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ENHANCEMENT OF SOLUBILITY DISSOLUTION RATE AND FORMULATION DEVELOPMENT OF EFAVIRENZ TABLETS EMPLOYING βCD AND LUTROL: A FACTORIALSTUDY

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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. As such it needs enhancement in the dissolution rate and bioavailability in its formulation development to derive its maximum therapeutic efficacy. The objective of the present study is enhancement of solubility, dissolution rate of efavirenz, a poorly soluble BCS-Class II employing β-CD and Lutrol. The individual and combined effects of β-CD and Lutrol in enhancing the solubility and dissolution rate of efavirenz were evaluated in a 2^2-factorial study. The feasibility of formulating the drug-β-CD-Lutrol solid inclusion complexes into tablets was also evaluated. Efavirenz -βCD-Lutrol inclusion complexes and their tablets were formulated employing selected combinations of β-CD (factor A) and Lutrol (factor B) as per 2^2 factorial design and were evaluated.

βCD alone gave higher enhancement in the solubility of efavirenz, (1.93 fold) than Lutrol and combination of βCD- Lutrol.βCD alone gave a higher enhancement (4.7 fold) in the dissolution rate of (K1) of efavirenz. There was no additional advantage of combining βCD and Lutrol in enhancing the dissolution rate of efavirenz.The dissolution efficiency (DE_{20}) of efavirenz was increased from 1.68 % for pure drug to 7.83, 7.87, and 8.37 % respectively with βCD, Lutrol and βCD – Lutrol complexes.Efavirenz -βCD – Lutrol inclusion complexes could be formulated into tablets by direct compression method and the resulting tablets fulfilled the official (IP 2010) specifications with regard to drug content, hardness, friability and disintegration time.Tablets formulated employing βCD (TF_a) and βCD- Lutrol (TF_{ab}) gave rapid and higher dissolution of efavirenz, 5.85 and 4.41 fold increase in K_1 when compared to formulation TF_1 (plain).These tablets also fulfilled the official (IP 2010) dissolution rate specification of NLT 70 % in 30 min prescribed for efavirenz tablets.Complexation with βCD alone and in combination with Lutrol is recommended for formulation of efavirenz tablets with fast dissolution characteristics.

Keywords: Efavirenz, β Cyclodextrin, Lutrol , Solubility, Dissolution Rate, Formulation Development, 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. As such it needs enhancement in the dissolution rate and bioavailability in their formulation development to derive its maximum therapeutic efficacy. 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 system 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 tours-shaped molecules with a hydrophilic outer surface and a liphophillic central cavity which can accommodate a variety of liphophillic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and

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bioavailability can be favourably affected[2,3].Cyclodextrins have been receiving increasing application in formulation in recent years due to their approval by various regulatory agencies[4,5]. Lutrol 400 is a polyethyleneglycol of molecular weight 400.It is widely used as a solvent and solubilizing agent for active substances and excipients in liquid and semisolid praparations[6]. Though cyclodextrins and Lutrol have been investigated individually for enhancing the solubility and dissolution rate of the poorly soluble drugs, no reports are available on their combined use in enhancing the solubility, dissolution rate, and formulation development of poorly soluble drugs.

The objective of the present study is enhancement of solubility, dissolution rate of efavirenz employing βCD and Lutrol. The individual and combined effects of βCD and Lutrol in enhancing the solubility and dissolution rate of efavirenz were evaluated in a 2^2-factorial study. The feasibility of formulating the drug-β-CD-Lutrol solid inclusion complexes into tablets was also evaluated . The overall objective of the study is development of efavirenz tablets with fast dissolution characteristics employing β-CD and Lutrol

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. Lutrol 400, dichloromethane (Qualigens) , Primojel, lactose, potato starch , talc , magnesium stearate were procured from commercial sources. All other materials used were of pharmacopoeial grade

Methods:

Estimation of Efavirenz:

UV spectrophotometric method based on the measurement of absorbance at 245nm 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 - LutrolComplexes:

Solid inclusion complexes of efavirenz – βCD – Lutrol were prepared as per 2^2 – factorial study by kneading method. Efavirenz, βCD and Lutrol were triturated in a mortar with a small volume of solvent dichloromethane. The thick slurry formed was kneaded for 45 min and then dried at 55°C until dry. The dried mass was powdered and sieved through mesh No. 120.

