RESEARCH PAPER

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Formulation and Evaluation of β-Cyclodextrin Complexes of Tenoxicam

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β-Cyclodextrin complexation of tenoxicam was attempted to enhance the solubility features of the drug. The stoichiometry and complex stability was determined by the phase solubility studies. The complex was characterised by infrared spectroscopy and X-ray diffraction studies. The complex prepared in 1:1 M ratio by various techniques were evaluated for its dissolution profile, thermal stability and photostability. The complex prepared by neutralisation method was found to yield very reliable and best results over that of the common solvent and kneading method.

The poor dissolution of relatively insoluble drugs has for long been a problem in the formulation of oral dosage forms. This limits the aspects such as absorption and bioavailability. Therefore, several approaches have been followed in improving the solubility of drugs, one being complexation using cyclodextrins[1]. Tenoxicam is a nonsteroidal antiinflammatory drug belonging to the class of oxicams. It has very poor aqueous solubility[2] and therefore an attempt has been made to prepare an inclusion complex of the drug with β-cyclodextrin with an aim of improving its extent and rate of dissolution.

MATERIALS AND METHODS

Tenoxicam was a gift sample from Recon Ltd., Bangalore, β-cyclodextrin was obtained from Biocon India Ltd., Bangalore. All other chemicals used were of analytical grade.

Phase solubility studies:[3]

Excess amount of tenoxicam was transferred to 50 ml of aqueous solution containing 0-10 mM concentration of β-cyclodextrin. These solutions were shaken for 5 days at 25±1° for equilibration. The solutions were filtered through Whatman no. 1 filter paper and the filtrate was estimated for tenoxicam spectrophotometrically at 368 nm.

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Preparation of complexes:

Kneading method:

β-Cyclodextrin was taken in a glass mortar and little water was added and mixed to obtain a homogenous paste. Tenoxicam was then added slowly while grinding. The mixture was ground for 1 h, during this process appropriate quantity of water was added to maintain suitable consistency. The paste was dried in an oven at 40° for 48 h. The dried complex was taken for study.

Common solvent method:

Tenoxicam and β-cyclodextrin were dissolved in 25% ammonia and the solvent was allowed to evaporate overnight at room temperature. The complex so prepared was pulverised and sifted through sieve no. 80.

Neutralisation complex:

Ingredients were dissolved in sufficient quantities of 0.1 N sodium hydroxide to dissolve and then mixed in a 100 ml beaker with constant stirring. Then 0.1 N hydrochloric acid was added slowly adjusting the pH to

7.55 to get the solid complex as precipitate. The solid was filtered and dried in an air circulation drier and stored in descicator.

The infrared spectra of complexes was recorded on a FTIR 8201PC, Shimadzu Corporation, Japan using KBr pellet method. Using a Philips, X-ray diffraction studies were conducted X-ray diffractometer Eindhoven Netherlands. The Nickel filtered copper radiation was used at a scanning speed of 1°/min[4].

Dissolution:[5]

The formulation equivalent to 20 mg of tenoxicam was taken for dissolution study in USP XXII dissolution testing apparatus which was maintained at 37±2° in 500 ml of pH 1.2 and pH 7.4 buffer media. Samples were withdrawn at various time intervals and the basket was replaced with equal volume of appropriate media. The sample were analysed for the drug content spectrophotometrically.

Accelerated stability studies:[6]

The samples were stored at various temperature conditions such as room temperature, 37, 45 and 60° for a period of 12 weeks and the samples were withdrawn at weekly intervals for the estimation of the drug content. The samples were also stored in transparent containers and exposed to direct sunlight at the rate of 6 h a day for a period of 12 weeks and the sampling was done similar to that of the thermal stability studies.

RESULTS AND DISCUSSION

The method followed for phase solubility study was found to be reliable and reproducible. The equilibrium period of 5 days was judged on attempting several trials of different periods of shaking. The curve obtained was of B_s type (Fig. 1). The initial ascending portion is followed by a plateau region and then a total decrease in solubilised tenoxicam concentration due to precipitation of microcrystalline complex at higher concentrations. This type of solubility curve indicate the formulation of a complex with 1:1 stoichiometry in the initial stages and the formation of complexes of multiple ratio in the later stages.

In the IR spectra, the peaks assignable to $-CH_3$ and and -OH groups does not show a shift in that of complex confirming the non interaction of these groups with β-cyclodextrin. But the peak assignable to the heterocyclic ring [1428 cm^{-1}] is found to be missing

