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Original Article

Characterization of Solid Binary Systems of Efavirenz and Hydroxypropyl-β-Cyclodextrin

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ABSTRACT: Efavirenz is a widely prescribed anti-retroviral drug that belongs to BCS class II and exhibit low and variable oral bioavailability due to its poor aqueous solubility and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. The aim of this study was to increase the solubility of Efavirenz (EFA) by complexing it with Hydroxypropyl-β-cyclodextrin (HPβCD). Solid binary systems were prepared by co-grinding and microwave irradiation methods. The interaction of EFA with HPβCD was evaluated by Phase solubility studies, *in vitro* dissolution studies and different analytical techniques including Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC). The apparent stability constant revealed EFA with HPβCD produces 1:1 M stoichiometric complex. The host guest interactions studied by FTIR and DSC confirmed true inclusion of EFA with HPβCD at 1:2 M. The Dissolution rates of EFA- HPβCD binary systems were faster when compared to physical mixture and pure drug. Overall the rank order of improvement in dissolution properties of Efavirenz with ratios is 1:2M > 1:1M and methods MW > CG > PM > Pure drug. One-way ANOVA suggest the DP_{60} and DE_{60} values were significantly higher ($P<0.05$) in solid binary systems prepared by microwave irradiation method when compared to co-grinding and its corresponding physical mixtures and pure drug.

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INTRODUCTION

Efavirenz (EFA) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used for the treatment of human immunodeficiency virus type 1 infection [1] (figure 1). Despite being widely used clinically, this drug has very low oral bioavailability (40%–45%) and high interindividual (56%) and intraindividual (22%) variability in its absorption [2,3]. This drug has been classified as a Biopharmaceutics Classification System Class II compound with high permeability but low aqueous solubility with a dissolution rate-dependent absorption [4,5]. The very low aqueous solubility (~3–9 g/mL) hinders its administration, oral absorption, and bioavailability [6]. By improving dissolution, it is possible to enhance its oral bioavailability [7].

In general, an intrinsic dissolution rate less than 0.1 mg/ (min cm^2) could be a rate limiting factor for oral drug absorption [8]. EFA has a very low intrinsic dissolution rate of 0.037 mg/min cm2, which suggests dissolution rate limited absorption problems for this drug [9]. Polymeric micellar solubilisation and cyclodextrin complexation have significantly increased the solubility of EFA [2,9].

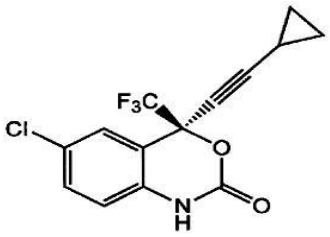

Figure 1: Structure of Efavirenz

A strategy used to increase the solubility, dissolution and bioavailability of poorly water-soluble compounds such as efavirenz is the formation of inclusion complexes with cyclodextrins (CDs) [10]. CDs are oligosaccharides which are formed by D-(+) glucopyranose units linked with alpha-1,4-glycosidic bonds and are obtained by enzymatic degradation of the starch by action of the enzyme cyclodextrin glycosyl transferase (CGTase). The natural cyclodextrins due to their physicochemical properties, their supramolecular structure with a hydrophobic internal cavity and a hydrophilic exterior, they can be used as host for a variety of guest molecules to form inclusion complexes by non-covalent bonds. Based on the structure and properties of drug molecule it can form 1: 1 or 1: 2 drug cyclodextrin complex as illustrated in figure 2.

Despite the fact that the natural CDs are widely used for the investigation and development of pharmaceutical formulations, they have some limitations. In particular, β-cyclodextrin shows a low aqueous solubility (1.85% w/v at 25°C) due to its rigid structure resulting from intramolecular formation of hydrogen bonds between its secondary hydroxyl groups. In order to counteract the low solubility of this cyclodextrin, chemically modified derivatives with higher solubility and lower toxicity have been developed, such as hydroxylpropyl-β-cyclodextrin (HPβCD), formed by substitution of the hydroxyl in position 2, 3 and 6 with 2-hydroxypropyl substituents [11,12].

