Original Article

Techniques And Polymers Used In Ocular Drug Delivery System

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Abstract

A distinctive anatomical and physiological feature of the eye's walls is the administration of optical medicine. The scientists were required to create novel phrasings to deliver medications to the eye at a controlled rate in order to avoid the need for repeated instillations due to the low optical bioavailability obtained from standard phrasings. The possibility of administering medications topically through the constrained precorneal area and releasing them gradually has been illustrated by natural polymers. Ideal ophthalmic drug delivery must be able to maintain drug release and stay in close proximity to the front of the eye for an extended period of time. Therefore, it is essential to improve the delivery of ophthalmic medications; one way to achieve this is by adding polymers of different colours, creating an in-place gel or colloidal suspension, or employing an erodible or non-erodible insert to prolong the pre corneal medication retention. In addition to polymer employed in modern pharmaceutical design and numerous potential routes of drug delivery into optical apkinsn, this review focused on controlled and sustained medicine delivery.

Keywords: Ophthalmic drug delivery, Bioavailability, Polymers, Controlled, Sustained.

INTRODUCTION

Due to its properties for drug disposition, the eye is the most fascinating organ. Due to its ease and safety for ocular chemotherapy, topical administration of medications is typically the method of choice. It is a huge difficulty for the formulator to get around (bypass) the eye's defences without enduring long-term tissue damage. Ocular delivery systems with high treatment efficacy continue to be made possible by the development of better, more sensitive diagnostic procedures and innovative therapeutic substances. There are numerous drawbacks to traditional ophthalmic formulations such solution, suspension, and ointment, which lead to low drug bioavailability in the ocular cavity. To achieve an ideal medication concentration at the active site for the right amount of time is the specific goal when creating a therapeutic system. A medicinal agent's ocular disposition and removal depend on both its physicochemical characteristics and the pertinent ocular anatomy and physiology. Therefore, an integrated understanding of the drug molecule and the limitations provided by the ocular route of administration is necessary for the successful design of a drug delivery system. Two categories can be made out of the different methods that have been used to lengthen the therapeutic effect of ophthalmic medicines and boost their absorption. The first is founded on the utilisation of sustained drug delivery systems, which offer the continuous and regulated supply of ophthalmic medications. The second includes optimising drug absorption into the cornea while limiting drug loss before the cornea. The perfect ophthalmic medication delivery system must be able to maintain drug release and stay close to the front of the eye for an extended period of time. Therefore, it is crucial to maximise ophthalmic medication delivery. One way to do this is by adding polymers of different grades, creating an in-situ gel or colloidal suspension, or employing an erodible or non-erodible insert to extend the pre corneal drug retention. [1]

The Anatomy of the Eye

The human eye is a portal to the phenomenon known as vision because of its exquisite detail and design. The eyeball measures about an inch wide and is spherical in shape. It contains numerous structures that cooperate to improve sight. The layers and internal structures that make up the human eye each serve a specific purpose. Below is an explanation of each eye part in depth.

A. Sclera

The strong white sheath that makes up the ball's outer layer is known as the sclera (the white part of the eye). The eye's roughly globe-shaped shape is maintained by a strong fibrous membrane. When compared to the front/anterior of the eye, it is significantly thicker toward the back/posterior of the eye. [2]

B. Conjunctiva

The anterior portion of the eyeball is protected by the conjunctiva, a thin, transparent mucous epithelial membrane that borders the inside of the eyelids. Palpebral and bulbar conjunctiva are the names for the separate parts of the conjunctiva. The conjunctiva is made up of two layers: the stroma beneath the outer epithelium (substantia propria). Conjunctiva and cornea, which are on the eye's exposed surface, are shielded by the tear film. Conjunctiva secretes significant amounts of electrolytes, fluid, and mucins, which help to produce the tear film**.** [3]

C. Cornea

At the front of the eye, there is a prominent, transparent bulge called the cornea. The adult cornea's surface has a radius of about 8mm. It performs a crucial optical function by refracting light that enters the eye, passes through the pupil, and then hits the lens (which then focuses the light onto the retina). The capillaries that terminate in loops at the cornea's periphery provide the required nutrition to the non-vascular (blood vessel-free) cornea. Numerous nerves that are descended from the ciliary nerves supply it. These seep into the cornea's layered tissue. As a result, it is very sensitive. [4]

D. Aqueous humour

A jelly-like material called aqueous humour fills the outer/front chamber of the eye. The "anterior chamber of the eye," which is situated immediately behind the cornea and in front of the lens, is filled with a watery fluid. The aqueous humour is a salt solution that is only very mildly alkaline and contains extremely small amounts of sodium and chloride ions. It is continuously made, primarily by the ciliary processes, and flows from the posterior chamber into the anterior chamber through the pupil. It then leaves via the trabecular pathway at the angle and the uveoscleral route. Aqueous humour from the anterior chamber is collected in Schlemm's canal, also known as the scleral venous sinus, and is then released into the bloodstream by the anterior ciliary veins. It is situated where the sclera and cornea meet. Aqueous humour turnover in humans occurs at a rate of 1% to 1.5% of anterior chamber volume per minute. Aqueous formation occurs at a rate of around 2.5 l/min. There are pressure-dependent and pressure-independent routes in aqueous humour. The trabecular meshwork-canal-venous Schlemm's system is known as the pressure-dependent outflow, whereas the pressure-independent outflow is known as the uveoscleral outflow and refers to any non-trabecular outflow. [5]

E. Pupil

Although the pupil frequently appears to be the dark "centre" of the eye, it is actually the circular opening in the iris's middle through which light enters the eye. The pupillary reflex controls the size of the pupil (and subsequently the amount of light admitted into the eye) (also known as the "light reflex"). [6]

F. Iris

The iris is a tiny, round, contractile veil that hangs behind the cornea and in front of the lens. The iris is a diaphragm with a range of sizes, and its job is to change the pupil's size to control how much light enters the eye. The coloured portion of the eye is it (shades may vary individually like blue, green, brown, hazel, or grey).

G. Ciliary Muscle

The middle layer of the eye's ciliary muscle is a ring of striated smooth muscles that manages accommodation for viewing things at various distances and controls the aqueous humour's flow into Schlemm's canal. Both sympathetic and parasympathetic nerves innervate the muscle. The lens's curvature changes as a result of ciliary muscle contraction and relaxation. The balance between two states—Ciliary Muscle tightened (which helps the eye focus on distant things) and Ciliary Muscle relaxed—can be used to characterise this process (This enables the eye to focus on near objects).

H. Lens

A thin clear capsule surrounds the transparent lens, which is a transparent structure. It is situated beneath the eye's pupil and is surrounded by the ciliary muscles. It facilitates the refraction of light entering the eye (which first refracted by the cornea). The retina receives an image from the lens's focus of light. This is made possible by the lens' ability to alter form in response to an object's proximity to the observer's eye. Accommodation refers to the process of the ciliary muscles contracting and relaxing to change the curvature of the lens. [7]

I. Vitreous Humour

The huge region that takes up around 80% of each eye in the human body is called the vitreous humour, often known as the vitreous body. The vitreous humour covers the space behind the eye's lens and is a completely transparent, thin, jelly-like fluid. It is an albuminous fluid that is encased in the hyaloid membrane, a thin, transparent membrane.

J. Retina

At the back of the human eye is the retina. The retina can be thought of as the "screen" on which an image is created by light that enters the eye through the cornea, aqueous humour, pupil, and lens before passing to the retina. The retina serves as more than just a screen for images to be generated; it also collects the data from those images and sends it in a form that can be used by the body to the brain. Therefore, the interior of the eye's retina, or "screen," is lined with light-sensitive tissue. It has

photosensitive cells (known as rods and cones) and the nerve fibres that connect them, which transform the light they perceive into Nerve impulses that go along the optic nerve and are then delivered to the brain.

