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DESIGN AND CHARACTERIZATION OF TRANSDERMAL PATCHES OF DICLOFENAC SODIUM USING BOX BEHNKEN FACTORIAL DESIGN

Joshi Hrushikesh[1*], Aditya Nath Pandey[2], Rajendra Patil[3]

[1]Mansarover Global University, Bhopal. M.P., India*

[2]Shivnagar Vidya Prasarak Mandals College of Pharmacy, Malegaon Bk Baramati.

[3]Delonex Society's Baramati College of Pharmacy, Burhanpur, Baramati.

Corresponding Author: Joshi Hrushikesh

Email: joshihrushikesh153@gmail.com

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Abstract

The development of transdermal patches for diclofenac sodium, an NSAID widely used for pain and inflammation, can enhance therapeutic efficacy and patient compliance while minimizing systemic side effects. This study utilizes Box-Behnken factorial design to optimize the formulation of transdermal patches containing diclofenac sodium, focusing on the effects of different polymer types and penetration enhancers on drug release and flux. Eudragit RL 100 and Eudragit RS 100 were used as the primary polymers, and penetration enhancers such as DMSO, oleic acid, and Tween 80 were evaluated. The study aimed to identify the optimal formulation parameters that maximize drug release and flux while ensuring desirable physical properties of the patches. Experimental results indicated that the optimized formulation, DFC 2005, demonstrated significant improvements in drug release and flux compared to other formulations. The optimized patches also met the criteria for physical properties such as smoothness, thickness uniformity, and folding endurance. Stability studies confirmed the formulation's robustness under various storage conditions. This approach demonstrates the efficacy of using Box-Behnken design for the systematic optimization of transdermal patches, providing a valuable framework for developing effective and patient-friendly transdermal delivery systems.

Keywords: Transdermal patches, diclofenac sodium, box-behnken design, eudragit RL 100, eudragit RS 100, penetration enhancers, drug release, formulation development

Introduction

Transdermal drug delivery systems (TDDS) offer a promising alternative to oral and injectable routes, providing continuous drug release over extended periods while minimizing systemic side effects. These systems, which deliver medication through the skin, can improve patient compliance and therapeutic efficacy. One such application is the development of transdermal patches for diclofenac sodium, a widely used nonsteroidal anti-inflammatory drug (NSAID) known for its effectiveness in managing pain and inflammation.

Diclofenac sodium is a potent NSAID with broad clinical use in treating conditions such as arthritis, muscle pain, and post-surgical inflammation. However, its oral administration is often associated with gastrointestinal adverse effects and poor patient adherence due to the frequency of dosing required (Verma et al., 2010). Transdermal delivery of diclofenac sodium can potentially circumvent these issues by providing controlled, localized drug release, thus reducing systemic side effects and improving patient compliance (Pillai et al., 2013).

Transdermal patches offer several advantages over traditional drug delivery methods. They provide a steady and controlled release of the drug, bypassing the gastrointestinal tract and first-pass metabolism in the liver, which can enhance bioavailability and minimize systemic toxicity (Hadgraft, 2004). Furthermore, transdermal systems can improve therapeutic efficacy by maintaining drug levels within the therapeutic range for prolonged periods (Jovanovic et al., 2014). The ability to deliver drugs non-invasively and at a controlled rate makes transdermal patches an attractive option for various therapeutic applications.

The Box-Behnken design (BBD) is a statistical tool used in experimental design and optimization, particularly in the pharmaceutical industry. It allows for the efficient evaluation of multiple factors and their interactions on the performance of a formulation (Box & Behnken, 1960). This design is particularly useful for optimizing the formulation of transdermal patches, where factors such as polymer type, penetration enhancers, and drug concentration can significantly influence the drug release profile and patch properties (Khan et al., 2020).

Eudragit RL 100 and Eudragit RS 100 are widely used polymers in the preparation of transdermal patches due to their favorable properties, including biocompatibility and controlled release characteristics. These polymers form a film matrix that can control the release rate of the drug from the patch. Eudragit RL 100 is known for its higher

permeability, making it suitable for drugs requiring enhanced skin penetration, while Eudragit RS 100 offers a slower release rate, which can be advantageous for achieving a prolonged drug effect (Zhu et al., 2016).

The primary objective of this study was to design and characterize transdermal patches of diclofenac sodium using Box-Behnken factorial design to optimize the formulation parameters. The study aimed to evaluate the effect of different factors, including polymer type and penetration enhancers, on the drug release rate, flux, and overall performance of the transdermal patches. The use of BBD allows for a systematic approach to formulation optimization, providing insights into the interactions between formulation variables and their impact on patch performance.

Material and Methods

Experimental Design

Drug permeation studies from solutions containing 1% w/v drug have been done in presence and absence of penetration enhancers. The data from these preliminary studies were useful to fix minimum and maximum concentrations of penetration enhancers to incorporate in drug loaded matrix type transdermal drug delivery systems.

The drug loaded matrix type transdermal drug delivery system were formulated and evaluated for their drug release kinetic and percentage cumulative drug release. The polymeric film which showed maximum percentage cumulative drug release was selected for incorporation of penetration enhancers at different levels of concentration by three factor three level Box Behnken factorial design.

Factorial Design

A three factor three level Box Behnken design (BBD) was employed in optimization of matrix type transdermal drug delivery system containing diclofenac sodium and flurbiprofen. The three penetration enhancers dimethyl sulfoxide, oleic acid and tween 80 were selected as independent variables. These independent variables (factors) were selected at three different levels i.e. low (-1), medium (0), and high (+1). The levels of factors and the obtained responses are shown in Table. These levels selected were based on initial trials (Tunçel et al., 2024). The dependent variables (response) studied in this research work were percentage cumulative release (Y1, %CDR) and flux (Y2, mcg/cm2/hr). Seventeen runs of the experiment were evaluated for responses (Y1) and Y2.

