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FORMULATION, *INVITRO*-EVALUATION AND SOLID STATE CHARACTERIZATION OF SOLID DISPERSION OF EFAVERENZ

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ABSTRACT

Efaverenz is an HIV-1 specific, non-nucleoside reverse transcriptase inhibitor (NNRTI).It is an antiretroviral agent indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection, which is not soluble in water and lower absorption in gastric fluid. In order to improve the solubility and oral absorption of the drug in gastric fluid and to enhance its dissolution rate, solid dispersion method is designed and evaluated. Solid dispersions of Efaverenz were prepared using Betacyclodextrin, Maltodextrin, HPMC 606, Plasdone K 32, and Polaxomer 407. Solid state studies like DSC and FTIR indicated the compatibility of polymers with the drug. *Invitro* dissolution studies indicated a significant increase in dissolution of Efavirenz when dispersed in polymers. Solid dispersions containing Efaverenz and Maltodextrin have shown maximum stability and drug release.

KEY WORDS: Efaverenz, Betacyclodextrin, Maltodextrin, HPMC 606, Plasdone K 32, Polaxomer 407 and Solid dispersion.

1. INTRODUCTION

Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Improvement in the extent and rate of dissolution is highly desirable for such compounds, as this can lead to an increased and more reproducible oral bioavailability and subsequently to clinically relevant dose reduction and more reliable therapy. Nowadays, pharmaceutical technology provides many approaches to enhance the dissolution rate of poorly soluble drugs. Physical modifications often aim to increase the surface area, solubility and/or wettability of the powder particles and are therefore focused on particle size reduction or generation of amorphous states. Several methods have been employed to improve the solubility of poorly water soluble drugs. A solid dispersion technique has been used by various researchers who have reported encouraging results with different drugs. There are various methods like freeze drying, physical mixing, fusion (melt) method and solvent evaporation are employed for the formulation of solid dispersion and this will helps in the reduction of dose of the drug. Efaverenz was choosen as a water-insoluble model drug and Betacyclodextrin, Maltodextrin, HPMC 606, Plasdone K 32, and Polaxomer 407 are hydrophilic polymers.

2. MATERIALS AND METHODS

2.1. Apparatus and chemicals: Efaverenz (99% purity) was obtained from Aurobindo Pharma Ltd., Hyderabad, India. Maltodextrin, Betacyclodextrin, Plasdone K 32 and Polaxomer were procured from RA Chem Pharma Ltd., Hyderabad. Other excipients used were of analytical grade. All chemicals used were purchased from Merck, Mumbai, India.

2.2. Dissolution testing of Efavirenz marketed tablets in different dissolution media: Conducted dissolution testing of Efaverenz tablets 200 mg in various dissolution medias like distilled water, acetate buffer, Phosphate buffer, 2% sodium lauryl sulfate(SLS) and 0.1 N HCL to know the release pattern of the Efaverenz from the tablet dosage form, using USP apparatus 2 (paddle type). From the dissolution data we can conclude that (Figures 28-32) Efaverenz drug release was very less in different media mentioned above. But the actual intestinal or gastric environment does not resemble the 2% SLS solution. So we have decided to improve the dissolution profile of Efaverenz by employing novel drug delivery system .We have chosen solid dispersion technique as preliminary screening technique to test whether the drug is suitable for novel drug release system or not. Next we have chosen 0.1 N HCL as dissolution media for testing solid dispersion formulation since 0.1 N HCL resembles more of a gastric environment.

2.3. Composition of Solid dispersion: Solid dispersions were prepared by melt solvent method as per the ratios given in table 1

2.4. Preparation of solid dispersions: Accurately weighed amount of pure drug dissolved in minimum quantity of methanol and transferred into glass beaker. Accurately weighed quantity of polymer was melt in china dish. Methanol with drug in dissolved form was transferred to china dish with molten polymer with continuous mixing. Then the mixture was cooled and dried at constant temperature (45^0C) for 24 hours to remove methanol from the mixture. The samples were sent for DSC and FTIR studies. A sample of solid dispersion equivalent to 200mg of drug was used for conducting dissolution studies. The same procedure was followed to all the ratios of polymers and the drug.

