



CODEN [USA]: IAJPBB

ISSN: 2349-7750

**INDO AMERICAN JOURNAL OF  
PHARMACEUTICAL SCIENCES**

SJIF Impact Factor: 7.187

Available online at: <http://www.iajps.com>

Research Article

**DEVELOPMENT AND EVALUATION OF FAST DISSOLVING  
TABLETS OF EFAVIRENZ BY SOLUBILITY ENHANCEMENT  
TECHNIQUE****N.Kartheek, Pasam Jyothirmayi, Abbineni Anusha, Dr. N.srinivasa Rao**

Vikas College Of Pharmacy, Vissannapeta, NTR District, Andhra Pradesh, India.

**Abstract:**

*Efavirenz (EFV) is an anti-retroviral agent with low aqueous solubility. To enhance the solubility of EFV by using the concept of mixed hydrotrophy. Initially, solubility of EFV was determined individually in sodium acetate, sodium citrate, urea and sodium benzoate at concentration of 10% w/v solutions. Highest solubility was obtained in 10% sodium benzoate solution. Highest solubility was obtained in 1:6:1 ratio of Urea + Sodium benzoate + Sodium acetate. This optimized combination was utilized in the preparation of solid dispersions by using distilled water as a solvent. Fourier-transform infrared to show no drug-hydrotropes interaction has occurred. Formulation of FAST dissolving tablets of Efavirenz using mixed hydrotrophy technique with different concentrations of super disintegrants such as Crosspovidone and Sodium Starch Glycolate were prepared by using direct compression method. Dissolution studies of prepared tablets were done using USP Type II apparatus. The batch CF3 tablets show 98.3% cumulative drug release within 40 min. The miraculous enhancement in solubility and bioavailability of Efavirenz was clear indication of the potent mixed hydrotrophy to be used in future for other poorly water-soluble drugs in which low bioavailability is a major concern.*

**KEYWORDS:** Efavirenz, Mixed hydrotrophy, Solid dispersions, fast dissolving tablets.

**Corresponding author:**

**N.Kartheek,**  
M Vikas College Of Pharmacy,  
Vissannapeta, NTR District,  
Andhra Pradesh, India.

QR code



Please cite this article in press N.Kartheek et al., *Development And Evaluation Of Fast Dissolving Tablets Of Efavirenz By Solubility Enhancement Technique*, Indo Am. J. P. Sci, 2024; 11 (01).

**INTRODUCTION:**

Efavirenz inhibits the activity of viral RNA-directed DNA polymerase (i.e., reverse transcriptase). Antiviral activity of efavirenz is dependent on intracellular conversion to the active Tri phosphorylated form. The rate of Efavirenz phosphorylation varies, depending on cell type. 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. Intracellular enzymes subsequently eliminate the HIV particle that previously had been uncoated, and left unprotected, during entry into the host cell. Thus, reverse transcriptase inhibitors are virustatic and do not eliminate HIV from the body. Even though human DNA polymerase is less susceptible to the pharmacologic effects of Tri phosphorylated Efavirenz, this action may nevertheless account for some of the drug's toxicity.

The solubility of poorly soluble drugs can be increased through a variety of methods, including modifying the physical and chemical properties and use of particle size reduction, crystal engineering, salt development, solid dispersion, and surfactants.

Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response.

Hydrotropic solubilization is a technique that can be used to improve the solubility of drugs that are poorly soluble. This technique involves adding a large amount of a second solute, known as a hydrotrope, which increases the aqueous solubility of the poorly soluble drug.

About 45% of new chemical entities coming from the discovery are poorly bioavailable. This exerts strong limits to the performance of a drug by necessitating administering a much higher dose than strictly required from the pharmacological point of view. This can induce harmful side-effects or create problems related to cost of treatment. Due to poor bioavailability the formulator may have to select the injection route instead of the oral route.<sup>[1]</sup> For a better oral bioavailability drug must be soluble in gastro-intestinal fluids that is, drug should be soluble in an aqueous medium and also possess permeability properties for good membrane diffusion in order to reach the bloodstream.<sup>[1,2]</sup>

**MATERIALS AND METHODS:**

**Materials:** Efavirenz was obtained from mylon pharmaceuticals, Hyderabad as gift sample. Sodium Starch Glycolate, and Cross povidone were supplied by yarrow chem products. Microcrystalline cellulose was collected from Thermo fisher scientific India Pvt. Ltd., Mumbai. Urea, sodium acetate, and sodium benzoate were obtained from Merck specialties Pvt. Ltd., Mumbai. All other chemicals are of analytical grade.

**Methods:**

Preformulation studies:

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. Solubility of Efavirenz was determined in water and methanol, ethanol, chloroform. Melting point,  $\lambda_{max}$  were determined. Micrometric, flow and derived properties were studied for given drug sample.

