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A REVIEW ON NOVEL NANOEMULGEL FOR OCULAR DRUG DELIVERY

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Abstract
Nanotechnology has been widely used the recent clinical trends, it enhances the potential of the delivery of the drug in ocular target site by reducing complete and partial side effects. Eye is a sophisticated and sensitive structure of the human body their physiology impart a significant role in the delivery of the drug and effectiveness of the drug at target site. Developing efforts in drug delivery has led to progresses of nanoparticle preparation for ocular drugs, Nanoemulgel, is a novel drug delivery system, and has garnered substantial consideration in current years due to its probable to revolutionize ocular drug delivery. Emulsion based nanotechnology or nanoemulgel is a design connected interference to recover the complete distribution and beneficial profile of fat-soluble drugs. Nanoemulgel is a multifaceted preparation of two dissimilar arrangements in which nano emulsion containing drug is fused into a gel base. The combination of these binary systems makes this invention valuable in numerous ways. Lipid based preparations can be easily unified and the permeation through epidermis of the integrated drugs can be boosted in numerous way due to the exceptionally dispersed nanoparticle of nano emulsion. Prior studies demonstrate that this preparation suggestively amended the adsorbtion, distribution, metabolism, excretion and pharmacodynamic parameters of the lipotropic drugs whereas; the character statics of nanoemulgel in ocular drug delivery is limited. The main focus of this study is to assess and describe the current potential and encounters face by the drug delivery system of the loaded drug in Nanoemulgel, and upcoming possibility of nanoemulgel invention for fetching an operative delivery system for hydrophilic drugs. In this assessment, we have briefly discussed the consequence of various studies on absorption, distribution, metabolism, excretion, binding of the drug to their receptor and affinity of the drugs distributed in ocular concluded via nanoemulgel. Reasonableness of use laterally with the foremost tasks to overawed for nanoemulgel invention has been deliberated.

Keywords: Nanoemulgel, ocular drug delivery, nanotechnology, gel-based systems, therapeutic efficacy.

1. Introduction:

Eye disease has been treated with various ophthalmic preparation but eye drops are convenience and ideal method of drug administration, Unfortunately, these formulation are used from the conventional period of era, their use is strongly habituated they have a drawback that did not reach the desired target site of the eye or internal structure of the eye such as retina epithelia cornea .Therefore, to acquire a beneficial efficacy, it is essential to spread high attentions in the ocular tissues. It may produce the side effects and cause the toxic effect on the body. To overcome this toxicity nano technology has been used, and attentive consideration on the expansion of new drug delivery tactics increasing ophthalmic residence time, with desired pharmacological action, thus refining the bioavailability, and diminishing adverse effect by refining patient care. The residence time of drugs has been increased at the eyes epithelium level by employed various approaches therefore use of gels is the new strategy, it composed of a 3D cross-linked polymer or a colloidal system occupied in a fluid. It also known as, hydrogels, water is the main component of the ophthalmic formulation. Hydrogels are proficient to absorbing large amount of liquid or biotic solutions, due to the occurrence of water loving groups, and liberating the drugs lured in them and disturbed the tonicity of the eye, it becomes the main reasons of irrevocable loss of visual in industrialized nations, these include diseases, retinopathy due to elevated hyperglycemia and closed angle glaucoma (Bastawrous et al., 2014,) Amid them, glaucoma is presently one of the foremost sources of irreparable complete vision loss (Mancino et al., 2018). The pathology of the glaucoma is connected with an higher intraocular pressure (IOP) It regard as a neurodegenerative disease (Mancino et al., 2018). The higher IOP is associated with the stressful condition of the cells of the eye, and subsequently dysfunction or death of the retinal ganglion cells (RGCs). (Gauthier and Liu, 2016). Glaucoma has been treated with the surgical procedure that mainly focused on reducing IOP, (Sena and Lindsley, 2017). Moreover, dryness of the eye is another complication that desires to be treated concomitantly in glaucoma patients, Glaucoma is mainly affect the elder population (Zhang et al., 2019). Consequently, in management for glaucoma dryness eye management is a typical task (Ratna and Rina, 2011,).

Ophthalmic formulations poses significant trials due to the unique biological fences of the eye. Conformist eye drop formulations often suffer from low bioavailability, rapid clearance, and poor patient compliance. To overcome these limitations, researchers have explored innovative drug delivery systems that can enhance drug retention time, improve corneal penetration, and minimize side effects. Nanoemulgel, a combination of nanotechnology and gel-based formulations, has emerged as a promising solution to address these challenges.

2.0 Synthesis Techniques and Characterization:

Several techniques are employed to synthesize nanoemulgel, including high-pressure homogenization, ultrasonication, and microfluidics. These methods ensure uniform distribution of nano emulsion within the hydrogel matrix. Advance techniques have been employed to measure and evaluate the particle size it includes dynamic light scattering, transmission electron microscopy, and rheological analysis are used to evaluate particle size, stability, and consistency of the nanoemulgel. Ocular iontophoresis, is a non-invasive skill to improve drug penetration using a insignificant electric current. This method offers larger flexibility to transport anticipated drug amount in a precise and acceptable manner. In prior studies, this system has been attested to distribute antibiotics, corticoid, proteins and other genetic factor into the ophthalmic with the effectiveness of giving or improving miscellaneous ophthalmological diseases (Weis et al,. 2023).

2.1 Biopharmaceutical Considerations:

Nanoemulgel formulation requires careful consideration of biocompatibility, cytotoxicity, and ocular irritation. Preclinical studies, with in vitro and in vivo valuations, are essential to establish safety and efficacy. Furthermore, the impact of nanoemulgel on corneal permeation, tear dynamics, and patient comfort should be thoroughly investigated.

