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The Futuristic trends in Ophthalmic Delivery: An Overview on Gel Forming Solution

Anshika Garg[1*], Anuradha Verma[1], Manish K.Singh[2], Ritu Chauhan[1], Babita Kumar[1]

[1]Department Of Pharmaceutics, Sanskar College of Pharmacy &Research, Ghaziabad, Uttar Pradesh, 201302, India.

[2]Bhupal Noble's University, Udaipur, Rajasthan, India

[*]Corresponding author: **Anuradha Verma**

Email: anuradha.singh@sanskar.org

ABSTRACT

Conventional ophthalmic dosage forms such as eye drops are the most accepted form of ophthalmic dosage forms but it has several limitations such as poor bioavailability and therapeutic response because of several precorneal and corneal barriers present in the eye. The Conventional dosage forms are not able to retain the drug in the eye for a long time due to its excretion along with tear and nasolacrimal drainage. The most challenging field for formulation scientists is to design an ocular drug delivery system capable of retaining the drug by maintaining the contact with ocular surface for a longer period of time. Various novel approaches have been developed to overcome the limitations of conventional dosage forms. Gel forming solution is one of those novel approaches. Basically, it is administered in the form of a solution, and after administration, it shows phase transition and gets converted to gel form because of various stimuli such as pH and ion activation. It provides longer residence time as compared to conventional dosage forms attributed to its phase transition nature and hence shows sustained and controlled drug action as required in the treatment of several chronic ocular disorders such as glaucoma. The major advantage of such formulations is that it does not require sophisticated equipment for manufacture, and can be easily administered by patients, unlike ocular implants and inserts. It offers several advantages over conventional dosage forms by improving the drug release profile and reducing toxicity. A lot of research is going on to formulate such systems so that ocular diseases can be managed. This article provides a review of various polymers, drugs used for the formulation of ophthalmic gel-forming solution, and also various marketed gel forming solution preparations. It also gives an insight into various patents, clinical trials, current challenges, and future prospects of this novel ophthalmic dosage form for effective drug delivery to the eye.

Keywords: *Ophthalmic; In-situ; Gel forming solution; Pre-corneal barriers; Phase transition; Drug delivery*

INTRODUCTION

Ophthalmic drug delivery is the best and most preferred route of drug administration for topical action at the ocular site, but the major limitation is the characteristic anatomical arrangements of tissues and the impermeability of the cornea which makes it difficult for the drug to cross the

barriers and thus shows reduced bioavailability. Conventional ophthalmic dosage forms have short ocular residence time and poor bioavailability due to extensive elimination along with tear and nasolacrimal drainage. It is one of the most challenging fields for pharmaceutical scientists to work in as ocular diseases such as glaucoma, dry eye disease, and ocular hypertension are very common nowadays. The major problem for the ocular formulation is retaining the required therapeutic concentration at the site of action to get the desired therapeutic action. Rapid precorneal elimination of drugs is mainly due to conjunctival absorption and lachrymation and also water-soluble drugs diffuse slowly through the cornea and hence show less bioavailability. Ocular drug delivery has several challenges because of various ocular barriers- static barriers and dynamic barriers. Static barriers include different layers of cornea, sclera, and retina, dynamic ocular barriers include choroidal and conjunctival blood flow, lymphatic clearance, and many more. Drug delivery to the posterior segment of the eye is a major hindrance. To overcome these hindrances, several improvements and development have been made over the past years,and various novel drug formulations such as niosomes, bio-adhesive gels, gel forming solutions have been developed[1-3]. These formulations can retain the drug for a longer time because drainage is less and thus optimum therapeutic concentration at the desired site of action can be maintained. They are also aimed to minimize or slow down the elimination rate of the drug. Drug delivery systems based on in-situ gel formation offer a great alternative to the instillation of eye drops because in-situ gels increase pre-corneal residence time[4]. Concerns about inadequate compliance and various systemic side effects with ophthalmic solutions have led to the use of a system with less frequent dosing schedules. Gel forming solution is a colourless, transparent solution that forms a gel on contact with monovalent and divalent cations present in the precorneal tear film[5].The use of polymers in conventional ocular dosage forms such as solutions and suspensions has been found efficient to increase bioavailability by prolonging contact time[6]. In-situ gelling polymers are used for prolonging contact time in the cornea and thus increasing ocular bioavailability. In-situ gelling polymers act by phase transition (sol-gel transition) due to stimuli, either physical stimuli (temperature) or chemical stimuli (pH, ions etc). Smart polymeric systems have proved to be efficient drug delivery systems to the ocular region[7-10]. This review demonstrates a brief summary about gel forming solutions, various polymers used in their formulation, mechanism of sol-gel transition, patents, clinical trials, current challenges and future prospects.

