FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF METOPROLOL SUCCINATE

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Abstract

The anti-hypertensive transdermal patches in the perspective of enhancing the bioavailability as well as in improving patient compliance, it has appear as a substitute for oral route permit self-administration, controlled and sustained drug delivery. This study will investigate the effects of metoprolol Succinate in treatment of hypertension with the interaction of hydroxy propyl methyl cellulose and ethyl cellulose. The present research work concludes that the patches prepared with different ratios of polymers shows sustained drug release for long period of time confirms that the delivery system prepared can be suitably used as sustained and controlled drug delivery. The Transdermal Patches of drug metoprolol Succinate can be utilized in the diseases hypertension, myocardial infarction and congestive heart failure, etc. It offers high patient compliance by ease in administration.

Keywords: Anti-hypertensive, Transdermal patches, Metoprolol succinate and HPMC.

Introduction

Hypertension is the chronic elevation of blood pressure that, in the long term, causes and and organ damage & results in increased morbidity and mortality occurs due to the abnormal functioning of the arterial pressure related to the central nervous system [1], rennin-angiotensin–aldosterone system endothelial dysfunction, genes and even due to certain environmental factors.

The basic component of Transdermal Drug Delivery System [2] includes inert polymer matrix in which the drug is dissolved or dispersed providing support & platform for drug release. There are Two basic designs of the patch system;

- Matrix or Monolithic: The polymer matrix [3] holds a large quantity of drug and controls the release from the device.

- Reservoir or Membrane: The rate controlling membrane [4] made of a polymer present between the drug layer and the adhesive layer that provides the rate limiting barrier for drug release from the device.

Many of the technologies have been successfully developed to provide the rate control over the release and skin permeation of drugs [5].

Materials and Methods:

Materials:

Table 1: List of Ingredients

S. No.	Name	Specification	Manufacturer
1.	Metoprolol Succinate	Pharma Grade	Bal Pharma Ltd. Rudrapur
2.	Hydroxy Propyl Methyl Cellulose	Analytical Grade	Classic Solvent PVT. LTD, Ahmedabad
3.	Ethyl Cellulose	Analytical Grade	Galaxy Chemicals, Ahmedabad
4.	Eudragit-L 100	Analytical Grade	Bal Pharma Ltd. Rudrapur
5.	Dibutyl Phthalate	Analytical Grade	Merk, Mumbai
6.	Dimethyl Sulphoxide	Analytical Grade	Merk, Mumbai
7.	Methanol	Analytical Grade	S. D. Fine Chemicals, Ahmedabad
8.	Dichloromethane	Analytical Grade	SolvoChem, Ahmedabad

Methods:

Preparation of Phosphate buffer (pH 6.8): 27.216 gm of Potassium dihydrogen phosphate (KH_2PO_4) was taken and dissolved in 200 ml of distilled water. To make 0.2 M KH_2PO_4 the volume was made upto 1000 ml with distilled water. Further 8 gms of Sodium hydroxide (NaOH) was taken and dissolved in 200 ml of distilled water [6] to make 0.2 M NaOH the volume was made upto 1000 ml with distilled water. To make Phosphate buffer pH 6.8, 250 ml of 0.2 M KH_2PO_4 and 112 ml of 0.2 M NaOH was mixed and the volume was made upto 1000 ml with distilled water.

Determination of λ_{max}: The UV spectrum of Metoprolol succinate was analyzed spectrophotometrically by using spectrophotometer (UV-1800 Shimadzu). 100 mg of the drug was accurately weighed and dissolved in sufficient quantity of Phosphate buffer (pH 6.8) and the final volume was made up to 100 ml to prepare the stock solution of solution of 1000 μg/ml. From the stock solution 1 ml was withdrawn and volume was made up to 100 ml with Phosphate buffer to obtain the solution of 10 μg/ml [7]. The resultant solution was scanned from 200 to 400 nm and the spectrum was recorded to obtain maximum wavelength λ_{max}.

