RESEARCH ARTICLE

Preparation of Mouth Dissolving Sublingual Film of Fixed Dose Combination of Hydrochlorothiazide and Losartan Potassium and Statistical Optimization of Film

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ABSTRACT

Fast-dissolving films (FDFs) are innovative dosage forms offering advantages such as improved patient compliance, rapid onset of action, precise dosing, and favorable taste. Particularly beneficial for patients unable to swallow or require immediate drug absorption, FDFs dissolve rapidly in the mouth, releasing medication directly into the oral cavity. The sublingual application enhances drug delivery due to the high permeability of the sublingual mucosa, bypassing hepatic first-pass metabolism. This route is advantageous for drugs like losartan potassium (LP) and hydrochlorothiazide (HCZ), which benefit from enhanced bioavailability and faster onset of action. Preformulation studies included UV spectroscopy for λmax determination (LP: 282 nm, HCZ: 250 nm), DSC for thermal analysis (LP: 289.11°C, HCZ: 104.76°C), and solubility studies confirming LP's solubility in acidic pH and HCZ's increased solubility in pH 6.7 buffer. Compatibility studies using FTIR and DSC validated stability with excipients. Formulation optimization with HPMC E15 resulted in films with characteristics like film weight (145.66–167.0 mg), thickness (0.246–0.326 mm), folding endurance (898.0–1274.0), pH (6.0–6.70), disintegration time (77.66–174.6 s), tensile strength (77.04–141.90 g/cm²), and drug release profiles (LP: 68.78–96.22%, HCZ: 59.49–95.43% at 21 minutes). In summary, this study successfully developed LP and HCZ FDFs with optimized characteristics, demonstrating their potential in hypertension management and improving therapeutic outcomes.

Keywords: Fast dissolving films, Patient compliance, Rapid onset of action, Sublingual administration, Enhanced bioavailability, Formulation optimization.

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INTRODUCTION

Fast-dissolving films offer numerous advantages, such as improved patient compliance, quick onset of action, precise dosing, and pleasant taste compared to other oral dosage forms. These films are easy to administer and handle. When placed in the mouth, they quickly disintegrate and dissolve, releasing the medication without needing water or chewing. This is ideal for children, the elderly, and those with difficulty swallowing, such as patients with emesis, motion sickness, dysphagia, or mental illness.[1-3]

Sublingual application of fast-dissolving films offers immediate drug absorption due to high permeability and vascularity, bypassing first-pass metabolism and increasing bioavailability. Losartan, an antihypertensive drug, and hydrochlorothiazide (HCTZ), a diuretic, can both benefit from this form. Losartan reaches removes plagiarism, and a sublingual film can improve its bioavailability. HCTZ has 45 to 55% oral bioavailability, which a fast-dissolving film can enhance. Combining losartan and HCTZ in a fast-dissolving film can effectively lower blood pressure, reduce stroke risk, and improve treatment outcomes.[4-7]

MATERIALS & METHODS

Materials

Losartan Potassium is supplied by Indoco Remedies Pvt Ltd, Hydrochlorothiazide by Merck India Pvt Ltd, and Hypromellose METHOCEL™ E3, E5, and E15 Premium are provided as complimentary samples by Colorcon Asia Pvt Ltd.

Preformulation Study of Drug

Confirm λmax for LP and HCZ by measuring absorbance of 5 µg/mL solutions in a combined solution of phosphate buffer at pH 6.7 and methyl alcohol from 200 to 400 nm, determine melting points using the capillary tube technique, record FTIR spectra over 4000 to 400 cm^{-1}, measure loss on drying

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Table 1: Placebo film formulation with HPMC E15 and HPMC E5

CODE	*F21*	*F22*	*F23*	*F24*	*F25*	*F26*
HPMC E 15	3% (300 mg)	4% (400 mg)	5% (500 mg)	(50 mg)	1% (100 mg)	2% (200 mg)
HPMC E5	0.5% (50 mg)	0.5% (50 mg)	0.5% (50 mg)	5% (50 mg)	4% (400 mg)	3% (300 mg)
PEG 400	(0.5 mL-5%)	(0.5 mL-5%)	(0.5 mL-5%)	(0.5 mL-5%)	(0.5 mL-5%)	(0.5 mL-5%)
Water qs (mL)	10	10	10	10	10	10
Film properties	GS	GS	GS	GS	GS	GS
Peelability	P	P	P	P	P	P
Tachyness	NS	NS	NS	NS	NS	NS
Clarity	C	C	C	C	C	C
DT	1.55 minutes	2 minutes 20 seconds	3 minutes	2 minutes	2.30 minutes	3 minutes 40 seconds

X: No result, GS: Good & stiff, P: Positive, NS: Non-sticky, C: Clear

by drying 0.1 g samples at 100°C for 4 hours, analyze DSC thermograms from 30 to 180°C at 5°C/min under nitrogen, determine saturation solubility using the shake flask technique at 37°C, and estimate %purity by measuring absorbance of methanol-dissolved samples at 282 nm (LP) and 250 nm (HCZ) using calibration curves.[1-8]

Powder characterization (physical properties)

For measuring the angle of repose, the funnel method was utilised. Bulk density (BD) was calculated by pouring 10 g of sample 50 mL graduated cylinder, tapped density (TD) was measured by tapping the sample until the volume was constant, Carr's index was calculated as ((TD - BD) / BD) x 100, Hausner's ratio was calculated as TD/ BD.[9]

Method of Analysis for fixed-dose combination of LP and HCZ (LH)

Simulated Salivary Fluid

Dissolve 8 g NaCl, 0.19 g $K_2HPO_4 \cdot H_2O$, and 2.38 g Na_2HPO_4 in purified water and dilute to 1000 mL (pH 6.7).[9]

Stock Solution

Dissolve 100 mg of losartan potassium (LP) or hydrochlorothiazide (HCZ) in simulated salivary fluid to make a 1-mg/mL solution, then dilute to 0.1 mg/mL (100 µg/mL).

