RESEARCH PAPER

Design and Optimization of Etravirine Tablets via Solid Dispersion with Hydrophilic Polymers

Hiren Parekh[1]*, Dr. Malay Chotaliya[2]

[1]*Research Scholar (Ph. D) R. K. University, Gujarat, India Department of Pharmaceutics, R. K. University, Gujarat, India*
[2]*School of Pharmacy, RK. University, Rajkot, Gujarat, India*

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ABSTRACT

Objectives: This study aimed to enhance the aqueous solubility and dissolution rate of Etravirine, a poorly soluble antiretroviral agent, using solid dispersion with hydrophilic polymers and systematic optimization.

Methods: Etravirine was characterized by FTIR, DSC, and XRD. Solid dispersions were prepared with HPMC 5 cps and PVP K30 via spray drying. A 2^3 factorial Design of Experiments (DoE) was employed to optimize disintegration time, dissolution, and assay parameters. Standard pharmacopeial methods were followed for tablet evaluation.

Results: HPMC 5 cps solid dispersion improved aqueous solubility ~3.4-fold compared to pure drug (0.409 vs. 0.12 mg/mL). The optimized formulation (ETR002) achieved over 93% drug release within 90 minutes, significantly outperforming the pure drug and comparable to the marketed reference (Intelence®, f2 = 75). Statistical analysis (ANOVA) confirmed the significance of Croscarmellose sodium and Crospovidone levels on dissolution and disintegration ($p < 0.05$).

Conclusion: Solid dispersion with HPMC 5 cps via spray drying is an effective strategy for enhancing Etravirine solubility and dissolution. The approach eliminates hazardous solvents such as MDC, offering a safer and scalable industrial process. Further in vivo pharmacokinetic and bioequivalence studies are warranted.

Keywords: *Etravirine, Solubility enhancement, Solid Dispersion, Liquisolid Method, Design of Experiment.*

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INTRODUCTION

Despite being a potent second-generation NNRTI for HIV-1 therapy, Etravirine (ETR) has limited water solubility and poor oral absorption, which pose challenges to its clinical effectiveness. These limitations present challenges for achieving consistent pharmacokinetic profiles and therapeutic outcomes in patients[1].

A range of formulation strategies such as micronization, co-crystallization, inclusion complexation, and solid dispersion have been widely employed to overcome such limitations. Among various solubility enhancement approaches, the use of solid dispersion with hydrophilic carriers such as Povidone K-30 and HPMC 5 cps has been found effective in improving drug dissolution rates[2-6].

Despite existing efforts in the literature, limited studies have specifically explored the comparative evaluation of multiple advanced formulation strategies for Etravirine. Moreover, there is a lack of studies employing statistical design methods such as DoE or RSM to thoroughly assess the joint effects of formulation components

Consequently, this work sought to explore and compare novel formulation strategies for improving the aqueous solubility and in vitro dissolution profile of Etravirine. Special emphasis was placed on employing solid dispersion via spray drying, optimized using a systematic factorial DoE approach to identify significant factors, desirability ranges, and response optimization. The findings aim to bridge current gaps and provide a comprehensive formulation strategy for clinical translation.

MATERIAL AND METHODS FOR SOLUBILITY ENHANCEMENT

MATERIALS:

Etravirine was generous gift sample from Emcure Pharmaceuticals, Pune, India. Povidone was gifted from BASF, Hypromellose is gifted from Shin Etsu, Magnesium Stearate was gifted from Peter Greven, Mannitol was gifted from Roquette, Microcrystalline cellulose is gifted from DuPont, Aerosil 200 is gifted from Evonik, Croscarmellose sodium is gifted from IFF, Crospovidone XL 10 is gifted from Ashland, Isopropyl Alcohol, and Acetone is gifted from Finar.

METHODS:

Preformulation Studies

Identification of Etravirine was performed using FTIR (ATR mode) over the 500–4000 cm^{-1} range, confirmed by UV analysis at 310 nm (see Figure 1, Table 4), with the resulting absorption bands corresponding to those of the

**Author for Correspondence:* Malaykumar.chotaliya@rku.ac.in

standard compound. This identification was further validated through UV analysis at 310 nm [7].

Drug–Excipient Interaction

Fourier-transform infrared (FTIR) spectra of the pure drug and its excipient blends were acquired using a Shimadzu IRAffinity-1S spectrometer (Shimadzu, Carlsbad, CA, USA) in the range of 500–4000 cm^{-1}. Samples were analyzed both before and after one month of accelerated stability testing at 40 °C and 75% relative humidity, to evaluate potential chemical interactions or degradation. Spectral changes, including peak shifts or losses, were assessed for signs of incompatibility (See Figure 5 to 15) [8,9].

Powder Blend Characterization

The flow characteristics of the powder blends were assessed by determining the angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. Each parameter was measured in triplicate, and values were reported as mean ± standard deviation (SD). The funnel method was used to determine tapped density (See Table 6) [10].

X-ray Diffraction (XRD)

X-ray Powder Diffraction (XRD) analysis was performed to determine the physical state of Etravirine in its pure form and within the formulated products. XRD is a widely used technique for identifying crystalline versus amorphous materials based on their diffraction patterns. Pure Etravirine exhibited multiple sharp, intense peaks in the 2θ range of 5° to 40°, confirming its crystalline nature. In contrast, the solid dispersion or formulated tablet showed a diffused halo pattern, indicating a transition to the amorphous form due to the absence of long-range molecular order.

This amorphization is desirable in enhancing solubility and dissolution rate. Stability samples subjected to accelerated climatic conditions (40 °C/75% RH for 3 months) retained the amorphous profile with no recrystallization peaks, demonstrating the physical stability of the formulation over time (See Figure 3 and 4).

Preparation of Solid Dispersions (Liquisolid)

Spray drying serves as a highly efficient method for the fabrication of solid dispersions, enabling the prompt evaporation of solvent and rapid transformation of drug–carrier solutions into solid particulate systems[11-14]. The liquisolid technique is an advanced formulation approach that integrates solid dispersion principles with liquid drug delivery systems, enabling the incorporation of poorly water-soluble drugs into solid dosage forms while enhancing their solubility and dissolution rate[15-17].

In this method, the drug is first dissolved or suspended in a non-volatile solvent with hydrophobic polymer (commonly known as the liquid vehicle), forming a liquid medication or solution. The resulting drug solution is absorbed onto a carrier like microcrystalline cellulose, and coated with a flow-enhancing agent such as colloidal silica to improve processability. The final powder can then be compressed into tablets or filled into capsules.

When applied to solid dispersion, the liquisolid approach allows the drug to be molecularly dispersed in the liquid phase before solidification, potentially converting the drug into an amorphous or solubilized state. This molecular dispersion and increased surface area lead to enhanced wettability, solubilization, and dissolution, thereby improving bioavailability[18-24].

Etravirine was obtained as a pure drug sample. Solubility Enhancing polymer such as Hypromellose and Povidone K-30, were used. Solvents such as Acetone and Purified water were selected as liquid vehicles for the liquisolid technique. All materials and solvents used were of pharmaceutical grade.

There are different type of polymer used for solubility enhancement of Etravirine API in different solvent system. Among them PVP and HPMC grade were selected.

Etravirine and the carrier polymers (HPMC 5 cps or PVP K30) were solubilized in a solvent system comprising acetone and water in varying proportions.

Etravirine and carrier Povidone K-30 or HPMC 5 cps (1:4) was dissolved in Acetone: Water in different ratio as per Table 1. Then evaporate the solvent and precipitate the powder and determine the solubility of different formulation. For Drug and carrier 1:4 ratio finalize and dissolve the API and carrier in different ratio of solvent system.

Also there was a different ratio of Drug: Polymer used for solubility enhancement of Etravirine API (eg. 1:2, 1:3, 1:4) in different ratio of solvent system of Acetone: water (60:40, 70:30,
80:20).

Table 1: Formulation of Solid dispersion of API + Polymer in different ratio

Formula (mg)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Etravirine	100	100	100	100	100	100	100	100	100
HPMC 5 cps	200	200	200	300	300	300	400	400	400
Acetone	8825	10290	11760	11775	13720	15680	14700	17150	19600
Water	5875	4410	2940	7825	5880	3920	9800	7350	4900
Formula (mg)	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Etravirine	100	100	100	100	100	100	100	100	100
Povidone	200	200	200	300	300	300	400	400	400
Acetone	8825	10290	11760	11775	13720	15680	14700	17150	19600
Water	5875	4410	2940	7825	5880	3920	9800	7350	4900

Solubility Studies

For solubility analysis, identical amounts of each solid dispersion formulation were introduced into 10 mL of distilled water and sealed in screw-capped vials. To achieve equilibrium, the vials were subjected to continuous agitation in a water bath shaker maintained at 37 ± 0.5 °C for a period of 24 to 48 hours. After incubation, the samples were filtered through 0.45 µm membrane filters. The filtrates were then analyzed for drug content using a UV-Visible spectrophotometer (set at 310 nm). (Refer Table 5, Figure 16).

Design of Experiments (DoE)

An experimental 2^3 factorial design evaluated the impact of three formulation variables—Croscarmellose sodium, Crospovidone XL 10, and Magnesium Stearate—on tablet performance parameters. These factors were varied according to the experimental matrix, while other excipient quantities remained fixed. The formulation compositions are listed in Table 2. Data analysis and visualization, including response surface and contour plots, were conducted using Design Expert software (Version 13, Stat-Ease, USA) (Refer Table 9 to Table 11) [25-27].

Table 2: Composition (mg) of formulations variables in the 2^3 factorial design

Batch No.	**Formulation Variables (Independent Variables)**		
	% w/w of Croscarmellose Sodium level	**% w/w of Crospovidone XL 10 level**	**% w/w of Magnesium Stearate level**
ETR001	3.3%	7.0%	0.5%
ETR002	5.3%	5.0%	0.3%
ETR003	7.3%	3.0%	0.5%
ETR004	3.3%	3.0%	0.5%
ETR005	7.3%	7.0%	0.1%
ETR006	3.3%	7.0%	0.1%
ETR007	3.3%	3.0%	0.1%
ETR008	5.3%	5.0%	0.3%
ETR009	7.3%	7.0%	0.5%

ETR010	5.3%	5.0%	0.3%
ETR011	7.3%	3.0%	0.1%

Tablet Formulation

Formulations (n=11) were prepared via top-spray granulation, then processed through standard unit operations—sifting, milling, blending, and lubrication—and compressed using an Elizapress EP 200 tablet press. Weighing of the drug, polymers, and other excipients was conducted with a Sartorius Cubis II analytical balance, calibrated and traceable, as per the factorial DoE matrix.