Preparation of Calibration Curve of Metoprolol succinate in phosphate buffer (pH 6.8): 100 mg of Metoprolol succinate [8] was accurately weighed and dissolved in sufficient quantity of phosphate buffer (pH 6.8) and the final volume was made up to 100 ml to prepare the stock solution of solution of 1000 μg/ml. From the stock solution 1 ml was withdrawn and volume was made up to 10 ml with phosphate buffer to obtain the solution of 100 μg/ml. This solution was further diluted to prepare solutions of 5μg/ml to 30μg/ml. Absorbances of each solution was measured at 223nm [9] using Shimadzu UV-1800 Spectrophotometer using pH 6.8 phosphate buffer as a reference standard. The calibration curve was prepared for solutions of 5μg/ml to 30μg/ml.

Compatibility studies:

FT-IR Spectroscopy: FT-IR spectroscopy was employed to ascertain the compatibility the drug Metoprolol Succinate and the selected polymers, FT-IR spectra of pure drug Metoprolol succinate was taken separately [10]. Further drug and polymers (HPMC and Ethyl cellulose) were mixed in the same ratio as shown in table 2 and scanned using Shimadzu FT-IR.

Table 2: Drug Polymer ratio for Compatibility studies

S. No.	Drug-Excipient	Ratio
1.	Metoprolol succinate: HPMC	1:1
2.	Metoprolol succinate: *EC*	1:1
3.	Metoprolol succinate: HPMC: *EC*	1:1:1

Formulation of Transdermal Patches:

Transdermal Patches of Metoprolol Succinate were prepared by solvent evaporation method. The polymer ethyl cellulose & HPMC were taken in required amount. About 20ml of solvent mixture of methanol:dichloromethane in the ratio of 1:1 was added and stirred well. When the polymers completely soulblized in mixture of solvent, added 0.5ml dibutylphthlate act as a plasticizer [11]. Then added 50mg of the drug metoprolol succinate to the polymer solution and finally added the 0.2ml of permeation enhancer dimethyl sulphoxide. This mixture was placed at one side for sometime to exclude any entrapped air and was then transferred into a previously cleaned and dried petri plate. Then the plate was kept a side for solvent evaporation and was covered by funnel to control evaporation of solvent. Allowed to dry at room temperature overnight [12], The dried films were separated and the backing membrane used was aluminium foil and stored in desiccators These films were further evaluated.

Table 3: Composition of Transdermal Patches of Metoprolol Succinate

Formulation	F1	F2	F3	F4	F5
Drug (ms)(mg)	50mg	50mg	50mg	50mg	50mg
HPMC	500mg	450mg	400mg	350mg	300mg
Ethyl Cellulose	500mg	550mg	600mg	650mg	700mg
Dibutylphthalate	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml
Dimethylsulphoxide	0.2ml	0.2ml	0.2ml	0.2ml	0.2ml
Methanol: Dichloromethane	1:1	1:1	1:1	1:1	1:1

Evaluation of transdermal patches of metoprolol succinate:

The physicochemical evaluation of transdermal patches is based on following parameters;

Physical Appearance: All the prepared Transdermal Patches were observed visually for colour, clarity, smoothness and flexibility [13].

Surface PH Measurement: The pH of prepared transdermal patches was measured with the help of calibrated pH meter. The average of three readings was recorded for patch [13, 14].

Thickness of Patch: The thickness of each transdermal patch was measured at six different places using a digital vernier calliper and average thickness of patches was measured [11, 14].

Weight Uniformity: The three different patches from each formulation weighed on electronic weighing balance and calculated the average weight of three patches. The individual weight should not deviate from the average weight of patch [15].

Folding Endurance: This test is done to determine the following capacity of the patches subjected to frequent extreme conditions of folding [16]. The folding endurance was determined by repeatedly folding a small strips of films at the same place till it broke.

Flatness: Three longitudinal patches were cut from each patch at different portion like centre, left, and right side. The initial length of strip was measured and then kept for two hours at room temperature. The variations in length due to non uniformity in flatness were measured by determing percent constriction by using the following formula [17]-

$$Flatness = \frac{Initial\ length\ of\ each\ strip\ in\ cm - Final\ length\ of\ each\ strip\ in\ cm}{Final\ length\ of\ each\ strip\ in\ cm} \times 100$$

Percentage Moisture Loss: The percentage moisture loss test is used to check the integrity of transdermal patches at drug condition. Accurately weighed of three 1 cm patches were kept in dessicators containing anhydrous calcium chloride [18] and exposed to an atmospheric room temperature.

$$\%\ Moisture\ Loss = \frac{Initial\ weight - Final\ weight}{Final\ weight} \times 100$$

Percentage Moisture Absorption: The Percentage Moisture Absorption test is carried out to check the physical stability of trandermal patches at high humid conditions. The weight of three 1 cm patches were weight accurately and then placed in dessicators containing saturated solution of potassium chloride , with the relative humidity 84% [18, 19]. The patches were removed after three days, weight and Percentage Moisture Absorption was calculated by the following formula-

$$\%\ Moisture\ Absorption = \frac{Final\ weight - Initial\ weight}{Initial\ weight} \times 100$$

Tensile Strength: To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film [17, 19]. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation.

