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Recent Advances in In-situ Gel Formulations

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Abstract: *In-situ gels are now recognized as one of the popular and accessible approaches. These systems have several advantages, including simple manufacturing, convenience of use, improved retention, and patient compliance by decreasing drug delivery frequency due to their distinctive solution to gel transition features. In-situ temperature-sensitive gel is a type of in-situ gel that looks as a solution at room temperature but transforms spontaneously into a gel at body temperature. The'sol-gel' process involves hydrolysing, polymerizing, or condensing the precursor to produce a particle suspension or solution. Such in-situ gel formation methods, which can be delivered in liquid form, gel at the completion site. In recent years, some researchers developed in-situ gelling methods for liposomes, microspheres, nanoemulsion, nanospheres, and so on. This review concentrated on the introduction, benefits, downsides, types of polymers, and acceptable qualities for making in-situ gel.*

Keywords: sol to gel (solution to gel), Nanoemulsion, Hydrolysing, Polymerising

I. INTRODUCTION

The absorption and dispersion of drugs through mucous membranes are the primary goal for administration of Medication. There are several method's of administration of Drug by In-situ gel, In Past Decade Formulation of Nasal Route of Drug Administration and Ocular Route of Drug Administration are Developed Exponentially due to its wide Application, Patient Compliance, Decrease Dosing Frequency and Greater Absorption with High Bioavailability

II. CLASSIFICATION OF IN-SITU GEL

1.Thermosensitive In-situ gel:

Thermosensitive In-situ gel is made from thermosensitive polymers, which is in liquid under its lower critical solution temperature and will be elated Whenever the surrounding temperature reaches or exceeds LCST. Materials including poloxamer, chitosan, poly (N-isopropyl acrylamide) are common temperaturesensitive In-situ gel.

Applications

1) Ophthalmic Drug Delivery: Temperature-sensitive gels might be utilized as occular drops that gel when in touch with the eye's surface, increasing medication retention and bioavailability.This is particularly useful for treatment of glaucoma, where prolonged drug action is needed without frequent reapplication

2) Nasal Drug Delivery: These gels can help deliver medications directly to the nasal passages, allowing for faster absorption into the circulation. The sol-to-gel conversion at body temperature aids in maintaining a high concentration of the medicine while inhibiting systemic adverse effects.

2. Nanoemulsion in-situ gel:

Nanoemulsion In-situ gel mainly uses the Polysaccharide derivatives produce a polymer solution to undergo chemical response with a large number of cations such as K+, Na+, Ca2+ in the liquid environment in human body, and then undergo conformational change, thus forming gel at the application site.

Applications

1) Enhanced Bioavailability, Nanoemulsions enhance the ability to dissolve and absorption of weakly water-soluble medicines, making them helpful carriers for oral, parenteral, and transdermal delivery systems. They can encapsulate both lipophilic and hydrophilic medications.

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2) Food Coatings, edible nanoemulsion coatings can increase the duration of storage of food goods by limiting moisture loss and oxidation, while also giving taste and color.

3. PH-sensitive in-situ gel:

PH responsive in-situ gel may accept or emit protons from the environment around it when the pH value of human body changes, which results in gelation reaction and slowly release drugs for a long time. The commonly used polymers include chitosan, cellulose acetate and its derivatives.

Applications-

1) Stomach-specific delivery: pH-sensitive hydrogels can be used for delivering drugs to the stomach during conditions like ulceritis. The gels remain intact release the medication in the stomach's acidic environment

2) Vaginal Drug Delivery pH-responsive polymers: Gels for vaginal medication delivery can be formulated using pH-responsive copolymers. These gels expand and release the medicine in reaction to the vaginal tract's slightly acidic pH, allowing for the targeted delivery of contraceptives or antibacterial agents.

