Int. J. Pharm. Investigation, 2023; 13(1):74-81.
www.jpionline.org

Original Article

Development, Optimization and Evaluation of Herbal Patch Formulation for Acne Treatment

Kinjal Patel[1,*], Keyur Patel[2], Maitreyi Zaveri[3]

[1]Research Scholar, Department of Pharmacognosy, K. B. Institute of Pharmaceutical Education and Research, Kadi Sarva Vishwa Vidyalaya, Gandhinagar, Gujarat, INDIA.
[2]Department of Pharmaceutics, K. B. Raval College of Pharmacy, Shertha, Gandhinagar, Gujarat, INDIA.
[3]Department of Pharmacognosy, K. B. Institute of Pharmaceutical Education and Research, Kadi Sarva Vishwa Vidyalaya, Gandhinagar, Gujarat, INDIA.

ABSTRACT

Background: More than 85% of young people around the world suffer from acne vulgaris, which is the most prevalent chronic inflammatory skin illness. The study's objective was to develop a herbal patch formulation contained quercetin, curcuminoids, and berberine HCl for the treatment of acne that utilizing ethyl cellulose and HPMC K4M as polymers and propylene glycol as a plasticizer. **Materials and Methods:** Drug excipient compatibility study was performed using FT-IR. Preliminary trial was done for screening of polymers and plasticizer concentrations. The combined influence of the two independent variables, namely the concentration of HPMC K4M and ethyl cellulose, on the dependent variables, tensile strength and cumulative % drug release at 24 hr, was examined using a 3^2 full factorial design. Patches were evaluated for physicochemical parameters. **Results:** Drug excipient compatibility study revealed that drug and excipients are compatible with each other. The optimized formulation (C0) showed tensile strength 2.56 kg/cm^2, cumulative percentage drug release of quercetin, berberine HCl, and curcuminoids at 24 hr were 94.02%, 64.66%, and 94.21%, respectively. Tensile strength increased with an amount of HPMC K4M and Ethyl cellulose increases, the cumulative percentage of drug release decreased as HPMC K4M and ethyl cellulose concentrations were raised. **Conclusion:** Optimized herbal patch formulation had shown good physico-chemical and mechanical properties. The research shows that the developed formulation has the potential to be a useful replacement for the present medications in the market.

Keywords: Acne, Berberine HCl, Curcuminoids, Ethyl cellulose, HPMC K4M, Quercetin.

Correspondence
Ms. Kinjal Patel
Associate Professor, Department of Pharmacognosy, K. B. Raval College of Pharmacy, Shertha, Gandhinagar-382423, Gujarat, INDIA.
Email id: kinjal9387@gmail.com
ORCID: 0000-0001-7799-6692

Received: 02-09-2022;
Revised: 28-09-2022;
Accepted: 11-10-2022.

INTRODUCTION

More than 85% of young people around the world suffer from acne vulgaris, which is the most prevalent chronic inflammatory skin illness. It affects areas having largest oil gland that includes trunk, face, and back. The pathogenesis of acne involved overproduction of sebum, hyper keratinization which blocks skin pores, inflammation and bacterial colonization by *Propionibacterium acnes*.[1,2] Topical or systematic antibiotics and retinoid are used for current treatment of acne. Most serious side effect of antibiotics is its resistance and unwanted side effects; Oral isotretinoin causes teratogenic effects. Nowadays, natural source of medicine are gaining attention to treat wide range of skin ailments due to its efficacy and minimum side effects.[3,4] The traditional and antiquated drug administration method used to give these herbal medicines to patients results in reduced drug efficacy because of poor solubility, poor stability in highly acidic pH, first pass hepatic metabolism, risk of toxicity, and poor stability that lowers drug level below therapeutic concentration in blood, resulting in minimal or no therapeutic effect.[5] Among the many advantages of transdermal drug delivery are the avoidance of hepatic first pass metabolism and the maintenance of steady blood levels over an extended period of time, hence dosing frequency is reduced that decreases gastrointestinal irritation and improved the patient compliance for long term treatment. Chances of overdose or under dose can be reduced by removing the patch from the target site at any time that will end the treatment.[5-7] Based on literature survey, we have chosen quercetin, curcuminoids, and berberine HCl for herbal patch formulation since they have anti-inflammatory, anti-acne, antibacterial, and antioxidant characteristics.[5,8-11] So the development of herbal patch formulation was the goal of the present work to enhance patient compliance and to control the drug release from patches to enhance bioavailability. For that preliminary screening was done for screening of polymers and plasticizers. The effect of

DOI: 10.5530/223097131792

Copyright Information:
Copyright Author (s) 2023 Distributed under Creative Commons CC-BY 4.0

Publishing Partner: EManuscript Tech. [www.emanuscript.in]

HPMC K4M and ethyl cellulose was examined using a 3^2 full factorial design.

MATERIALS AND METHODS

Materials

Berberine HCl, quercetin, curcuminoids were procured from Yucca enterprises (Mumbai); HPMC K4M (Hydroxy Propyl Methyl Cellulose K4M), EC (Ethyl Cellulose) and Eudragit RS100 were purchased from Astron Chemicals (India); PG (Propylene Glycol), DBT (Dibutyl Phthalate) and PEG400 (Polyethylene Glycol 400) were purchased from Chemdyes Corporation (Ahmedabad, Gujarat). Analytical-grade chemicals were employed throughout the study.