A solution of Efavirenz containing the concentration 10  $\mu\text{g/ml}$  was prepared in pH 0.1N HCL buffer. UV spectrum was taken using Thermo scientific (Evolution 201) double beam spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Equilibrium solubility studies in different hydrotropic agents 10% w/v, solutions of each hydrotropic agent viz., urea (U), sodium benzoate (B), sodium acetate (A), and tri-sodium citrate were prepared in water. For determination of solubility accurately measured 5 ml of above particular solution of hydrotropic agent was taken in a 10 ml vial and excess amount of drug (EFV) was added and mechanically shaken until saturated solution was formed. Each vial was shaken on the mechanical shaker for 12 h and hence that equilibrium solubility can be achieved, and the solution was allowed to equilibrate for 24 h. The solution was further centrifuged at 2000 r.p.m. for 10 min in ultra-centrifuge and further filtered through What man grade 41 filter paper. Aliquot was suitably diluted with distilled water and analyzed using UV spectrophotometer at 247 nm.

**Equilibrium solubility studies in blends**

Initially 2-3 hydrotropic agents were mixed in 1:1 ratio and dissolved in water to get clear solution, excess amount of drug (EFV) was added in above solution and mechanically shaken until saturated solution was formed and solubility in water was determined.

**Table 1. Equilibrium solubility of Efavirenz in different hydrotropic agents**

S.NO	Code of hydrotrope	Hydrotropic blend	Concentration (% w/v)	Individual concentration (% w/v)
1.	HS.1	U+SB	10	0.5
2.	HS.2	U+SA	10	0.5
3.	HS.3	U+SC	10	0.5
4.	HS.4	A+SB	10	0.5
5.	HS.5	A+SC	10	0.5
6.	HS.6	B+SC	10	0.5
7.	HS.7	U+SB+SA	10	0.375+0.5+0.125
8.	HS.8	U+SB+SA	10	0.25+0.625+0.125
9.	HS.9	U+SB+SC	10	0.125+0.375+0.5
10.	HS.10	U+SB+SA	10	0.125+0.750+0.12
11.	HS.11	SA+SB+U	10	0.375+0.5+0.125
12.	HS.12	SB+SA+U	10	0.25+0.625+0.125
13.	HS.13	SA+U+SB+SC	10	0.1+0.5+0.3+0.1
14.	HS.14	U+SA+SB+SC	10	0.1+0.5+0.3+0.1

#### Formulation of hydrotropic solid dispersions of Efavirenz

For preparation of hydrotropic solid dispersion, accurately weighed 0.750g sodium benzoate, 0.125 g of sodium acetate, 0.125 g of urea (so that total weight of the mixture was 1g) were taken in a 100 ml beaker and properly mixed. Further, minimum quantity of warm distilled water sufficient to dissolve the above hydrotropic blend was added. If minimum amount of water (approximately 5 ml) is used lesser will be the time required to evaporate it and chemical stability of drug may not be affected adversely during removal of the water.

Dissolution of the hydrotropic mixture was facilitated by agitation of a Teflon coated magnetic rice bead on a high-speed magnetic stirrer. After complete dissolution of above hydrotropic mixture, 1 g of EFV (drug to carrier ratio was 1:1) was dissolved in the above solution and temperature was maintained in the range of 55-60°C so as to facilitate the water evaporation. As soon as evaporation of water increases speed of rice magnetic bead automatically decreased due to increased viscosity and it stopped stirring. when most of the water was evaporated, this indicates

the formation of hydrotropic solid dispersion (wet). The wet solid dispersion thus obtained were spread on several watch glasses and the watch glasses were kept in hot air dry oven maintained at 50°C ± 2°C so that remaining moisture could also be evaporated easily and a constant weight with no further weight loss (due to evaporation) could be obtained. After complete drying, hydrotropic solid dispersions were crushed using a glass pestle mortar and passed through sieve no. 60 and were finally stored in an air tight glass bottle. [3,4]

#### Preparation of tablets by direct compression technique:

All the ingredients were passed through 60 mesh sieve separately. Solid dispersion equivalent to 600mg of EFV and microcrystalline cellulose were mixed in geometric proportion to get a uniform mixture. Then the other ingredients were weighed and mixed in geometrical order and tablets were compressed using flat round punch of 16mm sizes on a Rotary tablet Compression Machine.

#### FORMULATION DESIGN:

**Table 2. Formulation chart of Efavirenz Immediate release tablets (MCC)**

S.NO	Ingredients	MF1	MF2	MF3	MF4	MF5	MF6
1	EFV(HSD)	600	600	600	600	600	600
2	SSG	50	75	100	-	-	-
3	CP	-	-	-	50	75	100
4	MCC	330	305	280	330	305	280
5	Talc	10	10	10	10	10	10
6	Mg Stearate	10	10	10	10	10	10
7	Total	1000	1000	1000	1000	1000	1000

Table 3. Formulation chart of Efavirenz fast dissolving tablets (SSG &amp;CP):

S.No	Ingredients	CF1	CF2	CF3
1	EFV(ESD)	600	600	600
2	CP:SSG	50:50	50:75	50:100
3	MCC	280	255	230
4	MgSt	10	10	10
5	Talc	10	10	10
6	Total	1000	1000	1000

Table 4. Formulation chart of Efavirenz Immediate release tablets (EF1,HF1):