Preparation of Efavirenz-βCD –Lutrol Tablets:

Compressed tablets each containing 50 mg of efavirenz were prepared as per 2^2 – factorial study by direct compression method employing efavirenz- βCD -Lutrolinclusion complexes as per the formulae given in Table 3. Efavirenz - βCD – Lutrol complexes were initially prepared in each case. The dried βCD complex and other ingredients as per the formula were blended in a closed polyethylene bag and were compressed into tablets on a 8 - station tablet punching machine (Karnavathi Rimek Minipress II) 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 Paramount tablet disintegration test machine using water as test fluid.

Dissolution rate study:

The dissolution rate of efavirenz from the solid inclusion complexes and their tablets formulated employing βCD and Lutrol was studiedusing (Labindia DS 8000) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. Water (900ml) was used as dissolution fluid in the case of solid inclusion complexes. In the case of tablets water containing 2% SLS (900ml) was used as dissolution fluid as prescribed in IP 2010. A temperature 37±1°C was maintained throughout the study. βCD complex equivalent to 50 mg of efavirenz or 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 four times each (n=4).

Analysis of results:

Dissolution data were subjected to analysis as per zero order and first order kinetics and the first order dissolution rates (K_1) were calculated. Dissolution efficiency (DE_{20}) values were calculated as suggested by Khan[7]. Dissolution data were also analyzed by Analysis of Variance (ANOVA) as per 2^2 factorial studies

RESULTS AND DISCUSSION

The objective of the study is to enhance the solubility and dissolution rate of efavirenz bycyclodextrin complexation along with Lutrol and to evaluate the individual main effects and combined (or interaction) effects of β cyclodextrin (βCD) and Lutrol on the solubility and dissolution rate of efavirenz in a 2^2factorial experiment

The individual main effects and combined (interaction) effects of βCD (Factor A) and Lutrol(Factor B) on the aqueous solubility of efavirenz were evaluated in a 2^2-factorial experiment. For this purpose, two levels of βCD (0, 5 mM), two levelsof Lutrol (0, 2 %) were selected and the corresponding four treatments involved in the 2^2-factorial study were purified water (1);water containing 5 mM βCD (a); water containing 2% Lutrol (b); and water containing 5 mM βCD and 2% Lutrol (ab);

The solubility of efavirenz in the above mentioned fluids was determined (n=4) and the results are given in Table.1. The solubility data were subjected to Analysis of variance (ANOVA) to find out the significance of main and combined effects of βCD and Lutrol on the solubility of efavirenz. The results of ANOVA indicated that the individual and combined effects of βCD and Lutrol in enhancing the solubility of efavirenz were highly significant ($P < 0.01$). βCD alone gave 1.93 fold increase in the solubility of efavirenz. There was no advantage of combining βCD with Lutrol for increasing the solubility. .

To evaluate the individual and combined effects of βCD and Lutrol on the dissolution rate of efavirenz, solid inclusion complexes of efavirenz - βCD were prepared with and without Lutrol as per 2^2-factorial design. For this purpose two levels of βCD (0 and 1:2 ratio of drug : βCD) and two levels of Lutrol (0 and 2%) were selected and the corresponding four treatments involved in the 2^2-factorial study were efavirenz pure drug (1); efavirenz - βCD (1:2) inclusion complex (a); efavirenz - Lutrol (2%) complex (b); efavirenz - βCD (1:2) - Lutrol (2%) complex (ab).

The CD complexes were prepared by kneading method. All the solid inclusion complexes of efavirenz - βCD - Lutrol prepared were found to be fine and free flowing powders. Low coefficient of variation (c.v.) values (< 1.2 %) in the percent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared.

The dissolution rate of efavirenz alone and from βCD complexes was studied in distilled water. The dissolution of efavirenz followed first order kinetics with r (correlation coefficient) above 0.905. Dissolution efficiency (DE20) values were calculated as suggested by Khan[7]. The dissolution parameters are given in Table.2. The dissolution of efavirenz was rapid and higher in the case of efavirenz - βCD complexes prepared when compared to efavirenz pure drug as such. The dissolution rate (K1) values were subjected to ANOVA to find out the significance of the main and combined effects of βCD and Lutrol on the dissolution rate of efavirenz. ANOVA indicated that the individual main effects of βCD and Lutrol and their combined effects in enhancing the dissolution rate (K1) and dissolution efficiency (DE20) were highly significant ($P < 0.01$). βCDalone gave a higher enhancement (4.7 fold) in the dissolution rate of (K_1) of efavirenz. Lutrol alone gave 3.5 fold increase in the dissolution rate of efavirenz. Combination of β-CD and Lutrol gave a 4.6 fold increase in the dissolution rate. There was no additional advantage of combining βCD and Lutrol in enhancing the dissolution rate of efavirenz. The dissolution efficiency (DE_{20}) of efavirenz was increased from 1.68% for pure drug to 7.83, 7.87 and 8.37 % respectively with βCD, Lutrol and βCD – Lutrol complexes.

