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Design and Development of Ramipril Transdermal Patch For Treating Hypertension

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ABSTRACT

A good Transdermal patch containing can be formulated by solvent casting technique using as film former and propylene glycol as plasticizer such Transdermal patches are advantages in providing effective treatment for Hypertension with enhanced patient compliance. From the in-vitro release results observed that the films prepared by using different ratios of HPMCK 15M, PVPK30 and EC Transdermal Ramipril patches were formulated using DBP as a plasticizer and DMSO as a penetration enhancer proved to exhibit better release characteristics. It can be reasonably concluded that Ramipril can be formulated into Transdermal patches to prolong its release characteristics. Thus the formulation HPMCK15M and Ethyl Cellulose was found to be the best for controlled release. The Cumulative drug release from Formulation R10 was found to be 99.64% after 24 hrs. So the formulation R10 is emerged as ideal formulation for Ramipril because it showed better release with sustained effect as compared to other formulations.

1. INTRODUCTION

Currently, Transdermal drug delivery is one of the most promising methods for drug application through the skin to the systemic circulation. Transdermal drug delivery systems are pharmaceutical preparations intended to be applied on the unbroken skin in order to achieve the ingredients to the systemic circulation after passing through the skin barrier. They are defined as the self-contained, discrete dosage forms which when applied to the intact skin, deliver the drug(s) through the skin at a controlled rate to systemic circulation. Thus Transdermal film can increase the therapeutic value of Ramipril by avoiding specific problems with the drug like gastro-intestinal disturbances, low absorption, hepatic first-pass metabolism, short half-life. So, Transdermal film is one of the most feasible drug delivery system .The present study aims to formulate and evaluate Transdermal drug delivery for sustained release of Ramipril.

2. MATERIALS AND METHODS

Ramipril procured from Zydus Cadila, Ahmedabad, and HPMC K15M. EC, PVPK-30 gift sample from Micro advance research Centre, Bangalore, Glycerin, DMSO, DBP purchased from Finar chemicals Limited, Ahmedabad, Methanol purchased from Jiangsu Huaxi International trade Co Limited, China.

Development of transdermal films: In the present study matrix type Transdermal films of Ramipril were prepared by solvent casting method. Locally fabricated glass mould was used for this purpose. The Transdermal films were prepared using the polymers in different ratios. The polymeric solution of EC, HPMC K15M, PVP were prepared dissolving separately in ethanol. The solutions are mixed in different ratios using DBP as plasticizer. A weight amount of drug was dissolved in suitable solvent and dispersed in polymer mixture, poured into the hard rigid surface. Solvent evaporation was controlled by covering with the placement of funnel in its inverted position. After 24 hours the films were removed and kept in desiccators to remove any adhering solvents. Then the films were wrapped in aluminum foil, packed in self-sealing cover and kept in desiccators.

i. Uniformity of weight: This was done by weighing three different patches of individual batch taking the uniform size at random and calculating the average weight of 3. The tests were performed on films which were dried at 60°C for 4h prior to testing.

ii. Thickness: Thickness of all the membranes were measured at three different points on each membrane in digital caliper and average of three readings was taken.

iii. Folding endurance: This was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

iv. Swelling index: The polymeric Film were weighed accurately and allowed to swell on an agar gel plate contain 2% w/v. Individual membranes were weighed periodically until they showed a constant weight.

v. Percentage of moisture content: The Film were weighed individually and stored in desiccator consists of fused calcium chloride at room temperature for 24 hours. Individual membranes were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

vi. Percentage of moisture uptake: A weighed Film stored in a desiccator at room temperature for 24 hours was taken out and exposed to 84% relative humidity (a saturated solution of potassium chloride) in a desiccator until a constant weight for the membrane was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

vii. Tensile strength and extension: Tensile strength of the films was determined by using house field universal testing machine. The sensitivity of the machine was 1 mg – 500 mg. It consists of two load cell jaws. The upper one is movable and lower one was fixed. The films of specific size (4x1cms) was fixed between these grips and upper jaw was moved at a speed of 100 mm/min. (ISI STD speed) applying force gradually till the films break. The tensile strength of the films was taken directly from the dialed reading in kilogram and extension of film in mm.

viii. Drug content uniformity: A fabricated film was cut into small pieces and put in a 100 ml of phosphate buffer 7.4 pH solution. This is then stirred in a mechanical stirrer to get a homogenous solution and filtered. The filtrate of 1 ml was withdrawn and made up to 100 ml, again from this 1 ml was pipette out and made up to 10 ml with buffer 7.4 PH. The drug content was analyzed at 212 nm by UV Spectrophotometer.

