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Research paper

Solubility enhancement of celecoxib using β-cyclodextrin inclusion complexes

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Abstract

Celecoxib has very low water solubility. It forms a complex with β-cyclodextrin (βCD) both in aqueous and in solid state. It was observed that due to formation of the inclusion complex, the solubility and dissolution rate of celecoxib were enhanced. The formation of 1:1 complex with βCD in solution was confirmed by phase solubility and spectral shift studies. The apparent stability constants calculated by these techniques were 881.5 and 341.5 M^{-1}, respectively. The solid inclusion complexes of celecoxib and βCD were prepared by the kneading method using different molar proportions of βCD, and formation of solid inclusion complexes of celecoxib and βCD at different molar ratios were confirmed by differential scanning calorimetry. Enhancement of dissolution rates with increasing quantity of βCD in the complex was observed. It was also observed that the complexes exhibit higher dissolution rates than the pure drug and physical mixture.

Keywords: Cyclooxygenase-2 inhibitors; Cyclodextrin; Inclusion complex; Phase solubility

1. Introduction

Enzymatic hydrolysis of starch usually results in formation of glucose, maltose and a long range of linear and branched dextrins. However, a number of different microorganisms and plants produce certain enzymes called cyclodextrin glucosyltransferases (CGTs), which degrade starch to cyclic products called cyclodextrins. These are cyclic oligosaccharides consisting of a lipophilic central cavity and a hydrophilic outer surface. Because of such characteristics, cyclodextrins form inclusion complexes both in solution and in solid state, in which each guest molecule is surrounded by the hydrophobic environment of the cyclodextrin cavity. This can lead to alteration of the physical, chemical and biological properties of the guest molecules and can eventually have considerable pharmaceutical potential [1]. Out of the three parent cyclodextrins, β-cyclodextrin (βCD) appears most useful as a pharmaceutical complexing agent because of its complexing ability, low cost and other properties. There are two types of complex cyclodextrin forms with the guest molecules, type A (L) that forms in solutions and type B (S) which forms in solid complex [2]. Apart from the kneading [3], the solid drug can be complexed with βCD by freeze drying [4], spray drying [5], co-evaporation [6] or by roll mixing [7]. Therefore, βCD was selected to form an inclusion complex with celecoxib to enhance its solubility.

Celecoxib, 4-[5-(4-methyl phenyl)-3-(triflouromethyl)-1*H*-pyrazol-1-yl], is a non-steroidal anti-inflammatory drug (NSAID), which is a specific cyclooxygenase-2 (COX-2) inhibitor [8] for pain and inflammation. Celecoxib offers the unique therapeutic prospect of alternative pain and inflammation without untoward gastric tract, renal and platelet effects associated with conventional NSAIDs. Because, celecoxib is a COX-2-specific inhibiting agent 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 GI tract, kidney and platelets and that are formed under the control of cyclooxygenase-1 [9]. It is also used in the treatment of orthopedics, familial adenomatous polyps [10] and in dental practice [11]. It has comparable efficacy and superior gastric tolerability [12] and it is safer, when compared to the conventional NSAIDs [13]. The major

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drawback with celecoxib therapy is its poor aqueous solubility and dissolution in gastric fluid. Hence it is aimed to enhance the aqueous solubility and dissolution rate of celecoxib by forming an inclusion complex with βCD and their physico-chemical properties were investigated.

2. Materials and methods

2.1. Materials

Celecoxib (Lupin Laboratories, India), βCD (Cavitron, USA), and other reagents used were of analytical grade.

2.2. Preparation of solid complexes

(1) Physical mixtures: The physical mixture (1:1) was prepared by mixing of pulverized powder and then passed through sieve (#100).
(2) Complexes: Thick slurry was prepared by adding one-third water by weight to βCD. Under stirring the quantity of drug was added to it and then dried in an oven at 45 °C until dry. The dried mass was pulverized and sieved through mesh #100.

2.3. Determination of stability constant

2.3.1. Phase solubility studies

Solubility studies were performed according to the method reported by Higuchi and Connors [14]. Excess celecoxib was added to 30 ml of purified water (pH 6.8) containing various concentrations of βCD (0.002–0.01 M) in a series of 100 ml volumetric flasks and the mixture was shaken for 24 h at room temperature (25 °C) on a shaker (150 rev./min). Then, the samples were kept aside to achieve equilibrium. The aliquots were then filtered through Whatman filter paper no. 41. The filtered samples were diluted suitably and assayed for celecoxib, by measuring the absorbance at 252 nm [15]. The mixture was shaken until three consecutive samples estimated the same amount of drug.

