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(Research Article)

Effect of Polyvinylpyrrolidone on Complexation and Dissolution Rate of Beta Cyclodextrin and Hydroxypropyl Beta Cyclodextrin Complexes of Piroxicam

Otra Kumar[1], A. Prameela Rani[2]

[1]*Drugs Control Administration, Eluru, West Godavari District, India*
[2]*University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur, India.*

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ABSTRACT

Complexation of Piroxicam with β-Cyclodextrin and hydroxypropyl-β-Cyclodextrin in the presence and absence of polyvinylpyrrolidone and the effect of polyvinylpyrrrolidone on the solubilizing efficiency of Cyclodextrins and on the dissolution rate of Piroxicam from the Cyclodextrin complexes were investigated. The phase solubility studies indicated the formation of Piroxicam-β-Cyclodextrin and Piroxicam-hydroxypropyl-β-Cyclodextrin inclusion complexes at a 1:1 M ratio in solution, both in the presence and absence of polyvinylpyrrolidone. The complexes formed were quite stable. The solubility and dissolution rate of Piroxicam were markedly enhanced by complexation with β-Cyclodextrin and hydroxypropyl- β-Cyclodextrin. Piroxicam-hydroxypropyl-β-Cyclodextrin(1:2) inclusion complex gave a 36.52-fold increase in the dissolution rate of Piroxicam. Addition of polyvinylpyrrolidone resulted in higher complexation efficiency and markedly enhanced solubilizing efficiency of β-Cyclodextrin and hydroxypropyl-β-Cyclodextrin. Solid inclusion complexes of Cyclodextrins with polyvinylpyrrolidone gave several times higher rates of dissolution than those of Piroxicam and its complexes with Cyclodextrins alone.

Key Words: Piroxicam, Cyclodextrin, Dissolution, Polyvinylpyrrolidone,Complexation.

INTRODUCTION

Cyclodextrins(CD) are cyclic torus-shaped molecules with a hydrophilic outer surface and a liphophilic central cavity, which can accommodate a variety of liphophilic drugs. As a consequence of the inclusion process, many physicochemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably modulated[1-3]. Cyclodextrins have been receiving increasing application in pharmaceutical formulations in recent years due to their approval by various regulatory agencies[4,5]. However, the use of Cyclodextrins in solid oral dosage forms is limited to low dose drugs with large stability constants due to the mass limitations of oral dosage units[3]. Therefore, in case where the low complexation efficiency would require a large amount of CD than that acceptable for solid or liquid dosage forms, the enhancement of the complexation capacity of the chosen CD is of practical importance. On this subject, earlier papers are reported[2,6,7] the positive effect of the addition of small amounts of a suitable water-soluble polymer to a drug-CD system in improving both the complexing and solubilizing efficiencies of the CDs. Piroxicam is the most widely prescribed COX-2 inhibitor. The poor aqueous solubility and wettability of Piroxicam give rise to difficulties in the design of pharmaceutical formulations and lead to variable oral bioavailability. We have been working on the enhancement of solubility, dissolution rate and bioavailability of Piroxicam through complexation with Cyclodextrins[8]. In the present work, the effect of polyvinylpyrrolidone (PVP) on the complexation of Piroxicam with β- and hydroxypropyl-β-Cyclodextrins(HPβCD) was investigated. The effect of PVP on the solubilizing efficiency of Cyclodextrins and dissolution of Piroxicam from the CD complexes was also investigated.

MATERIALS AND METHODS

Piroxicam was a gift sample from M/s. Dr.Reddy's Laboratories, Hyderabad. β-CD and HPβCD were gift samples from M/s.Cerestar Inc.,USA. PVP(K40),Dichloromethane (Qualigens), Methanol (Qualigens) and Sodium lauryl sulphate (Qualigens) were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Phase Solubility Studies

Solubility studies were performed according to the method reported by Higuchi and Connors[9]. Excess drug (25mg) was added to 15ml of double distilled water (pH 6.8) containing various concentrations of βCD or HPβCD (3-15mM) in a series of 50ml of stoppered conical flasks, and the mixtures were shaken for 72h at room temperature (28^{o}C) on a rotary flask shaker. After equilibration, 2ml of aliquots were withdrawn at 1h intervals and filtered immediately using 0.45µ nylon disc filter. The filtered samples were diluted suitably and assayed for Piroxicam at 254nm against blanks prepared in the same concentration of βCD or HPβCD 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 in each case with and without addition of PVP. PVP was added at a concentration of 0.5% w/v to the solution containing CDs. The solubility experiments were conducted in triplicate.

