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A STATISTICAL APPROACH TO THE DEVELOPMENT OF TELMISARTAN TRANSDERMAL DELIVERY SYSTEM

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Abstract:

Transdermal patches of telmisartan with matrix type were prepared by solvent evaporation technique. In this investigation the matrix of HPMC E15: Eudragit RL100 were cast to achieved sustained release of the drug. A 3^2 factorial design was introduced to prepare the patches. The quantities of Hyroxypropyl methyl cellulose E15 (X_1), IPM (X_2) were selected as independent variable. The % drug permeated was selected as response variable. The prepared patches possessed satisfactory physicochemical characteristics. invitro permeation study were performed using modified KC diffusion cell. Kinetic data revealed that the drug release followed Korsemeyer-Peppas model and the mechanism of release was found to be non fickian diffusion. The results of the study shows that telmisartan could be administered transdermally through the matrix type TDDS which seemingly free of potentially hazardous skin irritation.

Keywords: *Telmisartan, statistical approach, Transdermal patches, HPMC, In-vitro and in vivo evaluation.*

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INTRODUCTION:

Transdermal drug delivery system (TDDS) is a topically administered system in the form of patches or semisolids (gels) that deliver drugs for the systemic effects at a predetermined and controlled rate [1-2]. Transdermal drug delivery system has many advantages over conventional modes of drug administration, it is convenient, it bypasses first pass metabolism and it provides a steady state plasma concentration of drug and long-term therapy in a single dose [1]. These advantages lead to improved patient compliance. However, the skin permeation of clinically useful drugs is generally poor with some exception (it has small molecular weight(<300Da) and lipophilic nature) because the stratum corneum functions as a barrier against foreign substances. To overcome this problem, many penetration enhancers that temporarily increase the permeability of skin have been examined. Study has been carried out to provide an anti-hypertensive drug in transdermal patchs [2-4]. In this study, the possibility of developing transdermal patches containing telmisartan was evaluated. In developing transdermal preparations, it is important to design an optimized pharmaceutical formulation that has an appropriate penetration with concomitant acceptable skin irritation levels [3-5]. For this purpose, it is considered important to discover the optimized formulations of enalapril maleate patch by employing a nonlinear response method (RSM). Using RSM, we can easily understand nonlinear relationships between causal factors and response variables and obtain a stable and reproducible simultaneous optimal solution. Telmisartan is an angiotensin II receptor antagonist used mainly for the treatment of hypertension. As with other angiotensin II receptor antagonists, Telmisartan is indicated for the treatment of hypertension. It belongs to BCS class II drug and the solubility is extremely low (0.09 mg/ml in water). Accordingly, Telmisartan shows variable oral bioavailability of 42–58%, leading to inadequate and varying pharmacological effects. So an alternative route like transdermal drug delivery system is chosen to deliver the drug to systemic circulation [6].

MATERIALS AND METHODS:

Material:

Telmisartan**,** was procured from Yarrow chemicals, Mumbai. HPMC E15 and Eudragit ERL100 from Lobachemie**,** and polyethylene glycol 400 from Thermo fischer scientific India Pvt.ltd. All other chemicals and solvents were of analytical grades.

Method:

Preparation of Transdermal Patch [7-9]:

The patches are prepared by solvent casting method using solvent evaporation technique. Plasticizer was incorporated at a concentration of (15% v/v). Backing membranes were cast by pouring and then evaporating 4% aqueous solution of polyvinyl alcohol in petridish, at 60ºC in a hot air oven for 6hr. The matrices were prepared by pouring the homogeneous dispersion of different blends of polymer with PVP in a solvent on the backing membrane in prefabricated glass moulds. The above dispersion was evaporated slowly at 40ºC for 2hr to achieve a drug-polymer matrix patch. The dry patches were kept in desiccators until use.

Preparation of Transdermal Patches Using Factorial Designs [10]:

A 3^2 factorial design was selected in the present study. The formulae were developed as 9 sets varying the variables (polymer combination and Penetration enhancer) following 3^2 full factorial design (3 levels) using Design Expert™ 11.1.2.0. The two independent variables selected were the ratio of the combination of HPMC E15: ERL100 (X_1) and the amount of penetration enhancer (X_2). The dependent variable selected for the response was drug release in 24hr. The formulations were shown in table no. 1.

