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Formulation and Development of Transdermal Gel with Antihypertensive Drug

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KEYWORDS

Transdermal, Hypertension, Homogeneity, Stability studies, Sustained release.

ABSTRACT

Introduction: Transdermal drug delivery systems (TDDS) offer a promising alternative by enabling the controlled release of drugs through the skin into systemic circulation. These gels can bypass gastrointestinal degradation and hepatic first-pass metabolism, potentially enhancing the bioavailability of antihypertensive agents. Hypertension is a widespread chronic condition that significantly increases the risk of cardiovascular diseases, stroke, and kidney failure.

Objectives: The present study focuses on the formulation and evaluation of transdermal gels containing Olmesartan medoxomil, an antihypertensive agent.

Methods: Weighed quantity of Carbopol 934P was soaked overnight in distilled water containing Sodium benzoate 0.2% w/v. HPMC K15M solution was prepared in water and homogenised. Both polymers were mixed with gradual stirring and methyl salicylate and propylene glycol were added to the mixture.

Results: The present investigation successfully demonstrated the formulation and optimization of transdermal gels containing Olmesartan medoxomil for effective antihypertensive therapy.

Conclusion: The developed transdermal gels offer a promising alternative to oral antihypertensive therapy, with the potential to improve patient compliance and achieve sustained drug delivery.

INTRODUCTION:

Hypertension is a widespread chronic condition that significantly increases the risk of cardiovascular diseases, stroke, and kidney failure[1]. Although oral antihypertensive medications are commonly used to manage blood pressure, they often face limitations such as poor bioavailability, frequent dosing requirements, and first-pass hepatic metabolism, which can reduce therapeutic effectiveness and patient adherence[2]. Transdermal drug delivery systems (TDDS) offer a promising alternative by enabling the controlled release of drugs through the skin into systemic circulation[3]. Among various TDDS formats, transdermal gels stand out due to their ease of application, non-invasiveness, and ability to maintain steady plasma drug levels over extended periods[4]. These gels can bypass gastrointestinal degradation and hepatic first-pass metabolism, potentially enhancing the bioavailability of antihypertensive agents[5]. This research focuses on the formulation and evaluation of transdermal gels incorporating antihypertensive drugs[6]. It aims to optimize the gel composition for effective skin permeation, stability, and patient acceptability. By exploring this delivery route, the study seeks to contribute to the development of more efficient and patient-friendly therapeutic options for long-term hypertension management.

OBJECTIVES: To develop olmesartan transdermal gel by using suitable techniques. To Study the effect of polymers concentration on drug release. To study release mechanism of drug. To perform preformulation study of drug. To study the effect of different permeation enhancers on the drug penetration. To evaluate the transdermal gel. To study the In-vitro drug release/permeation through excised rat abdominal skin. In-Vivo characterization of the formulation against hypertension induced laboratory animals. To carry out the stability studies of optimized formulations

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METHODS:

Development and evaluation of transdermal gel:

Selection of polymers: Preliminary screening was carried out using various polymers (HPMC, methyl cellulose, sodium alginate, Carbopol, HPC and CMC) combinations. Their effect on transdermal gel was assessed from the viscosity, homogeneity and clarity of the gel.

Selection of plasticizers: Plasticizers were selected based on parameters like nature, solubility, moisture content of resulting gel. Different plasticizers were tested like, propylene glycol, polyethylene glycol 400, glycerin, castor oil.

Drug excipients compatibility study: Drug and excipients were mixed and placed at room temperature for 24 hours. Drug excipients compatibility was checked by FT-IR spectroscopy.

Development of medicated transdermal gel: Weighed quantity of Carbopol 934P was soaked overnight in distilled water containing Sodium benzoate 0.2% w/v. HPMC K15M solution was prepared in water and homogenised. Both polymers were mixed with gradual stirring and methyl salicylate and propylene glycol were added to the mixture. Drug was accurately weighed, dissolved in ethanol in a stoppered glass vial. Weighed amount of menthol was added to drug solution which was then transferred to polymeric mixture and homogenized. The pH was adjusted to 6.8 by adding triethanolamine to induce gel formation by carbopol (125).

