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FORMULATION DEVELOPMENT OF EFAVIRENZ TABLETS EMPLOYING HP β CYCLODEXTRIN-PVP K30-SLS: A FACTORIAL STUDY

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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-HPβCD-PVP K30/SLS inclusion complexes into tablets and to evaluate the effects of HPβCD, PVP K30 and SLS on the dissolution rate and dissolution efficiency of efavirenz tablets in a 2^3 factorial study. A comparative evaluation of wet granulation and direct compression methods was made for the preparation of tablets employing drug-HPβCD-PVP K30/SLS inclusion complexes. Drug-HPβCD-PVP K30/SLS inclusion complexes were prepared by kneading method. Tablets each containing 50 mg of efavirenz were prepared by wet granulation and direct compression methods employing various HPβCD complexes as per 2^3 factorial design and the tablets were evaluated for dissolution rate and other physical properties.

Efavirenz tablets formulated employing dug-HPβCD-PVP K30/ SLS 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- HPβCD- PVP K30 /or SLS 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., HPβCD (factor A), PVP K30 (factor B) and SLS (factor C) were highly significant ($P < 0.01$) in enhancing the dissolution rate (K1) and dissolution efficiency (DE 30) of efavirenz in both wet granulation and direct compression methods. Among the three factors HPβCD (factor A) gave highest enhancement in the dissolution rate (K1) and dissolution efficiency (DE 30) of efavirenz tablets in both wet granulation and direct compression methods. SLS (factor C) alone gave low dissolution rate in both wet granulation and direct compression methods. Overall direct compression method gave higher dissolution rates (K1) and dissolution efficiency (DE 30) values than the wet granulation method in all the cases. Combination of HPβCD with either PVP K30 or SLS or both gave a

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significantly higher dissolution rate (K1) of efavirenz in both wet granulation and direct compression methods. Hence a combination of HPβCD with either PVP K30 or SLS or both is recommended to enhance the dissolution rate and efficiency of efavirenz tablets.

Key words: Efavirenz tablets, HPβ Cyclodextrin, PVP K30, SLS, Dissolution rate.

INTRODUCTION

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. 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, nanoparticles, 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]. Use of poly vinyl pyrrolidone (PVP K30) and/or sodium lauryl sulphate (SLS) is also reported[6-8] for solubilization and to enhance dissolution rate of poorly soluble drugs.

We have reported[9] earlier that combination of HPβCD with either PVP K30 or SLS or both 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-HPβCD-PVP K30 and efavirenz-HPβCD-SLS inclusion complexes into tablets and to evaluate the effects of HPβCD, PVP K30 and SLS 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-HPβCD-PVP K30 and efavirenz-HPβCD-SLS inclusion complexes. A comparative evaluation of the two methods of preparation was also made.

EXPERIMENTAL

Materials and methods

Efavirenz was a gift sample from M/s Hetero Drugs Limited, Hyderabad. HPβ-Cyclodextrin was gift sample from M/s. Cerestar Inc., USA. Methanol (Qualigens) and PVP K30, lactose, crospovidone, talc and magnesium stearate were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Estimation of Efavirenz

An UV spectrophotometric method based on the measurement of absorbance at 246 nm in water containing 2% SLS was used for estimation of efavirenz. The method obeyed Beer-Lambert's law in the concentration range of 1-10 μg /mL. When the standard drug solution was assayed repeatedly (n = 6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.60% and 1.0%, respectively. No interference from excipients used was observed.

Preparation of efavirenz-HPβCD-PVP K30/ SLS Complexes

Solid inclusion complexes of efavirenz, HPβCD, PVP K30 and SLS were prepared as per 2^3 – factorial study by kneading method. Efavirenz, HPβCD, PVP K30 and SLS 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-HPβCD-PVP K30/ SLS Tablets

Compressed tablets each containing 50 mg of efavirenz were prepared as per 2^3 – factorial study by (i) wet granulation and (ii) direct compression methods employing efavirenz-HPβCD-PVP K30/ SLS inclusion complexes. The formulae of the tablets prepared are given in Table 1.

Preparation of Tablets by Wet Granulation Method

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-HPβCD-PVP K30-SLS 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 and direct compression methods employing drug-HPβCD-PVP K30-SLS 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)**	(mg/table 50.0	-	-	-	-	-	-	-
Efa-HP βCD (1 : 2) (a)	-	150.0	-	-	-	-	-	-
Efa-PVP K30 (2%) (b)	-	-	54.4	-	-	-	-	-
Efa-HP βCD (1 : 2) -PVP K30 (2%) (ab)	-	-	-	154.4	-	-	-	-
Efa-SLS (2%) (c)	-	-	-	-	54.4	-	-	-
Efa-HP βCD (1 : 2) -SLS (2%) (ac)	-	-	-	-	-	154.4	-	-
Efa-PVP K30 (2%) -SLS (2%) (bc)	-	-	-	-	-	-	58.8	-
Efa-HP βCD (1 : 2) -PVP K30 (2%) -SLS (2%) (abc)	-	-	-	-	-	-	-	158.8
Crospovidone	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0
Talc	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4
Magnesium stearate	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4
Lactose	150.2	50.2	145.8	45.8	145.8	45.8	141.4	41.4
Total weight	220.0	220.0	220.0	220.0	220.0	220.0	220.0	220.0

