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Formulation and Development of Transdermal Patches with Antihypertensive Drug

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ABSTRACT

Olmesartan medoxomil was found to be water soluble as tested by the vessel shaking method. The formulation P9 had maximum release of all four drugs after 24 hr. However, the tensile strength of P9 batch was the least of all other factorial design batches. Based on Q24 values, batch P9 was selected as optimized batch. Though the tensile strength was low, it was not below the desirable limit. Among P1 to P9 formulations, P9 showed lowest tensile strength, highest % moisture content, % moisture uptake, WVTR and folding endurance. drug loaded patch and gel significantly restored the decreased serum nitric oxide levels compared to to MPA-induced hypertensive rats. On application of Patch (P9) and Patch (P8) restored the NO concentration (67.2 ± 3.7 and 65.3 ± 5.3 µmol/ml). The elevated MDA levels were significantly decreased by the drug loaded patch (P9) and patch (P8) (2.0 ± 0.05 and 2.1 ± 0.02 nmol/ml). The drug loaded patch (P9) and patch (P8) significantly restored the decreased GSH levels (8.9 ± 0.3 and 8.0 ± 0.1 µmol/mL, respectively). Overall, transdermal patches represent a safe, effective, and patient-friendly delivery system for antihypertensive therapy.

KEYWORDS: Transdermal, Hypertension, olmesartan indapamide, losartan, TDDS

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INTRODUCTION

First transdermal patch approved in 1979 by FDA was of Scopolamine for motion sickness. Nitroglycerine was the second patch authorized in 1981. A large variety of patches for transdermal application are available on the market[1]. Transdermal delivery not only allows for continuous, predetermined, and consistent drug administration, but also allows for regulatedinput of medicines with short biological half-lives and prevents pulsed entrance into systemic circulation, avoiding unwanted side effects. The oral route is the most common method of drug delivery, but it has some drawbacks, such as first pass metabolism (the rapid uptake and metabolism of an agent by the liver into inactive compounds immediately after enteric absorption and before it reaches the systemic circulation), drug degradation in the gastrointestinal tract due to enzymes, pH, and other factors. A new medication delivery method based on transdermal patches was developed to address these issues[2]. A Transdermal Drug Delivery System (TDDS) is a method of delivering drugs via the skin for local or systemic therapeutic effects. It is, together with oral medicine and injectable, one of the primary study topics for third-generation pharmacological preparations[3]. The drug's delivery technique, whichis easy, simple to use, non-invasive, and improves patient compliance, is one of the reasons behind this[4]. TDDS also minimizes drug concentration fluctuations in the blood, maintains stableplasma levels, reduces the risk of overdosing, and facilitates drug detection[5,6]. Simultaneously, it avoids issues associated with oral administration, such as the impact of the gastrointestinal environment (pH, enzyme activity, drug-food interaction) on therapeutic effectiveness and the 'first pass effect.' Transdermal drug delivery systems were commonly used to treat various skin disorders. Also, substantive applications have been found in the management of angina pectoris, pains, smoking, cessation & neurological disorders such as Parkinson's disease[7,8]. Transdermal patches, are one of the novel pharmaceutical dosage form for the delivery of drugs upon application to the skin and into the bloodstream. By nature the patches are expected to provide controlled/sustained/modified delivery of drugs for defined period of time with predefined rate. Because the skin is such an efficient barrier, only medicines with a low molecular weight may beadministered this way. Transdermal patches are currently accessible in a wide range of medicines. The first commercially available prescription patch was authorized by the US Food and Drug Administration in December 1979. Since then transdermal drugs continued to gain popularity along with further improvements to improve safety and efficacy. Further major step was the production of patches delivering peptide and even protein substances including growth hormone, insulin, and vaccines ect[9]. Transdermal patches can be categorized into three categories - first generation, second generation, and third generation. They are available in different sizes & having more than one ingredients. Once they apply on normal skin they deliver active ingredients into systemic circulation passing through skin barrier. A transdermal patch containing high dose of drug inside is retained on the skin for prolonged period of time and enters into blood systemic circulation by diffusion process[10].

