Research Article

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DEVELOPMENT AND *IN-VITRO* EVALUATION OF IMMEDIATE RELEASE TABLETS OF EFAVIRENZ

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ABSTRACT:

Immediate release tablets are those tablets which disintegrate and release the drug rapidly once it enters GIT. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer and lead to better patient compliance. They are also a tool for expanding markets, extending product life cycles and generating opportunities. Efavirenz is an anti retroviral drug with poor aqueous solubility. The present work involves the formulation development and invitro evaluation of immediate release Efavirenz tablets for enhancement of dissolution rate. Direct compression method was selected for the formulation of immediate release Efavirenz tablets. Tablets were prepared using different concentrations of Croscarmellose sodium, Crospovidone, and sodium starch glycolate as superdisintegrants. During the course of study it was found that the formula F8 containing Sodium starch Glycolate as superdisintegrant exhibited acceptable disintegration time and in vitro drug release. The Drug-excipient interaction was investigated by FTIR. Later they were subjected to stability studies after packing which showed acceptable results.

KEYWORDS:

Immediate release tablets, Efavirenz, Direct compression method, FTIR.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and then maintain the desired drug concentration [1]. Oral route is considered most natural, uncomplicated, convenient and safest due to its ease of administration, patient acceptance and cost effective manufacturing process [2]. Different types of tablet formulations are available, which could be broadly classified based on:

1. Route of administration such as tablets for oral delivery, sublingual delivery, buccal delivery, rectal delivery or vaginal delivery.
2. Formulation characteristics such as immediate release tablets, effervescent tablets, melt-in mouth or fast dissolving tablets, delayed release or extended release tablets. In all the cases, the general manufacturing process, machinery used for preparation of tablets and materials used are similar [3].

Immediate release solid oral dosage forms are classified as either having rapid or slow dissolution rates. Immediate release dosage forms are those for which ≥85% of labeled amount dissolves within 30 min. For immediate release (IR) tablets, the only barrier to drug release is simple disintegration or erosion stage, which is generally accomplished in less than one hour. For many substances, conventional immediate release formulation provide clinically effective therapy maintaining the required balance of pharmacokinetic and Pharmacodynamic profiles with an acceptable level of safety to the patients [4]. The immediate release preparations have the advantage of enhanced oral bioavailability through transmucosal delivery and pregastric absorption, convenience in drug administration to dysphasic patients, especially

the elderly and bedridden, and new business opportunities.

Efavirenz,(4S)-6-chloro-4-(2-cyclopropylethynyl)-4-(trifluoromethyl)-2,4-dihydro 1H-3,1-benzoxazin-2-one (Figure 1) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) and is used as part of highly active antiretroviral therapy (HAART) for the treatment of a human immunodeficiency virus (HIV) type 1. Efavirenz inhibits the activity of viral RNA-directed DNA polymerase (i.e., reverse transcriptase). It is believed that inhibition of reverse transcriptase interferes with the generation of DNA copies of viral RNA, which in turn are necessary for synthesis of new virions [5]

In the present study Sodium starch glycolate, Crospovidone and Croscarmellose sodium used as superdisintegrants, PVP as binder, Talc and Magnesium stearate as lubricants and SLS is used to enhance the drug release.

MATERIALS AND METHODS

Materials

Efavirenz was obtained as a gift sample from Intas Pharmaceuticals Ltd., Ahmedabad, and Gujarat, India. Croscarmellose sodium, Sodium Starch Glycolate and Crospovidone were gift sample from Signet Chemical Corporation, Mumbai. Povidone was obtained from Loba Chemical, Mumbai. All other chemicals used were analytical grade. Double distilled water was used in the study.

Methodology

PRE FORMULATION STUDIES

Drug-Excipient Compatibility Studies

The FTIR samples (Efavirenz Pure drug and formulations) were obtained, using Perkin Elmer FT-IR system Spectrum BX series (Beaconsfield, Buckinghamshire, UK), in the frequency range of 4000–550 cm^{-1}at 4 cm^{-1} resolution. The technique used very small amount of each sample which directly loaded into the system. Spectrum BX series software version 2.19 was used to determine peak positions [6, 7].

