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FORMULATION DEVELOPMENT OF EFAVIRENZ TABLETS EMPLOYING CYCLODEXTRIN - PVP INCLUSION COMPLEXES

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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. We have earlier reported that a combination of CDs (βCD, HPβCD) with PVP K30 has markedly enhanced both the solubility and dissolution rate of efavirenz. The objective of the present study is to evaluate the feasibility of formulating efavirenz –βCD–PVP K30 and efavirenz –HPβCD –PVP K30 inclusion complexes into tablets and to evaluate the effects of βCD, HPβCD and PVP K30 on the dissolution rate of efavirenz tablets. A comparative evaluation of two methods i.e. wet granulation and direct compression methods of preparation was also made. Efavirenz –CD (βCD / HPβCD)–PVP K30 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 CD complexes and the tablets were evaluated for dissolution rate and other physical properties.

Efavirenz-CD (βCD/ HPβCD) - PVP K30 solid inclusion complexes could be formulated into tablets by both wet granulation and direct compression methods. Tablets prepared by direct compression method disintegrated rapidly when compared to those prepared by wet granulation method. Tablets formulated employing βCD inclusion complexes disintegrated rapidly when compared to tablets formulated employing HPβCD inclusion complexes in both wet granulation and direct compression methods. Efavirenz dissolution was rapid and higher from the tablets formulated employing efavirenz-CD (βCD/ HPβCD) - PVP K30 inclusion complexes when compared to the tablets containing

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efavirenz alone and tablets containing PVP alone in both wet granulation and direct compression methods. Combination of βCD and HPβCD with PVP K30 gave a significantly higher dissolution rates (K_1) and dissolution efficiency (DE_{30}) values of efavirenz in both wet granulation and direct compression methods. Tablets formulated employing βCD inclusion complexes gave higher dissolution rates when compared to those formulated employing HPβCD inclusion complexes. Overall wet granulation method gave higher increase (no. of folds) in the dissolution rate when compared to direct compression method in all the cases. Hence a combination of CDs (βCD and HPβCD) with PVP K30 is recommended to enhance the dissolution rate and dissolution efficiency of efavirenz tablets. Both wet granulation and direct compression methods were found suitable to prepare efavirenz tablets with rapid disintegration and dissolution characteristics employing these CD-PVP inclusion complexes.

Key words: *Efavirenz tablets, Cyclodextrins, Polyvinyl pyrrolidone, Complexation.*

INTRODUCTION

About 95% of all new potential therapeutic drugs (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 BCS with low solubility and high permeability characters and pose challenging problems in their pharmaceutical product development process. Efavirenz belongs to Class II under BCS and exhibit low and variable bioavailability due to its poor aqueous solubility. As such it needs enhancement in the dissolution rate and bioavailability to derive its 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, microemulsion and self-emulsifying systems are available[1] to enhance the bioavailability of BCS Class II drugs. Among the various techniques, cyclodextrin complexation is an efficient approach for enhancing the dissolution rate and bioavailability of BCS – Class II Drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and 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 favorably affected.[2,3] Cyclodextrins have been receiving increasing application in pharmaceutical products in recent years due to their approval by various regulatory agencies.[4,5] It is reported in a few studies [6,7] that addition of small amounts of water soluble polymers such as PVP, HPMC, PEG to cyclodextrin systems has improved both the complexing and solubilizing efficiencies of CDs. We have earlier reported[8] that a combination of CDs (βCD, HPβCD) with PVP K30 has markedly enhanced both 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–PVP K30 and efavirenz –HPβCD –PVP K30 inclusion complexes into tablets and to evaluate the effects of βCD, HPβCD and PVP K30 on the dissolution rate of efavirenz tablets. Two methods i.e. wet

granulation and direct compression methods were tried for the preparation of efavirenz tablets. A comparative evaluation of the two methods of preparation was also made.