S NO	Ingredients	EF1(With out SD)	HF1(Without HSD)
1	EFV(ESD)	600	600
2	SSG	-	100
3	MCC	380	280
4	Talc	10	10
5	MgSt	10	10
6	Total	1000	1000

## EVALUATION:

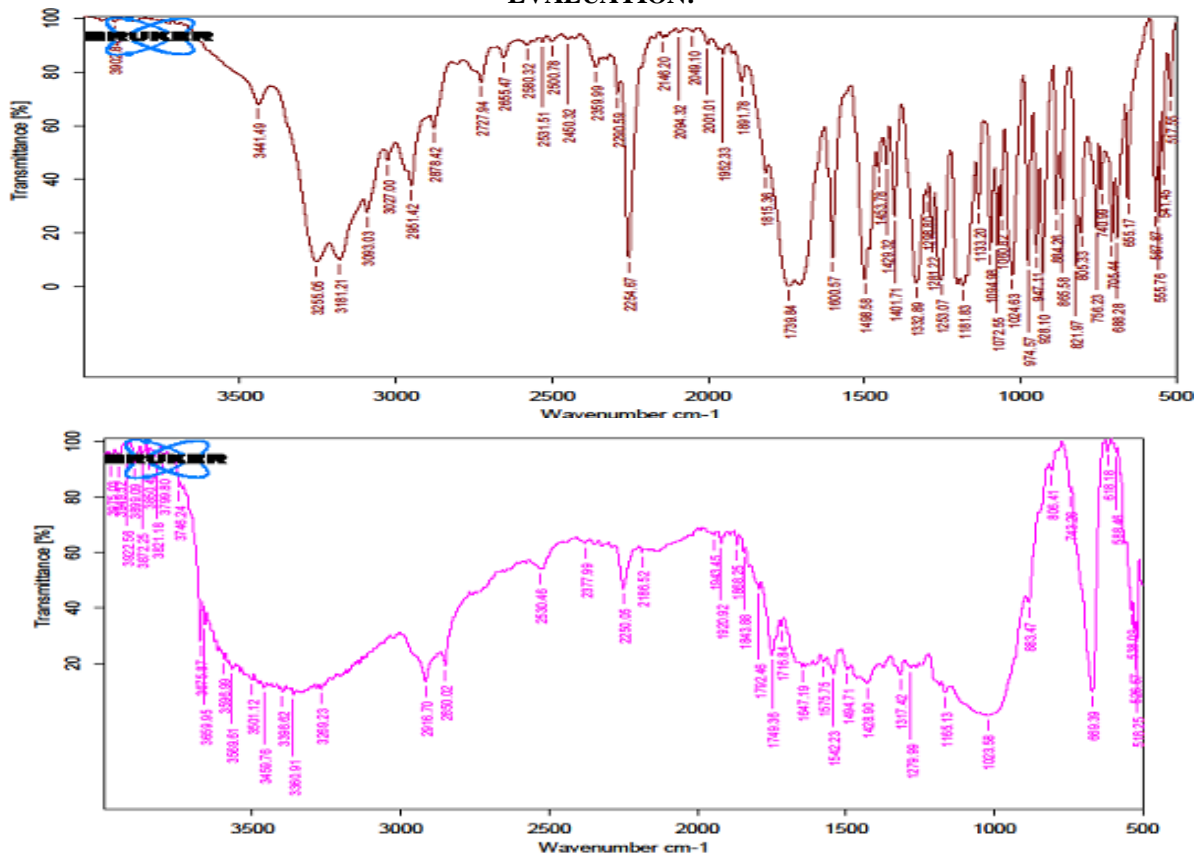


Figure 1: FTIR spectra of pure drug efavirenz and formulation

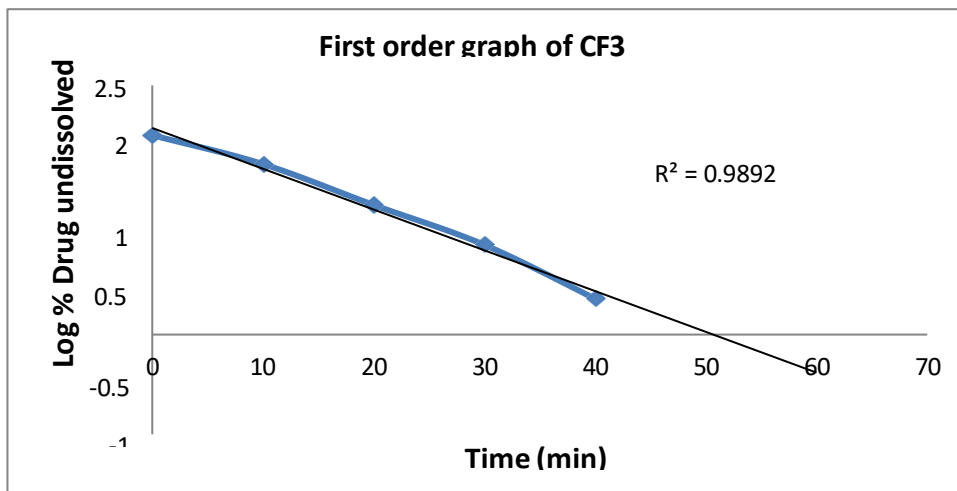


Fig 2 First order graph of CF3

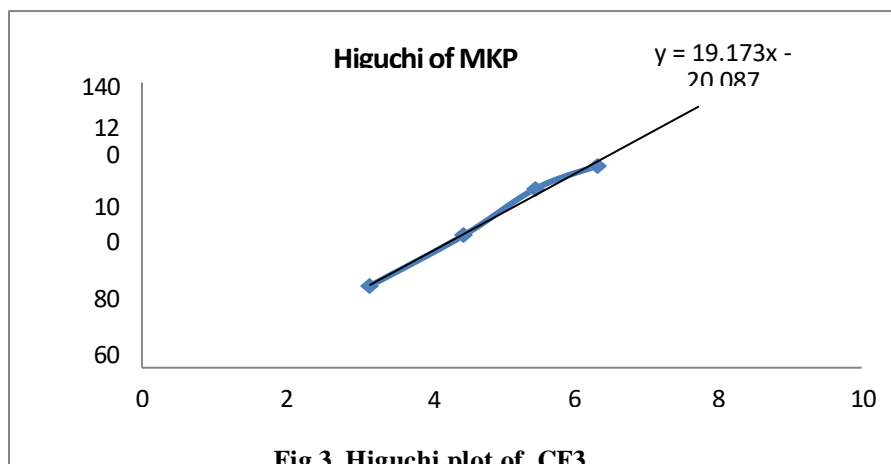


Fig 3 Higuchi plot of CF3

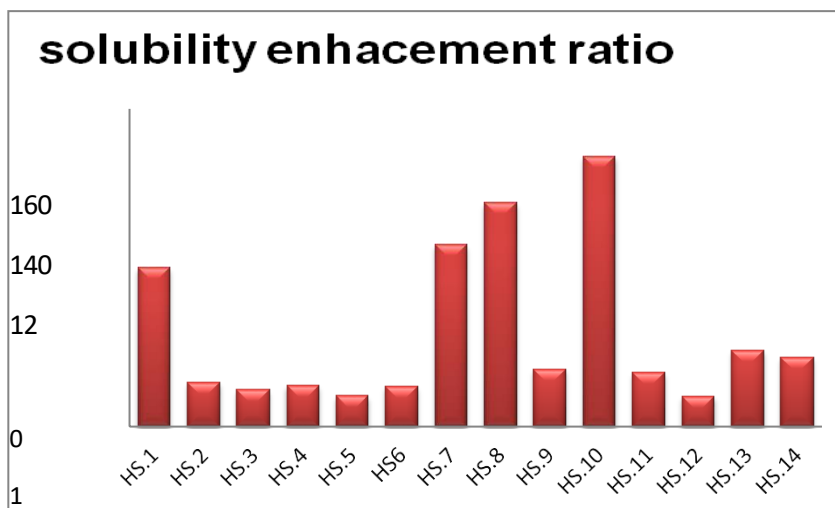


Fig 4 solubility enhancement ratio

## Micromeritic properties

Table no 5 Pre-Compression Parameters

Formulation	Angle of Repose ( $^{\circ}$ )	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner Ratio
LF1	27.63±0.69	0.520±0.02	0.623±0.02	16.37±0.75	1.19±0.06
LF2	28.91±0.85	0.525±0.02	0.623±0.02	15.73±0.71	1.18±0.05
LF3	27.82±0.82	0.560±0.03	0.660±0.06	15.15±0.62	1.17±0.04