4. Ion-sensitive gels:

Ion-sensitive gels are at In-situ gel that performs a solution to gel state change as an outcome alterations in ion concentration in the surrounding environment. These gels are particularly useful for drug Distribution

Mechanisms of Ionotropic Gelation = This process occurs when oppositely charged ions interact with polymer chains. For instance, divalent or multivalent cations (like Ca^{2+}) interact with negatively charged polymer chains it causes the development of a network with three dimensions. This network traps solvent, resulting in gel formation. The gelation can happen via external or internal methods

External Gelation-A polymer solution is introduced dropwise into a crosslinking solution, allowing ions to diffuse into the polymer droplets, promoting immediate gelation at the surface while creating a gradient of gelation throughout the droplet.

Internal Gelation-This method involves the presence of insoluble salts within the polymer solution, which dissolve upon contact with a solvent, triggering gelation In-situ

Applications- Because of its capacity to switch between solution to gel in reaction to change in ion concentration, ion-sensitive gels have showed promise in transdermal drug delivery applications.

5. Enzyme-sensitive gel:

Enzyme-sensitive gels utilize enzymatic cleavage mechanisms to achieve controlled degradation and drug release.

Mechanisms of Enzymatic Cleavage - Enzymatic cleavage in gels involves crosslinking with specific enzymes, such as matrix metallo proteinases (MMPs), which breaks down the gel network and releases encapsulated drugs or biomolecules. The hydrogel's composition also plays a role in its responsiveness, with chitosan hydrogels degrading in the presence of lysozyme, an enzyme secreted by inflammatory cells. Enzyme specificity can trigger gel degradation, with glucose oxidase initiating radical polymerization in certain hydrogels, allowing targeted drug delivery in tumor environments. The controlled release mechanism of drugs from enzyme-sensitive gels involves diffusion and degradation, with the mesh size increasing as the gel degrades. This mechanism can be adjusted by adjusting the enzyme concentration or crosslinking density.

Applications

1) Oral delivery: Ion-sensitive Gels can be customized to deliver medicines at precise regions of the gastrointestinal tract based on pH and ion concentrations. For example, pectin-based gels can release drugs in the colon by responding to the higher pH and presence of calcium ions.

2) Ophthalmic delivery: Ion-sensitive solution can be delivered as eye drop and form a gel when in contact with Lacrimal fluid, enhancing drug residence time and bioavailability for disease such as glaucoma.

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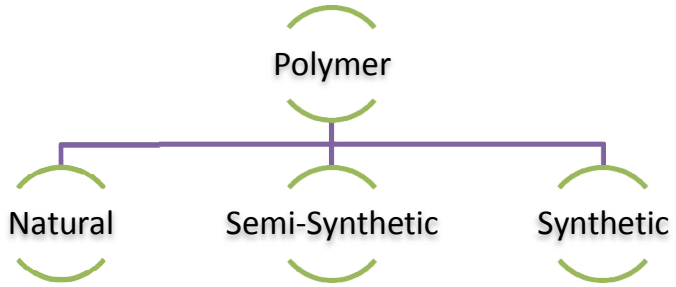
Classification of Polymers :



- Natural = Those which are obtained from animals and plants. Example for such polymers includes cellulose, starch, gelatin, chitin etc.
- Semi-Synthetic = These are those which are obtained by chemical modification of natural polymers. Examples include cellulose derivatives such as HPMC, starch derivatives, chitosan etc.
- Synthetic = These are those which are synthesized in laboratory or which are man-made polymers. Examples include PLGA, polyacrylates, polyethylene glycol etc

Polymers utilize in In-situ Gel :

