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(RESEARCH ARTICLE)

Optimised herbal transdermal patch of ethnobotanical plant *Costus igneus* N. E. br. Developed through response surface methodology

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Abstract

Costus igneus (Family: Costaceae) has been used by the aboriginal humans since long through oral route. In our laboratory, we used biodegradable polymer for release control of this transdermal patch. This transdermal patch could be affixed in the lower abdominal region which releases intraperitoneally after principal meals, twice a day; which could be terminated instantly by removing the patch externally. Our objective is Formulation, evaluation and statistical designing of a Transdermal patch containing ethnobotanical plant *Costus igneus.* As Transdermal Patch reduces can be removed when termination of treatment is necessary and it also has the capability to bypass the different chemical changes that a oral pill has to go through.

The Macro-physico evaluation parameters were calculated. The folding endurance was in between of 7 to 16, the maximum value was of the F_{OPT}, the Tensile strength was relatively similar in all the formulations. F_{OPT} showed the highest of all. In percentage elongation test the F_{OPT} showed good resilience, thickness was relatively acceptable for all the formulations. % moisture content and %moisture uptake was acceptable in all of the formulations showed a good and satisfiable range. The drug content was calculated according the total quercetin content taking pure quercetin API as the reference F_{OPT} had the highest drug content of 82.5%. The Response Surface Curve predicted the optimised formulation and the desirability score also gives us our optimised patch. The Kinetics for the optimum by the optimization of transdermal patch was observed in all the different type of plots. The F_{OPT} had a good linearity of 0.938 in regression co-efficient with Korsmeyer-Peppas Plot . It explains the release of drug's material through a polymeric matrix system while also considering Non-Fickian drug release mechanism. The different Response Surface Curve allows us to predict from the software that the F_{OPT} Formulation is the Gem of Ten. This would produce beneficial blood-sugar content reduction. If we can commercialise this Herbal Transdermal Patch then, it can be an innovation remedy for this chronic disease.

Keywords: Transdermal Patch; Factorial design; Drug Delivery System; Dose dependent response; Biodegradable; Homo-polymer; Pharmaceutics

1. Introduction

After a thorough investigation about the *Costus igneus* plant for the benefit of human, it is understood that the said insulin plant contains 18% protein [1], beta-sitosterol, diosgenin [2] and other closely related flavonoids [3,4] along with microquantities of anti-oxidants like ascorbic acid, beta-carotene, alpha-tocopherol, glutathione, steroidal components alkaloids, terpenoids and other macro and micro nutrients in considerable amount [5,6,7]. However, since more than 7000 years old Vedic era; through the only oral route as green leaves, pills, cookies etc. since long past were the only route of administration [8,9,10]. A NDDS with herbal components is a recent method under developmental experimentation [11]. The herbal active ingredients as said above, are degradable and susceptible to hydro, gastro, acidic environment of gastric calamities. Hence an approach was tried to keep the hydro-alcoholic leaf extract of this

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fiery spiral flag to keep stable with a modified release towards the herbal transdermal patch formulation with a pharmacology of Type-I and Type-II, gestational, neonatal diabetes, where insulin action is jeopardised [12-20]. In this approach a modified release kinetics is the talk of the day to control the metabolic polyol pathogenesis of increased blood sugar level and decreased insulin blood concentration and vice versa. The terminal pathogenesis of diabetic neuropathy, nephropathy, diabetic retinopathy(glaucoma); which exaggerates to the pandemic outburst all over the world. Isolated and purified quercetin were compared as the total herbal component for analytical and bio-analytical assay. [21,22] We all know pharmacologically active potent microcontent diosgenin and related cyclopentanoperhydrophenanthrene structured are evidently degradable in gastric environment. But a systematic kinetically module pharmacophores as a transdermal patch could enlighten a more stable and dependable formulatory coin [23-28].

A research gap explains there are no stable conclusion about the oral metabolic of site stability of the total herbo-pharmacophores in the gastric juice and its pre and post concentration in the human body till metabolic excretion. We know various authors have recommended and experimented methanolic, n-hexanoic or other solvent used for extraction of the *Costus igneus* leaves. But we have adored, pharmacologically acceptable ingredients; mainly water and ethanol. Other inactive ingredients stated below are consumable as per the drug control authority. Hence, their penetration from the ectoderm of the peritoneal cavity is the most suitable in comparison to other oral or parenteral (if any) route [29,30].

Figure 1 Flora of Insulin Plant in Medicinal Herbal Garden of Bengal School of Technology

Figure 2 Image from GPSMap Camera (Date and Time of Collection:- 08/02/2022, 12:28 PM

The Rationality can be described as to protect the Phytoconstituents of the Ethnobotanical Practice of Absorption-Through-Stomach (in the form of Pill, etc.). The vision of modernization of the Herbal components, mostly used by aboriginal people should be reconsidered and reoriented. In this direction, the research gap, was applicated with the herbal transdermal patch of Insulin plant. The Over-Burden, Dose-Dumping and Cumulative-Toxicity, if any, can be overcome by removing the Herbal Transdermal Patch of *Costus igneus* N.E.Br, instantly in emergency from the local supra-peritoneal cavity [31-34].

If we Hypothesize the study, it can be told that the 'Closely Related Structural Phyto-molecules' have a Unique Race, in the Biogenetic Process to subserve the ailments together in the Human and Animal of the Kingdom and thus varieties of this plant's Phytochemicals protect our living world.

2. Material and methods

2.1. Materials

HPMC K-15M, a Hydroxy Propyl Methyl Cellulose homopolymer with a slight moderate hydroxypropyl substitution which serves as our Polymer, was procured from Simson Pharma Ltd, Ethyl Cellulose which acts as the Plasticizer was procured from Loba Chemie Pvt. Ltd., Ethanol which will be the main Solubiliser was procured from CSS Analytical Reagents, Purified Water was prepared in a Double Distillation Facility in our Institute, Menthol, which acts as a Permeation Enhancer on skin, Brilliant Green as colouring agent and Quercetin as a standard reference for our Drug content was procured from Yarrow Chem Products Ltd. All other materials were of Analytical Grade.

