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Original Article

FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF METOPROLOL TARTRATE USING PERMEATION ENHANCERS OF NATURAL AND SYNTHETIC ORIGIN

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ABSTRACT

Objective: Oral metoprolol tartrate has a short elimination half-life (2-3h) and low bioavailability undergoes extensive first-pass metabolism and frequent dosing. The aim of the present investigation was to formulate, develop and evaluate metoprolol tartrate transdermal patches using various synthetic and natural penetration enhancers.

Methods: Enhancers used were eugenol, limonene, basil oil, urea and SLS (sodium lauryl sulphate). Polymer used was chitosan and PEG 400 used as a plasticizer. Transdermal Films were prepared by using solvent casting method. FTIR and DSC were studied to assess any interaction between the drug and polymers. Films were evaluated for Physico-chemical Characteristics like thickness, weight variation, folding endurance, moisture loss, moisture absorption and drug content. *In vitro* skin permeation studies were performed using Keshary chien cell For 24 h across rat skin.

Results: Chitosan was found to be a suitable polymer for matrix formation. 3.5% w/w was used to optimize to formulate transdermal patches. 1.5% of total solution v/v lactic acid was used for dissolution of chitosan. 2.5%v/v of total solution PEG 400 was used to provide plasticity and smoothness to the patches. From the evaluation of patches formulation, F10 containing Basil oil as penetration enhancer in the concentration of 1.5% v/v was found to be best among all batches because of its consistent release rate For 24 h and extent of drug release was 85.20%. It can be concluded that naturally occurring volatile oils i.e., terpenes appear acceptable permeation enhancer and shows the best permeation across skin as indicated by high percutaneous enhancement ability.

Conclusion: The developed transdermal patches are stable, non-irritating, and had increased efficacy of metoprolol and therefore had a good potential for hypertension treatment.

Keywords: Transdermal drug delivery system, Chitosan, PEG 400, Penetration Enhancers, Basil oil, Limonene, Eugenol, Urea, Sodium lauryl sulphate

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INTRODUCTION

Transdermal patches are pharmaceutical preparation, which delivers drugs directly into the systemic circulation after passing through the skin barrier [1]. It is convenient for the delivery of drugs having short biological half-life.

Transdermal patches are easy to remove and apply. This approach of drug delivery is more pertinent in case of chronic disorders such as hypertension, which require long term dosing to maintain therapeutic drug concentration [2].

Transdermal delivery of therapeutic agents has been used successfully for several decades. In 1981, the first transdermal patch; Transderm Scop was developed by Alza Followed by Transderm Nitro [3]. Many other patches were introduced as motion sickness (hyoscine), cardiovascular disease (clonidine and nitroglycerin), Chronic pain (fentanyl), smoking cessation (nicotine), hormone replacement (levonorgestrel) [4].

Transdermal delivery of cardiovascular drugs offer several advantages as avoiding hepatic first-pass metabolism, maintaining constant blood level for a longer period resulting in a reduction of dosing frequency, improved bioavailability, decreased gastrointestinal irritation and improved patient compliance [5].

More than 35 TDDS products have now been approved for sale in US and approximately 16 active ingredients are approved for use in TDDS products globally. Global burden of disease study reported that there were 5.2 million deaths from cardiovascular diseases in economically developed countries and 9.1 million deaths from the same cause in developing countries. Hypertension is directly responsible for 57% of all stroke deaths in India [6].

In the present study, we aimed to deliver cardioselective beta-blocker, metoprolol tartrate used for the treatment of mild and moderate hypertension and also for long term management of angina pectoris. Metoprolol tartrate has a bioavailability of 40-50% in oral dosage forms and the half-life is 3 to 7 h. This makes frequent dosing necessary to maintain therapeutic blood levels of the drug for long term treatment. Therefore, metoprolol tartrate is ideal drug candidate for transdermal drug delivery [7].