K. Macula

The macula is the name for the retina's central region. High numbers of photoreceptor cells, which transform light into nerve signals, are found in the macula. We can perceive small details, like newsprint, with the macula thanks to the great density of photoreceptors. The fovea, where our sharpest eyesight is located, sits in the exact middle of the macula.

L. Choroid

The unneeded energy is absorbed by the choroid layer, which is situated behind the retina and nourishes the outer regions of the retina. It is a dark brown membrane that is thin, extremely vascular (i.e., has blood vessels), and contains a pigment that absorbs extra light to prevent vision blur (due to too much light on the retina). One of the highest blood flows occurs in the choroid. The lamina fusa loosely fastens the choroid to the sclera's inner surface.

M. Optic nerve

The nearly 1 million nerve fibres that make up the optic nerve are in charge of carrying nerve signals from the eye to the brain. These nerve signals include data on an image that the brain can process. The optic disc refers to the front surface of the optic nerve as it appears on the retina. [8,9]

1. Classification of Ocular dosage form

- **Conventional Ophthalmic Dosage Forms**:

a) Eye Drops: It is described as a liquid preparation in which every ingredient is equally and totally soluble in solution. After instillation, the precorneal region absorbs the majority of the implanted volume.

b) Eye Gels: It is a semisolid preparation that is applied to the eye and is made up of tiny molecules that are permeated by a liquid. When utilising gels, the residence period is longer in the eye region, increasing the absorption rate and producing a sustained therapeutic impact.

c) Eye ointments: Eye ointments are sterile, semisolid preparations with a uniform appearance that are applied to the eyelid edge or conjunctiva. It has very little therapeutic impact because of its hydrophobic nature. It causes eyesight blurring because of its oily nature.

d) Eye Suspension: Suspensions are created by dispersing relatively insoluble pharmacological compounds that have been finely ground into an aqueous medium with the right suspending and dispersing agents. It must have particles with specific chemical properties and tiny enough size to not irritate the eyes15. The particles are better retained in cul-de-sacs, increasing the drug's bioavailability and producing a slow release effect. [10]

- **Novel Ophthalmic Dosage Forms**:

Many advancements have been made to enhance precorneal medication absorption and minimise precorneal drug loss in order to address the shortcomings of standard ophthalmic dosage forms

a) Mucoadhesives: In order to prolong their pre-ocular residence durations, mucoadhesives are characterised as substances that are kept in the eye thanks to non-covalent bonds formed with corneal conjunctival mucin.

b) Phase transition system: When injected into the cul-de-sac, these liquid dose forms change into gel or solid forms. Drug elimination is slowed down as a result of the substance's extended interaction with the cornea of the eye when it transforms into gel.

c) Niosomes: Niosomes are non-ionic surfactant-containing vesicles that can entrap both hydrophilic and lipophilic medicines in either an aqueous layer or a lipid-based membrane. It aids in preventing the medication from being metabolised by enzymes found near the tear/corneal surface**.**

d) Liposomes: Liposomes are tiny vesicles with aqueous compartments surrounded by membrane-like lipid layers. Phospholipid makes up the majority of the lipid layers. They have the capacity to integrate hydrophobic molecules into the lipid bilayers and to entrap hydrophilic compounds in the aqueous compartment.[11]

e) Nanoparticles: Nanoparticles are solid, polymeric particles with sizes between10 and 1000 nm. The medications are attached to tiny particles and then distributed in an aqueous medium25. These are not easily washed away by tears since they are so little.[12]

f) Contact lenses: The use of contact lenses as eyeglass replacements is becoming more and more common. Soft contact lenses soaked in medication have been suggested as a method for slow but extended drug delivery, particularly to ocular tissue The Pharma Research Year: 2009, Vol: 01 77.

g) Pharmacosomes: They are the vesicles that the amphiphilic medicines have created. Any medication with a free carboxy group can be esterified to a lipid molecule's hydroxyl group to create an amphiphillic prodrug. These become pharmacosomes after being diluted with tear.[13]

h) Ophthalmic inserts: Inserts are described as thin discs or tiny cylinders that fit into the lower or upper conjunctival sac and are constructed of the suitable polymeric material. Greater medication availability in relation to liquid and semisolid formulation may be the result of their prolonged persistence in the preocular area.[14]

2. Advantages of occuserts:

- Increased ocular residence time hence a prolonged drug activity and a higher bioavailability with respect to standard vehicle.
- Possibility of releasing drug at a slow constant rate.
- Accurate dosing (contrary to eye drop that can be improperly instilled by the patient and are partially lost after administration each insert can be made to contain a precise dose which is fully retained at the administration site).
- Reduction of systemic absorption (which occurs freely with eye drops via the nasolacrimal duct and nasal mucosa).
- Better patient compliance, resulting from a reduced frequency of administration and a lower incidence of visual and systemic side effects.
- Possibility of targeting internal ocular tissues through non corneal(conjunctival sectional) routes
- Increased shelf life with respect to aqueous solutions.
- Exclusion of preservative, thus reducing the risk of sensitivity reactions.
- Possibility of incorporating various level novel chemical/technological approaches, such as prodrugs, mucoadhesives, permeation enhancers, microparticulates, salts acting as buffers etc [15,16]

3. Disadvantages of occusert

- Initial discomfort, their movement around the eye.
- Occasional inadvertent loss during sleeps or while rubbing the eye.
- Interference with vision and a difficult placement.

4. Classification of occusert

They are classified on the basis of their solubility [17]

a) Insoluble ophthalmic inserts.

b) Soluble ophthalmic inserts.

c) Bioerodible ophthalmic inserts.

a) Insoluble ophthalmic inserts: Subcategorized under The Pharma Research Volume: 01 78, 2009 Inserts for diffusion. Inserts for osmosis. lenses for your eyes. Inserts for Diffusion: The medicine is contained in a central reservoir of the diffusional inserts that is semi-permeable and carefully constructed to allow the drug to diffuse out of the reservoir at a predetermined rate. The drug release from such a device is controlled by the lacrimal fluid penetrating through the membrane up until the required internal pressure is obtained to force the drug out the reservoir. The Fick's diffusion equation can be used to operate on its operating principle. J=-DAdc/dx J = pure flux D is the drug's difference co-efficient inside the polymer membrane. Drug concentration gradient within the membrane along the direction of drug flow: A = Area of Membrane dc/dx.[18]

Osmotic Inserts: Two different compartments make up the osmotic inserts. Sandwiched between the membrane regulating the flow rate is a compartment containing the medicine and another containing the osmotic solution. The tears cause an osmotic pressure in the osmotic compartment, which causes the medication to diffuse.

Contact Lenses: Contact lenses are made of hydrophilic or hydrophobic polymers that are covalently bonded to form a three-dimensional network that can hold water, aqueous medication solutions, or solid components. [19]

b) Soluble ophthalmic inserts: These inserts are completely soluble, so they don't need to be taken out of the application site. The medicine is released from these inserts because tear fluid seeps into them, causing a rapid rate of drug diffusion and forming a gel layer surrounding the core of the insert. [20]

c) Bioerodible Ophthalmic Inserts: The hydrophobic coating of the biodegradable inserts, which is largely impermeable, contains a material homogeneous dispersion of a medicine, whether it is present or not. When a device comes into touch with tear fluid, it causes a brief diversion of the matrix, which leads to the release of the drug from the system. [21]

NEW TECHNIQUES USED IN OCULAR

1. Solvent displacement method

It has been frequently employed to create nanoparticles and goes by the name of nanoprecipitation. The technique is based on the preformed polymer precipitating when a semi-polar solvent that is miscible with water is displaced, either with or without the use of a surfactant. This technique's fundamental idea is comparable to spontaneous emulsification, which occurs when a drug- and polymer-containing organic phase mixes with an external aqueous phase. In this procedure, a water-miscible organic solvent with a medium level of polarity is used to dissolve both the polymer and the medication (e.g. acetone and ethanol). The resultant organic phase is introduced into an aqueous phase that has been agitated and is stabilised using a surfactant. The fast diffusion of the organic phase into the aqueous phase causes the nanoparticles to develop instantly.[22,23]

