ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

A Factorial Study on the Effects of β Cyclodextrin, PVP K30 and SLS on the Solubility and Dissolution Rate of Efavirenz

KPR Chowdary* and A Naresh

University college of Pharmaceutical Sciences, Andhra University,Visakhapatnam – 530 003 (A.P.) India

ABSTRACT

The objective of the study is to evaluate the individual main effects and combined (or interaction) effects of β cyclodextrin (βCD), poly vinyl pyrrolidone (PVP K30) and sodium lauryl sulphate (SLS) on the solubility and dissolution rate of efavirenz in a series of 2^3 factorial experiments. The solubility of efavirenz in eight selected fluids containing βCD, PVP K30 and SLS as per 2^3 factorial study was determined. The solubility of efavirenz was markedly enhanced by βCD (3.01 fold), PVP K30 (2.49 fold) and SLS (226.96 fold) individually. Combination of βCD with PVP K30 and SLS gave a markedly higher enhancement in the solubility of efavirenz than is possible with them individually. βCD in combination with PVP K30 and SLS gave respectively 4.07 and 401.89 fold increase in the solubility of efavirenz. Solid inclusion complexes of efavirenz - βCD were prepared with and without PVP K30 and SLS as per 2^3-factorial design by kneading method and were evaluated. ANOVA indicated that the individual main effects of βCD, PVP K30 and SLS and their combined effects in enhancing the solubility and dissolution rate (K_1)and dissolution efficiency (DE_{30}) were highly significant ($P < 0.01$).βCD alone gave a 16.02 fold increase in the dissolution rate of efavirenz. βCD in combination with PVP K30 and SLS gave respectively 18.09 and 21.67 fold increase in the dissolution rate of efavirenz. βCD in combination with both PVP K30 and SLS gave highest enhancement (35.27 fold) in the dissolution rate of efavirenz. Combination of βCD with PVP K30 and SLS has markedly enhanced the solubility as well as dissolution rate of efavirenz than is possible with them individually. Hence a combination of βCD with PVP K30 and / or SLS is recommended to enhance the solubility and dissolution rate of efavirenz, a BCS class II drug.

Keywords: Efavirenz, β Cyclodextrin, PVP K30, SLS, Solubility, Dissolution rate, Factorial Study

Corresponding author
E-mail: prof.kprchowdary@rediffmail.com

ISSN: 0975-8585

INTRODUCTION

Efavirenz, a widely prescribed HIV-1 specific, non nucleoside reverse transcriptase inhibitor (NNRTI) drug belong to Class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It is practically insoluble in water. 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, microemulsions and self-emulsifying micro and nanodisperse systems 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 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 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.

Though cyclodextrin complexation and use of PVP K30 and surfactant, SLS for enhancing the solubility and dissolution rate of poorly soluble drugs have been investigated individually, no reports are available on their combined use in enhancing the solubility and dissolution rate. In the present investigation the individual main effects and combined (or interaction) effect of βCD, PVP K30 and SLS on the solubility and dissolution rate of efavirenz, a BCS class II drug were evaluated in a series of 2^3 factorial experiments.

In factorial experiments the effects of several factors of variation are studied and investigated simultaneously, the treatments being all the combinations of different factors under study. In these experiments an attempt is made to estimate the effects of each of the factors and also the interaction (or combined) effects, i.e., the variation in the effect of one factor as a result to different levels of other factors.

MATERIALS AND METHODS

Efavirenz was a gift sample from M/s. Hetero Drugs Ltd., Hyderabad. β- Cyclodextrin was a gift sample from M/s. Cerestar Inc., USA. Methanol (Qualigens), poly vinyl pyrrolidone, K30 (PVP K30) and sodium lauryl sulphate (SLS) 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 a phosphate buffer of pH 7.4 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 1-10µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variation were found to be 0.8% and 1.2% respectively. No interference by the excipients used in the study was observed.

Solubility Determination

Excess drug (50mg) was added to 15ml of each fluid taken in a 25ml stopped conical flask and the mixtures were shaken for 24 h at room temperature (28±1^{o}C) on Rotary Flask Shaker. After 24 h of shaking, 2ml aliquots were withdrawn at 2 h interval and filtered immediately using a 0.45µ disk filter. The filtered samples were diluted suitably and assayed for efavirenz by measuring absorbance at 246 nm. Shaking was continued until two consecutive estimations are the same. The solubility experiments were replicated for four times each (n=4).

