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Influence of water soluble polymers on hydroxypropyl-β-cyclodextrin complexation of rofecoxib

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Rofecoxib (Rb) is a nonsteroidal anti-inflammatory drug (NSAID) with poor aqueous solubility. The present study was undertaken to investigate the influence of water-soluble polymers namely sodium carboxymethyl cellulose (Na CMC), polyvinylpyrrolidine (PVP) and polyethylene glycol (PEG-6000) on hydroxypropyl β-cyclodextrin (HP β-CD) complexation of Rb. The complexes were prepared by kneading, autoclaving and precipitation techniques in 1 : 1 and 1 : 2 molar ratios. The aqueous solubility enhancement of Rb by these polymers is found to be of the following order: Na CMC > PVP > PEG-6000. Complexes were characterized by Fourier transform infrared (FTIR) spectroscopy, Nuclear magnetic resonance (NMR) and X-ray diffractometry (XRD) techniques. *In vitro* dissolution studies were carried out on tablets formulated from molar ratios of the complexes prepared by different techniques.

1. Introduction

Cyclodextrin (CD) inclusion complexes are considered as promising means of increasing the solubility and dissolution rate of poorly water soluble drugs (Beckers et al. 1991). Water insoluble drugs are usually characterized by low bioavailability, as their absorption is dissolution rate limited and consequently slow (Abdou 1989). Water soluble polymers such as hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose (NaCMC), polyethylene glycols (PEG's) and polyvinylpyrrolidine (PVP) have recently gained attention in these systems as they increase the solubilization efficiency of cyclodextrins by increasing the solubility and stability constant of the complexes, even when employed in small concentrations (Loftsson et al. 1996). Thus cyclodextrin complexation (with or without water soluble polymers) of hydrophobic drugs aim to act as a fast release dosage form with better dissolution or absorption characteristics (Loftsson et al. 1994).

Rofecoxib is a nonsteroidal anti-inflammatory (NSAID) drug with poor aqueous solubility, that exhibits anti-inflammatory, analgesic and antipyretic activities. (Schmidt et al. 2004; Harel, 2004; Barden et al. 2005; Matheson and Figgitt 2001).

The aim of this study was to improve the release properties of rofecoxib via complexation with HP β-CD and to study the influence of three water-soluble polymers namely Na CMC, PVP and PEG-6000 on the complexation efficiency of HP β-CD.

2. Investigations, results and discussion

Phase solubility studies of Rb clearly indicate that water soluble polymers like PVP, Na CMC and PEG-6000 potentially improve the aqueous solubility of the drug. The optimum concentration of the polymers rendering highest drug solubility are shown as Table 1.

Phase solubility studies of Rb confirmed the solubility enhancement capabilities of the CDs. HP-β-CD showed the formation of A_L type of phase solubility curves.

The apparent stability constant (K_S) were calculated with HP-β-CD alone and in presence of each water soluble polymer.

The diffractogram of Rb exhibited a series of intense lines which indicate its crystallinity. The clear disappearance of important crystalline peaks of Rb situated at 16.08 and 22.33 (2θ) in PH2 and AB1 systems, suggest the presence

Table 1: Optimum concentration of the polymers rendering the highest drug solubility

Polymer type	Concentration of the polymer (%w/v)	Highest Rb solubility (μg/ml)	Solubility enhancement
PVP	0.25	1.489	2.84 times
Na CMC	0.30	1.632	3.11 times
PEG-6000	0.15	1.082	2.06 times

Table 2: Apparent stability constant K_S of rofecoxib with several HP-β-CD derivatives

Type	K_S (M−1)
Rb-HP-β-CD	1106.28
Rb-HP-β-CD (0.25% w/v PVP)	1382.36
Rb-HP-β-CD (0.30% w/v Na CMC)	1769.90
Rb-HP-β-CD (0.15% w/v PEG-6000)	1336.81