Table 3: Formulation composition of Etravirine tablets

Sr. No.	Ingredients	ETR001	ETR002	ETR003	ETR004	ETR005	ETR006
1	Etravirine	200.00	200.00	200.00	200.00	200.00	200.00
2	HPMC 5 cps	600.00	600.00	600.00	600.00	600.00	600.00
3	Acetone	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
4	Purified Water	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
5	MCC PH 101	523.00	525.50	523.00	583.00	469.00	529.00
6	Aerosil 200	15.00	15.00	15.00	15.00	15.00	15.00
7	CCS (Ac-di-sol)	49.50	80.00	109.50	49.50	109.50	49.50
8	Crospovidone XL 10	105.00	75.00	45.00	45.00	105.00	105.00
9	Magnesium Stearate	7.50	4.50	7.50	7.50	1.50	1.50
Avg. wt. of Tablet		**1500.00**	**1500.00**	**1500.00**	**1500.00**	**1500.00**	**1500.00**

Sr. No.	Ingredients	ETR007	ETR008	ETR009	ETR010	ETR011
1	Etravirine	200.00	200.00	200.00	200.00	200.00
2	HPMC 5 cps	600.00	600.00	600.00	600.00	600.00
3	Acetone	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
4	Purified water	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
5	MCC PH 101	589.00	525.50	463.00	525.50	529.00
6	Aerosil 200	15.00	15.00	15.00	15.00	15.00
7	CCS (Ac-di-sol)	49.50	80.00	109.50	80.00	109.50
8	Crospovidone XL 10	45.00	75.00	105.00	75.00	45.00
9	Magnesium Stearate	1.50	4.50	7.50	4.50	1.50
Avg. wt. of Tablet		**1500.00**	**1500.00**	**1500.00**	**1500.00**	**1500.00**

Post-compression Quality Evaluation

Friability Test

Tablet friability was evaluated according to the guidelines outlined in USP <1216> to assess the mechanical strength and resistance of tablets to abrasion and shock. From each formulation batch, ten tablets were randomly selected, carefully cleaned to remove any dust, and accurately weighed using a calibrated analytical balance (Sartorius Cubis II, Germany).

The weighed tablets were then placed into a friabilator (Electrolab EF-2L, Electrolab Pvt. Ltd., Mumbai, India) and subjected to 100 revolutions at a speed of 25 rpm for a total duration of 4 minutes. Upon completion of the test cycle, the tablets were removed, dedusted again to eliminate any detached particles, and reweighed:

$F\% = (W_1 - W_2) / W_1 * 100$

Where F, W_1, and W_2 represent percentage weight loss, initial weight, and final weight, respectively.

Tablet thickness and diameter

The thickness and diameter of ten tablets, randomly chosen from each formulation, were measured using a digital Vernier caliper (Mitutoyo, Japan). Each measurement was performed in triplicate, and the results were reported as the Mean ± SD. Dimensional uniformity was considered acceptable if individual measurements fell within ±5% of the average.

Crushing strength

Tablet hardness, an indicator of mechanical robustness, was measured for ten randomly chosen units using the Electrolab EH-01 hardness tester. The data were used to assess compliance with mechanical strength specifications outlined in USP <1217>.

Uniformity of weight test

Tablet weight uniformity was evaluated by individually weighing twenty tablets randomly drawn from each batch. The mean weight and standard deviation were calculated, and compliance was determined per pharmacopeial standards: ≤2 tablets deviating >5% and none >10% from the mean.

Dissolution and Drug Release Studies

A primary stock solution of Etravirine (1000 µg/mL) was prepared by dissolving 100 mg of the drug in an appropriate diluent and diluting to 100 mL following sonication. Serial dilutions were then performed to obtain calibration standards in the concentration range of 2–6 µg/mL. The absorbance of each standard was measured at 310 nm using a Genesys 10 UV-Visible spectrophotometer (Thermo Fisher Scientific, UK). All samples were analysed in triplicate, and the results were reported as mean absorbance values ± standard deviation.

A linearity graph of the average absorbance of Etravirine against the concentration in ppm is plotted and is found to be a straight-line graph.

Drug release profiles

Dissolution testing of Etravirine tablets was performed using USP Apparatus II (paddle method) in 1800 mL of 1% SLS in 0.01 M HCl at 37 ± 0.5 °C and 50 rpm (Electrolab Pvt. Ltd., Mumbai, India). UV absorbance was measured at 310 nm, and results were reported as mean ± SD (n = 3). (Refer Table 12, Figure 23).

Standard Preparation

An accurately weighed amount of 100 mg of Etravirine reference standard was transferred into a 100 mL volumetric flask containing 25 mL of ethanol. The mixture was sonicated for approximately 5 minutes to ensure complete dissolution, and the volume was then brought up to the mark with ethanol to obtain the primary standard solution. From this solution, 10 mL was pipetted into a separate 100 mL volumetric flask and diluted to volume with ethanol to prepare the working standard solution.

Sample Preparation

Ten Etravirine tablets were weighed and crushed to a fine, uniform powder using a mortar and pestle. A quantity equivalent to 100 mg of Etravirine was accurately measured and transferred into a 100 mL volumetric flask containing 25 mL of ethanol. The mixture was sonicated for 5 minutes to ensure complete dissolution within 15 minutes. Subsequently, a 10 mL aliquot of the supernatant was taken and diluted to 100 mL with ethanol to obtain the final sample solution for analysis.

Formulation Optimization

Formulation optimization was carried out using a numerical optimization algorithm available in the Design-Expert® software, with the aim of achieving the target dissolution profile. The concentrations of the independent formulation variables were restricted within the predefined limits of the experimental design space. The formulation exhibiting the highest desirability value, as recommended by the software, was selected. This optimized composition was then used to prepare the final formulation in triplicate. The results of the stability study conducted on the optimized batch are summarized in Table 13.

RESULTS

Identification of Etravirine

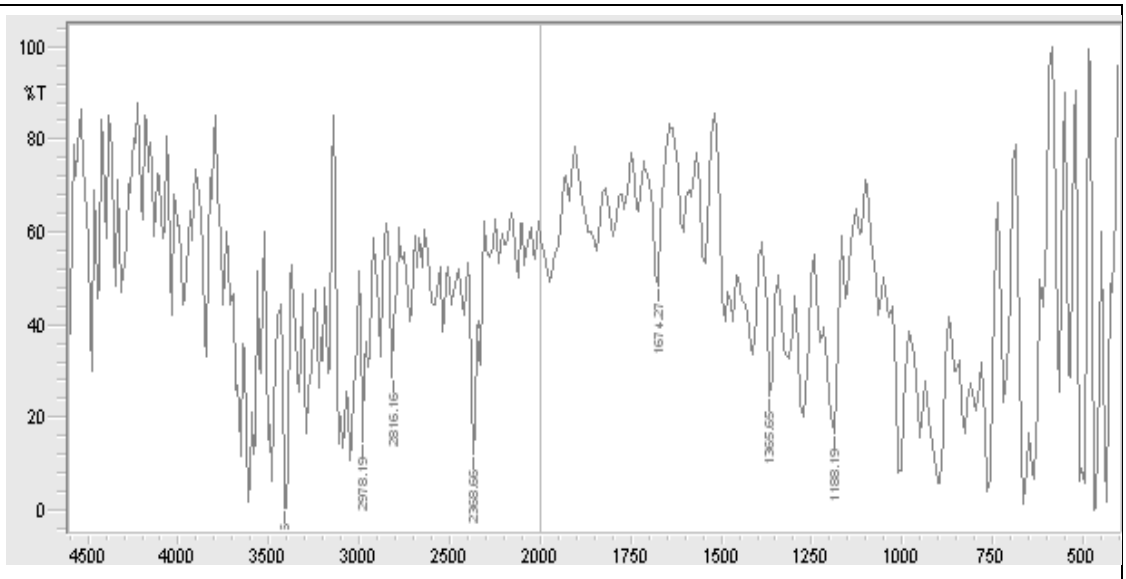

Figure 1: FTIR Spectra of Etravirine API in crystalline form

Table 4: Characteristic peaks of Etravirine API

Sr. No.	Peak observed	Characteristics
1	3410.26 cm^{-1}	Aromatic primary amine stretching
2	2368.86 cm^{-1}	Nitrile
3	2978.19 cm^{-1}	Aromatic C-H Stretching
4	650 cm^{-1}	C-Br
5	1365.65 cm^{-1}	Primary and Tertiary amine
6	1188.19 cm^{-1}	Ether C-O-C stretching

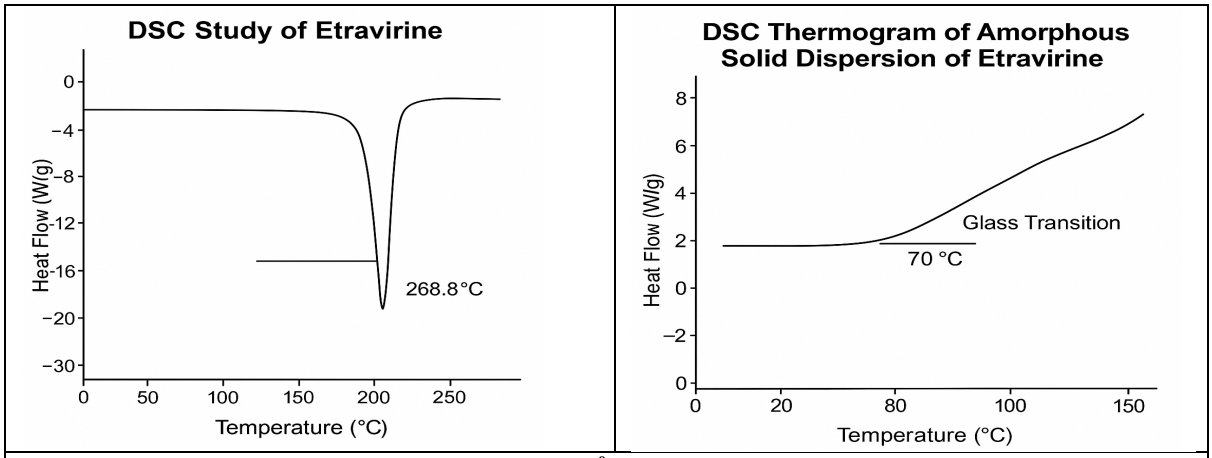

Figure 2: DSC thermogram of Etravirine (268.8^0 C) and Amorphous solid dispersion (Formula 9)

