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FORMULATION AND EVALUATION OF EFAVIRENZ NANOSUSPENSION FOR ENHANCED ORAL BIOAVAILABILITY

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ABSTRACT

Efavirenz is a poorly water-soluble antiretroviral drug belonging to Biopharmaceutical Classification System Class II, exhibiting limited dissolution and variable oral bioavailability. The objective of the present study was to formulate and evaluate efavirenz nanosuspension to enhance dissolution rate and improve oral bioavailability. Nanosuspensions were prepared by nanoprecipitation technique using Hydroxypropyl Methylcellulose (HPMC E15) as stabilizer and Sodium Lauryl Sulphate (SLS) as surfactant. A 2^2 factorial design was employed to optimize formulation parameters by considering polymer concentration and surfactant concentration as independent variables, while particle size, zeta potential, and drug release were selected as dependent responses. The prepared nanosuspensions were evaluated for particle size distribution, zeta potential, and in vitro drug release. The optimized formulation exhibited reduced particle size, satisfactory stability, and enhanced drug release when compared to pure drug suspension. The study concludes that nanosuspension technology is a promising strategy for improving the oral bioavailability of poorly soluble drugs such as efavirenz.[11]

KEYWORDS: Efavirenz, Nanosuspension, Nanoprecipitation, Oral bioavailability, HPMC E15, SLS.

1. INTRODUCTION

Bioavailability is defined as the rate and extent to which the active pharmaceutical ingredient reaches systemic circulation and becomes available at the site of action. Poor aqueous solubility is one of the major obstacles in oral drug delivery, especially for Biopharmaceutical Classification System Class II drugs, where dissolution is the rate-limiting step in absorption.[1,2]

Several techniques have been employed to improve the dissolution and bioavailability of poorly soluble drugs, such as micronization, solid dispersions, complexation, and lipid-based systems. Among these approaches, nanosuspension technology has gained considerable attention due to its ability to enhance dissolution by reducing particle size to the nanometer range.[3,4]

Efavirenz is a non-nucleoside reverse transcriptase inhibitor used in the management of HIV infections. However, its poor aqueous solubility limits its oral bioavailability. Therefore, formulation of efavirenz as nanosuspension may improve its dissolution behavior and therapeutic effectiveness.[1,2]

2. MATERIALS AND METHODS

2.1 Materials

Efavirenz was procured from Strides Arc Lab, Bengaluru. Hydroxypropyl Methylcellulose (HPMC E15), Sodium Lauryl Sulphate (SLS), methanol, and distilled water were used in the study. All chemicals and reagents were of analytical grade**.**

2.2 Preparation of Efavirenz Nanosuspension

Efavirenz nanosuspension was prepared by the nanoprecipitation method. The required quantity of efavirenz was dissolved in methanol to form the organic phase. HPMC E15 and SLS were dissolved in distilled water to form the aqueous phase. The organic phase was added dropwise into the aqueous phase under continuous magnetic stirring. Stirring was continued for one hour to ensure complete evaporation of solvent and formation of nanosuspension.[7,8]

2.3 Experimental Design

A 2^2 full factorial design was applied using Design-Expert software. Polymer concentration and surfactant concentration were selected as independent variables. Particle size, zeta potential, and percentage drug release were chosen as dependent variables. Four batches were prepared and evaluated.[11]

2.4 Evaluation Parameters

The prepared nanosuspensions were evaluated for

- **Particle size**
- Zeta potential[11]
- **Entrapment efficiency**
- **In vitro drug release**

Stability studies

Table 6: Independent variables with coded and actual levels.

Independent variables	High		Low	
	Coded	Actual	Coded	Actual
Concentration of Polymer (%) (A)	+	2.5	_	1
Concentration of surfactant (%) (B)	+	0.5	_	0.3

Table 7: Dependent variables with units.

Dependent variables	units
Particle size	nm
Zeta potential	mv
Drug release	%

Table 8: Factorial design layout for nanosuspension formulations.

Factorial batch code	A	B
F1	+	-
F2	+	+
F3	-	-
F4	-	+

Table 9: Composition of the Nanosuspension formulations.

Sl. No.	Name of Ingredients	Formulation Code			
		F1	F2	F3	F4
1.	Efavirenz	600mg	600mg	600mg	600mg
2.	HPMC	2.5%	2.5%	1%	1%
3.	SLS%	0.3%	0.5%	0.3%	0.5%
4.	Methanol(ml)	1	1	1	1
5.	Water(ml)	40	40	40	40

6.	Stirring speed(rpm)	1500	1500	1500	1500

Here is your content **paraphrased into concise article-style format (clear, structured, and compact)**

2.5 Characterization and Evaluation of Efavirenz Nanosuspension

The optimized efavirenz nanosuspension was subjected to various characterization and evaluation studies to determine its physicochemical properties, stability, and in vitro performance.

2.5.1 Scanning Electron Microscopy (SEM)

The surface morphology of the optimized nanosuspension was examined using Scanning Electron Microscopy (SEM). The sample was dried, mounted on an aluminum stub, and coated with a thin platinum layer under vacuum. The coated sample was then observed under vacuum at room temperature to analyze the shape and surface characteristics of the nanosized particles.

2.5.2 Fourier Transform Infrared Spectroscopy (FTIR)

Fourier Transform Infrared (FTIR) spectroscopy was performed to assess the compatibility between Efavirenz and the excipients used in the formulation. The nanosuspension was centrifuged, and the separated particles were dried. The dried sample was mixed with potassium bromide and compressed into pellets. The pellets were scanned in the wavelength range of 4000–400 cm^{-1} to identify characteristic functional groups and detect any possible drug–excipient interactions.

2.5.3 Particle Size and Polydispersity Index[9,10]

The particle size and polydispersity index (PDI) of the prepared nanosuspension were measured using a Malvern Zeta Sizer Nano ZS 90. The formulation was diluted appropriately with filtered distilled water before analysis. Particle size analysis was performed to determine the mean size of the nanoparticles, while PDI was used to evaluate the uniformity of particle size distribution.[9,10]

2.5.4 Zeta Potential Measurement[11]

The zeta potential of the nanosuspension was determined using the same instrument based on electrophoretic mobility measurements. Zeta potential provides information regarding the surface charge of nanoparticles and indicates the physical stability of the colloidal system.[11]

2.5.5 Drug Content Determination

The drug content of the nanosuspension was estimated by accurately measuring a specific volume of formulation and dissolving it in methanol. The resulting solution was suitably diluted with 1.5% sodium lauryl sulphate (SLS) solution and analyzed spectrophotometrically at 247 nm using a UV-visible spectrophotometer. The amount of drug present was calculated from the standard calibration curve of efavirenz.

2.5.6 Entrapment Efficiency

The entrapment efficiency was determined by centrifuging the nanosuspension to separate the unentrapped free drug from the nanoparticles. The supernatant was collected, diluted appropriately, and analyzed by UV spectroscopy at 247 nm. The entrapment efficiency was calculated using the following equation

Entrapment Efficiency (%) = Total Drug - Free Drug / Total Drug × 100

2.5.7 In Vitro Dissolution Studies

The in vitro dissolution study of efavirenz nanosuspension was carried out using the USP Type II (Paddle) dissolution apparatus. The dissolution medium consisted of 900 mL of 1.5% SLS solution, maintained at 37 ± 0.5°C, with a paddle speed of 50 rpm. At predetermined time intervals, aliquots were withdrawn and replaced with an equal volume of fresh dissolution medium to maintain sink conditions. The samples were analyzed spectrophotometrically at 247 nm to determine the percentage cumulative drug release.[12,13]

2.6 Statistical Analysis of Experimental Design

The prepared formulations were analyzed using Design-Expert software (Stat-Ease®, Minneapolis, MN, USA) to evaluate the effect of formulation variables on the selected responses. The dependent variables considered for optimization were**:**

- Particle size
- Zeta potential[11]
- Drug release
- The influence of independent variables on these responses was analyzed statistically using factorial design methodology.

2.7 Optimization of Formulation

Optimization of efavirenz nanosuspension formulations was performed by setting specific criteria for the independent variables and responses using Design-Expert software. The

optimized formulation was selected based on the desirability function approach to achieve minimum particle size, optimum zeta potential, and maximum drug release.[11]

The optimization criteria for formulation variables and responses are presented in Table 10

Table 10: Optimization criteria for efavirenz nanosuspension formulations.

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
A:Hpmc	is in range	1	2.5	1	1	3
B:SLS	is in range	0.3	0.5	1	1	3
Particle size	minimize	256.7	407.9	1	1	3
Zeta potential	minimize	-19.2	-8.13	1	1	3
Drug release	maximize	63.54	77.04	1	1	3

4.4.5 Stability studies

2.5.8 Stability Studies

The optimized efavirenz nanosuspension formulation was subjected to stability studies under two different storage conditions, namely refrigerated temperature (4°C) and room temperature (25 ± 2°C / 60 ± 5% RH), for a period of 60 days. Samples were withdrawn at predetermined time intervals of 0, 15, 30, and 60 days and evaluated for visual appearance, drug content, and entrapment efficiency.

The purpose of the study was to determine the physical and chemical stability of the formulation during storage. Any changes in color, phase separation, or sedimentation were observed visually, while drug content and entrapment efficiency were measured to identify possible degradation or drug leakage from the nanosuspension system. The results obtained from stability testing were used to assess the suitability of the optimized formulation for storage under different environmental conditions.

