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Enhancement of Solubility, Dissolution rate and Bioavailability of Efavirenz by Cyclodextrins and Solutol HS15 - A Factorial Study

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Abstract

Efavirenz widely prescribed anti-retroviral drug belongs to class II BCS 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 objective of the present investigation is to enhance the solubility, dissolution rate and bioavailability of efavirenz by the use of cyclodextrins (βCD and HPβCD) and surfactant, Solutol HS15. The individual main effects and combined (interaction) effects of cyclodextrins (βCD and HPβCD) and surfactant Solutol HS15 on the solubility and dissolution rate of efavirenz were evaluated in a series of 2^2 factorial experiments. The solubility of efavirenz in the fluids containing βCD, HPβCD and Solutol HS15 as per 2^2 factorial design was determined. Efavirenz-CD-surfactant complex systems were prepared employing selected combinations of CDs and surfactant in each case as per a 2^2 factorial design by kneading method and were evaluated. Pharmacokinetic evaluation was done on efavirenz– βCD (1:2) and efavirenz- βCD-Solutol HS15 (1:2:0.05) complexes in comparison to pure drug with a view to evaluate their *in vivo* performance in healthy rabbits.

The results of the present investigation clearly indicated that the individual main effects as well as combined effects of CDs (βCD and HPβCD) and surfactant Solutol HS15 in enhancing the solubility and dissolution rate (K_1) of efavirenz are highly significant ($P < 0.01$). Combination of Solutol HS15 with CDs (βCD and HPβCD) resulted in a much higher enhancement in the solubility and dissolution rate (K_1) of efavirenz than is possible with CDs and Solutol HS15 alone. βCD-Solutol HS15 combination gave 54.43 fold increase in the solubility and 5.95 fold increase in the dissolution rate (K_1) of efavirenz. In the *in vivo* pharmacokinetic evaluation, βCD has markedly enhanced both the rate (K_a) and extent (AUC) of absorption (i.e. bioavailability) of efavirenz. Addition of Solutol HS15 has further enhanced both the rate of absorption and extent of absorption of efavirenz from efavirenz – βCD- Solutol HS15 (1:2:0.05) complex. Efavirenz-βCD-Solutol HS15 inclusion complex exhibited a 4.92 fold increase in the absorption rate (K_a) and 1.85 fold increase in the $(AUC)_0^\infty$when compared to efavirenz pure drug. Hence a combination of cyclodextrins (βCD and HPβCD) and Solutol HS15 is recommended for enhancing the solubility, dissolution rate and bioavailability of efavirenz, a BCS Class II drug.

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INTRODUCTION

The most important property of a drug delivery system is its ability to deliver the active pharmaceutical ingredient (API) to the site of action in the body in an amount sufficient to produce the desired therapeutic response. This property of the drug delivery system is referred to as bioavailability. Bioavailability is more precisely defined as the rate and extent of absorption (availability) of drug to the systemic circulation. About 95 % of all new potential therapeutics (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pHs and consequent low dissolution rate. These drugs are classified as class II drugs under Bio-Pharmaceutical System (BCS) and pose challenging problems in their pharmaceutical product development process.

Several modern organic drugs belong to class II category under BCS and exhibit low and variable dissolution rates. These drugs need enhancement in dissolution rate and bioavailability to derive their maximum therapeutic efficacy. Several conventional methods such as micronization, chemical modification, use of surfactants and solubilizers, solid dispersion and a few new emerging technologies such as cyclodextrin complexation, mucoadhesive microspheres, nanoparticles, nanosuspensions, micro emulsion and self-emulsifying systems are available to enhance the bioavailability of BCS Class II drugs.

Efavirenz a widely prescribed anti-retroviral drug belongs to class II BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It is practically in-sooluble in water and aqueous fluids. As such its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. Among the various approaches complexation with cyclodextrins has gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably affected.[1,2] Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies[3,4]. Surfactants also increase the solubility of lipophilic water-insoluble drugs by micellar solubilization. Though cyclodextrin complexation and use of surfactants for enhancing the solubility and dissolution rate of poorly soluble drugs have been investigated individually, no reports are available on their combined use in enhancing the solubility and dissolution rate.

