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Novel Approach in Ophthalmic Drug Delivery: In-Situ Gelling System

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***Abstract*: Ophthalmic drug delivery is one of the most interesting and challenging endeavor facing the pharmaceutical scientist. The conventional ocularly drug delivery system like solutions, suspension and ointments show drawbacks such as increased precorneal elimination, high variability efficiency, and blood vision respectively so there was a need for developing advanced drug delivery system. Nowadays ophthalmic route of administration of drugs is rapidly progressing and more studies are going on in formulating ophthalmic drug delivery systems. There are many conventional dosage forms available in the market like ointments, eye drops etc. The main drawback with these types of formulations is rapid drainage of the instilled dose due to the lacrimal fluid secretions and blinking of the eye lids. In order to minimize this drainage and to increase the ocular residence time and corneal contact time, *in situ* gel forming formulations are developed. In these systems sol to gel transformation takes place due to the environmental changes like pH, temperature, ionic strength. Some polymers like sodium alginate, HPMC are frequently used to initiate these processes. These formulations can be assessed for viscosity, clarity, gel strength, gelling capacity, gelling time, texture, isotonicity, sterility, ocular irritancy, and anti-microbial efficacy, in vitro drug release, ex vivo release, in vivo absorption, in vivo retention and stability.**

***Keywords*: Ophthalmic gel, insitu, ocular drug delivery, evaluation.**

1. Introduction

In situ gels are applied as a solution or suspensions and are capable of undergoing rapid sol-to-gel transformation triggered by external stimulus such as temperature, pH etc. on instillation. The aim of present study was to formulate and evaluate pH responsive in situ gel for ophthalmic delivery [1]. Eye is the most interesting organ due to its drug deposition characteristics. Generally, application of the drugs is the method of choice under most circumstances because of its convenience and safety for ophthalmic chemotherapy. A significant challenge to the formulator is to circumvent (bypass) the protective barriers the eye without causing permanent tissue damage. Conventional ophthalmic formulations like solution, suspension, and ointment have many disadvantages which result poor bioavailability of drug in the ocular cavity. In situ forming gels the dosage forms which are liquid in nature outside the body and when they are instilled into the eye, they are converted into gel upon the environment changes like pH, temp. and upon ion activation. The formation of the gel increases the residence time in the eye which is helpful in prolonging the coronel contact time, reducing the drainage of the drug thus leading to an enhanced bioavailability. These formulations will also improve patient compliance by reducing freq. of administration [1]. The basic disadvantages associated with the use of ocular formation is rapid loss of both solutions and suspended solid. Ophthalmic ointments give blurred vision, leading to poor patient acceptance. These problems can be overcome by using in situ gel forming ocular drug delivery system, prepared from polymer, exhibit sol-to-gel phase transition due to a change in a specific physic-chemical parameter. (pH, temp, ion sensitive) [2].

A. Advantages of In-Situ Forming Gels

- Mainly used to maintain for the prolonged and controlled release of the drug from the formulation.
- The formation of the gel mainly increases the ocular contact time and residence time which is helpful for the enhancement of the bioavailability.
- Due to the secretion of the lacrimal fluids from the eye there will be rapid drainage of the drug which is the major drawback of the conventional dosage forms. This limitation can be overcome by the formation of gel.
- In situ forming gels will increase the patient compliance by the free of administration.
- Accurate dosing is possible which may not involve in the over dose and dose dumping.
- More comfortable with improved patient compliance when compared to other dosage form like ocular inserts etc.
- Drugs loss through nasolacrimal duct is minimized as it can lead to unwanted side effects.

B. Mechanisms of In-Situ Gelation

These are classified into following different mechanisms.

- Based on physiological stimuli (pH, temp, ionic strength or ion activation).

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- Based on physical changes (swelling, diffusion).
- Based on chemical reaction (photo-polymerization, enzymatic cross-linking and chemical polymerization).

C. Ideal Characteristics of In-Situ Drug Delivery System

- It should be biocompatible.
- It is capable of adhering to the mucus membrane.
- Preferred pseudo plastic behavior of polymer.
- Good tolerance and optical clarity is more preferred.
- It should influence the tear behavior.
- The polymer should be capable of decreasing the viscosity
- It should be capable of adherence to mucus and non-irritating.
- It should have pseudo plastic behavior.
- The polymer should be capable of decrease the viscosity with increasing shear rate there by offering lowered viscosity during blinking & stability of the tear film during fixation [3].