Full Factorial (3^2) design for optimization of formulation variables: A 3^2 full factorial design was applied for optimization of formulation variables like, concentration of Carbopol 934P, concentration of HPMC K15M and %w/w of menthol. Viscosity and Q24(% drug release at 24 hrs) were taken as dependent variables in this study.

Table No. 1: Design batches of transdermal gel using 3^2 full factorial

Formulation code	HPMC K15M (mg)	Carbopol 934P (mg)	Menthol (%w/w)	Drug (%w/w)	Propylene glycol (% w/w)	Methyl Salicylate (% w/w)	Sodium benzoate (% w/w)
G1	1000	500	4%	1 %	10 %	5 %	0.2 %
G2	1000	1000	4%	1 %	10 %	5 %	0.2 %
G3	1000	1500	4%	1 %	10 %	5 %	0.2 %
G4	2000	500	4%	1 %	10 %	5 %	0.2 %
G5	2000	1000	4%	1 %	10 %	5 %	0.2 %
G6	2000	1500	4%	1 %	10 %	5 %	0.2 %
G7	3000	500	4%	1 %	10 %	5 %	0.2 %
G8	3000	1000	4%	1 %	10 %	5 %	0.2 %
G9	3000	1500	4%	1.%	10 %	5 %	0.2 %

In vivo antihypertensive studies:

Chemicals and drugs: Pure active pharmaceutical ingradient Olmesartan medoxomil, Macleods Pharmaceuticals Ltd., Raniphool, Sikkim, India). Methylprednisolone acetate (MPA) injection (Depo-Medrol™) manufactured by Pfizer was purchased from a medical shop.

Animals care and Handling: The animal experimental protocol was approved by the Institutional Animals Ethical Committee (IAEC), Bhopal, (M.P). Approval

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Number, **Ref/08/IAEC/Pharmacy/2024 Dated: 20/04/2024.**

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.

RESULTS:

Organoleptic properties: Olmesartan medoxomil was a White to light yellowish-powder color, unpleasant odor and crystalline powder with bitter in taste. All above describe properties of Olmesartan complies with the standards as reported earlier.

Solubility: 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 determination: 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.

Development of Transdermal Gel:

Selection of polymers: All the preliminary trial batches of transdermal gel showed viscosity variation ranging from 2140 to 108000 cps as shown in Table. All the batches showed good clarity and homogeneity. Among all the polymers used, carbopol 934P was reported to have more gelling property. Carbopol 934P polymer proved to be a promising carrier for controlled release of active phytoconstituents in the gel formulation. Batch D7, which contained HPMC K15M and carbopol 934P, showed optimum viscosity. Therefore combination of HPMC K15M and carbopol 934P was selected.

Selection of plasticizers and permeation enhancers: Propylene glycol was selected as a plasticizer as it is hydrophilic in nature and suitable for hydrogel formulation. Menthol was selected as a permeation enhancer for gel.

Full Factorial design batches: A 3^2 full factorial design was used to optimize the variables for formulation of transdermal gel. Three factors were evaluated, each at 2 levels, and experimental trials were performed at all 9 possible combinations. Preliminary studies suggested that combination of HPMC K15M and Carbopol 934P may be able to achieve desired drug release. Hence amount of HPMC K15M, amount of Carbopol 934P and amount of menthol were assumed as independent variables in a 3^2 full factorial design. The amount of Carbopol 934P was taken as 500 mg, 1000 mg and 1500, amount of HPMC K15M was taken as 1000 mg, 2000 mg and 3000mg while amount of menthol was taken as permeation enhancer, which corresponded to -1, 0 and +1 levels, respectively. The factorial design batches were evaluated for physical appearance, clarity, homogeneity, spreadability, extrudability, pH and drug content study. Viscosity and Q24 (% cumulative drug release at 24 hrs) were taken as dependent variables. The results are presented in Table.