Preparation of Efavirenz IR tablets:

Formulation of Efavirenz IR tablets were prepared by direct compression employing various excipients as mentioned in Table 1. Efavirenz and PVP were shifted together trough mesh #40. Microcrystalline cellulose (Avicel PH 102) was passed through 40 # mesh and mixed well in the previous blend for 10 minutes. To this, superdisintegrants was added after shifting through 40 # mesh [8]. Sodium lauryl Sulphate was added to aid release. The above obtained blend was lubricated with magnesium stearate and talc after passing through 60 # mesh. The prepared powder blend was evaluated for various parameters like bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio. This blend was then compressed using a 16 station rotary compression machine (Cadmach, Ahmedabad, India).

EVALUATION

Pre Compression parameters of Powder Blend:

a) Bulk Density (Db): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is the bulk volume. From this the bulk density was calculated according to the formula mentioned below [9]. It is expressed in gm/ml and is given by

Db = M/ Vb

Where, M and Vb are mass of powder and bulk volume of the powder respectively.

b) Tapped Density (Dt): It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750

times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus) [10].

It is expressed in gm/ml and is given by

Dt = M / Vt

Where, M and Vt are mass of powder and tapped volume of the powder respectively.

c) Angle of Repose [13]: The flow properties of blend (before compression) were characterized in terms of angle of repose, Carr's index and Hausner's ratio. For determination of angle of repose (θ), the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel [11]. Angle of repose was calculated using following equation.

tan θ = (h/r)

Where, h = height of pile; r = radius of pile

d) Carr's index (or) % compressibility [11]: It indicates flow property of powders. It is expressed in percentage and is given by

C.I. = Dt – Db / Dt * 100

Where, Dt and Db are tapped density and bulk density respectively.

e) Hausner's ratio: Hausner's ratio is an indirect index of ease of powder flow. It was calculated by the following formula [12].

Hausner's ratio = Dt / Db

Where, **Dt** and **Db** are tapped density and bulk density respectively.

Post compression parameters of Tablets:

The formulated tablets were evaluated for the following physicochemical parameters.

a) Physical appearance

The general appearance of tablets involves measurement of number of attributes such as tablet size, shape, colour, presence or absence of odor, taste, surface texture and consistency of any identification marks [13].

b) Tablet Size

Thickness of the tablet was measured by using Vernier calliper in mm.

c) Weight variation test

Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual weights deviate from the average weight by more than the percentage and none deviates by more than twice the percentage. Official limit of Efavirenz IR tablets (F1-F9) percentage deviation is ±5% [14].

d) Hardness

Hardness of all batches was determined using Tablet hardness tester (Monsanto hardness tester). The test was carried out in triplicate for all batches as per USP XXIV monograph for uncoated tablets [14].

e) Friability

Tablets of all batches were used to evaluate friability as per USP XXIV monograph. Friability testing was done by Friability test apparatus (Lab India Friability Apparatus FT 1020).

f) Disintegration test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets and note down the time taken to disintegrate the tablets then average is calculated.

***g) In vitro* dissolution studies**

Dissolution test was carried out using USP XXIV (model DISSO, M/s. Lab India) rotating paddle method (apparatus II). The stirring rate was 50 rpm. 0.1 N hydrochloric acid was used as dissolution medium (900ml) and was maintained at 37 ± 0.5^0C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, wherever necessary and were analyzed for the Efavirenz at 247nm by using a double beam UV spectrophotometer (Shimadzu-2000). Each dissolution study was performed for three times and the mean values were taken [15].

RESULTS

PREFORMULATION STUDIES

Compatibility Studies by FTIR:

Compatibility of the drug with excipients is studied by the FTIR technique. The results show that the drug is compatible with the all excipients. Compatibility is characterized on the characteristic peaks in respective wave number (Figure no. 4 & 5).

Precompression Evaluation Parameters of powder Blend:

The powder blend was prepared by mixing of various ingredients mentioned and used for characterization of various flow properties of powder. The bulk density of all the formulations was found to be in the range of 0.480 to 0.589 gm/cm^3. The tapped density of all the formulations was found to be in the range of 0.561 to 0.695gm/cm^3. The Angle of Repose for all formulations was found to be between the 25º to 30º which show that the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 12 to 18 which indicating that the powder has good flow properties. All the formulations has shown the Hausner's ratio ranging between 0 to 1.2 indicating the powder has good flow properties (Table 3).