LF4	27.58±0.82	0.521±0.02	0.623±0.02	16.37±0.74	1.19±0.06
MF1	26.88±0.65	0.542±0.04	0.637±0.03	14.91±0.91	1.17±0.04
MF2	28.91±0.85	0.521±0.02	0.623±0.02	16.37±0.75	1.19±0.06
MF3	27.59±0.82	0.485±0.01	0.564±0.06	14.0±0.65	1.16±0.03
MF4	26.54±0.65	0.540±0.04	0.615±0.01	12.1±0.55	1.13±0.02
MF5	28.46±0.80	0.490±0.01	0.580±0.07	15.5±0.54	1.18±0.06
MF6	26.54±0.65	0.540±0.04	0.615±0.01	12.1±0.55	1.13±0.03
MF7	26.43±0.63	0.500±0.01	0.579±0.05	13.6±0.58	1.15±0.04
MF8	27.33±0.82	0.559±0.05	0.649±0.04	13.8±0.58	1.16±0.05
MF9	27.21±0.82	0.521±0.02	0.623±0.02	16.37±0.75	1.19±0.06
CF1	28.91±0.86	0.520±0.02	0.620±0.02	16.12±0.75	1.19±0.06
CF2	27.21±0.60	0.521±0.02	0.623±0.02	16.37±0.75	1.19±0.06
CF3	27.66±0.66	0.520±0.02	0.620±0.02	16.12±0.74	1.19±0.06
EF1	26.54±0.65	0.540±0.04	0.615±0.01	12.1±0.65	1.13±0.03
HF1	26.88±0.64	0.542±0.04	0.637±0.03	14.91±0.58	1.17±0.04

