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Review Article

Insights of Nanoemulsion as a Drug Delivery System: An Overview of Current Trends and Applications

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ABSTRACT

The ability of nanoemulsion to improve the solubility, bioavailability and stability of weakly water-soluble drugs has emerged their roles as promising drug delivery systems. Nanoemulsion is advanced colloidal systems made up of nanometer-sized droplets (usually 20-200 nm) scattered in two immiscible liquids and stabilized by surfactant. It offers a flexible substrate for enclosing both hydrophobic and hydrophilic medications. Owing to the tiny droplet size, there is more surface area available for absorption and more precise distribution to particular tissues or cells. Accordingly, nanoemulsion has drawn a lot of attention in a variety of industries, including medicine, cosmetics, food and agriculture. Its application in medical field includes drug delivery, drug administration and vaccine formulation. Nevertheless their benefits, some concerns may represent obstacles that hinder their applications such as formulation complexity, stability issues and industrial production scale-up. To get beyond these hurdles and completely realize the potential of nanoemulsion in commercial and therapeutic applications, more research and innovation are needed.

Keywords: Nanoemulsion, Formulations, Characteristic, Drug delivery, Application.

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INTRODUCTION

This review will go through different aspects of nanoemulsion, with an emphasis on their properties, applications and potential future scenes. It will give a thorough grasp of the state of nanoemulsion technology today and its prospective applications in various industries. The potentials and benefits of nanoemulsion over conventional formulations make them a promising tool for delivering medications.[1] They are colloidal dispersions of two immiscible liquids, usually water and oil, stabilized by surfactants and sometimes co-surfactant.[2-4] Remarkably, different types of nanoemulsion are available, oil-in-water, water-in-oil and bi-continuous nanoemulsion.[5,6] Oil-in-Water (O/W) nanoemulsion is composed of small oil droplets scattered in a continuous water phase. Frequently, this type is employed to deliver hydrophobic medications in watery settings. On the other side, Water-in-Oil (W/O) nanoemulsion is a continuous oil phase with tiny water droplets scattered throughout. Frequently, it utilized for hydrophilic medications in oil-based media and in topical preparations. Furthermore, other type is the bi-continuous nanoemulsion, in which the two phases; oil and water phases are combined to form linked networks.[7,8] However, this type is less prevalent yet still helpful in some cases.

Historical Overview for Nanoemulsion Development

Technological developments in drug delivery, chemistry of surfactant and colloidal science have all contributed to the development of nanoemulsion.[9] In brief, this is an outline of the past:

Fundamental of Emulsion Science: Early 20th Century

In the early 1900s, the bases of emulsion fabrication, stability and applications were investigated by scientists. They started examining emulsions, which are mixtures of two immiscible liquids in which one liquid is spread into the other.[10] The role of surfactants in decreasing the interfacial tension to stabilize emulsions was investigated. All these preliminary investigations helped in finding ways for how to develop emulsions and maintain them stable.[11]

Advances in Microemulsion Technology: Mid 20th Century

The idea of thermodynamically stable emulsions with droplet sizes in a nanometer range, namely; microemulsion was first proposed in the mid of the 20th Century.[12] Researchers commenced investigating their capability to dissolve hydrophobic materials. The pharmaceutical industry used emulsions and microemulsion in the development of medications for drug delivery, especially

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those that are poorly soluble in water.[13,14] On the other hand, the stability of microemulsion formulations presented certain challenges.[15]

Development of Nanoemulsion: Late 20th Century

During the end of 20th Century, developments in colloidal science gave rise to the creation of nanoemulsion, which are emulsions with droplet sizes most commonly ranging from 20 to 200 nanometers.[16,17] The fact that these are kinetically stable but not thermodynamically stable differentiates them from microemulsion.[18] Various preparation techniques have been developed for the preparation of nanoemulsion.[1,16,19] High-pressure homogenization, ultrasonic emulsification and microfluidization are some of these new techniques.[20-25] These methods helped to create nanoemulsion that were more stable and had more consistent droplet sizes. Researchers recognized various applications for nanoemulsion, mostly in the food, cosmetics and drug delivery sectors.[16,26-29] It is highly documented that nanoemulsion can protect sensitive chemicals and increases the drug bioavailability.[30,31]

Scientific and Technological Developments: Early 21st Century

The development and utilization of nanoemulsion has been grown significantly as a result of the integration of nanotechnology with emulsion science.[32,33] The processes controlling drug delivery effectiveness and nanoemulsion stability started to be clearer to researchers. Concerning with pharmaceuticals and cosmetics, regulatory agencies began to put criteria for the assessment and approval of nanoemulsion based products.[34,35]

Recent Developments: Commercialization and Innovation

Novel nanoemulsion formulations were recently designed for particular uses.[36,37] Targeted drug delivery systems and innovative skincare products, have been developed in recent years.[27] Additionally, various commercial nanoemulsion based products have made their way onto the market in a number of industries.[38] It can be found in food sectors (such as enriched beverages), cosmetics (such as anti-aging products) and medicines (such as intravenous formulations).[39-45] New techniques for developing and stabilizing nanoemulsion, as well as their possible applications in various fields including environmental science and agriculture, are still being investigated.[46]

Characteristics and Key Considerations in Nanoemulsion

The distinct properties of nanoemulsion reflect their performance and suitability for various applications. To optimize nanoemulsion for particular applications, it is essential to understand their properties. The followings are the principal characteristics that describe nanoemulsion:

Optical features

Owing to the small particle size of nanoemulsion, it seems to be transparent or translucent, which is much recommended for cosmetics and pharmaceutical preparations.[44] Additionally, the way of light interaction with the nanoscale droplets can change how the nanoemulsion looks, which is very crucial property for applications.

