Pharmacophore 2016, Vol. 7 (6), 458-471 USA CODEN: PHARM7 ISSN 2229-5402

Pharmacophore

(An International Research Journal)

Available online at http://www.pharmacophorejournal.com/

Original Research Paper

FORMULA OPTIMIZATION FOR RAPID DISSOLUTION OF EFAVIRENZ FROM DOSAGE FORM

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ABSTRACT

The formulation of poorly soluble drug for oral delivery is one of the biggest challenges for formulation scientists. Efavirenz, a non-nucleoside reverse transcriptase inhibitor is used as a part of highly active antiretroviral therapy treatment of a human immunodeficiency virus type I. It exhibits poor dissolution characteristics when administered in conventional oral dosage form with a bioavailability of just 40-45%. The objective of this study is to evaluate the effects of novel excipients such as Soluplus®, dioctyl sulphosuccinate and various superdisintegrants in increasing the dissolution efficiency of Efavirenz. Physical mixtures of Efavirenz with one or more of these excipients was used in different ratios for formula optimization to increase the dissolution rate of Efavirenz. Analytical techniques such as Fourier Transform Infra red spectroscopy (FTIR) and differential scanning calorimetry (DSC) were used to confirm compatibility of efavirenz with the excipients. Preliminary trials along with factorial studies were performed for finalization of formula. Dissolution studies performed revealed improvement in release profile as compared to conventional tablet. Short-term stability studies were performed on the optimized formula. Optimized formulation was subjected to analytical studies to confirm stability of formulation. Evaluation by X-ray diffraction (XRD), DSC and FTIR techniques revealed that the formulation was stable. Techniques such as solid dispersion of drug in solubilizing agent can be tried to bring about further enhancement in extent of drug release.

Keywords: Contour plots, Design of Experiment, Differential Scanning Calorimetry, Dioctyl sulphosuccinate, Efavirenz, Soluplus®

INTRODUCTION

Dissolution of drug from dosage form is the rate determining step for oral absorption and affects the in vivo absorption of drug. Currently only 8-10% of new drug candidates have both high solubility and permeability.[1] It is now possible to increase the solubility of poorly soluble drugs with the help of various techniques that have been well documented in literature.[1] Efavirenz, which belongs to BCS Class II, is a non-nucleoside reverse transcriptase inhibitor (NNTRI). It is synthetic purine derivative that is used as part of highly active antiretroviral therapy for treatment of a human immunodeficiency virus (HIV) type I.[1, 2] Efavirenz is also used in combination with other antiretroviral agents as part of an expanded post exposure prophylaxis regimen to prevent HIV transmission for materials associated with a high risk for HIV transmission (infected blood and body fluids). For HIV infection that has not been treated, efavirenz and lamivudine in combination with zidovudine or tenofovir is the preferred NNRTI-based regimen.[3]

Efavirenz is practically insoluble in water and soluble in methanol.[2]Although research is being carried out to improve the dissolution efficiency of efavirenz; there is still scope for development

of formulations with improved dissolution characteristics.In the present study, polyvinyl caprolactum-polyvinyl acetate-poly ethylene glycol graft copolymer(Soluplus®), an amphiphilic polymer with amphiphilic properties whichshows excellent solubilizing properties for BCS class II substances and offers the possibility of producing solid solutions was used to enhance dissolution of efavirenz from the formulation.[4,5] Varying ratios of drug andSoluplus®were mixed and evaluated to deduce the possible interactions, their physical mixtures were also formulated along with other excipients like superdisintegrant, dioctyl sulphosuccinate (DOSS) acting as plasticizer and sodium lauryl sulphate (SLS) and subjected to drug-excipient compatibility studies. The objective of this study was to develop an optimized formulation of efavirenz that could overcome the drawbacks of conventional therapy. The optimized formulation will be subjected to stability studies as per ICH guidelines.[3]

MATERIALS AND METHODS

Materials

Gift sample of Efavirenz was provided by Lee Pharma (Hyderabad, India). Other excipients were procured as gift samples from BASF India limited and Signet Chemical Corporation Pvt. Ltd. All other chemicals and solvents used were of Analytical grade.[8, 9, 10]

Analytical Method Development of Efavirenz

UV analysis

Various solvents such as 0.1 N HCl, NaOH, methanol, distilled water were used to dissolve the drug. Spectrophotometric scanning of the drug was carried out by UV spectrophotometer in the range of 200-400 nm.

Calibration curves

Calibration curve was drawn within the range 6-18µg/ml and coefficient of correlation was estimated.

Drug excipient compatibility studies

The drug was mixed with various excipients in the ratio 1:5 and 10:1 and exposed to 25°C, 40°C temperature, UV light for 24 hrs and observed visually for any physical changes.[11]

Drug content

Ten tablets were crushed in mortar and 5 mg of powder was transferred to volumetric flask. To the flask, methanol (10 mL) was added and sonicated for 5 minutes. Then volume was made up to 25 ml with distilled water (stock solution). The stock solution was diluted suitably to get a sample having concentration of 10µg/ml. This procedure was repeated six times. The absorbances were recorded spectrophotometrically at 247 nm and concentrations derived using standard equation.[12]

Dissolution studies

In vitro dissolution study was performed in a USP Type II dissolution test apparatus (Lab India) using 900 ml of1 % SLS at 37±0.5°C.[13] Aliquot of 5 ml was withdrawn at predetermined time intervals and equal amount of fresh medium was replaced to maintain sink conditions and sample was analyzed at 248 nm spectrophotometrically. The resultant concentration was calculated from standard equation.

Instrumental techniques of evaluation

Fourier-Transform Infrared Spectroscopy (FTIR)

Fourier-transform infrared (FTIR) spectrum of Efavirenz and final formulation was obtained using an IR spectrophotometer. The samples were scanned over the wave number range of 4000 to 650 cm^{-1}.

