7. SUMMARY AND CONCLUSION

The limitations of conventional dosage forms lead the way to advanced drug delivery systems those include sustained release dosage forms. But even drugs delivered through such extended release dosage forms are known to show variations in pharmacokinetics and or pharmacodynamics. Besides, few classes of drugs warrant timely availability of a fraction of dose for immediate therapeutic outcome and prolonged exposure of drug in blood for the maintenance of such outcome till subsequent dosing. Dual release drug delivery systems are found more promising dosage forms for achieving such release pattern and to optimize the therapeutic outcome.

With this objective, the present work was designed to prepare a dual release drug delivery systems comprising fast and delayed release pattern using solid dispersion and minitablets / pellets of aceclofenac to achieve a desired in vitro and in vivo profile and therapeutic needs to overcome the variation in drug concentration in the plasma and to improve patient compliance.

The compatibility studies were performed to find out the compatibility between the selected grades of excipients (HPMC-K100, MCC-101, PEG-6000) and the drug (aceclofenac) and the results revealed that there was no drug-excipients incompatibility.

Aceclofenac solid dispersions were prepared by solvent evaporation method using PEG 6000 as carrier at different ratios. The prepared solid dispersion was evaluated for percentage yield, drug content and in vitro characterization. Based on the in vitro release studies, the formulation ASD-4 (1:4 ratios) was chosen as optimized batch and incorporated into dual release capsules of aceclofenac.

Aceclofenac pellets were prepared using different concentrations of HPMC by extrusion spheronization technique. The prepared sustained release pellets were evaluated for size distribution analysis, bulk density, porosity, Carr’s consolidation index, friability, drug content uniformity and in vitro release characteristics. Based on
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*in vitro* release studies the formulation containing 15% HPMC (M3) was chosen as the optimized batch and incorporated into dual release capsules of aceclofenac. Aceclofenac mini tablets were prepared using different concentrations of HPMC. The prepared mini tablets were evaluated for weight variation, hardness, drug content, disintegration time and *in vitro* drug release studies. Based on the *in vitro* release studies formulation containing 40% HPMC (F3) was chosen as optimized batch and incorporated into dual release capsules of aceclofenac.

Two types of dual release dosage forms were formulated incorporating the optimized batch of solid dispersion (ASD4) with either pellets (M3) or mini tablets (F3). The amount of pellets/mini tablets equivalent to 200 mg of aceclofenac (sustained release) and amount of solid dispersion equivalent to 100 mg of aceclofenac (immediate release) were filled in gelatin capsule (size 2) and were evaluated for their *in vitro* and *in vivo* drug release.

The dual release capsules showed a biphasic *in vitro* release pattern with initial burst release and sustained release following the quasi-Fickian diffusion-based release mechanism. Compared with the marketed SR and IR tablets, the dual release capsules showed better *in vitro* release profile. The release models were plotted and regression coefficient values were calculated. It was observed that the developed dual release mini matrix tablets and pellets followed first order kinetics obeying Fickian diffusion.

Bioavailability studies for the optimized dual release formulations were carried out to estimate the pharmacokinetic parameters. The peak plasma concentration ($C_{\text{max}}$) was achieved in 2 h and 3 h for spheroids and mini matrix tablets respectively. The $C_{\text{max}}$ of dual release pellets and mini matrix tablets was found to be greater than that of IR and SR dosage forms indicating that higher plasma concentration could be achieved faster than the SR formulation. Thus the absorption lag time associated with SR formulations could be minimized using these formulations.

Further, there was significant increase in AUC$_{0-\alpha}$ in case of dual release pellets and mini matrix tablets than the IR and SR indicating the enhanced absorption of poorly water soluble aceclofenac which may be attributed to enhanced solubility by solid dispersion technique and greater surface area of multiparticulate dosage forms.
There was no significant variation in $K_e$ and $t_{1/2}$ for pellets and mini tablets, when compared with marketed SR formulation. This indicated that the developed formulations did not change any intrinsic pharmacokinetic parameters such as $K_e$ and $t_{1/2}$.

In conclusion, the dual release drug delivery systems developed were able to deliver a first fraction of the dose in shorter time for quick onset of action and deliver a second fraction at a sustained rate for continuous therapeutic effect for a longer period of time. These novel dosage forms have also resulted minimal variation in plasma drug concentration and thereby result in optimal therapeutic outcome with minimal risk of either dose dumping or subtherapeutic levels.

Future Prospective

This device can be a useful tool for the formulations of those active ingredients for which specific delivery patterns and/or input rates are needed or will be needed in the future when more accurate pharmacokinetics and clinical trials will be developed.