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STUDIES ON DICLOFENAC -β- CYCLODEXTRIN INCLUSION COMPLEXES

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ABSTRACT

This work was aimed at investigating diclofenac-**β**-cyclodextrin inclusion complexes in aqueous medium. Applying the method of phase solubility analysis, **β**-cyclodextrin formed a complex in 1:1 stoichiometry with diclofenac. The complex obeyed Beer's law. The stability constant, partition coefficient and solubility values were evaluated. The effect of pH on the stability of the complex was studied. The results indicated an increased aqueous solubility of diclofenac when complexed with ß-cyclodextrin. Maximum stability of the complex was at pH value of 4.0. This makes it possible for aqueous oral solution of diclofenac to be formulated.

Key words: *Cyclodextrin; inclusion complex; stability; diclofenac; phase solubility.*

Introduction:

Cyclodextrins are cyclic oligosaccharides containing a minimum of six D-(+)-glucopyranose units attached by α-1,4 linkages produced by the action of Bacillus macerans amylase on starch. The chemical and physical properties of the four most common natural cyclodextrins (α, β, γ, δ)? have been compared.[1] Cyclodextrins contain a relatively hydrophobic central cavity and hydrophilic outer surface. The β and γ forms are the most useful in pharmaceutical technology.[1] they have been used in drug incorporation and dissolution[2], drug solubilization[3], improvement of organoleptic properties and change in reactivity of drug or guest molecule[4], stabilization of labile drugs such as Benzocaine, vitamin A and fatty acids against heat, oxygen and water.[5] Cyclodextrins may accelerate degradation in some drugs like indomethacin inclusion in β -cyclodextrin at pH 8.0.[6] Inclusion complexes have been evaluated using different methods, which are specific for the particular property for which the complex was formed as – partition coefficient, partition rate, conductimetric titration, membrane permeation, phase solubility analysis, stability and water solubility.[7,8]

Diclofenac is a phenylacetic acid derivative and a potent cyclooxygenase inhibitor with anti-inflammatory, analgesic and antipyretic properties.[9] It is very slightly soluble in water (Less than 1:1000). The presence of cations (Na^+ or K^+) markedly affects the solubility of diclofenac. Diclofenac has been shown to undergo degradation in solution and in solid state.[9] This research was aimed at investigating the properties of diclofenac-β-cyclodextrin inclusion complexes for a possible development of a formulation regime for aqueous diclofenac solution for oral administration.

Materials and Methods

Materials

The following materials were used as procured from their local suppliers without further purification. Diclofenac powder (Ciba, England), β-cyclodextrin (S. A. Chemical, India) and chloroform (May & Baker, England). Distilled water was obtained from an all glass still. All other reagents and solvents were of analytical grade and were used as such.

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Methods

Preparation of the complex

A 5 % w/v solution of β-cyclodextrin was prepared in distilled water. An excess amount (5 g) of diclofenac (exceeding its solubility) was then added and the resulting suspension constantly agitated for 96 h. After equilibration, it was later filtered and the filtrate concentrated by freeze-drying.[10]

Beer's Plots

Increasing concentrations each of diclofenac and diclofenac-β-cyclodextrin complex were prepared in distilled water. Their absorbances were determined in a spectrophotometer (SP 8-100 UV-Vis. Double Beam, Pye Unicam, England) at 270 nm (λ_{max} for diclofenac) and 280 nm (λ_{max} for the complex) respectively. The absorbance values were plotted against the concentrations to yield the Beer's plots.

Analysis of the complex

Determination of partition coefficient

Aqueous solution of diclofenac was prepared and saturated with chloroform in a flask and shaken vigorously for 5 min. The mixture was poured into a separating funnel and observed until an equilibrium state was obtained at 37 ± 0.5^{0}C. The aqueous phase was collected and centrifuged and a portion was diluted adequately with water and analysed in a spectrophotometer at 270 nm. The above procedure was repeated for the complex.

Phase-solubility analysis

This was carried out according to method of Higuchi and Connors.[11] Diclofenac, in an amount exceeding its solubility (1g) was accurately weighed in a weighing balance (August Sauter, KG D-7470, Germany) and placed in test tubes containing 10 ml of distilled water (pH 7.0) in which various quantities of β-cyclodextrin were added. They were mixed very well and the test tubes kept in a shaker at room temperature for 96 h, after which the solutions were filtered and analysed spectrophotometrically at 280 nm. The phase solubility studies were further carried out in phosphate buffer at pH 4.0, 5.0 and 7.5.

