JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

IN-SITU GELLING OPHTHALMIC DRUG DELIVERY SYSTEM: A Review

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ABSTRACT:

Eye is the most vital organ of body.The usual ophthalmic dosage forms are accountfor 90% of c urrently accessible ophthalmic formulations.The smajor trouble encountered is quick precornel drug loss. There are significant efforts being made to develop innovative drug delivery systems for ophthalmic administration in order to increase the bioavailability of ophthalmic medications. Recent studies on ocular medication delivery devices are focused on Amalgamation of several drug delivery technologies, that includes to build up systems which is not only extend the contact time of the vehicle at the ocular surface, but which at the same time slow down the removal of the drug.There are numerous innovative dose forms, including collagen shield, in-situ gel,Liposomes, niosomes, dendrimers, ocular iontophoresis, ocular film, ocusert, nanosuspension, nanoparticulate system, etc.Due to significant tear fluid turnover and dynamics that cause quick drug removal from the eyes, conventional administration techniques frequently produce subpar bioavailability and therapeutic response. Ophthalmic in situ gels were created as a result to solve the bioavailability issues.

Keywords:

In-situ gel, Novel ocular drug delivery system, gelation, Ion-activated in-situ system, Sol to gel.

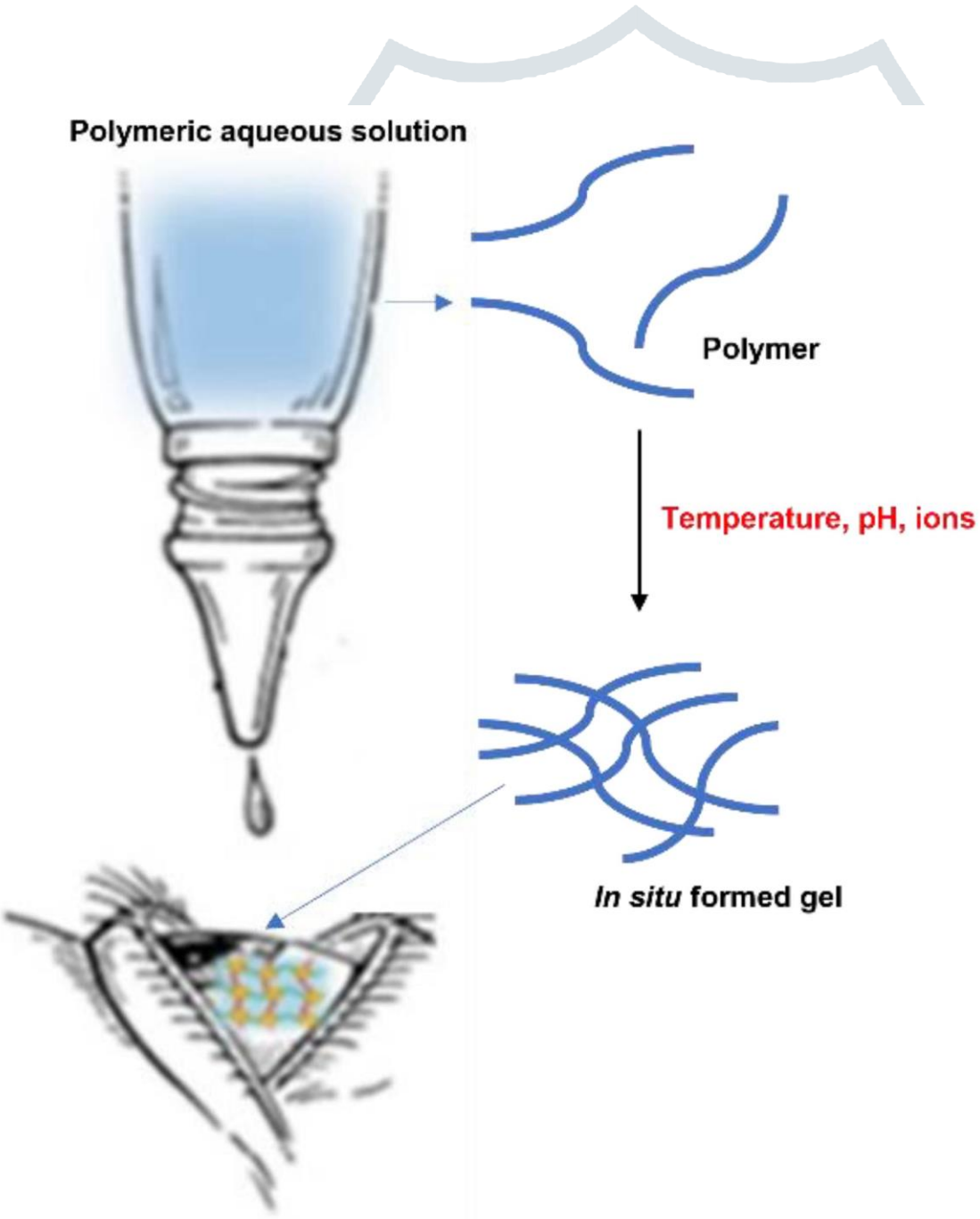
INTRODUCTION

The main aim of pharmacotherapeutics is the attainment of an effective drug concentrati on at the intended site of action for a sufficient period of time to elicit the response.A

major problem faced in ocular therapeutics is the attainment of an optimal concentration at the site of action. The formation of tears, ineffective absorption, brief residence duration, and impermeability of the corneal epithelium are the main causes of the low bioavailability of medications from ocular dosage forms.

Two issues with the drugs installed in the eye's poor bioavailability are:

- Binding by the lachrymal proteins.
- Drainage of the injected solutions, lachrimation, tear production, a small corneal surface area, and poor corneal.
- Evaporation and permeability of tears.
- Nonproductive absorption/adsorption.