In the present investigation, the effort has been made to enhance the bioavailability of metoprolol tartrate for the treatment of hypertension as well as angina pectoris by using various natural permeation enhancers such as basil oil, limonene, eugenol, urea and sodium lauryl sulphate. The previous studies had utilized synthetic agents but in this study natural permeation enhancers are also being explored for the bioavailability enhancement of metoprolol tartrate. Oral metoprolol tartrate has a short elimination half-life (2-3 h), and low bioavailability undergoes extensive first-pass metabolism and frequent dosing. The aim of the present investigation was to formulate, develop and evaluate metoprolol tartrate transdermal patches using various synthetic and natural penetration enhancers.

MATERIALS AND METHODS

Materials

Metoprolol tartrate was a gift sample from Ctx life science, Gujarat, India. Eugenol, limonene, sodium lauryl sulphate (sls), urea and basil oil from Central drug house. Chitosan has been received from Hi media. Other chemical and reagents were of analytical grades.

Animals

Wistar albino rats 150–200 g, and immature female wistar albino rats of 21–23 d old (40–60 g) were used in this study. They were procured from animal house, Amity Institute of Pharmacy, Amity University, Noida, UP. The animals were acclimatized for ten days under laboratory conditions. They were housed in polypropylene

cages and maintained at 27 °C±2 °C, relative humidity 65±10% under a 12-hour light/dark cycle. The animals were fed with rodent pellet diet and water ad libitum the protocol was approved by the Institutional Animal Ethics Committee (IAEC) and carried out in accordance with the Indian National Science Academy Guidelines for the use and care of animals. Animal skin was obtained from the animal house of Amity Institute of Pharmacy after CPCEA approval no. CPCSEA/AIP/2014/002.

Each experimental group had a separate set of animals and care was taken to ensure that animals used for one response were not employed elsewhere. Animals were habituated to laboratory conditions for 48 h prior to an experimental protocol which minimizes any nonspecific stress.

Methods

Determination of melting point and solubility studies

The melting point of the drug was determined by using Thieles tube method. The solubility of drug was determined after shaking the saturated solution of drug for 2 h at 25 ° C in water, chloroform, ethanol, acetone, and ether respectively.

FTIR analysis

FTIR spectra of pure drug and optimized formulation were obtained by FTIR spectrophotometer.

Differential scanning calorimetry

The DSC of the pure drug, polymer and physical mixture of drug-polymer at 1:1 was carried out.

UV analysis

The aqueous solutions of the pure drug and the patches containing metoprolol tartrate were filtered through whatmann filter paper and scanned for UV absorption between 200 and 400 nm [8].

Development of transdermal films

Solvent Casting method was used for the formulation of polymer matrix. The chitosan was weighed accurately as 3.5% w/w total solution. Chitosan was transferred to 20 ml beaker and lactic acid 1.5% v/v of polymer was used to solubilize the chitosan. Beaker is kept on magnetic stirrer at a moderate speed to obtain a homogeneous mixture. PEG 400 2.5% was used as plasticizer and transferred to beaker containing chitosan. Metoprolol tartrate and enhancers were added to the solution. Solution was made up to 18 ml with solvent and kept for 24 h to obtain homogeneous mixture of polymer, plasticizer and drug. After 24 h solution was transferred to teflon mould and was kept in oven at 40 °C overnight. After 24 h patches were scratched from mould. The patches thus formed were evaluated further for various parameters. The films were then packed in aluminum foil and stored in a desiccator until use at RH 40% and temperature 20 °C [9].

