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Research Article

EFFECT OF PVP ON CYCLODEXTRIN COMPLEXATION OF EFAVIRENZ FOR ENHANCING ITS SOLUBILITY AND DISSOLUTION RATE

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ABSTRACT

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. The objective of the present investigation is to study the complexation of efavirenz with two cyclodextrins, β-cyclodextrin (βCD) and hydroxypropyl β-cyclodextrin (HPβCD) alone and in the presence of polyvinyl pyrrolidone (PVP) by phase solubility study and to evaluate the feasibility of enhancing the solubility and dissolution rate of efavirenz employing the two cyclodextrins alone and with PVP. Solid inclusion complexes of efavirenz-βCD and efavirenz -HPβCD in 1:1 and 1:2 ratios were prepared with and without PVP K30 by three methods namely (i) physical mixing, (ii) kneading and (iii) co-precipitation and were evaluated.

The aqueous solubility of efavirenz was linearly increased as a function of the concentration of βCD and HPβCD alone and in the presence of PVP K30. The increase in solubility is due to the formation of a 1:1 M complex in solution in each case. The complexes formed between efavirenz-CD were quite stable. Addition of PVP has markedly enhanced the complexation and solubilizing efficiencies of βCD and HPβCD. The CD complexes of efavirenz prepared employing βCD and HPβCD alone and with PVP exhibited marked enhancement in the dissolution rate and dissolution efficacy of efavirenz. HPβCD gave higher enhancement in the dissolution rate and efficiency when compared to βCD. Complexes prepared by kneading method gave higher dissolution rate and DE_{30} values than those prepared by co-precipitation and physical mixing methods. The solid inclusion complexes of βCD and HPβCD with PVP gave higher rates of dissolution than those of efavirenz and its complexes with CDs alone. Efavirenz- βCD (1:2) kneaded complex gave a 10.42 fold increase in the dissolution rate of efavirenz, whereas in the presence of PVP K30, it gave a 26.28 fold increase. Efavirenz-HPβCD (1:2) kneaded complex gave a 24.41 fold increase in the dissolution rate of efavirenz, whereas in the presence of PVP K30, it gave a 46.64 fold increase. Hence a combination of CDs (βCD, HPβCD) with PVP K30 is recommended to enhance the solubility and dissolution rate of efavirenz, a BCS class II drug.

Keywords: Efavirenz, Cyclodextrin complexation, PVP, Solubility, Dissolution rate.

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. The objective of the present investigation is to study the complexation of efavirenz with two cyclodextrins, β-cyclodextrin (βCD) and hydroxypropyl β-cyclodextrin (HPβCD) alone and in the presence of polyvinyl pyrrolidone (PVP) by phase solubility study and to evaluate the feasibility of enhancing the solubility and dissolution rate of efavirenz employing the two cyclodextrins alone and with PVP.

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.), dichloromethane (Qualigens), methanol (Qualigens) were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

METHODS

Phase Solubility Studies

Solubility studies were performed according to the method reported by Higuchi and Connors[8]. Excess drug (efavirenz) (25 mg) was added to 15 ml of double distilled water (pH 6.8) containing various concentrations of βCD or HPβCD (3-15 mM) taken in a series of 50 ml stoppered conical flasks and the mixtures were shaken for 72 hr at room temperature (28^{o}C) on a rotary flask shaker. After 72 hr of shaking to achieve equilibrium, 2 ml aliquots were withdrawn at 1 h interval and filtered immediately using 0.45 μ nylon disc filters. The filtered samples were diluted suitably and assayed for efavirenz at 245 nm against blanks prepared in the same concentration of CDs in water so as to cancel any absorbance that may be exhibited by the cyclodextrin molecules. Shaking was continued until three consecutive estimations were the same. Phase solubility studies were conducted with and without the addition of PVP K30 in each case. In the series with PVP K30, the polymer was added at a concentration of 0.5% w/v to the solution containing CDs. The solubility experiments were conducted in triplicate (n = 3).

Preparation of Solid Inclusion Complexes:

In each case solid inclusion complexes of drug and cyclodextrins were prepared in 1:1 and 1:2 ratio by three methods namely, kneading, co-precipitation and physical mixing with and without the addition of PVP K30. In the series with PVP K30, the polymer was added at a concentration of 10 % w/w of the solid complex.

Kneading Method

Drug (efavirenz), cyclodextrin and PVP K30 were triturated in a mortar with a small volume of a solvent blend of water: methanol: dichloromethane (4:6:1). The thick slurry formed was kneaded for 45 min and then dried at 55 ºC until dry. The dried mass was powdered and sieved through mesh No. 120.

Co-precipitation Method

Methanolic solution of drug (efavirenz) was added to an aqueous solution of cyclodextrin and PVP K30. The resulting mixture was stirred for 45 min and the contents were dried at 55 ºC until dry. The dried mass was powdered and sieved through mesh No. 120.