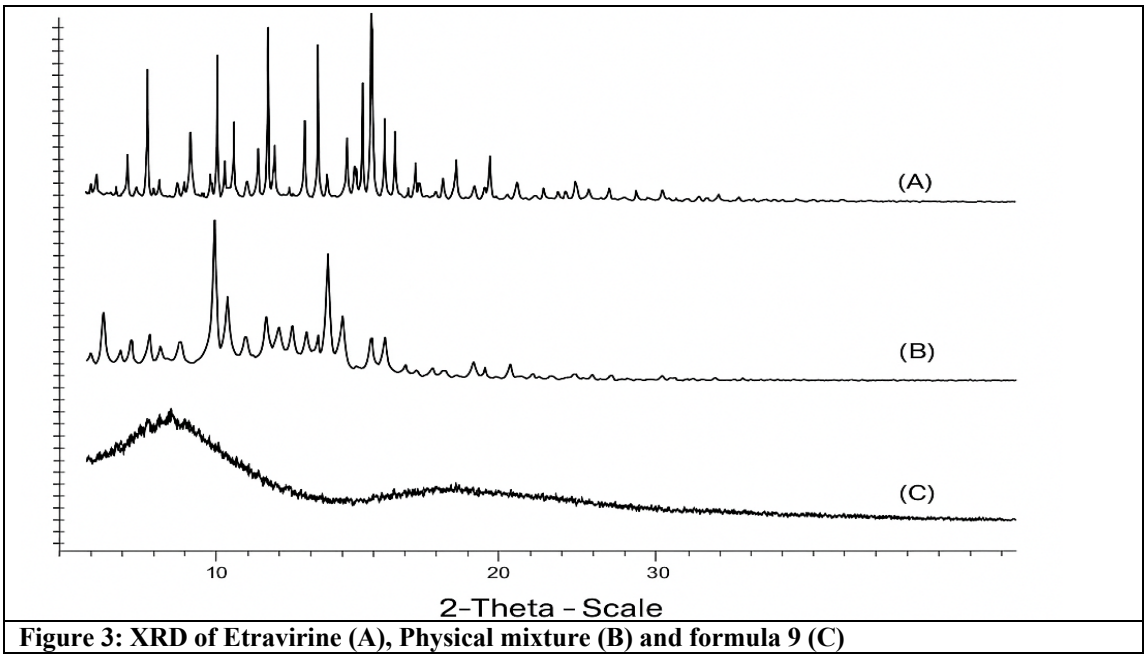

Figure 3: XRD of Etravirine (A), Physical mixture (B) and formula 9 (C)

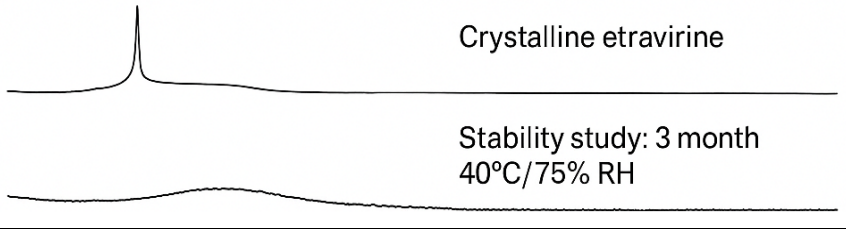

Figure 4: XRD of Etravirine API and 3 month stability sample of Etravirine tablet formulation (ETR002)

Preformulation Compatibility Studies

No indications of physicochemical interactions were observed in the FTIR spectra of the drug–excipient mixtures following accelerated stability testing at 40 °C / 75% RH. All the characteristic absorption bands present in the spectrum of the pure active pharmaceutical ingredient (API) were also clearly visible in the corresponding spectra of the binary mixtures, indicating the preservation of functional groups and compatibility between Etravirine and the excipients.