Table 1: Composition of metoprolol transdermal drug delivery systems

Formulation code	Drug	Polymer	Solvent	Plasticizer	Penetration enhancer
	Metoprolol tartrate (mg)	Chitosan (mg)	Lactic acid (ml)	PEG 400 (ml)	
F1	360	630	0.27	0.45	_
F2	360	630	0.27	0.45	Limonene (0.5% v/v)
F3	360	630	0.27	0.45	Limonene (1% v/v)
F4	360	630	0.27	0.45	Limonene (1.5% v/v)
F5	360	630	0.27	0.45	Eugenol (0.2%v/v)
F6	360	630	0.27	0.45	Eugenol (0.5% v/v)
F7	360	630	0.27	0.45	Eugenol (1%v/v)
F8	360	630	0.27	0.45	Basil oil (0.5% v/v)
F9	360	630	0.27	0.45	Basil oil (1% v/v)
F10	360	630	0.27	0.45	Basil oil (1.5% v/v)
F11	360	630	0.27	0.45	Urea (1% w/w)
F12	360	630	0.27	0.45	Urea (2% w/w)
F13	360	630	0.27	0.45	Urea (3% w/w)
F14	360	630	0.27	0.45	SLS (0.5% w/w)
F15	360	630	0.27	0.45	SLS (0.75% w/w)
F16	360	630	0.27	0.45	SLS(1%w/w)

Physico-chemical evaluation of prepared transdermal patches

Weight variation

Weight variation was determined by individually weighing randomly selected patches with the help of electronic balance. The average weight of a film and its standard deviation was calculated [10].

Folding endurance

The folding endurance would be defined as the number of folds required to break any polymeric Film. The folds on the patch have to be made at the same point, till it breaks. It was measured manually by repeatedly folding the patch at the same place till it broke. The number of folds a patch can sustain will dictate its folding endurance [11].

Percentage of moisture loss

The film was weighed accurately and placed in a desiccator containing 100 ml of saturated solution of calcium chloride (79.50% RH). After 3 d, the film was taken out and weighed, the percentage of moisture uptake was determined from the following formula

Percentage of moisture loss = (X-Y/Y) × 100

Where, X = initial weight, Y = final weight ..... [12]

Percentage of moisture content

The prepared patches are to be weighed individually and to be kept in desiccators containing fused potassium chloride (90%) at room temperature for 24 h. After 24 h the patches are to be reweighed and the percentage moisture content was determined from the following formula

Percentage of moisture content = (X-Y/Y) × 100

Where, X = initial weight, Y = final weight ..... [13]

Drug content

The patches (1.6 cm^2) were cut and added to the beaker containing 100 ml of phosphate buffer of pH 7.4. The medium was stirred with a magnetic bead. The contents were filtered using whatmann filter and the filtrate was examined for the drug content against the solution consisting of placebo patches spectrophotometrically at the wavelengths at which calibration curve has been plotted. The experiment was repeated to validate [14].

Thickness

The thickness of transdermal patches was measured at three different places using a micrometer and the average value were calculated.

Flatness

Longitudinal strips were cut out from the prepared medicated patch, the lengths of each strip were measured and then variation in the lengths due to the non-uniformity in flatness was measured. Flatness was calculated by measuring the construction of strips and a zero percent constriction is equal to a hundred percent flatness.

Percentage of constriction = $(I_1-I_2)\ I_2 \times 100$

Where, I_1 = initial length of each strip and

I_2 = final length of each strip ..... [15]

***In vitro* skin permeation studies**

An *in vitro* permeation study was carried out by using keshary-chien diffusion cell. Hair from the abdominal region was removed carefully; the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in phosphate buffer pH 7.4 before starting the experiment. Diffusion cell was filled with a diffusion medium and placed on a magnetic stirrer with a small magnetic bead for uniform distribution of the diffusing. The temperature of the cell was maintained at 37±0.5 °C using a thermostatically controlled heater. The isolated rat skin piece was mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. A sample volume of the definite volume was removed from the receptor compartment at regular intervals and an equal volume of fresh medium is to be replaced. Samples are analyzed spectrophotometrically at wavelength 275 nm [16].

***In vitro* drug release studies**

USP apparatus V paddle over disc method was used for assessment of the release of the drug from the prepared patches. A patch of known thickness was cut into definite shape, weighed and fixed over a glass plate with an adhesive. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples were withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer.