Preparation of Solid Complexes

Solid inclusion complexes of Piroxicam-βCD and Piroxicam-HPβCD were prepared in 1:1 and 1:2 ratios by kneading method with and with out the addition of PVP. PVP was added at a concentration of 10% w/w of the solid complex. Piroxicam, CD and PVP 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 45min and then dried at 55^{o}C. The dried mass was powdered and sieved through mesh No. 120. Piroxicam-PVP (9:1) solid complex was also prepared to study the effect of PVP on the solubility and dissolution rate of Piroxicam.

Estimation of Piroxicam

A UV spectrophotometric method based on the measurement of absorbance at 254 nm in water containing 1% sodium lauryl sulphate (SLS) was developed and used for the estimation of Piroxicam. The method obeyed Beer's law in the concentration range of 2-10 ug/ml. when a standard drug solution was assayed repeatedly (n=6), the relative error (accuracy) and relative standard deviation (precision) were found to be 0.8% and 1.2% respectively.

Dissolution Rate Study

The dissolution rate of pure Piroxicam and the Piroxicam from all CD inclusion complexes prepared was studied using DISSO 2000, Lab India 8-station dissolution rate test apparatus with a paddle stirrer. The dissolution rate was studied in 900ml of water containing 1% SLS. Piroxicam (50mg) or its inclusion complex equivalent to 50mg of Piroxicam, a speed of 50 rpm and a temperature of 37^{o}C were used in each test. Samples of dissolution medium (5ml) were withdrawn through a filter (0.45µ) at different time intervals, suitably diluted and assayed for Piroxicam by measuring absorbance at 254 nm. The volume withdrawn at each time was replaced with dissolution medium (5ml). The dissolution experiments were conducted in triplicate.

RESULTS AND DISCUSSION

The complexation of Piroxicam with β-CD and HP-β-CD was investigated by phase solubility studies. The phase solubility diagrams for the complex formation between Piroxicam and CDs in the presence and absence of PVP are shown in fig.1. The aqueous solubility of Piroxicam was found to increase linearly as a function of the concentration of CD. The phase solubility diagrams of Piroxicam-CD complexes can be classified as type A_L according to Higuchi and Connors[9]. Because the straight line had a slope<1 in each case, the increase in solubility was due to the formation of 1:1 M complex in solution with both β-CD and HP-β-CD in the presence of absence of PVP. The apparent stability constant (K_C) was calculated from the slope of the linear plot of the phase solubility diagram according to the equation:

$$K_C = \text{Slope}/S_o\,(1\text{-Slope})$$

where S_o is the solubility of the drug in the absence of CD. The estimated K_c values of various complexes are given in Table 1. The values of K_c indicated that the complexes formed between Piroxicam and CDs are quite stable.

To evaluate the effect of PVP, the solubilizing efficiency of CDs in the presence and absence of PVP was calculated as a ratio between drug solubility in aqueous solution of CD (15mM), with and without PVP, and drug solubility in water. The solubilising efficiency values are given in Table 1. β-CD alone gave a 5.76 fold increase in the solubility of Piroxicam, where as in the presence of PVP, it gave an 11.03-fold increase. Similarly HP-β-CD gave a 15.23 and 11.04-fold increase in the solubility of Piroxicam respectively in the presence

and absence of PVP. Thus, the addition of PVP markedly enhanced the solubilizing efficiency of β-CD and HP-β-CD. Among the two CDs, HP-β-CD exhibited higher solubilizing efficiency both in the absence and presence of PVP. The values of stability constant (K_c) were found to be higher in the presence of PVP, with both β-CD and HP-β-CD indicating higher complexation efficiency. A 2.57- and 1.31- fold increase in the K_c value was observed respectively with β-CD and HP-β-CD in the presence of PVP.