Post Compression Evaluation Parameters of Efavirenz IR Tablets:

All the tablets were observed visually and did not show any effect such as capping, chipping and lamination. The physical characteristics of Efavirenz IR tablets (F1 to F9) such as weight variation, thickness, hardness, friability and disintegration time were determined and results of the formulations found to be within the limits specified in official books (Table no.4). The thickness of the tablets of all formulations was found to be within the range of 5.20 to 5.24 mm. A difference in tablet hardness reflects difference in tablet density and porosity. The hardness of tablets was found to be in the range of 5.12 to 5.94 Kg/cm^2. Percentage friability of all formulations was found to be in the range of 0.21 to 0.38%.This indicates good handling property of the prepared tablets. The average weight of the tablet is 900mg. The USP Pharmacopoeial limit for percentage deviation is ± 5%. The weights of all tablets were ranged from 886.2mg to 925.5mg. Disintegration test was performed for all formulations and F8 shows less disintegration time (2 min) compared to other formulations (Figure 3).

In vitro dissolution studies were studied for all the formulations in 0.1N HCl using Dissolution Apparatus (Paddle type). The samples were withdrawn at different time intervals and cumulative % drug release was calculated. The results were shown in Table no.5 and Figure 4. Among all the formulated tablets F8 which is based on Efavirenz with 10% SSG gave the highest dissolution (99.25%) in 60 mins. Based on dissolution rate the superdisintegrants can be ranked as

Sodium Starch Glycolate > Crospovidone> Croscarmellose sodium.

Stability Studies:

Based on the drug release studies F8 is selected as a best formulation and conducted the stability studies on optimized formulation as per ICH guidelines. Stability studies are continued for a period of one month and Results of the stability study had shown no remarkable change in the release profile of Efavirenz IR Tablets after the stability shown in Table no.6.

CONCLUSION

In the present work efforts have been made to develop Efavirenz Immediate release tablet as a promising approach to enhance the drug release profile using Superdisintegrants. The results showed that the release of the drug was depended on different superdisintegrants used, in that Sodium starch glycolate can release drug faster compare to Crospovidone and Croscarmellose sodium and the best formulation (F8) containing 10 % SSG showed minimum disintegration time and better drug release profile as compare to other formulations.

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Conflict of interest statement

We declare that we have no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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Table 1: Formulation of Efavirenz IR tablets

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Efavirenz	600	600	600	600	600	600	600	600	600
PVP	45	45	45	45	45	45	45	45	45
CCS	45	--	--	67.5	--	--	90	--	--
SSG	--	45	--	--	67.5	--	--	90	--
CP	--	--	45	--	--	67.5	--	--	90
Talc	18	18	18	18	18	18	18	18	18
Magnesium Stearate	9	9	9	9	9	9	9	9	9
SLS	18	18	18	18	18	18	18	18	18
MCC	165	165	165	42.5	142.5	142.5	120	120	120
TOTAL (mg)	900	900	900	900	900	900	900	900	900

Table 2: Drug-Excipient compatibility Study

S.No	Structure	Wave number (cm^{-1})	Pure API	API+Excipients
1	C-OH (-COOH, stretching)	3405-3395	3405	3401
2	R_2NH amines, N-H stretching	3350-3310	3332	3325
3	Aromatic C-C, Stretching	1600-1585	1619	1610
4	Alkyl halides C-F, Stretching	1350-1000	1261	1255
5	Alkyl halides C-Cl, Stretching	850-750	760	760
6	R_2NH amines, C-N stretching	1230-1030	1176	1180

Table 3: Pre compression Parameters of Powder blend

Formulation	Bulk density (gm/cc)	Tapped density (gm/cc)	Angle of repose(°)	Carr's Index (%)	Hausner's Ratio
F1	0.495	0.577	26.43	14.21	1.16
F2	0.482	0.561	27.59	14.08	1.16
F3	0.527	0.625	28.91	15.68	1.18
F4	0.544	0.645	27.33	15.65	1.18
F5	0.538	0.613	26.54	12.23	1.13
F6	0.561	0.662	27.82	15.25	1.18
F7	0.589	0.695	29.11	15.25	1.17
F8	0.480	0.579	28.46	17.09	1.20
F9	0.545	0.640	26.88	14.8	1.17

