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Research Article

FORMULATION DEVELOPMENT OF EFAVIRENZ TABLETS EMPLOYING B CYCLODEXTRIN, SOLUPLUS AND PVP K30: FACTORIAL STUDY

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Abstract: Efavirenz, a widely prescribed HIV- 1 specific non – nucleoside reverse transcriptase inhibitor drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It is practically insoluble in water and aqueous fluids and as such it posses challenging problems in its formulation development. The objective of the present study is to formulate efavirenz tablets employing β cyclodextrin (β CD), Soluplus and PVP K30 alone and in combinations and to evaluate their effects on the dissolution rate of efavirenz tablets in a 2^3 factorial study. Efavirenz tablets were formulated employing β CD, Soluplus and PVP K 30 as per 2^3 factorial design and the tablets were prepared by direct compression method. The tablets prepared were evaluated for various physical properties, dissolution rate and dissolution efficiency. Dissolution data were analyzed by Analysis of Variance (ANOVA) of 2^3 factorial studies. Efavirenz – βCD – Soluplus- PVP K 30 solid inclusion complexes could be formulated into compressed tablets by direct compression method and the resulting tablets fulfilled the official (IP 2010) specifications with regard to hardness, friability, drug content, disintegration time and dissolution rate .Efavirenz dissolution was rapid and higher from the tablets formulated employing drug- βCD- Soluplus- PVP K 30 inclusion complexes when compared to the tablets containing efavirenz alone and market product tested. The individual as well as combined effects of the three factors involved i.e., βCD (factor A) ,Soluplus (factor B) and PVP K 30 (factor C) except abc combination were highly significant ($P< 0.01$) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of efavirenz. Combinations of β CD – Soluplus, β CD – PVP K 30 and Soluplus – PVP K 30 gave higher enhancement in the dissolution rate of efavirenz tablets than is possible with them alone. The tablets formulated employing drug- βCD- Soluplus- PVP K 30 inclusion complexes and market product tested fulfilled the official (I.P 2010) dissolution rate test specification of NLT 70 % in 30 min prescribed for efavirenz tablets. Hence combination of βCD with either Soluplus or PVP K 30 and combination of Soluplus with PVP K 30 is recommended to enhance the dissolution rate and dissolution efficiency of efavirenz in its formulation development.
Key**words:** Efavirenz tablets, Formulation development, β cyclodextrin, Soluplus, PVP K30, Dissolution rate, Factorial study

INTRODUCTION

Efavirenz, a widely prescribed HIV- 1 specific non – nucleoside reverse transcriptase inhibitor drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It is practically insoluble in water and aqueous fluids and as such it posses challenging problems in its formulation development. IP 2010 prescribed a dissolution rate test specification of NLT 70 % in 30 min for efavirenz tablets to check the quality commercial brands. In the present study efavirenz tablets were formulated employing β cyclodextrin (β CD), Soluplus and PVP K30 alone and in combinations and their effects on the dissolution rate of efavirenz tablets were evaluated in a 2^3 factorial study.

Several techniques[1] such as micronization, cyclodextrin complexation, use of surfactants and solubilizers, solid dispersion in water soluble and dispersible carriers, use of salts, prodrugs and polymorphs which exhibit high solubility, micro emulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs. 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[2,3]. Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies[4, 5]. Soluplus is a polymeric solubiliser with an amphiphilic chemical nature, which was particularly developed for solid solutions [6]. Soluplus is polyvinyl caprolactam – polyvinyl acetate – polyethylene glycol graft co- polymer. Soluplus increased the solubility and enhanced the bioavailability of actives in solid solutions. Itraconazole and fenofibrate showed significant increase in the bioavailability with Soluplus[6]. The solubility and dissolution rate of valsartan was effectively enhanced by using Soluplus in the form of solid dispersions[7]. Poly vinyl pyrrolidone (PVP K 30) is also reported[8, 9] to enhance the solubility and dissolution rate of poorly soluble drugs. In the present study βCD, Soluplus and PVP K 30 alone and in combinations were tried to enhance the dissolution rate of efavirenz tablets. The individual main effects and combined (or interaction) effects

of βCD, Soluplus and PVP K30 on the dissolution rate of efavirenz tablets were evaluated in a 2^3 factorial study.

