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Research Article

Formulation and evaluation of controlled release matrix Transdermal patches of Metoprolol Succinate

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ABSTRACT

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. The *in-vivo* kinetics was shows in the extent of bioavailability and in the rate of absorption. The optimized formulation were stable at accelerated conditions with level of significance P>0.05. Good correlation was observed between *in-vitro* and *ex-vivo*, *in-vitro* and *in-vivo* profile revealed the ability of the formulation to reproduce the *in-vitro* permeation pattern through the rat abdominal skin and rabbit. 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.

Keywords: Metoprolol succinate, Solvent casting technique, zero order kinetics, non-Fickian

INTRODUCTION

Transdermal drug deliveries 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 (Rawat S, 2008).

Traditionally, beta blockers were used as first line agents in the treatment of uncomplicated hypertension and recommended as a class by national and international guidelines despite paucity of evidence for their cardiovascular benefit (Vyas SP, 2002). Metoprolol succinate is widely used in the treatment of hypertension, angina pectoris, and arrhythmias, due to its β-selective adrenoceptor blocking property (Al-Saidan SM et al., 2004). 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% (Kendall MJ, 1991).

MATERIALS AND METHODS

Metoprolol succinate, Hydroxy propyl methyl cellulose K4M, Poly vinyl pyrrolidine K30, and Eudragit RL100 were procured from Drugs india, Hyderabad. All other chemicals used and received were of analytical grade.

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Table 1: Composition 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

Formulation of controlled release matrix transdermal patches of Metoprolol succinate

The controlled release matrix transdermal patches of Metoprolol succinate were prepared by the method of solvent casting technique (Rita B et al., 2011; Rao YM et al., 2007). 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 aluminium foil, which is used as a baking membrane. The Metoprolol succinate patches were stored in desiccators until further use. The compositions of formulation of both drug free and Metoprolol succinate transdermal patches were given in the table 1.

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. The results were presented in the table 2.

Thickness and weight

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 (Ramarao P et al., 2000). The weight of three different patches of same formulations was calculated by using digital balance and the mean of three patches were recorded (Mamatha T et al., 2009).

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 (Gupta R, et al., 2003).

$$\text{Flatness} = (L2 - L1) / L \times 100$$

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 (Raghuraman S, et al., 2002).

Surface pH

The warmed pH 6.8 isotonic phosphate buffer containing 2% w/v agar solution poured into a petridish and allowed to gel at room temperature was used for the determination of surface pH of the prepared patches.

Table 2: Physicochemical evaluation of transdermal patches

F. Code	Thickness (mm)	Weight (mg)	Flatness (%)	Folding endurance	Surface pH	PMA	PML	Q	Drug content (%)
MP1	0.216± 0.01	280.93± 1.22	100	300 ±1.0	7.43± 0.01	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	7.39± 0.01	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	7.41± 0.02	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	7.44± 0.05	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	7.39± 0.015	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	7.54± 0.03	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	7.36± 0.03	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	7.48± 0.01	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	7.38± 0.02	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	7.41± 0.01	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	7.43± 0.01	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	7.41± 0.03	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	7,47± 0.02	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	7.40± 0.01	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	7.42± 0.02	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	7.43± 0.01	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	7.42± 0.02	7.12± 0.04	5.14± 0.72	1.67± 0.34	98.9± 1.27

The patches were placed and the surface pH was measured with the help of pH meter. The average of three readings was recorded (Nafee NA, et al., 2003).

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 (Alagusundaram M, et al., 2011),

$$\text{Percentage Moisture Absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \text{X100}$$

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 (Alagusundaram M, et al., 2011),

$$\text{Percentage Moisture Loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{X100}$$

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

Table 3: Mechanical strength of Metoprolol succinate transdermal patches

Formulation code	Mechanical strength in kg/mm^2
MP1	9.76±0.088
MP2	8.89±0.099
MP3	8.78±0.069
MP4	13.64±0.073
MP5	10.76±0.049
MP6	13.25±0.075
MP7	11.45±0.083
MP8	9.46±0.059
MP9	13.65±0.124
MP10	9.47±0.562
MP11	10.83±0.121
MP12	12.23±0.058
MP13	12.67±0.061
MP14	15.65±0.057
MP15	11.87±0.048
MP16	13.43±0.036
MP17	12.98±0.053

Table 4: Draize scoring method

Sl.no.	Erythmea and Eschar formation	Oedema formation	Score assigned
1	No ertythmea	No oedema	0
2	Very slight erythmea	Very slight oedema	1
3	Well defined erythmea	slight oedema	2
4	Moderate to severe erythmea	Moderate oedema	3
5	Severe erythmea	Severe oedema	4

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 (Krishna R, et al., 1994).

$$Q = WL/S$$

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. The mean of three films was taken as drug content.

