Review Article

Optimization and Evaluation of Temperature Triggered in Situ Hydrogels for an Effective Treatment of Ophthalmic Preparations – A Perlustration

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ABSTRACT

This work reviews on the optimization and evaluation of pluronic polymers based thermo-responsive in-situ hydrogels which is used specifically for ophthalmic purposes. The method of preparation using cold method and different physicochemical properties that affect hydrogel preparations include pH, flow ability, transition of sol–gel, temperature, gelling capacity and rheological properties were briefly reviewed. Based on in-vitro release studies and gelling capacity, how the best formulation could be selected and analyzed has been widely discussed in this work. Literature reports on the study of different autoclaving (both before and after) and irritation studies in rabbits were reviewed. In addition, the aqueous humour analysis done using albino rabbits was also reported. Through this review, it was inferred that the increase in pluronic polymer concentration increase the physiochemical property of sol–gel transition temperature. Further, these types of hydrogels are widely established as secured especially for usage ophthalmic products and it might significantly improve drug bioavailability in humour analysis. It is concluded that the optimized in-situ hydrogels could be a promising substitute to conventional eye drops.

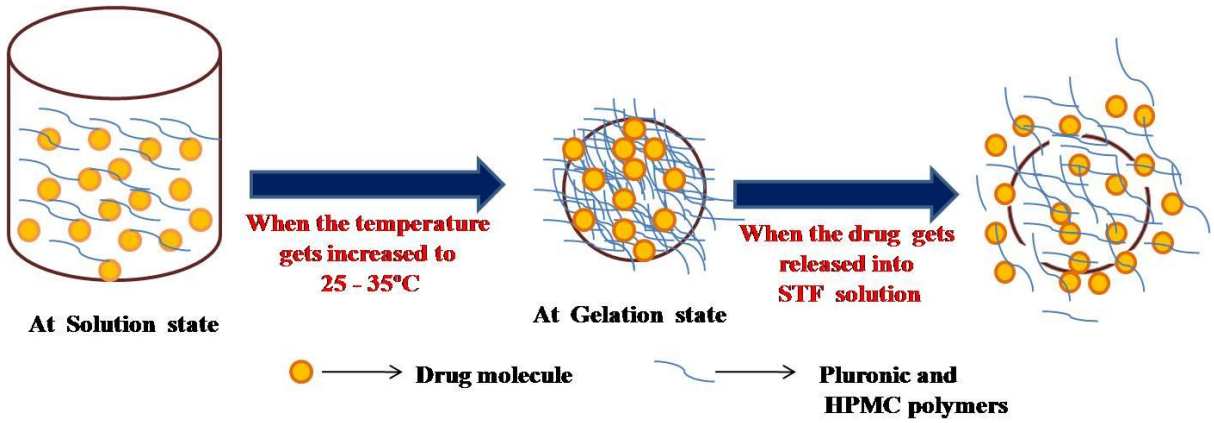
Keywords: Hydrogels, Opthalmic preparations, bioavailability, sol-gel.

INTRODUCTION

In human, eye is considered as an important organ in which the drug absorption on the eye tissues could not occur intensely. Though various drug delivery for ophthalmology include ointments, suspensions and inserts are available to surmount this issue, it is not widely used by patients owing to various demerits such as dosage heterogeneity of suspensions, complications in inserts administration and blurred vision due to ointments usage. [1]