Table 1: Formulation variables and their levels in Box-Behnken experimental design

Sr. No.	**Formulation Variables**				
1	**Independent variables**		**Level**		
			Low (-)	**Medium (0)**	**High (+)**
	1	A: DMSO (% v/v)	5	10	15
	2	B: OA (% v/v)	5	10	15
	3	C: T 80 (% v/v)	5	10	15
2	**Response variables**				
	1	R1: percentage cumulative drug release (%CDR)			Maximizing
	2	R2: Flux (mcg/cm^2/hr)			Maximizing

*A (DMSO)-dimethyl sulfoxide, B- (OA) - Oleic acid and C-Tween 80. (T 80)

Table 2: Design matrix in Box-Behnken design actual values for transdermal drug delivery system of Eudragit RL 100 and Eudragit RS 100 containing diclofenac sodium (DFC 2000)

Std	**Run**	**Actual Values**		
		Factor A : DMSO	**Factor B: Oleic Acid**	**Factor C: Tween 80**
14	**1**	**10**	**10**	**10**
9	2	10	5	5
6	3	15	10	5
5	4	5	10	5
12	5	10	15	15
8	6	15	10	15
2	7	15	5	10
7	8	5	10	15
16	**9**	**10**	**10**	**10**
10	10	10	15	5
13	**11**	**10**	**10**	**10**
17	**12**	**10**	**10**	**10**
11	13	10	5	15

15	**14**	**10**	**10**	**10**
3	15	5	15	10
4	16	15	15	10
1	17	5	5	10

ANOVA for Quadratic model

Final Equation in Terms of Coded Factors

R1 = + 50.51 - 0.8312 A + 2.60 B + 3.09 C - 0.4700 AB - 0.2925 AC + 0.7200 BC + 6.40 A^2 + 6.42 B^2 + 6.15 C^2

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

ANOVA for Quadratic model

Response 2: FLUX

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	1657.15	9	184.13	**22.98**	**0.0002**	**significant**
A-DMSO	71.64	1	71.64	8.94	0.0202	
B-Oleic Acid	192.37	1	192.37	24.01	0.0018	
C-Tween 80	262.78	1	262.78	32.80	0.0007	
AB	5.27	1	5.27	0.6574	0.4442	
AC	7.48	1	7.48	0.9336	0.3661	
BC	9.55	1	9.55	1.19	0.3111	
A^2	365.93	1	365.93	45.67	0.0003	
B^2	248.35	1	248.35	30.99	0.0008	
C^2	378.40	1	378.40	47.23	0.0002	
Residual	56.09	7	8.01			
Lack of Fit	56.09	3	18.70			
Pure Error	0.0000	4	0.0000			
Cor Total	1713.24	16				

Final Equation in Terms of Coded Factors

FLUX = + 83.64 - 2.99 A + 4.90 B + 5.73 C -1.15 AB - 1.37 AC + 1.55 BC + 9.32 A^2 + 7.68 B^2 + 9.48 C^2

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

Evaluation of optimized batches

Thickness Uniformity

The thickness of blank polymeric film was measured using digital micrometer (Mititoyo). The thickness was measured at five different points of the film and average of five readings was taken (Parivesh et al., 2010).

Percent Flatness

The films were cut into longitudinal strips, two from either and one from center of the film. The length of each strip was measured to the nearest centimeter without applying additional pressure. Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered to be equal to a hundred percent flatness (Patel et al., 2009).

Percentage Constriction= (L1-L2)/L2 x 100

Where, L1 is initial length of strip and, L2 is final length.

Moisture Uptake

A weighed polymeric film kept in desiccators at 40^0C for 24 h was taken out and exposed to two different relative humidity of 75% (saturated solution of sodium chloride) and 93% (saturated solution of ammonium hydrogen phosphate) in two different desiccators, respectively, at room temperature. Then the weights of film were measured periodically to constant weights (Kumar et al., 2018). The percent moisture uptake was calculated at each relative humidity as below.

Percentage Moisture Uptake = **[(**W_2-W_1**)** / W_1**]** **x**100

Where W_1= Initial weight in grams

W_2= Final weight in grams

Water Vapour Permeability

Glass vials of equal diameter were used as transmission cell. These transmission cells were washed thoroughly and dried in oven at 100^0 C for 30 minutes. Anhydrous calcium chloride, one gram was placed in the each cell and respective polymeric film

was fixed over brim. The cells were weighed accurately (Initial weight,W_1 gm) and placed carefully in a desiccator containing saturated solution of potassium chloride maintained at relative humidity (RH) of 84%. The cells were taken out off desiccator periodically and weighed accurately (Final Weight, W_2 gm) (Fokuhl et al., 2013). The amount of water vapor transmitted (gm/ 24 hrs / cm^2) was calculated as-

Water Vapour Transmission Rate = $(W_2-W_1)/A$

Where W_1= Initial weight in grams

W_2= Final weight in grams

A = area (cm^2)

Moisture Content

The polymeric film was weighed and kept in a desiccator containing anhydrous calcium chloride at 40^0C in a drier for at least 24 h or more until it showed a constant weight. The moisture content was the difference between the constant weight taken and the initial weight. The moisture content of the polymeric film was reported in terms of percentage (by weight) (Gannu et al., 2007).

