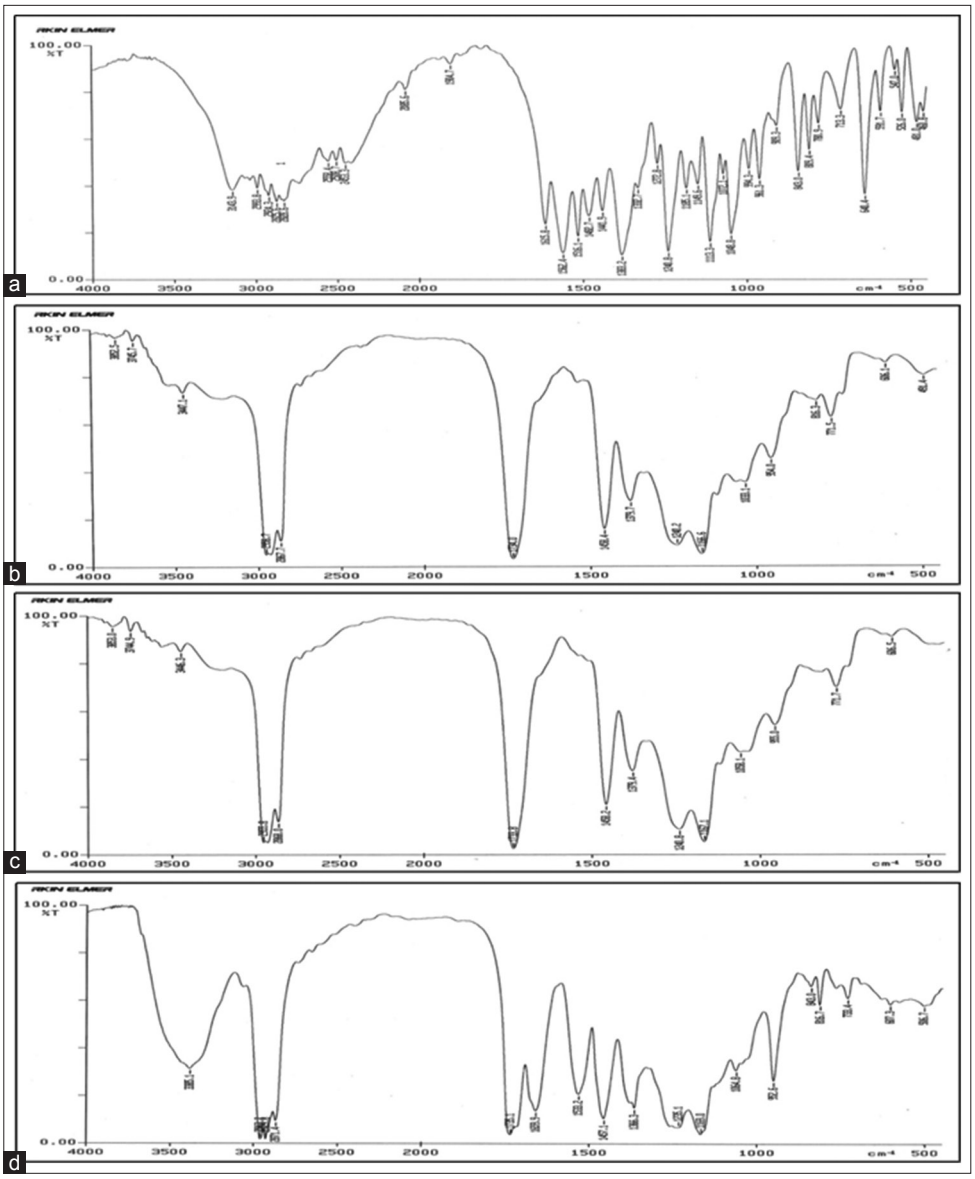

Figure 1: Attenuated total reflection spectra: (a) Metoprolol succinate, (b) Duro-Tak 387-2051, (c) Duro-Tak 387-2052, (d) Duro-Tak 87-2677

intimate mixing of drug in the adhesive. Where as, Duro-Tak adhesive 387- 2051 was found to be most compatible with the drug. Duro-Tak adhesive 387- 2052 also showed some interaction with the drug, but the interactions were minor and correspond to the intimate mixing of drug and adhesive.