The use of a gel system that is administered as drops into the eye and undergoes a solgel transition in the cul-de-sac may be used to address the low bioavailability and therapeutic response displayed by traditional ophthalmic solutions due to rapid precorneal clearance of the medication.Since only a very small portion of drugs that are systemically administered will reach the eye from the general circulatory system, topical administration clearly seems to be the preferred route for the therapeutic treatment of the majority of ocular problem .The eye initially appears to be a perfect, easily accessible target organ for topical therapy. However, the cornea, which serves as a physical and biological barrier, protects the eye well from the absorption of external substances, first by the eyelids and tear production. When any foreign substance or medication is applied to the surface of the eye, tear production increases right away, quickly washing the substance away. The eye can only hold a relatively modest capacity without overflowing under typical circumstances. The amount of commercial eye drops is around 30 l, which is similar to the size of a human's conjunctival sac.

Evaluations of in-situ gel system-

The prepared in-situ gel formulations underwent testing for clarity, pH measurement, gelling capacity, drug content, rheological study, in vitro diffusion study, isotonicity, antibacterial activity, in vivo ocular, and diffusion study.Testing in rabbits and accelerated stability studies.The in-situ pH All of the gel formulations were determined to have a 7.4 pH value. The Formulation should have the best viscosity possible to allow ffo Simple liquid (drops) instillation into the eye, which would Rapid sol-to-gel transition that is triggered by pH and temperatureOr ion exchange).

Physical parameters-

Testing is done on the in-situ gel formulation for clarity, pH, gelling ability, and drug content estimation.

Gelling capacity-

By adding a drop of the prepared formulation to a vial containing 2.0 ml of freshly made simulated tear fluid and visually observing the results, the gelling capacity of the formulation can be assessed. It is noted how long it took for it to gel.

Rheological evaluation -

Utilizing a Brookfield viscometer, a cone viscometer, and a plate viscometer, the viscosity data may be computed. The sampling tube contained the in-situ gel compositions. It was clear from the literature that the formulation's viscosity should range from 5 to 1000 mPas before gelling. And after the eye activates the ion gel, it will have a viscosity of between 50 and 50,000 mPas10, 13. Prior to each measurement, the samples are examined via a circulating bath linked to the viscometer adaptor at 25°C (room temperature) and 37°C +/- 0.5°C (thermostat). The spindle's angular velocity was increased by 20, 30, 50, 60, 100, and 200, and the formulation's viscosity wasmeasured.

