Review Article

Smart *In-Situ* Gels for Treatment of Glucoma

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Abstract

A series of progressive visual neuropathies known as glaucoma are defined by alterations in the optic nerve head as a result of retinal ganglion cell degeneration. It often happens when intraocular pressure rises over what a healthy eye can handle. Open-angle chronic glaucoma is the second-leading cause of blindness worldwide and a significant public health issue. The first step in treating glaucoma is to utilise common eye drops that contain medications like prostaglandins, carbonic anhydrase inhibitors, beta-blockers, etc. These eye drops generate lachrymal leakage, reduced corneal permeability, and repeated instillations, all of which contribute to poor availability. Ophthalmic in situ gels, which have recently been discovered by researchers, are among the greatest alternatives to eye drops that can be used to solve their drawbacks. Different polymers were used to create ophthalmic in situ gelling solutions that were pH-triggered, temperature-triggered, and ion activated. When administered into the eye, these formulations go through a phase transition from sol to gel and let the medicine stay in the body for longer. These formulations are also known as "smart gels" because they turn into gelling solutions when injected into the eyes. The idea of creating ocular in situ gels for the treatment of glaucoma is discussed in this article.

Keywords: Glaucoma, eye drops, ocular drug delivery, ophthalmic *in-situ* gels

1. Introduction

Ocular *in-situ* forming hydrogels are referring to polymer which can be administered as liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental change. Gelation can be triggered by temperature, pH, ions, solvent and UV. Three methods have been employed to cause phase transition on the surface: change in temperature, pH and electrolytic composition (1).In-situ hydrogels are providing such 'sensor' properties and can undergo reversible solgel phase transitions upon changes in the environmental conditions (2). An in-situ gelling system should be low viscous, free flowing liquid. This form is reproducible and allowed to be administered as eye drop. The gel form should be strong enough to withstand the shear forces in the cul-de-sac. In order to increase the effectiveness of the drug as a dosage form, it should be chosen which increases the contact time of the drug in the eye. This may prolong the residence time of the gel formed in-situ along with its ability to release drugs in sustained manner which will assist in enhancing its bioavailability. It will also reduce systemic absorption and reduce the need for frequent administration leading to improve patient's compliance (3). Glaucoma is a disease with a characteristic of the higher level of intraocular pressure which might hurt visibility. Sometimes advanced age, family history and black race are the main factors for the development of glaucoma (4). It is called the silent thief of sight. If the vision is lost, then it can't be recovered easily. So the main target of the treatment of this disease is preventing further loss. Untreated glaucoma can lead to permanent damage (5). Treatment of this disease is preventing further loss. Untreated glaucoma can lead to permanent damage (6).

2. Structure of eye and glaucoma overview

Eye is the most sensitive organ of the body which has special attributes to allow local drug delivery and non-invasive clinical assessment. In most of the cases ocular therapy requires administration of drugs in cul-de-sac as many parts of the eye are relatively inaccessible to systemically administered drugs. These drugs may require delivery to treat the pre-corneal regions for such infections or to provide intraocular treatment via the cornea for diseases like glaucoma (7).

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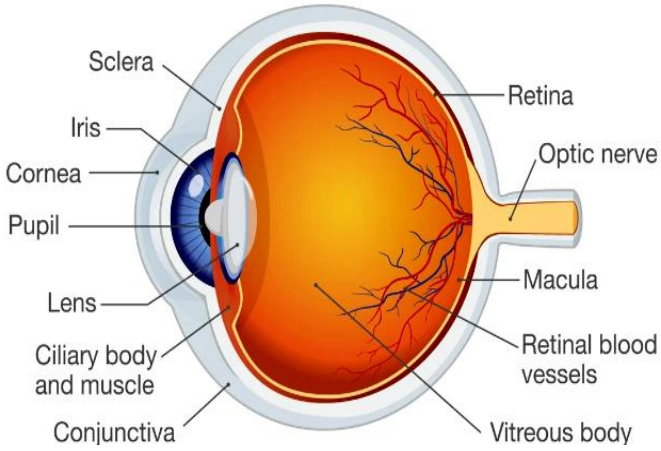

Figure 1: Anatomy of eye

An anatomy of eye is shown in Fig:1, where the internal structures of the eye and blood supply are illustrated in the same. The cornea, lens and vitreous body are all transparent media with no blood vessel. Oxygen and nutrients are transported to these non-vascular tissues by the aqueous humor (8).