The feasibility of formulating the solid inclusion complexes of efavirenz -βCD-Lutrol into compressed tablets was evaluated. Efavirenz (50 mg) tablets were formulated employing selected combinations of βCD (factor A) and Lutrol (factor B) as per 2^2 factorial design and tablets were evaluated. The physical parameters of the efavirenz tablets prepared are given in Table 4. The hardness of the tablets was in the range 3.5-4.0 kg/cm^2. Weight loss in the friability test was less than 0.67 % in all the cases. Efavirenz content of the tablets prepared was within 100±3 %. Tablet formulations TF_1 (plain) and TF_b (tablets containing Lutrol alone) disintegrated rapidly within 1 min-20 sec. Formulations TF_a and TFab which contain βCD and βCD – Lutrol respectively disintegrated slowly in 4-0 min and 4-20 min-sec respectively. As such all the efavirenz tablets formulated employing βCD and Lutrol fulfilled the official (IP 2010) standards with regard to hardness, friability, drug content and disintegration time of uncoated tablets.

The dissolution profiles of efavirenz tablets formulated are shown in Fig.1. All the dissolution parameters estimated (PD_{30} (percent dissolved in 30 min), T_{50}, DE_{20} and K_1) (Table 5) indicated rapid and higher dissolution of efavirenz from tablets formulated employing βCD – Lutrol complexes (TF_a, TF_b , TF_{ab}) when compared to tablets formulated with efavirenz alone (TF_1). Among all, tablets formulated, βCD (TF_a) and βCD- Lutrol (TF_{ab}) gave rapid and higher dissolution of efavirenz, 5.85 and 4.41 fold increase in K_1 when compared to formulation TF_1 (plain). Formulations TF_a and TF_{ab} gave respectively 76.06 % and 73.36 % dissolution in 30 min fulfilling the official (IP 2010) dissolution rate specification of NLT 70 % in 30 min. Hence efavirenz tablets with fast dissolution could be formulated employing βCD and βCD – Lutrol inclusion complexes.

CONCLUSIONS

1. βCD alone gave higher enhancement in the solubility of efavirenz, (1.93 fold) than Lutrol and combination of βCD- Lutrol.
2. βCD alone gave a higher enhancement (4.7 fold) in the dissolution rate of (K1) of efavirenz. There was no additional advantage of combining βCD and Lutrol in enhancing the dissolution rate of efavirenz.
3. The dissolution efficiency (DE_{20}) of efavirenz was increased from 1.68 % for pure drug to 7.83, 7.87, and 8.37 % respectively with βCD, Lutrol and βCD – Lutrol complexes.
4. Efavirenz -βCD – Lutrol inclusion complexes could be formulated into tablets by direct compression method and the resulting tablets fulfilled the official (IP 2010) specifications with regard to drug content, hardness, friability and disintegration time.
5. Tablets formulated employing βCD (TF_a) and βCD- Lutrol (TF_{ab}) gave rapid and higher dissolution of efavirenz, 5.85 and 4.41 fold increase in K_1 when compared to formulation TF_1 (plain).These tablets also fulfilled the official (IP 2010) dissolution rate specification of NLT 70 % in 30 min prescribed for efavirenz tablets.
6. Complexation with βCD alone and in combination with Lutrol is recommended for formulation of efavirenz tablets with fast dissolution characteristics.