MATERIALS AND METHOD

Preformulation Studies

Preformulation testing is the first step in the rational development of dosage forms of a drug. It can be defined as an investigation

of physical and chemical properties of drug substance, alone and when combined with excipients.

Development of Matrix Type Transdermal Patch

Selection of solvents: Solvent was selected based on solubility of drugs. Solubilities of drugs were determined in various solvents like methanol, ethanol, water, acetone, dichloromethane, chloroform, etc.

Selection of polymers: Preliminary screening was carried out to check the effect of various polymer combinations on transdermal patch formulation. Composition of preliminary trial batches A1 to A6 is shown in Table below. Polymeric films were evaluated based on their thickness, weight, % flatness and folding endurance.

Preparation of polymeric film: Various polymer combinations were accurately weighed and dissolved in dichloromethane: methanol (50:50). The polymeric dispersion was stirred for 2 min to remove entrapped air bubbles. Polyethylene Glycol 400 (PEG) was added to the polymeric dispersion, which was then casted in a petridish smeared with castor oil. Casting solvent was allowed to evaporate overnight at room temperature to obtain dry films.

Selection of plasticizers: Plasticizers were selected based on nature, solubility in solvents, polymer combinations and folding endurance of patch. Various plasticizers were tested like propylene glycol, polyethylene glycol 400, castor oil, glycerol, dibutyl phthalate.

Selection of backing membrane: Backing membrane works as a flexible film and provides low water vapor transmission and high oxygen transmission rates. Polyvinyl Alcohol (PVA) is used in the fabrication of transdermal drug delivery systems as the backing membrane. Preliminary trial of backing membrane was done using various concentration of PVA as shown in Table. Based on Water Vapor Transmission Rate (WVTR) and tensile strength, optimum concentration of PVA was selected.

WVTR is defined as the quantity of moisture transmitted through unit area of film in unit time. Glass cells were filled with 2 g of anhydrous calcium chloride and a film of specified area was affixed onto the cell rim. The assembly was accurately weighed and placed in a humidity chamber (80 ± 5% RH) at 27 ± 2 °C for 24 hrs. The cell was reweighed and WVTR was determined using following formula.

WVTR = Final Weight - Initial Weight/Area × 24

Selection of permeation enhancers: Penetration enhancers from natural origin offer several benefits over their synthetic counter parts. Therefore menthol was selected as permeation enhancer and was added at a concentration of 3-5% w/w in the patch.

Preparation of medicated Transdermal Patch: Backing membrane was prepared by casting 5% aqueous solution of PVA followed by drying at 60° C for 6 hrs. Drug loaded matrix type transdermal patches were prepared by solvent casting method. Petri-dish with total area of 38.465 cm^2 was used. Polymers were accurately weighed and dissolved in dichloromethane: methanol (50:50). The polymeric dispersion was stirred for 2 min to remove entrapped air bubbles. PEG 400 and menthol were added to the polymeric dispersion. Drug was accurately weighed, dissolved in ethanol and added to polymeric dispersion. Tween 80, a surfactant was also added to polymeric dispersion. The solution was casted on the backing membrane placed in a petridish and dried at room temperature for 24 hrs. An inverted funnel was placed over the petridish to prevent fast evaporation of the solvent. After 24 hrs the dried patches were taken out, cut into small pieces (9 cm^2) and stored in desiccators for further studies.

Full Factorial (3^2) design for optimization of formulation variables

A 2^3 full factorial design was applied for optimization of variables like, concentration of Eudragit RL 100, concentration of Eudragit RS 100 and %w/w of menthol. Tensile strength and Q24(% drug release at 24 hrs) were taken as dependent variables in this study.

