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Original Article

FORMULATION AND DEVELOPMENT OF EFAVIRENZ TABLETS BY PAPER TECHNIQUE USING CO-SOLVENCY METHOD

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ABSTRACT

Objective: The present study is to formulate and development of efavirenz tablets by paper technique using the co-solvency method, the drug is antiviral drug used for the treatment of HIV.

Methods: In this 7 formulation (F1-F7) were prepared by using different tissue papers like kitchen roll paper, hand kercheif paper, facial tissue paper, with different weights. The prepared tablets were evaluated for hardness, friability, thickness, content uniformity, disintegration time and *in vitro* dissolution study.

Results: Among all the formulations, F2 (kicthen roll paper with weight 250 mg) was consired to be the best formulation, which release up to 98.02% drug in 3 h. The results of stability studies of formulation F2 after a period of 2 mo indicated that the formulation was stable.

Conclusion: It was concluted that a paper tablet of efavirenz shows better results and it does not contain any excipient and increase the dissolution rate.

Keywords: Efavirenz, Tissue paper, Disintegration, *In vitro* dissolution

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INTRODUCTION

Oral drug delivery is the most efficient drug delivery due to its ease of administration, high stability, more patient compliance, less cost, manufactured easily. So most of the API available in the oral dosage form. As a result, pharmaceutical companies are designed most of the various new oral formulation. Apart from this many water-insoluble drugs are present class 2 means it as low solubility and high permeability the solubility of the drug increases, the bioavailability of the drug increases [1]. To enhance the solubility of the drug various solubility enhancement technique are like micronization, solid dispersion, conservation, co solvency, etc [2].

Co-solvency [3-5]

To increase the solubility of non-polar solvent it is mixed with water-miscible or partially miscible solvent popularly known as co solvency technique. It is widely used because it is very simple to prepare and evaluate.

Examples: -ethanol, propylene glycol, PEG 300,

Co-solvent was also used in other techniques like precipitation, p^H adjustment and solid dispersions. In parenteral low toxic solvents can be used widely like ethanol, propylene glycol, glycerine.

Advantages

1) It is very simple and accurate.

2) Shows a high degree of solubility when compare to other solubilization techniques.

3) When compare surfactants it has no toxicity problems.

4) It forms simple compounds, not complex compounds.

MATERIALS AND METHODS

Materials [6, 7]

Efavirenz, various types of papers were used and it contains pharmaceutical quality like kitchen roll paper, facial tissue, handkerchief paper were taken, ethanol.

Method

Estimation of efavirenz by UV spectrophotometric method [8]

A UV spectrophotometric method based on the measurement of absorbance at 247 nm in 2% SLS was used in the present study for the estimation of Efavirenz.

Preparation of standard curve of efavirenz

In this 10 mg of the drug (efavirenz) was accurately weighed and transferred into 10 ml volumetric flask, dissolved it is in a few ml of methanol and was made up to 10 ml to get a concentration 1 mg/ml stock solution. From the stock solution, further dilutions were made with SLS (2%w/v) to get the concentrations ranging from 2.5 µg/ml to 20 µg/ml. The absorbance was measured at 247 nm in UV-Visible Spectrophotometer. The absorbance was plotted against concentrations of drug vs time as shown in fig. 1. The method obeyed Beer's law in the concentration range of 2.5-20 µg/ml.

Sterilization of papers

Before performing the further steps, sterilization of papers can be done for various grades of papers like (kitchen roll, paper, facial tissue paper, and handkerchief paper) are kept in a hot ir oven at temperature ranges from 150-200 ° C for 10 min and the sterilized papers were used for further process.

Method for preparation of paper tablet using various papers [9]

In these sterilized papers are taken with certain parameters like the diameter of 10 mm and a mass of about 200 mg were produced by using a single punch tablet press. Before compression, the different types of paper were cut into pieces, each possessing a mass of about 200 mg. For this, the density of the paper was roughly determined by analysing the height and the respective mass/volume. Based on this the required area of paper was calculated, cut out and weighed to control the mass.