2. Formation of Situ Gel Based on Physiologic Stimuli

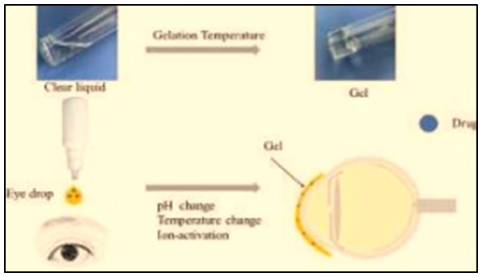

Fig. 1. In-SITU gelling in ocular drug delivery system

1) pH

In this the formation of gel is triggered due to the changes in the pH. The pH of the lacrimal fluids was found to be 7.4 at which formation of gel takes place. For example, cellulose acetate phthalate (CAP) is a polymer which exists in the form of a solution under pH of solution 4.5 and gel when it is present at pH of lacrimal fluid. The mechanism involved in this mainly deals with the ionizable groups of these polymers which can accept or release proton due to the changes in ph. Some examples of polymers used is poly vinyl acetyl di-ethyl amino acetate (AEA), combination of polymethacrylic acid and polyethylene glycol and carbomer [4], [5].

Polymers containing acidic or alkaline functional groups that respond to changes in pH are called pH sensitive polymers. The pH is an important signal, which can be addressed through pH responsive material gelling of the solution is triggered by a change in pH at pH 4.4 the formulation is free running solution which undergoes coagulation when the pH is raised by the tear fluid to pH 7.4. The pH change of about 2.8 units after instillation of the formulation (pH4.4) into the tear film leads to an almost instantaneous transformation of the highly fluid latex into viscous gel. The polymer with large number of ionizable groups are known as polyelectrolyte. Swelling of hydrogen increase as an external pH in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups [2].

2) Temperature

Temperature is most widely used stimulus in environmentally responsive polymer system. The formation of gel or the conversion of sol to gel takes place due to the changes in temp. Generally, the preparation is in form of solution at the temp around 20°C-25°C and it is converted into gel at temp of eye which is around 35°C-37°C.As the temp increases there will be destruction of polymeric chains which help in gel formation. Pluronic's are widely used thermosetting polymers. These are having hydrophobic part (polyoxy propylene) and hydrophilic part (ethelyne oxide). Pluronic F-127 is widely used for the preparation of colourless and transparent gels. This type of solution upon instillation into eye due to increase in temp it forms gels. The mechanism may be due to increased entanglement of the gel and also because of the intra molecular hydrogen bonding [6].

A. Classification of temperature sensitive system

1) Negatively thermo sensitive in situ gels

These are system having lower critical sol temp (LCTC), it is the critical solution temp below which the components of the mixture are miscible for all compositions. So, formation of gel takes place above this temp. Example of such type of polymers is poly-(N-isopropylacrylamide). It is soluble in water at LCST and above this temp it will be hydrophobia and starts precipitin from the sol.

2) Positively thermo sensitive in situ gels

These are having upper critical temp (UCST), it is temp above which all the components of the mixture are miscible in all proportions. So, on cooling this mixture below UCST it forms gel. Example of this type of polymers are poly (acrylic acid) (PAA), polyacrylamide.

3) Thermo reversible in situ gels

These are normal free flowing systems upon change in temp they form gel. Examples of this type of polymers are peplomers [2], [6].

4) Ion activation

In this type initially the dosage form is in sol form but when it come in contact with the monovalent or divalent ions which are present in lacrimal fluids of the eye it forms gel. Concentration of sodium ion in eye is 2.6g\L which is useful for the gal formation of some polysaccharide like Gelrite. Alginates also used as gelling agent and they are used along with HPMC where HPMC acts as agent for increasing viscosity. The mechanism involved is the formation of gel or phase transition takes place in presence of ion in the lacrimal fluid mainly because of the interaction of glucuronic aid in alginate chains. Some other examples of this type of polymers are hyaluronic acid, gellan gum, pectine, carrageenan. [6]