Table no 6: Pre-Compression Parameters:

Formulations	Wt variation(mg)	Thickness (mm)	Hardness (kg/cm <sup>2</sup> )	Drug content(%)	Friability(%)
LF1	999.3±0.34	6.21±0.83	4.5±0.37	98.96±0.47	0.31±0.026
LF2	999.2±0.34	6.23±0.83	4.5±0.35	98.91±0.65	0.31±0.025
LF3	998.1±0.30	6.22±0.80	4.5±0.37	98.15±0.52	0.32±0.026
LF4	999.1±0.30	6.23±0.83	3.6±0.37	99.25±0.60	0.31±0.025
MF1	997.2±0.25	6.21±0.80	3.5±0.37	98.85±0.4	0.30±0.025
MF2	999.1±0.30	6.23±0.83	4.0±0.35	99.31±0.58	0.31±0.026
MF3	998.3±0.30	6.23±0.84	4.3±0.36	99.96±0.24	0.32±0.026
MF4	999.5±0.34	6.20±0.83	3.6±0.35	99.3±0.28	0.30±0.025
MF5	999.9±0.34	6.22±0.80	3.5±0.37	99.36±0.38	0.31±0.026
MF6	998.2±0.34	6.23±0.83	3.4±0.35	99.75±0.29	0.32±0.026
MF7	997.2±0.25	6.22±0.82	3.8±0.33	99.21±0.40	0.32±0.026
MF8	999.9±0.34	6.21±0.82	3.5±0.38	99.56±0.38	0.31±0.025
MF9	998.2±0.32	6.15±0.81	3.3±0.36	99.61±0.49	0.29±0.024
CF1	999.9±0.34	6.22±0.82	3.5±0.37	98.98±0.60	0.31±0.025
CF2	998.2±0.32	6.23±0.83	4.2±0.39	99.03±0.56	0.32±0.026
CF3	999.9±0.34	6.21±0.82	3.5±0.38	99.36±0.58	0.31±0.025

EF1	997.2±0.25	6.21±0.82	3.8±0.34	97.76±0.69	0.30±0.025
HF2	999.2±0.33	6.23±0.83	4.5±0.38	98.76±0.56	0.31±0.026

**Table No 7: Wetting time, Water absorption ratio, Disintegration time of Designed Formulations.**

Formulation code	Disintegrating time	Wetting time
LF1	45	89
LF2	36	75
LF3	27	65
4F4	25	42
MF1	35	60
MF2	32	54
MF3	40	44
MF4	36	55
MF5	28	43
MF6	35	29
MF7	38	39
MF8	29	34
MF9	35	32
CF1	40	25
CF2	36	20
CF3	28	17
EF1	60	176
HF1	150	240
MKP	19	34

**Drug release kinetics data**

**Table no 8 : %drug release of LF1 To LF4 Formulations**

S.NO	TIME (MIN)	LF1	LF2
1	10	13.4	17.4
2	20	23.5	25.5
3	30	33.4	37.4
4	40	50.3	53.5
5	50	61.5	66.4
6	60	75.5	78.4

**Table no 9 : %drug release of MF1 To MF9 Formulations:**

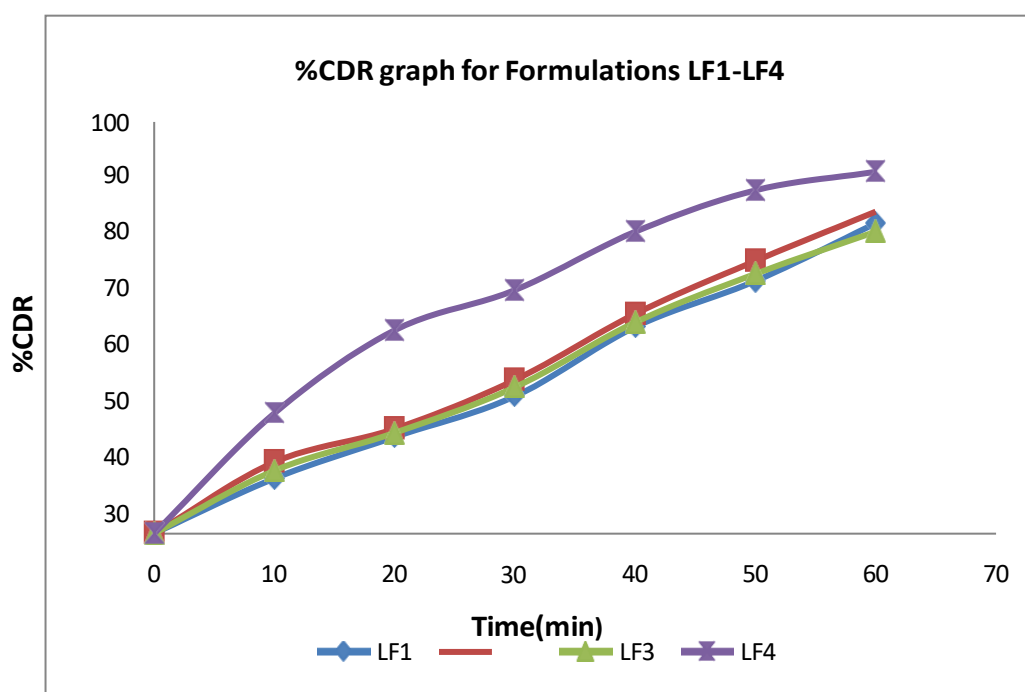
SNO	TIME	MF1	MF2	MF3	MF4	MF5	MF6
1	10	29.3	32.3	37.5	35.6	43.7	45.6
2	20	49.5	52.5	58.3	56.1	64.9	65.6
3	30	59.3	63.2	69.2	65.6	75.0	78.6
4	40	73.5	79.3	81.3	81.8	85.3	90.0
5	50	83.6	86.3	92.5	88.7	91.5	98.0
6	60	90.1	93.2		94.5	97.5	