Differential Scanning Calorimetry Studies (DSC)

The DSC patterns were recorded by a heat flow method. Efavirenz was heated in crimped aluminum pans with a pierced lid at a scanning rate of 10 ^{o}C/ min in an atmosphere of nitrogen gas purge (20ml/min). The DSC was calibrated for baseline using empty pans, and for temperature and enthalpy using indium.[14]

X-ray Powder Diffraction Analysis (XPRD)

The XRPD patterns of solid samples of efavirenz were recorded on X-ray diffractometer. The study was carried out on API as well as on stability samples of formulation to evaluate the effect of processing parameters on the drug.[15]

Formulation trials and evaluation of tablets

Non aqueous method of granulation was used with PVP K_{30} as binder. Soluplus®, [16] a novel

excipient with reported application in increasing solubility of drug was selected to improve the dissolution rate of efavirenz along with other ingredients like DOSS, superdisintegrant sodium starch glycolate.[17] Wetting agent sodium lauryl sulphate (SLS) was used intragranularly as well as extragranularly. PVP K_{30} acted as a binder. The granules were subjected to size reduction and were lubricated with 1% w/w magnesium stearate. Factorial design was applied to optimize tablet formulations while taking intragranular SLS and Soluplus® as independent variables at three different levels under investigations as mentioned in Table1.[18] 3-D contour plots were drawn to visualize the impact of changing variables at a glance. Formula of all nine factorial batches is shown in Table 2. Tablets containing equivalent to 50 mg of Efavirenz were prepared by non aqueous granulation method. The granules were then compressed on 8 station rotary compression machine using 11 mm flat faced punch. The formulations were evaluated for physical parameters as per Pharmacopoeial monograph.

In Vitro Drug Release Study

In vitro release test was performed using USP Type II dissolution test apparatus (Lab India) using 900 ml of 1 % SLS at 37±0.5°C, paddle speed –50 rpm. Aliquots of 5 ml were withdrawn at predetermined time intervals, and replaced with an equal volume of the fresh medium to maintain the total volume constant. Samples were filtered through Whatman filter paper no. 41 and assayed by UV spectrophotometry at 248 nm after suitable dilution. The cumulative percentage of drug released from the tablets was calculated and plotted as a function of time. The dissolution profile data was fitted to different kinetic models to determine the best fit model.

Stability Studies

Stability studies were performed according to ICH guidelines[3]. The effects of temperature, humidity and time on the physical characteristics and chemical properties of the tablet were evaluated for assessing the stability of the optimized formulations. The different parameters that were studied include dissolution test, hardness, thickness, friability, drug content as per ICH guidelines.

RESULTS AND DISCUSSION

Drug Content

Drug content was evaluated and was found to be in acceptable range indicating suitability of developed method (Table3).

Analytical Method Development of Efavirenz

UV analysis

UV spectrometric scanning showed absorption maxima at 247 nm and coincides with value reported in literature. Calibration curve was drawn within range 6-18 µg/ml. Spectra of efavirenz in distilled water is shown in(Fig. 1).Optical characteristics are reported in Table 4.

Dissolution studies

The dissolution data of formulated tablets is presented in (Fig.2). Conventional tablets (B No. EF13) demonstrated 29.5 % release of efavirenz after 30 min. As against this, tablets containing physical mixture of efavirenz with Soluplus® showed statistically significant increase in dissolution over the entire duration of the study. Factorial Batches (EF28-EF36) were superior as compared conventional batch and released around 75% drug in 30 minutes.

Fourier-transform infrared spectroscopy (FTIR)

The spectra were compared for characteristic peaks of efavirenz molecule and their presence or absence in physical mixture tablets were noted and are depicted in (Fig.3 and 4**)** respectively. The FTIR spectra of efavirenz and physical mixture of efavirenz and Soluplus®, showed identical peaks indicating that overall symmetry of the molecule was not significantly affected. This indicates that there was no chemical interaction between the drug and the excipients used in efavirenz formulation. Spectra of stability batches after 3 months at accelerated conditions were compared with those of pure drug and initial tablet sample. No change in peaks was seen indicating no change in chemical composition.

Differential scanning calorimetry studies (DSC)

DSC has been shown to be a powerful tool in characterization of solid state interactions between drug and polymer. Thermal analysis of Efavirenz by Differential Scanning Calorimetry showed a characteristic sharp endothermic peak at 136.7°C indicating the melting point of the drug. This fact confirmed that the API was pure and crystalline in nature (Fig.5). DSC thermogram of efavirenz-Soluplus® mixture showed a decrease in the glass transition temperature indicating that the drug has undergone transition from crystalline to amorphous state.Overlay of DSC scans of efavirenz with individual excipients confirmed absence of drug-excipient interaction (Fig.6)

X-ray powder diffraction analysis (XPRD)

XPRD was used to determine the crystallinity of drug in optimized formulation. The XPRD diffractogram of API showed numerous sharp, intense and narrow peaks reflecting high crystallinity. From (Fig. 7) it is observed that peak intensity of optimized formulation batches is lower and fewer number of peaks were seen. This confirms the hypothesis that amorphization of efavirenz has taken place due to processing with Soluplus®.

Optimization and evaluation of efavirenz formulation

Optimization of formula

Optimization of formula was done by Design of Experiment (DOE)technique. A full factorial design with two independent variables namely Soluplus® and SLS at three different levelswas drawn. The dependent variables that were evaluated include drug release in 1 hour, time for 50%drug release, time for 90% drug release, dissolution efficiency (DE) and mean dissolution time (MDT). Effect of change in levels of the independent variables was assessed by drawing 3D contour plots. (Fig.8). It was seen that as concentration of Soluplus® increased from 25 mg to 75 mg, with increase in SLS concentration from 2.5 to 7.5 mg, the amount of drug released in 1 hr increased. Thus increase in concentration of both lead to improved dissolution profile. At the same time, minimum time for 50% drug release was seen at Soluplus® concentration of 25 mg and SLS concentration of 5 mg.It is seen that 90% of drug released in minimum time when Soluplus® concentration is 75 mg and extragranular agent SLS 7.5 mg/tab. Thus, highest concentration of both give a release profile that shows minimum time for 90% release of the drug. Also, Dissolution efficiency is highest with lowest concentration of Soluplus® concentration 25 mg and extragranular agent SLS concentration 2.5 mg/tab. It was observed that mean dissolution time was independent of concentration of Soluplus® and SLS. Hence a somewhat flat plot obtained. Three of the batches that showed good release (EF28, EF32 and EF33) were subjected to evaluation by doing similarity and difference tests as per U.S.P (Table5). Based on results of the tests, the three batches do not vary with respect to dissolution profile. However, EF28 has minimum concentration of Soluplus® and SLS (Table 2) and was finalized for scaleup for stability studies. Amongst the different kinetic models applied to dissolution data, Korsmeyer-peppas was found to be the best fit model (Table 6). Also EF28 has highest value of dissolution efficiency justifying its selection as the finalized formula.