Table 1: Composition of Solid dispersion

Carrier	Drug: Carrier	Method
Beta cyclodextrin	1:1	Melt solvent
Maltodextrin	1:1	Melt solvent
Maltodextrin	1:2	Melt solvent
HPMC 606	1:1	Melt solvent
Plasdone K 32	1:2	Melt solvent
Plasdone K 32	1:3	Melt solvent
Polaxomer 407	1:3	Melt solvent
Polaxomer 407	1:4	Melt solvent

2.5. Dissolution rate determination: An ELECTROLAB dissolution test apparatus type II (Paddle) at rotation speed of 50 rpm was used for the study. Dissolution of the drug and solid dispersion was carried out on an equivalent of 200 mg of the Efaverenz in 0.1N HCL as dissolution media. The volume and temperature of the dissolution media were 900 ml and 37 ± 0.2^0C, respectively. After fixed time intervals, 10 ml of samples were withdrawn and replace the same fresh dissolution media so as to maintain sink condition. The samples were filtered through 0.2µm filters and further diluted with methanol in 25 ml volumetric flasks and these samples were assayed by UV spectroscopy at 246.5 nm. To increase the reliability of the observations, the dissolution studies were performed in triplicate.

3. RESULTS AND DISCUSSION

3.1. Solid state characterization: The solid state characterization of the pure drug, pure polymers and the solid dispersions were carried out by using DSC and FTIR studies. The study was carried out as follows

1. DSC study of Efaverenz pure drug.
2. DSC study of all individual polymers
3. DSC study of all ratios of solid dispersions
4. FTIR study of Pure drug
5. FTIR study of pure all individual polymers
6. FTIR study of all ratios of all solid dispersions
7. Interpretation of the results by using the above DSC and FTIR data

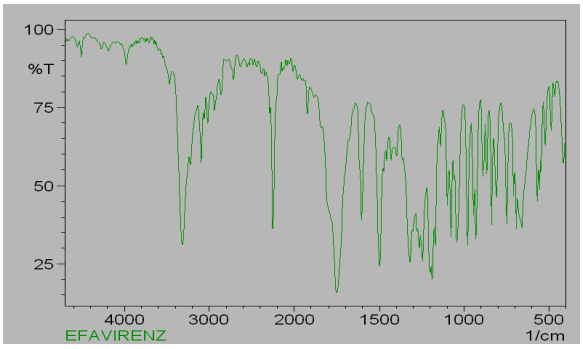

Fig.1. FTIR of Efaverenz pure drug

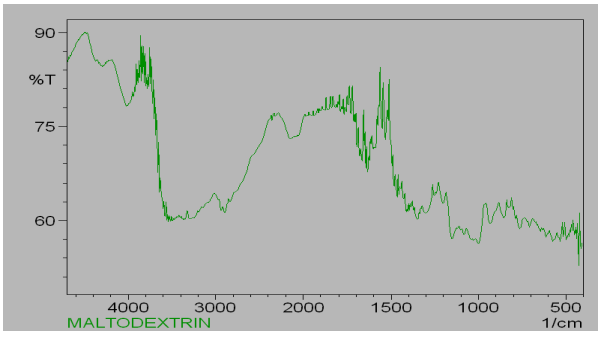

Fig.2.FTIR of Maltodextrin

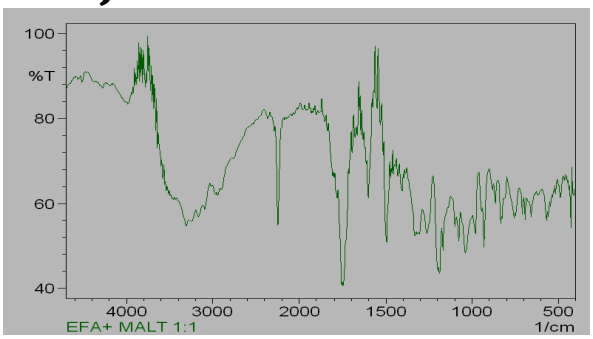

Fig.3.FTIR of Efaverenz: Maltodextrin(1:1)