Percentage Moisture Content = $[(W_2-W_1) / W_1] \times 100$

Where W_1= Initial weight in grams

W_2= Final weight in grams

Folding Endurance

A strip of polymeric films of specific area were cut and repeatedly folded at the same place till it broken. The number of times, the film folded without braking gave the value of folding endurance (Das et al., 2017).

Tensile strength

A small film strip (10 mm X 70 mm), free from air bubbles or any other physical imperfections was cut on a glass plate with a sharp blade. One end of the film was fixed between adhesive tapes to give support to film when placed in the film holder. Another end of the film was fixed between the adhesive tapes with a small pin sandwiched between them to keep the strip straight while stretching. A small hole was made in the adhesive tape near the pin in which a hook was inserted. A thread was tied to this hook, passed over the pulley and a small pan attached to the other end to hold the weights. A small pointer was attached to the thread, which travels over the scale fixed on the base plate. Weights were gradually added to the pan to increase the pulling force till the film was broken. To determine tensile strength, the film was pulled by means of a pulley system. The elongation was recorded as the distance

travelled by the pointer before break of the film on the scale (Bharkatiya et al., 2010). The weight required to break the film was noted as break force and Tensile strength was calculated as:

Tensile strength = F/A

Where F= Breaking force

A= Cross-sectional area of sample

Percent elongation

Percentage of elongation at break was calculated during the measurement of tensile strength by using formula as given bellow (Patel et al., 2012)

Percentage Elongation = [(L2-L1)/L1] x 100

Where L1= initial length of film

L2 = length of film at breaking point

Drug content and Content Uniformity

The drug content uniformity of the transdermal drug delivery system was determined by collecting 2 cm x 2cm size patch from different location of polymeric film and dissolved in 10 ml solvent with constant shaking for 24 h. Methanol was used as solvent after filtering the solutions, (through 0.45 micron), concentration of drug in solutions were determined spectrophotometrically. The percentage content of drug was calculated based on dry weight of drug and polymer used (Singh et al., 2016).

Skin irritancy studies

Patches were applied to the shaved skin on one side of the back of rats and secured using adhesive tape. On other back side of the rats, control patch (without drug) was secured in a similar way. The animal was observed for any sign of erythema or edema for a period of 48 h (Kawahara et al., 2007).

Stability studies

The short term stability studies of the formulated transdermal patches were carried out on prepared films at different temperature and humidity according to ICH guidelines: 25±2°C (60%RH) and 45±2°C (75%RH) a period of 60 days. The patches were wrapped in aluminum foil and stored in desiccator for stability study. The patches were characterized for drug content and other parameters at regular intervals (Parhi et al., 2018).

Results and Discussion

The study aimed to evaluate various formulations of diclofenac sodium (DS) in Eudragit RL 100 and Eudragit RS 100 patches to determine the optimal combination for effective transdermal delivery. The formulations were assessed based on their cumulative drug release (CDR), flux, and physicochemical properties, as well as their performance in skin irritation and stability studies.

Table No. 3 and Table No. 4 show that formulation DFC 2005 achieved the highest cumulative drug release (69.20%) and flux (112.5µg/cm²) among the tested formulations. This high release rate and flux indicate an efficient delivery system for diclofenac sodium. Formulation DFC 2005's performance is particularly notable as it demonstrates superior drug release compared to other formulations such as DFC 2004 (60.20% CDR and 96.65 µg/cm² flux) and DFC 2006 (65.33% CDR and 105.5 µg/cm² flux). This enhanced performance can be attributed to the optimal concentration of penetration enhancers in DFC 2005, which likely facilitated better drug permeation through the skin.

The release kinetics of DS from the patches were analyzed using zero-order, Higuchi, and Korsmeyer-Peppas (PK) models (Table No. 5). Formulation DFC 2005 exhibited a high correlation coefficient (R^2) for the zero-order (0.993) and Higuchi models (0.921), suggesting a controlled and sustained drug release pattern. The Korsmeyer-Peppas model further supported this with a release exponent (n) of 0.902, indicating non-Fickian diffusion, which implies a combination of diffusion and matrix erosion mechanisms in drug release. These results reinforce the suitability of DFC 2005 as a stable and efficient transdermal delivery system.

The physicochemical evaluations of DFC 2005 showed promising results. The thickness uniformity (103.00 µm ± 1.095), folding endurance (40.67 ± 2.08), and tensile strength (0.458 N/mm² ± 0.058) were all within acceptable ranges for transdermal patches, ensuring durability and ease of application. The moisture content (1.94% ± 0.08) and moisture uptake (2.35% ± 0.10) were relatively low, which is beneficial for maintaining patch integrity and preventing drug degradation. The high percent flatness (100.47% ± 0.42) further indicates a well-manufactured patch with minimal deviations from the intended design.

Skin irritation studies confirmed that DFC 2005 is non-irritant, showing no adverse reactions over 48 hours. This result is critical for ensuring patient safety and comfort during use. Stability studies (Table No. 15) demonstrated that DFC 2005 maintained a high drug content (97.08% ± 0.58) over 60 days at various conditions, indicating good

formulation stability. Although there was a slight decrease in drug content over time, it remained within acceptable limits, confirming that DFC 2005 is robust under typical storage conditions

Table No. 3: Results of % CDR and FLUX of Eudragit RL 100 and Eudragit RS 100 containing diclofenac sodium (DFC 2000)

F. Code	Response 1 CDR %	Response 2 FLUX mcg/Sq.cm
DFC 2001	50.51	83.64
DFC 2002	58.40	92.19
DFC 2003	58.40	92.62
DFC 2004	60.20	96.65
DFC 2005	69.20	112.5
DFC 2006	65.33	105.5
DFC 2007	61.10	95.88
DFC 2008	68.30	115
DFC 2009	50.51	83.64
DFC 2010	62.90	102.1
DFC 2011	50.51	83.64
DFC 2012	50.51	83.64
DFC 2013	61.82	96.41
DFC 2014	50.51	83.64
DFC 2015	66.50	107.7
DFC 2016	64.62	100.2
DFC 2017	61.10	98.79

