SUMMARY

Developed ISGS for FQ drugs viz. LFX, OFX (BCS Class I); and NFX, equivalent to 0.5%, 0.3% and 0.3% w/v were found to be promising. Suitable amount of different gelling agents, tonicity adjusting agent and antimicrobial preservative were added. The formulations were based on the use of three different mechanisms for phase transition from sol to gel viz. pH sensitive, ion sensitive and temperature sensitive are used.

The results of compatibility study indicate no interaction between drug and polymers. All the developed IS gel formulations were evaluated for appearance, clarity, gelation temperature, gelling efficiency, pH and mucoadhesive force. The contents, clarity, and pH of the formulations were found to be in acceptable range and the formulations were liquid at room temperature and refrigeration too.

On the basis of clarity, gelling capacity, bioadhesion force and in vitro drug release study of all the formulations, selected formulations viz. P1, S2, G3, C3, P4, S4, G5, C4, P7, S7, G7 and C7 were further subjected to rheological behavior and transcorneal permeation study.

Thin layer chromatography was carried out to check the drug polymer interaction after autoclaving for selected formulations. Rf values were found to be nearly same for standard drug and its formulation after autoclaving. Formulations shows shear thinning nature with increase in shear stress with increase in angular velocity. The results obtained from the rheological study of prepared ISGS suggested that the viscosity decreases in ascending order of the angular velocity. The viscosity was directly proportional to concentrations of polymers present in the formulations.
Higuchi matrix diffusion mechanism was observed from all ISG formulation. The release of drug from this matrix is regulated by diffusion/erosion. The overall release was diffusion-controlled. The best fit kinetic model was Higuchi matrix model. When compared using student t test ANOVA followed by Dunnet’s test was done to study transcorneal permeation after 2 hr. LFX and NFX IS gel formulations showed sustained release as compared to marketed eye drop. For OFX containing IS gel formulation, only P4 showed sustained release.

Amongst the four formulations developed based on three systems, for FQ drugs viz. LFX, OFX and NFX for further study two systems were considered viz. gellan based ion sensitive ISG system and PXM based thermosensitive ISGS.

The formulations were found to be isotonic when compared with marketed LFX eye drop. The result of antimicrobial efficacy study shown that there were no changes in the antimicrobial activity of FQ drugs viz. LFX, OFX and NFX due to formulation ingredients and working conditions as compared to reference formulation (marketed eye drop formulation).

For scintigraphic studies, the observation of the gamma camera images showed that both, developed thermosensitive and gellan based ion sensitive ISGS form good clear gel over the corneal surface immediately after administration. Marketed eye drop solutions were cleared very rapidly from the corneal region whereas; all ISGS were cleared at slow rate and showed good retention for longer duration.

IS gel forming abilities of the developed systems significantly controls precorneal drainage. Thus, increased residence time in eye would help to increase ocular bioavailability.
Superficial corneal opacity has been observed with gellan based systems on the rabbit eye after gamma scintigraphy study. Thermosensitive ISG system does not show any opacity on the rabbit eye.

Further optimized thermosensitive ISG medicated formulation containing LFX, OFX and NFX was found to be well tolerated and nonirritant. Combination of 18%w/v PXM 407 and 4%w/v PXM 188 with 0.2%w/v HPMC K4M and 0.25%w/v chitosan, showing mucomimetic properties as well as optical clarity. The optimized IS gel formulation and commercial eye drops were subjected to *in vivo* studies to determine drug concentration in aq. humor in the eyes of rabbits. The MIC\textsubscript{90} of drug in aq. humor was achieved by ISGS and remained up to study duration of 6 hr. In the marketed eye drops solution, initial increase in drug concentration was drop down after some time. $C_{\text{max}}$ of ISG formulation was found to be higher than marketed eye drops solution at the similar $T_{\text{max}}$ of 1 hr. $C_{\text{max}}$ of ISG formulations i.e. P1, P4 and P7 was found to be 1.6, 1.5 and 1.3 times higher than marketed eye drops solution respectively at the similar $T_{\text{max}}$ of 1 hr. The AUC\textsubscript{0-360min} of LFX is more than OFX and NFX. The results indicate the significant permeation of LFX than OFX and NFX. Also the IS gel formulation showed more AUC\textsubscript{0-360min} than their respected marketed eye drop formulations. The more AUC\textsubscript{0-360min} of IS gel formulations is because of increased contact time in the eye. The developed IS gel formulations improved contact time, there by improved bioavailability of drug as proved from high drug aq. humor concentrations.

Selected sterilized formulations viz. P1, P4 and P7 were stored at 5±3°C and 30±2°C/65% RH ±5% RH for duration of 90 days. The formulations were evaluated at predetermined intervals for assay, clarity, pH, liquid–gel conversion and transcorneal
permeation, no significant change was observed. The optimized systems of LFX, OFX and NFX are ISG based on thermogelation, gels at 33-34°C. The formulation should be stored at cool conditions or below 25°C. At these storage conditions (cool place) the developed systems remains in the form of clear solution. As degradation was found to be less than 5 percent, approximate shelf life of 24 months can be allotted to the optimized formulations.