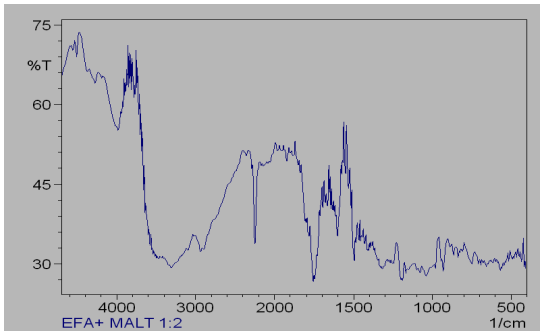

Fig.4.FTIR of Efaverenz: Maltodextrin(1:2)

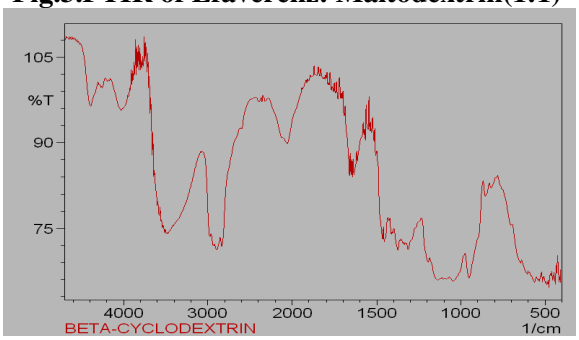

Fig.5.FTIR of Betacyclodextrin

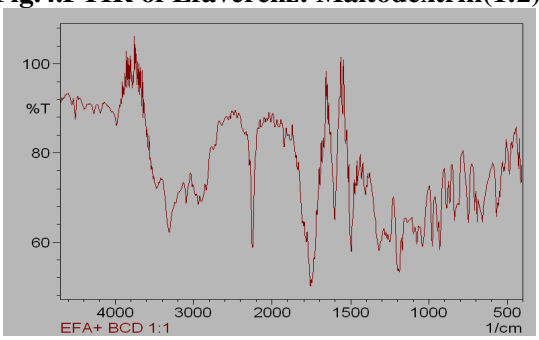

Fig.6.FTIR of Efaverenz: Betacyclodextrin (1:1)

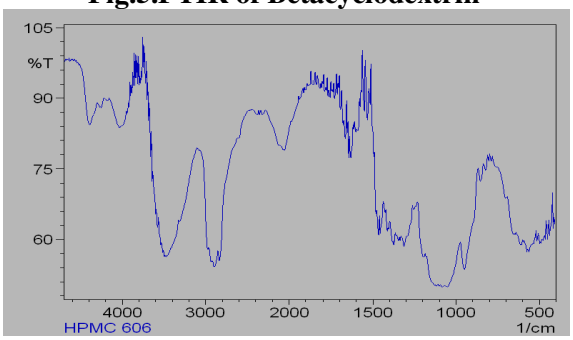

Fig.7.FTIR of HPMC 606

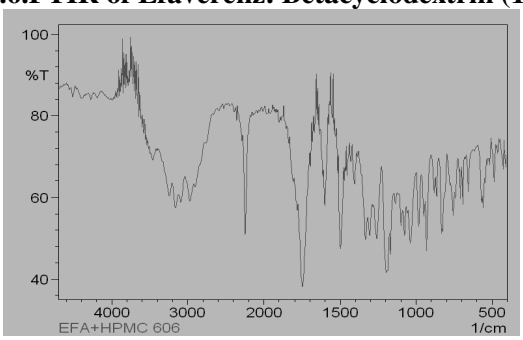

Fig.8.FTIR of Efaverenz: HPMC 606 (1:1)

