SUMMARY AND CONCLUSION

SUMMARY

In present study soluble ocular inserts of Moxifloxacin Hydrochloride using PVA, in-situ gelling system of MOXI and indomethacin using gellan, and scleral implants of indomethacin using sodium alginate (track field type), ethyl cellulose (film type) and gellan (film type) were fabricated and characterized and compared.

Soluble ocular inserts of MOXI using PVAL and PVAH alone and in various combinations were fabricated by a casting technique. The in-vitro drug release from the prepared inserts was studied using a continuous flow –through system. The anti-microbial efficacy of the developed inserts against common ocular pathogens like S. aureus ATCC 25923 and P. aeruginosa ATCC 27853 were evaluated using a modified in-vitro microbiological model. The drug release from the prepared inserts followed matrix diffusion kinetics showing an anomalous release mechanism. The microbiological model demonstrated the in-vitro effectiveness of the inserts and correlated well with the results of the in-vitro release study.

In-situ gelling systems of MOXI using gellan alone and in combinations with sodium alginate, and indomethacin using gellan were prepared by dissolving the polymer(s) in hot (75°C) acetate buffer pH 7.4, respectively. The above prepared systems were evaluated for drug content, viscosity, sterility and gelling efficiency. The drug release from the prepared MOXI and indomethacin systems were studied using a modified method reported in the literature. The antibacterial efficacy of the selected batches of the prepared MOXI system was evaluated using a rabbit eye model. The pharmacodynamic efficacy of the prepared indomethacin system was evaluated in uveitis induced rabbit eye model. The rheological studies of the prepared systems showed that viscosity increased with an increase in polymer concentration. In case of MOXI system containing both sodium alginate and gellan, sterilization by autoclaving caused a 10 to 15 % reduction in viscosity, while the viscosity of gellan based systems remained unchanged. In case of the gellan-sodium alginate preparations, the gellan concentration was kept constant at 0.3% and the concentration of sodium alginate was varied. The total polymer concentration
could not be increased beyond 1%w/v. The pharmacodynamic studies showed that the formulations were far more superior in inhibiting the growth of the microorganisms for longer duration in comparison to a marketed eye drop of MOXI. In case of indomethacin system, sterilization by autoclaving did not cause any decrease in the viscosity of the preparations. The pharmacodynamic studies showed the propensity of the systems to control the various clinical parameters of uveitis effectively for prolonged periods (24 hours).

Indomethacin implants with sodium alginate alone and/or in combinations with HPMC were prepared by compressing using 2x7.5 mm punches, which yielded track field type of implants. Devices were formulated with and without calcium chloride for studying the effect of cross-linking (in-situ), when the device comes in contact with the dissolution medium. The implants were evaluated for physico-chemical properties like weight variation, drug content uniformity, hardness and friability. The drug release kinetics was evaluated using agar diffusion (1 and 2% agar), static dissolution, continuous flow through and USP basket methods. In all the case the effect of parameters like particle size, HPMC concentration and calcium chloride concentration were studied. Out of the methods studies, the agar diffusion method and the continuous flow through method showed prolonged drug release and also simulated the in-vivo conditions to a certain extent as far as the placement of the device and ocular tissue fluid dynamics are concerned. Ethyl cellulose-based scleral implants of indomethacin, prepared by casting were fabricated. The effect of ethyl cellulose concentration, drug loading and plasticizer concentration on the in-vitro drug release characteristics were evaluated. Selected batches of the implants were subjected to pharmacodynamic studies, after scleral placement, in uveitis induced rabbit eyes. The pharmacodynamic studies showed a marked improvement in the various clinical parameters in the implanted eye when compared to the control eye in the rabbits and more importantly the implants were intact at the end the studies (10 days). Film type scleral implants of indomethacin with gellan gum and plasticizers were prepared by solvent casting. The effect of plasticizers like glycerol, propylene glycol (PG), polyethylene glycol (PEG) 200 and 400 on the void volume of free gellan film (placebo) was calculated from the water content of the film. The drug release from the prepared implant was determined using a static dissolution set up. Based on the results of the void volume and initial drug release studies, glycerol and PG were selected as the plasticizers for the gellan-based implants. The morphology of the drug free films (containing 10
and 40% of PG) and of untreated and cross linked drug-loaded films (before and after dissolution) were studied using scanning electron microscopy (SEM).

Further, the effect of plasticizer concentration, gellan concentration, effect of calcium chloride cross-linking technique and cross-linking time on in-vitro drug release characteristics were evaluated. Selected batches of the implants were subjected to pharmacodynamic studies, after scleral placement, in uveitis induced rabbit eyes. The release of indomethacin from the prepared implants seemed to depend on both gellan and plasticizer concentration. Cross-linking with 10% calcium chloride for 8 hours (surface) retarded drug release by a factor of 1.42 than non cross-linked implant and was found to be optimum. The pharmacodynamic studies showed a marked improvement in the various clinical parameters detailed as before, in the implanted eye when compared to the control eye in the rabbits. The scleral implants survived up to 3 weeks in-vivo.

**CONCLUSION**

In conclusion it may be said that the goal of this research work was fulfilled by formulating the modern ophthalmic drug delivery systems of Moxifloxacin Hydrochloride and scientifically proved its superiority over its tradition counterparts (Eye drops and Eye ointments). Delivery systems meant for delivering the drug both to the anterior (inserts and in-situ gelling systems) and posterior globe (implants) of the eye were able to sustain the drug release for prolonged periods following matrix diffusion kinetics. A single application of the in-situ gelling systems or the soluble insert has the potential to replace 4 to 12 instillations of topical solution/ointment and thus may constitute a valid once-a-day therapy. These systems being soluble are likely to be eliminated and hence do not require removal. Scleral implants likewise afford some unique advantages over systemic or vitreous application, in that they are free from undue toxicity. “Once a day therapy” is the current gold standard, and oral/systemic therapy for ocular diseases will eventually be supplemented by “site specific” delivery systems as the ones studied in the present investigations.
SCOPE OF THE RESEARCH WORK

The limited *in-vivo* studies undertaken in the present study show that avenues do exist towards better more user-friendly ocular drug delivery systems. “Once a day therapy” is the current gold standard, and oral/ systemic therapy for ocular diseases will eventually be supplied by “site specific’ delivery systems.

- To produce ocular inserts in large batches.
- To study the pharmacokinetics and pharmacodynamics in higher animal models other than rabbits and rats.
- To ascertain the observed promising results in humans.
- To extend product evaluation to clinical studies.