1.1 Spectrophotometric analysis efavirenz

From the spectral data, the absorption maxima obtained was 247nm with a characteristic peak as shown in Figure 10.

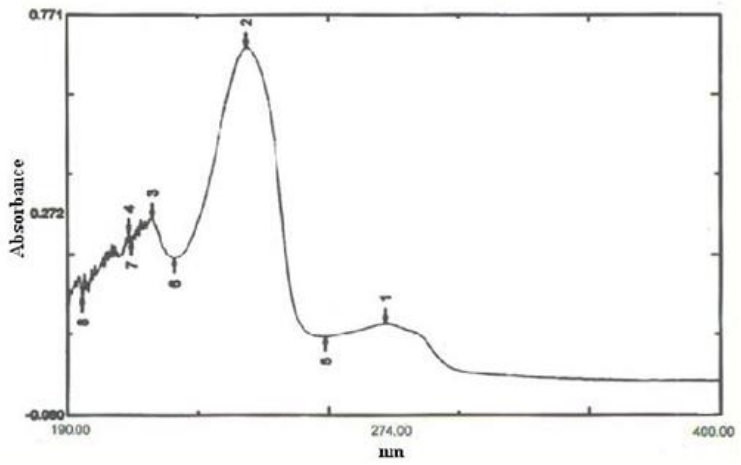


Figure 10: Absorption maxima for efavirenz.

The optical density was measured at 247nm. The absorbance data and statistical data were shown in Tables 11 and 12. Concentration versus optical density values are plotted and were given in the Figure 11.

Table 11: Calibration curve data of efavirenz.

Concentration (µg/ml)	Optical density values			
	I Set	II Set	III Set	Mean ±SD(n=3)
1	0.0535	0.062	0.0496	0.055±0.00634
2	0.100	0.109	0.112	0.107±0.00624
3	0.159	0.163	0.151	0.157±0.00610
4	0.215	0.208	0.221	0.214±0.00650
5	0.264	0.259	0.275	0.266±0.00818

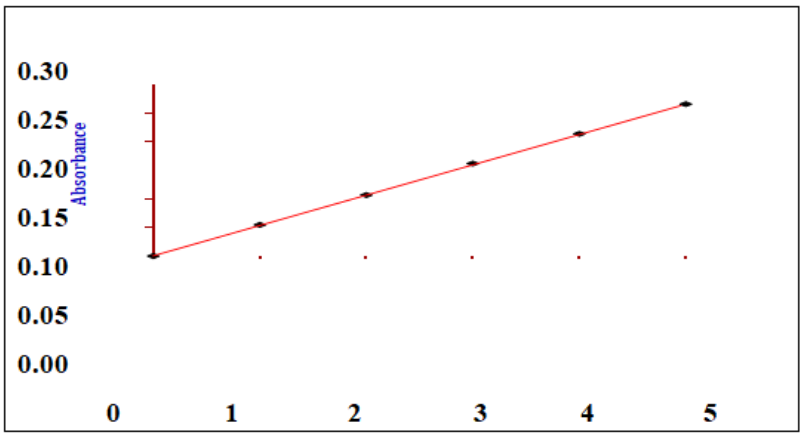


Figure 11: Calibration curve of efavirenz.

Table 12: Statistical data of the calibration curve of efavirenz.

Parameters	Values
Absorption maxima(nm)	247
Beer's law limit (µg/ml)	1-20

Molar absorptivity (1mole^{-1}/cm^{-1})	2.21×10^{-4}
Best-fit values ± SE	
Slope	0.0532 ± 0.0002619
Y-intercept	0.001 ± 0.0007928
X-intercept	-0.0188
1/slope	18.8
95% Confidence Intervals	
Slope	0.05247 to 0.05393
Y-intercept	-0.001201to 0.003201
X-intercept	-0.06086to 0.02233
Goodness of Fit	
R square	0.9999
P value	<0.0001
Equation	Y =0.0532*X + 0.001

1.2 Compatibility study of drug and excipients by FTIR

The FTIR spectra of efavirenz, SLS, HPMC are shown below to assess the compatibility of the drug with selected excipients.

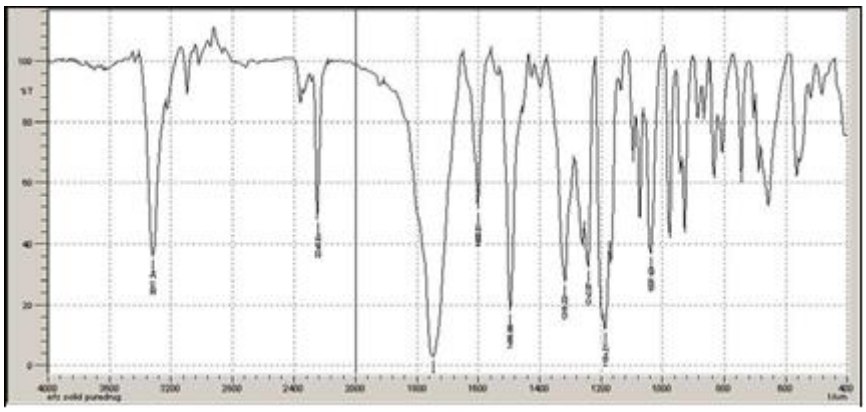


Figure 12: FTIR spectrum of Efavirenz.

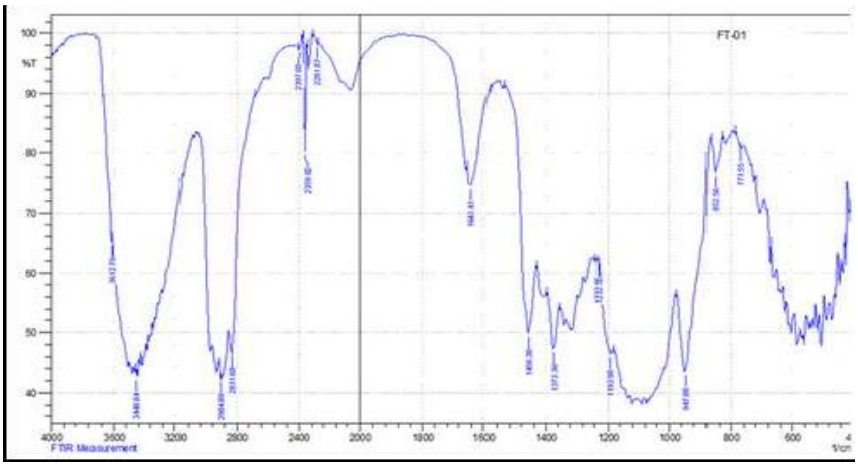


Figure 13: FTIR spectrum of HPMCE15.

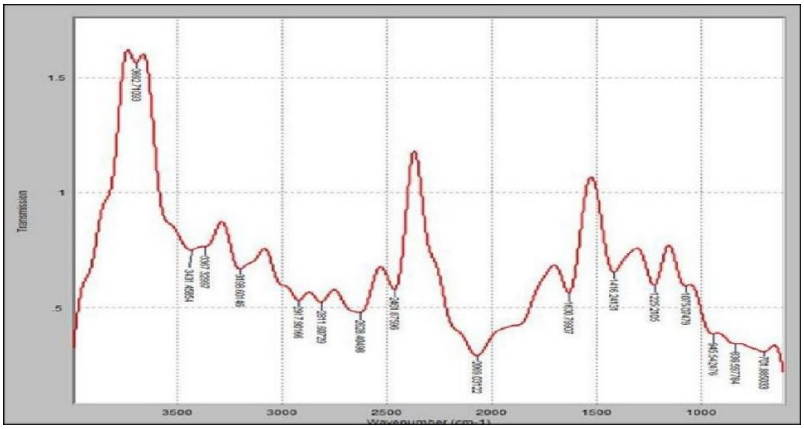


Figure 14: FTIR spectrum of SLS.

1.3 Formulation of efavirenz containing nanosuspensions

The Nanosuspension formulations (F1-F4) were formulated using Nanoprecipitation method as shown in Figure xx. The formulated nanosuspension batches were prepared with different quantities of SLS & HPMC, where the quantities of methanol and efavirenz remained constant in each formulation.[7,8]

1.4 Characterization of prepared nanosuspension Morphology of nanosuspension by SEM

The optimized nanosuspension formulation was characterized by SEM to study the surface morphology of the particles as shown in Figure 16 &17.

Figure 15: Formulated nanosuspension batches (F1-F4) of efavirenz.

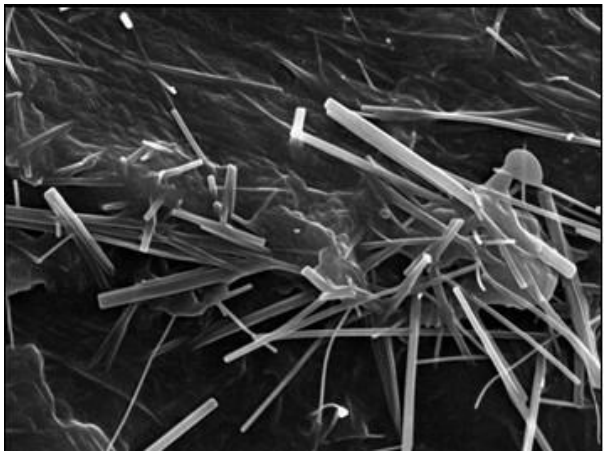


Figure 16: SEM image of optimized efavirenz nanosuspension at 5000x magnification showing clearly defined rod-shaped nanoparticles.