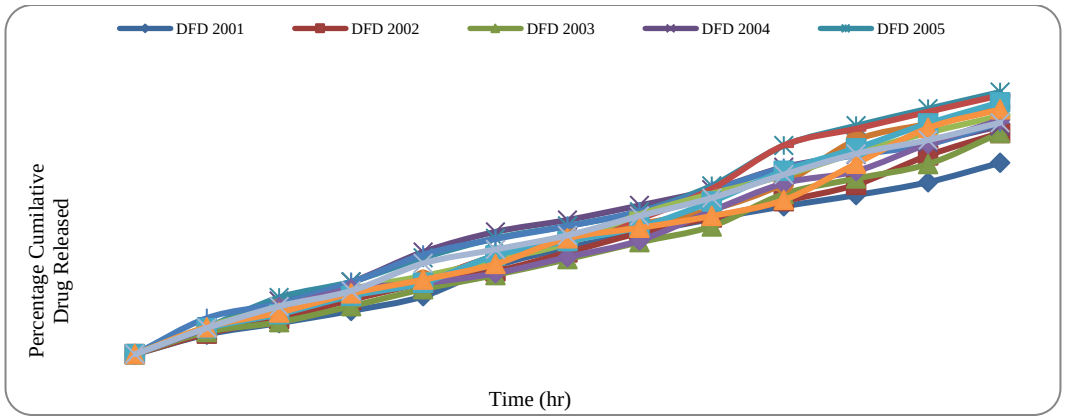
In vitro release of diclofenac sodium (DS) from Eudragit RL 100 and Eudragit RS 100 patches containing penetration enhancers (Box Behnken Design)

Table No. 4: In vitro release of diclofenac sodium (DS) from Eudragit RL 100 and Eudragit RS 100 patches containing penetration enhancers (Box Behnken Design)

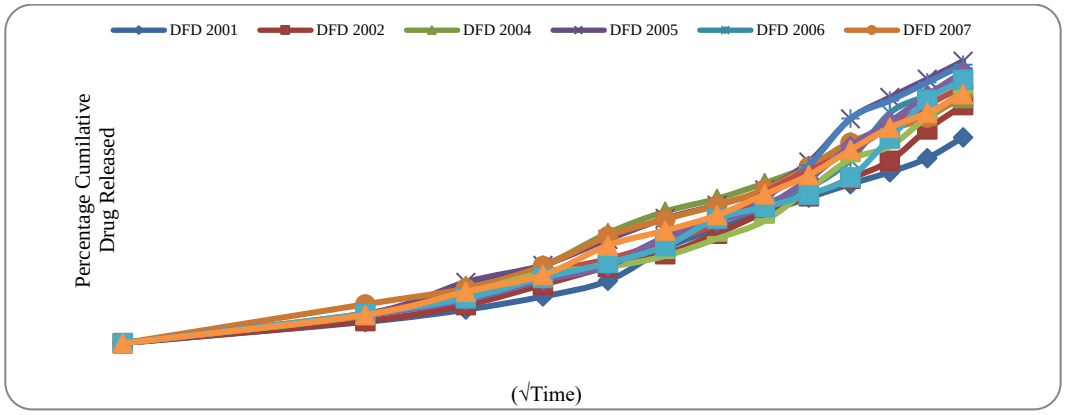
Sr. No.	Time (hr)	Percentage Cumulative Drug Released (%)												
		DFC 2001 S D (±)	**DFC 2002 S D (±)**	**DFC 2003 S D (±)**	**DFC 2004 S D (±)**	**DFC 2005 S D (±)**	**DFC 2006 S D (±)**	**DFC 2007 S D (±)**	**DFC 2008 S D (±)**	**DFC 2010 S D (±)**	**DFC 2013 S D (±)**	**DFC 2015 S D (±)**	**DFC 2016 S D (±)**	**DFC 2017 S D (±)**
1	0	**0.00 (±0.00)**	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
2	1	**5.21 (±0.012)**	5.43 (±0.026)	5.90 (±0.021)	6.93 (±0.023)	7.14 (±0.016)	6.84 (±0.019)	9.55 (±0.006)	6.84 (±0.019)	7.28 (±0.015)	6.78 (±0.023)	6.84 (±0.019)	7.17 (±0.015)	6.93 (±0.023)
3	2	**8.23 (±0.010)**	9.34 (±0.028)	8.46 (±0.019)	14.05 (±0.021)	14.98 (±0.010)	12.07 (±0.023)	13.42 (±0.012)	12.07 (±0.023)	12.39 (±0.024)	12.37 (±0.024)	10.57 (±0.026)	11.03 (±0.017)	12.65 (±0.035)
4	3	**11.46 (±0.014)**	14.35 (±0.027)	12.69 (±0.024)	19.08 (±0.021)	19.13 (±0.021)	15.78 (±0.015)	18.93 (±0.018)	15.78 (±0.015)	17.22 (±0.022)	17.20 (±0.022)	15.41 (±0.010)	16.06 (±0.020)	16.72 (±0.042)
5	4	**15.30 (±0.009)**	18.70 (±0.040)	17.18 (±0.027)	27.01 (±0.046)	25.47 (±0.026)	19.64 (±0.021)	26.28 (±0.039)	19.64 (±0.021)	20.65 (±0.029)	18.75 (±0.024)	18.90 (±0.022)	19.69 (±0.022)	23.98 (±0.068)
6	5	**23.25 (±0.017)**	21.87 (±0.036)	20.93 (±0.029)	32.29 (±0.055)	30.60 (±0.037)	25.98 (±0.026)	30.43 (±0.037)	25.98 (±0.026)	24.81 (±0.025)	21.38 (±0.029)	26.08 (±0.027)	23.82 (±0.005)	27.65 (±0.051)
7	6	**28.11 (±0.013)**	26.87 (±0.036)	25.08 (±0.025)	35.43 (±0.051)	33.86 (±0.038)	31.12 (±0.037)	33.81 (±0.037)	31.12 (±0.037)	29.29 (±0.023)	25.65 (±0.020)	29.86 (±0.035)	30.58 (±0.044)	31.40 (±0.044)
8	7	**31.98 (±0.026)**	32.04 (±0.035)	29.57 (±0.023)	39.27 (±0.043)	37.64 (±0.030)	34.37 (±0.038)	37.70 (±0.028)	35.78 (±0.016)	36.94 (±0.030)	30.02 (±0.023)	33.59 (±0.016)	33.36 (±0.048)	36.50 (±0.027)
9	8	**35.71 (±0.014)**	36.06 (±0.026)	33.77 (±0.020)	43.45 (±0.041)	44.49 (±0.035)	38.16 (±0.030)	43.27 (±0.041)	43.69 (±0.018)	42.37 (±0.040)	37.84 (±0.029)	40.28 (±0.030)	36.49 (±0.051)	41.26 (±0.018)
10	9	**39.04 (±0.019)**	40.39 (±0.039)	42.29 (±0.069)	49.36 (±0.031)	55.06 (±0.034)	45.03 (±0.018)	49.19 (±0.031)	55.14 (±0.027)	47.16 (±0.050)	45.12 (±0.063)	48.40 (±0.036)	40.71 (±0.037)	47.42 (±0.016)
11	10	**41.98 (±0.025)**	44.74 (±0.022)	46.36 (±0.055)	52.71 (±0.054)	60.29 (±0.034)	56.49 (±0.027)	52.53 (±0.054)	59.50 (±0.034)	53.17 (±0.060)	48.32 (±0.044)	54.35 (±0.014)	50.29 (±0.046)	52.89 (±0.026)
12	11	**45.41 (±0.023)**	52.47 (±0.039)	50.19 (±0.053)	55.88 (±0.030)	64.78 (±0.034)	60.84 (±0.034)	55.36 (±0.035)	63.98 (±0.034)	58.46 (±0.027)	55.55 (±0.034)	60.89 (±0.021)	59.71 (±0.014)	56.52 (±0.031)
13	12	**50.51 (±0.038)**	58.40 (±0.010)	58.40 (±0.027)	60.20 (±0.041)	69.20 (±0.031)	65.33 (±0.034)	61.10 (±0.036)	68.30 (±0.034)	62.90 (±0.017)	61.82 (±0.016)	66.50 (±0.029)	64.62 (±0.029)	61.10 (±0.019)