2.3.2. Spectroscopic studies

Complex formation between celecoxib and βCD was also studied by spectroscopic method. The concentration of the drug in these studies was 2.622×10^{-5} M whereas βCD concentration was increased from 0.002 to 0.01 M. The UV spectra of the drug were recorded on a Shimadzu (UV-2101PC, Japan) UV–Vis, scanning spectrophotometer. The change in the absorbance of celecoxib on the addition of various concentrations of the complexing agent, were measured at 252 nm to evaluate the stability constant of the complex.

2.4. Differential scanning calorimetry (DSC)

The samples were sealed in 40 μl aluminum pans, the lids were pierced and the DSC thermograms were recorded at a heating rate of 10 °C/min from 50 to 350 °C using nitrogen atmosphere.

2.5. Dissolution rate studies

The in vitro dissolution studies of pure drug, physical mixture and complexes were carried out in 900 ml of (i) 0.1 N HCl and (ii) phosphate buffer (pH 7.4), using USP 6-stage dissolution rate apparatus (Model-Electrolab programmable tablet dissolution test apparatus USP XXI/XXII, TDT-06P, India) with a paddle stirrer. In the present studies, samples equivalent to 100 mg of drug were taken. The paddle was rotated at 50 rev./min and a temperature of dissolution medium was maintained at 37 ± 0.5 °C. Samples of dissolution media were withdrawn at different time intervals, filtered with Whatman filter paper no. 41 and assayed for celecoxib using spectrophotometric method by measuring the absorbance at 252 nm.

3. Results and discussion

The phase solubility diagram for the complex formation between celecoxib and βCD is shown in Fig. 1. The aqueous solubility of celecoxib increased linearly with a slope 0.0633 ($r = 0.9989$), as a function of βCD concentration. The phase solubility diagram (Fig. 1) can be classified as type (A) according to Higuchi and Connors [2]. It is assumed that the increase in solubility observed was due to the formation of a 1:1 M inclusion complex. The stability constant (K_c) of celecoxib and βCD complex (1:1) was calculated as 881.5 M^{-1} from the linear plot of the phase solubility diagram according to the equation $K_c = \text{slope}/\text{So}\ X(1 - \text{slope})$, where So is the solubility of drug in the absence of βCD.

The UV spectra of celecoxib solution in the presence of increasing molar concentration of βCD were recorded. The changes in peak intensity are assumed to result from changes in the solvent microenvironment upon inclusion of the solute. The observed reduction in peak intensity may result from the transfer of the guest molecule from water to the CD cavity [16]. Because the molar absorptivities of the complex and drug differed at the same wavelength, it was possible to

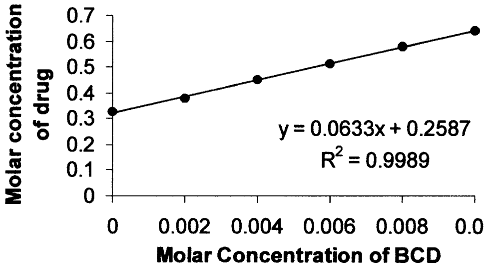

Fig. 1. Phase solubility diagram of celecoxib in aqueous β-cyclodextrin solution.

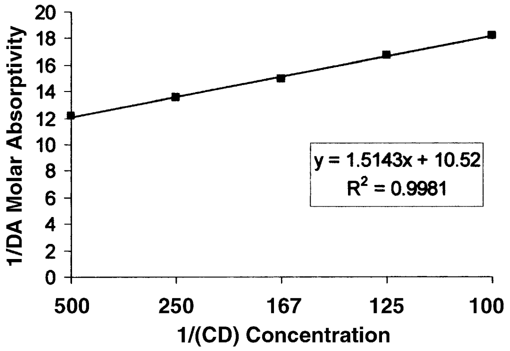

Fig. 2. Double reciprocal curve of celecoxib in aqueous β-cyclodextrin solution.

determine the stability constant from these spectral data by the double reciprocal plot [17]. The plot of $1/\Delta A$ versus 1/(CD) (Fig. 2) is linear indicating the presence of a 1:1 M complex. The apparent 1:1 M stability constant (K_c) was estimated from the Benesi–Hildebrand equation [18]

$$\frac{1}{\Delta A} = \frac{1}{(D)}K_c\Delta\varepsilon X\frac{1}{(\mathrm{CD})} + \frac{1}{(D)}\Delta\varepsilon$$

where ΔA is the difference of absorbance at 252 nm, (CD) the βCD concentration, (D) the drug concentration (constant), and $\Delta\varepsilon$ is the difference in the molar absorptivities between the complex and the free drug. The K_c value was calculated to be 341.5 M^{-1}.

