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Original Article

Analytical Quality By Design-Based Development And Validation Of A Stability-Indicating RP-HPLC Method For Simultaneous Determination Of Triamcinolone Acetonide And Econazole Nitrate In Pharmaceutical Cream Formulation

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ABSTRACT

This study reports the development and validation of a rapid, robust, and stability-indicating Reverse-Phase High-Performance Liquid Chromatography (RP-HPLC) method for the simultaneous estimation of Triamcinolone Acetonide (TRI) and Econazole Nitrate (ECO) in pharmaceutical cream formulations. A systematic Analytical Quality by Design (AQbD) approach employing a three-factor, five-level Central Composite Design (CCD) was utilized to optimize the chromatographic conditions. The critical method parameters (CMPs) investigated included the percentage of the aqueous phase, pH of the aqueous phase, and flow rate, while the critical analytical attributes (CAAs) comprised the tailing factor of TRI, tailing factor of ECO, and total chromatographic run time. The optimized chromatographic conditions consisted of a Kinetex® Biphenyl column (250 × 4.6 mm, 5 µm) using a mobile phase composed of Acetonitrile and 0.1 % hexanesulfonic acid in HPLC grade water (pH adjusted with orthophosphoric acid) at the optimized ratio, delivered at a flow rate of 1.0 mL min^{-1} with UV detection at 235 nm. The CCD optimization involved 19 experimental runs, and response surface methodology successfully established a Method Operable Design Region (MODR) that produced symmetrical chromatographic peaks with tailing factors close to 1.5 for both analytes and a total chromatographic run time of approximately 12 min. The optimized method exhibited excellent reproducibility and robustness, as confirmed by replicated centre-point experiments and statistical evaluation of the quadratic model. The developed method was validated in accordance with ICH Q2(R2) guidelines for system suitability, specificity, linearity, accuracy, precision, robustness, detection limit, quantitation limit, and solution stability. The validation results demonstrated excellent analytical performance with satisfactory linearity, acceptable accuracy and precision, and robust chromatographic behavior.

Keywords: RP-HPLC; Method Development; QbD Approach; Simultaneous Estimation; Central Composite Design; Triamcinolone Acetonide (TRI); Econazole Nitrate (ECO).

INTRODUCTION

Multidrug semisolid dosage forms, such as creams, represent a sophisticated approach in modern topical drug delivery. By incorporating two or more active pharmaceutical ingredients (APIs) into a single base, these formulations provide combined therapeutic actions, improve patient compliance, and enhance treatment efficacy for conditions such as skin infections, inflammation, and pain. The formulation of these creams requires rigorous attention to drug compatibility, stability, uniform distribution, and skin permeability. [1-2]

The pharmaceutical industry operates under rigorous regulatory frameworks, necessitating the development of precise and robust analytical methodologies to ensure the identity, strength, quality, and purity of drug products. As combination therapies—specifically those incorporating multiple active pharmaceutical ingredients (APIs) for localized dermatological treatments—become increasingly prevalent, [3-4]

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

This study addresses the simultaneous estimation of four chemically diverse drugs: Triamcinolone Acetonide (TRI), (1S,2S,4R,8S,9S,11S,12R,13S)-12-fluoro-11-hydroxy-8-(2-hydroxyacetyl)-6,6,9,13-tetramethyl-5,7-dioxapentacyclo[10.8.0.02,9.04,8.013,18]icosa-14,17-dien-16-one, [5] Econazole Nitrate (ECO), chemically 1-[2-[(4-chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]imidazole;nitric acid, [6] The simultaneous determination of these specific analytes is particularly complex due to their disparate polarities and structural characteristics.

Quality by Design (QbD) is a concept originally introduced by renowned quality expert Joseph M. Juran in his influential publications, most notably *Juran on Quality by Design*. While these principles have been implemented across various industries to improve product and process quality—most notably in the automotive sector—they have recently been adopted by the U.S. Food and Drug Administration (FDA) to transform how drugs are discovered, developed, and manufactured. [7-9]

Since the FDA first initiated this shift through its "Pharmaceutical cGMPs for the twenty-first century" program, QbD has become a cornerstone concept for the pharmaceutical industry. As further defined in the International Conference on Harmonisation (ICH) guidance on pharmaceutical development, QbD is "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management". Consequently, the scientific understanding gained during the method development process is now used to devise effective method control elements and manage identified risks. [10-12]

The aim of the analytical method is to separate and quantify the main compound while meeting the method performance criteria based on regulatory requirements, such as specificity, linearity, accuracy, precision, sensitivity, robustness, and ruggedness.

The study employs a systematic Quality by Design (QbD) approach, utilizing a three-factor, five-level Central Composite Design (CCD) via Design-Expert 13.0 software to optimize chromatographic conditions. The study specifically evaluates how variations in the percentage of the polar phase (water), the flow rate of the mobile phase, and the pH of the polar phase influence critical responses, including the tailing factors of Triamcinolone Acetonide (TRI), Econazole Nitrate (ECO) and the total chromatographic run time.