Drug excipient compatibility study

Chemical and physical interactions between drugs and polymers were studied by recording the IR spectra by KBr pellet method using FTIR. For drugs and physical mixtures of drugs with polymers, the spectra were taken in the wavelength range between 4000 and 400 cm^{-1}.[12]

Method of preparation of patch

Herbal drug-loaded patches were created using the solvent casting technique. We utilized a petri dish with a surface area of 36.29 cm^2. Selected polymers were first weighed, completely mixed with 10 ml of dichloromethane: methanol (1:1), and then left alone for two hours. Quercetin (7.5mg/2 cm^2), curcuminoids (20 mg/2 cm^2) and berberine HCl (0.5 mg/2 cm^2) were accurately weighed and dissolved in polymeric solution. Then plasticizer was added. The uniform dispersion finally casted on backing membrane [Backing membrane was created by pouring a 4% polyvinyl alcohol solution and drying it at 60°C for six hours] After that, patches were given a 24-hr 40°C drying period. The solvent was uniformly evaporated using an inverted funnel that was kept on the petri dish. The patches were cut into a 2 cm^2 area after the dried films were completely removed from the petri plate and kept in desiccators for subsequent evaluation investigations.[13,14]

Preliminary screening of polymers

Preliminary screening was done to check effect of various polymers on the formulation of herbal patches. Prepared patches were assessed for tensile strength, thickness, weight variation, and folding endurance.[7,13,14] Composition of preliminary trial batches for the selection of polymers is shown in Table 1.

Preliminary screening of plasticizers

Preliminary trial batches P1 to P9 were prepared using varying concentration DBT, PEG400 and PG for the optimization and selection of effective plasticizers. The prepared patches were assessed for drug content, thickness, weight variation, tensile strength, folding endurance, and cumulative percentage drug release at 24 hr. Composition of preliminary trial batches for the selection of plasticizers is shown in Table 2.

Physicochemical evaluation

Thickness

At several locations, thickness was measured using a micrometer screw gauge. The mean value and standard deviation was computed.[15]

Folding endurance

Patch was folded at the same place repeatedly till it broke. The value for folding endurance was the number of times the patch could be folded without breaking.[16]

Weight of patch

A predetermined size (2 cm^2) of dried patch was cut and weighed three times on a digital balance. The average weight and standard deviation was computed.[17]

Table 1: Composition of preliminary trial batches for the selection of polymers.

Ingredients	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12
HPMC K4M (mg)	300	-	-	200	150	100	200	150	100	-	-	-
EC (mg)	-	300	-	100	150	200	-	-	-	200	150	100
ERS100 (mg)	-	-	300	-	-	-	100	150	200	100	150	200
PG (%w/w)	10	10	10	10	10	10	10	10	10	10	10	10

Table 2: Composition of preliminary trial batches for the selection of plasticizers.

Ingredients	P1	P2	P3	P4	P5	P6	P7	P8	P9
HPMC K4M(mg)	200	200	200	200	200	200	200	200	200
EC (mg)	100	100	100	100	100	100	100	100	100
DBT (% w/w)	10	15	20	-	-	-	-	-	-
PEG400 (%w/w)	-	-	-	10	15	20	-	-	-
PG (% w/w)	-	-	-	-	-	-	10	15	20

Percentage moisture content

The patches were weighed separately and maintained in an activated silica-filled desiccator for 24 hr at room temperature. The weight of the patches was measured repeatedly until it remained constant. The difference between the initial and final weights with regard to the final weight was used to compute the percentage of moisture content.[18]

Percentage moisture uptake

In order to maintain 84% RH for 24 hr, the patches were weighed individually and maintained in a desiccator with a saturated solution of potassium chloride. Films were weighed several times until a constant weight was found. The difference between the final and initial weights with regard to the initial weight was used to compute the percentage of moisture uptake.[14]

Tensile Strength

A tensiometer was used to measure tensile strength. It has two grips for load cells. The upper one is adjustable, while the lower one is fixed. Between these grips, a patch is fixed, and pressure is exerted progressively until the patch breaks. The dial reading in kilograms is used to directly record the tensile strength.[13]

Tensile strength =Tensile load at break / cross section area

Drug content

Patch (2 cm^2) was placed in the ultrasonicator for 30 min after being dissolved in 100 ml of phosphate buffer (pH 7.4). The same buffer solution was then used to create an acceptable dilution. After that, the resultant solution was filtered through 0.45 µm membrane filters. Drug content was determined spectrophotometrically.[15]

In-vitro drug release study

For *in vitro* drug release studies, Franz diffusion cells were utilized. With phosphate buffer pH 7.4, the cellophane membrane was hydrated for 24 hr prior to usage. Patch was present in the donor compartment, while pH 7.4 phosphate buffer was present in the receptor compartment. The entire assembly was mounted on a magnetic stirrer, and the temperature of the receptor compartment was kept at 35±0.5°C by continually stirring the solutions at 50 rpm using magnetic beads. Sampling was done on regular interval and an equal volume of fresh buffer solution was introduced in the receptor compartment. Using spectrophotometry, the active components found in the samples withdrawn were determined. The cumulative percentage of drug release was plotted against time.[13]