The cornea is covered by a thin epithelial layer continuous with the conjunctiva at the cornea sclerotic junction. A layer of endothelium covers its posterior surface. The cornea is richly supplied with free nerve endings. Aqueous humour is secreted by the ciliary processes and flows out of the anterior chamber at a turnover rate of 1% per minute (9).

Glaucoma is a group of eye disease that result in the damage of optic nerve and vision loss. The most common type of glaucoma is open-angle glaucoma where the drainage angle for fluid within the eye remains open. Other types are closed angle glaucoma and normal-tension glaucoma. Open angle glaucoma develops slowly and there is no pain (10). Closed-angle glaucoma can present gradually. Some may have high eye pressure over years and never develop. The mechanism of open angle glaucoma is believed to be the slow exit of aqueous humour through the tubercular meshwork, while in closed angle glaucoma the iris blocked the tubercular meshwork (11).

Glaucoma affects one in 200 people aged fifty and younger and one in 10 over the age of eighty. If the condition is detected early, it is possible to arrest development or slow the progression of medical and surgical means. Untreated glaucoma can lead to permanent damage to optic nerve and results in visual field loss (12).

3. Approaches for in-situ gels:

There are mainly 3 approaches for the in-situ gel development. They are:

1) Temperature triggered system
2) Ion activated system
3) pH triggered system.

3.1. Temperature triggered systems:

Triggered system Temperature sensitive in-situ gels are the environment-sensitive in-situ gels which is commonly studied. Three main strategies are applied for the designing of these type of thermo hermos-sensitive gels. Thermo-sensitive in-situ gels are mainly classified into positively thermo hermos-sensitive, negatively thermos-sensitive, and thermally reversible gels. Such examples are cellulose derivatives, polymethacrylates and poloxamer (13).

3.2. Ion activated systems

Ion activated gelling system is triggered by cations mainly which are present in eye tear fluid. Polymers like sodium alginate, tamarind gum, gelrite, gellan gum are used with MC and HPMC. They provide sustained release of the drug by providing mucoadhesiveness. This system is based on the mechanism of ionic interaction of ions of polymer and divalent ions of tear fluid. When anionic polymers come in contact with cations, they form gel. Examples of this type of gelling systems are gellan gum and sodium alginate (14).

3.3. pH triggered systems

The pH sensitive polymers contain pendant acidic or basic groups. They either accept or release protons in response to change the environmental pH. The most anionic pH sensitive polymers are based on carbopol, carbomer known as PAA. Polymers form hydrogen bonds at higher pH with mucin to form in-situ gel. The pH triggered in-situ gels are therapeutically efficacious, stable and provides sustained release of the drug for a longer period of time. Such type of drugs is polyacrylic acid, polycarbophils etc.

This three approaches are done using cold method. Polymers with low critical temperature transition between ambient and physiologic temperature. On the other hand, pH triggered in-situ gels are more time longer than conventional eye drop. Furthermore human tear which is 2.6 g/l pH is particularly suitable to cause gelation of material when formulation administered topically (15). The three approaches which is for the formation of in-situ gel system is given in Fig. 2.

