Five

Summary & Conclusions
Meloxicam is an established NSAID in the treatment of rheumatic diseases, and offers the convenience of once daily administration. Although it is a preferential COX-2 inhibitor, however it has been implicated in causing peptic ulceration and gastrointestinal bleeding. Gastrointestinal adverse effects are possibly the most troubling aspect of NSAID therapy, with reported relative risk of serious complications. Consequently, there is considerable interest in developing new NSAIDs and/or formulations with better gastrointestinal tolerability.

Therefore, in the present study a novel physico-chemical approach has been used to combine the established NSAID, meloxicam with a cyclic macromolecule i.e. β-cyclodextrin or hydroxylpropyl β-cyclodextrin to improve the aqueous solubility of the drug, thus enhancing its dissolution rate, thereby showing a faster onset of action and less gastrointestinal mucosal toxicity. Following conclusions can be drawn from the results obtained:

Meloxicam showed a Bs type phase solubility curve with increasing concentration of β-CD and HPβ-CD suggesting the formation of 1:2 complex in solution state.

In solid state the complexes of meloxicam with β-CD and HPβ-CD were prepared by four methods viz., Grinding, solid dispersion, kneading and freeze drying technique in two molar ratio i.e., 1:1 and 1:2. These complexes were characterized using Differential scanning calorimetry (DSC), X-ray diffraction analysis (XRD), Fourier transform infrared spectroscopy (FT-IR), Scanning electron microscopy (SEM) and Nuclear magnetic resonance (NMR) methods. It was concluded from the results of these characterization methods that maximum complex formation was achieved by freeze drying technique in a 1:2 (drug: cyclodextrin) molar ratio with both β-CD and HPβ-CD as complexing agents. Partial complex formation was achieved by solid dispersion and kneading methods.

The complexes of meloxicam with β-CD and HPβ-CD as complexing agent in the molar ratio of 1:1 and 1:2 prepared by different techniques were subjected to dissolution studies. The dissolution data indicated that all the complexes showed an increased rate of dissolution and dissolution was more in alkaline medium, which may be due to ionisation of the drug molecule as it is a weakly acidic substance. Technique used from making the
complexes was found to have an influence on the dissolution rate. The complexes prepared by freeze drying method were found to yield a complex of higher rate of dissolution over solid dispersion and the later over the kneading and grinding method, supporting an earlier observation that maximum complex formation was achieved with freeze drying technique in a molar ratio of 1:2.

Solubility profile of complexes of meloxicam prepared using β-CD and HPβ-CD as complexing agent in a molar ratio of 1:2 by freeze drying method in pH 1.2 and pH 7.4 indicated that the acid solubility of meloxicam was enhanced considerably by formation of an inclusion complex with β-cyclodextrin and hydroxypropy β-cyclodextrin.

Final optimised formulation contained meloxicam-β-CD/HPβ-CD inclusion complex (FD, 1:2) equivalent to 15 mg of meloxicam, starch, talc, magnesium stearate and microcrystalline cellulose. Comparative release studies also showed significant increased dissolution of the drug as compared to the marketed formulation “Muvera” (Sun Pharmaceuticals).

The result of the release rate data indicated that the coefficient of variation was lower for first order rate constant than the corresponding zero order values thereby suggesting that the drug release followed first order kinetics.

Optimized formulation i.e. meloxicam-HPβ-CD freeze dried complex (1:2) gave a significant higher percentage inhibition of carrageenan induced inflammation in rat hind paw at the 1st and 2nd hour as compared to meloxicam-β-CD complex (FD, 1:2) and pure meloxicam (p=0.0000055 and p = 0.000471).

In the ulcerogenic studies, the meloxicam freeze dried dispersion prepared with HPβ-CD was significantly found to reduce the ulcerogenicity of the drug as compared to meloxicam-β-CD freeze dried dispersion and pure meloxicam (p=0.0032).

LD₅₀ of the optimised tablet containing meloxicam-HPβ-CD freeze dried complex (1:2) was found to be 478.6 mg/kg p.o. which was comparable to the reported LD₅₀ of pure meloxicam (470 mg/kg p.o.).
Toxicity studies were carried out to establish the safety profile of the developed formulation [Meloxicam-HPβ-CD (FD,1:2)] using rats as the model animal. There was found to be no significant change in the cellular structure of liver, kidney, heart, spleen and stomach in the test animals. Further, the values of urea, creatinine, bilirubin, SGOT, SGPT, alkaline phosphatase, hemoglobin, TLC and RBC were also similar to the control groups, proving the safety of the formulation.

The tablets containing complexed drug were subjected to accelerated stability studies to ascertain the chemical and physical stability of the formulation. The tablets containing meloxicam-β-CD (FD,1:2) inclusion complex and meloxicam-HPβ-CD (FD, 1:2) inclusion complex were kept at 40° ± 0.5°C and 75% ± 5% RH. No significant changes in the properties like weight, hardness, thickness friability and disintegration time of the formulation was observed. The rate constant for the drug decomposition was $1.34 \times 10^{-4}$/day and $1.38 \times 10^{-4}$/day for β-CD complex and HPβ-CD complex respectively.

On the basis of good in-vitro response and pharmacodynamic studies and toxicity studies and in-vivo evaluation of the optimised tablets containing meloxicam-HPβ-CD inclusion complex (FD, 1:2) was done on six healthy human volunteers in a cross-over study after approval from the Institutional ethical committee. The bioavailability results showed that the developed formulation had faster absorption than a conventional meloxicam tablet formulation. Furthermore, higher and significant ($p<0.5$) values of $C_{\text{max}}$, $T_{\text{max}}$, and $\text{AUC}_{0-72}$ were obtained.

It can be concluded that the developed formulated containing meloxicam-HPβ-CD freeze dried complex (1:2) will have significant advantages in terms of a faster onset of action and reduced ulcerogenicity as compared to the presently available conventional meloxicam tablet in the Indian Pharmaceutical market.
ACHIEVEMENTS

1. Investigations with the complexation of meloxicam with cyclodextrins has been carried out successfully.

2. Among the various complexes prepared, meloxicam-hydroxypropyl-β cyclodextrin (1:2) complex prepared by freeze drying method gave the best results in terms of solubility and dissolution rate of drug.

3. The above complexation reduced the ulcerogenic activity of meloxicam significantly.

4. The formulation is stable and capable of being marketed as tablets.

5. Bioavailability studies in healthy human volunteers showed higher $C_{\text{max}}$, $T_{\text{max}}$ and $\text{AUC}_{0-72}$.

6. Technology has been developed which can be commercialised for improved formulation of meloxicam.