ix. Surface PH: Surface pH of the patches was determined by the method described by Bottenberg et al. The patches were allowed to swell by keeping them in contact with 0.5 ml of double distilled water for 1 hour in glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1 minute

x. In-vitro drug release studies: A modified paddle over disc USP dissolution apparatus was used in these studies. A transdermal matrix ˆlm was mounted on the disc and placed at the bottom of the dissolution vessel. The dissolution medium was 900 ml of phosphate buffered saline of pH 7.4. The apparatus was equilibrated to 37±0.5°C and the stirrer paddle speed was set at 50 rpm. The samples were withdrawn at appropriate time intervals and analyzed at 212 nm using a spectrophotometer. The amount of drug released was calculated from the standard curve.

xi. Skin irritancy study: The primary skin irritation test was performed for prepared Transdermal films. Skin irritation test was performed since skin is a vital organ through which drug is transported. Skin irritation studies were performed on healthy rabbits (average weight: 1.5 to 2.25 kg). The dorsal surface (50 cm^2) of the rabbits was cleaned, and the hair was removed by shaving. The skin was cleansed with rectified spirit. The best formulation (RM4) was placed over the skin with the use of adhesive tape and was removed after 24 hours. The resulting skin reaction was evaluated according to the weight score as per Table 3 and compared with control group placing the placebo film.

Table.1.Formulation of Ramipril transdermal patches

Ingredients(Mg)	R1	R2	R3	R4	R5	R6
Ramipril	20	20	20	20	20	20
HPMC K15m	300	-	-	150	-	150
EC	-	300	300	150	150	150
PVP K-30	-	-	-	-	150	-
DBP (%)	30	30	30	30	30	30
DMSO	5	5	5	5	5	5
Methanol	20	20	20	20	20	20

Table.2.Formulation of Ramipril transdermal patches

Ingredients(mg)	R7	R8	R9	R10	R11	R12
Ramipril	20	20	20	20	20	20
HPMC K15M	400	-	-	200	-	200
EC	-	400	-	200	200	-
PVP K-30	-	-	400	-	200	200
DBP (%)	30	30	30	30	30	30
DMSO (%)	5	5	5	5	5	5
Methanol	20	20	20	20	20	20

Table.3.Possible score for skin irritation

Test	Skin reaction	Score
Erythema	Very slight erythema	1
	Well defined erythema	2
	Moderate to severe erythema	3
	Severe erythema	4
	Total possible erythema score	4
Edema	Very slight edema	1
	Well defined edema	2
	Moderate to severe edema	3
	Severe edema	4
	Total possible edema score	4
	Total score for primary skin irritation	8

3. RESULTS AND DISCUSSION

Compatibility study using differential scanning calorimetry (DSC): The DSC analysis of Ramipril alone showed a sharp endothermic peak at 112.55 C corresponding to its melting point, it indicate the drug sample was pure. The DSC analysis of Ramipril with sodium alginate and conjugated sodium alginate demonstrated negligible change in the melting point of Ramipril (112.55 C), which indicated that the polymer do not interact with the drug. The DSC thermograms of Ramipril and Ramipril with Ethyl cellulose, PVP K-30, HPMC 15 M.