Percentage of drug release was calculated using the following Formula:

Percentage drug release= Da/Dt ×100

Where Da= amount of drug released

Dt= amount of drug in the patch ..... [17]

Preliminary stability study of the optimized polymer matrix

The fabricated patches were properly packed in aluminum foil and kept stability studies at the following temperature and relative humidity (RH) for one month at 25 C and 65% RH [18].

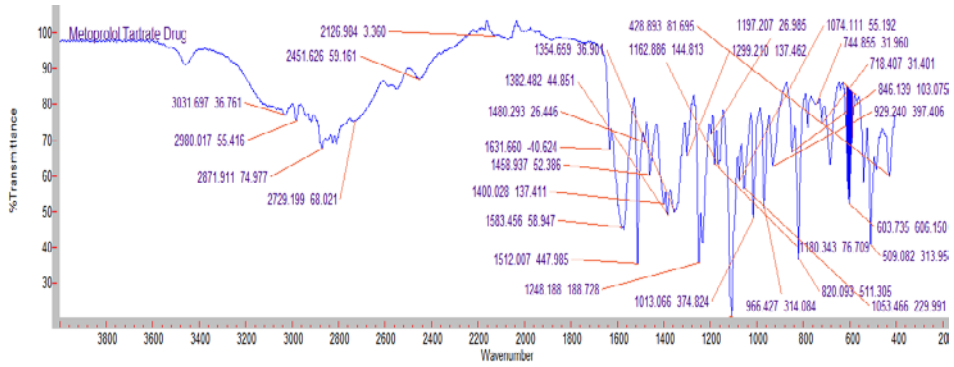

Fig. 2: FTIR of metoprolol tartrate

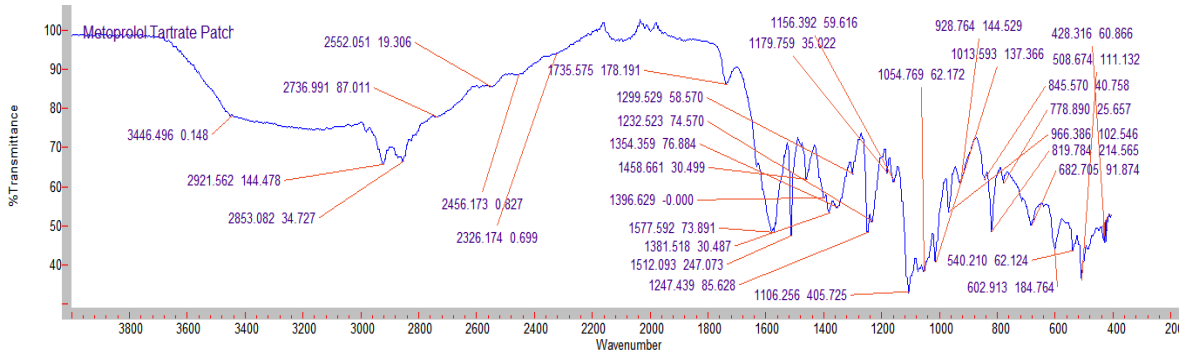

Fig. 3: FTIR of transdermal patches

RESULTS AND DISCUSSION

Investigation of physicochemical compatibility of drug and polymer

The physicochemical compatibility between the drugs and polymers used in the patches was studied by using differential scanning calorimetry (DSC). The sample was heated between 30 °C and 300 °C at the rate of 10 °C/min in an atmosphere of nitrogen (20 ml/min). The thermograms obtained for the drug, polymers, physical mixture of drugs with polymers and formulation (patch) were compared. The pure metoprolol tartrate peak was obtained at 125.8 °C. The DSC results suggest that the drug and polymers are compatible as found in fig. 1.