Following optimization and successful method finalization through various experimental trials, the procedure was validated in accordance with ICH Q2 R guidelines

MATERIAL AND METHOD

Material and chemical

The materials, chemicals, and instruments used in the experiment are documented as follows. The drug samples— Triamcinolone Acetonide (TRI), and Econazole Nitrate—were obtained from Yarrow pharm, with purities of ≥ 99.93%, and 98%, respectively. Reagents and chemicals utilized included HPLC grade water from Millie Queue Water, methanol from SD Fine Chem. Limited, acetonitrile from Merck Lab, and orthophosphoric acid.

Equipment

The chromatographic analysis is performed using an HPLC system equipped with a Photodiode Array (PDA) detector, The system utilizes a Phenomenex Kinetex C-8 column, which measures 250 mm in length with an internal diameter of 4.6 mm and 5 micron in size. The experimental design model was developed on Design-Expert 13.0 (Stat-Ease Inc., Minneapolis, USA).

Design of Experiments (CCD)

To optimize the chromatographic conditions, a three-factor, five-level Central Composite Design (CCD) was employed during the method development phase. This experimental design evaluated three independent variables: the ratio of the polar phase (water) in percent, the flow rate of the mobile phase in mL/min, and the pH of the polar phase. The efficacy of these variables was assessed based on several dependent responses, specifically the tailing factors for Triamcinolone Acetonide (TRI) and Econazole Nitrate (ECO) as well as the total chromatographic run time. Following the optimization process, the

conditions identified in Trial 9 were selected as the final method. These optimized parameters consist of a mobile phase composed of a 47:53 v/v ratio of acetonitrile to 0.1 % hexanesulfonic acid in HPLC grade water (with the water pH adjusted to 3.0 using orthophosphoric acid), a flow rate of 1 mL/min, and a detection wavelength of 235 nm. Additionally, the method is conducted at a column temperature ranging between 37°C and 38°C, with a total run time of 12 minutes.

Variables	Levels				
	-1.68179	**-1**	**0**	**+1**	**+1.68179**
Ratio of polar phase (HAS 0.1% in HPLC grade water) (%)	45	46	47	48	49
Flow rate of mobile phase (mL/min)	0.8	0.9	1.0	1.1	1.2
pH of polar phase	2.8	2.9	3.0	3.1	3.2

Table No.1 Levels for method optimization and selected variables in CCD for analysis of TRI and ECO

Preparation of Solution

Standard Stock Solutions: Accurately weighed amounts of TRI and ECO were dissolved in methanol in 10 mL volumetric flasks, sonicated to dissolve, and made up to the mark with diluent. Working Standards: Prepared by diluting stock solutions with Acetonitrile to achieve desired concentrations (e.g., 1 µg/mL for TRI and 10 µg/mL for ECO). Sample Solution (Cream Formulation): 10 g of cream (containing 0.1% TRI and 1% ECO) was transferred to a 100 mL volumetric flask, 100 mL of acetonitrile was added, and the mixture was sonicated for 15 minutes. The solution was filtered through a 0.45 µm nylon syringe filter and centrifuged at 3000 rpm for 10 minutes. A 1 mL aliquot was further diluted to 10 mL with acetonitrile.

Method Validation

The method was validated according to ICH Q2R guidelines: [13-14]

System Suitability

Assessed by six replicate injections of the standard solution; acceptance criteria included %RSD for retention time ≤ 2.5%, theoretical plates > 2000, and tailing factor ≤ 2.5.

Linearity:

Determined by analyzing five concentrations (10–50 µg/mL) of the analytes; calibration curves were plotted and R^2 values were evaluated.

Accuracy:

Performed via recovery studies at 80%, 100%, and 120% levels using the standard addition method.

Precision:

Evaluated through system precision (standard solution) and method precision (homogenous sample of a single batch analyzed six times).

Specificity:

Confirmed by injecting blank and placebo samples to ensure no interference at the analytes' retention times.

Robustness:

Assessed by making small, deliberate changes to flow rate (±0.1 mL/min), pH (±0.1 units), and organic phase composition (±10%).

Analysis of marketed formulation

The analysis was conducted on the marketed cream formulation " Ecozol Plus," manufactured by Opsonin Pharma., which has a label claim weight of 20 grams.