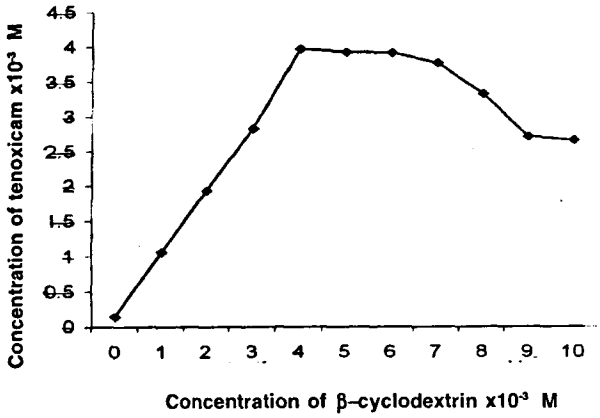

Fig. 1 : Phase solubility studies

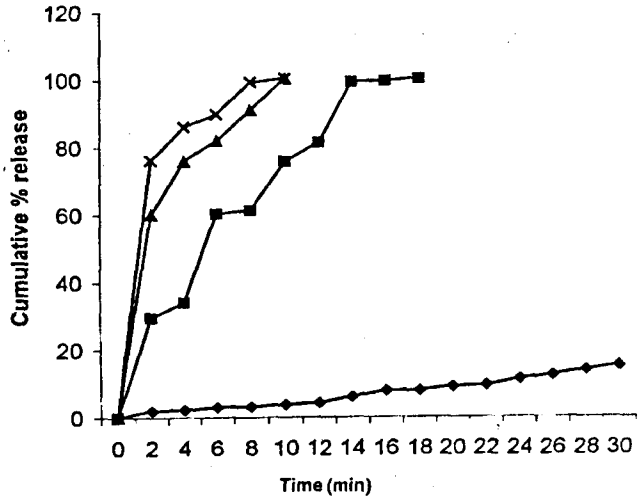

Fig. 2 : Dissolution profile of tenoxicam (◆) and its cyclodextrin complexes prepared by kneading (■), common solvent (▲) and (X) neutralisation technique at pH 1.2

in all the complexes prepared by various methods. This may be due to entrapment of the heterocyclic ring in the lipophilic core of β-cyclodextrin.

The powder X-ray diffraction pattern of the drugs is considerably affected by complexation with β-cyclodextrin owing to change in their crystalline nature. The appearance of new peaks and widening of existing peaks are an indication of chemical interaction between the complexing agent and the drug and change in the crystalline nature of the drug. In the complexes prepared by common solvent method and neutralisation method, the new peaks occurred almost at the same point and suppression of many peaks at 17.5, 17.7, 19 and 26.5 were observed. The peaks were less sharper than that in tenoxicam pure drug. Therefore,

TABLE 1 : FIRST ORDER DEGRADATION RATE CONSTANT (K) OF COMPLEXES PREPARED BY VARIOUS TECHNIQUES SUBJECTED TO STABILITY STUDIES

Method of Preparation	Room Temperature	37±1°	45±1°	60±1°	Direct light exposure
Pure drug (10^{-2})	1.02±0.43	1.34±0.32	1.52±0.12	1.59±0.70	4.88±0.70
Kneading method (10^{-3})	1.32±0.18	1.51±0.37	2.00±0.17	2.07±0.82	6.20±0.93
Common solvent Method (10^{-3})	0.69±0.08	0.83±0.18	0.94±0.24	1.12±0.32	4.32±0.89
Neutralisation Method (10^{-3})	0.54±0.12	0.62±0.19	0.70±0.10	0.72±0.22	3.30±0.77

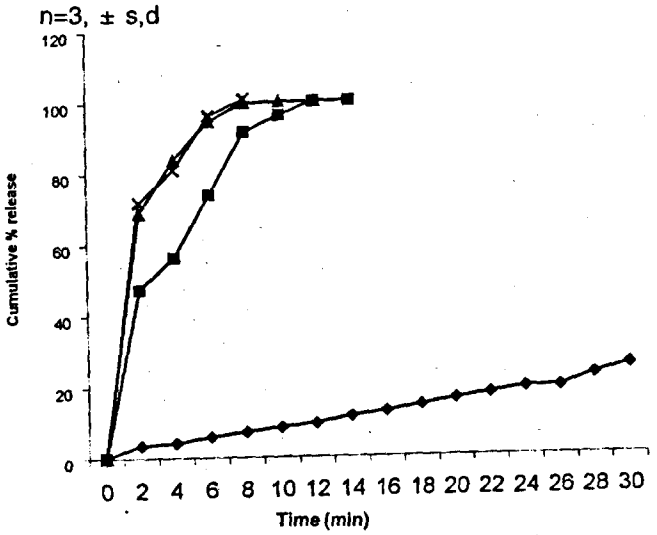

Fig. 3 : Dissolution profile of tenoxicam (◆) and its cyclodextrin complexes prepared by kneading (■), common solvent (▲) and neutralisation technique (X) at pH 7:4

the complex may be regarded as a mixture of crystalline and amorphous forms.

The dissolution studies revealed that all the formulations showed an increased rate and was more in alkaline medium which may be due to an ionisation of the drug as it is a weak acid. The complexes prepared by various techniques was found to have an influence on the dissolution rate. The one prepared by neutralisation method was found to yield a complex of higher rate of dissolution over common solvent and the latter over the kneading method. The dissolution profiles of the pure drug and the formulations in pH 1.2 and pH 7.4 buffer media are shown in Fig. 2 and 3.

The complexes prepared by various techniques were found to exhibit a better stability over the pure drug at all storage conditions as well as when exposed to sunlight. Of all, the complex prepared by neutralisation method was superior with respect to resistance to thermal and photodegradation. The results in terms of first order degradation constant are shown in the Table 1.

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