G. Saravanan et al. / Journal of Pharmacy Research 2014,8(2),167-173

Research Article
ISSN: 0974-6943

Available online through
http://jprsolutions.info

Formulation by 2^3 factorial design and evaluation of controlled release transdermal patches of metoprolol succinate

G. Saravanan*[1],Sarath Chandiran Irisappan [2],K.N. Jayaveera [3]

[1*]Assistant Professor, Dr. Samuel George Institute of Pharmaceutical Sciences, Markapur-523316, Andhra Pradesh, India
[2] Professor & Principal, Gokula Krishna College of Pharmacy, Sullurpet-524121, Nellore dist, Andhra Pradesh, India
[3] Prof & Head, Department of Chemistry, JNTU Anantapur, Anantapuram – 515 002, Andhra Pradesh, India.

Received on:21-11-2013; Revised on: 12-12-2013; Accepted on:10-01-2014

ABSTRACT

The aim of present investigation is the development and evaluation of Transdermal drug delivery system for Selective $ß_1$ receptor blocker of Metoprolol succinate. Optimization of formulations of matrix transdermal patches was carried out by 2^3 factorial design. Formulation of controlled release matrix transdermal patches of Metoprolol succinate was done by solvent casting method by using different polymers like HPMC K4M, PVP K30 and Eudragit RL100. Formulated matrix transdermal patches were evaluated for physiochemical parameters like thickness and weight, Flatness, Folding endurance, Mechanical strength, Percentage moisture absorption, Percentage moisture loss, Water vapor transmission rate and Drug content. Surface morphology was examined by Scanning electron microscopy. All prepared formulations indicated good physical stability. Skin irritation studies were performed through rat skin by Draize scoring method. In-vitro permeation studies of formulations were performed by using Franz diffusion cells. The satisfactory results were obtained in all prepared formulation and based on the results MP14 (HPMCK4M-71.25mg, PVP K30-4.75mg and Eudragit RL100-19mg) was the best one when compared to other. The in-vitro kinetics shows the zero order drug release followed by non-fickian diffusion mechanism.

Keywords: Metoprolol succinate, Factorial design, solvent casting method, Draize scoring method, In-vitro permeation studies, Franz diffusion cell.

1. INTRODUCTION

Transdermal drug delivery systems are topically applied medicated patches which deliver the drug(s) in to systemic circulation at a predetermined and controlled rate. A drug is kept in a relatively high dosage inside of a patch, which is allowed to stick to skin surface for a specified period. The drugs enter in to systemic circulation by diffusion mechanism. The high concentration of drug in the patch and low in the blood makes the drug to diffuse into the blood for an extended period of time and maintains constant drug concentration in the blood. This technique has many advantages than traditional methods. Compared to the oral route, transdermal drug delivery is devoid of GI absorption, enzymatic/pH associated deactivation and reduced pharmacological dosing due to the shortened metabolisation pathway compared to oral route. Transdermal therapy is multi-day therapy with a single application and the therapy can be terminated simply by removing the patch[1]. Metoprolol succinate is widely used in the treatment of hypertension, angina pectoris, and arrhythmias, due to its ß-selective adrenoceptor blocking property[2]. The drug is freely soluble in water and the half-life of Metoprolol succinate is about 3-4 h, and its oral bioavailability has been reported to be about 50%. By considering the above points the Metoprolol succinate might be a right and suitable candidate for the design of matrix transdermal patches.

***Corresponding author.**
G. Saravanan
Assistant Professor,
Dr. Samuel George Institute of Pharmaceutical Sciences,
Markapur-523316,
Andhra Pradesh, India.

2. MATERIALS & METHODS

Metoprolol succinate was obtained from Drugs india, Hyderabad as gift sample .Dibutyl phthalate, Hydroxy propyl methyl cellulose K4M were from Karnataka fine chem. Industries, Bangalore.Dicalcium phosphate and Lactose were purchased from Sd fine chemicals, Mumbai. Disodium hydrogen phosphate and Isopropyl alcohol were obtained from Qualigens fine chemicals, Mumbai. Eudragit RL100, Guargum and Magnesium stearate were from Rankem limited, Mumbai.

