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Review on Smart in Situ Gels for Site Specific Delivery of Anti-Fungal: Opportunities and Challenges

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ABSTRACT

Aims: The aim of this study is to explore the potential of in situ gel systems as innovative drug delivery vehicles, particularly for the treatment of invasive fungal infections (IFIs) in patients undergoing hematopoietic cell transplantation. The study emphasizes the advantages of in situ gelling systems in delivering antifungal agents locally or systemically with improved therapeutic efficacy and prolonged residence time.

Methodology: The study involves the evaluation of in situ gel systems composed of synthetic, natural, or semi-synthetic polymers that exhibit a sol-to-gel transition in response to biological stimuli such as temperature, pH, or ionic strength. These gels can be formulated alone or in combination with mucoadhesive polymers to enhance site-specific drug retention. The potential of these gels as carriers for nanoparticles or microparticles is also considered. The clinical background includes the assessment of systemic Candida infections during the pre-engraftment phase in hematopoietic cell transplant patients and a comparison of the effectiveness of fluconazole, amphotericin B, and caspofungin as antifungal agents.

Conclusion: In situ gel systems offer a promising strategy for the delivery of antifungal agents in immunocompromised patients, particularly those undergoing hematopoietic cell transplantation. Their stimuli-responsive behavior, prolonged residence time, and compatibility with nanoparticle carriers make them highly suitable for improving antifungal therapy. Integration with mucoadhesive polymers may further enhance therapeutic efficacy by increasing localization and bioavailability at the site of infection.

Results: Systemic Candida infections were previously reported in 15–25% of cases during the pre-engraftment phase. The introduction of fluconazole prophylaxis has significantly reduced early infection rates. Caspofungin has emerged as a superior alternative due to its broad-spectrum activity and lower toxicity compared to amphotericin B. In situ gel systems have demonstrated the ability to respond to endogenous stimuli and effectively transition into gels post-injection, allowing for controlled and localized drug delivery.

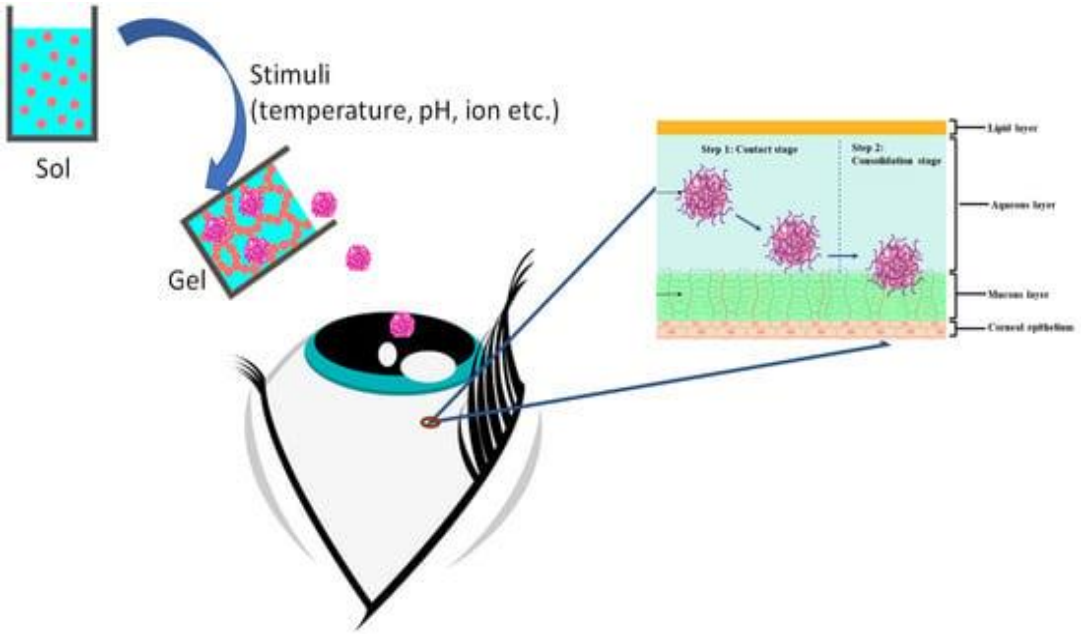
Keywords: *In situ, ocular delivery, Anti-fungal, site specific, Sustained release, smart polymer.*

1. INTRODUCTION

1.1Antifungal

Worldwide, one of the main causes of skin diseases is fungus infection. It is estimated that 40 million people in developing and impoverished nations suffer from fungal infections. Typically, during the first stage, fungi target the skin's surface before desquamating their way into the deeper layer. One of the most common fungi that cause superficial cutaneous infections is Candida species[1,2,3]. Cutaneous mycoses are fungal infections that manifest in the deeper layers of the skin. A popular term for fungal diseases of the skin is "dermatophytes." Fungi like Tinea corporis, Tinea pedis, and Tinea cruris are frequently implicated in various dermatomycoses [4,5,6]. When a fungal infection spreads further into the skin, it is referred to as "subcutaneous mycosis."[7]Treatment for both superficial and deep fungal infections involves antifungal chemotherapy.

