International Research Journal of Pharmaceutical and Applied Sciences (IRJPAS)
Available online at **www.irjpas.com**
Int. Res J Pharm. App Sci., 2013; 3(1): 269-273

Research Article

FORMULATION DEVELOPMENT OF EFAVIRENZ TABLETS EMPLOYING B CYCLODEXTRIN- POLOXAMER 407- PVP K30 - A FACTORIAL STUDY

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(Received: 10 December, 2012; Accepted: 20 December, 2012, 2013; Published: 29 December, 2012)
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Abstract: 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. The objective of the study is to evaluate the feasibility of formulating efavirenz –βCD– Poloxamer 407 /PVP K30 inclusion complexes into tablets and to evaluate the effects of βCD, Poloxamer 407 and PVP K30 on the dissolution rate and dissolution efficiency of efavirenz tablets in 2^3 factorial study. Drug – βCD- Poloxamer 407 / PVP K30 inclusion complexes were prepared by kneading method. Tablets each containing 100 mg of efavirenz were prepared by wet granulation method employing various βCD complexes as per 2^3 factorial design and the tablets were evaluated for dissolution rate and other physical properties. Efavirenz – βCD– Poloxamer 407 and efavirenz –βCD –PVP K30 inclusion complexes could be formulated into compressed tablets by wet granulation method. Efavirenz dissolution was rapid and higher from the tablets formulated employing drug- βCD- Poloxamer 407/ PVP K30 inclusion complexes when compared to the tablets containing efavirenz alone. The tablets formulated employing drug- βCD- Poloxamer 407/ PVP K30 inclusion complexes fulfilled the official (I.P 2010) dissolution rate test specification of NLT 70 % in 30 min prescribed for efavirenz tablets.The individual as well as combined effects of the three factors involved i.e., βCD (factor A), Poloxamer 407 (factor B) and PVP K30 (factor C) were highly significant ($P< 0.01$) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of efavirenz. Among the three factors Poloxamer 407 (factor B) gave highest enhancement in the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of efavirenz tablets. βCD alone gave low dissolution rates. Combination of βCD with Poloxamer 407 or PVP K30 gave a significantly higher dissolution rate (K_1) of efavirenz. Hence Poloxamer 407 alone or a combination of βCD with either Poloxamer 407 or PVP K30 is recommended to enhance the dissolution rate and efficiency of efavirenz tablets.
Key**words** Efavirenz Tablets, β Cyclodextrin, Poloxamer 407, PVP K30, Dissolution Rate

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. As such its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. 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[2-5] and use of. Poloxamer 407 (surfactant) [6-8] and PVP[9,10] have gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs..

We have reported[11] earlier that combination of β – cyclodextrin (βCD) with Poloxamer 407 and/or PVP K30 has markedly enhanced the solubility and dissolution rate of efavirenz, a BCS class II drug than is possible with them individually. The objective of the present study is to evaluate the feasibility of formulating efavirenz – βCD– Poloxamer 407 and efavirenz –βCD –PVP K30 inclusion complexes into tablets and to study the effects of βCD, Poloxamer 407 and PVP K30 on the dissolution rate of efavirenz tablets in a 2^3 factorial study.

EXPERIMENTAL

Materials

Efavirenz was a gift sample from M/s. Eisai Pharmatechnology and Manufacturing Pvt. Ltd., Visakhapatham. β Cyclodextrin was gift sample from M/s. Cerestar Inc., USA. Methanol (Qualigens), poly vinyl pyrrolidone (PVP K30) and Poloxamer 407 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- Poloxamer 407/ PVP K30 complexes

Solid inclusion complexes of efavirenz, βCD, Poloxamer 407 and PVP K30 were prepared as per 2^3 – factorial study by kneading method. Efavirenz, βCD, Poloxamer 407 and PVP K30 were triturated in a mortar with a small volume of solvent consisting of a blend of water: 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 - Poloxamer 407/ PVP K30 tablets

Compressed tablets each containing 100 mg of efavirenz were prepared as per 2^3 – factorial study by wet granulation method employing Efavirenz- βCD - Poloxamer 407/ PVP K30 inclusion complexes as per the formulae given in Table 1. Lactose was used as filler. Crospovidone (5%), talc (2%) and magnesium stearate (2%) were incorporated, respectively as disintegrant and lubricants. Purified water was used as granulating fluid in wet granulation method. The required quantities of drug, drug- βCD- Poloxamer 407 - PVP inclusion complexes and lactose were mixed thoroughly in a mortar by following geometric dilution technique. Water was added and mixed thoroughly to form dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60° C for 4 h. Dried granules were passed through mesh No. 16 to break aggregates. Crospovidone (5%) and lubricants talc (2%) and magnesium stearate (2%) were passed through mesh No. 100 on to dry granules and blended in a closed polyethylene bag. The tablet granules 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.