In order to circumvent the above complications, about 90% of commercial ophthalmic formulations were obtainable as water soluble drugs and are specifically as eye drops.[2] The significant advantage being as eye drops are mainly for effortless administration onto the eyes with an exact dosage. Nevertheless, the important demerit of eye drops is even the best formulation could not be used especially for eye disorders since it is linked with sudden elimination of precorneal membrane during various protective mechanisms include nasolacrimal duct drainage and blinking eyes. The repeated administration of the drug is required for different ocular disorders such as conjunctivitis, glaucoma and dry eye syndrome. In conventional eye drops, the main limitation is about <1% of poor ocular drug bioavailability and this may lead precorneal loss factors such as non-productive absorption, relative drug impermeability to corneal epithelial membrane, rapid tear turnover and transient residence time in the cul-de-sac. In order to avoid this issue, in-situ gel system is having a potential and acts as an alternate to conventional eye drops. In-situ gel undergoes a transformation from sol-gel transition in the cul-de-sac. At present, literature reports are mainly based on the gel technology methods specifically on the development of in-situ gel formulations for ophthalmic usage. The prepared in-situ formulation is primarily had assuring polymer which could undergo sol-gel transition state during a change in environmental factors such as pH, temperature and specific. In this study, thermo-responsive in-situ gel formulations have been widely focused. When the thermo-responsive in-situ liquid formulation comes in contact with an eye, it underwent sol-gel transition and this is mainly happened due to temperature drift from lower to higher temperature. The sol-gel transition state of various ophthalmic formulations is determined using various techniques include differential scanning calorimeter, UV-Visible spectroscopy and Rheology. It must forms as a gel at pre-corneal temperature (35^{o}C) and is formulated in such a way in order to repel from fridge before it is administrated as the cold eye drops may cause eye irritation.

Pluronics is, also recognized as poloxamers, one of the prominent polymers which is having an excellent thermo-responsive performance. Pluronics is a triblock copolymer which shows amphiphilic nature due to the presence of hydrophobic propylene oxide domains and hydrophilic ethylene oxide domains in a chemical structure of poly (ethylene oxide)-(b-poly(propylene oxide)-(b-poly (ethylene oxide) (PEO–PPO–PEO).



The changes in micellar structure at different temperature and concentrations explain the principle of the gelation mechanism of pluronics. Though it has advantages, the main limitation of the polymer is their low mucoadhesive nature. In order to circumvent this problem, ophthalmic formulations were prepared by mixing pluronics with polymers which has mucoadhesive property especially carbopol, sodium hyaluronate and etc.

The overview of different literature reported on the thermo-responsive in-situ gel formulations are briefly discussed in this study.

Literature reported on the development and evaluation in-situ gel formulation of clindamycin HCl for their application in vagina. Though the vaginal preparations are considered as safer, it has still complications include frequent dosing and escape that cause uneasiness to patient. The vaginal drug delivery system is said to be proficient only when the delivery of the system should be at infectional site for an extended time period. The authors have suggested the dosage forms of in-situ gel formulations contain thermosensitive polymers such as poloxamer127 and poloxamer188 and pH activated polymers such as chitosan and Carbopol974p. These polymers were combined in order to obtain the property of both solution and gels and hence an exact dosage could be administered easily. During administration, the in-situ gel formulations are in solution state which undergoes transformation into gel after it is administrated into vaginal cavity. Clindamycin HCl was used along with concentration ratio (% w/v) of P127 and P188 as 23:7 and the prepared formulation was found to be an effective proportion for sol-gel transition temperature at 37˚C. In addition, about 0.1% HPMC and 0.9% NaCl were added as bioadhesive polymer and isotonic agent in order to provide strength to the prepared formulation. The clarity and appearance were found to be satisfactory and drug content in the formulations was in the range of 98.1-101%. The authors have concluded that the combination of poloxamer 127/188 functions as an effective bio-responsive polymer and Clindamycin in situ gel is one of the effectual formulation specifically for vaginal application.[3]

The authors have reported on the evaluation of two in-situ gelling systems specifically for ocular drug delivery of Moxifloxacin. Moxifloxacin, fourth fluoroquinolone generation was used for the preparation of the formulations. In this study, about 7 formulations (P1-P7) of temperature triggered in-situ gel and 9 formulations. The pH triggered insitu gels were prepared using pluronic and carbopol 934 respectively. Based on gelling capacity for CL formulations, gelation temperature for PL formulations, rheological properties, *in-vitro* drug elease and mucoadhesion property, the developed formulations were evaluated. Among different formulations, P6 and C5 had an optimum gelation temperature of around 33.9˚C. Comparing to mucoadhesive index of 1.947 Pa for P6, C5 had higher index of 7.325 Pa. Due to higher amount of Mox, the drug P6 was on the aqueous humour area remained for 8 hrs after injecting it onto the eyes. Hence, C_{max} and $AUC_{(0-\infty)}$ of P6 showed 2.8 fold increment than C5. The authors have concluded that PL based in-situ gelation is one of an effective and efficient drug delivery system especially for ocular bioavailability than CL based gelling system.[4]