In these various types of tissue, papers were taken up to the 200 mg weight of paper [kitchen roll, disposable Handkerchief, facial tissue]. This paper acts as a matrix. They were cut into 6*6 sizes, and then the drug was dissolved ethanol and the solution is dispersed in water. Then the Dissolved drug solution was loaded into the papers

with pipette drop wise and the dried. The procedure was continued until the required quantity of the drug was loaded into that papers and then again the papers were cut into 1*1 sizes and the papers were compressed. The tablet was obtained.

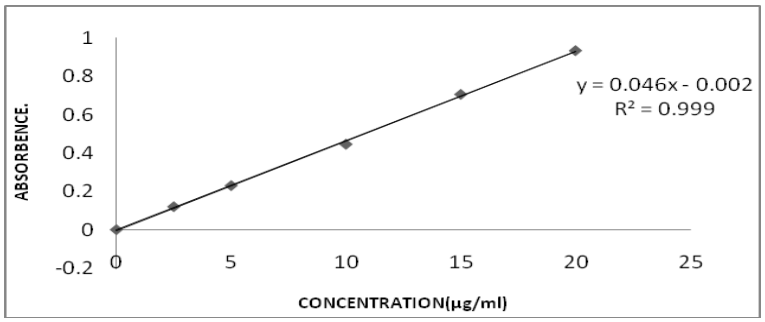

Fig. 1: Calibration curve of efavirenz

Table 2: Interpretation of FTIR spectra of pure drug

Ingredients	F1	F2	F3	F4	F5	F6	F7
Efavirenz	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
Ethanol	2 ml	2 ml	2 ml	2 ml	2 ml	2 ml	2 ml
Kicthen roll tissue paper	100 mg	200 mg	300 mg	---	---	---	---
Hand kercheif tissue paper	---	---	---	100 mg	200 mg	300 mg	---
Facial tissue paper	---	---	---	---	---	---	200 mg
Total	150 mg	250 mg	350 mg	150 mg	250 mg	350 mg	250 mg

RESULTS AND DISCUSSION

Drug–paper compatibility studies

- **Fourier transform infrared (FT-IR) studies**

FT-IR spectra of efavirenz and various papers were recorded in the range of 400 to 4,000 cm-1 using a Jasco -FT-IR spectrophotometer (Jasco, Essex, UK) by the KBr disc method. The spectra are shown in fig. 2

Differential scanning calorimetry

DSC thermograms of pure efavirenz and optimized formulation were recorded on DSC. Samples (15 mg weighed to a precision of 0.1 mg) were placed in aluminum pans and the lids were crimped using a TA crimper. The thermal behavior of the samples was investigated at a scanning rate of 10°/min, covering a temperature range of 25-200° against an empty aluminum pan as reference. The instrument was calibrated with an indium standard. The DSC thermograms.

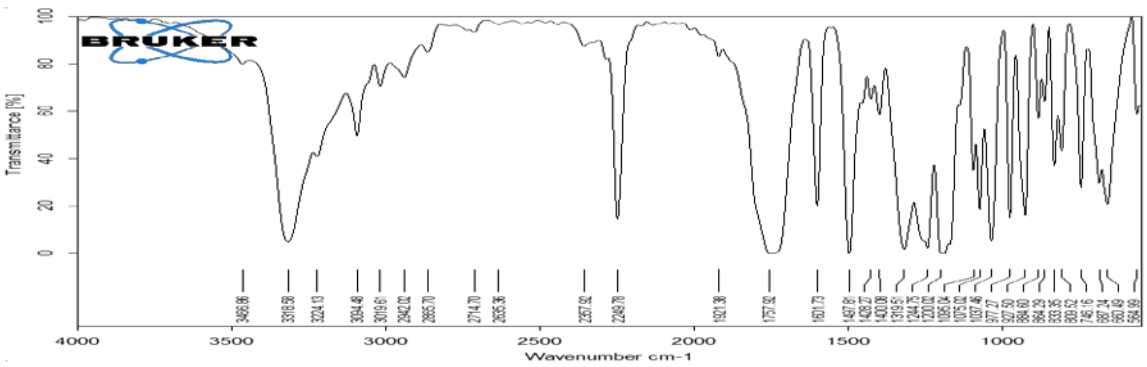

Fig. 2: FITR of pure drug

Table 3: FITR of drug with paper

S. No.	Wave number (cm^{-1})	Bonds
1.	1601.73	NH
2.	1244.75	Cl
3.	1319.51	CH_3
4.	3318.58	OH
5.	1428.27	CH_2
6.	1200.07	CF_3
S. No.	**Wave number (cm^{-1})**	**Bonds**
1.	1683.81	NH
2.	1244.13	Cl
3.	1338.64	CH_3
4.	3545.38	OH
5.	1417.27	CH_2
6.	1338.38	CF_3