All the formulations exhibited Newtonian and pseudoplastic flow characteristics before and afte r gelling in the fluid respectively.

Invitro drug release studies-

With the use of a Franz diffusion cell, an in vitro release investigation of an in-situ gel solution was completed. The mixture was put in the donor compartment, and the freshly made fake tear fluid was put in the receptor section.A membrane of the dialysis compartment between the donor and receptor is positioned (0.22 m pore size). The entire apparatus was set down ontheThermostatically controlled magnetic stirrer.The temperature of themedium was kept at 37°C plus or minus 0.5°C. A sample of 1 ml is Withdrawn at predetermined time interval of 1hr for 6 hrs and sameA quantity of new media is added.The samples that have been withdrawn are diluted to 10ml in a volumetric flask with the appropriate solvent before being assessed by UV spectrophotometer at the appropriate nm using reagent blank. Utilising an equation created from a standard calibration curve, determine the drug content. The determined %CDR, or percent cumulative drug release Curve fitting for data on medication release is also used to the obtained data. For their kinetics, the best fit model is examined for the Krosmeyers-Peppas and Fickinian diffusion mechanisms.

Texture analysis-

The texture profile analyzer, which primarily showed gel strength and ease of administration in vivo, is used to evaluate the consistency, stiffness, and cohesion of in-situ gel. Higher values of adhesiveness of gels are needed to maintain an intimate contact with mucus su rface.

Isotonicity evaluation-

The ophthalmic preparations' isotonicity is a key property. Maintaining isotonicity is necessary to avoid tissue damage and eye discomfort. Since all ophthalmic preparations demonstrated good release characteristics, gelling capacity, and the necessary viscosity, they were all put through isotonicity testing. A few drops of blood are combined with the formulations before they are examined under a 45X microscope and contrasted with commercially available standard ophthalmic formulations.

Drug-polymer interaction study and thermal analysis-

Fourier Transform Infrared (FTIR) spectroscopy can be used to examine interactions. The approach of using the KBr pellet method can be used to examine the nature of the interacting forces during the gelation process. For in situ forming polymeric systems, thermo gravimetric analysis (TGA) can be used to calculate the amount of water in hydrogel. Differential scanning calorimetry (DSC) was utilised to compare the thermograms of the formulation to those of pure active components employed for gelation.

Antibacterial activity-

Antibiotic concentrations are used to measure the microbiological growth of bacteria, and this growth must be compared to that caused by known antibiotic concentrations in standard preparations. The serial dilution method is used to conduct microbiological assays.

Ocular irritancy test-

Prior to commercialization, the Draize irritancy test was created to assess an ophthalmic product's potential for causing eye irritation. According to the Draize test, 100 l of drug is typically injected into the lower cul-de-sac and applied to the eye, with observations of various criteria made at predetermined intervals of 1 hour, 24 hours, 48 hours, 72 hours, and 1 week after administration. For the investigation, three male rabbits weighing 1.5 to 2 kg are employed. A cross-over research is conducted after the sterile formulation has been administered twice daily for seven days (after a pre-cross-over study saline washing period of three days). Rabbits are periodically checked for signs of redness, edoema, and eye watering.

Accelerated stability studies-

According to International Conference on Harmonization (ICH) stated Guidelines, formulations are put in ambient colour vials and sealed with aluminium foil for a short duration accelerated stability assessment at 402 °C and 755% RH. Every month, samples are examined for rheological evaluation, in vitro dissolution, drug content, clarity, pH, gelling capacity, and clarity.

Statistical analysis-

Multivariate tests were used to statistically analyse the findings from the experiments on mucoadhesive strength and release investigations. Using different SPSS software, a statistically significant difference was investigated, and a difference was deemed significant at P 0.05.