Literature reported on the development and characterization of pH responsive sustained drug release in-situ gel for ophthalmic formulation which contains ciprofloxacin Hcl as drug content. Ciprofloxacin Hcl is one of the broad spectrum antibiotics and is specifically used for corneal ulcer treatment of the infections related to eyes. The main limitations of using conventional eye drops are rapid dilution after instillation, easy wash out, poor drug retention. Hence, an alternative therapeutics must be required by circumventing the above problems. In this study, sodium alginate, a mucoadhesive polymer, was mixed along with drug in order to achieve the immediate gel formation. This immediate gelling was achieved mainly due to the interaction of divalent cation (Ca^{+2}) present in lachrymal fluid with sodium alginate resulting in the formation of calcium alginate. In order to improve the viscosity and sustained drug release, hydroxy Propyl Methyl Cellulose (HPMC K4M and E5 OLV) was used. The authors had evaluated the developed formulations for different characteristics such as pH measurement, clarity, drug content, gelling capacity, In-vitro drug release and rheological study. From this study, the authors have inferred that in-situ gel based could be

an substitute to conventional systems especially in the ophthalmic drug delivery.[5]

Neomycin sulphate, an anti-bacterial agent, has poor ocular bioavailability and rapid precorneal elimination when the drug is administered as conventional eye drops. In order to get round this problem, temperature-triggered in-situ gel formulation of neomycin sulphate was developed to afford sustained drug release based on polymeric carriers that could go through sol-to-gel transition upon there is a change in temperature. The formulation of neomycin sulphate in situ gel was done using poloxamer 407 and hydroxyl propyl methyl cellulose (HPMC). The specific nature of HPMC functions as viscosity enhancer. After preparing the formulations, the authors had evaluated certain characteristics studies were performed. The authors have concluded that the developed formulation was stable and provided sustained drug release up to 8 h and it could be a feasible different to conventional eye drops.[6]

In this study, the objective of temperature triggered in-situ gel formulation was adopted using sodium alginate, ALG and poloxamer 407, P407. This was formulated in such a way in order to achieve gel formation on the eyes along with other targets such as sustained drug release profile, improved ocular delivery and prolonged eye contact. The different concentrations of the drug were used to develop the formulations and the optimization was done based on gelling capacity. With respect to ocular bioavailability, the optimized formulation had highest shelf life and sustained drug release profile. Further, *in-vitro* study showed sustained drug release and followed the mechanism of non-Fickian diffusion. The authors had suggested that about 15% (w/v) of P407 and 2% (w/v) of HPMC had an effective FLZ ocular bioavailability in rabbits eyes rather than FLZ as a control solution. Hence, it was concluded that the particular optimized in-situ formulation could be a potential drug delivery system of FLZ with improved activity of sustained drug release and ocular bioavailability.[7]

The initial preparation was done using cold method and further the physicochemical properties were investigated. Among the development of different formulations based on varying concentrations of drug, an optimized formulation was chosen and looked into their eye irritation potency in rabbits. The authors had reported that the sol–gel transition temperature was not affected by using carbopol 940 whereas pH, transparency and gelling capacity were much affected. Along with pseudo plastic flow behaviour, the sol–gel transition temperatures of 32-35^{o}C were exhibited for an optimized formulation. Furthermore, diclofenac sodium bioavailability was considered safer for ophthalmic usage and it could improve aqueous humour significantly. The authors had concluded that the in-situ gel have found to be an effective and efficient and as a substitute to the conventional eye drop.[8]

The authors had developed thermo sensitive drug vehicles specifically for glaucoma therapy in order to overcome problems in the existing conventional eye drops such as naso lachrymal drainage, poor bioavailability and rapid precorneal elimination. The preparation for the formulation was carried out using cold method. While preparation, thermo sensitive polymer, pluronic F-127 was mixed with HPMC-E 50 LV and betaxolol hydrochloride which have the nature of viscosifying agent and anti-glaucoma effects respectively. After formulating the drug, the authors had evaluated pH, *in-vivo* ocular irritation study and sterility test. Through this study, it was concluded that the optimized formulation of betaxolol had sustained release over 7 hours and it exhibited excellent ocular tolerance.[9]