Optimization of dosage form by 3^2 full factorial design

Based on preliminary screening results, the concentration of HPMC K4M (X_1) and concentration of EC (X_2) were taken as independent factors, whereas tensile strength (Y_1), cumulative percentage release of quercetin at 24 hr (Y_2), cumulative percentage release of berberine HCl at 24 hr (Y_3) and cumulative percentage release of curcuminoids at 24 hr (Y_4) were taken as dependent variables (Table 3).[19,20]

Accelerated stability study

Accelerated stability study was done for optimized patch at 40°C and 75% RH for three month using humidity chamber. Patch was analyzed for tensile strength and cumulative percent drug release at 24 hr.[21,22]

RESULTS AND DISCUSSION

Preliminary screening of polymers

Prepared batches B1 to B12 were assessed for tensile strength, weight variation, thickness, and folding endurance. Among all the trial batches, Batch B4 which contained HPMC K4M and EC as polymers was found to have desirable properties and exhibited good tensile strength and folding endurance so HPMC K4M and EC were used for optimization of formulation. Results of preliminary trial batches for the selection of polymers are shown in Table 4.

Drug excipients compatibility study

There were minor changes in IR spectra of drug mixture alone and combination with polymers but it was with in reported values. It demonstrates the compatibility of drugs and excipients. Results are shown in Figure 1A and 1B.

Preliminary screening of plasticizers

Results of preliminary trial batches for the selection of plasticizers are shown in Table 5. Results of batches P1 to P3 showed good physicochemical parameters but they were dry and less flexible than other batches. Results of batches P4 to P6 also suggested that obtained patches having poor flexibility and mechanical strength compared to P8 batch. Results of batches P7 to P9 showed good mechanical strength and all physicochemical parameters were in uniform range. Batch P9 contained concentration 20% w/w of PG was highly hygroscopic and sticky nature. Hence, among all

Table 3: Optimization of formulation as per 3^2 full factorial design

Batch code	Coded value		Uncoded value	
	X_1	X_2	X_1= concentration of HPMC K4M (mg)	X_2=concentration of EC (mg)
C1	-1	-1	150	50
C2	0	-1	200	50
C3	1	-1	250	50
C4	-1	0	150	100
C5	0	0	200	100
C6	1	0	250	100
C7	-1	1	150	150
C8	0	1	200	150
C9	1	1	250	150

Table 4: Results of preliminary trial batches for the selection of polymers.

Batch code	Thickness (mm)	Weight of patch (mg)	Tensile strength (kg/cm²)	Folding endurance
B1	0.44±0.020	325.6±2.08	1.42±0.02	68.33±2.08
B2	0.33±0.011	298.3±0.57	1.08±0.02	42.66±2.08
B3	0.41±0.041	331.6±2.08	1.20±0.015	47±2
B4	0.42±0.023	338.6±2.51	2.54±0.032	119.6±2.05
B5	0.41±0.030	310.3±1.52	1.32±0.015	99±1.60
B6	0.37±0.011	326±2	1.13±0.029	81.66±2.68
B7	0.46±0.04	345.3±1.52	1.76±0.025	104.3±1.52
B8	0.42±0.011	337±1.73	1.44±0.025	96±2.64
B9	0.38±0.02	327.3±2.08	1.15±0.026	83.33±3.21
B10	0.41±0.030	337.6±1.15	0.99±0.02	67±1
B11	0.34±0.030	327±2	0.77±0.020	68.66±4.16
B12	0.4±0.02	316.6±1.15	0.65±0.020	62.66±2.08

Values expressed as mean ± S.D, n = 3.

Table 5: Results of preliminary trial batches for the selection of plasticizers.

Batch code	Thickness (mm)	Weight of patch (mg)	Tensile strength (kg/cm²)	Folding endurance	% Drug content		
					Quercetin	Berberine HCl	Curcuminoids
P1	0.38±0.030	337±2.64	1.78±0.03	109.6±3.51	97.71±1.38	95.75±0.53	96.75±0.25
P2	0.40±0.030	338.3±2.51	1.78±0.011	206±2.64	98.58±0.46	96.92±1.23	97.25±0.50
P3	0.41±0.025	340.3±1.15	1.85±0.036	221.3±2.08	98.58±1.38	95.99±0.93	97.31±0.41
P4	0.40±0.015	337.3±1.52	1.75±0.015	105.6±3.05	98.14±1.84	98.45±0.60	97.58±0.25
P5	0.40±0.049	339±1	1.96±0.032	192±3	98.36±0.92	97.04±0.93	96.42±0.34
P6	0.41±0.025	340±2.64	2.11±0.025	210.6±2.51	97.71±0.92	95.87±0.73	97.64±0.50
P7	0.40±0.020	338.6±2.51	2.03±0.030	121.3±2.08	98.14±1.84	98.45±0.93	97.97±0.41
P8	0.42±0.020	340.6±1.52	2.98±0.032	202.6±1.51	98.14±1.06	97.92±1.53	98.2±1.09
P9	0.41±0.015	343.6±3.21	2.69±0.030	263.3±1.52	97.27±1.84	99.03±0.20	98.7±0.88

Values expressed as mean ± S.D, *n*= 3.

