RESEARCH ARTICLE

Formulation Optimization and Characterization of Transdermal Patches of Luliconazole and Posaconazole by Response Surface Methodology

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ABSTRACT
In the present study the transdermal drug delivery system of two anti-fungal drugs i.e., luliconazole and posaconazole was reported using surface response method. Independent variable like HPMC, E-5 and PEG and dependent variable i.e., folding endurance and in vitro release study were taken in consideration. 15 formulations having varying concentration of polymers and permeation enhancer were formulated using solvent casting method. Results indicates that R1 (folding endurance) and R2 (% drug released) ranged from 62 to 88 and 76.22 to 92.46 %. Validated values were found to be much closed to the optimized values and results were closed to the selected batches as obtained by the software's.
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INTRODUCTION

Transdermal patches are comparatively novel formulations that can address limitations associated with traditional drug delivery systems. Transdermal patches provide controlled release of drugs, hence can avoid systemic side effects.[1] A recent review suggested only 2% people faced systemic adverse effects of transdermal patches containing diclofenac drug, hence, considered systemic side effects to be rare with transdermal patches.[2] Another advantage offered by transdermal patches is better patient adherence. There are a number of studies that have suggested better patient adherence to treatment regime with use of transdermal patches. Transdermal patches offer unique advantages that make them promising for drug delivery. They provide a visible reminder of treatment, integrating seamlessly into daily routines and promoting adherence, especially among forgetful patients or caregivers. The visual indication of patch application reassures caregivers that the medication is being administered correctly and allows for quick removal in case of adverse reactions. Additionally, patches minimize the risk of accidental overdose, making them safer for use. This combination of convenience and safety enhances confidence in treatment, potentially allowing for optimized dosing and improved patient outcomes.[3]

MATERIALS AND METHODS

Materials

The drugs Luliconazole (LN) & Posaconazole (PN) were obtained as gift sample. All the material used in the experiments was of analytical grade and purchased from authentic vendor. Other chemicals were purchased from Signa Aldrich.

Preformulation Parameteres

The study was performed using standard methods and in this study organoleptic properties, melting point and maximum wavelength were deterimined for both the drug luliconazole (LN) and posaconazole (PN).

DSC Study

It was determined using DSC-60 model.

Methods

Formulation of Matrix type Transdermal Patches

The Transdermal patches [Matrix type] (TP) were formulated using solvent casting method casted on a glass mould. Matrix type TP containing Luliconazole (LN-50 mg) & Posaconazole (PN-50 mg) were prepared using 2 polymer i.e., HPMC E5, Ethyl cellulose, Emulsifier i.e., Span 80 and permeation enhancer i.e., Propylene glycol by solvent evaporation technique using petridish. The polymers like EC, and permeation enhancer PEG were selected as rate controlling polymers as they are biodegradable, easily affordable, economic, and non-toxic. The TP was formulated by using solvent casting methods. For this polymer HPMC E5 in 10-30 % w/v, EC in 5-20 % w/v and permeation enhancer PEG 5-15 % w/v concentration was taken. Polymers were dissolved in solvent mixture (25 ml) in the ration 1:1 of Methanol: Dichloromethane. After 6 hr of swelling the drug was mixed containing span 80 and methonal was added. After 2 hr it was transferred in petriplate and was dried at room

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Table 1: List of independent variables selected in experimental design

S. No.	Independent variables	Level of variation		
		Low	Medium	High
1.	X1- HPMC E-5 (% w/v)	10	20	20
2.	X2- EC (% w/v)	5	12.5	20
3.	X3- PEG (%w/v)	5	10	15

temperature. The formulated TP was removed very carefully of size 4 cm^2 and was further evaluated.[4,5]

Optimization of Transdermal Patches

The formulation of Luliconazole (LN) & Posaconazole (PN) was optimized by Central Composite design [Design-Expert-13®]. The list of independent variables is shown in table 1, the response or dependent variables are R1 [Folding endurance] and R2 [% Drug Release] and experimental designs for TP formulation is shown in table 2 The concentration of polymer HPMC E-5 (X1), concentration of polymer EC (X2) and permeation enhancer PEG (X3) were selected as three independent variables and folding endurance (R1) and % drug release (R2) were selected as response variables. Further, statistical validity using ANOVA and 3D-response surface plots were established to find the compositions of optimized formulation.[6,7]