Table No. 5: Release rate constants, flux and permeation coefficients of diclofenac sodium (DS) released from Eudragit RL 100 and Eudragit RS 100 patches with penetration enhancers (Box Behnken Design)

Sr. No.	Formulation Code	Zero Order Model		Higuchi Model		PK Model			Flux (µg / Sq.cm.)	Permeation Coefficient (cm/Hr)
		k	R^2	k	R^2	k	R^2	n		
1	**DFC 2001**	**4.24**	**0.992**	**15.81**	**0.925**	**4.73**	**0.996**	**0.956**	**83.64**	**0.01115**
2	DFC 2002	4.67	0.995	17.21	0.905	4.17	0.998	1.048	92.19	0.01229
3	DFC 2003	4.69	0.991	17.15	0.886	3.46	0.998	1.125	92.62	0.01235
4	DFC 2004	4.90	0.985	17.15	0.886	8.50	0.998	0.792	96.65	0.01289
5	DFC 2005	5.70	0.993	21.21	0.921	7.05	0.993	0.902	112.50	0.01500
6	DFC 2006	5.35	0.988	19.63	0.893	4.96	0.992	1.020	105.50	0.01407
7	DFC 2007	4.86	0.991	18.44	0.956	8.25	0.998	0.799	95.88	0.01278
8	DFC 2008	5.83	0.989	21.35	0.889	4.13	0.995	1.152	115.00	0.01533
9	DFC 2009	4.24	0.992	15.81	0.925	4.73	0.996	0.956	83.64	0.01115
10	DFC 2010	5.17	0.996	19.16	0.916	5.35	0.998	0.992	102.10	0.01361
11	DFC 2011	4.24	0.992	15.81	0.925	4.73	0.996	0.956	83.64	0.01115
12	DFC 2012	4.24	0.992	15.81	0.925	4.73	0.996	0.956	83.64	0.01115
13	DFC 2013	4.89	0.983	17.91	0.885	4.46	0.991	1.036	96.41	0.01285
14	DFC 2014	4.24	0.992	15.81	0.925	4.73	0.996	0.956	83.64	0.01115
15	DFC 2015	5.46	0.992	19.98	0.891	4.53	0.997	1.066	107.70	0.01436
16	DFC 2016	5.08	0.982	18.63	0.886	4.68	0.991	1.028	100.20	0.01336
17	DFC 2017	5.01	0.997	18.75	0.937	6.39	0.999	0.909	98.79	0.01317



(a) Zero order kinetic



(b) Higuchi plot

Figure 1: In-vitro release profile of diclofenac sodium (DS) from Eudragit RL 100 and Eudragit RS 100 patches containing penetration enhancers (a) Zero order kinetic, (b) Higuchi plot