The authors had reported on the formulation and evaluation of timolol maleate in situ gel for ocular delivery based on the concepts of both pH and temperature triggered in situ gelation. In this study, a thermosensitive polymer, pluronic F-127 was combined with pH-sensitive polymer, chitosan which could acts as both permeation enhancer and gelling agent. The evaluation of different *in vitro* parameters such as gelation temperature and pH, clarity, rheological studies, sterility, isotonicity, ocular irritation, drug release profile and transcorneal permeation study were done for an optimized formulation. The authors had shown that the developed formulation was clear and available as an isotonic solution, which could undergo sol-gel transition at pH 6.9–7.0 and temperature above 35^{o}C. From the results, the authors had inferred that the developed formulation had been proved ocular retention time is increased.[10]

Literature reported on the designing and evaluation of the modified chitosan-moxifloxacin HCl based in-situ gel. The evaluation of different parameters such as rheological study, drug content, in vitro drug release studies, release kinetics and gelation temperature were done for an optimized formulation. All prepared formulations showed drug content of 98.8±0.2% and satisfactory pH of 6.2±0.2. The authors had reported that when there was increase in the concentration of each polymeric component, phase change temperature and *in vitro* drug release was quiet decreased. An optimized formulation has an anti bacterial efficacy against *Staphylococcus aureus* and it confirmed that the optimized formulation could retain their nature against bacterial infection and has prolonged drug release effect. The authors had concluded that the combination of polaxomer 407 and modified chitosan with moxifloxacin HCl could be a potential satisfactory substitute for sustained drug release.[11]

In prior to manufacturing, all the ophthalmic products must be sterilized and it should ensure products sterility. This could be done through sterilization by autoclaving (steam sterilization) or filtration. In large scale productions, autoclaving is the prior option to be done for

most of the ophthalmic solutions whereas few products could not be sterilized through autoclaving due to distortion of their physicochemical properties during autoclaving conditions. As a result, manufacturers should sterilize certain ophthalmic solutions. Literature supports for this study examined whether the autoclave conditions does affect the physicochemical properties.

This study reviews the optimization of thermo responsive NSAID/ophthalmic in-situ gels and evaluation of their physicochemical properties, studies on eye irritant, *in vivo* studies, and to determine the effect of autoclave for formulations.

Experimental design

The preferred design was Box–Behnken design engaged to optimize the in situ gel formulation using Design-Expert software (Version 7.1.6.). This cubic design is characterized by center point replicates and a set of points present at the midpoint of each edge of the multidimensional cube that circumscribes the region of interest. Design matrix consisting of 17 experimental runs was constructed.[12-14]

The computer-generated equation of the design nonlinear quadratic model is as follows:

$$Y= A_0+A_1X_1+A_2X_2+A_3X_3+A_4X_4+A_5X_5+A_6X_1X_3+A_7X_1^2+A_8X_2^2+A_9X_3^2$$

where, A0: the intercept representing the arithmetic average of all of 17 runs; A1, A2, A3, A4, A5 A6, A7, A8, and A9: The responses obtained after the preparation of these 17 formulations were filled in the design.

Preparation of thermo sensitive gel:

The preparation of ophthalmic in situ gel was done with slight modifications of "Cold Method".[15] The definite quantity of drug was dissolved in phosphate buffer saline in aseptic condition. Further, preservative benzalkonium chloride was added at the same time. Separately the polymeric solution was prepared and kept aside for 24 hours for appropriate mixing. Finally, the drug and polymeric solution was mixed well and the future quantity of the isotonic agent was also added to it.

Evaluation of in situ gel

Drug Content Uniformity

100 µl of the prepared ophthalmic in situ gel formulation was taken and it was poured into 100ml standard flask, make the volume with STF.[16] Amount of drug from the prepared ophthalmic formulations was evaluated by using UV spectrophotometrically (Perkin Elmer Lamba 35) at particular λ_{max}. The obtained results were measured in triplicates.