Droplet size and distribution

The normal range of droplet sizes for nanoemulsion is 20-500 nanometers.[47-49] The high surface area-to-volume ratio produced by the small droplet size improves the interaction between the nanoemulsion and biological membranes, enhancing the absorption and bioavailability of the materials that are entrapped.[3] Actually, reduced droplet size results in enhanced drug solubility, increased stability and frequently, enhanced emulsion clarity or transparency.[50] Moreover, the risk of phase separation can be decreased and consistent performance is enhanced by uniform droplet sizes.[51] Regarding the distribution of droplet sizes within the nanoemulsion, it can be evaluated through measuring the Polydispersity Index (PDI). A smaller value of PDI (closer to 0) usually is more preferable since it points toward a uniform distribution, which provides an indication for better stability and efficacy.[52]

Stability

In contrast to microemulsions, nanoemulsion are not thermodynamically stable, but they are kinetically stable.[16] This means that they do not gradually split into different phases. Certain factors can affect the stability and help to avoid aggregation and coalescence.[53] Adequate surfactant concentration is an essential factor to avoid droplet coalescence and keep the nanoemulsion stable.[49] Another factor is Zeta Potential, which emphasize the stability by measuring the electric charge at the droplet surface. Stronger repulsion between droplets is indicated by higher absolute values of zeta potential, which can be either positive or negative value and this will decrease the possibility of aggregation.[54,55] Furthermore, nanoemulsion can become unstable due to Ostwald ripening phenomena. In that case, smaller droplets dissolve and re-deposit onto larger ones. Adding stabilizers or employing oils with poor water solubility can alleviate this problem.[56] Environmental factors, mainly; temperature, pH and ionic strength can greatly influence the stability of nanoemulsion. Investigating the formulation's stability under different environmental conditions is essential. Certain additives, including; co-surfactants, polymers, or other stabilizers can be used to improve the stability of nanoemulsion.[16] These additives can add more steric or electrostatic barriers to the formulation to prevent coalescence.

In order to check stability of nanoemulsion, shelf-life study is employed in which several parameters can be evaluated over time

to assess their stability when kept under normal conditions.[57] Moreover, accelerated stability test can be performed to predict long-term stability in which nanoemulsion is kept under extreme conditions, mainly; high temperature and humidity.

Viscosity and Rheology

Viscosity is very essential parameter since it influences the flow properties and spreadability of the nanoemulsion. When compared to conventional emulsions, nanoemulsion often has a higher viscosity, which facilitates its application.[58] Generally, in oral and injectable formulations, lower viscosity is frequently preferable; nevertheless, for prolonged release in topical applications, a higher viscosity may be desirable. Viscosity is determined utilizing instruments such as rheometers and viscometers, which can reveal information about the flow properties of the nanoemulsion in different conditions.[59] Concerning with rheology, it is the study of material flow and deformation behavior. It includes characteristics such as viscosity, elasticity and plasticity in nanoemulsion. The rheological behavior of nanoemulsion affects how it is handled and applied.[60]

Surface tension

Surface tension is the force that acts to minimize the surface area of the liquid by acting on its surface. Surfactants help to form small droplets in nanoemulsion by reducing the surface tension between the water and oil phases.[49] Subsequently, it lessens the tendency for coalescence, which adds to the stability of the droplets. Measuring surface tension using a tensiometer is a common method of evaluating the performance of surfactants in the nanoemulsion formulation.[61] Producing nano-sized droplets requires an efficient surface tension reduction.

Advantages of Nanoemulsion in Drug Delivery

Lately, nanoemulsion are extensively used and applied in various fields especially in the food industry, cosmetics and drug delivery sectors owing to their several advantages as shown in Figure 1.

Long-term Stability

The practical application of nanoemulsion is heavily influenced by their long-term stability. The term "stability" describes the capability of nanoemulsion to keep its initial properties like appearance, droplet size, distribution and efficacy over a prolonged period of time under diverse storage conditions. Generally, nanoemulsion exhibit kinetic stability due to the small droplet size and the use of suitable surfactants, which provides resistance to phase separation and droplet coalescence over an extended period of time.[16] An outline of the variables influencing long-term stability and methods to improve it is provided below:

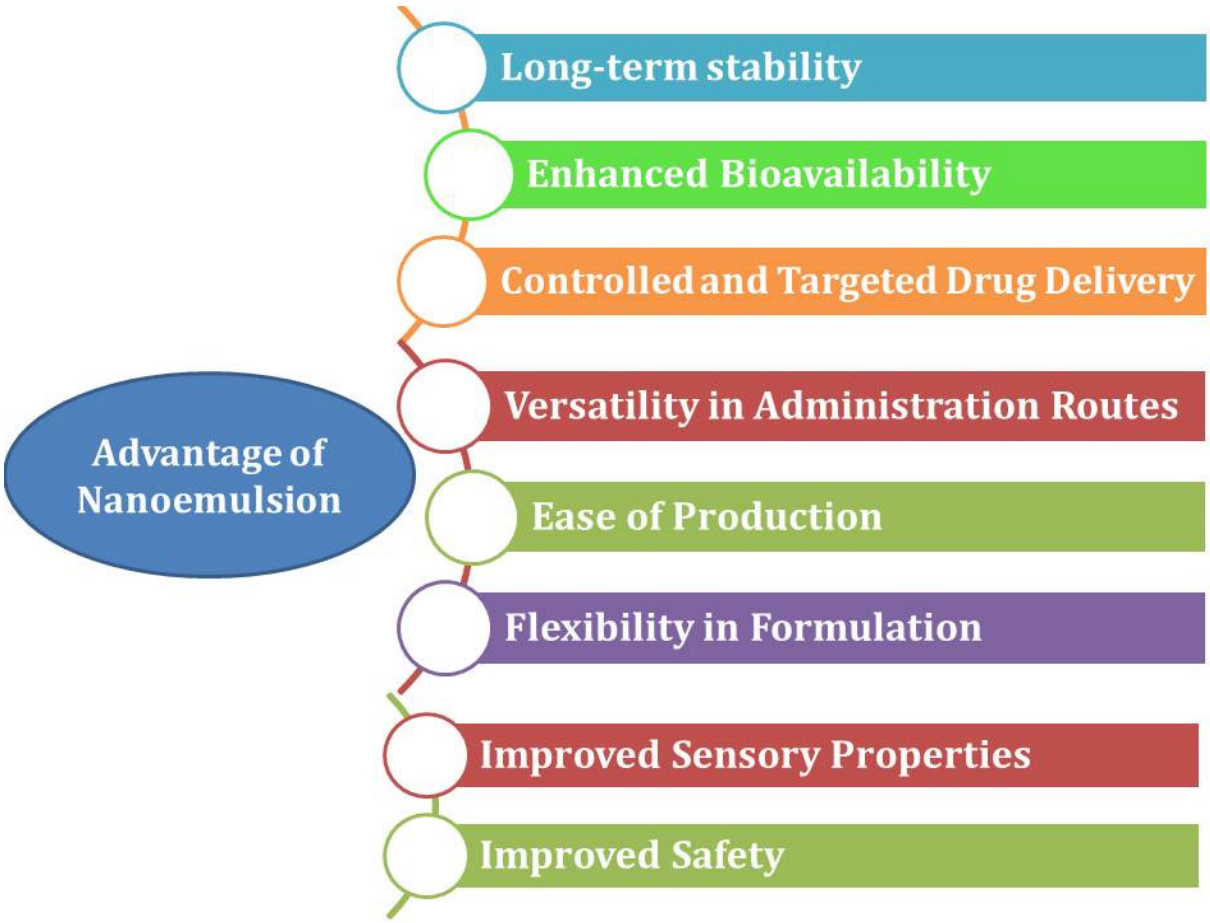

Figure 1: Illustrative chart displaying the advantages of Nanoemulsion.

The small droplet size which is characteristic for nanoemulsion helps to offer more stability and less likely to cream or sediment because they are subject to less gravitational stress.[44]

Stability depends on a uniform droplet size distribution, which is shown by a low PDI. Greater probability of larger droplets coalescing or smaller droplets going through Ostwald ripening could result from a higher PDI.[62] By minimizing Ostwald ripening, the formulation can be made more stable over time with a uniform droplet size distribution in the nanoemulsion.[63]

Surfactants are essential for stabilizing nanoemulsion because they lessen the interfacial tension between the water and oil phases.[49] Stability is influenced by surfactant type and concentration; to avoid droplet coalescence and keep stability over time, an ideal concentration is required.

The repulsion between droplets is influenced by zeta potential, which is a measurement of the electrical charge on the droplet surface. Stability is improved by a high absolute value of zeta potential, either positive or negative, which inhibits aggregation and coalescence. As the zeta potential becomes closer to zero, there may be less electrostatic repulsion between the droplets, which could result in phase separation and decreased stability.[64]

Temperature variations have an impact in the viscosity, surfactant solubility and Ostwald ripening rate. Instability can result from droplet coalescence accelerating at high temperatures.[65]

The charge on the droplets can change due to changes in pH or ionic strength, which could destabilize the nanoemulsion.[66]

Strategies to Improve Long-Term Stability

Selecting the Component of the Formulation

Selecting the appropriate surfactant and co-surfactant can greatly improve the stability of nanoemulsion. Steric and electrostatic stabilization can be achieved by using different surfactant combinations.[67]

By reducing Ostwald ripening and increasing stability, oils with limited solubility in the aqueous phase can be used. The active ingredient's compatibility and the intended stability profile should be taken into consideration when selecting the oil phase.

Utilization of Stabilizers

The steric stability can be obtained upon adding polymers and polyelectrolytes since they can stop droplet aggregation and coalescence.[68] These stabilizers encircle the droplets in a protective layer, improving the long-term stability.

To keep the stability and efficacy of the nanoemulsion that are prone to oxidation, antioxidants can be added to stop the deterioration of the oil phase and active components.[69]

Controlling the Environmental Conditions

Instability of nanoemulsion that caused by temperature variations can be avoided by storing nanoemulsion at specific temperatures, usually in a cool, dry location.[70]

To further improve the stability of nanoemulsion, choose packaging materials that are suitable for protecting against light, air and moisture.[71]

Enhanced Bioavailability

The ability of nanoemulsion to increase the bioavailability of Active Pharmaceutical Ingredients (APIs), especially those that are poorly water-soluble, is one of the most important benefits of using them in drug administration. The percentage of drug that reaches the bloodstream upon introduction to the body and is thereafter available for therapeutic effect is referred to as bioavailability. Nanoemulsion increase bioavailability in a number of ways:[72]

The problem with hydrophobic medications is their poor solubility in water, which restricts their ability to be absorbed when taken orally or through other ways. A drug's efficacy is typically decreased by poor bioavailability resulting from low solubility. The role of nanoemulsion is to effectively solubilize hydrophobic drugs in an aqueous phase by enclosing them within their oil phase. This solubilization increases the drug's bioavailability by facilitating improved drug absorption in the gastrointestinal system or across other biological membranes.[73]

Nanoemulsion' small size and lipid-based structure make it easier for them to pass through biological membranes. This is especially helpful for drugs that have to pass through cellular barriers such as the blood-brain barrier, the intestinal epithelium, or other barriers.[27] Improved permeability and consequent bioavailability are advantages of using nanoemulsion in many routes of administration, such as oral, topical, intravenous and others.