One of the primary or secondary infections brought on by Candida species is candidiasis . The trachea, lung, gastrointestinal tract, fingers, nails, skin, vagina, throat, and mouth may be the only areas affected. When the immune system is seriously compromised, Candida species can result in invasive candidiasis (IC), which includes deep-seated tissue infections and blood-derived infections (candidemia) [8,9,10]



Graphical Abstract[51]

1.2Antifungal treatment

Since topical application ensures direct access and a higher retention rate at the target, it may be the most effective method of combating the main skin dermatophytes. Avoiding pre-systemic metabolism and reducing systemic toxicity are two more benefits of topical administration. Topical administration of certain medications, such as ketoconazole, itraconazole, and clotrimazole, involves rubbing or distributing them onto the skin [11].

1.3 In situ gels

In recent years, numerous innovative drug delivery methods have been tested. In situ gels are particularly noteworthy among these systems because they offer a profitable strategy that is on par with both traditional and innovative strategies. In situ gel systems are delivery vehicles made of natural, semisynthetic, or synthetic polymers that have the special ability to change from sol-gel when biological stimuli are applied.

1.3.1 Importance of in situ gel in controlled antifungal therapy [12].

1) It aids in the controlled and prolonged release of medications.
2) In situ gel is resilient to a range of physiological stresses.
3) In situ gels containing locally given antifungal drugs are more effective in penetrating the oral mucosal layer.
4) boosting the efficacy of its treatment

2. OVERVIEW OF IN SITU GELS

2.1 *In-situ* gel system

Among the greatest new drug delivery methods is in situ gel. It aids in the controlled and prolonged release of medications. The formulation of the in situ gel system is such that, although initially in solution, it will transform into gel form under certain physiological circumstances. There are numerous types of polymers that could be applied to different medication delivery systems. In situ gelling systems have many uses and benefits in modern life. In situ gel is resilient to a range of physiological stresses.

Because in situ gel contains monovalent and divalent cations, it changes from a solution to gel when it comes into contact with bodily fluids.

2.2 These systems have several benefits over conventional formulation

1) Continuous drug release because of the gel network that forms after being influenced by physiological stimulation
2) Easy administration similar to a traditional eye drop formulation repeatable and accurate dosing.
3) Ease of fabrication, and prolonged retentivity at the site of action.

4) Simple sterilization and scaling up, as well as combination system engineering (by selecting polymers with multiple function penetration enhancer/mucoadhesion/in situ gel property).

In situ gel systems with special qualities might be referred to as the preferred antifungal solution due to the aforementioned benefits. In response to a biological stimulus, in situ gel systems exhibit a phase change from sol to gel [13,14].

2.3 Classification of system *in situ* gel

A. Temperature-sensitive gelling system

The most often researched class of stimuli-sensitive polymer systems in drug delivery research is most likely temperature-sensitive in situ gelling systems. A change in temperature acts as an external stimulation for these systems [15]. It is known as the lower critical solution temperature (LCST) at which the sol--gel transition takes place. Sol to gel conversion is thought to be primarily caused by differences in solubility at various temperatures. Hydrogen bonding between the water molecule and the hydrophilic groups on the polymeric surface promotes better dissolution of the polymer chains at temperatures lower than the LCST, and the system stays in the state of solution. The hydrogen bonds in the system deteriorate when the temperature rises over LCST. Consequently, the sol--gel transformation is facilitated by an increase in the hydrophobic contact [16].

B. pH-sensitive gelling system

Another crucial bioenvironmental factor at the ocular location is pH, which instantly forms a gel when biostimulus is received. These polymers' sensitivity to pH is caused by ionizable groups on their surface, which show a dramatic shift in ionization and water solubility at a particular pH (pKa) [17]. While many synthetic and natural polymers show pH sensitivity, the focus of this discussion will be on polymers that have been specifically researched.

3. SMART POLYMER FOR IN SITU GELATIN

1) Natural polymers and derivative

Mother Nature has bestowed many blessings upon humanity. Among these are polymers with in situ gelling capabilities. Novel in situ gel systems with desired properties have been created using these polymers, either by themselves or in conjunction with other materials [18].

2) Synthetic polymers

Even though many synthetic polymers with desired thermosensitive in situ gel characteristics have been created, the discussion will only cover derivatives that are used in administration. Readers seeking a deeper knowledge are referred to another source[17,19].