B. In situ gel formation based on physical changes

1) Swelling

Some's substance like mineral 18-99 (glycerol mono-oleate) which is having- lipid like properties, it swells when it comes into formation of gel like substance and also having the bio adhesive the contact time and helps in sustained release of the

drug. After the ation, it can be degraded by enzymatic activity. In situ formation may also occur when material absorbs water from surrounding environment and expand to desire space. One such a substance is mineral (glycerol mono-oleate), which is polar liquid that swells in water to from lyotropic liquid crystalline phase structures. It has some bio adhesive properties and can be degraded in vivo by enzymatic action. In situ formation may also occur when material absorbs water from surrounding environment and expand to occur desired space. One such substance is mineral 18- 99 (glycerol mono-oleate), which is polar 1400 lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some Bio adhesive properties and can be degraded in vivo by enzymatic action [4], [8].

2) Diffusion

In this mechanism, diffusion of the solvent from the matrix takes place which help in the polymer matrix. The solvent used in such type of system is N methyl-pyrrolidone (NMP). This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N –methyl pyrrolidone (NMP) has been shown to be useful solvent for such a system. Drug Release from in Situ Gels Diffusion controlled (Drug diffusion from the non-degraded polymer) swelling controlled (Enhanced drug diffusion due to the polymer) chemically controlled (Drug release due to polymer degradation and erosion) [4]. This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N-methyl-pyrrolidone (NMP) has been shown to be useful solvent for such system [8].

C. In situ gel formation based on chemical reaction

1) Enzymatic cross-linking

In this approach the gel formation takes place due to interaction with enzymes. This is having large benefits when compared to other types because these are no need of using special monomers ache other synthetic derivatives which will trigger the formation of gel. A novel drug delivery system in this approach is intelligent drug delivery system where, insulin and glucose oxidase are entrapped in a cationic pH sensitive polymer which can release insulin based on the glucose level in the blood. Here maintaining the level of enzyme will be helpful for the formation of the gel.

2) Photo-polymerization

This technique is helpful in the formation of in situ gel. Here some substance like monomers and some initiators are used which are helpful for the formation of the gel when electromagnetic radiation is applied. Certain functional groups like acrylateon the monomers undergo photo polymerization when exposed to electromagnetic radiation or in the presence of photo imitator. Usually, longer wave length of light like UV-visible range can be used as shorter wavelength light is having energy and can be harmful to the biological issues. Examples of some initiators used are2,2 dimethoxy-2-phenyl acetophenone (gets polymerized when exposed to ultraviolet radiation), camphoroquinonne and ethyl eosins (gets polymerized to visible light). These initiators and some of the polymers used can be biodegraded in the body with the use of the enzymes. These dosage forms can be introduced in liquid and by the exposure to radiation they directly get polymerized to form a gel and these types of systems can also be formulated as inserts. Hence, this helps in attaining controlled drug delivery.

3) Chemical cross linking

Polysaccharides may undergo sol gel transition due to the presence of ions. K carrageenan forms brittle and rigid gel in presence of k+, Na+,Ca2+, and Mg2+. Similarly, alginic acid and pectine undergo gelation in the presence of divalent/polyvalent cations. Due to the presence of Na+, Ca2+ and Mg2+ in tear fluids, the above polymers can undergo gelation in situ upon contact with tear fluids [8].

3. Evaluation Tests for In Situ Forming Gels

A. Viscosity and rheology

Viscosity and rheological properties of in situ forming drug delivery systems can be assessed by using Brookfield rheometer or some other types of viscometers such as Ostwald's viscometer. The viscosity of these formulations should be such that no difficulties are envisaged during their administration by patients, especially during parenteral and ocular administration.

Rheology studies should be done for the prepared formulation as it very much important for this type of formulations which undergo sol-gel transition. The viscosity of the dosage form can be determined with the help of Brookfield viscometer, Ostwald viscometer, and cone and plate viscometer [5,8].

