RESEARCH ARTICLE

Formulation and Evaluation of Naringin Loaded Transdermal Patches using 3^2 Full Factorial Design

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ABSTRACT

The main goal of the current study was to maximize the bioavailability of naringin by prolonging the drug's release using transdermal patches. Ethyl cellulose (EC) served as the lipophilic component and hydroxy propyl methyl cellulose (HPMC) as the hydrophilic matrix in the preparation of transdermal patches. A 3^2-complete factorial technique was used to build the optimal design matrix, altering the ratio between the hydrophilic and lipophilic matrices. To create the best optimum formulation, three alternative ratios of EC and HPMC were employed. The patches had pH values ranging from 5.28 ± 0.006 to 5.62 ± 0.015. The transdermal patches had thicknesses ranging from 0.514 ± 0.004 to 0.697 ± 0.004 mm. The average weight of the prepared transdermal patches ranged from 194.67 ± 0.578 to 241.67 ± 1.528 mg. The transdermal patches' moisture content ranged from 7.23 ± 0.158 to 10.33 ± 0.158%. Tensile strength values of the prepared transdermal patches ranged from 9.59 ± 0.006 to 10.41 ± 0.035 kg/cm^2, while the drug content varied from 94.7 ± 0.6 to 97.33 ± 0.208%.

Keywords: Optimization, Transdermal, Naringin, Ethylcellulose, Matrix.

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INTRODUCTION

The majority of medications that are used in clinical medicine work by interfering with the structure and function of cells and cell membranes through concentration-dependent, reversible interactions at certain receptor sites. Sometimes, in order to achieve and keep the prescribed drug's concentration within the therapeutically effective range, it is necessary to take a single dosage many times. As a result, there are variations in the medication levels in plasma.[1,2] Medication delivered via healthy skin with controlled release is one definition of a transdermal drug delivery system. Nowadays, oral therapy and transdermal distribution are the most fruitful areas of novel drug delivery research. Approximately 40% of drug delivery candidate items are being clinically assessed and have a link to the dermal or transdermal system. For the purpose of treating localized or systemic disorders, a transdermal patch is an adhesive patch that has been medicated and put to the skin to provide a time-released amount of medication.[3]

Many medication delivery methods that use a subdermal implant to administer sustained-release treatment have been developed recently. Public release has been made of three systems that provide drug delivery techniques suitable for transdermal medicine administration. Many antihistaminic drugs meet the criteria needed to be used effectively in a transdermal drug delivery system. Among the benefits are high potency, suitable physicochemical characteristics, sufficient skin penetration, and lack of cutaneous irritation.[4]

Naringin is a disaccharide dihydroxy flavanone present in plants, which has been widely reported to be a potent antioxidant compound. The use of naringin has been limited owing to its low oral bioavailability. Previous reports related to the improvement of bioavailability of naringin utilized the formulation of nanoparticles and nanosuspension of naringin.[5,6] Also, reports related to sustained release formulations of naringenin,[7] a precursor for naringin have been found in the literature.[8-11] In the proposed research work, it was hypothesized to prepare transdermal patches of naringin with the objective of delivering naringin over the long term at a consistent pace to control inflammation.

MATERIAL AND METHODS

Yarrow Pharmaceuticals provided the naringin, while different sources provided the hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), and other necessary chemicals.

Drug Excipient Compatibility Studies by FTIR

The infrared spectra of naringin and its physical interaction with polymers and excipients were obtained using FTIR. Spectra showed evidence of both pure drug and a physical mixture of drug and polymer.[12]

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Standard Curve of Naringin

At 295 nm, the greatest absorption of naringin in ethanol was noted. At the aforementioned wavelength, several medication concentrations were used to create the calibration curve. About 50 mL of ethanol were used to dissolve 5 mg of naringin to create a new stock solution[13] in a 10 mL volumetric flask and then used the same buffer to build up the solution until it reached the desired level to create a 100 µg/mL solution. This stock solution was obtained in 5 mL, and by adding ethanol to achieve 10 µg/mL, the volume was raised to 50 mL. Transfer 2, 4, 6, 8, and 10 mL of this mixture into a 10 mL volumetric flask. Next, ethanol will be added to generate solutions of 2, 4, 6, 8, and 10 µg/mL, increasing the amount to 10 mL. The absorbance of each dilution was measured at 295 nm using a UV spectrophotometer with ethanol as the reference blank. A calibration curve was then generated.