The objective of the present investigation is to enhance the solubility, dissolution rate and bioavailability of efavirenz by the use of cyclodextrins (βCD and HPβCD) and surfactant, Solutol HS15. The individual main effects and combined (interaction) effects of cyclodextrins (βCD and HPβCD) and surfactant Solutol HS15 on the solubility and dissolution rate of efavirenz were evaluated in a series of 2^2 factorial experiments.

Experimental

MATERIALS

Efavirenz was a gift sample from M/s Amoli Organics Pvt., Ltd., Mumbai, β-cyclodextrin and hydroxy propyl β-cyclodextrin were gift samples from Signet Chemical Corporation Pvt., Ltd., Mumbai..Solutol HS15 was a gift sample from Dr. Reddy's Laboratories Ltd, Hyderabad.Polyvinyl pyrrolidone (PVP K-30) and Crosscarmellose sodium were gift samples from M/s Natco Pharma Ltd., Hyderabad. Talc, I.P. Magnesium stearate, I.P. and Lactose, I.P. were procured from commercial sources. All other materials used were of pharmacopoeial grade.

METHODS

Determination of solubility:

The solubility of(efavirenz in the following four selected fluids as per 2^2 factorial study was determined to evaluate the individual and combined effects of the cyclodextrins and the surfactant on the solubility of efavirenz. The two levels of CD (factor a) are 0 and 5 mM. The two levels of surfactant (factor b) are 0 and 2%.

The selected fluids as per 2^2 factorial studies are as follows:

For Efavirenz- βCD-Solutol HS15 system

Statistical code as per 2^2 – Factorial Design	Description
(1)	Purified water
(a)	Water containing βCD (5 mM)
(b)	Water containing Solutol HS15 (2 %)
(ab)	Water containing βCD (5 mM) and Solutol HS15 (2 %)

For Efavirenz- HPβCD-Solutol HS15 system

Statistical code as per 2^2 – Factorial Design	Description
(1)	Purified water
(a)	Water containing HPβCD (5 mM)
(b)	Water containing Solutol HS15 (2 %)
(ab)	Water containing HPβCD (5 mM) and Solutol HS15 (2 %)

Procedure:

Excess drug was added to 15 ml of the selected fluid taken in a 25ml stoppered conical flask and the mixtures were shaken for 72 h at room temperature (28ºC) on a rotary flask shaker to achieve equilibrium. After 72 hrs of shaking, 2 ml of aliquots were withdrawn and filtered immediately using 0.45µ disc filter. The filtered samples were diluted suitably and assayed at 246 nm in the case of efavirenz. In each case the solubility determinations were replicate 4 times (n=4).

Preparation of Drug -CD- Surfactant systems:

To evaluate the individual and combined effects of cyclodextrins and surfactant on the dissolution rate of efavirenz drug -CD-surfactant systems were prepared employing the following selected combinations of CD and surfactant in each case as per a 2^2 factorial design. The two levels of CD (factor a) is 0 and 1:2 ratio of drug: CD respectively. The two levels of surfactant (factor b) are 0 and 2%. The following are the selected treatments as per 2^2 factorial designs in each case to evaluate the individual and combined effects.

The selected treatments (products) as per 2^2 – factorial study in each case are as follows.

For Efavirenz- βCD-Solutol HS15 system

Statistical code as per 2^2 – Factorial Design	Description
(1)	Efavirenz pure drug
(a)	Efavirenz-βCD (1:2) binary system
(b)	Efavirenz-Solutol HS15 (2 %) binary system
(ab)	Efavirenz-βCD-Solutol HS15 (1:2:0.02) ternary system

For Efavirenz- HPβCD-Solutol HS15 system

Statistical code as per 2^2 – Factorial Design	Description
(1)	Efavirenz pure drug
(a)	Efavirenz-HPβCD (1:2) binary system
(b)	Efavirenz-Solutol HS15 (2 %) binary system
(ab)	Efavirenz-HPβCD-Solutol HS15 (1:2:0.02) ternary system

The above mentioned binary and ternary systems were prepared by kneading method employing βCD, HPβCD and Solutol HS15.

Preparation method:

Required quantities of drug, βCD and surfactant were taken in a clean and dry mortar. Kneading fluid consisting of water: alcohol (1:1) was added and mixed to get thick slurry. The slurry was thoroughly mixed and kneaded for 45 min .Additional quantities of kneading fluid was added to maintain the mixture as thick slurry during the kneading process. After kneading for 45 min the mixture was transferred to a petridish and dried in an oven at 60ºC. The dried powder was passed through mesh No.100.

