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Inclusion Complexation of Ketoprofen with β-Cyclodextrins

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Ketoprofen, a non-steroidal anti-inflammatory agent, is chemically a propionic acid derivative having poor aqueous solubility. This study describes method of inclusion complexation of ketoprofen with β-cyclodextrin (β-CD) and hydroxypropyl β-cyclodextrin (HP-β-CD). The solid complexes were prepared by various methodologies such as physical mixture, co-precipitation, kneading and freeze drying. The drug and cyclodextrins were used in molar ratio of 1:1. These complexes were characterized by U.V., FT-IR, ^{1}H-NMR Spectroscopy, Differential Scanning Calorimetry, and X-ray diffractometry. Freeze drying method was found to be the method of choice for successful inclusion complexation of Ketoprofen with β-CD and HP-β-CD.

Ketoprofen is primarily used as an anti-inflammatory analgesic for treatment of osteoarthritis[1] and rheumatoid arthritis[2]. Ketoprofen is believed to act by inhibition of prostaglandin synthesis[3,4]. Non-steroidal anti-inflammatory drugs, which are generally very slightly soluble in water and cause adverse reactions due to a stimulant property to stomach upon oral administration. These adverse reactions can be overcome by giving their aqueous solution along with β-cyclodextrins (β-CD)[5].

β-Cyclodextrins are cyclic oligomaltoses which have been shown to improve solubility, dissolution rate and stability of a number of drugs by inclusion complexation[6]. Chemically modified β-cyclodextrins overcome the inherent low solubility characteristics of the natural β-cyclodextrins[7,8].

The present investigation throws light on enhancement of aqueous solubility of ketoprofen by using different methods of complex formation with β-CD and HP-β-CD as well as to study the host-guest interaction by sophisticated analytical techniques.

MATERIALS AND METHODS

Ketoprofen was procured from Rhone Poulenc, Mumbai, India, β-cyclodextrin was a generous gift from American Maize Company, U.S.A. and hydroxypropyl-β cyclodextrin from Nihon Shokuhin Kako co. Ltd. Japan. All the reagents and solvents used were of analytical grade.

Preparation of the Complexes

Kneading Method : β-CD and Ketoprofen at a 1:1 molar ratio were wetted with ethanol (96% v/v) : distilled water (4:6) solution. It was kneaded to get a paste and then dried in a vaccum dessicator for 4 h.

Coprecipitation Method : Coprecipitate of ketoprofen-β–CD (1:1 mole ratio) was prepared by the solvent method using ethanol in a beaker with constant stirring at 60° which were subsequently dried.

Freeze Drying Method : A mixture of β-Cd and Ketoprofen (1:1 mole ratio) was dissolved in aqueous ammonia solution. The solution was stirred for 2 h and freeze dried (Edward Freeze dryer). The HP-β-CD. Ketoprofen complex in the solid state was prepared in a similar way.

In order to study the effect of processing parameters, drug alone (without cyclodextrins) was subjected (treated

