A REVIEW ON NEWER METHODS TO IMPROVE SOLUBILITY BY INSITU GELS.

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ABSTRACT

In situ gelling formulations are dosage forms in the shape of a sol when they enter the body, but they change into gel kinds under physiological conditions. The shift from sol to gel is dependent on one or a combination of triggers, such as a change in pH, temperature control, UV irradiation, or the presence of certain ions or molecules. Such systems can be employed in a variety of ways for local or systemic drug delivery, as well as carriers for drug-induced Nano and micro particles. In-situ gel, collagen shields, Nano-emulsified system, iontophoresis, Nano-micelles, emulsions, micro-needles, and dendrimers are all discussed in this article. These innovative techniques provide a huge technological barrier, as well as a patient compliance issue with dosing forms. Traditional drug delivery methods are washed away in a short amount of time, resulting in low bioavailability and therapeutic responses due to fast drug clearance from the eye due to high tear fluid turnover and dynamics. In-situ gelling frameworks are polymer-based fluids that display stage progress on the visual surface because of an adjustment of a particular physicochemical boundary like temperature, ionic strength or pH set off in-situ frameworks because of which the arrival of medication can be supported for longer periods of time, restoratively more strong, non-aggravation and stable than ordinary eye drops.

Keywords: *in-situ gel, nano-emulsion, dendrimers, nano-micelles, collagen shields, micro needles, iontophoresis.*

1.INTRODUCTION:

Gels are soft, stable, or solid-like substances that are made up of at least two components, one of them being a liquid present in significant amounts. The state of gel refers to a mixture of liquids and solids i.e., either semi solids or semi liquids. Gels are divided into two categories (i.e., physical and chemical). Hydrogen, electrostatic, and Vander Waal linkages are all weak bonds found in physical gels. In situ gels are liquids or suspensions that gel upon contact with bodily fluids or physicochemical changes such as pH, temperature, ionic concentration, UV radiation, the presence of certain molecules or ions, external triggers, and so on. Despite the vast variety of gels, one kind in particular, smart polymer gels, is the focus of pharmaceutical research[1]. Smart polymers, for example, can carry and administer the medicine on their own due to their capacity to respond to a stimulus by displaying physical or chemical changes in the environment. In-situ gel systems have piqued ophthalmologists' interest in recent years. Because of the bio-adhesiveness of the formed gel that has been developed, in-situ gel forming systems have shown their promise in expanding the residence time[2]. The bulk of these systems are unique in that they are sol-state prior to injection and then gel in the body. As a result, they are distinguished by simplicity of administration, extended residence duration, and sustained drug release at the administration site, as well as a reduction in administration frequency and improved patient compliance and comfort. The fact that these formulations may be taken by numerous ways to create a local or systemic impact of the medication contained is one of the reasons for their enormous popularity. They can also be employed as vehicles for nano- and micro-drug delivery systems[3].

Given the intricacy of the eye's highly specialised anatomy, designing Ocular Drug Delivery Systems (ODDS) is a significant problem for pharmaceutical researchers[4]. Gellanic gum, alginic acid, and xyloglucan are examples of natural polymers employed in the ocular delivery system. Several combinations of anti-inflammatory, antibacterial, and autonomic drugs are utilised to treat intraocular glaucoma stress in the local ophthalmic administration approach to relieve intraocular glaucoma stress. In ocular preparations, viscosity enhancers such as Poly Vinyl alcohol, Carbomers, Carboxy Methyl Cellulose, and Hydroxy Propyl Methyl Cellulose are used to improve the viscosity of these formulations, resulting in enhanced precorneal residence duration and bioavailability. Smooth polymer approaches for delivering pharmaceuticals seem promising; once delivered, these polymers are converted from sol to gel. The implications of employing biodegradable polymers in medicinal applications are now clear[5]. A polymer

called carbomer 934p allows the product to be physically stable and resuspended with ease[6]**.** The goal of new ocular medication delivery systems is to keep effective drug concentration at the appropriate spot in the eye for a long time[7].