3.1 PH- sensitive polymer

These polymers' sensitivity to pH is caused by ionizable groups on their surface, which show a dramatic shift in ionization and water solubility at particular pH values (pKa). The current discussion will only cover polymers that have been specifically researched for drug delivery, even though many natural and synthetic polymers demonstrate pH sensitivity[20]. Example: **Carbopol**

There are several molecular weights of carbopols with side chains that are cross-linked, branching, and linear. Compared to other natural or synthetic polymers (such as cellulose derivatives), carbopols have superior mucoadhesive properties, which is why they are being thoroughly researched for drug delivery. Carbopol 934 is the most widely documented carbopol polymer, consisting of 62% carboxyl groups made from repeated acrylic acid units cross-linked with either allylsucrose or pentaerythritol allylethers[20].

3.2 Thermo-sensitive polymer.

The most often researched class of stimuli-sensitive polymer systems in drug delivery research is most likely temperature-sensitive in situ gelling systems. A change in temperature acts as an external stimulation for these systems. It is known as the lower critical solution temperature (LCST) at which the sol--gel transition takes place. Sol to gel conversion is thought to be primarily caused by differences in solubility at various temperatures. The system stays in the form of solution at temperatures below the LCST because of hydrogen bonding between the water molecule and the hydrophilic groups on the polymeric surface, which promotes better dissolution of the polymer chains [16].

Example: **Poloxamers**

Depending on the block ratio, poloxymers come in a variety of grades with varying gelation characteristics. Pluronic F127 is the polymer that has been examined the most in pharmaceutical technology out of all the grades that are available. Since the first discovery that concentrated water solutions of Poloxamer may create thermoreversible gels, Poloxamer has made

significant strides. There has been a lot of work done to pinpoint the precise mechanism of sol-gel interconversion. Such interconversion could be caused by a change in micellar characteristics as a function of temperature and concentration [21].

3.3 Ion-sensitive polymer.

The presence of an ionic environment, supplied by the ocular site (Ca++ and other ions found in tear fluid), causes some polymers to undergo phase change. For the purpose of creating the in situ gel system for ocular delivery, this characteristic has thus been thoroughly investigated. Alginates, b-Carrageenan, and gellan gum have all been extensively studied for this purpose.

Examples: Gellan Gum

The linear, anionic hetero polysaccharide gellan gum is made up of rhamnose, glucose, and glucuronic acid in a 2:1:1 molar ratio as the polymer backbone joined to form a tetrasaccharide repeat unit Sphingomonas elodea is the secretor of this microbial substance. Gelrite is a deacylated form of the naturally occurring polysaccharide that is sold commercially. It is safe and effective despite having a microbiological origin, as evidenced by its regulatory approval as a pharmaceutical excipient and controlled-release commercial product (Timoptic XE) for the treatment of glaucoma[20]. As the list of various Anti-Fungal Drugs In-Situ gel with their Mechanism are mentioned below in **Table-1**.

4. ANTIFUNGAL DRUG USED IN IN SITU GELS [22]

Drug	**Mechanism**	**Potential target**
Terbinafine	Inhibit biosynthesis of ergosterol	Squalene epoxidase[21]
Imidazoles,fluconazoles,Miconazoles Ketoconazoles	Inhibit biosynthesis of ergosterol	Cytochrome P450
Amorolfine	Inhibit biosynthesis of ergosterol	Sterol reductase and isomerase[22]
Amphotericin B and nystain	Inhibitbiosynthesisof ergosterol	Altermembraneintegrity
Tolnaftate	Inhibit biosynthesis of ergosterol	Squalene epoxidase
Griseofulvin	Inhibit fungal mitotic process	Interferein microtubules function[20]

Table-1- List of various Anti-Fungal Drugs In-Situ gel with their Mechanism.

