Influence of Hydrophilic Polymers on Celecoxib Complexation With Hydroxypropyl β-Cyclodextrin

Submitted: January 24, 2006; Accepted: June 7, 2006; Published: September 29, 2006

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ABSTRACT

Complexation of celecoxib with hydroxypropyl β-cyclodextrin (HPβCD) in the presence and absence of 3 hydrophilic polymers—polyvinyl pyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), and polyethylene glycol (PEG)—was investigated with an objective of evaluating the effect of hydrophilic polymers on the complexation and solubilizing efficiencies of HPβCD and on the dissolution rate of celecoxib from the HPβCD complexes. The phase solubility studies indicated the formation of celecoxib-HPβCD inclusion complexes at a 1:1M ratio in solution in both the presence and the absence of hydrophilic polymers. The complexes formed were quite stable. Addition of hydrophilic polymers markedly enhanced the complexation and solubilizing efficiencies of HPβCD. Solid inclusion complexes of celecoxib-HPβCD were prepared in 1:1 and 1:2 ratios by the kneading method, with and without the addition of hydrophilic polymers. The solubility and dissolution rate of celecoxib were significantly improved by complexation with HPβCD. The celecoxib-HPβCD (1:2) inclusion complex yielded a 36.57-fold increase in the dissolution rate of celecoxib. The addition of hydrophilic polymers also markedly enhanced the dissolution rate of celecoxib from HPβCD complexes: a 72.60-, 61.25-, and 39.15-fold increase was observed with PVP, HPMC, and PEG, respectively. Differential scanning calorimetry and X-ray diffractometry indicated stronger drug amorphization and entrapment in HPβCD because of the combined action of HPβCD and the hydrophilic polymers.

KEYWORDS: Celecoxib, complexation, hydroxypropyl β-cyclodextrin, hydrophilic polymers, dissolution rate.

INTRODUCTION

With the advent of high-throughput screening techniques, the discovery of biologically active molecules is taking place at a pace never seen before. Most of the chemical entities that are being discovered are lipophilic and have poor aqueous solubility, so they pose difficulties to the biopharmaceutical scientist in their formulation. Unless a drug is delivered to its target area at a rate and concentration that minimize side effects and maximize therapeutic effects, the drug is not beneficial to the patient and, though potentially useful, may be discarded. Cyclodextrins (CDs), with their ability to form molecular inclusion complexes with drug substances, will affect many of the physicochemical properties of the drugs without affecting their intrinsic lipophilicity or pharmacological properties.[1,2] As a consequence of the inclusion process, many physicochemical properties, such as solubility, dissolution rate, stability, palatability, and bioavailability, can be favorably affected.[3-5] CDs are thus offering new hope to formulation scientists in their efforts to develop an effective drug delivery system. CDs are effectively used as drug carriers and in foods and flavors, cosmetics, packing materials, textiles, separation processes, environmental protection efforts, fermentation, and catalysis.[6]

CDs are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity that can accommodate a variety of lipophilic drugs. The number of applications of CDs in pharmaceutical formulations has been increasing in recent years because of their approval by various regulatory agencies.[7,8] However, the use of CDs in solid oral dosage forms is limited to low-dose drugs with large stability constants because of the mass limitations of oral dosage units.[5] Therefore, in cases where the low complexation efficiency would require a larger amount of CD than is acceptable for solid dosage forms, the enhancement of the complexation capacity of the chosen CD is of practical importance. It has been reported[9] that the addition of small amounts of polyvinyl pyrrolidone (PVP), a water-soluble polymer, to a naproxen–hydroxypropyl β-cyclodextrin system has improved the complexing and solubilizing efficiencies of hydroxypropyl β-cyclodextrin (HPβCD).