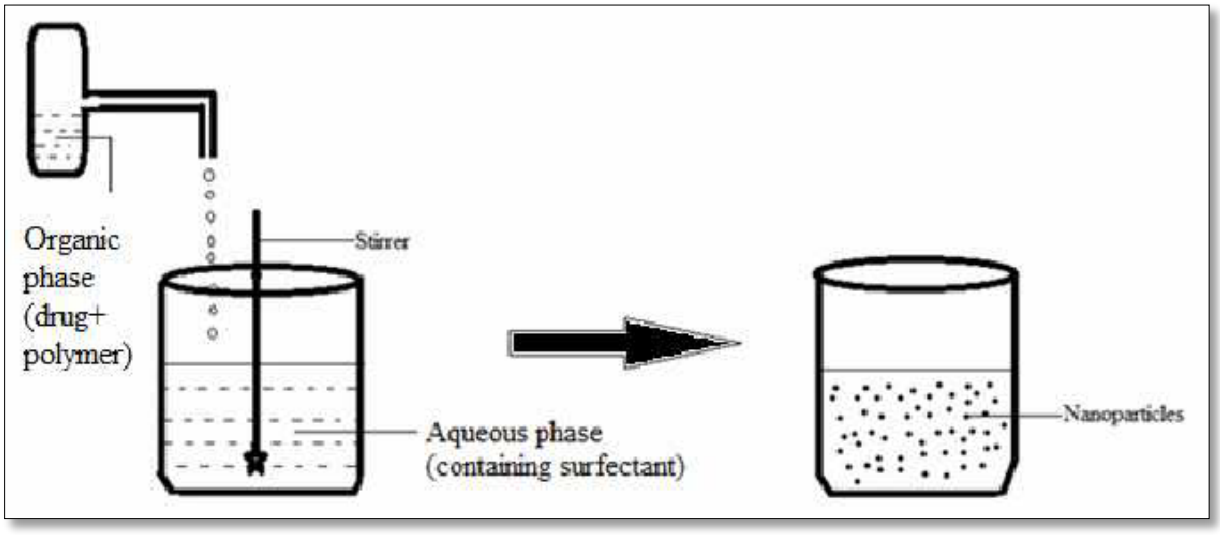


Fig. 1: solvent displacement method

This method was employed by **Mandal et al**. to create an ocular delivery system for sulfacetamide-loaded Eudragit RL-100 nanosuspension. Sulfacetamide-containing Eudragit RL-100 nanosuspensions were created using acetone and 1% w/v pluronic F-109 as a surfactant. The formulation variable used was the medication to polymer ratio. The findings suggested that nanosuspension might be used as a viable delivery method for treating bacterial infections of the eyes. [24]

Yadav et al. reported the investigation of carvedilol-loaded Eudragit E-100 nanoparticles by nanoprecipitation approach utilising poloxamer F407 as polymeric stabiliser, and they hypothesised the viability of formed nanoparticles for the treatment of hypertension. The size range of the produced nanosuspension particles was 190-270 nm. It was discovered that the amount of Eudragit E-100 directly affected the nanoparticle size. 41 With the use of PLGA, this technique can also be utilised to encapsulate some fluoroquinolones, such as sparfloxacin, for prolonged ocular drug administration.[98,99]

Using the nanoprecipitation process, **Gupta et al**. explored sparfloxacin-loaded PLGA nanoparticles for sustained ocular drug delivery. The created PLGA nanoparticle was shown to increase precorneal residence time and ocular penetration. It was also discovered to be more stable and have a longer shelf life than commercially available formulations. Another publication from the same study mentions the encapsulation of levofloxacin-like fluoroquinolone nanoparticles. [25]

Levofloxacin was made into a nanosuspension utilising the solvent evaporation method using PLGA as the biodegradable polymer. The study focuses on particle size distribution, and it was discovered that all formulations have monodisperse systems with polydisperse indices of less than 0.1. According to the results of a transcorneal permeation study, levofloxacin-loaded PLGA nanoparticles have a significantly higher permeation capacity than commercially available levofloxacin eye drops. It was also determined that the formulation of levofloxacin-encapsulated PLGA nanosuspension provides prolonged retention with improved tolerability and prolonged release at the corneal site. [26,27]

Acyclovir was reported to be released from a nanosuspension created by mixing tween 80 as a surfactant with Eudragit RS-100 as a sustained polymer, according to **Kerur et al**. The study found that acyclovir's polymeric ophthalmic nanosuspension could release the medication for a long time and had a higher bioavailability.[28]

By using the solvent evaporation method, **Pignatello et al**. were able to determine the stability of cloricromene in ophthalmic formulation and increase bioavailability at the ocular level. The resulting nanosuspensions had a positive surface charge and acceptable mean particle sizes for ophthalmic applications. Additionally, a significant polydispersity index was observed, which denotes a high degree of particle size variability. When nanoparticles were generated in saline without tween or with the least amount of tween, greater chemical stability of ester medication was seen.[29,30]

For the treatment of severe dry eye syndrome, **Aksungur et al**. developed nanoparticles encapsulating cyclosporine (CsA) utilising poly lactide co-glycolic acid (PLGA), Eudragit RL-100, and/or PLGA coated with carbopol. [103] With Eudragit RL, the smallest nanoparticles were produced. CsA released from nanoparticles followed a Weibull model of release. It was discovered that the physicochemical characteristics of the polymer caused nanoparticle size to decrease when Eudragit-RL concentration increased. According to the study, the particle size of the freeze-dried cyclosporine nanoparticles somewhat increased.[30,31]

Adibkia et al. created Eudragit RS100 loaded piroxicam nanoparticles using a comparable technique to treat rabbits with endotoxin-induced uveitis and reduce inflammatory symptoms (EIU). The study recommended using the non-invasive PiroxicamEudragit RS-100 nanosuspensions as a safer controlled ocular administration system for inhibiting the symptoms of uveitis.[32]

Another study looked into the possibilities of improving drug distribution to the ocular mucosa by using amphotericin B nanoparticles made using solvent evaporation. The study contains a molecular weight cutoff of 12,000–14,000 Da and

investigated the release of amphotericin B from nanoparticles utilising diffusion cells and dialysis membrane. Particle size and particle size distribution were significantly influenced by the ratio of drug to polymer as well as the organic phase to aqueous phase ratio. Amphotericin B nanoparticles' positive zeta potential and small particle size contribute to extending the corneal contact period.[33,34]

Using the same technique, Ahuja et al. created a nanoususpension of diclofenac-loaded Eudragit S100 for ocular administration. Cryoprotectant mannitol (5%w/v) was added. The formulation including Eudragit S100 (lyophilized with cryoprotectant) had an average particle size and entrapment efficiency of 172 nm and 95.77%, respectively, whereas the formulation containing Eudragit S100 (lyophilized without cryoprotectant) had values of 2720 nm and 92.56%. Average particle size and polydispersibility index of nanosuspensions are crucial factors in determining their biological performance, physical stability, dissolution rate, and saturation solubility.[35,36,37]

The aggregation of suspended particles during the lyophilization stage is what causes the larger average particle size and lower value of zeta potential in the formulation containing Eudragit S100 lyophilized without mannitol compared to formulation containing Eudragit S100 lyophilized with mannitol. The study notes that Eudragit S100 nanosuspension is a successful ocular delivery strategy for diclofenac due to its greater entrapment efficiency and sustained in vitro release. [38]

Using two distinct polymers, poly[Lac(Glc-Leu)] (PLDA) and poly(lactide-co-glycolide), Agnihotri et al. studied a diclofenac-loaded biopolymericnanosuspension for ocular administration generated by emulsion and solvent evaporation technique (PLGA). The research showed that corneal adhesion and stability during storage, particularly at low temperatures, were improved by the nanosuspensions. The outcomes suggested that nanosuspension might be used as a possible delivery strategy for topically treating inflammatory eye diseases.[39]

Utilizing sodium lauryl sulphate (SLS) and hydroxypropyl methyl cellulose (HPMC) as surfactants and microfluidic reactors, some steroids, such as hydrocortisone, can be encapsulated.[40,41]

The results showed that spherical particle-based nanosuspensions with mean particle sizes of 500–64 nm, zeta potentials of -18–2.84 mV, and polydispersity indices of 0.21–.026 were discovered. The feasibility of preparing hydrocortisone as a nanosuspension for ocular medication delivery was also determined.