The high surface area-to-volume ratio of nanoemulsion is caused by their incredibly small droplet sizes. The drug can make more extensive contact with the absorption sites, like the mucosal lining of the gastrointestinal tract if it possesses large surface area. Furthermore, the drug is able to enter the bloodstream more rapidly and effectively due to the increased surface area, which speeds up the dissolving and absorption processes.[74]

Difficult gastrointestinal conditions, which include an acidic pH and enzymes, can affect the stability of formulations. Therefore, nanoemulsion can protect encapsulated drugs from breaking down by ensuring that a larger percentage of the drug is preserved and ready for absorption, this protection increases the drug's bioavailability.

Oral Administration: Medications taken orally frequently go through first-pass metabolism, where a substantial amount of the medication may be broken down before entering the

bloodstream. As a result, the bioavailability of the drug is decreased. Nanoemulsion can be absorbed via the lymphatic system, bypassing the liver's first-pass metabolism. This route of absorption permits a greater amount of the medication to enter the systemic circulation unaltered and consequently, the bioavailability can be increased.[75]

The greater surface area, higher permeability and improved solubilization of nanoemulsion all help to speed up the absorption of drugs and the therapeutic impact will be fast as well.

Lower doses may be needed to produce the intended therapeutic effect since nanoemulsion can greatly increase a drug's bioavailability. By lowering the dose, you can reduce the possibility of side effects and increase patient compliance.[76]

Controlled and Targeted Drug Delivery

The controlled and targeted drug delivery is greatly enhanced by nanoemulsion, which makes them a desirable platform for pharmaceutical research. Controlled release of drugs is likely to formulate nanoemulsion so that drugs are released progressively over time, providing a sustained therapeutic influence. A consistent concentration of the medication in the bloodstream or at the target site can be achieved by slowing down the release of the drug as a result of the small droplet sizes or by using particular surfactants or polymers.[77]

The medication is protected from enzymatic breakdown and other metabolic processes by being encapsulated in the oil phase of a nanoemulsion. This encapsulation contributes to the drug's prolonged duration of action.[44] Controlled drug release offers a decrease in dosing frequency, which can improve patient compliance and provide more convenient treatment plans.

The Enhanced Permeability and Retention (EPR) effect is a phenomenon that nanoemulsion can take advantage of in order to achieve targeted drug delivery.[78] EPR effect occurs when molecules preferentially gather in inflammatory or tumorous areas because they have leaky vasculatures. This passive targeting allows for higher drug concentrations at the target site while minimizing exposure to healthy tissues. Cancer cells, which are the target sites, can undergo modification in their surfaces with ligands, antibodies, or peptides that attach to their receptors. Active targeting ensures that therapeutic medicines are delivered exactly to the target site.[79]

Versatility in Administration Routes

Ability of nanoemulsion to be administered through a variety of routes is one of its main advantages; this allows them to be used to deliver a wide range of therapeutic substances through different routes. Because of its adaptability, nanoemulsion can be applied in a variety of medical and cosmetic settings, which enhances patient compliance and treatment results. An outline of the benefits of nanoemulsion for various delivery methods is provided below:

Oral delivery: Nanoemulsion can increase the oral bioavailability of drugs by increasing the solubility and stability of poorly soluble medications in the gastrointestinal tract.[72]

Topical and transdermal delivery: Nanoemulsion are perfect for topical and transdermal applications because they can improve the active components' penetration into the skin. They are effective in delivering both lipophilic and hydrophilic medications.[44]

Intravenous delivery: Hydrophobic medications can be more safely and effectively delivered systemically when administered intravenously owing to the suitability of nanoemulsion for intravenous administration.[80]

Pulmonary delivery: Aerosolized nanoemulsion can be inhaled to deliver medication straight to the lungs. Treatment for respiratory diseases such lung infections, asthma and Chronic Obstructive Pulmonary Disease (COPD) is especially successful with this approach. Pulmonary nanoemulsion lowers the possibility of adverse reactions via achieving high local concentrations with less systemic exposure. Additionally, patients are more likely to stick to their treatment plans using pulmonary administration since it is non-invasive and simple to be utilized using nebulizers or inhalers.[81] In addition to, intranasal drug delivery, which depends on administering the medication through the nasal cavity

Ease of Production

One of the main benefits of nanoemulsion is their simplicity of production. Scalable techniques can be used to create nanoemulsion, including; High-pressure homogenization, microfluidization and ultrasonic emulsification. Both large-scale industrial manufacturing and small-scale laboratory production are suitable applications for these techniques.[1] Stable nanoemulsion may be produced with comparatively easy and affordable methods, which make them a desirable choice for commercial applications.