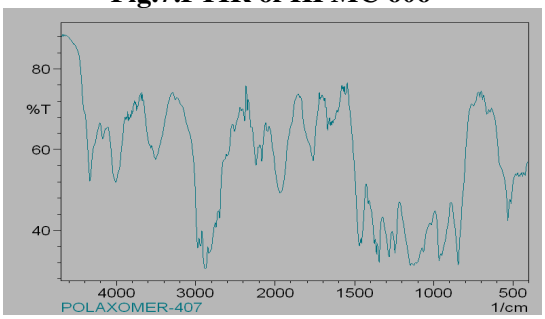

Fig.9.FTIR of Polaxomer 407

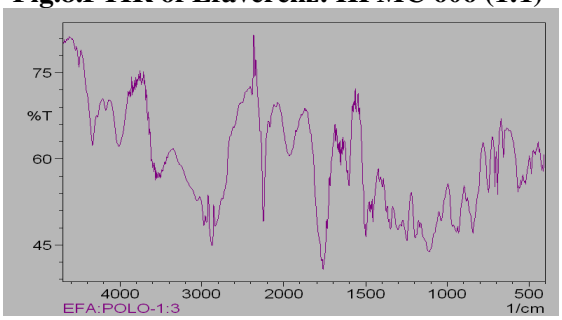

Fig.10.FTIR of Efaverenz : Polaxomer 407 (1:3)

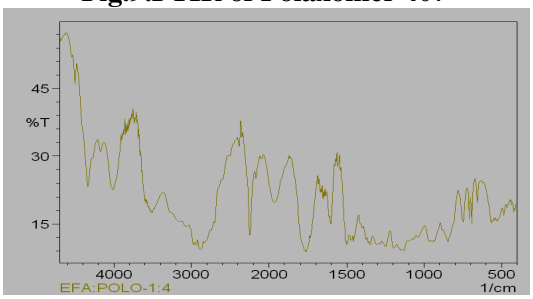

Fig.11.FTIR of Efaverenz : Polaxomer 407 (1:4)

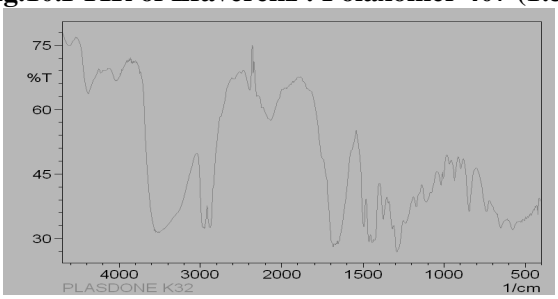

Fig.12.FTIR of Plasdone K 32

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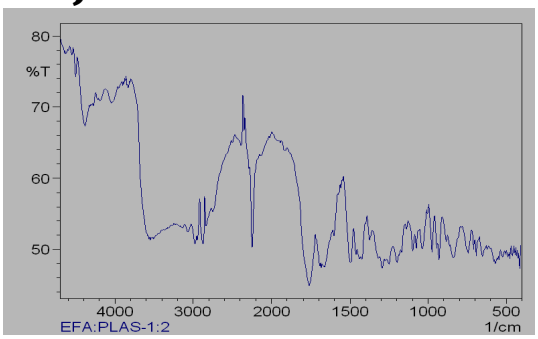

Fig.13.FTIR of Efaverenz :Plasdone K 32(1:2)

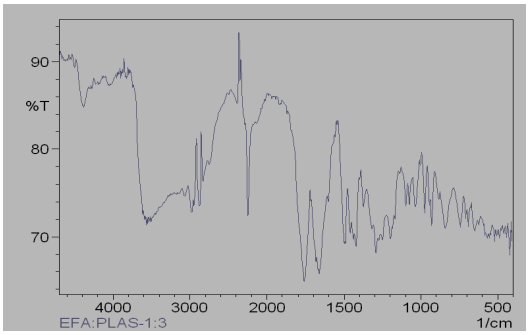

Fig.14.FTIR of Efaverenz :Plasdone K 32(1:3)