Table 4: Post compression parameters of Efavirenz IR tablets

Formulation	Weight Variation(mg)	Thickness (mm)	Hardness (kg/cm^2)	Percentage of weight loss (%)	Disintegration time (min)
F1	895.3	5.21	5.12	0.29	5
F2	888.1	5.20	5.94	0.32	4
F3	910.5	5.20	5.33	0.21	3
F4	915.7	5.21	5.20	0.21	4
F5	886.2	5.21	5.71	0.30	3
F6	891.9	5.24	5.89	0.31	3
F7	910.3	5.20	5.26	0.22	3
F8	925.5	5.23	5.66	0.32	2
F9	895.7	5.22	5.58	0.29	3

Table 5: Comparative % drug release profiles of all formulations (F1-F9)

Time (min)	Cumulative % Drug release								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0		0	0
5	11.41	20.92	16.53	16.47	22.37	18.73	24.38	27.51	26.04
10	15.86	26.89	23.94	26.55	30.32	28.46	35.72	38.64	37.9
15	22.54	33.63	28.46	42.44	47.65	43.89	47.92	52.02	48.35
30	31.78	41.13	38.86	49.03	55.96	52.87	61.77	69.14	63.25
45	40.57	50.87	44.93	61.77	65.78	62.54	83.03	84.88	85.55
60	51.77	59.38	53.23	77.86	85.83	81.12	95.87	99.25	97.73

Table.6: Various physicochemical parameters after stability study

Conditions	Parameter	Initial data	Data after one month
Room temperature	Hardness(kg/cm^2)	5.66	5.66
Room temperature	Friability (%)	0.32	0.31
Room temperature	Disintegration time (min)	2	2
Room temperature	% drug release	99.25	99.17
Intermediate	Hardness(kg/cm^2)	5.66	5.64
Intermediate	Friability (%)	0.32	0.32
Intermediate	Disintegration time (min)	2	2
Intermediate	% drug release	99.25	99.19
Accelerated	Hardness(kg/cm^2)	5.66	5.65
Accelerated	Friability (%)	0.32	0.32
Accelerated	Disintegration time (min)	2	2
Accelerated	% drug release	99.25	99.23