The stability constant estimated by a spectral shift technique was relatively small when compared to that obtained by the phase solubility studies. However, as stated by Choudhary [19], it should be noted that the use of the spectral shift technique is certainly not the method of first choice when the drug has low aqueous solubility, because the difference in the absorption will be too small to allow for a reliable determination. In contrast, the phase solubility method provides a much better determination in these cases [20].

The thermal behavior of celecoxib–βCD solid complexes was studied using DSC in order to confirm the formation of the solid complex. DSC thermograms of rofecoxib solid complexes are shown in Fig. 3. The DSC thermograms of rofecoxib exhibited an endothermic peak at 166.8 °C corresponding to its melting point. βCD alone showed a broad endothermic peak representing a loss of water molecule, a dehydration process. The thermograms of physical mixture and complexes are different from the pure drug, which gives clear evidence that there is formation of the complexes. The disappearance of endothermic peaks with these systems gives clear evidence that there is formation of the complexes of celecoxib and βCD at different molar ratios.

The thermal behavior data of celecoxib–βCD inclusion complexes are given in Table 1, which shows that there is deviation in peak height in all the complexes that have been prepared in different molar ratios. Even the physical mixture showed the deviation in peak height. This shows that there is a formation of inclusion complex in all the cases. However

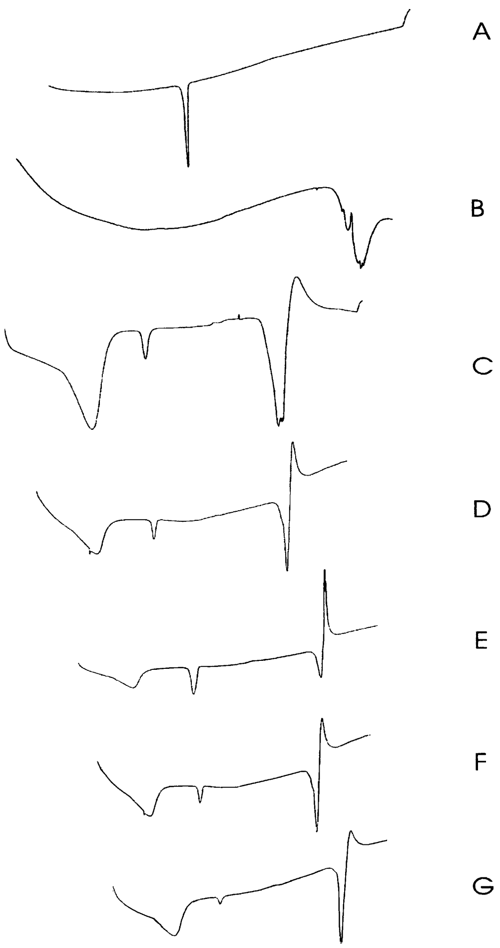

Fig. 3. DSC thermograms of celecoxib BCD. (A) Pure drug. (B) Cyclodextrin. (C) Physical mixture (drug: cyclodextrin, 1:1). (D) Drug: cyclodextrin (1:0.25). (E) Drug: cyclodextrin (1:0.5). (F) Drug: cyclodextrin (1:1). (G) Drug: cyclodextrin (1:2).

Table 1
Thermal behavior of celecoxib–βCD inclusion complexes

Content	Quantity of drug in complexes (mg)	Theoretical peak height, $\Delta J/g$	Observed peak height, $\Delta J/g$	% Difference
R	3.80	–	21.29	–
CPM	1.23	6.89	3.25	52.84
C1	3.35	18.77	9.33	50.29
C2	2.99	16.75	8.05	51.95
C3	2.28	12.77	4.71	63.69
C4	1.45	8.13	1.96	78.82

C, celecoxib; CPM, physical mixture of celecoxib and -βCD (1:1); C1, celecoxib–βCD complexes (1:0.25); C2, celecoxib–βCD complexes (1:0.5); C3, celecoxib–βCD complexes (1:1); C4, celecoxib–βCD complexes (1:2).