2.2. Extraction of Active Constituents

Fresh Leaves of *Costus igneus* N.E.Br collated of our Medicinal garden, then washed with tap water and then dried in shade, away from sun rays until crushable. Then they were subjected to smaller particle size by means of Grinding in a Mixer-Grinding. The veins were removed and the crushed leaves were again subjected to small particle size using grinder. 100 grams of the crushed powder was taken in a beaker and solvent comprising of a combination of 50:50 :: EtOH: H_2O was made to produce 250 ml of the Extract. Maceration was performed for 72 Hours in a Beaker, with the sample kept at a thermostatic temperature of 30-35 °C with occasional stirring. After Maceration, Centrifugation was performed at 3000 RPM for 30 minutes [38,39]. The Extract was filtered to get rid of the Marc and the filtrate was used. This filtrate was used to formulate the Transdermal Patch [35,36].

2.3. Preparation of Patch Matrix

For all the ten formulations starting from F-1 to F-9 and $F_{OPT,}$ accurately weighed amount of HPMC K-15M, Ethyl Cellulose was taken in a clean beaker. EtOH was poured slowly as a solvent and stirring was done properly. The Insulin Plant Extract was added after the HPMC K-15M and Ethyl Cellulose forms a homogeneous gel. The Gel was then stirred using a Mechanical Stirrer. Menthol which serves as a Permeation Enhancer and Brilliant Green Colour for increasing elegance was added thereafter. The Homogenous Gel was then transferred to a Petri-Dish, spread evenly and then covered with Aluminum foil and was shade dried for the next seven days at 40% RH until the solvent evaporates leaving a solid matrix. The Matrix was cut into a 2cm x 2cm Square size [37]. The matrix was affixed in the backing material (Linen) using adhesives and a liner is applied in the adhesive layer. This forms a Matrix Type Transdermal Patch and was kept for further evaluations [38].

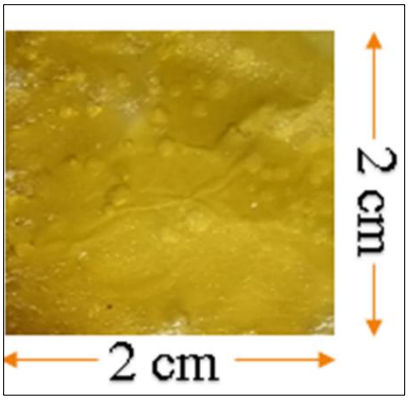

Figure 3 Insulin Plant Transdermal Patch Matrix cut in a 2cm x 2cm Square

2.4. Experimental Design

3^2 (twofactor andthree-level)factorial design had experimented forthe optimizationof Insulin Plant Transdermal Patch. The amount of polymer namely HPMC K-15M is the originally selected independentvariable(factor), which changed at three-levels (lower, mid, and higher). The other independent variable arbitrarily selected was Ethyl Cellulose at three stages (lower, mid, and higher). Many trials of formulations of Insulin Plant Transdermal Patch formulated as per the instruction of 3^2 factorial-design .The factorial design for collected causative trialformulations which is represented in Table 1. The Tensile Strength (Kg/cm^2), % Moisture content and Drug Content (mg/ml) was experimented as the only dependent variables that are originally the responses. Design-Expert Software Version 10.0 (Stat-Ease Incorp, USA) had been implemented for the production and evaluation of the mathematical experiment design .The inactive and their divisions in DOE is shown in Table 2.

Table 1 Factorial Divisions for Independent Variables with other non-variable ingredients

Independent variables	**USAGE**	**-1**	**0**	**+1**
HPMC K-15M(mg)	Polymer	150	200	250
Ethyl Cellulose(mg)	Plasticizer	100	120	150
Other excipients	**Usage**	**0**	**0**	**0**
Insulin Plant Extract(ml)	Active Herbal Ingredient	5	5	5
Ethanol(ml)	Solvent	5	5	5
Menthol(mg)	Permeation Enhancer	0.5	0.5	0.5
Brilliant Green	Colouring Agent	As required	As required	As required

Table 2 Design of Experiments by Factorial Design as designed by Design Expert

Excipients	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**	**F-9**	**F_{Opt}**
HPMC K15M(mg)	150	150	150	200	200	200	250	250	250	270.711
Ethyl Cellulose	100	120	150	100	120	150	100	120	150	160.355
Insulin Plant Extract (ml)	5	5	5	5	5	5	5	5	5	5
Ethanol(ml)	5	5	5	5	5	5	5	5	5	5
Menthol (mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Brilliant Green	As required	As required	As required	As required	As required	As required	As required	As required	As required	As required

For the optimization, the transdermal patch, the independent variables were modelled upon response effects by the use of the 'first-order' polynomial equation which considers independent-variables along with the reactions of different experimental results or responses. The 3^2 Factorialdesign has 3 levels with 2 factors.The Polynomial-equation that describes it is as per below:

$$P = m_0 + m_1K + m_2L + m_3M + m_4KL + m_5KM + m_6LM,$$

Here, P is the dependent variable, while m_o is the intercept; m_1 , m_2 , m_3 , m_4 , m_5 , m_6, and m_7 are regression coefficients; K, L and M are independent variables and KL, KM, and LM are the various molecular collision changes between variables. One-wayANOVA has calculated for measuring the implication for the model having a P- Value < 0.05 and considering every representable alterables.

In our experimentation, we have taken the various concentrations of HPMC K15M and Ethyl Cellulose as the absolute Independent variables. Their levels were set in three different concentrations as Low, Mid and High. The Dependent variables were the Drug Content, Moisture content and the tensile strength as they are dependent on the concentrations of the previous independent variables [39].