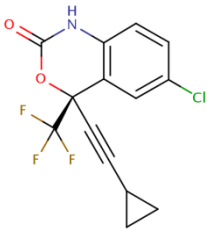

Figure: 1 Structure of Efavirenz

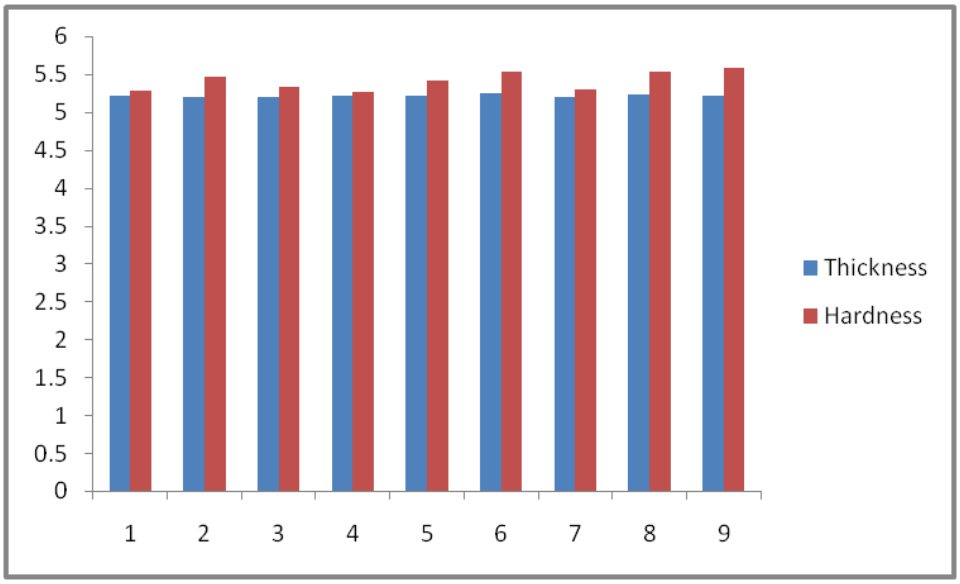

Fig.2: Comparative graph of Thickness & hardness

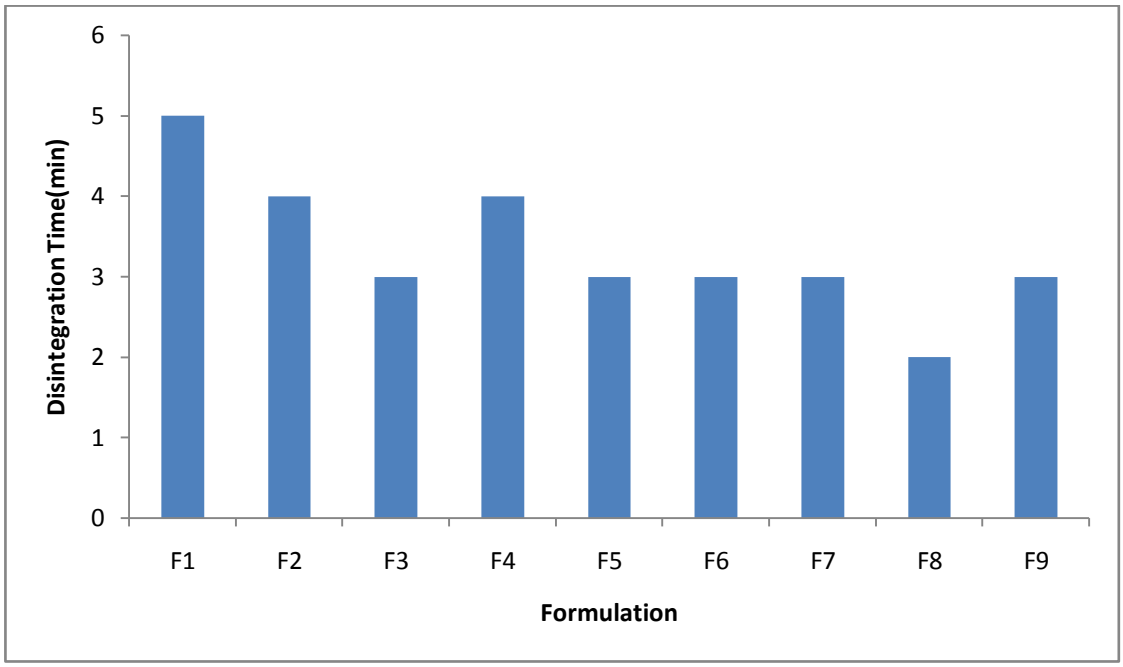

Fig.3: Comparative graph of Disintegration time for all formulations

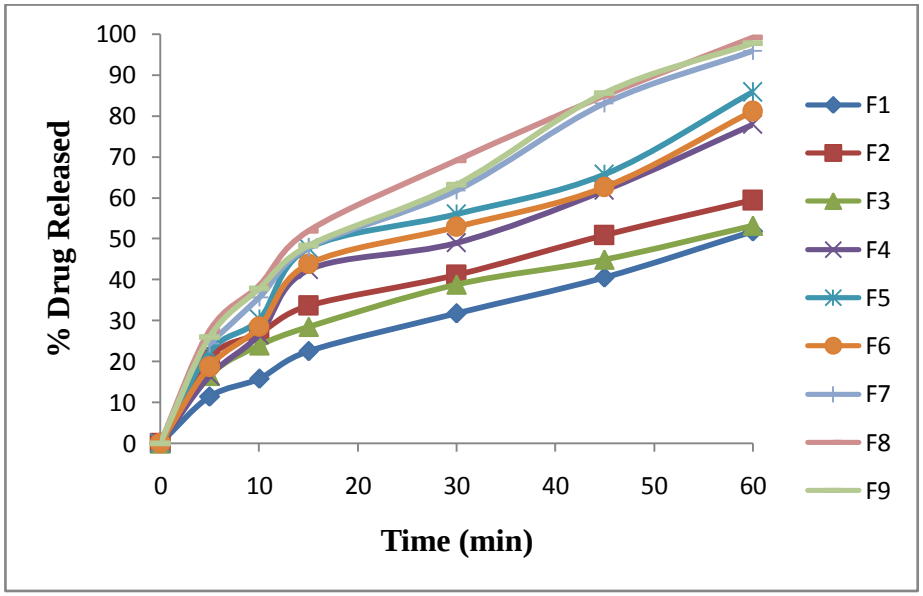