Physical Mixing

The physical mixtures of respective ratios were prepared by mixing powders of drug, cyclodextrin and PVP K30 in a dry mortar and the powder was sieved through mesh No. 120.

Content of Active Ingredient

From each batch of CD complexes prepared, four samples of 50 mg each were taken into 100 ml volumetric flask. Methanol was added and mixed to dissolve the drug and the solution was made up to 100 ml with methanol. The solution was then suitably diluted with water containing 2% SLS and assayed for efavirenz content at 245 nm.

Dissolution Rate Study

Dissolution rate of efavirenz and its CD complexes 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. Efavirenz or its CD complexes equivalent to 50 mg of efavirenz were used in each test. 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 dissolved. All dissolution rate experiments were conducted in triplicate (n=3).

RESULTS AND DISCUSSION

The complexation of efavirenz with βCD and HPβCD alone and in the presence of PVP K30 was investigated by phase solubility studies. The phase solubility diagrams for the complex formation between efavirenz - βCD and efavirenz - HPβCD in the presence and absence of PVP K30 are shown in Figs.1 and 2.

Presence and Absence of PVP

The aqueous solubility of efavirenz was increased linearly as a function of the concentration of CD with both βCD and HPβCD. The phase solubility diagrams of efavirenz-βCD and efavirenz-HPβCD complexes can be classified as type A_L according to Higuchi and Connors[8]. Because the straight line had a slope <1 in each case, the increase in solubility was due to the formation of a 1:1 M complex in solution with βCD and HPβCD both in the presence and absence of PVP. The apparent stability constant (K_c) in each case was calculated from the slope of the corresponding linear plot of the phase solubility diagram according to the equation, K_c = Slope/S_o (1-Slope), where S_o is the solubility of the drug in the absence of solubilizers. The estimated K_c values of various complexes are given in Table 1.

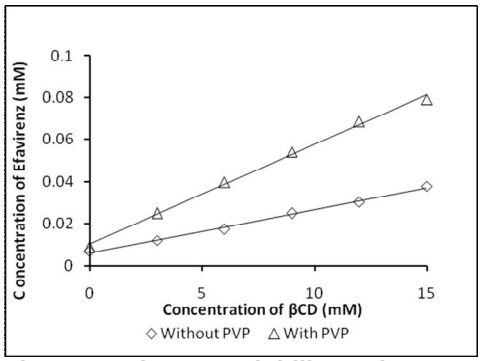

Fig. 1: Phase Solubility Diagrams of Efavirenz - βCD in the Presence and Absence of PVP

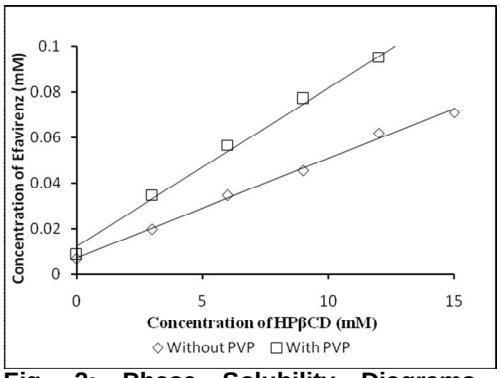

Fig. 2: Phase Solubility Diagrams of Efavirenz - HPβCD in the

Table 1: Apparent Stability Constants of Various Efavirenz - CD complex systems with and without PVP

S. No	System	Kc (M^{-1})	Complexation Efficiency* (No of folds of increase in Kc)
1	Efv – Bcd	303.3	-----
2	Efv - βCD- PVP	706.4	2.33
3	Efv – HPβCD	640.3	------
4	Efv - HPβCD- PVP	1024.9	1.60

* Ratio between Kc of βCD or HPβCD with and without PVP.

The values of K_c indicated that all the complexes formed between efavirenz and CDs are quite stable. The values of stability constant (K_c) were found to be higher in the presence of PVP K30 indicating higher complexation efficiency in the presence of PVP K30. A 2.33 and 1.60 fold increase in the K_c value was observed respectively with βCD and HPβCD in the presence of PVP K30.

Table 2: Effect of CDs and CD –PVP on the Solubility of Efavirenz and their Solubilizing Efficiencies

S.No	System	Solubility of Efavirenz (mM) in		Solubilizing Efficiency*
		Water	CD(15mM) solution	
1	Efavirenz	0.0068	---	---
2	Efv- βCD	---	0.0378	5.56
3	Efv- βCD- PVP	---	0.0791	11.63
4	Efv- HPβCD	---	0.0711	10.45
5	Efv- HPβCD- PVP	---	0.1139	16.75

* Ratio between drug solubility in aqueous solution (15 mM) of CD (with and without PVP) and in water.