Evaluation of optimized formulation of efavirenz

The stability batches were evaluated for precompression and post compression parameters as per Indian Pharmacopoeia 2010 and results are reported in Table 7 and 8. Thus, tablets tested for weight variation, uniformity of content, hardness and disintegration time showed results within pharmacopeial limits.

Dissolution Data of optimized formulation

In vitro dissolution study of optimized formulation showed faster drug release, with minimum disintegration time, good mechanical strength. Drug release was in compliance with the Pharmacopeia for release obtained within 30 minutes and around 98 % drug was released at the end of 120 min. (Fig9 and 10).

Stability study

Two batches EF37 and EF38 (optimized formula) were manufactured and put up on stability at 25°C/60%RH, 40°C/75%RH and were evaluated

as per stability protocol as shown in Table 9 and 10. The blend was evaluated for pre compression parameters as shown in Table 6 and7. In vitro dissolution was within acceptable limit as shown in (Fig.9 and 10). It can be concluded that formulation was stable for three months under conditions of accelerated testing. FTIR, DSC and XPRD scans of stability batches are reported in Fig 11, 12 and 13.

CONCLUSION

In present study, we investigated the possibility of preparing tablets using physical mixtures of Soluplus® and efavirenz with other excipients. Drug-excipient compatibility was assessed by exposing physical mixtures of drug and each excipient to higher temperature and UV light. The samples were evaluated by instrumental techniques such as UV, FT-IR, XRD and DSC. No incompatibility was seen. The release profile of compressed tablets indicates that almost 100% of the drug is released in 2 hours. As the final conclusion, it is obvious that the formulation was able to achieve preset goal of increasing the solubility of Efavirenz. Since physical mixtures with novel excipient (Soluplus®) improved the solubility, the study can be extended further by preparing solid dispersions of efavirenz with Soluplus®. This will aid in dispersing efavirenz at molecular level, further enhancing rate of dissolution of drug as well as dissolution efficiency. Also there is scope for trying out other dissolution enhancing excipients in the formula. This will help in improving bioavailability without incurring cost of investing in specialized equipment as conventional manufacturing equipment can be used in processing of solid dispersions.

ACKNOWLEDGEMENT

The authors are grateful to Gahlot Institute of Pharmacy for providing valuable insights and premises to carry out experimental work. The authors are thankful to BASF India and LEE Pharma for providing excipients and drug sample respectively. The authors also acknowledge IIT Mumbai for providing facilities to carry XPRD studies.

Table 1: Formulation design for three different levels for variables as per factorial design

Coded level	-1	0	+1
X1: SOLUPLUS (mg/tablet)	25	50	75
X2: SLS (mg/tablet)	2.5	5	7.5

Table 2: Formulation of tablets as per factorial design

Ingredients	(mg/tablet)								
	EF28	EF29	EF30	EF31	EF32	EF33	EF34	EF35	EF36
Efavirenz	50	50	50	50	50	50	50	50	50
Soluplus	25	25	25	50	50	50	75	75	75
Microcrystalline cellulose	202	199.5	197	177	174.5	172	152	149.5	147
DOSS	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
SLS	2.5	5	7.5	2.5	5	7.5	2.5	5	7.5
PVP K 30	8	8	8	8	8	8	8	8	8
Sodium starch glycolate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sodium lauryl sulphate	5	5	5	5	5	5	5	5	5
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Tablet weight	250	250	300	300	300	300	300	300	300

Table 3: Drug content of factorial batches

Batch no.	Assay (%w/w)
EF28	104%
EF29	106%
EF30	101.5%
EF31	103.6%
EF32	106%
EF33	104%
EF34	103.2%
EF35	101.6%
EF36	106%

Table 4: Optical characteristics of efavirenz

Parameters	Observed values
λmax (nm)	247 nm
Beer's range (µg/ml)	6-18 µg/ml
Correlation Coefficient (r^2)	0.999
Regression equation	Y=0.0406x+0.0771
Intercept (a)	0.0771
Slope (b)	0.0406
LOD	3.86
LOQ	11.703

Table 5: Results for similarity and difference factor

BATCHES	SIMILARITY FACTOR(f2)	DIFFERENCE FACTOR(f1)
EF28-EF32	58.35%	4.653%
EF28-EF33	50.43%	3.169%

Table 6: Fitting of data to kinetic models

Formulation code	Zero order	1st order	Higuchi	Korsmeyer peppas	D.E (%)	MDT
EF28	0.7272	0.665	0.8478	0.914	91.26	18.48
EF29	0.8327	0.7901	0.9287	0.9755	82.14	20.74
EF30	0.6584	0.5361	0.791	0.8226	75.01	22.19
EF31	0.6506	0.5031	0.7823	0.7909	72.49	23.52
EF32	0.8248	0.7638	0.921	0.9636	87.20	21.033
EF33	0.7659	0.7087	0.8776	0.9284	93.31	16.26
EF34	0.67	0.5807	0.7943	0.8534	76.44	17.59
EF35	0.6266	0.5297	0.758	0.8096	83.66	19.95
EF36	0.6307	0.5445	0.7713	0.8371	91.61	17.87

Table 7: Data for pre compression parameters of stability batches

Formulation Code	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility Index	Hausner's Ratio	Angle of repose(θ)
EF37	0.227	0.263	13.68	1.15	27.52
EF38	0.25	0.277	9.74	1.10	25.87

Table 8: Data for post compression parameters for stability batches

Formulation Code	Assay (%)	Weight variation(mg)	Hardness (kg/cm^2)	$t_{50\%}$(mins)	$T_{90\%}$ (mins)
EF37	100.8%	296.3±14.81	7	20	60
EF38	110.4%	297.1±14.85	4	10	30