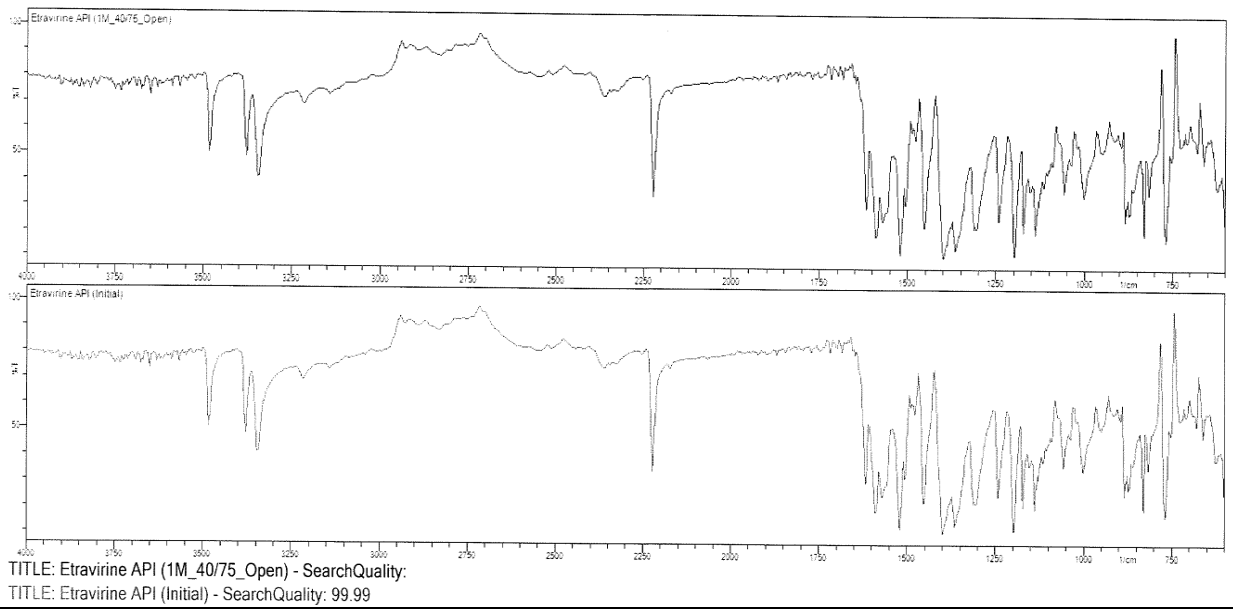

Figure 5: FTIR Spectra of Etravirine API

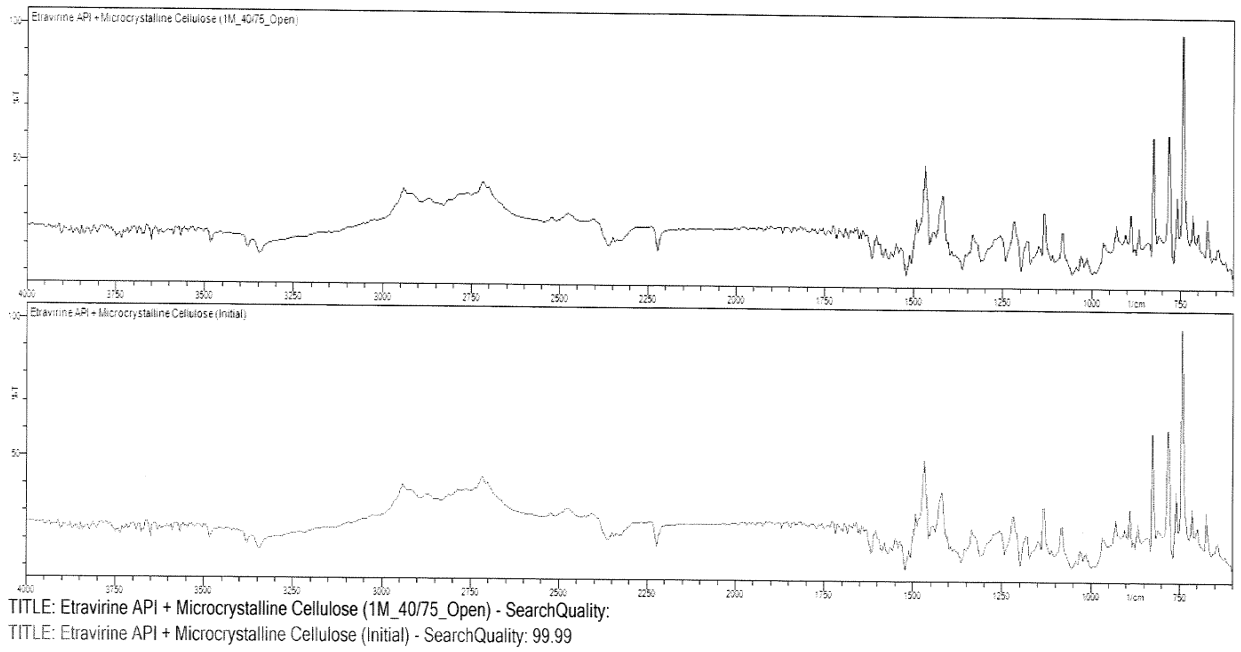

Figure 6: FTIR Spectra of Etravirine API + Microcrystalline cellulose

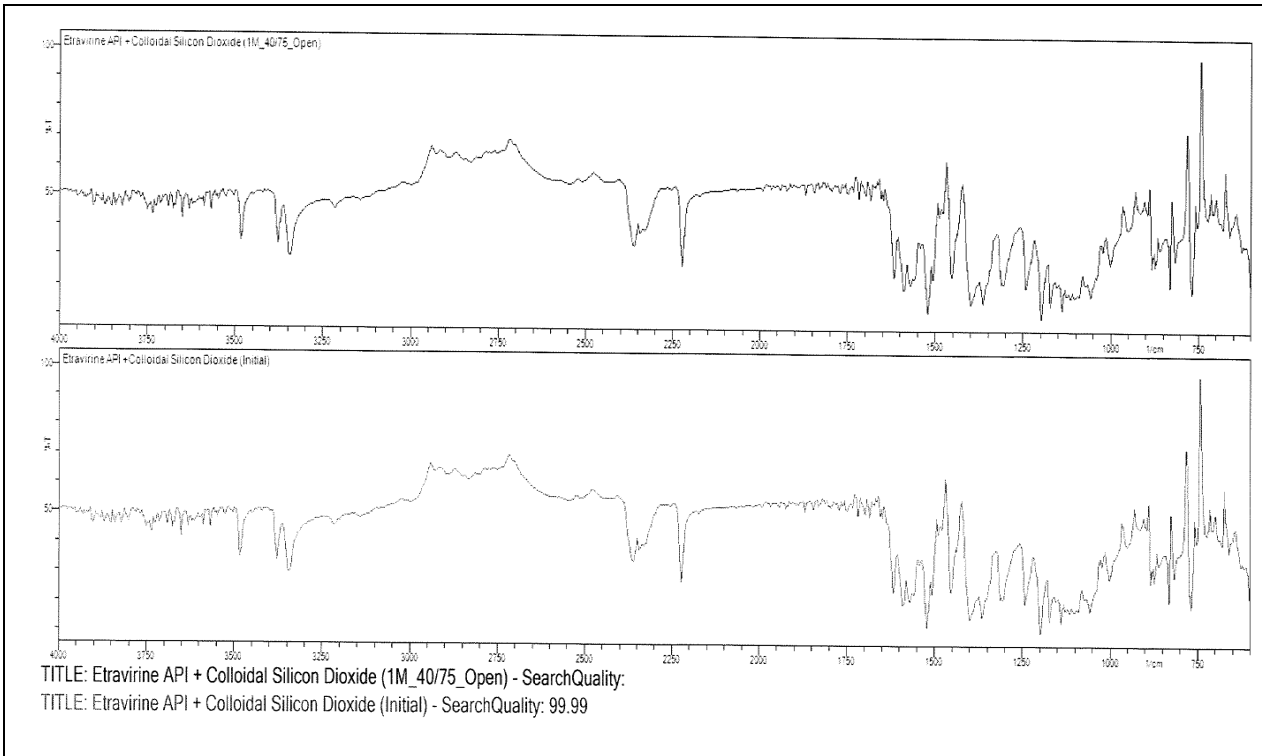

Figure 7: FTIR Spectra of Etravirine API + Colloidal Silicon Dioxide

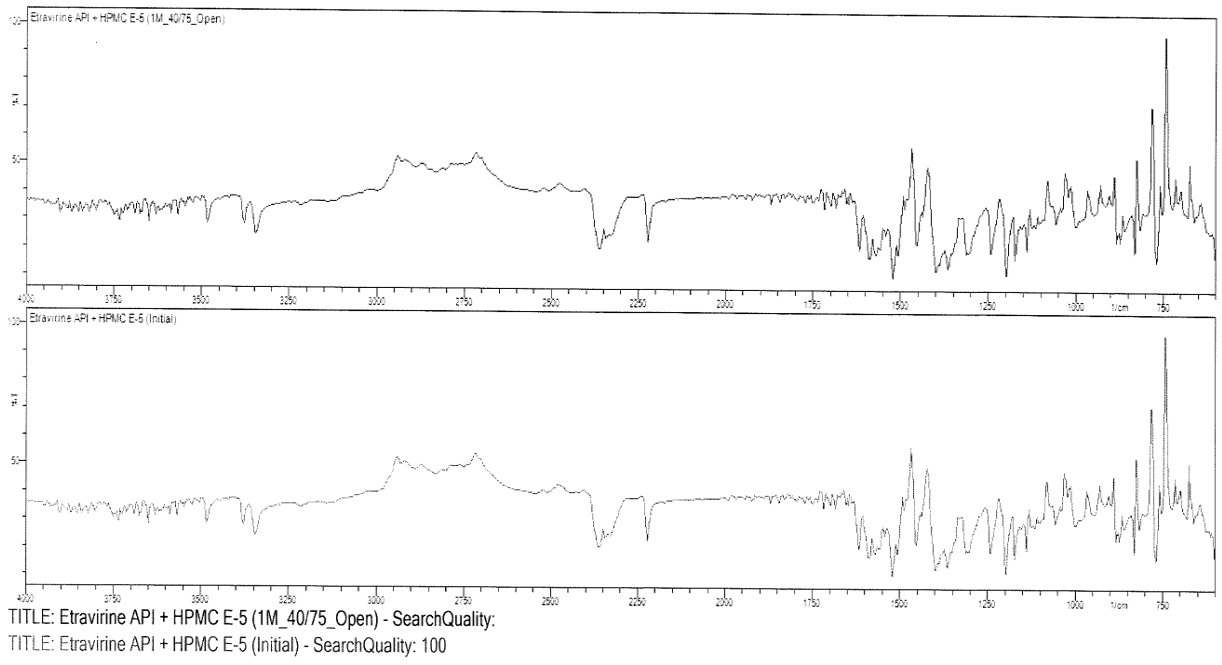

Figure 8: FTIR Spectra of Etravirine API + HPMC 5 cps

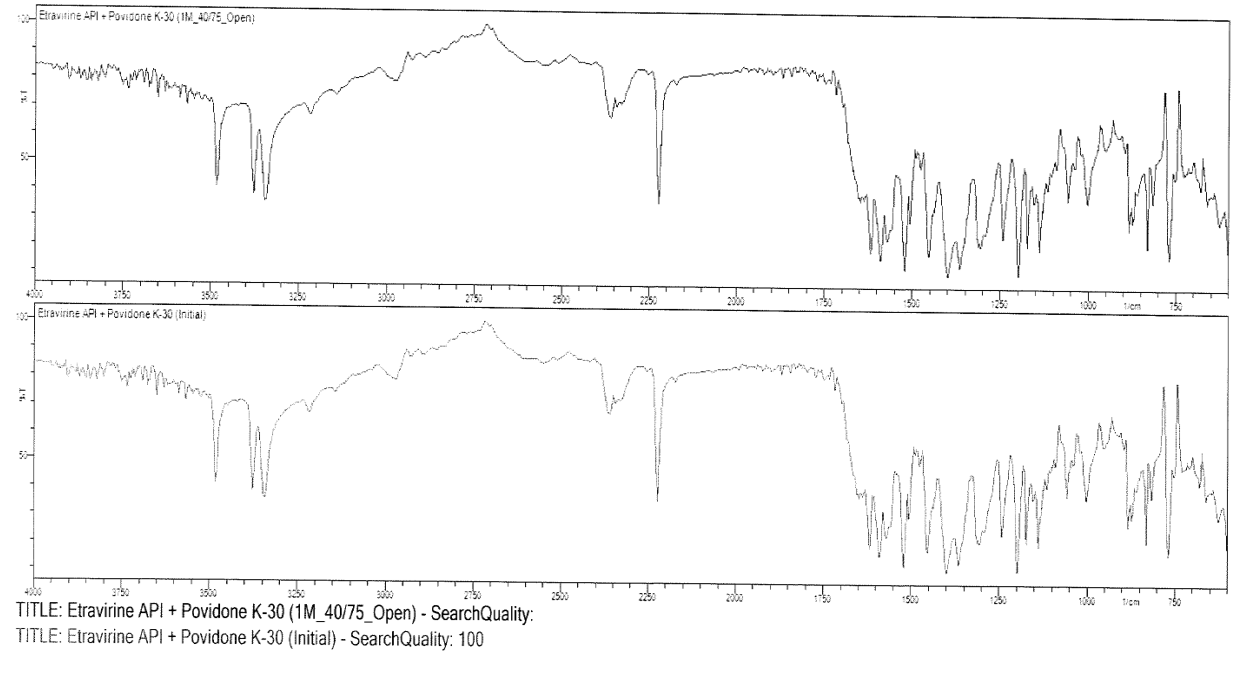

Figure 9: FTIR Spectra of Etravirine + Povidone K-30

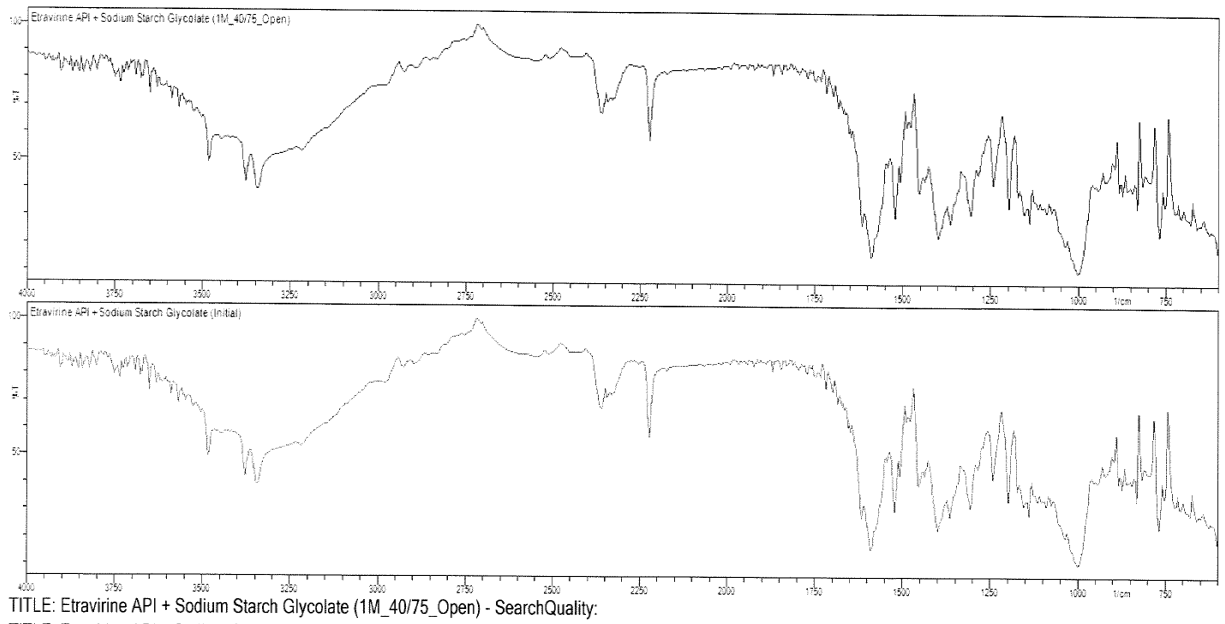

Figure 10: FTIR Spectra of Etravirine API + Sodium Starch Glycolate

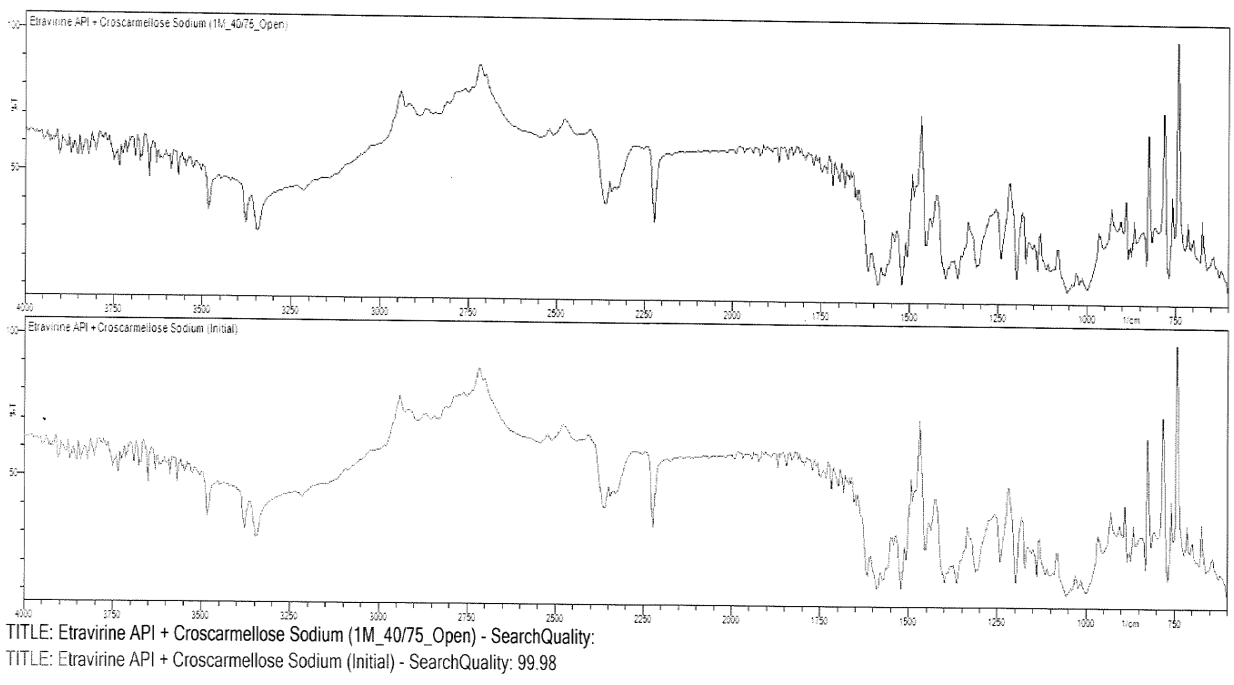

Figure 11: FTIR Spectra of Etravirine API + Croscarmellose Sodium

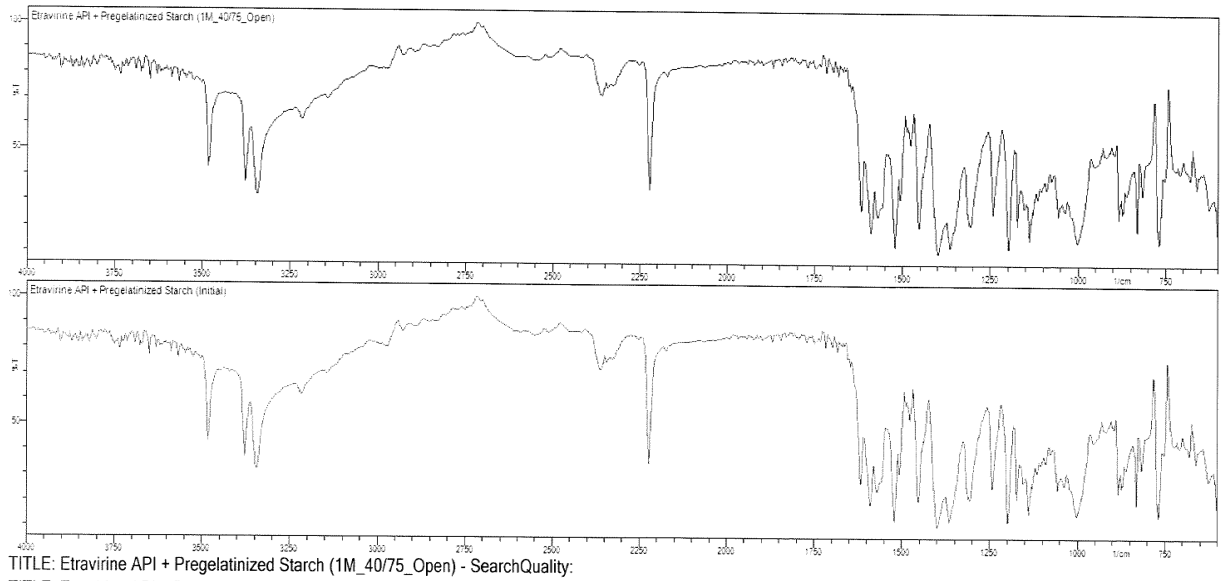

Figure 12: FTIR Spectra of Etravirine API + Pregelatinized Starch

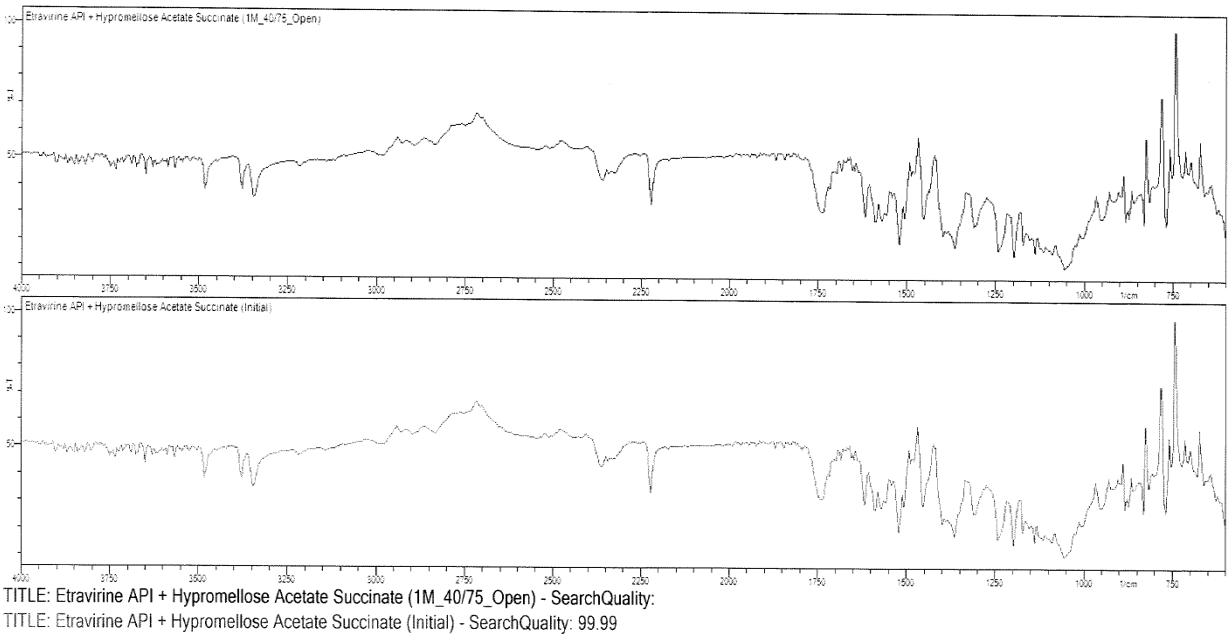

Figure 13: FTIR Spectra of Etravirine API + HPMC Acetate Succinate

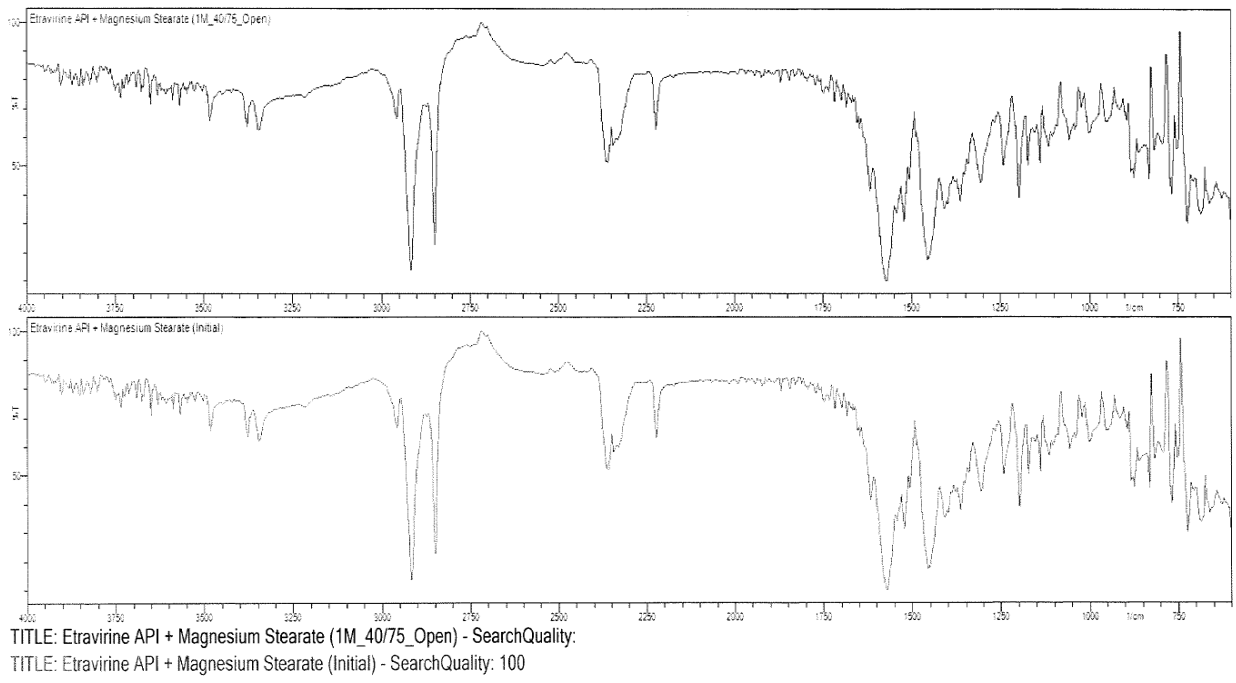

Figure 14: FTIR Spectra of Etravirine API + Magnesium Stearate

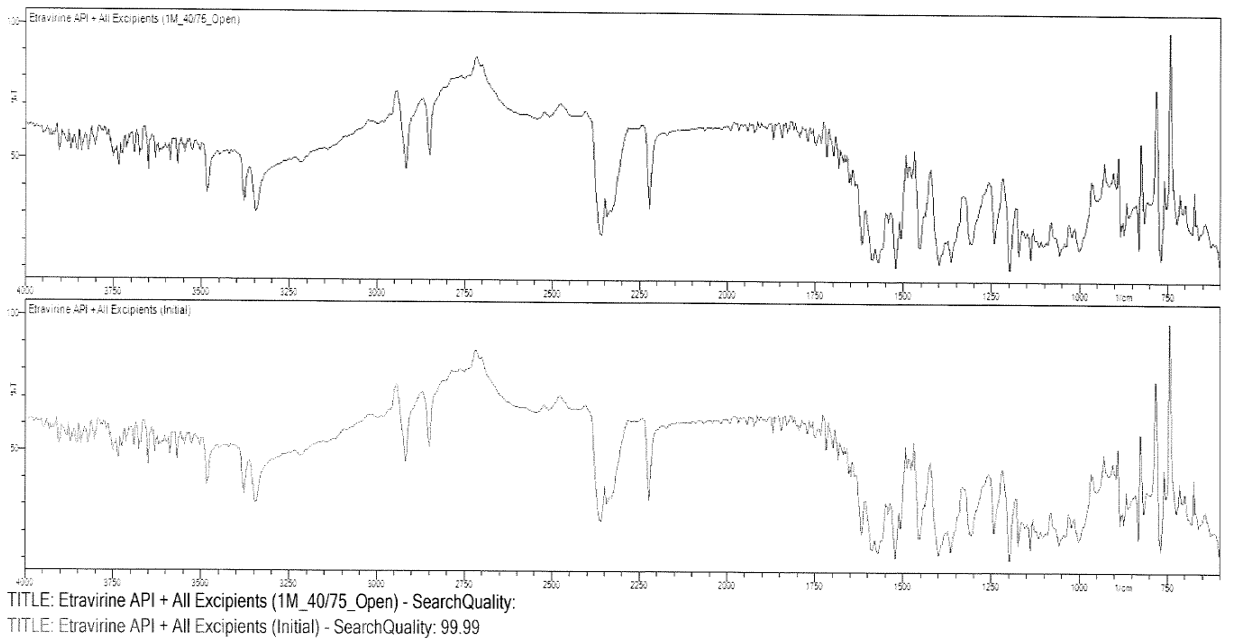

Figure 15: FTIR Spectra Etravirine API + All Excipients of Final Formulation

Solubility of Etravirine API:

Table 5: Solubility in water for different trials

Sr. No.	Formulation	Solubility in water (mg/ml)*	% RSD
1	Formula 1	0.129 ± 0.01	5.88
2	Formula 2	0.268 ± 0.02	7.12
3	Formula 3	0.294 ± 0.00	1.53
4	Formula 4	0.158 ± 0.01	3.86
5	Formula 5	0.320 ± 0.02	6.23
6	Formula 6	0.298 ± 0.01	3.53

7	Formula 7	0.212 ± 0.01	5.89
8	Formula 8	0.388 ± 0.01	2.97
9	Formula 9	0.409 ± 0.01	2.69
10	Formula 10	0.133 ± 0.01	9.01
11	Formula 11	0.173 ± 0.00	2.89
12	Formula 12	0.176 ± 0.01	8.18
13	Formula 13	0.148 ± 0.01	4.88
14	Formula 14	0.189 ± 0.00	0.53
15	Formula 15	0.191 ± 0.01	3.06
16	Formula 16	0.139 ± 0.01	5.41