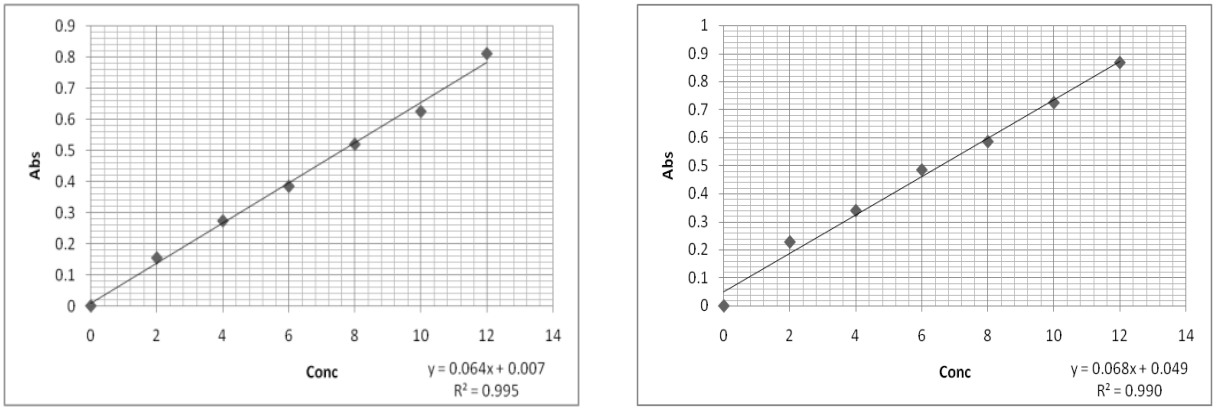

Figure 1: Calibration Curve Luliconazole (LN) & Posaconazole (PN)

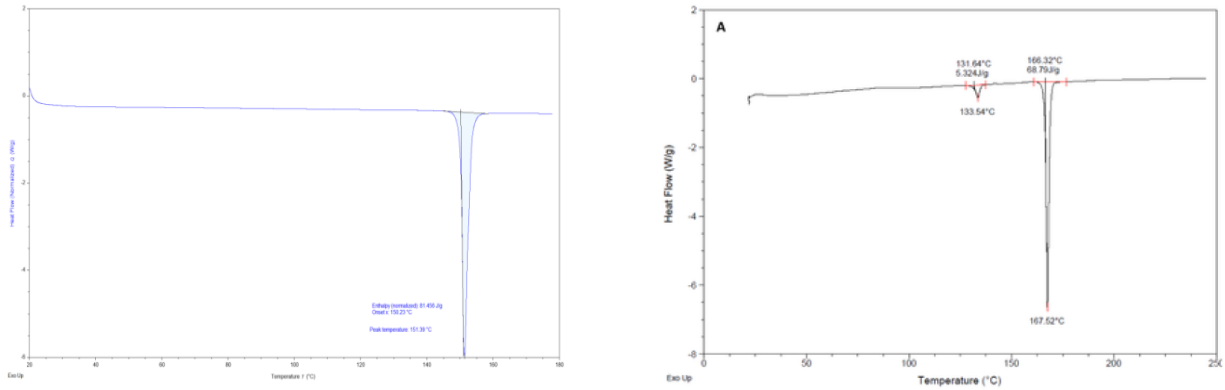

Figure 2: DSC thermogram of Luliconazole (LN) & Posaconazole (PN)