Celecoxib, which is chemically designated as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide is a specific cyclooxygenase-2 inhibitor[10] widely prescribed for pain and inflammation. It inhibits the conversion of arachidonic acid to the prostaglandins that mediate pain and inflammation, while having no effect on the formation of the prostaglandins that mediate normal homeostasis in the gastrointestinal tract, kidney, and platelets and that are formed under the control of cyclooxygenase-1.[11] It is

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also used in the treatment of arthropathies and adenomatous polyps,[12] and in dentistry.[13] It has comparable efficacy and superior gastric tolerability[14] and is safer when compared with conventional nonsteroidal anti-inflammatory drugs.[15] The major drawback of celecoxib is its poor aqueous solubility and dissolution in gastric fluid. Hence, we sought to enhance the aqueous solubility and dissolution rate of celecoxib through formation of an inclusion complex with HPβCD. The enhancement of solubility and dissolution rate of celecoxib through complexation with CDs has been reported.[16] In the present work the effect of 3 hydrophilic polymers—PVP, hydroxypropyl methylcellulose (HPMC), and polyethylene glycol (PEG)—on the complexation of celecoxib with HPβCD was investigated. The effect of the hydrophilic polymers on the solubilizing efficiency of HPβCD and the dissolution rate of celecoxib from the HPβCD complexes was also investigated.

Materials and Methods

Materials

Celecoxib was a gift sample from M/s Dr Reddy's Laboratories (Hyderabad, India). HPβCD was a gift sample from M/s Cerestar Inc. (Hammond, IN) PVP (K-40), HPMC (E-5), PEG 4000, dichloromethane (Qualigens, Mumbai, India), methanol (Qualigens), and sodium lauryl sulfate (Qualigens) were procured from commercial sources. All other materials used were of pharmacopeial grade.

Methods

Phase Solubility Studies

Solubility studies were performed according to the method reported by Higuchi and Connors.[17] Excess drug (25 mg) was added to 15 mL of double-distilled water (pH 6.8) containing various concentrations of HPβCD (3-15mM) in a series of 50-mL stoppered conical flasks. The mixtures were shaken for 72 hours at room temperature (28 ± 0.5°C) on a rotary flask shaker. After 72 hours of shaking to achieve equilibrium, 2-mL aliquots were withdrawn at 1-hour intervals and filtered immediately using a 0.45-μ nylon disc filter. The filtered samples were diluted suitably and assayed for celecoxib at 254 nm against blanks prepared in the same concentration of HPβCD in water so as to cancel out any absorbance that might be exhibited by the CD molecules. Shaking was continued until 3 consecutive estimations were the same. Phase solubility studies were conducted with and without the addition of hydrophilic polymers. In the series with hydrophilic polymers, the polymer was added at a concentration of 0.5% wt/vol to the solution containing HPβCD. The solubility experiments were conducted in triplicate.

Preparation of Solid Complexes

Solid inclusion complexes of celecoxib-HPβCD were prepared in 1:1 and 1:2 ratios by the kneading method, with and without the addition of hydrophilic polymers. In the series with hydrophilic polymers, the polymer was added at a concentration of 10% wt/wt of the solid complex. Celecoxib, HPβCD, and hydrophilic polymers 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 minutes and then dried at 55°C until dry. The dried mass was powdered and sieved through mesh No 120.

Estimation of Celecoxib

A UV spectrophotometric method based on the measurement of absorbance at 254 nm in water containing 1% sodium lauryl sulfate was developed and used for the estimation of celecoxib. The method obeyed Beer's law in the concentration range of 1 to 10 μg/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 celecoxib alone and from its CD inclusion complexes was studied using the DISSO 2000 (Lab India, Mumbai, India), an 8-station dissolution rate test apparatus with a paddle stirrer. The dissolution rate was studied in 900 mL of water containing 1% sodium lauryl sulfate. Sodium lauryl sulfate was added to the dissolution fluid to maintain sink conditions. Celecoxib (50 mg), or its inclusion complex equivalent to 50 mg of celecoxib; a speed of 50 rpm; and a temperature of 37 ± 1°C were used in each test. Samples of dissolution medium (5 mL) were withdrawn through a filter (0.45 μ) at different time intervals, suitably diluted, and assayed for celecoxib by measuring absorbance at 254 nm. The dissolution experiments were conducted in triplicate.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) thermograms of the drug, polymer, CD, and prepared solid binary and ternary systems were recorded on the DSC 2920 Model (TA Instruments MDSC 2920, New Castle, DE). Samples (2-5 mg) were sealed in aluminum pans and scanned at a heating rate of 10°C min^{-1} over a temperature range of 30 to 250°C under a nitrogen gas stream.