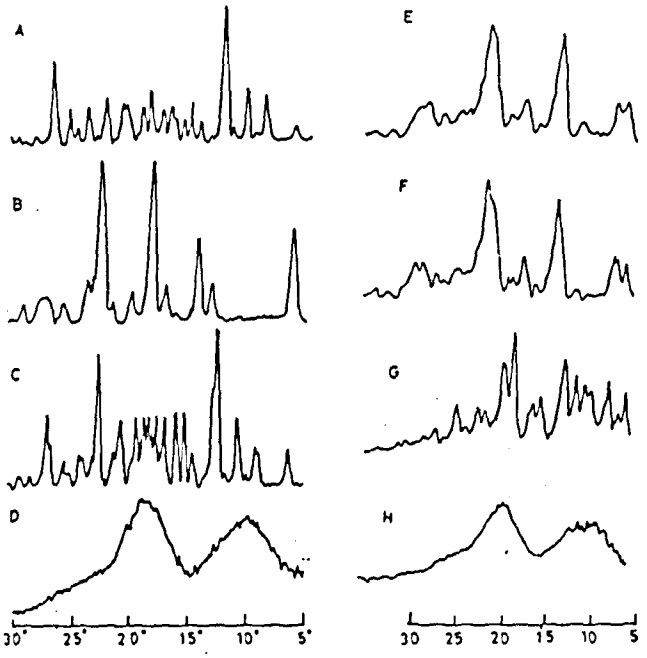


Fig. 1 : X-ray Diffractogram A/B-Cyclodextrin; B/ Ketoprofen; C/ Physical mixture of β-CD and Ketoprofen; D/ HP-β-CD; E/ Kneaded complex (β-CD-Ketoprofen); F/ Coprecipitated complex (β-CD Ketoprofen); G/ Lyophilised complex (β-CD-Ketoprofen); H/ Lyophilised complex (HP-β-Cd-Ketoprofen)

drug) to kneading or co-precipitation or freeze drying method before characterization.

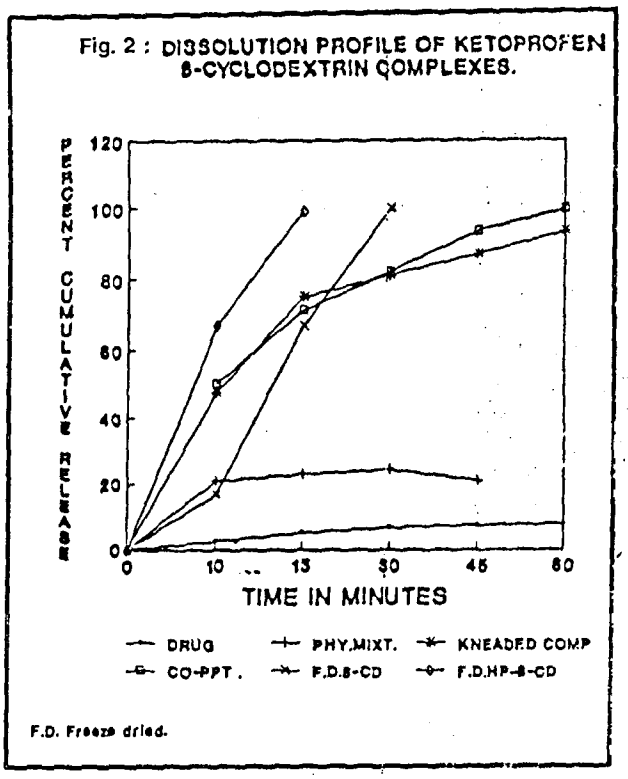
Characterization of Ketoprofen, Physical Mixture and complexes.

U.V. Visible Spectrophotometric studies : An accurately weighed quantity of drug-cyclodextrin complexes were dissolved in distilled water and the absorbance was recorded at 253 nm and was observed for any spectral changes.

FT-IR Studies : The FT-IR spectra were recorded by using KBr disc as reference on a Jasco F.T. Infrared Spectrophotometer model 281.

Differential Scanning Calorimeter Studies : Thermal analysis was carried out using a Perkin Elmer DSC Model 7 with a temperature increase of 10°. The scanning range was 0-200 °.

X-ray Diffraction Studies : X-ray Diffractometry was



carried out using a Philips Powder, Diffractometer Model PW 17291 with a gonoimeter using a Nickel filter cuk$_\alpha$ radiation operating at 30 KW and 20 mamps in the range of 40 degrees. The scanning rate employed was 1° per min.

Nuclear Magnetic Resonance Spectoscopy : The Bruker ^{1}HNMR Spectrometer AMX500 with 500MHz frequency was used for the studies. Deuterium Oxide was used for complex evaluation.

***in vitro* Dissolution Studies :** Dissolution studies were conducted for Ketoprofen, physical mixture and inclusion complexes using USP XXII Apparatus I The speed of rotation was set at 100 rpm. The dissolution medium used was 0.1N hydrochloric acid and the bath temperature was maintained at 37±0.2°. Samples of 5 ml were collected at 5, 10, 15, 30, 45 and 60 minutes intervals. The samples were filtered and the filtrates were analysed Spectrophotometrically at 253 nm.