Table 2
Dissolution profile of celecoxib in 0.1 N hydrochloric acid

Time (min)	Mean percentage of drug dissolved (± SD)*					
	C	CPM	C_1	C_2	C_3	C_4
5	0.22 (3.75)	0.48 (3.00)	0.82 (1.94)	1.23 (1.63)	1.84 (1.85)	2.24 (1.22)
10	0.61 (3.95)	1.22 (3.44)	1.83 (1.45)	4.39 (1.25)	6.23 (1.75)	7.22 (2.85)
15	1.43 (3.08)	2.59 (3.25)	3.61 (1.77)	6.42 (1.52)	8.08 (1.49)	9.63 (1.58)
30	2.47 (2.05)	4.24 (2.65)	5.58 (1.63)	8.59 (1.74)	10.61 (1.85)	14.26 (1.85)
45	4.19 (2.55)	7.63 (2.15)	10.41 (1.25)	14.21 (1.51)	15.76 (1.66)	17.42 (1.92)
60	8.99 (3.78)	12.36 (4.00)	14.22 (1.84)	16.74 (1.65)	19.45 (1.39)	21.79 (1.57)
k min^{-1} × 10^{-3}	1.5	3.01	6.50	10.5	19.01	33.5
DE$_{15}$%	0.46	1.166	2.11	3.05	7.15	11.25
r	0.9724	0.9625	0.9620	0.9825	0.9718	0.9702

$n = 6$. C, celecoxib; CPM, physical mixture of celecoxib and -βCD (1:1); C1, celecoxib–βCD complexes (1:0.25); C2, celecoxib–βCD complexes (1:0.5); C3, celecoxib–βCD complexes (1:1); C4, celecoxib–βCD complexes (1:2).

Table 3
Dissolution profile of celecoxib in phosphate buffer (pH 6.8)

Time (min)	Mean percentage of drug dissolved (± SD)*					
	C	CPM	C_1	C_2	C_3	C_4
5	1.2 (3.15)	2.7 (1.87)	4.2 (1.72)	6.3 (1.78)	8.4 (1.63)	9.33 (2.85)
10	2.1 (2.25)	3.9 (1.58)	5.4 (1.64)	7.5 (1.23)	9.6 (1.55)	10.80 (1.42)
15	3.3 (2.56)	5.1 (1.75)	6.3 (1.45)	9.6 (1.52)	12.6 (1.85)	15.58 (2.05)
30	4.2 (2.73)	7.2 (2.05)	10.8 (1.48)	14.7 (1.74)	18.3 (1.38)	21.24 (1.54)
45	7.2 (2.11)	11.1 (1.67)	14.4 (1.35)	18.3 (1.51)	22.8 (1.69)	25.8 (1.88)
60	12.31 (3.94)	17.7 (1.85)	21.6 (1.39)	24.3 (1.64)	29.4 (1.28)	32.04 (1.59)
k min^{-1} × 10^{-3}	1.25	6.5	8.5	13.0	18.5	29.5
DE$_{15}$%	2.15	2.75	3.16	6.45	9.89	14.25
r	0.9895	0.9913	0.9764	0.9880	0.9845	0.9816

$n = 6$. C, celecoxib; CPM, physical mixture of celecoxib and -βCD (1:1); C1, celecoxib–βCD complexes (1:0.25); C2, celecoxib–βCD complexes (1:0.5); C3, celecoxib–βCD complexes (1:1); C4, celecoxib–βCD complexes (1:2).

the greatest deviation observed in 1:2 complex, shows that maximum complexation of drug has occurred in this combination.

The dissolution characteristics of celecoxib and celecoxib–βCD inclusion complex systems are given in Tables 2 and 3. The dissolution data were evaluated on the basis of (i) dissolution efficiency (DE$_{15}$%) at 15 min and (ii) dissolution rate constant k_1 min^{-1} during the initial period (i.e. at initial 10 min). The dissolution of celecoxib during 0–10 min period followed first order kinetics. The correlation coefficients (r) between log percent dissolved and time were in the range of 0.9620–0.9913 for various complexes. In both the dissolution medias the dissolution rate (k_1) and dissolution efficiency (DE) were highest for 1:2 complex. It was also observed that these gradually increased as the concentration of βCD increased. A 22- and 23- fold increase in dissolution rate in 0.1 N HCl and phosphate buffer (pH 7.4), respectively, were observed with 1:2 complexes when compared to that of the pure drug.

Thus the results of the studies indicated the formation of celecoxib–βCD inclusion complexes at 1:1 ratio in aqueous solution with a stability constant 881.5 M^{-1}, whereas solid complexes prepared at different combinations of drug and βCD exhibited higher rate of dissolution and dissolution efficiency than the corresponding physical mixture and pure drug.

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