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IMPROVEMENT OF DISSOLUTION PROPERTIES OF *EFAVIRENZ* BY INCLUSION COMPLEXATION USING CYCLODEXTRIN

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ABSTRACT

Efavirenz (EFV) is an oral antihuman immunodeficiency virus type 1 drug with extremely poor aqueous solubility. Thus, its gastrointestinal absorption is limited by the dissolution rate of the drug. The objective of this study was to characterize the inclusion complexes of EFV with β-cyclodextrin (β-CD) and ϒ-CD to improve the solubility and dissolution of Efavirenz. The Binary inclusion complexes of Efavirenz were prepared by physical mixture, solvent evaporation method, kneading method in (1:1) ratios of two types cyclodextrins. The pre and post parameters are excellence values obtained from all the ratios it over all formulations ϒ-CD kneading method showed the heisted percentage of drug release compared other methods. It can be concluded that the inclusion complexation technique is an effective approach for the dissolution rate improvement of poorly water soluble drugs such as Efavirenz.

KEYWORDS: Efavirenz, Inclusion complexation.

INTRODUCTION

Any drug from a given dosage form to be absorbed must be present in the form of solution at the site of absorption. Low aqueous solubility is one of the major problems encountered during formulation development of new chemical entities especially in the process of generic product development. More than 40% new chemical entities developed in pharmaceutical industry are practically insoluble in water. Various techniques are used for the enhancement of the solubility of poorly soluble drugs includes physical and chemical modifications of drug like particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant, hydrotropy, co-solvency, use of surfactants, complexation etc. Inclusion

complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule into the cavity of another molecule or host molecules. The most commonly host molecules are cyclodextrins. Cyclodextrins are nonreducing, crystalline, hydrophilic outer surface. Due to the chair conformation of the glucopyranose units, the cyclodextrins are shaped like a truncated cone.[2] In aqueous solutions cyclodextrins are able to form inclusion complexes with many drugs by taking up a drug molecule or more frequently some lipophilic moiety of the molecule, into the central cavity. No covalent bonds are formed or broken during the complex formation and drug molecules in the complex are in rapid equilibrium with free molecules in the solution.

Efavirenz (EFV) is an anti-retroviral agent and is a good example of the problems associated with low aqueous solubility. Low aqueous solubility is a major problem faced during formulation development of new drug molecules Efavirenz is practically insoluble in water. Hence, purpose of this research was to enhance the solubility of EFV by using the inclusion complexation.

The aim of this study was to formulate inclusion complexes were made to enhance dissolution rate along with EFV using cyclodextrins β-CD, ϒ-CD. Efavirenz is in a class of medications called non-nucleoside reverse transcriptase inhibitors (NNRTIs), was selected as the active pharmaceutical ingredient in the study.

MATERIALS AND METHODS

Materials

Efavirenz was gifted by hetero labs HYD, cyclodextrins β-CD from Rouette Pharma, FRANCE, ϒ-CD are from ISP Technologies, USA, methanol from SD fine chemicals Ltd. Mumbai, sodium lauryl sulphate from Loba Chemi, Mumbai.

METHODS

Physical mixtures

The physical mixtures of EFV and β-CD, ϒ-CD in 1:1 were obtained by mixing individual components that had previously been sieved (75-150µm) together with a spatula.

Solvent Evaporation Method

Inclusion complexes of EFV were prepared by dissolving carriers β-CD, ϒ-CD and EFV at their corresponding ratio in common volatile solvent like methanol using a glass

mortar. They were mixed by slight pressure for 15 min. Then the solvent was allowed to evaporate in hot air oven at 45 0C for 2h. The dried mass were passed through 100 # mesh and stored in desiccators at room temperature until further use. The complexes were made in different ratios with respect to drug and polymers.

Kneading Method

EFV and carrier β-CD, ϒ-CD were weighed according to their corresponding molar ratio. EFV and carrier were transferred to a mortar pestle. The mixture was reduced the size by continuous stirring with pestle. Water-methanol mixture (1:1 v/v) ratio was added to the above physical mixture and continuously stirred until the slurry mass was formed. Slurry mass was collected and dried in a hot air oven for 2 hrs at 50 °C, dried mass was collected and further dried in desiccators over for 24 hrs. The dried mass were collected and passed through 100 # mesh, and packed it in a closed container. The complexes were made in different ratios with respect to drug and β-CD, ϒ-CD as shown in Table.