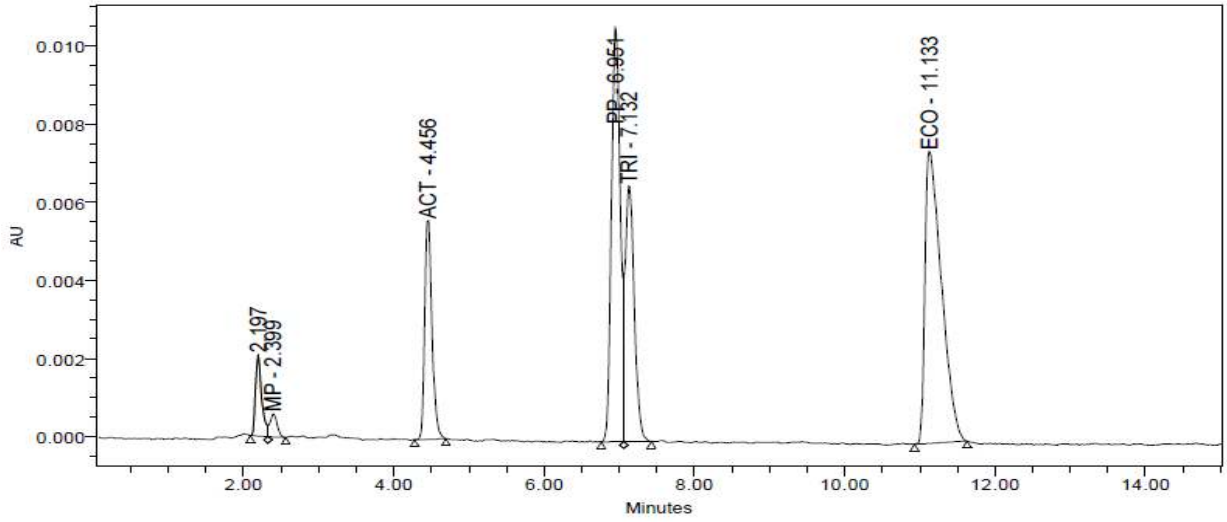
To prepare the sample solution, 10 grams of the cream were transferred to a 100 mL volumetric flask, combined with 100 mL of acetonitrile, and sonicated for 15 minutes to ensure complete dissolution. This solution was subsequently filtered through a 0.45 µm nylon syringe filter and centrifuged at 3000 rpm for 10 minutes. A 1 mL aliquot of the resulting clear supernatant was then transferred to a 10 mL volumetric flask and diluted to the mark with acetonitrile.

RESULT AND DISCUSSION

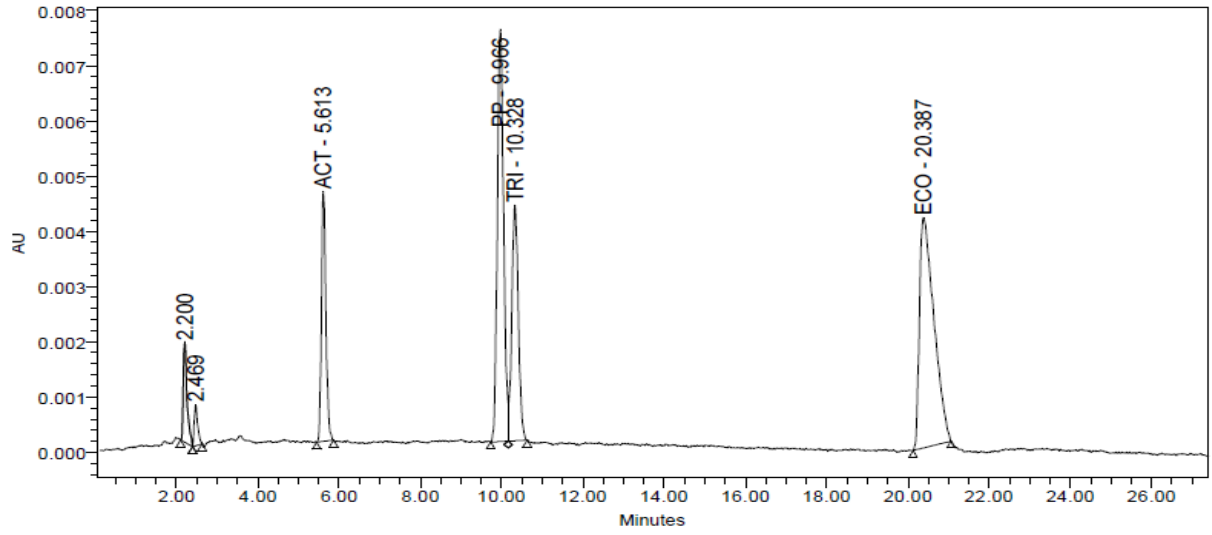
Design of Experiments (CCD)

A three-factor, five-level Central Composite Design (CCD) was employed to evaluate the influence of percentage of polar phase (water, X_1), flow rate (X_2), and pH of the polar phase (X_3) on the chromatographic performance. The selected response variables included the tailing factor (TF) of Triamcinolone Acetonide (TRI), Econazole Nitrate (ECO) and the total chromatographic run time (RT). A total of 19 experimental runs comprising factorial, axial, and centre points were performed, as presented in Table no. 2

The centre point experiments (Runs 4, 5, 13, and 19) demonstrated good reproducibility with minimal variation in the response values, confirming the reliability of the experimental design and indicating insignificant pure experimental error.