Physicochemical characterization of transdermal patches

Seven formulations were formulated and designated as F_1, F_2, F_3, F_4, F_5, F_6 and F_7. The detailed composition of the patch formulation is shown in Table 1. The first four formulations (F_1-F_4) contain 5% w/v drug, whereas the formulations F_5-F_7 contain 2.5 % w/v drug. In formulation F_7, 2.5% w/v drug concentration was selected because at 5% w/v concentration drug crystallized out during solvent evaporation. The prepared transdermal patches were evaluated for various physicochemical parameters such as weight variation, thickness uniformity, drug content uniformity, and adhesive properties. The physico-chemical characteristics are summarized in Table 3.

All the formulations exhibited uniform weight with standard deviation values indicating the uniformity of the patches. The weight of the patch varied between 45.6 ± 4.45 mg and 63.6 ± 3.578 mg. The thickness of transdermal patches was measured by micrometer in which thickness of the patches varies between 0.231 ± 0.0138 mm and 0.31 ± 0.0154 mm. Low standard deviation values ensure uniformity of the patch prepared by solvent evaporation technique. The area of the patch was found to be 0.785 cm^2.

The drug content uniformity was determined for all the seven formulations by UV-Spectrophotometric method. It

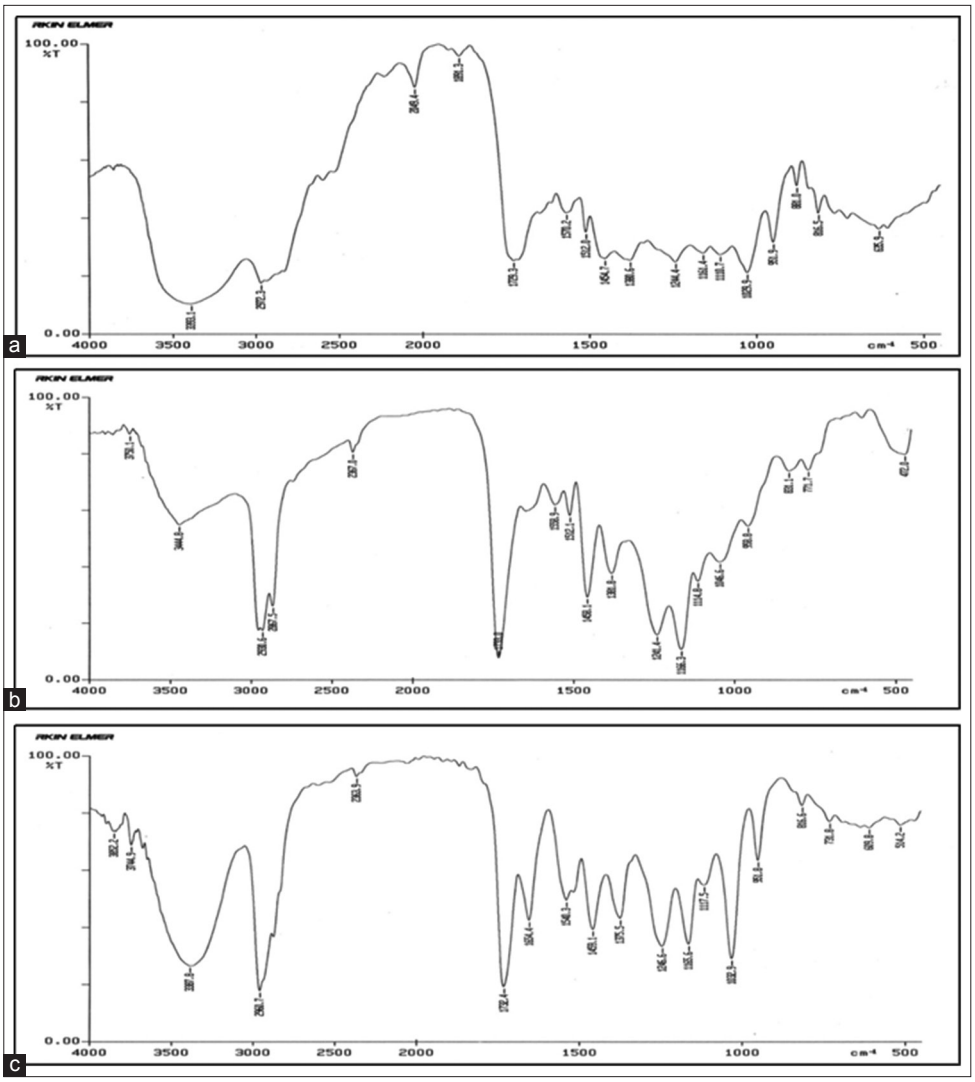

Figure 2: Attenuated total reflection spectra: (a) Duro-Tak 387-2051 and metoprolol succinate, (b) Duro-Tak 387-2052 and metoprolol succinate, (c) Duro-Tak 87-2677 and metoprolol succinate