Formulation of Transdermal Patches[14,15]

Using the solvent casting method, naringin-loaded transdermal patches were created in a 38.46 cm^2 petridish. The polymers were carefully weighed and dissolved in 10 mL of water-ethanol to produce a clear solution. (1:1) solution, and stirred for 30 minutes using a magnetic stirrer before being set aside (Table 1). The naringin was carefully weighed, dissolved in the previously described solution, and then mixed to create a translucent solution. In order to improve permeability, propylene glycol (15% w/w of total polymer) and plasticizer, polyethylene glycol 400 (30% w/w of total polymer), were added. Following a drying time of 24 hours at room temperature and lubrication with glycerin, the uniform solution was transferred to a petri plate. The petri dish was covered with an inverted funnel to stop the solvent from evaporating too quickly. The dried patches were removed after 24 hours and kept for later research in a desiccator.

Evaluation of Transdermal Patches[16]

General appearance

We assessed the homogeneity, transparency, clarity, color, and smoothness of the formulated patches.

Table 1: Formula for naringin loaded transdermal patches

Ingredients	*Naringin*	*HPMC (mg)*	*EC (mg)*	*PEG-400 (%w/w)*	*Propylene glycol (%w/w)*
P1	180	100	50	30	15
P2	180	125	75	30	15
P3	180	150	75	30	15
P4	180	125	75	30	15
P5	180	100	100	30	15
P6	180	125	75	30	15
P7	180	100	75	30	15
P8	180	125	75	30	15
P9	180	150	50	30	15
P10	180	125	75	30	15
P11	180	125	100	30	15
P12	180	125	50	30	15
P13	180	150	100	30	15

Uniformity of weight test

By weighing each formulated patch separately and comparing its weight to the average weight of the prepared patches, the patches were exposed to mass variation. Patch weight was measured with an analytical balance that was calibrated. For every formulation, the analysis was done in triplicate.

Thickness

Using a vernier caliper, the thickness of each patch was measured at six separate locations, and the average was determined.

Surface pH

Using a pH meter that was calibrated, the transdermal patches' surface pH was determined. A 1-cm^2 section of transdermal patch and 1-mL of distilled water were incubated for 2 hours at room temperature (25 ± 2°C) in a test tube. The pH of the surface was measured using the wet patch after the water in the test tube was decanted. The pH electrode was placed in the swollen section of the patch three times in order to get the average pH.

Folding endurance

To evaluate the durability of folding, one patch was folded repeatedly from the same position until it cracked or broke. The number of times the film could be folded from the same position without cracking or breaking is used as a measure of folding endurance.

Tensile strength

The produced patches' tensile strength was assessed using a lab-made pulley apparatus. The beginning patch length was calculated using a scale. The transdermal patch was secured to a weighing pan by a rope that crossed a pulley on one side and a weighing balance hook on the other. The pan was gradually filled with weight until the patch broke or fractured. The tensile strength was calculated using the total weight of the pan. The force necessary to cause the transdermal patch to shatter or crack was determined using the following equation:

$$Tensile\ Strength = F/[a * b\,(1 + L/I)]$$

Where, F is the force required to fracture the patch, an is its width, and b is its thickness (measured in centimeters). The patch's length (L) is measured in centimeters, and its elongation (I) is measured in centimeters before it breaks or cracks.

The following formula was used to calculate the transdermal patches' % elongation:

$$\%\ Elongation = (Lf - Li)/Li * 100$$

Where Li is the patch's initial length and Lf is the patch's length before breaking.

Drug content test

Three 4 cm^2 pieces were taken from each patch by slicing off zones from different areas.[17] These parts were dissolved in ten milliliters of ethanol and placed on a vortex shaker for an hour in order to completely dissolve the patches. Following the completion of the final solutions by 0.1 mL of the solution was removed using a Whatman paper filter and diluted to 10 mL in a second volumetric flask. The absorbance of this solution was

measured at 295 nm using a UV-visible spectrophotometer, which made it possible to calculate the drug concentration.