ADVANTAGES:

- Lowered dosing concentration.
- Decrease dosing Frequency.
- Increase bioavailability by Improved precorneal residence time and by decreased nasolacrimal drainage of the drug[8]
- Provide sustained and controlled drug delivery.
- Ocular bioavailability is increased due to improved precorneal residence time.
- Decrease the drainage of drugs.
- Enhances bioavailability.
- Usage of natural polymers provides biocompatibility and biodegradation[9].
- Obstacles like ocular drainage, lacrimation, and conjunctival absorption are avoided.
- Drug nasolacrimal drainage is reduced, which might result in unwanted side effects owing to systemic absorption.
- In case of hydrophobic drugs, the extent of drug loading is limited.[11]

IDEAL CHARACTERISTICS OF INSITU GEL:

- It must be able to stick to the mucous membrane
- With an increase in shear rate, it should be possible to reduce viscosity.
- It should have an impact on tear production.
- It should have high optical clarity and tolerance.
- It needs to be compatible[1].
- It has pseudo plastic and viscoelastic properties.
- It is antimicrobial and bio adhesive.
- It can transform to a hydrogel at ocular pH.
- Stability in the presence of heat, light, air or reasonable levels of moisture.[10]

METHODS OF FORMATION OF IN- SITU GEL DRUG DELIVERY SYSTEMS

There are four generally documented processes that generate in situ gel preparation.

Thermally triggered system:

Temperature-sensitive in situ medication delivery Gels are the most well-studied type of environmentally sensitive polymer system. Polymers are liquid at room temperature (20-25°C) and gel at physiological temperature (35-37°C) in this gelling system. The phase transition temperature for an ideal temperature triggered in situ gelling solution should be higher than room temperature (25° C) so that it may be conveniently delivered to the eye and gelled at precorneal temperature. Poloxamers, also known as Pluronic® in the industry, are thermoreversible polymers that are often employed to create thermosensitive in situ gelling systems. When a novel 'protein polymer' is injected into the system as a solution, it undergoes an irreversible change to a gel, forming a hard, durable gel in a very short time.

pH triggered in situ gelling system:

pH driven in situ gelling systems are solutions that transition to the gel phase when exposed to the pH of the lachrymal fluid. Electrostatic, hydrophobic contact, and hydrogen bonding occur at particular pH levels, resulting in inter-diffusion and a conformational change in the polymer, which causes swelling. Hence sol to gel transition takes place. Similarly, PMA and polyethylene glycol mixes have been employed to induce gelation in response to pH changes. In comparison to other polymers such as cellulose derivatives and polyvinyl alcohol, polyacrylic acid has excellent muco adhesive characteristics. In reaction to blood glucose levels, cationic pH-sensitive polymers containing immobilised insulin and glucose oxidase can expand and release stored insulin in a pulsatile way.

Ion triggered in situ gelling system:

The solution viscosity rises when the tear fluids are exposed to ionic concentrations in this sort of physiological stimulus in situ gelling device. Ion sensitive polymers form crosslinks with cations (monovalent and divalent) found in lacrimal fluid on the ocular surface, extending medication retention duration. Polymeric compounds can undergo phase transformations in the presence of different ions, and some polysaccharides can degrade in an ion-sensitive environment. In the presence of monovalent and divalent cations, such as Mg2+, Ca2+, Na+, and K+, anionic polysaccharides such as gellan gum create in-situ gels. [5,10,11]

APPROACHES FOR CREATING *INSITU* GELS:

This paper will provide a brief overview of various approaches for creating *in-situ* gels and various research work related to these novel systems.

NANO EMULSIFIED SYSTEM:

By overcoming the limits of ocular barriers, a novel pH induced nano-emulsified in-situ gel for ophthalmic distribution of antibiotic medicines can improve permeability and residence duration. Because of its inherent advantages, nano-emulsions (NE) have been frequently reported as a medication delivery technique for ocular distribution. Only a few of the advantages include enhanced penetration into deeper layers of the ocular anatomy and into the aqueous humour through the cornea, as well as simplicity of sterilizing.

Once the medication is given, the adsorption of Nano droplets on the cornea acts as a reservoir, limiting the drug's outflow[12].