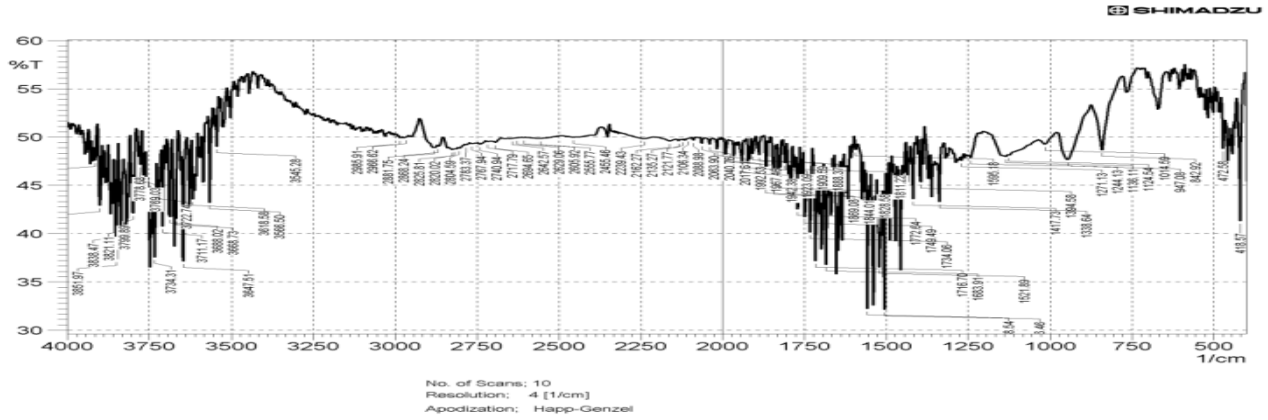

Fig. 3: FITR of drug with paper

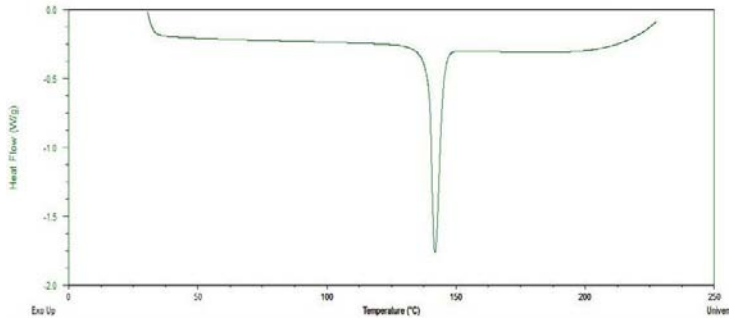

Fig. 4: Thermogram of the efavirenz

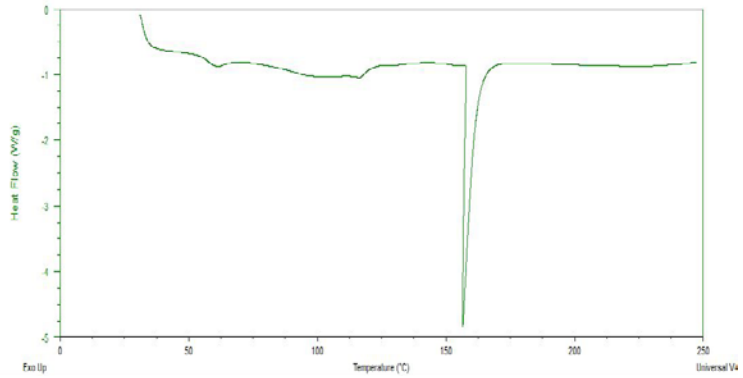

Fig. 5: Thermogram of drug with paper (F2)

Post-compression parameters [10, 11]

Hardness

The tablet Hardness can be determined by using monsanto hardness tester**.** In this tablet was placed on the lower plunger and reading was adjusted to zero. Then plunger was turned against a spring with force until tablet was fractured and the final reading was noted. Then hardness was by removal from final values with initial values. Then hardness of tablet obtained.