Measurement of mechanical strength

The mechanical strength (Peh KK, 1999) 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. The tensile strength and elongation at break were measured using the formula. The results were presented in the table 3 and represent in the figure 1.

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

$$\text{Elongation at break (\%mm}^2) = \frac{\text{Increase in length (mm)}}{\text{Original length (mm)}} \text{X} \frac{100}{\text{Cross sectional area (mm}^2)}$$

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±1°C) 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

Table 5: 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

Table 6: In-vivo kinetic parameters of MP14

Parameters	Formulation MP14
C_{max} (µg/L)	839.80
t_{max} (h)	9
$t_{1/2}$ (h)	4.78
K_{el} per h	0.145
$AUC_{(0-24)}$ (µg.h/L)	10731.20
$AUC_{(0-\infty)}$ (µg.h/L)	11281.54

Table 7: Stability studies of best formulation MP14

Parameters	2nd month	4th month	6th month	p value
Physical appearance	No Change	No Change	No Change	-
Flatness	100±0.005	100±0.100	99.50±0.125	0.4325
Folding endurance	311.33±0.322^{ns}	310.78±0.231^{ns}	310.33±0.452^{ns}	0.6532
Drug content	99.97±0.132^{ns}	99.76±0.125^{ns}	99.66±0.213^{ns}	0.8363
Mechanical strength	15.63±0.125^{ns}	15.23±0.121^{ns}	15.22±0.152^{ns}	0.5231
In-vitro drug release	99.75±0.453^{ns}	99.13±0.321^{ns}	98.92±0.425^{ns}	0.7521

All values are expressed as Mean±SD; ^{ns} = non significant

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 (Mutalik S, et al., 2005). The grades of draize scoring method were presented in the table 4 and the obtained results for best formulation MP14 were presented in the table 5.

***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±1°C) 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 aluminium 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 (Brain R et al., 1999).

***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 (Vijay SJ et al., 2012). 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 kintetic 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. Zero order is cumulative amount of drug release vs time. Equation is $C=K_o t$, where K_o is the zero order rate constant expressed in units of concentration/time and t is the time in hours. First order is Log cumulative percentage drug remain-

ing vs time. Equation is Log C=Log C_o-Kt/2.303, where C_o is the initial concentration of drug, K is the first order constant and t is the time. Higuchi model is the cumulative percent drug release vs square root of time. Equation is $Q=Kt^{1/2}$, Where K is the constant reflecting the design variables of the system and t is the time in hours. Korsmeyer peppas is the log cumulative percentage of drug release vs log time. The exponent n was calculated through the slope of straight line. $M_t/M_\infty = kt^n$ where, M_t/M_∞ is the fractional solute release, K is the kinetic constant characteristic of the drug polymer system, t is the release time and n is the exponent. The correlation coefficient values (r) from zero order, first order and Higuchi's model indicate the kinetic of drug release and diffusion exponent values (n) from Korsmeyer peppas model indicate the mechanism of drug release.

***In-vivo* drug absorption study using rabbits**

Based on the *in-vitro* evaluation studies, the best formulation MP14 were selected for *in-vivo* evaluation. Six male New Zealand white rabbits (2-2.5 kg) were selected for the *in-vivo* study, which was already checked for absence of any diseases (Thimmasetty J, et al., 2008). The dose of Metoprolol succinate was adjusted based on the rabbit weight and such a way that the patches were designed as the composition of best formulations. The optimized formulation MP14 were cut and placed over the dorsal surface of the skin and the hairs were removed by suitable means. One ml of blood sample was taken by syringe, which already contained 1 ml of heparin solution to prevent blood clotting (Basak SC, et al., 1997). These blood samples were subjected for centrifuging at 2,500 rpm for about 30 minutes. One ml of supernatant was taken, and after suitable dilution, analyzed at 274 nm using UV spectrophotometer. The study was approved by the institutional ethical committee.

***In-vivo* drug absorption kinetics**

The pharmacokinetic parameters such as C_{max}, t_{max}, $t_{1/2}$, AUC_{0-t}, K_{el} and bio availability were calculated from the plasma concentration time profiles of absorption data followed by topical administration of best formulation MP14.

