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# INCLUSION COMPLEXATION OF LORAZEPAM WITH β - CYCLODEXTRIN

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## ABSTRACT

The preparation of an inclusion complex of Lorazepam, a benzodiazepine antianxiety agent with β - cyclodextrin is described. The inclusion compound was prepared by the homogeneous coprecipitation method in the molar ratio of 1:2 of the drug and β -cyclodextrin respectively. The formation of inclusion complex was evaluated by UV spectral studies, IR studies, X-ray diffractometry, and Differential Thermal Analysis. The solubility and in-vitro drug release studies indicated that the complex form of the drug significantly increase the solubility and the dissolution rate

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compared to the free form. Tablets prepared with Lorazepam- β -cyclodextrin complex also showed a significant increase in dissolution of the drug indicating that β -cyclodextrin plays an important role in the solubilization of the drug.



## INTRODUCTION

Cyclodextrins have been one of the subjects of interest for numerous industries including those engaged in the pharmaceutical field.[1]. This is due to their particular structure that imparts interesting physico-chemical properties. Today, cyclodextrins are known for their ability to molecular encapsulate a wide variety of drugs into their hydrophobic cavity, resulting in the enhancement of water solubility and drug dissolution rate.

Cyclodextrins (also called Cycloamylose,Schardinger dextrins or Cycloglycans) are cyclic malto oligo-sachharides in which the glucose units are linked by α-1, 4 glycosidic bonds.[2] Due to their particular arrangement of the glucose units, it imparts the molecule a cone like structure which makes the exterior of the cone hydrophilic and interior of the cone hydrophobic in nature.[3] This characteristic of the polymer has led to the encapsulation of drugs into its cavity resulting in the improvement in solubility and drug release [4-8].

In the present study, the effect of β -cyclodextrin on the solubility and invitro drug

release[9] of Lorazepam was investigated. β -cyclodextrin was used for the study, as it has bigger cavity size of (7.5 °A) and is the least toxic among the other natural cyclodextrins.

## MATERIALS AND METHODS

Materials :

Lorazepam and β -cyclodextrin were generously donated by Cipla Ltd ( India) and Nihon Shokuhin Kako Co. Ltd., Tokyo ( Japan), respctively. They were used as such after checking their purity.

All the reagents and solvents used were of analytical grade.

Methods :

Solubility studies

The solubility studies were carried out according to Higuchi & Conners [10]. Solutions containing various concentrations of β -cyclodextrin in distilled water were added to excess amounts of Lorazepam and were shaken at room temperature for 24 hrs. After equilibrium, the solutions were carefully filtered through whatman No.41 filter paper and the portion of the final solutions were analysed for drug contents at 233 nm using a Beckman DB 25 spectrophotometer. The presence of trace amounts of β -cyclodextrin did not interfere with the estimation.

Preparation of Lorazepam- β -cyclodextrin Complex

The solid complexes were prepared by taking different ratios of Lorazepam : β -cyclodextrin

calculated on the molecular weight basis (e.g. 1:0.5, 1:1, 1:1.5 & 1:2) by the coprecipitation method [11].

Lorazepam was dissolved in ethanol at room temperature to which required moles of β -cyclodextrin in distilled water was added. The mixture was stirred at room temp., for 1 hr and then slowly evaporated on a boiling water bath. The inclusion complex precipitated as a crystalline powder was pulverised, sieved ( 100 #) and stored in a dessicator till free from any traces of the organic solvent.

Physical mixtures of Lorazepam and β -cyclodextrin were also prepared in the same molar ratio by gradually mixing both the powders in the vials, sieving and storing the mixture in dessicator till further use.

Evalution of Inclusion Complex :

Characterisation of inclusion complex in solid state :

1. IR spectral studies :

The IR spectra of the free drug, inclusion complex and the physical mixture were taken in Nujol using Perkin Elmer Infrared Spectrophotometer Model - 281.