Table No. 2: Experimental Runs and Measured Responses of Transdermal gel

Formulation code	**% w/w of Carbopol 934P (X1)**	**% w/w of HPMC 15M (X2**	**Viscosity (1×10^3) (Centipoise)**	**Q24 (% Drug release at 24 hr)**
G1	0.5	1.0	50.31 1.22	80.12
G2	0.5	2.0	45.22 1.72	82.92
G3	0.5	3.0	53.24 1.02	89.88
G4	**1.0**	**1.0**	**58.35 2.02**	**94.23**

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G5	1.0	2.0	65.34 1.01	82.34
G6	1.0	3.0	70.23 1.21	79.22
G7	1.5	1.0	64.22 2.73	71.74
G8	1.5	2.0	70.29 1.02	65.32
G9	1.5	3.0	81.22 1.31	62.53

Evaluation of prepared Transdermal Gel: The factorial design batches were evaluated for homogeneity, spreadability, clarity, extrudability, pH and drug content study. All gel formulations were found to contain 98.29 – 99.92 % of drugs. They were yellowish in color, clear and showed good homogeneity, spreadability and extrudability. The spreadability and extrudability were better in G1, G2, G3 and G5. However, homogeneity and clarity were best in G4. The pH of all formulations was 6.7 -7.2. As the concentration of menthol increased in the formulations, the viscosity decreased. Among G1 to G9 formulations, G4 showed very good homogeneity, spreadability, extrudability and optimum viscosity.

In-vitro drug release study: In-vitro drug release data of 3^2 full factorial design batches of transdermal gel for drug are given in Table below. The formulation G3 and G4 had shown higher % release of drugs compared to all other formulation. This may be due to high % of Carbopol 934P. From the graph of cumulative % drug release vs. time, it can be concluded that the drug release appeared to increase more with an increasing amount of the Carbopol 934P as compared to HPMC K15M. A marked effect of menthol on release of drugs was observed.

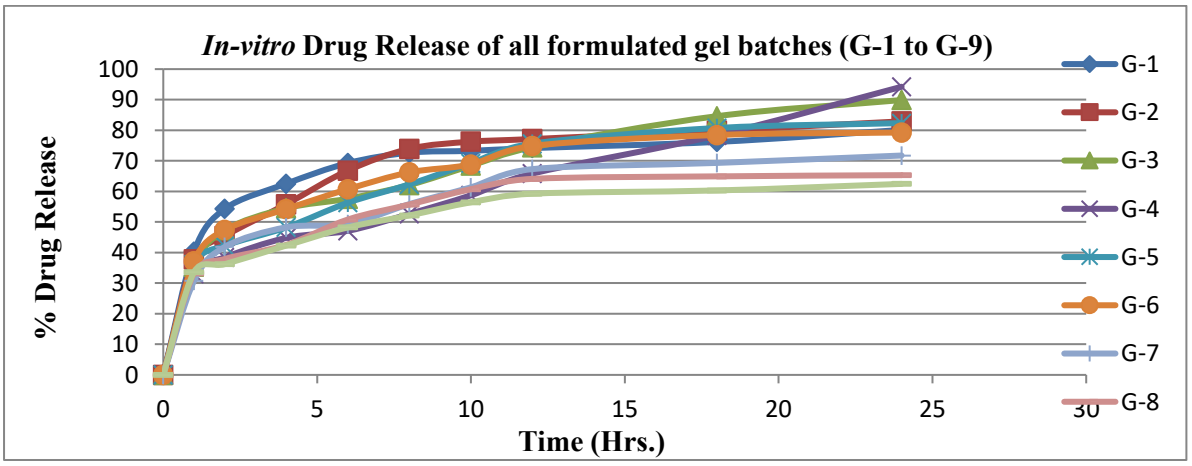

Figure No. 1: In-vitro Drug Release of all formulated gel batches (G-1 to G-9)