2.5. Macro-Physico Evaluations

2.5.1. Folding Endurance Test

Folding Endurance test is performed by physically Folding a short strip of specified dimension (4cm^2) of the Patch by half at the exact base upto the patch breakage. The repetitive times the patch was folded gives us Folding Endurance Value; FoldingEndurance Test helps us to evaluate the plasticizer efficiency also polymeric-patch-strength.

2.5.2. Tensile Strength

The Tensile Strength is a Physical Parameter that provides us how much tension is needed to break the Patch of a specified area 2cm x 2cm. It was measured using Tensiometer and the reading of each Formulation was noted in Kg.

2.5.3. % Elongation Test

The %elongation break test can be performed by observing the initial patch length denoted by L1 and elongating it until the patch breaks. The length at which it breaks denoted by L2. Then it was calculated by applying the formula,

$$\% \text{ Elongation} = \frac{\text{L2} - \text{L1}}{\text{L1}} \text{ x } 100$$

2.5.4. Thickness

The patch thickness is measured using Screw Gauge with three various positions. The average of the calculation was done with three different observations was recorded in all cases.

2.5.5. % Moisture Content

The transdermal patches were Initially individually weighed(W1) and placed into a desiccator. Fused Calcium Chloride was placed inside the desiccator at a steady roomtemperature, twenty four hours. The patches were weighed after 24 hours(W2) and the % moisture content was calculated as below:

$$\% \text{ Moisture Content} = \frac{W2 - W1}{W2} \, X \, 100$$

2.5.6. % Moisture Uptake

The initial weight(W1) of the Transdermal Patch was measured. Then they were kept into a desiccator during twenty four hours comprising overconcentrated Potassium Chloride, for getting 84%Relative Humidity. A constant room temperature was maintained. The Final Weight(W2) was recorded and the %moisture uptake computed as:

$$\% \text{ Moisture Uptake} = \frac{W2 - W1}{W2} \, X \, 100$$

2.5.7. Determination of Drug Content

The Drug content was measured through dissolving a piece of insulin plant and polymer matrix (4 cm^2) from every formulation in 100ml pH 6.8 PBS by homogenization for Twenty-four hours with shaking from time to time. Then, 5ml of the dissolvedsolution was withdrawn and was dilutedwith the same isotonic PBS to 20ml. Resulting solution was thoroughly filtered using a 0.45mm Whatman-filterpaper. Following the dilution, the values of the absorbance was measured in maximum wavelength(λ_{max}) by utilizing UV-Visible spectro-photometer (Shimadzu UV - 1800) 256 nm [40]. Drug content was determined as per total quercetin content. Total Quercetin was calculated as mean ± SD (n = 3) and expressed as weight of quercetin equivalent (QE) at 100 mg extract [40]. From the Standard curve of Quercetin the total quercetin content was determined for each formulation by recording their absorbance and calculating the concentration from the Standard Curve.

2.5.8. In Vitro Drug Release Studies

For the *In Vitro* release studies the prepared matrix of each formulations, Franz Diffusion Cell was used at pH 6.8. The patches were affixed on the mouth of the Franz Diffusion Cell, then the cell was constantly run at a preserved 37±0.5 °C and at 50 R.P.M. The samples were withdrawn and stored at specified timeintervals. Each samples of the each formulation was then analyzed in an UV-Visible Spectrophotometer for finding the drug release pattern.

2.5.9. Kinetic Analysis of Release Data

For the analysis of kinetical mechanism of release of drug from the prepared matrices of transdermal patch of *Costus igneus* N.E.Br, *In Vitro* drug dissolution data were investigated to various mathematical models as follows:

- Zero-order : Zero-order kinetics explains the constant elimination of the drug regardless of the plasma drug concentration, following a linear fashion of elimination phase until the system becomes completely saturated. The equation for Zero-Order is as follows,

$$\mathbf{Q_t = Q_0 + K_0 t}$$

- First-order :
  First-order kinetics is explained when a constant proportion of the drug is eliminated per unit time. The change in drug concentration with respect to time is dependent on concentration. The equation for First-Order is as follows,

$$\mathbf{\log Q_t = \log Q_0 + \frac{K_1 t}{2.303}}$$

- Higuchi :
  Higuchi model explains the drug release from an insoluble matrix as a square root of a time-dependent process. The equation for Higuchi Plot is as follows,
  - $\mathbf{\frac{Q_t}{Q_0} = K_H t^{1/2}}$
- Hixson-Crowell
  The Hixson Crowell model describes that drug particles and dissolution rate are considered as rate of drug release and not by the diffusion. The equation for Hixson-Crowell is as follows,

$$\mathbf{\sqrt[3]{Q_0} - \sqrt[3]{Q_t} = K_{HC} t}$$

  Korsmeyer-Peppas.
  Korsmeyer-Peppas model is used for the explanation of drug release from polymeric systems. The equation for Korsmeyer-Peppas is as follows,

$$\mathbf{F = \left(\frac{Q_t}{Q}\right) = K_{Kp} t}$$

Where,
Q_0 = Initial amount of Drug
Q_t = Cumulative amount of Drug release at Time "t"
Q = Total amount of drug in dosage form
K_0 = Zero-Order release Constant
K_1 = First-Order release Constant
K_H = Higuchi release Constant
K_{HC} = Hixson-Crowell release Constant
K_{Kp} = Korsmeyer-Peppas release Constant
F = Fraction of drug released at Time "t"
t = Time in hours

2.6. Statistics

Statistics was opt for accomplishment by Design-Expert 10.0(Stat-Ease Incorp,USA).Other datas were scrutinised by natural mathematical calculation of statistic**.**