B. Sol- gel transition temperature and gelling time

Sol-gel transition temperature is the temperature at which the formation of gel takes place. To determine this temperature, the prepared formulation which is in the sol form is kept in a test tube and heated by increasing the temperature and the final temperature at which gel formation takes place is noted. The time required for the generation of gel is noted as gelling time. This evaluation test is carried out for the formulations which are formulated by using thermo sensitive polymer. For these tests the sample is kept in tube and kept the sample tube at specific temperature and then heated at specified rate. The conversion in gel is checked by tilting the test tube, no movement of sample seen one can say that gel is formed. Gelling time can be defined as time required for first detection of gelation as mentioned above [9], [4].

1) Gel strength

It can be assessed by using a device called rheometer. For the evaluation purpose initially the formation of the gel should be done by using appropriate mechanism. Later into the beaker containing gel a probe is inserted. Then different loads are kept on the probe. The changes in the load on the probe can be measured as the function of depth of immersion of the probe below the surface. Sol form. The gel containing beaker is raised at certain rate, to push the probe slowly down through the gel. For evaluation of gel strength rheometer is used. The gel is prepared in beaker as mentioned in the formulation from the changes in load from gel to empty space can be measured as a

function of depth of immersion of probe below the gel surface. [5,9].

2) Texture analysis

The consistency, cohesiveness and firmness of the dosage form can be determined by using texture analyzer. Texture analysis can be helpful in determining or assessing the syringe ability of the sol. higher values of the adhesiveness of the gel is needed in order to attain intimate contact and to increase the contact time.

It is very important for the ophthalmic formulation to have proper spread ability and adhesive properties in order to easily spread on the conjunctiva surface and the formed gel should properly adhere to the surface in order to enhance the retention time and helps in sustained drug release. To determine consistency, firmness and cohesiveness of in situ gel is determined by using texture profile analyzer which indicates gel strength and ease of application. In vivo to maintain the intimate contact of gel with mucus surface, polymer should have high adhesiveness value. With the help of texture profile analyzer, the consistency, firmness and cohesiveness of in-situ gel can be analyzes. These studies may indicate gel strength and easiness in administration. For intimate contact of gel with mucus membrane the value of adhesiveness should be high [6].

3) Clarity

Clarity of the prepared formulation can be estimated by visual observation. The prepared formulation is kept under light alternatively against black and white backgrounds for the particles. When HPMC is used as a polymer, at high temperatures it will get precipitated so after autoclaving of HPMC containing formulation it forms a cloudy mass. It can be disappeared and retains original clarity after standing it for overnight and then the clarity of the formulation is visualized. And also, UV-visible Spectro-photometer can also be used for the measurement of percentage transmission of the light through the formulate the clarity of the formulations before and after gelling will be determined by visual inspection of the formulations under fluorescent light, alternatively against white and black backgrounds. Ion under the visible region at 490nm wavelength by using reference standard most preferably water. The clarity of the formulations before and after gelling can be determined by visual examination of the formulations under light alternatively against white backgrounds. With the help of visual inspection under black and white background the clarity of formulation is determined [10], [6].

4) Isotonicity

Istonicity is the important parameter which should be measured properly especially for the ophthalmic preparations as the difference in isotonicity will lead to the damage of the tissue and it causes irritation to the eye. Hence, all the ophthalmic formulations should be tested for isotonicity measurement. Isotonicity of the ophthalmic preparation can be measured by mixing the small amount of the formulation in few drops of blood and it is observed under microscope at 45x magnification and compared with the standard ophthalmic marketed formulation [10].

5) Ocular irritancy test

Ocular irritancy test should be done before marketing the product and the test used for knowing about the ocular irritancy is Draize irritancy test. With respect to the Draize test the amount of medicament applied in the lower conjunctival sac is about 100µL and after administration different criteria or several parameters are considered and the observations can be done at a time interval of 1,24,48,72 hours and one week respectively after the instillation of the dose. For conducting this test healthy rabbits (male) three in number are chosen. Each rabbit weight is around 1.5 to 22 kilo grams. Then the dosage form is instilled into the eyes of the rabbit and the formulation should be in a sterilized form. The administration of the dose should be continued for one week by giving the dose in alternate days. Generally cross-over design is taken into practice. And the rabbits used for this design should be washed with saline for three days before the test is carried out. And the results can be evaluated by testing the rabbit eye or by visual inspection of the rabbit eye for the appearance of redness, swelling, inflammation and also can be checked for the excess secretions from the eye. These studies are performed on male albino rabbits (weight 1-2kg). The modified Draize technique is used for checking ocular irritation potential. The formulation is placed in lower cul-de-sac and irritancy is tested at time interval of 1hr, 2hr, 48hr, 72hr, and 1 week after administration. then observes the rabbits are observed periodically for redness, swelling& watering of eyes. [7], [3]