EXPERIMENTAL

MATERIALS

Efavirenz was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. β - cyclodextrin and hydroxypropyl β- cyclodextrin were gift samples from M/s Cerestar Inc., USA, Polyvinylpyrrolidone (PVP, K-30, Sigma Chemical Co.), Crospovidone, dichloromethane (Qualigens), methanol (Qualigens), lactose IP, talc and magnesium stearate 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% 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 1-10 µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.68% and 1.02% respectively. No interference by the excipients used in the study was observed.

Preparation of Efavirenz-CD (βCD/ HPβCD) - PVP K30 Complexes

Solid inclusion complexes of efavirenz-CD (βCD / HPβCD) - PVP K30 were prepared by kneading method. Efavirenz, βCD/ HPβCD 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-CD (βCD/HPβCD) - PVP K30 Tablets

Compressed tablets each containing 50 mg of efavirenz were prepared by (i) wet granulation and (ii) direct compression methods employing

efavirenz- βCD- PVP K30 and efavirenz- HPβCD - PVP K30 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-CD (βCD/HPβCD) - 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^{o} 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.

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 Thermonic tablet disintegration test machine using water as test fluid.

Dissolution Rate Study

Dissolution rate of efavirenz tablets prepared was studied in water containing 2% SLS (900 ml) employing USP 8 station Dissolution Rate Test Apparatus (M/s Labindia Disso 8000) with a paddle stirrer at 50 rpm. Sodium Lauryl Sulphate (SLS) was added to the dissolution fluid to maintain the sink condition as prescribed in I.P. 2010. A temperature of 37±1°C was maintained throughout the study. Samples of dissolution fluid (5 ml) were withdrawn through a filter (0.45 µm) at different intervals of time, suitably diluted and assayed for efavirenz at 245 nm. The dissolution fluid withdrawn at each sampling time was replaced with fresh dissolution fluid and suitable correction is made in calculating the amount of drug dissolved. All dissolution rate experiments were conducted in triplicate (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[9].

RESULTS AND DISCUSSION

The efavirenz-CD (βCD/ HPβCD) - PVP K30 inclusion complexes 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 efavirenz-CD (βCD/ HPβCD) - 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 efavirenz-CD (βCD/ HPβCD) - PVP K30 inclusion complexes were reported earlier[8].

The feasibility of formulating efavirenz-CD (βCD/ HPβCD) - 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. The formulae of efavirenz tablets prepared employing the above mentioned cyclodextrin inclusion complexes are given in Table 1.

Efavirenz-CD (βCD/ HPβCD) - PVP K30 solid inclusion complexes could be formulated into tablets by both wet granulation and direct compression methods. 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.

Table 1: Formulae of Efavirenz Tablets Prepared by Wet Granulation and Direct Compression Methods Employing Drug- CD –PVP K30 Inclusion Complexes

Ingredient (mg / tablet)	**Efavirenz Tablet Formulation***					
	F1/F7	**F2/F8**	**F3/F9**	**F4/F10**	**F5/F11**	**F6/F12**
Efavirenz	50.0	-	-	-	-	-
Efv - PVP K30 (2%)	-	51.0	-	-	-	-
Efv - βCD (1:2)	-	-	150.0	-	-	-
Efv - βCD (1:2) - PVP K30 (2%)	-	-	-	153.0	-	-
Efv - HPβCD (1:2)	-	-	-	-	150.0	-
Efv - HPβCD (1:2) - PVP K30 (2%)	-	-	-	-	-	153.0
Crospovidone	15.0	15.0	15.0	15.0	15.0	15.0
Talc	6.0	6.0	6.0	6.0	6.0	6.0
Magnesium Stearate	6.0	6.0	6.0	6.0	6.0	6.0
Lactose	223	222	123	120	123	120
Total weight	300.0	300.0	300.0	300.0	300.0	300.0

*F1-F6: Wet Granulation Method; F7-F12: Direct Compression Method; Efv: Efavirenz; βCD: β cyclodextrin; HP βCD: Hydroxy propyl β cyclodextrin; PVP K30: Poly vinyl pyrrolidone K30;

Table 2: Physical Properties of Efavirenz Tablets Prepared Employing Drug- CD –PVP K30 Inclusion Complexes by Wet Granulation Method.