Accelerated Stability Study of Olmesartan loaded Gel:

Table No. 3: Accelerated stability study of Olmesartan loaded Gel (G3)

Evaluation Parameter	**Initial**	**Results after 90 days**		
		2-8 ^{O}C	**Room temp.**	**40 ^{O}C**
Viscosity (Centipoise)	53.24 ± 1.02	53.22 ± 1.73	52.32 ± 0.97	51.42 ± 0.81

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Q24 (% Drug release at 24 hr)	89.88	88.12	87.42	85.64
Appearance	Clear	Clear	Clear	Clear
Homogeneity	Homogenous	Homogenous	Homogenous	Homogenous
Spreadability	+++	+++	+++	+++
Extrudability	+++	+++	+++	+++
Determination of pH	6.8 ± 0.1	6.7 ± 0.2	7.1 ± 0.1	6.9 ± 0.1
Drug content	98.29	98.64	97.21	98.21
In-vitro drug release	89.88	89.73	85.16	86.34

- No, + satisfactory, ++ good, +++ very good

Table No. 4: Accelerated stability study of Olmesartan loaded Gel (G4)

Evaluation Parameter	**Initial**	**Results after 90 days**		
		2-8 ^{O}C	**Room temp.**	**40 ^{O}C**
Viscosity (Centipoise)	58.35 ± 2.02	58.19 ± 1.31	57.42 ± 1.62	55.82 ± 1.52
Q24 (% Drug release at 24 hr)	94.23	92.26	93.73	91.72
Appearance	Clear	Clear	Clear	Clear
Homogeneity	Homogenous	Homogenous	Homogenous	Homogenous
Spreadability	+++	+++	+++	+++
Extrudability	+++	+++	+++	+++
Determination of pH	7.0 ± 0.2	7.1 ± 0.1	6.8 ± 0.2	6.9 ± 0.1
Drug content	99.72	98.92	98.21	97.16
In-vitro drug release	94.23	95.36	94.16	93.19

- No, + satisfactory, ++ good, +++ very good

In-vivo antihypertensive studies:

Table No. 5: 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

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Group-IV	MPA + Gel (G4)	119.72	164.51	142.14	133.27	120.53
Group-V	MPA + Gel (G3)	120.43	163.17	145.21	130.21	121.42

Table No. 6: 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/ gel 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 + Gel (G4)	119.72	164.51	120.53	26.73 %
Group-V	MPA + Gel (G3)	120.43	163.17	121.42	25.59 %

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 Gel (G4) and Gel (G3) restored the NO concentration (74.2 ± 3.2 and 72.3 ± 2.7 µmol/mL) as compared to the MPA-induced hypertensive rats group (38.4 ± 2.6 µmol/mL).