Table 1: Solubility of Efavirenz in Various Fluids as per 2^2 Factorial Study (n = 4)

Fluid	Solubility (mg/100 mL) x ± sd	Increase in Solubility (No. of folds)
Purified water	1.76±0.184	--
Water containing βCD (5 mM)	3.41±0.184	1.93
Water containing Lutrol 400 (2 %)	1.33±0.114	0.75
Water containing βCD (5 mM) and Lutrol 400 (2 %)	1.11±0.684	0.63

Table 2: Dissolution Parameters of Efavirenz βCD –Lutrol 400 Complexes Prepared as per 2^2 Factorial Design

Formulation	PD_{10} (%)	DE_{20} (%)	Increase in DE_{20} (no. of folds)	K_1 X 10^3 (min^{-1})	Increase in K_1 (no. of folds)
F_1	1.88	1.68		1.50	
F_a	8.99	7.83	4.66	7.65	4.71
F_b	8.34	7.87	4.68	5.35	3.57
F_{ab}	8.29	8.37	4.98	6.91	4.60

Table 3: Formulae of Efavirenz Tablets Prepared Employing βCD-Lutrol 400 as per 2^2 Factorial Design

Ingredient (mg/tablet)	Formulation			
	TF_1	**TF_a**	**TF_b**	**TF_{ab}**
Efavirenz	50	50	50	50
β-cyclodextrin	-	100	-	100
Lutrol (400)	-	-	5	5
Primojel	12.5	12.5	12.5	12.5
Talc	5	5	5	5
Magnesium stearate	5	5	5	5
DCV(Lactose –starch granules)	177.5	77.5	172.5	72.5
Total weight (mg)	250	250	250	250

Table 4: Physical Parameters of Efavirenz Tablets Prepared Employing βCD-Lutrol 400 as per 2^2 Factorial Design

Formulation	Efavirenz content (mg/tablet)	Hardness (Kg/cm^2)	Friability (% Wt loss)	Disintegration Time (min-sec)
TF_1	49.6	3.5	0.67	1-15
TF_a	49.8	4.0	0.50	4-0
TF_b	50.2	3.0	0.65	1-20
TF_{ab}	50.5	3.5	0.52	4-20

Table 5: Dissolution Parameters of Efavirenz Tablets Prepared Employing βCD-Lutrol as per 2^2 Factorial Design

Formulation	Dissolution Parameter				0fficial Dissolution Rate Specification
	PD_{30} (%)	**T_{50} (min)**	**DE_{20} (%)**	**$K_1 X 10^2$ (min^{-1})**	
TF_1	26.82	> 60	14.85	1.40	NLT 70% in 30 min in water containing 2% SLS (IP 2010)
TF_a	76.06	7.5	52.49	8.15	
TF_b	20.62	> 60	10.32	0.92	
TF_{ab}	73.36	12.5	41.59	6.15	

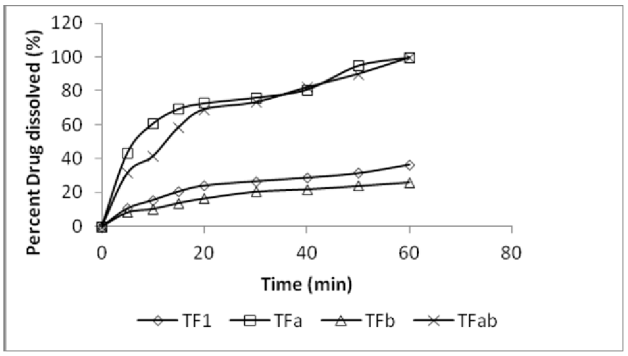

Fig 1: Dissolution Profiles of Efavirenz Tablets Prepared Employing βCD-Lutrol 400 as per 2^2 Factorial Design

REFERENCES

1. Chowdary, K.P.R.and Madhavi, B.L.R., Novel Drug Delivery Technologies for insoluble Drugs, **Indians Drug**, 42(9),557-562,2005.
2. D.Ducheneand D. Woussidjewe, in ed.:S.Dumitriu, **Polysaccharides in Medical Applications,** Marcel Dekker, New York, p. 575(1996).
3. D.O.Thompson, **Crit. Rev. Ther.Drug Carrier Syst**.14, 1(1997).
4. A.R.Hedges, Chem**.Rev**. 98, 2035(1998).
5. T.B.Patel, L.D.Patel, T,B.Patel, S.H.Makwana and T.R.Patel .**Int.J. Pharm., Pharmaceutical Sci**., 2, 138, (2010).
6. **Hand Book of Pharmaceutical Excipients;** Raymond C Rowe, Paul J Sheskey and Marian E Quinn, 6th edition, Pharmaceutical Press. P.517 (2009).
7. Khan, K.A., **Journal of Pharmacy and Pharmacology**. 27, 48-49, (1975).