By removing the mucous layer and breaking tight junctional complexes, NEs improve ocular drug penetration. Instead of include these polymers as in situ gel polymers in the NE form, the drug's therapeutic efficacy was increased employing poloxamers. When a medicine is discharged from the system, it will gradually diffuse into the continuous aqueous phase, hence NE may prolong its release duration. The dose form stays in the eye for longer

since the NE changes into a gel that is not readily eroded or damaged by tears because to the in-situ gelling polymer.[13]

The volume of formulations for nano-emulsion liquid dosage forms must be small enough to deliver the therapeutic amount of medication in a captured form. One of the important standards for selecting oils is the drug's solubility in the oil phase. In the case of ophthalmic administration, the globule size is a key factor since it determines drug release rate, absorption, and eye discomfort. NEs are able to deliver the required medication dosages into the cornea and aqueous fluid due to their tiny size.

Nirav Patel et al. created a unique cationic *insitu* nano-emulsified in-situ ophthalmic gel of loteprednol etabonate for improved ocular permeability and retention duration, resulting in increased ocular bioavailability. NE had the lowest risk of ocular irritation and had considerably (p50.01) larger Cmax and AUC (0–10 h), delayed Tmax, longer mean residence length, and increased (2.54-fold times) bioavailability when compared to the marketed formulation. In the treatment of a number of ocular inflammatory conditions, LE's cationic nano-emulsified in-situ ophthalmic gel provides a superior alternative dosage form to currently available formulations[14].

COLLAGEN SHIELDS:

One of the most useful biomaterials is collagen. Collagen has been the most often utilized material in applications because to its excellent biocompatibility and safety due to biological properties such as biodegradability and low antigenicity[15].

The collagen shield has a contact lens-like shape. It will be dehydrated when it arrives and will need to be rehydrated before using. Drug transport and ocular epithelial regeneration were both assisted by collagen shields. The corneal epithelium is protected from the action of the eyelids by the mechanical qualities of the shield, and the collagen in the lens may aid recovery. Collagen shields used for drug administration are susceptible to absorption and subsequent medication discharge. When a water-soluble pharmaceutical is used in a rehydration solution, it becomes trapped in the interstices of the collagen matrix. When the barrier disintegrates, the drug is released. Water-soluble drug-soaked shields reached corneal and aqueous levels equivalent to traditional topical treatment.

Antibiotics, antifungals, anti-inflammatory medications, immunosuppressive drugs, and anticoagulant pharmaceuticals have all been administered to the eye using collagen shields.

Collagen corneal shields were originally created to protect the ocular surface as corneal bandage lenses; however they are currently utilised to protect the ocular surface[16].

Advantages:

- Treatment is independent of patient compliance.
- Can be delivered through bandaged eye.
- When using topical eye drops on an uncovered eye, the risk of self-inoculation durin
- g the postoperative period is increased.

Disadvantages:

- Non economical
- Less visual acuity
- Discomfort Ness to patients

IONTOPHORESIS:

Iontophoresis is a noninvasive method of improving the dispersion of charged medication molecules across biological membranes such as the skin, joints, nails, and ocular structures by using a low-amplitude electrical current. Ocular iontophoresis is a painless, rapid, and safe way to administer a high concentration of medication to a particular area. The amount of medication given is directly tied to and limited by the applied current (milliamperes [mA]), the time of usage (min), and the surface region reached while using iontophoresis. The present iontophoresis profile can be tweaked to get the appropriate medicine penetration kinetics. During iontophoresis, drug penetration and molecular transport are principally performed by electro-repulsion and electro-osmosis. Electro-repulsion, or the orderly movement of ions in the presence of an electric field, is the most important mechanism for electro-transport of ionized compounds. Electro-osmosis, on the other hand, is the flow of liquid along the anode-cathode direction caused by an electric potential applied across a negatively charged membrane, and it is more essential in the iontophoresis of high molecular weight medications[17].

Iontophoretically administered antibiotics may have improved bactericidal activity and lower disease severity. Can help to reduce the risk of intraocular injections and implants causing negative side effects. Iontophoresis has been shown to be effective in treating bacterial keratitis[18].