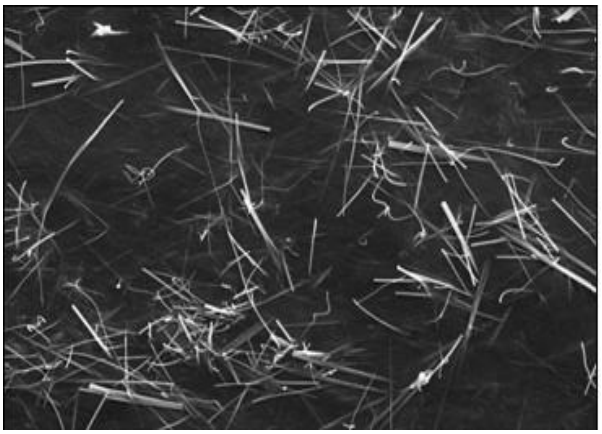


Figure 17: SEM image of optimized efavirenz nanosuspension at 1500x magnification showing distribution of rod-shaped particles across the field.

FTIR spectra of nanosuspension formulations

The FTIR spectra of nanosuspension formulation are shown in Figure18-21

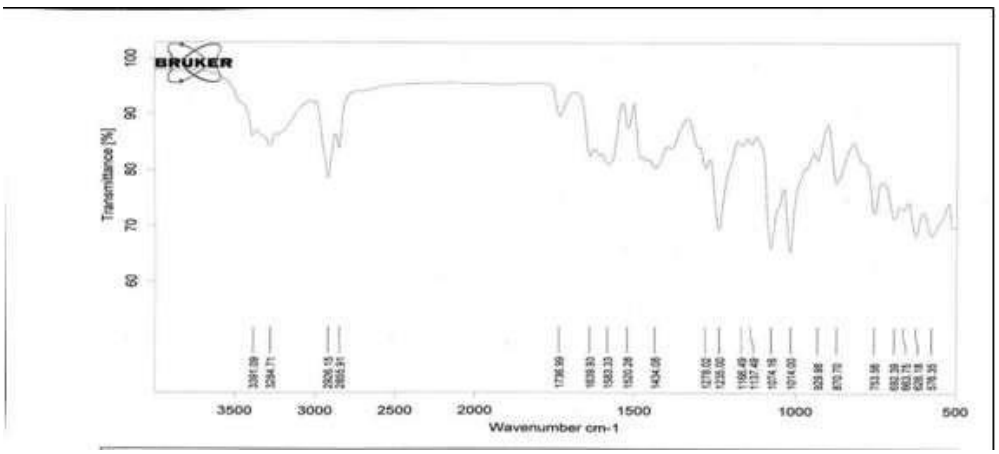


Figure 18: FTIR spectrum of F1.

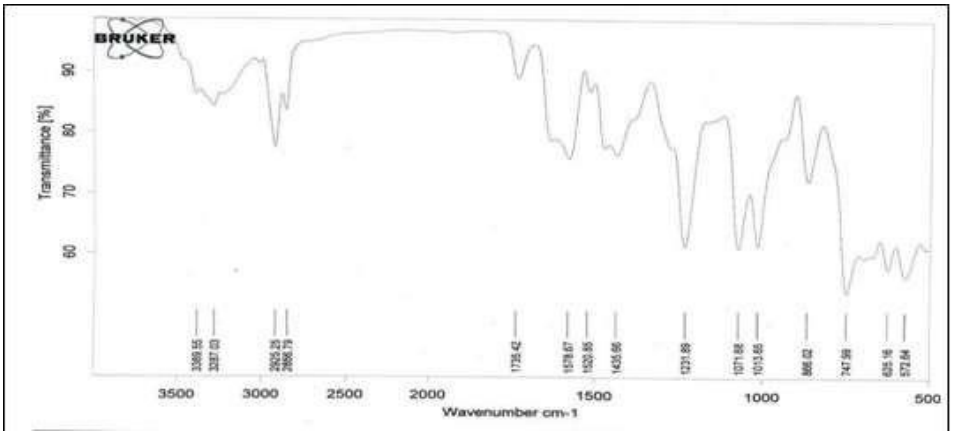


Figure 19: FTIR spectrum of F2.

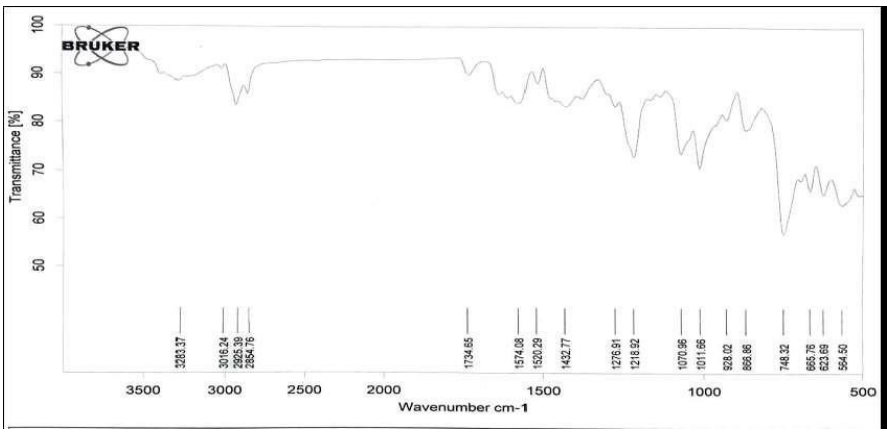


Figure 20: FTIR spectrum of F3.

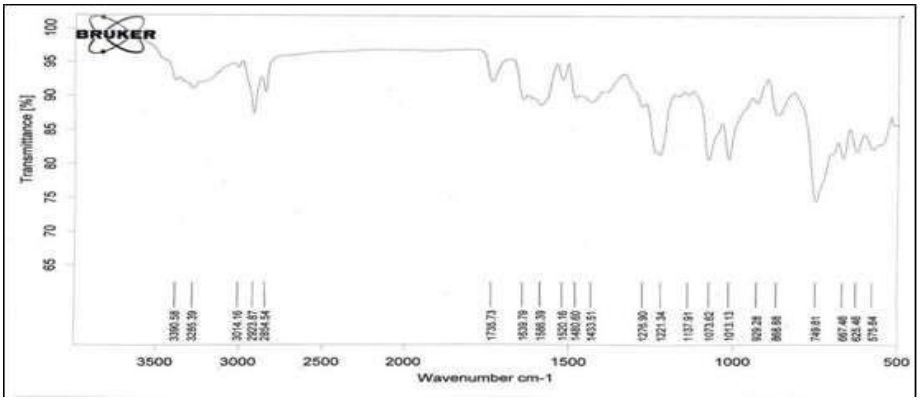


Figure 21: FTIR spectrum of F4.

1.5 Evaluation of prepared nanosuspension Particle size analysis

The prepared efavirenz nanosuspensions were analyzed for particle size, as shown in Figure19-25. The particle size of the formulations ranged between 256.7nm and 407.9nm. From the results, it was observed that all the formulations exhibited particle sizes within the nanometer range (<1000 nm), which are suitable for enhancing solubility and dissolution.

Polydispersity Index (PDI)

The polydispersity index of the nanosuspensions ranged from 0.357 to 0.379, as representedin Table 13.

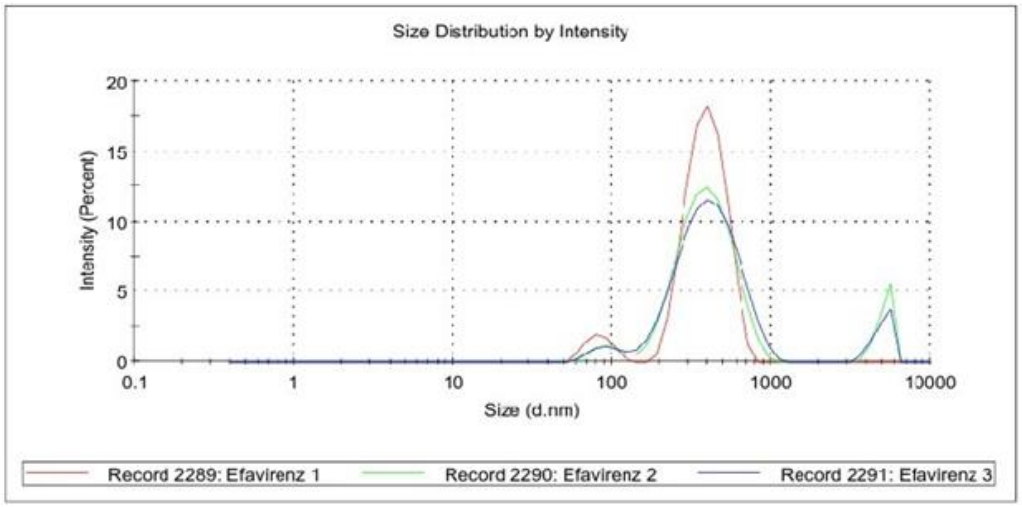


Figure 22: Particle size distribution of F1.