2. Differential Thermal analysis ( DTA) :

The inclusion complex, free drug and the physical mixture were subjected to DTA studies using an Automatic Recarding Homemade DTA set up ( Bhabha Atomic Research Centre, Tromby, India). Alumina was used as a reference at scanning rate of $4^{o}C$/min.

3. X-ray diffraction studies :

Power X-ray diffraction was carried out using a Philips Diffractometer model PW - 170 with a gonoimeter

using a nickel filter Cu K ( $\alpha$ ) radiation operating at 30 Kilowatts and 20 milliamps in the range of $20^{o}$ and 10 - $60^{o}$ and scanning rate of $2^{o}$/min.

Characterisation of inclusion complex in aqueous state

1. UV spectral studies :

The inclusion complex was accurately weighed and sufficiently diluted with distilled water to produce a final concentration of 10 mcg/mL. This solution was scanned spectrophotometrically in UV region. The plot of absorbance vs wavelength was made and compared with the plot of the free drug.

2. In - vitro drug release studies :

In vitro drug release was carried out using a USP XXII type II dissolution apparatus with 500 mL. distilled water as dissolution medium at 37 $\pm$ $0.5^{o}$C and 100 rpm for 30 min. The aliquots were diluted and analysed for drug content spectrophotometrically at 233 nm. $T_{50}$ and $T_{90}$ were also determined.

Preparation of Tablets :

Tablets of lorazepam (2mg) were prepared from inclusion complexes and pure drug by wet granulation method using starch (paste) 10%, talc 1%, Magnesium stearate 1% and Ac-Di-Sol 0.5 % . Lactose was used as a diluent to make a final tablet weight of 150 mg. The granules were compressed using single stroke cadmach tablet machine.

The tablets prepared were evaluated for all pharmacopoeial parmeters including in-vitro drug release studies.

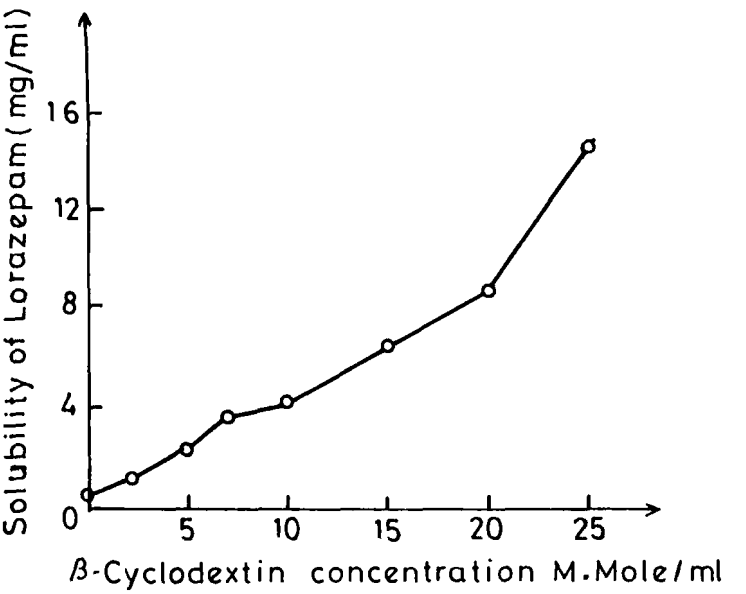


FIG.1 : PHASE SOLUBILITY DIAGRAM

## RESULTS AND DISCUSSION

Phase solubility diagram :

Fig. 1 shows the phase solubility diagram for Lorazepam along with β -cyclodextrin in water at room temperature. It can be seen that the solubility of Lorazepam increased almost linearly as a function of β -cyclodextrin concentration & hence the solubility curve could be classified as Higuchi Type A in which a complex is formed in the stoichiometry of 1:2.

