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A Review on Ophthalmic In Situ Gels

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ABSTRACT

The field of ocular drug delivery is one of the most challenging and interesting field for pharmaceutical scientist. In ophthalmic in situ gels various polymers are used. Generally hydrogels are used. These polymers will increase solution viscosity the field of ocular drug delivery is one of the most challenging and interesting field for pharmaceutical scientist. From last 10 to 20 years the field has been significantly improved[1]. Due the site of delicacy and the many restrains of the site of application caution has to be taken during formulation of new product[2.] According to physiology of eye this organ is impermeable to foreign substances. It is difficult to formulation to cross the protective barriers of eye so that drug reaches to site of action in sufficient concentration.[1] Novel drug delivery systems aimed to overcome the biological barrier which can obstruct efficient ocular drug delivery.[3] Crossing protective barrier without damaging the permanent tissue is major challenge to formulator during formulation. Some common diseases which are cured by topical drug delivery are blepharitis, conjunctivitis, keratitis, trachoma, glaucoma etc[4]. The major disadvantages of conventional formulation such as solutions, suspensions, emulsions, ointments etc. are poor bioavailability, increased precorneal elimination, high variability in efficacy respectively.[5] Because of convenience and safety for ophthalmic chemotherapy optical application of drug is most preferred formulation.

Keywords: Hydrogels, Drug Release, Corneal Permeation

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INTRODUCTION

By using polymers which will increase solution viscosity to improve drug retention on the corneal surface[6] Due to chemical or physical cross linking of individual polymer chain of hydrogels ,they form polymeric network that that absorb large quantity of water while remaining insoluble in aqueous solutions. Due to high water content they resembles to natural living tissue more than any other class of synthetic biomaterial because of high water content of the material contributes to biocompatibility. Due to low interfacial tension it shows minimal tendency to absorb proteins from body fluids[7]. The ability of hydrogels of drug loading and drug release this polymers allow the use of dry swollen polymeric network as drug delivery system for oral, nasal etc routes of administration. Because of the ability of polymer of water absorption and swell, tends to liquid gel transition[8] there are two types of hydrogels

1. Preformed hydrogels
2. In situ forming gels

Preformed hydrogels are simple viscous solutions which do not undergo any modification after administration. Preformed hydrogels are used as tear substitute. After administration this preformed hydrogels shows blurred vision, crusting of eyelid, and lachrymation [9]

Thus *In situ* gels can be "Instilled as eye drops and undergo an immediate gelation when in contact with the eye". In situ-forming gels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental changes. Three different types of polymers form to improve drug retention on corneal surface. Drug release from in situ gels is depending on various stimuli viz temperature, pH, ion induced etc. In situ gel formation is depend on chemical mechanism, physical mechanism etc.

In situ gel by three different mechanisms such as change in pH, change in temperature & ionic interaction. Increase in solution viscosity by using polymers improves retention of product on the corneal surface[10]. More recently, the approach to improve precorneal retention is based on the use of mucoadhesive polymers. The principle for use of bioadhesive vehicles relies on their ability to interact with the mucin-coating layer present at the eye surface. The polymers chosen to prepare ophthalmic hydrogels should meet some specific rheological characteristics. It is generally well accepted that the instillation of a formulation should influence tear behavior as little as possible. Because tears gave a pseudoplastic behavior, pseudoplastic vehicles would be more suitable as compare to Newtonian formulations, which have a constant viscosity independent of the shear rate, whereas pseudoplastic solution exhibit decreased viscosity with increasing shear rate, thereby

offering lowered viscosity during blinking and stability of the tear film during fixation[11]. In comparison with traditional formulations, these systems have the advantages of

- Prolonged drug release
- Reduced systemic side effects
- Reduced number of administrations
- Better patient compliance[8]

Sol to gel conversion

In Polymeric System Hydrogel forming solution is formed by simple sol to gel transition in water without external stimuli or chemical reaction. The sol phase means flowing fluid on the other hand gel system means non flowing fluid. Above the critical concentration of polymer gel phase appear. The critical gel concentration is inversely related to molecular weight of polymer. The formation of physical junction is prior requirement in determination of gelation. The physical junction should be strong enough to entropically driven dissolving forces of the solvent. The determination of physical junction depends on experimental methods. It is generally performed by inversion of test tube, if you tilt test tube containing sol will deform the liquid and flow in the direction of tilt on the other hand if you tilt the test tube containing gel the system will not deform and does not have flow as well. The flow rate is depend on time, inversion rate, quantity of solution, Diameter of test tube[6]

DRUG RELEASE FROM IN SITU GELS

Hydrogels are hydrophilic in nature due to which they can incorporate large amount of water. Therefore drug release mechanism of hydrogels is different from hydrophobic polymers. Both simple and sophisticated models are developed to check the release of drug from hydrogel as a function of time.