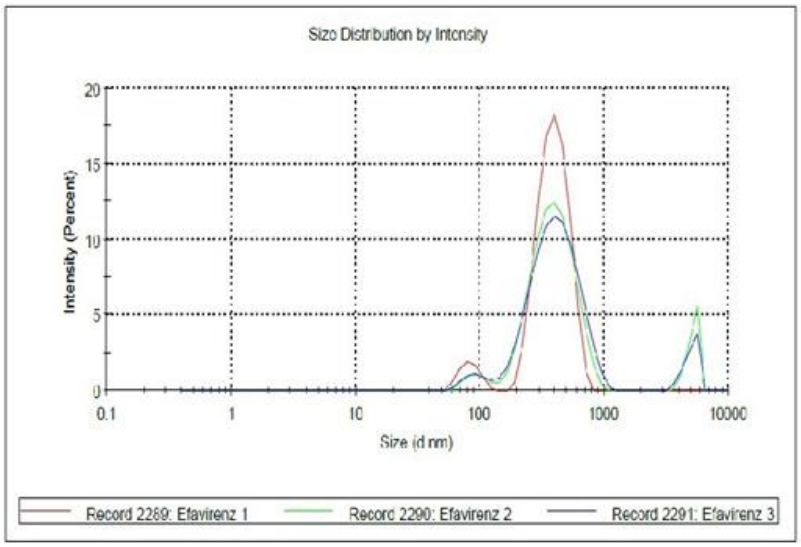


Figure 23: Particle size distribution of F2.

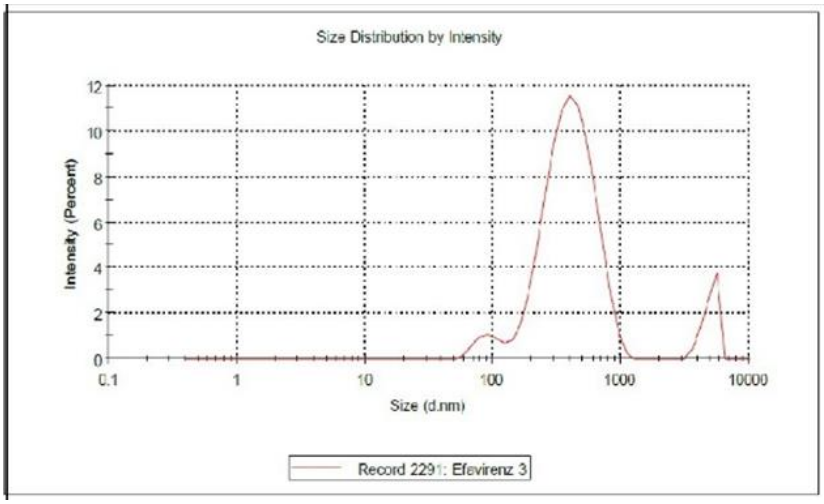


Figure 24: Particle size distribution of F3.

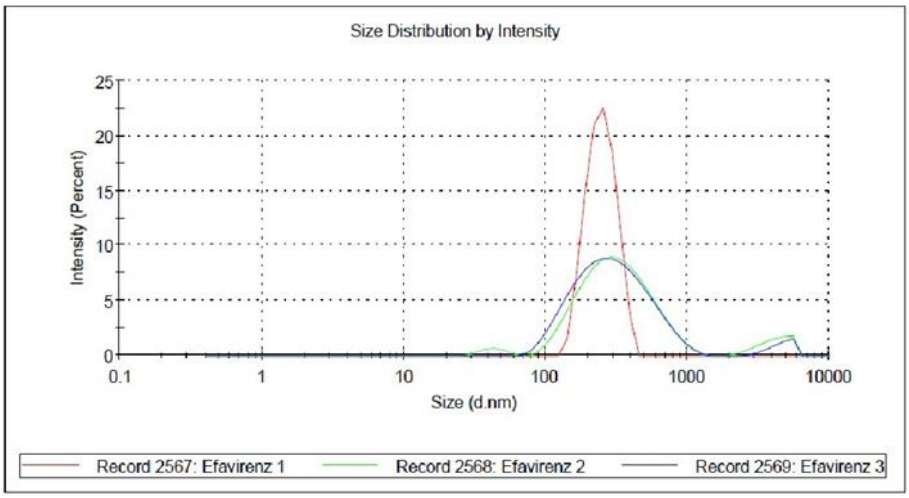


Figure 25: Particle size distribution of F4

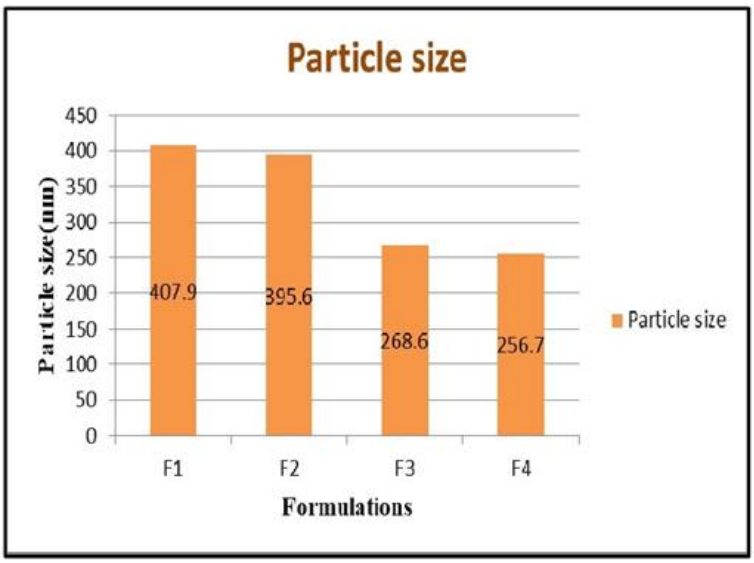


Figure 26: Comparative particle size of efavirenz nanosuspensions Zeta potential.[11]

The zeta potential values of the nanosuspensions were found to be in the range of –8.13 mV to –19.2 mV, as shown in Figure 27-30.[11]

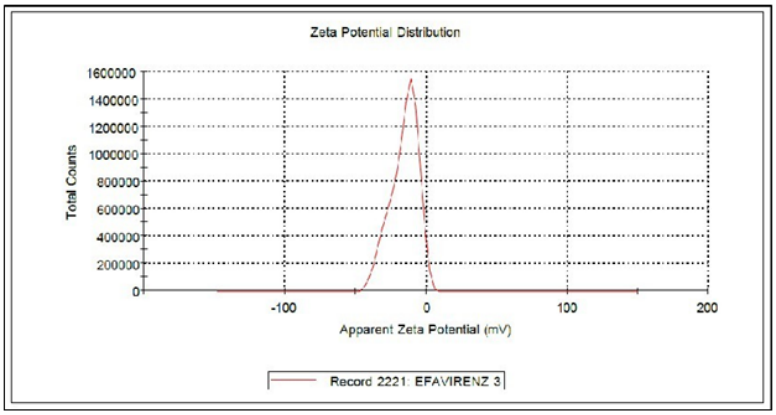


Figure 27: Zeta potential graph of F1.[11]

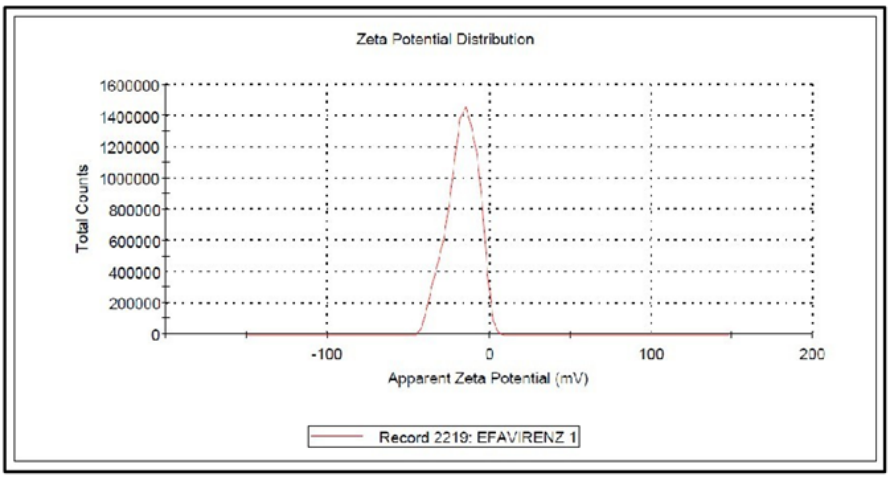


Figure 28: Zeta potential graph of F2.[11]

Figure 29: Zeta potential graph of F3.[11]