CLASSIFICATION OF OPHTHALMIC DRUG DELIVERY SYSTEMS

Various dosage forms for ophthalmic drug delivery are summarized in Table 1 and a brief classification is also shown through Figure 1.

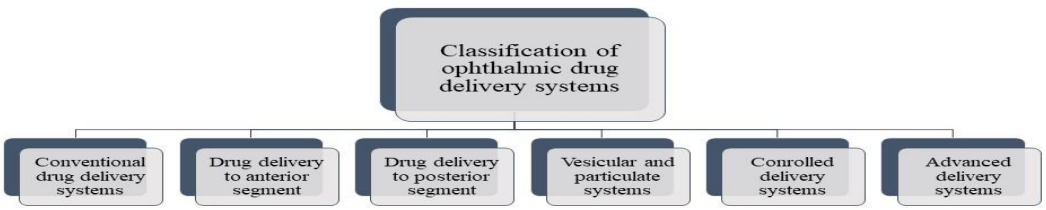

Figure 1: Classification of ophthalmic drug delivery systems

Table 1: Ophthalmic drug delivery systems

TYPE OF DELIVERY SYSTEM	DOSAGE FORM
Conventional drug delivery system	• Eye drops • Ointments and gels
Drug delivery to anterior segment	• Contact lens • Cul de sac inserts • Subconjunctival/ episcleral implants
Drug delivery to posterior segment	• Intravitreal implants • Injectable particulate systems
Vesicular and particulate systems	• Liposomes • Niosomes • Discomes • Pharmacosomes • Nanoparticles • Microparticles
Controlled delivery systems	• Gel forming Solution/ in situ gels • Dendrimer • Collagen shield
Advanced delivery systems	• Cell encapsulation • Gene therapy • Stem cell therapy • Protein and peptide therapy • SiRNA therapy • Aptamer • Oligonucleotide therapy • Scleral plug therapy

FATE OF OCULAR FORMULATION ADMINISTERED THROUGH EYE

The general process of absorption of the drug from the site of administration to the target site after topical instillation is quite complex. A series of events are involved in the drug absorption into the eye. It starts with drug instillation followed by dilution in tear fluid, diffusion through mucin layer and then penetration to cornea and then to aqueous humor. Drug distribution to the site of action (e.g, iris-ciliary body) starts after complete absorption of drug from dosage form. Corneal absorption is the most common route of drug absorption into the eye, parallel absorption via the conjunctiva/sclera pathway is a less followed pathway[11]. Figure 2 represents the series of precorneal events along with the kinetics of drug after administration.