MATERIALS AND METHODS-

The source of the antibiotic was Smruthi Organics Pvt ltd in Solapur. Hydroxypropylmethyalcellulose and Carbopol 940 were purchased from Orchid Pharmaceutical Ltd. In Chennai. We bought pluronic F-127 from Sigma Labs Pvt Ltd in Mumbai, India. From E. Merck Ltd, Mumbai, India, sodium chloride, sodium hydrogen carbonate, calcium chloride dihydrate, and sodium hydroxide pellets were bought.

Estimation of Ciprofloxacin hydrochloride using spectrophotometer method –

In simulated artificial tear fluid with a pH 7.4 buffer, a straightforward, straightforward, and repeatable approach was established to estimate the amount of ciprofloxacin hydrochloride. The approved technique for ciprofloxacin hydrochloride in 0.1N Hcl, however, demonstrates the l max at 278 nm Beers range of 2-20 mcg/ml. Ciprofloxacin hydrochloride exhibits l max at 272 nm in the range of 5 to 40 mcg/m in stimulated artificial tear fluid with a pH of 7.4.

Preparation of formulation –

PH-triggered system:

Aqueous solutions of various concentrations of carbopol 940 and hydroxypropylmethyalcellulose of various grades formulation code (Hcl, Hc2 —— Hc7) were created in order to determine the composition that would function best as an in-situ gelling system. By adding a drop of the system to a vial containing 2 ml of freshly prepared artificial tear fluid that had been equilibrated at 37 oC, watching the gel formulation, and timing how long it took for the gel to form and dissolve, the gelling capacity was evaluated. Calcium chloride (0.008g), sodium bicarbonate (200g), sodium chloride (0.670g), and filtered water were the components of the artificial tear fluid used (q.s. 100.0g). To measure the viscosity, a brook field synochroelectric viscometer (RVT type) was inserted into the tiny volume adaptor.

Temperature dependent system:

Ndergo gelation as a result of a rise in temperature when in contact with bodily fluids (35–37°c). The most used heat setting polymers in ophthalmology are pluronic. They are composed of an ethylene oxide- and polyoxypropylene-based hydrophobic and hydrophilic component, respectively, in the centre. Transparent and colourless gels are produced using pluronic F-127. Following a temperature increase, the progressive desolvation of the polymer, increased polymeric network entanglement, and intramolecular hydrogen bonding may all help to promote gelation.In 12 beakers, each containing 100 m of filtered water, 1.5 g of HPMC was dissolved, and the mixtures were agitated for an hour. Following an hour of stirring, HPMC solutions with varying concentrations of Pluronic F-127, ranging from 3 to 17, were mixed. The Pluronic solutions that had not yet completely dissolved the polymer were kept in the refrigerator (approximately 24 hours). Using a Brook Field Viscometer (Model D-III + programmed Rheometer), these polymer solutions of various concentrations of HPMC and Pluronic F-127 were assessed for gelling capability and viscosity in order to determine the ideal concentration suited for usage as in-situ gelling system. The Pluronic and HPMC E50 LV concentration of 15% was chosen since it has good characteristics for viscosity and gelling

Ion activated system:

Gelrite is the brand name for Gellan gum, an anionic exocellular polysaccharide that is water soluble and gels when exposed to cations. The presence of monovalent or divalent ions, such as Na + and Ca +, triggers the sol-gel transition process. Other factors that affect the phase transition include the concentration of polysaccharide, the preparation's temperature, and the type and concentration of cations. In-situ gel preparation with Gelrite was chosen.

Sterility studies:

The sterility test is a crucial component of ophthalmic preparations. The goal of the sterility test is to identify any live bacteria, fungus, or yeast in or on sterilised preparations. The test has to be done in a way that prevents unintentional product contamination while it's being done.