2.1. Preparation of controlled release transdermal patches of metoprolol succinate:

The controlled release matrix controlled transdermal patches of Metoprolol succinate were prepared by solvent casting technique, which is the method most widely, used by a good number of the researchers for the preparation of transdermal as well transbuccal patches/films. The composition is as shown in Table 1.

Table .1 Compositions of transdermal patches of Metoprolol succinate

Formulation code	HPMC K4M (mg)	PVP K30 (mg)	Eudragit RL100 (mg)
MP1	95	—	—
MP2	—	95	—
MP3	—	—	95
MP4	90.25	4.75	—
MP5	85.50	9.50	—
MP6	80.75	14.25	—
MP7	76.00	19.00	—
MP8	71.25	23.75	—
MP9	90.25	—	4.75
MP10	85.50	—	9.50
MP11	80.75	—	14.25
MP12	76.00	—	19.00
MP13	71.25	—	23.75
MP14	71.25	4.75	19.00
MP15	71.25	9.50	14.25
MP16	71.25	14.25	9.50
MP17	71.25	19.00	4.75

Drug loaded in each patch: 47.5 mg
Plasticizer: Dibutylphthalate (30%w/w)
Backing membrane: Aluminium foil

2.2.Optimization of formulations of matrix transdermal patches by 2^3 factorial designs

A two factor three level full factorial design was used for systemic study of combination of drug and polymers. The linear interactive model is shown in following equation.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2$$

Where Y is the dependent variable, b_0 is the arithmetic mean response and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor from its low to high values. The interaction term (X_1X_2) shows how the response values change when two factors are simultaneously changed.

A 2^3 factorial design was applied for the experiment where two variables (X_1, X_2) were the amount matrix forming polymer and diluents. The levels of drug and polymer initially adjusted at 1:2 (-1+1) ratio for individual polymers like HPMC K4M, PVP K30 and Eudragit RL100. Further the quantity of drug and controlled release matrix forming polymer adjusted in combination as like 1: (1.5:0.5) i.e., (-1:0:+1). By this way totally 17 formulations were prepared, using HPMC K4M, PVP K30 and Eudragit RL100 by solvent casting technique.

2.3. Formulation of controlled release matrix transdermal patches of Metoprolol succinate by solvent casting method

The controlled release matrix transdermal patches of Metoprolol succinate were prepared by solvent casting technique[3-6] employing 'O' shape ring placed on a glass surface as substrate by using different polymers like HPMC K4M, PVP K30 and Eudragit RL100.

The calculated quantities of polymers were dispersed in ethanol (70% v/v). An accurately weighed 47.5 mg Metoprolol succinate was incorporated in polymeric solutions after levigation with dibutylphthalate (30%w/w) which served the purpose of plasticizer as well as permeation enhancer. The solution was mixed occasionally to get semisolid consistency. Then the solution was subjected to sonication in a bath sonicator to remove the air bubbles Then this were casted on a glass surface employing 'O' shape ring having 4 cm in diameter is covered with funnel to controlling the evaporation of solvent and allowed to dry at room temperature over night. The dried patches were removed and covered with aluminum foil, which is used as a baking membrane. The Metoprolol succinate patches were stored in desiccators until further use.

2.4. Physiochemical evaluation of matrix transdermal patches of Metoprolol succinate

The prepared matrix transdermal patches of Metoprolol succinate was evaluated for physicochemical characteristics like thickness, weight, flatness, folding endurance, surface pH, percentage moisture absorption, percentage moisture loss, water vapor transmission rate and drug content as shown in Table 2. The procedures are as follows;

Thickness

The thickness of each patch was calculated by using a digital vernier caliper at six various positions of the patches and the average thickness were calculated[7].

Weight

Three different patches of same formulations were separately weighed by using digital balance and the mean of three patches were recorded[8].