17	Formula 17	0.201 ± 0.02	9.74
18	Formula 18	0.216 ± 0.02	8.02
*Means ± SD, n = 3			

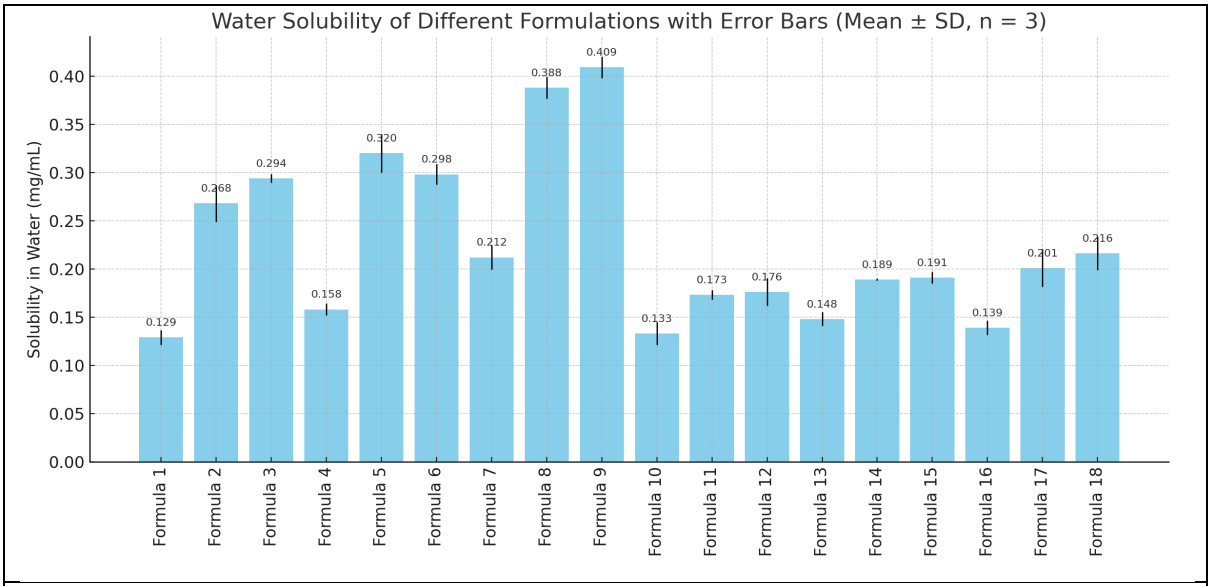

Figure 16: Solubility of Different Formula in Purified water

Table 6: Characterisation of powder blend (Optimized Formulation)

Notably, Formula 9 achieved 0.409 mg/mL solubility, representing a ~3.4-fold increase compared to pure drug (0.12 mg/mL).

Batch No.	**ETR002**
Bulk Density	0.450
Tapped Density	0.535
Carr's Index	15.888
Hausner's Ratio	1.189

Statistical analysis

Design-Expert software was used to analyse the experimental data statistically. The data were evaluated to determine the best-fit model describing the correlation between independent factors and response variables, based on parameters like R^2 and p-value.

Contour plots and response surface graphs illustrating the effects of formulation variables on the response parameters are depicted in Figures 17 through 20.

Table 7: Physical Parameters

Batch No.	**Average weight of 10 tablets (mg)**	**Thickness (mm) (Average of 10 Tablets)**	**Hardness (kP) (Average of 10 tablets)**	**% Friability**
ETR001	1504.63±1.89	7.43±0.02	25.12±1.92	0.12±0.01
ETR002	1498.45±2.30	7.46±0.03	23.48±1.80	0.20±0.02

ETR003	1502.12±1.68	7.45±0.02	24.44±2.32	0.18±0.02
ETR004	1502.90±2.33	7.45±0.02	25.63±1.44	0.14±0.01
ETR005	1500.35±3.21	7.49±0.01	26.40±2.30	0.15±0.02
ETR006	1498.68±2.44	7.43±0.03	23.56±1.98	0.14±0.01
ETR007	1507.32±1.90	7.48±0.02	24.44±3.20	0.21±0.03
ETR008	1493.55±2.80	7.44±0.02	25.90±2.87	0.09±0.01
ETR009	1502.78±3.20	7.42±0.03	24.68±2.76	0.14±0.02
ETR010	1505.24±2.10	7.50±0.03	23.78±1.90	0.16±0.02
ETR011	1495.60±1.88	7.48±0.01	24.40±2.34	0.20±0.02

Table 8: Optimization of Formulation variables & Response

Batch No.	Formulation Variables (Independent Variables)			Responses (Dependent Variables)		