Drug-polymer interaction studies

FTIR spectroscopy

The drug was characterized by FTIR spectroscopy. The spectrum was recorded using FTIR Spectrophotometer (Agilent). The scanning range was 4000 to 600 cm-1. The spectrum of Metoprolol tartrate is shown in fig. 2.

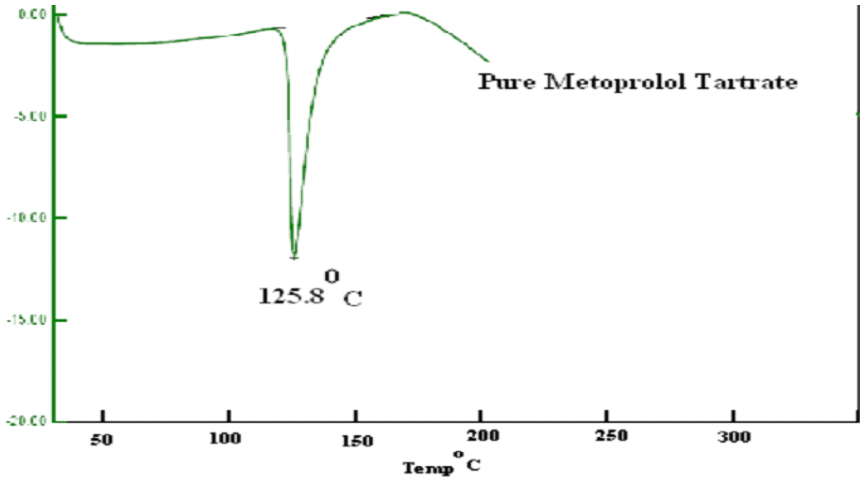

Fig. 1: DSC of metoprolol tartrate

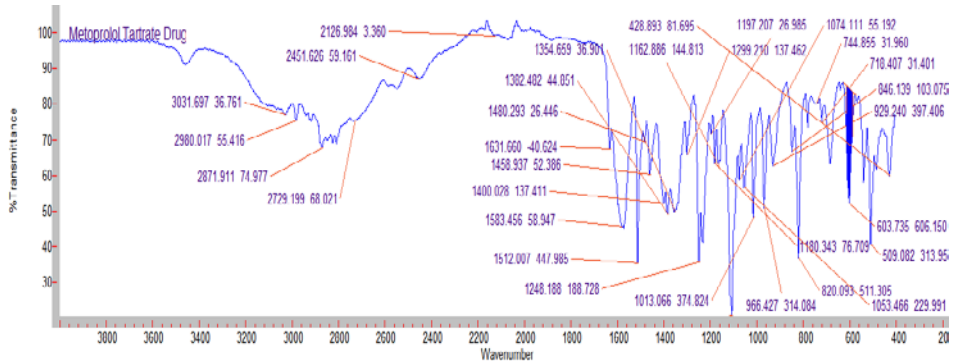

Fig. 2: FTIR of metoprolol tartrate

FTIR spectra of pure Metoprolol Tartrate, chitosan, PEG 400, lactic acid and physical mixtures of these excipients with the drug were recorded on Agilent FTIR spectrophotometer. The instrument was operated under dry air purge and the scans were collected with the resolution of 4 cm-1 over the region 4000-400 cm-1. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks and appearance of new peaks due to polymer interaction, shown in fig. 3.