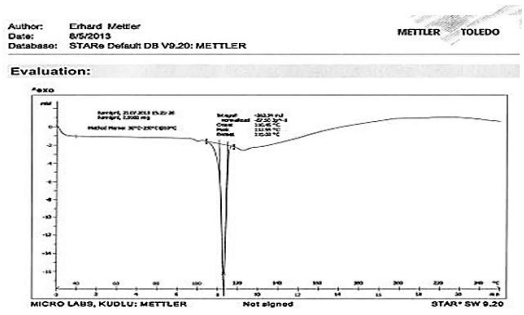

Figure.1.Differential scanning colorimetry of Ramipril

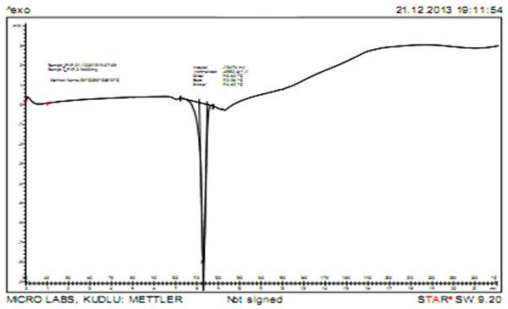

Figure.2.Differential scanning colorimetry of Rmipril with EC

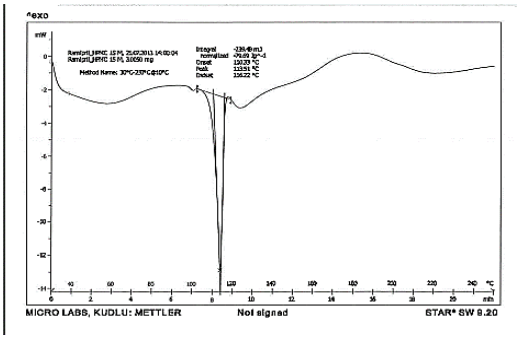

Figure.3.Differential scanning colorimetry of Rmipril with HPMC K 15 M

Table.4.Evaluation of formulated patches

Formulation code	Weight Variation test	Thickness	Folding endurance	% moisture absorption	% moisture loss	Swelling index
R1	0.4563±0.004509	0.2146±0.002517	88	6.415±0.17003	9.51266±2.682658	61.5333±1.078579
R2	0.468 ±0.002646	0.2113±0.003512	67	11.7936±0.0055	3.658±0.017321	47.3066±0.941081
R3	0.4453±0.003512	0.203±0.002	69	7.288±0.01026	4.30533±0.012702	99.7±0.277128
R4	0.4926±0.005033	0.2016±0.002517	78	5.7593±0.02478	1.8563±0.021362	103.42±0.428576
R5	0.4956±0.003512	0.2073±0.001528	72	3.9373±0.018193	4.066±0.001732	87.0133±1.708957
R6	0.4793±0.006658	0.205±0.005292	75	6.185±0.01601	4.47466±0.0004619	93.2366±1.062324
R7	0.5816±0.004509	0.2426±0.001528	71	8.8146±0.014799	5.756667±0.020207	63.7066±0.404145
R8	0.5693±0.006658	0.2616±0.003512	85	7.7476±0.004359	3.93033±0.004041	60.83333±3.608439
R9	0.5763±0.004041	0.2886±0.001528	82	5.5113±0.010066	3.91633±0.021362	55.70667±0.404145
R10	0.5923±0.004163	0.2273±0.002517	81	5.4643±0.017349	4.05333±0.057735	69.63±0.34641
R11	0.5913±0.003512	0.2316±0.003055	98	6.4673±0.022539	3.91133±0.000577	57.61333±0.525389
R12	0.5843±0.002082	0.2293±0.004509	92	8.8633±0.022539	2.10766±0.004619	74.72±0.277128

Table.6.Evaluation of formulated patches

Formulation code	Appearance	Surface PH	Tensile strength	Water vapour transmission rate	% of drug Release
R1	Transparent	5.3	3.156667±0.011547	0.014933±0.000404	97.4±0.45
R2	Transparent	5.1	2.803333±0.132791	0.0034±0.000346	97.98±0.42
R3	Transparent	5.8	3.176667±0.011547	0.006833±0.000577	99±0.25
R4	Transparent	5.6	3.29±0.034641	0.0094±0.000346	97.37±0.48
R5	Transparent	5.4	3.29667±0.0132791	0.009367±0.000289	97.00±0.75
R6	Transparent	5.2	3.51±0.121244	0.002±0.000693	97.52±1.4
R7	Transparent	5.5	3.513333±0.063509	0.011867±0.000808	97.99±0.79
R8	Transparent	5.6	3.67±0.017321	0.013567±0.000808	98.82±0.39
R9	Transparent	5.3	3.58±0.242487	0.0149±0.000346	97.9±0.70
R10	Transparent	5.8	3.73333±0.092376	0.006633±0.000231	98.95±0.43
R11	Transparent	5.7	3.32333±0.196299	0.009167±0.001097	97.8±0.52
R12	Transparent	5.4	3.106667±0.011547	0.011333±0.000115	98.2±0.48