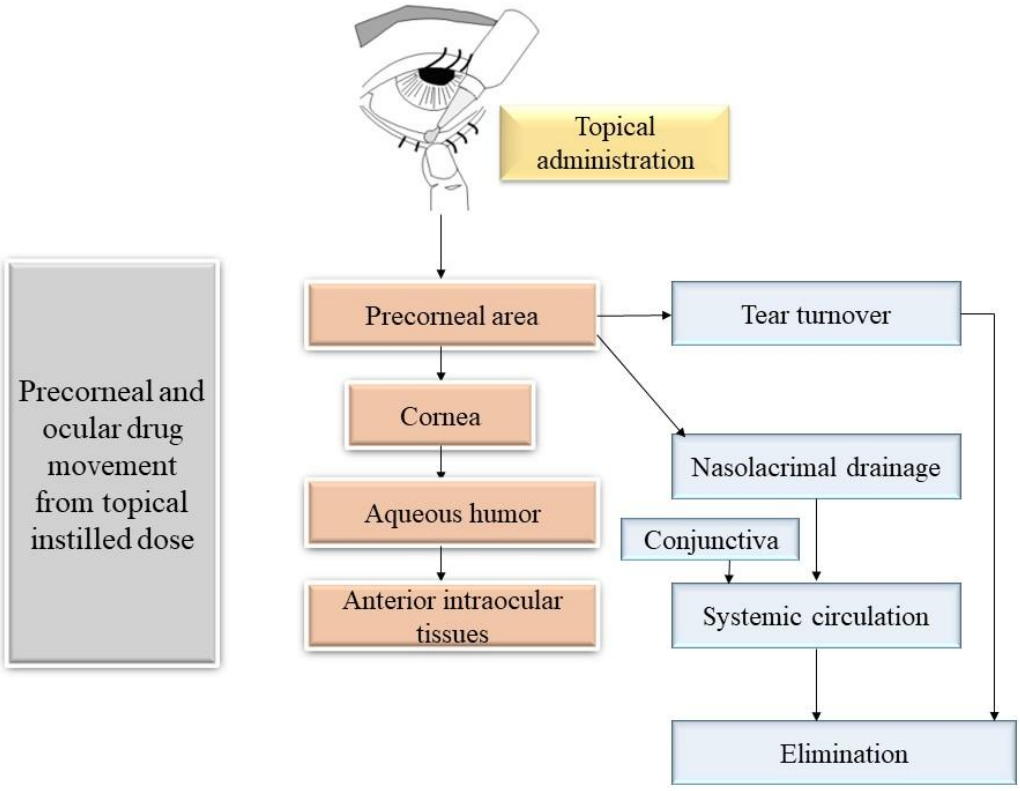

Figure 2: Fate of ocular formulation administered through eye

ADVANTAGES OF GEL-FORMING SOLUTION[12]

- Controlled and sustained action, thus a reduction in dosing frequency and therefore, more patient compliance
- Less blurred vision as compared to other viscous formulations
- Ease of administration, no special device or specialization required.
- Increased bioavailability due to increased precorneal residence time.
- Reduced systemic side effects due to reduced nasolacrimal drainage.
- Natural polymers provide biocompatibility and biodegradation

MECHANISM OF SOL-GEL TRANSITION[13-15]

The various approaches for sol to gel transitions are-

- Temperature triggered sol – gel transition
- pH induced sol – gel transition
- Ion activated systems

  Figure 3 illustrates the various mechanism of sol to gel transition upon ocular administration.

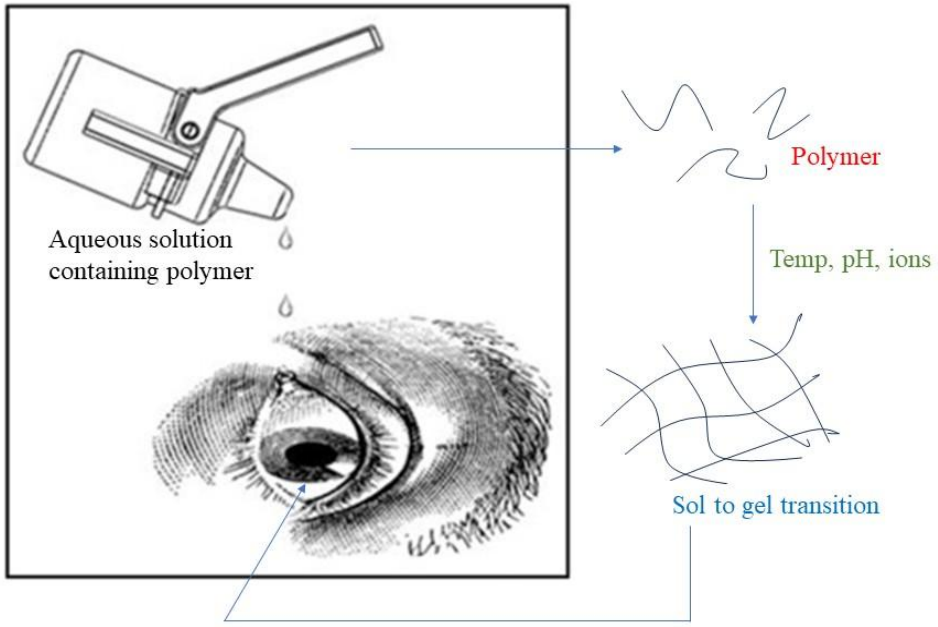

Figure 3: Mechanism of sol to gel transition

Temperature triggered sol – gel transition

This is one of the most commonly studied class of polymer systems. In this system, polymers are in liquid phase at room temperature (20-25^0 C) and undergoes sol to gel transition at physiological temperature (35-37^0 C). For optimum temperature triggered systems, the ideal temperature for sol to gel transition should be more than room temperature so that it can be easily administered in the eye and can show phase transition at room temperature. Figure 4 illustrates the temperature triggered sol to gel transition.