Tensile strength= F/a.b (1+L/l)

F is the force required to break; **a** is width of film; **b** is thickness of film; **L** is length of film; **l** is elongation of film at break point.

Water Vapour Permeability: Glass vials of the same diameter were washed thoroughly and dried to a constant weight in an oven. About 1 gm of fused Calcium chloride was taken in the vials & the polymeric transdermal patches about $1cm^2$ area were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber at 85 % RH condition for a period of 24 hours [20]. The vials were removed and weighed at various time intervals like 3, 6 and 24 hr to note down the weight gain. *Water Vapour Permeability = W/A,* Water Vapour Permeability is expressed in gm/m^2 per 24 hours; W is the amount of vapour permeated through the patch (gm/24 hrs). A is the surface area of the exposure samples (m^2).

Drug Content: The prepared patches of 1 cm2 were cut in three equal parts and kept in a 100 ml pH 6.8 phosphate buffer [21] and stirred for 24 hours and filtered. The filtrate was suitably diluted and determined by UV Spectrophtometer, the drug content then calculated by the mean of three patches.

In Vitro Drug Release: In vitro drug release study of prepared metoprolol succinate transdermal patches was carried out by using USP Paddle Type II dissolution test apparatus at 750 rpm in 900 ml of pH 6.8 phosphate buffer medium at the temperature $37 \pm 0.5°C$ for 24 hours [22]. 5 ml of samples were

withdrawn at predetermined time interval, filtered, diluted suitably and analysed by UV Spectrophtometer at 223 nm.

Stability Studies: Stability Studies were conducted according to the ICH guidelines [21, 23] by storing the transdermal drug delivery system samples at 40± 0.5°C and 75±5%. Relative humidity for two months. The samples were withdrawn at 0, 30 and 60 days and analyze suitability for the drug content.

Result and Discussion:

λ_{max} **Determination:** U.V. Spectrophotometer (Shimadzu 1800) was used to determine absorption maxima of the drug Metoprolol Succinate. The $_{max}$ for drug Metoprolol Succinate in Phosphate Buffer pH 6.8 was found at 223nm. Figure 1 shows the λ_{max} of Metoprolol Succinate in Phosphate Buffer pH 6.8.
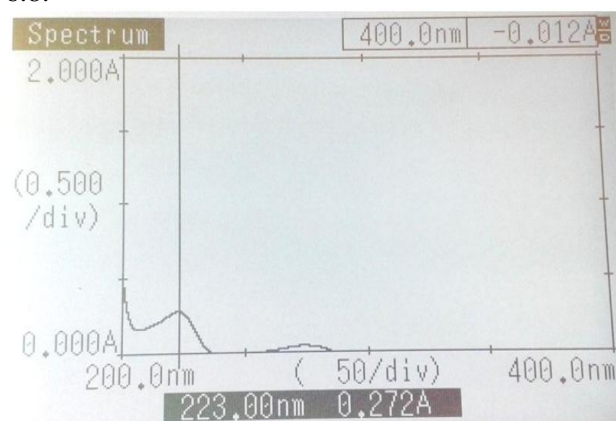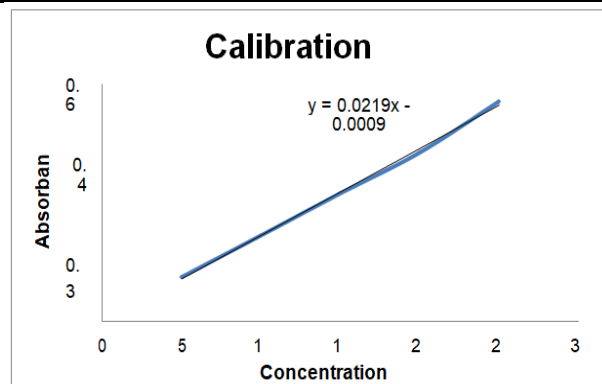

Figure 1: Absorption Maxima of Metoprolol succinate in Phosphate buffer pH 6.8

Calibration curve of Metoprolol succinate: The Calibration curve of drug (Metoprolol Succinate) was prepared in Phosphate Buffer pH 6.8 at 223nm shows the UV absorption. A straight line with $R^2 = 0.998$ for Phosphate Buffer pH 6.8 was found, indicating that the drug follows Beer's law within the specified concentration range.