Table 3: Physico-chemical characteristics of transdermal patches of metoprolol succinate

F.C.	Weight variation* (mg)	Thickness** (mm)	Drug content** (mg)
F_1	45.6 (±4.45)	0.231 (±0.0138)	3.62 (±0.020)
F_2	53.2 (±4.324)	0.232 (±0.0130)	3.62 (±0.034)
F_3	52.8 (±3.633)	0.238 (±0.0103)	3.78 (±0.036)
F_4	46 (±4.301)	0.261 (±0.0138)	3.22 (±0.026)
F_5	50.8 (±3.347)	0.237 (±0.0097)	2.055 (±0.050)
F_6	63.6 (±3.578)	0.31 (±0.0154)	2.400 (±0.043)
F_7	46.8 (±4.868)	0.236 (±0.0102)	2.47 (±0.026)

*Indicates values are average of five observations, **Indicates values are average of three observations and figures inside the parenthesis are standard deviation (±sd) values

was found in all formulations. The result of the drug content varies between 2.055 ± 0.050 mg and 3.62 ± 0.026 mg. It was considered that the drug is dispersed uniformly throughout the patch. The cumulative percent permeated, in *in vitro* permeation studies were calculated on the basis of drug content in the respective patch.

Evaluation of adhesive properties of patches

Pressure-sensitive adhesives adhere to the skin surface with no more force than applied finger-pressure, have a strong holding force, and are tacky in nature. Tackiness is taken into consideration when these adhesives are used for the drug matrix or other transdermal patches to adhere onto the skin surface.[14] With a little pressure, a liquid-like flow in the adhesive wets the skin surface and forms a strong bond to the skin. On removal of pressure, the adhesive layer remains adhered to the skin because of its visco-elastic characteristics. A good transdermal pressure-sensitive adhesive should be removed from the skin surface without leaving a residue. Tackiness is the ability of a polymer to adhere to the substance with low contact pressure. This measurement is

used to quantify or realize the sticky feel of the material. In this study, thumb tack tests of various formulations were performed and the degree of tackiness was determined. The results were listed in Table 4.

The Duro-Tak polymeric matrices had noticeable levels of tackiness. Out of the 7 types of polymeric matrices tested, six were very sticky in nature and one had insufficient tackiness to apply onto the skin. Only three of the formulations: Duro-Tak 387-2051 and Duro-Tak 387-2052 at 2.5-5% w/v drug level had acceptable tackiness. The patches from these formulations were easily removable, did not leave residue on the skin's surface, and did not inflict pain during removal. Out of these three varieties, Duro-Tak 387-2051 had the greatest degree of acceptability with regard to the adherence capacity and ease of removal. This composition was selected for further studies.

In vitro permeation studies

In vitro skin-permeation study is predictive of the *in vivo* skin-permeation performance of a drug. A permeation study was conducted across abdominal rat skin using phosphate buffer as an *in vitro* study fluid in the receptor compartments of Franz diffusion cells at 38 ± 0.5°C. True absorbance of the drug was measured by deducing the absorbance of the control sample from the absorbance of the test sample.[15] The result of *in vitro* drug permeation from different formulations were shown in Table 5.

In vitro skin permeation of metoprolol succinate from Duro-Tak 387-2051, Duro-Tak 387-2052, and Duro-Tak 87-2677 and combination of Duro-Tak 387-2051 and Duro-Tak 387-2052 [(50:50 (F_3) and 80:20(F_4)] polymeric transdermal matrix patches was conducted in a Franz diffusion cell through rat abdomen skin. Phosphate buffer (pH 6.0) was taken as a receptor media. The cumulative amount of drug release from various formulations ranged from 6 to 12 h. The permeation of the drug from formulation F_1 was very controlled, and gradual enhancement of the drug permeation through the skin was noticed. This may be attributed to the fact that in the first few hours, drug permeation was more dependent on the drug concentration at the skin surface and the initial bursting effect provided the sink condition. After the 8th h, the skin permeation of the drug eventually slowed down because of the slow release of drug from the patches to the skin's surface. From formulation F_2, in the beginning only 19.39% of the drug was released but burst release of drug was observed after 2 h and the entire drug was released at the end of 6th h.