Table No. : Design batches of transdermal patch using 3^2 full factorial

Formulation code	Concentration of Eudragit RL100 (X1)	Concentration of Eudragit RS100 (X2)	Drug in ethanol (mg)	PEG (ml)	Tween-80 (ml)	Menthol (%)
P1	200	200	25	0.2	0.15	3
P2	200	500	25	0.2	0.15	3
P3	200	800	25	0.2	0.15	3
P4	500	200	25	0.2	0.15	3
P5	500	500	25	0.2	0.15	3
P6	500	800	25	0.2	0.15	3
P7	800	200	25	0.2	0.15	3
P8	**800**	**500**	**25**	0.2	0.15	**3**
P9	**800**	**800**	**25**	0.2	0.15	**3**

All the reading were recorded in triplicate manner (n=3) and expressed as (Mean ± SD)

***In-vivo* Antihypertensive Studies**

Animals care and Handling:

The animal experimental protocol was approved by the Institutional Animals Ethical Committee (IAEC), Bhopal, (M.P). Approval Number, **Ref/08/IAEC/Pharmacy/2024 Dated: 20/04/2024.** Male & female Wistar albino rats (200-250g) were

provided by Institution, Bhopal Madhya Pradesh, India. The animals were housed in standard conditions of temperature (25±2^{0}C) and 12:12 h light-dark cycle. The rats were fed with commercial diet and water *ad Libitum*. The experiment was approved by the Institutional Ethics Committee, (M. P.).

Antihypertensive activity: Healthy male Albino Wistar rats were (weighing approximately 250 ± 25g) selected for this study, and all the animals were healthy during the study. The dose for the rats was determined based on the body weight and surface area ratio. Forty two rats were taken and divided into seven groups (Group I to VII) each carrying six rats. Group I was considered as control and hypertension was induced in other rats (Group II to VII) by injecting MPA (20mg/kg/week) subcutaneously for two weeks. Treatments given to each group were indicated in Table.

Table No. : Experimental design and group distribution of animal

S. No.	Groups	Treatments	No. of rats in groups	BP Measurement intervals (h)
1	Group-I	Normal control	6	0, 1,2, 3, 4, 6, 8, 10, 12, 24
2	Group-II	Only MPA	6	0, 1,2, 3, 4, 6, 8, 10, 12, 24
3	Group-III	MPA + Olmesartan pure	6	0, 1,2, 3, 4, 6, 8, 10, 12, 24
4	Group-IV	MPA + Patch (P9)	6	0, 1,2, 3, 4, 6, 8, 10, 12, 24
5	Group-V	MPA + Patch (P8)	6	0, 1,2, 3, 4, 6, 8, 10, 12, 24

RESULT AND DISCUSSION

Preformulation Studies:

Olmesartan medoxomil was found to be water soluble as tested by the vessel shaking method. From the solubility testing the solution was saturated and it was found that freely soluble in 0.1 N HCl, soluble in methanol, ethanol, chloroform, distilled water, 6.8 pH phosphate buffer and 0.1 N NaOH. Melting point of the drug Olmesartan was found to be 177 ^{O}C which is within the range of 175-178 ^{O}C. It complies with the purity of the drug sample. Lambda (λ) max of Olmesartan was determined in phosphate buffer pH 6.8 as 252 nm. From the standard calibration curve, it was observed that the drug obeys Beer's law in the concentration range of 2-12µg/ml in phosphate buffer of pH 6.8. Drug showed good linearity with the regression of co-efficient (R^2) of 0.998 and the equation for this line found 0.049x-0.015 which used in the calculation of the drug content as well as in dissolution study. Solubility of drugs in different solvents was determined. Ethanol was selected as a solvent for all drugs as they were found to be soluble in ethanol. All the trial batches were almost similar as far as % flatness was concerned. However, among all the trial batches, batch A6 exhibited maximum folding endurance. Moreover, the density of batch A6, as reflected from its thickness and weight (mg/cm^2), was the highest among all the 6 batches. Hence batch A6 which contained Eudragit RL 100 and Eudragit RS 100 as polymers was found to have desirable properties. Eudragit RL 100 is relatively more permeable to water than Eudragit RS 100.