A plot of total molar concentration of the drug (diclofenac) against the total molar concentration of β-cyclodextrin gave phase-solubility diagrams from where the apparent stability constants, K_C were calculated for all the pH values using their regression lines according to the following equation.

$$K_c = \frac{\text{Slope}}{[S_o\,(1-\text{Slope})]} \quad \text{.....(1)}$$

where So is the solubility of pure drug without β-cyclodaextrin.

Solubility determination

An excess quantity of diclofenac was weighed out and dissolved in 10 ml of distilled water. An excess quantity of the complex solution was also dissolved in 10 ml of distilled water and both resultant solutions shaken vigorously at 37 oC for 96 h, and filtered. A 10-fold dilution was done on a sample from each solution with distilled water (pH 7.0) and the samples analysed spectrophotometrically as before. The absorbance values were converted to concentration by reference to the appropriate Beer's plot.

Results and Discussion

Diclofenac and its complex with β-cyclodextrin obeyed Beer's law. Regression analysis of the two Beer's plots (not shown) showed that the straight lines could be individually described by these regression equations.

$$A_{270nm} = 8.7257[Dicl] + 0.0009 \quad \text{……(2)}$$

$$A_{280nm} = 0.202[D-\beta-cyclod] + 0.0067 \quad \text{……(3)}$$

where [Dicl] represents the concentration of diclofenac, [D-β-cyclod] represents the concentration of the complex and A is the absorbance

Partition coefficient

Diclofenac had a partition coefficient value of 21.31 whereas the complex was 0.27 and was much lower than the drug alone such that the apparent solubility of diclofenac in the aqueous solution was significantly increased by its complexation with β-cyclodextrin, unlike the pure diclofenac that has more affinity for the non-aqueous phase. This represented approximately 78.93-fold increase in aqueous solubility of diclofenac.

Phase solubility analysis

The result of the phase solubility analysis carried out on the complexes is presented in Fig. 1.

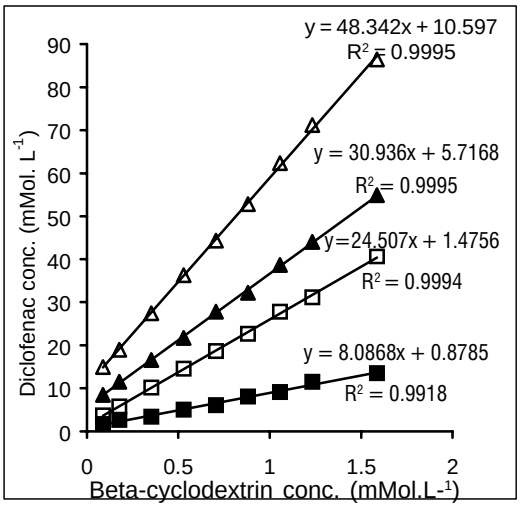

Fig. 1. Phase solubility analysis of the diclofenac-β-cyclodextrin complexes.
■ pH 4.0, □ pH 5.0, ▲ pH 7.0, △ pH 7.5

Fig. 1 shows that the solubilities of the various concentrations of β-cyclodextrin in the complex linearly increased with increasing concentrations of the β-cyclodextrin at all the pH values studied. As a result, the phase solubility diagram gave an A_L-type of curve, which is first order with respect to the cyclodextrin, and first or higher order with respect to the drug.[10,11] This indicates the formation of a soluble complex of constant composition between the diclofenac and the β-cyclodextrin. The experimental slopes that were less than one in all cases thus indicated that the stoichiometry of the complexation was 1:1 between the diclofenac and β-cyclodextrin.

From equation 1, the apparent stability constants, K_C of the diclofenac-β-cyclodextrin complex calculated from the slopes of the phase solubility diagrams were 53.50, 50.9, 48.5 and 47.9 L mol^{-1} respectively at pH 4.0, 5.0, 7.0 and 7.5. This indicates that unionized diclofenac interacted more strongly with β-cyclodextrin compared to the ionized form, since K_C decreased with increase in pH, and diclofenac being acidic in nature.

Conclusion

The formulation of diclofenac in aqueous oral form as an inclusion complex with β-cyclodextrin may have the advantage of improving its solubility and bioavailability as well as stability. This may increase compliance in paediatric management of febrile conditions. It should however, be noted that this is the result of a preliminary study of β-cyclodextrin inclusion complexation with diclofenac.

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