Iontophoretic device:

A direct current power source and two electrodes are used to manufacture the iontophoretic devices. The ground electrode is implanted at a distant region on the body, and the ionised drug is inserted in the same-charged electrode compartment

Approaches for retaining drug in to iontophoretic device:

In an iontophoretic device, medicines can be retained in one of two ways.

- The more typical method is to immerse a metal electrode extended from the current supply in the medicinal solution while filling an eye cup with it. An eye cup with an internal diameter of 5–10 mm is placed over the eye during iontophoretic therapy, and a medicinal solution is continually poured into the cup. The eye cup includes two ports: one for the medicinal solution and one for aspirating air bubbles that may interrupt the current supply, resulting in a tiny negative pressure that keeps the applicator in place.
- The second strategy employs a drug-saturated gel as a delivery probe. The gel was partially extruded from a plastic tube, allowing it to come into direct contact with the eye.

Transcorneal iontophoresis:

Transcorneal iontophoresis is a method of delivering a high concentration of medication to the anterior portion of the eye (cornea, aqueous humour, ciliary body, iris, and lens), which can be used to treat keratitis, glaucoma, dry eyes, corneal ulcers, and ocular inflammations. The lens barrier prevents transcorneal iontophoresis drugs from reaching the back of the eye.

Trans scleral iontophoresis:

This barrier is bypassed via transscleral iontophoresis, which allows medications to be delivered directly into the vitreous and retina via the choroid. To avoid current injury to the retina, the iontophoretic device is positioned on the conjunctiva, over the pars-plana region. For posterior ocular illnesses such as endophthalmitis, uveitis, retinitis, optic nerve atrophy, juvenile retinoblastoma, and age-related macular degeneration, transscleral iontophoresis is a potential treatment option (AMD).[19]

EMULSION:

Emulsion-based formulations have the benefit of enhancing medicine solubility and bioavailability. The two types of emulsion systems utilized commercially as carriers for active therapeutic substances are oil in water (o/w) and water in oil (w/o). The o/w emulsion is commonly used and recommended for ocular medication administration over the w/o method. To boost the ocular bioavailability of lipophilic medications, many oil-in-water emulsions have been authorised and are presently in clinical studies. Because the o/w emulsion causes less discomfort and has a better ocular tolerance, it is preferred. Emulsions have been demonstrated to increase precorneal residence time, drug corneal penetration, drug release stability, and hence ocular bioavailability in a number of studies. Emulsion has been demonstrated to reduce medication release while increasing chemical stability and precorneal residence time. When compared to uncoated emulsions, emulsion surface coating with chitosan enhanced the mean residence length and half-life of the emulsion by 1.5 and 1.8 times, respectively, in a tear fluid pharmacokinetic study[20].

Micro emulsions might be a good way to boost the eye's natural defenses. They are stable and have a large capacity for dissolving the medications since they are created using low-cost procedures such as auto-emulsification or energy supply, and they can be readily sterilized. The micro emulsion serves as a reservoir for the medication, preventing it from leaking out of the cornea. Microemulsions are liquids having Newtonian characteristics. The microemulsion dosage type had a delayed and delayed pharmacological effect when compared to the pharmacological impact of regular eye drops. They are viscous, but only in contrast to nanodroplet systems. They are thermodynamically stable and, by default, can make soluble lipophilic medicines, but this depends on the lipophilic phase used[21].

Tetsuya Tajika et al. looked examined the ocular distribution and excretion of tritium-labelled difluprednate (H-DFBA) ophthalmic emulsion 0.05 percent in pigmented rabbit eyes after a single or repeated instillation. A single or repeated dosage of 25 mg/50 mL H-DFBA 0.05 percent ophthalmic emulsion was administered to pigmented rabbits' right eyes. The radioactivity of the right and left ocular tissues, as well as urine, blood, plasma, and faeces, was measured using a liquid scintillation counter. The distribution of radioactivity surrounding ocular tissues was also investigated with autoradiography. The radioactivity distributed in the front area and was promptly removed after administering 3 H-DFBA ophthalmic emulsion 0.05 percent into rabbit eyes. Difluprednate and its metabolites have gotten into the posterior retina and choroid, as evidenced by the presence of radioactivity in these tissues. These findings show that difluprednate, when applied as a topical ophthalmic emulsion, quickly reaches the anterior and posterior parts of the eye, implying that it might be utilised to treat ocular inflammation in these areas[22].s

NANO MICELLES:

Nanomicelles are the most generally utilized transporter frameworks to plan remedial specialists into clear fluid arrangements. By and large, these nanomicelles are made with amphiphilic atoms[23].