Fig.4: Comparative Percentage drug release Profile of all formulations

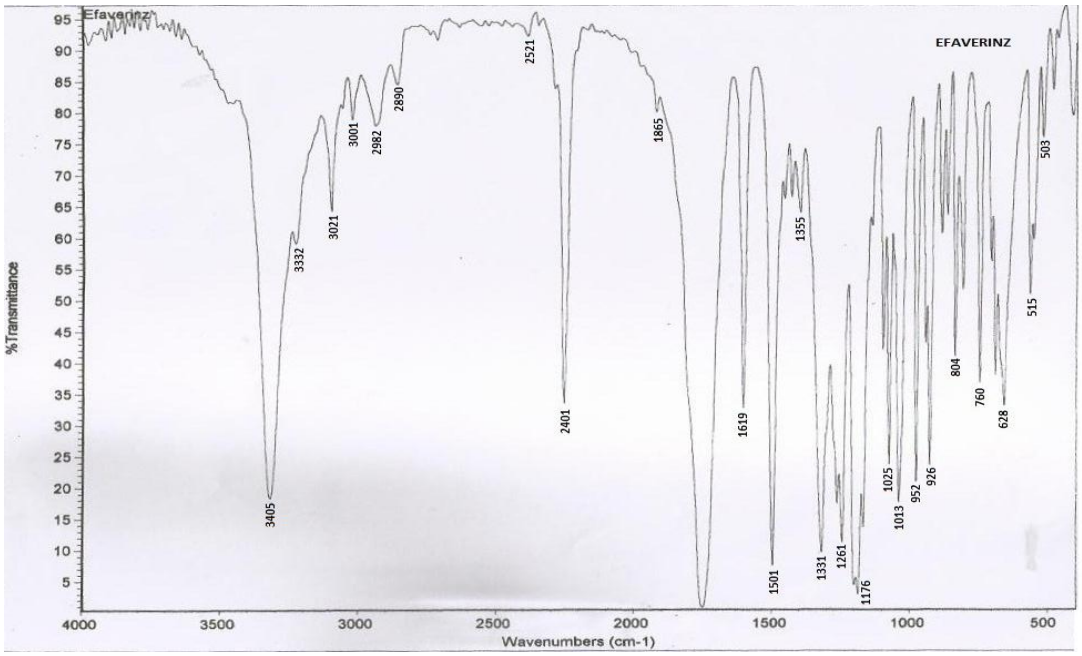

Figure.5: FTIR of Pure Efavirenz

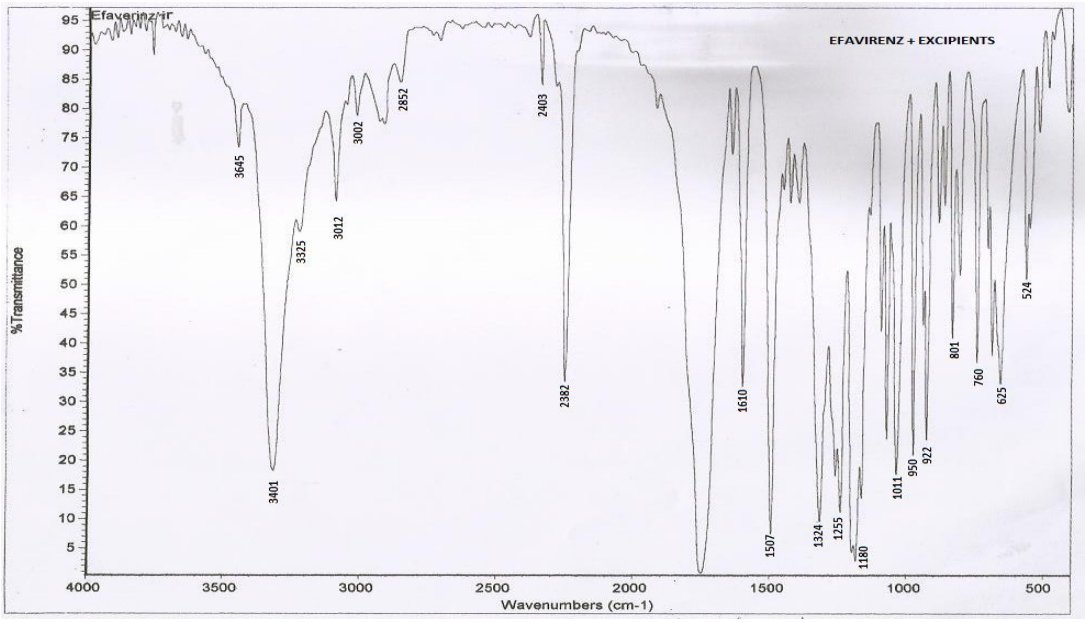

Figure.6: FTIR of Pure Efavirenz with Excipients

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