X-ray Diffractometry

X-ray powder diffraction patterns were recorded using a Phillips X'pert Pro powder diffractometer (Almelo, Netherlands)

with monochromatized Cu Kα radiation (λ = 1.54056). The samples were scanned at room temperature in the continuous scan mode over the 5° to 50° 2θ range with a 0.1 2θ step size and with a counting time of 0.6 seconds.

Results and Discussion

The phase solubility diagrams for the complex formation between celecoxib and HPβCD in the presence and absence of hydrophilic polymers are shown in Figure 1. The aqueous solubility of celecoxib was increased linearly as a function of the concentration of HPβCD. The phase solubility diagrams of celecoxib-HPβCD complexes can be classified as type A_L according to Higuchi and Connors.[17] Because the straight line had a slope <1 in each case, the increase in solubility was due to the formation of a 1:1M complex in solution with HPβCD in the presence and absence of hydrophilic polymers. 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 = Slope/S_o(1 – 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 celecoxib and HPβCD are quite stable.

To evaluate the effect of hydrophilic polymers, the solubilizing efficiency of HPβCD was calculated in each case as the ratio of the drug solubility in aqueous solution (15 mM) of HPβCD (with and without hydrophilic polymers) to the drug solubility in water. The solubilizing efficiency values are given in Table 1. HPβCD alone yielded a 10.45-fold increase in the solubility of celecoxib, whereas in the presence of hydrophilic polymers it yielded a 15.28-, 13.54-, and 11.48-fold increase with PVP, HPMC, and PEG, respectively. Thus the addition of hydrophilic polymers markedly enhanced the solubilizing efficiency of HPβCD. The values of the stability constant (K_c) were found to be higher in the presence of hydrophilic polymers, indicating higher complexation efficiency. A 1.43-, 1.29-, and 1.15-fold increase in the K_c value was observed in the presence of PVP, HPMC, and PEG, respectively.

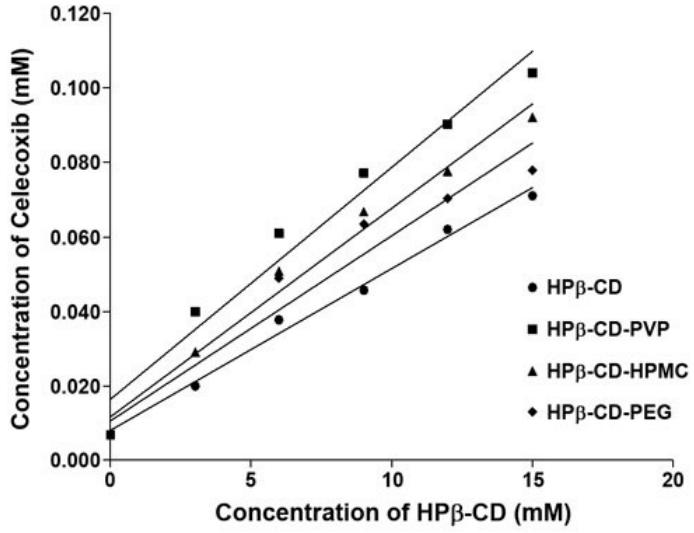

Figure 1. Phase solubility diagrams of celecoxib–hydroxypropyl β-cyclodextrin complexation in the presence and absence of hydrophilic polymers.

Table 1. Effect of PVP, HPMC, and PEG on the Apparent Stability Constant (K_c) and Solubilizing Efficiency of Celecoxib-HPβCD Complexes*

Sample	K_c (M^{-1})	Solubilizing Efficiency†
C-HPβCD	634.9	10.45
C-HPβCD-PVP	908.9	15.28
C-HPβCD-HPMC	819.1	13.54
C-HPβCD-PEG	727.9	11.48

*PVP indicates polyvinyl pyrrolidone; HPMC, hydroxypropyl methylcellulose; PEG, polyethylene glycol; HPβCD, hydroxypropyl β-cyclodextrin; and C, celecoxib.
†Ratio of drug solubility in aqueous solution (15mM) of cyclodextrin (with or without hydrophilic polymers) to drug solubility in water.