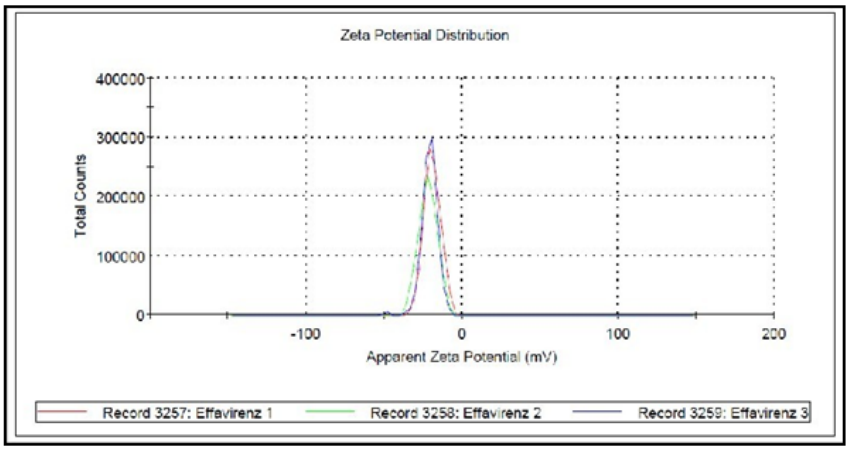


Figure 30: Zeta potential graph of F4.[11]

Table 13: Evaluation of Efavirenz nanosuspension

Formulation	Particle size (nm)	PDI	Zeta potential (mV)
F1	407.9	0.379	-11.7
F2	395.6	0.365	-16.8
F3	268.6	0.379	-8.13
F4	256.7	0.357	-19.2

3.3 Drug Content and Entrapment Efficiency

The drug content of the prepared efavirenz nanosuspension indicates the actual amount of drug present in the formulation in comparison with the theoretical quantity used during preparation. Entrapment efficiency, on the other hand, represents the percentage of drug successfully incorporated within the nanosized particles after separation of the unentrapped free drug by centrifugation.

Both parameters were determined by UV-visible spectrophotometric analysis at a wavelength of 247–248 nm using 1.5% sodium lauryl sulphate (SLS) solution as the dissolution medium. The drug content results confirmed uniform distribution of Efavirenz in the nanosuspension formulations, while the entrapment efficiency values indicated effective incorporation of the drug within the nanoparticulate system.

The values obtained for drug content and entrapment efficiency of all prepared formulations are presented in Table 14. The results revealed satisfactory drug loading and efficient entrapment of efavirenz, indicating that the selected formulation variables were suitable for the preparation of stable nanosuspensions.

Table 14: Drug content and entrapment efficiency of nanosuspension formulations.

Sl. No	Formulation code	Drug content	Entrapmentefficiency (%)
1	F1	91.54%	87.44%
2	F2	92.32%	89.26%
3	F3	94.24%	90.88%
4	F4	95.19%	93.28%

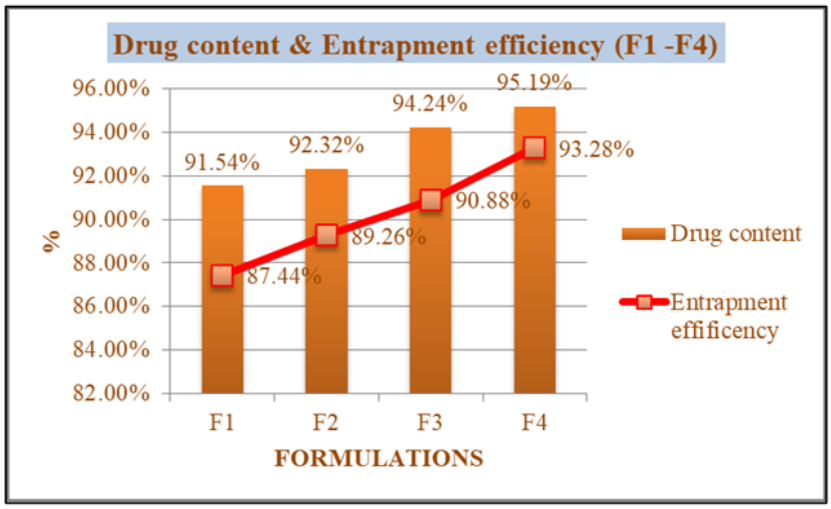


Figure 31: Comparison of drug content and entrapment efficiency (%) of efavirenz nanosuspension formulations (F1-F4).

1.6 In vitro dissolution

The in vitro drug release study of efavirenz nanosuspension formulations (F1-F4) was carried out and the cumulative percentage drug release was compared with pure drug and marketed formulation as shown in Table 15.

Table 15: Cumulative percentage drug release data of efavirenz nanosuspension formulations (F1-F4) compared with pure drug and marketed formulation.

Sl. No.	Time (mins)	Cumulative % drug release					
		Pure drug	F1	F2	F3	F4	Marketed formulation
1	0	0	0	0	0	0	0
2	5	8	63.54	71.72	72.40	77.07	20.09
3	10	11.98	64.15	73.83	73.50	78.04	31.76
4	15	14.08	64.76	74.17	74.65	79.46	49.23
5	30	15.24	66.72	78.71	76.95	80.27	62.44
6	45	20.45	68.35	79.80	78.71	82.37	73.21
7	60	26.69	70.85	81.90	80.34	84.88	80.53

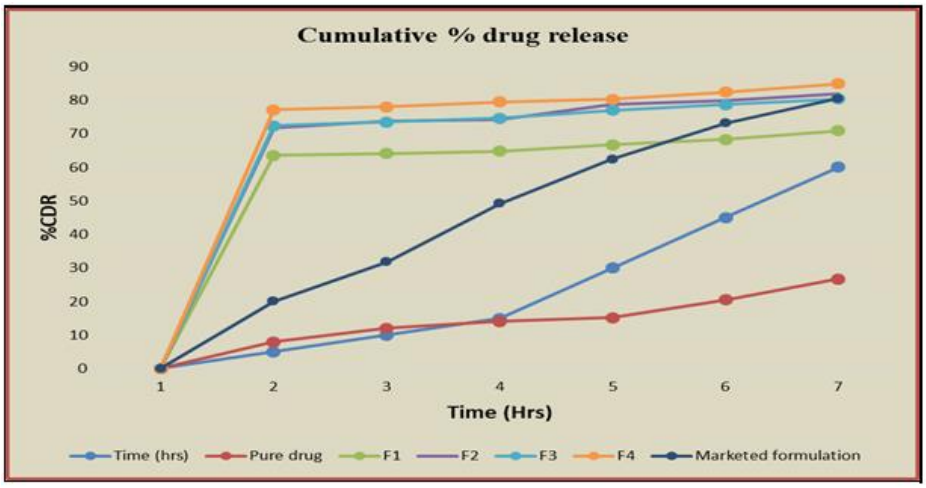


Figure 32: Cumulative percentage drug release profile of efavirenz nanosuspension formulations (F1-F4) compared with pure drug and marketed formulation.

1.7 Analysis of design

The values of the selected responses of formulations F1 to F4 were entered in the design as follows

Table 16: Design summary of factors and responses.

	Factor 1	Factor 2	Response 1	Response 2	Response 3
Run	**A:Hpmc %**	**B:SLS %**	**Particle size**	**Zeta potential**	**% drug release**
1	2.5	0.5	395.6	-16.8	71.2
2	2.5	0.3	407.9	-11.7	63.54
3	1	0.5	256.7	-19.2	77.04
4	1	0.3	268.6	-8.13	72.4

Evaluation of model

1. Particle size

Table 17: Fit Summary/

Source	Sequential p- value	Lack of Fit p- value	Adjusted R^2	Predicted R^2	
Linear	0.0014		1.0000	1.0000	**Suggested**

ANOVA for Linear Model

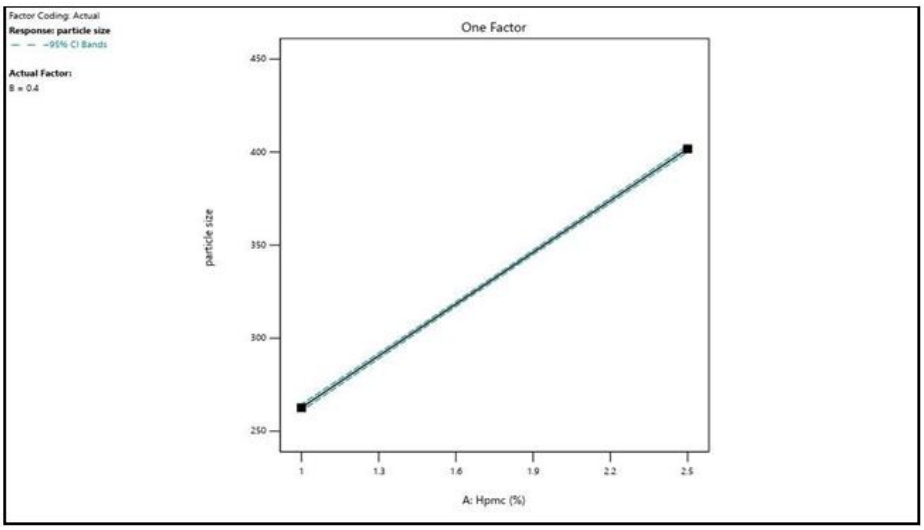
Table 18: Response 1: Particle size.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	19495.22	2	9747.61	2.437E+05	0.0014	**significant**
A-Hpmc	19348.81	1	19348.81	4.837E+05	0.0009	
B-SLS	146.41	1	146.41	3660.25	0.0105	
Residual	0.0400	1	0.0400			
Cor Total	19495.26	3				

Factor coding is **Coded** Sum of squares is **Type III – Partial**

The **Model F-value** of 243690.25 implies the model is significant. There is only a 0.14% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.