Percent moisture content

One by one, the transdermal films were weighed and then kept at room temperature in desiccators with fused calcium chloride for a whole day. After a day, the films were reweighed, and the moisture content percentage was determined using the supplied procedure.

$$\text{Percentage of moisture content} = \frac{\text{Initial weight} - \text{Final weight x 100}}{\text{Initial weight}}$$

In-vitro permeation study

Franz diffusion cells with a 30 mL receptor compartment capacity were used in transdermal patch *in-vitro* penetration investigations.[18] The prepared patch with a 4 cm^2 surface area was placed between the diffusion cell's donor and receptor compartments before the dialysis membrane was inserted. The receptor compartment of the diffusion cell was filled with phosphate buffer saline pH 7.4. The receptor compartment's solution was continuously mixed at a speed of 50 rpm using magnetic beads, and the complete assembly was fixed to a magnetic stirrer to maintain a temperature of 37 ± 0.5ºC. After the appropriate dilution with ethanol, the 1-mL aliquots were taken at various intervals (0, 2, 4, 6, 8, 12 and 24 hours), and the drug concentration was determined using UV light at 295 nm. After each sample extraction, the receptor phase was swapped out for the same volume of 37ºC phosphate buffer, and the amount of drug that permeated each square centimeter of patches was measured as a function of time.

RESULTS AND DISCUSSION

Drug-Polymer Compatibility Study

The compatibility of naringin with HPMC and ethyl cellulose was investigated using the FTIR spectra of the pure drug and the physical combination. Comparing the drugs and the physical combination with polymers' FTIR spectra revealed

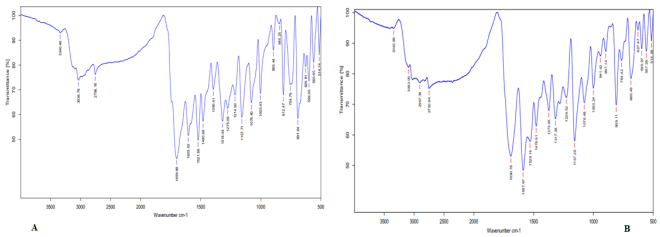

Figure 1: (A) FTIR spectra of naringin (B) Physical mixture naringin with HPMC and EC

that no peaks were eliminated. Only the intensities of the already-existing peaks varied (maybe due to the coupling of absorption frequencies) (Figure 1). This shows that the medication and the matrix-forming polymers are compatible. The stretching and bending vibrations caused by OH (3340.56 cm^{-1}), C=O (1699.89 cm^{-1}), C=C (1603.53 cm^{-1}), and C-O-C (1003.43 cm^{-1}) were seen in the FTIR spectra of naringin.

The formulation and release study concentrations of naringin were determined using the regression equation (Abs = 0.057 conc -0.005) derived from the calibration curve.

Results of Evaluation of the Patches

Ethyl cellulose (EC) served as the lipophilic component and hydroxy propyl methyl cellulose (HPMC) as the hydrophilic matrix in the getting transdermal patches ready. As a permeation enhancer, propylene glycol (15% polymer weight) was used to aid in the medication's penetration into the dermis., and PEG-400 (30% polymeric weight) was employed as the plasticizer to achieve the elasticity of the patches. The most popular and easiest way to create transdermal patches is the solvent-casting process. The solvents from the patch can be gradually evaporated with the assistance of an inverted funnel. A 3^2-complete factorial technique was used to build the optimal design matrix, altering the ratio between the hydrophilic and lipophilic matrices. To create the best optimum formulation, three alternative ratios of EC and HPMC were employed.