Formulation	Hardness (Kg/sq. cm)	Friability (% weight loss)	DT (min-sec)	Drug Content (mg/ tablet)
F1	4.5	0.75	0-48	50.6
F2	5.0	0.68	6-31	49.3
F3	5.0	0.70	3-01	49.5
F4	5.5	0.45	4-31	49.8
F5	5.5	0.55	8-45	50.1
F6	6.0	0.80	7-54	49.6

Table 3: Physical Properties of Efavirenz Tablets Prepared Employing Drug- CD –PVP K30 by Direct Compression Method

Formulation	Hardness (Kg/sq. cm)	Friability (% weight loss)	DT (min-sec)	Drug Content (mg/ tablet)
F7	4.5	0.92	0-10	49.2
F8	5.0	0.80	4-15	49.3
F9	4.5	0.81	0-08	50.4
F10	4.5	0.76	1-34	50.3
F11	6.0	0.51	2-12	50.6
F12	6.0	0.79	4-45	49.7

All the tablets prepared were found to contain efavirenz within 100±5% of the labeled claim. Hardness of the tablets was in the range 4.5-6.0 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 efavirenz-CD (βCD/ HPβCD) - PVP K30 inclusion complexes also disintegrated rapidly within 4 min 45 sec. Whereas tablets prepared by wet granulation method employing efavirenz-CD (βCD/ HPβCD) - PVP K30 inclusion complexes disintegrated relatively slowly and the disintegration times of these tablets were in the range 3- 9 min. Tablets formulated employing βCD inclusion complexes disintegrated rapidly when compared to tablets formulated employing HPβCD inclusion complexes in both wet granulation and direct compression methods. Tablets prepared by direct compression method disintegrated rapidly when compared to those prepared by wet granulation method. However all the tablets prepared employing efavirenz-CD (βCD/ HPβCD) - 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 IP 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_{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 efavirenz-CD (βCD/ HPβCD) - PVP K30 inclusion complexes when compared to the tablets containing efavirenz alone and tablets

containing PVP alone in both wet granulation and direct compression methods.

Table 4: Dissolution Parameters of Efavirenz Tablets Prepared Employing Drug- CD –PVP K30 Inclusion Complexes by Wet Granulation and Direct Compression Methods

Formulation	Wet Granulation Method				Formulation	Direct Compression Method			
	T_{50} (min)	Dissolution Rate ($K_1 \times 10^2$) (min^1) ($\bar{x} \pm$ s. d.)	Increase in K_1 (no. of folds)	Dissolution Efficiency (DE_{30}) (%) ($\bar{x} \pm$ s. d.)		T_{50} (min)	Dissolution Rate ($K_1 \times 10^2$) (min^1) ($\bar{x} \pm$ s. d.)	Increase in K_1 (no. of folds)	Dissolution Efficiency (DE_{30}) (%) ($\bar{x} \pm$ s. d.)
F1	30	1.27±0.0009	-	34.61±0.605	**F7**	20	1.63±0.001	-	42.05±3.206
F2	20	3.02±0.0054	2.39	40.45±1.578	**F8**	6	3.80±0.0012	2.34	63.96±2.449
F3	3	7.18±0.0021	5.67	76.31±1.596	**F9**	4	8.41±0.0024	5.17	77.94±1.316
F4	3	14.43±0.0027	11.39	82.75±0.261	**F10**	3	11.43±0.0017	7.03	78.37±0.598
F5	5	8.42±0.0030	6.65	69.35±0.698	**F11**	5	7.70±0.0019	4.74	68.92±1.496
F6	3	13.91±0.0115	10.98	81.07±0.614	**F12**	3	8.50±0.0006	5.22	83.23±0.458