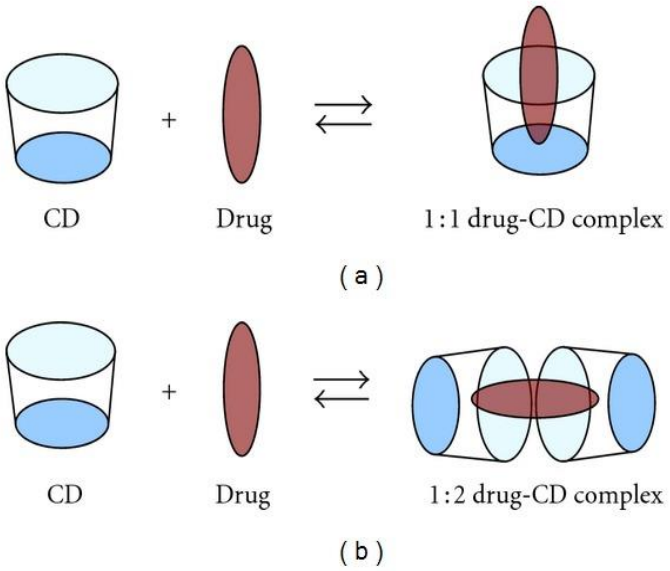

Figure 2: Drug- Cyclodextrin complexation

Hydroxypropyl-β-cyclodextrin (HPβCD) is a chemically modified derivative of β-cyclodextrin that has been reported to be safer and less irritating than the parent cyclodextrin [13,14]. The aforementioned derivative also provides higher solubility and stability to inclusion compounds than β-cyclodextrin [13]. Therefore, based on the above-mentioned benefits HPβCD was selected in this study.

Hence in this present work, our aim was to study the effect of HPβCD on EFA and their effect on its pharmaceutical properties (i.e. aqueous solubility, dissolution properties and bioavailability).

MATERIALS AND METHODS

Materials

Efavirenz (EFA) was a gift sample from Strides Pharma Ltd., Bangalore, India. Hydroxypropyl-β-cyclodextrin (HPβCD) was obtained from Glenmark Pharma Ltd., Nasik, India. All other reagents and solvents used were of analytical grade.

Methods

Preparation of solid binary systems

The following binary systems of efavirenz and HPβCD were prepared at 1:1 and 1:2 molar ratios.

Physical Mixtures: The physical mixtures of efavirenz and HPβCD in 1:1 and 1:2 M were obtained by mixing individual components that had previously been sieved (75-150 µm) together with a spatula.

Co-grinded systems: Efavirenz was triturated with HPβCD in a glass mortar for 30mins; the resulting grinded powder was passed through sieve no 80.

***Microwave irradiated systems*:** The aqueous solution of cyclodextrin was added slowly into a solution of efavirenz dissolved in methanol with constant stirring. The mixture was subjected for irradiation in microwave oven for 90 seconds at 60^0c, after reaction completes add adequate amount of methanol to remove the residual HPβCD. The resulting mixture was stirred for 1hour and evaporated under vacuum until dry. The resulting powder was pulverized and passed through sieve no 80.

Detection of solid binary systems in solution state

***Phase Solubility Studies*:** Excess amounts of efavirenz (50mg) were added to 25ml HPβCD solutions (ranging in concentration from 0.5 to 4×10^{-4}M) prepared in 1.5% w/v sodium lauryl sulphate solution in a series of 25ml stoppered conical flasks. The mixtures were shaken for 48hrs at room temperature (28°C) on a rotary flask shaker. After 48hrs of shaking to achieve equilibrium, 2ml aliquots were withdrawn at 12hrs intervals and filtered immediately using a 0.45µm nylon disc filter. The filtered samples were diluted and assayed for efavirenz by measuring absorbance at 247nm. Shaking was continued until three consecutive estimations were the same. The solubility experiments were conducted in triplicate. The blanks were performed in the same concentrations of HPβCD in 1.5% w/v sodium lauryl sulphate in order to cancel any absorbance that may be exhibited by the CD molecules. The apparent stability constants were calculated from the solubility diagrams.

Detection of solid binary systems in solid state

***FTIR studies*:** Fzourier transform IR spectra were recorded on a Shimadzu FTIR-281-spectrophotometer. The spectra were recorded for efavirenz, HPβ-CD and solid binary systems. Samples were prepared in KBr disks prepared with a hydrostatic press at a force of 5.2T Cm^{-2} for 3 min. The scanning range was 450-4000cm^{-1} and the resolution was 1 cm^{-1}.

***Differential scanning calorimetry*:** Thermograms of efavirenz, HPβCD and solid binary systems were recorded on a Sieko, DSC 220C model differential scanning calorimeter (Tokyo, Japan). About 10mg of samples were sealed in aluminium pans and heated at a rate of 10^0C/min from 30°C-300°C.