4. Mechanism of in-situ gel formation

Mechanism of in-situ gels are based on two categories. They are:

1) Physical stimuli
2) Chemical reactions

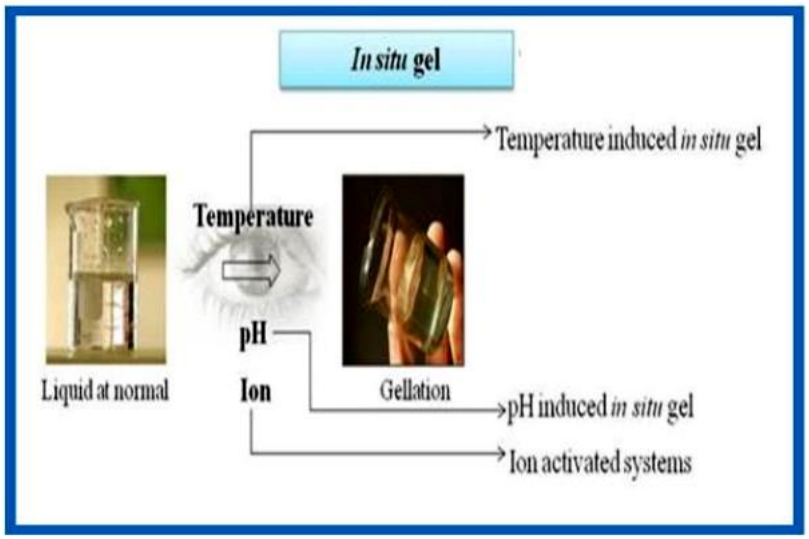

Figure 2: Overview of ophthalmic in-situ gelling mechanism

4.1. Physical stimuli

When a material absorbs water from the surrounding environment in-situ formation may also occur and expand to the desired space (16).

Diffusion: This process solvent diffuses from the polymer solution into surrounding tissues and results in precipitation or solidification of the polymer matrix. The most commonly used polymer for this approach is N-methyl pyrrolidone (NMP) (17).

Swelling: The polar lipid swells from inside to outside and slowly release the drug. It has some bio-adhesive properties and degraded *in-vivo* enzymatic reaction (18).

4.2. Chemical stimuli

Chemical reaction that result in-situ gelation may involve precipitation of inorganic solids by ionic cross-linking and enzymatic cross-linking. The ionic polymers undergo a phase transition to form a

gel. In the enzymatic cross linking, the gels are formed by the fluid that are present. This process have some advantages over chemical and photochemical methods (19).

5. Advantages of Opthalmic *In-Situ* Gels:

In situ drug delivery system has numerous benefits over the conventional ophthalmic dosage forms such as promotes bioavailability, less affected by nasolacrimal drainage thereby reduces absorption into the eye tissues and prevent the systemic adverse effects. This novel drug delivery system combines both solution and gel which ease the introduction of formulation into the eyes and increases patient compliance.

Furthermore reduces the frequency of dosage form as the in-situ gel retains the contact time of drug in the eye and the effective therapeutic will be achieved (20).

The advantages are given below in details:

1. It provides sustained and controlled drug delivery.
2. It increases accurate dosing. To overcome the side-effects of pulsed dosing produced by conventional system.
3. It provides targeting within the ocular globe so as to prevent the loss to other ocular tissues.
4. It increases the ocular bio-availability of the drug by increasing the corneal contact time. This can be achieved by effective adherence to the corneal surface.
5. It provides better housing of delivery system.
6. It provides comfort, better compliance to the patient and to improve the therapeutic performance of the drug.
7. It circumvents the protective barriers like drainage, lacrimation and conjunctival absorption.
8. It is easy to application other than the conventional eye drops (21).

6. Conventional eye drops for glaucoma:

Treatment of glaucoma usually begins with eye drops followed by surgery. If there is a good candidate for glaucoma eye drop then the patent may be described more than one type to achieve the best IOP control (22).A wide range of drugs are available for the treatment of glaucoma in conventional eye drops.

Some conventional eye drops for glaucoma with brand names is given in Table 1 (23).