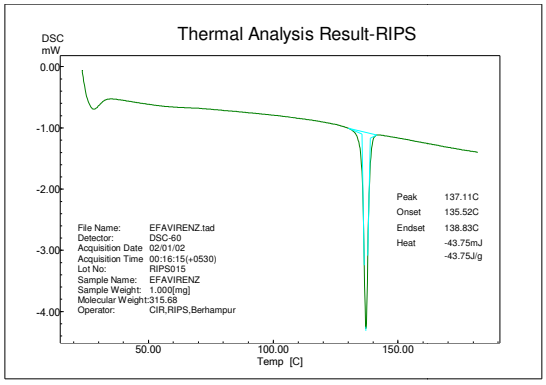

Fig.15. DSC of Efaverenz pure drug

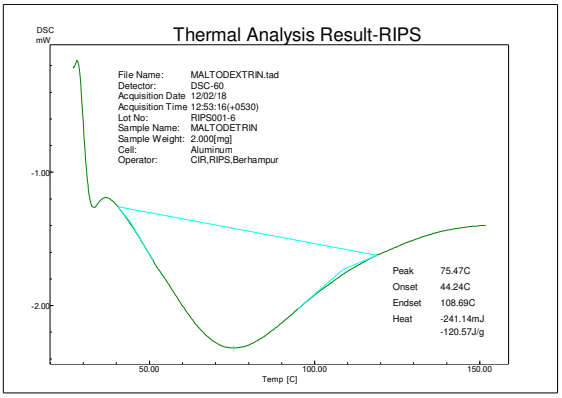

Fig.16. DSC of Maltodextrin

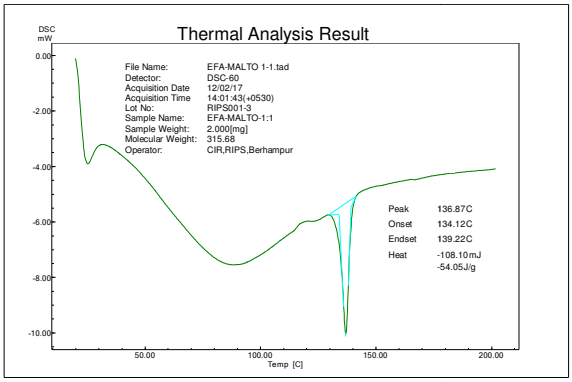

Fig.17. DSC of Efaverenz : Maltodextrin(1:1)

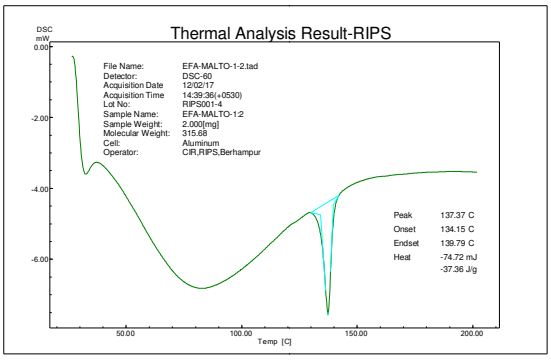

Fig.18. DSC of Efaverenz : Maltodextrin(1:2)