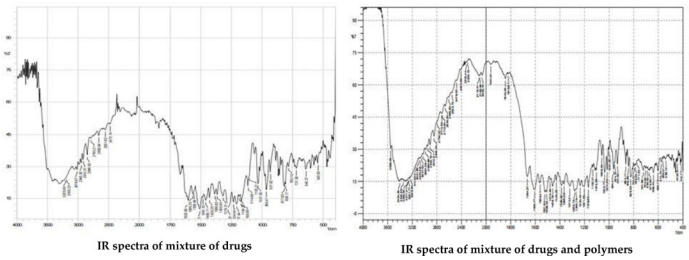


Figure 1: A: IR spectra of mixture of drugs, B: IR spectra of mixture of drugs and polymers.

three plasticizers, PG with 15% by weight of the polymer's total dry weight was selected for further study as it shows promising results for physicochemical parameters and also shows good drug release as shown in Figure 2A, 2B, 2C.

Optimization of dosage form by 3² full factorial design

Results for 3² full factorial design batches are shown in Table 6, 7 and Figure 3A, 3B, 3C.

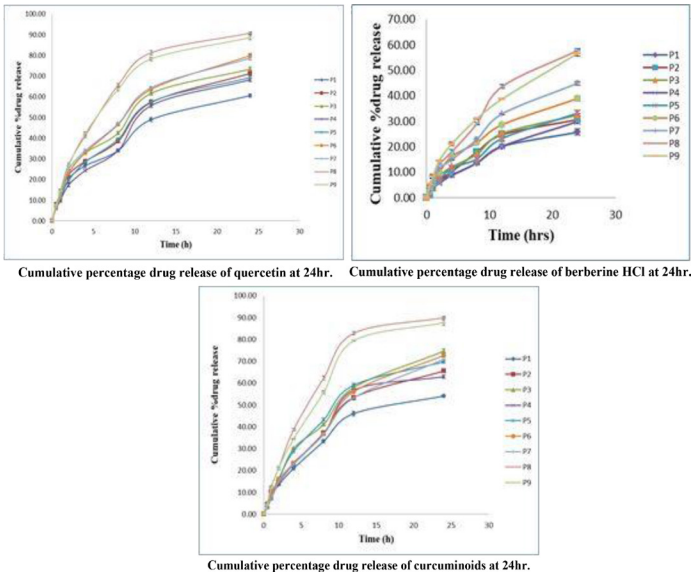


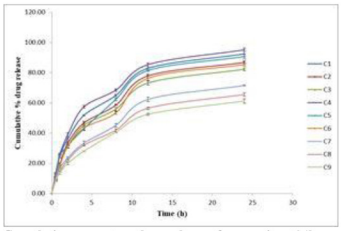
Figure 2: A: Cumulative percentage drug release of quercetin at 24hr, B: Cumulative percentage drug release of berberine HCl at 24hr, C: Cumulative percentage drug release of curcuminoids at 24hr.

Table 6: Results of 3^2 full factorial design batches.

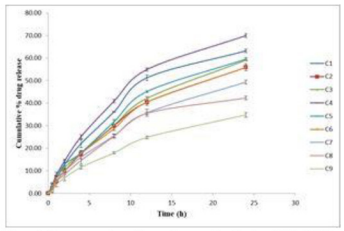
Batch code	Thickness (mm)	Weight of patch (mg)	Tensile strength (kg/cm²)	Folding endurance	% Moisture content	% Moisture uptake	% Drug content		
							Quercetin	Berberine HCl	Curcuminoids
C1	0.33± 0.030	328.6±1.52	2.013± 0.87	103± 2	1.433± 0.47	2.117± 0.52	99.34± 0.46	97.16± 1.23	97.47± 0.69
C2	0.37± 0.011	334.3±2.08	2.176± 0.95	115.6± 2.08	2.110± 0.28	1.771± 0.27	97.71± 0.92	99.18± 0.30	98.81± 0.69
C3	0.45± 0.011	343±2	2.306± 0.96	145.6± 3.05	2.810± 0.48	2.147± 0.34	99.01± 0.92	98.92± 0.73	97.81± 0.09
C4	0.38± 0.02	330.6±0.57	2.483± 1.05	172± 1	0.800± 0.35	1.388± 0.34	99.34± 0.46	98.57± 0.73	97.53± 0.44
C5	0.43± 0.064	341± 2	3.101± 1.06	190.3± 1.52	1.388± 0.62	1.370± 0.61	96.40± 0.75	96.92± 0.73	97.2± 0.16
C6	0.44± 0.02	342.3±1.52	3.416± 1.13	194± 1.73	1.482± 0.59	1.169± 0.29	97.38± 1.38	99.15± 0.35	98.97± 0.41
C7	0.41± 0.030	338±1	2.119± 0.93	216± 2.64	1.104± 0.18	0.594± 0.29	99.49± 0.25	96.57± 0.81	97.42± 0.34
C8	0.45± 0.030	336.6±2.08	3.598± 1.74	256.6± 2.08	1.017± 0.70	0.905± 0.29	98.69± 1.38	99.03± 1.13	97.47± 0.34
C9	0.46± 0.02	345.3±2.51	3.921± 1.95	288± 2.64	1.011± 0.17	1.101± 0.17	99.01± 1.84	97.51± 0.53	97.7± 0.60

Table 7: Results of 3^2 full factorial design batches.