*W: Wet Granulation Method; D: Direct Compression Method; Efa: Efavirenz;
HP βCD: Hydroxy Propyl β cyclodextrin; PVP K30: Poly Vinyl Pyrrolidone K30; SLS: Sodium Lauryl Suphate
** Figures in parentheses are codes as per 2^3 Factorial Design

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., 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 Thermionic tablet disintegration test machine using water as test fluid.

Dissolution rate study

The dissolution rate of efavirenz tablets prepared was studied in 2% SLS in 1000 mL of water using Disso 2000 (Labindia), 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature 37±0.5^{o}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, suitably diluted and assayed at 246 nm for efavirenz. The samples of dissolution fluid withdrawn at each time were 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-HPβCD-PVP K30/SLS 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-HPβCD-PVP K30/ SLS 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 feasibility of formulating efavirenz-HPβCD-PVP K30/ SLS 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 HPβCD, PVP K30 and SLS on the dissolution rate and efficiency of efavirenz tablets, tablets each containing 50 mg of efavirenz were formulated employing solid inclusion complexes of drug-HPβCD-PVP K30/ SLS as per 2^3 factorial design. For this purpose two levels of HPβCD (0 and 1 : 2 ratio of Drug : HPβCD) and two levels of each of PVP K30 and SLS (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); efavirenz -HPβCD (1 : 2) inclusion binary complex (a); efavirenz-PVP K30 (2%) binary mixture (b); efavirenz-HPβCD (1 : 2) – PVP K30 (2%) ternary complex (ab); efavirenz – SLS (2%) binary mixture (c); efavirenz-HPβCD (1 : 2) – SLS (2%) ternary complex (ac); efavirenz – PVP K30 (2%) – SLS (2%) ternary complex (bc); efavirenz-HPβCD (1 : 2)- PVP K30 (2%) – SLS (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 summarised in Table 4.

Table 2: Physical properties of efavirenz tablets prepared employing drug-HPβCD-PVP K30/ SLS 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	5.5	0.18	3-40	49.9
WT_a	5.6	0.12	3-18	50.1
WT_b	5.8	0.12	3-02	50.2
WT_{ab}	5.7	0.08	2-25	50
WT_c	5.8	0.14	2-36	49.9
WT_{ac}	5.7	0.16	2-47	50.1
WT_{bc}	5.9	0.10	2-20	50.0
WT_{abc}	6.0	0.06	2-12	50.0

Table 3: Physical properties of efavirenz tablets prepared employing drug-HPβCD-PVP K30/ SLS 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	5.4	0.32	2-56	49.7
DT_a	5.5	0.21	2-15	49.8
DT_b	5.8	0.27	2-08	50.1
DT_{ab}	6.0	018	1-45	50.0
DT_c	5.4	0.21	1-54	49.9
DT_{ac}	5.7	0.24	1-30	50.1
DT_{bc}	5.8	0.10	1-10	50.2
DT_{abc}	6.0	0.08	1-0	50.0

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- 6.0 Kg/cm^2. Percentage weight loss in the friability test was less than 0.40% in all the cases. Efavirenz tablets formulated employing dug-HPβCD-PVP K30 / SLS inclusion complexes and prepared by direct compression method disintegrated rapidly when compared to those made by wet granulation method. However all the tablets prepared by both wet granulation and direct compression methods employing HPβCD-PVP K30/SLS 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 2% SLS in water. 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_{50}, 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-HPβCD-PVP K30/SLS 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 (HPβCD, PVP K30, SLS) in enhancing the dissolution rate and efficiency of efavirenz tablets. The individual as well as combined effects of the three factors involved i.e., HPβCD (factor A), PVP K30 (factor B) and SLS (factor C) were highly significant ($P< 0.01$)