Table 2: Characterization of naringin loaded transdermal patches

Formulation	*Thickness (mm)*	*Average weight (mg)*	*Moisture loss (%)*	*Drug content (%)*	*Folding endurance*	*Surface pH*	*Tensile strength*
P1	0.514 ± 0.004	194.67 ± 0.578	7.23 ± 0.158	94.73 ± 0.404	74.33 ± 0.578	5.28 ± 0.006	9.59 ± 0.006
P2	0.564 ± 0.004	225.67 ± 2.309	7.87 ± 0.058	95.7 ± 0.173	77.67 ± 0.578	5.36 ± 0.006	9.4 ± 0.016
P3	0.633 ± 0.003	241.33 ± 1.528	10.33 ± 0.158	97.27 ± 0.153	83 ± 1.000	5.57 ± 0.026	10.52 ± 0.015
P4	0.563 ± 0.004	223.33 ± 2.082	7.87 ± 0.058	95.87 ± 0.058	79 ± 1.000	5.61 ± 0.012	9.93 ± 0.021
P5	0.537 ± 0.003	197.33 ± 2.082	7.13 ± 0.058	94.7 ± 0.6	74.67 ± 0.578	5.39 ± 0.025	9.61 ± 0.013
P6	0.565 ± 0.003	224 ± 3.000	7.77 ± 0.058	95.57 ± 0.265	80.33 ± 0.578	5.57 ± 0.025	9.83 ± 0.113
P7	0.526 ± 0.004	197.67 ± 1.548	7.2 ± 0.100	94.7 ± 0.600	73.67 ± 0.578	5.58 ± 0.040	9.62 ± 0.01
P8	0.562 ± 0.004	230.33 ± 1.528	7.73 ± 0.058	95.7 ± 0.265	77.67 ± 0.578	5.58 ± 0.031	9.83 ± 0.021
P9	0.592 ± 0.003	241.67 ± 4.163	10.13 ± 0.058	97.17 ± 0.115	82	5.59 ± 0.02	10.33 ± 0.025
P10	0.565 ± 0.003	223.67 ± 2.517	8.07 ± 0.058	95.6 ± 0.173	78.33 ± 1.458	5.61 ± 0.015	9.77 ± 0.029
P11	0.609 ± 0.002	219.33 ± 2.082	8.07 ± 0.058	95.8 ± 0.100	77.67 ± 0.578	5.58 ± 0.021	9.8 ± 0.025
P12	0.541 ± 0.003	224.67 ± 0.577	7.87 ± 0.058	95.53 ± 0.231	78 ± 1.000	5.59 ± 0.021	9.81 ± 0.035
P13	0.697 ± 0.00	241.67 ± 1.528	9.9 ± 0.1	97.33 ± 0.208	83 ± 1.000	5.62 ± 0.015	10.41 ± 0.035

The evaluation of the patches was done for various physical parameters as per procedure and the results are reported in Table 2.

Every patch that has been created was visually inspected to assess its physical appearance. The patches' outside look produced excellent outcomes. It was discovered that every prepared patch had a smooth, opaque, non-sticky, homogenous, and flexible texture.

The pH values of the patches, as indicated in the table, varied from 5.28 ± 0.006 to 5.62 ± 0.015, indicating their appropriateness for human usage and perhaps indicating that applying the patches will not cause skin irritation.

The transdermal patches had thicknesses ranging from 0.514 ± 0.004 to 0.697 ± 0.004 mm. The type and concentrations of the polymers may be to blame for this variation in thickness; that example, a higher concentration of the hydrophilic polymer HPMC would result in a thicker transdermal patch. The produced transdermal patches had weight variations ranging from 194.67 ± 0.578 to 241.67 ± 1.528 mg. According to the weight variation data, a higher HPMC content was linked to a higher patch weight. This might be a result of HPMC producing a heavier patch since it has a higher affinity for water and can absorb more moisture. Because the HPMC polymer is more hygroscopic than EC, there is a chance that the patches will retain more water and weigh heavier overall. The moisture level of the transdermal patches varied between 7.23 ± 0.158 and 10.33 ± 0.158%. Again, the mixtures with more HPMC concentrations had higher moisture content. Because HPMC is hydrophilic, it has the ability to both absorb and retain water in transdermal patches.

For patches, folding endurance is crucial because higher folding endurance keeps patches from breaking or becoming damaged quickly and makes them appear high-quality. Every transdermal patch that was created had a high folding endurance of more than 70 times. This indicates that every transdermal patch satisfies the standards for a standard patch. The folding endurance of the transdermal patches was not significantly impacted by the polymer concentrations (HPMC and EC), while the folding endurance increased with a larger HPMC content. The plasticizer PEG400 was utilized to create a flexible patch composition. The tensile strength values of the prepared transdermal patches ranged from 9.59 ± 0.006 to 10.41 ± 0.035 kg/cm^2, falling within the permitted limits for this type of patch.

All the transdermal patch formulations exhibited uniform drug content and with a minimum variability within the batch. The drug content ranged from 94.7 ± 0.6 to 97.33 ± 0.208% (Figure 2). This drug content range is deemed suitable for transdermal application.

The aforementioned figure made it abundantly evident that an increase in HPMC concentration led to an increase in drug loading in the patch. This might be because HPMC, a hydrophilic polymer, has an affinity for naringin, which has strong water solubility. The increased loading of naringin was a direct result of HPMC's water retention.

In-vitro Permeation Study

Franz diffusion cell was used to measure the quantity of medication that seeped through or was released from the transdermal patches. According to the *in-vitro* drug release research, at the end of the 24-hour release trial, P9 released the most medication (88.21 ± 1.286%), whereas P5 released the least (56.47 ± 1.066%). Formulated patches with higher concentrations of the hydrophilic polymer HPMC and lower concentrations of the lipophilic polymer EC were shown to release drugs more quickly. The study also showed that the formulation's drug release and burst impact increased with the amount of hydrophilic polymer (Figure 3).