Table no. 1: Formulation variables in 3^2 factorial design of Enalapril Maleate Transdermal Patch

Batch	Variable level coded formulation		Level used, Actual (Coded)		
	X_1	X_2	Low (-1)	Medium (0)	High (+1)
ET1	-1	-1			
ET2	-1	0			
ET3	-1	+1			
ET4	0	-1			
ET5	0	0			
ET6	0	+1			
ET7	+1	-1			
ET8	+1	0			
ET9	+1	+1			
Independent variables					
X_1 = HPMC E15: ERL100			4:6	6:4	8:2
X_2 = IPM (%)			5	10	15

Evaluation of Transdermal Patch [11-12]:
All the formulations of EM transdermal patches prepared were evaluated for the following parameters,

Thickness:
The thickness of the laminate was assessed at six different points of the prepared patch using a thickness gauge micrometer (0.01mm, Mitutoyo, Japan). For each formulation, three randomly selected laminated were used.

Weight variation:
The weight variation for each batch was determined using Sartorius electronic balance (Model CP-224 S), Shimadzu, Japan. Six patches from each batch (3.14 cm^2), were weighed individually and the average weight was calculated.

Flatness:
The flatness was measured manually for the prepared films. Longitudinal strips were cut out from each film, one from the center and two from either side. The length of each strip was measured and the variation in the length because of non-uniformity in flatness was measured by determining percentage constriction, considering 0% constriction is equivalent to 100% flatness. Flatness was determined using the below-given formula:
% Constriction = [(l1 – l2)/ l2] * 100
Where,
l1 = Initial length of each strip
l2 = Final length of each strip
The flatness for EM matrices was measured in triplicate and average reading was considered.

Folding endurance:
The folding endurance was measured manually for the prepared films. The folding endurance of the films was determined by repeatedly folding a strip measuring 2x2 cm in size at the same place till it breaks. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

Determination of Moisture content (Loss on drying):
Three patches from each batch (3.14cm^2), were weighed individually and the average weight was calculated. This weight was considered as an initial weight. Then all the patches were kept in a desiccators containing activated Silica at normal room temperature for 24hr. The final weight was noted when there was no further change in the weight of the individual patch. The percentage of moisture absorption was calculated as a difference between initial and final weight concerning final weight.
% Moisture content = [(Initial weight – Final weight)/ Final weight]* 100

Determination of Moisture absorption:
Three patches from each batch (3.14cm^2), were weighed individually and the average weight was calculated. This weight was considered as an initial weight. Then all the patches were kept in a desiccators containing 200ml saturated solution of Sodium chloride (Relative humidity of 75%) at normal room temperature for 72h. The final weight was noted when there was no further change in the weight of the individual patch. The percentage of moisture absorption was calculated as a difference between final and initial weight concerning initial weight. The % Moisture absorption was determined using the following formula:
% Moisture absorption = [(Final weight – Initial weight)/ Initial weight]* 100

Determination of Water vapor transmission rate (%WVTR):
For this study vials of equal diameters were used as transmission cells. The cells were weighed accurately and initial weight was recorded, and then kept in a closed desiccators containing 200ml saturated solution of potassium chloride. The cells were taken out and weighed after 6, 12, 24, 36, 48, and 72hr of storage. The amount and rate of water vapor transmitted were calculated by the difference in weight using the below-given formula:
% Water vapor transmission rate = (Final weight-Initial weight)/ time * Area

Tensile strength:
It is determined by using a modified pulley system. The force required to break the film is considered as tensile strength and it is measured as kg/cm^2.

Percentage elongation break test:
The percentage elongation break is determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula
Elongation percentage = L1-L2/L2 × 100
Where, L1 is the final length of each strip and L2 is the initial length of each strip.

Drug content:
The patch was dissolved in pH 7.4 phosphate buffer. Then solvent methanol to make polymer soluble were added to the mixture and the remaining volume as made up with pH 7.4 phosphate buffer to 100ml in

100ml volumetric flask. Then 1ml was withdrawn from the solution and diluted to 10ml. The absorbance of the solution was taken at 296nm and concentration was calculated.

