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Rofecoxib-β-cyclodextrin inclusion complex for solubility enhancement

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Complex formation of rofecoxib and beta-cyclodextrin in aqueous solution and in solid state and the possibility of improving the solubility and dissolution rate of rofecoxib via complexation with cyclodextrin were investigated. Phase solubility studies indicated the formation of an 1 : 1 complex in solution and the value of apparent stability constant was 769 M^{-1}. Solid inclusion complexes of rofecoxib and cyclodextrin were prepared by the kneading method in different molar ratios. Differential scanning calorimetry studies indicated the formation of solid inclusion complexes of rofecoxib and cyclodextrin at different molar ratios and the solid complexes exhibited a higher rate of dissolution than the physical mixture and the pure drug.

1. Introduction

Rofecoxib, 4-[4-(methylsulfonyl) phenyl]-3-phenyl-2-(5 H) furanone is practically insoluble in water (0.0086 mg/ml) and its oral absorption is dissolution rate limited [1]. The very poor aqueous solubility of the drug causes difficulties in formulation of dosage forms and may lead to a variable bioavailability. Therefore, an attempt is made to enhance the aqueous solubility of rofecoxib by complexation with β-cyclodextrin.

Among the cyclodextrins, β-cyclodextrin (βCD) is the most widely studied compound for drug complexation. Apart from the kneading method, the solid complex can be prepared by freeze-drying, spray drying, co-evaporation [2] or by roll mixing [3].

In the present project, the possibilities of improving the solubility and dissolution rate of rofecoxib via complexation with βCD were explored and their physicochemical properties were investigated.

2. Investigations, results and discussion

The phase solubility diagram for the complex formation between rofecoxib and βCD is shown in Fig. 1. The aqueous solubility of rofecoxib increased linearly ($r = 0.9732$), as a function of βCD concentration. The diagram is of type A_L according to Higguchi and Connors [4]. Because the straight line had a slope 0.0331, it was assumed that the increase in solubility observed was due to the formation of a 1 : 1 M complex. However, it was observed that the solubility increases linearly with the increase in concentration of βCD. The stability constant Kc was calculated from a linear plot of the phase solubility diagram according to the equation Kc = Slope/So*(1-slope), where So is the solubility of drug in the absence of βCD. The stability constant of rofecoxib βCD (1 : 1) complex was found to be 769 M^{-1}. The UV spectra of rofecoxib solution in the presence of increasing molar concentrations of βCD were studied. 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 [5]. Because the molar absorptivity of the complex and drug differed at the same wavelength, it was possible to determine the stability constant from these spectral data by the double reciprocal plot [6]. 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 (Kc) was estimated from the Benesi-Hildebrand equation [7].

$$1/\Delta A = 1/(D)\ Kc\ \Delta\varepsilon \times 1/(CD) + 1/(D)\ \Delta\varepsilon$$

where ΔA is the difference of absorbance at 276 nm, (CD) is the βCD concentration; (D) is the drug concentration (constant) and $\Delta\varepsilon$ is the difference in the molar absorptivities between the complex and the free drug. The Kc value was calculated to be 48 M^{-1}.

The phase solubility method is performed in saturated solutions under non-ideal conditions whereas the spectrophotometric method is performed in dilute solutions under