To evaluate the effect of PVP K30 on the solubilizing efficiency of βCD and HPβCD, the solubilizing efficiency was calculated in each case as the ratio between drug solubility in aqueous solution (15mM) of βCD and HPβCD (with and without PVP) and in water. The solubilizing efficiency values are given in Table 2. βCD alone gave a 5.56 fold increase in the solubility of efavirenz, where as in the presence of PVP K30 it gave a 11.67 fold increase . HP βCD alone gave a 10.45 fold increase in the solubility of efavirenz, whereas in the presence of PVP K30 it gave a 16.75 fold increase. Thus the addition of PVP K30 has markedly enhanced the solubilizing efficiency of both βCD and HPβCD. HPβCD exhibited higher solubilizing efficiency when compared to βCD, both alone and in the presence of PVP K30.

Solid inclusion complexes of efavirenz-βCD and efavirenz -HPβCD in 1:1 and 1:2 ratios were prepared with and without PVP K30 by three methods namely (i) physical mixing, (ii) kneading and (iii) co-precipitation. All the complexes prepared were found to be fine and free flowing powders. There was no significant loss of drug during the preparation of solid inclusion complexes in all methods. Low c.v values (< 1.5%) in the percent drug content ensured uniformity of drug content in each batch.

The dissolution rate of efavirenz from CD complex systems prepared was studied in water containing 2% SLS as prescribed in IP 2010. The dissolution of efavirenz was rapid and higher from all the cyclodextrin inclusion complexes prepared when compared to efavirenz pure drug. The dissolution data were analyzed as per zero order and first order kinetics. The dissolution data obeyed first order kinetic model in all the cases with correlation-coefficient (r) values greater than 0.9104. The first order dissolution rates (K_1) were calculated from the slopes of the corresponding linear plots. Dissolution efficiency (DE_{30}) values were calculated as per Khan[9]. T_{50} (time taken for 50% dissolution) values were recorded from the dissolution profiles. The dissolution parameters are summarized in Tables 3 and 4.

Table 3: Dissolution Parameters of Efavirenz - βCD-PVP Complex Systems

S.No	Complex System	Method of Preparation								
		Physical Mixing			Co-precipitation			Kneading		
		T_{50} (min)	DE_{30} (%)	K_1 (min^{-1})	T_{50} (min)	DE_{30} (%)	K_1 (min^{-1})	T_{50} (min)	DE_{30} (%)	K_1 (min^{-1})
1	Efavirenz	> 60	19.94	0.0078	-	-	-	-	-	-
2	Efv-βCD-(1:1)	> 60	24.70	0.0101	22	41.1	0.037	7.5	55.5	0.0527
3	Efv-βCD-(1:2)	49	26.90	0.0011	8.0	57.1	0.047	3.5	72.3	0.0813
4	Efv-PVP(9:1)	> 60	22.29	0.0085	> 60	24.51	0.0089	47.5	28.1	0.0124
5	Efv-βCD-PVP(1:1:0.2)	53	30.16	0.0106	8.0	58.1	0.060	4.5	68.8	0.0650
6	Efv-βCD-PVP(1:2:0.3)	40	33.14	0.0115	3.5	69.4	0.065	2.0	84.0	0.2050

All CD complexes exhibited higher rates of dissolution and dissolution efficiency values than efavirenz indicating rapid and higher dissolution of efavirenz from its CD complexes. The K_1 and DE_{30} values were increased as the proportion of CD in the complex systems was increased in each case. The increase in K_1 (no. of folds) with various CD system is shown in Table 5.

Table 4: Dissolution Parameters of Efavirenz - HPβCD-PVP Complex Systems

S.No	Complex System	Method of Preparation								
		Physical Mixing			Co-precipitation			Kneading		
		T_{50} (min)	DE_{30} (%)	K_1 (min^{-1})	T_{50} (min)	DE_{30} (%)	K_1 (min^{-1})	T_{50} (min)	DE_{30} (%)	K_1 (min^{-1})
1	Efavirenz	> 60	19.94	0.0078	-	-	-	-	-	-
2	Efv-HPβCD-(1:1)	57.5	29.30	0.0103	6.0	60.46	0.052	4.0	75.02	0.0953
3	Efv-HPβCD-(1:2)	45	31.87	0.0108	3.5	71.93	0.0803	2.5	83.4	0.1904
4	Efv-PVP(9:1))	>60	22.20	0.0087	>60	24.55	0.0089	47.5	28.10	0.0124
5	Efv-HPβCD-PVP(1:1:0.2)	45	34.36	0.0117	4.0	71.82	0.1089	2.5	82.6	0.1766
6	Efv-HPβCD-PVP(1:2:0.3)	35	36.55	0.0126	2.0	81.49	0.1291	2.0	88.97	0.3638