***In-vitro* permeation study:**

In-vitro permeation study of formulated EM matrix patch was carried out on modified Franz diffusion cell having 2.0cm diameter and 18ml capacity. Dialysis membrane (Himedia) having a molecular weight cut-off range 12000–14000kDa was used as a diffusion membrane. Pieces of dialysis membrane were soaked in phosphate buffer pH 7.4 for 24 hrs before the experiment. The diffusion cell was filled with phosphate buffer pH 7.4; the dialysis membrane was mounted on the cell. The temperature was maintained at 34 ± 0.5ºC. At predetermined time points, 1ml samples were withdrawn from the acceptor compartment, replacing the sampled volume with phosphate buffer pH 7.4 after each sampling, for 24hrs. The samples withdrawn were filtered and used for analysis. The amount of permeated drug was determined using a UV- spectrophotometer at 296nm. The experiments were done in triplicate. The amount of drug released/cm^2 of the patch was calculated for different formulations.

Kinetics of the drug release:

To know the mechanism of the drug release from the patches, the results obtained from the in-vitro permeation studies were analysed by various kinetic models. 1. Zero order drug release: cumulative % drug release Vs time. 2. First order drug release: log cumulative% drug retained Vs time 3. Higuchi's diffusion equation: cumulative %drug release Vs square root of time 4. Peppas-korsemeyer exponential: log cumulative % drug release Vs log time.

Analysis of release data:

The rate and mechanism of release of enalapril maleate from the prepared patchs were analysed by fitting the release data into zero-order, first order, Higuchi and the release data were also analysed as per Korsemeyer-Peppa's equation.

***Invivo* Study [13-15]:**

The study was approved by the institutional ethical committee (approval no. **1504/PO/Re/S/11/CPCSEA Dated 9/8/2019)**. The animals were provided by Vidyabharati College of Pharmacy, Amravati, Maharashtra, India. The animals were kept under standard laboratory conditions in 12hrs light/dark cycle at 25±2ºC. The animals were housed in polypropylene cages, 4 cages, with free access to standard laboratory diet and water *ad libitum.*

For Pharmacokinetic study, i.e. drug release experiments were studied for the selected formulations showing highest *invitro* drug permeation. The study was performed using *albino Wistar* rat as animal model. The animals were selected after examination of the skin for abnormalities. Rats weighing between 230 to 250gm were selected for the study. About 10cm^2 skin was shaved on the dorsal side. Prior to application of optimized formulations, rats were kept under observation for 24hrs for any ill effects of shaving. The rats were divided into two groups (n=6). Group I was administered oral dose of drug calculated on the basis of body surface area and group II received optimized formulation. The formulations were applied on the shaved skin surface. The blood samples (about 2ml) were withdrawn from the tail vein at predetermined time interval in heparinized tubes. Blood samples were centrifuged for 30min at 5000rpm and the plasma was separated and stored at -20 ºC, till observation and analysis. The blood samples were analyzed for the drug content by HPLC method.

RESULTS AND DISCUSSION:

Table no. 2: Physiochemical evaluation of EM matrix Patch using factorial design

Batch	TT1	TT2	TT3	TT4	TT5	TT6	TT7	TT8	TT9
Thickness (mm)	0.260± 0.02	0.248± 0.01	0.332± 0.05	0.321± 0.07	0.328± 0.05	0.320± 0.01	0.239± 0.04	0.241± 0.09	0.329± 0.05
Weight variation (mg)	189.3± 6.8	187.7± 5.9	176± 5.7	193.5± 5.1	182± 3.1	180± 4.2	190± 2.5	180± 3.1	180.6± 5.1
Flatness (%)	100	100	100	100	100	100	100	100	100
Folding endurance	135.± 4.34	143± 3.11	168± 7.52	138± 5.23	169± 3.88	180± 4.61	146± 4.51	155± 4.12	168± 5.11
Moisture content (%)	6.73± 0.20	4.78± 0.35	3.78± 0.25	12.45± 0.77	11.74± 0.44	6.81± 0.21	7.55± 0.57	8.94± 0.33	6.71± 0.66
Moisture absorption (%)	4.41± 0.11	3.05± 0.57	3.39± 0.25	4.89± 0.21	5.78± 0.74	3.01± 0.11	4.74± 0.47	4.15± 0.15	4.56± 0.49
Water Vapor transmission rate (%)	0.5305± 0.03	0.5072± 0.04	0.4835± 0.04	0.4418± 0.03	0.3904± 0.05	0.3782±0 .038	0.3684± 0.05	0.3279± 0.05	0.3184± 0.05
Tensile Strength(Kg /mm^2)	0.423± 0.003	0.323± 0.004	0.219± 0.005	0.645± 0.006	0.556± 0.007	0.341± 0.002	0.534± 0.004	0.526± 0.005	0.397± 0.007
Elongation (%)	15.48± 1.11	18.61± 0.77	22.46± 1.14	27.17± 1.34	31.76± 0.86	35.92± 1.25	41.88± 1.65	18.56± 0.87	25.25± 0.85
Drug content (%)	93.89	90.34	94.78	91.41	90.52	95.75	92.64	91.21	94.15