Simultaneous Estimation

Prepare 10 ppm solutions, scan with UV spectrophotometer, identify wavelengths, create dilutions (5–40 µg/ml for LP, 5–50 µg/mL for HCZ), measure absorbances, formulate simultaneous estimation equations using absorptivity coefficients.[10]

Cx = (A2ay1-A1ay2) / (ax2ay1-ax1ay2), Cy= (A1ax2-A2ax1) / (ax2ay1-ax1ay2)

Where Cx = concentration of LP, ax1 = absorptivity of LP at 260.6 nm, A1 = absorbance at 260.6 nm, Cy = concentration of HCZ, ax2 = absorptivity of LP at 324 nm; ay1 = absorptivity of HCZ at 260.6 nm, A2 = absorbance at 324.0 nm, ay2 = absorptivity of HCZ at 324 nm.

Drug-excipient compatibility was assessed using DSC and FTIR to ensure no adverse reactions affecting shelf life or formulation safety.

Formulation of LH Sublingual Film

Placebo films were created through the solvent casting process with HPMC E15, PEG 400, and honey, using water and ethanol as solvents, while LH-mouth dissolving films included HPMC E15, PEG 400, sucralose, and raspberry syrup to mask bitterness and ensure safety (Tables 1 and 2 and Figure 1).

The process for preparation of mouth dissolving sublingual film

Mouth Dissolving Sublingual Film Optimization using 2^3 (Factorial Design)

An eight-formulation factorial design optimized the mouth-dissolving sublingual film for losartan potassium and

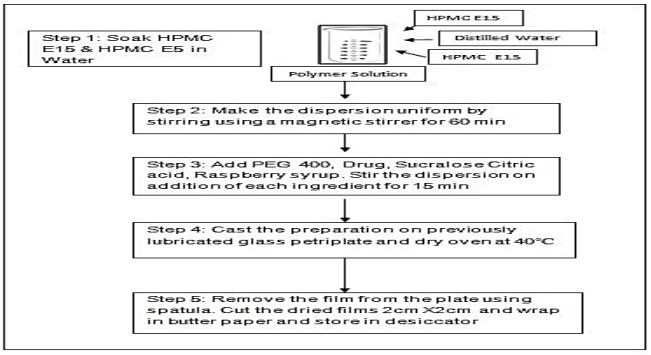

Figure 1: process for the preparation of mouth-dissolving sublingual film

Table 2: LP and HCZ MDF film formulation

S. No.	*Ingredients*	*Quantity*	*Use*
1	Losartan potassium	25 mg/film	Antihypertensive
2	Hydrochlorothiazide	12.5 mg/film	Antihypertensive
3	HPMC E15	3.5–4%	Agent of film-forming
4	HPMC E5	0.5–1%	Film-forming agent
5	PEG 400	2.5–5%	Plasticiser
6	Citric acid	10 mg	Saliva stimulating agent
7	Sucralose	10 mg	Sweetener
8	Raspberry syrup	1 mL	Flavoring agent
9	Water qs	10 mL	Solvent

Table 3: Composition of 2^3 factorial DSP MDF formulation

Ingredients	*LHI*	*LHII*	*LHIII*	*LHIV*	*LHV*	*LHVI*	*LHVII*	*LHVIII*
LP (mg)	794	794	794	794	794	794	794	794
HCZ (mg)	496	496	496	496	496	496	496	496
HPMC E15 (mg)	300	500	300	500	300	500	300	500
HPMC E5 (mg)	50	50	100	100	50	50	100	100
PEG 400 (mL)	0.2	0.2	0.2	0.2	0.4	0.4	0.4	0.4
Citric acid (mg)	10	10	10	10	10	10	10	10
Sucralose (mg)	10	10	10	10	10	10	10	10
Raspberry syrup (mL)	1	1	1	1	1	1	1	1
Water qs (mL)	10	10	10	10	10	10	10	10