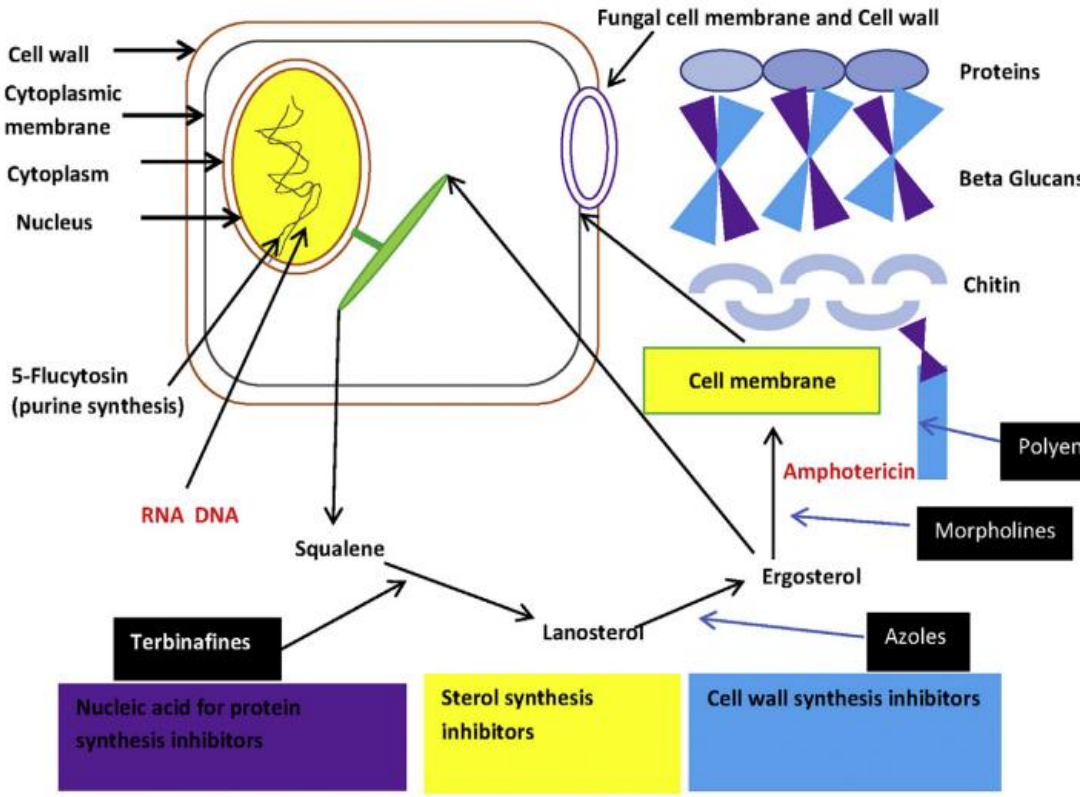


Figure 1. Targeting sites for drug [22].

4.1 Anti-fungal agents used in skins:- A list of various anti-fungal drugs are mentioned below in **TableNo-2.**

Nanomaterial	**Name of fungi**	**Infection cause by fungi**	**Result**	**Outcome**
SLNs	*Candida spp.*	Vaginal infection and candidiasis	Not as good as the stuff on the market	Non-irritating sustained release hydrogel [23]
Liposomes	*C.albicans*	Cutaneous candidosis	Low lipid increase penetration	Liposomes lead to the elimination of parkeratosis and localized thickening.[24]
microneedles	*C.albicans,e.coli*	Skin candidias	The stratum corneum was penetrated.	Antifungal drug sereve wasplaced by microneedles as TDDS for antifungal[25]
Niosomes	*C. albicans*	Skin candidiasis	Meanzone inhibition	Reduce toxic affect

			was larger	prolong apply[26]

Table-2- List of various anti-fungal drugs used in skin.

4.2 Systemic vs local antifungal

A systematic Topical therapy should be continued since it lowers the dosage and length of time needed for systemic treatment. The medication interactions and systemic side effects that describes Systemic agents cause research articles, whereas topical agents do not. Gentian violet, an aniline dye, was used as a treatment in the early 20th century, but due to resistance and adverse effects, including coloring of the oral mucosa, it was replaced by nystatin, a polygene antibiotic[27].

By attaching to sterols in fungal cell membranes, they change the permeability of the membrane. Both nystatin and amphotericin are applied locally in the mouth and are not absorbed from the digestive system. Clotrimazole and ketoconazole are medications in this class. Systemic antifungal can cause can result in more serious adverse effects, such as drug interactions, allergic reactions, and liver damage, than topical therapies.

Various delivery methods can be used to administer local therapies. Douching, nebulization, atomization, inhalations, irrigation, spray, drips, or powder insufflations are some methods used to give topical therapy. The way that medication is administered to the paranasal sinuses before and after sinus surgery differs significantly [28].

5. SITE- SPECIFIC DELIVERY APPROACHES[29,30].

5.1. oral drug delivery system.

It may be possible to distribute medications to particular areas of the GI tract using pH-sensitive hydro gels. The creation of silicone microspheres that either produced prednisolone in the stomach media or had gastro protective properties was made possible by hydro gels composed of different ratios of cross-linked PEG and PAA derivatives. Cross-linked dextran hydrogels swell more quickly at high pH levels, while other polysaccharides such amidaded pectins, inulin, and guar gum were studied to enhance a possible colon-specific medication delivery method. A complexed calcium ion is present in both the sodium alginate and gellan formulations, and it releases these ions into the stomach's acidic environment to undergo a gelation process.

