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

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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. A comparative evaluation of wet granulation and direct compression methods was made for the preparation of tablets employing drug – βCD – Poloxamer 407 / PVP K30 inclusion complexes. 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 and direct compression methods employing various βCD complexes as per 2^3 factorial design and the tablets were evaluated for dissolution rate and other physical properties. Efavirenz tablets formulated employing dug – βCD – Poloxamer 407 / PVP K30 inclusion complexes and prepared by direct compression method disintegrated rapidly when compared to those made 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 in both wet granulation and direct compression methods. 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 in both wet granulation and direct compression methods. 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 in both wet granulation and direct compression methods. βCD alone gave low dissolution rates in both wet granulation and direct compression methods. Combination of βCD with Poloxamer 407 or PVP K30 gave a significantly higher dissolution rate (K_1) of efavirenz in both wet granulation and direct compression methods. Overall direct compression method gave higher dissolution rates (K_1) and dissolution efficiency (DE_{30}) values than the wet granulation method in all the cases. 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. Direct compression method was more suitable to prepare efavirenz tablets with rapid disintegration and dissolution characteristics employing drug- βCD - Poloxamer 407 / PVP K30 inclusion complexes.

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 in soluble in water and aqueous fluids. As such its oral absorption is dissolution rate limited and it requires enhancement in the solubility and dissolution rate for increasing its oral bioavailability. 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, nano-particles, nanosuspensions, micro emulsion and self-emulsifying systems are available to enhance the solubility, dissolution rate and bioavailability of poorly soluble BCS Class II drugs [1].

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]. Poloxamer 407 is a polyethylene oxide-polypropylene oxide- polyethylene oxide triblock co-polymer of non-ionic nature and is used as a solubilising agent [6-8].

We reported[9] earlier that combination of cyclodextrins (βCD and HPβCD) with Poloxamer 407 and PVP K30 or Poloxamer 407 and PVP K30 alone have 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 evaluate the effects of βCD, Poloxamer 407 and PVP K30 on the dissolution rate of efavirenz tablets in a 2^3 factorial study.

Two methods i.e. wet granulation and direct compression methods were tried for the preparation of efavirenz tablets employing efavirenz- βCD- Poloxamer 407 and efavirenz- βCD- PVP K30 inclusion complexes. A comparative evaluation of the two methods of preparation was also made.

MATERIALS AND METHODS

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.

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^{o}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 (i) wet granulation and (ii) direct compression methods employing Efavirenz- βCD - Poloxamer 407/ PVP K30 inclusion complexes. The formulae of the tablets prepared are given in **Table 1**.

TABLE 1: FORMULAE OF EFAVIRENZ TABLETS PREPARED BY WET GRANULATION AND DIRECT COMPRESSION METHODS EMPLOYING DRUG- BCD – POLOXAMER 407- PVP K30 INCLUSION COMPLEXES AS PER 2^3 FACTORIAL STUDY

Ingredient (mg / tablet)	Efavirenz Tablet Formulation*							
	WT_1/DT_1	WT_a/DT_a	WT_b/DT_b	WT_{ab}/DT_{ab}	WT_c/DT_c	WT_{ac}/DT_{ac}	WT_{bc}/DT_{bc}	WT_{abc}/DT_{abc}
Efavirenz (1)**	100.0	-	-	-	-	-	-	-
EF- βCD (1:2) (a)	-	300.0	-	-	-	-	-	-
EF - P 407(2%) (b)	-	-	102	-	-	-	-	-
EF - βCD (1:2) - P 407(2%) (ab)	-	-	-	306	-	-	-	-
EF - PVP K30 (2%) (c)	-	-	-	-	102.0	-	-	-
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	11.0	18.0	11.0	18.0	11.0	18.0	11.0	18.0
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	28.0	98.2.	22.0	98.2	22.0	96.2	16.0
Total weight	220.0	360.0	220.0	360.0	220.0	360.0	220.0	360.0

*W: Wet Granulation Method; D: Direct Compression Method; 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

Preparation of tablets by Wet Granulation Method: Lactose was used as filler. Crosspovidone (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. Crosspovidone (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., Ahmadabad) to a hardness of 5- 6 kg/cm^2 using 9 mm flat punches. In each case 100 tablets were compressed.