Table 9: Stability data batch EF 37

TEST	STATION						
	Initial	One Month		Two Months		Three Months	
		25°C/60% RH	40°C/75% RH	25°C/60% RH	40°C/75% RH	25°C/60% RH	40°C/75% RH
Appearance	White	White	White	White	White	White	White
Weight Variation(mg)	296.3±14.81	---	---	---	---	---	---
Hardness (kg/cm^2)	7	---	---	8	7	9	7
thickness(cm)	0.47	---	---	---	---	---	---
Disintegration time	1 Min 30 Sec	2 Min	1 Min 40 Sec	2.5 Mins	1 Min 45 Sec	3 Min	2 Mins
Assay (UV method)	100.8%	98.88%	95.26%	107%	98%	98%	95.4%
Dissolution $t_{10\%}$	✓	✓	✓	✓	✓	✓	✓
$t_{50\%}$	20 min	25 min	25 min	20 min	25 min	30 min	25 min
DSC	✓	---	---	---	---	✓	✓
FTIR	✓	---	---	---	---	✓	✓
XRD	✓	---	---	---	---	✓	✓

Table10: Stability data batch EF 38

TEST	STATION						
	Initial	One Month		Two Months		Three Months	
		25°C/60 % RH	40°C/75 %RH	25°C/60 % RH	40°C/75 % RH	25°C/60 % RH	40°C/75 % RH
Appearance	White	White	White	White	White	White	White
Weight Variation (mg)	297.1±14.85	---	---	---	---	---	---
Hardness	4	---	---	6	5	7	4
thickness(cm)	0.47	---	---	---	---	---	---
Disintegration time	1 Min 30 Sec	2 Min	1 Min 40 Sec	2 Mins	1 Min 50 Secs	3 Mins 30 Secs	2 Mins
Assay (UV method)	110%	93%	105.6%	94.4%	103%	110.8%	108%
Dissolution t10%	✓	✓	✓	✓	✓	✓	✓
t50%	10 mins	20 mins	10 mins	20 mins	10 mins	30 mins	10 mins
DSC	✓	---	---	---	---	✓	✓
FTIR	✓	---	---	---	---	✓	✓
XRD	✓	---	---	---	---	✓	✓

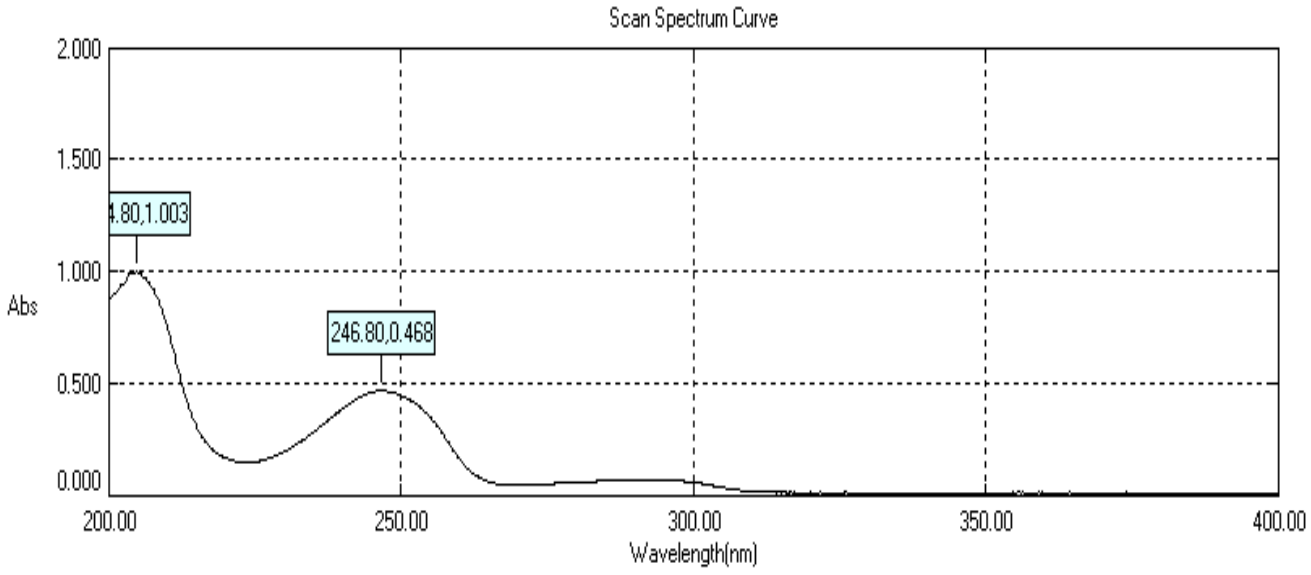

Figure 1: Spectra of Efavirenz in distilled water

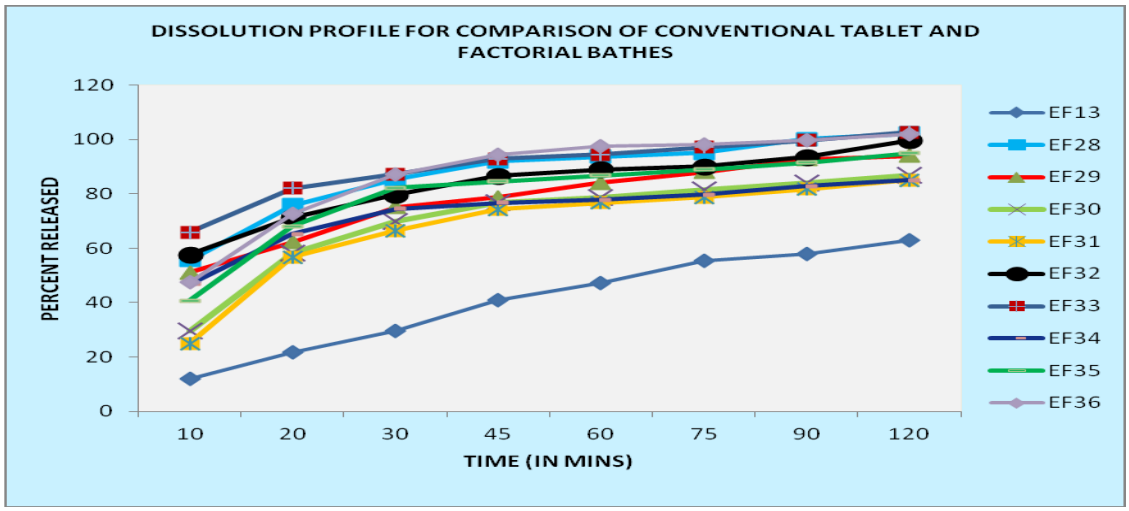

Figure 2: Dissolution profile for comparison of conventional and factorial batches (Physical mixtures with Soluplus®) EF13-Conventional batch; EF28-36: Factorial batch