Table 5: Enhancement of Dissolution Rate of Efavirenz by Various CD Complex Systems

S.No	Complex System	Method of Preparation		
		Increase in K_1 (No of Folds)*		
		Physical Mixing	Co-precipitation	Kneading
1	Efv-βCD(1:1)	1.29	4.74	6.75
2	Efv-βCD(1:2)	1.40	6.02	10.42
3	Efv-PVP(9:1)	1.10	1.14	1.60
4	Efv- βCD -PVP(1:1:0.2)	1.36	7.69	8.33
5	Efv- βCD -PVP(1:2:0.3)	1.47	8.33	26.28
6	Efv-HPβCD(1:1)	1.32	6.66	12.20
7	Efv-HPβCD(1:2)	1.39	10.29	24.41
8	Efv- HPβCD-PVP(1:1:0.2)	1.51	13.96	22.64
9	Efv- HPβCD -PVP(1:2:0.3)	1.62	16.55	46.64

* Ratio of K_1 of CD complex systems and uncomplexed drug.

HPβCD gave higher enhancement in the dissolution rate and efficiency when compared to βCD. Complexes prepared by kneading method gave higher dissolution rate and DE_{30} values than those prepared by co-precipitation and physical mixing methods. The higher dissolution rates and DE_{30} values observed with kneaded complexes may be due to the better drug-CD inclusion during the kneading process. The PVP alone gave a marginal increase (1.60 fold) in the dissolution rate of efavirenz. Efavirenz – βCD (1:2) kneaded complex gave a 10.42 fold increase in the dissolution rate of efavirenz, whereas in the presence of PVP K30, it gave a 26.28 fold increase. Efavirenz – HPβCD (1:2) kneaded complex gave a 24.41 fold increase in the dissolution rate of efavirenz, whereas in the presence of PVP K30, it gave a 46.64 fold increase. The higher dissolution rate observed with efavirenz-CD systems containing PVP K30 is due to the enhancement of complexation and solubilization efficiencies of cyclodextrins by the added PVP K30, an hydrophilic polymer and also due to the stronger drug amorphization and better inclusion due to the combined action of CD and the hydrophilic polymer, PVP K30. Because of the enhancement in cyclodextrin complexation, solubilization efficiency of CDs and also dissolution rate by the presence of PVP K30, a low amount of CD can be used to get the desired dissolution rate and efficiency.

CONCLUSION

The aqueous solubility of efavirenz was linearly increased as a function of the concentration of βCD and HPβCD alone and in the presence of PVP K30. The increase in solubility is due to the formation of a 1:1 M complex in solution in each case. The complexes formed between efavirenz– CD were quite stable. Addition of PVP has markedly enhanced the complexation and solubilizing efficiencies of βCD and HPβCD.

The CD complexes of efavirenz prepared employing βCD and HPβCD alone and with PVP exhibited marked enhancement in the dissolution rate and dissolution efficacy of efavirenz. HPβCD gave higher enhancement in the dissolution rate and efficiency when compared to βCD. Complexes prepared by

kneading method gave higher dissolution rate and DE_{30} values than those prepared by co-precipitation and physical mixing methods. The solid inclusion complexes of βCD and HPβCD with PVP gave higher rates of dissolution than those of efavirenz and its complexes with CDs alone. Efavirenz – βCD (1:2) kneaded complex gave a 10.42 fold increase in the dissolution rate of efavirenz, whereas in the presence of PVP K30, it gave a 26.28 fold increase. Efavirenz – HPβCD (1:2) kneaded complex gave a 24.41 fold increase in the dissolution rate of efavirenz, whereas in the presence of PVP K30, it gave a 46.64 fold increase. Hence a combination of CDs (βCD , HPβCD) with PVP K30 is recommended to enhance the solubility and dissolution rate of efavirenz, a BCS class II drug.

REFERENCES

1. Chowdary KPR and. Madhavi BLR. Indian Drugs. 2005;42(9):557.
2. Holvet C, Heyden YV and Plaizer – Vercanmmen, J Pharmazine. 005;60(8):598.
3. Veda H, Ou D, Endo T, Narge H, Tomono K and Nagari T. Drug Dev. Ind Pharm. 1998;24(9):863.
4. Thomson Do. Crit Rev Ther. Drug Carries Syst. 1997;1:14.
5. Hedges AR. Chem Rev. 1998;98: 2035.
6. Koester LS, mayorga P and Bassani VL. Drug Dev Ind Pharm. 2003;29(2): 139.
7. Mura P, Faucci MT and Bettinetti GP. Eur J Pharma Sci. 2001;13:187.
8. Higuchi, T. and Connors, K.A., Adv. Anal. Chem. Instr., 4. 117, 1965.
9. Khan, K.A., J.Pharm. Pharmacol., 27,48,1975.