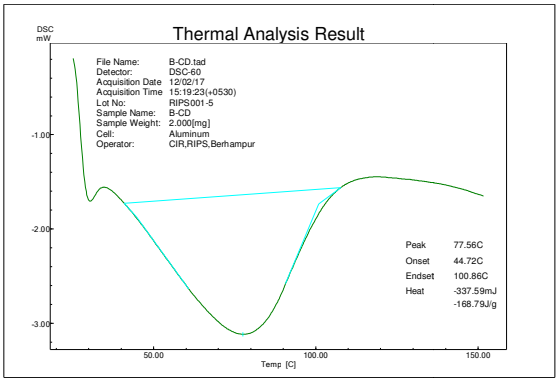

Fig.19. DSC of Betacyclodextrin

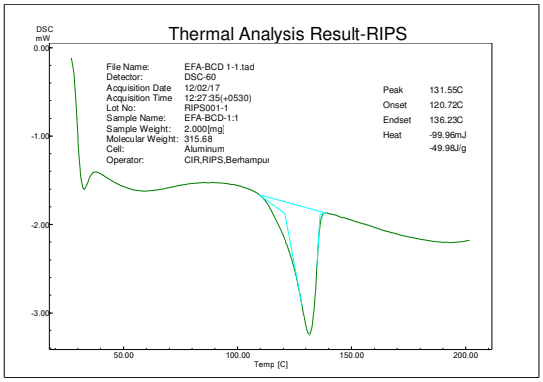

Fig.20. DSC of Efaverenz : Betacyclodextrin (1:1)

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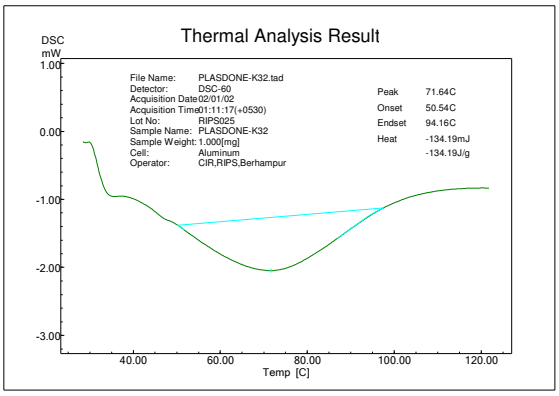

Fig.21. DSC of Plasdone K 32

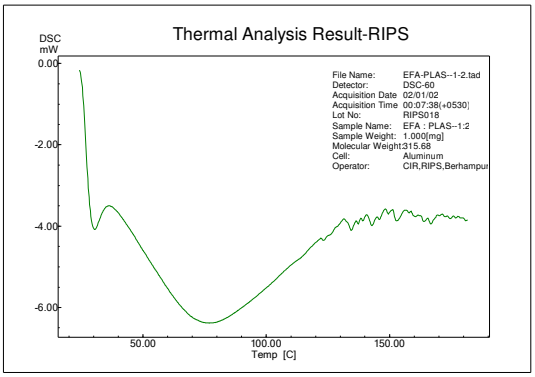

Fig.22. DSC of Efaverenz: Plasdone K 32(1:2)

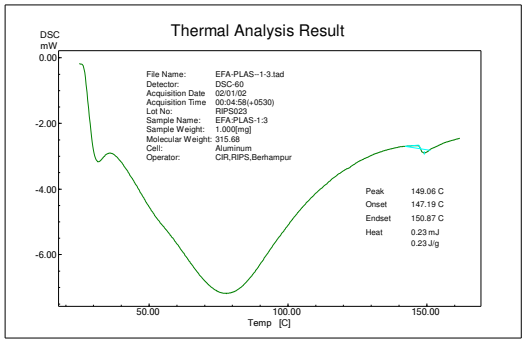

Fig.23. DSC of Efaverenz : Plasdone K 32(1:3)