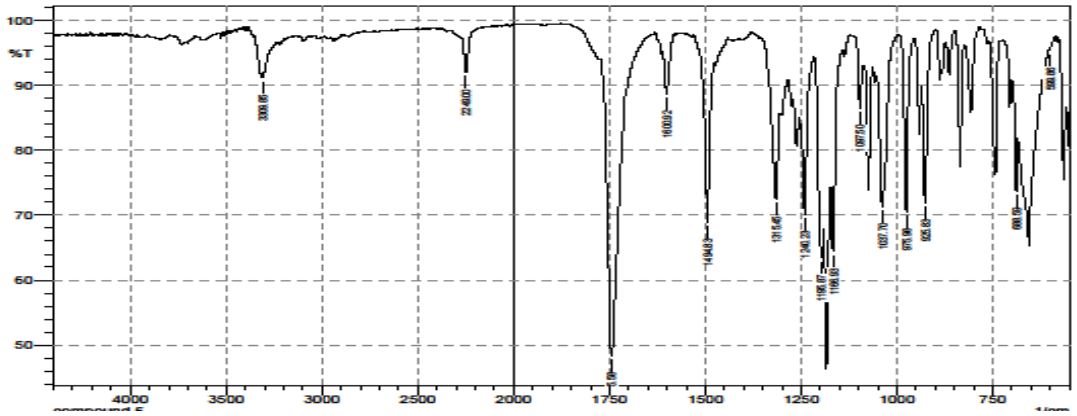

Figure 3: FTIR spectrum of pure drug efavirenz

N-H stretching-3309.85
C=O stretching-1745.8

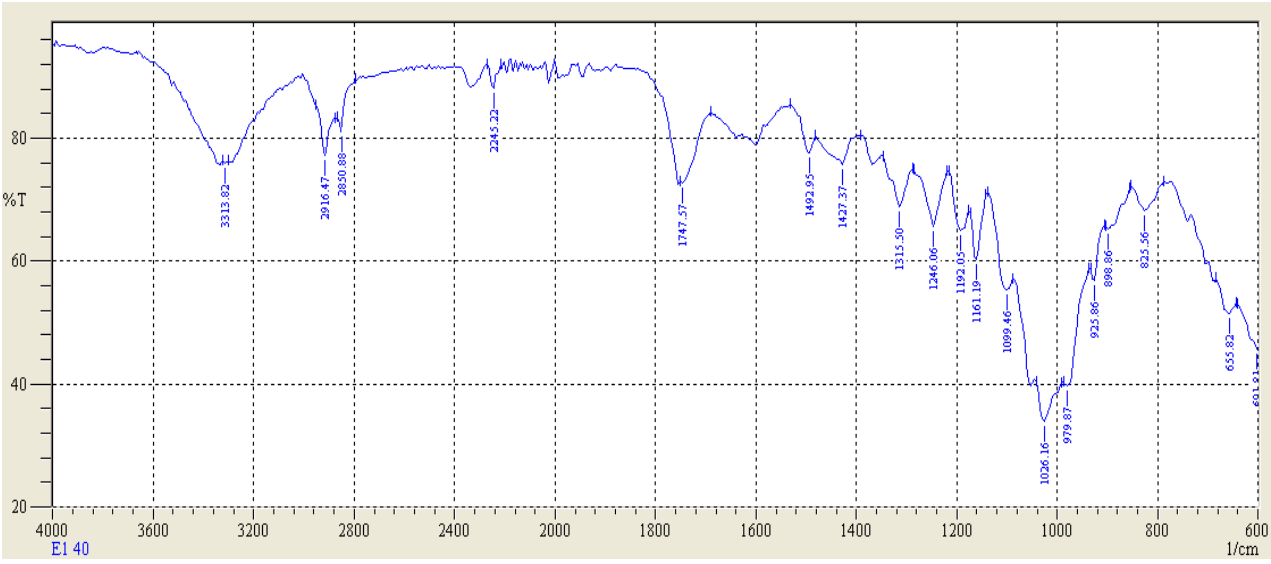

Figure 4: FTIR spectrum of efavirenz tablet (EF 37)