	% w/w of Crosscarmellose Sodium level	% w/w of Crospovidone XL 10 level	% w/w of Magnesium Stearate level	% Assay	Disintegration Time (sec.)	% Dissolution at 90 min.
ETR001	3.3%	7.0%	0.5%	99.1%	180 sec.	89%
ETR002	5.3%	5.0%	0.3%	99.6%	150 sec.	93%
ETR003	7.3%	3.0%	0.5%	101.4%	160 sec.	91%
ETR004	3.3%	3.0%	0.5%	98.5%	465 sec.	79%
ETR005	7.3%	7.0%	0.1%	100.2%	100 sec.	98%
ETR006	3.3%	7.0%	0.1%	97.8%	225 sec.	87%
ETR007	3.3%	3.0%	0.1%	100.6%	420 sec.	82%
ETR008	5.3%	5.0%	0.3%	98.9%	140 sec.	94%
ETR009	7.3%	7.0%	0.5%	99.9%	115 sec.	96%
ETR010	5.3%	5.0%	0.3%	100.1%	170 sec.	92%
ETR011	7.3%	3.0%	0.1%	98.0%	180 sec.	96%

Table 9: ANOVA for selected factorial model Response 1: Assay

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	10.68	5	2.14	5.90	0.0369	significant
A-Croscarmellose Sodium	1.53	1	1.53	4.23	0.0948	
B-Crospovidone XL 10	0.2812	1	0.2812	0.7773	0.4183	
C-Magnesium Stearate	0.6613	1	0.6613	1.83	0.2344	
AC	1.90	1	1.90	5.25	0.0705	
ABC	6.30	1	6.30	17.41	0.0087	
Residual	1.81	5	0.3618			
Lack of Fit	1.08	3	0.3608	0.9932	0.5372	not significant
Pure Error	0.7267	2	0.3633			
Cor Total	12.49	10				

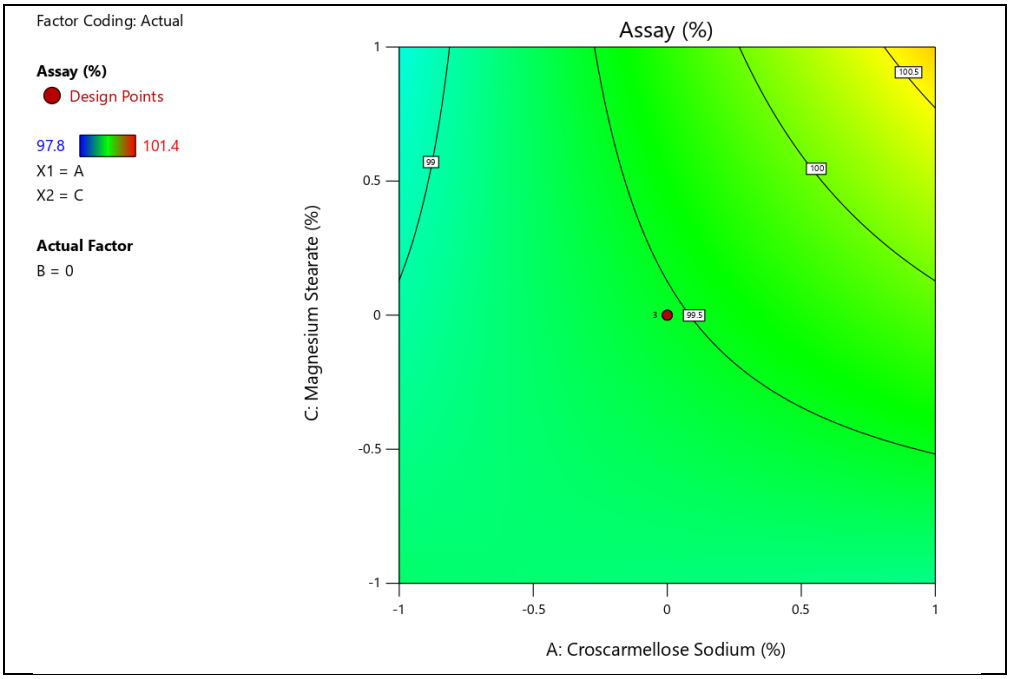

Figure 17: Contour Plot for factorial model Response 1: Assay

Table 10: ANOVA for selected factorial model Response 2: % Dissolution

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	331.00	6	55.17	8.64	0.0279	significant
A-Croscarmellose Sodium	242.00	1	242.00	37.89	0.0035	
B-Crospovidone XL 10	60.50	1	60.50	9.47	0.0370	
C-Magnesium Stearate	8.00	1	8.00	1.25	0.3257	
AB	8.00	1	8.00	1.25	0.3257	
AC	4.50	1	4.50	0.7046	0.4485	
BC	8.00	1	8.00	1.25	0.3257	
Residual	25.55	4	6.39			
Lack of Fit	23.55	2	11.77	11.77	0.0783	not significant
Pure Error	2.00	2	1.0000			
Cor Total	356.55	10				