Mean±SD *n=3

The thickness of each patch was measured at a 3 different points and SD value were calculated. In case of ratio of HPMC: ERL100 (4:6) 0.260-0.332±5.9mm, while ratio 8:2, 0.320-0.328±5.9, and ratio 6:4 0.239-0.329±5.9mm respectively. All the prepared patches were weighed individually, and the average weight of the patch was found in the range of 176.3-190.5mg. All the prepared patches were weighed individually, and the flatness of the patch was found nearly equals i.e., 100%. The folding endurance of all formulations ranged between 215-315. The ratio of HPMC: ERL100, 4:6 found to be 135±7.52 - 168±4.34, while 8:2 ratio 138±4.61 - 180±4.51 and 6:4 ratio 144±4.51 - 168±5.11respectively. The results of moisture content have indicated that, all transdermal systems have specific moisture content in them. Percentage moisture content ranged from 3.78±0.25 - 12.45±0.33%. The results of moisture absorption have indicated that HPMC have more moisture absorbing capacity as it is a hydrophilic polymer. Percentage moisture absorption ranged from 3.39±0.74 - 5.78±0.11%. An increase release rate of drug from transdermal patches may be related to eater vapor permeation of the film. The percentage varies from 3.279±0.05 - 5.305±0.03.

The results of tensile strength have indicated that, all transdermal formulation have specific strength for various films it ranges from 0.219±0.13 - 0.645±0.54Kg/mm^2. The percentage of elongation if inversely proportional to the tensile strength of the patches it ranges from 15.48±1.11 - 41.88±1.65%. Both Eudragit and HPMC patches showed uniform drug content and the values ranged from 90.52 - 94.15%. *Invitro* permeation studies were carried out for all 9 formulations using dialysis membrane as barrier. The maximum and the minimum drug release obtained for optimized were 78.16 and 94.48% respectively.

Kinetics of Drug Release data:

In this study, different formulations released variable amount of enalapril maleate through membrane into the *invitro* fluid. To study the drug diffusion kinetics and mechanism the results were fitted to zero, first order, Higuchi and the release data were also analysed as per Korsemeyer-Peppa's plot.