An optimum combination of the Eudragit RL 100 and Eudragit RS 100 could be able to achieve desired release profile. So other batches were eliminated and concentration of Eudragit RL 100 and Eudragit RS 100 were assigned as independent variable in 3^2 factorial designs in order to understand their effect and to optimize concentration of both for desired release profile. As all the drugs are lipophilic in nature, hydrophilic plasticizer was preferred. Polyethylene glycol 400 was selected as a plasticizer as it showed maximum folding endurance and is hydrophilic in nature. Among the five trial batches of transdermal patches prepared for selection of backing membrane, the one prepared using 5% polyvinyl alcohol (PVA) exhibited low water vapour transmission rate (WVTR) and sufficient tensile strength. Increasing the concentration of PVA beyond 5% did not lead to significant change in WVTR and tensile strength. Hence 5% PVA was selected as a backing membrane for all further batches of transdermal patches. Menthol, a monocyclic monoterpene free from toxic effects, has been approved as a penetration enhancer in the transdermal delivery of several drugs. From the review of literature, menthol was found to enhance the transdermal transport in the range of 0-12.5%. Penetration enhancers from natural origin offer several benefits over synthetic and chemical permeation enhancers, such as sustainable mass production from a renewable resource and lower cost depending on the type of extraction used. So menthol was selected as a permeation enhancer.

Optimization of Full Factorial Design Batches

A 3^2 full factorial design was used to optimize the variables for formulation of transdermal patch. Three factors were evaluated, each at 2 levels, and experimental trials were performed at all 9 possible combinations.

The formulation P9 had maximum release of all four drugs after 24 hr. However, the tensile strength of P9 batch was the least of all other factorial design batches. Based on Q24 values, batch P9 was selected as optimized batch. Though the tensile strength was low, it was not below the desirable limit.

Table No. : Experimental Runs and Measured Responses of 3^2 Full Factorial Design Batches of Transdermal Patch

Formulation code	Concentration of Eudragit RL100 (X1)	Concentration of Eudragit RS100 (X2)	Tensile strength (Kg/cm^2)	Q24 (% Drug release at 24 hr)
P1	200	200	3.53 ± 0.03	73.82
P2	200	500	3.37 ± 0.02	77.71
P3	200	800	3.12 ± 0.04	79.02
P4	500	200	2.85 ± 0.02	82.91
P5	500	500	2.45 ± 0.03	83.01

P6	500	800	2.31 ± 0.05	85.92
P7	800	200	2.04 ± 0.05	87.15
P8	800	500	1.77 ± 0.01	88.13
P9	800	800	1.59 ± 0.23	90.21

All the reading were recorded in triplicate manner (n=3) and expressed as (Mean ± SD)

Evaluation of transdermal patches:

Table : Result of Evaluation parameters of 3^2 Full Factorial Design Batches of Transdermal Patch

Formulation code	Thickness (mm)	Weight (g/9cm^2)	% Flatness	Folding endurance
P1	0.36 ±0.02	0.293 ±0.012	99.02 ±0.32	70.66 ±2.12
P2	0.39 ±0.03	0.301 ±0.020	99.43 ±0.43	63.43 ±1.83
P3	0.30 ±0.01	0.315 ±0.031	99.20 ±0.20	57.82 ±1.23
P4	0.28 ±0.01	0.325 ±0.044	98.23 ±0.32	68.53 ±1.05
P5	0.25 ±0.04	0.336 ±0.053	99.36 ±0.53	63.33 ±0.25
P6	0.22 ±0.04	0.374 ±0.047	99.53 ±0.41	53.81 ±1.25
P7	0.56 ±0.03	0.323 ±0.031	98.93 ±0.52	70.43 ±2.19
P8	**0.47 ±0.05**	**0.361 ±0.024**	**99.36 ±0.55**	**62.83 ±0.27**
P9	**0.41±0.02**	**0.411 ±0.021**	**99.34 ±0.35**	**54.82 ±0.64**

All the reading were recorded in triplicate manner (n=3) and expressed as (Mean ± SD)

Table : Result of Evaluation parameters of of 3^2 Full Factorial Design Batches of Transdermal Patch