2.2 Nanomedicine for Ocular Drug Delivery

Ocular system is a very sensitive and complicated moreover; relocating medicine through the eyes is a challenging duty due to fundamental features for example enhanced elimination of eye-drops from the eye, exterior due to quick drainage from the nasal lacrimal route, conversion of drugs across the blood-ocular barrier, and the cornea. Also, drug diffusion to the superficial of the eye due to the associated structure cornea conjunctiva and sclera. The infusion of the drug through visual tissue is simplified by nanomedicines. Present data of the various studies in nanomedicines as a beneficial tactic supported in therapeutic effect of the targeted drug -related to cataract and diabetic retinopathy by dropping pressure. vision impairment improved by nanomedicines via increase the release of drug and therapeutic profile along with reducing the adverse-effects of medications. Numerous methods has been introduce by the researcher in the nanoparticle and opted this novel technology imporve the drug release at the tergeted site mainly in the ocular diseases (Qamar, et al., 2020).

Figures and Tables:

Table 1: Comparison of Nanoemulgel with Conventional Ocular Formulations

Parameter	Nanoemulgel	Conventional Eye Drops
Particle Size (nm)	<100	>1000
Drug Release Profile	Sustained	Rapid
Corneal Permeability Enhancement	High	Limited
Ocular Residence Time (minutes)	Prolonged	Short
Patient Compliance	Improved	Variable

Stability	Enhanced	Limited

Table 2: Examples of Nanoemulgel Formulations for Ocular Drug Delivery

Drug	Nanoemulsion Components	Hydrogel Components	Target Application
Timolol	Lipid (Oil), Surfactant, Co-surfactant	Carbomer, Sodium Hyaluronate	Glaucoma
Cyclosporine	Lipid (Oil), Surfactant, Co-surfactant	Pluronic F127, Hydroxypropyl Cellulose	Dry Eye Syndrome
Antibiotic Peptide	Lipid (Oil), Surfactant, Co-surfactant	Chitosan, Xanthan Gum	Ocular Infections
Bevacizumab (Monoclonal Antibody)	Lipid (Oil), Surfactant, Co-surfactant	Gelatin, Polysaccharide	Macular Degeneration

Figure 1: Method of preparation of Nanoemulgel

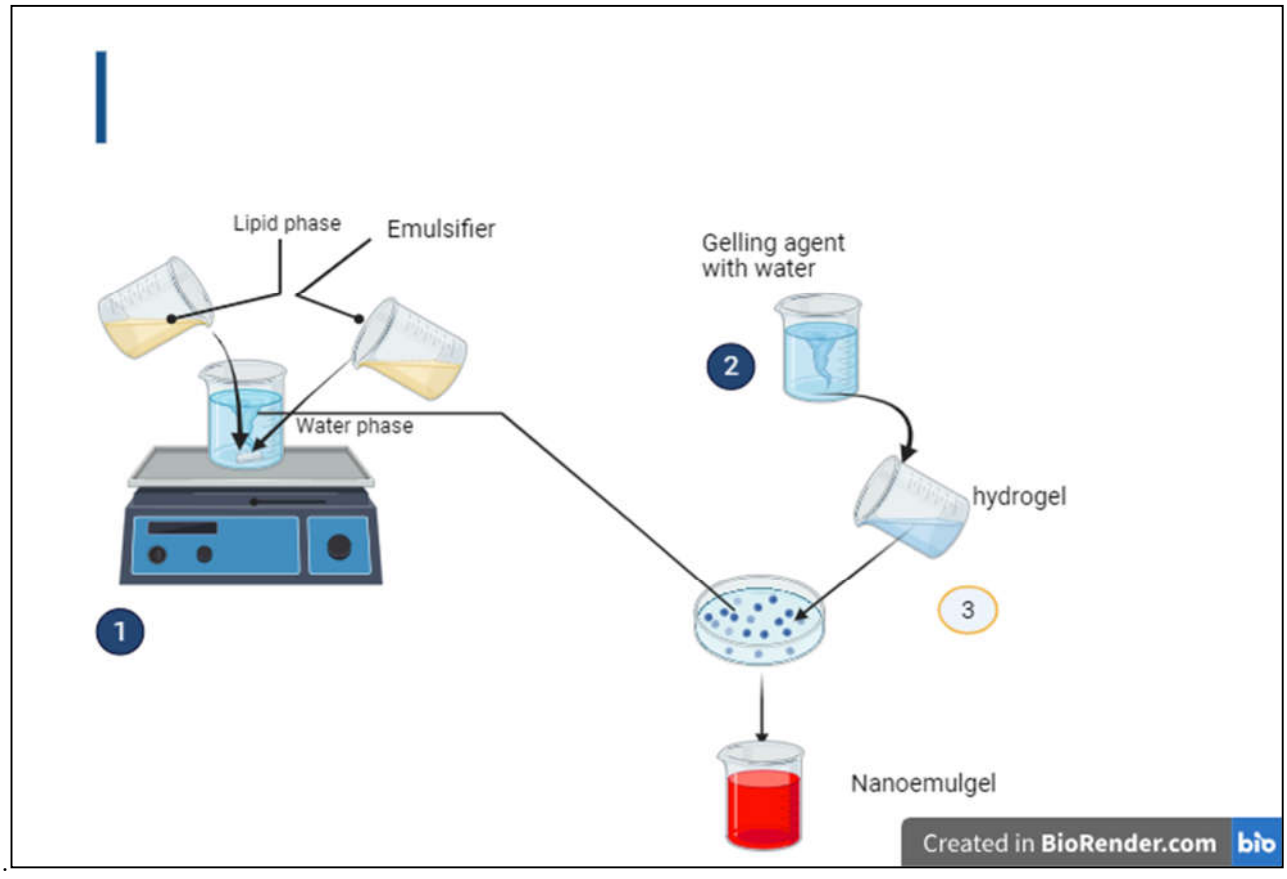

Fig 1: Method of preparation of Nanoemulgel

3.0 Nanoemulgel Formulation and Advantages:

Nanoemulgel is formulated by combining nanoemulsion and hydrogel components. Nanoemulsions consist of oil and water phases stabilized by surfactants and co-surfactants, resulting in droplets with a nanometer-scale diameter. This fine dispersion can improve the solubility and permeability of poorly water-soluble drugs. Hydrogels, on the other hand, provide a viscous and hydrating environment, increasing ocular residence time and patient comfort. The integration of nanoemulsion into hydrogel matrices offers several advantages. First, the nanometer-sized droplets in nanoemulsions provide a high surface area for drug absorption, leading to enhanced drug bioavailability. Second, hydrogels can sustain drug release over an extended period, reducing the frequency of administration. Third, the gel-based consistency enhances