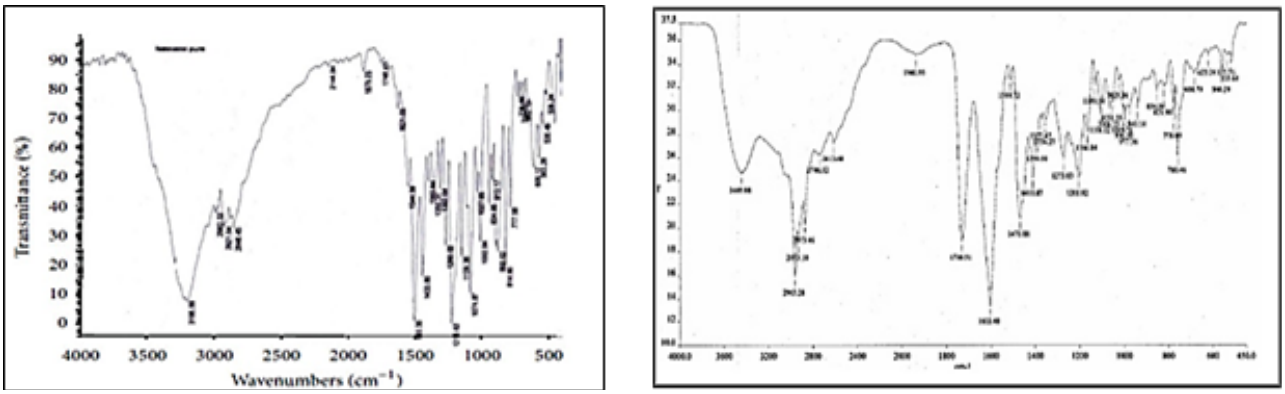

Figure 2: FTIR characteristic peaks of LP and HCZ pure drug

hydrochlorothiazide, evaluating the effects of HPMC E15, HPMC E5, and PEG 400 on DT (Disintegration Time), TS (tensile strength), drug releases at 21 minutes (Table 3).

Three Factor Two Level Design

Independent variables included X1 (HPMC E15) at 3.0 and 5.0%, X2 (HPMC E5) at 0.5 and 1.0%, and X3 (PEG 400) at 2 and 4%, with dependent variables being DT in seconds (Y1), TS in g/cm² (Y2), drug release percentages of losartan potassium (Y3) and hydrochlorothiazide (Y4) at 21 minutes.

Characterization of Mouth Dissolving Sublingual Film

Physical properties such as appearance, weight, thickness, folding insurance, pH and tensile strength were assisted for the LH films. USP apparatus was used to test disintegration in simulated salivary fluid at 37 ± 2°C; *in-vitro* drug release was measured at various intervals using a modified dissolution apparatus and spectrophotometry; assay involved dissolution in simulated fluid and spectrophotometric analysis; statistical optimization was performed with Design Expert software to find the impact of formulation variables on DT, TS, drug release, analyzed by two-way ANOVA; morphology was observed with scanning electron microscopy; and stability was assessed after 90 days of storage at 4 ± 2°C and 75 ± 5% RH, evaluating weight, thickness, folding endurance, assay, and drug release.[11-16]

Evaluation Parameters

Films were evaluated for physical appearance, surface texture, mechanical properties, tensile strength, and elasticity, with ideal characteristics being flat, stiff, robust, and easily dissolving. Key measurements included tensile strength (TS), percent elongation (%E), folding endurance (FE), disintegration time (DT), film thickness, drug content uniformity, surface pH, %moisture loss, *in-vitro* drug release, morphology *via* SEM, and separability classified as good, moderate, or poor.[17-19]

RESULTS & DISCUSSION

The observations and measurements recorded from the conducted experiments mentioned are presented systematically with the statistical treatment.

Preformulation study

Characterization of pure APIs (Table 4)

- *FTIR spectroscopy*

The FTIR spectrum of losartan potassium and hydrochlorothiazide individually disclosed characteristic peaks, which are shown respectively (Figure 2).

- *DSC study*

To verify the physical state of LP and HCZ in the finished dosage form, DSC of LP and HCZ were carried out (Figure 3).

Table 4: Characterization results of the pure drugs

S. No	*Tested parameters*		*Results*	
	LP		*HCZ*	
1.	Physical pppearance		White Powder	White Powder
	λmax (UV spectroscopy)			
2.	Methanol (nm)		282	250
	Phosphate buffer (PB) pH 6.7 (nm)		280	250 n
3.	Melting point (°C)		268–271	266–268
4.	LoD		0.087% (NMT 0.5%)	0.41% (NMT 0.5%)
5.	Equilibrium solubility study (mg/ml)	Methanol	0.569	0.653
		Water	0.041	0.160
		0.1 N HCl, pH 1.1	0.215	0.081
		Phosphate buffer of pH 6.7	0.115	1.321
		Phosphate buffer of pH 7.4	0.102	1.384
6.	%Purity		99.65% (98.0–102.0%)	99.86 % (98.0–102.0%)
7.	Characterization of powder			
	Angle of repose (º)		28.30	16.46
	BD (g/mL)		0.3125	0.4137
	TD (g/mL)		0.3448	0.5578
	Carl's index		9.368	42.361
	Hausner's ratio		1.1033	1.7328