Characterisation of the complex in solid state :

1. IR spectral studies :

For the inclusion complex, a simple superimposition of the drug and β -cyclodextrin was seen. The C-O

stretching prominent in the spectra of pure Lorazepam and the physical mixture, was completely absent for the complex. It could, probably, be due to the restriction of the C-O group of Lorazepam into the β-cyclodextrin cavity resulting in the disappearance of the C-O band.

2. Differential Thermal Analysis (DTA) :

The endothermic cooling peaks of Lorazepam-β-cyclodextrin physical mixture & the solid complexes in the ratios of 1:1.5 and 1:2 were compared.(Fig. 2) It was observed that a sharp endothermic peak at 165°C was obtained for Lorazepam, indicating the melting point of the drug. β-cyclodextrin showed a prominent cooling peak at 100°C. The physical mixture of the molar ratio 1:2 showed a sharp endothermic peak at 164°C and prominent peaks of β-cyclodextrin. However, in the cases of the complexes, the peaks were totally different in nature and the endothermic peak of the drug was at 161°C (1:1.5) and 160 C° (1:2) respectively. The peak of β-cyclodextrin was totally absent in the case of 1:2 inclusion complex.

3. X-ray diffration studies :

It was seen that the spectrum of the physical mixture was simply a superimposition or summation of the drug and β-cyclodextrin, but that of the inclusion complex gave somewhat diffused diffraction pattern showing that a new solid phase was formed, indicating the formation of the complex. (Fig. 3)

Characterisation of inclusion complex in aqueous state

1. UV Spectral studies :

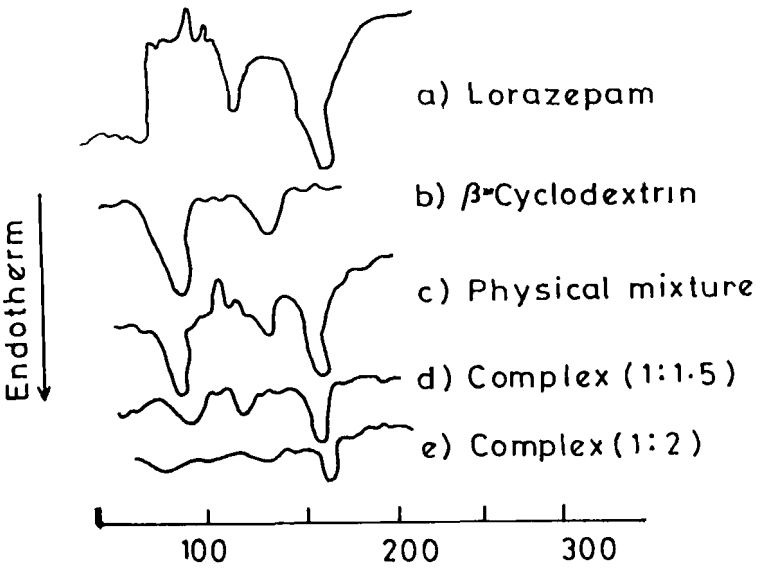


FIG. 2 : DIFFERENTIAL THERMAL ANALYSIS



No bathochromic shift was observed in the presence of β-cyclodextrin and also the intensity of the absorbance maxima evidently decreased in the complex as a result of partial shielding of the chromophore electrons into the β-cyclodextrin cavity.

2. In-vitro drug release studies :

Fig. 4 & 5 report the in-vitro drug release profilies of Lorazepam β-cyclodextrin complex in water at 37°C. It was found that about 97% drug release was obtained from the inclusion complex ( 1:2) as compared to 33% release from pure Lorazepam at the end of 30 min. The $T_{50}$ and $T_{90}$ values were less for the inclusion complex than the drug, indicating a faster dissolution and drug release from the inclusion complex. The tablets prepared from inclusion complex of lorazepam (1:2) showed 96% drug released