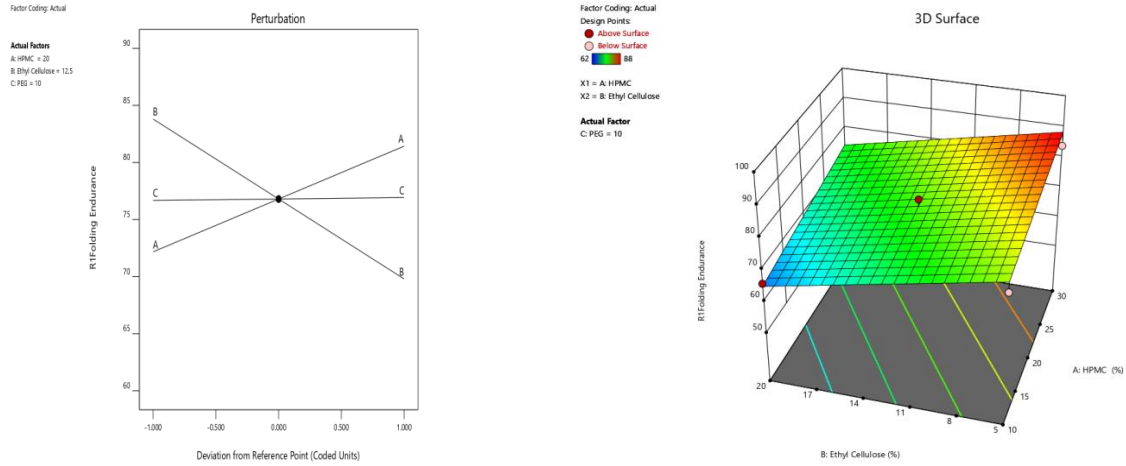

Figure 3: 3D surface plot of TP for Folding Endurance

Table 2: Central composite experimental design for transdermal patches

S. No.	Std. Run	Batch No.	Factor 1 A:HPMC %	Factor 2 B:Ethyl cellulose %	Factor 3 C:PEG%
1.	5	TP-1	10	12.5	5
2.	8	TP-2	30	12.5	15
3.	10	TP-3	20	20	5
4.	11	TP-4	20	5	15
5.	6	TP-5	30	12.5	5
6.	3	TP-6	10	20	10
7.	12	TP-7	20	20	15
8.	14	TP-8	20	12.5	10
9.	1	TP-9	10	5	10
10.	15	TP-10	20	12.5	10
11.	13	TP-11	20	12.5	10
12.	9	TP-12	20	5	5
13.	2	TP-13	30	5	10
14.	7	TP-14	10	12.5	15
15.	4	TP-15	30	20	10

Table 3: Effect of independent variables on response variables

Batch No.	Independent variable			Response variables	
	X1 % w/v	X2 % w/v	X3 % w/v	R1	R2
TP-1	10	12.5	5	78±1.27	78.25
TP-2	30	12.5	15	85±1.34	84.66
TP-3	20	20	5	66±1.54	80.05
TP-4	20	5	15	88±1.68	92.46
TP-5	30	12.5	5	82±1.58	82.56
TP-6	10	20	10	66±1.18	76.22
TP-7	20	20	15	76±1.28	84.88
TP-8	20	12.5	10	79±1.76	81.74
TP-9	10	5	10	76±1.28	82.35
TP-10	20	12.5	10	79±1.76	81.74
TP-11	20	12.5	10	79±1.76	81.74
TP-12	20	5	5	84±1.44	85.88
TP-13	30	5	10	84±1.44	90.88
TP-14	10	12.5	15	62±1.28	78.55
TP-15	30	20	10	68±1.28	76.88

RESULTS AND DISCUSSION

Preformulation Studies

Drugs were observed to be white crystalline powder and white solid powder having melting point 152-154^{0}C & 171-172^{0}C respectively for LN & PN. At 296 and 260 nm, the calibration curve of LN and PN were taken. The calibration curve was mentioned in figure 1.

DSC Analysis

DSC thermograms of the Luliconazole (LN) & Posaconazole (PN) showed in figure 2. DSC thermogram of Luliconazole (LN) showed sharp endothermic peak at 151.39^{0}C which DSC thermogram of Posaconazole (PN) showed sharp endothermic peak at 167.52^{0}C.

Optimization of Transdermal Patches of Luliconazole (LN) & Posaconazole (PN)

There were total 15 runs as per experimental design and were prepared in randomized manner. Design software suggest linear model as best fir for both responses. The effects of both variables were shown in table 3. Further, statistical validity were performed using ANOVA test to create R^2, adjusted R^2, predicted R^2, standard deviation and % coefficient of variance.