The permeation of the drug from formulation F_3 (50:50, Duro-Tak 387-2051 and Duro-Tak 387-2052) was almost same as that of formulation F_1 with 91% of drug was released in 8 h. Changing the composition of polymeric matrices (80:20, Duro-Tak 387-2051 and Duro-Tak 387-2052) resulted in significant decrease ($P < 0.05$) in the amount of drug released in the 1st h compared to formulation F_1 with 26.14% of drug was released compared to 38.72%. This could be due to the increase in hydrophobicity of the polymeric matrix. Decreasing the concentration of drug resulted in decreased

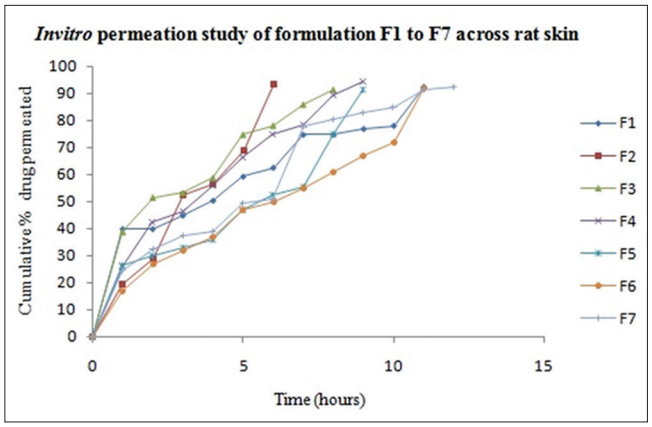

Figure 3: Plot of cumulative percent drug permeated versus time across rat skin for formulations F_1-F_7

Table 4: Degree of tackiness of the experimental patches

Formulation code	Degree of tackiness		
	Very tacky	Acceptable	Less tacky
F_1		+++	
F_2		++	
F_3	+++		
F_4	+++		
F_5		+++	
F_6		++	
F_7			++

+ Indicates lowest corresponding property, ++Indicates medium corresponding property, +++indicates highest corresponding property

Table 5: *In vitro* permeation study of formulations F_1-F_7 on rat skin

Time (h)	Cumulative % drug permeated						
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
1	39.83	19.39	38.72	26.14	26.37	16.75	24.37
2	39.83	28.78	51.43	42.29	30.26	26.75	32.46
3	44.8	52.54	53.09	46.64	33.18	31.75	37.32
4	50.33	56.4	58.61	55.96	36.1	36.75	38.94
5	59.17	69.11	74.64	66.52	46.81	46.75	49.47
6	62.48	93.42	77.95	75.21	52.65	50.08	51.09
7	74.64		85.69	78.32	55.57	55.08	77.81
8	74.64		91.21	89.5	75.03	60.91	80.24
9	76.85			94.47	91.58	66.75	82.67
10	77.95					71.75	85.1
11	92.32					91.75	91.57
12							92.38

permeation of drug from polymer matrices as evidenced from formulation F_5 and F_6. Formulation F_7 was made up of Duro-Tak 87-2677, although, released the drug very slowly but due to poor tackiness, this formulation was not further explored.

There was noticeable and slow, but steady, flux of drug during permeation. The permeability coefficient, P from various formulations ranged from 0.19 to 0.51/h.

The combined data obtained from *in vitro* permeation study was shown graphically according to various modes of data treatment [Figure 3].

Drug release kinetics

The data from the *in vitro* study were fitted to various kinetic models to determine the kinetics of drug release. The main models are zero order, first order, Higuchi equations to understand the drug release from the transdermal patch. The coefficient of regression and release rate constant values for zero, first and Higuchi models were computed and are listed in Table 6.