ocular retention by minimizing the rapid drainage associated with traditional eye drops. Moreover, the gel matrix can protect the drug from degradation, improving stability.

3.1 Potential Applications of Nanoemulgel:

Nanoemulgel holds immense potential for treating a wide range of ocular disorders. Conditions such as glaucoma, dry eye syndrome, and infections require precise and sustained drug delivery. Nanoemulgel can provide controlled release of therapeutic agents, ensuring optimal drug concentrations at the target site. Additionally, the enhanced permeability of nanoemulsions can facilitate the delivery of macromolecular drugs, such as proteins and nucleic acids, to address more complex ocular diseases.

3.2 Topical Drug Delivery

solutions, lotions, creams, patches, gels are the topical preparations that used from ancient time it has been reported previously But the drawback of the formulation limited to the competent stratum corneum and epidermis of the skin. The subcutaneous layer is a formed keratinocytes with a medium of lipid that spread up to 10–20 μm thick, the penetration of the drug to achieve a desire therapeutic effect is a typical task, due to this reason amount of drug reaching the target site is lesser and they have low permeation result less therapeutic effect. Consequently, the research has been proposed that mainly focuses on the development of topical formulations for skin and ophthalmic route with proper permeability and confirming distribution by numerous mechanisms. The way of research work in current years has targeted towards novel transporter arrangements with the determined to modify the permeability of aquaphobic drugs through the skin. New preparation progress techniques and strategies are incipient in new years (Donthi, Munnangi, Krishna, Saha, Singhvi, & Dubey, 2023).

3.3 Development of a Mupirocin Nanoemulgel

Nano emulsion is a most reliable strategy to improve the permeability and it is most effective method or formulation, the best example is nano emulsion of Mupirocin (MUP), it works against living microorganism with improved skin penetrability; the nano emulsion has limitations, regarding the viscosity, spread ability, and retention on the skin. nanoemulgel formulation is the most appropriate strategy to overcome these limitations, faced by the nano emulsion these formulation would improve its pharmacokinetic and physicochemical properties (Alhasso, Ghori, & Conway, 2023)**.**

3.4 Lipophilic drugs

The cell membrane is made up of P.L.L.P means protein lipid -lipid protein layer in this way Lipophilic drugs can be easily unified and the skin penetrability of the united preparations can be improved in numerous way due to the exceptionally dispersed droplets of nano emulsion phase. The Nanoemulgel is an invention related to progress the lipophilic drug in blood enhanced their therapeutic profile. These formulations directly impact the ADME and pharmacodynamic parameter of the fat-soluble drugs and amended meaningfully. A cumulative trend in topical nanoemulgel reduced the patient compliance and improve the better satisfactoriness good therapeutic and safety profile of the preparation, they also escaping the abdominal side effects (Sengupta & Chatterjee, 2017).

3.5 Development of Combined Therapy for Treating Psoriasis

The use of Babchi oil as a formulation constituent in topical methoxsalen formulation allows for extended use and improved penetration of the medication, which results in considerable epidermal effect and improved anti-psoriatic efficacy. Psoralens, or synthetic methoxsalen, and natural Babchi oil have been combined to create nanoemulgel compositions. Zeta potential, mean droplet size, and entrapment efficiency are the properties of prepared nanoemulsions. To create a nanoemulgel, more nanoemulsion formulation(s) were added to the carbopol gel basis in order to further maximize the desired outcome. The produced nanoemulgel formulations underwent analyses for ex vivo skin penetration, pH, drug content determination, spreadability, and viscosity investigations. Nanoemulgel (NG2) demonstrated greater penetration and localized deposition of methoxsalen throughout the skin in ex vivo skin permeation when compared normal gel (Bhardwaj, Gaur, & Tiwari, 2022).

3.6 In vitro and in vivo Evaluation of Anti-Inflammatory agents:

Rheumatoid arthritis is an autoimmune disorder, which essentially means it targets the joints. Nonetheless, every organ system - heart, eyes, skin and whatever else nook or cranny of the body is in range. Rheumatic diseases in the (adult) human are perhaps among some of the most deleterious and debilitating disorders leading to disability, affecting locomotors such as joints etc. These mainly include arthritic group problems. Osteoarthritis and rheumatoid arthritis (RA) indicate classic appearances of these articular issues. Introduction the paramount predominate symptom in Rheumatoid Arthritis (RA), an autoimmune disorder is joint pain which produces limited mobility, lack of sleep/ insomnia especially at night time and, physical disability leading to progressively higher health-related costs ultimately chronic inflammation through life. C. Several pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 are upregulated in RA They need to be targeted biologically in order for active RA to be effectively managed using drugs. Topical drug delivery is the application of a medicine directly to the skin The delivery of fat-soluble drugs is a major drawback associated with gels. The evidence support the studies that nanosized creations can encourage drug delivery by inducing momentary interruption in a highly systematized lipid bilayer structure. A nano emulsion is considered a translucent, temperature sensible, stable and optically isotropic colloidal arrangement having dewdrop size of 20–200 nm. Nano emulsions are