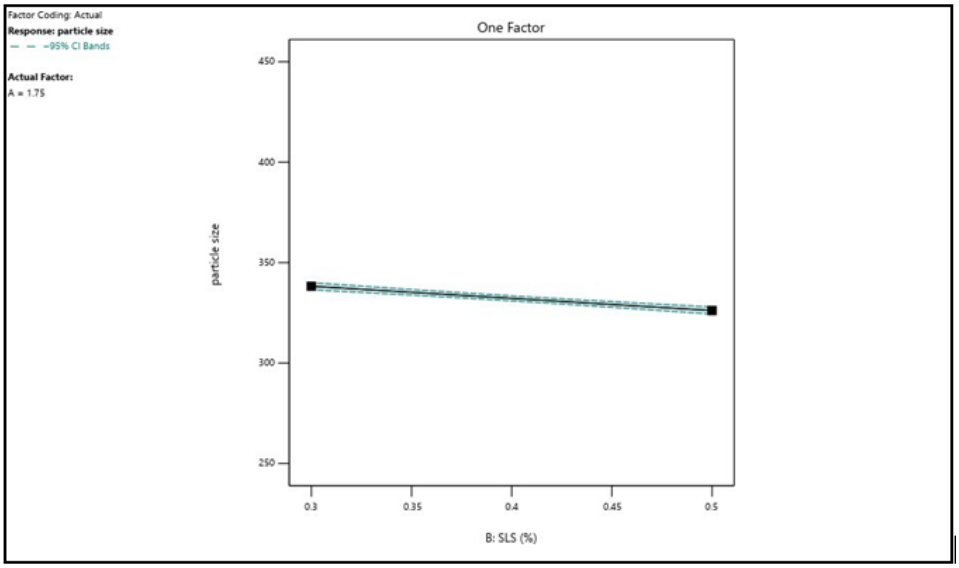


Figure 33: Effect of HPMC and SLS on Response – I.

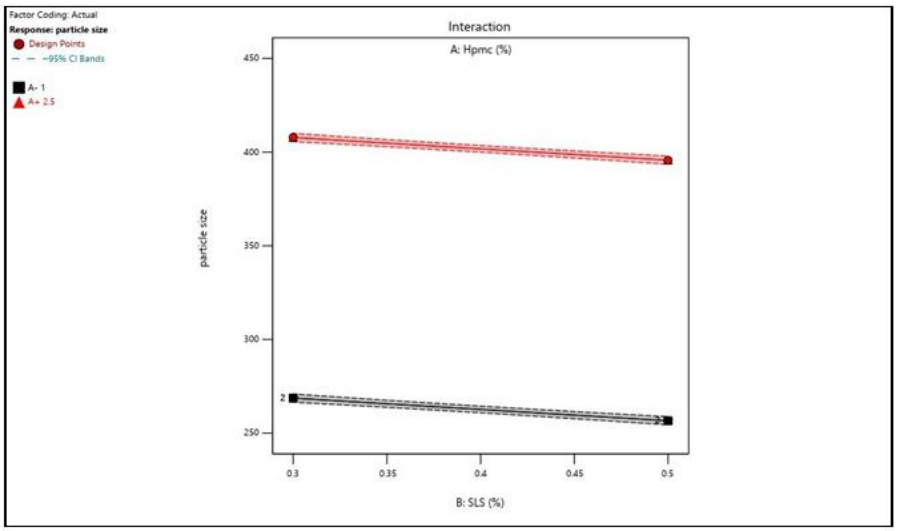


Figure 34: Interaction profile of HPMC and SLS on the response I.

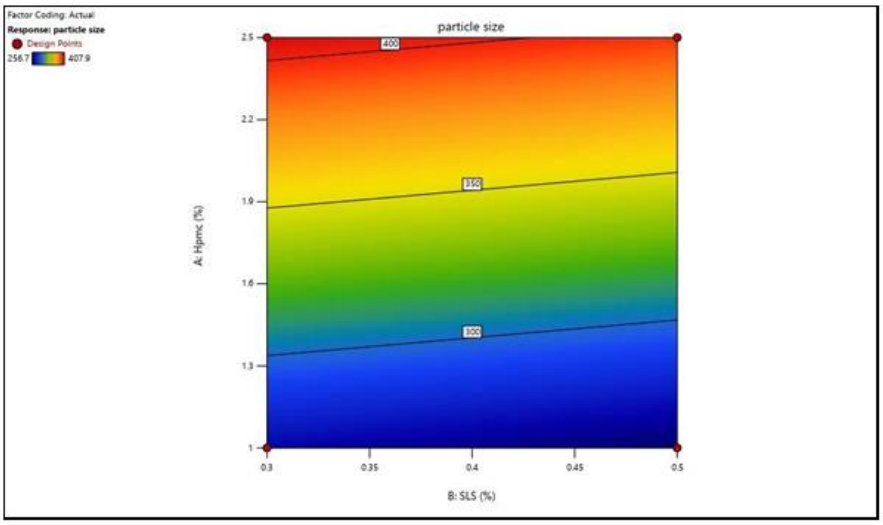


Figure 35: Contour plots for response I.

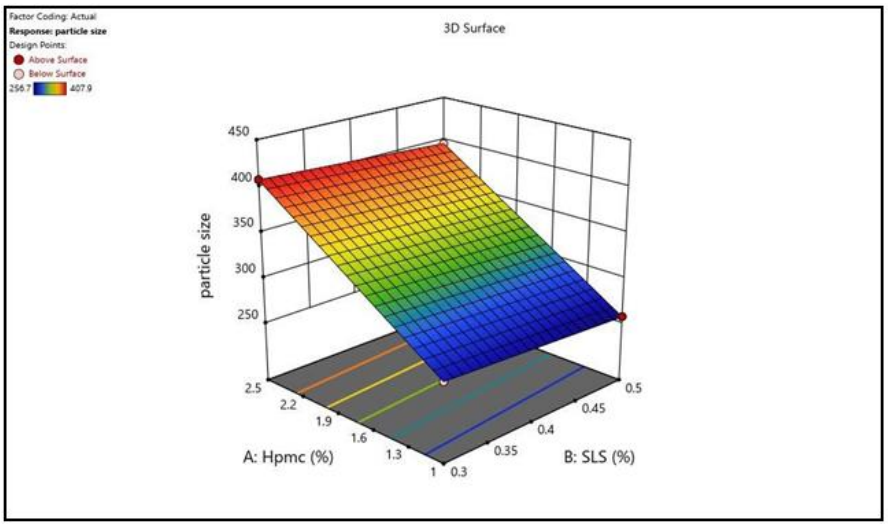


Figure 36: 3-Dimensional plots for Response I.

2. Zeta potential[11]

Table 19: Fit summary.

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.3456		0.6418	-0.9105	**Suggested**

ANOVA for Linear Model

Table 20: Response 2: Zeta potential.[11]

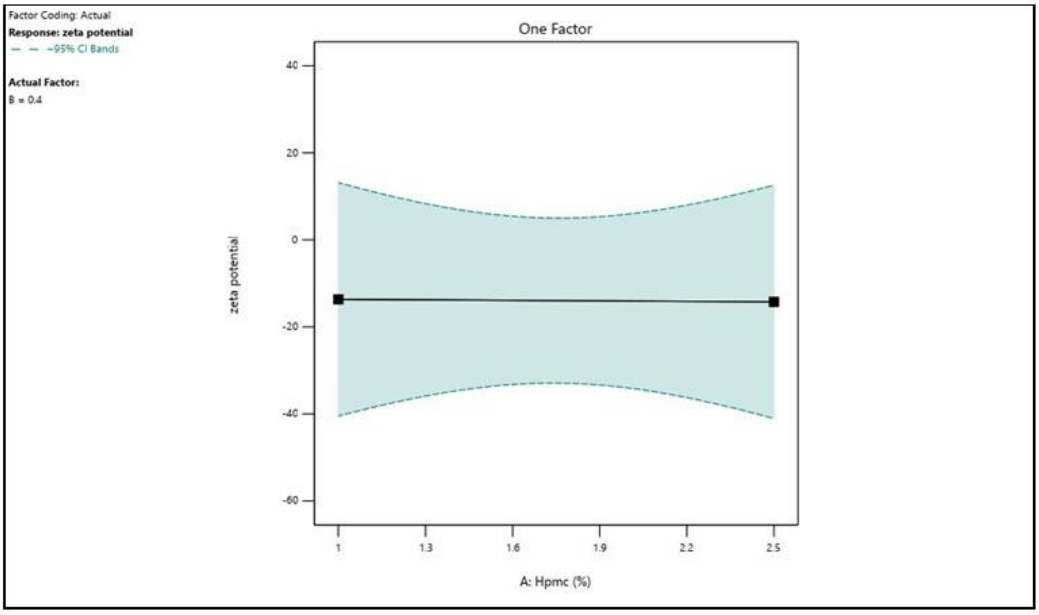
Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	65.71	2	32.85	6.84	0.0321	**significant**
A-Hpmc	0.3422	1	0.3422	0.0384	0.8768	
B-SLS	65.37	1	65.37	7.34	0.2252	
Residual	8.91	1	8.91			
Cor Total	74.62	3				

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 6.84 implies the model is significant. There is a 3.21% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case B is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.