Flatness

Three longitudinal strips were cut from each patch at different portion like centre, left and right side. The length of each strip was measured and kept for 2 h. The variation in length because of non uniformity in flatness if any was measured by determining percent constriction by using the formula[9]

Flatness = (L2 - L1) / L × 100

Where,

L1 is the initial length of each strip, L2 is the final length of each strip.

Folding endurance

Folding endurance test carried out by using three patches from each formulation and folded repetitively up to 300 times manually or till it broke at the same place. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance and the mean of three patches were recorded[10-12].

Percentage moisture absorption (PMA)

The physical stability of the transdermal patches at high humid conditions tested by the percent moisture absorption test. The weight of three 1 cm patches was weighed accurately immediately after cutout and then placed in desiccators containing saturated solution of aluminium chloride, keeping the RH at 79.5%. The films were removed after three days, weighed and percentage moisture absorption was calculated by the following formula[14];

Percentage moisture loss (PML)

The integrity of transdermal patches at dry condition is checked by percentage moisture loss test. The weight of three 1 cm patches was weighed accurately immsediately after cutout and then placed in desiccators containing fused anhydrous calcium chloride. The films were removed after three days, weighed and percentage moisture loss was calculated by the following formula[14].

Water vapor transmission rate (Q)

The vials of the same diameter were used as transmission cells for this study and cells were cleaned thoroughly and dried in a hot air oven. About 1 g of calcium chloride was taken in the cell and the polymeric transdermal patches measuring 1 cm^2 area were fixed over the edge with an adhesive. The initial weight was recorded, and then kept in a closed desiccators containing saturated solution of potassium chloride. The humidity in the desiccators was set up in between 80 – 90% RH. The cells were taken out and weighed after 18, 36, 54 and 72 h. From increase in weights the amount of water vapor transmitted and the rate at which water vapor transmitted (Q) were calculated by using the following formula[14,15].

$Q = WL/S$

Where,

Q -water vapor transmission rate, W -water vapor transmitted in mg, L – patch thickness in mm, S - exposed surface area in cm^2.

Drug content estimation

The patches of 1cm^2 were cutout in three equal parts and placed in a 100 ml phosphate buffer (pH6.8). The contents were subjected for stirring up to 24 h followed by filtration. The filtrate is suitably diluted and the absorbance was measured at 274 nm by using UV Spectro photometer[16,17]. The mean of three films was taken as drug content.

Scanning electron microscopy (SEM)

Scanning electron microscopy[18] has been used to determine particle size distribution, surface topography and texture and to examine the morphology of fractured or sectioned surface. The same generally used for generating three dimensional surface relief images derived from secondary electrons. The surface of transdermal patches having the proportions of drug and polymer under microscopical examination can give the information of morphology and porosity of the patch study.

Measurement of mechanical strength

The mechanical strength[19-21] of the matrix transdermal patches of Metoprolol succinate was measured by using specially designed apparatus consists of microprocessor force gauze attached with motor equipped with stand and cell. The patches containing no visual damage having 20 mm in diameter were cutout and placed between two clams at the distance of 3 cm. The two clamps are placed such a way that should not cause any damage to the patch while experiment under progress. The lower clamp was held at fixed position and the upper clamp is moving at a speed of 2 mm/sec till the patch was broke. Then the broken point followed by elongation was recorded.

Skin irritation studies through rat abdominal skin by Draize scoring method

The skin irritation studies were performed through rat abdominal skin for safer application of matrix controlled transdermal patches of Metoprolol succinate to humans for the therapeutic benefit. The skin irritation studies were carried out with male albino rats weighing between 125 to 132g. The selected rats were isolated under room temperature (25±1oC) with RH 60±5% and placed in cages of three each. The rats were cleaned by shaving without causing any peripheral damage to the skin. The rats were divided into 5 groups (n=3). The animals of group I (normal without any treatment), Group II, (control applied with adhesive tape USP). Transdermal patches were applied onto nude abdominal skin of rats of group III and IV (drug free and drug loaded) and group V (0.8% v/v aqueous solution of formalin) The formalin solution serves as standard irritant. The animals were applied with new patch, formalin solution each day for 7 days and finally the sites of application were graded according to a Draize scoring scale[22].