Flexibility in Formulation

A variety of active components, from small molecules to big macromolecules like proteins and nucleic acids, can be encapsulated in nanoemulsion. Owing to the flexibility of nanoemulsion, unique formulas for particular purposes can be created. By co-encapsulating many drugs or active substances, nanoemulsion can be used to create multipurpose products and combination therapies.[82]

Improved Sensory Properties

Nanoemulsion can be transparent or translucent due to their small droplet size, which is desirable for a more appealing appearance in pharmaceutical and cosmetic products. In topical formulations like lotions and creams, a smooth, non-greasy

texture is often appreciated and nanoemulsion can deliver such characters.[83]

Improved Safety

Compared to conventional emulsions or other drug delivery systems, nanoemulsion considered to be less irritant, which makes them appropriate for sensitive skin or mucosal tissues. A lot of nanoemulsion formulations make use of non-toxic and biocompatible components, which lowers the possibility of negative responses and makes them safer to use in cosmetic and pharmaceutical products.[84]

Applications of Nanoemulsion in Drug Delivery

Nanoemulsion has shown significant attention in the field of drug delivery attributable to their distinctive physicochemical properties, adaptability and versatility. As nanoemulsion can increase the solubility, stability and bioavailability of medicinal drugs, they have become a vital drug delivery platform. Therefore, they can be utilized to treat a variety of illnesses and ailments using a variety of delivery methods. They can be administered through a variety of routes, including oral, topical, intravenous, pulmonary, ophthalmic and intranasal.[85] By utilizing the advantages of nanoemulsion, every approach can improve treatment results, via controlled release, targeted administration, or better drug absorption. Furthermore, biocompatibility and safety of nanoemulsion make them appropriate for a variety of medicinal uses, such as vaccine delivery and cancer therapy.[86] The following are some significant applications of nanoemulsion in drug delivery.

Oral Drug Delivery

Nanoemulsion improves the oral bioavailability of poorly water-soluble pharmaceuticals by increasing the solubility of these drugs and encouraging their absorption in the gastrointestinal tract.[87] For instance, paclitaxel and cyclosporine have been shown to have better absorption when administered in nanoemulsion form.[88] Nanoemulsion can increase the amount of medication that reaches the bloodstream and protect them against degradation, by shielding from the harsh, acidic stomach environment. This is especially advantageous for medications that are susceptible to enzyme breakdown or pH variations. Table 1 illustrates different nanoemulsion formulations used for oral delivery of different drugs and their key findings.

Topical and Transdermal Drug Delivery

Nanoemulsion has emerged as a crucial technique in topical and transdermal drug administration since they can deliver therapeutic agents in a regulated manner. They are incredibly effective in delivering medications through the skin as a result of their small droplet size, which promotes stratum corneum penetration.[44] Actually, the stratum corneum represent skin's outermost layer that serves as a significant barrier to drug penetration. Because of their small droplet size and large surface area, nanoemulsion can break down the stratum corneum's lipid bilayers, which allow medications to penetrate deeper layers of the skin. Acne, eczema, psoriasis and fungal infections can all be effectively treated with this improved penetration. Nanoemulsion is very effective in delivering hydrophobic (lipophilic) medications. These medications can be efficiently applied to the skin by encapsulating them in to the oily phase of the nanoemulsion, which enhances therapeutic results.

Drugs can be included into nanoemulsion and being released gradually over time, ensuring a long-lasting therapeutic impact.[98] Therefore, it lowers the frequency of application and enhances patient compliance, especially in chronic illnesses where sustained medication action is necessary. The controlled release nanoemulsion helps to minimize the possibility of systemic or local adverse effects that are frequently related to topical formulations, helping to keep drug concentrations within the therapeutic window. Additionally, volatile substances such as essential oils that are frequently utilized in cosmetic and certain medicinal products can be effectively encapsulated and stabilized by nanoemulsion.[99] Therapeutically, antibiotics, antifungals and corticosteroids can be delivered via nanoemulsion to treat a variety of skin conditions. Further, they can be utilized in cosmetic treatments that have anti-aging and moisturizing properties, as well as in the delivery of medications for ailments like fungus infections, psoriasis and acne. Table 2 displays different nanoemulsion formulations used for topical and transdermal delivery of different drugs.

Intravenous Drug Delivery

Intravenous (IV) drug delivery using nanoemulsion has shown great promise due to its great benefits over conventional formulations. Their capacity to encapsulate hydrophobic medications, improve drug stability and offer controlled release makes them especially well-suited for intravenous systemic administration.[27] An outline of the advantages and uses of nanoemulsion in intravenous medication delivery is provided below:

Encapsulation of Hydrophobic Drugs

The solubility of hydrophobic medicines is one of the main issues with intravenous medication delivery. These medications can be encapsulated in their oil phase by nanoemulsion, which can convert poorly soluble substances into IV administration-ready formulations. This increases the bioavailability of medications that would be challenging to systemic delivery. Concerning with the conventional IV formulations, they necessitate the use of organic solvents in order to dissolve hydrophobic medications, which can be hazardous and cause unfavorable reactions. Such solvents are not required in case of nanoemulsion, providing a safer option for drug administration.[107]

Table 1: Formulation components, biological activity and key findings for Oral Nanoemulsion.