EXPERIMENTAL

Materials

Efavirenz was a gift sample from M/s. Eisai Pharmatechnology and Manufacturing Pvt. Ltd., Visakhapatnam. β Cyclodextrin was gift sample from M/s. Cerestar Inc., USA. Soluplus was a gift sample from BASF, the chemical company, Hyderabad. Methanol (Qualigens) and poly vinyl pyrrolidone (PVP K30) were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Methods

Estimation of Efavirenz

A UV Spectrophotometric method based on the measurement of absorbance at 245 nm in water containing 2 % Sodium lauryl sulphate (SLS) was used for the estimation of efavirenz. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 0-10 µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.85% and 1.20 % respectively. No interference by the excipients used in the study was observed.

Preparation of Efavirenz - βCD - Soluplus - PVP K30 Complexes

Solid inclusion complexes of efavirenz – βCD - Soluplus - PVP K30 were prepared as per 2^3 – factorial study by kneading method. Efavirenz, βCD, Soluplus and PVP K30 were triturated in a mortar with a small volume of solvent consisting of a blend of dichloromethane: methanol (1:1). The thick slurry formed was kneaded for 45 min and then dried at 55°C until dry. The dried mass was powdered and sieved to mesh No. 120.

Preparation of Efavirenz- βCD – Soluplus- PVP K 30 Tablets

Compressed tablets each containing 50 mg of efavirenz were prepared as per 2^3 – factorial study by direct compression method employing efavirenz- βCD - Soluplus - PVP K 30 inclusion complexes as per the formulae given in Table 1. All ingredients as per the formula were blended in a closed polyethylene bag and were compressed into tablets on a 16- station tablet punching machine (M/s Cadmach machineries Pvt. Ltd., Ahmedabad) to a hardness of 5- 6 kg/cm^2 using 9 mm flat punches. In each case 100 tablets were compressed.

Evaluation of tablets:

Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time of the tablets prepared was determined using a Thermonic tablet disintegration test machine using water as test fluid.

Dissolution rate study:

The dissolution rate of efavirenz from the tablets formulated employing βCD ,Soluplus and PVP K was studied in 900 ml water containing 2 % Sodium lauryl sulphate (SLS) using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature 37±1°C was maintained throughout the study. One tablet containing 50 mg of efavirenz was used in each test. Samples of dissolution media (5 ml) were withdrawn through a filter (0.45 µ) at different intervals of time, suitable diluted and assayed for efavirenz at 245 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid. The dissolution experiments were replicated three times each (n=3).

Analysis of results:

Dissolution data were subjected to analysis as per zero order and first order kinetics and the corresponding dissolution rates were calculated. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[10]. Dissolution data were also analyzed by Analysis of Variance (ANOVA) as per 2^3 factorial studies.

RESULTS AND DISCUSSION

Efavirenz, a widely prescribed anti retroviral drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Its oral absorption is dissolution rate limited and it requires enhancement in the solubility and dissolution rate for increasing its oral bioavailability. We have earlier reported[11] that the solubility and dissolution rate of efavirenz could be markedly enhanced by complexation with β cyclodextrin in the presence of Soluplus and PVP K 30. Combination of βCD with Soluplus and PVP K30 gave significantly higher dissolution rates (K_1) and dissolution efficiency (DE_{20}) when compared to βCD alone. In the present study efavirenz tablets were formulated employing β cyclodextrin (βCD), Soluplus and PVP K30 alone and in combinations and their effects on the dissolution rate of efavirenz tablets were evaluated in a 2^3 factorial study.