Yoncheva et al. described a method for coating and preparing pilocarpine-loaded poly (lactic-coglycolic acid) (PLGA) nanoparticles using solvent evaporation. For coating, a variety of mucoadhesive polymers including chitosan, sodium alginate, and poloxamers were utilised. Only the particles coated with chitosan had positive surface charges; all other particles had negative surface charges. Their negative (22.8 mV) surface charge was transformed to a positive (61.0 mV) surface charge. To determine the produced nanoparticles' mucoadhesive characteristics, the Hitachi U-1500 used turbidimetric measurements of the particles. After local ocular application, it was determined that encapsulating the nanoparticles with chitosan would be a viable strategy for extending their residence time.[42,43]

The goal of the study was to increase the availability of ibuprofen sodium (IBU) at the intraocular level by manufacturing polymeric nanoparticle solutions from inert polymer resins (Eudragit RS100) for ophthalmic controlled delivery.[44]

The quasi-emulsion solvent diffusion process was modified to create the nanosuspensions. After inducing an ocular insult, the rabbit eye's in vivo effectiveness was evaluated (paracentesis). The study concluded that even at lower concentrations of the free drug in the conjunctival sac from nanoparticulate formulation, an inhibition of the miotic response to the surgical trauma was achieved when compared to a control aqueous eye-drop formulation. It also revealed that there was no toxicity of IBU-loaded nanosuspension on ocular tissues. [46,47]

Flurbiprofen-loaded acrylate polymer nanosuspensions employing the quasi-emulsion solvent diffusion approach have been published in another section of the same study. The objective of the trial is to increase the drug's intraocular availability for the prevention of the myosis brought on by extracapsular cataract surgery. For in vivo anti-inflammatory experiments, the rabbit eye was employed following the creation of an ocular trauma. Additionally, ocular tissues exposed to nanosuspensions with FLU did not exhibit any harm. In spite of the fact that the nanoparticle system produced a lower concentration of free medication in the conjunctival sac than the control eye-drop formulation, it was determined that a suppression of the miotic response to the surgical trauma was acquired. A greater drug level was detected in the blood after the nanosuspensions were applied.[45]

For the treatment of cytomegalovirus retinitis, gangliclovir (GCV) as antiviral medication loaded nanoformulations were created utilising reverse-phase evaporation. The goal of this study was to compare the potential of several mucoadhesive nanoformulations for the topical administration of ganciclovir to the eyes. GCV mucoadhesive nanoemulsions (GCV-NEs), chitosan nanoparticles (GCV-NPs), and GCV mucoadhesive venomal dispersion are some of the several nano-formulations that were developed for the experiments (GCV-NDs). The results showed that the produced formulations had no hazardous or irritating properties. The use of GCV nanoformulatios as a possible delivery mechanism for topical instillation-based therapy of ocular infections was further concluded.[48,49,50]

In order to generate biodegradable nanoparticles for colloidal drug delivery systems, Mohammadi et al. used the nanoprecipitation process with PLGA as the biodegradable polymer. The investigation of clarithromycin nanosuspension's antibacterial properties utilised Staphylococcus aureus. Since the nanoparticle formulation had an equal antibacterial effect at a concentration of 1/8 of the intact drug, it was discovered that the intact drug CLR was less effective than nanoparticle

formulation against S. aureus. The study showed that the produced CLR nanoparticles had increased minimum inhibitory concentrations (MICs) and were more effective against S. aureus.

It has been reported that the double emulsion-solvent evaporation method used by Eudragit to create brimonidine tartrate nanoparticles for the treatment of open-angle glaucoma. The created brimonidine tartrate nanoparticles were discovered to have a limited particle size range and increased drug loading. The findings of the in vivo ocular irritation and tolerance studies showed that the nanoparticle formulations were well tolerated and showed no symptoms of irritation. In vivo studies using the nanosuspensions result in a sustained decrease in intraocular pressure (IOP) and medication release.

Using a single emulsion process, Javadzadeh et al. created naproxen nanoparticles with poly (lactic-co-glycolic acid). The aqueous phase volume, drug/polymer ratio, and homogenization speed were taken into account as process variables to produce the best preparation conditions. According to the study, it is possible to create PLGA nanoparticles with adequate physicochemical properties that will enhance a drug's anti-inflammatory effects once it is administered intravenously or topically.[51,52,53]

Poly (D,L-lactidecoglycolide) nanoparticles for contact lens care made by a double emulsion-solvent evaporation process were described by Jimenez et al. To determine the ideal lactic acid proportion in the copolymer and the parameters for the second sonication, a factorial design was used. It was shown that when the second sonication period was shortened, bigger particle size nanoparticles were produced and the efficiency of entrapment increased as the lactic acid proportion increased. PLGA 50:50 NPs were chosen for future development over PLGA 75:25 NPs because they settled quickly with diverse particle sizes in the sediment as opposed to the earlier nanoparticles, which formed aggregates. Tetronic 1304 was added, which initially encouraged the quick release of the enzyme and reduced the zeta potential (zeta) up to neutral values following gamma irradiation. Glycerol was added to the nanoparticles, which resulted in the highest entrapment effectiveness of Methyl trypsin (>90%). After the in vitro HETCAM test and the in vivo Draize test, it was found that nanoparticle formulations displayed a tolerable level of ocular irritation. After 3 days or longer, and with very little enzyme produced, the nanoparticles were shown to be useful as a lens care cleanser. [54]

2. Homogenization

The creation of nanosuspension is also done using this technique. The procedure can be broken down into three steps: first, the drug powders are dispersed in a stabiliser solution to create the presuspension; next, the presuspension is homogenised by a high-pressure homogenizer at a low pressure multiple times. Pre-milling is another name for it, and when the pre-milled suspension was homogenised at a high pressure for 10 to 25 cycles, the necessary nanosuspensions were created.[55]

Nanosuspensions of essentially insoluble glucocorticoid medications, such as hydrocortisone, prednisolone, and dexamethasone, were created using the high pressure homogenization process. As a surfactant, pluronic F68 (1% w/v) was employed. It was determined that glucocorticoid nanosuspensions improve the speed and volume of ocular drug absorption as well as the intensity of pharmacological activities. Additionally, it was noted that when nanosuspension viscosity increased, the duration of medication action increased.[56,57]

3. Ionic gelation

In the ionic gelation process, the hydrophilic polymer's positive or negative charge forms a compound with a multivalent cationic (such as calcium chloride) or polyanionic (such as sodium tripolyphosphate) ion to produce very viscous gel particles with a size in the nanometer range. For the creation of chitosan nanoparticles, Calvo and colleagues invented the ionic gelation process. This technique involves combining polymer and polyanion solutions to create nanoparticles. Electrostatic interactions between negatively charged anion and positively charged amino groups found in polymers are the fundamental process by which nanoparticles are formed. In other words, it is clear that in the ionic gelation procedure, the substance experiences a phase shift from liquid to gel as a result of interaction. The obtained chitosan nanoparticles generally are of small size in the range of 200-500nm.[58,59,60]