The nature of Nano-micelles may be polymeric or surfactant. Nanomicellar formulation-based technology for ocular medication delivery is now attracting a lot of attention. The high drug encapsulation capability, simplicity of manufacturing, compact size, and hydrophilic ion properties may be the causes. The bioavailability of the therapeutic drugs are improved by formulating into micellar form. Nano-micelles are used for ocular gene delivery. Topical ocular administration of small compounds using nanomicellar formulations is a feasible method. Nanomicelles are also being used for posterior ocular medication delivery in a few different ways. With the use of topical drops of mixed nanomicellar formulations, the scientists have recently achieved great progress in delivering therapeutic medicines to the posterior ocular tissues. The gelling capacity mainly depends on amount of polymer used in the formulation. while presence of other barriers is not considered in the nano-micelles insitu gels[24].

Advantages:

- Administration of accurate & reproducible quantity of drug.
- Increased precorneal contact time.
- Prolonged drug release.
- Drug delivery to deeper tissues.

- Reduced frequency of administration.
- Patient compliance.
- Easy to administer.

Han Kang et al., worked on Cyclosporine A micellar delivery system for dry eyes CsA eye drops are well-known in the pharmaceutical sector as a treatment for dry eye condition. Alternative ocular pharmaceutical formulations for this disease, with the exception of Restasis, are essentially non-existent due to stability and patient compliance difficulties.MS-CsA that is transparent and capable of improving patient compliance. MS-CsA formulations were created using the non-ionic surfactant Cremophor EL, ethanol, and phosphate buffer. Histological evidence of greater goblet-cell density and clinical evidence of better tear production in dry eyes revealed that MS-CsA had a strong therapeutic impact. Our findings clearly suggest that MS-CsA might be an excellent alternative treatment for dry eyes[25].

DENDRIMERS:

Dendrimers are nanoparticles made of synthetic polymers with a highly organized branching structure, which enhances the drugs aqueous solubility, bioavailability and biocompatibility and hence can be used for administering the drug through various routes. Dendrimers can be utilized in a number of ways to deliver medications. To target specific ocular components, dendrimer modification is used. A dendrimer is a gel-forming agent with a wide range of applications. The use of injectable treatments based on dendrimers to treat anterior and posterior segment problems looks to be promising. For decades, dendrimer injections have been delivered subconjunctivally. Nanoparticles delivered by this delivery site are protected against tear drainage washout, however, permeation through the scleral cavity is still required. The single element that defines the size of dendrimers is their surface charges. Dendrimers are tiny enough (in most formulations) that they will eventually reach systemic circulation, regardless of how they were administered initially[26].

Dendrimers can also reduce toxicity, and when used correctly, they allow the medicine to be delivered to the target location while maintaining the acceptable pharmacokinetic parameters. Dendrimers can exhibit several surface groups, allowing for easier targeting, preparation, and functionalization. In the interior cavities of first-generation dendrimers, hydrophobic medicinal molecules can be enclosed. Because of their systematic, electrophoretic, dimensional length scaling, and other biomimetic properties, they're called "artificial proteins".[27]

Dendrimers also appear to possess bio adhesive properties that are relatively strong compared to polymers such as Carbopol. It is possible to explain the bio-adhesion of these dendrimers by the nature and significance of the surface groups in these polymers. To manage drug loading and release from dendrimers, the physicochemical characteristics of dendrimers can be altered. Dendrimers behave as condensed polycations under a range of chemical and physiological circumstances, and may attach to negatively charged polyanionic nucleic acids, such as DNA or RNA, to create dendriplexes, thanks to the presence of their peripheral multivalent functional groups. Dendrimers must avoid aggregation and be tiny enough to disperse across the body's initial line of defence at exposed surfaces, and have a muco-inert surface to ensure optimal ocular distribution[28].