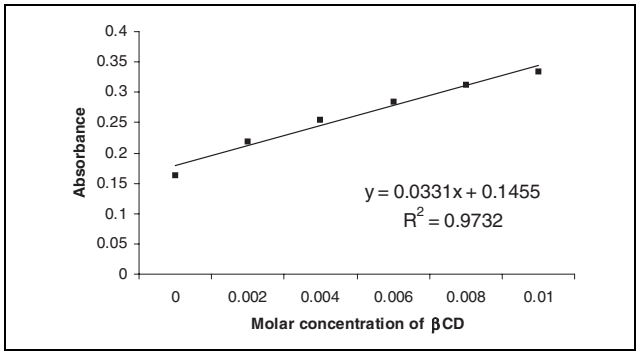

Fig. 1: Phase solubility diagram of rofecoxib in aqueous β-cyclodextrin solution

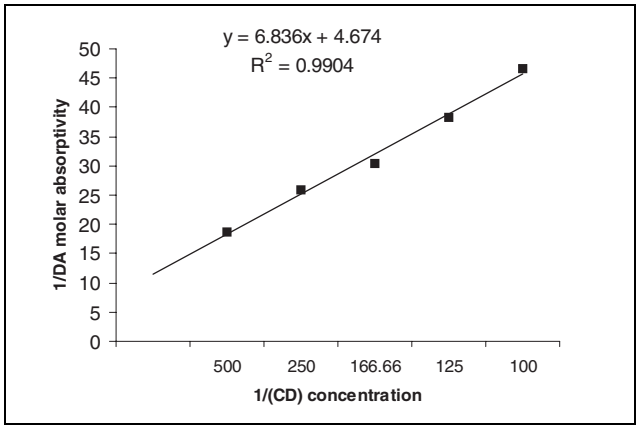

Fig. 2: Double reciprocal plot of rofecoxib in aqueous β-cyclodextrin solution

closer to ideal conditions and therefore the latter is more reliable. It has been observed that the stability constant estimated by the spectral shift technique was relatively small when compared to that obtained by the phase solubility studies. Since the spectral shift technique is not the first choice when the drug has low aqueous solubility, as the difference in the absorption is too small to allow for a reliable determination, therefore the phase solubility method provides a much better determination in such cases [8]. The solid complexes were prepared by the kneading method at different concentrations (1 : 0.25, 1 : 0.5, 1 : 1, and 1 : 2). The thermal behavior of rofecoxib 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 the Fig. 3. The thermogram of rofecoxib exhibited an endothermic peak at 208 °C corresponding to its melting point. βCD alone showed a broad endothermic segment representing a loss of water molecule. The thermograms of the physical mixture and the complexes are different from those of the pure drug, which gives a clear evidence that there are formations of the complexes.

The thermal behavior data of rofecoxib βCD inclusion complexes are shown in Table 1. The Table 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 an inclusion complex in all the cases. However, the highest deviation observed in the 1 : 2 complex shows that maximum complexation of drug has occurred in this combination.

The dissolution characteristics of rofecoxib and rofecoxib βCD complexes are given in Table 2 and 3. The dissolution data were evaluated on the basis of the dissolution rate constant K_H. The dissolution of rofecoxib followed first order kinetics. The correlation coefficient between log percent dissolved and time was in the range of 0.95–0.99 for various complexes. It was observed that, in comparison to the pure drug, both physical mixture and βCD complexes showed an enhanced dissolution rate. It was found that although the physical mixture of drug and βCD does not show substantial increase in solubility, the rate of drug release was significantly promoted in comparison to

Table 1: Thermal behavior of rofecoxib -βCD inclusion complexes

Content	Quantity of drug in complexes (mg)	Theoretical Pk. Ht. to be obtained (ΔJ/g)	Observed Pk. Ht. (ΔJ/g)	Difference (%)
R	4.04	–	31.78	–
RPM.	1.58	12.43	7.25	41.6
R1	3.2	25.17	7.73	24.8
R2	2.44	19.09	8.53	55.5
R3	1.86	14.63	8.18	44.0
R4	1.62	12.4	2.3	81.9

R = rofecoxib, RPM = Physical mixture of rofecoxib and -βCD (1 : 1), R1 = rofecoxib-βCD complexes (1 : 0.25), R2 = rofecoxib-βCD complexes (1 : 0.5), R3 = rofecoxib-βCD complexes (1 : 1), R4 = rofecoxib-βCD complexes (1 : 2),