From the correlation coefficient values, it was found that the permeation followed zero order kinetics. Furthermore, lower variation was obtained for zero order release rate constant as compared with first order release rate constants indicating a zero order release pattern from the formulations. Higuchi equation explains the matrix diffusion mechanism of drug permeation from the transdermal patches.

Effect of penetration enhancer

From the results obtained in the *in vitro* experiments, F_1 has selected for the further studies. The optimization was therefore effected by casting the patch at various drug concentrations viz., 1%, 2%, 3% and 4% w/v and using permeation enhancer (*l*-menthol). Total seven formulations were prepared as shown in Table 2.

Formulations containing Duro-Tak 387-2051 were contains 1%, 2%, 3% and 4% w/v Metoprolol succinate. They are designated as F_8, F_9, F_{10} and F_{11}. Formulations containing Duro-Tak 387-2051 were contains 2%, 4%, 6% w/v permeation enhancer (*l*-menthol). They are designated as F_{12}, F_{13}, and F_{14}. The patches were then evaluated for various physico-chemical tests such as weight variation, thickness uniformity, drug content uniformity, and i*n vitro* permeation study.[12]

The results of all the physico-chemical characteristics are summarized in Table 7. The results showed that the physico-chemical characteristics of the optimized batches were satisfactory with respect to weight variation, thickness uniformity and drug content uniformity.

The fabricated transdermal patches were subjected to *in vitro* permeation study across excised rat skin using Franz diffusion cell. The results of *in vitro* drug permeation from different formulations are depicted in Table 8.

From the results obtained, it was observed that as the concentration of drug was increased rate of permeation

Table 6: Release kinetic models

F.C.	Zero order	Higuchi equation	First order	Peppas equation	
	R^2	R^2	R^2	*n*	R^2
F_1	0.9620	0.9358	0.9567	0.3737	0.8973
F_2	0.9667	0.9419	0.9424	0.8642	0.9698
F_3	0.9754	0.9616	0.9551	0.4116	0.9510
F_4	0.9856	0.9888	0.9187	0.5748	0.9905
F_5	0.9074	0.825	0.9759	0.5360	0.8382
F_6	0.9718	0.9419	0.9389	0.6560	0.9806
F_7	0.9456	0.9346	0.9265	0.5935	0.9347

Table 7: Physico-chemical characteristics of transdermal patches of metoprolol succinate

F.C.	Weight variation* (mg)	Thickness** (mm)	Drug content** (mg)
F_8	48 (±3.536)	0.223 (±0.0182)	0.55 (±0.041)
F_9	49.2 (±3.194)	0.245 (±0.0136)	1.08 (±0.035)
F_{10}	51.8 (±3.899)	0.256 (±0.0114)	1.49 (±0.026)
F_{11}	51.4 (±2.966)	0.252 (±0.0075)	1.98 (±0.031)
F_{12}	38 (±2.345)	0.232 (±0.0083)	1.86 (±0.040)
F_{13}	43 (±2.550)	0.244 (±0.0114)	1.86 (±0.033)
F_{14}	50.6 (±1.817)	0.247 (±0.0067)	2.45 (±0.022)

*Indicates values are average of five observations, **indicates values are average of three observations and figures inside the parenthesis are standard deviation (±sd) values

Table 8: *In vitro* permeation study of formulations F_8-F_{14} on rat skin

Time (h)	Cumulative % drug permeated						
	F_8	F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}
1	25.58	22.40	35.03	36.46	20.53	24.83	34.36
2	33.09	46.48	36.37	42.52	35.59	32.36	45.79
3	53.09	63.14	48.45	50.60	45.26	43.11	55.59
4	70.72	77.03	56.51	61.11	59.24	56.02	61.3
5	94.54	89.07	57.85	67.77	68.92	64.62	70.28
6		90.07	82.01	71.81	79.67	81.82	77.95
7		95.37	82.01	75.85	82.90	93.65	87.43
8			94.76	87.97	89.35	95.81	94.69
9				96.21	95.21		
10							

also significantly ($P < 0.05$ F_8 compared to F_9, F_{10} and F_{11}) increased in the 1st h. Thereafter, the rate of permeation again suddenly increased in the case of formulation F_8, F_9 and F_{10} and then slow down but overall there was no significant difference ($P < 0.05$, F_8 compared to F_9, F_{10}, F_{11}) in the rate of permeation between formulations F_8-F_{11}.