Rheological studies:

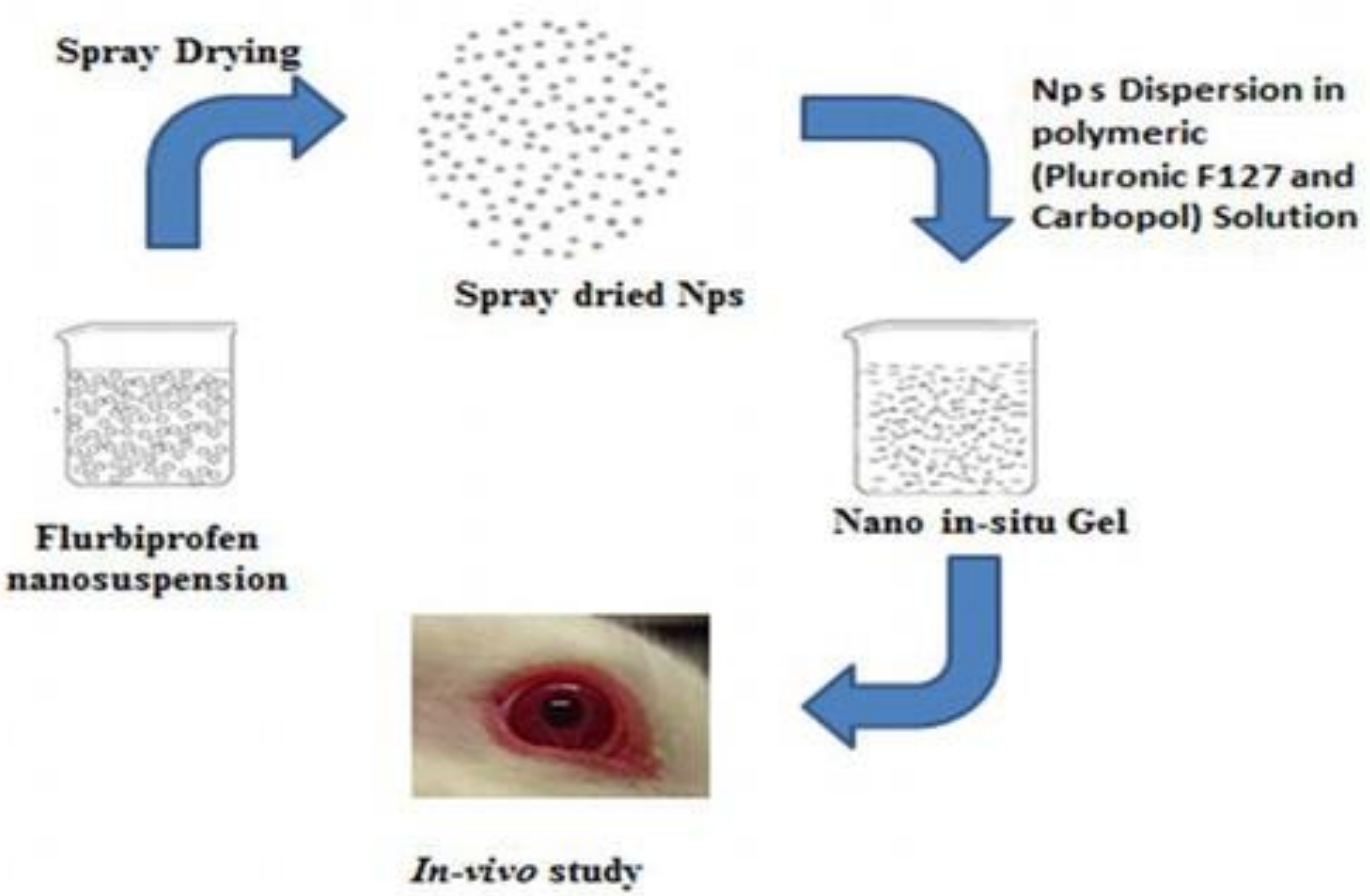
A Brookfield synchroelectric viscometer was used to measure the rheological characteristics of solutions and gels. The produced formulation was added to the brook field synchroelectric viscometer's tiny adaptor, and the angular velocity gradually increased from 10 to 100 rpm. The angular velocity hierarchy was turned around. The viscosity was determined using the average of the two readings. After that, the mixture was put into an ointment jar, and simulated lachrymal fluid was added to raise the pH to 7.4.