3. Results

3.1. Optimization of Transdermal Patch

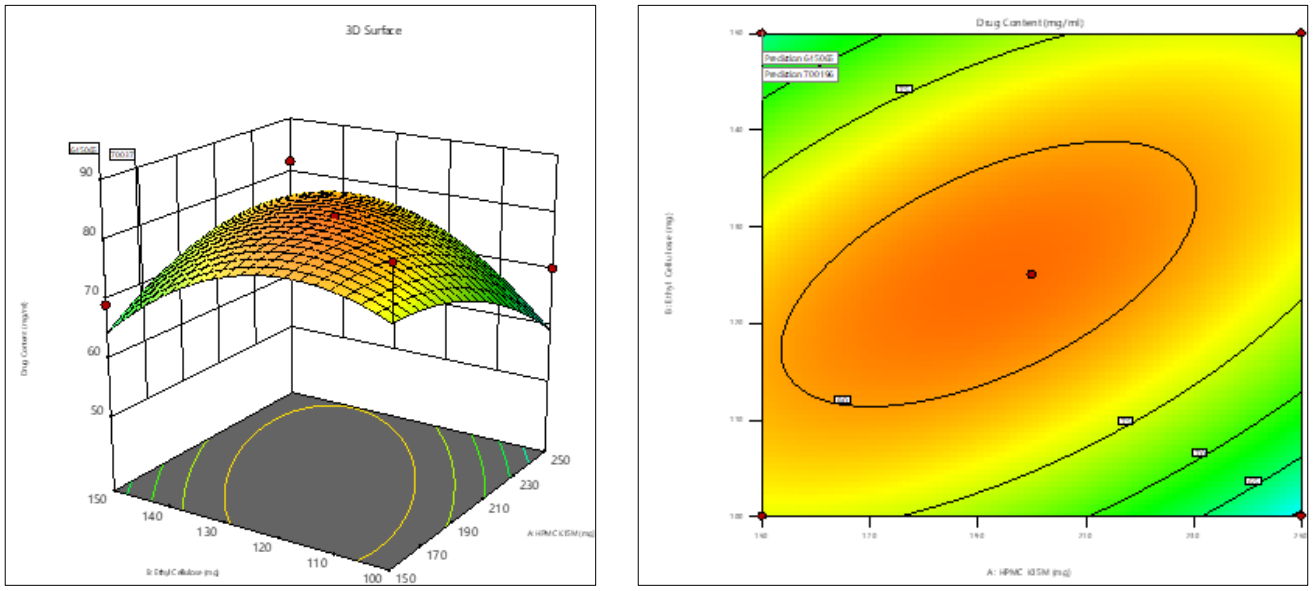

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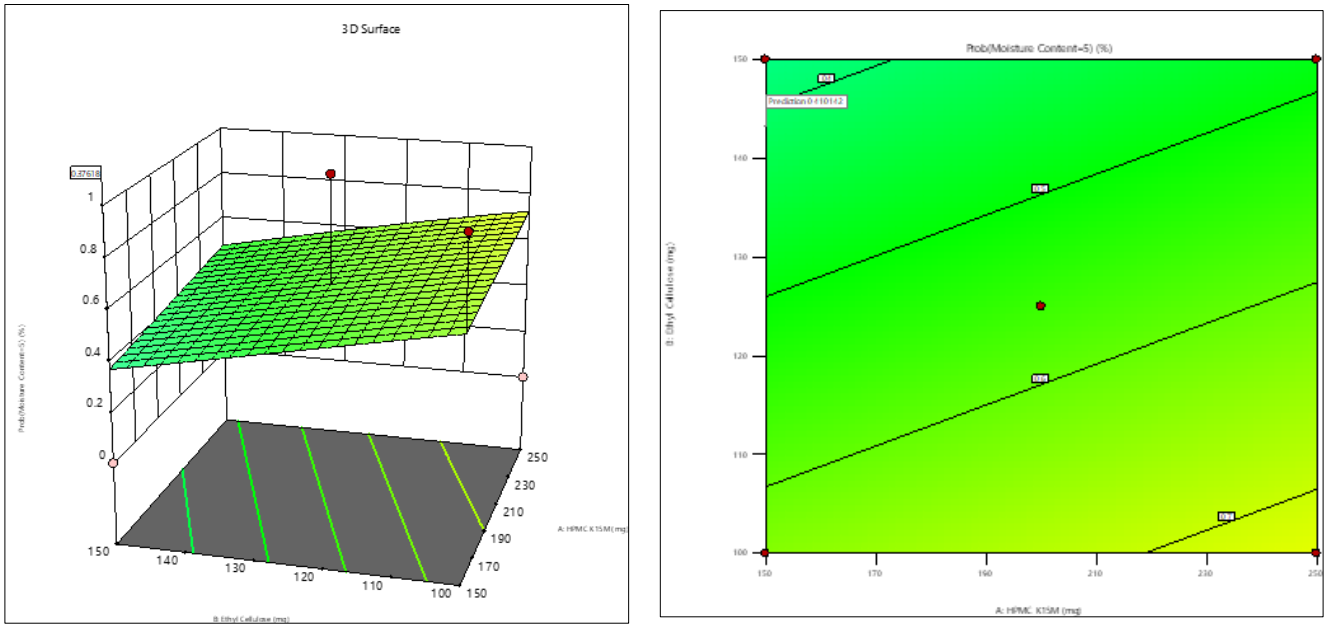
Figure 4 Effect of Ethyl Cellulose and HPMC for Drug Content in Transdermal Patch visulaized using (a) 3D Response Surface Curve and (b) Contour Plot



a b

Figure 5 Effect of Ethyl Cellulose and HPMC for Moisture Content in Transdermal Patch visulaized using (a) 3D Response Surface Curve and (b) Contour Plot