Th.F. Vandamme worked on Poly(amidoamine) dendrimers as ophthalmic vehicles for ocular delivery of pilocarpine nitrate and tropicamide, the purpose of this study was to see if controlled incremental increases in the size and molecular weight of PAMAM dendrimers as ocular medicine delivery vehicles would have any effect. The data imply that ocular residency length is influenced by bio adhesive dendrimer size, molecular weight, charge, and molecular geometry, in addition to size and molecular weight. The prolonged corneal residence time that these polymers cause, as well as the improved bioavailability of medications contained in eye drops, are undeniable benefits. Finally, the use of aqueous PAMAM dendrimers via the ocular channel has been shown to be of interest[29].

MICRONEEDLES:

Microneedles are a new medication delivery device that has a lot of potential in the healthcare area. They may be used to treat a number of ocular illnesses. Microneedles (MNs) are tiny polymer or steel objects that vary in diameter from a few micrometres to 200 nano-meters. MNs are least intrusive in nature given that they include

micro-sized projections. MNs have the capacity to no longer solely overcome the barriers of presently used traditional transport systems, however additionally to go ocular obstacles to exactly goal pills at the required web site of action. Because of trends in pharmaceutical technology, MNs now allow for localised, effective, much less invasive, and centered medicine administration in the eye. MNs have the practicable to pace up percutaneous medicine delivery. These micron-sized needles are easy to insert into the eye and can be used for a vary of purposes. These needles are less painful than standard hypodermic needles, and they can be designed to administer medicine for longer periods of time[30].

SOLID COATED MICRONEEDLES:

Solid coated MNs are those that are designed to penetrate tissue and rapidly destroy the coating. They can then be removed. The jabbing will make a micron-sized channel, which will empower for successful or designated drug conveyance. Strong MN's chief capacity is to make pores in the sclera or cornea of the eye. Strong covered MNs have covering plans applied to the surface with the goal that when jabbed in the visual tissue, the covering detailing breaks up and the medicament is conveyed. As strong MNs, metals, for example, treated steel and silicon tests are utilized.

HOLLOW MICRONEEDLES:

Micron-sized needles having the formulation entirely inside the needles are known as hollow MNs. Several formulations, including as nanoparticles and microparticles, are used to give the drug through hollow MNs. In some cases, hollow MNs can be manufactured out of borosilicate micropipette tubes, biodegradable polymers, or stainless steel. The drug is released from the MNs' hollow spaces, and the patch is removed when the medication has been given to the ocular tissue by pricking it. A diffusion release mechanism is used to release the medicine from the hollow MNs, allowing for faster drug delivery to a precise area within the eye.

DISSOLVING POLYMERIC MICRONEEDLES:

To tackle the numerous drawbacks of hollow and solid coated MNs, such as manufacturing, application, infusion difficulties, and accuracy, dissolving polymeric When compared to hollow and solid coated MNs, polymeric MNs have been produced as a method of demonstrating their usefulness in ocular tissue. They're made of a variety of biodegradable, biocompatible polymers that are simple to introduce into the ocular tissue. Applying a Microneedle (MN) patch to the ocular tissue before dissolving polymeric MNs is the initial step, and then releasing the medicine that has already been integrated into the polymeric needle patch into the eye tissue[31].

CONCLUSION:

In these systems a new carrier is incorporated to provide sustained drug delivery in a much better and more efficient way. Surfactant nano-micelles in addition to their numerous technological advantages such as their size for ocular application and high capacity for drug encapsulation, can be further enhanced in their effectiveness by insitu gelling systems. Lipid emulsions also delays the drug release from the delivery system, hence reduces the pre corneal drug loss. The new technology minimizes drug-induced toxicities in the body of the patient as well as vision loss. In addition, these nano carrier devices ensure sustained drug release, improve specificity when targeting moiety is used, and reduce the needed dosage. This method of drug delivery avoids non-specific drug tissue accumulation and delivers therapeutic levels of drug into targeted ocular tissues.

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