The folding endurance (R1) and % drug release (R2) ranged from 62 to 88 and 76.22 to 92.46 % respectively. The response models were created using Design expert software and coded for the factor levels to estimate the quantitative impacts of various combinations of factor levels on folding endurance and % drug release. Full model equations could be used to represent the specified model. The 3D surface plots in Figures 3 and 4provide a comprehensive visualization of the interaction between the drug and polymer concentration on both folding endurance and % drug release. These plots are instrumental in understanding how changes in formulation variables impact the performance of transdermal patches. The curvature of the surfaces suggests that a quadratic relationship is present, which aligns with the chosen quadratic model. These insights are critical for fine-tuning the formulation parameters to achieve maximum folding endurance while ensuring controlled drug release, thus enhancing the overall therapeutic efficacy of the

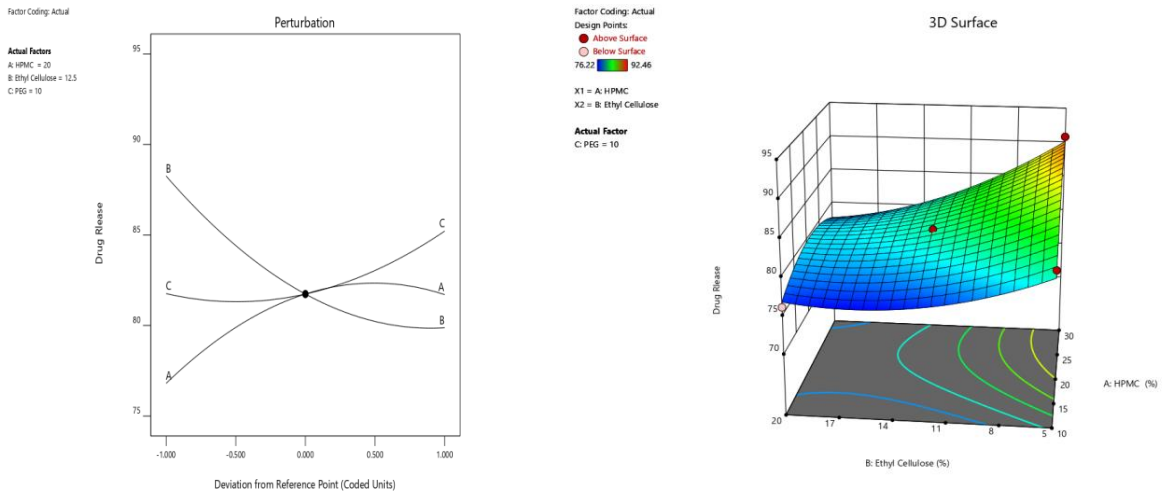

Figure 4: 3D surface plot of TP for % Drug Release

Table 4: Optimized batch formulation of TP

Number	HPMC	Ethyl Cellulose	PEG	Folding Endurance	Drug Release	Desirability
1	22.557	5.343	14.706	84.780	92.481	1.000

Table 5: Validated values of independent variables and response variables for Transdermal patches

Type of Variable	Variables	Optimized Value	Validated Value (n=3)
Independent	X1- HPMC E-5 (% w/v)	22.557	22.557
	X2- EC (% w/v)	5.343	5.343
	X3- PEG (%w/v)	14.706	14.706
Response or Dependent	R1- Folding endurance	84.780	84.216
	R2 - % Drug release	92.481	92.142

transdermal formulation.

The results obtained and observations of optimization on Design Expert a total 100 slution were found and the optimized formulation is as given in number 1. The data of optimized formulation were presented in table 4. In table 5validated values of the optimised batch were presented for both the variables and it was found to be much closed to optimised batches. Results were found to be very close to the batch selected from solutions given by software

CONCLUSION

The results indicate that the drug loaded Transdermal patches prepared showed good percent drug release. The final optimized patches containing drug have good physicochemical and mechanical parameters and it enhanced the percent drug release.

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