Preparation of tablets by Direct Compression Method: All the materials required as per the formulae were blended in a closed polyethylene bag. The blends were directly compressed into tablets on a 16- station tablet punching machine (M/s Cadmach machineries Pvt. Ltd., Ahmadabad) 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 as such and from 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. Efavirenz or efavirenz 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 [10].

RESULTS AND DISCUSSION: The efavirenz- βCD- Poloxamer 407 / PVP K30 inclusion complexes as per 2^3 factorial design were prepared by kneading method

with a view to enhance the solubility and dissolution rate of efavirenz, a BCS class II drug. All the solid inclusion complexes of Drug- βCD- Poloxamer 407 / PVP K30 prepared were found to be fine and free flowing powders. Low coefficient of variation (c.v) values (< 1%) in the percent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared. The dissolution rate characteristics of these βCD- Poloxamer 407 / PVP K30 inclusion complexes were reported earlier.

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 and direct compression methods. 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). The formulae of efavirenz tablets prepared as per 2^3 factorial design employing the above mentioned cyclodextrin inclusion complexes are given in Table 1. 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 **Tables 2-3** and the dissolution parameters of the tablets prepared are summarized in **Table 4**.

All the tablets prepared were found to contain efavirenz within 100±5% of the labelled 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. In both wet granulation and direct compression methods plain tablets formulated employing efavirenz alone disintegrated within 1 min. All the tablets prepared by direct compression method employing βCD– Poloxamer 407/ PVP K30 inclusion complexes also disintegrated rapidly within 2 min 50 sec. 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.

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)
WT_1	5.0	0.75	0-48	100.6
WT_a	5.5	0.61	5-16	99.8
WT_b	5.0	0.70	3-01	99.5
WT_{ab}	6.0	0.69	4-24	99.4
WT_c	6.5	0.55	8-45	100.1
WT_{ac}	5.5	0.60	12-14	100.6
WT_{bc}	5.0	0.73	9-02	101.0
WT_{abc}	5.5	0.64	13-00	101.2

TABLE 3: PHYSICAL PROPERTIES OF EFAVIRENZ TABLETS PREPARED EMPLOYING DRUG-βCD – POLOXAMER 407/ PVP K30 BY DIRECT COMPRESSION 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)
DT_1	5.0	0.92	0-10	99.2
DT_a	6.0	0.80	1-10	99.3
DT_b	6.5	0.81	0-08	101.4
DT_{ab}	5.5	0.76	1-25	101.3
DT_c	5.0	0.51	2-20	102.6
DT_{ac}	6.0	0.79	2-50	101.7
DT_{bc}	6.5	0.82	0-20	99.3
DT_{abc}	5.0	0.61	2-30	98.9

TABLE 4: DISSOLUTION PARAMETERS OF EFAVIRENZ TABLETS PREPARED EMPLOYING DRUG- BCD – POLOXAMER 407/ PVP K30 INCLUSION COMPLEXES BY WET GRANULATION AND DIRECT COMPRESSION METHODS AS PER 2^3 FACTORIAL STUDY