In-vitro drug permeation and kinetic studies

The in-vitro permeation study of fabricated transdermal patches of Metoprolol succinate was carried out by using excised rat abdominal skin using franz diffusion cell composed of preparation of rat abdominal skin, in-vitro drug permeation and in-vitro kinetics.

Preparation of rat abdominal skin

Male albino rats were selected weighing between 125 to 132g and isolated under room temperature (25±1oC) with RH 60±5% and placed in cages. The rats were sacrificed by excessive chloroform inhalation. The rat abdominal skin was carefully separated without damaging of epidermis layer and washed thoroughly with distilled water to remove adhering fat before that the hairs of the skin were removed by suitable means. The epidermis was washed, dried in desicator, covered in aluminum foil and stored at 4±1°C. At the time of use, the epidermis was rehydrated by immersing in water for 1 h at room temperature[23,24].

In-vitro drug permeation studies

The in-vitro permeation study of fabricated transdermal patches of Metoprolol succinate was carried out by using excised rat abdominal skin and franz diffusion cell[25,26]. The skin was sandwiched between donor and receptor compartments of the diffusion cell. The isolated appropriate size of patch was placed between the donar and receptor compartments of diffusion cell such a way that stratum corneum of the skin continuously remain contact with transdermal patch in the donar compartment. Teflon bead was placed in the receptor compartment filled with 12 ml of phosphate buffer pH 7.4. The cell contents were stirred with a magnetic stirrer and a temperature of 37±0.5°C was maintained throughout the experiment. Samples of 2 ml were withdrawn through the sampling port at different time intervals for a period of 24 h, simultaneously replacing equal volume by phosphate buffer pH 7.4 after each withdrawal. The samples were analyzed spectrophotometrically at 274 nm. Samples collected from drug free patch used as a blank.

In-vitro drug kinetic studies

To know the release kinetics, the data obtained from in-vitro drug release studies were plotted in various kinetic models like zero order, first order, higuchi model and koresmeyer peppas.

Ex-vivo skin permeation of best formulation through rat abdominal skin

An ex-vivo permeation study of Metoprolol succinate from transdermal patches of MP14 was carried out using isolated rat abdominal skin from male albino rats weighing between 125 to 132g by using franz diffusion cell at 37±0.5°C198. Abdominal skin of full thickness was excised were mounted between the donor and receptor compartment such a way that stratum corneum of the skin continuously remain contact with transdermal patch in the donar compartment. It was left overnight on the receptor fluid for stabilization and optimization.

Stability studies and statistical analysis

The formulation MP14 was selected and the stability studies were carried out at accelerated condition of 40±2 0C, 75±5% RH conditions, stored in desiccators, the patches were packed in aluminum foil and kept in above said condition for period of six months. The films were analyzed periodically for their physical appearance, flatness, folding endurance, drug content, mechanical strength and in-vitro drug release. Results were analyzed by One-way ANOVA followed by Tukey's test and the differences were considered statistically significant at $p<0.05$.

3. RESULTS AND DISCUSSION

The prepared matrix transdermal patches of Metoprolol succinate was evaluated for physicochemical characteristics like thickness, weight, flatness, folding endurance, surface pH, percentage moisture absorption, percentage moisture loss, water vapor transmission rate and drug content.

The weight and thickness of three patches of each formulation were taken with the help of digital vernier caliper and digital balance. The patches were thin and fall within the range of 0.212 to 0.235 mm and almost uniform weight in the range of 269.31 to 283.56mg. In order to know the constriction of patches on storage, the prepared patches were subjected to flatness test. The results indicate there is no significant constriction of patches on storage. Recovery is possible in the tune of 99.5 to 100 as shown in Table 2.

The folding endurance was found to be greater than 300 times in case of all the formulations. This makes the system acceptable for movement of skin, indicating good strength and elasticity. Folding endurance test reveals that the films would maintain the reliability with skin during administration. The formulation MP14 gave the maximum value because of the HPMC K4M patches having high amount of Eudragit RL100 along with PVP K30 as shown in Table 2.