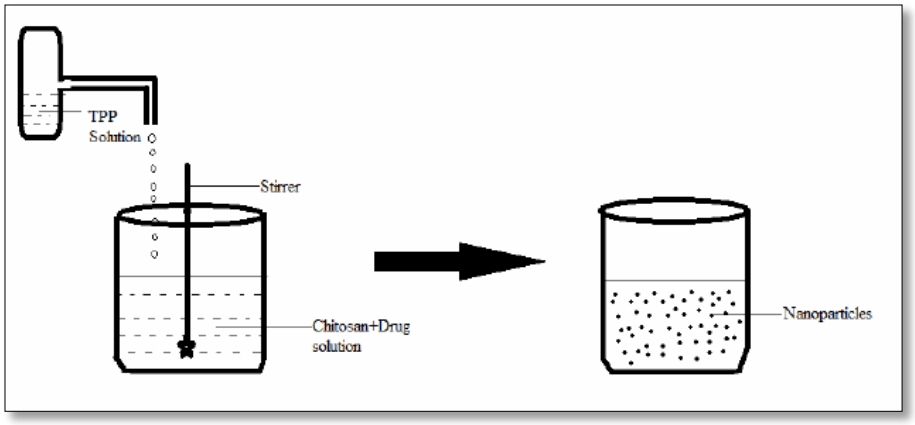


Fig. 2: Ionic gelation technique.

zeta potential. According to the results of the permeation investigation, fluconazole's optimised formulation had higher penetration (%) than the drug's commercial formulation.[60]

For ocular drug delivery, a comparison of chitosan- and soya-lecithin-loaded MMF nanosuspensions and ophthalmic soya-lecithin-loaded MMF suspensions was conducted. Preocular medication retention time was extended by the use of soy lecithin and chitosan-loaded nanosuspension technology. The modified chitosan nanosuspension demonstrated improved formulation stability and higher zeta potential values.

In another study hybrid nanoparticle based on cationized gelatine, polyanions dextran sulphate (DS) and chondroitin sulphate (CS) were prepared by Zorzi et al. for ocular gene therapy. It was reported that these systems can be used as a carrier for plasmid DNA by avoiding the DNAse I degradation. It was observed that the in vitro toxicity of the nanoparticles to human corneal cells can be reduced by the introduction of CS or DS in the formulation without compromising the transfection efficiency. These systems are prospective carriers for the development of safer and more valuable nanomedicines for ophthalmic delivery. [61]

In a different study, Jain et al. assessed the PLGA-chitosan Rhodamine loaded nanoplexes for their interaction with ocular mucosa, as well as its viability as an ocular delivery system, using ex vivo and in vivo studies. Fluorescent RhodamineNanoplexes were made using the ionotropic gelation process (Rd-Nanoplexes). For the investigation of corneal retention, uptake, and penetration of Nanoplexes, spectrofluorimetry and confocal microscopy were employed. Confocal microscopy of the corneas allowed researchers to observe the paracellular and transcellular uptake of the Nanoplexes. The ocular tolerability and in vivo uptake of the Rd-Nanoplexes in rabbit corneas were assessed. As an uptake mechanism, it was thought that adsorptive endocytosis and the opening of tight junctions between epithelial cells would occur. After exposure to Nanoplexes, no change was microscopically seen on the ocular surface.

To increase indomethacin's ocular bioavailability, chitosan-loaded nanoparticles and nano emulsions were created.[62,63] Chitosan nanoparticles were created using the ionic gelation method, while a nanoemulsion was created using the emulsification method. According to in vivo investigations, rabbits treated with nanoemulsion as opposed to nanoparticle preparation showed clearer healing of corneal chemical ulcers and moderately efficient prevention of polymorph nuclear leukocytic infiltration (PMNLs). As opposed to indomethacin medication solution, the high indomethacin level in the aqueous humour and inner ocular structure of rabbit eyes was reached with topical instillation of chitosan nano emulsion. The produced chitosan nanoparticles were able to make intimate contact with the cornea, resulting in a long-lasting, gradual drug release that improved transport to both internal and exterior ocular tissues.[64]

4. Milling method

To make nanosuspensions, high-shear media mills or pearl mills are employed. A milling chamber, a milling shaft, and a recirculation chamber make up the media mill. High energy and shear pressures are produced as a result of the drug impaction with the milling media, providing the energy required to break down the drug's microparticles into nanoparticles. Aluminium oxide, zirconium oxide, or strongly cross-linked polystyrene resin are ceramic-sintered to form the balls or milling medium, which have a high resistance to abrasion. Planetary ball mills are used to obtain sizes less than 0.1 m. The milling chamber is charged with the milling medium, water or another suitable buffer, the medication, and the stabiliser throughout the media milling process. After that, pearls or milling media are rotated at a very high shear rate.[65,66]

5. Supercritical fluid method

Due to the environmental safety of supercritical fluids, this method has being looked at for the production of biodegradable micro and nanoparticles. Common techniques involving supercritical fluids include supercritical anti-solvent (SAS), rapid expansion of supercritical solution (RESS), and precipitation with compressed anti-solvent process (PCS). One liquid solvent

and another supercritical fluid are used in the supercritical anti-solvent method. They are both perfectly miscible with one another. Since the solute is not soluble in the supercritical fluid, the instantaneous precipitation of the solute resulting from the liquid solvent's extraction by the supercritical fluid causes the production of nanoparticles. Nanoparticles of the medication dexamethasone phosphate can be made using the SAS process.[67,68]

Table 1: Summary of methods used for preparation of polymeric nanoparticles for ocular delivery

METHOD	DRUG	CATEGORY	POLYMER	STABILIZER	REFERENCES
Solvent displacement method	Sulfacetamide	Antibiotic	Eudragit RL 100	Pluronic F109	40
	Carvedilol	Non-selective beta blocker	Eudragit E100	Poloxamer 407	41
	Sparfloxacin	Fluroquinolone Antibiotic	PLGA	PVA	42
	Levofloxacin Cloricromen	Antibiotic	PLGA Eudragit RS 100 Eudragit RL 100	PVA Tween 80	43 45
	Cyclosporine	Immuno-Suppressant	PLGA Eudragit RL 100	PVA	46
	Piroxicam	NSAID	Eudragit RS 100	PVA	47
	Amphotericin B	Antifungal	Eudragit RS 100	PVA	48
	Diclofenac	NSAID	Eudragit S100	Poloxamer 188	49
	Diclofenac	NSAID	Eudragit S100	Tween 80	50
	Hydrocortisone	Glucocorticoid	HPMC	SLS	51
	Pilocarpine	Para-sympathomimetic alkaloid	PLGA Chitosan	-	52,53
	Ibuprofen	NSAID	Eudragit RS 100	-	54
	Flurbiprofen	NSAID	Eudragit RS 100R Eudragit RL 100R	- -	54 55
	Ganciclovir	Antiviral	Chitosan	-	56
	Clarithromycin	Macrolide Antibiotic	PLGA	-	57
	Brimonidine	Non-selective beta blocker	Eudragit	TPP	58
	Naproxen	NSAID	PLGA	-	59
Homogenization	Prednisolone Dexamethasone	Anti-inflammatory	Hydroxy ethyl cellulose	Pluronic F68	62
Ionic Gelation	Fluconazole	Triazole antifungal	Gum cordial	Di octyl sodium sulfosuccinate	65
	Mycophenolate mofetil	Immuno-suppressant	Chitosan	Pluronic F68	66
	Brimonidine tartrate	Non-selective beta blocker	Chitosan		67
	Econazole nitrate	Antifungal	Chitosan		69
	5- Fluro Uracil	Anticancer	Chitosan		71
	Indomethacin	NSAID	Chitosan		74
Milling	Cyclosporine A	Immunosuppressant		PVA	77

POLYMERS USED IN OCULAR FORMULATION Significant research has been put into developing ocular delivery systems that offer regulated and prolonged medication release in recent years. A delivery system known as a "in situ gelling system" undergoes a phase change from liquid to viscous gel depending on the pH, temperature, and electrolyte content when it is injected. In situ forming drug delivery systems provide several benefits over conventional formulations, including as enhanced bioavailability, convenience of administration, and astraight forward production procedure. As a result, the benefits of both solutions and gels, such as their simplicity of administration and extended residence times, are combined in this delivery system. As a result, it improves patient compliance, lowers dosage frequency, and boosts bioavailability.