EVALUATION OF FLOW PROPERTIES

Bulk density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/mL and is given by.

$$D_b = M/V_0$$

Where, M is the mass of powder

V_0 is the Bulk volume of the powder.

Tapped density

Tapped density was determined by using graduated cylinder. An accurately weighed sample was carefully added to the graduated cylinder with the aid of funnel. The initial volume was noted and the sample was tapped on a horizontal base. Tapping was continued until no further reduction in sample volume was observed. Volume was noted and tapped density is calculated by using the following formula.

$$D_t = M/V_t$$

Where, M is the mass of powder.

V_t is the Bulk volume of the powder.

Compressibility Index(CI) and Hausner's ratio (H)

In recent years the compressibility index and the closely related Hausner's ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of the bulk density, size, shape, surface area, moisture content and cohesiveness of the materials. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of the powder.

$$\text{Carr's index} = \frac{\rho t - \rho b}{\rho t} \times 100 \quad --- \quad (6)$$

$$\text{Hausner's ratio} = \frac{\rho t}{\rho b} \quad --- \quad (7)$$

Angle of repose

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and horizontal plane. The angle of repose was determined by funnel method suggested by Newman.

Fixed funnel method was adopted for measuring the angle of repose. In this method, powder was passed through a funnel (8 cm diameter at top and 1.7cm diameter at efflux tube) that is fixed at predetermined height (2cm) and allowed to pass with or without shaking to get precise vibration. Following equation was used for the calculation of angle of repose value

$$\text{Angle of repose} = \tan^{-1}\left(\frac{h}{r}\right)$$

Where 'r' is the radius of pile and 'h' is height of pile measured.

Table-20 lists flow characterization of powders based on values of CI, HR and Angle of repose.

Table: Reference ranges to assess flow properties of powders.

S.No	Flow character	Compressibility index	Hausner's ratio	Angle of repose
1	Excellent	≤10	1.00-1.11	25-30
2	Good	11-15	1.12-1.18	31-35
3	Fair	16-20	1.19-1.25	36-40
4	Passable	21-25	1.26-1.34	41-45
5	Poor	26-31	1.35-1.45	46-55
6	Very poor	32-37	1.46-1.59	56-65
7	Very very poor	>38	>1.6	>66

Fourier Transform Infrared spectroscopy

(a) Pure EFV

The FT-IR spectrum of EFV is shown in Important vibrations detected in the spectrum of EFV are attributed to the stretching of different bonds vibrations:2249.41 cm^{-1} is stretching of Typical Exocyclic Triple bond Stretching, 1745.99cm^{-1} is stretching of C=O bond, 1601.14 cm^{-1} is stretching vibrations of C-N bond,1185.12 cm^{-1} is stretching of C-F bond and 658.30 cm^{-1} is C-CL stretching .Therefore no reaction has observed between drug and carrier when compared to Pure drug and the data.

(b) EFV with ϒ-CD's

The FT-IR spectrum of EFV+ϒ CD's is shown Important vibrations detected in the spectrum of EFV are attributed to the stretching of different bonds vibrations. 1745.84$cm^{-1}$is stretching of C=O bond, 1602.47 $cm^{-1}$is stretching vibrations of C-N bond,1184.59 cm^{-1} is stretching of C-F bond and 655.07 $cm^{-1}$is C-CL stretching .Therefore no reaction has observed between drug and carrier.

(c) EFV with β - CD's

The FT-IR spectrum of EFV+ β - CD's is shown Important vibrations detected in the spectrum of EFV are attributed to the stretching of different bonds vibrations. 1744.43$cm^{-1}$is stretching of C=O bond, 1602.07 $cm^{-1}$is stretching vibrations of C-N bond, 1184.83 cm^{-1} is stretching of C-F bondand 654.82 cm^{-1} is C-CL stretching .Therefore no reaction has observed between drug and carrier.

