SUMMARY AND CONCLUSIONS

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Although there are many approaches available for improving dissolution rate and oral bioavailability each method is having its own limitations. Preparation of solid mixtures attracted the attention of many researchers for the enhancement of the dissolution rate. In the preparation of these solid mixtures carrier plays an important role and many carriers belonging to different classes were tried.

In the present research work two poorly water soluble non-steroidal anti-inflammatory drugs viz. Etoricoxib (EXB) and Celecoxib (CXB) were selected. The absorption of these drugs is dissolution rate limited and hence it is proposed to prepare solid mixtures for improving their dissolution rate and oral bioavailability.

Poly vinyl pyrrolidone-K 30, PEG 6000 and Mannitol are receiving more and more attention both in pharmaceutical formulations and drug carrier systems. Many of the PVP-K 30, PEG 6000, Mannitol which are being used as carriers which increase the dissolution rate of the poorly soluble drugs due to their hydrophilic nature associated with complex formation and increasing wettability, thereby reducing interfacial tension of drug in the dissolution medium. Hence in the present investigation the applicability of polymers PVP-K 30, PEG 6000 and Mannitol was successfully tested in the development of solid mixtures for poorly water-soluble drugs by using different methods of preparation.
Physical mixing (PM), kneading technique (KT) and solvent evaporation (SE) methods were used for the preparation of solid mixtures of the selected drugs Etoricoxib and Celecoxib with polyvinyl pyrrolidone (PVP-K 30), PEG 6000 and Mannitol as carriers. Solid mixtures using PVP-K 30, PEG-6000 and Mannitol were prepared in drug to carrier weight ratios of 1:1, 1:3, 1:6 and 1:9 for Etoricoxib and 1:1, 1:2, 1:4 and 1:6 for Celecoxib respectively. The same ratios were used for all the three methods used in the present investigation.

All the solid mixtures prepared were found to be fine and free flowing powders. Low c.v. Values in the percent drug content ensured drug content uniformity in each batch and reproducibility of the methods of preparation.

A simple economic and reproducible method was developed for the estimation of Etoricoxib in bulk and its pharmaceutical dosage forms using 0.1N HCL. The maximum absorbance was obeyed at 234 nm.

A new dissolution method for Etoricoxib was developed, as there is no official dissolution medium reported in the literature. 0.75% w/v of SLS in 0.1 N HCL was found to be the suitable dissolution medium.

The dissolution studies were carried out on all the prepared solid mixtures. For comparison dissolution of pure drugs were also done. Dissolution of solid mixtures was rapid compared to pure drug.
Different dissolution parameters like $DE_{10}$, $DE_{20}$, $T_{50}$ and $T_{90}$ were calculated. The $DE_{10}$ and $T_{50}$ values obtained for the solid mixtures prepared by different methods like PM, KT and SE using different drug-polymer ratios were subjected for statistical analysis using one way analysis of variance test. The statistical analysis data and different dissolution parameters confirmed that the solid mixtures of EXB: PVP-K 30 1:6 SE, EXB: PEG-6000 1:6 SE and EXB: MANNITOL 1:6 KM and solid mixtures of CXB: PVP K-30 1:4 SE, CXB:PEG 6000 1:4 SE and CXB: MANNITOL 1:4 KM were found to be optimized solid mixtures among different groups of solid mixtures prepared with Etoricoxib and Celecoxib respectively. In case of PVP K-30 and PEG 6000 and Mannitol increase in the drug-polymer ratio beyond 1:6 for Etoricoxib and 1:4 for Celecoxib caused decreased release rates. This may be due to the high viscosity generated by the polymers in the microenvironment of drug polymer particles during dissolution, reducing the diffusion rate of drug, thereby decreasing the dissolution efficiency.

The release of drug from the solid mixtures followed first order kinetics with a good positive correlation compared to Zero order. The mechanism of drug release was by erosion as per Hixon-Crowell equation.

Drug-carrier interaction studies were carried on the optimized solid mixtures by Fourier Transform Infrared Spectroscopy (FTIR), X-ray Diffraction (XRD), Differential Scanning Calorimetry (DSC) and Scanning electron microscopy (SEM) studies.