- Sodium Alginate: Sodium alginate is naturally occurring copolymer. The alginate sodium is an alginic acid salt containing β-Dmannuronic acid residues. Alginate salt is extremely attractive due to its disintegration and non-toxicity, as well as its sticky properties.
- Gellan Gum : Gellan Gum is a soluble in water also called as Gel Rite it is an FDA approved Polysaccharide. Gellan gum forms gels due to temperature fluctuations or the existence of cations (e.g., Na +)
- Xyloglucan: Tamarind seeds have a plant-based polysaccharide. The polysaccharide is chemically constituted of a sequence of (1-4)-Dglucan with particles of (1-6)-D xylose. It is used to provide pilocarpine and timolol via rectal, oral, and ocular routes.
- Chitosan: Chitosan, naturally occurring, flexible polymer derived from chitin, is rotten, hot, and not toxic. It is biocompatible and dispersible in strong solutions as high as pH 6.2.
- Carbopol: Carbopol is pH-based polymer that creats a tiny viscous gel in basic pH but stays in solution in an acidic range.
- Pluronic F-127 : Pluronic triblock copolymers consist of a central block of water hating polypropylene oxide surrounded by water loving polyethylene oxide blocks available in various stages, they are prone to temperature changes and can be identified by their assigned marks.
- Xanthan gum: Xanthomonas campestris makes xanthan gum, a very high atomic weight, consisting of prolong chain with glucose and mannose. It forms a strong gel when mixed with polymers due of its weak structure, it produces very viscous fluids even at minimal concentrations. [1]

Mechanism of Drug Release :

Understanding drug release mechanisms is critical for creating and manufacturing controlled release devices, as a regulated energy source is required for precise timing. Chemical and biological processes regulate drug relese, such as diffusion, dissolution, swelling osmosis, erosion, and targeting, with controlled drug delivery systems classified by mechanism.

1. Diffusion :

Diffusion is the movement of mass of molecule from one region of a system to another, affected by factors such as concentration gradients. It lowers concentration differences via spontaneous matter flux, particularly at the system/water interface. This process is important in medicine because it allows active chemicals to be taken and eliminated through the body, eventually reaching the intended location in a tissue or cell.

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Molecules move over time through thermal or Brownian motion, yet drug molecules interact in macroscopic solutions. Diffusion is a kinetic process occurs in non-equilibrium systems and is driven by solute concentration gradients. It occurs in volume groups with individual solutes, and increasing concentrations.

Fick used the Fourier principle of heat flow to explain mass transfer, claiming that diffusion is determined by the concentration gradient, distance, and percent of mass moving over.

The rate-controlling step in this system is drug diffusion through an insoluble polymer barrier, by Fick's first law and based on a particle concentration gradient.

$$J = -D.dc/dx$$

Where,

J= Flux

D= Diffusion Coefficient

dC/dX= rate of change in concentration across the membrane X.

2. Dissolution :

Drug molecules are transferred to surrounding mediums by dissolution, with solutions that are saturated having solutes under their solubility limit and supersaturated ones having solutes above it. Recognizing the connection between physicochemical qualities and their usefulness in drug release management is critical because both human and animal organisms include considerable amounts of water and hydrophobic substances, which provide the conditions in which medications must work. Non-covalent interactions hold highly organized arrangements of atoms and molecule together to form crystalline solids. Their shape, size of particles, and solvation/hydration are all affected by their processing conditions. Their physicochemical properties, such as solubility, might differ based on crystallization. Some instances, particles are transformed to amorphous, transparent state with varying thermalstabilities. The inter conversion of solid structures has the potential to change the agent's solubility, stability, and biological function.

Dissolution is the movement of medication ions or molecule from the solid state to a liquid vehicle, with saturated solutions containing the solute reaching its limit of solubility. The speed of a medicine's disintegration forecasts its discharge from the therapeutic system.

When a solid drug particle's surface came into touch with a dissolving fluid, molecules dissolve and are removed. Factors such as solvating medium, area of surface, and diffusion coefficient all influence this process.

Surface area of the drug particles (larger surface area = faster dissolution)

Concentration of dissolved drug (higher concentration = slower release)

The Rate of dissolutions is Given by :

$$\frac{dc}{dt}\ k\ Cs - Cb$$

Where,

dc/dt = rate of the drug dissolution

K = rate constant pf dissolution

Cs = drug concentration in stagnant layer

Cb = drug concentration in the bulk of the solution at time

3. Erosion :

These therapies, whether implanted or injected, are popular because to their non-retrieval mechanism, which is divided into two categories.

(1) Systems of physical immobilization

(2) Systems of chemical immobilization

Surface erosion:

Erodible systems, also known as biodegradable or erodible, are created when a therapeutic component is physically trapped by a polymeric net and then released following erosion. These systems are useful for medicinal applications

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since they dissolve in the body after administration, requiring no invasive intervention to remove. Chemical immobilization takes place when an active ingredient is attached chemically to a polymeric structure or a component of the structure.