5.2 ocular drug delivery system.

Most often, inulin is employed in ocular delivery systems. Different substances, including autonomic medications, anti-inflammatory agents, and antibacterial agents, are employed in local ophthalmic administration systems to relieve intraocular tension in glaucoma. Ophthalmic in-situ gels were created to address the bioavailability issue because conventional administration systems frequently lead to poor availability and therapeutic response because of high tear fluid turnover and dynamics, which causes the medication to be rapidly removed from the eye. Enhancers of viscosity, such as carbomers, polyvinyl alcohol, carboxymethyl methyl cellulose, and hydroxypropyl methyl cellulose, are used to increase the viscosity of formulations to extend the precorneal residence time and boost bioavailability while making them simple to manufacture. Drug penetration in the cornea is developed using penetration enhancers such surfactants, chelating agents, and preservatives.

5.3 Nasal medication delivery system

In the nasal in-situ gel system, momethasone furoate is utilized to assess the effectiveness of xanthan gum and gallan gum as in-situ gel producing polymers for the treatment of allergic rhinitis. The effect of in-situ gel on antigen-induced nasal symptoms in sensitized rats was reported in an animal investigation that uses an allergic rhinitis paradigm. In comparison to the commercially available product Nosonex (Momethasone Furoate suspension 0.05%), in-situ gel was observed to limit the increase in nasal symptoms.

5.4 System for delivering drugs vaginally and rectal

There are numerous pharmacological formulations that can be administered via the rectal route, including liquid, semisolid (ointments, creams, and foams), and solid dosage forms (suppositories). An anti-inflammatory medication called acetaminophen is made as a rectal in situ gel using polycarbophil and the synthetic polymer-forming in situ gelling liquid suppository F188 and 407, which is thought to be an efficient technique that improves bioavailability[30].

6. PHYSICOCHEMICAL EVALUATION OF *IN* SITU GELLING FORMULATIONS

6.1. Measurement of Gelation Temperature:

A 25 mL beaker containing 10 mL of cold sample solution was set up in a low temperature water bath at room temperature. The sample solution was submerged in a thermometer for continuous observation. A magnetic bar was used to heat the solution while swirling it at 200 rpm. The temperature at which gelation caused the magnetic bar to stop moving was known as the gelation temperature (*T*gel) [31][32].

6.2. Drug Content Uniformity.

In situ gelling formulations' drug concentration was ascertained by precisely dissolving a weighed quantity of formulation (1 mL) in 100 mL of simulated tear fluid. For the formulation to fully dissolve and produce a clear gel solution, it was shook for two to three minutes. After passing the solution through a Millipore membrane filter (0.45 μm), UV-Vis-Spectrophotometry was used to determine the drug content [33].

6.3. Rheological Studies.

By taking into account the viscosity of the instilled formulation, it is crucial to determine the duration of the drug's residency in the eye. Using a Brookfield viscometer, the prepared solutions were allowed to gel at physiological temperature before their viscosity was measured. Plotting the shear rate against shear stress graph allowed for the flow pattern to be verified.

6.4. Bioadhesion Strength.

The mucin-polymer mucoadhesive strength of the gel composition was measured using a straightforward viscometic technique. Viscosities of 15% (w/v) porcine gastric mucin dispersions in STF were evaluated using a Brookfield viscometer at a shear rate of 100 rpm at 37°C, either in the presence (ηt) or absence (ηm) of various formulations. Viscometric measurements were made for homogeneous distribution throughout the sample precisely three minutes after the shear force was applied. Using the formula $\eta t = \eta m + \eta p + \eta b$, viscosity components of mucoadhesion (ηb) were computed, where ηp is the viscosity of the corresponding pure polymer solution. Based on the formula $F = \eta b \cdot \sigma$, where σ is the rate of shear/sec, the force of mucoadhesion (F) was determined [34].

6.5. In Vitro Drug kinetic release.

In order to conduct the in vitro drug permeation tests, the donor and receptor compartments of an all-glass modified Franz diffusion cell were separated by the in situ gelling formation on a Millipore membrane filter (0.15 mm). All air bubbles were removed from the receptor compartment of an all-glass device after newly made simulated tear fluid (pH 7.0) was added. The Millipore membrane filter was covered with 1 mL of test solution, and a glass cover slip was used to close the donor cell's aperture. A magnetic stir bead was used to stir the receptor fluid continuously while maintaining a temperature of 37 C. The permeation investigation lasted for ten hours, after which samples were removed from the receptor and their contents examined using a spectrophotometer to measure absorbance [35].