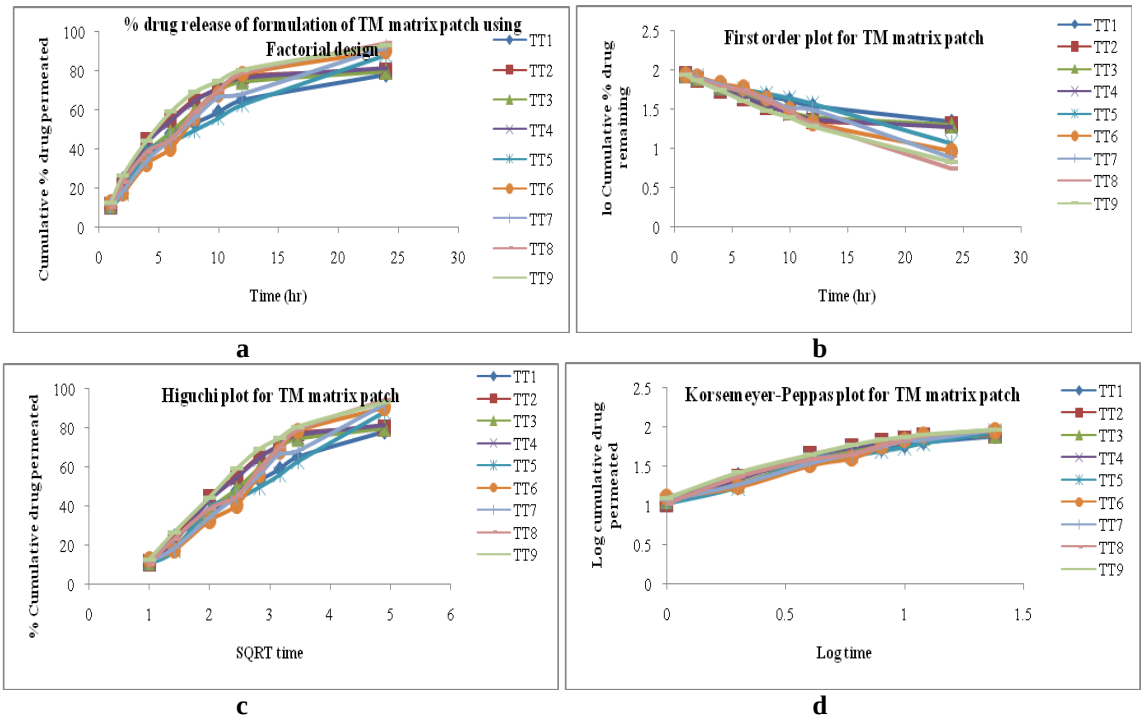


Figure No. 1: Release kinetics of Enalapril Maleate Transdermal Patch a. Zero order plot b. First order c. Higuchi plot d. korsemeyar-Peppas Model

Table no. 3: Kinetics of drug release of formulation of EM matrix patch using Factorial design

Batch	Zero order	First order	Higuchi Model	Korsemeyer-Peppas Model	
	R^2	R^2	R^2	R^2	n
TT1	0.7270	0.9388	0.9761	0.9628	0.5087
TT2	0.7509	0.9666	0.9793	0.9642	0.5072
TT3	0.7326	0.9201	0.9974	0.9674	0.5059
TT4	0.7555	0.9855	0.9662	0.9663	0.5056
TT5	0.7464	0.9602	0.9694	0.9631	0.5033
TT6	0.8543	0.9535	0.9821	0.9735	0.5057
TT7	0.8169	0.9670	0.9829	0.9661	0.5086
TT8	**0.8008**	**0.9708**	**0.9782**	**0.9878**	**0.5790**
TT9	0.9454	0.9674	0.9868	0.9850	0.5088

The *invitro* permeation data were fit to different equations and kinetic models to explain permeation profile (Table No. 3, Figure No. 1)). The coefficient of correlation of each of the kinetics was calculated and compared. The *invitro* permeation profiles of all the different formulations of transdermal patches did not fit to zero order behaviour truly and they could be beat expressed by Higuchi's equation for the release of drug from a homogenous polymer matrix type delivery system that depends on diffusion characteristics. The data was further treated as per Korsmeyer-Peppas equation. It was observed that formulations were best fitted to higuchi model. Batch TT8 has R^2 value (0.9878) and n value (0.5790). The slope (n) values obtained by this equations indicated that the drug released by Fickian diffusion predominated with all formulations.

EXPERIMENTAL DESIGN [16]:

The evaluation of data for optimization process was carried out by Design Expert Software™ 11.1.2.0. The 3^2 factorial design was used to optimize the formulation variables and the data generated was used to fit in a quadratic polynomial equations for dependent variable as shown in the equation 1.

$$y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_1X_2 + \beta_4X_1^2 + \beta_5X_2^2 + \varepsilon \quad \text{..... 1}$$

In this equation, y is a dependent variable; β_1, β_2, β_3, β_4, and β_5 are constant regression coefficient of the factor (linear terms), their interaction and quadratic terms, respectively; β_0 is the arithmetic mean response of the 9 runs and ε is random error.

For estimation of quantitative effects of the different combination of factors and the factor levels on the percentage drug release, the response models were calculated with Design Expert software by applying coded values of factor levels. The model described could be represented as:

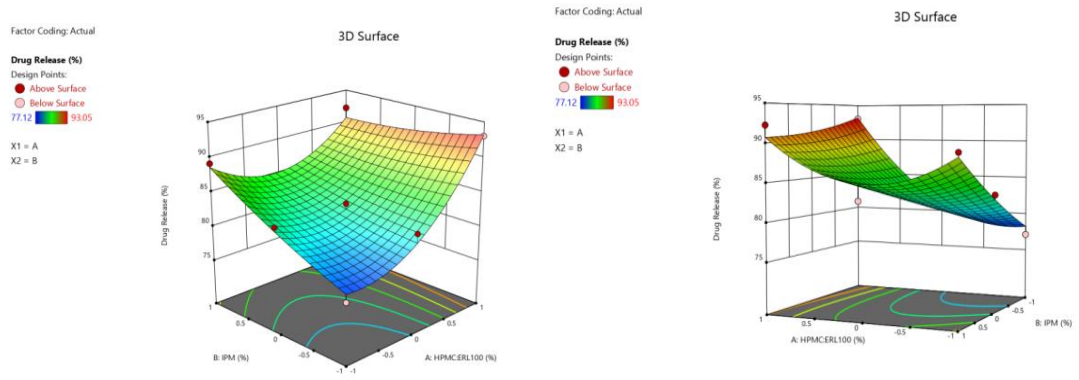
Coded level: Percentage Drug Release (Y_1) = 82.60 + 4.27A + 1.97B - 3.21AB + 4.49A^2 + 0.61B^2 2