Trail 4



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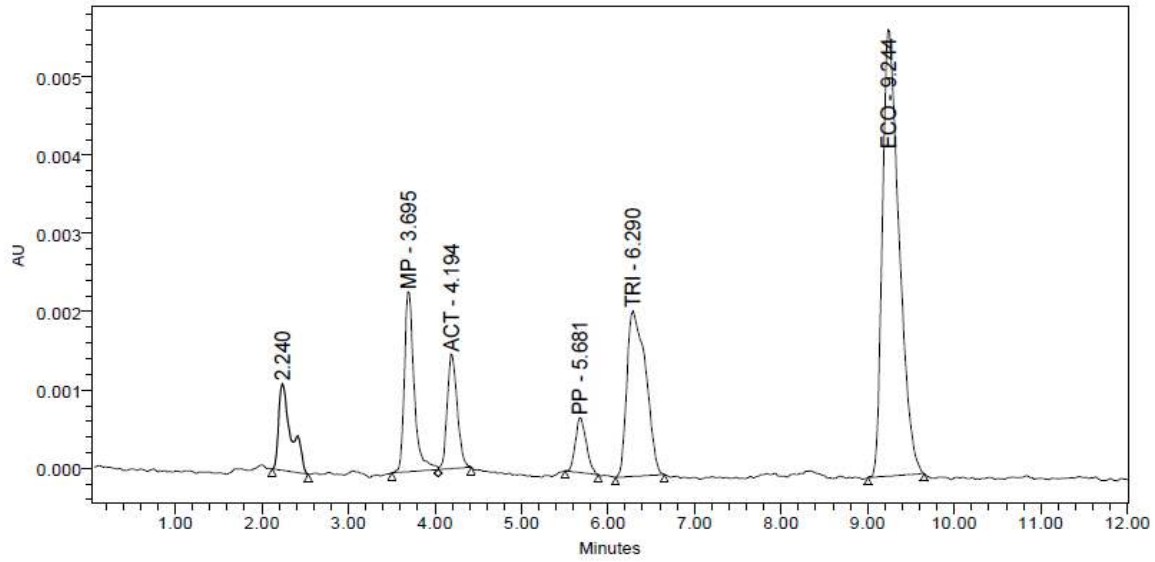

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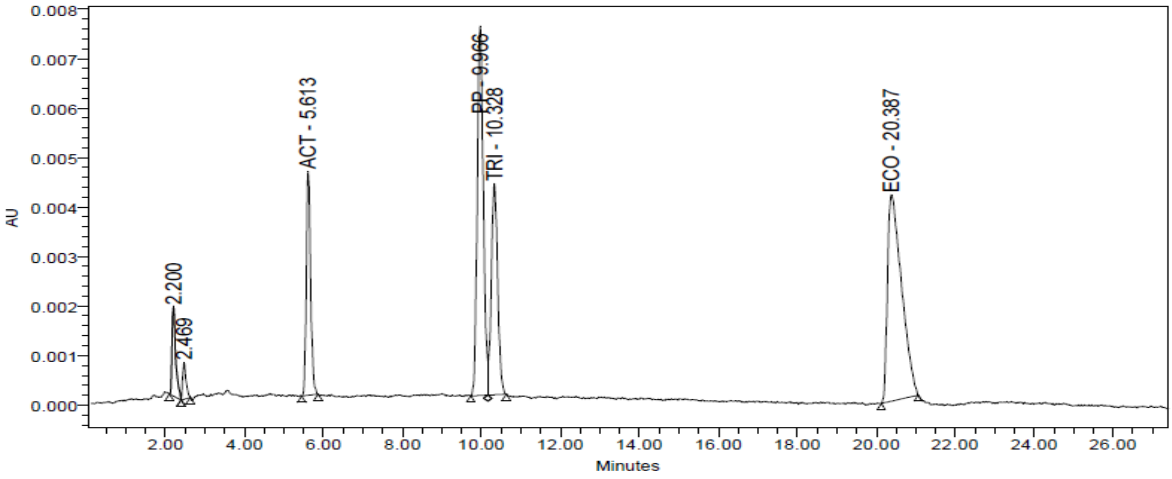

Trail 19

the statistics are given in Table 2. The contour (2D) plots and 3D plot of responses with respect to all factors are shown in Figure 01-03. for TF TRI, TF ECO and RT respectively. The optimum conditions were calculated using numerical optimization. To achieve the composite desirability (D), the response criteria were set as (lower–upper):

The three-dimensional response surfaces and contour plots demonstrated significant linear, interaction, and quadratic effects of the selected factors. The optimized design space was identified near the center region of the experimental domain, where minimal tailing factors for all analytes and an acceptable chromatographic run time were simultaneously achieved. These findings confirmed that CCD is a suitable experimental design for systematic optimization of the RP-HPLC method, enabling robust separation with improved peak symmetry and reduced analysis time.