All the solid complexes prepared were found to be fine and free-flowing powders. The angle of repose (θ) was below 20°. The free flow may be due to the inclusion of the drug in HPβCD. Low coefficient of variation (CV) (<1.0%) values in the percentage of drug content indicated uniformity of drug content in each batch of solid inclusion complex prepared. The dissolution rate of celecoxib alone and from various solid inclusion complexes was studied in water containing 1% sodium lauryl sulfate. Sodium lauryl sulfate was included in the dissolution medium to maintain sink conditions. The dissolution profiles of various complexes are shown in Figure 2. The dissolution of celecoxib was rapid and higher from all the solid inclusion complexes when compared with celecoxib pure drug. The dissolution of celecoxib alone and 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_{30}) values based on the dissolution data were calculated as per Khan.[18] $T_{50\%}$ (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 celecoxib, indicating rapid and higher dissolution of celecoxib from its HPβCD complexes. The K_1 and DE_{30} values were increased as the proportion of HPβCD in the complex was increased. The increase in K_1 (folds) with various CD systems is shown in Table 2. The addition of hydrophilic polymers markedly enhanced the dissolution rate and efficiency of celecoxib

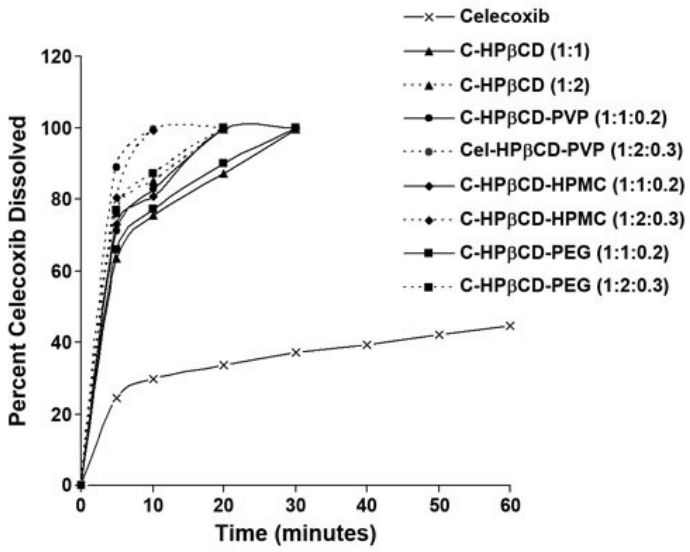

Figure 2. Dissolution profiles of celecoxib and its hydroxypropyl β-cyclodextrin complexes.

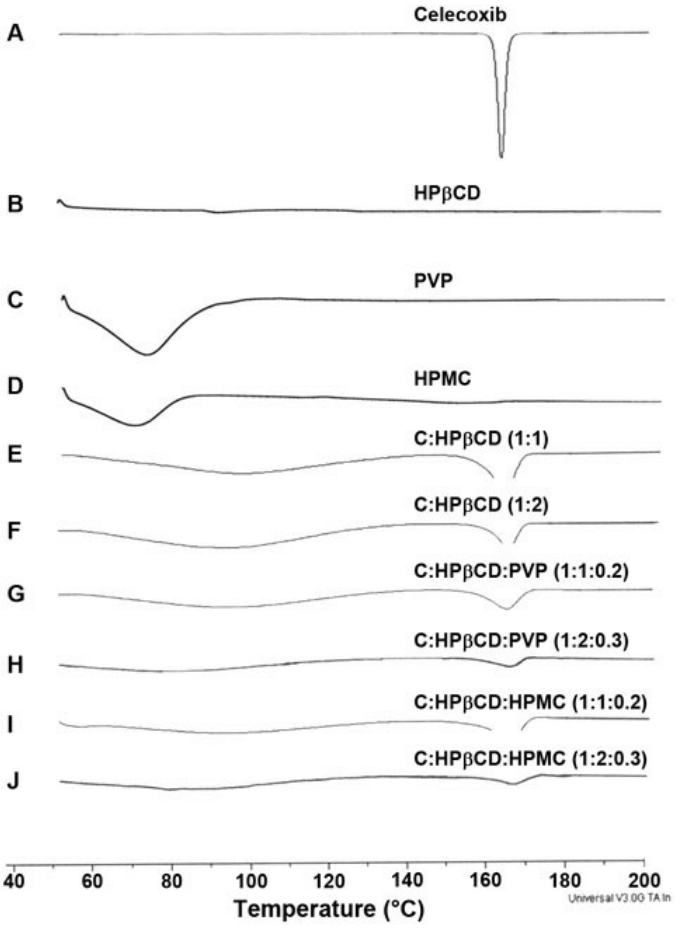

Figure 3. Differential scanning calorimetry thermograms of celecoxib and its cyclodextrin complex systems with and without hydrophilic polymers.