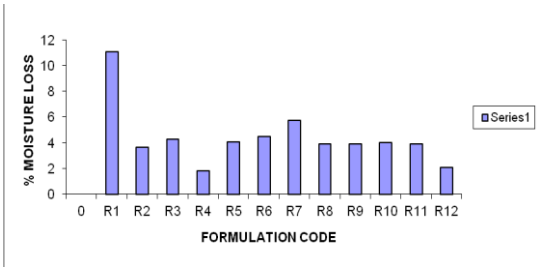

Figure.4. Percent moisture loss of TDDS patches

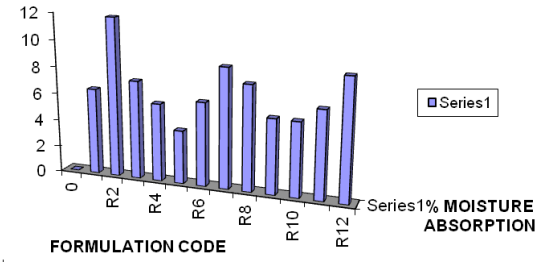

Figure.5. Percent moisture absorption of TDDS patches

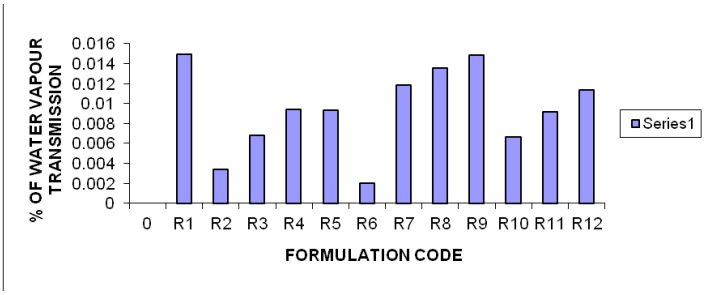

Figure.6.Water vapour transmission study of TDDS patch

Table.7.Diffusion studies for R10

Time	Concentration	Time	Concentration
1	17.69	8	36.99
2	20.91	10	45.21
4	30.56	12	77.21
6	32.15	24	93.29

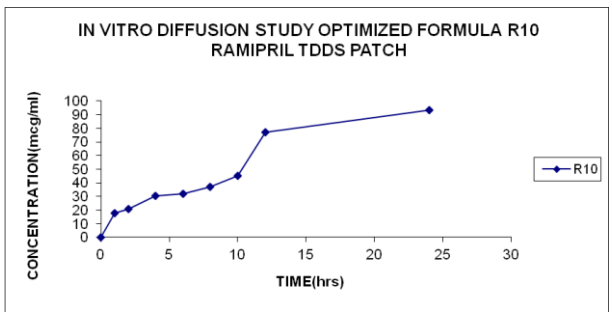

Figure.7.In-vitro diffusion studies for optimized R10

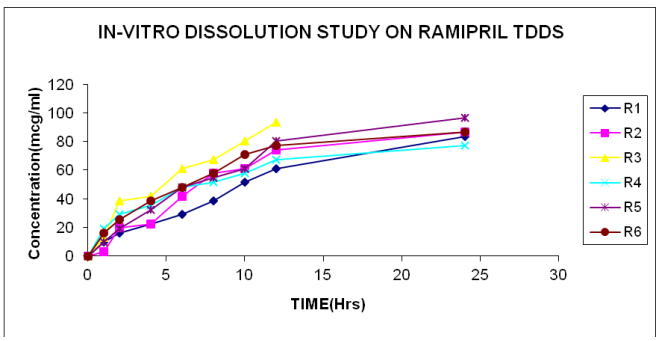

Figure.8.Dissolution profiles for R1- R6

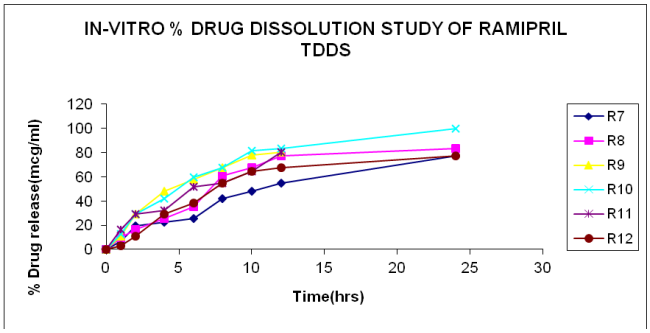

Figure.9.Dissolution profiles for R7-R12

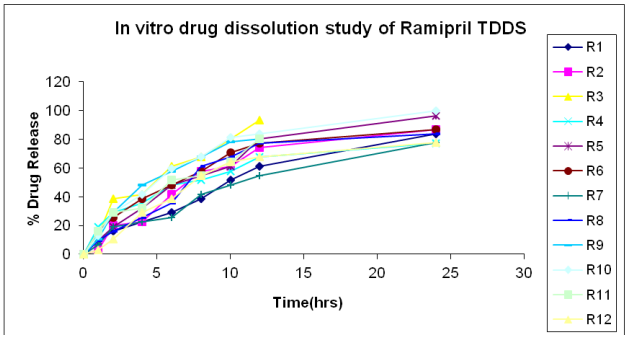

Figure.10.Dissolution profile for Ramipril TDDS

Stability studies:

