$_{\infty}$), ln $AUC_{(0-\infty)}$ at 90% confidence interval both the formulations were found to be bioequivalent. For the present test preparation all the acceptance criteria were completely fulfilled as per the guidance of CPMP for bioequivalence studies i.e 0.80 to 1.20 for untranformed data and 0.80 to 1.25 for the logtranformed data. Thus, bioequivalence between the test and standard preparation was demonstrated.

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Inclusion Complexation of Meloxicam with β-Cyclodextrin

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Inclusion complexes of meloxicam with β-cyclodexirin (β-CD) were prepared by various methods like grinding, kneading, solid dispersion and freeze drying. The prepared complexes were evaluated by FTIR, X-ray diffraction, differential scanning calorimetry and scanning electron microscopy. The *in vitro* dissolution rate of drug-β-CD complex was faster compared to the drug alone.

Cyclodextrins are cyclic maltooligosaccharides which have been extensively used to increase aqueous solubility of poorly soluble drugs[1-2]. Amongst the existing cyclodextrins, β-cyclodextrin (β-CD) has been used extensively to modify their physico-chemical properties[3-4]. Meloxicam is a preferential cox-2 inhibitor which is used in the treatment of osteoarthritis and rheumatoid arthritis[5-6]. The major drawback of this drug is its low aqueous solubility which delays its absorption from GI tract and its prolonged use is associated with incidence of side effects that include GI perforations, ulcerations and bleeding. Therefore, an attempt has been made to improve the aqueous solubility of meloxicam by complexing it with β-CD.

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Meloxicam and β-CD were gift samples from Sun Pharmaceuticals Ltd, Mumbai and Carestar Inc., USA, respectively. Other reagents and chemicals were of analytical reagent grade. The solubility studies[7] were performed by adding an excess amount of meloxicam to the aqueous solution of β-CD (MW-1135) at various concentrations (2-8 mM/l). The contents were stirred for 72 h at 30±1°. After equilibrium, the samples were filtered and absorbance read at 362 nm.

The inclusion complex was prepared in two molar ratios, 1:1 and 1:2. Physical mixture (PM) was prepared by triturating together the powders for 30 min in a clean, dry pestle and mortar. The kneaded dispersion (KN) was prepared by wetting the powders with water. It was kneaded to get a paste like consistency and stirring continued till it starts peeling off from the walls of the mortar. It was then dried in a hot air oven at 60° for 20 min. Solid dispersion (SD) was prepared by wetting the powders with 50% v/v ethanol. It was stirred to get a paste and rest of the procedure followed was the same as that mentioned for kneaded dispersion[8]. The freeze dried (FD) product was prepared by freeze drying a 25% aqueous ammonia solution containing meloxicam and β-CD in a benchtop lyophillizer. The solid obtained was sieved through 85 mesh.

DSC of the samples was carried out using DuPont model 910 (USA) system at a scanning range of 50-500°/10°/min. XRD of the samples was performed using high power X-ray diffractometer RU-200B from M/s Riguao, Japan. The scanning speed was 4° min. The FT-IR spectra of samples were recorded on FT-IR Magma IR 750 by Nicolet series II instrument using the KBr disc technique. Scanning was done from 4000 to 500 cm^{-1}. SEM of samples were performed using Joel scanning microscope JSM-840 with a 10 KV acceleration voltage.

Dissolution studies were conducted for pure meloxicam and for inclusion complex using USP Veego paddle type apparatus at 37±1° at 100 rpm. The dissolution medium used was 900 ml of 0.5% w/v sodium lauryl sulfate in distilled water[4]. The drug and the inclusion complex was filled in hard gelatin capsule shell so as to contain 15 mg meloxicam/capsule. At various time intervals, 5 ml sample was withdrawn and replaced with fresh dissolution medium. The absorbance of filtered sample was read at 362 nm. Experiment was performed in triplicate.