Optimization of Formulation

With 13 runs and a 32 complete factorial approach, the results from the release research were optimized. The two independent parameters influencing the drug's release (response) at 24 hours from the patches were the concentration of HPMC and EC (Table 3).

Using the Design Expert 7.0.0 trial version, the data was examined, and a quadratic model was created to forecast the drug's release from the formulations. The program generated three ideal options.

The software looked for the residual sum of squares and lack of fit in the several mathematical models that may be

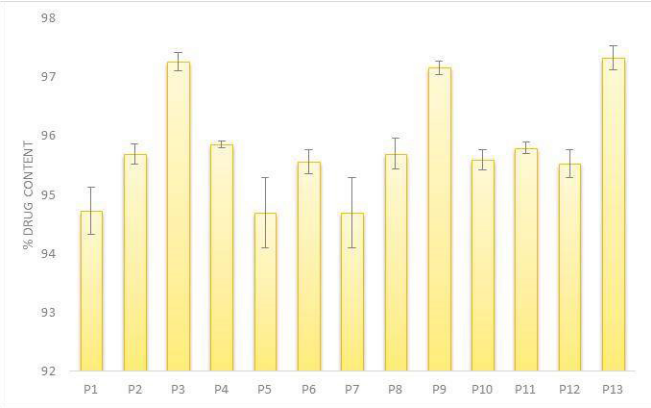

Figure 2: Drug content in the formulated transdermal patches

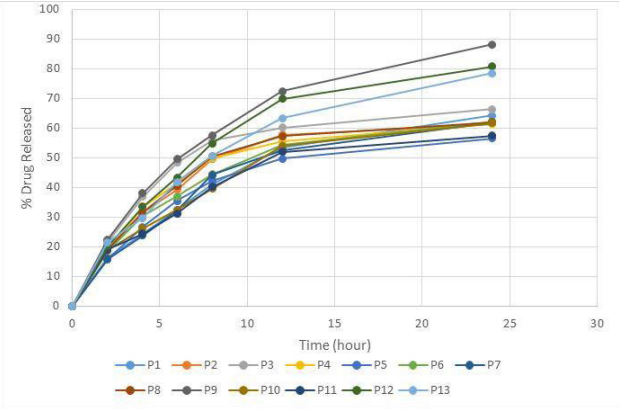

Figure 3: Release of naringin from transdermal patches (*in-vitro*)

Table 3: Data utilized for optimizing the formulation

Formulation	HPMC (mg)	EC (mg)	%Release of naringin
P1	100	50	64.13
P2	125	75	61.39
P3	150	75	66.28
P4	125	75	61.54
P5	100	100	56.47
P6	125	75	62.07
P7	100	75	61.95
P8	125	75	61.88
P9	150	50	88.21
P10	125	75	61.64
P11	125	100	57.43
P12	125	50	80.75
P13	150	100	78.49

created for improving the formulation. The study proposed two linear and quadratic models to anticipate the release. However, it was discovered that the cubic model was remarkably significant; however, it was aliased and so excluded (Table 4).

The mathematical model for estimating the maximal release of naringin from the patches was created by processing the quadratic model using ANOVA (Equation 1).

$$\text{Release} = +164.32638 - 0.62897*\text{HPMC} - 1.97851*\text{EC} - 0.000824*\text{HPMC}*\text{EC} + 0.00410786*\text{HPMC}^2 + 0.012068*\text{EC}^2 \quad \text{(Equation 1).}$$

The statistical parameters for the equation 1 are presented in Table 5.

The model's F-value of 7.08 indicates that it is significant. The chance of noise generating a "Model F-value" of this size is only 1.15%. Model terms with "Prob > F" values less than 0.0500 are considered significant. The "Lack of Fit F-value" of 852.15 suggests that the Lack of Fit is significant. This large of "Lack of Fit F-value" could only be due to noise in 0.01% of the situations. The general mean is thought to anticipate your reaction more accurately than the current model if the "Pred R-Squared" value is negative. "Adeq Precision" determines the signal-to-noise ratio. The ratio need to be more than 4. An adequate signal is suggested by our 8.977 ratio. This model may be used to traverse the design area (Figure 4).

Three numerical solutions were produced by the program after the findings were processed to optimize the drug's release from the patches (Table 6).