Preparation of Efavirenz-βCD complexes

Solid inclusion complexes of efavirenz - βCD in 1:2 ratio with and without PVP K30 (2%) and SLS (2%) as per 2^3 factorial design were prepared by kneading method. Efavirenz, βCD, 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.

Dissolution Rate Study

The dissolution rate of efavirenz as such and from βCD complexes prepared was studied in 1000 ml of phosphate buffer of pH 7.4 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. Efavirenz or Efavirenz-βCD complex equivalent to 50 mg of efavirenz was used in each test. Samples of dissolution media (5ml) were withdrawn through a filter (0.45µ) at different intervals of time, suitable diluted and assayed for efavirenz at 246 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 Data

Dissolution rate data were analysed as per zero order and first order kinetic models to assess the kinetics of dissolution of drug from the βCD complexes prepared. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[9]. Solubility and dissolution data were subjected to Analysis of Variance (ANOVA) to find out the significance of the main individual and combined effects of the factors involved.

ISSN: 0975-8585

RESULTS AND DISCUSSION

The individual main effects and combined (interaction) effects of βCD (Factor A), PVP K30 (Factor B) and SLS (Factor C) on the aqueous solubility of efavirenz were evaluated in a 2^3-factorial experiment. For this purpose, two levels of βCD (0, 5 mM), two levels of PVP K30 (0, 2%) and two levels of SLS (0, 2%) were selected in each case and the corresponding eight treatments involved in the 2^3-factorial study were purified water (1), water containing 5mM βCD (a); water containing 2% PVP K30 (b); water containing 5mM βCD and 2% PVP K30 (ab); water containing 2% SLS (c); water containing 5mM βCD and 2% SLS (ac); water containing 2% PVP K30 and 2% SLS (bc) and water containing 5mM βCD and 2% of each of PVP K30 and SLS (abc).

Table 1: Solubility of Efavirenz in Various Fluids as per 2^3 – Factorial Study

Fluids (Code as per 2^3 – Factorial Experiment)	Solubility (mg/ml) (n=4) (x±sd)	Increase in Solubility (Number of Folds)
Distilled water (1)	0.02 ± 0	-
Water containing 5 mM βCD (a)	0.05 ± 0.001	3.01
Water containing 2% PVP K30 (b)	0.04 ± 0	2.49
Water containing 5mM βCD and 2% PVP K30 (ab)	0.07 ± 0.002	4.07
Water containing 2% SLS (c)	3.90 ± 0.097	226.96
Water containing 5mM βCD and 2% SLS (ac)	6.91 ± 0.126	401.89
Water containing 2% PVP K30 and 2% SLS (bc)	5.03 ± 0.128	292.82
Water containing 5mM βCD, 2% PVP K30 and 2% SLS (abc)	8.47 ± 0.082	492.87

Table 2: ANOVA of Solubility Data of Efavirenz in Various Fluids Prepared as per 2^3 – Factorial Study

Source of variation	D.F	S.S	M.S.S	F-Ratio	Significance
Total	31	340.53	10.98		P<0.01
Treatments	7	340.39	48.63	8044.83	
a	1	21.18	21.18	3504.69	P<0.01
b	1	3.76	3.76	621.38	P<0.01
ab	1	0.09	0.09	14.91	P<0.01
c	1	291.35	291.35	48201.70	P<0.01
ac	1	20.39	20.39	3372.95	P<0.01
bc	1	3.52	3.52	582.19	P<0.01
abc	1	0.10	0.10	15.97	P<0.01
Error	24	0.15	0.01		

$F_{0.01\,(7,\,24)} = 3.50$; $F_{0.05\,(7,\,24)} = 2.43$; $F_{0.01\,(1,\,24)} = 7.82$; $F_{0.05\,(1,\,24)} = 4.26$

The solubility of efavirenz in the above mentioned eight fluids was determined (n=4) and the results are given in Table 1. The aqueous solubility of efavirenz was markedly enhanced by βCD alone and in combination with PVP K30 and SLS. The solubility data were subjected to Analysis of Variance (ANOVA) to find out the significance of main and combined effects of βCD, PVP K30 and SLS on the solubility of efavirenz. The results of ANOVA are shown in Table 2. The

ISSN: 0975-8585

individual and combined effects of βCD, PVP K30 and SLS in enhancing the solubility of efavirenz were highly significant ($P < 0.01$). Among the three factors, SLS (factor C) gave highest enhancement (226.96 fold) in the solubility of efavirenz. βCD alone gave a 3.01 fold increase in the solubility of efavirenz. Whereas βCD in combination with PVP and SLS respectively gave 4.07 and 401.89 fold increase in the solubility of efavirenz. βCD in combination with both PVP K30 and SLS gave highest enhancement (492.87 fold) in the solubility of efavirenz. Combination of βCD with PVP K30 and SLS has given a markedly higher enhancement in the solubility of efavirenz than is possible with them individually.