Differential Scanning Calorimetric analysis

The DSC Thermograms were recorded using a differential scanning calorimeter. Approximately 2-5 mg of each sample was heated in a pierced aluminum pan from 25°C to 300°C at a heating rate of 10°C/min under a stream of nitrogen. The DSC thermogram of EFV exhibits endothermic peak at 140.0°C corresponding to its melting point and is confirmed by literature data. Solid Dispersion of EFV andβ - CD's showed endothermic peak at 137.8°C which shows a weak interaction in the Solid Dispersion. The thermogram of Solid Dispersions showed a shift in the endothermic peaks of both drug as well as polymer. This data suggests the complete amorphization of drug in the polymer. Moreover some degree of interaction was reported which was dictated by the shift in the endotherms to a lower value. The endothermic peak as shown in graph.

***IN-VITRO* EVALUATION TESTS**

Calibration Curve of Efavirenz The calibration curve of EFV was obtained in the range of 2-10 µg/mL at the wave length of 246 nm. It has shown good linearity with a regression coefficient of 0.999 (r^2 value).The data were given in table.

Drug content estimation Solid Dispersions of EFV with various Carriers i.e. ϒ-CD's, β-CD's were prepared by physical mixture, Solvent Evaporation method and Kneading method with mass ratios (1:1). The results are shown in the Table. The percentage drug content for all the prepared dispersions were found to be in the range of 93.09±0.09 to 99.05±0.60 indicating uniform drug distribution.

In-vitro dissolution studies of EFV Solid Dispersion

The quantity of Solid Dispersion equivalent to 50mg of EFV was placed in dissolution medium. The dissolution study of dispersion was conducted using dissolution testing apparatus II (paddle method) in 900 ml of 2%W/V SLS solution at 37±0.5°C and at speed of 50 rpm. Aliquots of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain volume after each sampling and analyzed Spectrophotometrically at 246 nm against suitable blank using UV-visible Spectrophotometer (Elico SL150). The dissolution experiments were conducted in triplicate. Mean percent ± SD of Efavirenz at different time intervals are reported in tables.

Solubility studies

In the present work the drug is added to Buffers like pH 1.2 HCL Buffer, pH 4.6 Acetate Buffer, pH 6.8 Phosphate buffer, pH 7.2 Phosphate Buffer and also 1%SLS, 2%SLS Solutions as follows.

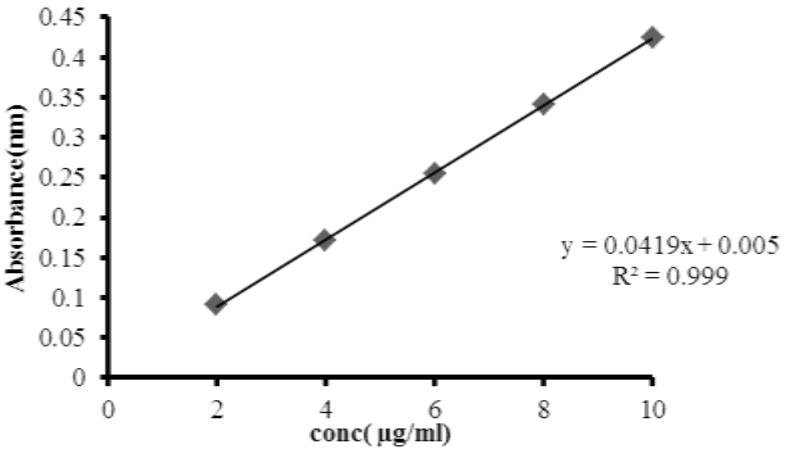
An excess of Efavirenz was added to 5mL of each fluid in a 25 mL stoppered conical flasks and the mixture were shaken for 48 hrs at room temperature (25±1°C) on a rotary flask shaker. After 48 hrs of shaking 1 mL aliquots were withdrawn and filtered immediately using a 0.45µ nylon disc filter. The filtered samples were diluted suitably and assayed for drug measuring absorbance at 246 nm. Shaking was continued until three constructive estimations were same. The solubility experiments were run in triplicate.

The results of solubility studies revealed that EFV is more soluble in 2%SLS Solution. The order of solubility is 2%SLS>1%SLS>1.2 pH >DW>6.8 pH>7.2 pH>4.6 pH. The data were given in table.