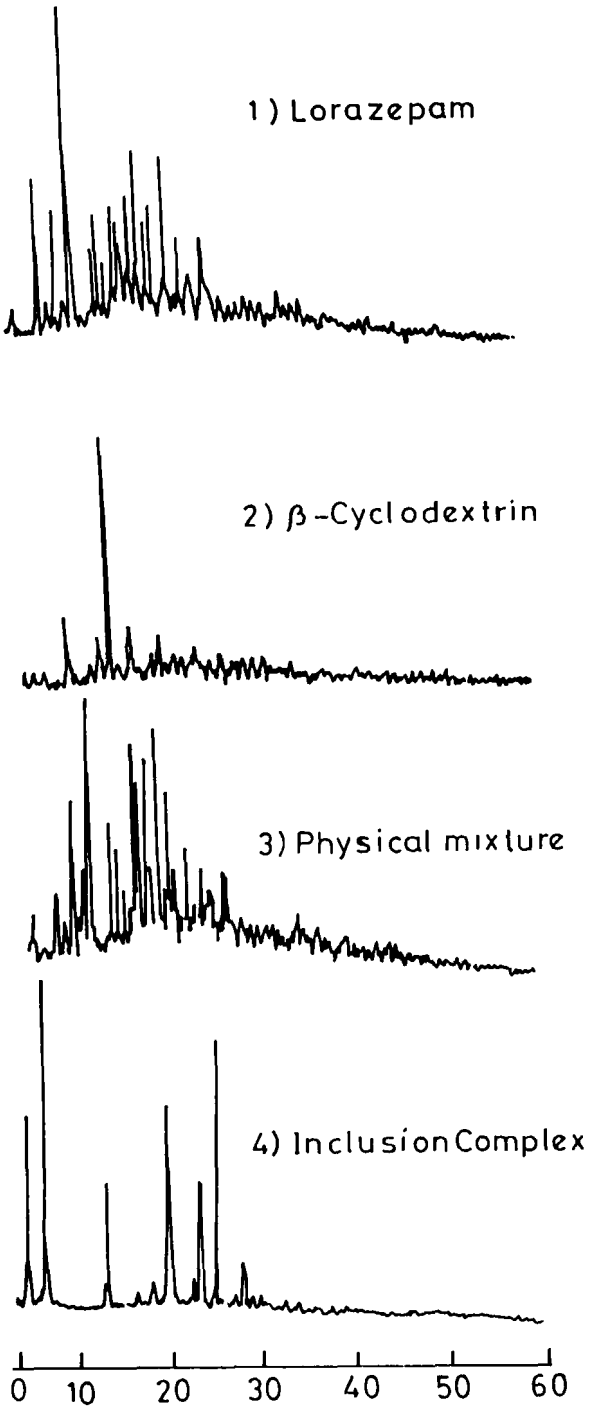


FIG. 3: X-RAY DIFFRACTION STUDIES

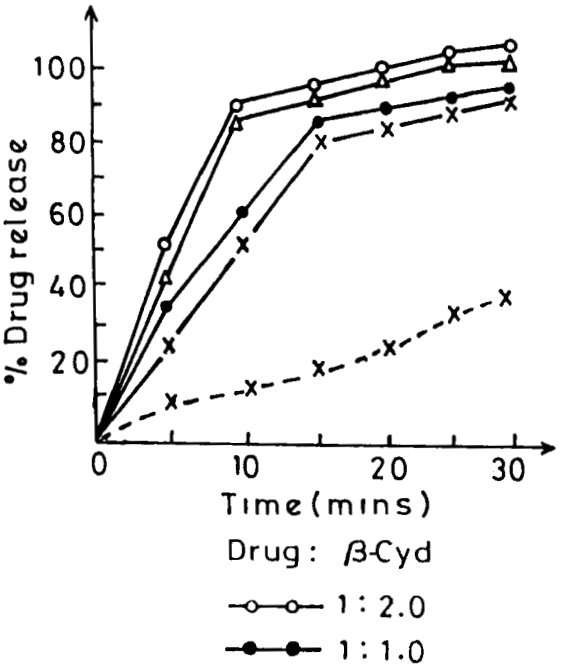


FIG. 4 : DRUG RELEASE PROFILES OF LORAZEPAM

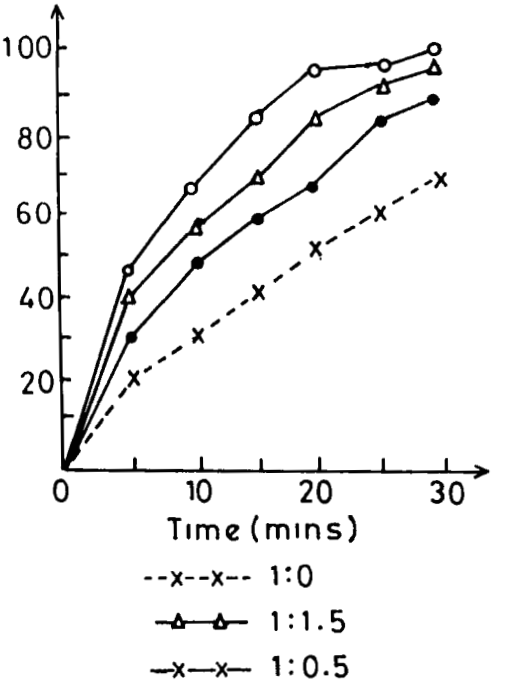


FIG. 5 : DRUG RELEASE PROFILES OF TABLET

TABLE 1

| Lorazepam : β-cyclodextrin | $T_{50}$ (min.) | $T_{90}$ (min.) |
|---|---|---|
| 1 : 0.5 | 7.5 | 38.1 |
| 1 : 1.0 | 6.6 | 30.7 |
| 1 : 1.5 | 6.1 | 25.9 |
| 1 : 2.0 | 2.3 | 17.4 |

compared to 65% release from control tablets. The control tablets showed $T_{50}$ value of 20.68 min while that for the inclusion complex (1:2) tablets had 6 min. (Table 1)

## CONCLUSION

An inclusion complex of Lorazepam and β-cyclodextrin could be prepared by the coprecipitation method. The optimum ratio of Lorazepam & β-cyclodextrin on molar basis was found to be 1:2. The inclusion complex and tablets prepared from it were found to have improved in-vitro drug release compared to control samples.

