Summary & Conclusions
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Pharmaceutical preparations are applied to the eye to treat surface or intraocular conditions including infections of the eye or eyelids caused due to bacterial, fungal and viral pathogens, like allergic or infectious conjunctivitis or inflammation, elevated intraocular pressure and glaucoma. Pharmaceutical dosage forms and drug delivery systems applied topically to the eye includes solutions, suspensions, gels, ointments, inserts, drug impregnated contact lenses, etc. Though these dosage forms are well accepted by the patients due to greater uniformity of dosage and easy administration, they are mainly suffering with major problem of rapid precorneal drug loss that is due to a relative brief contact time between the medication and absorbing surfaces. Ophthalmic ointments even though they have increased contact time, it interferes with vision causing blurring due to its oily nature. Eye rejects oily fluids, so portion of the ointment is expelled upon its application. These dosage forms are drained into the nasal cavity and transferred into the blood stream and their high concentrations in the blood causing unwanted and unwarranted side effects. So, there is a need of developing a safe ophthalmic formulation that can be easily administered that cannot be easily expelled from the eye, that cannot interfere with vision, greater uniformity of dosage, which delivers precise dosage and mainly controlled release of drug from the delivery system. In the present research work, we have formulated a sol-gel system, which is combined with ease of administration of liquid forms with the prolonged residence time of inserts. Sol-gel systems are liquids in the container and thus can be instilled as eye drops and gels on contact with the tear fluid thereby it provides increased contact time with the possibility of improved drug absorption and increased duration of therapeutic effect.
In the present research work, initially diclofenac sodium (as a model drug) sol-gel systems were prepared using 0.3% and 0.4% carbopols and viscolizers in the selected concentrations and subjected to viscosity studies and in vitro drug release studies. The results of viscosity study indicate that the increased concentration of carbopol increases the viscosity and the added viscolizers in selected concentrations were helped in improving the viscosity of the formulations. *In vitro* drug release studies were carried out for about six hours by dynamic dialysis technique, nearly 60-70% of the drug was released within six hours.

Similarly Timolol Maleate sol-gel systems were prepared using the optimized concentrations of carbopol and viscolizers. The formulations prepared were evaluated for several parameters like viscosity, drug-polymer interaction, drug content uniformity, sterility, *in vitro* drug release, *in vivo* evaluation or therapeutic efficacy and ocular safety or eye irritation. The viscosity results showed that the increased concentration of carbopol increases the viscosity of the formulation and the added viscolizers in their selected concentrations helped in improving the viscosity. To know the in situ gelling property of each carbopol used and also to know the effect of added viscolizer, the viscosity results of timolol maleate sol-gel systems were fitted to two-way classification of ANOVA studies, the ANOVA results showed that, the three types of carbopols i.e., carbopol 934p, 971p and 974p were not same in their gelling property and the selected concentrations of viscolizers significantly improving the viscosity of the formulations. In all the cases, the F-calculated values were greater than F-table values, so, it rejects null hypothesis in favour of alternate hypothesis. To know the rheological behaviour of the timolol maleate sol-gel systems, some selected formulations containing each of carbopol and viscolizer were plotted for log viscosity versus log speed, the plots were fairly linear and the slope values calculated were less than 1.
indicating pseudoplastic behaviour (shear thinning) of the systems is an ideal property (desirable property) of sol-gel systems.

The drug-polymer interactions was studied by infrared spectral analysis, infrared spectra of pure timolol maleate and formulations were scanned. The spectra of formulations were identical with the spectra of pure drug timolol maleate and the spectral data suggests that the intactness of the thiadiazole ring structure of timolol maleate indicated by the absence of additional peaks which occurs due to the opening of the thiadiazole ring, hence the drug was not reacted with the polymers used in the study.

The drug content uniformity was carried out on all the timolol maleate formulations by direct UV-spectrophotometric method as described by Mazzo and Lopper. The results of drug content uniformity study showed that the drug content in all the formulations was in between 93.06% to 99.81% indicating the greater uniformity of the dosage in the formulations.

Ophthalmic preparations will come in contact with sensitive ocular tissues after their application, so, preparations should be sterile and hence the formulations prepared were subjected to test for sterility for detecting the presence of viable forms of micro-organisms. The sterility tests were performed for aerobic, anaerobic bacteria and fungi by using alternative thioglycollate medium and soyabean casein digest medium as per the IP procedure. The observation of the test showed that there was no evidence of microbial growth in the formulations tested for bacteria and fungi, the results concluded that the formulations passed the test for sterility and they were sterile.

Timolol maleate sol-gel systems were evaluated for in vitro drug release studies for about 8 hours in 7.4 pH phosphate buffer as diffusion medium,
nearly 69.65% to 99.18% of the drug was released from the formulations within a period of 8 hours. To know precisely, the rate and mechanism of drug release, the in vitro data was fitted to first order and Higuchi’s equation, the results showed that the drug release from the formulation follows first order release kinetic by diffusion controlled mechanism. The data were also treated to Peppa’s exponential equation, the slope values of exponential equation indicated that the release was found to be Fickian diffusion controlled in all the cases.

Timolol maleate sol-gel system was also evaluated for in vivo evaluation i.e., it was evaluated to check its ability to lower the intraocular pressure in albino rabbits, a comparative evaluation was also performed with commercially available eye drop. The marketed eye drop suddenly lowers the intraocular pressure to a minimum and afterwards there was a sudden increase in the intraocular pressure to the original reading, whereas timolol maleate sol-gel systems lower the intraocular pressure slowly to a minimum and thereafter a gradual increase in the intraocular pressure, this was mainly due to the high viscosity of the preparations, which helps in sustained release of timolol maleate from the formulations.

Finally, the formulation was evaluated for ocular safety in rabbit by the procedure of modified Draize technique. Here the measurement of injury to the eye i.e., to cornea, conjunctiva and iris was measured at 1st, 24th and 48th hour after the instillation of the formulation. The results of the study showed that the scores scored were less than the maximum total score indicating there was no irritation to the ocular tissues and hence the formulation was safe.
From results and discussion of the research work, following conclusions can be drawn:

- Carbopol 971p at 0.4% was found to be ideal in-situ gelling polymer for ophthalmic preparations.

- Hydroxypropyl methylcellulose at 0.3% was found to be the best viscolizer among others used in sol-gel systems.

- The preparations were free from any drug-polymer interaction.

- There was a greater uniformity of dosage in all the formulations prepared.

- The preparations passed the sterility test.

- Anti-glaucoma studies revealed that the designed formulation was ideal in the treatment when compared to the marketed ones.

- The preparations were found to be free from eye irritation.