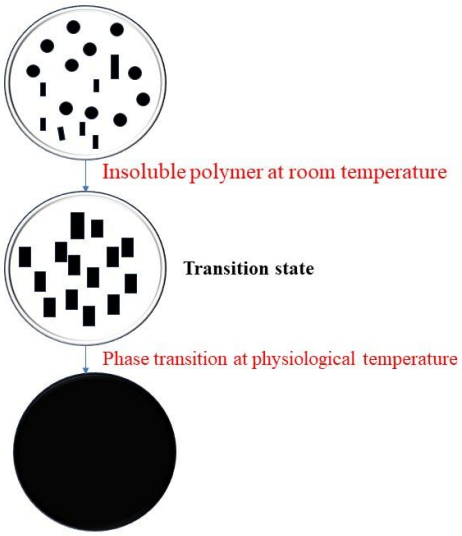

Figure 4: Schematic of temperature triggered sol to gel transition

pH induced sol – gel transition

pH induced systems are liquid at room temperature while it undergoes sol to gel transition at pH of the lachrymal fluid. Carbopol is a pH-sensitive polymer which shows pH triggered gelation upon ocular administration. pH induced systems contain polymers that are either weakly acidic or basic in nature which either accept or donate protons in response to change in the pH. Interdiffusion and conformational changes leads to swelling at specific pH. Figure 5 illustrates pH induced sol to gel transition.

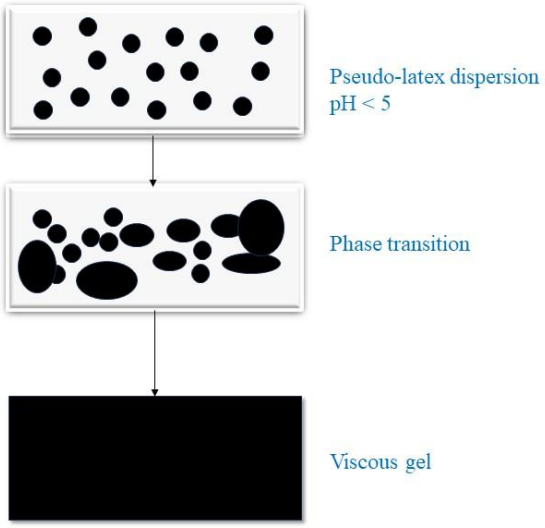

Figure 5: Schematic of pH induced sol to gel transition

Ion activated systems

These are the systems in which the solution viscosity increases upon exposure to ionic concentrations of tear fluids. Ion sensitive polymers cross links with the monovalent and divalent cations present in the lachrymal fluid on ocular surface and thus increases the retention time. Figure 6 illustrates the ion activated system of sol to gel transition.

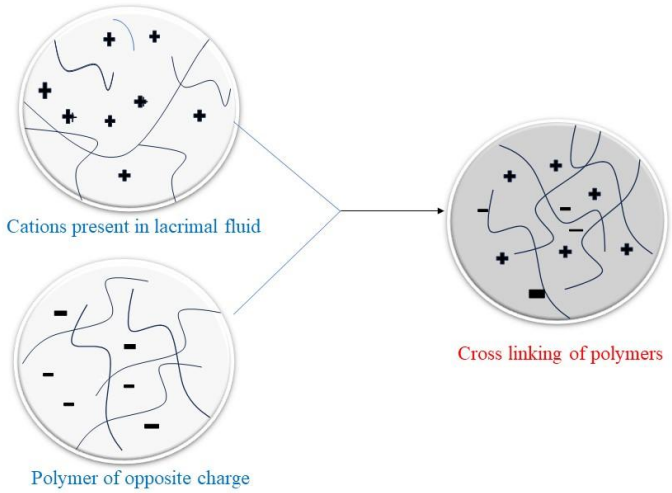

Figure 6: Schematic of ion activated system

POLYMERS USED IN OCULAR GEL FORMING SOLUTION

1. **Carbopol:**

It is a pH sensitive polymer, also known as carbomer, acrylic acid polymer etc.