Estimation of drug content in drug-CD-surfactant complexes prepared:

Drug-CD-surfactant complex powder equivalent to 50 mg of the medicament was taken into a boiling test tube and extracted with 4 x 10 ml quantities of methanol. The methanolic extracts were collected into 50 ml volumetric flask and the volume was made up to 50 ml with methanol. The solution was subsequently diluted with water containing 2%SLS in the case of efavirenz and assayed for the drug content by the UV spectrophotometric method.

Dissolution Rate study on Drug-CD-Surfactant Systems:

The dissolution rate of medicament from the drug-CD-surfactant systems prepared was studied in water containing 2% SLS (900 ml) using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature of 37°C ± 1°C was maintained throughout the study. Complex system equivalent to 50 mg of drug was used in each test. Samples of dissolution media (5 ml) were withdrawn through a filter (0.45µ) at different intervals of time, suitably diluted and assayed for efavirenz at 246 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid. The dissolution experiments were replicated four times each (n=4).

Pharmacokinetic Evaluation

Pharmacokinetic evaluation was done on efavirenz–βCD (1:2) and efavirenz- βCD-Solutol HS15 (1:2:0.05) complexes in comparison to pure drug with a view to evaluate their *in vivo* performance. Pharmacokinetic evaluation was done in healthy rabbits weighing 1.5 – 2.5 kg (n=6) of either sex in a cross over study at a dose equivalent to 10 mg/kg

In vivo study protocols were approved by the Institutional Animal Ethics Committee (Regd. .No 16/01/a/CPCSEA/125). A wash out period of one month was given between testing of two products.

After collecting the zero hour blood sample (blank), the product in the study was administered orally in a capsule shell with 10 ml of water. No food or liquid other than water was permitted until 4 hours following the administration of the product. Blood samples (3 ml) were collected from marginal ear vein at 0.5, 1, 2, 3, 4, 6, 8 and 12 hours after administration. The blood samples were collected in heparinized tubes and were centrifuged at 10000 rpm for 10 min and the plasma separated was collected into dry tubes. All the samples were stored under refrigerated conditions prior to assay on the same day. Plasma concentrations of efavirenz were determined by a known HPLC method.[5]

From the time versus plasma concentration data, various pharmacokinetic parameters such as peak concentration (C_{max}), time at which peak occurred (T_{max}), Area under the curve (AUC), elimination rate constant (K_{el}), biological half - life ($t_{1/2}$), percent absorbed to various times and absorption rate constant (K_a), were calculated in each case as per known standard methods.

From the time versus plasma concentration data, various pharmacokinetic parameters such as peak concentration (C_{max}), time at which peak occurred (T_{max}), Area under the curve (AUC), elimination rate constant (K_{el}), biological half - life ($t_{1/2}$), percent absorbed to various times and absorption rate constant (K_a), were calculated in each case as per known standard methods [6,7].

RESULTS AND DISCUSSION

Efavirenz, a widely prescribed anti-retroviral drug is poorly soluble in water and aqueous fluids and exhibit low and variable oral bioavailability. It require enhancement in solubility and dissolution rate for increasing its oral bioavailability. In the present study two cyclodextrins (βCD and HPβCD) and a surfactant (Solutol HS15) were tried to enhance the solubility, dissolution rate and bioavailability of efavirenz. The individual main effects and combined (interaction) effects of cyclodextrins and the surfactant on the solubility and dissolution rate of

efavirenz were evaluated in a series of 2^2 factorial experiments.