Fitting of Data to the Model

A 3^2 statistical experimental design as the RSM requires 9 experiments. All the responses observed for 9 formulations prepared were simultaneously fit to first order, second order, and quadratic models using Design Expert 11.1.2.0. It was observed that the best fit model was quadratic model and Sum of squares is Type III -partial. A positive value represents an effect that favours the optimization, while a negative value indicates an inverse relationship between the factor and response. It is evident that all the two independent variables, viz. the ratio of polymer (X_1), and IPM (X_2) have positive effects on the response, viz. % drug release.

The quantitative effects of the different combination of factors and factor levels on the percentage drug release was calculated using response surface models. The significant p value ($p<0.05$), R^2, adjusted R^2, and coefficient of variation values of this model indicated that the assumed regression model was significant and valid for each considered response. The values of the coefficients in the model are related to the effect of these variables on the response. Form this model quadratic was best, indicating that combination of above system had the greatest potential influence on the TM matrix patch.

3D response surface plots give a representation of the variations in each response when the two factors are simultaneously changed from lower to higher level. It gives a three-dimensional curvature of the change in response at different factor levels. It also gives the variation in design points from the predicted response value. The 3-D response surface (Fig.. 2) and counter plot (Fig. 3) were drawn to estimate the effects of the independent variables on response and to select the optimal formulation.



a **b**

Figure no. 2: Response Surface plot of EM matrix Patch using factorial design

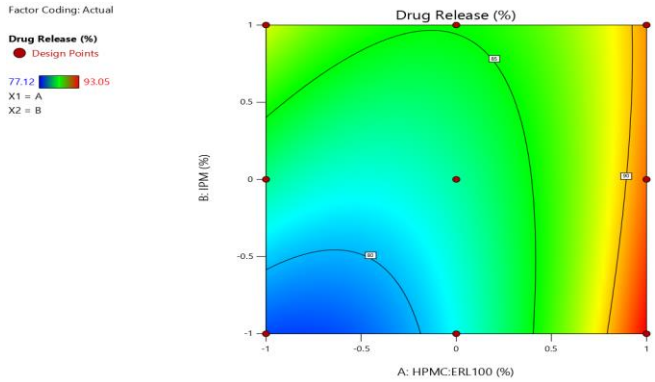


Figure No 3: Counter Plot EM matrix Patch using factorial design

Data Analysis:

The percentage of drug release (dependent variable) obtained at various levels of the three independent variables (X_1, and X_2) was subjected to multiple regression to yield a polynomial equation. The value of correlation coefficient (r^2) of the equation was found to be 0.9446, indicating good fit. VIF value found to be 1, indicating model is significant. According to table no.4, the result calculated using equation 6 was statistically significant with $p<0.005$, indicating that the developed model exhibited good agreement between the response Y_1 and the significant variables. The value of lack of fir for the equation more than 0.05 indicating that the proposed statistical model fit well. The ANOVA result for Y_1 provides F value 10.23 as compared to the critical values from the cut off point for F distribution (=0.05) (Table no. 4). These F value suggested that the derived quadratic models have significant influence on the response R^2 and adjusted R^2 value for Y1 were 0.8522, 0.3520, respectively demonstrate the accuracy of the test and the fitness of the results with prepared model. The percentage drug release measured for the different formulations showed wide variation (i.e. vales ranged from 78.14 to 94.48%). The results clearly indicate that the percentage drug release is strongly affected by the variables selected for the study. The main effects of X_1 and X_2 represents the average result of changing one variable at a time from its low level to its high level. The interaction terms (X_1X_2, X_1X_3 , X_2X_3, X_1^2, X_2^2, X_3^2) shows how the percent drug release changes when two variables are simultaneously changed. The negative coefficient for all three independent variables an unfavourable effect on the percentage drug release, while positive coefficients for the interactions between two variables indicate a favourable effect on percentage drug release.