Structure- Figure 7 illustrates the chemical structure of Carbopol.

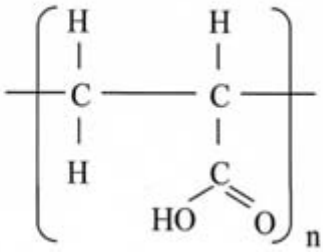

Figure 7: Structure of Carbopol

Properties of Carbopol[16-23]

1. Carbopol is a member of the modified crosslinked acrylic acid polymer family. It is an acrylic acid polymer with allyl sucrose or allyl ethers of pentaerythritol that is synthesized at high molecular weight.
2. Carbomer commercially available as Carbopol is a fluffy white hygroscopic powder with a slight odour. When Carbopol is dispersed in water, each of its polymers swells up to 1000 times its former volume.
3. It shows non-Newtonian rheology and exhibits viscoelastic properties.
4. It shows sol to gel transition in an aqueous solution when its pH is raised above pKa of about 5.5.
5. Carbopol 940 with a concentration of 0.1% can be used as gelling agent for ophthalmic drops and is able to prolong the contact time after administration into the eye.

Table 2: Various grades of Carbopol along with their viscosities and cross-linking density.

Grade	Viscosity (Pas)	Cross linking density
Carbopol 910	3000-7000	Lowest
Carbopol 934	30500-39400	Lowest
Carbopol 940	40,000-60,000	Highest
Carbopol 981	4000-11,000	Intermediate

Marketed products of Carbopol

71G NF, 971P NF and 934P NF are used in oral formulations while Ultrez10NF is used in topical formulations.

Table 3: Uses of Carbopol

Use	Concentration (%)
Gelling agent	0.5-2.0
Emulsifying agent	0.1-0.5
Suspending agent	0.5-1.0

Mechanism[24-27]

The mucoadhesive property of Carbopol is attributed to four different mechanisms of interactions between mucin and poly acrylic acid i.e., electrostatic interaction, hydrogen bonding, hydrophobic interaction, and interdiffusion. It is a tightly coiled molecule which upon dispersion in water dissociates to form flexible coil. It is a pH sensitive polymer and hence, increase in pH of the solution leads to swelling. Electrostatic repulsion occurs between anionic molecules at higher pH resulting in swelling of the polymer.

2. **Xanthan gum:**

   It is a high molecular weight polysaccharide, also known as corn sugar gum[28].

   Structure- Figure 8 illustrates the chemical structure of xanthan gum.

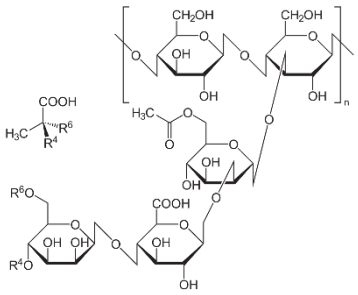

Figure 8: Structure of Xanthan gum

Properties[29-34]

1. Studies have shown that xanthan gum solution shows an increase in viscosity as its concentration in the solution increases.
2. The viscosity of the polymer solution decreases with the increase in shear rate and hence it showed shear thinning behaviour.
3. For lower concentrations of xanthan gum decrease in temperature does not show significant change in the viscosity of the solution.
4. During heating, solutions of xanthan gum undergo a conformational transition and change from a rigid state at low temperature to a flexible state at high temperature.

Uses of Xanthan gum

1. Binding agent
2. Suspending agent
3. Emulsifying agent
4. Release control agent

Table 4: Marketed products of xanthan gum

Trade name	Application
Keldent	formulation of toothpaste
Kelflo	aid in animal feed formulation
Kelgum	used in the form of blends to overcome formulation challenges
Keltrol	food and personal care applications
Kelzan	used in suspension and emulsion formulation
Xantural	syrups and ideal for controlled release formulations
Xanvis	used in water based circulating systems

Mechanism[35-38]

It does not form gel readily by the usual gelation method. It forms gel when aqueous solutions are annealed at high temperatures and then cooled subsequently.

3. Gellan gum:

It is an ion-sensitive polymer. It is also known as Gelrite®. Gellan gum has a tetrasaccharide unit consisting of one rhamnose unit, two glucose units, and one glucuronic acid unit. It is available in two forms: High Acyl (HA) gellan and Low Acyl (LA) gellan[39-41].