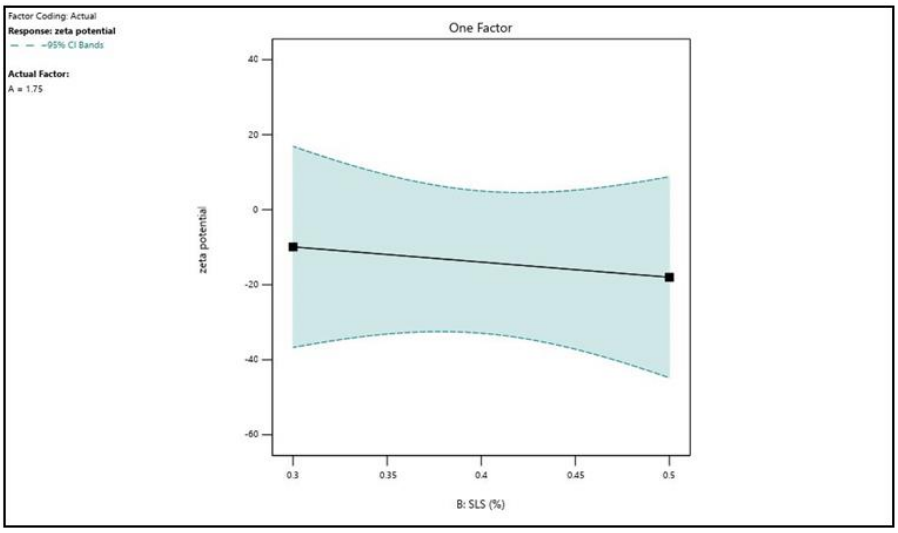


Figure 37: Effect of HPMC and SLS on Response – II.

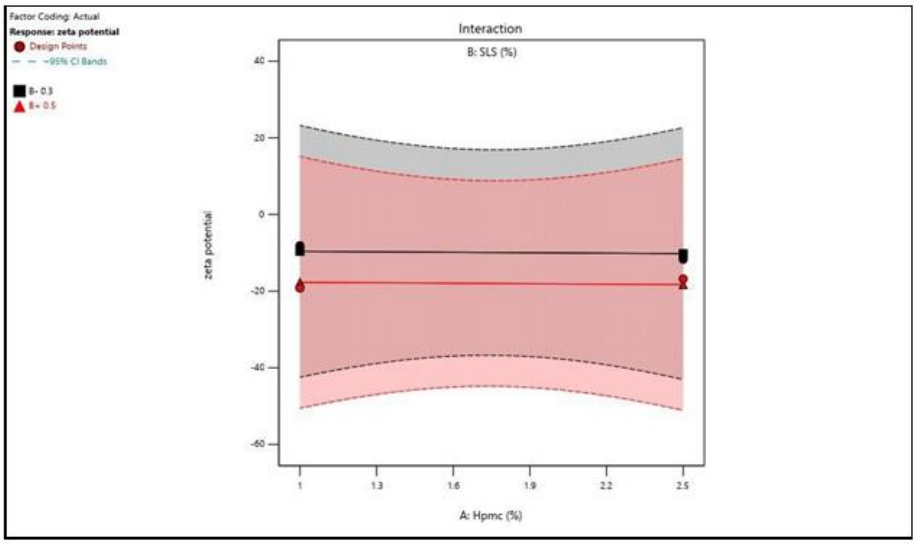


Figure 38: Interaction profile of HPMC and SLS on the response II.

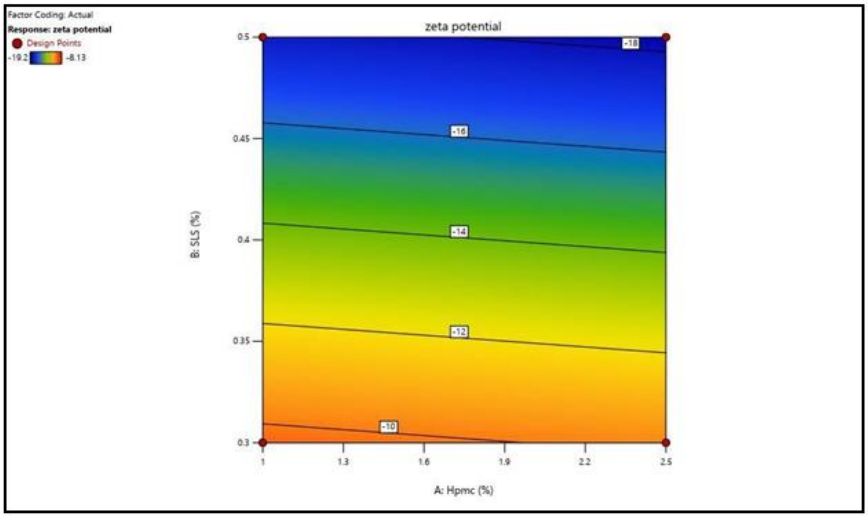


Figure 39: Contour plots for response II.

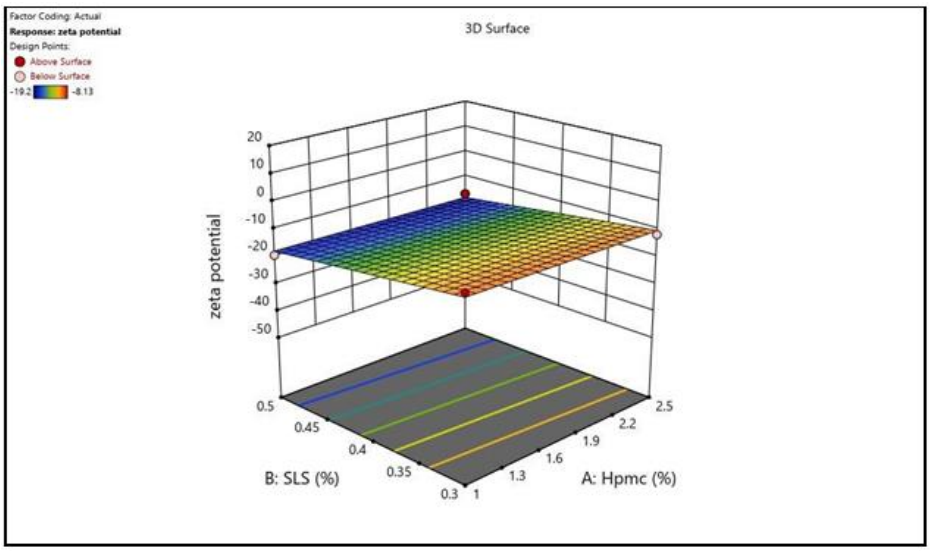


Figure 40: 3-Dimensional plots for Response II.

3. Drug release

Table 21: Fit summary.

Source	Sequential p-value	Lack of Fitp-value	Adjusted R^2	Predicted R^2	
Linear	0.1556		0.9273	0.6124	**Suggested**

ANOVA for Linear Model

Table 22: Response 3: Drug release.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	91.85	2	45.92	15..44	0.0058	significant
A-Hpmc	54.02	1	54.02	23.69	0.1290	
B-SLS	37.82	1	37.82	16.59	0.1533	
Residual	2.28	1	2.28			
Cor Total	94.13	3				

Factor coding is **Coded**.

Sum of squares is **Type III – Partial**

The **Model F-value** of 15.44 implies the model is significant. There is a 0.58% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