Formulation component	Biological action	Particle size (nm)	Key findings	Reference
Docetaxel and cyclosporine	Antitumor activity	30 nm	Self-nanoemulsifying drug delivery system effectively co-incorporated Docetaxel and cyclosporine. The intestinal permeability of Docetaxel was improved. It had an oral bioavailability 9.2-fold higher if compared to Docetaxel solution. It demonstrated an impressive antitumor effect with less toxicity.	89
Pioglitazone and *Nigella sativa*	Hypoglycemic activity	167.1 nm	The study revealed that Pioglitazone loaded nanoemulsion showed good stability and suitable characterizations. It also revealed a noteworthy drop in blood sugar, supporting the prospective utility of nanoemulsion as drug nanocarriers.	90
Low molecular weight heparin	Anticoagulant activity	Below 150 nm	Different types of nanoemulsion for oral delivery of low molecular weight heparin (LMWH) were developed. It was found that nanoemulsion increase the oral bioavailability of low molecular weight heparin more effectively than by biodegradable formulations.	91
Mebudipine, ethyle oleate and ethanol	Antihypertensive activity	22.8 nm	The study revealed that nanoemulsion could effectively improve the oral bioavailability of Mebudipine. The usage of nanoemulsion was found to potentially lower the dosage required for clinical research.	92
Candesartan cilexetil and Cinnamon oil	Angiotensin II type-1 receptor blocker	24- 39 nm	The outcomes of the study showed that nanoemulsion is an ideal method for enhancing solubility and dissolution of candesartan. Compared to conventional dosage forms and due to the high physiochemical stability of nanoemulsion, this drug delivery system has shown promise in addressing issues related to chronic cardiovascular illnesses.	93
Letrozole, Peppermint oil and Castor oil	Anticancer activity	80 nm	The study showed that the developed nanoemulsion demonstrated a noteworthy rise in Letrozole solubility as compared to the commercially available traditional tablet dose form.	94
Hesperetin, Medium chain triglycerides and castor oil	Antioxidant effects, anti-inflammatory and anti-aging.	100 nm	Nanoemulsion formulation presents a sustainable approach for increasing the bioavailability of hesperetin.	95
Ramipril and castor oil	Antihypertensive drug.	80.9 nm	The study revealed significantly greater extent of absorption than the conventional capsule formulation. It demonstrated how to improve the formulation of nanoemulsion for the delivery of hydrophobic drugs.	96
Diclofenac and sesame oil	Anti-inflammatory and analgesics.	122 nm	The results indicate that diclofenac-loaded nanoemulsion may be used as a possible medication delivery method to treat and manage inflammatory conditions and reduce pain.	97

Reduced Systemic Toxicity

Nanoemulsion can be designed to target specific organs, decreasing the amount of medication that is exposed to non-target tissues. This strategy reduces systemic adverse effects and raises the therapeutic index of the drug. It was documented that adding ligands to the surface of nanoemulsion can target cancer cells while avoiding healthy tissues.[86]

Applications in Cancer Therapy

An extensive research has been done on the use of nanoemulsion in the administration of chemotherapeutic medications such as docetaxel, doxorubicin and paclitaxel. These medications are frequently hydrophobic and have a high potential for toxicity. Loading them in a nanoemulsion form will increase their solubility, boost therapeutic efficacy and lessen side effects. Additionally, combination therapy can be utilized owing to the

ability of nanoemulsion to co-encapsulate numerous medications. This is especially helpful for treating cancer, as several pathways involved in tumor growth and resistance can be targeted by delivering diverse therapeutic drugs at the same time.[108]

Controlled and Sustained Release

When drug is formulated in the form of nanoemulsion, it can be maintained in the bloodstream to release the drug gradually. For long-term therapy or chronic illnesses in particular, this regulated release minimizes the need for frequent dosing and sustains therapeutic drug concentrations for extended periods of time. Table 3 demonstrated different nanoemulsion preparations applied for Intravenous delivery of different drugs.[98]

Pulmonary Drug Delivery

Nanoemulsion has demonstrated great promise, providing a new method for treating respiratory conditions and inhaling systemic medications.[116] Because of their small droplet size and special qualities, nanoemulsion are especially well-suited for targeting the lungs, resulting in more effective drug delivery and better therapeutic effects.

Nanoemulsion' droplet sizes can be carefully adjusted to lie between the ideal ranges for deep lung deposition. Because of this, the medication can enter the alveoli and be absorbed into the bloodstream, which makes nanoemulsion useful for both local and systemic drug administration.

By extending the period that drugs remain in the lungs, nanoemulsion can provide a longer duration of exposure to the therapeutic agent. This is especially helpful when treating long-term respiratory conditions, as sustained release drugs.

Nanoemulsion was proved to be useful for treating localized respiratory disorders including cystic fibrosis, asthma and Chronic Obstructive Pulmonary Disease (COPD).[117] Nanoemulsion can limit systemic side effects and lower the required dose by delivering the medicine directly to the site of action, hence increasing patient safety.

Table 2: Formulation components, biological activity and key findings for topical and Transdermal Nanoemulsion.

Formulation component	Biological action	Particle size (nm)	Key findings	Reference
Imiquimod, oleic acid and rose oil	Skin anticancer activity	152- 470 nm	The study demonstrated the possible utilization of Imiquimod in nanoemulsion form as a skin cancer prevention tool. Drug release was greatly enhanced by nanoemulsion. This new strategy has been validated to be a potential carrier for the topical delivery of Imiquimod.	100
Amphotericin B	Antifungal activity	112- 174 nm	The goal of this study was to create an Amphotericin B nanoemulsion formulation for the treatment of cutaneous candidiasis. The findings indicated that the nanoemulsion might be the best therapeutic option for treating fungal infections.	101
Meloxicam and abrafil® 1944 CS	Treating osteoarthritis and rheumatoid arthritis	60 nm	The goal of this study is to prepare a nanoemulsion to deliver meloxicam transdermally. The produced nanoemulsion exhibited a potential for enhancing meloxicam's transdermal efficacy in the treatment of osteoarthritis, rheumatoid arthritis and other joint conditions.	102
Carvedilol and Oleic acid	Analgesic activity	39.5 nm	The findings suggest that nanoemulsion can be employed as a possible vehicle for enhancing carvedilol transdermal delivery.	103
Soft extract of stem bark of *Rapanea ferruginea*	Anti-inflammatory activity	57 nm	The developed nanoemulsion demonstrated appropriate characteristics as a vehicle for applying *Rapanea ferruginea* extract topically and as a means of enhancing the anti-inflammatory effect.	104
Terbinafine hydrochloride, clove oil and olive oil	Antifungal activity	222-924 nm	Topical delivery of terbinafine hydrochloride using clove and olive oils have the potential to be highly effective carriers.	105
Lornoxicam and almond oil	Anti-inflammatory activity.	63-168 nm	The study demonstrated that a stable drug delivery system can be formed by preparting lornoxicam containing nanoemulsion-based formulation. These formulations show promise in terms of enhanced solubility, great potential for skin penetration and physicochemical properties	106

Nanoemulsion have the ability to encapsulate and protect sensitive biological molecules, mainly; peptides, proteins and nucleic acids, which facilitate their pulmonary delivery.[3] Combining nanoemulsion with specific biologic medicines is being helpful in the treatment of inflammatory illnesses, genetic disorders and respiratory infections.