Friability

The friability of the tablet was determined by roche friability test apparatus. About 20 tablets were selected and check there initial weight. Then they placed in apparatus and rotated for 100 revolutions. Then the tablets were taken and dedusted and check the final weight of the tablets. The percent friability was calculated by the formula.

Friability = [(initial weight–final weight)/initial weight] × 100.

Weight variation

20 tablets were selected randomly and weighed. The average weight of the 20 tablets was calculated. then average weight of the individual tablet should not be more than 10%. Standard deviation and average weight were calculated.

Drug content

Five tablets from each formulation were randomly selected, accurately weighed, and an average weight per tablet was calculated. Each tablet was cut into small pieces and a known amount of drug that is equivalent to 50 mg of Efavirenz was transferred into a 100-ml volumetric flask 2% SLS was used to dissolve the drug and solution was made up to the mark. The solution was strained and from which 1 ml was withdrawn into a

10-ml volumetric flask and diluted with buffer. The resultant solution was determined spectrophotometrically at 247 nm.

Disintegration test

In this apparatus, six baskets are present the tablet placed on each basket. 2% SLS buffer is used as the disintegration medium. The temperature of the liquid was maintained at 37 ° c±2 ° c. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets, not less than 16 of the total of 18 tablets should disintegrate complete**ly**

***In vitro* drug release study**

In this rotating paddle, (USP type 2) apparatus were selected. The dissolution medium contains 900 ml of 2% SLS buffer. The efavirenz paper tablets were taken. The release study was performed at 37 °C±0.5 °C with a rotation speed of 100 rpm.

The 5 ml of the sample was withdrawn at a time interval of 2, 10, 20, 40, 60, 90, 120, 150, 180 min and replaced with 5 ml of dissolution medium the amount of Efavirenz released was determined by UV Spectrophotometer at 247.0 nm.

Table 4: Disintegration time

Formulation code	Disintegration time (sec)
F1	80 sec
F2	60 sec
F3	112 sec
F4	150 sec
F5	70 sec
F6	180 sec
F7	160 sec

Table 5: Post compression parameters of tablet

Form no.	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (%)	Drug content uniformity
F1	4.8	3.1±0.21	0.12±0.031	5.1±0.12	93±0.15
F2	5.5	3.2±0.31	0.22±0.056	5.6±0.24	98.7±0.02
F3	6.0	3.8±0.28	0.28±0.041	5.9±0.29	91.2±0.33
F4	4.9	3.2±0.22	0.13±0.32	5.5±0.11	92.1±0.12
F5	5.6	3.5±0.11	0.32±0.12	6.0±0.31	96.2±0.09
F6	6.1	3.6±0.31	0.24±0.19	5.3±0.57	90.3±0.31
F7	5.4	3.1±0.25	0.23±0.25	5.4±0.32	92.3±0.25

Table 6: *In vitro* dissolution data of efavirenz paper tablet

Time	% Drug release						
(h)	F1	F2	F3	F4	F5	F6	F7
0.5	10.71±0.57	38.12±0.23	7.29±0.89	14.32±0.52	20.31±1.21	9.28±1.4	22.31±0.89
1	19.13±0.11	45.31±0.09	13.12±1.12	20.32±3.01	32.88±0.6	15.32±3.27	35.89±0.98
1.5	32.58±1.3	64.54±0.91	26.33±2.31	31.96±3.32	54.36±0.56	27.96±0.87	48.63±0.36
2	45.96±2.2	74.12±0.69	38.99±0.78	47.32±1.10	69.81±1.58	37.41±1.32	59.98±1.47
2.5	59.89±0.32	88.06±0.21	47.61±3.21	56.11±0.99	75.8±2.65	48.35±0.65	68.54±0.96
3	67.35±0.09	98.02±0.03	56.32±2.98	65.57±2.11	87.3±0.97	55.69±1.98	78.96±2.98
3.5	76.11±0.54	-----	69.87±1.69	79.88±3.50	95.7±0.11	63.21±2.9	89.22±0.21
4	87.16±0.78	-----	79.12±1.47	91.22±1.32	-----	78.96±3.2	96.13±0.11
4.5	95.27±0.69	-----	85.21±0.25	97.34±0.11	-----	87.32±1.2	-----
5	----	-----	90.36±0.36	----	-----	92.11±0.96	-----