Some of the commercial anti-glaucoma which are available in market are used globally. Some types of eye drop work by helping fluid drain from eye. These includes: Prostaglandin like Xalantan, Travatan Z, Zioptan etc. Other types of eye drops include Alpha-adrenergic agonists like Iopidine, Beta blockers and carbonic anhydrase inhibitors (24).

7. Selection of *In-Situ* Gel over Conventional Eye Drops:

Conventional eye drops which are used globally have some side-effects such as:

1) They have poor bio-availability, because of rapid precorneal elimination, conjunctival absorption drainage by gravity and normal tear turnover.
2) Systemic absorption of drug and additives through nasolacrimal duct may result in undesirable effect.
3) Frequent instillation of medication leads to poor patient compliance.

Table 1: Conventional eye drop formulation for glaucoma treatment

Generic	Brand	Company	Location	Dosing
Apraclonidine	Iopidine	Alcon	EU	Unit
Betaoxide	Betoptic	Alcon	US/EU	Unit
Carteol	Several	Several	EU	Unit
Dorzolamide	Trusopt	Merck	EU	Unit
Pilocarpin	Several	Several	EU	Unit
Timolol FC	Fotil	Santeen	EU	Unit
Tafluprost	Taflotan	Santeen	EU	Unit
Timolol	Several	Several	EU	Unit/Multidose
Travoprost	Travatan-2	Alcon	US	Multidose

4) Amount of drug delivered during application may vary. The drop size of ocular medication is not uniform and dose delivered is generally not correct (25).

Because of these disadvantages, conventional eye drops are somehow avoided. In order to overcome the demerits smart in-situ ophthalmic gelling solution which are liquid preparations upon instillation undergoing a phase transition in the ocular cul-de-sac to form a viscoelastic gel and this provides a response to environmental changes (26).

This novel drug delivery system promotes the importantly ease and convenience of administration, deliverance of accurate dose as well as to prolong the residence time of drug in contact with mucosa. In situ hydrogels can be instilled as eye drops and undergo an immediate gelation when in contact with the eye. In-situ gel forming ophthalmic drug delivery systems prepared from polymers that exhibit reversible phase transitions and pseudo plasticbehaviour to minimize interference with blinking. This can be formulated as a liquid dosage form suitable to be administered by instillation with the eye which upon exposure to physiological conditions, changes to the gel phase and increase the pre-corneal residence time of the delivery system (27).

8. Evaluation of opthalmic *in-situ* gels:

The prepared in-situ gel formation was evaluated for clarity, pH measurement, gelling capacity, drug content, rheological study, isotonicity, antibacterial activity, in-vitro diffusion study, in-vivo ocular testing and accelerated stability studies.

8.1. Texture analysis: The firmness, consistency and cohesiveness of hydrogels are evaluating by using texture analyser which mainly indicates the syringeability of sol so formulation can easily be administered *in-vivo* (28).

8.2. Physical parameters: The formulated in-situ gel solution is tested for clarity pH, gelling capacity and drug content estimation.

8.3. Gelling capacity: The gelling capacity of the prepared formulation is determined by placing a drop of the formulation in a vial containing 2.0 ml of freshly prepared stimulated tear fluid and visually observed (29).

8.4. Rheological studies: The viscosity measurement can be calculated using Brookfield viscometer, cone and plate viscometer. The in-situ gel formulations were placed in the sampler tube. It was evident that, the formulation before should have a viscosity of 5 to 1000 mPas. The samples are analysed both at room temperature. The angular velocity of the spindle was increased 20,30,50,60,100,200 and the viscosity of the formulation is measured (30).