***Dissolution Studies*:** *In vitro* dissolution studies of efavirenz, physical mixture and solid binary systems prepared were carried out in 900ml of 1.5%w/v sodium lauryl sulfate (SLS) solution using a USPXXI type 2-dissolution rate test apparatus by powder dispersed amount method (powder samples were spread over the dissolution medium). Sample equivalent to 100mg of efavirenz, speed of 75rpm and a temperature of 37°C were used in each test. A 5ml aliquot was withdrawn at different time intervals, filtered using a 0.45µm nylon disc filter and replaced with 5ml of fresh dissolution medium. The filtered samples were suitably diluted, if necessary and assayed for efavirenz by measuring the absorbance at 247nm.The dissolution experiments were conducted in triplicate. The results were computed by using dissolution software PCP DISSO V3.0.

RESULTS

***Phase solubility studies*:** The apparent stability constants ($K_{1:1}$) were calculated from phase solubility diagrams by using following equation [15].

$$K_{1:1} = \frac{\text{Slope}}{So(1\text{-Slope})}$$

Where S_o is intercept. The apparent stability constant value was $4.789M^{-1}\pm0.001$ for HPβCD and increase in solubility was 3.139 as shown in table 1 and figure 3.

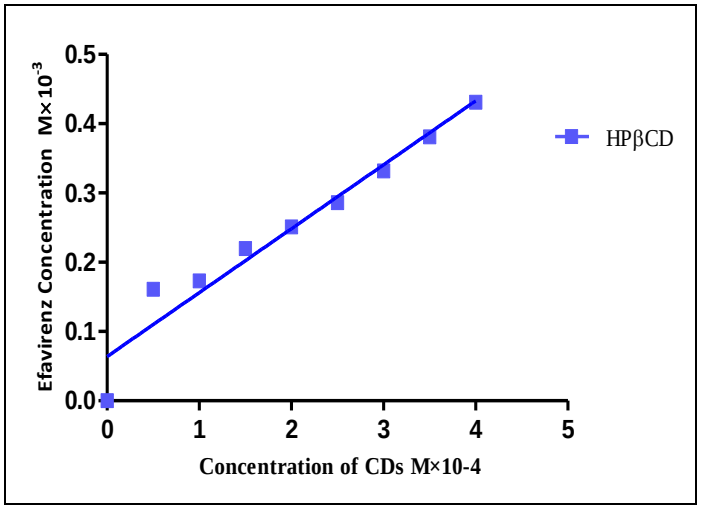

Figure 3: Phase Solubility Profile

Table 1: Summary of efavirenz- HPβCD Phase Solubility Studies*

CD	Type of Phase Solubility Diagram	Stability Constant M^{-1}	Increase of Solubility (S_t/S_o)
HPβCD	A_L	4.789	3.139

* CD, cyclodextrin; S_t, solubility of efavirenz in 25mM of CD solutions; S_o, solubility of efavirenz without CDs

***FTIR studies*:** Infrared spectroscopy has been widely used to investigate drug polymer interactions in solid binary systems [16]. The FTIR spectrum of pure efavirenz, physical mixture and its solid binary systems prepared by all methods are shown in figure 4 and table 2**.** The FTIR characteristic efavirenz bands are the same spectrum as mentioned in the literature [17].

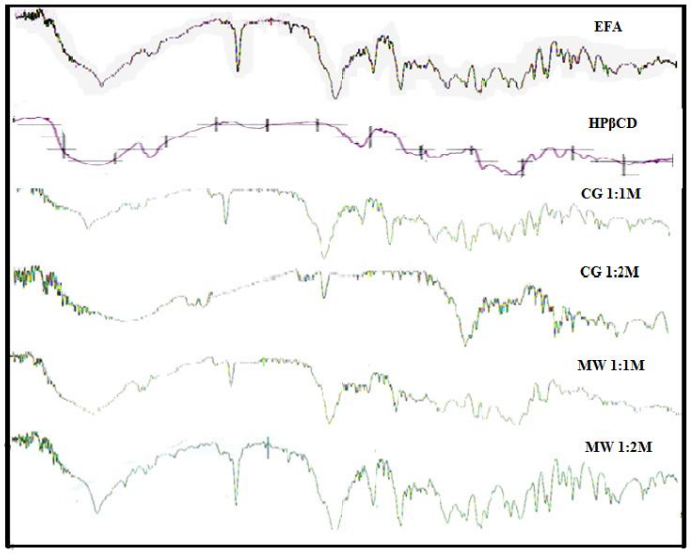

Figure 4: FTIR spectra of efavirenz, HPβCD and its solid binary systems

Table 2: Comparative FTIR data of efavirenz, physical mixture and solid binary systems.