Structure- Figure 9 illustrates the chemical structure of Gellan gum.

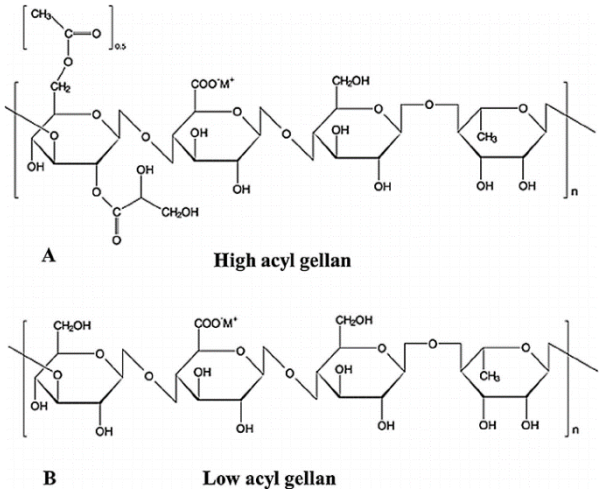

Figure 9: Structure of High acyl gellan and low acyl gellan

Properties[42-43]

1. The high acyl gellan forms a soft, elastic and non-brittle gel while the low acyl gellan forms firm, non-elastic and brittle gels.
2. Gellan gum forms a gel on cooling, setting temperature varies due to the presence of cations.
3. Low acyl gellan gum settles at around 25^0C, while high acyl gellan gum settles at around 65^0C in the absence of cations. With the addition of ions such as calcium and sodium, the setting temperature increases. Gellan gum sets rapidly once setting temperature has been reached. It is known as "snap" setting.
4. The gel structure increases sharply with increasing cation concentration. Both high acyl and low acyl gel gellan gum show this sharp increase in gel structure.
5. Low acyl gellan gum gels become less brittle and more elastic with increasing concentrations of sugars. High acyl gellan gum gels are more elastic in the presence of more than 60% total soluble solids content.
6. Low acyl gellan gum has a brittle texture, adding high acyl gellan gum to it reduces its brittleness. A variety of textures can be obtained with a blend of low-acyl and high-acyl gellan gum.
7. Gellan Gum shows Newtonian flow behaviour at a concentration below 0.9% and plastic flow behaviour above 1.0%.

Uses of gellan gum

1. Thickening agent
2. Binding agent
3. Stabilizer

Table 5: Marketed products of Gellan gum

Trade name	Use / application
Gelrite	gelling agent for microbial cultural media
Gelzan	tissue culture media in microbiological assay
Gelgro	Substitute of agar
Kelcogel	food, beverage, personal care formulations

Mechanism[44]

It is an ion-sensitive polymer. It produces a cation induced gelation due to cross linking between negatively charged helices and positively charged cations (Na^+, Ca^{2+}, Mg^{2+}). Divalent ions promote more gelation as compared to monovalent ions.

VARIOUS STUDIES CONDUCTED ON GEL FORMING SOLUTION

- An experimental study was done by Balasubramaniam J *et al*2003, on gellan gum-based indomethacin in-situ gel as a replacement for steroids for uveitis. The optimum concentration of gellan was 0.5% w/v above this concentration the gelation occurs at 40^o C. This composition was able to sustain the release of the drug for 8 hours period in-vitro and thus it can be seen as an alternative to standard suspension of indomethacin[45]
- A study done by Amal El-Kamel 2006, on carteolol hydrochloride and Gelrite (Gelrite formulation 0.4% w/v containing 1% drug) based in-situ gel showed improved bioavailability as compared to a marketed aqueous solution (Arteoptic® 1%) and thus can be a potential alternative because of its efficacy[46]
- A study done by Naoaki Takiyama *et al*2006, suggests that one daily dose of Timolol maleate gel forming solution is equivalent to twice the daily dose of timolol maleate aqueous solution[46]
- Another study by Shedden AH *et al*2001, also suggests that a timolol gel forming solution 0.5% one daily dose and timolol aqueous solution 0.5% twice daily are equivalent[47]
- A study was conducted byChakkittakandiyil A 2012, to investigate the safety and efficacy of timolol maleate gel forming solution 0.5% or 0.1% for infantile hemangiomas was performed. According to the study, timolol maleate gel forming solution was found to be effective[48]
- A study done by Rosenlund E.F 1996, suggests that the ocular hypotensive effect of 0.5% timolol gel forming solution once daily is as effective as 0.5% timolol solution administered twice daily[49]
- Another study done by Kim Y.C *et al*2022, suggests that gel forming eye drop was able to enhance the intraocular delivery of a kinase inhibitor[50]
- A study done by Schenker H *et al*1999, showed that a twice daily dose of timolol maleate solution is equally effective as once daily dose of timolol maleate gel forming solution for lowering intraocular pressure (IOP)[51]