C=O-147.57
N-H stretching – 3323.3

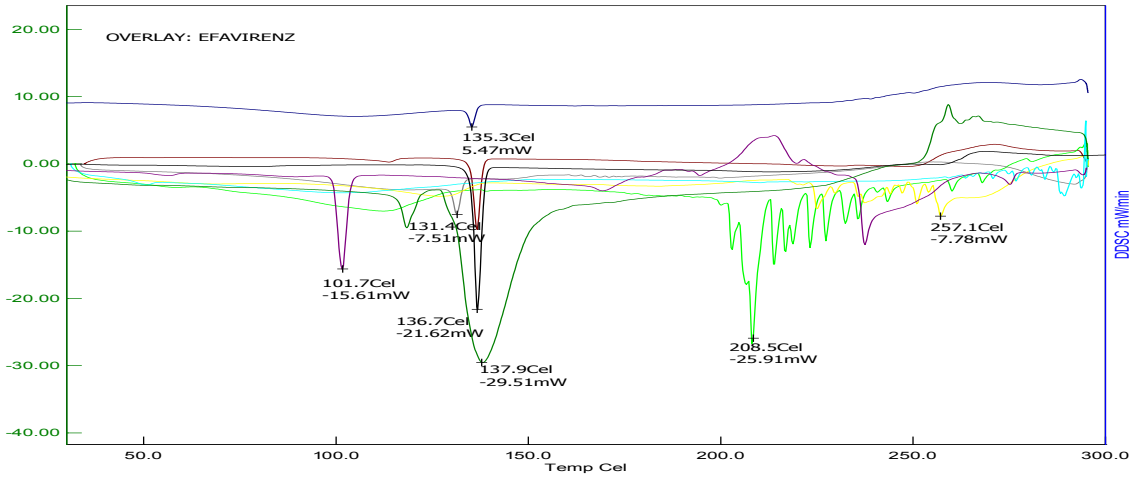

Figure 5: DSC scan for pure drug efavirenz

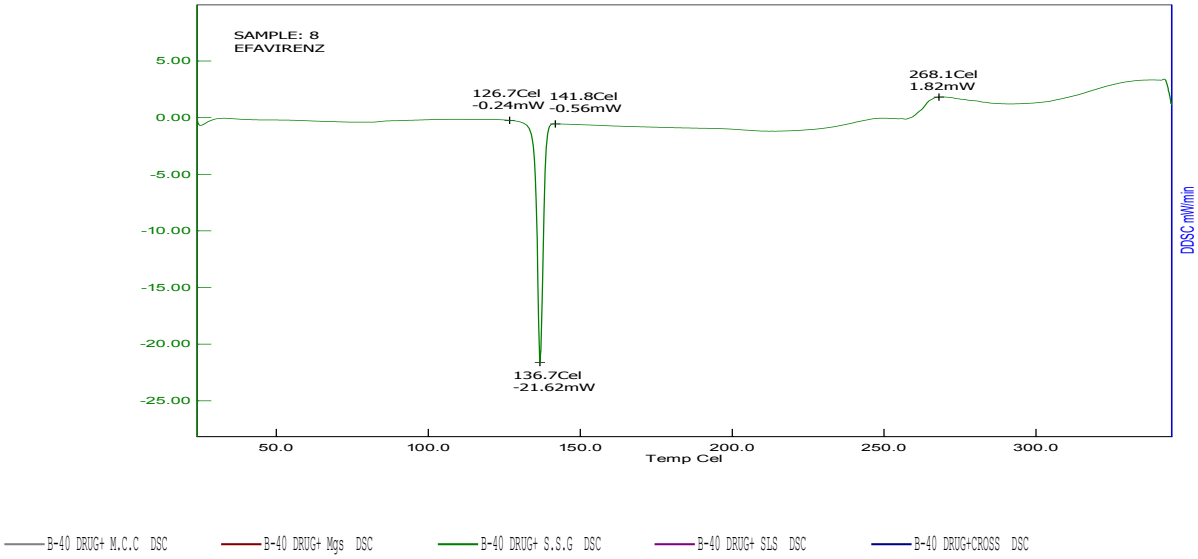

Figure 6: Overlay of DSC scan for drug with all excipient

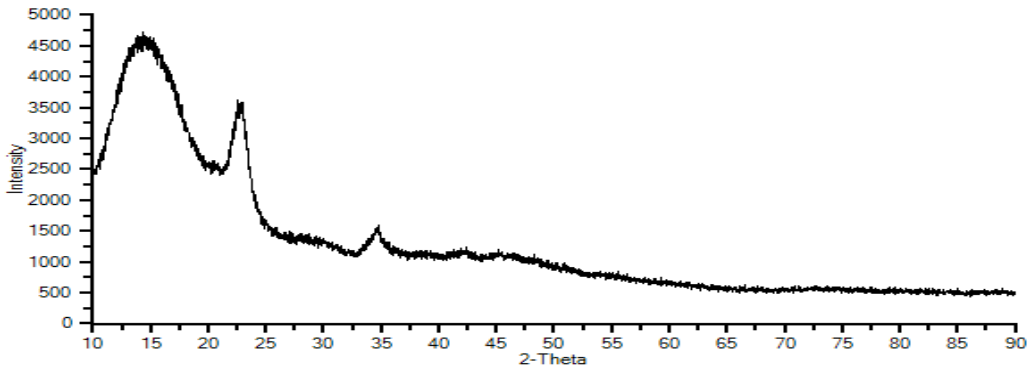

Figure 7 : XRD scan of efavirenz

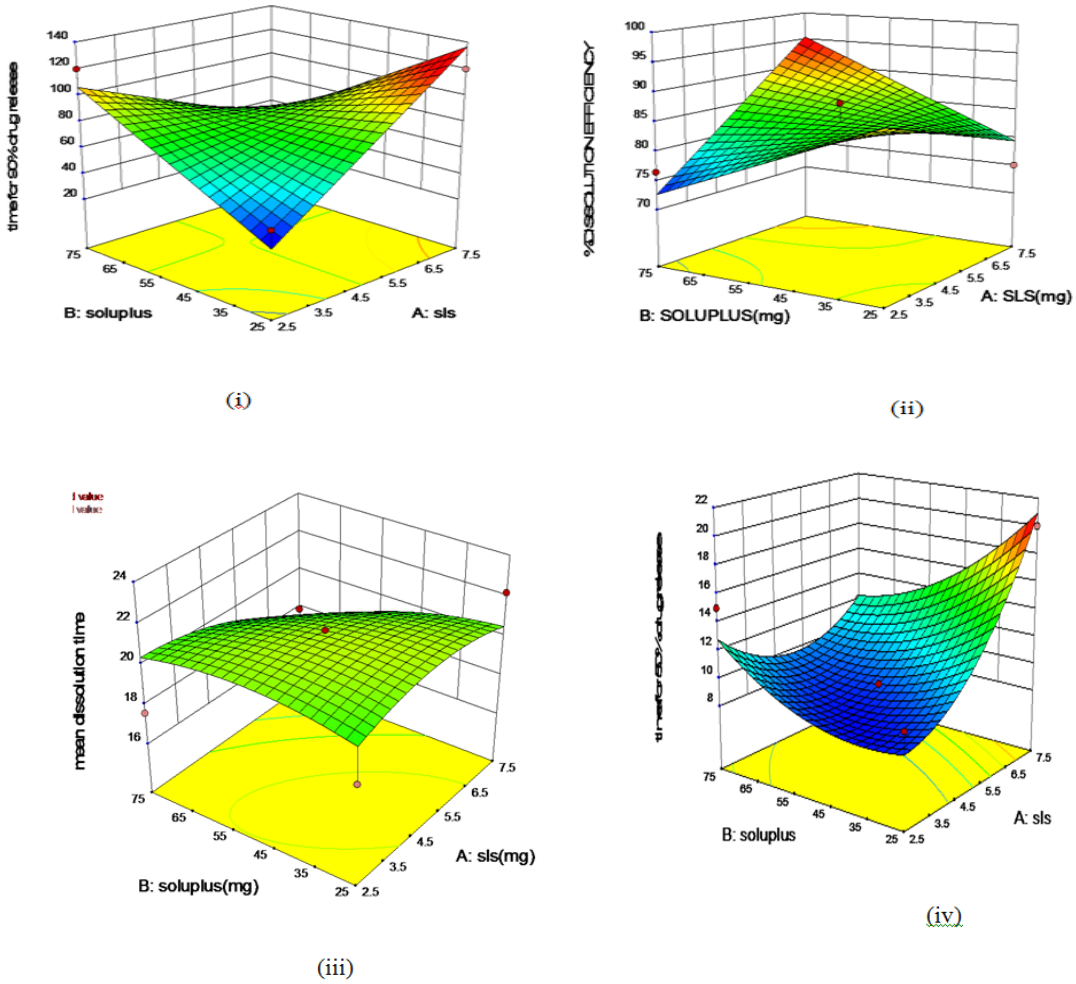

Figure 8 : 3D contour plots for factorial batches for selection of best optimized formula