The results of solubility studies with βCD and Solutol HS15 are given in Table 1

Table -1: Solubility of Efavirenz in Various Fluids (N=4) as Per 2^2 Factorial Study (Efavirenz-βCD-Solutol HS15)

Fluid	Solubility(mg/100 ml) $\bar{x}$ ± sd	Increase in solubility (no. of folds)
Purified water	1.20 ± 0.09	--
Water containing βCD(5mM)	5.23 ± 0.347	4.35
Water containing Solutol HS15 (2%)	36.45 ± 1.316	30.37
Water containing βCD (5mM) and Solutol HS15 (2%)	65. 32 ± 2.47	54.43

The solubility of efavirenz was markedly enhanced by βCD and Solutol HS15. A 4.35 and 30.37 fold increase in the solubility of efavirenz was observed respectively with βCD (5mM) and Solutol HS15 (2%) when used alone. A combination of βCD (5mM) and Solutol HS15 (2%) gave a 54.43 fold increase in the solubility of efavirenz. The solubility data were subjected to Analysis of Variance (ANOVA) to find out the significance of individual main and combined (interaction) effects of βCD and Solutol HS15 on the solubility of efavirenz. ANOVA indicated hat the individual main effects of βCD and Solutol HS15 as well as the combined effects are highly significant ($P<0.01$). A combination of βCD and Solutol HS15 has resulted in a much higher enhancement on the solubility of efavirenz than is possible with them individually. This may be due to better inclusion of drug molecules in the presence of Solutol HS15.

The results of solubility studies with HPβCD and Solutol HS15 are given in Table 2

Table -2: Solubility of Efavirenz in Various Fluids (N=4) as Per 2^2 Factorial Study (Efavirenz-HPβCD-Solutol HS15)

Fluid	Solubility(mg/100 ml) $\bar{x}$ ± sd	Increase in solubility (no. of folds)
Purified water	2.46 ± 0.21	--
Water containing HPβCD(5mM)	4.68 ± 0.34	1.90
Water containing Solutol HS15 (2%)	32.73 ± 0.89	13.30
Water containing HPβCD (5mM) and Solutol HS15 (2%)	46.20 ± 1.40	18.78

The solubility of efavirenz was markedly enhanced by HPβCD and Solutol HS15. A 1.28 and 30.37 fold increase in the solubility of efavirenz was observed respectively with HPβCD (5mM) and Solutol HS15 (2%). A combination of HPβCD (5mM) and Solutol HS15 (2%) gave a 14.76 fold increase in the solubility of Efavirenz. ANOVA indicated that the individual main effects of HPβCD and Solutol HS15 as well as the combined effects are highly significant ($P<0.01$). Solutol HS15 exhibited greater enhancement in the aqueous solubility (30.37 fold) of efavirenz. The order of increasing enhancement observed with various CDs and Surfactant was Solutol HS15 > βCD >HPβCD. Among all the combinations, βCD-Solutol HS15 exhibited greater enhancement in the aqueous solubility (54.43 fold) of efavirenz. The order of increasing enhancement observed with various combinations was βCD- Solutol HS15 > HPβCD-Solutol HS15.Thus combination of Solutol HS15 with CDs (βCD and HPβCD) resulted in a much higher enhancement in the solubility of efavirenz than is possible with CDs alone.

To evaluate the individual main and combined effects of cyclodextrins (βCD and HPβCD) and surfactant, Solutol HS15on the dissolution rate of efavirenz, solid inclusion complexes of Drug-CD-Surfactant were prepared in each case as per 2^2 factorial design. All the solid inclusion complexes prepared were found to be fine and free flowing powders. Low C.V values (< 1.5%) in the percent drug

content indicated uniformity of drug content in each batch of solid inclusion complexes prepared.

The dissolution rate of efavirenz from various Drug-CD-Surfactant complexes prepared was studied in water containing 2% SLS.

Drug-CD and Drug-CD-Surfactant complexes gave rapid and higher dissolution of efavirenz when compared to efavirenz pure drug. The dissolution was much higher in the initial 5-10 min. The dissolution data were analyzed as per zero order and first order kinetics. Dissolution of efavirenz from all CD-Surfactant complexes prepared followed first order kinetics with correlation coefficient (r^2)values in the range 0.9223-0.9730. The dissolution rate constants were calculated in each case separately for 0-5 min. and 5-30 min. and the average of the two was calculated and reported as dissolution rate (K_1). The first order dissolution rates (K_1) and Dissolution efficiency (DE_{15}) values, calculated as per Khan[8] are given in Table 3-4. The dissolution rates (K_1) and Dissolution efficiency (DE_{15}) values were several times higher in the case of CD-Surfactant complexes when compared to efavirenz pure drug.