Nanoemulsion intended to be inhaled offer a rapid onset of action, which make them perfect for treating acute illnesses such as allergic reactions or asthma episodes.[118] The lungs' enormous surface area facilitates the drug's rapid absorption into the bloodstream, which has immediate therapeutic effects. Regarding chronic treatment, the effectiveness of drug delivery using nanoemulsion can result in a decrease in dosage frequency, which can improve patient compliance.

The delivery of bronchodilators, corticosteroids and other anti-inflammatory medications used in the treatment of asthma and COPD has been investigated using nanoemulsion.[119] Their capacity to increase medication absorption and retention in the lungs can lessen flare-ups and improve symptom management. Moreover, nanoemulsion for systemic pulmonary drug delivery provide a non-invasive substitute for injections.[81] Fast-acting drugs can enter the bloodstream and attain therapeutic concentrations via the alveolar epithelium, offering a useful delivery system for medications such as insulin or vaccinations. In addition, drugs loaded in nanoemulsion taken via pulmonary route may have increased bioavailability, since it protect the drugs from enzymatic breakdown in the lungs and encourage effective absorption. As presented in Table 4, various investigations utilized nanoemulsion formulations for delivering drugs via pulmonary route. In the Table 4, various studies focused on using nanoemulsion preparations for pulmonary delivery of different drugs

Ocular Drug Delivery

Nanoemulsion has appeared as a viable platform for ocular drug delivery.[61] This is attributed to the exceptional capacity to increase drug solubility, increase penetration across ocular barriers and their ability to offer sustained drug release. In addition, nanoemulsion are very valuable in this field because of the delicate structure of the eye and the difficulties in delivering medications to particular ocular tissues.[127] This is thorough examination of specific challenges found in ocular medication delivery:

Obstacles in ocular drug delivery

Several physiological and anatomical barriers make it difficult to deliver medications to the eye, including:[128]

Corneal Barrier: Hydrophilic drug delivery is restricted by the corneal epithelium, which functions as a robust barrier to drug penetration.

Tear Film and Lacrimation: Blinking and quick tear turnover can wash away the applied formulations, shortening their duration of contact with the ocular surface.

Blood-Ocular Barriers: These barriers, which resemble the blood-brain barrier, prevent some chemicals from entering the bloodstream and reaching the ocular tissues.

Limited Absorption: The fast disposal and poor absorption of traditional eye drops lead to limited bioavailability.

Advantages of Nanoemulsion as an Ocular Drug Delivery

Several advantages provided by nanoemulsion are used for treating a variety of eye problems since they have significant benefits over conventional ocular drug delivery systems.[129] Moreover, these advantages aid in overcoming the previously mentioned challenges as shown in Figure 2.

Applications of Nanoemulsion in Ocular Drug Delivery

Ocular treatments have found that nanoemulsion constitute an extremely efficient delivery system. Attributable to their capacity to increase drug solubility, increase penetration through ocular barriers and offer prolonged drug release; nanoemulsion can be used for various ocular disorders. The following represent the main uses of nanoemulsion in ocular drug delivery are listed below:

Treatment of Eye Infections

Commonly, certain eye infections can occur, such as bacterial conjunctivitis or keratitis, which require treatment using antibacterial compounds. Antibacterial nanoemulsion has the ability to directly deliver antibiotics to the site of infection. Nanoemulsion results in continuous release and increased penetration of the drug, which maintain effective concentrations at the infection site and consequently, better treatment outcomes. Other infections such as fungal keratitis or viral conjunctivitis can be treated with antifungal or antiviral nanoemulsion, offering efficient therapy.[131]

Treatment of Glaucoma

Proper control of Intraocular Pressure (IOP) is essential for the treatment of glaucoma, the primary cause of blindness. Distribution and absorption of several anti-glaucoma medications are enhanced by being formulated in form of nanoemulsion.[132] These medications can more successfully reach the target tissues inside the eye due to their small droplet size and improved penetration qualities, which lower IOP more effectively. Further, this nanoemulsion can provide extended pharmacological action, minimizing the need for frequent administration and increases patient adherence to treatment strategies.

Table 3: Formulation components, biological activity and key findings for Nanoemulsion intended for Intravenous Administration.