Table 4: Dissolution parameters of Efavirenz tablets prepared employing drug-HPβCD-PVP K30/SLS 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				
	PD_{10} (%)	T_{50} (min)	Dissolution rate ($K_1 \times 10^2$) (min^{-1}) (x ± s. d.)	Increase in K_1 (No. of folds)	Dissolution efficiency (DE_{30}) (%) (x ± s. d.)
T_1	12.68 ± 0.53	> 60	0.60 ± 0.0001	-	14.15 ± 0.18
T_a	52.91 ± 0.35	8	6.72 ± 0.0057	11.15	53.76 ± 0.31
T_b	39.08 ± 0.69	12	3.30 ± 0.0004	5.48	46.28 ± 0.36
T_{ab}	68.82 ± 0.35	5	7.65 ± 0.0007	12.69	64.66 ± 0.03
T_c	26.05 ± 0.87	37	1.50 ± 0.000	2.49	30.18 ± 0.52
T_{ac}	56.02 ± 0.69	7	7.43 ± 0.0002	12.32	58.31 ± 0.15
T_{bc}	59.83 ± 0.69	5	7.45 ± 0.0003	12.35	60.98 ± 0.16
T_{abc}	75.50±0.69	3	9.73 ± 0.0006	16.13	73.04 ± 0.27

Formulation code as per 2^3 factorial design	Wet granulation method				
	PD_{10} (%)	T_{50} (min)	Dissolution rate ($K_1 \times 10^2$) (min^{-1}) (x ± s. d.)	Increase in K_1 (No. of folds)	Dissolution efficiency (DE_{30}) (%) (x ± s. d.)
T_1	18.79 ± 0.87	> 60	0.78 ± 0.0002	-	21.13 ± 0.12
T_a	69.51 ± 0.35	3	7.18 ± 0.0009	9.22	67.09 ± 0.30
T_b	59.25 ± 0.80	6	6.48 ± 0.0018	8.40	60.81 ± 0.42
T_{ab}	75.97 ± 0.72	4	7.93 ± 0.0009	10.19	73.75 ± 0.08
T_c	37.00 ± 0.69	19	3.14 ± 0.0004	4.03	41.61 ± 0.20
T_{ac}	72.05 ± 0.53	4	7.60 ± 0.0008	9.76	69.60 ± 0.06
T_{bc}	74.24 ± 0.53	4	7.67 ± 0.0007	9.85	71.19 ± 0.25
T_{abc}	85.99 ± 0.20	2	10.33 ± 0.0009	13.26	80.64 ± 0.19

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 HPβCD (factor A) 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. SLS (factor C) alone gave low dissolution rate 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.

HPβCD alone gave a dissolution rate (K1) of 6.72 x 10^{-2} and 7.18 x 10^{-2} min^{-1} respectively in the wet granulation and direct compression methods. PVP K30 alone gave a dissolution rate (K1) of 3.30 x 10^{-2} and 6.48 x 10^{-2} min^{-1} respectively in the wet granulation and direct compression methods. SLS alone gave a dissolution rate (K1) of 1.50 x 10^{-2} and 3.14 x 10^{-2} min^{-1} respectively in the wet granulation and direct compression methods. Whereas HPβCD in combination with PVP K30 gave a dissolution rate (K1) of 7.65 x 10^{-2} and 7.93 x 10^{-2} min^{-1} respectively in the wet granulation and direct compression methods. Similarly HPβCD in combination with SLS gave a dissolution rate (K1) of 7.43 x 10^{-2} and 7.60 x 10^{-2} min^{-1} respectively in the wet granulation and direct compression methods. HPβCD in combination with both PVP K30 and SLS gave a dissolution rate (K1) of 9.73 x 10^{-2} and 10.33 x 10^{-2} min^{-1} respectively in the wet granulation and direct compression methods. Combination of HPβCD with either PVP K30 or SLS or both gave a significantly higher dissolution rate (K1) of efavirenz in both wet granulation and direct compression methods. All the efavirenz tablets formulated employing drug-HPβCD-PVP K30/ SLS inclusion complexes are 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 fulfill the official dissolution rate specification. Hence a combination of HPβCD with either PVP K30 or SLS or both is recommended to enhance the dissolution rate and efficiency of efavirenz tablets.

CONCLUSIONS

(i) Efavirenz tablets formulated employing dug-HPβCD-PVP K30 / SLS inclusion complexes and prepared by direct compression method disintegrated rapidly when compared to those made by wet granulation method.

(ii) Efavirenz dissolution was rapid and higher from the tablets formulated employing drug-HPβCD-PVP K30 /or SLS inclusion complexes when compared to the tablets containing efavirenz alone in both wet granulation and direct compression methods.

(iii) The individual as well as combined effects of the three factors involved i.e., HPβCD (factor A), PVP K30 (factor B) and SLS (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.

(iv) Among the three factors HPβCD (factor A) 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. SLS (factor C) alone gave low dissolution rate in both wet granulation and direct compression methods.

(v) 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. Combination of HPβCD with either PVP K30 or SLS or both gave a significantly higher dissolution rate (K_1) of efavirenz in both wet granulation and direct compression methods.

(vi) Hence a combination of HPβCD with either PVP K30 or SLS or both 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-HPβCD-PVP K30 / SLS inclusion complexes.

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