Table.8.Physicochemical evaluation of formulation R10 during stability studies

Parameters	0 days*	30 days*		60 days*	
		A	B	C	D
Weight Uniformity (mg)	0.592	0.593	0.596	0.596	0.597
Folding endurance	81	78	75	74	71
Patch Thickness (mm)	0.227	0.227	0.227	0.228	0.229
% Drug content	98.95	98.90	98.91	98.91	98.85
%Moisture Content	5.061	5.065	5.062	5.064	5.062
%Moisture uptake	4.056	4.006	4.051	4.016	4.026
WVTR (gm/cm^2/hr)10^{-4}	0.0067	0.0069	0.0060	0.0062	0.0071

Table.8.Score of skin irritation for Ramipril TDDS

Test	Skin reaction	Score
Erythema	Very slight erythema	0
	Well defined erythema	0
	Moderate to severe erythema	0
	Severe erythema	0
Edema	Very slight edema	0
	Moderate to severe edema	0
	Severe edema	0
Total primary score for erythema and edema [for primary irritation]		0

Skin irritation studies: No sign of erythema or edema was observed.

Scanning Electron Microscopy (SEM Study): Photomicrograph of the Transdermal film are shown below. It is vivid from SEM photomicrographs that the films were discrete, uniform distribution of polymers.

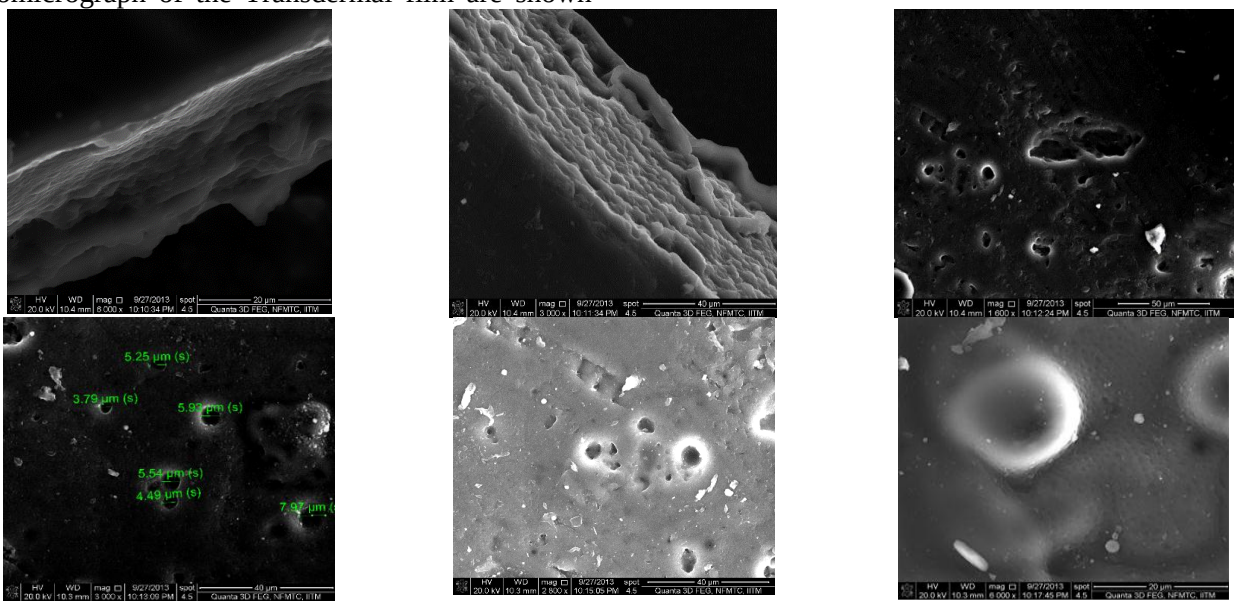

Figure.11.SEM analysis of Optimized formula

4. CONCLUSION

It can be concluded that the formulation has achieved of Transdermal drug delivery system ie extended release and reduced frequency of administration and has also avoided the first pass effect .RM4 emerged as the most satisfactory formulation in so far as its technological properties were concerned. On the stability studies it concluded that there is no change in the physical characteristics of Ramipril patches and the cumulative %drug release. Thus the formulated patches were stable. Therefore, Ramipril patch may be a potential formulation for the management of patients with chronic hypertension as a long term release formulation in Transdermal drug delivery system

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