The feasibility of formulating efavirenz- βCD - Soluplus – PVP K30 solid inclusion complexes into tablets was evaluated by preparing efavirenz tablets employing the solid inclusion complexes by direct compression method. To evaluate the individual and combined effects of βCD, Soluplus and PVP K 30 on the dissolution rate and dissolution efficiency of efavirenz tablets, tablets each containing 50 mg of efavirenz were formulated employing solid inclusion complexes of drug- βCD - Soluplus – PVP K 30 as per 2^3 factorial design. For this purpose two levels of βCD (0 and 1: 2 ratio of Drug : βCD) and two levels of each of Soluplus and PVP K 30 (0 and 1%) were selected and the corresponding eight treatments involved in the formulation of tablets as per 2^3-factorial study were efavirenz pure drug (1); EF- βCD (1:2) inclusion binary complex (a); EF - Soluplus (1%) binary mixture (b) and EF - βCD (1:2) – Soluplus (1%) ternary complex (ab); efavirenz – PVP K30 (1%) binary complex (c); efavirenz- βCD (1:2) - PVP K30 (1%) ternary complex (ac); efavirenz - Soluplus (1%) - PVP K30 (1%) ternary complex (bc) and efavirenz-βCD (1:2) - Soluplus (1%) - PVP K30 (1%) complex (abc).

All the prepared tablets were evaluated for drug content, hardness, friability and disintegration time and dissolution rate of efavirenz. The physical properties of the

tablets prepared are given in Table 2. The dissolution profiles of various tablets formulated are shown in Fig. 1.The dissolution parameters of the tablets prepared are summarized in Table 3.All the tablets prepared were found to contain efavirenz within 100 ± 2% of the labeled claim. Hardness of the tablets was in the range 5.0- 6.5 Kg/cm^2. Percentage weight loss in the friability test was less than 0.5 % in all the cases. All the tablets formulated employing efavirenz - βCD - Soluplus - PVP K30 inclusion complexes disintegrated rapidly within 2 min.

The dissolution rate of efavirenz from the tablets prepared was studied in 900 ml of water containing 2 % SLS as prescribed in I.P 2010. Dissolution of efavirenz from all the tablets prepared followed first order kinetics with the correlation coefficient (r) values above 0.915. Efavirenz dissolution was rapid and higher from the tablets formulated employing drug- βCD- Soluplus - PVP K 30 inclusion complexes when compared to the tablets containing efavirenz alone. Dissolution parameters, K_1 and DE_{30} were subjected to ANOVA to find out the significance of the individual and combined effects of the three factors (βCD, Soluplus and PVP K 30) in enhancing the dissolution rate and efficiency of efavirenz tablets. The individual as well as combined effects of the three factors involved i.e., βCD (factor A) ,Soluplus (factor B) and PVP K 30 (factor C) except abc combination were highly significant ($P< 0.01$) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of efavirenz.

Tablets containing efavirenz - β CD – Soluplus – PVP K 30 inclusion complexes gave rapid and higher dissolution of efavirenz when compared to control formulation F_1 prepared using efavirenz alone. β CD alone gave a 4.9 fold increase in the dissolution rate of efavirenz tablets. Where as in combination with Soluplus and PVP K 30 it gave respectively 5.63 and 5.38 fold increase in the dissolution rate of efavirenz tablets. Soluplus and PVP K 30 alone and in combination also gave higher enhancement in the dissolution rate of efavirenz tablets. Among all efavirenz tablets formulated employing Soluplus and PVP K 30 combination gave highest enhancement (7.51 fold) in the dissolution rate of efavirenz tablets. Combinations of β CD – Soluplus, β CD – PVP K 30 and Soluplus – PVP K 30 gave higher enhancement in the dissolution rate of efavirenz tablets than is possible with them alone. All the tablets formulated employing efavirenz- β CD – Soluplus – PVP K 30 gave higher dissolution than the market product tested.

I.P 2010 prescribed a dissolution rate specification of NLT 70% in 30 min for efavirenz tablets. All the efavirenz tablets formulated employing with drug- βCD – Soluplus – PVP K 30 inclusion complexes and market product fulfilled the official (I.P) dissolution rate specification of efavirenz tablets. Whereas plain tablets formulated employing efavirenz alone (F_1) did not fulfill the official dissolution rate specification. Hence combination of βCD with either Soluplus or PVP K 30 and combination of Soluplus with PVP K 30 is recommended to enhance the dissolution rate and dissolution efficiency of efavirenz tablets.