Schematic representation of 3Dcontour plots for (i)time for 90% dissolution, (ii) dissolution efficiency, (iii) mean dissolution time and (iv) time 50% release of drug.

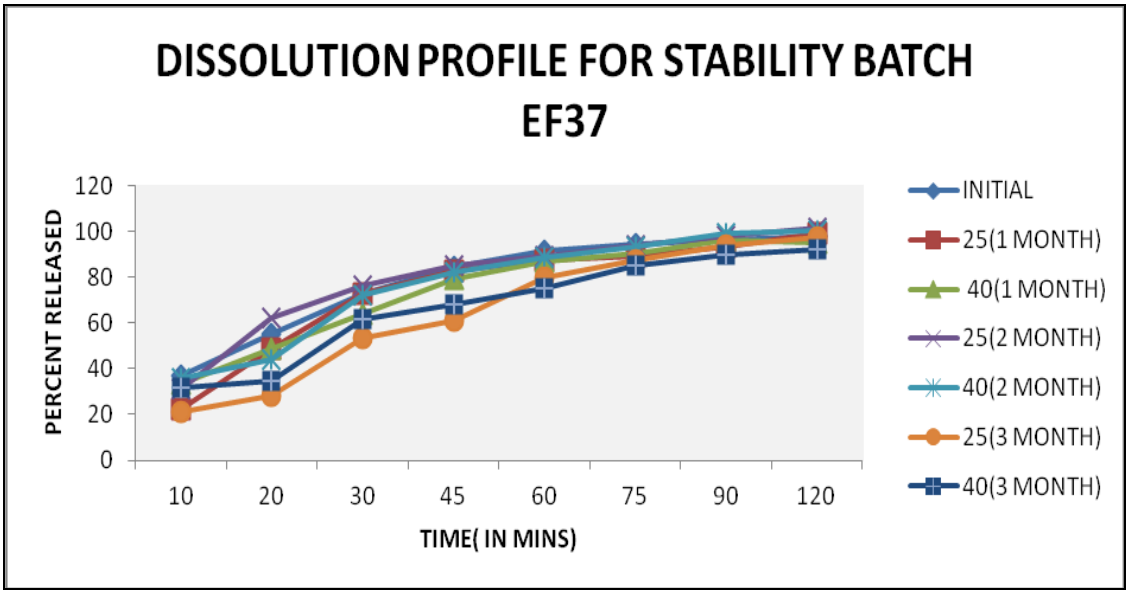

Figure 9: Dissolution data for final formulation along with release for stability batch 37

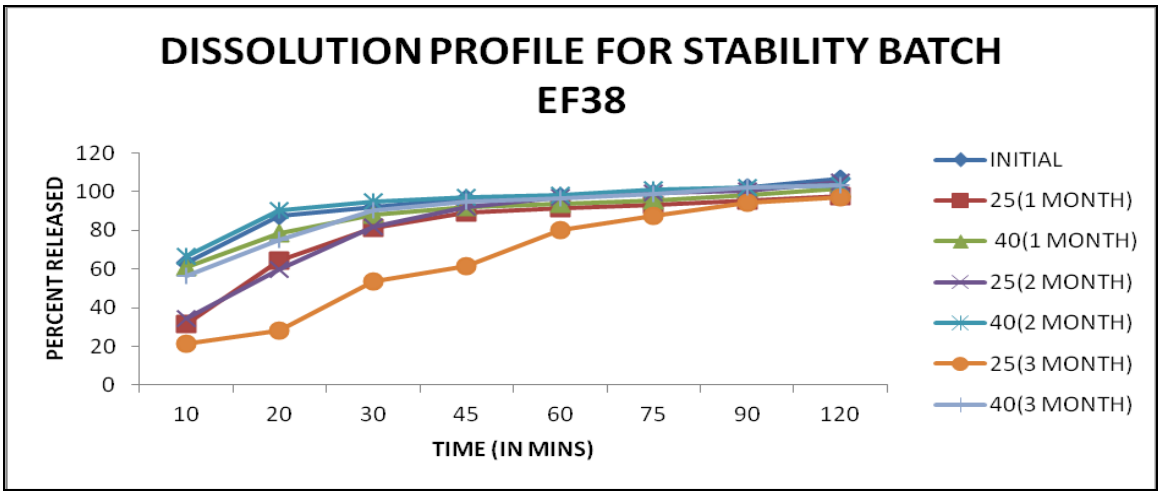

Figure 10: Dissolution data for final formulation along with release for stability batch 38