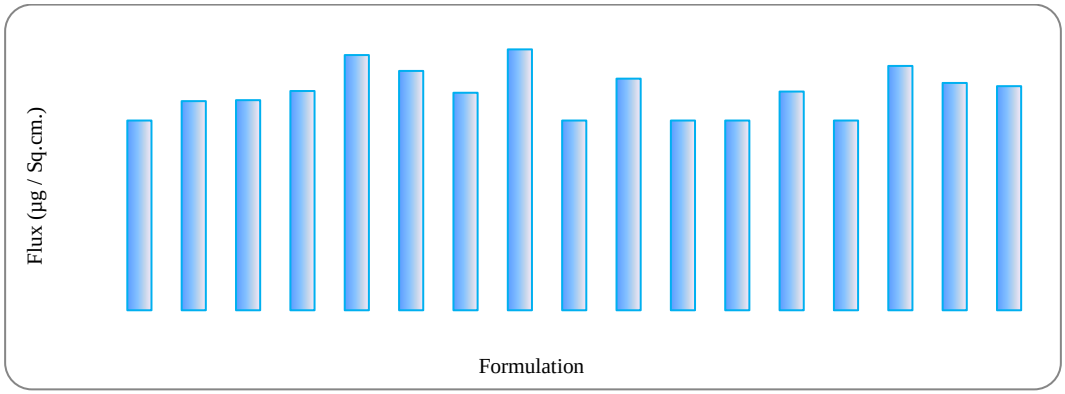
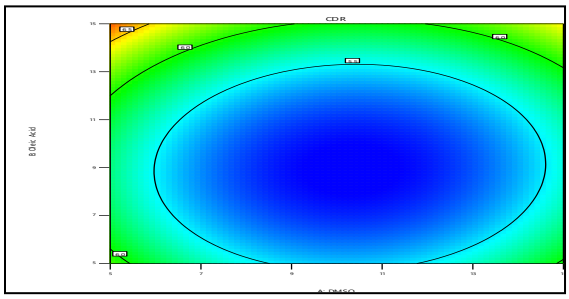
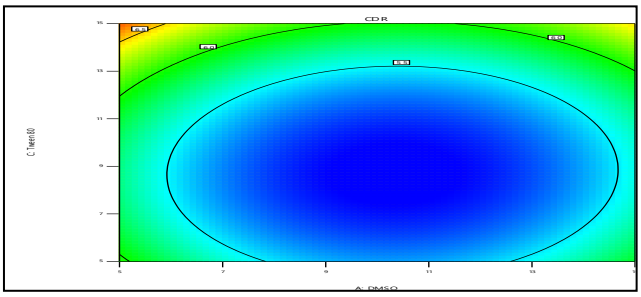


Figure 2: Flux (µg/cm^2) of diclofenac sodium (DS) released from Eudragit RL 100 and Eudragit RS 100 patches containing penetration enhancers

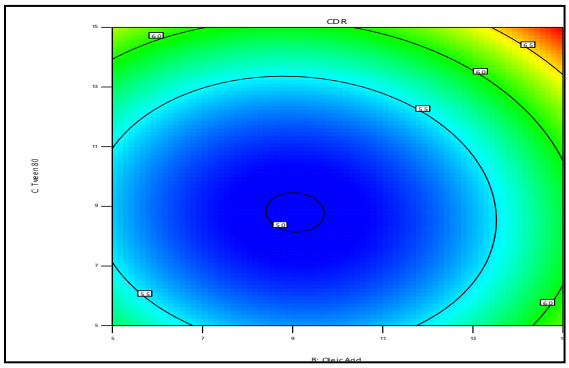
Different graphs of % CDR diclofenac sodium (DS) released from Eudragit RL 100 and Eudragit RS 100 patches