Run	%Polar phase (HAS 0.1% in HPLC grade water)	Flow rate (mL/min)	pH of polar phase	Response factors		
				TF (TRI)	TF (ECO)	RT
1	1.68179	0	0	4.5	4.2	25
2	-1	1	1	3.5	2.9	26
3	0	0	-1.68179	3.9	3.2	20
4	0	0	0	1.5	1.6	15
5	0	0	0	1.6	1.6	16
6	0	1.68179	0	4.6	4.1	18
7	1	-1	-1	3.2	3.1	21
8	0	-1.68179	0	3.9	3.5	26
9	-1	-1	-1	3.8	3.6	29
10	0	0	1.68179	4.6	4.5	25
11	0	0	0	1.8	1.53	20
12	-1	1	-1	4.2	3.6	23
13	0	0	0	1.5	1.45	15
14	1	1	1	4.2	3.8	18
15	1	-1	1	4.4	3.8	25
16	-1	-1	1	3.5	3.1	24
17	-1.68179	0	0	3.6	3.45	28
18	1	1	-1	3.6	3.4	25
19	0	0	0	1.6	1.6	15

Table N0.2 Response factors and independent variables fitted in central composite design CCD for analysis of TRI and ECO

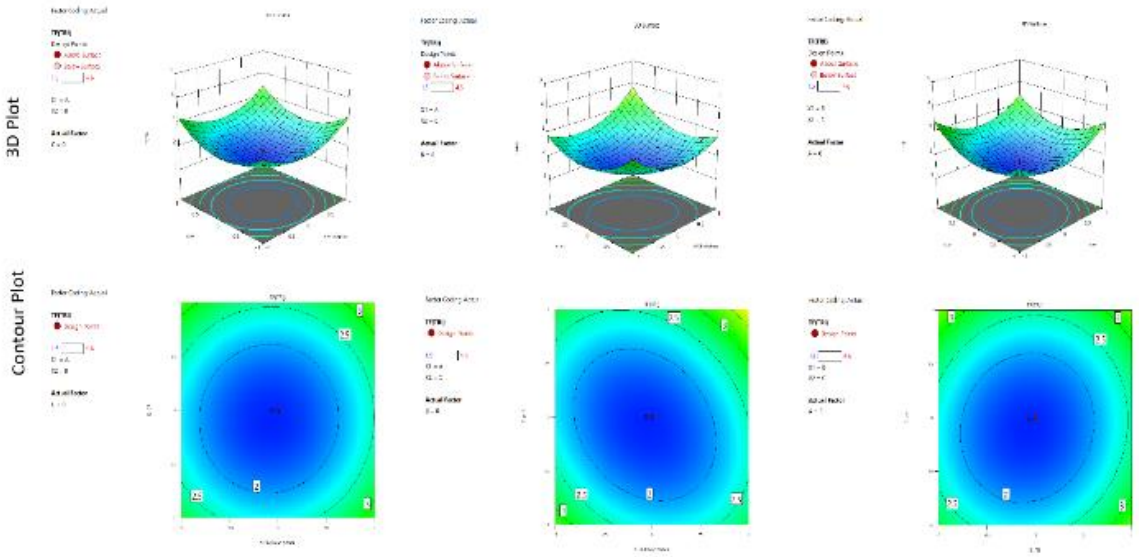

Figure No. 1 Surface response plot outcome of CCD analysis (3D plot and Contour Plot) for Tailing factor of TRI

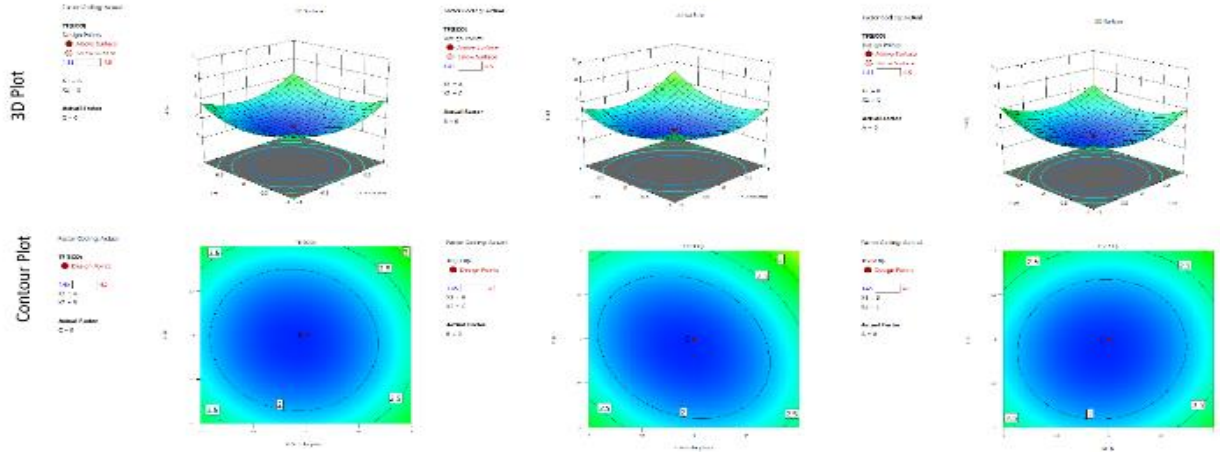

Figure No. 2 Surface response plot outcome of CCD analysis (3D plot and Contour Plot) for Tailing factor of ECO