6) Anti-microbial efficacy

The prepared ophthalmic formulations were tested for anti-microbial activity according the USP procedure one of such procedures used for ophthalmic in situ gels is USP 31<51> procedure in which it is mentioned effectively about the testing criteria for anti-microbial activity. In this test the samples are taken from the respective batches to be tested are selected and the test samples are inoculated with E. coli, Staphylococcus aureus, Pseudomonas aeruginosa, and these samples inoculated for one month (around 28 days) at 22.5°C ±2.5oC and the inoculum amount should be in the range of 105-106cfu/ml. Then for the time period of 7,14 and 28 days any indication for the growth of organisms or any increase in the turbidity is seen, by this we can notice effectiveness of the preservative.

The preservative used is said to be anti-microbially effective only if there is a 1-log decrease in the growth of the microorganisms and at the 7th day of the incubation and also if there is a 3-log decrease in the concentration in the growth or concentration of the microorganisms in the 14th day of incubation and from then there should be no much decrease in the growth from 14-28 days this is said according to USP 31. This antimicrobial efficacy tests can also be done by using simple procedure called cup and plate technique. In this test agar is used as nutrient medium in which the test organisms are inoculated and incubated for their growth later two solutions namely test and standard are prepared and the standard solution is the sterile solution of the drug whereas the test is the diluted solution to different concentrations from the test formulation. Later wait for around two hours which leads to the proper diffusion of the applied formulation later these plates are incubated for one day at 37°C. Then the zone of inhibition of the organisms in the plate is tested and can be compared with

the control. The study process should be done in the sterile area such as laminar air flow cabin. For obtaining proper results positive and negative controls should be maintained [9].

7) In vitro drug release studies

These studies for the ophthalmic formulations can be assessed by using diffusion studies. Here, these studies can be performed by using dialysis cell apparatus (Franz diffusion cell). This will be having donor compartment and receptor compartment and these two compartments can be separated by a cellulose membrane called cellulose membrane and this membrane is soaked in the simulated tear fluid overnight. The solution of the formulation can be incorporated into the donor compartment and the samples are taken from the receptor compartment and after the collection of the samples they are replaced with the same amount of simulated tear fluid. The phosphate buffer oh pH 7.4 will acts as a simulated lacrimal fluid.

The conditions maintained are a proper magnetic stirrer is used for proper stirring and the temperature is maintained at 37°C ±0.5ºC and the samples are collected for every one hour and the study is continued for six hours. And the obtained samples can be tested for the amount of drug or absorbance can be measured by using some spectrophotometric methods like UV-visible, HPLC etc. Dilutions of the obtained samples can be done if required and the dilution can be done by using some solvent. The amount of drug present is calculated by using the equation which is obtained from the calibration curve and from this the percentage cumulative drug release can be calculated. The information or data obtained can be fitted into the curves for drug release studies. The common plots used for this are fiction diffusion and kerseymere - peppas model or kinetics [9].

8) Ex vivo studies

This evaluation method is similar to the In vitro studies but here corneal membrane of goat is used instead of the synthetic semipermeable membrane. Cornea is removed from the eye of the goat carefully and washed properly with the cold saline and this tissue can be preserved in the simulated tear fluid prior to use. The test is carried out in the Franz diffusion cell where donor and receptor compartments are present. The sample or the required quantity of the formulation is kept into the donor compartment. And the phosphate buffer of pH 7.4 is used as the simulated lacrimal fluid. Intimate contact should be maintained with the membrane and the fluid in the donor compartment. The temperature of the cell is maintained at 37^0c and magnetic stirrer is used for continuous stirring and the samples are taken at specific time intervals and their absorbance can be measured [9].

9) In vivo studies

In this study the test animals used are rabbits the weight of each rabbit should be around 2.5 to 3kg. The rabbits should be healthy and should be devoid of any contamination. While using these test animals' permissions should be taken and the guidelines of the ministry of social justice and empowerment and from the government of India should be followed. One eye of the rabbit can be served as the control and into the other eye the test sample is given which is around 50µL and the eye lids are closed for some time after the instillation into the eye mainly to avoid the drainage of the dosage form [9].