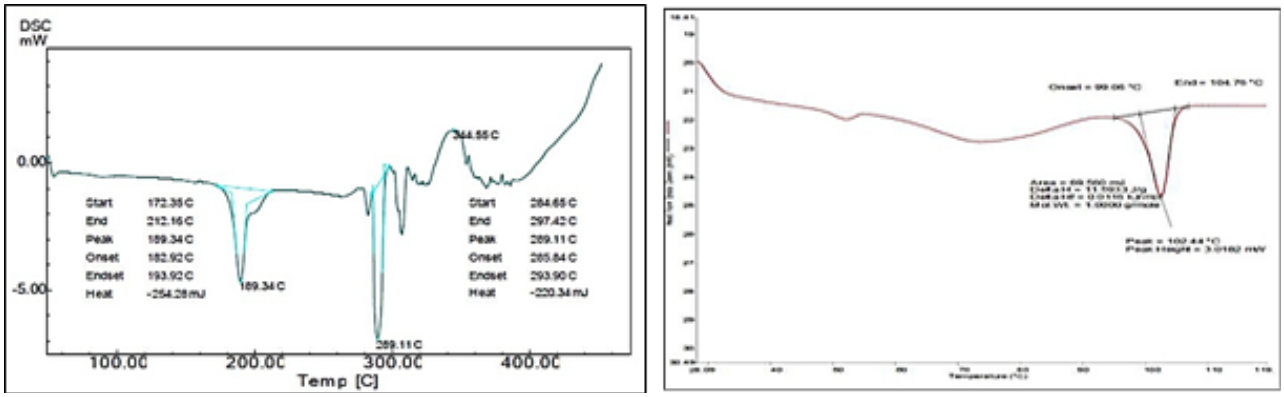

Figure 3: DSC thermogram of LP and HCZ pure drug

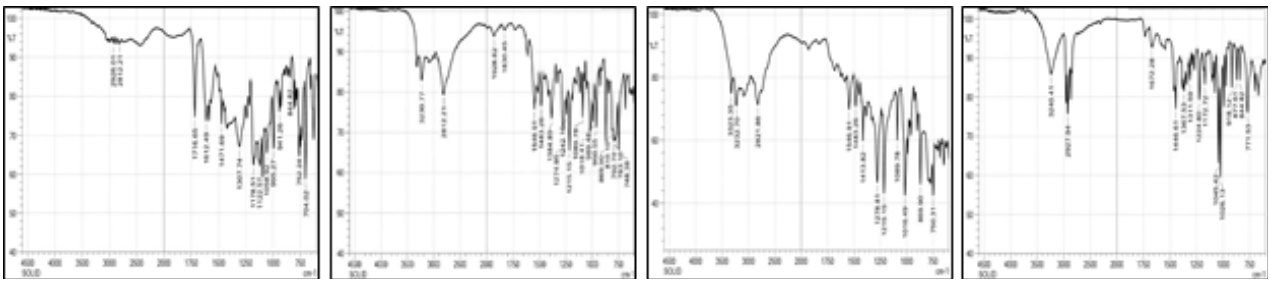

Figure 4: (a) Infrared spectra of LP (b) HCZ (c) LP and HCZ, and (d) LP and HCZ with excipients

- *Compatibility studies of Drugs and excipients*

Drug-excipient compatibility studies over one month showed no physical changes or interaction, as confirmed by FTIR spectroscopy, which indicated no shift in characteristic peaks of losartan potassium and hydrochlorothiazide (Figure 4).

- *Analytical method development and validation*

The standard curve for losartan potassium was developed using methanol and phosphate buffer, with 282 nm as the selected wavelength for quantitative estimation based on UV spectrophotometric analysis (Figure 5).

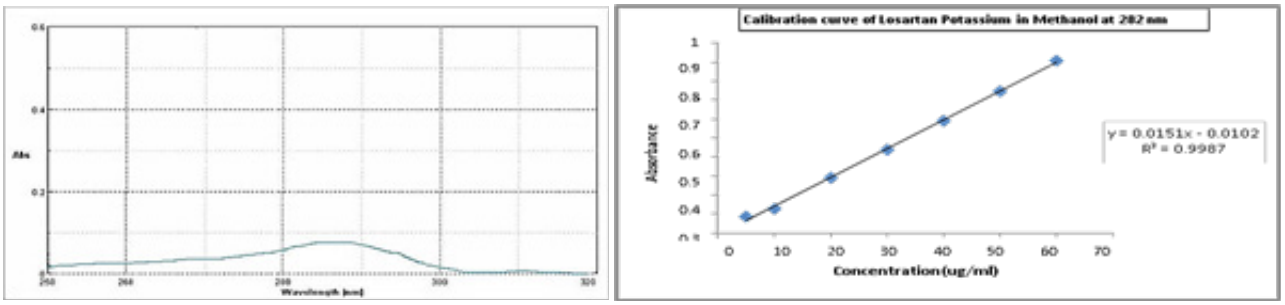

Figure 5: UV scan and Calibration curve of LP in methanol at λmax 282nm

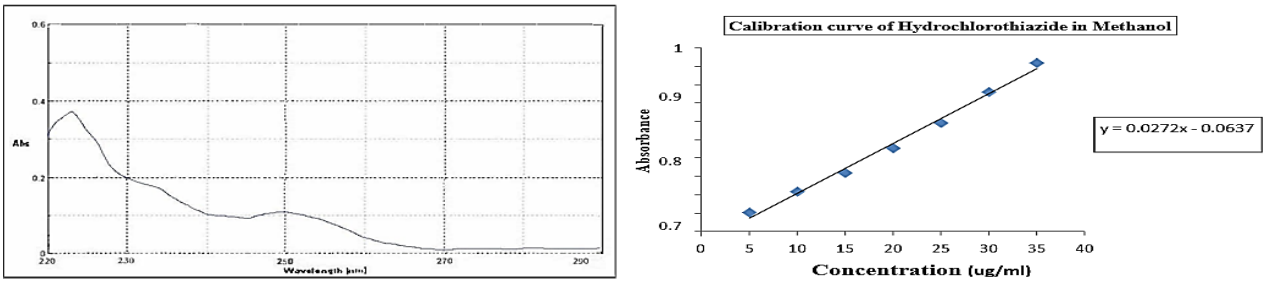

Figure 6: UV scan and calibration curve of HCZ

Losartan potassium reveals max. absorbance at 282 nm. In the range of 5 to 60 µg/mL, it shows compliance with Beer's law.