The phase solubility diagram for meloxicam-β-CD system in water can be characterized as Bs type phase solubility curve[7] which suggests that the molar ratio of the complex is 1:2 (fig. 1). Sanoferajan *et al.*[9] in a study on complexation of tenoxicam (a structurally similar NSAID to meloxicam) with β-CD also observed a Bs type curve during phase solubility study.

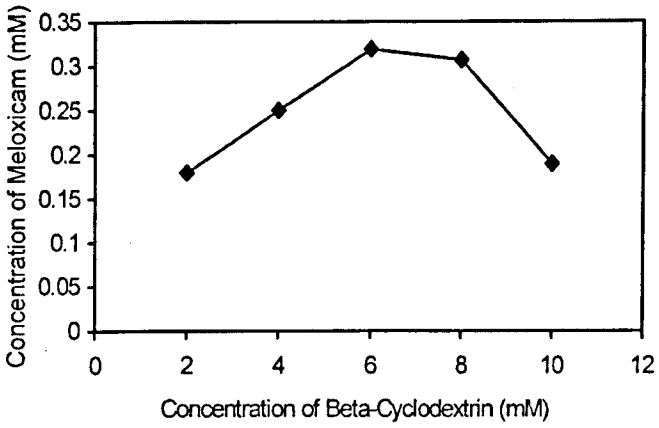

Fig. 1: Phase solubility diagram.

Effect of increase in concentration of β-cyclodextrin on the solubility of meloxicam.

The DSC graph for pure meloxicam shows a sharp endotherm near 252° which is indicative of its melting temperature followed by an exotherm which signifies that after melting, meloxicam decomposes. The thermograms of PM (1:1 and 1:2, drug-β-CD) are a combination of peaks of β-CD and meloxicam. In the thermograms for the KN (1:1 and 1:2) the intensity of the endotherm at 252° (which corresponds to the melting temperature of meloxicam) diminishes in intensity indicating partial complex formation. The DSC pattern of meloxicam β-CD complexes prepared by SD method shows diminished intensity of the drug melting endotherm indicating partial complex formation. In the FD complex the endothermic peak of the drug at 252° is not observed in 1:2 ratio and a very diminished endotherm is seen in 1:1 ratio, indicating that the drug has been engulfed in the cyclodextrin cavity (fig. 2). The XRD of the pure drug shows peaks that are sharp and intense signifying its crystalline nature. Peaks for PM (1:1 and 1:2, drug-β-CD) show diffused peaks with low intensity. In KN technique (1:1 and 1:2) most of the peaks can be seen indicating existence of crystalline nature. In case of SD (1:1 and 1:2) broad peaks of low intensity are there indicating partial amorphization of meloxicam. In FD complex, peak of meloxicam is completely missing in complex prepared in molar ratio of 1:2 suggesting complete amorphization of meloxicam. FT-IR spectra of meloxicam shows a distinct peak at 3291 cm^{-1} and β-CD

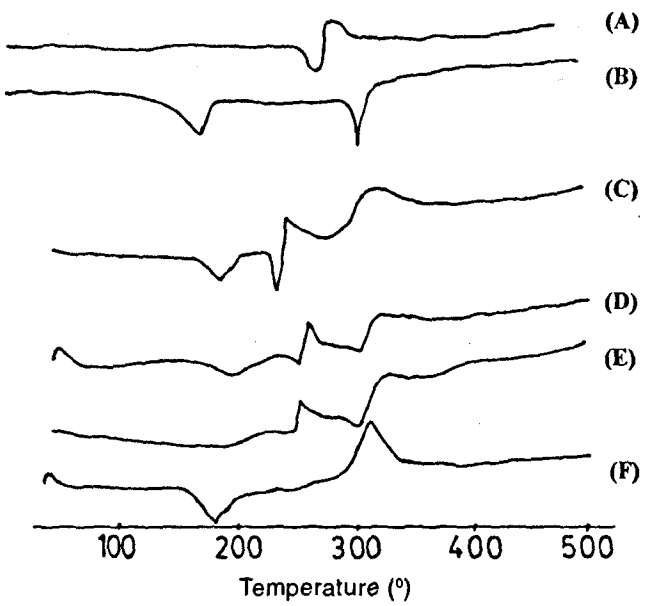

Fig. 2: Differential scanning thermograms of prepared complexes.