Formulation code	% moisture content	% moisture uptake	WVTR(g/cm^2) 24hr	Drug content (%w/w)
P1	1.32 ±0.09	2.32± 0.02	2.32± 0.23	98.92
P2	1.23 ±0.03	2.33 ±0.03	2.63± 0.22	97.72
P3	1.22 ±0.02	2.64 ±0.01	2.83± 0.63	98.88
P4	2.12± 0.01	3.22± 0.02	3.32± 0.24	99.03
P5	2.16 ±0.03	3.64± 0.01	3.74± 0.42	100.01
P6	2.43 ±0.03	3.84± 0.07	3.98± 0.23	98.87
P7	3.22 ±0.03	4.02± 0.09	4.23 ±0.45	99.82
P8	**3.41 ±0.02**	**4.15± 0.02**	**4.33 ±0.23**	**100.14**
P9	**3.83 ±0.03**	**4.42± 0.07**	**4.74 ±0.27**	**99.85**

All the reading were recorded in triplicate manner (n=3) and expressed as (Mean ± SD)
Among P1 to P9 formulations, P9 showed lowest tensile strength, highest % oisture content, % moisture uptake, WVTR and folding endurance.

7.4 *In-vitro* drug release study

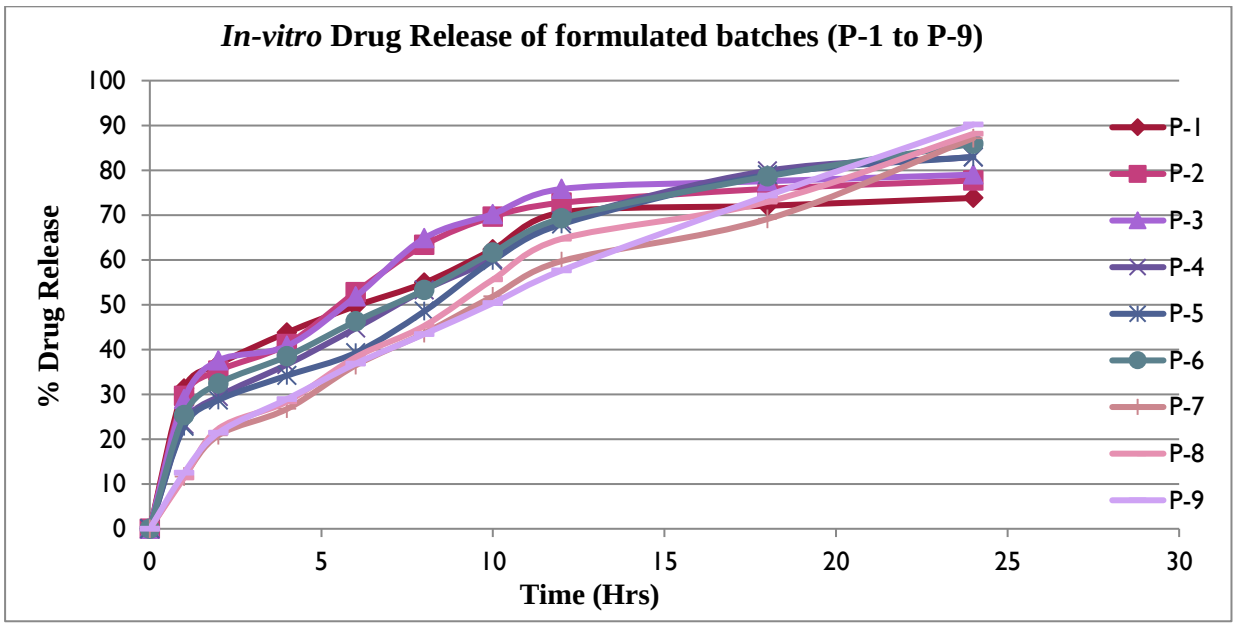

Figure : *In-vitro* Drug Release of all formulated batches (P-1 to P-9)

Table No. 7.20: Drug release Kinetics of Olmesartan loaded Patch (P-8)