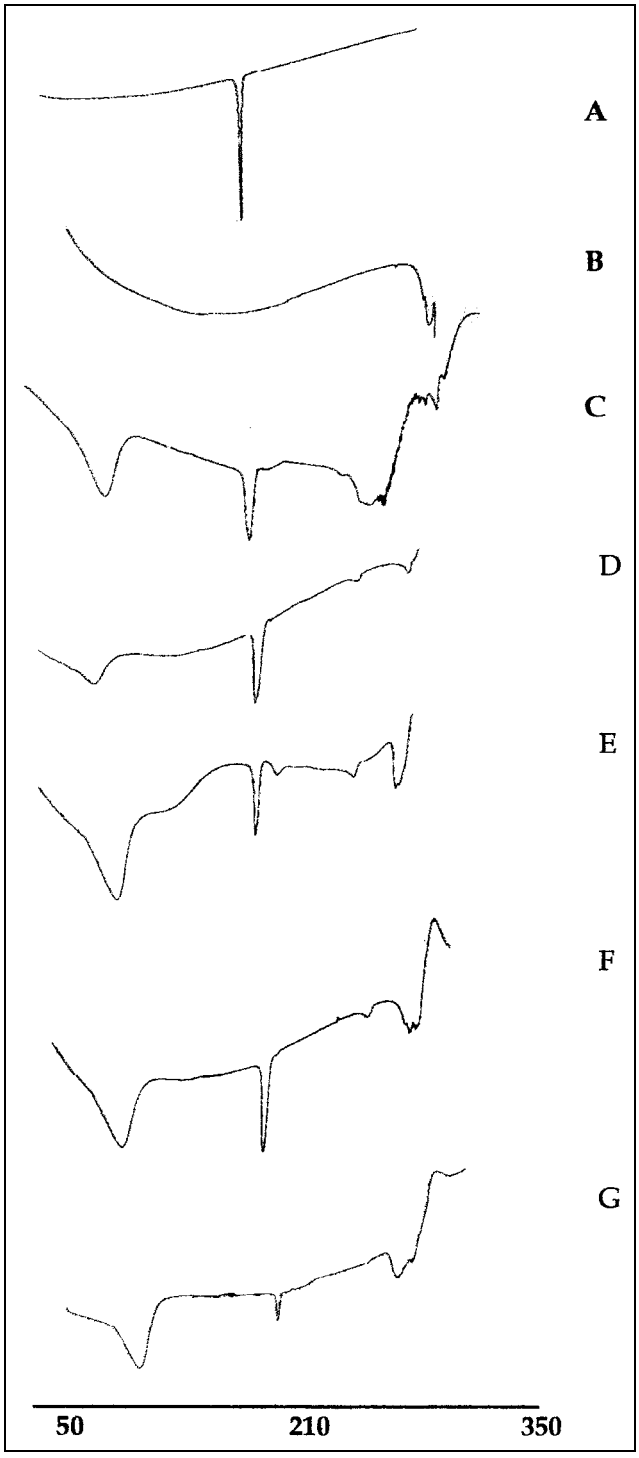

Fig. 3: DSC thermograms of rofecoxib β-cyclodextrin.
A – Pure drug, B – Cyclodextrin, C – Physical mixture (Drug: cyclodextrin, 1 : 1), D – Drug: cyclodextrin, (1 : 0.25), E – Drug: cyclodextrin, (1 : 0.5), F – Drug: cyclodextrin, (1 : 1), G – Drug: cyclodextrin, (1 : 2)

Table 2: Dissolution profile of rofecoxib in 0.1 N hydrochloric acid

Time (min)	Mean percentage of drug dissolved (± SD)*					
	R	RPM	R1	R2	R3	R4
5	9.61 (3.75)	8.53 (3.00)	20.45 (1.94)	22.54 (1.63)	26.45 (1.84)	33.04 (1.93)
10	12.11 (3.95)	11.83 (3.44)	22.62 (1.45)	24.45 (1.22)	33.52 (1.62)	38.62 (1.83)
15	20.07 (3.08)	18.73 (3.25)	26.52 (1.77)	34.15 (1.52)	39.11 (1.61)	42.63 (1.74)
30	25.5 (2.05)	24.53 (2.65)	32.98 (1.63)	35.23 (1.74)	42.83 (1.53)	48.63 (1.60)
45	31.71 (2.55)	28.77 (3.15)	38.25 (1.25)	39.22 (1.51)	47.21 (1.47)	54.32 (1.37)
60	35.39 (3.78)	34.82 (4.00)	41.34 (1.84)	43.32 (1.64)	51.98 (1.40)	58.36 (1.28)
K_H	7.68	6.99	17.25	21.77	25.02	29.95
r	0.959	0.965	0.984	0.930	0.958	0.953

n = 6, * SD = standard deviation
R = rofecoxib, RPM = Physical mixture of rofecoxib and -βCD (1 : 1), R1 = rofecoxib-βCD complexes (1 : 0.25), R2 = rofecoxib-βCD complexes (1 : 0.5), R3 = rofecoxib-βCD complexes (1 : 1), R4 = rofecoxib-βCD complexes (1 : 2),
K_H Higuchi rate constant [9]