Drug release in erodible systems is essentially determined by the kinetic deterioration of the suitable connection, with two distinct constraints to consider: surface erosion and bulk erosion. Surface erosion occurs when solvent invasion is slow and hydrolysis is rapid. Hydrophobic polymers shield their chemical bonds from water exposure, allowing hydrolysis to occur only on or near the surface. This results in a decrease in size over time.

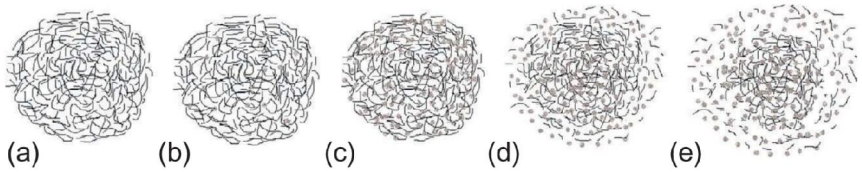

Fig:1. A diagram showing the stages of system surface erosion.

Bulk erosion:

In Bulk erosion systems occurs in three stages: release of medicines from the system's surface or linked cracks, latent degradation, and active agent release. The quick disintegration in the inside results from the buildup of autocatalytic degradation products, whereas leaching causes delayed erosion at the outermost layer. Thicker matrices may deteriorate more quickly than thinner ones. This process occurs when autocatalytic erosion products accumulate.[2]

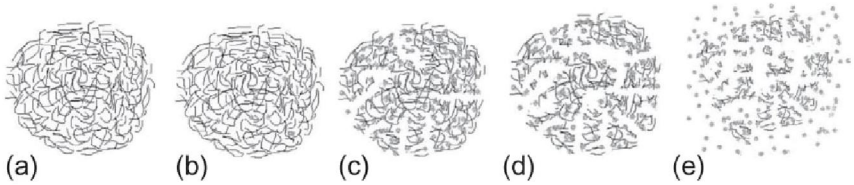

Fig: 2. A graphical representation of the steps of bulk erosion

4. Swelling

Polymers are often employed in controlled medication release systems because of their hydrophilic nature and contact with water molecules. When surrounded by water, their polymer chains can develop chemical or physical linkages, allowing them to expand. This swelling mechanism is comparable to osmosis in that water enters the polymer quickly and dissolution is gradual due to the need for disentangling. This increase in volume and space in chains of polymers can be exploited to regulate the release of active substances from polymer materials like matrices and reservoirs.

The relevance of swelling can be evaluated by the shape of the matrix or membrane, especially in reservoir systems. A polymer system's size and volume grow as it absorbs water during drug administration. However, separation and dissolving of the medication. [2]

According to the Flory-Rehner theory, swelling can be expressed as an equilibrium among the entropy of chains of polymers and the energy of mixing [3]. The matrix's volume falls and dissolves when the whole copolymer is swelled, resulting in a "swellable-soluble polymer." Material swelling is sometimes limited and the matrix remains due to insufficient compatibility between water and polymer.

Water intake and swelling in polymers are influenced by a combination of osmosis, electrostatic forces, and entropy-favored disintegration forces. The swelling of a polymer is determined by its High Water Affinity and cross-link density.

Types of Swelling:

1. Fickian swelling: Water diffusion is slower than polymer relaxation.
2. Non-Fickian swelling: Water diffusion is faster than polymer relaxation.
3. Anomalous swelling: Combination of Fickian and Non-Fickian swelling.

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Swelling controlled dissolution systems consist of polymers at ambient and human body temperatures. They can be classified into physical as well as chemical agents. Polymers have chains connected together by covalent bonds, whereas physical polymers have functional groups that react with ions or aldehydes. When exposed to water, the transparent polymer near the surface softens and swells, allowing water to infiltrate farther. This creates an oscillating front that separates a swelling outermost layer from a dry internal center, allowing water to infiltrate farther. Cross-link , ionic , and hydrophilic are the three most important components of swelling process

Biochemical polymers are linked by covalent bonds, whereas physical polymers feature functional groups that react with ions or aldehydes. Controllable medication delivery can benefit from customized swelling kinetics, that might be achieved by varying cross-linked density. The softening of chains of polymers typically results in a glass-to-rubber conversion.