Checking the physical stability of the film at high humid conditions and integrity of the film at dry conditions, the films were evaluated for PMA and PML. The formulation MP7 shows high value (HPMCK4M-76mg and PVP K30-19mg) and MP14 (HPMCK4M-71.25mg, PVP K30-4.75mg and Eudragit RL100-19mg) shows low value of PMA. For PML the formulation MP14 shows low value and MP11 shows high value (HPMCK4M-80.75mg and Eudragit RL100-14.25mg) as shown in Table 2.

Water vapor transmission studies indicated that all the films were permeable to water vapor. The obtained results indicate, all formulations were permeable to water vapor. The observed results of content uniformity indicated that the drug was uniformly dispersed in the transdermal patches and with minimum intra batch variability. Recovery was possible to the tune of 98.4 to 99.9 . The maximum drug content was observed in MP14 as shown in Table 2. The scanning

Table .2 Physicochemical evaluation of transdermal patches

Formulation Code	Thickness (mm)	Weight (mg)	Flatness (%)	Folding endurance	Mechanical strength in kg/mm^2	PMA	PML	Q	Drug content (%)
MP1	0.216±0.01	280.93±1.22	100	300±1.0	9.76±0.088	5.21±0.07	4.97±0.12	1.58±0.35	99.7±1.10
MP2	0.235±0.03	263.39±0.21	99.8	299±2.0	8.89±0.099	6.32±0.04	4.14±0.72	2.67±0.34	98.9±1.20
MP3	0.213±0.02	271.48±0.54	99.7	300±2.0	8.78±0.069	6.24±0.09	4.74±0.10	1.17±0.34	98.1±1.26
MP4	0.224±0.04	286.56±0.57	100	298±4.0	13.64±0.073	6.32±0.11	5.14±0.20	1.24±0.35	99.76±1.15
MP5	0.228±0.05	291.62±0.43	99.5	296±5.0	10.76±0.049	7.13±0.09	5.08±0.03	1.98±0.08	98.76±1.15
MP6	0.231±0.01	210.31±1.09	99.9	306±1.0	13.25±0.075	6.21±0.06	4.88±0.02	2.39±0.32	98.43±1.20
MP7	0.226±0.03	281.71±1.13	99.6	305±2.0	11.45±0.083	7.86±0.27	6.44±0.10	1.87±0.35	99.7±1.05
MP8	0.211±0.04	272.53±1.98	99.8	302±3.0	9.46±0.059	7.18±0.13	7.13±0.08	2.48±0.52	98.6±1.20
MP9	0.222±0.02	272.29±1.87	100	299±3.0	13.65±0.124	6.34±0.12	9.12±0.07	1.58±0.43	99.1±1.11
MP10	0.236±0.02	274.31±1.59	99.9	297±4.0	9.47±0.562	7.12±0.13	8.06±0.06	2.48±0.59	98.2±2.11
MP11	0.215±0.01	274.42±1.78	100	291±6.0	10.83±0.121	3.56±0.25	9.21±0.06	2.44±0.48	99.1±1.04
MP12	0.214±0.03	272.35±0.99	100	300±2.0	12.23±0.058	7.02±0.23	4.84±0.08	1.69±0.20	99.9±1.05
MP13	0.206±0.01	270.72±0.19	99.5	304±2.0	12.67±0.061	8.26±0.24	5.72±0.01	1.91±0.38	98.9±1.25
MP14	0.212±0.01	271.45±0.75	100	311±1.0	15.65±0.057	4.89±0.22	6.13±0.02	1.32±0.20	99.9±1.01
MP15	0.231±0.03	282.34±0.43	100	302±3.0	11.87±0.048	7.02±0.06	7.45±0.52	1.94±0.31	99.3±1.21
MP16	0.217±0.01	272.16±0.80	100	301±3.0	13.43±0.036	6.21±0.07	5.97±0.12	1.58±0.35	99.7±1.21
MP17	0.233±0.01	283.12±0.37	100	299±2.0	12.98±0.053	7.12±0.04	5.14±0.72	1.67±0.34	98.9±1.27

electron microscopy photographs revealed that the surface topography, morphology, texture and uniform distribution of drug and polymer as shown in Figure 1 & 2.