combination the of oils and surface-active agent usually in association with co-surfactants. the main drawbacks thes formulations. are low viscosity and spread ability. The researchers transformed nano emulsion, into nanoemulgel by mixing with gelling agents to overcome the limitation for active topical drug delivery. Nanoemulgel have the characteristics that include staining less , thixotropy, emollient, non-sticky, good spread ability, pleasing appearance and easily removal . Analgesics can be appropriate therapies for the moderation of tenderness and pain in joints, but their obstinate use is connected with numerous toxic effects, non-compliance of the patient and low efficiency. Non-steroidal anti-inflammatory drugs (NSAIDs) are extensively involved in the treatment of rheumatic diseases. The derivative of salicylic acid with extended period incorporated with the NSAID'S for effective trials that accepted to minimize side effects and to avert impairment of the associated organs such as liver & kidney. Local application of DIF as topical agent could be an auspicious technique to reduce the adverse effects related to oral route (Bashir, et al., 2021).

3.7 Chrysin Nanoemulgel for the Treatment of Skin Cancer

The current therapies for skin cancer are ineffective, which poses a significant barrier for the creation of innovative nan ocarriers. Techniques: Using a cutting edge strategy, Because of their systemic adverse effects and low transcutaneous penetration, we created a nanocomplex system made of hydrophobic chrysin dissolved in a lipid mixture and then nano emulsified. The flavone chysin, which is isolated from passion flowers, shows promise as an anti-cancer agent, but its poor solubility limits its application. To determine the optimal self-nanoemulsifying zone, pseudo-ternary phase diagrams were created by adjusting the amounts of oil, Tween 80, Caproyl 90 surfactant, and co-solvent Transcutol HP. Different physicochemical features of nanoemulsifying compositions loaded with chyprin were characterized. Findings: The mean droplet size of this thermodynamically stable, self-emulsifying drug delivery system was 156.9 nm. Currently available treatments for skin cancer are inefficient due to systemic side effects and poor transcutaneous permeation, thereby presenting a formidable challenge for the development of novel nanocarriers. Methods: We opted for a novel approach and formulated a nanocomplex system composed of hydrophobic chrysin dissolved in a lipid mix, which was further nanoemulsified. Chrysin, a flavone extracted from passion flowers, exhibits potential anti-cancer activities; however, it has limited applicability due to its poor solubility. Pseudo-ternary phase diagrams were constructed to identify the best self-nanoemulsifying region by varying the compositions of oil, Caproyl 90 surfactant, Tween 80, and co-solvent Transcutol HP. Chrysin-loaded nanoemulsifying compositions were characterized for various physicochemical properties. Results: This thermodynamically stable, self-emulsifying drug delivery arrangement exhibited a callous bead size of 156.9 nm,

The current therapies for skin cancer are ineffective, which poses a significant barrier for the creation of innovative nan ocarriers. Techniques: Using a cutting-edge strategy,viscosity of 9100 cps upon dispersion in gel and a polydispersity index of 0.26. The gel's mechanical evaluation using the Texture Analyzer revealed that its adhesiveness was 500 g and its hardness was 487 g. Significant improvements in transdermal captivation, as evaluated by flux, the apparent absorbency factor, the steady-state diffusion coefficient, and drug deposition, were seen upon ex vivo permeation through the abdomen skin of rats. A decrease in dosage was ensured by the greatly increased therapeutic efficacy shown in in vitro cytotoxicity on the A375 and SK-MEL-2 cell lines. Using the L929 cell line for biocompatibility testing, the product's safety was determined. In summary: A potential technological option for efficient localized transcutaneous distribution is aqueous, gel-based, topical, nano emulsified chrysin, which will assist lower the frequency and overall dosage utilization and eventually enhance the therapeutic profile (Nagaraja, Basavarajappa, Attimarad, & Pund, 2021).

3.8 Minocycline-Loaded Nanoemulgel for the Treatment of Acne Rosacea

sebum natural procedure of the oil glands present in the epidermal layer of skin is natural moisturiser assistances to preserve the skin saturated. Congestion of the emollient secreters may ultimately develop the skin complaint and polyps. A skin condition acne is a widely chief disorder of hair follicles in the skin. The topical sensory system directed to four major areas involved in disease evolution: at which bacteria are more prone which result inflammatory retort to biological intermediary's transport through the cell membrane. Macrolides, and sodium sulfacetamide are the drug that most widely used in the treatment of acne. In the topical preparation, salicylic acid (0.5 to 2%) used as membrane permeation enhancers. The most commonly prescribed antibiotic agents, are as tetracycline, erythromycin, ampicillin, metronidazole, and minocycline. the use of sunscreens has essential importance to skin. Minocycline nanoemulgel is the best approaches regarded for desired therapeutic effects The As opposed to systemic distribution, the alleged formulation may, as anticipated, improve cutaneous drug absorption, assist in the delivery of poorly lipophilic drugs, increase drug retention duration in the targeted location, and have fewer adverse effects. (Siddiqui, et al., 2022).

3.9 Crisaborole Loaded Nanoemulgel For Atopic Dermatitis

Atopic dermatitis (AD) is a long-term skin irritation that impairs quality of life. CB is a 2% ointment that is marketed as a topical PDE4 inhibitor. However, its solubility in water is low. Because of the improved skin penetration and higher solubility of CB, an o/w nanoemulsion will have a greater therapeutic impact. Patients can apply the nanoemulgel with even greater ease thanks to the addition of a gelling agent. (Kataria, et al., 2023).