Solid inclusion complexes of Piroxicam-β-CD and Piroxicam-HP-β-CD in 1:1 and 1:1 ratios were prepared with and without PVP by kneading method. All the solid complexes prepared were found to be fine and free flowing powders were found to be fine and free flowing powders. Low C.V. (<1.0%) values in percent drug content indicated uniformity of drug content in each batch of solid inclusion complex prepared. The dissolution rate of pure Piroxicam and Piroxicam from various solid inclusion complexes including Piroxicam-PVP (9:1) system was studied in water containing 1% SLS. SLS was included in the dissolution medium to maintain sink condition. The dissolution profiles of various complexes are shown in fig.2. The dissolution of Piroxicam from all the solid inclusion complexes was more rapid and higher when compared to Piroxicam pure drug. The dissolution of pure Piroxicam and Piroxicam from various complexes followed first order kinetics (r>0.980). Dissolution rate constants (K_1) were calculated from the slopes of the first order linear plots of the dissolution data. Dissolution efficiency (DE_{50}) values based on the dissolution data were calculated as per Khan[10]. T_{50} (Time taken for 50% dissolution) values were recorded from the dissolution profiles. The dissolution parameters are summarized in Table-2.

All CD complexes exhibited higher rates of dissolution and dissolution efficiency values than Piroxicam and Piroxicam-PVP (9:1) system, indicating more rapid and higher dissolution of Piroxicam from its CD complexes. The K_1 and DE_{50} values increased as the proportion of CD in the complex was increased. The increase in K_1 (folds) with various CD systems is shown in Table-2.

HP-β-CD gave higher enhancement in the dissolution rate and efficiency of Piroxicam when compared to β-CD. A 36.52-fold increase in the dissolution rate of Piroxicam was observed with Piroxicam-HP-β-CD (1:2) complex. PVP alone gave only a marginal increase in the dissolution rate of Piroxicam. A 1.83-fold increase in the dissolution rate was observed with Piroxicam-PVP (9:1) system, whereas addition of PVP has markedly enhanced the dissolution rate and efficiency of Piroxicam from CD complexes. Piroxicam- β-CD (1:2) complex gave a 13.21-fold increase in the dissolution rate of Piroxicam, whereas Piroxicam – β-CD-PVP (1:2:0.3) complex gave a 17.84-fold increase. Similarly Piroxicam-HP-β-CD (1:2) and Piroxicam-HP-β-CD-PVP (1:2:0.3) complexes gave 36.52 and 72.42 fold increase in the dissolution rate of Piroxicam respectively. Thus inclusion of PVP in the CD complexes has markedly enhanced both complexation and solubilizing efficiencies of the CDs, and the solid inclusion complexes of CDs with PVP gave higher rates of dissolution – several times higher than those of Piroxicam andits comples with CDs alone. Because of the enhancement in CD complexation andsolubilizing efficiencies by the presence of PVP, Piroxicam-HP-β-CD–PVP (1:1:0.2) complex gave a dissolution rate equal to that of Piroxicam-β-CD (1:2)complex. These observations indicate that in the presence of PVP, a low amount of CD can be used to get the desired dissolution rate and efficiency.

Thus, the results of the study indicated the formation of Piroxicam-β-CD and Piroxicam-HP-β-CD inclusion complexes at a 1:1 M ratio in solution both in the presence and absence of PVP. The complexes formed are quite stable. The solubility and dissolution rate of Piroxicam were markedly enhanced by complexation with β-CD and HP-β-CD, and addition of PVP resulted in higher complexation efficiency and markedly enhanced the solubilizing efficiency of β-CD and HP-β-CD. Thus, addition of PVP, a water-soluble polymer, could be a strategy that can be employed to improve the usefulness of Cyclodextrins.

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Table-1: Effect of PVP on Stability constant (K_c) and Solubilizing efficiency of Cyclodextrins

Sample	K_c (m^{-1})	Solubilizing Efficiency
P-βCD	310.52	5.76
P-HPβCD	695.54	11.03
P-βCD-PVP	798.84	11.04
P-HPβCD-PVP	912.14	15.23

Table-2: Dissolution parameters of various Piroxicam Solid complexes

Product	Percent Dissolved in 10 min	T_{50} (min)	DE_{30} (%)	K_1 (min^{-1})	Increase in K_1 (folds)*
Piroxicam	29.66±1.04	>60	28.94	0.0076	-
P-βCD (1:1)	55.12±1.74	8.0	54.42	0.0521	6.95
P-βCD (1:2)	73.84±2.06	3.0	72.28	0.0992	13.21
P-HPβCD (1:1)	75.34±1.32	3.5	74.92	0.1576	20.89
P-HPβCD (1:2)	85.14±1.05	1.5	82.75	0.2746	36.52
P-PVP (9:1)	36.12±1.57	27.0	37.82	0.0132	1.83
P-βCD-PVP (1:1:0.2)	71.92±1.72	4.0	68.82	0.0912	12.15
P-βCD-PVP (1:2:0.3)	88.82±2.14	2.0	82.15	0.1329	17.84
P-HPβCD-PVP (1:1:0.2	82.97±1.21	2.5	81.44	0.2948	39.43
P-HPβCD-PVP (1:2:0.3)	99.57±1.53	1.0	89.24	0.5445	72.42