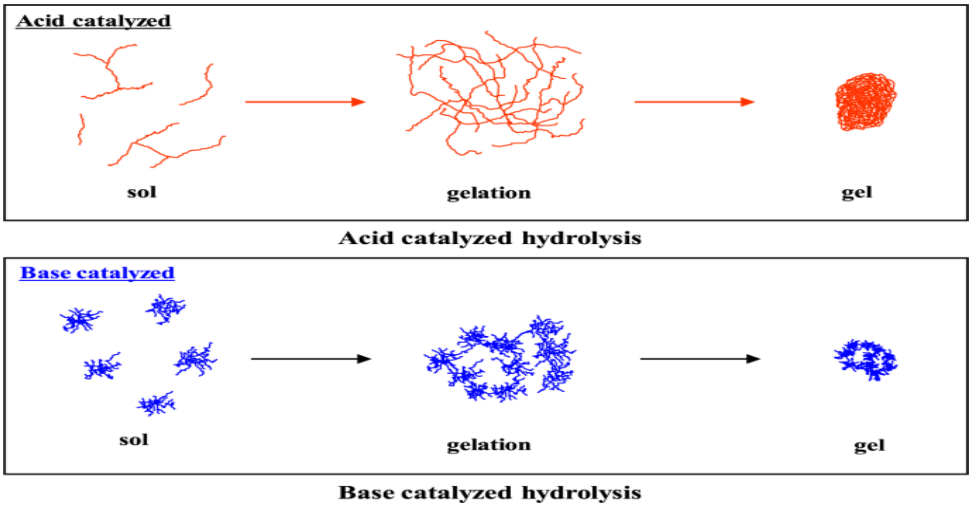


Fig.3: Mechanism of sol-gel transition

Classification of in situ gelling system

1. pH sensitive in situ gelling system

2. Temperature sensitive in situ gelling system

3. Ion sensitive in situ gelling system

1. pH sensitive in situ gelling system

In this system, the solution begins to gel when the pH is increased from 5-7.4. A hydrogel is produced when mucin and a polymer form a hydrogen bond as a result of a higher pH. Carbopol, polyacrylic acid, polyethylene glycol, and cellulose acetate phthalate latex are examples of pH-dependent polymers.[69]

Mechanism for pH sensitive gelling System

Each pH-sensitive polymer has a pendant acidic or basic group that can accept or release protons based on the pH of the environment. Hydrogel swelling increases for weakly acidic groups but decreases for weakly basic groups when the external pH rises. [70]

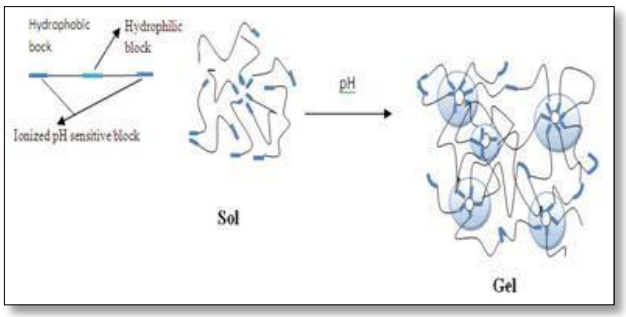


Fig. 4: Mechanism of pH sensitive in situ gelling system

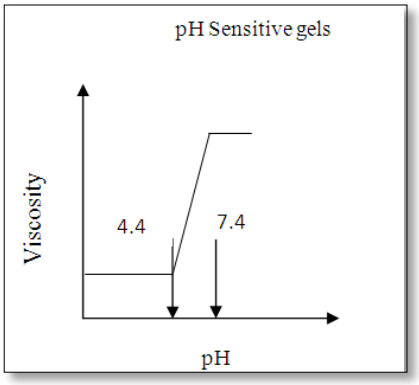
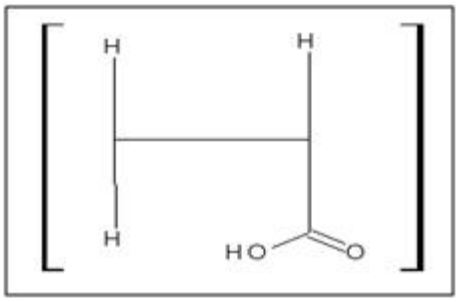


Fig. 5: Graphical representation of pH sensitive in situ gelling system

Polymers used in pH sensitive in situ gelling system

- **Carbomer**



Scheme 1: Structure of Carbomer

Mechanism

Carbomer, a cross-linked polyacrylic acid derivative with a high molecular weight, possesses the strongest mucoadhesive property. Water is soluble in vinyl polymer. A sol to gel transition occurs in aqueous solution when the pH is raised above the pKa of around 5.515. As the concentration of carbomer increases, its acidic nature may irritate the eyes. The use of cellulose will lessen the polymer concentration in addition to enhancing gelling capabilities. A range of carbomer grades are available on the market, including carbopol 981, which has the maximum cross linking density, and carbopol 940, which has the lowest cross linking density (intermediate cross linking density). Carbopol is used as a gelling, emulsifying, and suspending agent.[71]

Srividyaetal., developed a pH triggered ophthalmic delivery of ofloxacin by using carbopol and HPMC, results indicated that it produce sustained release over a period of 8 hours.

A carbopol/pluronic-based ocular in situ gelling system was developed by **Lin HR et al**. The bioavailability and gel strength were significantly improved in the mixture of 0.3% carbopol and 14% pluronic solution.

Pandey et al., developed ocular in situ gel of levobunolol hydrochloride. The combination of mucoadhesivecarbopol and viscosity enhancer HPMC provide sustained action over a period of time.

Mohanambal et al., developed carbpol/HPMC based pH triggered ocular in situ gel of levofloxacin. The developed formulation was stable, non-irritant and sustained release over a period of time. [72]

- **Polycarbophil**

Polycarbophil is lightly cross linked polyacrylic acid having excellent mucoadhesive property.

Mechanism

Despite being insoluble in water, the polymer chain can cling to the mucus layer due to its propensity to expand in a neutral medium. The polycarbophil carboxylic acid group binds to mucin via hydrogen bonds. Noveon®AA-1 polycarbophil, a high molecular weight polyacrylic acid polymer with divinyl glycol cross-links, displays sol-gel transition.[73]

Cellulose acetate latex (CAP latex), another pH-sensitive polymer, flows as a liquid at pH 4.8 and gels at pH 7.4.

2. Temperature sensitive in situ gelling system

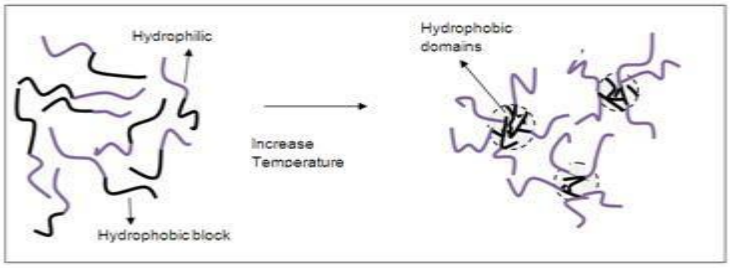


Fig. 6: Mechanism of temperature sensitive in situ gelling system

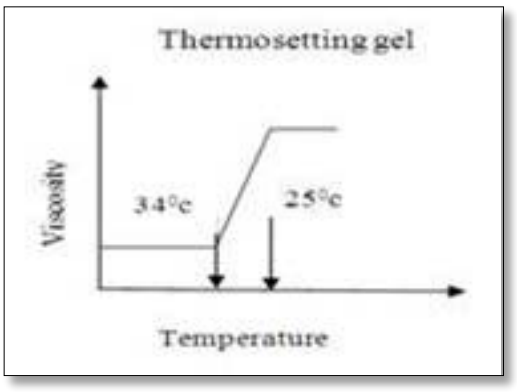
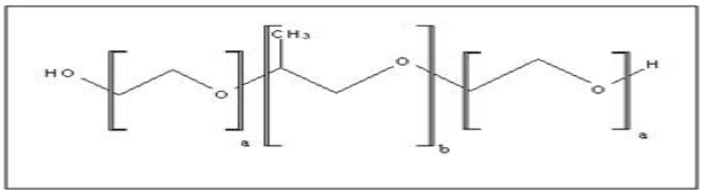


Fig.7: Graphical representation of temperature sensitive in situ gelling system

Polymers used in temperature sensitive gelling system

- **Poloxamer**



Scheme 2: Structure of Poloxamer

Poloxamer are water soluble tri-block copolymer consisting of two polyethylene oxide (PEO) and polypropylene oxide (PPO) core in an ABA configuration.