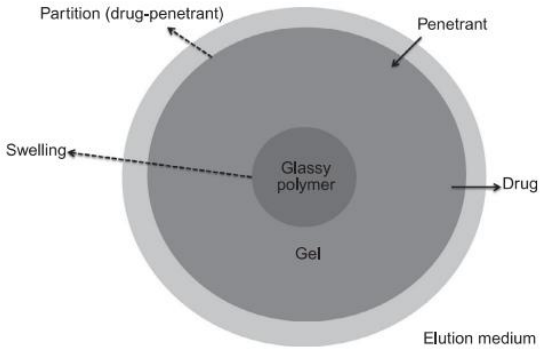

Fig:3

Application of In-situ Gel :

1. Oral medication Delivery: In-situ solutions produce a gel in the gastrointestinal tract, allowing for long-term medication release. This is especially important for pharmaceuticals that have to be absorbed gradually over time.[8]
2. Optical Drug Delivery: The gels used in eye drops improve drug absorption and efficacy through prolong contact time on the optical layer. They are triggered by the warmth of the eyeball and the pH of the tear fluid [9].
3. Nasal medication Delivery: In-situ gels provide systemic medication delivery. The gelation process helps to keep the medicine in the nasal passages and enhances uptake. [10]
4. Rectal and Vaginal Drug Delivery: Rectal and vaginal gels can deliver drugs topical or systemically. They give a prolong release of the medication, enhancing clinical outcomes. [11]
5. Injectable. Localized drug distribution is achieved using in-situ solutions. Upon injection, they form a gel depot at the location of administration, releasing the drug for an extended period.
6. Intraperitoneal Medication Delivery : These formulations can be used for delivering drugs directly into the peritoneal cavity, providing a controlled release and reducing the frequency of administration[12]
7. Dermal Delivery System: The thermally changeable Pluronic F127 was investigated for percutaneous indomethacin administration, with in-vivo tests indicating potential for topical application.[6]

A. Nasal Drug Delivery System:

The nasal passageway is the major element of the airway and serves as an entrance for breathed air. The septum of the nose divides it into two lateral parts, which are protected by a mucous. The nasal cavity is separated into three sections: vestibular, respiratory, and olfactory. The vestibular area is the entry to the nostrils, covered by mucus and ciliated hairs. The respiratory region, measuring about 130 cm², includes ciliated and non-ciliated epithelium, goblet cells, basal cells, blood capillaries, and trigeminal and olfactory neurons. The olfactory layer is found in the top section of the nasal cavity.

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The nasal cavity is rich in olfactory sensory cells and trigeminal neurons, which connect to the brain's olfactory lobe. The olfactory neuroepithelium is structure with a capacity to regenerate, allowing for direct medication delivery to the central nervous system. However, the specific process of nose-to-brain medication targeting is not entirely understood. Some hypotheses propose that the major mechanism is neurological, through olfactory and trigeminal nerve cells, while additional pathways involve CSF2, the lymphatic system, and vascular absorption.