from CD complexes. The celecoxib-HPβCD (1:2) complex yielded a 36.57-fold increase in the dissolution rate of celecoxib, whereas in the presence of hydrophilic polymers, it yielded a 72.60-, 61.25-, and 39.15-fold increase with PVP, HPMC, and PEG, respectively. The order of hydrophilic polymers in enhancing the solubilizing efficiency and dissolution rate of HPβCD complexes was PVP > HPMC > PEG. Thus, inclusion of hydrophilic polymers in the CD complexes markedly enhanced both the complexation and solubilizing efficiencies of the HPβCD, and the solid inclusion complexes of HPβCD with hydrophilic polymers yielded rates of dissolution several times higher than those of celecoxib and its complexes with HPβCD alone.

DSC was used to characterize the celecoxib-HPβCD solid complexes prepared with and without hydrophilic polymers. The DSC thermograms of various products are shown in Figure 3. The DSC curve of celecoxib (A) showed a single sharp endothermic peak at 167°C, corresponding to its melting point. HPβCD, PVP, and HPMC showed (B, C, D) broad endothermic peaks associated with loss of water. In the thermogram of celecoxib-HPβCD (E, F), the intensity (or height) of the endothermic peak at 167°C was reduced, indicating an interaction of celecoxib with HPβCD. With the celecoxib-HPβCD-PVP (G, H) and celecoxib-HPβCD-HPMC systems (I, J) the endothermic peak at 167°C was

Table 2. Dissolution Parameters of Various Celecoxib-HPβCD Solid Inclusion Complexes*

Product	Percent Dissolved in 10 Minutes	$T_{50\%}$ (min)	DE_{30} (%)	K_1 (min^{-1})	Increase in K_1 (folds)†
Celecoxib	29.63 ± 1.06	>60	28.91	0.0075	—
C-HPβCD (1:1)	75.29 ± 1.37	3.5	74.94	0.1573	20.97
C-HPβCD (1:2)	85.04 ± 1.05	1.5	83.75	0.2743	36.57
C-HPβCD-PVP (1:1:0.2)	82.97 ± 1.21	2.5	82.47	0.2959	39.45
C-HPβCD-PVP (1:2:0.3)	99.57 ± 1.71	1.0	89.23	0.5445	72.60
C-HPβCD-HPMC (1:1:0.2)	80.57 ± 1.92	2.5	82.11	0.2670	35.60
C-HPβCD-HPMC (1:2:0.3)	98.99 ± 1.85	1.0	87.96	0.4594	61.25
C-HPβCD-PEG (1:1:0.2)	77.25 ± 1.25	3.5	76.83	0.1767	23.56
C-HPβCD-PEG (1:2:0.3)	86.99 ± 1.05	1.5	84.41	0.2936	39.15

*HPβCD indicates hydroxypropyl β-cyclodextrin; DE, dissolution efficiency; C, celecoxib; PVP, polyvinyl pyrrolidone; HPMC, hydroxypropyl methylcellulose; and PEG, polyethylene glycol.
†Ratio of K_1 of CD complexes to K_1 of celecoxib.

markedly reduced and even disappeared in 1:2:0.3 systems (H, J), indicating the absence of crystalline drug and its complete complexation with HPβCD.

X-ray diffractometry patterns of celecoxib and its various complexes with HPβCD are shown in Figure 4. X-ray diffractometry of celecoxib exhibited diffraction peaks indicating a crystalline nature. The diffraction peaks were much reduced or were absent in the case of the binary (celecoxib-HPβCD) and ternary (celecoxib-HPβCD-PVP/HPMC) systems, respectively. The disappearance of celecoxib crystalline peaks confirmed the stronger drug amorphization and entrapment in HPβCD due to the combined action of HPβCD and the hydrophilic polymers.