Properties

It has an extended drug residence duration and good thermal setting properties, and it is marketed as Pluronic®. It functions as a solubilizing, emulsifying, and gelling agent. A clear, colourless gel is produced by poloxamer.[74]

Several molecular weights are available, each with a different gelling behaviour depending on the ratio and distribution of hydrophilic and hydrophobic chains.[75].

Table 2: Classification of poloxamer

Poloxamer	Molecular weight
124	2200
188	8400
237	7959
338	14600
407	12600

Mechanism of gelling action

It has a polypropylene oxide-based centre hydrophobic component and hydrophilic components on either side of it (polyethylene oxide). It functions as a viscous liquid at room temperature (25o C) and changes into a transparent gel at a higher temperature (37o C) 31. Small micellar subunits are formed in solution at low temperatures, and as the temperaturerises, the viscosity increases, causing the swelling that results in the formation of a massive micellar cross-linked network.[76]

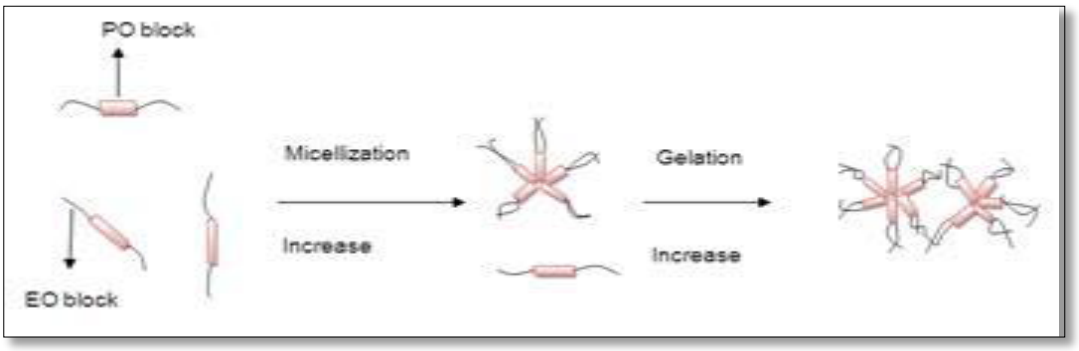


Fig.8: Gelling mechanism of Poloxamer

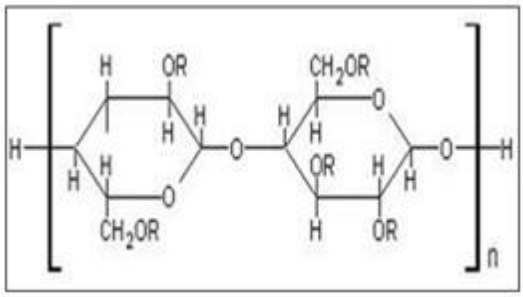
Kamel et al., developed a Pluronic F 127 based in situ gelling system containing timolol maleate for sustained ocular delivery. In vivo study showed that ocular bioavilability of Pluronic F127gel based formulation increased by 2.5 fold as compared with aqueous timolol solution.[77]

Qui et al., developed a pluronic and carbopol based ocular in situ gelling containing puerarin. Incorporation of carbopol enhance mucoadhesive force and provide sustained drug release over a period of 8hrs. [78]

Qian Y et al., formulated temperature sensitive poloxamer based in situ gelling system of methazolamide, for increasing corneal residence time and bioavailability. From the study, in vitro release shows that diffusion controlled release of drug from poloxamer solution over a period of 10 hours.[78]

Cao F et al., developed poloxamer/carbopol based ophthalmic in situ gelling system of azithromycin. Addition of carbopol 974 could increase the solubility of azithromicin by salt effect and enhance mucoadhesive property. The formulation exhibited 24 hour sustained release. [78]

- **Cellulose derivative**



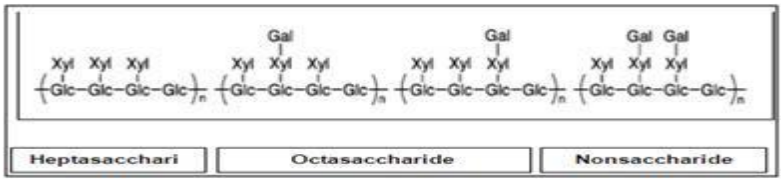
Scheme 3: **Structure of HPMC K4M**

The glucan chain with the repeating 1,4-D-glucopyranose unit makes up cellulose. Sol-gel phase transitions in natural polymers including HPMC, MC, and EC are temperature-sensitive.[79]

Mechanism

Hydrophobic interactions between molecules with methoxy substitutions lead cellulose solution to gel. When temperatures are low, molecules are hydrated and there is little contact between polymers, however when temperatures are high, polymers lose their water of hydration.[81]

- **Xyloglucan**



Scheme 4: **Structure of Xyloglucan**

When more than 35% of the galactose residues are eliminated, xyloglucan, which is a water-soluble hemicellulose derived from vascular plants, displays thermally sensitive activity. It is made up of a (1,4)-D-glucan backbone chain (GLC) and branches (1,6)-D-xylose, which are partially replaced by (1-2)-D-galactoxylose (GAL).[80]

Properties

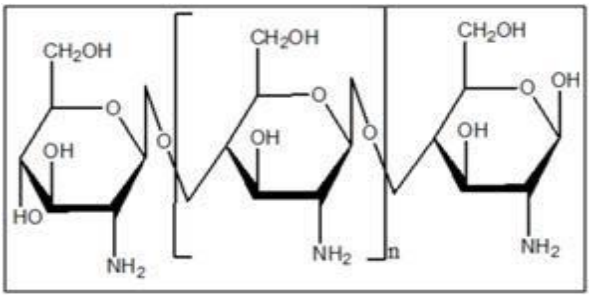
The three distinct oligomers that make up xyloglucan—heptasaccharide, octasaccharide, and nonsaccharide—differ in the number of galactose side chains. Its non-toxicity, biodegradability, and biocompatibility make it a popular choice for drug delivery through the oral, rectal, and ophthalmic routes. Similar to poloxamer, when heated to refrigerator temperature or cooled from a higher temperature, it shows signs of gelation. But xyloglucan differs in that it gels at lower concentrations (1–2%wt).[81]

Mechanism

While xyloglucan's original form does not exhibit gelation, its diluted solutions undergo a so-gel transition upon heating as a result of partial -galactosidase breakdown. The galactose removal ratio and polymer concentration have an inverse relationship with the transition temperature.

Miyasaki S et al., developed xyloglucan based ocular in situ gelling system of pilocarpine. That results degree of enhancement of miotic response followed by sustained release of pilocarpine. [82]

- **Chitosan**



Scheme 5: Structure of Chitosan

A naturally occurring polymer created by deacetylating chitin, chitosan is a cationic polysaccharide made up of copolymers of glucosamine and N-acetylglucosamine. Because of electrostatic interactions between negatively charged mucin and positively charged amino groups, chitosan has the ability to adhere to mucous membranes. It is a polysaccharide that is non-toxic, biocompatible, biodegradable, bioadhesive, and antibacterial.[83]

Mechanism

The mucoadhesive feature results from an ionic contact between the negatively charged sialic acid residues of mucins and the positively charged amino groups of chitosan, which depends on the pHof the environment. It is employed as a viscosifying agent in artificial tear compositions because to its bioadhesive, hydrophilic, and good spreading qualities.