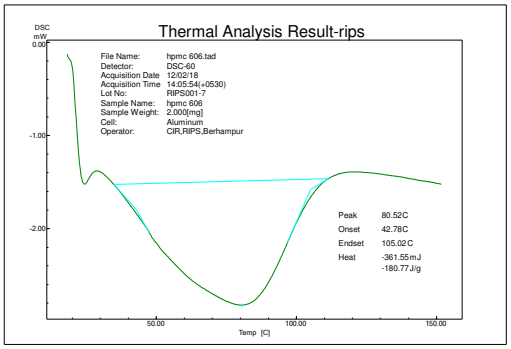

Fig.24. DSC of HPMC 606

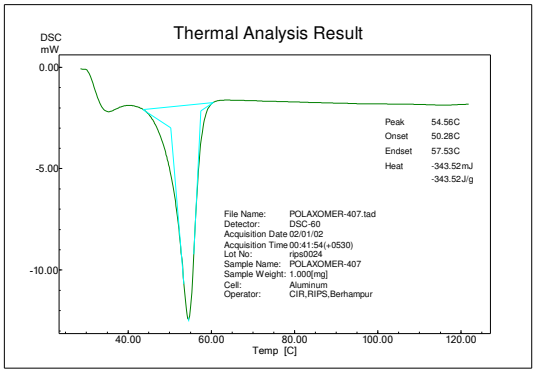

Fig.25. DSC of polaxomer 407

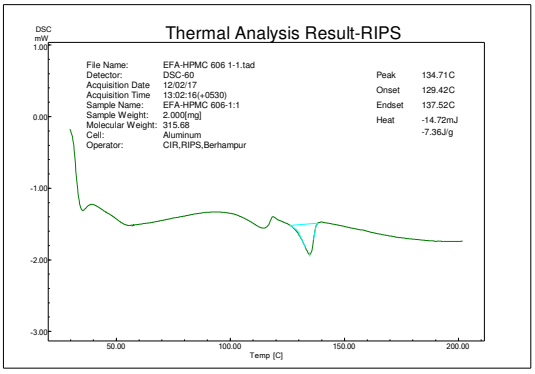

Fig.26. DSC of Efaverenz : HPMC 606 (1:1)

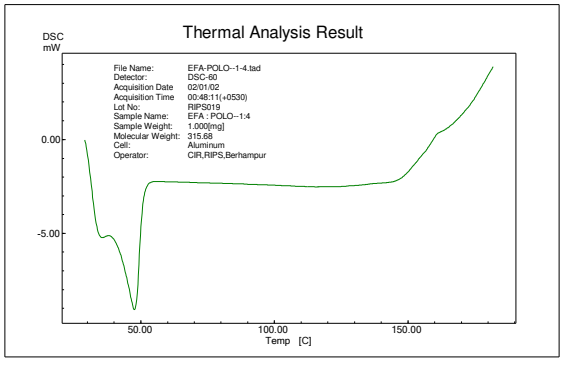

Fig.27. DSC of Efaverenz : polaxomer 407(1:4)

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3.2. Dissolution testing of Efaverenz marketed tablets in different dissolution media