Tablets formulated employing efavirenz-βCD-PVP K30 and efavirenz- HPβCD-PVP K30 inclusion complexes gave higher dissolution rates and dissolution efficiency values when compared to those formulated employing efavirenz- βCD and efavirenz- HPβCD complexes in both wet granulation and direct compression methods. In the wet granulation method βCD-PVP K30 (F4) gave an 11.39 fold increase in the dissolution rate of efavirenz tablets when compared to plain tablets (F1) .Whereas βCD alone (F3) gave only a 5.67 fold increase in the dissolution rate. Similarly HPβCD alone (F5) gave a 6.65 fold increase and in combination with PVP K30 (F6) it gave a 10.98 fold increase in the dissolution rate of efavirenz tablets when compared to plain tablets (F1). In the direct compression method βCD-PVP K30 (F10) gave a 7.03 fold increase in the dissolution rate of efavirenz tablets when compared to plain tablets (F1) .Whereas βCD alone (F9) gave a 5.17 fold increase in the dissolution rate. Similarly HPβCD alone (F11) gave a 4.74 fold increase and in combination with PVP K30 (F12) it gave a 5.22 fold increase in the dissolution rate of efavirenz tablets when compared to plain tablets (F1). Tablets formulated employing βCD-PVP K30 inclusion complexes gave higher dissolution rates when compared to those formulated employing HPβCD-PVP K30 inclusion complexes. Overall wet granulation method gave higher increase (no. of folds) in the dissolution rate when compared to direct compression method in all the cases.

Thus combination of βCD and HPβCD with PVP K30 gave a significantly higher dissolution rates (K_1) and dissolution efficiency (DE_{30}) values of efavirenz in both wet granulation and direct compression methods. I.P 2010 prescribed a dissolution rate specification of NLT 70% in 60 min for efavirenz tablets. All the efavirenz tablets formulated employing efavirenz-CD (βCD/ HPβCD) - 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 fulfill the official dissolution rate specification. Hence a combination of CDs (βCD and HPβCD) with PVP K30 is recommended to enhance the dissolution rate and dissolution efficiency of efavirenz tablets. Both wet granulation and direct compression methods were found suitable to prepare efavirenz tablets with rapid disintegration and dissolution characteristics employing efavirenz-CD (βCD/ HPβCD) - PVP K30 inclusion complexes.

CONCLUSIONS

1. Efavirenz-CD (βCD/ HPβCD) - PVP K30 solid inclusion complexes could be formulated into tablets by both wet granulation and direct compression methods.

2. Tablets prepared by direct compression method disintegrated rapidly when compared to those prepared by wet granulation method.
3. Tablets formulated employing βCD inclusion complexes disintegrated rapidly when compared to tablets formulated employing HPβCD inclusion complexes in both wet granulation and direct compression methods.
4. Efavirenz dissolution was rapid and higher from the tablets formulated employing efavirenz-CD (βCD/ HPβCD) - PVP K30 inclusion complexes when compared to the tablets containing efavirenz alone and tablets containing PVP alone in both wet granulation and direct compression methods.
5. Combination of βCD and HPβCD with PVP K30 gave a significantly higher dissolution rates (K_1) and dissolution efficiency (DE_{30}) values of efavirenz in both wet granulation and direct compression methods.
6. Tablets formulated employing βCD inclusion complexes gave higher dissolution rates when compared to those formulated employing HPβCD inclusion complexes.
7. Overall wet granulation method gave higher increase (no. of folds) in the dissolution rate when compared to direct compression method in all the cases.

Hence a combination of CDs (βCD and HPβCD) with PVP K30 is recommended to enhance the dissolution rate and dissolution efficiency of efavirenz tablets. Both wet granulation and direct compression methods were found suitable to prepare efavirenz tablets with rapid disintegration and dissolution characteristics employing these CD-PVP inclusion complexes.

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