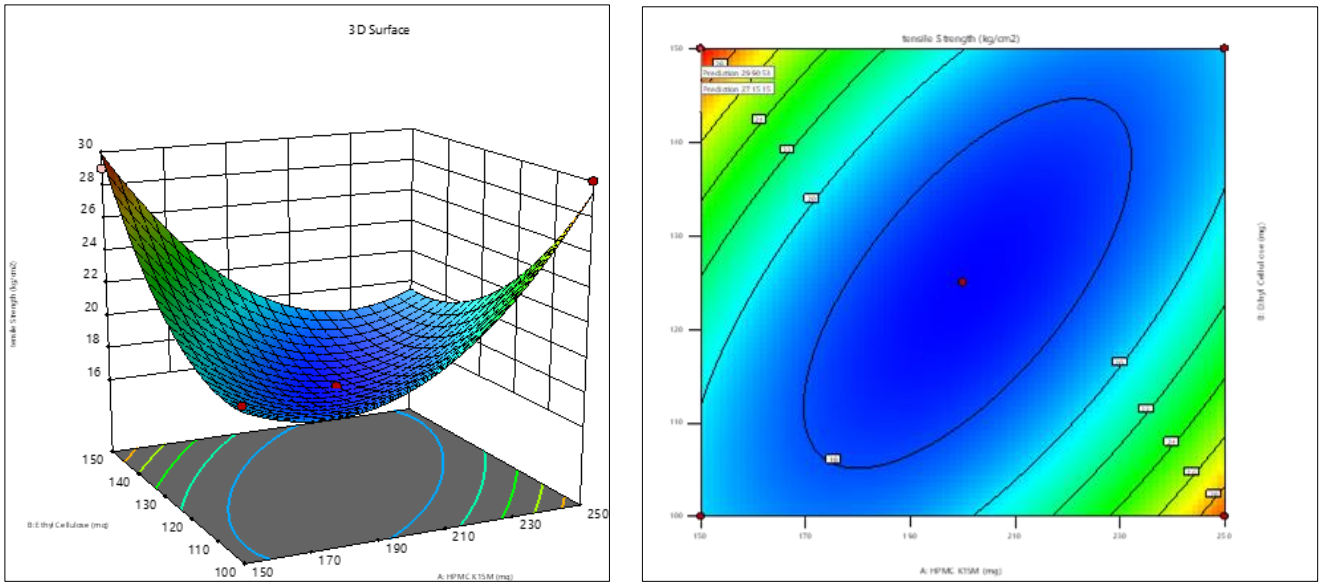


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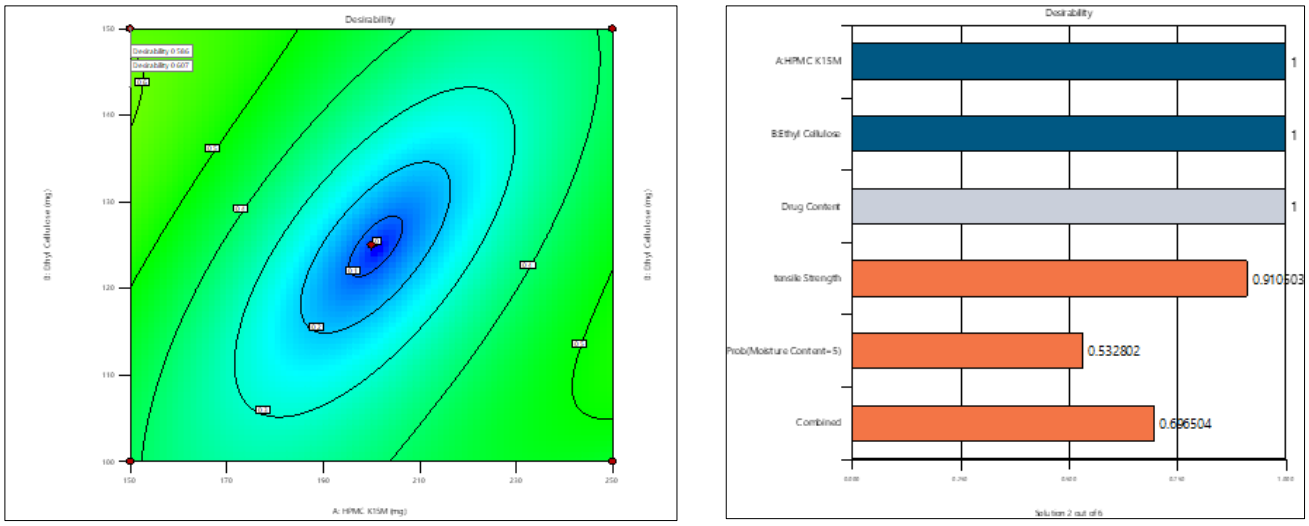
Figure 6 Effect of Ethyl Cellulose and HPMC for Tensile Strength in Transdermal Patch visulaized using (a) 3D Response Surface Curve and (b) Contour Plot



a b

Figure 7 Desirability Index for Transdermal Patch formulation visulaized using (a) 2D Contour Plot and (b) Desirability Points

3.2. Macro-Physico Evaluations

Each Evaluations were repeated three times and the average of all the three was taken as the result and tabulated in Table 3,

Table 3 Macro-Physico Evaluations of Each Patch Form (mean ± S.D., n = 3)..

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	$F_{Opt.}$
Folding Endurance Test	7±1	8±1	8±1	12±1	13±1	15±1	10±1	11±1	11±1	16±1
Tensile Strength(kg/cm^2)	22±1	24±1	26±1	27±1	29±1	30±1	17±1	19±1	20±1	30.2±1
% Elongation Break test	17.5±1	19±1	21±1	23±1	23.5±1	26±1	22±1	23.5±1	24±1	27±1
Thickness(mm)	0.22±1	0.22±1	0.23±1	0.27±1	0.3±1	0.3±1	0.32±1	0.32±1	0.34±1	0.23±1
%Moisture Content	5±1	5±1	5±1	4±1	4±1	4±1	5±1	4±1	5±1	4±1
% Moisture Uptake	10±1	9.5±1	11±1	8.1±1	8.5±1	8±1	9.5±1	9.5±1	9.8±1	8±1