Fig: 1 SEM photograph of drug free patch

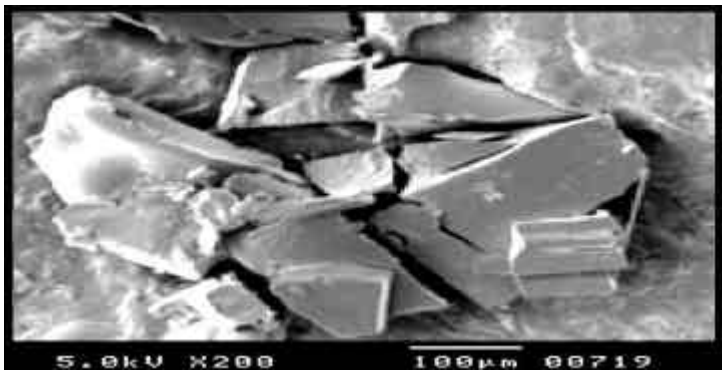

Fig: .2 SEM photograph of drug loaded patch

The tensile strength is an important phenomenon to show the flexibility and convenience of the patches during storage and administration in the skin. The mechanical strength is the measure of the force applied for the patches for elongation until it breaks. The maximum mechanical strength was noted in the formulation MP14 due to the cationic nature of the Eudragit RL100 and bond formation with film forming polymer of PVP K30. Whereas the formulation MP3 shows less mechanical strength due to the presence of cationic Eudragit RL100 alone with no combination.

The skin irritation studies were performed through rat abdominal skin for safer application of matrix controlled transdermal patches of Metoprolol succinate to humans for the therapeutic benefit. The drug free and drug loaded should not cause any significant irritation and no erythmea formation when compared to the normal and control group of animals as shown in Table 3.

Table .3 Scores assigned for skin irritation studies

Groups	Scores assigned Erythmea and eschar formation	Oedema formation
Group I (Normal)	0	0
Group II (Applied with adhesive tape)	1	0
Group III (Drug free patch)	0	0
Group IV (Drug loaded patch)	0	0
Group V (0.8% v/v aqueous solution of formalin)	2	2

The *in-vitro* permeation study of fabricated transdermal patches of Metoprolol succinate was carried out by using excised rat abdominal skin using franz diffusion cell. Distinguishable difference was observed in the release of Metoprolol succinate in all formulations (Figure 3&4) as shown in Table 4. The *in-vitro* drug release and Higuchi's plot have shown that the drug release followed zero order kinetics, which was known from the regression value (r). Eudragit RL100 is the cationic polymer, hence in optimum level it provides the controlled release of Metoprolol succinate extended period of time by means of bonding between anionic polymer of hydroxypropylmethyl cellulose and povidone. The data of zero order, first order release, Higuchi's and peppas of all formulations MP1-MP17 were presented in respective Table 5. The correlation coefficient values (r) indicate that the kinetic of drug release was of zero order. The mechanisms of drug release from all formulations by Peppas model indicates the non-fickian, whereas the formulation MP1, MP2 and MP3 indicates the fickian mechanism of drug diffusion evidenced with diffusion exponent values (n) as shown in Table 5.