Table 1: Formulae of Efavirenz Tablets Prepared by Wet Granulation Method Employing Drug- βCD – Poloxamer 407- PVP K30 Inclusion

Ingredient (mg / tablet)	Efavirenz Tablet Formulation							
	T_1	T_a	T_b	T_{ab}	T_c	T_{ac}	T_{bc}	T_{abc}
Efavirenz (1)**	100	-	-	-	-	-	-	-
EF- βCD (1:2) (a)	-	300	-	-	-	-	-	-
EF - P 407(2%) (b)	-	-	102	-	-	-	-	-
EF - βCD (1:2) - P 407(2%) (ab)	-	-	-	306	-	-	-	-
EF - PVP K30 (2%) (c)	-	-	-	-	102	-	-	-
EF - βCD (1:2) - PVP K30 (2%) (ac)	-	-	-	-	-	306	-	-
EF - P 407(2%) - PVP K30 (2%) (bc)	-	-	-	-	-	-	104	-
EF - βCD (1:2) - P 407 (2%) - PVP K30 (2%) (abc)	-	-	-	-	-	-	-	312
Crospovidone	11	18	11	18	11	18	11	18
Talc	4.4	7.0	4.4	7.0.	4.4	7.0	4.4	7.0
Magnesium Stearate	4.4	7.0	4.4	7.0	4.4	7.0	4.4	7.0
Lactose	100.2	28	98.2.	22	98.2	22	96.2	16
Total weight (mg)	220	360	220	360	220	360	220	360

EF: Efavirenz; βCD: β cyclodextrin; P 407: Poloxamer 407; PVP K30: poly vinyl pyrrolidone K30; ** Figures in parentheses are codes as per 2^3 Factorial Design

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 prepared 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 100 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[12].

RESULTS AND DISCUSSION

The feasibility of formulating efavirenz- βCD - Poloxamer 407/ PVP K30 solid inclusion complexes into tablets was evaluated by preparing efavirenz tablets employing the solid

inclusion complexes by wet granulation method. To evaluate the individual and combined effects of βCD, Poloxamer 407 and PVP K30 on the dissolution rate and efficiency of efavirenz tablets, tablets each containing 100 mg of efavirenz were formulated employing solid inclusion complexes of drug- βCD - Poloxamer 407/ PVP K30 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 Poloxamer 407 and PVP K30 (0 and 2%) 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 - Poloxamer 407 (2%) binary mixture (b); EF - βCD (1:2) – Poloxamer 407 (2%) ternary complex (ab); EF – PVP K30 (2%) binary mixture (c); EF - βCD (1:2) – PVP K30 (2%) ternary complex (ac); EF – Poloxamer 407 (2%) - PVP K30 (2%) ternary complex (bc); EF - βCD (1:2)- Poloxamer 407 (2%) - PVP K30 (2%) inclusion complex (abc).

Table 2: Physical Properties of Efavirenz Tablets Prepared Employing Drug-βCD – Poloxamer 407/ PVP K30 by Wet Granulation Method as per 2^3 Factorial Study

Formulation code as per 2^3 factorial design	Hardness (Kg/sq. cm)	Friability (% weight loss)	DT (min-sec)	Drug Content (mg/tablet)
T_1	5.0	0.75	0-48	100.6
T_a	5.5	0.61	5-16	99.8
T_b	5.0	0.70	3-01	99.5
T_{ab}	6.0	0.69	4-24	99.4
T_c	6.5	0.55	8-45	100.1
T_{ac}	5.5	0.60	12-14	100.6
T_{bc}	5.0	0.73	9-02	101.0
T_{abc}	5.5	0.64	13-00	101.2

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.

Table 3: Dissolution Parameters of Efavirenz Tablets Prepared as per 2^3 Factorial Study Employing Drug-βCD-Poloxamer 407/ PVP K30 Inclusion Complexes

Formulation code as per 2^3 factorial design	Wet Granulation Method			
	T_{50} (min)	Dissolution Rate ($K_1 \times 10^2$) (min^{-1}) ($\bar{x}$) (cv)	Increase in K_1 (no. of folds)	Dissolution Efficiency (DE_{30}) (%) ($\bar{x}$) (cv)
T_1	30	1.18 (1.6)	-	35.6 (1.2)
T_a	15	3.52 (1.8)	2.98	49.6 (1.4)
T_b	3	14.10 (1.2)	11.95	82.8(0.8)
T_{ab}	5	7.75 (0.8)	6.56	61.6(0.7)
T_c	3	7.20 (0.6)	6.10	77.2(1.5)
T_{ac}	8	4.52 (0.7)	3.83	58.7(1.6)
T_{bc}	3	14.26 (0.6)	12.08	83.6(1.8)
T_{abc}	4	6.73 (0.4)	5.70	57.7(1.1)