The addition of *l*-menthol at 6% w/v level to the transdermal patch formulation significantly ($P < 0.05$ F_{14} compared to F_1) increased the amount of drug permeated. Whereas, at 2 % and 4 % w/v level there was no significant ($P < 0.05$) difference in amount of drug permeated per unit time. However, it was interesting to note that on addition of 2% and 4% w/v *l*-menthol resulted in significantly ($P < 0.05$ F_{12} and F_{13} compared to F_1) decreased permeation of drug in the 1st h.

The combined data obtained in *in vitro* permeation study is shown graphically according to various modes of data treatment [Figure 4].

Statistical kinetics

The data from the *in vitro* study were fitted to various kinetic models to determine the kinetics of drug release. The main models are zero order, first order, Higuchi equations to understand the drug release from the transdermal patch. The coefficient of regression and release rate constant values for zero, first and Higuchi models were computed and the listed in Table 9.

The results of the curve fitting into various mathematical kinetics models indicate the *in vitro* Metoprolol Succinate permeation behavior of these transdermal patches. When respective correlation coefficients were compared, it was found that *in vitro* metoprolol Succinate permeation followed the zero-order (R^2 = 0.955-0.998). The values of the diffusional exponent (n) determined from *in vitro* metoprolol Succinate permeation from all these pressure-sensitive adhesive-based transdermal patches ranged between 0.685 and 0.948 [Table 9] following anamolous transport which refers to the controlled release of drug by the combination of both diffusion and erosion of the matrix.[16]

Skin irritation studies

The skin irritation test of the metoprolol succinate transdermal patch F1 (optimized patch) after application onto the skin of healthy rats was examined up to 24 h for flushing of skin (redness), papules, wheals, erythema and edema, if any. Any significant development of flushing of skin (redness), papules, wheals, erythema, and edema on the surface of rat skin was not found. The results of the skin irritation study were depicted in Figure 5 and Table 10. These results indicated the safety and acceptability of these transdermal patches without any sign of skin irritation.[14,17]

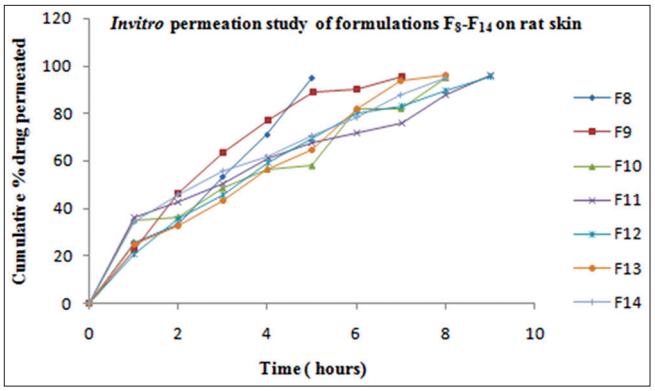

Figure 4: Plot of cumulative percent drug permeated versus time across rat skin for formulations F_8-F_{14}

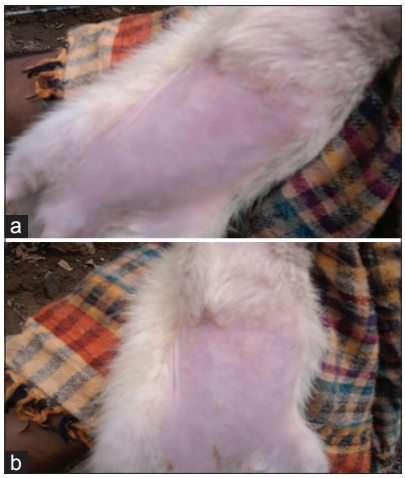

Figure 5: Skin irritation studies. (a) Rat skin before application of patch, (b) rat skin after application of patch

Table 9: Release kinetic models of patch formulations

F.C.	Zero order	Higuchi equation	First order	Peppas equation	
	R^2	R^2	R^2	n	R^2
F_8	0.9756	0.9300	0.9906	0.8184	0.9431
F_9	0.9614	0.9190	0.7963	0.7442	0.9619
F_{10}	0.9556	0.9125	0.9631	0.5054	0.8951
F_{11}	0.9887	0.9708	0.9698	0.4453	0.9655
F_{12}	0.9985	0.9642	0.8725	0.7054	0.9938
F_{13}	0.9867	0.9647	0.9649	0.7	0.9720
F_{14}	0.9961	0.9882	0.961	0.4831	0.9898