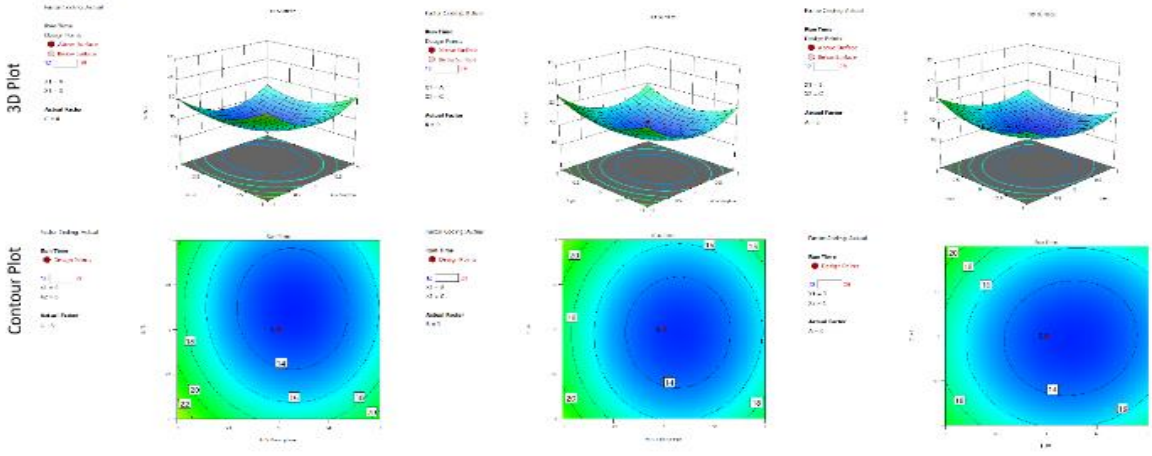

Figure No. 3 Surface response plot outcome of CCD analysis (3D plot and Contour Plot) for Run time

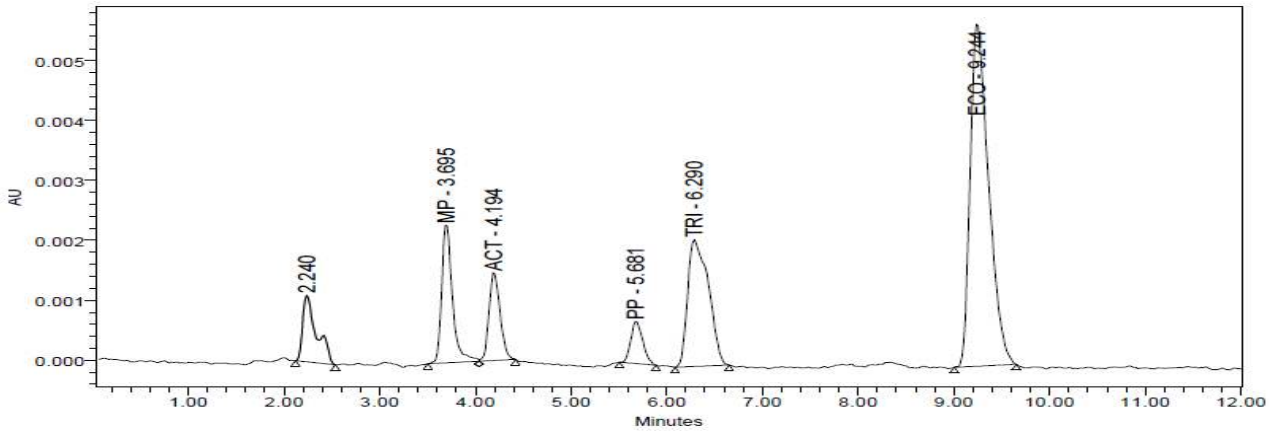

Figure No. 4 Optimized chromatogram of standard solution mixture containing 01ug/ml of TRI, and 10 ug/ml of ECO

METHOD VALIDATION

System suitability: -

All System suitability parameters (Retention Time, Peak Area, Tailing Factor) for TRI, ECO were calculated for n=6 replicates to study the system suitability of HPLC method all the result were within acceptable limits, confirming the suitability of the instrument, reagents, and column. as shown in Table 3

Parameter	compound	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Mean	SD	%RSD
Retention Time	TRI	6.290	6.265	6.341	6.242	6.301	6.299	6.289	0.033856	0.538288
	ECO	9.244	9.278	9.212	9.219	9.312	9.281	9.257	0.039185	0.423771
Peak area	TRI	81940	81421	82013	81987	82121	81998	81913	248.4984	0.303367
	ECO	118832	118645	118972	118898	118612	118998	118826	164.12	0.138118
Tailing Factor	TRI	1.52	1.51	1.51	1.54	1.54	1.53	1.52	0.013784	0.903872
	ECO	1.52	1.51	1.53	1.51	1.56	1.57	1.53	0.02582	1.683906

Table No.03: Observation of System suitability Parameters

Linearity:-

The linearity of the HPLC detector response for determination of TRI and ECO was evaluated by analyzing a series of different concentrations of each compound. The calibration range was established with respect to the practical range necessary (according to content and ratio of each compound in the cream formulation), to give accurate, precise and linear results. Seven concentrations were chosen, ranging from 0.5-1.5 ug/mL TRI and 05-15 µg/mL ECO and the linearity was determined. Characteristic parameters for regression equations of the HPLC method are given in Table 04-. The R^2 values for all four drugs were found to be ≥ 0.9945, indicating a high level of linearity and a consistent detector response across the tested concentration ranges.