## REFERENCES

1) J. Cohen and J. L. Lach, J. Pharm. Sci., 52,132 (1963)
2) J. Szejtli, in "Controlled Drug Bioavailability", Vol -3, eds, V. F. Smolen and L. Ball, A Wiley, Interscience publication, 365 (1985).

3) D. Duchene and D. Wouessidjewe, Acta Pharma. Technol., 36, 1, (1990).
4) D. Duchene, F. Glomot, C.Vaution, in "Cyclodextrins And Their Industrial Uses". eds, Duchene, D, De sante, Paris, 6 (1987).
5) Y. Nakai, K. Yamamoto, K. Terado and H. Horibe, J.Incl. Phenon., 2,523 (1984).
6) K. Vekana, S. Narisawa, F. Hirayana and M. Otagiri, Int. J. Pharm., 19,327 (1983).
7) K. Uekama and T. Fujinaga, Int. J. Pharm., 10, 1 (1982).
8) O.T. Corrigan and C.T. Stanley, J.Pharm.Pharmacol., 34, 621, (1982).
9) The United States Pharmacopoeia, XXII, Mack Printing Company,Easton,PA 18042, 780, (1990).
10) T.Higuchi and K. Connors. Adv. Anal. Chem. Instr., 4,117 (1965).
11) G. Puglisi, N. A. Santagati, and R. Pignatello, Drug Dev. Ind. Pharm., 16, 395 (1990).