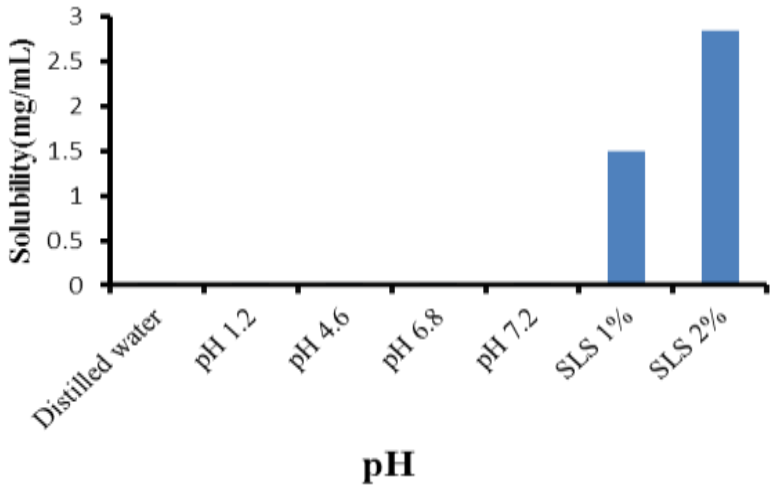
RESULTS

Calibration data of FEV.

SI No.	Concentration (µg/mL)	Absorbance (at 246 nm)
1	2	0.091
2	4	0.171
3	6	0.254
4	8	0.341
5	10	0.425



Calibration Curve of Efavirenz



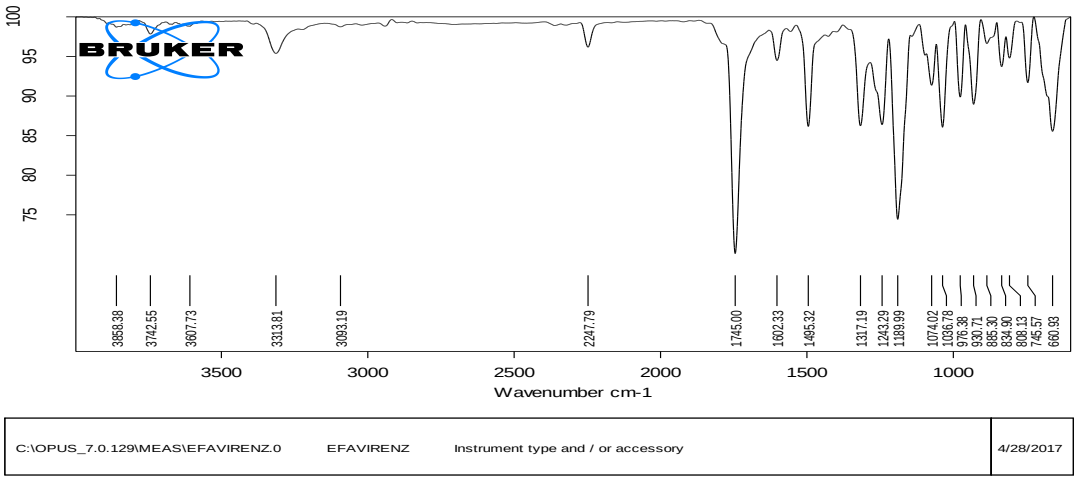
Solubility studies of EFV various solvent.

Table: Pre compression Evaluation of Solid Dispersions.