- Another study by Halper LK *et al*2002, suggests that timolol gel forming solution QD has better efficacy in lowering IOP as compared to levobunolol hydrochloride BID with fewer effects on heart rate[52]
- A study done by Sawarkar S *et al*2016, showed that an in-situ gel forming solution of moxifloxacin hydrochloride has better attributes than conventional dosage forms and hence can be used for the treatment of various ocular infections[53]
- A study conducted by Tripathi R *et al* 2022, suggests that a novel ophthalmic gel forming solution of Gemifloxacin mesylate has beneficial effects in treating ocular infections and can be a potential alternative to conventional eye drops[54]

MARKETED PRODUCTS OF OCULAR GEL FORMING SOLUTION[55]

Various marketed products of ocular gel forming solution are given in Table 6**.**

Table 6: Marketed products of ocular gel forming solution

Polymer	**Brand Name**	**Therapeutic Agent**	**Manufacturing Company**
Gellan Gum	Timoptic® XE	Timolol maleate	Merck
Xanthan Gum	Timoptic® GFS	Timolol maleate	Alcon

GFS: Gel forming solution

PATENTS ON OCULAR GEL FORMING SOLUTION

Table 7 summarizes various patents available on ocular gel forming solution.

Table 7: Patents on ocular gel forming solution

Patent no.	**Title of Patent**	**Approach**	**Inventors**	**Year**
WO2011018800A2	A novel in situ gel forming solution for ocular drug delivery	In situ gelling of solution comprising of natural polysaccharide using various mechanisms such as thermal gelation, ionic gelation etc	Nandan Mohan Chandavarkar, Kour Chand Jindal, Rajkumar Malayandi	2011

353075	A stable gel forming solution	Ophthalmic gel forming solution comprising of low concentration of preservative	Aditi Panandikar, Kavita Inamdar, Yogesh Bhide, Suryakant Tarapur	2020
WO2021/198911A1	A sterilization process of timolol gel forming solution through aseptic filtration	Sterilization process of timolol maleate gel forming solution using aseptic filtration	Manish Kumar Singh, Sai Kiran Jana, MallinathHarwalkar, Kishor Deo, Deepak Bahri	2021

ONGOING CLINICAL TRIALS

Various clinical trials conducted on ocular gel forming solution have been summarized in the Table 8. The information has been accessed from https://clinicaltrials.gov

Table 8: Ongoing clinical trials on gel forming solution

S.No.	Intervention / Treatment	Condition	Study type	Phase	Sponsor	Identifier
1.	BETOPTIC S (Betaxolol HCl) and timolol gel forming solution)	Glaucoma or ocular hypertension	Interventional, randomized, double blind	III	Alcon research	NCT00061542
2.	Timolol gel forming solution	Open angle glaucoma or ocular hypertension	Interventional, randomized, crossover design	IV	Vistakon pharmaceuticals	NCT00804648
3.	Al37807 ophthalmic suspension vs timolol gel forming solution	Glaucoma or ocular hypertension	Interventional, randomized, parallel design	II	Alcon research	NCT00620256
4.	LUMIGAN® vs TRAVATAN Z® and TIMOLOL GFS	Glaucoma or ocular hypertension	Interventional, randomized, parallel design	IV	Allergan	NCT02097719
5.	LUMIGAN® vs TRAVATAN Z®, Timolol Maleate- EX and Timolol	Glaucoma or ocular hypertension	Interventional, randomized, parallel design	IV	Allergan	NCT01881126

	GFS					
6.	AL-37807, XALATAN, Timolol GFS	Open angle glaucoma or ocular hypertension	Interventional, randomized, parallel design	II	Alcon Research	NCT00287521

EVALUATION AND CHARACTERIZATION OF OCULAR GEL-FORMING SOLUTION[56-57]