RESULTS AND DISCUSSION

The FT-IR Spectra of freeze dried complexes demonstrated a shift of carbonyl band of ketoprofen from 1697.5 cm^{-1} to 1660.86 cm^{-1} which confirms complex formation. The DSC thermograms in which, the

Table 1 - Disolution Data of Complexes

Type of complexes	T_{25} (Min.)	T_{50} (Min.)	T_{90} (Min.)	Rate constant (K)
Physical Mixture	16	35	58	0.024
Co-precipitation	11	22	42.5	0.824
Kneading	12	25	48.0	0.759
FreezeDrying (β-CD)	7.0	14	26.0	3.718
Freeze Drying (HP-β-CD)	4.0	8.0	14.0	6.664

endothermic peak of drug at 94° is shifted to 90° indicating inclusion complex formation in case of co-precipitated and kneaded complex. The endothermic peak of drug is completely diminished in the thermograms of freeze dried complexes (β-CD and HP-β-CD). The X-ray diffraction studies (Figure.1) showed broadening of the peaks indicating existence of a new solid phase. The peaks at 2.1, 8.5 10.5 and 18.8° of the drug observed in the plot of the physical mixture are not evident in case of freeze dried complex. This confirms ketoprofen complexes with HP-β-CD in freeze dried complex. NMR Spectra of the complexes and the free drug, reveals that under the conditions employed (500 MHz) only shift changes of the signal occurred. There were no new peak that could be assigned to the complex itself[10,11]. Significant difference was not observed in FT-IR spectra, DSC thermograms and X-ray spectra for ketoprofen and treated ketoprofen indicating drug is not undergoing any changes due to processing parameters.

Dissolution profiles of ketoprofen, physical mixture and their respective complexes are illustrated in Figure 2. The dissolution profile for co-precipitated complex has T_{50} and T_{90} values of 22 and 42.5 min. respectively. The kneaded complex shows 25 and 48 min of. T_{50} and T_{90} values which indicates the coprecipitated complex have better dissolution profile as compared to kneaded complex. The freeze dried complex shows 14 and 26 min of T_{50} and T_{90} values respectively, which exist better than coprecipitated complex. Ketoprofen alone shows lower dissolution compared to complexes. The physical mixture showed a slight improvement in dissolution over that of drug. The dissolution rate of HP-β-CD complex appears to exhibit a faster dissolution rate in comparison with β-CD complex.

In conclusion, the results obtained demonstrate that aqueous solubility and dissolution rate of ketoprofen were significantly increased when complexed by freeze drying technology. The X-ray diffraction, DSC studies, FT-IR and proton NMR for freeze dried complexes showed clear evidence of complexation.

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REFERENCES

1. Famaly, J.P., Colinet, E. and Scan., **J. Rheumatolo.,** 1976, 5, 129.
2. Howard, D.L.G. **Current Therapeutic Research.,** 1978, 23, 678.
3. Lundstan, S.O.A. and Leissner, K.H., **Lancet** 1982, 1, 1096.
4. Kubata, T., Komatus, H, Kawamato, H and Yamada J., **Arch. Int. Pharma. dyn.** 1979, 237, 169.
5. Hamada, Y, Nambu. N. and Nagai, T., **Chem. Pharm Bull.,** 1975, 23, 1205.
6. Vekama, K. and Otagiri, M., **CRC. Crit, Rev.Ther. Drug Carrier System,** 1987, 3, 1.
7. Torres-Labandeira, J.J., Davignon P. and Pitha, H. **J. Pharm. Sci.,** 1990, 80, 384.
8. Loftsson, T. and Bodor, N., **Acta Pharm. Nord,** 1989, 1, 185.
9. Silverstein, R. M., Bassler, C.G. and Morrill, T.C., **Identification of organic compounds** Fifth edition, John wiley and sons, Inc., 1991, 1.
10. Luoutras, Y.H., Vraka V. and Gregoradis, G., J. Pharm. Pharmac **J. Pharm. Pharmacol.** 1997, 49, 127.
11. Djedaini F. Lin S. Perly B. and Wouessidjew, D., **J. Pharm. Sci.** 1990, 79, 643.