- *Preparation of standard curve of Hydrochlorothiazide*

Hydrochlorothiazide was analyzed using methanol and phosphate buffer, with 250 nm selected for quantitative estimation based on UV spectrophotometric analysis showing absorption maxima at this wavelength (Figure 6).

Hydrochlorothiazide reveals max. absorbance at 250 nm. In the range of 5 to 40 µg/ml HCZ complize with Beer's law.

- *Simultaneous estimation of LP and HCZ in phosphate buffer pH 6.7*

The method was validated per ICH guidelines. (Figure 7 and Table 5).

Formulation of MDF

Preliminary Screening for Placebo Films

Distilled water was chosen as the solvent for preparing mouth-dissolving sublingual films, with no cosolvent added. Preliminary trials showed HPMC E15 was excellent for film formation, and HPMC E5 worked well at 5%. A combination of HPMC E15 and E5 was used, with PEG 400 as a plasticizer. Formulations F21 to F26 produced transparent, smooth films, with F21, F22, and F23 being easily peelable. Thus, higher HPMC E15 and lower HPMC E5 concentrations were selected. Sucralose and raspberry syrup were used as sweeteners and flavoring agents, respectively (Table 6).

Optimization of DSP Mouth-Dissolving Sublingual Film by 2^3 Factorial Design

The fixed-dose combination mouth-dissolving sublingual films of losartan potassium (LP) and hydrochlorothiazide (HCZ) were prepared using the design of the experiment. The

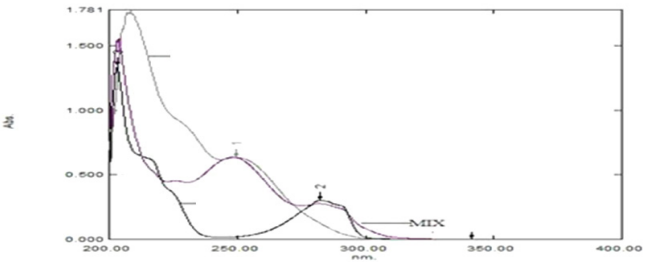

Figure 7: The overlain spectra of LP and HCZ

Table 5: Precision and accuracy data

Accuracy and precision data for quantification of HCZ in availability of LP		
Amount of hydrochlorothiazide added (µg/mL)	*Within day * (Amount found ± SD)*	*Between day * (Amount found ± SD)*
10	10.04 ± 0.05	10.07 ± 0.04
20	20.03 ± 0.03	20.12 ± 0.12
30	30.17 ± 0.22	30.23 ± 0.19
Precision and accuracy data for quantification of LP in the availability of HCZ		
Amount of losartan potassium added (µg/mL)	*Within day * (Amount found ± SD)*	*Between day * (Amount found ± SD)*
2	2.05 ± 0.06	2.03 ± 0.18
4	4.06 ± 0.15	4.10 ± 0.03
6	6.07 ± 0.12	6.15 ± 0.04

SD: Standard deviation, *: Mean of each 6 readings

films weighed between 145.66 ± 3.055 and 167.0 ± 0.001 mg, with thickness ranging from 0.246 ± 0.011 to 0.326 ± 0.011 mm. Folding endurance was 898.0 ± 3.0 to 1274.0 ± 3.60.

Table 6: Assessment of palliative films of HPMC E15 and HPMC E5

Code	*F21*	*F22*	*F23*	*F24*	*F25*	*F26*
Folding endurance	788 ± 4.5	856 ± 3.6	976 ± 4.5	689 ± 5.0	632 ± 4.5	659 ± 5.0
Surface pH	6.65 ± 0.01	6.67 ± 0.02	6.70 ± 0.022	6.62 ± 0.01	6.66 ± 0.02	6,66 ± 0.01
DT (s)	75s ± 2.51	85s ± 3.0	115s ± 4.5	121s ± 2.51	105s ± 3.6	90s ± 1.08
Thickness (mm)	0.22 ± 0.03	0.22 ± 0.02	0.23 ± 0.05	0.21 ± 0.06	O.21 ± 0.02	0.22 ± 0.01
Surface texture	Even	Even	Even	Even	Even	Even
Clarity	Clear	Clear	Clear	Clear	Clear	Clear

Mean ± SD (n = 3) expresses results.

Table 7: MDF evaluation physiochemically

CODE	*W (mg)*	*T(mm)*	*FE*	*Surface (pH)*	*Assay(%)LP*	*Assay (%)HCZ*
LH1	145.66 ± 3.055	0.246 ± 0.011	898.0 ± 3.0	6.21 ± 0.03	97.65 ± 0.963	100.65 ± 1.035
LH2	161.0 ± 2.0	0.316 ± 0.005	932.33 ± 2.516	6.26 ± 0.02	98.41 ± 0.870	99.06 ± 0.697
LH3	146.0 ± 3.0	0.25 ± 0.01	980.0 ± 2.00	6.32 ± 0.03	100.95 ± 2.053	97.49 ± 0.212
LH4	154.66 ± 1.527	0.266 ± 0.005	1053.66 ± 3.21	6.24 ± 0.01	98.95 ± 0.843	98.3 ± 1.433
LH5	157.03 ± 1.732	0.29 ± 0.01	1154.0 ± 2.0	6.45 ± 0.03	97.46 ± 0.848	98.99 ± 0.681
LH6	166.33 ± 2.309	0.306 ± 0.011	1207.33 ± 2.516	6.40 ± 0.02	100.74 ± 1.087	97.84 ± 0.371
LH7	159.66 ± 1.527	0.29 ± 0.017	1247.33 ± 2.516	6.50 ± 0.03	99.88 ± 1.147	98.21 ± 1.232
LH8	167.0 ± 0.001	0.326 ± 0.011	1274.0 ± 3.60	6.46 ± 0.01	100.99 ± 1.532	98.40 ± 0.829