**Table 10: %drug release of CF1 TO CF3 Formulations:**

S.NO	TIME	CF1	CF2	CF3
1	10	26.2	25.4	37.4
2	20	45.31	51.3	78.4
3	30	75.3	77.3	91.5
4	40	89.3	89.2	98.3
5	50	96.5	97.2	
6	60			

**Table 11: comparison %drug release of HF1, EF1, MKP,CF3 Formulations**

S.NO	TIME	HF1 (without SD)	EF1 (with SD)	MKP	CF3
1	10	15.3	9.5	31.2	37.4
2	20	32.2	19.2	57.2	78.4
3	30	46.2	25.3	78.6	91.5
4	40	59.2	33.6	88.7	98.3
5	50	72.2	46.1	94.5	
6	60	80.2	55.3	98.0	





**Fig 5 :%CDR graph for LF1 To LF4Formulations**

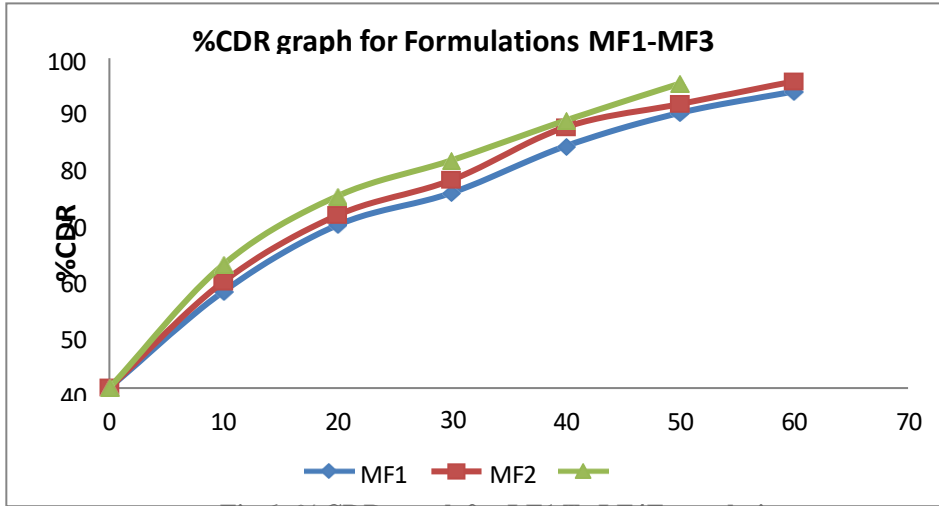


Fig 6: %CDR graph for LF1 To LF4 Formulations

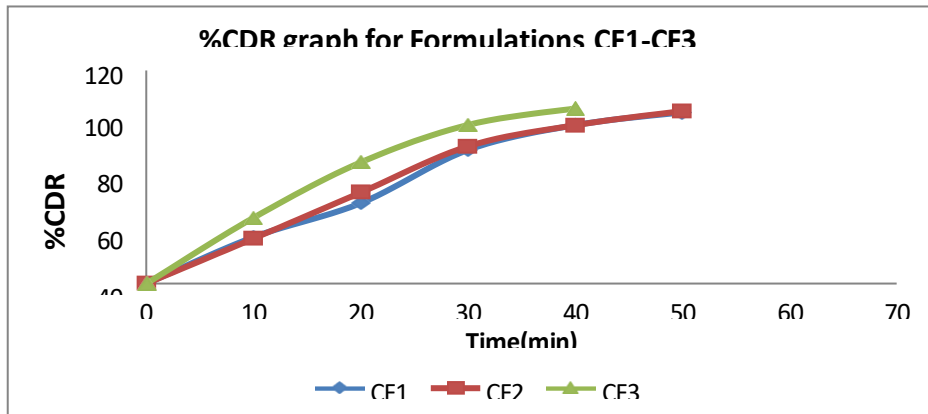


Fig 7: %CDR graph for CF1 To CF3 Formulations

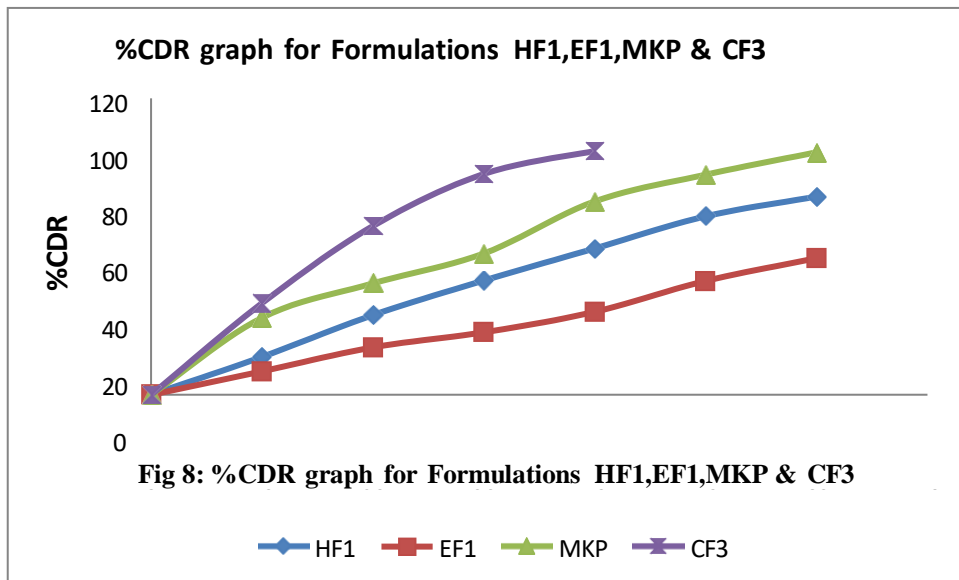


Fig 8: %CDR graph for Formulations HF1, EF1, MKP & CF3

### RESULTS AND DISCUSSION:

Physical characterization of Efavirenz tablets were studied. Hardness of the developed formulations varies from  $3.3 \pm 0.36$  kg/cm<sup>2</sup> to  $4.5 \pm 0.38$  kg/cm<sup>2</sup> for hydrotropic solid dispersions. Thickness of the Efavirenz solid dispersions varied from  $6.20 \pm 0.83$  to  $6.33 \pm 0.83$  mm. The average weight of twenty tablets of EFV was calculated for each formulation which varied from 997.2 to 999.5 mg, which Complies the official requirement as per IP. Friability of the developed formulations varied from  $0.29 \pm 0.023\%$  to  $0.32 \pm 0.024\%$  loss for EFV which was less than 1% as per official requirement of IP. The drug content was estimated for all the formulations and the results obtained between the range 90% to 99.37. All the formulations were found within the limit. The most important parameter that needs to be optimized in the development of fast dissolving tablets is the disintegration time of tablets. In the present study disintegration time of all batches were found. Among them, formulations with super disintegrants disintegrate in the range of 89 sec to 240 sec and for the formulation without super disintegrants shows disintegration with in 176 sec, fulfilling the official requirements.