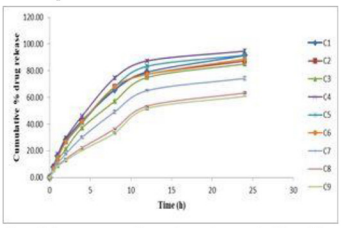
Batch code	Dependent variables			
	Tensile strength (kg/cm²)	Cumulative % drug release at 24 hr		
		Quercetin	Berberine HCl	Curcuminoids
C1	2.013±0.87	92.38±1.68	63.21±0.72	91.43±1.53
C2	2.176±0.95	86.76±1.37	55.89±1.08	87.31±0.62
C3	2.306±0.96	82.27±0.92	59.08±0.35	85.15±1.08
C4	2.483±1.05	95.14±1.09	69.97±0.82	94.75±1.51
C5	3.101±1.06	90.63±1.33	59.55±0.68	91.71±0.81
C6	3.416±1.13	85.34±1.05	55.89±1.52	88.82±1.22
C7	2.119±0.93	71.48±0.53	49.34±0.82	74.34±1.52
C8	3.598±1.74	65.52±1.26	42.3±0.83	63.39±0.88
C9	3.921±1.95	61.23±1.48	34.82±1.03	60.77±0.54



Cumulative percentage drug release of quercetin at 24hr.



Cumulative percentage drug release of berberine HCl at 24hr.



Cumulative percentage drug release of curcuminoids at 24hr.

Figure 3 A: Cumulative percentage drug release of quercetin at 24hr, B: Cumulative percentage drug release of berberine HCl at 24hr, C: Cumulative percentage drug release of curcuminoids at 24hr.

Full and reduced model for Tensile strength (Y_1)

Full model equation

$$Y_1 = 3.12 + 0.5X_1 + 0.52X_2 - 0.22X_1^2 - 0.28X_2^2 + 0.38X_1X_2$$

Table 8: Summary output of regression for effect X_1 and X_2 on Y_1.

R-Squared	0.9721	
Adj R-Squared	0.9521	
Source of variation	Sum of squares	P value
Model (Quadratic)	4.32	< 0.0001
X_1	1.53	< 0.0001
X_2	1.65	< 0.0001
X_1^2	0.14	0.0277
X_2^2	0.22	0.0094
X_1X_2	0.57	0.0008

Based on ANOVA results, the developed quadratic model was highly significant as shown by the extremely low probability value <0.0001 (Table 8). The R^2 value was determined to be 0.9721, indicating that a quadratic model may exhibit 97.21% of response variability. According to the regression coefficient values of the variables and 3D surface plots (Figure 4), tensile strength increased with an increase in HPMC K4M and EC. In this case the b_2 value is more than b_1 value, indicating tensile strength increases more with an increase in EC when compared to HPMC K4M.

Full and reduced model for cumulative percentage release of quercetin at 24 hr (Y_2)

Full model equation

$$Y_2 = 90.48 - 5.03X_1 - 10.53X_2 + 0.14X_1^2 - 13.96X_2^2 - 0.035X_1X_2$$

Based on ANOVA results, the developed quadratic model was highly significant as shown by the extremely low probability value <0.0001 (Table 9). The R^2 value was determined to be 0.9994, indicating that a quadratic model may exhibit 99.94% of response variability. According to the regression coefficient values of the variables and 3D surface plots (Figure 5), As HPMC K4M and EC concentrations rose, the percentage drug release fell. In this case the b_2 value is more negative than b_1 value, indicating EC had a more release retardant effect compare to HPMC K4M at

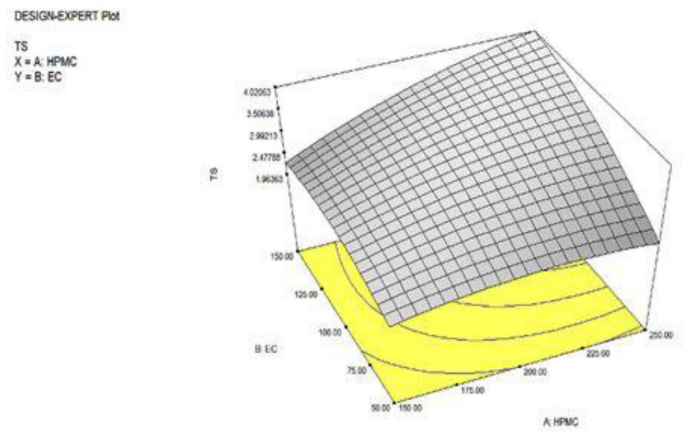


Figure 4: 3D surface plot of response Y_1.

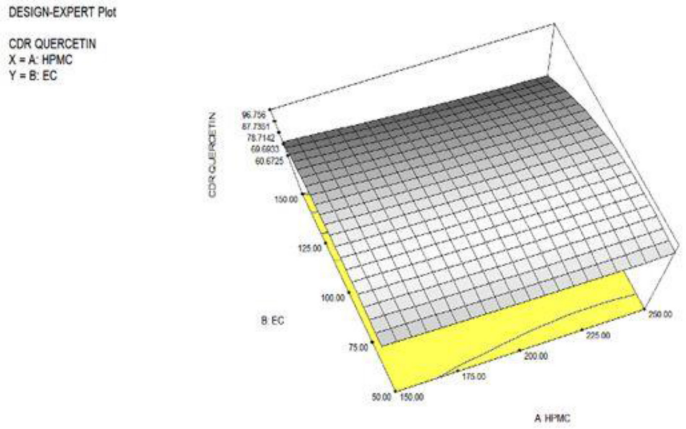


Figure 5: 3D surface plot of response Y_2.