Table 4: Absorbance of Metoprolol Succinate in phosphate buffer pH 6.8

S. No.	Concentration (μg/ml)	Absorbance of metoprolol Succinate at 223nm
1.	5	0.113
2.	10	0.218
3.	15	0.324
4.	20	0.427
5.	25	0.556

Figure 2: Calibration curve of Metoprolol succinate in phosphate buffer (pH 6.8)

FT-IR Spectroscopy: FT-IR spectrum of the drug sample was obtained by FT- IR (Shimadzu FTIR8101A). The IR spectral analysis of Metoprolol Succinate showed principal peaks observed at wave numbers 3734.48, 3629.37, 2363.34, 2341.16, 1731.76, 1615.09, 1516.74, 1316.18, 669.178 cm^{-1}, confirming the purity of Drug.
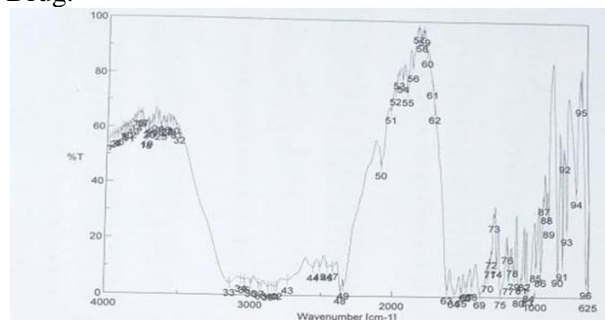
Figure 3: FT-IR Spectra of Metoprolol succinate

Table 5: IR study of drug-polymer mixture

S No.	Functional Groups present	Wavenumbers (cm^{-1})			
		Metoprolol succinate	Metoprolol succinate-HPMC mixture	Metoprolol succinate-EC mixture	Metoprolol succinate-HPMC- EC mixture
1.	-NH$_2$	3734.48	3736.4	3734.48	3734.48
2.	-OH	3629.37	3630.34	3627.45	3625.52
3.	-COOH	2363.34	2360.44	2360.44	2359.48
4.	-CH$_2$-CH$_2$(symmetric)	2341.16	2342.12	2341.16	2341.16
5.	- C=O (Anhydride)	1731.76	1733.69	1731.76	1731.76
6.	-C=C	1615.09	1615.09	1615.09	1616.06
7.	-C-C (Aromatic)	1516.74	1516.74	1516.74	1516.74
8.	-C-NO$_2$	1316.18	1316.18	1316.18	1316.18
9.	-C-H	669.178	669.178	669.176	669.176

Physicochemical Evaluation of Trandermal Patches:

Table 6: Physicochemical Evaluation of Transdermal Patches

| Parameters	F1	F2	F3	F4	F5
Surface pH	7.43 0.01	7.39 0.02	7.38 0.01	7.42 0.02	7.38 0.02
Thickness(m m)	0.17 0.037	0.19 0.018	0.18 0.042	0.17 0.031	0.18 0.021
Weight Uniformity (gm)	1.44 0.0018	1.48 0.0014	1.43 0.0017	1.43 0.0015	1.46 0.0017
Folding Endurance	135 5.32	132 4.57	130 6.92	127 5.09	125 4.92
Flatness	98%	97%	99%	99%	98%
% Moisture Loss	10.98 1.88	10.23 2.23	9.78 1.46	9.08 1.31	8.37 1.29
% Moisture Absorption	8.19 1.94	7.82 1.53	7.06 1.67	6.73 1.48	5.13 1.32
Tensile strength (kg/mm^2)	3.86 0.051	4.13 0.045	4.28 0.045	3.43 0.062	3.74 0.055
Water Vapour Permeability (gm/m^2/24hrs)	12.18 1.6	12.32 2.2	11.21 1.9	11.16 2.4	12.26 2.0
Drug content	98.99 0.53	98.97 0.48	97.89 0.65	97.96 0.38	98.93 0.72

Mean SD, n=5

In vitro **Drug Release:** In Vitro Drug Release study indicated that when the polymer concentration increased or changed, the amount of drug permeation increased, initial rapid dissolution of the polymers occurs when the patch is in the contact with the hydrated skin, resulting in the accumulation of high amounts of drug on the skin surface and thus leading to the saturation of the skin with drug molecules at all times. Drug release study of F1 formulation (97.86%) was better than the other formulations.