CONCLUSION

PSA Duro-Tak 387- 2051, Duro-Tak 387- 2052, Duro-Tak 87- 2677 and combination of Duro-Tak 387- 2051 and Duro-Tak 387- 2052 in ratio of 50:50 and 80:20 were used to develop drug-in-adhesive transdermal patch systems of metoprolol succinate. These extremely hydrophobic PSAs showed sufficient promise in controlling the release

Table 10: Skin irritation study

Time in days	F_1		
	F	P	E
1	–ve	–ve	–ve
2	–ve	–ve	–ve
3	–ve	–ve	–ve
4	–ve	–ve	–ve
5	–ve	–ve	–ve
6	–ve	–ve	–ve
7	–ve	–ve	–ve

–ve: No allergic manifestation observed, F: Flushing of skin (redness), P: Papules and wheals, E: Erythema and oedema

of extremely hydrophilic drug when used alone or in combination with other adhesives. These PSAs, with the exception of Duro-Tak 87-2677, exhibited favorable physicochemical properties for the development of the formulation. Some drug excipient interactions between drug and PSAs were also noticed.

In conclusion, the present data confirm the feasibility of PSAs, Duro-Tak 387- 2051, Duro-Tak 387-2052 and their combination in the development of transdermal patch system of metoprolol succinate. However, further studies (*in vivo*) are required to monitor the drug level in the blood after the application of patch on the skin.

REFERENCES

1. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, *et al*. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): Summary. BMJ 2004;328:634-40.
2. Rastogi V, Yadav P. Transdermal drug delivery system: An overview. Asian J Pharm 2012;6:161-70.
3. Rastogi V, Yadav P, Upadhyaya P. Brief view on antihypertensive drug delivery through transdermal patches. Int J Pharm Sci Res 2012;3:1955-70.
4. Shingade GM, Aamer Q, Sabale PM, Grampurohit ND, Gadhave MV, Jadhav SL, *et al*. Review on: Recent trend on transdermal drug delivery system. J Drug Deliv Ther 2012;2:66-75.
5. Mohamed A, Yasmin S, Asgar A. Matrix type transdermal drug delivery systems of metoprolol tartrate: *In vitro* characterization. Acta Pharm 2003;53:119-25.
6. Murthy TE, Mallikarjuna RP, Murali K. Design and development of piroxicam transdermal films. Pharmacol Rev 2004;56:145-7.
7. Ghosh TK, Adir J, Xiang S, Onyilofur S. Transdermal delivery of metoprolol II: *In vitro* skin permeation and bioavailability in hairless rats. J Pharm Sci 1995;84:158-60.
8. Chein YW. Transdermal Drug Delivery Systems and Delivery Systems. 2nd ed. New York: Marcel Dekker, Inc.; 1992. p. 301.
9. 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.
10. 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.
11. Bijaya G, Harivardhan RL, Raghvendra VK, Jasmina K. Comparison of skin permeability of drugs in mice and human cadaver skin. Indian J Exp Biol 2000;38:42-5.
12. Kulkarni R, Doddayya H, Marihal SC, Patil CC, Habbu PV. Comparative evaluation of polymeric films for transdermal application. East Pharm 2000;93:109-11.
13. 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.
14. Sharma N, Agrawal G, Rana A, Alibhat Z, Kumar D. A review: Transdermal drug delivery system: A tool for novel drug delivery system. Int J Drug Dev Res 2011;3:70-84.
15. Sintov AC, Shapiro L. New microemulsion vehicle facilitates percutaneous penetration *in vitro* and cutaneous drug bioavailability *in vivo*. J Control Release 2004;95:173-83.
16. Rastogi V, Yadav P, Kumar A, Porwal M, Mishra AK, Verma N, *et al*. Enhancement of skin permeation of glibenclamide from ethyl cellulose - polyvinyl pyrrolidone based transdermal patches using olive oil and mustard oil as penetration enchancer: *In vitro*, *ex vivo* and *in vivo* evaluation. Drug Deliv Lett 2015;5:109-21.
17. Singh MC, Naik AS, Sawant SD. Transdermal drug delivery systems with major emphasis on transdermal patches: A review. J Pharm Res 2010;3:2537-43.

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