Polymers used in in situ gels

Polymer should be applied safely as polymer therapeutics or as a agent in tissue regeneration and repair. If the polymer is not used as drug it works as drug carrier, reducing immunogenicity, toxicity or degradation it also improve circulation time. In this case polymer should be water soluble. Non-toxic, non-immunogenic and it should be safe at all stages of drug delivery (from administration to elimination).

If the polymer is non degradable, its size should be below renal threshold for easy elimination which will avoid accumulation of polymer in body. E.g. poly (meth) acrylates.

If the polymer is degradable, the toxicity of immune response of degradation product should be considered.

Stimuli responsive polymers mimics' biological system but external stimulus such as temp or pH results in change in properties. The change can be in its solubility, conformation, hydrophilic/ lipophilic balance release of active component.[12]

Different environmental conditions can cause reversible sol-to-gel phase transition. There are various stimuli which are responsible for formation of hydrogels are-

1) Physical stimuli- change in temperature, electric fields, light, pressure, sound and magnetic field.
2) Chemical stimuli- change in pH, ion activation from biological fluids.
3) Biological stimuli include change in glucose level.

Out of all this stimuli only temperature, pH, ion activated stimuli are used for ophthalmic formulations.[5, 13]

Drug release from in situ Gels is Shown in Table no-01

Table 1: Drug Release From In Situ Gels

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)

1) Temperature induced in situ gel system

Some polymers and hydrogels are temperature responsive will transform from sol to gel is induced by increase in temperature. The body temperature is sufficient to trigger sol to gel conversion no external temperature is required to trigger sol to gel conversion. The system which is set should tolerate small changes in temperature. Temperature sensitive hydrogels are classified in three categories negatively thermo sensitive, positively thermo sensitive and thermally reversible gels. Some hydrogels are negative temperature sensitive (Insoluble upon heating) and they have lower critical solution temperature and if heated at above lower critical solution temperature it will contract[14]. Gelling of these solutions is enhanced by change in temperature which will further sustain the drug release. Due to change in temperature there is change in hydration state which will cause volume phase transition where intra and intermolecular hydrogen bonding of the polymer molecule favored compared to solualisation by water. This condition can be achieved by using drug polymer which is in solution form at room temperature and transform into gel at body temperature[8]. Some polymers are soluble upon heating known as upper critical solution temperature. The change in hydration state causes volume phase transition which leads to inter and intra molecular hydrogen bonding of polymer which leads insolubility of that compound.

e.g poloxamer- it is a thermosetting polymer, when concentration of poloxamer is increased the contact time and elasticity of the drug is increased and sol to gel conversion is decreased.[5, 9]

2) pH induced in situ gel systems

In this case transition of sol to gel triggered by change in pH. The polymers which shows pH dependent transition and has acidic or basic groups which upon change of pH either accept or release proton. Weakly acidic (anionic) group shows swelling with reference to increase in pH where as weakly basic (cationic) groups at decreased pH[14] .The anionic pH sensitive polymers e.g carbopol, carbomer and its derivatives. At pH 4.4 the formulation is in solution form but when it is instilled in eye its pH is changes from 4.4 to 7.4 due to change in pH the formulation is from sol to gel.

e.g cross-linked polyacrylic, derivatives of carbomer etc[5]

3) *In situ* formation based on physical mechanism

a) Swelling

In situ conversion of sol to gel some time may also occur when material absorb water on the surface from surrounding and expand to get desired space.

e.g myverol 18-99, it is polar lipid which form pyotropic liquid crystalline structure after swelling in water.

b) Diffusion

In the method of diffusion the solvent is diffused from polymer solution in to the surrounding tissue which leads to precipitation or solidification of polymer matrix.

e.g N methyl pyrolidone used as solvent for such system.

c) *In situ* formation based on chemical reaction

The chemical reactions which include in gelation may involve precipitation of in organic solids from supersaturated ionic solutions, enzymatic process and photo initiated processes.

d) Ion induced In situ gel systems

Sometimes polymers may convert from sol to gel in presence of various ions. Some polysaccharides come under ion sensitive polymers. It is assumed that the rate of gelation is depend on osmotic gradient across gel surface. The osmolality of the solution may influence the sol to gel transition in eye. In tear fluid generally mono or divalent cations are present which form clear gel of aqueous polymer solution[8]. Gellan gum is an anionic polysaccharide that undergoes gelling in presence of mono and divalent cation. The Na,Ca,Mg ions which are present in the tear fluid generally initiate the sol to gel transition. In presence of divalent cation(Ca) alginic acid undergo gelation.