Batches	Batches	Batches	Batches
EFA	3318cm^{-1}	2251 cm^{-1}	1749 cm^{-1}
EFA: HPβCD CG 1:1	3315cm^{-1}	2249cm^{-1}	1747cm^{-1}
EFA: HPβCD MW 1:1	3387cm^{-1}	2249cm^{-1}	1778cm^{-1}
EFA: HPβCD CG 1:2	3329cm^{-1}	2249cm^{-1}	1747cm^{-1}
EFA: HPβCD MW 1:2	3356cm^{-1}	2249cm^{-1}	1778cm^{-1}

***DSC Studies*:** DSC thermograms of efavirenz and its solid binary systems were shown in figure 5. The DSC thermogram of efavirenz exhibited an endothermic peak at 136.87°C, similar to the peak value reported in the literature [18] corresponding to its melting point and DSC thermogram of HPβCD showed broad endothermal peak at 68.58°C.

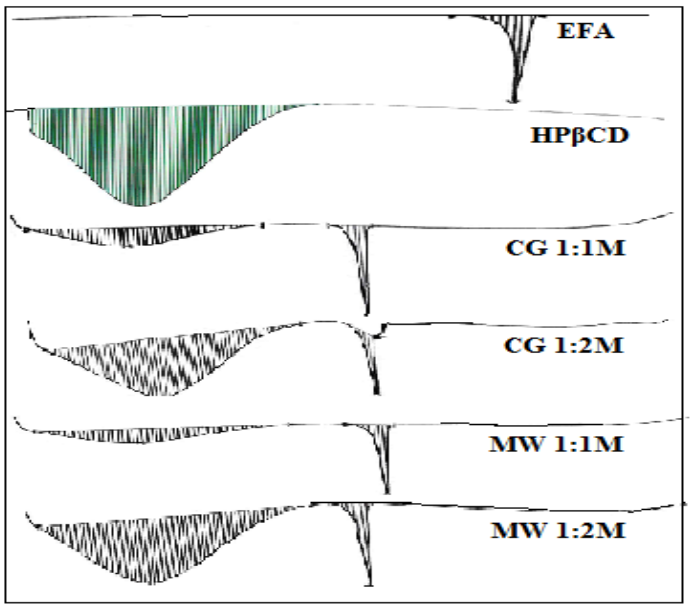

Figure 5: DSC Thermograms of efavirenz, HPβCD and Its Solid Binary Systems

***Dissolution studies*:** In the present investigation, dispersed amount method is used to investigate the various dissolution parameters of efavirenz and its solid binary systems. The dissolution data of efavirenz and its solid binary systems were studied by using dissolution software PCP DISS0 V.3.0**.** DP_{30}, DP_{60}, DE_{30}, DE_{60}, MDT_{30}, MDT_{60}, RDR_{30}, RDR_{60}, T_{50} values were calculated from the dissolution software and are given in table 3 and the dissolution profiles are shown in figure 6.

The dissolution data obtained were subjected to model fitting and the model which fits the observed dissolution data was evaluated by correlation coefficient (r) between the variables involved. The calculated `r' values in various models for all complexes are summarized in table 4. One-way ANOVA was used to test the statistically significant difference between pure drug and prepared solid binary systems.

Significant differences in the means of DP_{60} and DE_{60} were tested at 95% confidence. The DP_{60} and DE_{60} values of efavirenz, physical mixture and its corresponding solid binary systems are shown in table 5 and table 6.

Table 3: Dissolution parameter data of efavirenz, efavirenz: HPβCD physical mixtures and its solid binary systems

Batches	DP_{30}	DP_{60}	DE_{30}	DE_{60}	RDR_{30}	RDR_{60}	T_{50}
Pure Drug	8.3	16.0	4.69	8.55	1.0	1.0	239.1
PM 1:1M	14.3	26.5	7.81	14.24	1.63	1.59	135.1
PM 1:2M	19.2	34.8	11.26	20.11	2.25	2.34	97.3
CG 1:1M	32.9	55.0	19.51	31.35	3.61	3.46	52.1
CG 1:2M	42.0	66.4	25.46	39.11	4.56	3.99	38.2
MW 1:1M	57.2	81.7	28.99	49.15	6.05	5.16	24.5
MW 1:2M	58.9	88.4	29.41	52.88	6.11	5.86	24.2