4.0 Cumin as Skin Infiltration Enhancer.

Complex mixtures of terpene/terpenoids, phenylpropanoids, and trace amounts of other volatile chemical compounds make up essential oils. The annual perennial plant known as cumin (Cuminum cyminum L.), which comes to the Apiaceae family, can reach an elevation of around 25 cm. Researchers are growing more interested in the use of cumin essential oils due to the chemical makeup of cumin seeds, which are rich in these oils. The oxygenated monoterpenes or

monoterpene hydrocarbons found in the cumin essential oils were the primary cause of the attraction. Terpenes have been demonstrated to be among the safest and most successful. The stratum corneum barrier function, which restricts the penetration of most exogenous substances, makes a very small number of formulations commercially available despite the products' enormous potential for dermal application. Additionally, it is difficult to overcome the epidermis poor permeability. The epidermis increased permeability makes it possible to administer medications via the skin in a secure and effective manner. Many chemical classes have been investigated and studied, including alcohols, azones, chelating agents, essential oils and their components, pyrrolidones, sulphoxides, and surfactants. Nanolipoidal systems are one of the novel and distinctive medication delivery methods. One of the most successful methods of delivering lipophilic active agents among the several nanolipoidal delivery techniques (such as liposomes, solid lipid nanoparticles, nanostructured lipid carriers, microemulsion, and nanoemulsion) is nanoemulsion. A nano-vehicle with excellent transdermal performance, the nanoemulsion may effectively deliver lipophilic compounds to the skin while preserving the constituent components. It can integrate a wide variety of lipophilic elements. A nanoemulsion with a gelling component is called a nanoemulgel. A medication from nanoemulgel can penetrate the skin via both transcellular and paracellular pathways, but a drug from nanoemulsion can only enter the skin via the transcellular route, according to a variety of experimental data about emulgel dosage forms (Morteza-Semnani, et al., 2021).

4.1Nanoemulgel for Nose-to-Brain delivery

The FDA has authorized quetiapine hemifumarate (QF), a second-generation atypical antipsychotic, to treat mental diseases including schizophrenia. QF relates with cytochrome P450 2D6 and catalyzes the breakdown of 7-hydroxyquetiapine, which is then supplementary oxidized by enzyme known as human myeloperoxidase/H2O2 to yield reactive free radicals. QF is very effective against schizophrenia (Li and Cameron, 2012). Leukopenia and thrombocytopenia are caused by these radicals, which also unintentionally lower white blood cell numbers. Only around 9% of QF's current oral tablet formulations have bioavailability, which is quite low (Zhou et al., 2020). In order to keep the medication concentration within the therapeutic window, high dosages and frequent infusions of QF are therefore required. On the other hand, oral QF passes straight through the GI epithelium and into the circulation.

However, because of the BBB's tight connections, parenteral administration appears to be ineffective in increasing enough QF concentrations in the brain. Consequently, it is critical to develop and enhance medication delivery strategies, guaranteeing the site-specific, secure, and effective distribution of QF to desired locations by special administration method. As a result of their ability to facilitate direct therapeutic delivery from the nose to the brain while avoiding the powerful BBB, nose-to-brain administration strategies have garnered significant attention from researchers studying CNS therapies these days (Cunha et al., 2022). In this case, a variety of channels, including the cranial and lymphatic nerve pathways, help carry drugs from the nose to the central nervous system (Gadhave et al., 2022).

Antipsychotics may be successfully transported to the brain through exposed nerve terminals using the intranasal (IN) route (Gadhave et al., 2019b). Additionally, by avoiding enzymatic degradation and first-pass removal, this method enables non-invasive injection and direct CNS distribution (Banks, 2012). It also has some benefits, such as lowering dosage and dose intensity, which improve patient compliance and comfort. Nevertheless, there are several drawbacks to IN administration, such as mucociliary clearance, a defense mechanism that speeds up the removal of applied delivery systems from the nasal cavity quickly (Bhavna et al., 2014). The intranasal route of drug penetration is hindered by these nasal defense mechanisms, which limit the nasal residence duration for administered formulations. In order to get around this problem, mucoadhesive and gel-forming polymers like poloxamer and chitosan can be used (Qu et al., 2021).

4.2 Atorvastatin-Loaded Nanoemulgel on Wound-Healing Efficacy

Inflammation, granulation, and tissue remodelling are all intricate parts of tissue repair and wound healing. It has been demonstrated that atorvastatin (ATR), among other statins, has the ability to enhance the impact of wound healing. (ATR gel, ATR emulgel, and ATR nanoemulgel) were assessed in terms of their ex vivo drug penetration, in vitro drug release, and physical characteristics, including rheological behavior. The developed ATR gel compositions were equivalent and had acceptable physical characteristics. Drugs released from gel, emulgel, and nanoemulgel have different release characteristics. The formulation of ATR into nanoemulgel resulted in a considerable ($p < 0.05$) enhancement in its skin penetration capacity. Studies on in vivo wound healing revealed that the greatest % wound contraction was shown by ATR nanoemulgel. After 21 days of ATR, histopathological evaluation revealed a noticeable improvement in the skin's histological architecture (Morsy, et al., 2019).

4.3 Ebselen nanoemulgel for fungal infection

Fungal infections of the skin, hair, and nails known as superficial mycoses afflict thousands of individuals globally. When treating superficial or systemic fungal infections, emerging resistance to azole antifungals is a typical issue. Organoselenium compound ebselen (EB) has shown encouraging action against pathogenic yeasts. The limited dynamic and kinetic solubility of EB in water significantly restricts the applicability of traditional formulations. The innovative topical EB nanoemulgel for improving permeability and solubility, derived from a saturation solubility analysis. Even at a dose of 100 µM, terbinafine shown little efficacy against Candida albicans and Candida tropicalis, but EB-P demonstrated significant antifungal action at 20 µM. Based on available data, topical EB nanoemulgel appears to be a viable substitute for current candidiasis treatment therapies. (Vartak, Menon, Patki, Billack, & Patel, 2020).