Table 7: *In vitro* dissolution kinetics of efavirenz paper table

Formulation code	Zero-order		First-order		Hixson Crowell	
	R^2	K_0	R^2	K_1	R^2	K_H
F1	0.919	0.821	0.854	0.011	0.923	0.01
F2	0.992	1.25	0.940	0.016	0.972	0.023
F3	0.896	0.562	0.872	0.009	0.897	0.015
F4	0.956	1.01	0.925	0.010	0.948	0.019
F5	0.984	0.654	0.964	0.015	0.948	0.007
F6	0.876	0.747	0.864	0.007	0.823	0.012
F7	0.965	0.99	0.957	0.012	0.954	0.018

Table 8: Drug content during stability studies

% Drug release (F2)		
Time (weeks)	**30 °C/70 RH**	**45 °C/75 RH**
1^{st}week	99.52	99.01
3^{rd}week	99.02	98.67
5^{th}week	98.87	98.10
8^{th}week	97.53	97.00

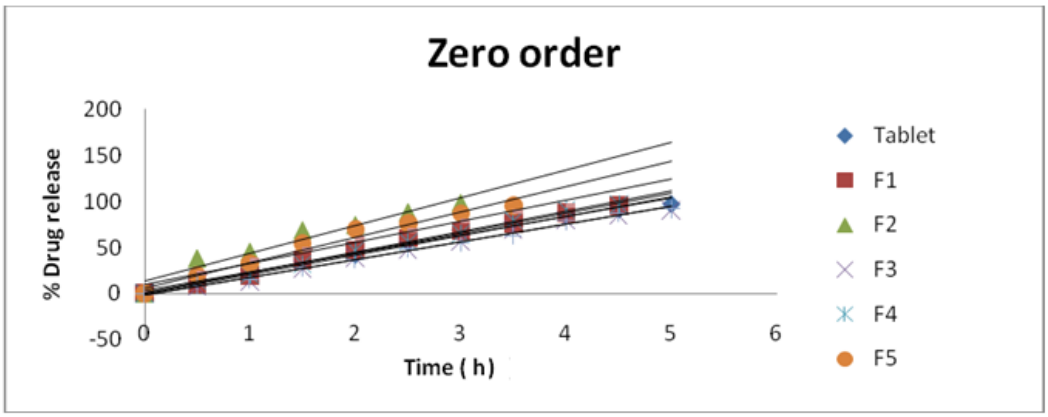

Fig. 6: Zero-order plot

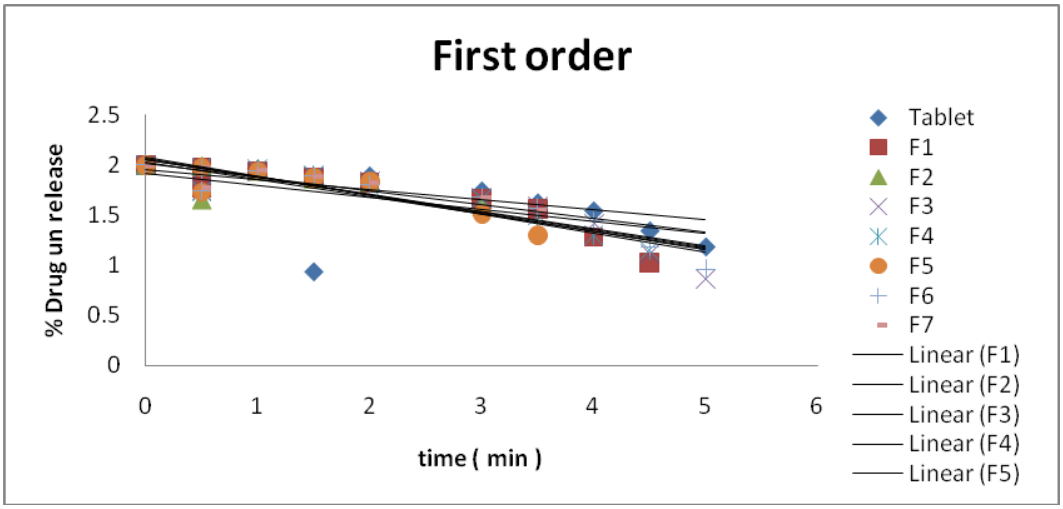

Fig. 7: First order plot

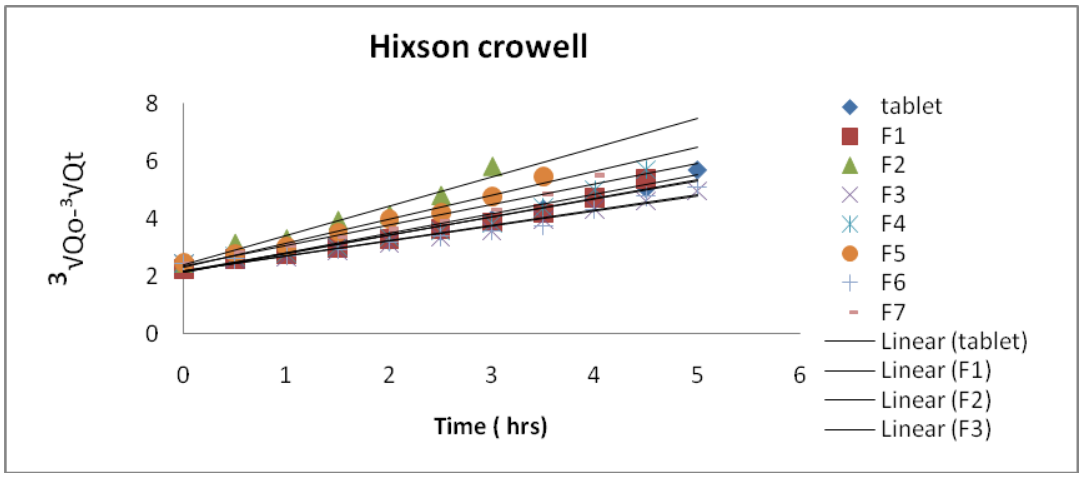

Fig. 8: Hixson crowell

Stability studies

After storage, changes are not present. The drug content was found to be uniform. The drug release data are shown in indicated that there are no significant changes in the drug release even after storage at 40 °C. The slow drug release characteristics of the product are found to be stable and unaltered.

CONCLUSION

Efavirenz (EFV), an anti-human immunodeficiency virus (anti-HIV) drug that works by inhibiting the non-nucleoside reverse transcriptase of HIV and is used as a part of the highly active antiretroviral therapy. This drug-related to class 2 which means the drug having low solubility and high permeability.

The paper tablet has potential advantages it does not contain any excipients and it increases the solubility by cosolvency technique and increases the dissolution and bioavailability of the drug. The paper tablet was prepared by cosolvency technique and incorporated in various papers like kitchen roll, hand Kerchief, facial tissue with various weights are taken and incorporated drug into it. the evaluated results are confirmed that prepared formulation exhibit satisfactory results.

The paper tablet contains efavirenz; among all the formulation F2, shows better release 98.02 for 180 min. From the order of release, it observed that the prepared formulation follows zero-order release kinetics. Other parameters like hardness, friability, weight variation, thickness are also within the limit so the F2 is the optimized formulation. The DSC and FTIR of the pure drug and the paper-containing drug are also conducted. All the parameters are within the limit. The disintegration time of the f2 formulation is 6o sec. the stability of the tablet are also attained. So the drug can be released efficiently from the paper and shows its action.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICTS OF INTERESTS

Authors declare no conflicts of interest

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