Ocular gel-forming solutions are evaluated and characterized on the basis of the following parameters:

1. **Visual appearance and clarity**
   Clarity of the formulation is inspected by visual inspection against a black background.
2. **Texture analysis**
   The consistency, firmness and cohesiveness of the formulation is analyzed using texture analyzer. It is mainly analyzed to check the syringeability of solution to check the sol-gel transition.
3. **pH-** ThepH is an important parameter to be evaluated. pH of the formulation should remain in an ideal range that is non-irritant to the eyes. It is measured using digital pH meter.
4. **Sol-gel transition temperature**
   Sol-gel transition temperature can be defined as the temperature at which the phase transition of sol is first noted.
5. **Gelling capacity**
   Gelling time is defined as the time period required for gelation of sol phase. It is the time taken by the formulation to show gelation from sol phase. It is determined by placing a drop of the formulation in a vial containing freshly prepared simulated tear fluid.
6. **Gel strength**
   Gel strength of the formulation is evaluated using rheometer. Depending on the mechanism followed by the gelling agent, a specified amount of gel is prepared from sol and raised at certain temperature. The change in the load on the probe is measured by its immersion below the gel surface.
7. **Rheology**
   Rheology of the formulation is an important aspect of ocular formulations. Rheologic properties such as viscosity are measured using Ostwald's viscometer. Viscosity of the formulation should be in such limits that they do not interfere during administration by the patients.
8. **Isotonicity**
   All the ophthalmic formulations should be isotonic to prevent tissue damage or irritation to the eyes. It should possess osmotic pressure within the range of 290-310 mOsml/kg. it can be determined using osmometer.
9. **In vitro drug release study**
   It is done using a Franz diffusion cell. Freshly prepared artificial tear fluid is placed in the receptor compartment. The dialysis membrane is placed between the donor and the receptor compartment, the whole assembly is kept on a magnetic stirrer, and temperature is maintained at 37± 0.5^{o} C. medium is stirred continuously at 20 rpm for 1 hour. Samples are withdrawn at the predetermined time periods and replaced with the dissolution medium. Samples collected are analyzed using UV-visible spectrophotometry or HPLC.
10. **Sterility Testing**
    It is performed as per the guidelines laid down by Indian Pharmacopoeia. Direct inoculation method of sterility testing is used. In this method, 2 ml of sample is removed using sterile

pipette and aseptically transferred to fluid thioglycolate medium and soyabean casein digest medium separately. The mediums are inoculated for 14 days at 30^{o} C.

CURRENT TRENDS

Research done in the last decade reveals the inclination of researchers towards combination approach, combining several polymers to get synergistic effect and thus reduction in the concentration of polymers used. The combination approach increases the therapeutic effectiveness of the drug entrapped in polymeric matrices. The formulation containing combination of polymers is even better than conventional dosage forms in terms of efficacy and simplicity of fabrication[58].

FUTURE PERSPECTIVES

Over the past decade, ocular drug delivery has been extensively investigated. The shortcomings of the current ocular drug delivery systems such as drainage and low bioavailability create challenges, and allow novel technologies to come up with effective treatment for ocular disorders. For the majority of the ocular disorders such as cataracts, glaucoma, and many others, eye drops are considered to be the most effective but the major problem is drainage with tears ultimately resulting in low bioavailability. Formulation scientists are exploring the field of novel dosage forms for formulating effective ocular dosage forms. Thus, novel formulations for ophthalmic drug delivery such as gel forming solution have a promising future because it overcomes the majority of the shortcomings seen in conventional dosage forms and provides the optimum bioavailability required for action. Further research and investigation in the field of ocular drug delivery needed to prove the efficacy of such novel formulations is being done by formulation scientists[59-61].

CONCLUSION

The utilization of gel forming agents for ophthalmic delivery provides various advantages over conventional dosage forms. The use of biocompatible, biodegradable, and water-soluble polymers for ophthalmic formulation can make excellent drug delivery systems. In recent years researchers have drawn interest, and there is a scope to provide an advanced technique in drug delivery. A novel carrier can incorporate into these systems to obtain sustained drug delivery in a much improved and extreme manner. These systems, as they can administer in solution form, undergo gelation at the site of action. Finally, in situ, gels are easy to apply and offer patient comfort and compliance.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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