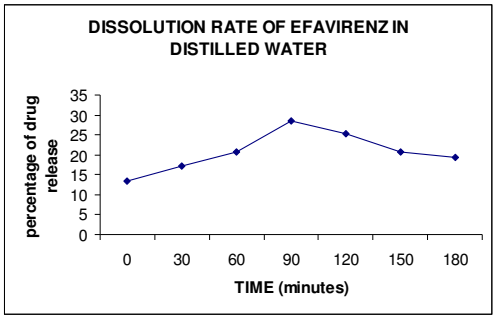


Fig.28. Dissoltion of Efaverenz tablets 200 mg in distilled water

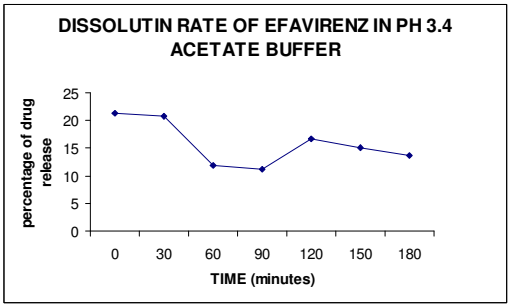


Fig.29. Dissolution rate of Efaverenz tablets 200 mg in ph 3.4 acetate buffer

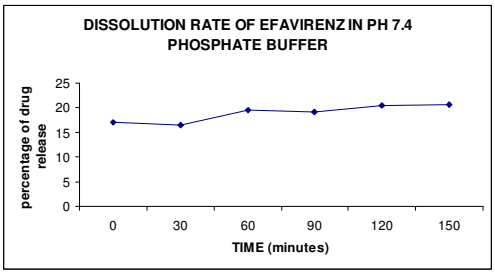


Fig.30. Dissolution of Efaverenz tablets 200 mg in ph 7.4 phosphate buffer

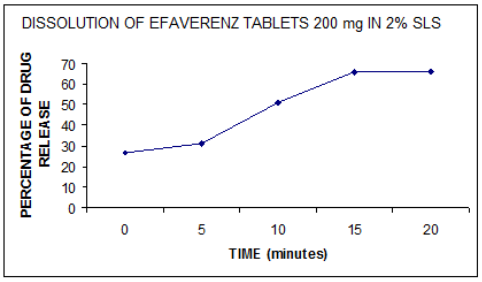


Fig.31. Dissolution rate of Efaverenz tablets 200 mg in SLS

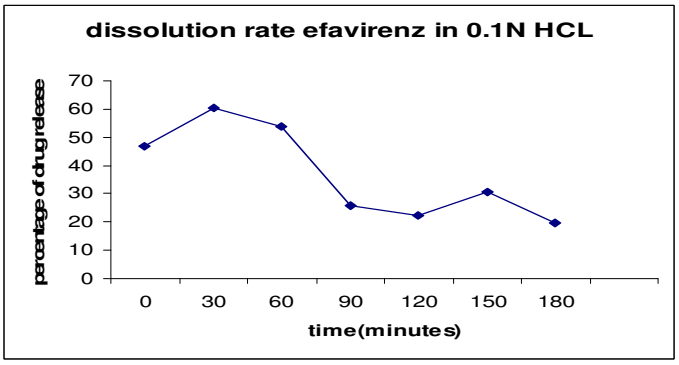
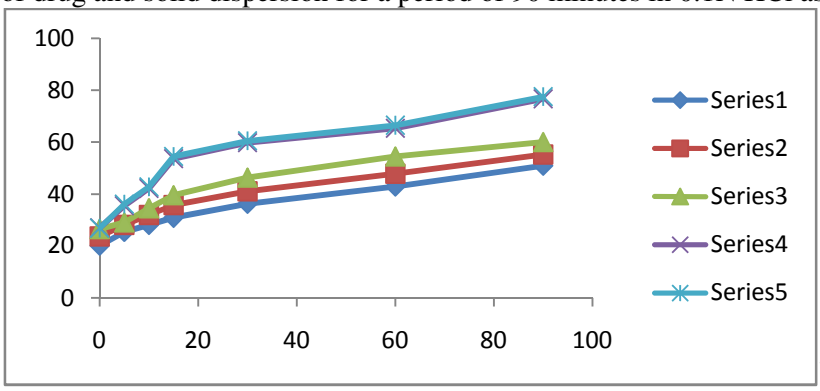


Fig.32. Dissolution rate Efaverenz in 0.1 N HCl

3.3. In Vitro Dissolution Study of Solid Dispersion: Dissolution studies were conducted for different ratios of drug and solid dispersion for a period of 90 minutes in 0.1N HCl as dissolution medium. (Fig.33)



Series1: Efaverenz: Maltodextrin (1:1)
Series2: Efaverenz: Maltodextrin (1:2)
Series3: Efaverenz: Betacyclodextrin (1:1)
Series4: Efaverenz: Polaxomer 407 (1:3)
Series5: Efaverenz: Polaxomer 407 (1:4)

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Fig.33.Dissolution studies of solid dispersions of various ratios of drug and polymers

4. CONCLUSION

Dissolution studies indicated a significant increase in dissolution of Efaverenz when dispersed in polymers. Solid dispersions containing Efaverenz: Maltodextrin1:2 and 1:1 ratios have shown remarkable promise in increasing the dissolution rate and these two ratios have shown great stability as per the DSC data. So we can conclude that we can select Maltodextrin as a hydrophilic polymer for our further studies on solid dispersions.

5. ACKNOWLEDGEMENT

The authors are thankful to Aurobindo drugs Ltd., Hyderabad, India, for providing the gift sample of Efaverenz and RA Chem Pharma Ltd., for providing the gift sample of Plasdone k 32, Maltodextrin, and Betacyclodextrin, also thankful to Nimra College of Pharmacy, Vijayawada for providing the necessary facilities to carry out the research work.

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