10) In vivo scintigraphy studies

In this study technique used is gamma scintigraphy. This technique is mainly used for the evaluation of the controlled release of ophthalmic formulation and to know about its retention time in the eye. Generally, the lab animals like rabbits are used in this study but preferably human volunteers can also be used as the physiology differences may exist when compared to human and other animals [9].

11) Accelerated stability studies

Accelerated stability studies can be done to know about half life and the stability of the formulation. In this the samples to be tested are selected from the respective batches and they are properly enclosed in the ambient colour container and these can be properly covered with aluminium foils. Accelerated stability studies can be done by maintaining the temperature at 40±2°C and the percentage relative humidity is 75±5% as per ICH guidelines. Later the samples are taken and can be tested for all evaluation parameters like Appearance, pH, clarity, rheological studies, diffusion studies, drug content, gelling capacity etc. Formulated gel preparations are kept at different temperature conditions like 25°C to 28°C ambient temperature (temperature in the working area), 4+-1°C (refrigerated temperature) and 37+-2°C (temperature in the incubator) for 6week.The following parameters of the gel such as colour, consistency, drug content and degradation rate constant (K) are studied. To assess the shelf life, the samples are subjected to stability studies.

12) Gelling capacity

In proportion of 25:7 the in-situ gel is mixed with simulated tear fluid respectively. The gelation is accessed visually by noting time taken for gelation and time taken for dissolution of formed gel. The gelling ability of the prepared formulations will be determined either visually or by SEM. By visual inspection the gelling capacity is determined by pouring a drop of the solution in a vial containing 2 ml of artificial tear fluid which should be freshly prepared and equilibrated at 37◦C, and both the time of gelation and the time taken for the gel formed to dissolve will be noted. The composition of the artificial tear fluid [10].

13) Sterility testing

Sterility testing was performed for aerobic and anaerobic bacteria and fungi by using fluid thioglycolate soybean casein digest medium respectively as per Indian Pharmacopeia. The method used for sterility testing was direct inoculation method.

It is determined by taking 1ml of the formulation and diluting it to 100ml with distilled water. 1 ml was withdrawn and further diluted to 10 ml with distilled water. Concentration was determined at 200-400nm by using UV visible.

14) Spectroscopy.

Interaction studies can be performed in three ways one is by using UV, second is by taking IR spectra and third is by using DSC instrument. In first method by UV the solutions of Polymer and drug prepared separately and in combinations and are autoclaved. The ultraviolet spectra taken before and after autoclaving using double beam ultraviolet visible spectrophotometer. Compare both the spectra for any possible

change in solution content due to interactions between different ingredients. In the second method the IR spectra was taken by using FTIR spectrophotometer. The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi on KBr-press and the spectra was scanned in the wave number range of 6000-400 cm-1. The FTIR graph of pure drug and combination of drug with excipient are recorded, and then compared. In the third method DSC scan isrunned for individual component and the mixture for the interaction study. The interaction studies were carried out to check any possible physiochemical interaction among the formulation ingredients. If UV spectra, IR spectra and DSC graph of the ingredients before and after mixing found to be identical and no additional peak emerged or existent peak shifted that confirms the formulation ingredients were compatible to each other and no physicochemical reaction taking place [6].

4. Mechanism of Ocular Drug Absorption

Small drug molecules can efficiently cross the mucosal membrane whereas some drugs and peptides unable to cross the mucosal membrane. Simple solution has very low bioavailability when the drug is instilled into the eye firstly it penetrates through cornea and then through non corneal routes. The drugs which absorb poorly through cornea are diffused across cornea and sclera.

1) Corneal permeation

The corneal permeation of drug occurs from the precorneal space through diffusion across corneal membrane. The rate of absorption is depending on rate and extend of transport process. The transport of drug molecule across biological membrane depends on physicochemical properties of the permeating molecule and its interaction with the membrane. The cornea consists of three primary layers viz. epithelium, stroma, endothelium, the trans corneal permeation of drug depend on physicochemical properties of diffusing drug and the resistance offered by every layer varies greatly. Epithelium Layer is lipoidal in nature hence it has a diffusional barrier and offers high resistance to ionic or other water soluble or polar species. Compounds with low polarity have greater diffusional resistance in hydrophilic stroma layer Due to this lipophilic and hydrophilic structure of corneal membrane difficulty occurs in selection of drug candidate for ocular drug delivery [3], [4].