Table 9: Summary output of regression for effect X_1 and X_2 on Y_2.

R-Squared	0.9994	
Adj R-Squared	0.9989	
Source of variation	Sum of squares	P value
Model (Quadratic)	1442.23	< 0.0001
X_1	151.6	< 0.0001
X_2	665.29	< 0.0001
X_1^2	0.051	0.5461
X_2^2	538.54	< 0.0001
X_1X_2	4.90	0.8501

24 hr. The coefficients X_1^2 and X_1X_2 were determined to have significance values of $P = 0.5461$ and $P = 0.8501$, respectively. In order to create a reduced model, they were therefore excluded from the full model.

Reduced model equation on the basis of p value,

$$Y_2 = 90.48 - 5.03X_1 - 10.53X_2 - 13.96X_2^2$$

Full model for cumulative percentage release of berberine HCl at 24 hr (Y_3)

Full model equation

$$Y_3 = 59.67 - 5.46X_1 - 8.62X_2 + 2.96X_1^2 - 10.87X_2^2 - 2.6X_1X_2$$

Based on ANOVA results, the developed quadratic model was highly significant as shown by the extremely low probability value <0.0001 (Table 10). The R^2 value was determined to be 0.982, indicating that a quadratic model may exhibit 98.2% of response variability. According to the regression coefficient values of the variables and 3D surface plots (Figure 6), As HPMC K4M and EC concentrations rose, the percentage drug release fell. In this case the b_2 value is more negative than b_1 value, indicating EC had a more release retardant effect compare to HPMC K4M at 24 hr.

Table 10: Summary output of regression for effect X_1 and X_2 on Y_3.

R-Squared	0.982	
Adj R-Squared	0.9691	
Source of variation	Sum of squares	P value
Model (Quadratic)	982.26	< 0.0001
X_1	178.54	< 0.0001
X_2	445.83	< 0.0001
X_1^2	24.26	0.0181
X_2^2	326.42	< 0.0001
X_1X_2	26.99	0.0143

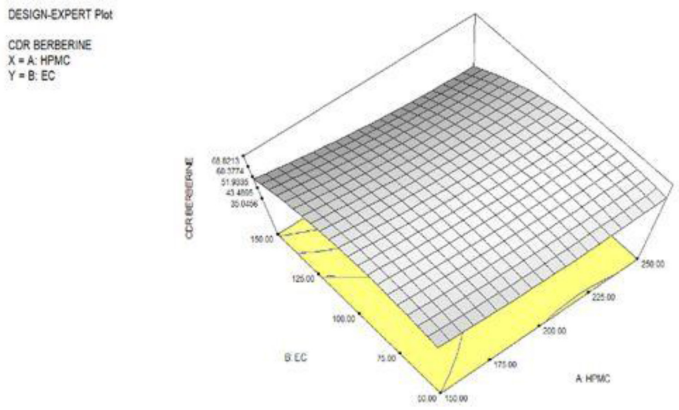


Figure 6: 3D surface plot of response Y_3.

Full and reduced model for cumulative percentage release of curcuminoids at 24 hr (Y_4)

Full model equation

$$Y_4 = 91.37 - 4.3X_1 - 10.9X_2 + 1.28X_1^2 - 15.15X_2^2 - 1.82X_1X_2$$

Based on ANOVA results, the developed quadratic model was highly significant as shown by the extremely low probability value <0.0001 (Table 11). The R^2 value was determined to be 0.9916, indicating that a quadratic model may exhibit 99.16% of response

Table 11: Summary output of regression for effect X_1 and X_2 on Y_4.

R-Squared	0.9916	
Adj R-Squared	0.9856	
Source of variation	Sum of squares	P value
Model (Quadratic)	1536.18	< 0.0001
X_1	110.77	0.0001
X_2	712.64	< 0.0001
X_1^2	4.53	0.1623
X_2^2	634.28	< 0.0001
X_1X_2	13.29	0.0318

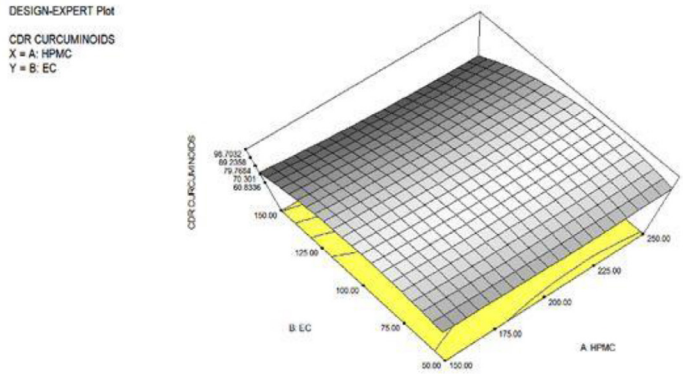


Figure 7: 3D surface plot of response Y_4.

variability. According to the regression coefficient values of the variables and 3D surface plots (Figure 7), As HPMC K4M and EC concentrations rose, the percentage drug release fell. In this case the b_2 value is more negative than b_1 value, indicating EC had a more release retardant effect compare to HPMC K4M at 24 hr. The coefficient X_1^2 was determined to have significance value of $P = 0.1623$. In order to create a reduced model, it was therefore excluded from the full model.