e.g. Gellan gum [5]

Table no 02 shows mechanism & Example of various stimuli sensitive polymers

Table 2 Stimuli Sensitive Polymer

Stimuli	Mechanism	Examples
Temperature	Formulation is liquid at room temperature(20-25^{0}C) which undergoes gelation in contact with body fluid (35-37^{0}C). Temp increases degradation of polymer chains which leads to formation of hydrophobic domains & transition of an aqueous liquid to hydrogel network	Poloxamer/ phloronics Xyloglucan cellulose derivative
Ionic interactions	Formulation undergoes liquid-gel transition under influence of an increase in ionic strength gel formation takes plae because of complexation with polyvalent cations (like Ca+) in lacrimal fluid.	Chitosan, Gellan Gum/ Gelrite Alginate
PH Change	Sol to gel transition when pH rise from 4.2-7.4. At higher pH polymer forms hydrogen bond with mucin which leads to formation of hydrogel network.	Pseodolatexes carbomer (acrylic acid) cellulose acetate, phthalate latex

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 have very low bioavailability when the drug is instilled into the eye firstly it penetrate through cornea and then through non corneal routes. The drugs which absorb poorly through cornea are diffused across cornea and sclera.

Figure 1 Ocular Drug Absorption

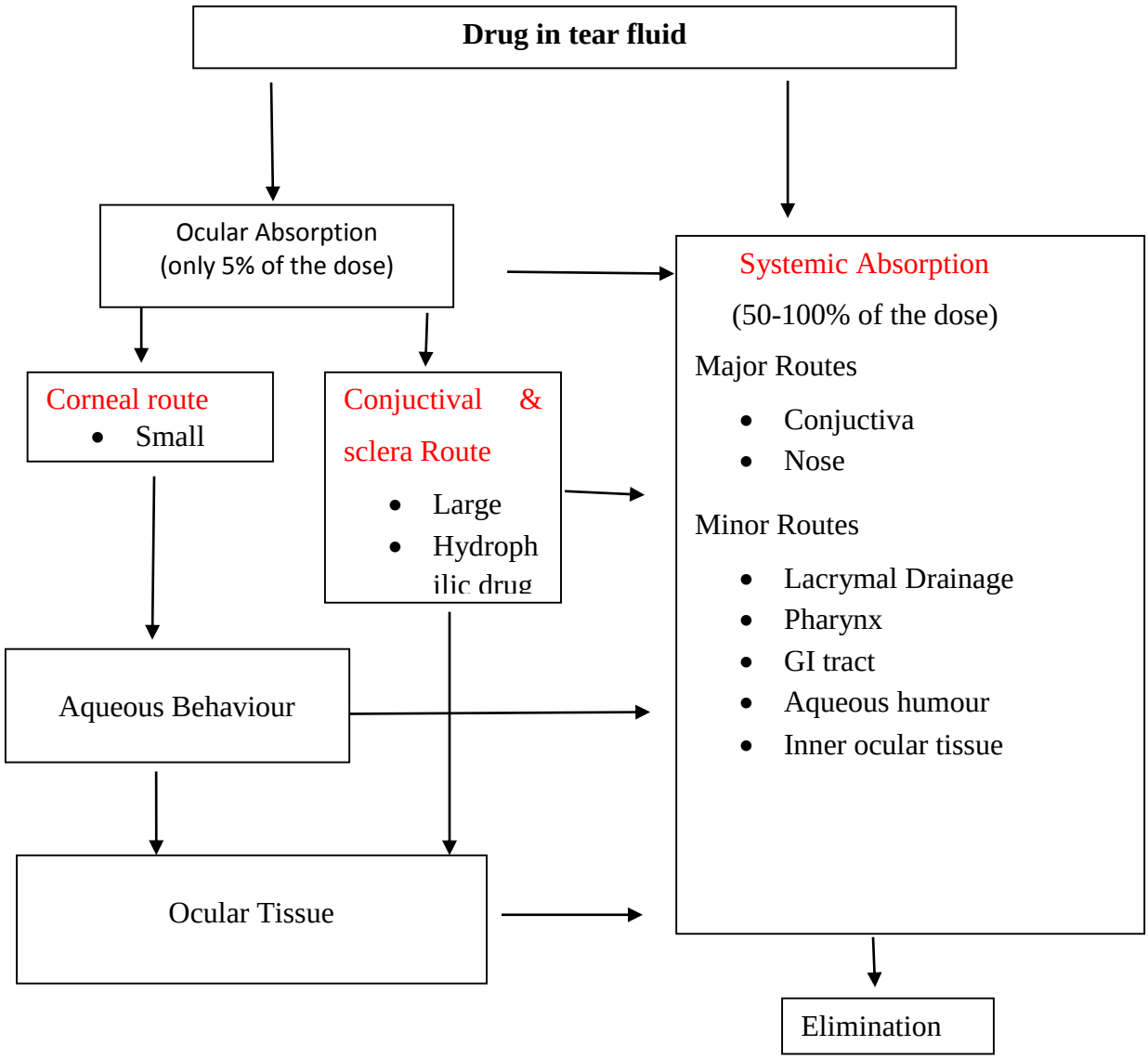

Figure 1: Ocular Drug Absorption

Corneal permeation:-

The corneal permeation of drug occurs from the precorneal space through diffusion across corneal membrane. The rate of absorption is depend 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 consist 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 have 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.

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 conjuctival stroma offers less resistance then the corneal epithelium[15].

EVALUATION PARAMETERS: -

Clarity: -

With the help of visual inspection under black and white background the clarity of formulation is determined.[16]

Texture analysis: -

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.[17]

sol-gel transition temperature and gelling time:-

This evaluation test is carried out for the formulations which are formulated by using thermo sensitive polymer. For these test 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. [18]

Gel strength:-

For evaluation of gel strength rheometer is used. The gel is prepared in beaker as mentioned in the formulation from sol form. The gel containing beaker is raised at certain rate, to push the probe slowly down through the gel. 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. [18]

In vitro drug release studies:-

Franz diffusion cell is used to determine in vitro release study of in situ gel. In this instrument two compartments are present, in which formulation is placed in donor compartment and freshly prepared stimulated tear fluid in receptor compartment. The dialysis membrane is placed (0.22 µm pore size) between receptor donor compartments. The whole assembly is placed on thermostatically controlled magnetic stirrer. The temperature is maintained at 37ºc± 0.5ºc. 1 ml sample is withdrawn at time interval of one hour for six hours. This sample is diluted to 10 ml volumetric flask with suitable solvent and analyzed by UV using reagent blank. With the help of