W= weight, FE= Folding Endurance, T= Thickness, LH=Losartan & Hydrochlorothiazide

Mean ± SD (n=3) expresses the results

Table 8: MDF evaluation physiochemically

CODE	*DT (s)*	*TS g/cm²*	*DR – LP 21 min*	*DR – HCZ 21 min*
LH1	77.66 ± 2.081	77.04 ± 1.09	96.22 ± 0.91	95.43 ± 0.99
LH2	94.0 ± 3.065	139.12 ± 1.84	89.93 ± 0.95	84.48 ± 0.55
LH3	109.33 ± 2.081	84.07 ± 2.06	74.91 ± 0.96	81.47 ± 1.11
LH4	130.0 ± 2.00	141.90 ± 1.76	68.78 ± 0.85	59.49 ± 0.94
LH5	100.66 ± 1.527	43.32 ± 1.74	97.06 ± 0.93	94.37 ± 0.86
LH6	165.0 ± 2.00	101.53 ± 1.07	90.55 ± 0.98	85.67 ± 0.944
LH7	138.33 ± 1.527	52.39 ± 1.67	82.42 ± 0.91	76.60 ± 0.95
LH8	174.6 ± 1.527	108.27 ± 1.75	78.63 ± 0.76	70.55 ± 0.98

DT =Disintegration Time, DR-Drug release, TS=Tensile strength

Mean ± SD (n=3)expresses the results

The pH ranged from 6.0 ± 0.01 to 6.70 ± 0.01. Disintegration time varied between 77.66 ± 2.081 and 174.6 ± 1.527 seconds. Tensile strength was 77.04 ± 1.09 to 141.90 ± 1.76 g/cm². At 21 minutes, drug release was 68.78 ± 0.85 to 96.22 ± 0.91% for LP and 59.49 ± 0.94 to 95.43 ± 0.99% for HCZ. LP1 and LP5 released drug completely by 21 minutes, HCZ6 by 24 minutes; further formulations completed release by 30 minutes (Tables 7 and 8, Figures 8 and 9).

Statistical Optimization of MDF

Statistical optimization of MDF was done using Design Expert software. Utilizing regression analysis (*p-value*, adjusted R^2, predicted R^2), with significant terms ($p < 0.05$) and ANOVA at a 5% significance level, the best-fit model was chosen.

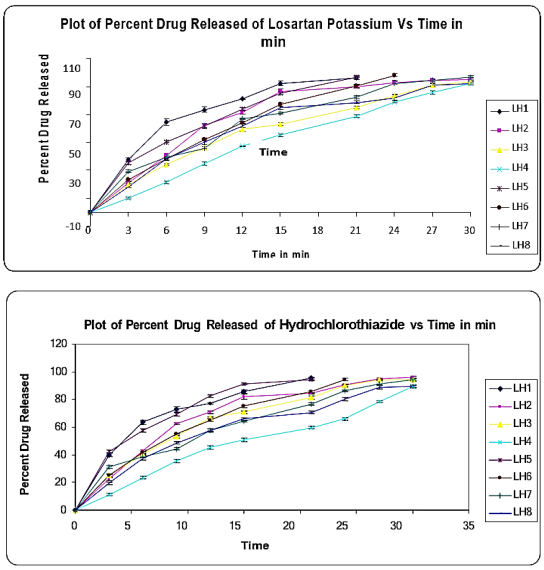

Figure 8: *In-vitro* drug release study of LP and HCZ from 2^3 factorial MDF

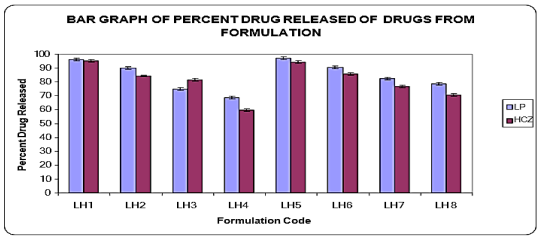

Figure 9: Percent drug released of LP and HCZ from MDF

Table 9: For Disintegration time, ANOVA and regression analysis

Outputs	*DF*	*SS*	*MS*	*F*	*P-value Prob > F*
Model	4	8042.91	2010.73	23.89	0.0130
HPMC E15	1	2369.47	2369.47	28.15	0.0131µ
HPMC E5	1	1653.13	1653.13	19.64	0.0214
PEG 400	1	3513.73	3513.73	41.74	0.0075
HPMCE15* PEG 400	1	506.57	506.57	6.02	0.0914
Residual	3	252.54	84.18	-	-
Total	7	8295.45		-	Significant