Reduced model equation on the basis of *p* value,

$$Y_4 = 91.37 - 4.3X_1 - 10.9X_2 - 15.15X_2^2 - 1.82X_1X_2$$

Optimization of formulation

Selection of optimum formulation was done on the basis of criteria of minimum and maximum values of dependent variables. From the Figure 8, it could be concluded that batch with X_1 = 156.11 and X_2 =94.28 was selected as optimized batch which has desirability 1. Result of evaluation parameters of optimized batch are shown in Table 12. Comparisons between observed and predicted responses for optimized batch are shown in Table 13.

Actual response of optimized batch was measured and compared with the predicted response. The percentage error was discovered to be less than 5%, demonstrating good agreement between the observed and predicted values. Consequently, it was determined that this design was valid.

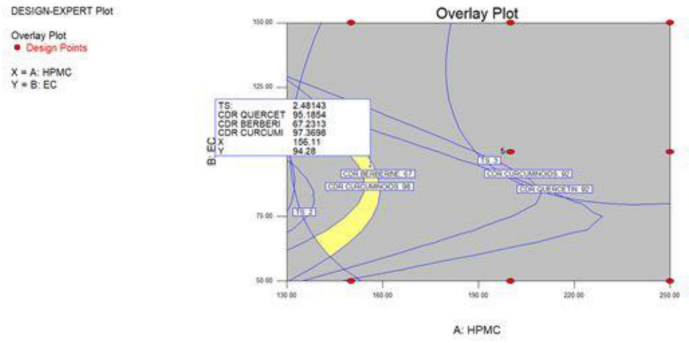


Figure 8: Optimized batch from overlay plot.

Table 12: Result of evaluation parameters of optimized batch (C0).

Evaluation of optimized batch	Results
Tensile strength (kg/cm²)	2.56±0.81
Cumulative % drug release of quercetin at 24 hr	94.02±1.17
Cumulative % drug release of berberine HCl at 24 hr	64.66±0.89
Cumulative % drug release of curcuminoids at 24 hr	94.21±1.53
Thickness (mm)	0.40±0.03
Weight of patch (mg)	337.3±1.52
Folding endurance	193.3±2.51
% Moisture content	1.10 ± 0.63
% Moisture uptake	0.89 ±0.29
% Drug content of quercetin	98.69±1.38
% Drug content of berberine HCl	99.03±0.85
% Drug content of curcuminoids	98.85±0.74

Table 13: Comparison between responses of optimized batch (C0).

Evaluation parameters	Predicted value	Actual value	% Error
Tensile strength (kg/cm²)	2.48	2.56±0.81	3.23
Cumulative % drug release of quercetin at 24 hr	95.19	94.02±1.17	1.23
Cumulative % drug release of berberine HCl at 24 hr	67.23	64.66±0.89	3.82
Cumulative % drug release of curcuminoids at 24 hr	97.37	94.21±1.53	3.25

Accelerated stability study

Drugs remained stable in patch formulation at accelerated conditions for 90 days as no significant variations in tensile strength and cumulative percent drug release at 24 hr was observed at mentioned conditions (Table 14).

CONCLUSION

A herbal patch formulation using HPMC K4M and ethyl cellulose as a polymer that has demonstrated strong physicochemical and mechanical properties was optimized using a 3^2 full factorial design. Tensile strength increased with an increase in HPMC K4M

Table 14: Results of optimized patch under accelerated stability testing conditions.

Stability conditions	Sampling time	Tensile strength (kg/cm^2)	Cumulative percent drug release at 24 hr		
			Quercetin	Berberine HCl	Curcuminoids
Accelerated condition (40±2°C and 75±5% RH) (Batch C0)	Initial (0 day)	2.56	94.02± 1.17	64.66± 0.89	94.21± 1.53
	30 days	2.52	94.16± 1.77	64.59± 0.38	94.34± 1.12
	60 days	2.59	95.32± 0.31	65.15± 0.92	93.99± 1.63
	90 days	2.49	93.97± 1.26	64.12± 1.45	93.86± 0.23

and ethyl cellulose concentration, and cumulative percentage drug release reduced with an increase in HPMC K4M and ethyl cellulose concentration, according to all criteria and evaluation of the experimental design. An FTIR investigation of drug excipient compatibility revealed no interactions between drugs and excipients. The study shows that the developed formulation has the potential to be employed as a powerful substitute for the medications that are currently on the market.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

%: Percentage; **°C:** Degree Celsius; **RH:** Relative humidity; **kg:** Kilogram; **cm:** Centimeter; **hr:** hour; **SD:** Standard deviation; **HPMC K4M:** Hydroxy propyl methyl cellulose K4M; **EC:** Ethyl cellulose; **PG:** Propylene glycol; **DBT:** Dibutyl phthalate; **PEG400:** Polyethylene glycol 400.