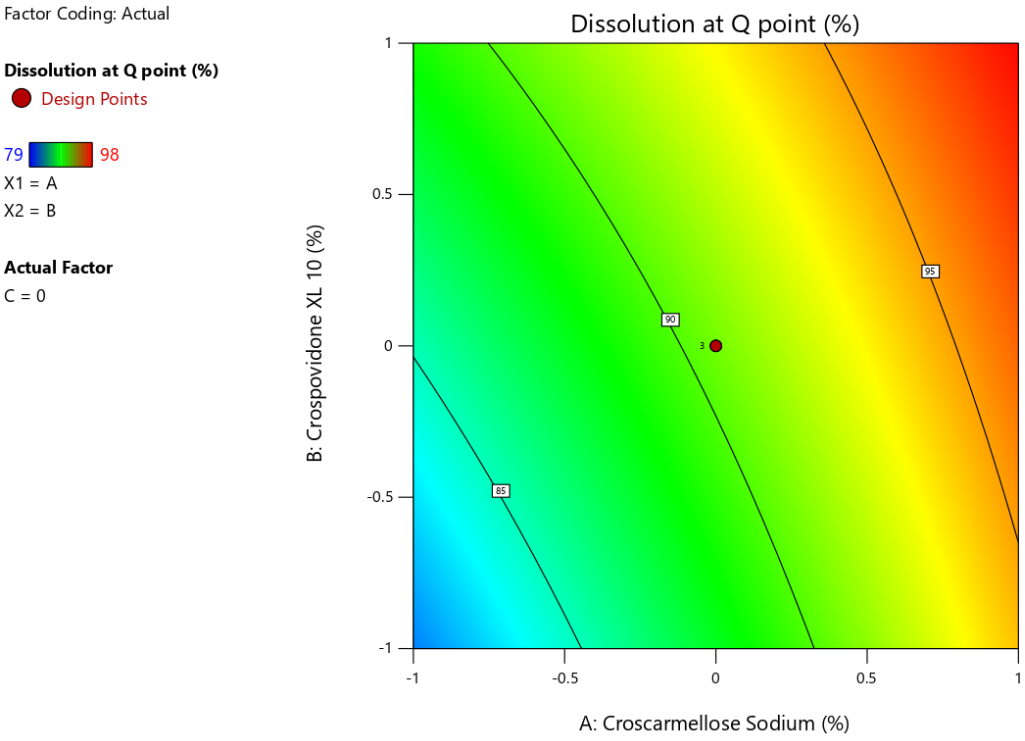

Figure 18: Contour Plot for factorial model Response 2: % Dissolution

Table 11: ANOVA for selected factorial model Response 3: Tablet Disintegration Time

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1.290E+05	5	25808.13	8.15	0.0190	significant
A-Croscarmellose Sodium	67528.12	1	67528.12	21.33	0.0057	
B-Crospovidone XL 10	45753.12	1	45753.12	14.45	0.0126	
C-Magnesium Stearate	3.13	1	3.13	0.0010	0.9762	
AB	15753.13	1	15753.13	4.98	0.0761	
AC	3.13	1	3.13	0.0010	0.9762	
Residual	15832.10	5	3166.42			
Lack of Fit	15365.44	3	5121.81	21.95	0.0439	significant
Pure Error	466.67	2	233.33			
Cor Total	1.449E+05	10				