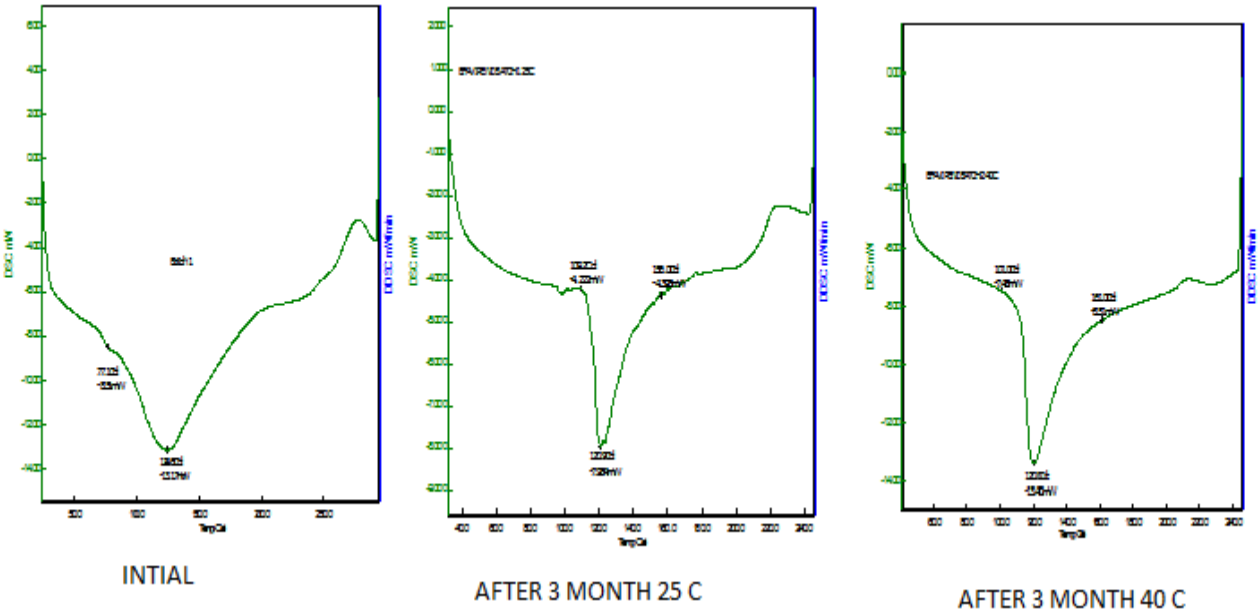

Figure 11: DSC scans for stability batch (EF 37)

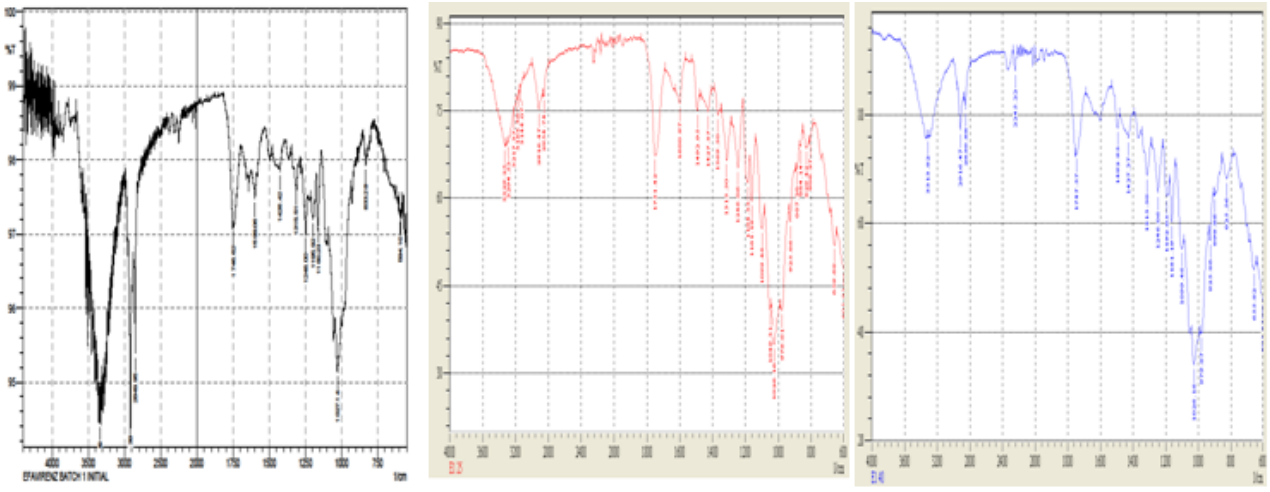

Figure 12: FTIR scans for stability batch (EF 37)

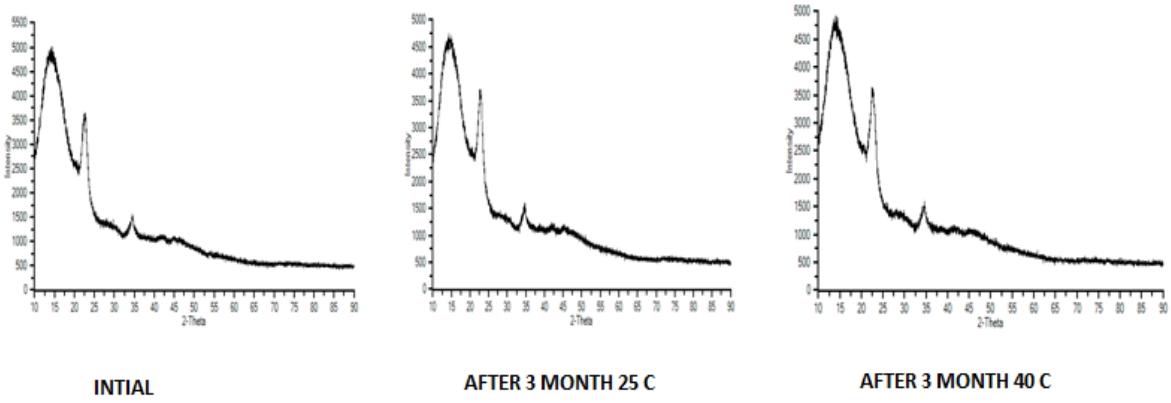

Figure 13: XPRD scans for stability batch (EF 37)

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Cite This Article: Smita, Nayak; Shivali, Singh and Vaidhun, Bhaskar (2016), "Formula optimization for rapid dissolution of efavirenz from dosage form", ***Pharmacophore***, Vol. 7 (6), 458-471.

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