4.4 Capsaicin Nanoemulgel for Diabetic Neuropathy

One of the most common side effects of type 1 diabetes is diabetic somatic neuropathy (T1D). Numerous therapies were looked into in an effort to lessen the agony this disease caused. Naturally occurring lipophilic alkaloid capsaicin has been shown to be a safe and effective therapy for chronic pain conditions.. Marketed conventional topical formulations has limited therapeutic benefits of capsaicin, they have limited bioavailability. It has been hypothesized

The capsaicin nanoemulgel improves its effectiveness against neuropathic pain by increasing skin penetration. Nanoemulsions are created by utilizing the low-energy emulsification technique with co-surfactants such as propylene glycol, ethanol, and isopropyl alcohol, and eucalyptus oil as the oily phase and Tween 80 as a surfactant. Phase diagrams of pseudo-ternaries were created in order to study and improve the formulation. The best formulation was then created as a nanoemulgel and tested for skin penetration using Franz diffusion cells and diabetic neuropathy (DN) treatment using diabetic mice that had been given alloxan. With 0.05% capsaicin, the chosen nanoemulsion is made up of 68% water, 24% surfactant, and 8% oil. Nanosized globules with a comparatively short polydispersity index are its defining characteristic. The nanoemulgel showed a roughly 4-fold rise in capsaicin cumulative permeation relative to the usual gel, and the treated diabetic mice showed an improvement in its antinociceptive qualities. In conclusion, the chosen capsaicin nanoemulgel appears to be a viable transdermal formulation that might potentially relieve T1D patients' diabetic neuropathy. **(Saab, Raafat, & El-Maradny, 2021)**.

4.4Nanoemulgel for the diabetic wound:

The goal of the current study was to create and describe a tocotrienol-rich naringenin nanoemulgel that may be used topically to diabetic chronic wound situations. As time went on, the solubility research was used to determine the segments of the nano emulsion; polymer such as Capryol 90 and tocotrienols as the oil, Solutol HS15, as surfactant and Tanscutol P as cosurfactant, were used in the preparation of nanoemulgel. The technique used to create to achieve the desired globule size, polydispersity index (PDI), zeta potential, viscosity, mucoadhesive stuff, spread ability, in vitro release, and release mechanism of optimized thermodynamically stable nanoemulgel were assessed. Moreover, a rise in the mucoadhesive characteristic of the nanoemulgel correlated with a reduction in the release rate as the concentration of polymers in the gels rose. The nanosized globules of the disseminated stage were uniformly distributed (PDI, 0.452 ± 0.03) in the optimized nanoemulgel (NG1), which had a zetapotential, stickiness, and high spread ability. The in vitro dissolution of naringenin in phosphate buffer saline demonstrated a continuous release profile from the formulated nanoemulgel (NG1) over a 24-hour period, reaching a high of 74.62 ± 4.54%. On the other hand, 89.17 ± 2.87% was released from the nanoemulsion, which might be attributed to the absence of a polymer coating on the scattered oil droplets. Furthermore, the nanoemulgel's in vitro release kinetics adhered to the Higuchi model with non-Fickian diffusion and first-order release. As a result, the research's hopeful findings clearly point to a bright future in **(Yeo, Yew Chieng, Choudhury, Pandey, & Gorain, 2021).**

4.5Thymoquinone Loaded Topical Nanoemulgel for Wound Healing

Natural bioactive thymoquinone has strong therapeutic action against a variety of diseases, including wound healing. Its therapeutic effectiveness is limited by its low skin permeability and poor water solubility. The aim of the present study was to strengthen thymoquinone's biopharmaceutical characteristics in order to increase its epidermal efficacy in injury. Using a high-energy emulsification process, a nano emulsion-based hydrogel scheme was created and described as a nanotechnology-mediated drug delivery strategy to increase the therapeutic effectiveness of thymoquinone. Since black seed oil naturally contains thymoquinone, it was used to increase the created nanoemulsion system's drug loading capability and use ultrasonication to shrink the oil droplet size to less than 100 nm. Thymoquinone nanoemulgel has been demonstrated to exhibit thixotropic and pseudoplastic behavior when applied topically. The comparative analysis of nanoemulgel system demonstrated a significant improvement in skin penetrability, faster, earlier healing in wounded areas, and deposition characteristics following topical administration to the conventional hydrogel system, The healing efficacy was also compared with that of commercially available silver sulfadiazine (1%) cream. The investigation's findings indicate that, in preclinical studies, topical administration of thymoquinone using a nanoemulgel technology speeds up the healing process of wounds. **(Algahtani, Ahmad, Shaikh, Abdel-Wahab, Nourein, & Ahmad, 2021)**.

4.6Glimepiride-Loaded Nanoemulgel

The oral hypoglycemic medication glimepiride (GMP) is widely used in the management of type 2 diabetes. The administration of GMP by transdermal distribution has been extensively studied as a potential substitute for oral administration; nevertheless, the limited solubility and penetration of GMP impede its delivery. In order to improve the hypoglycemic impact, the current study aimed to create a topical nanoemulgel Guanine mono phosphate and report on the solubility improved glimepiride in conjunction with hypoglycemic agent. To create the final nanoemulgel formulations, nanoemulsions including clove oil, was generated. Xanthan gum (3%, w/w) was then used for gelling. Particle size, zeta potential, pH, conductivity, viscosity, and in vitro skin penetration tests were used to assess each formulation. The hypoglycemic action of the in vivo. The outcomes confirmed that, commercially available GMP, the nanoemulgel improved the hypoglycemic efficacy and increased in vitro skin penetration as when compared to pure GMP. topical nano emulsion-based GMP gel are proposed as potential useful substitutes for oral medication in the management of diabetes. **(Razzaq, et al., 2021)**.