Gelation temperature (GT)

About 10ml of the ophthalmic solutions was taken in the vial with a magnetic beadle and placed on the water bath maintained at low temperature. Accuracy of 0.1°C temperature was measured using thermometer was dipped into the solution.[17, 18] The formulation was heated to the rate of 1°C per 1-2minutes speed of 100rpm while stirring. During to gelation, the magnetic stirrer gets stopped at which temperature is said to be gelation temperature (GT). Moreover, the results were taken in triplicate value.

Gelling capacity

In order to determine the gelling capacity of ophthalmic formulations, 100µL of the prepared solutions was dropped in 2ml bottle of STF solutions. Gelation was examined as recommended procedure. The formulation undergoes sol to gel transition as said in the above procedure. Gelling capacity increases with increasing concentration of gelling agent both at higher and lower concentration of viscofying agent.[19]

Rheological studies

Among the rheological studies, the most important was determination of viscosity of in situ gel was expressed in centipoises (cP). It was then examined using viscometer attached with spindle 63 (Brookfield Viscometer DV2T). And also obtained datas were performed for triplicate. Further, the formulations were determined by using following techniques as UV spectroscopy, DSC and rheological properties.[20]

Autoclaving sterilization

Further, 10 g of ophthalmic in situ gel was taken, screwed the test tubes with caps and were placed in autoclave. All the test tubes containing formulations were exposed to steam for 20 min at 121°C, under a pressure of 15 psi. Subsequently, also evaluate their physicochemical properties.[21]

***In vitro* drug release studies**

In vitro release study of the prepared formulations was done using dialysis bag membrane method. About 3 ml of sample was withdrawn on 1 hr interval for about 8 hrs and substituted with fresh STF fluid. Further, the samples withdrawn for every hr were subjected to UV visible spectrophotometry analysis to measure the cumulative % drug release. The data was taken in triplicates.[22,23]

Ocular irritancy test

The rabbits were housed in cages at 27°C and fed with standard diet and water. The left and right eyes of white rabbits were marked as control and test respectively. The control eye has no sample mentioned as blank whereas the test eye was injected with 0.1 ml of formulation. Further, the eyes were observed at different time intervals such as 1, 24, 48, 72 hrs and 1 week after having an exposure with the optimized formulation. The ocular changes were graded using scoring system which incorporates score rating and any alteration on conjunctiva, eyelids, cornea and iris. In addition, the eyes of white rabbits were also observed regularly for redness, swelling and watering of the eye.[24-26]

***In vivo* studies**

Animals were divided into the two groups each group consists of 6 male white New Zealand rabbits. The study was done to evaluate the concentration of drug in the aqueous humour after 0, 30 min, 1, 2, 4, 6, and 8 hrs following instillation of the developed formulation and marketed formulation. The rabbits received a single dose of 40 µl of the tested preparation in the cul-de-sac of the right eyes and left eyes serves as control. At different times post instillation the intramuscular injection of ketamine hydrochloride 15mg/Kg, Xylazine 1.5mg/Kg. 50 µl aqueous humour was withdrawn with the help of 26 gauze needle attached to 1ml disposable syringe inserted through the corneal sclera junction and slightly upwards into anterior chamber. The samples were collected and stored at -80^{o}C until the assay was carried out by HPLC method.[27]

Accelerated stability studies

The developed formulations were placed in amber coloured vials and sealed with aluminium foil for a short terms accelerated stability study at higher temperature as per International Conference on Harmonization (ICH) guidelines. Formulations are evaluated for each month as per the recommended guidelines. [28]

CONCLUSION

The in situ ophthalmic gels prepared provide enormous advantages over conventional dosage forms like extended therapeutic plasma drug concentration, excellent stability and biocompatibility features making this test products very valuable. This type of optimization by DOE experts helps easy to predict the best formulations. These in situ gels can administered in drop form and produce appreciably less inconvenience with vision. This type of dosage form is used in the treatment of glaucoma, dry eyes syndrome, shoran's syndrome, trachoma etc.

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