Table 3: Increase in DE_{15} and K_1 values of Efavirenz by βCD and βCD –Solutol HS15

CD complex	DE_{15} (%)		$K_1 \times 10^2$ (min^{-1})	
	$\bar{x}$	Increase (no. of folds)	$\bar{x}$	Increase (no. of folds)
Efavirenz	1.83	-	0.20	
βCD	11.80	6.44	1.10	5.50
Solutol HS15	6.74	3.68	0.69	3.45
βCD-Solutol HS15	11.95	6.53	1.19	5.95

Table 4: Increase in $DE_{30}$and K_1values of Efavirenz by HPβCD and HPβCD –Solutol HS15

CD complex	DE_{30}(%)		$K_1 \times 10^2$ (min^{-1})	
	$\bar{x}$	Increase (no. of folds)	$\bar{x}$	Increase (no. of folds)
Efavirenz	21.89	-	1.06	
HPβCD	78.39	3.58	17.21	16.23
Solutol HS15	86.36	3.94	18.13	17.10
HPβCD-Solutol HS15	86.68	3.96	24.6	11.47

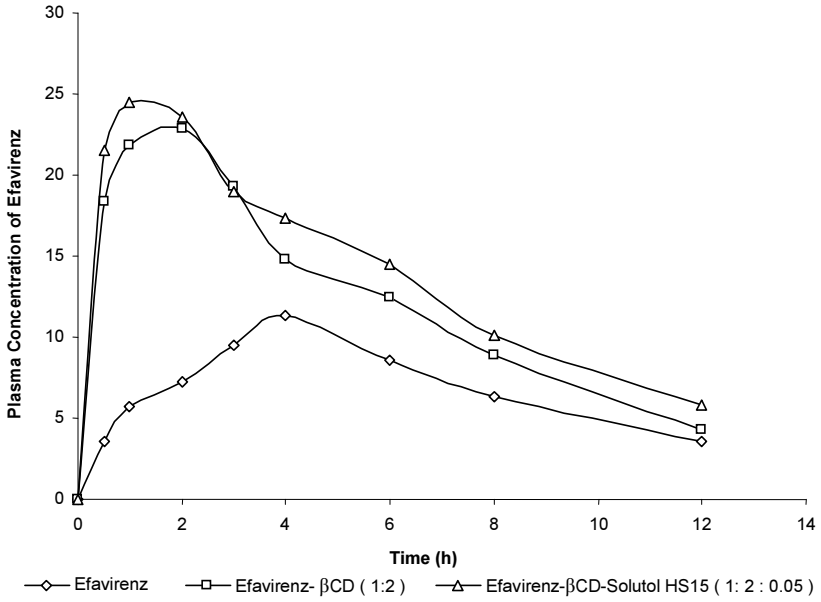

Fig. 1 Plasma Concentrations of Efavirenz Following the Oral Administration of Efavirenz and its CD Complexes in Rabbits.

Among the individual effects, CDs (βCD and HPβCD) gave higher enhancement in the K_1 and DE_{15} of efavirenz than the surfactant Solutol HS15. The order of increasing enhancement in K_1 and DE_{15} observed with various CDs and surfactant was βCD > HPβCD >Solutol HS15. βCD gave highest increase in DE_{15} (6.44 fold) and K_1 (5.50 fold) of efavirenz. The results of ANOVA indicated that all individual and combined effects were highly significant ($P < 0.01$). Among other combined effects, βCD-Solutol HS15 gave highest enhancement in K_1 (5.95). βCD alone gave an increase of 5.50 fold in the dissolution rate of efavirenz. Combination of βCD with Solutol HS15 has further enhanced the dissolution rate(K_1) of efavirenz by 5.95 folds.

Plasma concentrations of efavirenz following the oral administration of efavirenz and its CD complexes are shown in Fig.1. Pharmacokinetic parameters estimated are summarized in Table 5.

The biological half- life ($t_{1/2}$) estimated from the elimination phase of the plasma level curves was found to be 4.77, 3.91 and 4.58 h respectively following the oral administration of efavirenz, and its CD complexes, efavirenz - βCD (1:2) and efavirenz – βCD- Solutol HS15 (1:2:0.05).The close agreement of the $t_{1/2}$ values in the three cases indicated that the elimination characteristics of efavirenz have not changed when it was administered as CD complexes.