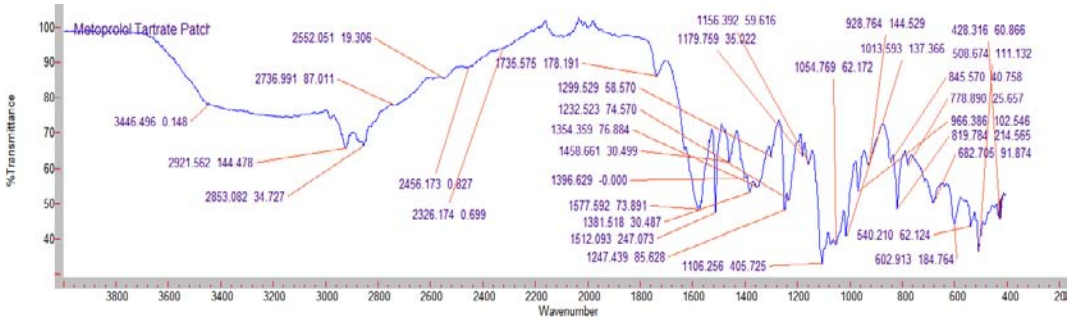

Fig. 3: FTIR of transdermal patches

Physicochemical characterization of patches

Chitosan 3.5% w/w in combination with 1.5% v/v lactic acid and PEG 400 along with varying concentration of penetration enhancers (natural as well as synthetic) were used for the formulation of transdermal films in the ratios as depicted in table 1.

The results of the physicochemical characterization of the patches are shown in table 2. The weights ranged between 426 mg and 526 mg, which indicates that different batches' patch weights were relatively similar. Good uniformity of drug content among the batches was observed with all formulations and ranged from 78.09% to 94.25%. The results indicate that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability. The flatness study showed that all the formulations had the same strip length before and after their cuts, indicating 100% flatness as depicted in table 2.

Thus, no amount of constriction was observed; all patches had a smooth, flat surface; and that smooth surface could be maintained when the patch was applied to the skin. Folding endurance test

results indicated that the patches would not break and would maintain their integrity with general skin folding when applied. The folding endurance was found to be best in the patches containing basil oil as penetration enhancers as depicted in table 2.

The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long term storage. The moisture uptake of the formulations was also low, which could protect the formulations from microbial contamination and reduce bulkiness.

The moisture loss varied with different penetration enhancers. It was found that batches containing basil oil as penetration enhancers were best in terms of moisture loss since they had minimum water loss. The moisture loss was lowest in the patches without penetration enhancers as depicted in table 2.

Table 2: Physicochemical properties of transdermal patches*

Formulation code	Folding endurance±SD	Weight variation(mg)±SD	Moisture loss (%)±SD	Moisture absorption (%)±SD	Drug content (%)±SD	Flatness (%)	Thickness (mm)±SD
F1	198±2.21	426±0.005	2.23±0.02	4.0±0.005	78.09±0.0432	100	0.53±0.007
F2	180±2.23	523±0.004	4.92±0.07	3.59±0.061	80.66±0.023	100	0.52±0.017
F3	189±2.20	521±0.002	3.62±0.03	5.1±0.025	88.12±0.029	100	0.53±0.010
F4	190±2.27	526±0.002	4.71±0.05	6.21±0.021	89.67±0.039	100	0.55±0.016
F5	188±2.36	524±0.003	2.94±0.06	4.18±2.21	80.18±0.051	100	0.53±0.015
F6	195±2.78	520±0.001	3.28±0.02	6.12±1.98	87.20±0.042	100	0.51±0.012
F7	191±3.21	522±0.001	5.23±0.04	8.49±1.99	90.32±0.051	100	0.55±0.015
F8	200±1.23	510±0.002	2.12±0.03	4.08±0.22	82.03±0.005	100	0.52±0.018
F9	193±1.45	498±0.003	3.72±0.01	3.07±0.12	91.53±0.023	100	0.55±0.016
F10	203±1.89	493±0.002	1.28±0.03	3.02±0.22	94.25±0.09	100	0.54±0.019
F11	172±2.22	499±0.004	2.52±0.05	4.2±0.006	89.20±0.028	100	0.53±0.013
F12	185±2.34	500±0.006	3.89±0.06	2.5±0.002	90.15±0.02	100	0.55±0.015
F13	187±3.21	497±0.002	4.50±0.02	3.23±0.005	89.25±0.024	100	0.56±0.012
F14	197±2.10	495±0.001	3.01±0.05	4.82±0.281	88.10±0.0432	100	0.52±0.016
F15	196±2.45	494±0.003	5.64±0.02	2.28±0.22	90.12±0.044	100	0.54±0.019
F16	192±2.98	496±0.003	4.93±0.03	3.69±0.226	86.99±0.042	100	0.55±0.011

*All values are expressed as mean±SD (n = 10).