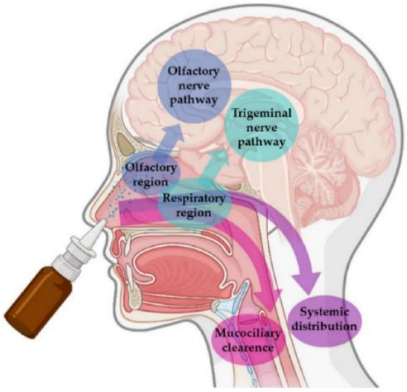

Fig.4

The transport of drugs from the nasal passages to the brain happens via the olfactory and trigeminal nerves, with the olfactory neurological pathway generally the most prevalent. This mechanism is characterized by passive diffusion and endocytosis, also known as paracellular transport. The trigeminal nerve connects the nasal passages to the cerebellum, pons, frontal cortex, and olfactory bulb. Controlling drug transport along a single route is difficult. Another process involves medication absorption through the lymphatic system and cerebrospinal fluid (CSF), which connects the nasal passages to the CSF of the CNS' subarachnoid area. The distribution and transit of medicines in the CSF are determined by their characteristics. The olfactory region of the nasal cavity contains numerous olfactory and trigeminal nerve
When medications interact with nerve endings, they travel to the brain through the lamina propria and cell transport systems. The medication enters the brain through the cribriform plate and is distributed to various brain regions by bulk flow and perivascular transport.[7]

Challenges of Nasal Drug Delivery :

1. Mucociliary elimination prevents extraneous particles from entering the body and leads to poor medication retention. However, fast clearance and short drug stay in the nasal passages limit medication uptake.
2. Enzymatic loss: The nasal cavity's epithelial limitation & lumen include exo- and endo-peptidase enzymes that breakdown proteins and peptides. This limits the bioavailability of peptide-based bioactives, requiring the use of prodrugs, enzyme-blockers, or innovative drug carrier systems.
3. Poor invasion and low medication bioavailability = the nasal passageway has a thin mucous membrane that is lipophilic, making it appropriate for smaller lipophilic molecules. However, the nasal route limits the absorption of polar medicines, which have just a 10% bioavailability. To improve nasal absorption of polar medicines, suitable absorption enhancers such as phospholipids, surfactants, bile salts, cationic compounds, cyclodextrins, and fatty acids can be utilized. Novel carrier methods and surface modification can both improve nasal absorption.
4. Nasomucosal toxicity: How medications are administered affects their passage from the nose to the brain. Regular nasal drops introduce the medicine into the respiratory system, sending it to the circulatory system and respiratory organs. However, patients find it uncomfortable to maintain an upright head position.

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III. IN-SITU FORMULATION FOR NASAL DRUG DELIVERY

In-situ gel of Disulfiram

- Researcher used Disulfiram-loaded nanoemulsion In-situ gel (DSF-INEG) in rat brains to treat Glioblastoma with copper ions in a non-invasive, direct, and low-toxicity way.
- DSF-INEG-Cu successfully suppressed C6 & U87 cells from growing in vitro and shown outstanding brain-targeting by nose-to-brain administration. It improved tumor growth inhibition in rats, leading in longer median survival durations and the potential for therapeutic GBM treatment.
- The solubility of DSF was 63.3 ± 1.9 µg/mL, satisfying sink conditions.
- The viscosity of the Disulfiram was found to be 55.9 ± 2.8 s (n = 3), and it could remain up to 24 hours, This was useful in resolving limitation about rapid mucociliary elimination.
- TEM scans revealed a roughly spherical form for INEG and DSF-INEG.
- The DLS measurement revealed that both the molecule dimension and zeta potential for the formulation was 63.4 ± 1.1 nm and -23.5 ± 0.2 mV, respectively.
- DAPI staining revealed that DSF-INEG/Cu therapy dramatically increased GBM cell death in C6-U87 cells, leading to better cell absorption of DSF.
- Disulfirams anti-carcinogenic mechanisms are not fully explored, but it's believed that its cytotoxicity is enhanced by copper. This copper-copper complex can inhibit cellular proteasome, IkB degradation, and NFkB nuclear translocation. DSF also inhibits DNA methyltransferase activities and elevates radical oxygen species. Studies show nose-to-brain transport is potential for treating GBM.[13]

In-situ gel of Atomoxetine

- The study evaluates the effectiveness of atomoxetine filed tiny lipoid carrier (NLC)-loded temperature-sensitive In-situ hydrogel in targeting the brain after nasal delivery.
- Atomoxetine formulation was created using melt emulsification and ultrasonication.
- Atomoxetine formulation was optimized for nanoparticle size of 108 nm, entrapment rate of 84.12%, and zeta potential of -42.3 mV. AXT-NLC was discovered to be spherical.
- The AXT-NLC13G4 formulation, optimized for in-situ gel generation, had a viscosity of 2532 ± 18 Cps at 37°C and produced the gel at 28-34°C.
- Atomoxetine nano emulsion constant delivery AXT (92.89 ± 3.98% over 12 hours).
- When administered intravenously, Atomoxetine formulation produced 51.91% higher BTP than only Atomoxetine (28.64 percent).[14]