6.6. Antifungal Studies.

Selected sustained release in situ gel formulations were tested on Aspergillus fumigatus and Candida albicans to determine their antifungal efficacy and long-lasting effects. Before being autoclaved at 121°C for 15 minutes, saboured dextrose was dissolved in hot distilled water to create the nutritional agar medium. Diffusion technique test organisms were previously seeded in the nutrient agar medium (10 CFU/mL) . A micropipette was used to transfer test samples into a petri dish filled with nutritional agar media. The plates were incubated for 24 hours at 25°C after being left for 30 minutes. After 24 and 120 hours, measurements were made of the diameters of the zone of inhibition for Candida albicans and As per gillus fumigates [36].

7. RECENT ADVANCES AND PATENTS IN SMART IN SITU GELS FOR ANTIFUNGAL DELIVERY.

1. Peptides

Evolutionarily varied animals, such as prokaryotes, plants, insects, and vertebrates, create a novel class of antibiotics called antimicrobial peptides (AMPs). While certain AMPs may be anionic, the majority are cationic molecules. With comparable physicochemical characteristics, several families of antimicrobial cationic peptides include a broad range of structural motifs, including defensins, cecropins, melittins, magainins, indolicidins, and protegrins. They demonstrated a wide range of antibacterial activity, including some of the more dangerous infections that are clinically important and resistant to antibiotics, albeit some of them have been proven to be less effective than traditional antibiotics[37].

2. Phenyl alkane nitriles

A new class of chemicals, esters of 2-phenylalkane nitriles of the general formula, were patented by MCS Laboratories, Modesto, CA, USA.

In C-3, the compounds had an OH. 3-acetoxy-2-substituted or unsubstituted phenyl propanenitrile, 3-acetoxy-2-phenylpropanenitrile, and 3-acetoxy-2-phenylbutanenitrile are examples of typical esters of the invention. With the caveat that at least two of them must be hydrogen, Y1–Y5 can be either hydrogen, halogen, methyl, -CHF2, -CF3, -OCHF2, -OCF3, C1–C5 alkoxy, phenoxy, or -SF5. The invention's most potent esters (Figure 11B and C) are reasonably harmless to mammals and especially effective against T. mentagrophytes and C. albicans (MICs < 16 µg/ml). The active ingredients may be administered topically or orally as granules, powder, dust, emulsion, paste, gel, suspension, [38]

3. Cyclic guanidines

A series of cyclic guanidine derivatives were patented in 2012 by the Universita degli Study di Siena, Italy. These derivatives are represented by the general formula of Figure 15A, where R1 = H, propargyl, benzyl, cyclopropylmethyl, but-2-enyl, isobutenyl, and prenyl; n1 and n2 are numbers that are equal or different and range from 4 to 8 [39].

7.1 Novel polymer blends and nanogels

The use of polymers and modified polymers in a variety of drug delivery systems, such as gene delivery, implants, and nano-based methods, has greatly improved therapeutic interventions. Drug administration by implants that use biodegradable polymers, such as poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL), has been shown to be effective in sustained release, improving patient compliance. Polymers and gene delivery systems work together to effectively target the distribution of genetic material and overcome the difficulties associated with gene therapy. Micelles, dendrimers, and nanogels are examples of polymer-based nanoparticles that offer precise control over release kinetics, better bioavailability, and improved absorption in nano-based drug delivery[40].

Nanogels are hydrogels that are cross-linked and have a size between 20 and 200 nm. Pharmaceutical formulations have shown great success using nanogel-based nanoplatforms. The ability of nanosystems to integrate with polymeric materials is one of its unique strengths. These qualities are particularly helpful in polymeric drug delivery applications. For maximum stability, the drug-carrier size is intended to be nanoscale, which increases the surface area and inner space. Additionally, it permits loaded medications to circulate for a longer duration. Photolithographic, modified pullulan, emulsion polymerization, reverse microemulsion polymerization, inverse miniemulsion polymerization, and free radical crosslinking polymerization techniques are all methods for creating nanogel[41].

7.2 Recent patents and innovation

Ocular Thermosensitive & Mucoadhesive In Situ Gels

1. Ketoconazole nanoparticles in poloxamer-based thermosensitive ocular gel Ketoconazole nanoparticles in a thermosensitive ocular gel based on poloxamer. This formulation, which was created to treat fungal keratitis, had a gelation temperature of about 34.7 °C and greatly improved drug release and solubility, increasing antifungal efficacy against Malassezia furfur[42].

2. Itraconazole nanocrystal-laden thermosensitive ocular gel

Media-milled itraconazole nanocrystals were incorporated into a Pluronic F127-based thermosensitive gel. In ex vivo porcine eye models, this yielded a ~93 % reduction in *Candida albicans* compared to standard suspensions [43].