2) Non- corneal permeation

Primary drug permeation is through sclera likely to be diffusion across the intercellular aqueous media (structurally similar stroma). The conjunctiva composed of epithelial layer underlying stroma. The conjunctival stroma offers less resistance than the corneal epithelium [10].

5. Research Works

Following are the some of the works carried out on some of the drugs used to treat ophthalmic diseases based on in situ gel forming drug delivery:

1) Moxifloxacin hydrochloride

Moxifloxacin hydrochloride is the drug mainly used in the treatment of some infections occurred in the eye like conjunctivitis etc. It is formulated as the in-situ gel forming formulation by using sodium alginate and HPMC as polymers [9]

2) Sesbania grandiflora

It is an extract of flower which is also mainly used to treat some bacterial infections noticed in the eye. Here, the polymers used are Pluronic F127 and chitosan where phase transformation takes place due to change in temperature [9].

3) Dexamethasone and ciprofloxacin hydrochloride

The use of ciprofloxacin is it acts as an antibiotic which is used to treat bacterial infections of the eye and dexamethasone is a potent anti-inflammatory drug used to treat inflammation caused during infection. To formulate this combination of drugs is gellan gum [9].

4) Olopatadine hydrochloride

Oloptadine HCl is the drug mainly used in the treatment of allergic reactions it is a class of anti-histaminic drug to formulate this drug as In-situ forming gel the polymers used are carbopol and HPMC E-50LV acts as a PH triggered system [9].

5) Norfloxacin

Norfloxacin is the drug which is mainly used to treat bacterial infections like conjunctivitis. The polymers used to formulate this drug are carbopol-940 and HPMC-E50LV and the formation of gel takes place due to pH change [9].

6) Ketorolac

Ketorolac is an on-steroidal anti-inflammatory drug. Here the polymers used arecarbopol 940 and HPMC. Here also gel formation takes place due to the changes inpH [8].

7) Dorzolamide Hydrochloride:

This drug is mainly used in the treatment of glaucoma. The polymers used for formulating this drug are sodium alginate and Hydroxy propyl cellulose. The main mechanism involved in the formation of the gel is due to the presence of calcium ions in the lachrymal fluid [7]

8) Ciprofloxacin

Ciprofloxacin is mainly used for the treatment of eye infections like macrocystis, ulceration in cornea, conjunctivitis etc. The polymers used for formulating this drug are poly acrylic acid and HPMC [7].

9) Voriconazole

This drug is mainly used fungal keratitis which causes vision loss. It is a broad-spectrum antifungal drug. The polymers used to formulate this drug are sodium alginate and HPMC K15M [10].

10) Pilocarpine

It is the drug which is used in the treatment of glaucoma. And the polymers used are sodium alginate which mainly consists of glucuronic acid residues which are helpful for the formation of gel in the presence of calcium ions [7].

11) Timoptic-XE

This formulation is supplied from Merck and Co. Inc., which is sterile and buffered product and is isotonic with the eye. The drug present in this is Timolol maleate. It is mainly used to decrease the increased intra ocular pressure. Each ml of this solution contains 3.4mg of the drug. The other ingredients present in this are tromethamine, gellan gum, mannitol and water [7].

6. Conclusion

In recent times several infections related to eye are rapidly increasing even though they are not so serious an action should be taken as the eye problems should need rapid recovery and relief from the symptoms. Hence, several types of dosage forms are formulated such that they should not cause any irritation to the eye and they should be comfortably administered as the eye is having secretions like lacrimal fluid which causes more loss of the drug and also naso-lacrimal drainage is present which leads to poor bio-availability and the contact time of the drug. So, in order to avoid these problems, the ophthalmic formulations can be generated as solution forms in which some polymers are included and these polymers can be useful for formation of gel when comes into contact with eye. Drugs used for several diseases like conjunctivitis; cataract can be formulated as In-situ gel forming dosage forms.

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