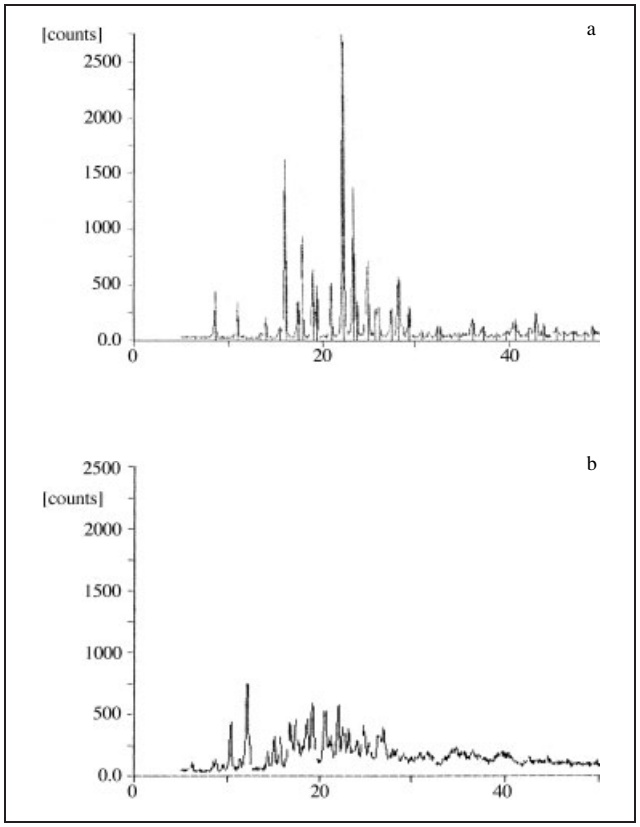

Fig. 1: a: XRD spectrum of pure drug (Rb); b: XRD sprectrum of Rb-HP β-CD complex

of a new solid phase with lower crystallinity than the drug, where a possible complexation of Rb inside the cyclodextrin cavity was contemplated as shown in Figs. 1a and 1b.

In the IR spectra of inclusion complexes the peaks at 2925, between 690–1000 and 1740 cm^{-1} are masked and/or flattened which gives proof of strong inclusion complex formation. The characteristic band of Rb at 1150 cm^{-1} also showed reduced intensity in complex systems, which may have resulted from its restriction within CD cavity.

Rofecoxib shows a CH_3 peak between 3.22 and 3.53 ppm and a CH peak at 5.51. The aromatic portion of the molecule gives a multiple peak between 7.26 and 8.22. The observations of the spectra were sufficient to confirm the complex formation as evident from difference in spectra of Rb before and after complexation with the CD's as shown in Figs. 2a and 2b. Position of proton signals in Rb were shifted marginally in some and significantly in others, which clearly indicates the existence of complexation between the drug and the CD's.

In vitro dissolution performances of the tablets fabricated from complexes prepared by the precipitation method was compared with conventional tablets. A 1 : 2 molar ratio of Rb : HP-β-CD showed 77.7% drug dissolved in 60 min.

In conclusions the complexation with HP-β-CD improved the solubility of Rb, also water soluble polymers have shown an synergistic effect in increasing the aqueous solubility of Rb. The FTIR, XRD and NMR studies of the complexes showed significant evidence of complexation. The rate of dissolution of Rb from HP-β-CD complexes of the drug prepared by precipitation was found to be significantly higher than that from complexes prepared by other methods.

3. Experimental

3.1. Materials

Refecoxib, PVP, Iodium CMC and HP β-CD were generously donated by Ranbaxy Research Laboratories, Gurgaon, India. Polyethylene glycol 6000