In the present study wetting time of all batches were found. Among them, formulations with super disintegrants, wetting time is in the range of 45 sec to 150 sec and for the formulation without super disintegrants shows wetting time with in 60 sec, fulfilling the official requirements. The post compression parameters like Hardness, Friability, Disintegration time, Weight variation, wetting time values were found to be within the IP limits.

HSD formulations of EFV were prepared and optimized by taking different parameters into consideration. SSG & CCS as Super Disintegrants in 5% concentration. MF1-MF6 Formulations MCC is selected based on above formulation results as diluents. In these formulations Sodium starch glycolate, Crosspovidone, and SSG were selected as super disintegrates, in different concentrations. Sodium starch glycolate is used as the super disintegrate in the formulation MF1 – MF3 at the concentrations of 5%, 7.5%, 10%, respectively. Maximum drug release is seen with MF3(SSG) 92.5% at the end of 50 min. Cross-povidone is used as the super disintegrate in the formulation MF4–MF6 at the concentrations of 5%, 7.5%, 10%, respectively. Maximum drug release is seen with MF6(CP), 98.5% at the end of 50 min. Based on drug release further I designed the combination of super disintegrants as CF1-CF3 in three different ratios (1:1, 1:2, 1:3) of CP:SSG Super disintegrants are selected

based on drug release. Maximum drug release is seen with formulation CF3 (CP: SSG) 98.3 % at the end of 40 min.

Finally the best formulation was compared with pure drug formulation, HSD formulation without any super disintegrants & marketed formulation. Pure drug formulation EF1 shows maximum drug release of 55.3% at the end of 60 min. HSD formulation without super disintegrant (EF1) shows maximum drug release of 81.2% at the end of 60 min and finally conducted marketed tablet dissolution test, shows maximum drug release 98.0 % at the end of 60 min. Among all these formulations CF3 shows best release of 98.3 % at the end of 40 min. The data obtained from the comparison of marketed formulation and pure drug formulation with the optimized formulation CF3 it was revealed that the optimized formulation CF3 shows better results than that of marketed formulation and pure drug formulation.