Table No. 4: A Summary of ANOVA for response Y_1 for fitting to quadratic model For VH matrix patch

Source	Sum of Squares	df	Mean Square	F-value	p-value
Model	214.96	5	42.99	10.23	0.0421
A-HPMC:ERL100	109.4	1	109.4	26.02	0.0146
B-IPM	23.29	1	23.29	5.54	0.1
AB	41.22	1	41.22	9.8	0.052
A^2	40.32	1	40.32	9.59	0.0534
B^2	0.7442	1	0.7442	0.177	0.7023
Residual	12.61	3	4.2		
Std. Dev.	2.05		**R^2**	0.9466	
Mean	86.00		**Adjusted R^2**	0.8522	
C.V. %	2.83		**Predicted R^2**	0.3520	
			Adeq Precision	8.959	

Search for the Optimum Formulation:

The search for the optimized formulation composition was carried out using the desirability function approach with Design Expert software, criterion being one having the maximum desirability value. The optimization process was performed by setting the responses within selected ranges. Target ranges for the % drug release on TM matrix (Y). The suggested formulation was considered as optimized batch (TT8). The composition of TT8 and the responses predicted by software are listed in table no. 5. Batch TT8 was found to exhibit the value of observed parameters close to the values predicted by software.

Table no. 5: Simultaneous optimal solution by RSM For VH matrix patch

Response	Pred. Mean	Pred. Median	Observed	Std. Deviation	SE Mean	95% CL Low	95% CL High	95%TL Low	95% High
% Drug Release	91.3	91.36	90.01	2.05	1.528	86.49	96.22	72.34	110.38

Table no. 188: Pharmacokinetic parameter for ET8 formulation

Sr. No	Pharmacokinetic Parameter	Unit	Control Group (Drug Solution)	Test Group# (Formulation)
1	C max	ng/mL	377.929±4.633	921.16±3.436
2	T max	hrs	2	2
3	AUC $_{Last}$	ng/mL/hrs	2285.63±0.02684	5639.41±0.006793
4	AUC $_{Extra}$	ng/mL/hrs	239.098±5.245	6215.92±8.198
5	AUC $_{(0 \text{ to } \omega)}$	ng/mL/hrs	2514.73±5.244	6975.90±6.883
6	Elimination Rate Constant (K_e)	1/ hrs	0.3045±0.005966	0.00726±0.00056
7	Half Life of Drug ($t_{1/2}$)	hrs	3.4870±0.0001784	6.3185±0.03322
8	Mean Resituate Time (MRT)	hrs	5.6324±0.04911	10.7078±0.009557
9	Clearance (CL)	l/ hrs	4.21596±0.02356	1.39629±0.064
10	Absorbance Rate Constant (Ka)	-	6.26±0.001121	6.96406±0.01327
11	Volume of Distribution (Vd)	mL	16398.1635±0.08069	12635.9578±1.818
12	Volume of Distribution (Vd)	L	18.2981±0.0801	12.70393±0.00181
13	AMUC $_{(Last)}$	ng/L*(hrs)2	9907.68±0.06258	8215.8±0.8412
14	AMUC $_{(Extra)}$	ng/L*(hrs)3	4019.74±1.53	32415.8±0.1095
15	AMUC $_{(0 \text{ to } \omega))}$	ng/L*(hrs)4	12927.3±0.2028	90904.7±0.04057
# P value <0. 0001, Significantly different (P < 0.05)?:Yes, One- or two-tailed P value?:Two-tailed				

From the result it was observed that (TT8) telmisartan half life, area under curve, mean residence time, volume of distribution was found to be increased and elimination rate constant, clearance rate were decreased.

CONCLUSION:

The results of the present study demonstrated that telmisartan can be considered for transdermal patch containing HPMC E15 and Eudragit RL100 polymers combination and IPM as penetration enhancer for controlled release of the drug over a period of 24 hrs for the management of hypertension. It was found that there was an increase in the drug release by increasing the concentration of hydrophilic polymer HPMC E15. From the pharmacokinetics result it was observed that telmisartan half life, area under curve, mean residence time, volume of distribution was found to be increased and elimination rate constant, clearance rate was decreased. Here, it was concluded that addition of penetration enhancer is needed to attain the required concentration of telmisartan in plasma. The optimized formulation of matrix patch should be carried out on human volunteers to confirm improved pharmacokinetic parameters.

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