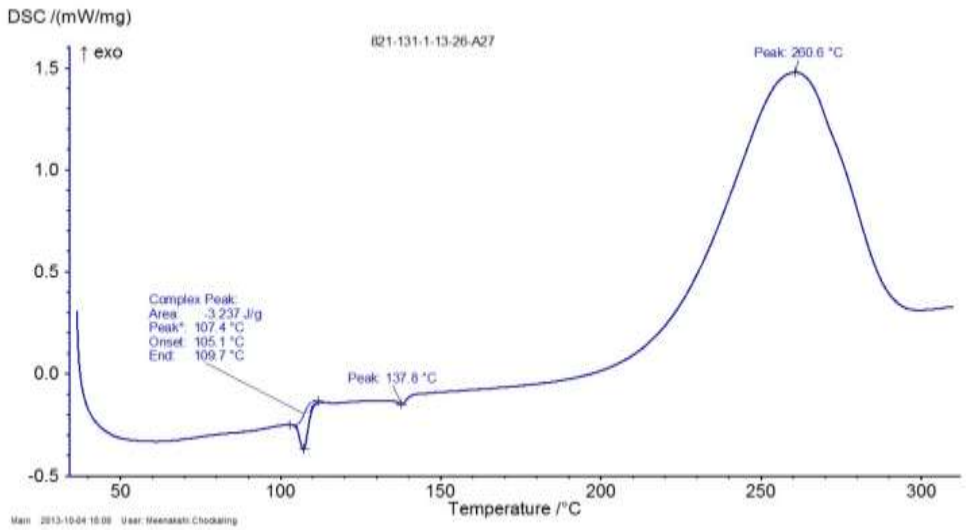
Solid Dispersions	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose	Flow comment
ϒ-CD PM 1:1	19.86±0.45	0.62±0.57	0.89±0.20	17.64	1.038	GOOD
ϒ-CD SE 1:1	20.18±0.47	0.74±0.64	0.90±0.54	18.87	1.022	GOOD
ϒ-CDKM1:1	24.06±0.54	0.83±0.44	0.91±0.05	19.78	1.011	GOOD
β-CD PM 1:1	20.86±0.45	0.72±0.57	0.92±0.20	18.64	1.336	GOOD
β-CD SE 1:1	22.18±0.47	0.84±0.64	0.95±0.54	17.87	1.021	GOOD
β-CD KM 1:1	26.06±0.54	0.93±0.44	1.01±0.05	9.78	1.103	EXCELLENT

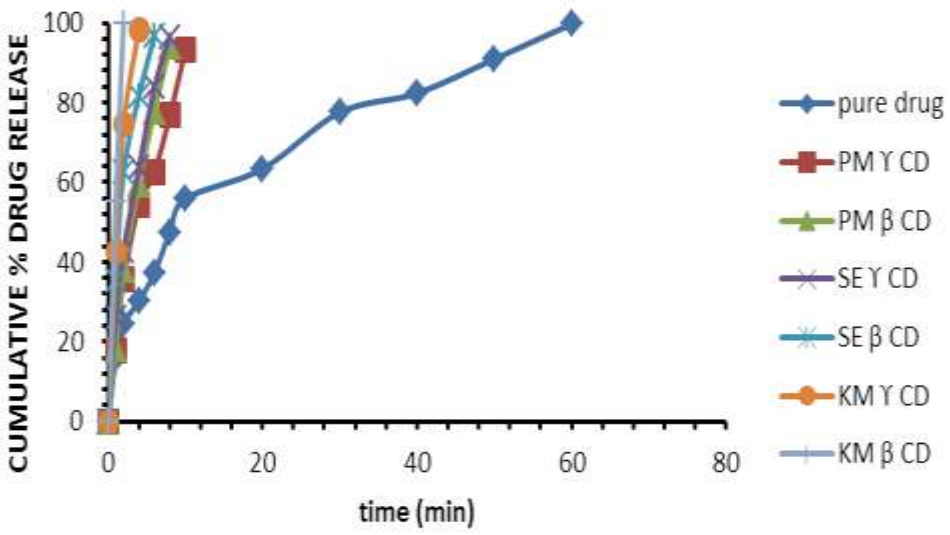
Characterization of Solid Dispersions of Pure EFV and various Carriers

FT-IR studies.



(DSC) of EFV: β-cd Kneading method





***In-vitro* Dissolution Studies of EFV Solid Dispersions with Various Carriers and ratio.**

Time (min)	pure drug	PM Ɣ CD	PM β CD	SE Ɣ CD	SE β CD	KM Ɣ CD	KM β CD
0	0	0	0	0	0	0	0
1	15.85±5.36	17.82±0.03	18.0±0.15	26.03±0.45	35.4±1.97	42.84±6.29	55.0±3.64
2	24.40±0.25	35.55±0.18	38.0±0.02	42.78±1.51	62.5±0.91	74.60±3.95	99.95.±0.60
4	30.14±0.54	54.17±1.21	59.5±5.16	63.63±0.60	81.7±1.82	98.24±0.90	
6	37.25±2.5	62.56±0.90	77.8±1.81	83.84±1.21	96.72±0.60		
8	47.47±2.0	76.75±2.12	94.10±0.60	96.53±0.30			
10	55.9±0.58	93.09±0.09					
20	63.39±4.23						
30	77.56±0.36						
40	82.36±0.35						
50	90.94±3.75						
60	99.72±3.75						

DISCUSSION

Calibration Curve of Efavirenz The calibration curve of EFV was obtained in the range of 2-10 µg/mL at the wave length of 246 nm. It has shown good linearity with a regression coefficient of 0.999 (r^2 value).