### CONCLUSION:

Efavirenz is one of a new class of anti-viral drugs called non-nucleoside reverse transcriptase inhibitor (NNRTI). It offers the unique therapeutic prospect of treatment and management of disease and so used extensively as a single component formulation. It has poor solubility and undergoes first pass metabolism thus having poor bioavailability (46%). It is highly permeable drug and is having poor solubility limitation. So it was logically decided to enhance its solubility and design fast dissolving tablets by different solubility enhancement techniques so as to fulfill the object & an attempt was made to prepare mixed hydrotropic solid dispersions. The aim of this study was to improve the solubility thereby increase dissolution profile. On optimizing the formulations CF3 with mixed hydrotropic solid dispersions with combination of super disintegrants (CP & SSG), it was clearly observed that the drug was released immediately, 98.3 % within 40 mins by best formulation. So, the % of drug release was instantaneous in optimized formulation. Among all these formulations, after comparing the solubility and dissolution profile it was found CF3 give desired dissolution profile of Efavirenz more than 98.3 % release in 40 min. The present research work concludes that the hydro trophy is a novel, safe and effective way to enhance solubility of poorly aqueous soluble drugs.

### REFERENCES:

1. Sikarra D, Shukla V, Kharia AA, Chatterjee DP. Research article techniques for solubility enhancement of poorly soluble

- drugs: An overview. *J Med Pharm Allied Sci.* 2012; 1: 1–22.
2. **Behera AL, Sahoo SK, Patil SV.** Enhancement of solubility: A pharmaceutical overview. *Pharm Lett*, 2010; 2: 310–8.
  3. **Limbachiya MI, Agarwal M, Sapariya A, Soni S.** Solubility enhancement techniques for poorly soluble drugs: Review. *Int J Pharm Sci Rev Res*, 2011; 4: 71–86.
  4. **Saleh AM, El-Khordagui LK.** Hydrotropic agents: A new definition. *Int J Pharm.* 1985; 24: 231–8.
  5. **Kapadiya N, Singhvi I, Mehta K, Karwani G, Dhrubo JS.** Hydrotrophy: A promising tool for solubility enhancement: A review. *Int J Drug Dev Res*, 2011; 3: 26–33.
  6. **Kim JY, Kim S, Papp M, Park K, Pinal R.** Hydrotropic solubilization of poorly water-soluble drugs. *J Pharm Sci.* 2010; 99: 3953–65. **Lee J, Lee SC, Acharya G, Chang CJ, Park K.** Hydrotropic solubilization of paclitaxel: Analysis of chemical structures for hydrotropic property. *Pharm Res*, 2003; 20: 1022–30
  7. **Kwan K C,** Oral bioavailability and first-pass effects, *Drug Metabolism and Disposition*, Vol. 25, 12.
  8. **Petri N, Bergman E, Forsell P, Hedeland M, Bondesson U, Knutson L and Hans Lennernäs H,** First-pass effects of verapamil on the intestinal absorption and liver disposition of fexofenadine in the porcine model, September 2010, 38(9)
  9. **Dresser G K, Kim R B, and Bailey DG,** Effect of grapefruit juice volume on the reduction of Fexofenadine bioavailability: possible role of organic anion transporting polypeptides. *Clin Pharmacol Ther* 2005, 77: 170–177
  10. **Fromm M F, Busse D, Kroemer H K, and Eichelbaum M (1996)** Differential induction of prehepatic and hepatic metabolism of verapamil by rifampin. *Hepatology* 24: 796–801
  11. **The Biopharmaceutics classification system (BCS) guidance,** Center for Drug Evaluation and Research, US Food and Drug Administration, 2001, <http://www.fda.gov/cder>.
  12. **Wu C.Y., Benet L.S.,** Predicting drug disposition via application of BCS: Transport /Absorption elimination interplay & development of a biopharmaceutical drug disposition classification system. *Pharmaceutical research*, 22(1): 23-27, (2005)
  13. **Shinde AJ. et al,** “Solubilization of poorly soluble drugs: A Review”, *Pharmainfo.net* 2007; 5: 6.
  14. **Shiv M.** Solubility Enhancement: Need. *pharmainfo.net*. 2009.
  15. **.P. B. Myrdal and S. H. Yalkow**
  16. **AMartin, Solubility and Distribution**
  17. **Varun Raj Vemula\*1, Venkateswarlu Lagishetty1, Srikanth Lingala 2** Volume 5, Issue 1, November – December 2010; Article-007 Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system
  18. **Patil S.K., Wagh K.S., Parik V.B., Akarte A.M., Baviskar D.T.,** Strategies for solubility enhancement of poorly soluble drug. *International journal of pharmaceutical science review and research*, 8(2): 74-80, (2011)
  19. **Chaudhari A., Nagachi U., Gulati N., Sharma V.K., Khosa R.K.,** Enhancement of solubilisation and bioavailability of poorly soluble drugs by physical and chemical modification; A recent review. *Journal of advance pharmacy education and research*, 2(1): 32-67, (2012)
  20. **Blagden N., de Matas M., Gavan P.T., York P.,** Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. *Advanced Drug Delivery Reviews*, 59(7): 617–630, (2007)