*Ratio between K_1 of CD complex and K_1 of Piroxicam. T_{50} is time taken for 50% dissolution; DE_{30} is dissolution efficiency upto 30 min; and K_1 is first order dissolution rate constant

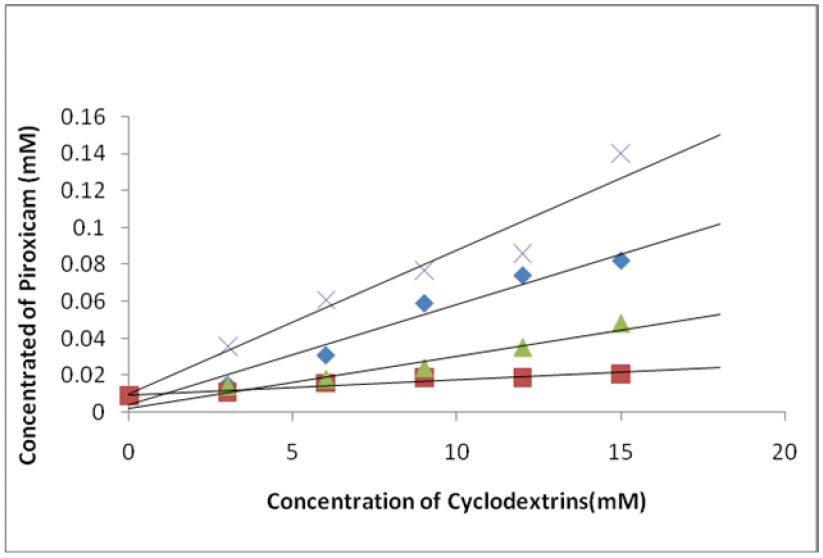

Fig. 1: Phase solubility diagram of Piroxicam-CD complexation Phase solubility diagram for Piroxicam-β-CD (Δ) and Piroxicam-HPβCD ( ))with (……) and without (.) PVP

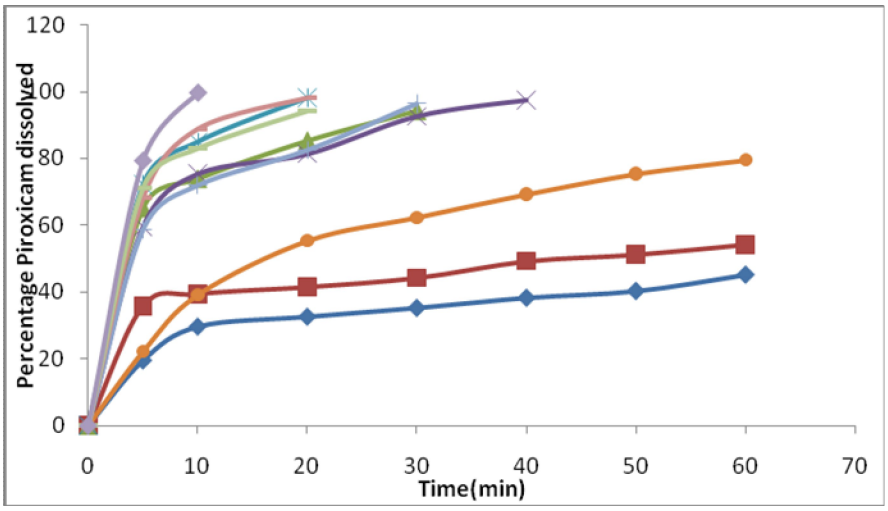

Fig. 2: Dissolution profiles of Piroxicam and its CD complexes Dissolution profiles of Piroxicam and its CD complexes P-βCD, P-HPβCD, P-βCD-PVP, P-HPβCD-PVP; Drug:CD ratios 1:1 (.), 1:2 (---) and P-PVP (9:1) (+)

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***Corresponding Author:** *Otra Kumar,*
Drugs Control Administration,
Eluru, West Godavari District, India
Email ID : annu9052434991@gmail.com