Formulation code as per 2^3 factorial design	Wet Granulation Method				Direct Compression 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}) (%) (x) (cv)	T_{50} (min)	Dissolution Rate ($K_1 \times 10^2$)(min^{-1}) ($\bar{x}$) (cv)	Increase in K_1 (no. of folds)	Dissolution Efficiency ($\overline{DE_{30}}$)(%) (x) (cv)
T_1	30	1.18 (1.6)	-	35.6 (1.2)	20	1.53(1.1)	-	43.1(1.5)
T_a	15	3.52 (1.8)	2.98	49.6 (1.4)	4	6.14(0.8)	4.01	74.5(1.8)
T_b	3	14.10 (1.2)	11.95	82.8(0.8)	3	11.50(0.7)	7.64	79.4(1.6)
T_{ab}	5	7.75 (0.8)	6.56	61.6(0.7)	3	7.92(0.6)	5.17	76.9(1.1)
T_c	3	7.20 (0.6)	6.10	77.2(1.5)	4	8.46(1.2)	5.53	78.9(0.8)
T_{ac}	8	4.52 (0.7)	3.83	58.7(1.6)	3	6.52(1.4)	4.26	79.8(0.6)
T_{bc}	3	14.26 (0.6)	12.08	83.6(1.8)	3	8.65(1.2)	5.65	84.3(1.2)
T_{abc}	4	6.73 (0.4)	5.70	57.7(1.1)	4	6.62(1.6)	4.32	76.6(1.4)

However, all the tablets prepared employing βCD–Poloxamer 407/ PVP K30 inclusion complexes by both wet granulation and direct compression methods 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. The correlation coefficient (r) values were higher in the first order model than those in the zero order model in all the cases. The dissolution parameters (T_{90}, K_1 and DE_{30}) of various tablets are summarized in Table 4.

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 in both wet granulation and direct compression methods. Dissolution parameters, K_1 and DE_{30} in each case 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 in both wet granulation and direct compression methods. 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 in both wet granulation and direct compression methods. Poloxamer 407 alone gave a 11.95 and 7.64 fold increase in the dissolution rate of efavirenz tablets respectively in wet granulation and direct compression methods when compared to the corresponding plain tablets.

βCD alone gave a dissolution rate (K_1) of 3.52 x 10^{-2} and 6.14s x 10^{-2} min^{-1} respectively in the wet granulation and direct compression methods. Whereas βCD in combination with Poloxamer 407 gave a dissolution rate (K_1) of 7.75 x 10^{-2} and 7.92 x 10^{-2} min^{-1} respectively in the wet granulation and direct compression methods. Similarly βCD in combination with PVP K30 gave a dissolution rate (K_1) of 4.52 x 10^{-2} and 6.52 x 10^{-2} min^{-1} respectively in the wet granulation and direct compression methods.

Thus, combination of βCD with Poloxamer 407 or PVP K30 gave a significantly higher dissolution rate (K_1) of efavirenz in both wet granulation and direct compression methods. Overall direct compression method gave higher dissolution rates (K_1) and dissolution efficiency (DE_{30}) values than the wet granulation method in all the cases. 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 and prepared by both wet granulation and direct compression methods fulfilled the official (I.P.) dissolution rate specification of efavirenz tablets. Whereas plain tablets formulated employing efavirenz alone did not fulfil 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 efficiency of efavirenz tablets. Direct compression method was found more suitable to prepare efavirenz tablets with rapid disintegration and dissolution characteristics employing drug- βCD - Poloxamer 407 / PVP K30 inclusion complexes.

CONCLUSIONS:

1. Efavirenz tablets formulated employing drug – βCD – Poloxamer 407 / PVP K30 inclusion complexes and prepared by direct compression method disintegrated rapidly when compared to those made by wet granulation method.

2. 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 in both wet granulation and direct compression methods.

3. 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 in both wet granulation and direct compression methods.

4. 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 in both wet granulation and direct compression methods.

5. βCD alone gave low dissolution rates in both wet granulation and direct compression methods. Combination of βCD with Poloxamer 407 or PVP K30 gave a significantly higher dissolution rate (K_1) of efavirenz in both wet granulation and direct compression methods.

6. Overall direct compression method gave higher dissolution rates (K_1) and dissolution efficiency (DE_{30}) values than the wet granulation method in all the cases.

7. 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.

8. Direct compression method was more suitable to prepare efavirenz tablets with rapid disintegration and dissolution characteristics employing drug- βCD - Poloxamer 407 / PVP K30 inclusion complexes.

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