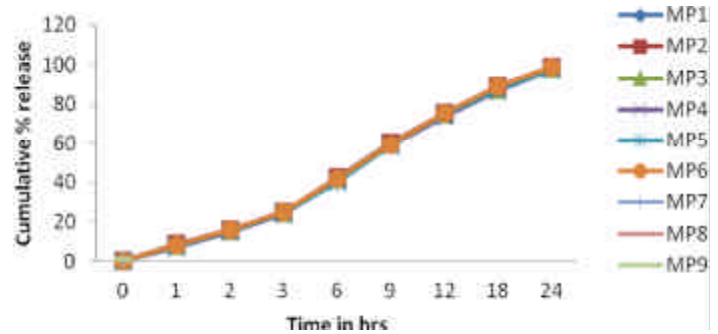

Figure .3 In-vitro drug release profile for formulation MP1 to MP9

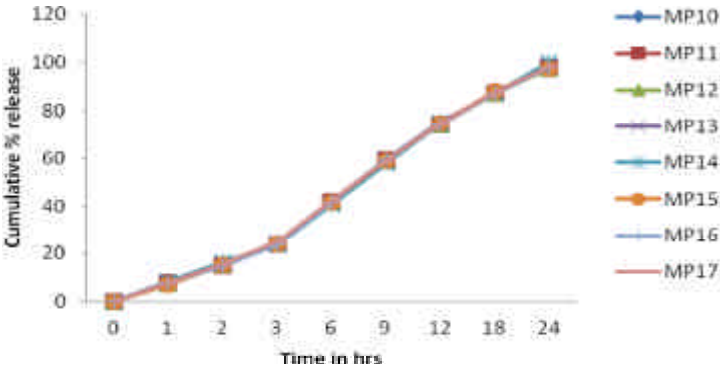

Figure .4 In-vitro drug release profile for formulation MP10 to MP17

Table .4 *In-vitro* drug release data for formulation MP1 to MP9

Time in h	Cumulative % release MP1	MP2	MP3	MP4	MP5	MP6	MP7	MP8	MP9
0	0	0	0	0	0	0	0	0	0
1	12.4	13.5	11.3	7.9	8.8	8.2	7.2	7.5	8.2
2	23.8	25.2	21.4	15.8	16.1	15.4	14.9	15.2	16.1
3	34.4	37.8	32.2	24.9	25.2	24.4	23.8	24.3	25.2
6	55.9	57.8	53.1	41.8	42.4	42.1	41.7	40.4	42.1
9	80.8	82.9	78.6	59.2	60.3	59.8	58.8	58.9	59.5
12	88.9	90.4	87.2	75.7	75.9	74.8	73.7	74.8	75.7
18	98.4	98.9	97.6	88.9	89.3	87.7	86.9	87.3	89.2
24				98.5	98.7	98.2	97.3	97.8	98.8

Table .4 In-vitro drug release data for formulation MP10 to MP17

Time in h	Cumulative % release							
	MP10	MP11	MP12	MP13	MP14	MP15	MP16	MP17
0	0	0	0	0	0	0	0	0
1	8.1	7.8	7.5	8	8.2	7.2	7.7	7.9
2	15.6	15	15.2	15.7	16.4	15.1	14.9	15.7
3	24.5	24	24.1	24.8	23.8	24.3	23.9	24.9
6	41.7	41.8	42	40.9	40.4	41.5	41.6	42.4
9	59.4	59.5	59.1	59.4	57.8	59.1	59.3	59.2
12	75.2	74.3	74	75.2	74.6	74.7	74.3	74.6
18	87.3	87.4	87.2	87.8	87.3	88.2	87.2	87.5
24	98.1	97.9	97.6	98.3	99.8	97.7	98	98.3

Table 5. Diffusion characteristics of Formulations MP1-MP17

Formulation code	Correlation coefficient values (r)			Diffusion exponent value (n)
	Zero Order	Higuchi's Model	First order	
MP1	0.951	0.985	0.988	0.323
MP2	0.944	0.985	0986	0.310
MP3	0.957	0.985	0.991	0.341
MP4	0.966	0.983	0.972	0.805
MP5	0.965	0.988	0.970	0.782
MP6	0.966	0.988	0.973	0.800
MP7	0.966	0.988	0.982	0.828
MP8	0.966	0.988	0.977	0.818
MP9	0.966	0.988	0.966	0.796
MP10	0.965	0.988	0.973	0.800
MP11	0.966	0.988	0.976	0.814
MP12	0.966	0.988	0.979	0.818
MP13	0.966	0.988	0.971	0.802
MP14	0.971	0.988	0.907	0.794
MP15	0.966	0.987	0.982	0.829
MP16	0.966	0.987	0.974	0.817
MP17	0.966	0.989	0.970	0.803

The effectiveness of the permeation enhancer through stratum corneum layer of the skin could provide means for Metoprolol succinate administration can be determined through permeation in rat abdominal skin. The ex-vivo permeation study of optimized formulation (MP14) rat abdominal skin was shown in Table 6 & Figure 5.