Table 4: Model fitting values of efavirenz, physical mixture and its solid binary systems

Batches	$K_1 \times 10^2 (min)^{-1}$		$K_H \times 10^2 (mg^{1/3}.min^{-1})$	
	R	K	R	K
Pure Drug	0.9951	-0.0029	0.9936	-0.0009
PM 1:1M	0.9972	-0.0051	0.9952	-0.0016
PM 1:2M	0.9926	-0.0071	0.9867	-0.0021
CG 1:1M	0.9974	-0.0133	0.9905	-0.0037
CG 1:2M	0.9972	-0.0182	0.9866	-0.0047
MW 1:1M	0.9935	-0.0283	0.9787	-0.0064
MW 1:2M	0.9520	-0.0566	0.9857	-0.0085

Table 5: ANOVA data obtained for DP_{60} by using Dunnett multiple comparison tests for efavirenz: HPβCD physical mixtures and solid binary systems at 1:1 and 1:2 ratios

Batches	Comparison	Number of points	Mean	SD	SEM	Mean difference	q	P value
Pure Drug	----------	3	16.12	0.117	0.0679	-----	-----	-----
PM 1:1M	EFA vs PM 1:1M	3	26.56	0.121	0.0699	-10.438	11.48	**P<0.01
CG 1:1M	EFA vs CG 1:1M	3	34.84	0.109	0.06341	-18.719	20.58	**P<0.01
MW 1:1M	EFA vs MW 1:1M	3	53.38	2.933	1.693	-37.264	40.98	**P<0.01
PM 1:2M	EFA vs PM 1:2M	3	66.44	0.131	0.07566	-50.315	55.33	**P<0.01
CG 1:2M	EFA vs CG 1:2M	3	81.76	0.114	0.06567	-65.644	72.19	**P<0.01
MW 1:2M	EFA vs MW 1:2M	3	88.44	0.092	0.05326	-72.317	79.53	**P<0.01

Where, ns* not significant, P< 0.05*(significant), P< 0.01** (very significant) and P< 0.001*** (highly significant)

Table 6: ANOVA data obtained for DE_{60} by using Dunnett multiple comparison tests for efavirenz: HPβCD physical mixtures and solid binary systems at 1:1 and 1:2 Ratios

Batches	Comparison	Number of points	Mean	SD	SEM	Mean difference	q	P value
Pure Drug	----	3	8.55	0.099	0.057	-----	-----	-----
PM 1:1M	EFA vs PM 1:1M	3	14.25	0.110	0.063	-5.697	66.292	**P<0.01
CG 1:1M	EFA vs CG 1:1M	3	20.11	0.106	0.061	-11.554	134.45	**P<0.01
MW 1:1M	EFA vs MW 1:1M	3	31.35	0.100	0.057	-22.801	265.33	**P<0.01
PM 1:2M	EFA vs PM 1:2M	3	39.11	0.104	0.060	-30.554	355.56	**P<0.01
CG 1:2M	EFA vs CG 1:2M	3	49.14	0.115	0.066	-40.590	472.35	**P<0.01
MW 1:2M	EFA vs MW 1:2M	3	52.88	0.100	0.057	-44.327	515.83	**P<0.01

Where, ns* not significant, P< 0.05*(significant), P< 0.01** (very significant) and P< 0.001*** (highly significant

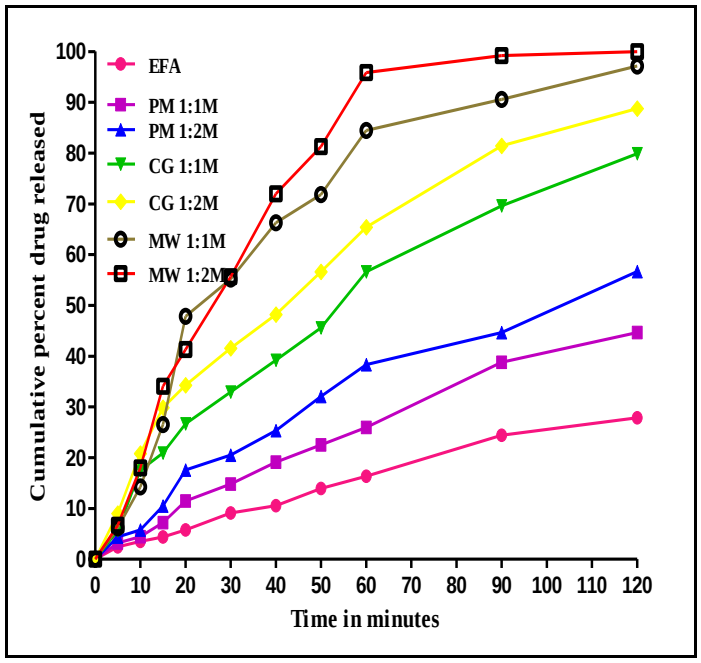

Figure 6: Comparative release profiles of efavirenz, efavirenz: HPβCD physical mixtures and its solid binary systems