The principal absorption peaks of pure drug were found in all the prepared solid mixtures indicating no chemical interaction between drug and polymers in FTIR studies. In XRD studies Etoricoxib and Celecoxib exhibited characteristic diffraction pattern,
whereas in the case of solid mixtures with all the carriers, the sharp diffraction peaks have been changed. There was considerable decrease in the intensity of the sharp peaks in the diffractograms of solid mixtures indicating the reduced crystallinity of the drug in all the solid mixtures. This could be due to partial conversion of the drug to amorphous state from crystalline state. DSC studies indicated the formation of solid solution of drug and polymer with PVP-K 30 and PEG-6000 and MANNITOL. SEM studies the crystalline charters of Etoricoxib and Celecoxib was absent, and the crystals of the components (EXB, CXB and PVP-K 30) could not be differentiated. These microscopic observations indicated a good physical interaction of drug particles with PVP-K 30.

From the patient acceptance point of view tablets are the most preferred oral dosage forms and hence tablets of the optimized solid mixtures were compressed to evaluate the efficacy of these solid mixtures in the tablet dosage form. For comparison tablets of pure drugs were also compressed. Etoricoxib solid mixtures of EXB: PVP-K 30 1:6 SE, EXB: PEG 6000 1:6 SE, EXB: Mannitol 1:6 KM, compressed by wet granulation, whereas for other Celecoxib solid mixtures viz. CXB: PVP-K 30 1:4-SE, CXB: PEG-6000 1:4-SE and EXB: Mannitol 1:4 KM by using wet granulation technique was used to compare the method of tablet preparation. Wet granulation technique was alone used for all the Etoricoxib and Celecoxib solid mixtures by wet granulation technique only. Direct compression could not be used due to bulk of the powder. The prepared tablets complied with all the Pharmacopoeial and other standards. Though there was a decrease in the drug release compared to the respective solid mixtures the prepared tablets from optimized EXB: PVP-K 30 1:6 SE, EXB: PEG-6000 1:6 SE and EXB: MANNITOL 1:6 KM and CXB: PVP-K 30 1:4 SE and CXB: PEG-6000 1:4 SE and CXB: MANNITOL 1:4 KM
solid mixture gave faster dissolution compared to the respective commercial formulations. The release followed First order kinetics with erosion mechanism.

Reproducibility studies are performed for solid desperations of ETORICOXIB: PVP-K 30 1:6 SE prepared by solvent evaporation technique and CELECOXIB: PVP- K 30 1:4 solvent evaporation method. Five batches of solid dispersions are prepared under similar set of conditions and drug content of all the batches was calculated. The drug content values are subjected to one-way ANOVA test and it is concluded that there is no significant difference in the batches prepared.

Reproducibility studies are also performed for tablets containing ETORICOXIB: PVP-K 30 1:6 SE and CELECOXIB: PVP-K 30 1:4 SE ratio solid dispersions prepared by solvent evaporation technique. Five batches of tablets are prepared under similar set of conditions. The half-lives of all the batches are calculated. The half-lives values are subjected to one-way ANOVA test and it is concluded that there is no significant difference in the batches prepared.

The anti-inflammatory activity of Eterocoxib and its solid dispersion systems was evaluated by carrageenan induced rat paw oedema model employing Zeitlin’s apparatus to measure the paw thickness.

The inflammation due to carrageenan was markedly inhibited by Eterocoxib and its solid dispersion systems. EXB: PVP-K 30 exhibited a rapid onset and greater extent of anti-inflammatory activity when compared to Eterocoxib and corresponding solid dispersions. A good correlation was observed between in vitro dissolution rate (K₁) and in vivo anti-inflammatory activity of Solid dispersions of Eterocoxib.
The inflammation due to carrageenan was markedly inhibited by Celecoxib and its solid dispersion systems. CXB: PVP-K 30 1:4 SE exhibited a rapid onset and greater extent of anti-inflammatory activity when compared to uncomplexed Celecoxib. A good correlation was observed between *in-vitro* dissolution rate ($K_1$) and *in-vivo* anti-inflammatory activity of solid dispersions of Celecoxib.

The stability studies indicated no significant physical changes in the prepared tablets. The dissolution rate and pattern of release were not altered for both the drugs.

Thus the above study clearly indicated the applicability of the preparation of solid dispersions for improving the dissolution rate and oral bioavailability of the Etoricoxib and Celecoxib.