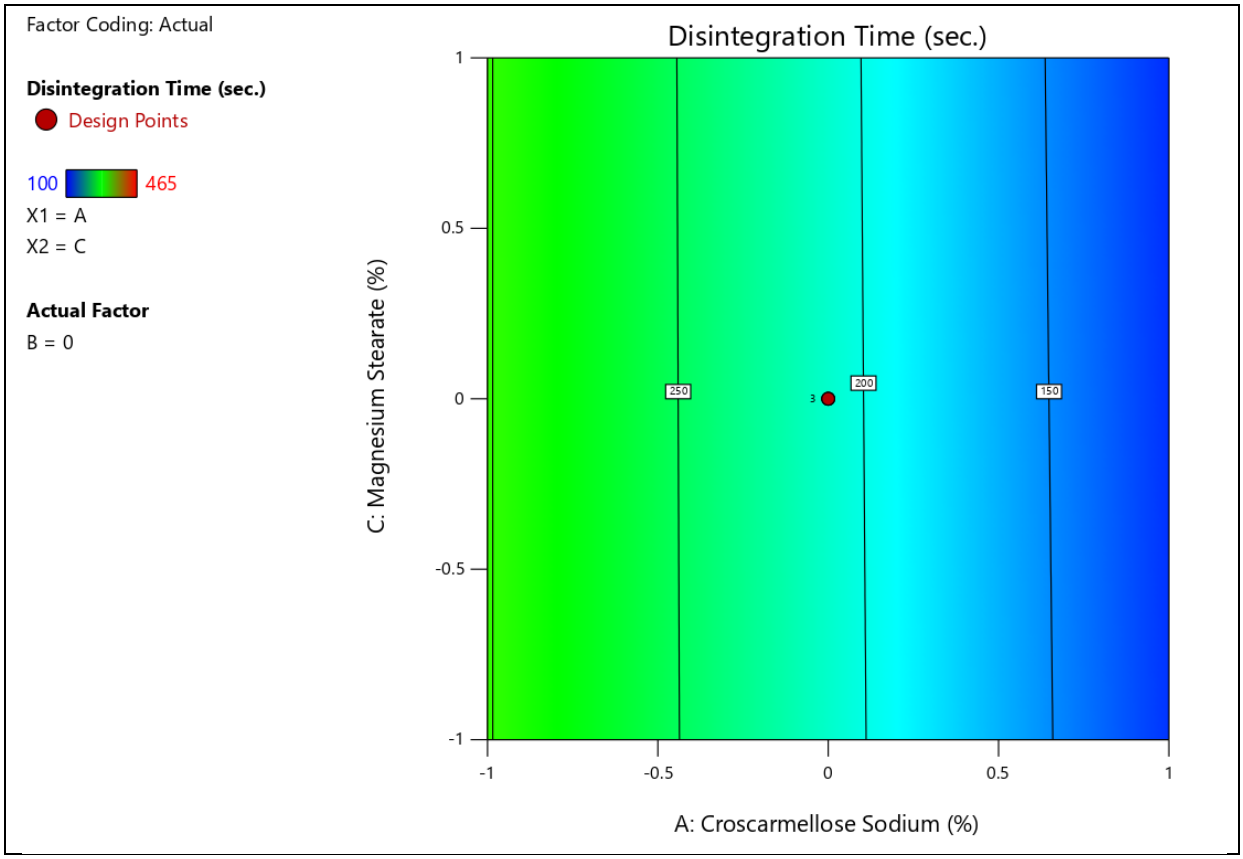

Figure 19: Contour Plot for factorial model Response 3: Disintegration Time

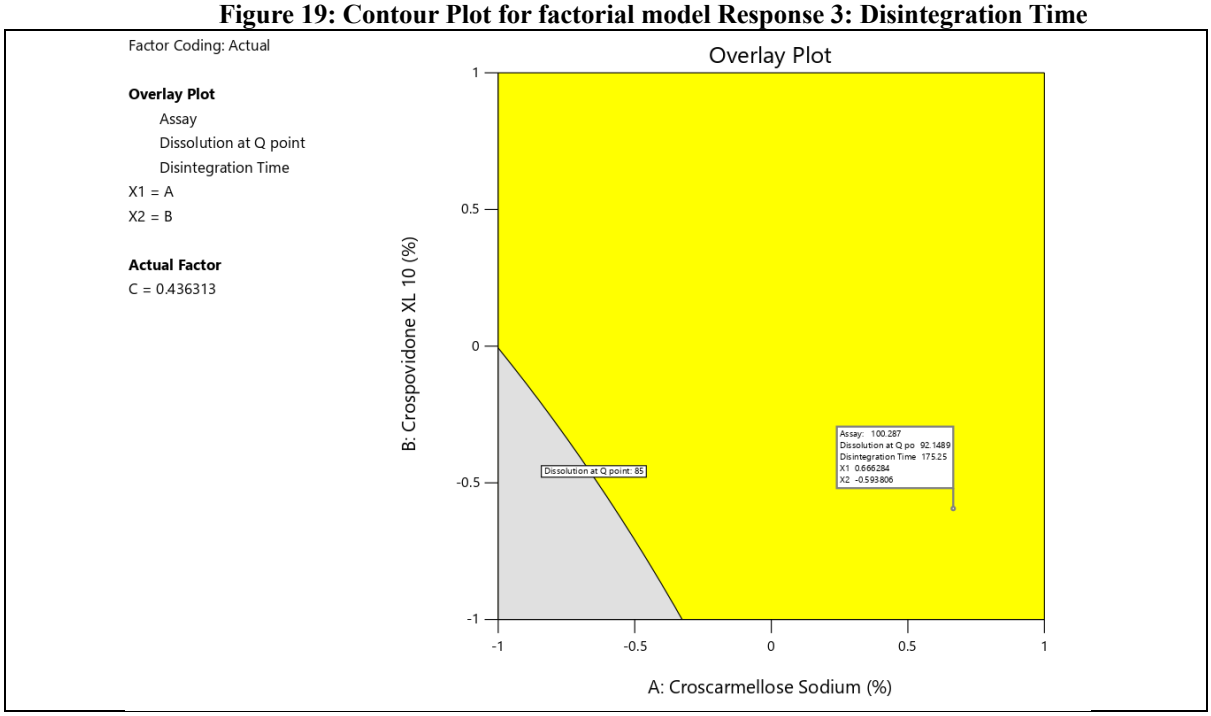

Figure 20: Overlay Plot for factorial design

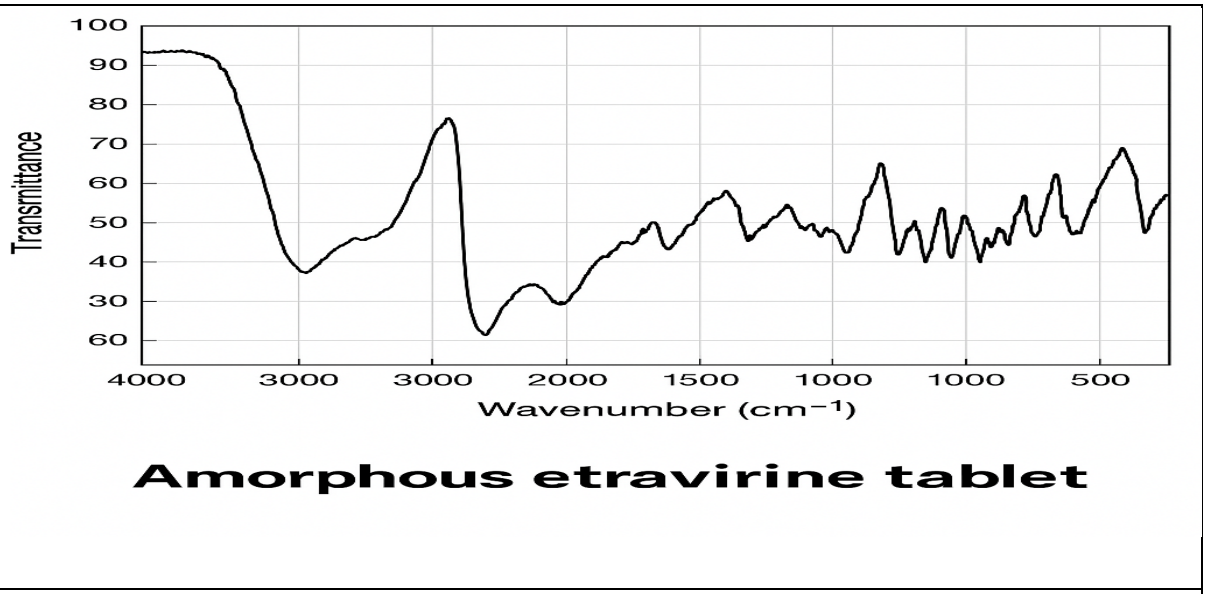

Figure 21: FTIR spectra of Amorphous Etravirine Tablet formulation (ETR002)

Formulation optimization

Comparative Dissolution Profile of Reference product (**INTELENCE 200 mg; Mfg. by: Janssen Cilag S.p.A., Latina, IT**) and Test Product (Formulation 2, Batch No. ETR002) performed as per OGD recommendation media.

Reference Product | **Test Product (ETR002)**

Figure 22: Images of Reference and Test Product

Table 12: % Drug release of Reference and Test Product of Etravirine in OGD recommendation media

Time (min.)	Reference Product (INTELENCE 200 mg)	Test Product 200 mg (ETR002)
0	0	0
15	40.75±2.14	38.68±3.18
30	49.48±2.31	52.20±3.45
45	66.81±1.91	69.56±4.78
60	75.34±1.72	81.44±3.24
90	95.12±1.10	93.45±2.60
120	98.32±0.75	96.44±2.10
F2	**75**	

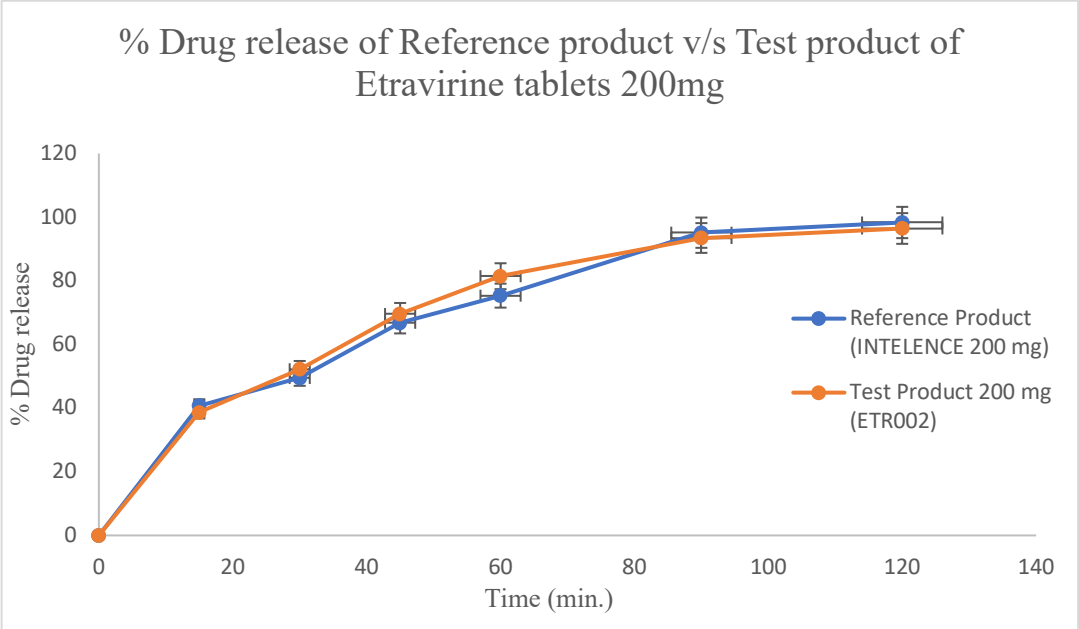

Figure 23: Comparative drug release profiles of optimized Etravirine formulation (ETR002) vs. marketed product (Intelence®).

Statistical analysis (t-test, $p < 0.05$) indicated no significant difference between the optimized formulation (ETR002) and the marketed reference (Intelence®), supporting bioequivalence in vitro.

Table 13: Stability Study Data (Optimize Formulation ETR002)

	Description	Assay (%)	% Drug Dissolution at 90 min.	Disintegration Time (sec.)
Initial	*	99.60±1.20	93.45 ± 2.60	150 ± 3.42
1 Month (40^0 C/75% RH)	*	98.68±0.75	91.55 ± 2.18	168 ± 3.78
3 Month (40^0 C/75% RH)	*	99.14±1.10	92.46 ± 1.88	180 ± 4.80
3 Month (25^0 C/60% RH)	*	99.85±0.84	95.72 ± 3.38	155± 7.42

*Off white capsule shape uncoated tablet debossed with "EM" on one side and "140" on other side

DISCUSSION

The FTIR analysis of the API revealed spectral features that closely aligned with those of the reference standard and the official Etravirine spectrum, indicating that the active ingredient conforms to the established physicochemical profile of Etravirine.

Mechanistically, HPMC 5 cps likely enhanced solubility due to its low viscosity, hydrogen bonding capacity, and improved wettability compared to PVP K30, which forms more viscous dispersions that can hinder drug release. These findings align with prior reports on HPMC-based solid dispersions improving dissolution of poorly soluble antivirals.

DSC is a critical tool in confirming the crystalline to amorphous conversion of Etravirine, its compatibility with carriers, and its thermal stability during formulation and storage. Amorphization confirmed by DSC supports enhanced solubility and bioavailability in solid dispersions or other advanced formulations.

The disappearance of distinct peaks in the XRD spectra of the solid dispersion suggested a transition from crystalline to amorphous state." The XRD pattern of the physical mixture shows a noticeable reduction in the number and intensity of peaks, suggesting a partial loss of crystallinity. In contrast, the optimized formulation ETR006 exhibited a complete absence of characteristic diffraction peaks, confirming its amorphous nature (Fig. 10). The enhancement in the drug's dissolution rate can be attributed to the significant reduction in crystallinity, which in turn improves solubility and consequently enhances bioavailability.

The XRD spectrum of pure Etravirine displayed multiple sharp peaks indicating its crystalline nature, with characteristic 2θ values at approximately 10.5°, 14.1°, and 21.6°. In contrast, the spray-dried solid dispersion exhibited a broad halo with no distinguishable peaks, confirming the

conversion of the drug into its amorphous form. The 3-month stability sample stored at 40°C/75% RH retained the amorphous profile, indicating good physical stability of the formulation."

The preferred attributes of Etravirine formulations included, with over 85% of the drug being released within approximately 90 minutes. The highest desirability was observed through analysis of the various dependent variables on Design-Expert, which aligned with a formulation similar to that of F2. This desirability index was regarded as satisfactory to direct the attainment of the desired product specifications. Consequently, this formulation was identified as the optimized batch that would targeted the ideal pharmacokinetic parameters.

Limitations: This study is restricted to in vitro evaluations. Further in vivo pharmacokinetic and scale-up studies are essential to confirm clinical translation.

CONCLUSION

Etravirine tablets were successfully formulated and optimized using a 2^3 factorial design. The optimized batch (ETR002) showed >93% drug release in 90 minutes with good stability over 3 months, meeting pharmacopeial quality standards. Compared to conventional spray drying methods using carcinogenic MDC, the present aqueous top-spray granulation process is safer, simpler, and more scalable. These findings highlight the industrial significance of this approach for developing robust formulations of poorly soluble drugs. Future work should include in vivo pharmacokinetic studies and bioequivalence testing to confirm clinical relevance.

The 2^3 factorial design conducted using Design Expert® successfully identified the significant factors and their interactions influencing the selected response variable(s). Statistical analysis confirmed the adequacy of the model, as indicated by a high coefficient of determination (R^2), significant p-values ($p < 0.05$), and non-significant lack of fit ($p > 0.05$), demonstrating a good fit between the experimental data and the model predictions.

The model optimization suggested an ideal set of parameters within the design space to achieve the desired formulation. These results confirm that the factorial design approach is effective in systematically evaluating and optimizing formulation parameters.

The optimized formulation was effectively developed into a stable tablet dosage form using suitable excipients. The final tablets met all pharmacopeial standards for weight variation, hardness, friability, disintegration time, and dissolution rate.

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