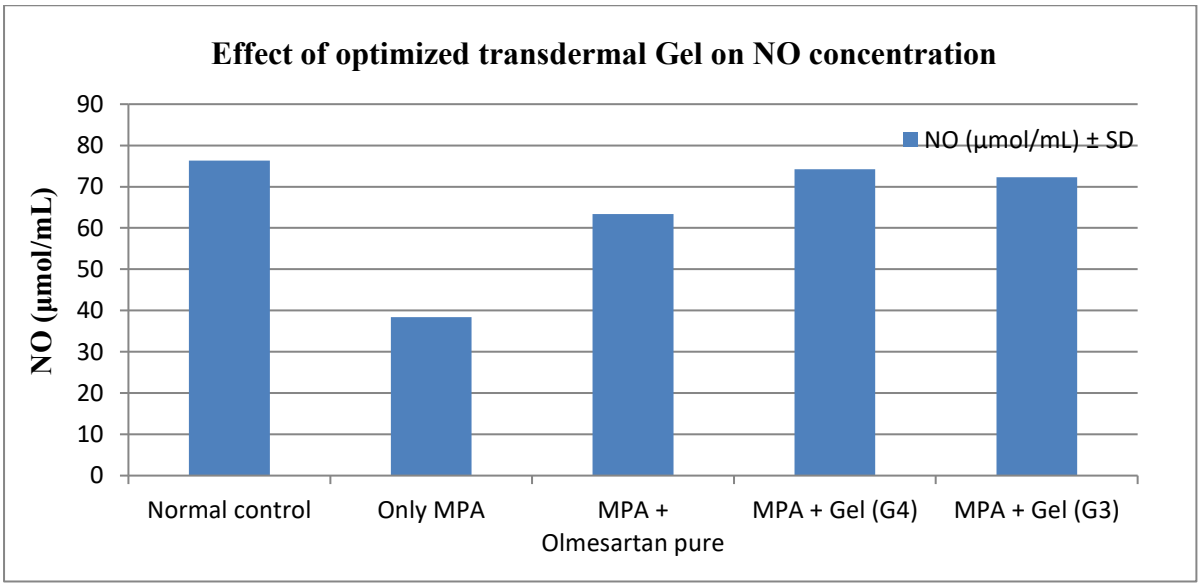

Figure 2: Effect of optimized transdermal Gel on NO concentration

Determination of Malondialdehyde (MDA): The elevated MDA levels were significantly decreased by the drug loaded gel (G4) and gel (G3) (1.7 ± 0.01 and 1.8 ± 0.02 nmol/mL, respectively) in the liver homogenate compared to to MPA-induced hypertensive rats (3.5 ± 0.01nmol/mL).

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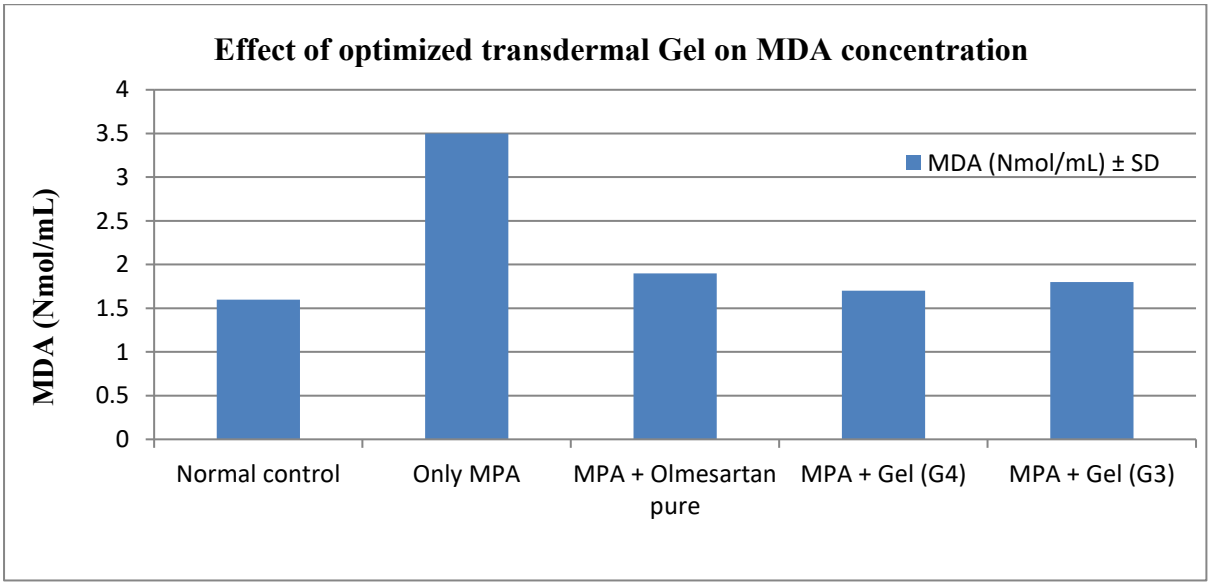

Figure 3: Effect of optimized transdermal Gel on MDA concentration

Determination of Glutathione (GSH): The drug loaded gel (G4) and gel (G3) also significantly restored the decreased GSH levels (10.9 ± 0.1 and 9.5 ± 0.2 µmol/mL, respectively) in liver homogenate compared to MPA-induced hypertensive rats (7.2 ± 0.3 µmol/mL).