Analysis of Metoprolol succinate in plasma

The plasma samples were analyzed using a reversed phase high performance liquid chromatographic (HPLC) method. The HPLC system composed of an Agilent compact LC 1120 pump and a Rheodyne sample injector fitted with a 20 µl sample loop. The detector was operated using a wavelength of 272 nm. A ODS (Octadecyl silane) C18 column (10 µm, 250x4.6 mm) fitted with a guard column was used for separation. The mobile phase consisted of acetonitrile and methanol at the ratio of 7.5:2.5. The pH was adjusted to 1.2 by using triethyl amine. The mobile phase filtered through a 0.45 µm membrane filter (Sartorius USA) and was then degassed by ultrasonication. Analysis was run at a flow rate of 1.0 ml/min and quantification was by peak height. The *in-vivo* parameters were calculated from the measured concentration of Metoprolol succinate in plasma at various time intervals, C_{max}, t_{max}, $t_{1/2}$, AUC_{0-t}, K_{el}, and Bioavailability by using Wagner-Nelson method and the data's are run through the M_BV6 software. The Wagner-Nelson method is one method of calculating absorption kinetics, from plasma concentration time data (Cp vs t) following on oral administration of formulations. C_{max} and t_{max} were directly obtained from plasma concentration-time data. The area under the curve is calculated using the trapezoidal rule and the value of kel is estimated from the terminal log-linear portion of the curve, using a least squares linear regression analysis on the last 4 points. By using kel, the bioavailability (Fa) was calculated as a function of time. The *in-vivo* kinetic parameters of the best formulation were presented in the table 6.

Stability studies and statistical analysis

The formulation MP14 was selected and the stability studies were carried out at accelerated condition of 40±2 ^{0}C, 75±5% RH conditions, stored in desiccators, the patches were packed in aluminium 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 $p<0.05$ and the data were presented in the table 7.

RESULTS AND DISCUSSION

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 compositions of formulation of both drug free and Metoprolol succinate transdermal patches were given in table 1. 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 results were presented in the table 2.

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 with in 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