Kinetics Model	Patch (P-8)		Patch (P-9)	
	Linearity Equation	R^2	Linearity Equation	R^2
Zero order	y = 3.487x + 13.06	0.932	y = 3.510x +11.72	0.963
First order	y = -0.035x + 1.996	0.981	y = -0.038x + 2.019	0.960
Higuchi model	y = 18.26x – 3.294	0.983	y = 18.26x – 3.294	0.983
Peppas-Korsmeyer model	y = 0.625 + 1.099	0.986	y = 0.602x + 1.109	0.995

***In-vivo* antihypertensive studies**

Table No. : Effect of optimized formulations on BP in MPA induced Hypertensive rats

Groups	Treatments	Mean systolic BP (mm-Hg)				
		Pre-treatment	1 hour	6 hours	12 hour	24 hours
Group-I	Normal control	120.15	120.32	120.47	120.56	121.72
Group-II	Only MPA	121.22	164.76	161.63	158.62	160.18
Group-III	MPA + Olmesartan pure	118.82	163.72	150.31	147.55	146.62
Group-IV	MPA + Patch (P9)	119.56	164.47	143.26	132.17	125.21
Group-V	MPA + Patch (P8)	120.64	162.73	146.32	135.28	126.37

Table No. : Effect of optimized formulations on BP in MPA induced Hypertensive rats

Groups	Treatments	Mean systolic BP (mm-Hg)			
		Pre-treatment	Post-MPA treatment	Post patch treatment	% Reduction in BP
Group-I	Normal control	120.15	-	-	-
Group-II	Only MPA	121.22	164.76	-	-
Group-III	MPA + Olmesartan pure	118.82	163.72	146.62	10.45 %
Group-IV	MPA + Patch (P9)	119.56	164.47	125.21	23.87 %
Group-V	MPA + Patch (P8)	120.64	162.73	126.37	22.34 %

Determination of Serum Nitric Oxide (NO) Concentration: The drug loaded patch and gel significantly restored the decreased serum nitric oxide levels compared to to MPA-induced hypertensive rats. On application of Patch (P9) and Patch (P8) restored the NO concentration (67.2 ± 3.7 and 65.3 ± 5.3 µmol/ml)

Determination of Malondialdehyde (MDA): The elevated MDA levels were significantly decreased by the drug loaded patch (P9) and patch (P8) (2.0 ± 0.05 and 2.1 ± 0.02 nmol/ml).

Determination of Glutathione (GSH): The drug loaded patch (P9) and patch (P8) significantly restored the decreased GSH levels (8.9 ± 0.3 and 8.0 ± 0.1 µmol/mL, respectively).

Table No. : Effect of optimized transdermal Patch and Gel on NO concentration

Groups	Treatments	NO (µmol/mL) ± SD	MDA(Nmol/mL) ± SD	GSH (µmol/mL) ± SD
Group-I	Normal control	76.3 ± 7.3	1.6 ± 0.01	11.8 ± 0.2
Group-II	Only MPA	38.4 ± 2.6	3.5 ± 0.01	7.2 ± 0.3
Group-III	MPA + Olmesartan pure	63.4 ± 5.1	1.9 ± 0.03	9.3 ± 0.1
Group-IV	MPA + Patch (P9)	67.2 ± 3.7	2.0 ± 0.05	8.9 ± 0.3
Group-V	MPA + Patch (P8)	65.3 ± 5.3	2.1 ± 0.02	8.0 ± 0.1

CONCLUSION

The formulation and development of transdermal patches for antihypertensive drugs present a promising alternative to conventional oral therapies, especially for chronic conditions like hypertension that require long-term management. It was concluded from the studies that transdermal patches offer controlled and sustained drug release, improving therapeutic efficacy and reducing dosing frequency. Bypass first-pass metabolism, enhancing bioavailability of antihypertensive drugs. Physicochemical evaluations (e.g., thickness, tensile strength, moisture content) confirm patch stability and uniformity. In-vitro permeation studies showed steady drug diffusion, aligning with zero-order or Higuchi kinetics, depending on the polymer matrix. Patient compliance was improved due to non-invasive administration, reduced side effects, and ease of use. Overall, transdermal patches represent a safe, effective, and patient-friendly delivery system for antihypertensive therapy.

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