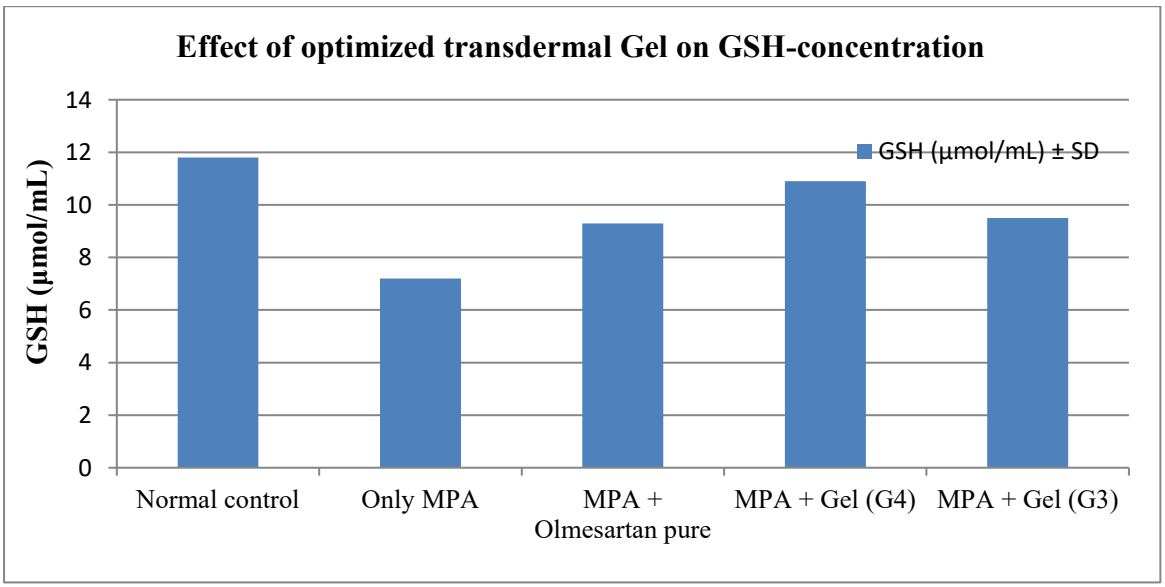

Figure 4: Effect of optimized transdermal Gel on GSH-concentration

Histopathological Examination of Heart: Examination of the heart of the normal control group revealed that the heart tissues were within the normal limit, where the muscle fibers were arranged in bundles parallel to each other. Microscopic examination of heart tissues in MPA-induced hypertensive rats showed dilatation of blood capillaries, hemorrhage, myocardial fibrosis and cellular infiltration between the cardiac tissues. The cross sections of the heart of rats in the drug loaded patch or gel showed less degeneration in the cardiac muscle bundles with no hemorrhage observed and decreased cellular infiltration.

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DISCUSSION:

The present investigation successfully demonstrated the formulation and optimization of transdermal gels containing Olmesartan medoxomil for effective antihypertensive therapy. Through systematic evaluation of polymers, plasticizers, and permeation enhancers, Carbopol 934P and HPMC K15M emerged as suitable gelling agents, with menthol enhancing drug permeation. Among the factorial design batches, formulations G3 and G4 exhibited favorable physicochemical properties, optimal viscosity, and superior drug release profiles.

In-vitro and in-vivo studies confirmed the therapeutic potential of these gels, showing significant blood pressure reduction and improved biochemical markers in hypertensive animal models. Stability assessments further validated the robustness of the optimized formulations under various storage conditions. Overall, the developed transdermal gels offer a promising alternative to oral antihypertensive therapy, with the potential to improve patient compliance and achieve sustained drug delivery.

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