Table 7: Drug release study

Time (hrs)	Cumulative percentage drug release (%)				
	F1	F2	F3	F4	F5
2	13.26 0.89	13.96 0.68	12.88 0.36	12.01 1.86	11.47 0.84
4	20.87 1.86	24.57 0.93	24.12 1.05	25.68 1.30	26.16 0.56
6	36.12 1.61	31.26 1.05	32.55 0.77	34.96 0.64	30.87 1.18
8	45.31 1.46	43.94 1.12	40.27 0.56	39.93 0.87	34.34 1.62
10	58.98 1.33	53.72 0.53	49.54 1.16	43.69 0.93	40.28 1.39
12	69.23 0.56	66.42 1.48	63.91 1.21	63.18 1.41	58.89 0.51
14	76.53 1.48	74.72 1.02	73.69 0.92	71.27 1.13	69.56 0.85
16	82.71 0.79	80.94 1.23	76.38 1.36	74.42 1.02	72.95 0.66
24	97.86 1.08	94.69 0.97	93.13 0.57	90.73 0.69	88.42 1.78

Mean SD, n=5

Figure 7.9: Cumulative % drug release of Transdermal Patch F1 to F5
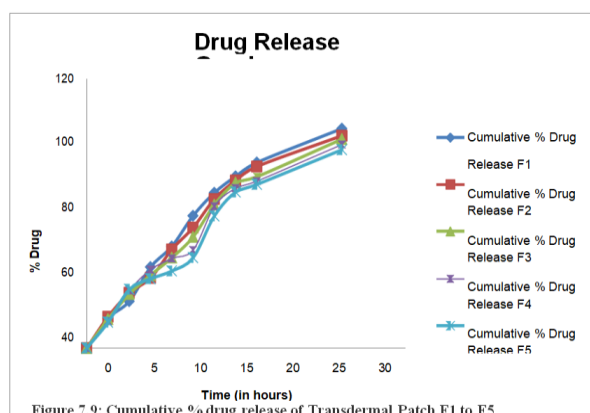
Stability Studies: All the prepared patch formulations were stored at temperature 40˚C and 75% RH for a period of two months and further re-evaluated for the drug release and drug content. The results shows that there was no signs of deterioration of patches and no change in drug release and drug content after two months. The results are given in the table 8.

Table 8: Comparative stability study of different formulation

S. No.	Batches	pH	Drug release (%)	Drug content (%)
1.	F1	7.43 0.01	97.86 1.08	98.99 0.53
2.	F3	7.39 0.02	94.69 0.97	98.97 0.48
3.	F5	7.38 0.01	93.13 0.57	97.89 0.65
4.	F7	7.42 0.02	90.73 0.69	97.96 0.38
5.	F9	7.38 0.02	88.42 1.78	98.93 0.72

Conclusion:

All the Transdermal Patches formulated were evaluated for their physicochemical evaluation parameters pH, thickness, weight uniformity, folding endurance, moisture uptake, and moisture content, drug content, tensile strength, water vapour permeation, in vitro drug release and stability studies. The five formulations F1 to F5 were

prepared using polymers in combination Hydroxy Proply methyl Cellulose and Ethyl Cellulose. Dibutyl phthalate used as plasticizer and Dimethyl sulphoxide as a permeation enhance Methanol and chloroform used as solvents. They were used in order to achieve better sustained and controlled drug release over a period of 24 hours. % Drug release study reveals that from all the five formulations. F1 formulation containing HPMC and EC in the same ratio emerged as better formulation because it showed better release with sustained effect as compared to other formulations of Metoprolol Succinate. Stability of the prepared patches were observed for two months shows no change in pH, drug content and drug release when calculated.

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