Table 6. *Ex-vivo* permeation studies of best formulation MP14

Formulation code	Correlation coefficient values (r)			Diffusion exponent value (n)
	Zero Order	Higuchi's Model	First order	
MP1	0.951	0.985	0.988	0.323
MP2	0.944	0.985	0986	0.310
MP3	0.957	0.985	0.991	0.341
MP4	0.966	0.983	0.972	0.805
MP5	0.965	0.988	0.970	0.782
MP6	0.966	0.988	0.973	0.800
MP7	0.966	0.988	0.982	0.828
MP8	0.966	0.988	0.977	0.818
MP9	0.966	0.988	0.966	0.796
MP10	0.965	0.988	0.973	0.800
MP11	0.966	0.988	0.976	0.814
MP12	0.966	0.988	0.979	0.818
MP13	0.966	0.988	0.971	0.802
MP14	0.971	0.988	0.907	0.794
MP15	0.966	0.987	0.982	0.829
MP16	0.966	0.987	0.974	0.817
MP17	0.966	0.989	0.970	0.803

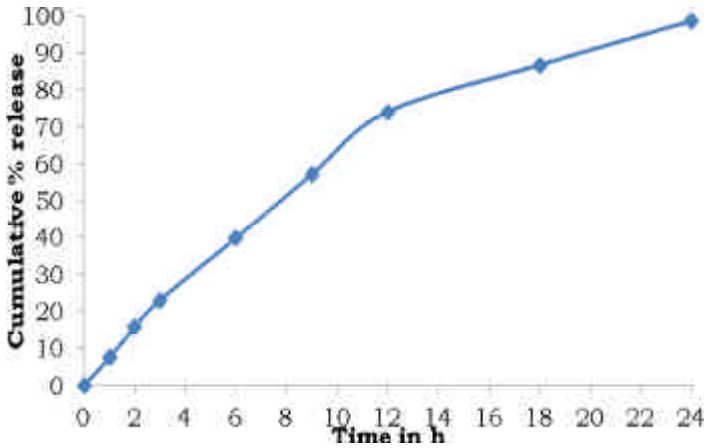

Fig: 5. *Ex-vivo* permeation plot of MP14

CONCLUSION

The controlled release matrix transdermal patches of Metoprolol succinate were prepared by the method of solvent casting technique employing 'O' shape ring placed on a glass surface as substrate by using different polymers like HPMC K4M, PVP K30 and Eudragit RL100. The dibutylphthalate (30%w/w) used as plasticizer and permeation enhancer, whereas aluminium foil served as a baking membrane. The prepared matrix transdermal patches of Metoprolol succinate was evaluated for physicochemical characteristics like thickness, weight, flatness, folding endurance, surface pH, percentage moisture absorption, percentage moisture loss, water vapor transmission rate and drug content. The satisfactory results were obtained in all prepared formulation and based on the results MP14 (HPMCK4M-71.25mg, PVP K30-4.75mg and Eudragit RL100-19mg) was the best one when compared to other. The in-vitro kinetics shows the zero order drug release followed by non-fickian diffusion mechanism. Hence the controlled release matrix transdermal patches of Metoprolol succinate which are used mainly in minimizing dose and help to improve the patient compliance and Metoprolol succinate is a drug of choice for delivery through the control release via matrix transdermal patches.

ACKNOWLEDGMENT

The authors are thankful to Dr. A.Sathish, Secretary of Dr. Samuel George Institute of Pharmaceutical sciences, Markapur, Prakasam Dist, A.P, India for availing the laboratory facilities during the course of research studies.

Conflict of Interest

We declare that we have no conflict of interest

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Source of support: Nil, Conflict of interest: None Declared