Table 3: *In vitro* cumulative drug release of metoprolol transdermal drug delivery systems

S. No.	Formulation code	Cumulative percentage drug release
1	F1	58.03±1.90
2	F2	69.86±0.90
3	F3	72.5±1.99
4	F4	79.26±1.09
5	F5	69.12±1.23
6	F6	75±1.98
7	F7	80.12±1.54
8	F8	80.12±1.54
9	F9	75.5±1.90
10	F10	85.201±0.30
11	F11	60.96±1.19
12	F12	72.5±1.98
13	F13	75.22±1.67
14	F14	58.07±1.65
15	F15	65.521±1.23
16	F16	60.25±0.45

*All values are expressed as mean±SD (n = 10)

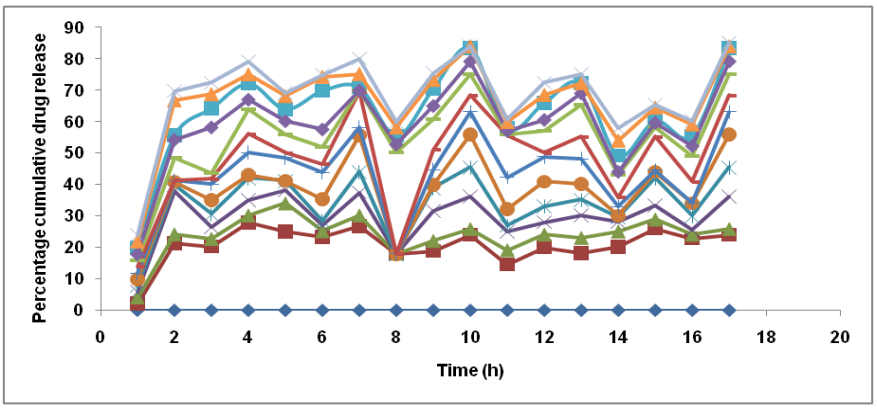

Fig. 4: *In vitro* skin permeation profile of metoprolol from transdermal patches, data are mean±SE (n=6)

In vitro skin permeation studies

The *in vitro* skin permeation studies were carried out using keshary chien cell for a period of 24 h. The patches were 15 cm^2 in area and were prepared by solvent casting method by using PEG 400 as a plasticizer. In order to know whether the patches would release drug in desired fashion *in vitro* permeation studies in Keshary chien cell was carried out. Along with that, diffusion studies were also evaluated in phosphate buffer pH7.4 [23-25] The *in vitro* permeation of various formulations were the *in vitro* release of formulations from F1 to F16 were found in the range of 58.03% to 80.20%, as depicted in table 3. From the evaluation of patches formulation, F10 containing basil oil as penetration enhancer in the concentration of 1.5% v/v was found to be best among all batches because of its consistent release rate for 24 h and extent of drug release was 85.20% as depicted in fig. 4 and table 3. The formulation F10 have achieved highest drug release as compared to other polymers.

CONCLUSION

The patches are containing basil oil as penetration enhancer were best in terms of physicochemical properties as well as drug release. The formulation F10 was found to be best among all batches because of its consistent release rate for 24 h, and extent of drug release was 85.20%. It can be concluded that naturally occurring volatile oils i.e., terpenes appear acceptable permeation enhancer and shows the best permeation across skin as indicated by high percutaneous enhancement ability.

The developed transdermal patches are stable, non-irritating and had increased efficacy of metoprolol and therefore had a good potential for hypertension treatment. However, pharmacodynamics and pharmacokinetic evaluation of these systems in human volunteers is necessary to confirm these findings.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors report no conflicts of interest

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