8.5. In-vitro drug release studies: In-vitro release study of in-situ gel solution is carried out by using Franz diffusion cell. The formulation placed in donor compartment and freshly prepared stimulated tear fluid in receptor compartment. Between donor and receptor compartment dialysis membrane is placed. The whole assembly is placed on the thermostatically controlled magnetic stirrer. 1 ml of sample is withdrawn at predetermined time interval of 1hr for 6hrs and same volume of fresh medium is replaced. The withdrawn samples are diluted to 10 ml in a volumetric flask with respective solvent and analysed by UV spectrophotometer at respective nm using reagent blank. The drug content calculated using the equation generated from standard calibration curve. The % cumulative drug release calculated. The data obtained is further subjected to curve fitting for drug release data (31).

8.6. Antibacterial activity: The microbiological growth of bacteria is measured by concentration of antibiotics and this has to be compared with that produced by known concentration of standard preparation of antibiotic. To carry out microbiological assay serial dilution method is employed (32).

8.7. Isotonicity evaluation: Isotonicity is important characteristic of the ophthalmic preparation. Isotonicity has to be maintained to prevent tissue damage or irritation of eye. All ophthalmic preparations are subjected to isotonicity testing, since they exhibited good release characteristics and gelling capacity and the requisite viscosity. Formulations are mixed with the few drops of blood and observed under microscope at 45X magnification and compared with standard marketed ophthalmic formulation (33).

8.8. Ocular irritancy test: The Draize irritancy test was designed for the ocular irritation potential of the ophthalmic

product prior to marketing. According to the Draize test, the amount of substance applied to the eye is usually placed into the lower cul-de-sac with observation of the various criteria made at a designed required time interval of 1hr, 24hrs, 48hrs, 72hrs and 1 week after administration. Three rabbits (male) weighing 1.5 to 2 kg are used for the study. The sterile formulation is instilled twice a day for a period of 7 days, and a cross over study is carried out. Rabbits are observed periodically for redness, swelling and watering of the eye (34).

8.9. Accelerated stability studies: Formulations are placed in ambient colour vials and sealed with aluminium foil for a short term accelerated stability study as per International Conference on Horizontal (ICH) states Guidelines. Samples are analysed every month for clarity, pH, gelling capacity, drug content, rheological evaluation and in-vitro dissolution (35).

8.10. Hen's egg test-chorioallantonic membrane: HET-CAM test is performed by incubating the eggs for 10 days. Relative humidity is about 70% with automatic turning once per hour. After the incubation period, a portion of each egg shell is removed and a drop of water is placed onto the air sac membrane to avoid capillary damage during its removal. The CAM is then carefully exposed to 0.1ml or 0.1gm of test substances. Then CAM is exposed tp a saline solution and 1% SDS solution. Each CAM is observed microscopically after 5 minutes of lysis and coagulation36 .coagulation (36).

9. *In-situ* gel formulations for the treatment of glaucoma:

Several researches have worked on the responsive in-situ gel for the treatment of ocular drug delivery. In situ gel has various advantages like administration of accurate dose and enhanced ocular retention time. These liquids basically convert into a viscoelastic gel in the ocular surface (37). It has been reported that Nifedipin (NF) is effective in reducing the elevated glaucoma problem due to vasodilation of eye vascular smooth muscle.NF loaded in-situ gels are prepared using Poloxamer 407(P407) and Hydroxypropyl methyl cellulose. NF in-situ gel can avoid the undesirable systemic side-effects.The objective of the current study is to prepare NF loaded in-situ gel composed of Poloxamer407 (P407),Poloxamer188 (P188) and Hydroxypropyl methylcellulose K4M (HPMC).Box-Behnken design (BBD) will be used to optimize NF in-situ gel formation according to percent drug release, gelation temperature and gelation time (38).

10. Conclusion

In-situ gelling system is the most idyllic approach for the treatment of glaucoma. This system is preferred over other systems for ocular drug delivery because it is convenient to use, reduce the retention time and can easily be applicable for the children and aged person and creates significant impact on the patients. That's why it's highly appreciable and in future more study is required to reconnect in-situ formulation for the treatment of various ocular chronic diseasediseases.

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Conflict of Interest

The authors proclaim no conflict of interest.

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