Table 5: ANOVA for response surface quadratic model

Std. Dev.	*5.189624*	*R-Squared*	*0.834958*
Mean	66.32538	Adj R-Squared	0.717071
C.V. %	7.824491	Pred R-Squared	-0.67792
PRESS	1916.67	Adeq precision	8.977267

Table 6: Solutions for maximizing release

Number	*HPMC*	*EC*	*Release*	*Desirability*
1	150	50	87.47246	0.976763
2	150	100	72.87579	0.516881
3	150	93.9	71.42565	0.471193

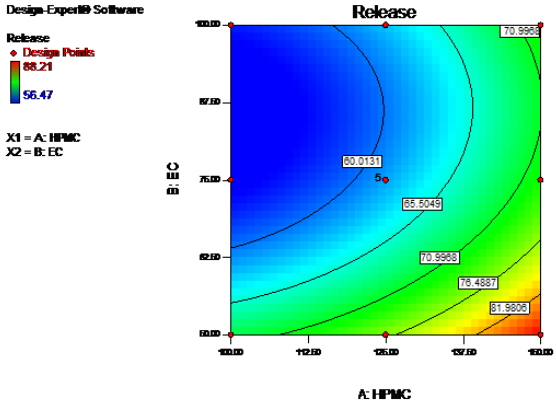

Figure 4: Surface response graph for the selected model

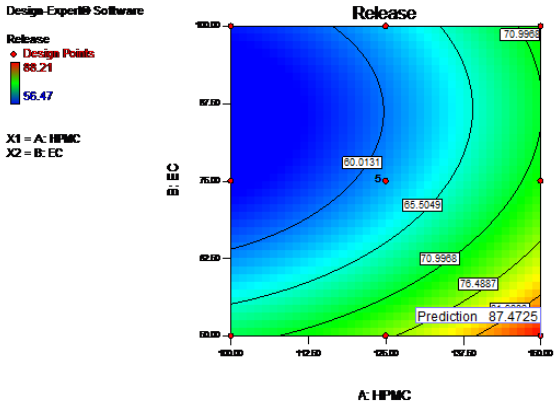

Figure 5: Contour plot predicting release in relation of HPLC and EC with selected model

Table 4: Model summary statistics

Source	*Std. deviation Dev.*	*R-Squared*	*Adjusted R-Squared*	*Predicted R-Squared*	*PRESS*	
Linear	6.65087	0.612759	0.53531	0.194647	919.9437	Suggested
2FI	7.00222	0.613687	0.484916	-0.73356	1980.227	
Quadratic	5.189624	0.834958	0.717071	-0.67792	1916.67	Suggested
Cubic	0.270894	0.999679	0.999229	0.992259	8.84268	Aliased

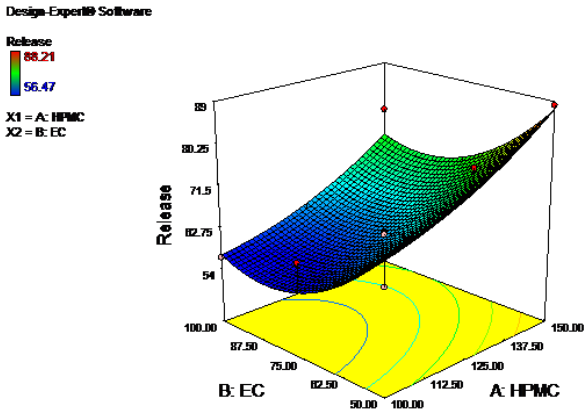

Figure 6: 3D-surface plot predicting release in relation of HPLC and EC with selected model

The model that was chosen had the lowest amount of EC and the highest degree of HPMC. Figures 5 and 6 show, respectively, the contour plot and the 3D-surface plot of the effects of variables on release.

CONCLUSION

The primary objective of the current study was to create transdermal patches containing naringin for the treatment of inflammation. Hydroxypropylmethylcellulose (HPMC) and ethylcellulose (EC) were used as the polymeric release regulating matrix to create the formulation. It was anticipated that the formulation would address the issues of poor distribution, high metabolism, and low bioavailability related to oral naringin dosing. The transdermal patches' capacity to maintain naringin release for over 24 hours was sufficiently convincing to resolve the issues related to oral delivery. The formulation P9 had the greatest drug loading and released the most drug. Therefore, it can be said that P9 was the optimal formulation since it had the right amount of potency and medication release to successfully control inflammation all day long. The optimization study found that for the patches to release the most naringin in 24 hours, a larger proportion of hydrophilic polymers and a smaller proportion of lipophilic polymers were advantageous.

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