% level	TRI Conc. (µg/ml)	Mean	ECO Conc. (µg/ml)	Mean
50	0.5	19219	05	39424
80	0.8	53139	08	77930

100	1.0	81979	10	118809
120	1.2	112500	12	152261
150	1.5	141295	15	206178
R^2Value	0.9941		0.9949	

Table no. 04 Observation of linearity of TRI & ECO

Accuracy:-

Accuracy was determined by standard addition method at three levels Standard solution, Accuracy-80%, Accuracy-100% and Accuracy-120% solutions were injected in to HPLC system. Amount found and amount added for TRI and ECO, individual recovery and mean recovery values were also calculated. The average % recovery of TRI & ECO, was calculated and The excellent recoveries of standard addition method (Table 5) for HPLC suggested good accuracy of the proposed method.

Sr. no.		**1**	**2**	**3**
Level		**80%**	**100%**	**120%**
Amount added μg/ml	**TRI**	0.8	1	1.2
	ECO	8	10	12
Mean Area±%RSD (n=6)	**TRI**	147011±0.78	164420±1.1	180818±1.0
	ECO	214191±0.91	238044±0.79	261830±1.0
Mean Area Recovered (n=6)	**TRI**	65001	82410	98808
	ECO	95269	119122	142908
Amount Recovery (µg/mL) (n=6)	**TRI**	0.7925	1.0048	1.2048
	ECO	0.8011	1.0016	1.2016
%Recovery	**TRI**	99.06	100.48	100.40
	ECO	100.13	100.16	100.13

Table No.05: Accuracy study of TRI and ECO by standard addition method at (80%, 100% and 120%)

Precision:-

The precision of the method was determined by intraday studies. The peak areas of all two drugs were calculated for each trial. The experiment was repeated three times in a day for intra-day precision Prepare 20 µg/mL solutions from a standard solution and inject Six times in a day on to analytical column. The percentage relative standard deviation (%RSD) was calculated and lower % RSD indicates that there are less variation and there is high precision all % RSD value given in table no.6 & table no.7

Parameter	compound	Run 1	Run 2	Run 3	Run4	Run 5	Run6	Mean	SD	%RSD
Peak area	TRI	81832	81940	81898	82010	81901	81889	81911	59.385744	0.07249979
	ECO	119012	118832	118899	118841	118901	118870	118893	65.136011	0.054785635
Retention Time	TRI	6.214	6.290	6.262	6.291	6.211	6.289	6.259	0.0380039	0.607140301
	ECO	9.144	9.244	9.201	9.221	9.211	9.241	9.210	0.0365385	0.396712722

Table No. 06: Observation for System precision

Parameter	compound	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Mean	SD	%RSD
Peak area	TRI	82109	82100	82091	82117	82109	82110	82106	9.121403	0.0111093
	ECO	118922	118981	118988	118921	118999	118899	118952	42.462532	0.03569729
Retention Time	TRI	6.114	6.163	6.129	6.112	6.156	6.142	6.136	0.0213260	0.3475560
	ECO	9.090	9.101	9.151	9.149	9.162	9.095	9.124	0.0326231	0.3575267

Table No. 07: Observation for Method precision

Specificity:-

Studies with blank and placebo solutions confirmed no interference at the retention times of the analytes, indicating the method is specific. Shown in figure no.08 (**Blank chromatogram)** figure no.09 **(**placebo chromatogram**)**