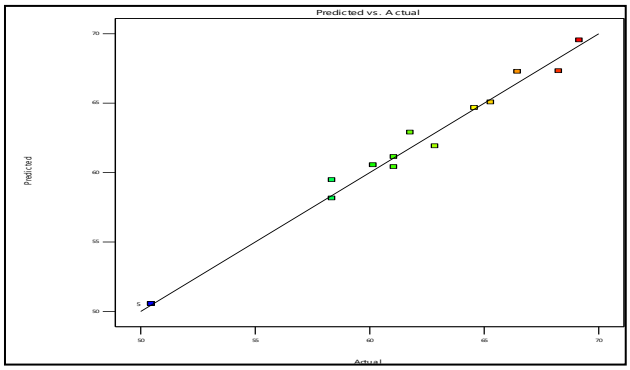
AB – DMSO and Oleic Acid



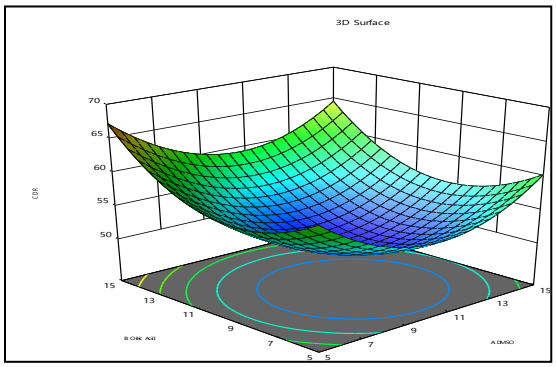
AC – DMSO and Tween 80



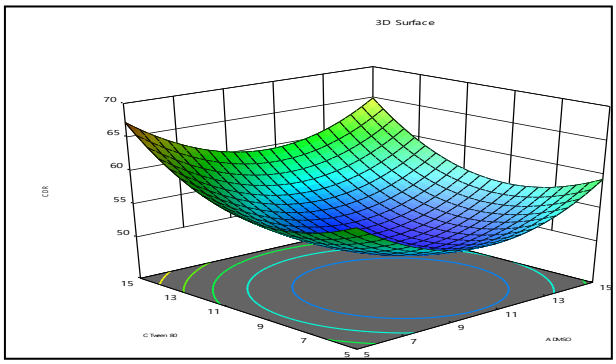
BC- Oleic Acid and Tween 80



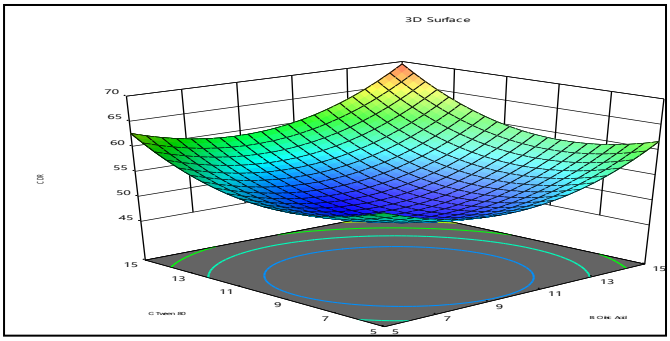
Predicted VS Actual



AB - DMSO and Oleic Acid



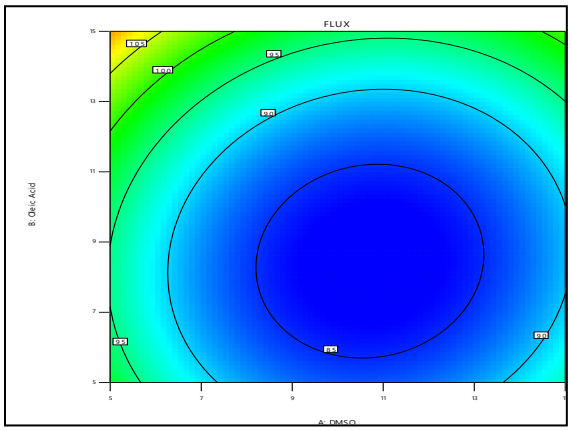
AC - DMSO and Tween 80



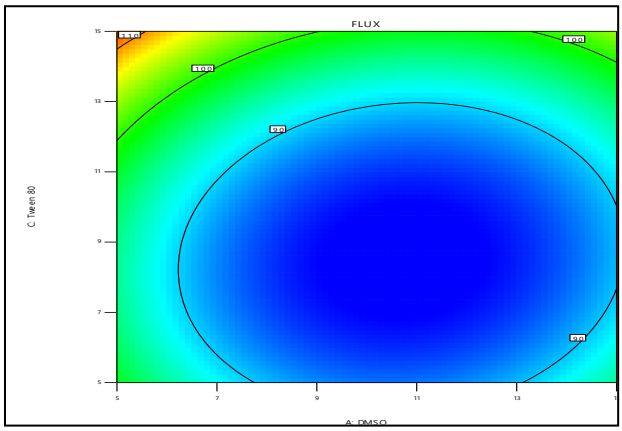
BC- Oleic Acid and Tween 80

Figure 3: Different graphs of % CDR diclofenac sodium (DS) released from Eudragit RL 100 and Eudragit RS 100 patches

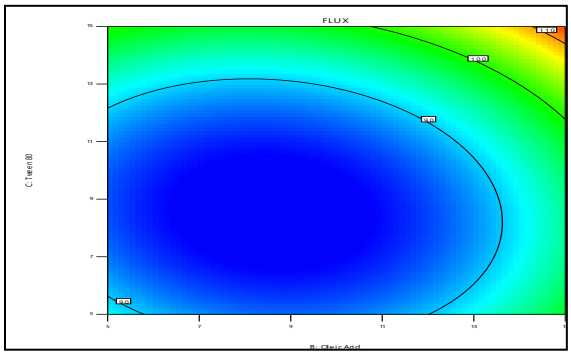
Different graphs of FLUX diclofenac sodium (DS) released from Eudragit RL 100 and Eudragit RS 100 patches