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

Time (min)	Mean percentage of drug dissolved (± SD)*					
	R	RPM	R1	R2	R3	R4
5	2.88 (1.85)	3.28 (1.85)	8.77 (1.85)	10.44 (1.85)	12.43 (1.85)	16.07 (1.85)
10	3.74 (1.85)	5.33 (1.85)	9.13 (1.85)	11.69 (1.85)	15.36 (1.85)	18.76 (1.85)
15	5.36 (1.85)	9.42 (1.85)	10.36 (1.85)	13.42 (1.85)	18.76 (1.85)	21.66 (1.85)
30	8.77 (1.85)	11.69 (1.85)	12.56 (1.85)	15.31 (1.85)	24.66 (1.85)	28.57 (1.85)
45	10.25 (1.85)	13.09 (1.85)	17.29 (1.85)	19.75 (1.85)	27.64 (1.85)	33.04 (1.85)
60	12.11 (3.94)	15.85 (1.85)	19.15 (1.29)	22.82 (1.05)	32.55 (1.41)	35.17 (1.33)
K^H	2.92	2.17	6.73	9.02	12.64	14.55
r	0.918	0.969	0.943	0.935	0.988	0.952

n = 6, * SD = standard deviation
K_H Higuchi rate constant [9]
R = rofecoxib, RPM = Physical mixture of rofecoxib and -βCD(1 : 1), R1 = rofecoxib-βCD complexes (1 : 0.25), R2 = rofecoxib-βCD complexes (1 : 0.5), R3 = rofecoxib-βCD complexes (1 : 1), R4 = rofecoxib-βCD complexes (1 : 2)

pure drug and βCD complexes, whereas in the complexes it was observed that the amount (%) of drug released had increased greatly, although there were not much appreciable difference in the rates of release of the respective complexes. The highest dissolution rate was observed with the 1 : 2 complex when compared with pure drug.

3. Experimental

3.1. Material

Rofecoxib (Ranbaxy Laboratories, India), β-cyclodextrin (Cavitron, USA), and other reagents were used of analytical grade.

3.2. Methods

3.2.1. Preparation of solid complexes

Physical mixtures: The physical mixture (1 : 1) was prepared by mixing of pulverized powder of drug and β-cyclodextrin in 1 : 1 ratio then passed through sieve (100)
Solid complexes: A thick slurry was prepared by adding one third water by weight to β-cyclodextrin and then various ratios of rofecoxib were added with stirring. The paste was then dried in an oven at 45 °C until dry. The dried mass was pulverized and sieved through mesh no 100.

3.2.2. Phase solubility studies

Solubility studies were performed according to the method reported by Higuchi and Connors [4]. Excess rofecoxib was added to 30 ml of purified water (pH 6.8) containing various concentrations of βCD (0.002 M to 0.01 M) in a series of 100 ml volumetric flasks and then the mixture were shaken for 24 h at room temperature (25 °C) at 150 RPM. The mixture was then kept aside to achieve equilibrium. These mixtures were then filtered through Whatman filter paper No 41 and assayed for rofecoxib by measuring the absorbance at 276 nm, against blank solutions. The mixture was shaken till three consecutive samples estimated same amount of drug.

3.2.3. Spectroscopic studies

Complex formation between rofecoxib and βCD was also studied by spectroscopic methods. The concentration of the drug in these studies was 3.18×10^{-5} M whereas the βCD concentration was increased from 0.002 to 0.01 M. The UV spectra of drug were recorded on a Shimadzu UV-2101PC, UV-VIS scanning spectrophotometer. The changes in the absorbance of the drug on addition of various concentration of the complexing agent were measured at 276 nm to evaluate the stability constant of a complex.

3.2.4. Differential scanning calorimetry

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

3.2.5. Dissolution rate studies

The in vitro dissolution studies of pure drug, physical mixture and complexes (equivalent to 25 mg of rofecoxib) were carried out in 900 ml of dissolution media (0.1 N HCl and phosphate buffer pH 7.4), using USP 6-stage dissolution rate apparatus (Model-Electrolab programmable tablet dissolution test apparatus USP XXI/XXII, TDT-06P) with a paddle stirrer. The media was stirred at 50 rpm and maintained the temperature 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 rofecoxib measuring the absorbance at 276 nm.

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