4.7Levofloxacin-loaded monoterpene-based nanoemulgel: MRSA ocular infections

The development of novel antimicrobial drugs was required due to the rise of Methicillin-resistant Staphylococcus Aureus (MRSA) strains, which are a major cause of ocular keratitis globally. The main component of the oil produced from citrus peel, known for its antibacterial, antifungal, anticancer, and gastroprotective properties, is d-limonene. Levofloxacin is put into a nanoemulsion made of limonene, Tween®80, and propylene glycol at a ratio of 5:4:1. The physiochemical features of the formed limonene-based nanoemulsion loaded with levofloxacin, such as droplet size, polydispersity index, zeta potential, and in-vitro drug release, were examined, and the stability over a period of three months was evaluated. Additionally, using the biofilm test and killing kinetics of the biofilm-forming MRSA strain, in-vitro antimicrobial susceptibility was examined. Using the HET-CAM test, the in-situ nanoemulgel ocular irritation was investigated. The outcomes showed that limonene-based levofloxacin-loaded
The development of novel antimicrobial drugs was required due to the rise of Methicillin-resistant Staphylococcus Aureus (MRSA) strains, which are a major cause of ocular keratitis globally. The main component of the oil produced from citrus peel, known for its antibacterial, antifungal, anticancer, and gastroprotective properties, is d-limonene. Levofloxacin is put into a nanoemulsion made of limonene, Tween®80, and propylene glycol at a ratio of 5:4:1. The physiochemical features of the formed limonene-based nanoemulsion loaded with levofloxacin, such as droplet size, polydispersity index, zeta potential, and in-vitro drug release, were examined, and the stability over a period of three months was evaluated. Additionally, using the biofilm test and killing kinetics of the biofilm-forming MRSA strain, in-vitro antimicrobial susceptibility was examined. Using the HET-CAM test, the in-situ nanoemulgel ocular irritation was investigated. The results indicated that the limonene-derived loaded with levofloxacin had a particle size of 119 ± 0.321 nm and increased the eradication efficiency of MRSA biofilm; the loaded nanoemulgel's minimum inhibitory concentration (MIC) was 3.12 mg/ml, which was much lower than the drug's MIC of 6.25 mg/ml. Similar to the sodium chloride solution (negative control), which had an irritation score of zero as opposed to 9.87 for the positive irritant group (1%w/v sodium lauryl sulfate), the HET-CAM test revealed no evidence of bleeding, coagulation, or lysis for the loaded nanoemulgel. To sum up, our study established a solid basis for future research on limonene nanoemulgel as a possible adjunctive therapeutic agent for strains of bacteria that are resistant to treatment. **(Mehanna, Mneimneh, & Jalil, 2020)**.

5.0Drawback of Recent Strategies of Nanoemulgel

The permeability of **nanoemulgel** has been enhanced by usage of chemicals and syntheic solvents the is the foremost disadvantage of the recent strategies. These formulation stable for a extensive period would prime to several skin complications as well; countless restrictions postured by the skin, There are certain characteristics in order to be appropriate for the topical route of administration.

Appendices:

Appendix A: Methodological Checklist

[Include descriptive title and relevant content]

Please note that the contents of the manuscript, references, figures, tables, and appendices are placeholders. You should replace them with the actual content and details of your research on nanoemulgel for ocular drug delivery. Make sure to adhere to the submission requirements provided by the Pharmacy Education Journal.

Conclusion:

Nanoemulgel has the potential to revolutionize ocular drug delivery by addressing the limitations of conventional formulations. The integration of nanoemulsions with hydrogel matrices offers enhanced drug bioavailability, sustained release, and improved patient compliance. As researchers continue to refine the formulation and characterization techniques, nanoemulgel holds promise for the effective treatment of various ocular disorders. This innovative approach exemplifies the intersection of nanotechnology and pharmaceutical science, driving advancements in ocular therapy. As we know the conventional preparations have so much disadvantage in their release profile at the target site, limited corneal permeability results ocular residence time become too short that directly affect stability of the preparation. Nanotechnology is the emerging tool to overcome these challenge of the convention prerparation after the comparison the nanoemulgel preparation to the conventional eye preparation they also improve the patient compliance.

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Conflict of Interest:

The authors declare no conflicts of interest related to this work.

References:

1. Algahtani, M. S., Ahmad, M. Z., Shaikh, I. A., Abdel-Wahab, B. A., Nourein, I. H., & Ahmad, J. (2021). Thymoquinone Loaded Topical Nanoemulgel for Wound Healing: Formulation Design and In-Vivo Evaluation. Molecules , 26, 3863.
2. Alhasso, B., Ghori, M. U., & Conway, B. R. (2023). Development of a Nanoemulgel for the Topical Application of Mupirocin. Pharmaceutics , 15, 2387.
3. Almostafa, M. M., Elsewedy, H. S., Shehata, T. M., & Soliman, W. E. (2022). Novel Formulation of Fusidic Acid Incorporated into a Myrrh-Oil-Based Nanoemulgel for the Enhancement of Skin Bacterial Infection Treatment. Gels , 8, 245.