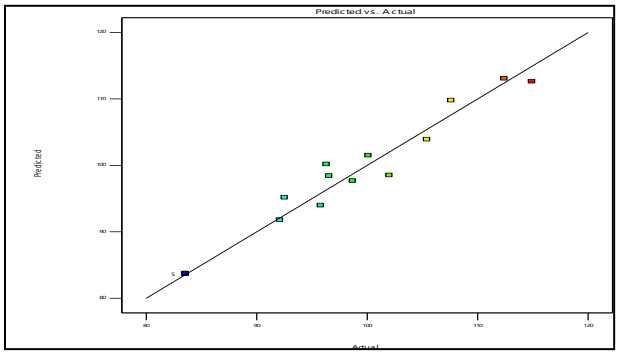
AB- DMSO and Oleic Acid



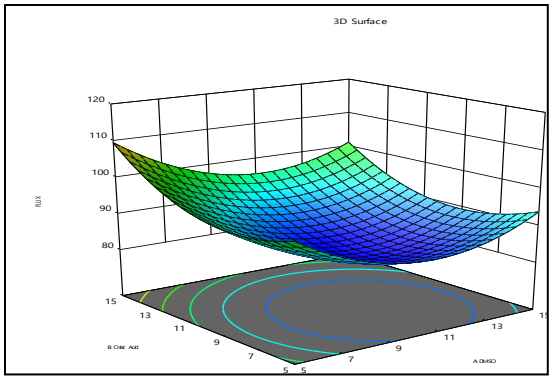
AC- DMSO and Tween 80



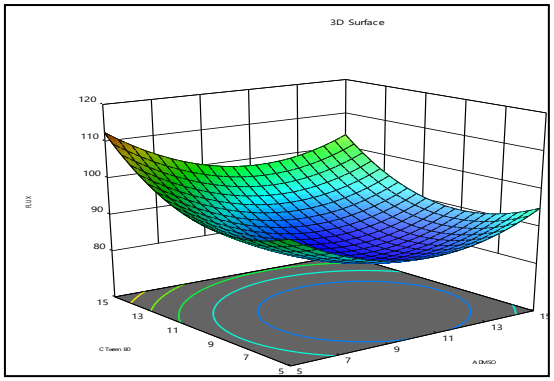
BC- Oleic Acid and Tween 80



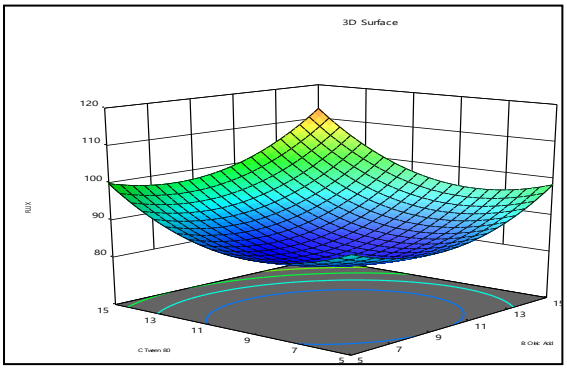
Predicted vs Actual



AB- DMSO and Oleic Acid



AC- DMSO and Tween 80



BC- Oleic Acid and Tween 80

Figure 4: Different graphs of FLUX diclofenac sodium (DS) released from Eudragit RL 100 and Eudragit RS 100 patches

Experimental Data with predicted response

On the basis of experimental data with predicted response formulation DFC 2005 was selected as optimized formulation.

F. Code	Factor A : DMSO	Factor B: Oleic Acid	Factor C: Tween 80	Flux		% CDR	
				Actual Value	Predicted Value	Actual Value	Predicted Value
DFC 2005	10	15	15	69.20	69.49	112.50	112.98

Results of Organoleptic Evaluation of optimized formulations by DOE (Box Behnken Design)

Table No 6: Results of Organoleptic Evaluation of optimized formulations

Sr. No.	Polymeric Film Code	Smoothness	Clarity	Brittleness	Overall Appearance
1	DFC 2005	+++	+++	NA	Good

Table No 7: Results of optimized formulations thickness uniformity (n=5)

Sr. No.	Film Code	Thickness (µm)						SD (±)
		Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Avg	
1	DFC 2005	102	103	105	103	102	103.00	1.095

Table No 8: Results of optimized formulations Folding Endurance (n=3)

Sr. No.	Film Code	Folding Endurance				SD (±)
		Trial 1	Trial 2	Trial 3	Avg.	
1	DFC 2005	39	40	43	40.67	2.08

Table No 9: Results of Percentage Moisture Content

Sr. No.	Film Code	Percentage Moisture Content.				SD (±)
		Trial 1	Trial 2	Trial 3	Avg.	
1	DFC 2005	1.98	1.85	1.99	1.94	0.08

Table No 10: Results of Moisture Uptake or Absorption

Sr. No.	Film Code	Percentage Moisture Uptake				SD (±)
		Trial 1	Trial 2	Trial 3	Avg.	
1	DFC 2005	2.25	2.36	2.45	2.35	0.10

Table No 11: Results of Physicochemical Properties Percent Flatness

Sr. No.	Film Code	Percent Flatness				SD (±)
		Trial 1	Trial 2	Trial 3	Avg.	

1	DFC 2005	100.00	100.80	100.6	100.47	0.42

Table No 12: Physicochemical Properties Tensile Strength

Sr. No.	Film Code	Tensile Strength (N/mm^2)	SD (±)	Modulus of Elasticity	SD (±)	Percentage elongation (%)	SD (±)
1	DFC 2005	0.458	0.058	0.905	0.033	36.58	0.32

Table No 13: Results of percentage drug content

Sr. No.	Film Code	Percentage Moisture Uptake				SD (±)
		Trial 1	Trial 2	Trial 3	Avg.	
1	DFC 2005	96.65	97.74	96.85	97.08	0.58

Table No 14: Results of skin irritation study

	After 12 hrs	After 24 hrs	After 36 hrs	After 48 hrs
Blank Patch	**A**	**A**	**A**	**A**
DFC 2005	**A**	**A**	**A**	**A**

A – No reaction, B – Slight patchy erythema, C-Slight but Confluent or Moderate but patchy erythema, D-Moderate erythema, E-Severe erythema with or without edema.

Table No 15: Results of stability study of optimized formulations DFD 2005

F. Code	Initial Drug Content	25 ± 2^0C (60±5% RH)			40 ± 2^0C (75±5% RH)		
		15 days	30 days	60 days	15 days	30 days	60 days
DFD 2005	99.70	99.65	99.50	98.85	98.85	97.75	96.65

Conclusion

In summary, formulation DFC 2005 emerged as the most promising among the tested formulations. It not only provided the highest cumulative drug release and flux but also showed

favorable physicochemical properties, non-irritancy, and stability. The data supports DFC 2005 as an optimized formulation for effective and safe transdermal delivery of diclofenac sodium. This formulation's performance aligns well with the desired characteristics of a high-quality transdermal patch, making it a suitable candidate for further clinical evaluation and potential therapeutic use.

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