standard calibration curve drug content is calculated. The % cumulative drug release is also calculated.[19]

Ocular irritancy test: -

These studies are performed on male albino rabbits (weight 1-2kg). The modified draize technique is used for checking ocular irritation potential.[20]

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.[21] then observes the rabbits are observed periodically for redness, swelling & watering of eyes. [22]

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 [23]

Rheological studies: -

With the help of Brookfield viscometer, cone and plate viscometer the viscosity of formulation is determined. viscosity of Formulation should be 5-100mPas, before gelling and after ion gel activation by eye will have viscosity ranging from 50-50,000 mPas [24,25]

Isotonicity evaluation: -

In case of ophthalmic preparations isotonicity is maintained prevent tissue damage or irritation of eye. The formulation is mixed with few drops of blood & observed under microscope at 45x magnification and compared with standard marketing formulations.[26]

Sterility testing:-

To carry out sterility testing formulation should be incubated at 300-350 degree Celsius for not less than 14 days in fluid thioglycolate media. Incubation of formulation at 200-250 degree Celsius in soya bean casein digest medium. Thioglycolate medium used to find growth of bacteria where as soya bean casein medium is for fungi in formulation. [27]

Accelerated stability studies:-

Place formulation in amber color vial and sealed it with aluminum foil for accelerated stability studies at 40± 20 c and relative humidity 75±5% as mentioned in ICH and placed the vial for stability studies. After every month sample is analyzed for clarity, pH, gelling capacity, drug content, rheological evaluation and in vitro dissolution.[2]

Texture analysis:-

With the help of texture profile analyzer the consistency, firmness and cohesiveness of insitu 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.[23]

Advantages of in situ drug delivery system [29, 30]

1. More comfortable compared to insoluble & insoluble formulations
2. Less blurred vision as compared to ointments.
3. Due to increased viscosity precorneal residence time is increased and nasolacrimal drainage is decreased.
4. Due to increased residence time frequent instillation is not required.
5. Ease of administration

CONCLUSION

In these review we saw introduction to ophthalmic in situ gels. The various type of polymers which used for gelling are seen. The sol is converted in to the gel by various stimuli. The drug release from the gels is also covered. The ocular drug absorption is by corneal or non corneal permeation. The various evaluation parameters are also covered in this review.

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