Vaginal Antifungal In Situ Gels

1. Stimuli-responsive (pH/thermo) spray gel with miconazole nitrate

Miconazole nitrate Chitosan + Poloxamer 407 + HPMC produced a stimuli-responsive (pH/thermo) spray gel that gels at ~31 °C and pH ~4.2, providing sustained release over 24 hours with superior antifungal activity compared to conventional creams.

2. Bioadhesive-thermosensitive gel-flake system for itraconazole [44]

Itraconazole bioadhesive-thermosensitive gel-flake system used "gel flakes" for solid dispersion in a PF-127/PF-68/HPMC matrix. In animal models, itraconazole tissue retention was maintained (>4 mg after 8 hours), and the number of C. albicans colonies was reduced by >90% [45].

Emerging and Adjacent Technologies

1.Clay–zwitterion membranes embedded with terbinafine HCl

Terbinafine HCl-embedded clay–zwitterion membranes A 2025 arXiv study investigates clay-based wound dressings containing the antifungal terbinafine, providing prolonged release and suppression of Candida albicans—a new related technology that differs from a traditional in situ gel [46].

2. ZIF-8-based antifungal formulations for keratitis

Antifungal formulations for keratitis based on ZIF-8

An novel approach to treating keratitis that goes beyond conventional gel forms is a metal-organic framework (ZIF-8) that provides antifungal and anti-inflammatory advantages [47].

8. OPPORTUNITIES AND CHALLENGES IN SITU GEL SYSTEM OPPORTUNITES[48,49]

1) In situ gel extends the retention period and increases bioavailability.
2) Reduced frequency of medicine administration allows for immediate drug administration.
3) Delivers and controls medications continuously.

4) Natural polymers that are biocompatible and biodegradable make up in-situ gel.
5) Because of its hydrophilicity, it provides significant in vivo function, extending the in-vivo release cycle.
6) To prevent a barrier of defense, as the absorption of a water connection
7) Increase the drug's therapeutic response and improve patient contact.
8) Just supply eye tissue to prevent the loss of other ocular tissue.

Challenges:-

1) Only a small amount of the medication can be administered, and a lot of liquids is needed.
2) Gel stability issues are caused by high chemical breakdown and the need for large amounts of fluid.
3) You can postpone eating and drinking for a few hours after taking the medication.
4) The sun's form is decreasing significantly

9. IN SITU GEL SYSTEM FOR OCULAR DRUG DELIVERY.

For the local treatment of eye diseases, topical administration via the ocular channel has been widely utilized. Poor BA related to traditional eye drops is caused by physiological limitations like the corneal epithelium's lipophilic temperament, restricted absorption area, and a number of elimination factors like nasolacrimal drainage, tear turnover, and tear evaporation that shorten the duration of medication contact with the corneal surface. A diagram showing the difficulties in the transportation and destiny of a medication molecule[8]. In **Figure 2** shows the exact The drug's initial barrier to be absorbed is the precorneal tear film. The outermost layer, which is made up of lipid and oil and stops tears from evaporating, is the first of its three levels. The middle layer is made up of aqueous salt solution, while the innermost layer is made up of mucous. Ocular membranes include the vascularized conjunctiva and the nonvascularized cornea. Five or six layers of non-keratinized squamous cells make up the corneal epithelium, which is thought to be the main route for ocular medication penetration.

" The main obstacle to ocular delivery is the removal of the implanted dose due to several causes (Figure 1), which can be successfully addressed through formulation engineering. The sole remedy for this issue is the creation of a formulation with an enhanced retention time[9].