Differential scanning thermograms of meloxicam (A); β-cyclodextrin (B); and complexes prepared by Physical Mixture (C); Kneading (D); Solid Dispersion (E); and Freeze Drying (F) methods.

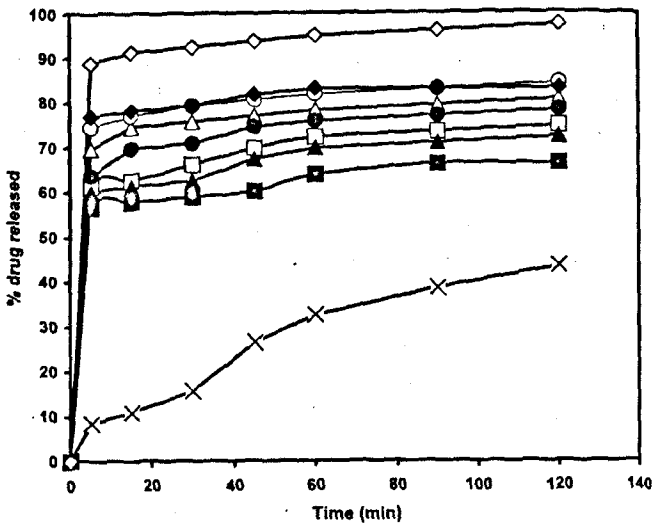

Fig. 3: Dissolution profiles of meloxicam and its complexes with β-cyclodextrin.

The *in vitro* dissolution rate profiles of pure meloxicam drug powder (-×-) and complexes with β-cyclodextrin prepared by Physical Mixture 1:1 (-■-); Physical Mixture 1:2 (-□-); Kneading 1:1 (-▲-); Kneading 1:2 (-△-); Solid Dispersion 1:1 (-●-); Solid Dispersion 1:2 (-○-); Freeze Drying 1:1 (-◆-) and Freeze Drying 1:2 (-◇-) methods.

shows a sharp peak at 3400 cm^{-1}. The PM, KN and the SD (1:1) show peaks corresponding to both meloxicam and β-CD. In the PM (1:2) the position and intensity of hydroxyl group decreases and they appear at 3390 cm^{-1}. However, the intensity of the amide band at 3311 cm^{-1} has increased indicating interaction of amide linkage with hydroxyl groups of β-CD, Almost identical spectra are seen for meloxicam β-CD inclusion complex prepared by KN and SD method. IR spectra of FD dispersion (1:1) show the partial overlapping of amide band at 3290 cm^{-1} in pure meloxicam with the hydroxyl band at 3262 cm^{-1} supporting interaction of meloxicam with β-CD. In 1:2 complex, the amide band at 3290 cm^{-1} is completely overlapped with hydroxyl band at 3383 cm^{-1} indicating interaction between meloxicam and β-CD and complex formation by FD method.

The SEM photomicrographs of PM of meloxicam-β-CD system shows the crystalline structure. The features of both crystals in the SD were not easily detectable. Furthermore, the micrograph of the FD system showed an amorphous product with the presence of small size particles tending to aggregation.

The dissolution profile of the inclusion complexes prepared by different methods is shown in fig. 3. It can be seen that after 15 min only 10.8% pure drug is dissolved and even after 120 min only 43.2% drug goes into solution whereas in case of meloxicam-β-CD inclusion complex prepared by FD method in a 1:2 molar ratio 91.2% drug was released within 15 min and almost complete release (95%) was seen after 60 min (Table 1). Nath and Shivakumar[10] have recently reported a similar increase in dissolution of meloxicam in presence of β-CD and PVP. It can be concluded that an inclusion complex of meloxicam with β-CD could be prepared successfully by FD method in a molar ratio of 1:2 and this was confirmed by solubility studies, DSC, XRD, FT-IR and SEM. Dissolution studies of the FD complex exhibited almost complete *in vitro* dissolution profile.

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