Drug content estimation Solid Dispersions of EFV with various Carriers i.e. Ɣ-CD's, β-CD's were prepared by physical mixture, Solvent Evaporation method and Kneading method with mass ratios (1:1). The percentage drug content for all the prepared dispersions were found to be in the range of 93.09±0.09 to 99.05±0.60 indicating uniform drug distribution.

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In the present work the drug is added to Buffers like pH 1.2 HCL Buffer, pH 4.6 Acetate Buffer, pH 6.8 Phosphate buffer, pH 7.2 Phosphate Buffer and also 1%SLS, 2%SLS Solutions as follows.

The results of solubility studies revealed that EFV is more soluble in 2%SLS Solution. The order of solubility is 2%SLS>1%SLS>1.2 pH >DW>6.8 pH>7.2 pH>4.6 pH.

Evaluations of flow properties: Flow properties of complexation like bulk density, tapped density, Hausner's ratio, Carr's index and Angle of repose were evaluated Among the formulation prepared with drug and β-CDs, containing showed good flow characteristics while improved flowability was observed with increase in ratio of polymer. Among the complexation prepared ϒ-CD containing EFV (1:1) ratio showed passible and good flow characteristics, whereas, no much improvement in flowability was observed with increase in the ratio of polymer. lowest amount of polymer showed only passable flow properties which indicate the need for further increment in ratio of polymer.

***In vitro* dissolution studies**

In physical mixture(PM I) dissolution study of EFV with γ- CD's in 1:1 ratio, the data showed that 35.55±0.18% of drug was released within 2 minutes. The drug release in physical mixture (PM II) EFV with β- CD's in 1:1 ratio was found to be 38.0±0.02% within 2 min. For initial periods of time for 1min, the drug release in 1:1 with γ- CD's and β- CD's was found to be 17.82±0.03% and 18.0±0.15% respectively this indicates that as the carrier is changed the dissolution is increased. The complete dissolution in 1:1 with γ- CD's and β- CD's obtained in 10 and 8 min respectively.

In Solvent Evaporation(SE I) dissolution study of EFVwith γ- CD's in 1:1 ratio, the data showed that 42.78±1.51% of drug was released within 2 minutes. The drug release in solvent evaporation method (SE II) 1:1 ratio was found to be 62.50±0.91% within 2 min. For initial periods of time for 1min, the drug release in 1:1 with γ- CD's and β- CD's was found to be 26.03±0.45% and 35.4±1.97% respectively this indicates that carrier is changed the dissolution is increased. The complete dissolution in 1:1 with γ- CD's and β- CD's in 8 and 6min respectively.

In kneading method (KM I) dissolution study of EFVwith γ- CD's in 1:1 ratio, the data showed that 74.60±3.95% of drug was released within 2 minutes. The drug release in kneading method (KM II) 1:1 ratio was found to be 99.05±0.60% within 2 min. For initial periods of time for 1min, the drug release in 1:1 with γ- CD's and β- CD's was found to be 42.84±6.29% and 55.0±3.64% respectively this indicates that carrier is changed, the dissolution is increased. The complete dissolution in 1:1 with γ- CD's and β- CD's is obtained in 4 and 2 min respectively.

All the Solid Dispersions in combined carriers gave much higher rates of dissolution, several times higher than the dissolution rate of pure drug. EFV: β- CD's (KM II) with kneading method in 1:1 Solid Dispersion gave a 2.265fold increase (K_1) in the dissolution rate of Efavirenz.

CONCLUSIONS

In the present investigation studies were carried out on enhancement of dissolution rate of EFV by Solid Dispersion technology (physical mixture, solvent evaporation, Kneading method) employing various water dispersible carriers. A ϒ-CD's, β-CD'swas evaluated as carriers for Solid Dispersions and for enhancing the dissolution rate of poorly soluble drugs. Among all β- CD's in the ratio 1:1 (KM II) was found to be good carrier for Solid Dispersions for enhancing the dissolution rate of Efavirenz.

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