4. Bashir, M., Ahmad, J., Asif, M., Khan, S.-U.-D., Irfan, M., Y Ibrahim, A., et al. (2021). Nanoemulgel, an Innovative Carrier for Diflunisal Topical Delivery with Profound Anti-Inflammatory Effect: in vitro and in vivo Evaluation. International Journal of Nanomedicine , Volume 16, 1457–1472.
5. Bhardwaj, S., Gaur, P. K., & Tiwari, A. (2022). Development of Topical Nanoemulgel Using Combined Therapy for Treating Psoriasis. ASSAY and Drug Development Technologies , 20, 42–54.
6. Cassano, R., Di Gioia, M. L., & Trombino, S. (2021). Gel-Based Materials for Ophthalmic Drug Delivery. Gels , 7, 130.
7. Donthi, M. R., Munnangi, S. R., Krishna, K. V., Saha, R. N., Singhvi, G., & Dubey, S. K. (2023). Nanoemulgel: A Novel Nano Carrier as a Tool for Topical Drug Delivery. Pharmaceutics , 15, 164.
8. Kataria, S., Roy, S., Chaurasia, M., Awasthi, H., Fatima, Z., Prasad, R., et al. (2023). Crisaborole loaded nanoemulgel for the mitigation of atopic dermatitis in mice model. Drug Development and Industrial Pharmacy , 49, 521–535.
9. Konstas, A. G., Schmetterer, L., Katsanos, A., Hutnik, C. M., Holló, G., Quaranta, L., et al. (2020). Dorzolamide/Timolol Fixed Combination: Learning from the Past and Looking Toward the Future. Advances in Therapy , 38, 24–51.
10. Mehanna, M. M., Mneimneh, A. T., & Jalil, K. A. (2020). Levofloxacin-loaded naturally occurring monoterpene-based nanoemulgel: a feasible efficient system to circumvent MRSA ocular infections. Drug Development and Industrial Pharmacy , 46, 1787–1799.
11. Moosa, R. M., Choonara, Y. E., du Toit, L. C., Tomar, L. K., Tyagi, C., Kumar, P., et al. (2014). In vivo evaluation and in-depth pharmaceutical characterization of a rapidly dissolving solid ocular matrix for the topical delivery of timolol maleate in the rabbit eye model. International Journal of Pharmaceutics , 466, 296–306.
12. Morsy, Abdel-Latif, Nair, Venugopala, Ahmed, Elsewedy, et al. (2019). Preparation and Evaluation of Atorvastatin-Loaded Nanoemulgel on Wound-Healing Efficacy. Pharmaceutics , 11, 609.
13. Morteza-Semnani, K., Saeedi, M., Akbari, J., Eghbali, M., Babaei, A., Hashemi, S. M., et al. (2021). Development of a novel nanoemulgel formulation containing cumin essential oil as skin permeation enhancer. Drug Delivery and Translational Research , 12, 1455–1465.
14. Nagaraja, S., Basavarajappa, G. M., Attimarad, M., & Pund, S. (2021). Topical Nanoemulgel for the Treatment of Skin Cancer: Proof-of-Technology. Pharmaceutics , 13, 902.
15. Ni, X., Guo, Q., Zou, Y., Xuan, Y., Mohammad, I. S., Ding, Q., et al. (2020). Preparation and characterization of bear bile-loaded pH sensitive in-situ gel eye drops for ocular drug delivery. Iranian Journal of Basic Medical Sciences , 23.
16. Qamar, Z., Qizilbash, F. F., Iqubal, M. K., Ali, A., Narang, J. K., Ali, J., et al. (2020). Nano-Based Drug Delivery System: Recent Strategies for the Treatment of Ocular Disease and Future Perspective. Recent Patents on Drug Delivery & Formulation , 13, 246–254.
17. Razzaq, F. A., Asif, M., Asghar, S., Iqbal, M. S., Khan, I. U., Khan, S.-U.-D., et al. (2021). Glimepiride-Loaded Nanoemulgel; Development, In Vitro Characterization, Ex Vivo Permeation and In Vivo Antidiabetic Evaluation. Cells , 10, 2404.
18. Rizg, W. Y., Hosny, K. M., Mahmoud, S. S., Kammoun, A. K., Alamoudi, A. J., Tayeb, H. H., et al. (2022). Repurposing Lovastatin Cytotoxicity against the Tongue Carcinoma HSC3 Cell Line Using a Eucalyptus Oil-Based Nanoemulgel Carrier. Gels , 8, 176.
19. Saab, M., Raafat, K., & El-Maradny, H. (2021, October). Transdermal Delivery of Capsaicin Nanoemulgel: Optimization, Skin Permeation and in Vivo Activity Against Diabetic Neuropathy. Advanced Pharmaceutical Bulletin .
20. Sengupta, P., & Chatterjee, B. (2017). Potential and future scope of nanoemulgel formulation for topical delivery of lipophilic drugs. International Journal of Pharmaceutics , 526, 353–365.
21. Siddiqui, A., Jain, P., Alex, T. S., Ali, M. A., Hassan, N., Haneef, J., et al. (2022). Investigation of a Minocycline-Loaded Nanoemulgel for the Treatment of Acne Rosacea. Pharmaceutics , 14, 2322.
22. Taha, M., Alhakamy, N. A., Md, S., Ahmad, M. Z., Rizwanullah, M., Fatima, S., et al. (2022). Nanogels as Potential Delivery Vehicles in Improving the Therapeutic Efficacy of Phytopharmaceuticals. Polymers , 14, 4141.
23. Tan, A. Y., LeVatte, T. L., Archibald, M. L., Tremblay, F., Kelly, M. E., & Chauhan, B. C. (2002). Timolol Concentrations in Rat Ocular Tissues and Plasma After Topical and Intraperitoneal Dosing. Journal of Glaucoma , 11, 134–142.
24. Thrimawithana, T. R., Young, S., Bunt, C. R., Green, C., & Alany, R. G. (2011). Drug delivery to the posterior segment of the eye. Drug Discovery Today , 16, 270–277.
25. Vartak, R., Menon, S., Patki, M., Billack, B., & Patel, K. (2020). Ebselen nanoemulgel for the treatment of topical fungal infection. European Journal of Pharmaceutical Sciences , 148, 105323.
26. Wei, D., Pu, N., Li, S.-Y., Wang, Y.-G., & Tao, Y. (2023). Application of iontophoresis in ophthalmic practice: an innovative strategy to deliver drugs into the eye. Drug Delivery , 30.
27. Yeo, E., Yew Chieng, C. J., Choudhury, H., Pandey, M., & Gorain, B. (2021). Tocotrienols-rich naringenin nanoemulgel for the management of diabetic wound: Fabrication, characterization and comparative in vitro evaluations. Current Research in Pharmacology and Drug Discovery , 2, 100019.