Table 1: Formulae of Efavirenz Tablets Prepared Employing βCD, Soluplus and PVP K 30

Ingredient (mg / tablet)	Efavirenz Tablet Formulation							
	F_1	F_a	F_b	F_{ab}	F_c	F_{ac}	F_{bc}	F_{abc}
Efavirenz (1)*	50	-	-	-	-	-	-	-
EF- βCD (1:2) (a)	-	150	-	-	-	-	-	-
EF – Soluplus (1%) (b)	-	-	52.3	-	-	-	-	-
EF - βCD (1:2) – Soluplus (1%) (ab)	-		-	152.3	-	-	-	-
EF – PVP K 30 (1%) (c)		-	-	-	52.3	-	-	-
EF - βCD (1:2) – PVP K 30 (1%) (ac)	-	-	-	-	-	152.3	-	-
EF – Soluplus (1%) – PVP K 30 (1%) (bc)	-	-	-	-	-	-	54.6	-
EF – βCD (1:2) - Soluplus (1%)) – PVP K 30 (1%) (abc)	-	-	-	-	-	-	-	154.6
PVP K30	2.3	-	-	-	-	-	-	-
Crosscarmellose sodium	9.2	9.2	9.2	9.2	9.2	9.2	9.2	9.2
Talc	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3
Magnesium Stearate	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3
Aerosil	1.15	1.15	1.15	1.15	1.15	1.15	1.15	1.15
Avicel PH 102	162.75	65.05	162.75	62.75	162.75	62.75	160.45	60.45
Total weight (mg)	230	230	230	230	230	230	230	230

EF: Efavirenz; βCD: β cyclodextrin; ***** Figures in parentheses are codes as per 2^3 Factorial Design

Table 2: Physical Properties of Efavirenz Tablets Prepared Employing βCD, Soluplus and PVP K 30

Formulation code as per 2^3 factorial design	Hardness (Kg/sq. cm)	Friability (% weight loss)	DT (min-sec)	Drug Content (mg/tablet)
F_1	5.0	0.55	1-20	50.2
F_a	5.5	0.40	1-50	49.6
F_b	5.0	0.45	1-30	49.8
F_{ab}	6.0	0.65	1-45	50.2
F_c	5.0	0.60	0-57	50.1
F_{ac}	5.5	0.55	1-10	49.8
F_{bc}	5.0	0.45	1-15	49.9
F_{abc}	5.5	0.65	1-32	50.2

Table 3: Dissolution Parameters of Efavirenz Tablets Prepared Employing βCD, Soluplus and PVP K 30

EF-β CD Complex	Composition	PD_{10} (%)	Dissolution Rate ($K_1 \times 10^2$) (min^{-1})	Increase in K_1 (no of folds)	Dissolution Efficiency (DE_{30}) (%)	Increase in DE_{30} (no of folds)
F_1	EF	49.46	1.82	-	48.55	-
F_a	EF- βCD (1:2)	84.36	8.92	4.90	80.46	1.65
F_b	EF-Soluplus (1%)	86.33	9.38	5.15	85.18	1.75
F_{ab}	EF- βCD (1:2) – Soluplus (1%)	89.88	10.26	5.63	85.10	1.75
F_c	EF – PVP K 30 (1%) (c)	90.90	10.09	5.54	85.67	1.76
F_{ac}	EF - βCD (1:2) – PVP K 30 (1%) (ac)	89.84	9.80	5.38	85.46	1.76
F_{bc}	EF – Soluplus (1%)) – PVP K 30 (1%) (bc)	87.94	13.67	7.51	84.92	1.74
F_{abc}	EF – βCD (1:2) - Soluplus (1%)) – PVP K 30 (1%) (abc)	85.56	9.22	5.06	81.39	1.67
commercial	-	57.73	4.14	2.55	63.71	1.31

Table 4: ANOVA of Dissolution Rate (K_1) Data of Efavirenz Tablets Prepared Employing βCD, Soluplus and PVP K 30