REFERENCES

1. Olutunmbi Y, Paley K, English JC. Adolescent female acne: Etiology and management. J Pediatr Adolesc Gynecol. 2008;21(4):171-6. doi: 10.1016/j.jpag.2007.07.004, PMID 18656070.
2. Karodi RS, Mahendrakumar CB, Bhise K. Evaluation of anti-acne activity of hydroalcoholic extract of *Punica granatum* Linn. J Pharmacogn Phyther. 2013;5(9):160-3.
3. Prasad SB, Kaur D,. Y. Formulation of topical gel from extract of *Berberis aristata* DC for acne. Int J Drug Deliv Technol. 2019;9(1):104-8. doi: 10.25258/ijddt.9.1.17.
4. Kaur D, Prasad SB, Verma S. Formulation and evaluation gel from extract of *Plumbago indica* for acne. Int J Drug Deliv Technol. 2016;6(3):95-8. doi: 10.25258/ijddt.v6i3.8895.
5. Kriplani P, Guarve K, Singh Baghel U. Formulation optimization and characterization of transdermal film of curcumin by response surface methodology. Chin Herb Med. 2021;13(2):274-85. doi: 10.1016/j.chmed.2020.12.001, PMID 36117499.
6. Chien YW. Novel drug delivery system: drugs and pharmaceutical sciences. 2nd ed. Marcel Dekker Inc; 2007. p. 301-75.
7. Barry B. Transdermal drug delivery. In: Aulton ME, editor, Pharmaceutics: The Design and manufacture medicine. 3rd ed. Churchill Livingstone; 2007. p. 565-92.
8. Batubara I, Kuspradini H, Muddathir AM, Mitsunaga T. *Intsia palembanica* wood extracts and its isolated compounds as Propionibacterium acnes lipase inhibitor. J Wood Sci. 2014;60(2):169-74. doi: 10.1007/s10086-013-1388-5.
9. Majewski G, Bohm R, Ross M. Acne treatment compositions and methods of use. US20080070875A1. 2008.
10. Patel K, Zaveri M. Spectrophotometric multicomponent determination of quercetin, berberine HCl and curcumin by double divisor ratio spectra derivative method. Int J Bot Stud. 2021;6(5):7-8.
11. Slobodníková L, Kost'álová D, Labudová D, Kotulová D, Kettmann V. Antimicrobial activity of *Mahonia aquifolium* crude extract and its major isolated alkaloids. Phytother Res. 2004;18(8):674-6. doi: 10.1002/ptr.1517, PMID 15476315.
12. Pavia D, Lampman G, Kriz G. Introduction to spectroscopy: A guide for students of organic chemistry. 3rd ed. Thomson learning; 2013. p. 14-101.
13. Prajapati ST, Patel CG, Patel CN. Formulation and evaluation of transdermal patch of repaglinide. ISRN Pharmacol. 2011;2011:1-9. doi: 10.5402/2011/651909, PMID 22389856.
14. Kharia A, Singhai AK. Gilhotra R. Formualtion and evaluation of transdermal patch for the treatment of inflammation. J Pharm Sci Res. 2020;12(6):780-8.
15. Singh A, Bali A. Formulation and characterization of transdermal patches for controlled delivery of duloxetine hydrochloride. J Anal Sci Technol. 2016;7(1):25. doi: 10.1186/s40543-016-0105-6.
16. Lakhani P, Bahl R, Bafna P. Transdermal Patches: Physiochemical and *in-vitro* evaluation methods. Int J Pharm Sci Res. 2015;6(5):1826-36. doi: 10.13040/IJPSR.0975-8232.6(5).1826-36.
17. Ali HSM, Hanafy AF. Glibenclamide nanocrystals in a biodegradable chitosan patch for transdermal delivery: Engineering, formulation, and evaluation. J Pharm Sci. 2017;106(1):402-10. doi: 10.1016/j.xphs.2016.10.010. PMID 27866687.
18. Patel NA, Patel NJ, Patel RP. Design and evaluation of transdermal drug delivery system for curcumin as an anti-inflammatory drug. Drug Dev Ind Pharm. 2009;35(2):234-42. doi: 10.1080/03639040802266782, PMID 18785045.
19. Amin MJ, Patel KS, Patel DR, Patel ZP, Bajag JV. Formulation and evaluation of sustained-release pellets of lornoxicam. Int J Appl Pharm. 2021;13(4):221-7. doi: 10.22159/ijap.2021v13i4.41601.
20. Trivedi H, Patel K, Oza NA, Sagar S. Int-Part ii: Optimization of isosorbide dinitrate sustained release layer in antihypertensive bilayer tablet. J Appl Pharm. 2020;12(5):219-26.
21. Ah YC, Choi JK, Choi YK, Ki HM, Bae JH. A novel transdermal patch incorporating meloxicam: *in vitro* and *in vivo* characterization. Int J Pharm. 2010;385(1-2):12-9. doi: 10.1016/j.ijpharm.2009.10.013, PMID 19833177.
22. Shinkai N, Korenaga K, Mizu H, Yamauchi H. Intra-articular penetration of ketoprofen and analgesic effects after topical patch application in rats. J Control Release. 2008;131(2):107-12. doi: 10.1016/j.jconrel.2008.07.012, PMID 18680771.

Cite this article: Patel K, Patel K, Zaveri M. Development, Optimization and Evaluation of Herbal Patch Formulation for Acne Treatment. Int. J. Pharm. Investigation. 2023;13(1):74-81.