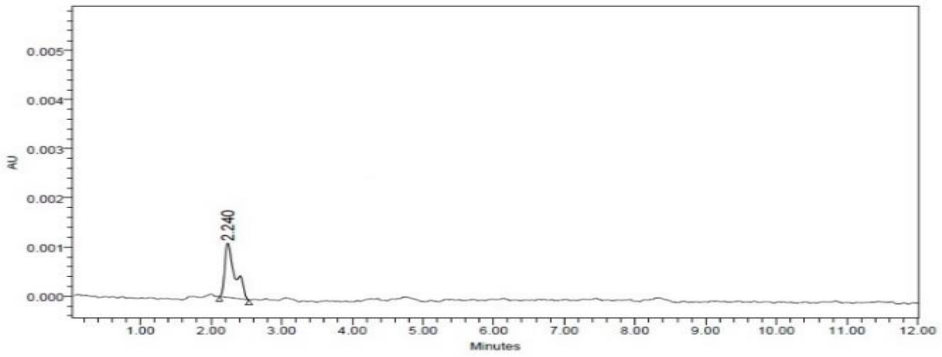

Figure no.08 Blank chromatogram

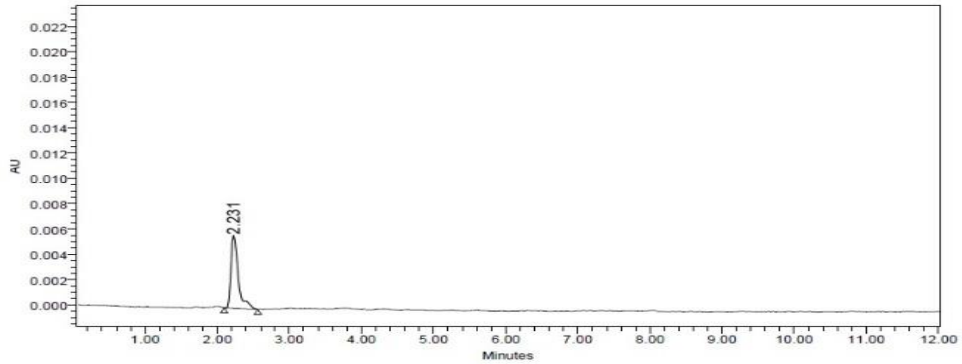

Figure no.09 Placebo chromatogram

Robustness:-

Various factors were assessed to check the robustness of the method. Deliberate variations in flow rate (±0.1 mL/min), pH (±0.1 units), and organic phase composition (±10%) were tested. The method was also found to be robust for the factors thus studied and method remained robust within the tested ranges. the data of all factor given in table 8-10

Parameter	TRI	ECO
Flow Rate 0.9ml/min	74740	116823
	74982	116898
	74808	116908
	74914	116845
	74908	116878
Mean	74877	116872
SD	87.00038314	32.16623488
%RSD	0.116191581	0.027522697
Retention Time in Min.	6.988	10.289
	7.057	10.301
	7.101	10.311
	6.975	10.299
	6.999	10.306
Mean	7.019	10.302
SD	0.048704894	0.007641989
%RSD	0.693818376	0.074179667
Flow Rate 1.1ml/min	91210	119246
	91189	119189
	91211	119276
	91260	119119
	91217	119210
Mean	91217	119208
SD	23.31237154	53.58606784
%RSD	0.025556954	0.044951612
	5.783	8.647

Retention Time in Min.	5.804	8.611
	5.798	8.632
	5.776	8.658
	5.745	8.642
Mean	5.775	8.638
SD	0.025435539	0.015970807
%RSD	0.440429531	0.18487583

Table No. 08: Robustness study for change in flow rate ±10% (±0.1ml/min)

Parameter	**TRI**	**ECO**
pH 2.9 (-0.1 unit)	81940	118863
	81987	118871
	82009	118793
	81899	118849
	81953	118871
Mean	81957	118853
SD	38.18071066	30.62025473
%RSD	0.046586366	0.025763132
Retention Time in Min.	6.283	9.099
	6.241	9.110
	6.263	9.141
	6.289	9.117
	6.278	9.129
Mean	6.272	9.120
SD	0.017458522	0.015158056
%RSD	0.278356541	0.166191571
pH 3.1 (+0.1 unit)	80954	117832
	81021	117742
	80999	117828

	81011	117849
	80854	117763
Mean	80949	117796
SD	76.94521861	45.21688
%RSD	0.095054142	0.038386
Retention Time in Min.	6.270	9.086
	6.278	9.089
	6.268	9.074
	6.269	9.079
	6.241	9.091
Mean	6.261	9.085
SD	0.016018	0.007014271
%RSD	0.255826	0.077207167

Table No. 09 : Robustness study for change in pH ± 0.1 units.

Parameter	TRI	ECO
Organic Phase Change (-10%)	83850	118971
	83743	118898
	83841	118984
	83856	118914
	83865	118927
Mean	83837	118937
SD	46.79601123	33.51069
%RSD	0.055818072	0.028175
Retention Time in Min.	8.142	14.445
	8.133	14.432
	8.148	14.440
	8.139	14.417
	8.144	14.321

Mean	8.141	14.396
SD	0.005164	0.058862552
%RSD	0.063427	0.408881299
Organic Phase Change (+10%)	82745	118451
	82689	118488
	82714	118530
	83098	118563
	82748	118498
Mean	82790	118505
SD	152.5734796	38.18726
%RSD	0.184289003	0.032224
Retention Time in Min.	5.263	6.854
	5.298	6.864
	5.241	6.721
	5.301	6.870
	5.287	6.896
Mean	5.279	6.850
SD	0.02311493	0.065551252
%RSD	0.43782423	0.956929304

Table No. 10: Robustness study for change in Organic Phase ± 10%.

Application of validated method

The HPLC method was successfully applied to the determination of TRI and ECO in cream formulation without the interference of excipients therein. The results of the assay are shown in Table 11

	TRI	**ECO**
Standard	N=6	N=6
Mean Area	81940	118832
Test Preparation Cream	N=6	N=6
Mean Area	82010	118922
Observed in mg	1.00 mg	10.00 mg

Label claim in mg	1 mg	10 mg
% Assay	100.08	100.07

Table No. 11: Result of marketed formulation TRI & ECO (Ecozol Plus)

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