Response	*P Value*	*R^2*	*Adjusted R^2*	*Predicted R^2*	*Adequate precision*	*SD*	*CV%*
Y_1	0.0131	0.9697	0.9291	0.7836	14.4876	9.18	7.43

Reduced Model Equation = $+44.3575-6.6625X_1+57.50X_2-10.8725X_3+7.9575X_1*X_3$

Abbreviations: DF = Degree of Freedom, MS = Mean of Square, SS = Sum of Square

Table 10: Tensile strength using ANOVA and regression analysis

Outputs	*DF*	*SS*	*MS*	*F*	*p-value Prob > F*
Model	3	9259.68	3086.56	845.23	< 0.0001
HPMC E15	1	6844.50	6844.50	1874.32	< 0.0001
HPMC E5	1	82.05	82.05	22.47	0.0090
PEG 400	1	2333.13	2333.13	638.91	< 0.0001
Residual	4	14.61	3.65	-	-
Total	7	9274.28		-	Significant

Response	*p-value*	*R^2*	*Adjusted R^2*	*Predicted R^2*	*Adequate precision*	*SD*	*CV%*
Y_2	<0.0001	0.9984	0.9972	0.9937	73.3102	1.91	2.04

Reduced Model Equation= $+18.08 + 29.25 *X_1+ 12.81*X_2- 17.07750* X_3$

Abbreviations: DF = Degree of freedom, SS = Sum of Square, MS = Mean of square

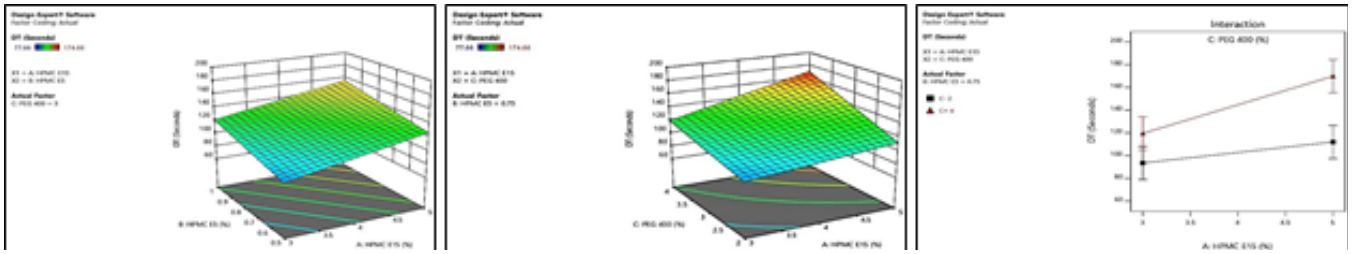

Figure 10: Response Surface Plot of Effect of (a) HPMC E15 and E5 (b) PEG 40P and HPMC E15 on Disintegration Time and (c) Interaction Plot Showing Effects of PEG 400 and HPMC E 15

Effect of Variables (Formulation) on DT

A 2^3 factorial design indicated that a linear model is the greatest fit for disintegration time (response Y1). The regression analysis and ANOVA summary showed a significant model ($p < 0.0130$). The predicted R^2 (0.7835) was in considerably complies with the adjusted R^2 (0.9290), with a difference of less than 0.2. Adequate precision was 14.4875, model F-value was 23.89, indicating significance (Table 9 and Figure 10).

Examination of the impact of formulation variable on the tensile strength of LH MDF

Impact of formulation factors on LH MDF Tensile Strength

The 2^3 factorial design showed a linear model as the best fit

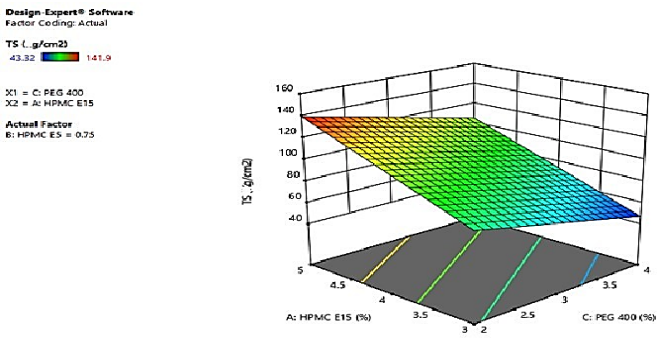

Figure 11: Plot of surface response showing the Effect of HPMC E15 and PEG400 on MDF tensile strength

Table 11: For LP drug release, ANOVA and regression analysis

Outputs	*DF*	*SS*	*MS*	*F*	*p-value Prob > F*
Model	4	735.87	183.97	228.27	0.0005
HPMC E15	1	64.52	64.52	80.06	0.0029
HPMC E5	1	595.47	595.47	738.86	0.0001
PEG 400	1	44.27	44.27	54.94	0.0051
HPMCE 5* PEG 400	1	31.60	31.60	39.21	0.0082
Residual	3	2.42	0.8059	-	-
Total	7	738.29		-	Significant

Response	*P Value*	*R^2*	*Adjusted R^2*	*Predicted R^2*	*Adequate precision*	*SD*	*CV%*
Y3	0.0005	0.9967	0.9924	0.9767	38.9447	0.8977	1.06