3.3. Drug Content

Table 4 Concentration vs Absorbance Chart for Quercetin

Standard Curve of Quercetin		
Sl no.	**Concentration (PPM)**	**Absorbance (λmax=256nm)**
1	10	0.285
2	20	0.345
3	30	0.478
4	40	0.529
5	50	0.633
6	60	0.701
7	70	0.799
8	80	0.891
9	90	1.002
10	100	1.199

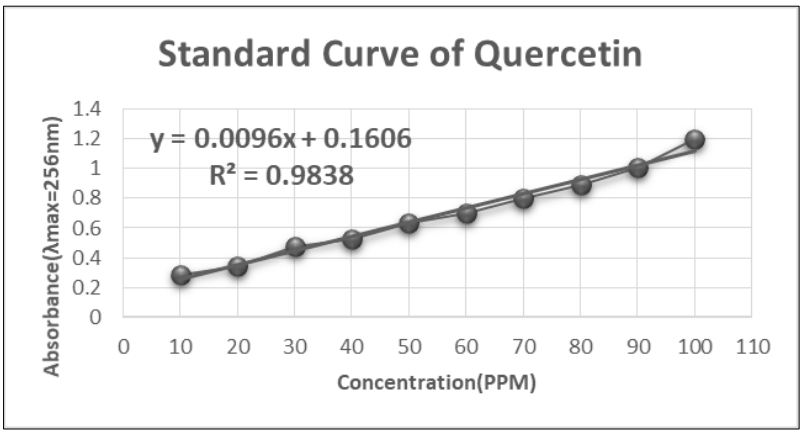


Figure 8 Standard Calibration Curve of Quercetin by employing Absorbance(nm) vs Concentration (PPM) at Maximum Absorbance of 256 nm

Table 5 Drug Content of Each Formulation in terms of Total Quercetin Content

	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**$F_{Opt.}$**
% Drug Content (Total Quercetin Content)	51.9	61.9	68.4	81.6	82	85.2	70.3	61.7	69.2	87.7

3.4. ANOVA for Quadratic model

Table 6 ANOVA for the Response of Drug Content in Transdermal Patch by using Design Experts

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	433.97	5	86.79	0.4818	0.7779	not significant
A-HPMC K15M	15.94	1	15.94	0.0885	0.7855	
B-Ethyl Cellulose	11.42	1	11.42	0.0634	0.8175	
AB	191.82	1	191.82	1.06	0.3780	
A^2	53.79	1	53.79	0.2986	0.6228	
B^2	208.95	1	208.95	1.16	0.3604	
Residual	540.49	3	180.16			
Cor Total	974.46	8				

P-values less than 0.0500 indicate model terms are significant. In this case there are no significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve our model.

Table 7 ANOVA for the Response of Tensile Strength in Transdermal Patch by using Design Experts

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	164.27	5	32.85	29.96	0.0092	significant
A-HPMC K15M	0.2500	1	0.2500	0.2280	0.6656	
B-Ethyl Cellulose	0.0858	1	0.0858	0.0782	0.7979	
AB	100.00	1	100.00	91.21	0.0024	
A^2	63.92	1	63.92	58.30	0.0047	
B^2	25.10	1	25.10	22.90	0.0174	
Residual	3.29	3	1.10			
Cor Total	167.56	8				

The Model F-value of 29.96 implies the model is significant. There is only a 0.92% chance that an F-value this large could occur due to noise.

Table 8 ANOVA for the Response of Moisture Content in Transdermal Patch by using Design Expert**s**

Source	**df**	**χ^2**	**p-value**
Model	2	0.6048	0.7390
A-HPMC K15M	1	0.0901	0.7641
B-Ethyl Cellulose	1	0.5177	0.4718

3.5. ML (Maximum Likelihood) analysis χ^2 Log Likelihood Ratio p-values

P-values less than 0.0500 indicate model terms are significant. In this case there are no significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve our model.