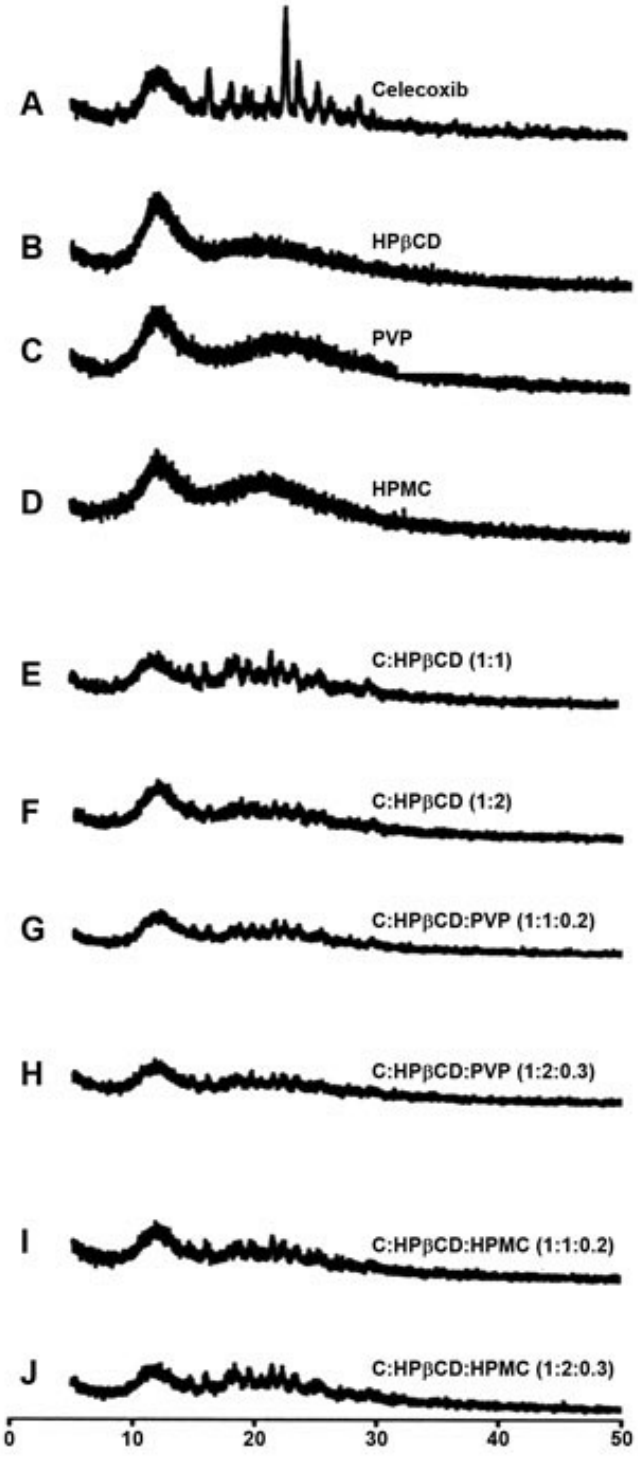

Figure 4. X-ray diffractograms of powder samples of celecoxib and its cyclodextrin complex systems with and without hydrophilic polymers.

The much-enhanced dissolution rate observed with celecoxib-HPβCD systems containing hydrophilic polymers was due to (1) the enhancement of the complexation and solubilization efficiencies of HPβCD by the added hydrophilic polymers, and (2) the stronger drug amorphization and better inclusion caused by the combined action of HPβCD and the hydrophilic polymers.

Because of the enhancement in the HPβCD complexation and solubilizing efficiencies caused by the presence of hydrophilic polymers, a low amount of CD can be used to obtain the desired dissolution rate and efficiency. Thus, addition of hydrophilic polymers could be a strategy for improving the usefulness of CDs.

CONCLUSIONS

Celecoxib formed inclusion complexes with HPβCD at a 1:1M ratio in solution in the presence and absence of hydrophilic polymers. The addition of hydrophilic polymers resulted in a higher complexation efficiency and markedly enhanced the solubilizing efficiency of HPβCD. Solid inclusion complexes of HPβCD with hydrophilic polymers yielded rates of dissolution several times higher than those of celecoxib and its complexes with HPβCD alone.

ACKNOWLEDGMENTS

S. Vijaya Srinivas is grateful to Council for Scientific Industrial Research (CSIR) (New Delhi, India) for the award of CSIR-Senior Research Fellow (SRF) to work on cyclodextrin complexation for enhancing dissolution and bioavailability.

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