Reduced Model Equation = $+132.885 -2.84*X_1-58.36*X_2 - 3.61*X_3+7.95*X_2*X_3$

Abbreviations: DF = Degree of Freedom, MS = Mean of Square, SS = Sum of Square

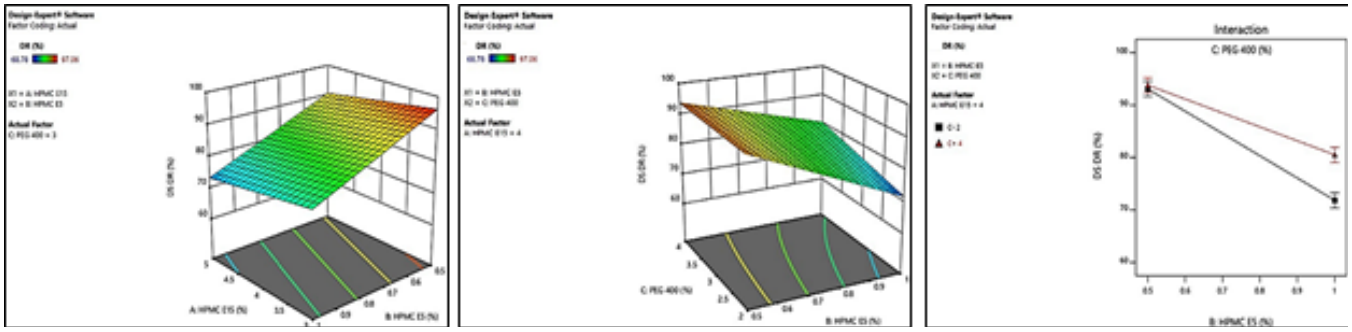

Figure 12: Response surface plots illustrate (a) the impact of polymers on LP drug release, (b) the effect of PEG 400 and HPMC E 15, and (c) their interaction on LP drug release

Table 12: HCZ drug release, ANOVA and regression analysis

Outputs	*DF*	*SS*	*MS*	*F*	*p-value Prob > F*
Model	2	929.30	464.65	27.97	0.0019
HPMC E15	1	284.17	284.17	17.10	0.0090
HPMC E5	1	645.12	645.12	38.83	0.0016
Residual	5	83.07	16.61	-	-
Total	7	1012.36		-	Substantial

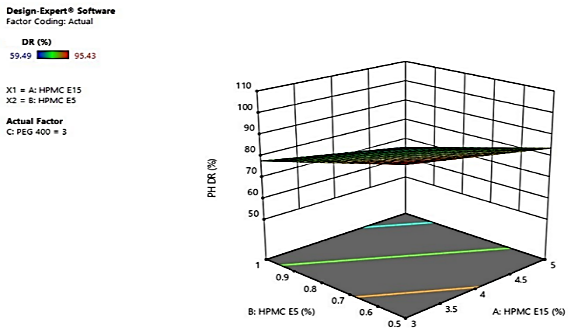

Figure 13: Surface plot showing the impact of HPMC E5 and HPMC E15 on HCZ drug release

($p < 0.0001$), with predicted R^2 (0.9937) and adjusted R^2 (0.9972), precision of 73.310, and a significant F-value of 845.23 (Table 10 and Figure 11).

Impact of Formulation Factors on MDF LP Release

The 2^3 factorial design for LP drug release from LH-MDF at 21 minutes identified a linear model as the best fit ($p = 0.0005$). Predicted R^2 (0.9767) and adjusted R^2 (0.9924) matched closely, with an adequate precision of 38.9447, a model F-value of 228.27, confirming (Figure 12 and Table 11).

Table 13: Regression analysis

Response	*p-value*	*R^2*	*Adjusted R^2*	*Foretold R^2*	*Acceptable precision*	*SD*	*CV%*
Y4	0.0019	0.9179	0.8851	0.7899	11.9711	4.08	5.03

Reduced Model Equation = $+131.78750 -5.96*X_1-35.92*X_2$

Abbreviations: DF = Degree of Freedom, SS = Sum of Square, MS = Mean of Square

Impact of Formulation Variables on HCZ Release from DSP-MDF

The 2^3 factorial design for HCZ drug release from LH-MDF at 21 minutes identified a linear model as the best fit ($p = 0.0019$). Predicted R^2 (0.7899) and adjusted R^2 (0.8851) were closely matched, with an adequate precision of 11.9711 and a model F-value of 27.97, confirming significance (Figure 13 and Tables 12 and 13).

The response surface graph shows that an increase in the polymer concentration, i.e. percentage of HPMC E5 and HPMC E15 decreases the release of the drug.

CONCLUSION

In conclusion, the analysis of losartan potassium and hydrochlorothiazide confirmed their purity and adherence to pharmacopeial standards. The UV spectrophotometric method for concurrent estimation in sublingual films was robust and accurate. Statistical optimization using Design Expert 11.0 identified significant factors for multiple responses in mouth-dissolving films (MDFs). For disintegration time (Y1), HPMC E15, HPMC E5, and PEG 400 were significant, with a model F-value of 23.89 ($p = 0.0130$). Tensile strength (Y2) was influenced by these factors, with a model F-value of 845.23 ($p < 0.0001$). Drug release of losartan potassium (Y3) and hydrochlorothiazide (Y4) were significantly affected, with model *p-values* of 0.0005 and 0.0019, respectively. Batch LH1 was optimized to balance disintegration time and drug release effectively.

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