In-situ gel of Rizatriptan

- The research project intends to produce a nasal gel containing rizatriptan for migraine therapy.
- Riztriptan, a specific 5-HT1B / 5-HT1D receptor agonist, is utilized for the relief of migraines.
- The gel's clarity was observed that is clear
- The Rizatriptan formulation mucoadhesive strength at 72.2 dyne/cm2, while the formulation had the drug content of 96.45%
- The gelation temperature is 37.12 ℃ , resulting in a gel strength is 14.4 seconds.
- The F4 formulation is considered optimized as its gelation temperature is close to body temperature.
- The formulation has a Higest release rate of 99.12%, according to the Total Drug Delivery data.
- The study suggests that nasal In-situ gel can enhance the absorption of rizatriptan in the brain, potentially serving as a viable alternative to parentral and oral formulations. [15]

B. Occular Drug Delivery System

Adipose tissue occupies the region between the eyes and the orbital region. The orbital bone walls and fat assist to shield the eye from harm. The anterior segment of the eye contains the cornea, conjunctiva, iris, pupil, ciliary body,

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anterior chamber, aqueous humor, lens, and trabecular meshwork, whereas the back part contains the vitreous fluid, sclera, retina, choroid, macula, and optic nerve. [17,18]

- **Sclera:** The sclera is a strong fibrous tissue which creates the outermost part of eyeball, allowing the eye to maintain its globe structure. It is larger on the Back side of the eye than on the anterior.
- **Conjunctiva:** The conjunctiva is a transparent layer which borders the inner side of the eye and surrounds the front one-third of the eyeball. It has two layers: an outer epithelial and an underlying stroma.
- **Iris:**It is a sperical-shaped muscular curtain placed in front of the lens. It is governed by iris muscle, which adjust pupil size to regulate light intake.

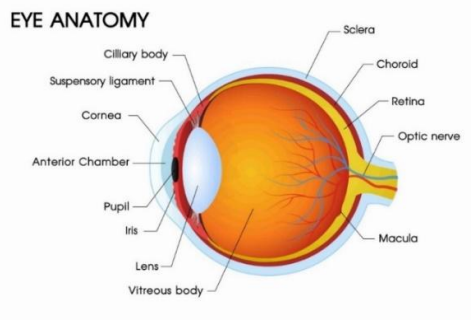

Fig.5

Cornea: The cornea is a visible translucent protrusion at the anterior, having a radius of around 8mm. Its main optical function is to refract light that reaches the eye, travel across the pupil and lens before focusing on the retina. The cornea dose not contain veins, obtains nourishment from capillaries and is highly sensitive to neurons from ciliary neurons that penetrate the tissue of the cornea.[19]

Ciliary Muscle: The ciliary muscles, a group of soft muscles situated in the inner eye layer, regulate the area available for recognizing things at different range.

The Lens: The lens is clear convex shape, flexible substance made up of tissue layers in a capsule and deflected by tiny fibers called zonules from the ciliary muscles. [17,20]

Pupil: The pupil, or black core of the eye, is a round aperture in the iris that permits light to come in. The pupillary reflex, or "light reflex," regulates pupil size and light admittance.

Optic nerve: The optic nerve arrangement is about 10 lakhs nerve cells, transmits nerve information from an eye to nervous system and Brain, carrying picture information that the brain processes.

Challenges of Occular Drug Delivery :

1. Lacrimal fluid quickly eliminates implanted substances from the eye surface, with a turnover rate of 1 µl/min. Systemic absorption helps to remove non-productive drugs.
2. The corneal epithelium, which is made up of developing epithelial cells, inhibits medication absorption through lacrimal fluid to the eye, with transcorneal diffusion serving as the predominant route of drug entrance.
3. The blood-ocular barrier defends the eye from xenobiotics, with the front barrier protecting plasma albumin from reaching the humor and the posterior barrier limiting drug distribution to the retina. Drug distribution routes vary depending on the target tissue.