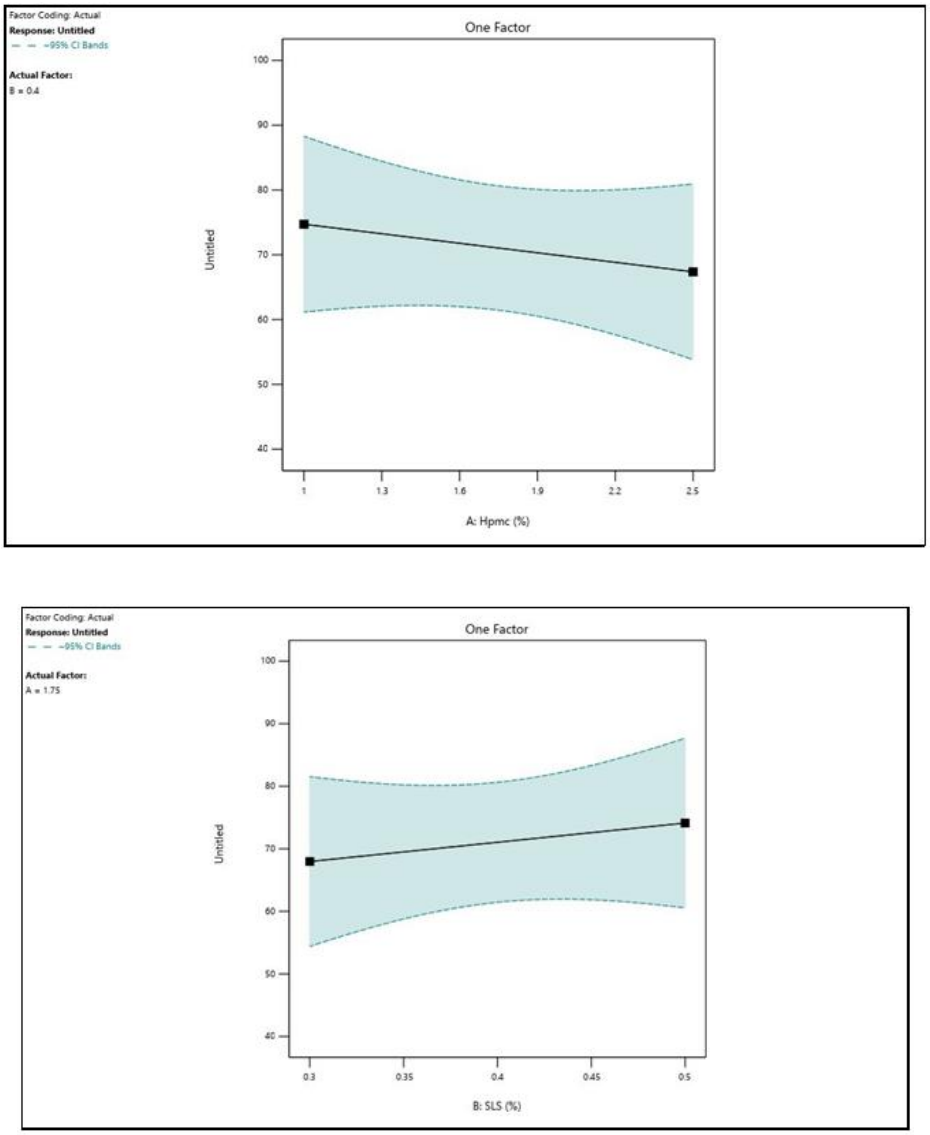


Figure 41: Effect of HPMC and SLS on Response – III

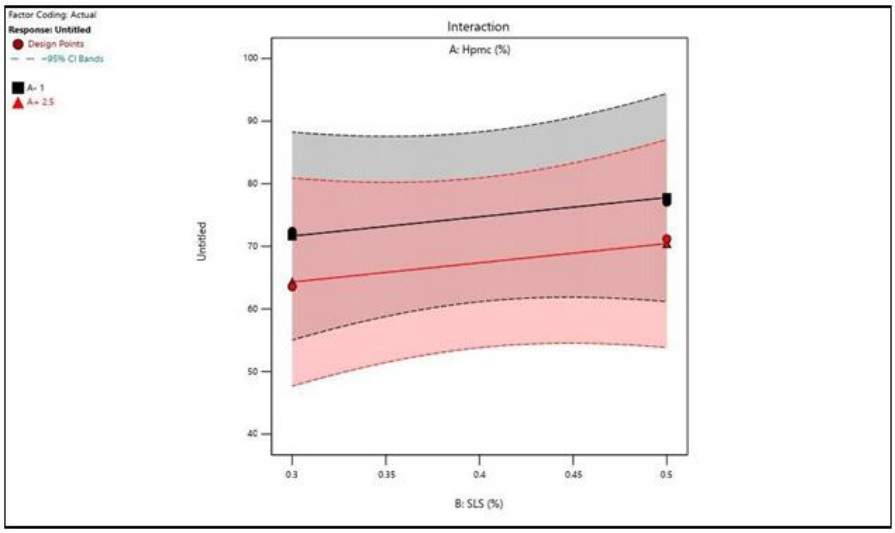


Figure 42: Interaction profile of HPMC and SLS on the response III.

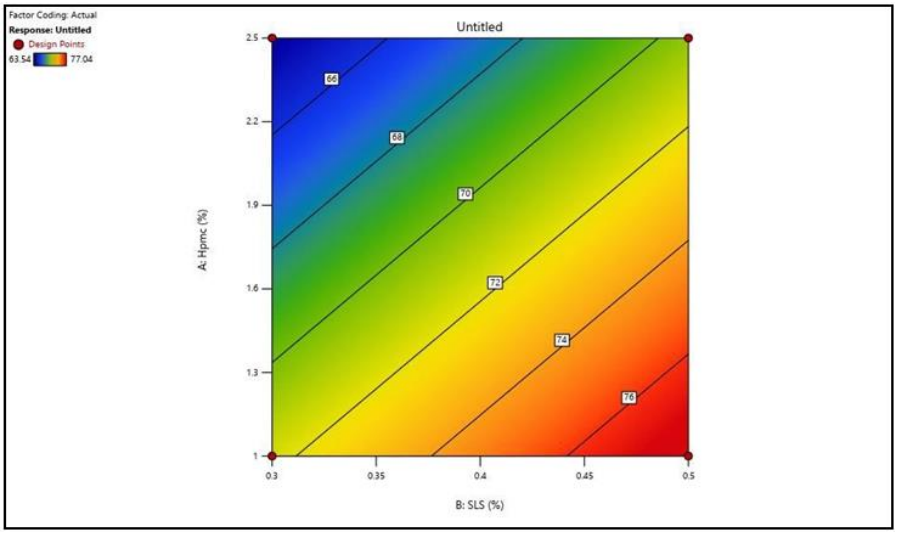


Figure 43: Contour plots for response III.

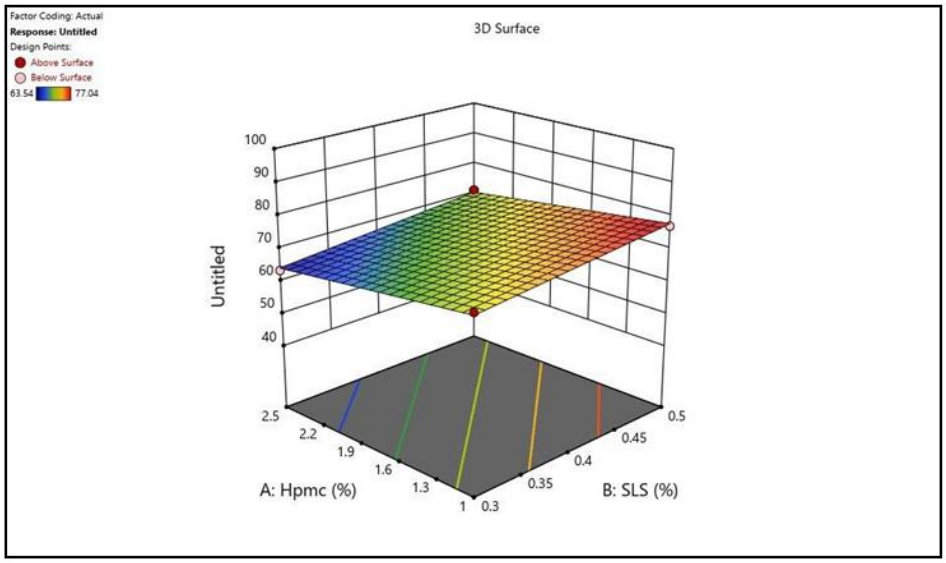


Figure 44: 3-Dimensional plots for Response III.

5.8 Solutionfor optimization

Based on the criteria selected for optimization, 5 solutions were suggested by the design expert software which are mentioned below,

Table 23: Solution for optimization

Number	Hpmc	SLS	Particle size	Zeta potential	Untitled	Desirability	
1	**1.00108**	**0.5**	**256.7**	**-17.7079**	**77.7897**	**0.953**	**Selected**
2	1.00889	0.5	257.424	-17.711	77.7515	0.951	
3	1.00001	0.48862	257.289	-17.2475	77.445	0.936	
4	1.00001	0.483506	257.598	-17.0407	77.2878	0.928	
5	1	0.478511	257.9	-16.8388	77.1342	0.921	

As the suggested optimized formulation was found to be similar to F4, formulation F4 was considered to be the optimized formulation.

5.9 Stability studies

The stability of the optimized efavirenz nanosuspension was evaluated for 60days at refrigerated temperature (4± 2°C) and room temperature (25± 2°C) as shown in Table 24 & 25. Samples were periodically analyzed for visual appearance, drug content, and entrapment efficiency.

Table 24: Stability studies of nanosuspension at 4℃

Sl. No.	Days	Visual appearance	Drug content (%)	Entrapment efficiency (%)
1.	0	Off white, milky	95.19	93.28
2.	15	No change	95.02	93.06
3.	30	No change	94.85	92.98
4.	60	No change	94.12	92.36

Table 25: Stability studies of nanosuspension at room temperature

Sl. No.	Days	Visual appearance	Drug content (%)	Entrapment efficiency (%)
1.	0	Off white, milky	95.19	93.28
2.	15	No change	94.82	92.76
3.	30	No change	94.21	92.46
4.	60	No change	93.56	91.87

RESULTS AND DISCUSSION

The nanoprecipitation technique successfully produced efavirenz nanosuspensions with nanosized particles. The optimized formulation showed improved dissolution characteristics due to enhanced surface area.[14,15]

The particle size was significantly influenced by stabilizer concentration. Increased polymer concentration improved stabilization but excessive polymer led to increased viscosity and particle size. Surfactant concentration improved wettability and enhanced dissolution.

The optimized formulation exhibited satisfactory zeta potential values, indicating physical stability. In vitro drug release studies demonstrated improved dissolution of efavirenz nanosuspension compared to the pure drug, confirming enhancement of solubility and bioavailability.[11]

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