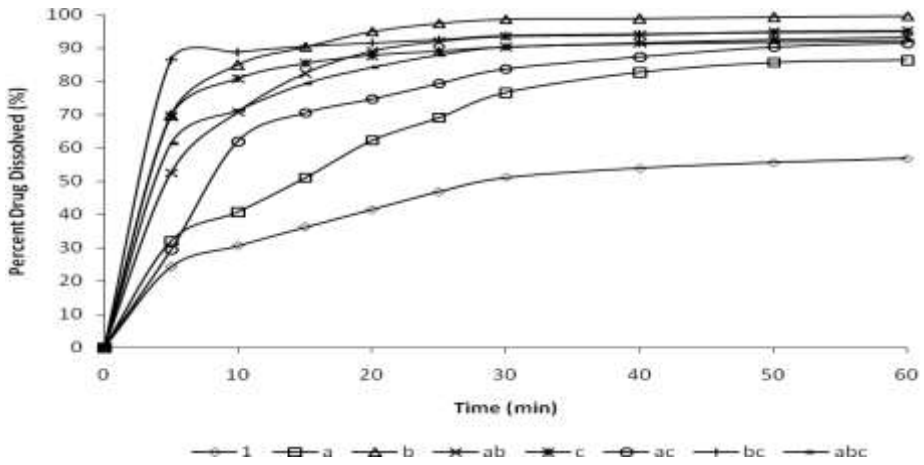

Fig. 1: Dissolution Profiles of Efavirenz Tablets Formulated Employing βCD, Poloxamer 407 and PVP K30 by Wet Granulation Method as per 2^3 Factorial Design

All the tablets prepared were found to contain efavirenz within 100±5% 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 0.92% in all the cases. Plain tablets formulated employing efavirenz alone disintegrated within 1 min. Whereas tablets prepared by wet granulation method employing βCD– Poloxamer 407/ PVP K30 inclusion complexes disintegrated slowly and the disintegration times of these tablets were in the range 3- 13 min. However all the tablets prepared employing βCD– Poloxamer 407/ PVP K30 inclusion complexes fulfilled the official (I.P) disintegration time specification of uncoated tablets.

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 0.950. Efavirenz dissolution was rapid and higher from the tablets formulated employing drug- βCD- Poloxamer 407/ PVP K30 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, Poloxamer 407, PVP K30) 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), Poloxamer 407 (factor B) and PVP K30 (factor C) were highly significant ($P< 0.01$) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of efavirenz. Among the three factors Poloxamer 407 (factor B) gave highest enhancement in the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of efavirenz tablets. βCD alone gave a dissolution rate (K_1) of 3.52×10^{-2} min^{-1}. Whereas βCD in combination with Poloxamer 407 and PVP K30 gave a dissolution rate (K_1) of 7.75×10^{-2} and 4.52×10^{-2} min^{-1} respectively. Thus combination of βCD with Poloxamer 407 or PVP K30 gave a significantly higher dissolution rate (K_1) of efavirenz.

I.P 2010 prescribed a dissolution rate specification of NLT 70% in 30 min for efavirenz tablets. All the efavirenz tablets formulated employing drug- βCD - Poloxamer 407 / PVP K30 inclusion complexes fulfilled the official (I.P) dissolution rate specification of efavirenz tablets. Whereas plain tablets formulated employing efavirenz alone did not fulfill the official dissolution rate specification. Hence Poloxamer 407 alone or a combination of βCD with either Poloxamer 407 or PVP K30 is recommended to enhance the dissolution rate and dissolution efficiency of efavirenz tablets.

CONCLUSIONS

- Efavirenz – βCD– Poloxamer 407 and efavirenz –βCD –PVP K30 inclusion complexes could be formulated into compressed tablets by wet granulation method.
- Efavirenz dissolution was rapid and higher from the tablets formulated employing drug- βCD- Poloxamer 407/ PVP K30 inclusion complexes when compared to the tablets containing efavirenz alone.
- The tablets formulated employing drug- βCD- Poloxamer 407/ PVP K30 inclusion complexes fulfilled the official (I.P 2010) dissolution rate test specification of NLT 70 % in 30 min prescribed for efavirenz tablets.
- The individual as well as combined effects of the three factors involved i.e., βCD (factor A), Poloxamer 407 (factor B) and PVP K30 (factor C) were highly significant ($P< 0.01$) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of efavirenz.
- Among the three factors Poloxamer 407 (factor B) gave highest enhancement in the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of efavirenz tablets.
- βCD alone gave low dissolution rates. Combination of βCD with Poloxamer 407 or PVP K30 gave a significantly higher dissolution rate (K_1) of efavirenz.
- Hence Poloxamer 407 alone or a combination of βCD with either Poloxamer 407 or PVP K30 is recommended to enhance the dissolution rate and efficiency of efavirenz tablets.

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