Table 3: Dissolution Parameters of Efavirenz- βCD Complex Systems Prepared as per 2^3 Factorial Study

EFA-βCD Complexes	Composition	$K_1 x 10^3$ (min^{-1})	Increase in K_1 (no.of folds)	DE_{30} (%)	Increase in DE_{30} (no.of folds)
F_1	EFA	0.23	--	1.04	--
F_a	EFA - βCD (1:2)	3.71	16.02	8.52	8.17
F_b	EFA - PVP K30 (2%)	2.44	10.52	4.52	4.34
F_{ab}	EFA - βCD (1:2) - PVP K30 (2%)	4.19	18.09	11.25	10.79
F_c	EFA - SLS (2%)	3.80	16.41	8.63	8.28
F_{ac}	EFA - βCD (1:2) - SLS (2%)	5.02	21.67	17.75	17.03
F_{bc}	EFA - PVP K30 (2%) - SLS (2%)	4.67	20.15	12.36	11.86
F_{abc}	EFA - βCD (1:2) - PVP K30 (2%) - SLS (2%)	8.18	35.27	21.30	20.43

EFA - Efavirenz; βCD – β Cyclodextrin; PVP K30 - Poly vinyl pyrrolidone K30; SLS – Sodium lauryl sulphate

To evaluate the individual and combined effects of βCD, PVP K30 and SLS on the dissolution rate of efavirenz, solid inclusion complexes of efavirenz - βCD were prepared with and without PVP K30 and SLS 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 PVP K30 and SLS (0 and 2%) were selected and the corresponding eight treatments involved in the 2^3-factorial study were efavirenz pure drug (1); efavirenz - βCD (1:2) inclusion binary complex (a); efavirenz - PVP K30 (2%) binary complex (b); efavirenz - βCD (1:2) – PVP K30 (2%) ternary complex (ab); efavirenz – SLS (2%) binary complex (c); efavirenz - βCD (1:2) – SLS (2%) ternary complex (ac); efavirenz - PVP K30 (2%) – SLS (2%) ternary complex (bc) and efavirenz - βCD (1: 2) – PVP K30 (2%) SLS (2%) complex (abc).

The βCD complexes were prepared by kneading method. All the solid inclusion complexes of efavirenz -βCD - 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 dissolution rate of efavirenz alone and from βCD complexes was studied in phosphate buffer of pH 7.4. The dissolution of efavirenz followed first order kinetics with r (correlation coefficient) above 0.91. The dissolution parameters are summarized in Table 3. The dissolution of efavirenz was rapid and higher in the case of all efavirenz – βCD binary and ternary complex systems prepared when compared to efavirenz pure drug as such.

ISSN: 0975-8585

Table 4: ANOVA of K_1 Values of Efavirenz - βCD – PVP K30 – SLS Complexes Prepared as per 2^3 – Factorial Study

Source of Variation	D.F	S.S	M.S.S	F-Ratio	Significance
Total Treatments	23 7	0.0001 0.0001	0.00000 0.00002	1397.39	P<0.01
a	1	0.00004	0.00004	3396.56	P<0.01
b	1	0.00002	0.00002	1538.18	P<0.01
ab	1	0	0	10.75	P<0.01
c	1	0.00005	0.00005	4215.62	P<0.01
ac	1	0	0	8.99	P<0.01
bc	1	0	0	60.63	P<0.01
abc	1	0.00001	0.00001	551.01	P<0.01
Error	16	0	0		

$F_{7,16}(0.01) = 4.03$; $F_{7,16}(0.05) = 2.66$; $F_{1,16}(0.01) = 8.53$; $F_{1,16}(0.05) = 4.49$

Table 5: ANOVA of DE_{30} values of Efavirenz - βCD – PVP K30 – SLS Complexes Prepared as per 2^3 – Factorial Study