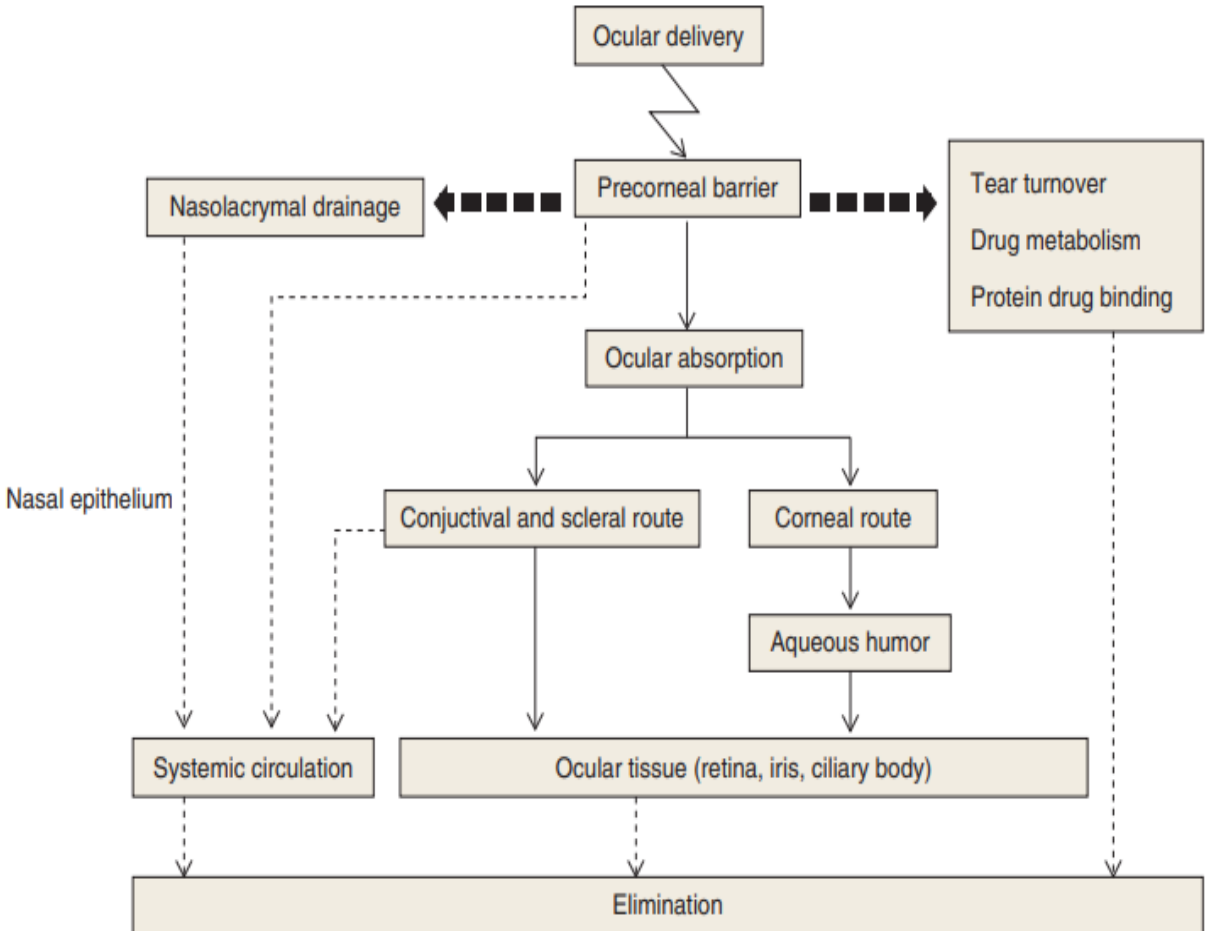


Figure no.2 Movement of drug and barriers in ocular delivery.

10. CONCLUSION

Researchers have made a tremendous effort over the last 20 years to develop a number of innovative strategies that can effectively circumvent the challenges presented by traditional ocular formulations. Unquestionably, one of the greatest outcomes of these efforts is the creation of in situ gel-based delivery methods. Since their inclusion in the medication regimen, the field of ocular delivery has advanced at an exceptionally rapid pace; this excitement is evident in the large number of published findings and continuing studies in the field.

Improving the ocular BA of the supplied formulation by extending its duration of contact with the eye tissues is the most important problem in the realm of ocular delivery. Their distinct phase transition characteristics (sol--gel transformation) may be the reason for the excitement surrounding in situ gel systems.. Additionally, these systems provide strong sustained-release characteristics and eliminate the harmful effects and systemic absorption of the drug that is retained by the polymeric matrix.

The in situ gelling technique extended the duration of the drugs' residence at the site of action/absorption, hence increasing the effectiveness of local or systemic medications delivered through non-parenteral routes. The performance of the formulation is further improved by the use of mucoadhesive agents or the use of polymers that have the ability to interact with the mucosa or mucus in addition to in situ gelling capabilities. In the past year, the most popular and effective method has been using the same formulation of polymers with distinct in situ gelation methods to take advantage of a synergistic interaction between them.

List of short abbreviation-

LCST Lower Critical Solution Temperature, **UCST** Upper Critical Solution Temperature. **PSG** pH-Sensitive Gel types respond to pH variations, employing polymers such as **PAA** Polyacrylic Acid, **HPMC** Hydroxypropyl Methylcellulose, **CP** Carbopol that gel in the presence of physiological pH. **ISG** Ion-Sensitive Gel systems gel upon contact with ionic fluids, using materials like **GELLAN** Gellan Gum, **ALG** Sodium Alginate, **XG** Xanthan Gum that respond especially to divalent

ions such as calcium. **MRG** Multi-Responsive Gel, **SPIG** Stimuli-Responsive In Situ Gel respond to a combination of stimuli such as temperature, pH, ions. To enhance mucosal adhesion and site-specific retention, **MBP** Mucoadhesive Biopolymer..

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