In-Vitro release studies of Ciprofloxacin Hydrochloride In-Situ gels:

Using a modified USP XXIII dissolving testing apparatus, the in-vitro release of Ciprofloxacin hydrochloride from the produced formulations was investigated through cellophane membrane.The dissolving medium employed was freshly made pH 7.4 buffered artificial tear fluid. A glass cylinder with a specific design (open at both ends, 5 cm in diameter) was tied to one end with a cellophane membrane that had previously been soaked overnight in the dissolution medium. A 2 ml volume of the formulation was then accurately pipetted into this assembly. The cylinder was suspended in 100 ml of dissolution medium kept at 37°C so that the membrane barely touched the surface of the receptor medium. The cylinder was connected to the metallic drive shaft. At hourly intervals, 1 ml volume aliquots of the receptor media were pulled out of the shaft while it was rotating at 50 rpm. To quantify absorbance, the aliquots were diluted with receptor media.

Anti microbial efficacy studies:

The "cup plate technique" agar diffusion test was used to determine this. These solutions were poured into cups bored into sterile nutritional agar that had previously been seeded with test organisms (Pseudomonas aeruginosa and Staphylococcus aureus). Sterile solutions of Ciprofloxacin hydrochloride (standard solution) and the developed formulations were di-luted at different concentrations (test solutions). The agar plates were incubated at 37°C for 24 hours after allowing the solutions to diffuse for 2 hours. Comparing each cup's zone of inhibition (ZOI) to a control revealed differences. With the exception of the incubation, the entire procedure was completed in a laminar airflow unit. Both positive and negative controls were maintained the study.



Formulation and Evaluation of Thermosensitive Flurbiprofen

Accelerated stability studies:

Studies on the stability of materials under accelerated temperatures are typically conducted at 400, 500, and 600 C as well as at room temperature and below zero C. The samples were kept under a variety of conditions, including 40 °C and room temperature with a 75% relative humidity. The samples were taken out at weekly intervals and their drug concentration was spectrophotometerically determined at 272 nm under fluorescent lighting.

Comparative evaluation of In-Vitro drug release from marketed prepa-

Rations with In-Situ gel formulations-

For the preliminary tests and in-vitro release studies, in-situ gels of various compositions and commercially available eye drops and eye ointments were used. For the in-vitro release research, a modified dissolution testing apparatus was used. The release investigation was conducted using a pH 7.4 buffer and 100 ml (simulated artificial tear fluid). Preliminary evaluation evaluations of the selected formulations' aesthetic appeal, clarity, pH, and medication concentration were all conducted.

RESULTS AND DISCUSSION:

The generated formulations underwent tests for visual appearance, pH, drug content by UV spectrophotometer at 272 nm, clarity by visual observation against a black and white background, sol-gel transition, sterility, in-vivo release studies, antibacterial investigations, and accelerated stability studies.

CONCLUSION

In the rapidly developing field of ophthalmic drug delivery, most researchers are taking on challenges to address various issues with this delivery. Steady advancement in the understanding of guidelines and procedures for ocular medication absorption and disposition and ongoing technological advancements have unquestionably introduced various enhancements to ophthalmic delivery systems' effectiveness.increased patient compliance is the main goal of a successful controlled release product, and in-situ gels deliver on this goal.utilizing polymeric in-situ gels for the controlled release of different medications has a number of benefits over traditional dosing forms.The In situ gel dosage forms are extremely dependable due to the drug's prolonged and sustained release, good stability, and biocompatibility properties. For the in-situ gel formulations, the use of biodegradaqble and water soluble polymers can increase their acceptability and make them excellent drug delivery systems.In-situ activated gel-forming devices appear to be more popular because they can be supplied in drop form and cause noticeably less vision discomfort.

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