Source of Variation	D.F	S.S	M.S.S	F-Ratio	Significance
Total Treatments	23 7	916.82 916.64	39.86 130.95	11849.64	P<0.01
a	1	390.25	390.25	35313.82	P<0.01
b	1	68.19	68.19	6170.28	P<0.01
ab	1	0.33	0.33	29.73	P<0.01
c	1	451.79	451.79	40882.54	P<0.01
ac	1	5.54	5.54	501.64	P<0.01
bc	1	0.43	0.43	38.57	P<0.01
abc	1	0.12	0.12	10.93	P<0.01
Error	16	0.18	0.01		

$F_{7,16}(0.01) = 4.03$; $F_{7,16}(0.05) = 2.66$; $F_{1,16}(0.01) = 8.53$; $F_{1,16}(0.05) = 4.49$

The dissolution parameters (K_1 and DE_{30}) were subjected to ANOVA to find out the significance of the main and combined effects of βCD, PVP K30 and SLS on the dissolution rate of efavirenz. The results of ANOVA are shown in Tables 4 and 5. ANOVA indicated that the individual main effects of βCD, PVP K30 and SLS and their combined effects in enhancing the dissolution rate (K_1) and DE_{30} were highly significant ($P < 0.01$). βCD, PVP K30 and SLS alone gave respectively 16.02, 10.52 and 16.41 fold increase in the dissolution rate of efavirenz. βCD in combination with PVP K30 and SLS gave respectively 18.09 and 21.67 fold increase in the dissolution rate of efavirenz. βCD in combination with both PVP K30 and SLS gave highest enhancement (35.27 fold) in the dissolution rate of efavirenz.

Thus the results of the study indicated that combination of βCD with PVP K30 and SLS has markedly enhanced the solubility as well as dissolution rate of efavirenz than is possible with them individually. Hence a combination of βCD with PVP K30 and / or SLS is recommended to enhance the solubility and dissolution rate of efavirenz, a BCS class II drug.

ISSN: 0975-8585

CONCLUSION

The solubility of efavirenz was markedly enhanced by βCD (3.01 fold), PVP K30 (2.49 fold) and SLS (226.96 fold) individually. Combination of βCD with PVP K30 and SLS gave a markedly higher enhancement in the solubility of efavirenz than is possible with them individually. βCD in combination with PVP K30 and SLS gave respectively 4.07 and 401.89 fold increase in the solubility of efavirenz. ANOVA indicated that the individual main effects of βCD, PVP K30 and SLS and their combined effects in enhancing the solubility and dissolution rate (K_1)and dissolution efficiency (DE_{30}) were highly significant ($P < 0.01$). βCD alone gave a 16.02 fold increase in the dissolution rate of efavirenz. βCD in combination with PVP K30 and SLS gave respectively 18.09 and 21.67 fold increase in the dissolution rate of efavirenz. βCD in combination with both PVP K30 and SLS gave highest enhancement (35.27 fold) in the dissolution rate of efavirenz. Combination of βCD with PVP K30 and SLS has markedly enhanced the solubility as well as dissolution rate of efavirenz than is possible with them individually. Hence a combination of βCD with PVP K30 and / or SLS is recommended to enhance the solubility and dissolution rate of efavirenz, a BCS class II drug.

REFERENCES

[1] Chowdary KPR, Madhavi BLR. Indian Drugs 2005; 42(9): 557-562.
[2] Fromming KH, Szejtli J. Cyclodextrins in Pharmacy. Kluwer Academic Publications, Dordrecghi, 1994; p 20.
[3] Duchene D, Woussidjewe D, Dumitriu S. Polysaccharides in Medical Applications. Marcel Dekker, New York, 1996; 575- 602.
[4] Thompson DO. Crit Rev Ther Drug Carrier Syst 1997; 14 (1): 1-104.
[5] Hedges AR. Chem Rev 1998; 98: 2035-2044.
[6] Giri TK, Hemant B, Amit A, Tripathi DK. Int J Applied Biology and Pharmaceutical Tech 2010; 1 (2): 793-800.
[7] Aejaz A, Jafar M, Dehghan MHG, Adil Shareef S. International Journal of Pharmacy and Pharmaceutical Sciences 2010; 2 (1): 182-190.
[8] Dehghan MHG, Saifee M, Hanwate RM. J Pharm Sci Tech 2010; 2 (9), 2010, 293-297.
[9] Khan KA. J Pharm Pharmacol 1975; 27: 48- 49.