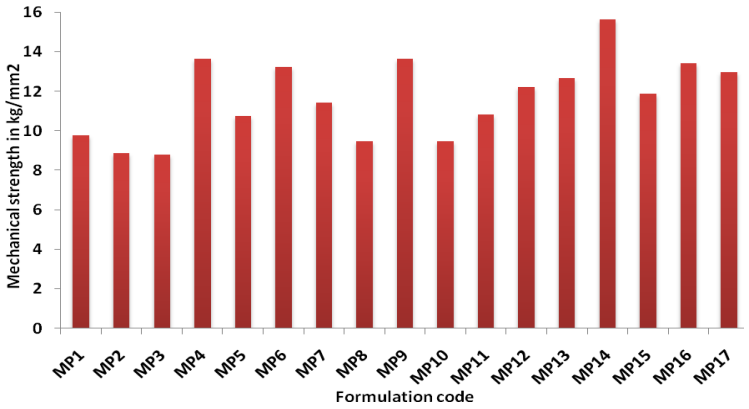

Figure 1: Mechanical strength of Metoprolol succinate patches

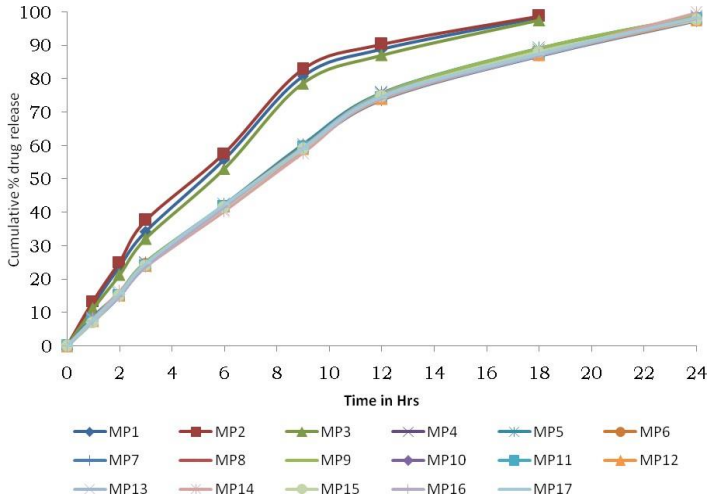

Figure 2: Cumulative % drug release plot

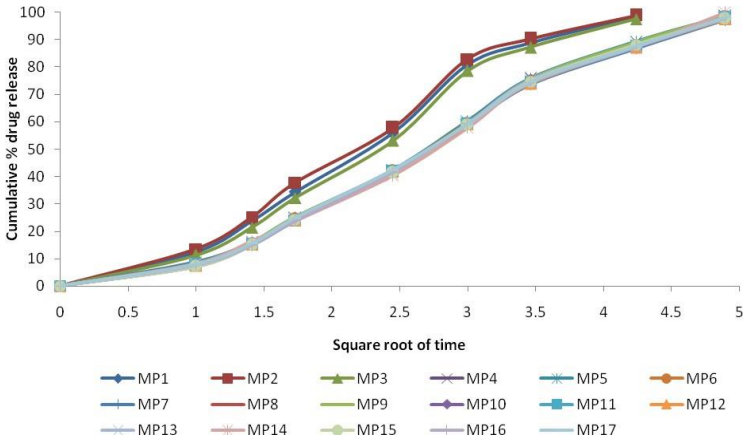

Figure 3: Higuchi's plot

of patches on storage. Recovery is possible in the tune of 99.5 to 100. 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. Considering the nature and anatomy of the skin at exposed in various climatic condition, the formulations should possess the pH is closed to the skin pH. It is very important to avoid skin irritation during administration. The results were found in the range of 7.36 to 7.47 which is very close to skin pH.

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

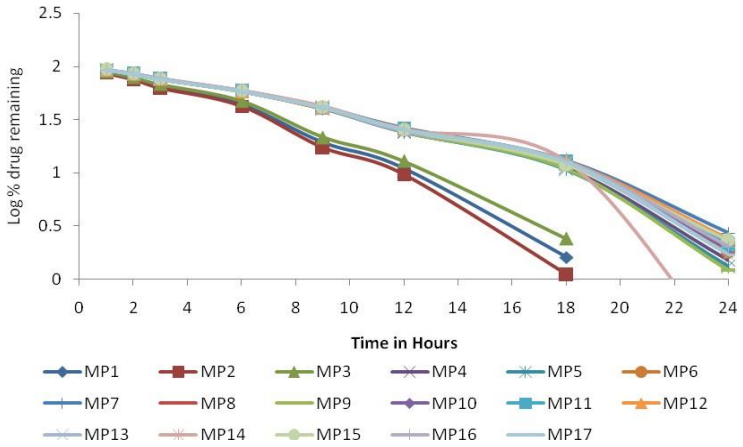

Figure 4: First order plot

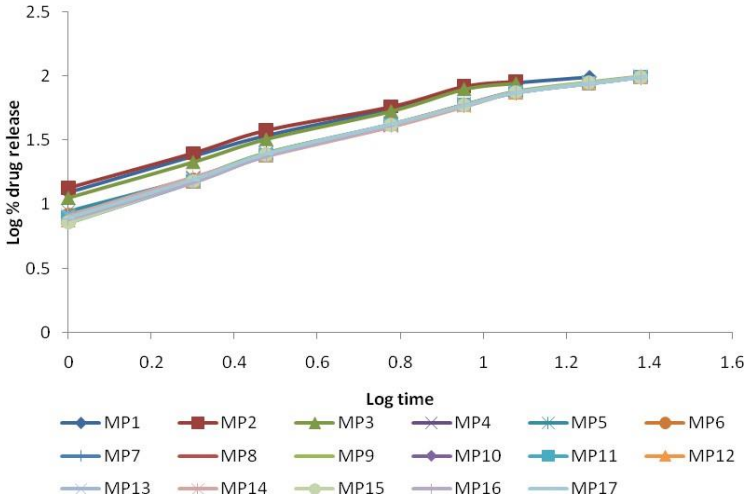

Figure 5: Koresmeyer peppa's plot

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). 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.

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. The results of all formulations were shown in the figure 1 and the data are presented in the table 3. 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.

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. 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 represented in figures 2 to 5. The obtained results in these formulations were plotted in

various model treatments as cumulative percentage release of drug versus square root of time (Higuchi's), log cumulative percentage release versus log time (Peppas) and log percentage remaining versus time (first order). To find out the mechanism of drug release from hydrophilic matrices, the *in-vitro* drug permeation data of each formulation were calculated with different kinetic drug release equations. 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).

CONCLUSION

Based on the *in-vitro* evaluation studies, the best formulation MP14 were selected for *in-vivo* evaluation. Six male New Zealand white rabbits (2-2.5 kg) were selected for the *in-vivo* study, which was already checked for absence of any diseases. The *in-vivo* studies of optimized formulation shows zero order release pattern and also shows more compatibility of the skin during topical administration of transdermal patches. The rabbits did not show any inflammation or any other sensitization reactions at the administration site. The study was approved by institutional ethical committee. The pharmacokinetic parameters such as C_{max}, t_{max}, $t_{1/2,}$ $AUC_{0\text{-}t}$, K_{el} and bio availability were calculated from the plasma concentration time profiles of absorption data followed by topical administration of best formulation MP14.

The stability of the best formulation MP14 at accelerated conditions shows satisfactory results in physical appearance, flatness, folding endurance, drug content, mechanical strength and *in-vitro* drug release over the period of six months. Results were analyzed by One-way ANOVA followed by Tukey's test and the differences were considered statistically significant at $p<0.05$.

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