IV. IN-SITU FORMULATION FOR OCCULAR DELIVERY

In-situ gel of Nepafenac

- Nepafenac is a NSAID primarily used in ophthalmology, converting into amfenac after penetrating the cornea. Nepafenac, a medication used to treat pain and inflammation associated with cataract surgery, inhibits COX enzymes, reducing the production of prostaglandins.
- The maximum wavelength of Nepafenac was determined by ultraviolate spectroscopy is 258 nm. Formulation is Transparent

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- The ophthalmic formulations of Nepafenac In-situ gel contain a of 98.99 percent of Drug
- The formulation must have optimal viscosity for easy application into the eye, rapid sol-to-gel transition, and sustained drug release without dissolving or eroding for extended periods. The gealing time was found to be 14 sec
- The viscocity of the Formulation Befor gelation is 106 and After Gelation is 1200 [26]

In-situ gel of Gentamicin

- The study developed an in-situ gel containing gentamicin bilosomes to improve therapeutic activity for surface eye disease, overcoming limitations of eye drops due to short corneal residence and low bioavailability.
- Gentamicin Biosomes has the vesicle size of 185.1±4.8nm 4, zeta potential 27.6 mV
- The entrapment effectiveness is 81.86±1.29%, with round shape.
- Gentamicin Biosomes released 78.08 ± 4.73% of extended release over 12 hours.
- The optimized in-situ gel (GE-BMopt-IG4) has 99.16±1.02% gentamycin content
- Study suggests that Biosomes in-situ gel can enhance the therapeutic efficacy of Gentamicin, but further preclinical studies are needed. [27]

In-situ gel of Norfloxacin

- Norfloxacin is an antibiotic that is use in the treatment of the conjunctivitis.
- Patients with ocular irritation or chronic conjunctivitis may benefit from using norfloxacin ophthalmic solution, which has been demonstrated to be beneficial in treating ocular infections.
- Norfloxacin In-situ gel was developed to improve treatment efficacy by extending contact time, providing regulated release, reducing administration frequency.
- It was determined that all of the formulations' clarity was adequate.
- The pH of the formulations is in the range of 5.4-7.2
- The formulation contains 99.7% of the drug.
- The formulations exhibited instantaneous gelation in only 60 seconds and demonstrated stability over several hours. [33]

Future Directions

1. **Advancements in Smart Materials:** Research is likely to lead to the development of more sophisticated smart materials that can respond to a broader range of stimuli, including light, electric fields, and biological signals.
2. **Tissue Engineering and Regenerative Medicine:** In situ gels can serve as scaffolds for cell growth and tissue regeneration. Future research may lead to their application in complex tissue engineering.
3. **Diagnostics and Biosensors:** In situ gels may also have promising applications in diagnostics and biosensors, where they can be engineered to respond to specific biomarkers, providing real-time information about disease
4. As the applications of in situ gels expand, regulatory bodies will likely develop new guidelines and frameworks to ensure the safety and efficacy of these materials in clinical settings.
5. **Gene Therapy:** Nasal delivery could serve as a non-invasive route for administering gene- based therapies, enhancing access to the CNS.

V. CONCLUSION

In-situ gels provide benefit over typical dosing methods. In-situ gels are composed of biocompatible, biodegradable, and water-soluble polymers. Formulation might result in exceptional and improved medicine delivery systems. It also contributes significantly to improving patient comfort and compliance. We evaluated many traditional formulations that were turned into novel in-situ formulations, which resulted in overcoming the limitations and problems of traditional aspects of the Dosage System with no adverse effects. Different Invitro Evaluation Parameters of the Nasel Drug

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Delivery System and Occular Dug Delivery System are researched, and conclude that the Insitu gel system has the scope and capacity to overcome the limitations and produce the Novel Drug Delivery.

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