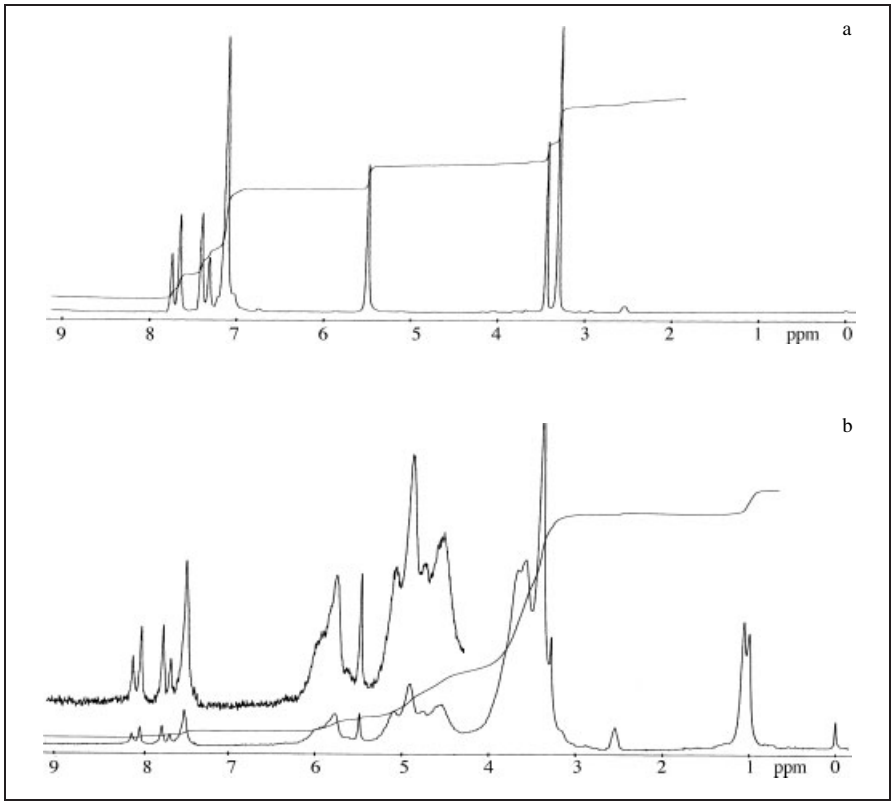

Fig. 2
a: NMR spectra of pure drug (Rb); b: NMR spectra of Rb-HP-β-CD complex

(PEG-6000) was obtained from S.D. Fine Chem. Ltd., Mumbai, India. All other chemicals used were of analytical reagent grade.

3.2. Phase solubility studies

Solubility measurements were conducted according to the method of Higuchi and Connors (1965). An excess amount (20 mg) of the drug was added to a constant volume (20 ml) of aqueous solution of various water-soluble polymers (Na CMC, PVP and PEG-6000) ranging from 0 to 0.5% w/v concentrations. The solutions, contained in stoppered conical flasks were shaken at room temperature for 48 h and then equilibrated for next 3 days. After equilibration, solutions were filtered through a G-2 sintered filter and after appropriate dilutions, samples were analyzed spectrophotometrically (Jasco, Model 7800, Japan). The solubility of the drug was plotted against polymer concentration and the optimum concentration of each polymer which rendered maximum drug solubility was determined.
Similarly phase solubility studies were performed on HP-β-CD, to study the effect on the aqueous solubility of Rb caused by HP-β-CD alone and in presence of each 0.25% w/v PVP, 0.30% w/v Na CMC and 0.15% w/v PEG-6000. The amount of dissolved drug was plotted against the cyclodextrin (HP-β-CD) concentrations. The apparent stability constants (K_S) were calculated using the following equation:

$$K_S = \frac{\text{slope}}{S_0(1 - \text{slope})} \quad (1)$$

where, S_0 is the solubility of drug without cyclodextrin.

3.3. Preparation of inclusion complexes

HP-β-CD complexes of Rb were prepared by the following methods without and with the addition of selected optimum concentration of Na CMC, PVP and PEG-6000.

3.3.1. Heating in a sealed container (autoclaving)

A slurry of Rb and HP-β-CD in weighed amounts (1 : 1 and 1 : 2 molar ratios) was prepared in a flask containing distilled water. The slurry was heated in an autoclave at 120 °C for 40 min. During heating, HP-β-CD and their complex were almost dissolved. The hot solution was then removed from the autoclave and allowed to slowly cool at room temperature with continuous shaking, until the solid complexes precipitate out completely. The precipitated complexes were filtered and dried in a hot air oven (110 °C) and stored in a desiccator.

3.3.2. Kneading

For preparing 1 : 1 molar ratio complexes, Rb and HP-β-CD were taken in a mortar and pestle and kneaded thoroughly by adding small amounts of water for about 1 hr. The paste obtained was then dried in a hot air oven at 100 °C. The dried powdered complexes were passed through sieve # 82 and stored in a desiccator. The complexes of 1 : 2 molar ratios were also prepared by the same method.

3.3.3. Precipitation

To prepare complexes of 1 : 1 and 1 : 2 molar ratios by this method, calculated amount of Rb and β-CD/HP-β-CD were dispersed in distilled water and then heated to 85–90 °C for 15–20 min followed by slow cooling at room temperature. The complexes were separated out, filtered and dried in a hot air oven (110 °C) and stored in a desiccator.

3.4. Characterization of inclusion complexes

All the prepared complexes were characterized in solution form through UV spectroscopy and in solid state through Fourier transformed infrared (FTIR) spectroscopy, Nuclear magnetic resonance (NMR) and X-ray diffractometry (XRD) techniques.

3.5. In vitro dissolution studies

All the prepared complexes, fabricated and commercial tablets were subjected to *in vitro* dissolution studies using an USP XXII digital dissolution rate test apparatus. Distilled water (900 ml) was used as dissolution medium, maintained at 37 ± 0.5 °C throughout the study. Stirring speed of the paddle was maintained at 100 rpm. The aliquots were withdrawn at 10 min intervals for a period of 60 min. The dissolution medium was compensated with the same volume of fresh distilled water for maintaining sink conditions. The aliquots were analyzed spectrophotometrically at 263 nm. The cumulative percent release of Rb from each batch was calculated and plotted against the sampling time intervals.

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