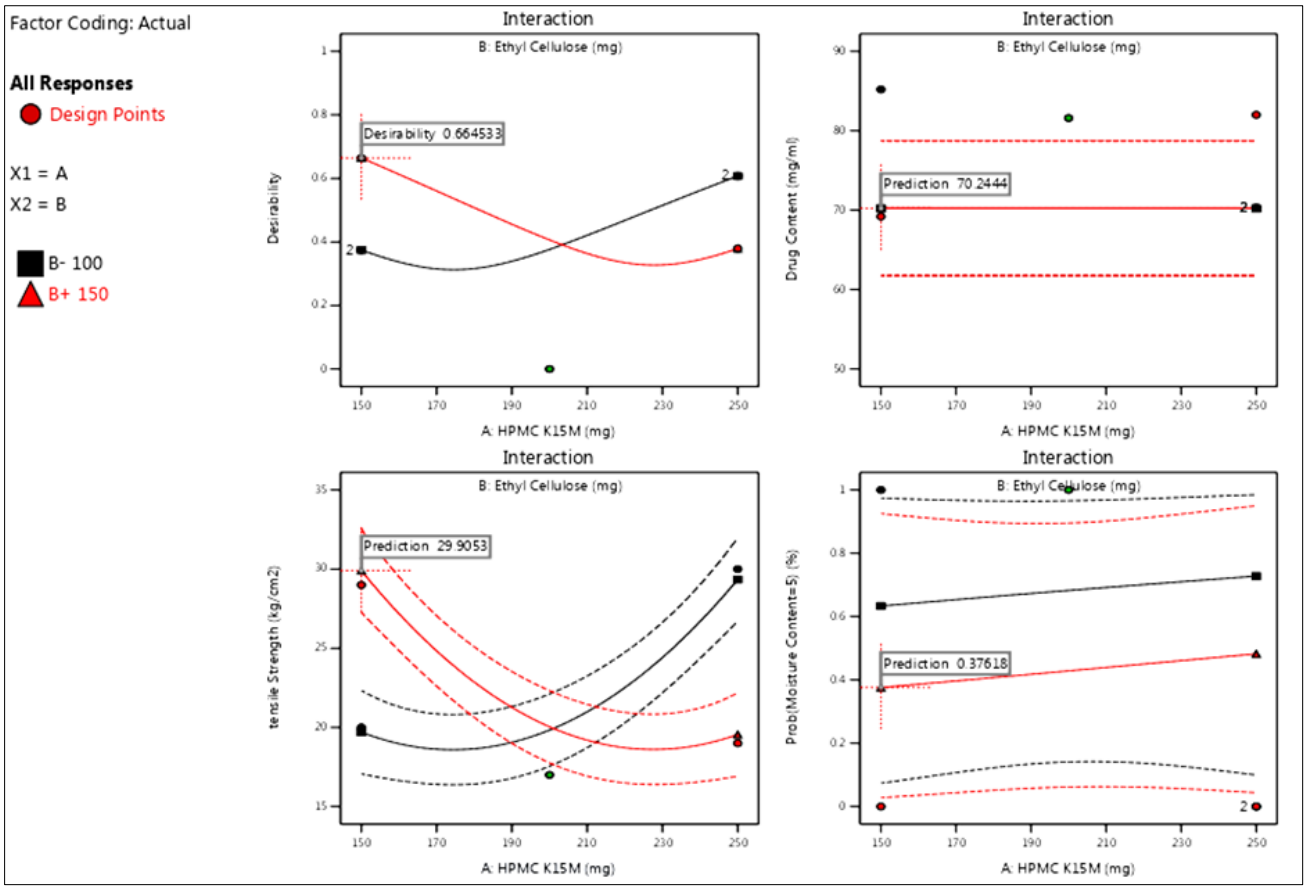


Figure 9 Graphical representation of possible interactions in Transdermal Patch Matrices using Design Expert Software

Table 9 Various Constraints and their importance value according to Design Experts software

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
A:HPMC K15M	is in range	150	250	1	1	3
B:Ethyl Cellulose	is in range	100	150	1	1	3
Drug Content	none	51.9	85.2	1	1	3
tensile Strength	maximize	17	30	1	1	3
Moisture Content	minimize	0.001	0.999	1	1	3

Table 10 Two-sided T-test with Confidence= 95%for the Confirmation of various constraints

Solution	Predicted Mean	Predicted Median	Observed	Std Dev	n	SE Pred	95% PI low	Data Mean	95% PI high
Drug Content	70.2444	70.2444		11.0367	1	11.6337	43.4172		97.0717
tensile Strength	29.9053	29.9053		1.04709	1	1.33479	25.6574		34.1532
Moisture Content	0.37618	0.37618		0.484426	1	N/A	0		1

Standard error (SE) not calculated on original scale

Table 11 Two-sided Point Prediction with Confidence = 95% and Population = 99%for Patch Formn

Solution 2 of 6 Response	Predicted Mean	Predicted Median	Observed	Std Dev	SE Mean	95% CI low for Mean	95% CI high for Mean	95% TI low for 99% Pop	95% TI high for 99% Pop
Drug Content	70.2444	70.2444		11.0367	3.67889	61.7609	78.728	14.7617	125.727
tensile Strength	28.8365	28.8365		1.04709	0.771154	26.3824	31.2907	19.1461	38.527
Moisture Content	0.388621	0.388621		0.487437	N/A	0.0331277	0.92183	N/A	N/A

Standard error (SE) not calculated on original scale.

3.6. In Vitro Drug Release

Table 12 Cumulative %Drug Release with respect to time for each formulation

		Formulations									
Sl No.	Time(in min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F_{Opt}
1	10	1.55	1.72	1.89	2.02	2.29	2.34	1.12	1.44	2.1	2.33
2	20	6.9	7.1	7.5	7.9	8.33	9.12	6.12	6.88	7.05	10.71
3	30	11.23	12.6	12.98	14.44	20.45	21.77	10.22	12.33	15.88	28.11
4	45	19.67	20.11	21.2	20.67	30.11	34.66	18.79	20.87	22.33	38.51
5	60	25.29	28.46	31.79	31.33	42	49.66	21.55	28.23	30.75	48.05
6	75	35.76	37.04	39.22	40.02	56.78	60.34	32.86	36.34	39.68	52.21
7	90	40.12	42.33	45.98	51.95	62.11	67.1	40.12	42.13	46.5	69.91
8	105	46.11	48.44	50.44	59.33	69.12	72.3	47.98	49.44	50.23	75
9	120	50.21	52.43	55.34	70.22	75.34	80.5	52.56	55.33	58.22	82.1