DISCUSSION

Phase solubility studies: The solubility of efavirenz increases linearly with an increase in the concentration of CDs giving A_L type solubility diagrams. The increase in solubility in the systems is due to one or more molecular interactions between Efavirenz and CD form distinct species or complexes.

The cavity size of HPβCD seems to be optimal for entrapment of efavirenz molecule and consequently provides the greatest solubilisation effect. The stability constant value that was observed with HPβCD indicates efavirenz interacts strongly with HPβCD and produces 1:1M stoichiometric complex.

***FTIR studies*:** Efavirenz has strong absorption peak at 1747cm^{-1} which was assigned to drug carbonyl stretching vibration. The characteristic carbonyl stretching (CO) vibration of efavirenz appeared at 1747cm^{-1} in the physical mixtures, co-grinded and microwave irradiated products with HPβCD.

In the spectra of microwave irradiated complex this band was broader and was shifted towards lower wave number at 1747-1768cm^{-1}. On the other hand, the C=O stretching band of efavirenz in microwave irradiated complex shifted to higher frequency, shifting is from 1747cm^{-1} (Efavirenz) to 1768-1789 cm^{-1}. These results indicate the formation of inclusion complex suggesting the formation of hydrogen bonds between the carbonyl groups of efavirenz and the hydroxyl groups of the host cavities during complexation processes. The observed changes in the FTIR spectra of the solid binary systems may be explained by the different preparation methods. From the FTIR spectra the patterns of the physical mixtures correspond to superimposing of FTIR spectra of the two components.

Moreover, the vibrations of efavirenz are shifted towards higher frequencies, suggesting the breakage of existing bonds as a result of inclusion complex formation with reduced intensities.

***DSC Studies*:** The DSC curves of the efavirenz and HPβCD compared with its solid binary systems prepared by all methods confirm not only an interaction between the drug and HPβCD but also a real inclusion. The DSC curve of efavirenz was compared with the inclusion complexes of efavirenz- HPβCD prepared by co-grinded and microwave irradiated methods. DSC curves indicate progressive reduction in efavirenz endothermal peak intensity in efavirenz-HPβCD inclusion complexes at 1:1M and 1:2M ratios prepared by co-grinding and 1:1M microwave irradiation method. These point to partial interaction between efavirenz and HPβCD, but in case of efavirenz-HPβCD 1:2M microwave irradiated inclusion complex more reduction in efavirenz endothermal peak indicates strong interaction between efavirenz and HPβCD.

***Dissolution Studies*:** The results of the dissolution rate studies indicated higher dissolution rate of efavirenz from solid binary systems when compared to efavirenz itself and the corresponding physical mixtures. The DE_{30} and DE_{60} values of the binary systems that were prepared by the co-grinded and microwave irradiated methods were relatively high when compared with the values from the physical mixtures and efavirenz alone. Overall the rank order of improvement in dissolution properties of efavirenz with methods is MW > CG > PM. The DE_{30} and DE_{60} values of the efavirenz- HPβCD microwave irradiated complexes were higher than those of the complexes prepared by co-grinding method. The DP_{60} and DE_{60} values of solid binary systems prepared by microwave irradiation and co-grinding method are significantly higher ($P<0.01$) when compared to DP_{60} and DE_{60} values of pure efavirenz, physical mixture and its corresponding solid binary systems.

CONCLUSION

The results of the phase solubility studies reveal that the solubility of efavirenz increases in the presence of HPBCD. However, the calculated apparent stability constants allowed concluding that efavirenz forms stable inclusion complex with HPβCD. We consider the results obtained by FTIR Spectroscopy and DSC Analysis to serve as proof for the formation of inclusion complex between efavirenz and HPβCD at 1:1 and 1:2 molar ratios by co-grinding and microwave irradiation methods with a good performance of dissolution profile. Further higher and significant ($p <0.05$) DP_{60} and DE_{60} values of solid binary systems signified that the complexation effectively enhances the solubility of efavirenz, which consequently increase its dissolution and bioavailability.

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