Source of Variation	D F	S.S	MSS (SS/DF)	F – Ratio	Significance
Total	23	238.27	10.35	-	-
Treatment	7	230.27	32.89	65.80	P<0.01
error	16	7.30	0.45	-	-
a	1	4.49	4.49	9.85	P<0.01
b	1	50.95	50.95	111.62	P<0.01
ab	1	42.26	42.26	92.59	P<0.01
c	1	55.54	55.54	121.67	P<0.01
ac	1	62.82	62.82	137.63	P<0.01
bc	1	12.05	12.05	26.41	P<0.01
abc	1	1.95	1.95	4.283	P>0.05

$F_{0.01}(7, 16) = 4.03$; $F_{0.05}(7, 16) = 2.66$; $F_{0.01}(1, 16) = 8.53$; $F_{0.05}(1, 16) = 4.49$

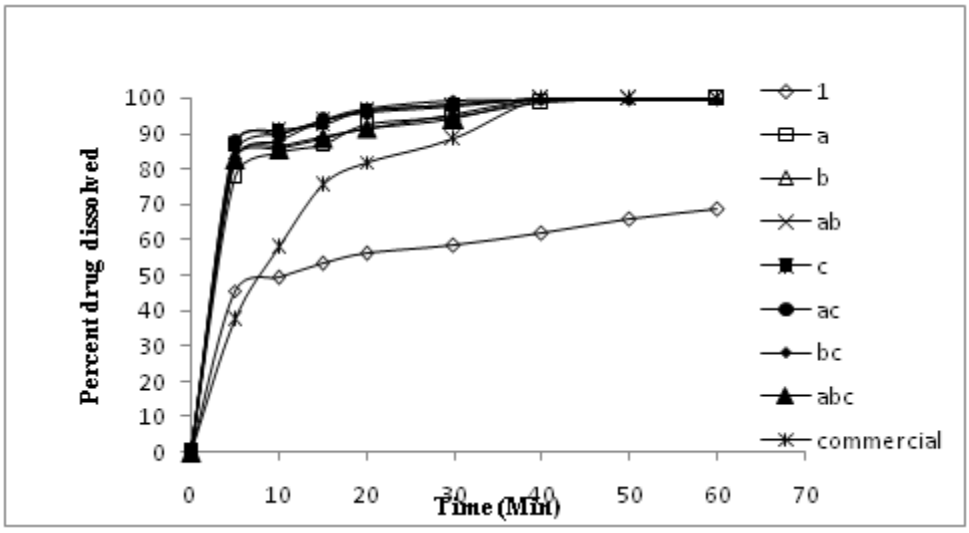

Fig.1: Dissolution Profiles of Efavirenz Tablets Prepared Employing βCD, Soluplus and PVP K 30.

CONCLUSIONS

Efavirenz – βCD – Soluplus- PVP K 30 solid inclusion complexes could be formulated into compressed tablets by direct compression method and the resulting tablets fulfilled the official (IP 2010) specifications with regard to hardness, friability, drug content, disintegration time and dissolution rate .

Efavirenz dissolution was rapid and higher from the tablets formulated employing drug- βCD- Soluplus- PVP K 30 inclusion complexes when compared to the tablets containing efavirenz alone and market product tested.

The individual as well as combined effects of the three factors involved i.e., βCD (factor A) ,Soluplus (factor B) and PVP K 30 (factor C) except abc combination were highly significant (P< 0.01) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of efavirenz.

Combinations of β CD – Soluplus, β CD – PVP K 30 and Soluplus – PVP K 30 gave higher enhancement in the dissolution rate of efavirenz tablets than is possible with them alone.

The tablets formulated employing drug- βCD- Soluplus- PVP K 30 inclusion complexes and market product tested fulfilled the official (I.P 2010) dissolution rate test specification of NLT 70 % in 30 min prescribed for efavirenz tablets.

Hence combination of βCD with either Soluplus or PVP K 30 and combination of Soluplus with PVP K 30 is recommended to enhance the dissolution rate and dissolution efficiency of efavirenz in its formulation development.

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