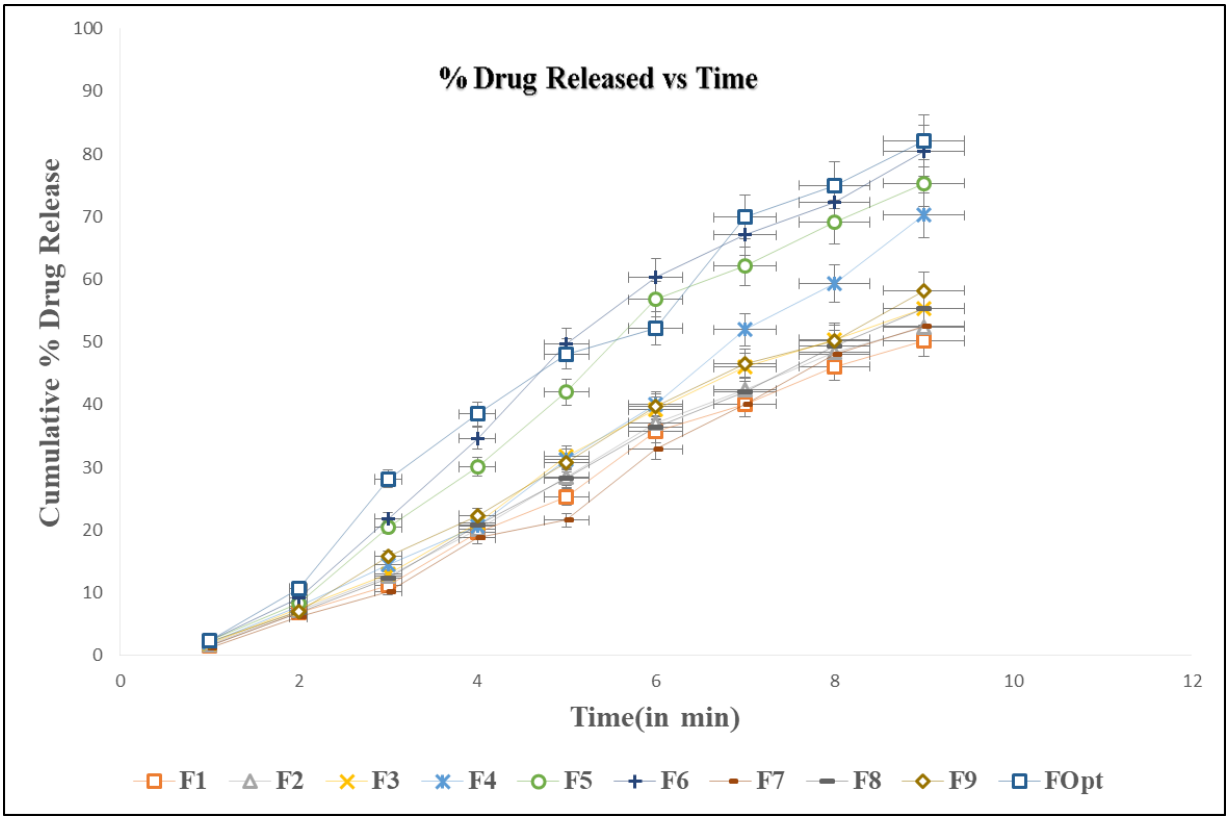


Figure 10 *In-Vitro* drug release vs Time from various Insulin Plant Transdermal Patch matrix(F-1 to F-Opt). Values represented in (mean ± S.D., n = 3)

3.7. *In-Vitro* Release Kinetics

Table 13 Release Kinetics of each formulation in terms of their Regression Coefficient

Release Kinetics	F1	F2	F3	F4	F5	F6	F7	F8	F9	F_{Opt}
Zero-Order (R)	0.987	0.992	0.990	0.991	0.986	0.987	0.977	0.992	0.991	0.978
First-Order (R)	0.974	0.981	0.979	0.978	0.959	0.970	0.964	0.984	0.984	0.984
Hixson-Crowell (R)	0.979	0.986	0.984	0.983	0.972	0.979	0.969	0.988	0.987	0.984
Higuchi (R)	0.846	0.855	0.851	0.856	0.842	0.849	0.838	0.857	0.866	0.904
Korsmeyer-Peppas (R)	0.658	0.666	0.661	0.669	0.651	0.669	0.651	0.669	0.663	**0.938**

4. Discussion

All the finding of the Macro-physico evaluation landed a good knowledge of the various physical and chemical parameters. The folding endurance was in the range of 7 to 16 ,the highest was of the F_{OPT} thus it showed highest flexibility. The Tensile strength was relatively optimum in all formulations. F_{OPT} showed the highest of all. In percentage elongation break test the optimized patch showed good resilience, thickness was relatively considerable for all the formulations. The %moisturecontent and %moistureuptake were evolved to comply and all the formulations showed a good and satisfiable range. The drug content was according total quercetin content as per the experimental UV-Visible Spectroscopy analysis using Beer-Lambert Law at 256nm of Maximum absorbance. The Response Surface Curve shows us the optimised formulation of the transdermal patch and the desirability score also gives us our optimised patch. The Kinetics for the optimum by the optimization of transdermal patch was observed in all the different type of plots. The different interaction in between the excipients were measured by the Design Expert software. The different Models we used were Zero-Order, First-Order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas Plot. The Korsmeyer-Peppas Plot was employed mostly as it explains the release of drug's material through a polymeric matrix system while also considering Non-Fickian drug release mechanism. This kinetic modelling is applied on the moment the release

mechanism is unknown for a Novel Drug Delivery System. The F_{OPT} showed a high linearity of 0.938 in regression coefficient with the Korsmeyer-Peppas kinetic mechanism. Thus, it complies with the type of release mechanism we are opting for.

5. Conclusion

The different Response Surface Curve allows us to predict from the software that the F_{OPT} Formulation is the Gem of Ten, which would produce beneficial blood-sugar content reduction, probably after principle meals would benefit the mankind where diabetes is a grow to be a pandemic all over the world. If we switch over to Insulin Plant Transdermal Patch then we can get remedy from this severe disease.

Future prospect

Now, search is going on for the moiety which gives anti-diabetic activity and the scientists impact Flavo-Alkaloid to be the prime medicament in diabetes. *Costus igneus* was phytochemically analysed to contain Alkaloid, Flavonoid, Triterpenoid, Saponin, Tannins and Glycoside. Whether an enzyme is present is under experimentation, by electrophoresis.

50% of the blood polyol disorder people, who are suffering, converted to diabetic neuropathy. Other than diabetic neuropathy which covers the most detrimental pathogenetic disorder, diabetic nephropathy, diabetic retinopathy (leading to glaucoma), gestational diabetes are other subserving consequences.

Compliance with ethical standards

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Disclosure of conflict of interest

The Authors declares no conflict of interest.

Plant authentication

The Plant of which the extract was used in formulation was authenticated from Botanical Survey of India, Kolkata-700064 under Authentication Number BSI/PLANT CHEM/ 001-2023 having Sample Number BST/MPHARM/GSROY/RDS/001.

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