Table-5: Summary of Pharmacokinetic Parameters Estimated Following the oral Administration of Efavirenz Products

Parameter	Efavirenz	Efavirenz-βCD (1:2) Complex	Efavirenz-βCD-Solutol HS15 (1:2:0.5) Complex
C_{max} (µg/ml)	11.35±0.7	22.82±0.8	24.52±1.4
T_{max} (h)	4.0	2.0	1.0
K_{el} (h^{-1})	0.1450	0.1768	0.1513
$t_{½}$ (h)	4.77	3.91	4.58
$(AUC)_0^{12h}$	86.82	149.92	168.61
$(AUC)_0^{\alpha}$	111.50	174.35	207.27
BA (%)	100	156.36	185.89
K_a (h^{-1})	0.4859	1.7583	4.920
Percent Absorbed			
0.5 h	23.43	64.84	75.05
1.0 h	38.68	82.76	90.85
2.0 h	54.06	99.39	100.0

Efavirenz was found to be absorbed slowly when given orally and a peak plasma concentration (C_{max}) of 11.35±0.7µg/ml was observed at 4.0 h after administration. The absorption rate constant (K_a) was found to be 0.4859 h^{-1}.All the pharmacokinetic parameters namely C_{max}, T_{max}, K_a and $(AUC)_0^{\infty}$indicated rapid and higher absorption and bioavailability of efavirenz when administered as CD complexes. Higher C_{max} values and lower T_{max} values were observed with the CD complexes when compared to those of efavirenz as such. The absorption rate constant (K_a) was found to be 1.7583 h^{-1} 2.3918 h^{-1} respectively with efavirenz - βCD (1:2) and efavirenz – βCD- Solutol HS15 (1:2:0.05) complexes, whereas in the case of efavirenz K_a was only 0.4859 h^{-1}. A 3.62, and 4.92 fold increase in the K_a was observed respectively with efavirenz - βCD (1:2) and efavirenz – βCD- Solutol HS15 (1:2:0.05) complexes when compared to efavirenz pure drug. $(AUC)_0^{\infty}$ (extent of absorption) was also much higher in the case of CD complexes when compared to efavirenz pure drug. $(AUC)_0^{\infty}$was increased from 111.50µg.h /ml for efavirenz pure drug to 174.35 and 207.27 µg.h/ml for efavirenz - βCD (1:2) and

efavirenz – βCD- Solutol HS15 (1:2:0.05) complexes respectively. A 1.56 and 1.85 fold increase in $(AUC)_0^\infty$ was observed respectively with Efavirenz - βCD (1:2) and efavirenz – βCD- Solutol HS15 (1:2:0.05) complexes when compared to efavirenz pure drug.

Thus βCD has markedly enhanced both the rate (K_a) and extent (AUC) of absorption (i.e. bioavailability) of efavirenz. Addition of Solutol HS15 has further enhanced both the rate of absorption and extent of absorption of efavirenz from efavirenz – βCD- Solutol HS15 (1:2:0.05) complex.

CONCLUSION

The results of the present investigation clearly indicated that the individual main effects as well as combined effects of CDs (βCD and HPβCD) and surfactant Solutol HS15 in enhancing the solubility and dissolution rate (K_1) of efavirenz are highly significant ($P < 0.01$). Combination of Solutol HS15 with CDs (βCD and HPβCD) resulted in a much higher enhancement in the solubility and dissolution rate (K_1) of efavirenz than is possible with CDs and Solutol HS15 alone. βCD-Solutol HS15 combination gave 54.43 fold increase in the solubility and 5.95 fold increase in the dissolution rate(K_1) of efavirenz.

In the *in vivo* pharmacokinetic evaluation, βCD has markedly enhanced both the rate (K_a) and extent (AUC) of absorption (i.e. bioavailability) of efavirenz. Addition of Solutol HS15 has further enhanced both the rate of absorption and extent of absorption of efavirenz from efavirenz – βCD-Solutol HS15 (1:2:0.05) complex. Efavirenz -βCD-Solutol HS15 inclusion complex exhibited a 4.92 fold increase in the absorption rate (K_a) and 1.85 fold increase in the $(AUC)_0^\infty$when compared to efavirenz pure drug.

Hence a combination of cyclodextrins (βCD and HPβCD) and Solutol HS15 is recommended for enhancing the solubility, dissolution rate and bioavailability of efavirenz, a BCS Class II drug.

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