GratieriT et al., developed chitosan/poloxamer based in situ gelling system. The results indicated that chitosan improves the mechanical strength of poloxamer and increase mucoadhesive activity.

Felt O et al., developed chitosan based ophthalmic gel for enhancing corneal residence time when compared to tobrex [85].

3. Ion Sensitive Gelling System

Cations (Na+, Mg++, and Ca++) in the tear fluid cause gelation to occur. These can be accomplished using polymers like gellan gum and sodium alginate.

Gelation is caused by an ionic interaction between tear fluid's divalent ions and the polymer. Gel is created when cationic ions and anionic polymers are in contact.[84]

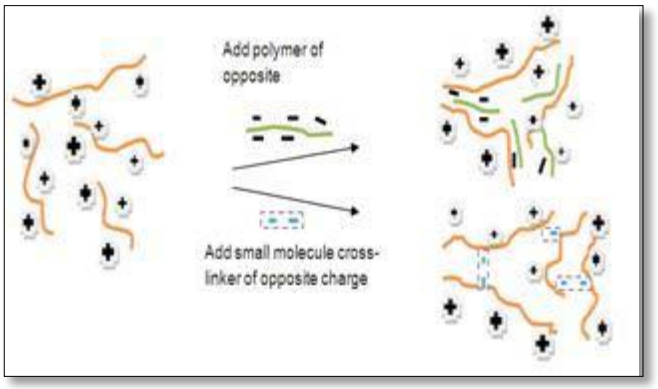


Fig.9: mechanism of ion sensitive in situ gelling system

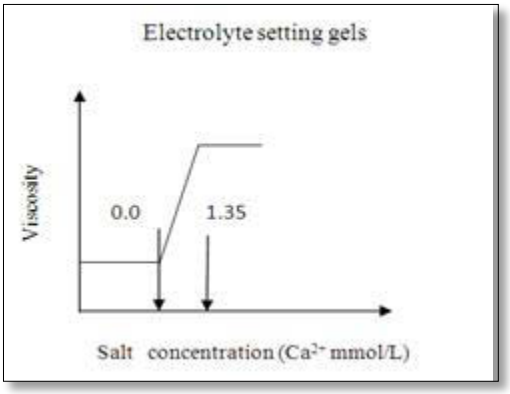
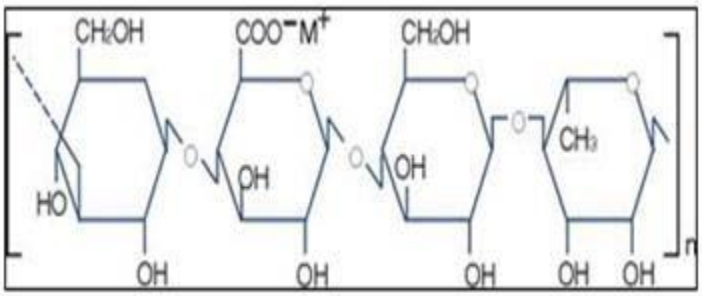


Fig.10: graphical representation of ion activated in situ gelling system

Polymers used for ion sensitive in situ gelling system

- **Deacetylatedgellan gum (Gelrite)**



Scheme 5: Structure of Gelrite

Gellan gum is an anionic hetero polysaccharide, secreted by microbe Sphingomonas elodea. It consists of glucose, rhamnose, glucuronic acid and are linked together to give a tetrasaccharide unit.[85]

Properties

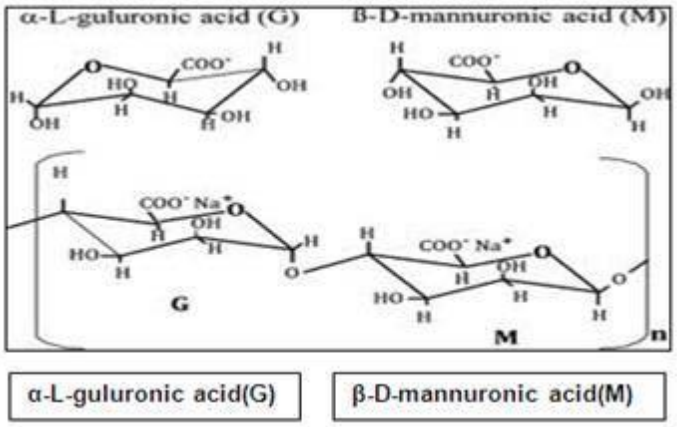
Gellan gum is treated with alkali to remove the acetyl group, resulting in the creation of gelrite, which is deacetylated gellan gum. Because calcium ions are present, gelrite gels when it is injected[82]. In order to build three dimensional networks by aggregating double helical segments by complexation with cations and hydrogen bonding with water, double helical junction zones must first arise. Ophthalmology uses thermoplasticity, pseudoplasticity, and thixotropy extensively. is employed as a stabilising and suspending agent in the food sector.[85]

Mechanism

Due to the cross-linking of negatively charged helices with monovalent or divalent cations (Na+, Ca+, or Mg+), gellan gum causes cation-induced in situ gelation (Ca2+, Mg 2+, K+, and Na+). Comparatively speaking, divalent ions and monovalent cations are better in promoting gelation. Gelation increases the drug's bioavailability and increases the drug's residence time at the absorption site. [86]

Rajas N J et al., developed gelrite based ocular in situ gel of levofloxacin hemihydrate for bacterial infections. The developed formulation shows better corneal residence time and sustained release of the drug.[86]

- **Sodium Alginate**



Scheme 9: Structure of sodium alginate

Brown algae are used to make the gum sodium alginate. It is an alginic acid salt. It is a linear block polysaccharide made up of 1,4 glycosidic linkages connecting two type monomers, -D-mannuronic acid and -L-glucuronic acid residues. Because of its carboxylic group, it exhibits good mucoadhesive properties. It is non-toxic and biodegradable.

Mechanism

Alginate's two monomers, -D-mannuronic acid (M) and -L-glucuronic acid (G), are structured as either a block of M-M molecules or a block of G-G molecules with an alternating sequence (M-G) block. When the G block of the polymer interacts with calcium moieties, a homogeneous gel is created. The G: M ratio, the kind of cross-linker employed, and the concentration of alginate solution all affect the hydrogel's mechanical strength and porosity.

CONCLUSION

Due to the complexity of the numerous diseases and the existence of ocular barriers, effective management of ophthalmic diseases is a difficult problem for pharmaceutical experts. The identification of transporters on ocular tissues and chemical modification of pharmacological molecules to target such transporters have helped in part to address challenges in ocular medication delivery. Transporter specificity aids in focusing on particular tissues, reducing adverse effects and enhancing bioavailability. After a single application, therapeutically effective medication levels should ideally be sustained for a long time. Invasive drug delivery techniques cannot be regarded as secure, efficient, or patient-friendly. Many of these restrictions could be circumvented, and periocular drug delivery could also provide sustained drug levels in a variety of ocular illnesses affecting both the anterior and posterior parts of the eye. Many medication compounds with poor ocular barrier absorption may benefit from the targeted lipid prodrug method. The condition of present therapy could be considerably improved by colloidal drug delivery technologies, and I might become a viable alternative following periocular administration. Designing and creating novel ocular medication delivery systems will continue to be driven by developments in nanotechnology and noninvasive drug and gene delivery approaches. For both anterior and posterior segment eye problems, noninvasive sustained medication

administration needs to receive more attention. Additionally, ongoing advancements in gene therapy seem to be a very promising field for treating a variety of ocular illnesses. However, the discovery of drugs in this area would be substantially accelerated by a thorough understanding of the intricacies related to healthy and diseased circumstances, physiological barriers, and pharmacokinetics.

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