Formulation component	Biological action	Particle size (nm)	Key findings	Reference
Paclitaxel and myrrh oil	Antitumor activity	132-238 nm	The study revealed that PEGylated nanoemulsion of myrrh essential oil is a promising nanocarrier for Paclitaxel passive targeting.	109
Date Palm Extract and arachis oil	Antitumor activity	115-235 nm	The developed PEGylated nanoemulsion of date palm extract showed appropriate characteristics that are essential for the stability of nanoemulsion and the study will pave the way for upcoming adjuvants for cancer therapy.	110
Quercetin, curcumin and sefsol oil	Antitumor activity	< 30 nm	The current study demonstrates how an oil-based nanocarrier such as nanoemulsion, can be used to deliver curcumin and quercetin intravenously for the treatment of breast cancer.	111
Resveratrol and coconut oil	Anti-alzheimer	110- 363 nm	This study highlights the advantages of eating fruits rich in resveratrol and adding it to nanoemulsion offers a potentially effective treatment option for Alzheimer's.	112
Centella asiatica crude extract and Virgin coconut oil	Anti-epileptic	57- 125 nm	The prepared nanoemulsion with *Centella asiatica* L leaf crude extract has demonstrated good physicochemical properties, making it a viable regimen for use in future research in a pharmaceutical application, particularly in the treatment of epilepsy.	113
Brucine and arachis oil	Anticancer activity	> 140 nm	Brucine could be successfully incorporated into PEGylated nanoemulsion, which suggested to be an effective drug carrier for passively delivering BRU to tumor cells, resulting in favorable anti-tumor activity and therapeutic effect.	114
Indinavir and lactoferrin	Treatment of HIV infection	112 nm	The study concluded that applying lactoferrin nanoemulsion obviously enhances the brain penetration of indinavir.	115

Management of Dry Eye Syndrome

Nanoemulsion can be developed in order to function as lubricants or artificial Tears that provides the ocular surface sustained hydration for treating dry eye syndrome.[133] These formulations can relieve discomfort and improve eye health by simulating normal tear films. Frequently, inflammation is accompanying with dry eye condition that require treatment with anti-inflammatory medications, such as cyclosporine A. These anti-inflammatory drugs can be delivered using nanoemulsion providing long-lasting therapeutic benefits, improving the ability to retain drugs on the ocular surface.[134]

Treatment of Diseases on the Ocular Surface

Allergic conjunctivitis requires treatment using antihistamines or corticosteroids that can be applied topically to the eye using nanoemulsion.[135] Rapid and efficient drug delivery is ensured by the small droplet size, which also offers prompt relief from symptoms like redness, itching and swelling. Other ocular surface disorder is the corneal problems like corneal ulcers and dystrophies. The therapeutic agents that help in treating such problems can be applied to the cornea using nanoemulsion.

Retinal Diseases

Despite the challenges, nanoemulsion are being investigated as a mean of delivering medications to the retina and the posterior portion of the eye.[129] This is especially important when treating diseases like diabetic retinopathy and Age-related Macular Degeneration (AMD). The capacity of the nanoemulsion to deeply enter the tissues of the eyes may enhance the delivery of medication to the retina. Furthermore, nanoemulsion can be utilized as carriers for gene delivery in the treatment of retinal disorders, representing a non-viral vector option for ocular gene therapy.[136]

Treatment and Prevention of Cataract

The clouding of the eye's lens, which causes vision impairment, is a hallmark of cataracts, one of the primary causes of blindness globally. Even though surgery is still the most effective treatment for cataracts, non-surgical approaches such as those that use nanoemulsion drug delivery systems are gaining popularity as a means of treating and preventing cataracts. Nanoemulsion represent a viable strategy since they can increase drug solubility, provide sustained release and improve the delivery of therapeutic agents directly to the lens.[98] The best treatment is to protect against oxidative stress by delivering antioxidants directly to the lens. These antioxidants work on neutralizing the free radicals,

shielding the lens proteins from oxidative damage, which is the major contributing factor in the development of cataracts.[128] Since most of the antioxidants are weakly soluble in water, it is challenging to formulate them into traditional eye drops. Encapsulating these lipophilic antioxidants in the oily phase of nanoemulsion, results in enhancing their stability and solubility in aqueous solutions.

Table 5 displays numerous investigations performed utilizing nanoemulsion formulations for delivering drugs through ocular pathway.

Nanoemulsion in Cancer therapy

Recently, nanoemulsion has become a promising platform for cancer therapy. This is ascribed to its capability to increase drug solubility, decrease systemic toxicity, distribute chemotherapeutic agents more effectively and provide targeted administration.[86] Researchers and medical professionals are creating safer, more effective cancer treatments by utilizing the special qualities and properties of nanoemulsion. An outline of the uses and benefits of nanoemulsion in cancer treatment is provided in Figure 3.

One of the most interesting applications is the co-delivery of multiple therapeutic agents that termed as combination therapy.[143] These multiple drugs can work synergistically to enhance the therapeutic effectiveness, lower the dosages needed and reduce the toxicity. The combination could be between chemotherapeutic agent and sensitized as in radiation therapy or with imaging agent like fluorescent dyes providing simultaneous therapy and imaging.[144] Moreover, photodynamic and photothermal therapy are very remarkable application. In case of photodynamic therapy, photosensitizing chemicals can be delivered to tumors via nanoemulsion.[145] These drugs produce Reactive Oxygen Species (ROS) that cause cancer cells to die when they are activated by light. On the other hand, for photothermal therapy, chemicals that absorb Near-Infrared (NIR) light and transform it into heat can be encapsulated in nanoemulsion to cause thermal ablation of tumor cells.[146] When paired with chemotherapy, photothermal therapy can be a potent and minimally invasive cancer treatment. Table 6 demonstrates several research studies that were executed for cancer therapy using nanoemulsion formulations.

Nanoemulsion in Vaccine Delivery

Nanoemulsion has distinctive properties that enhance vaccine durability, effectiveness and immunogenicity. Therefore, more studies are being carried out on the nanoemulsion as a novel vaccine delivery system. A number of benefits come with using nanoemulsion to deliver vaccines, including better antigen distribution, boosted immune responses and the possibility of

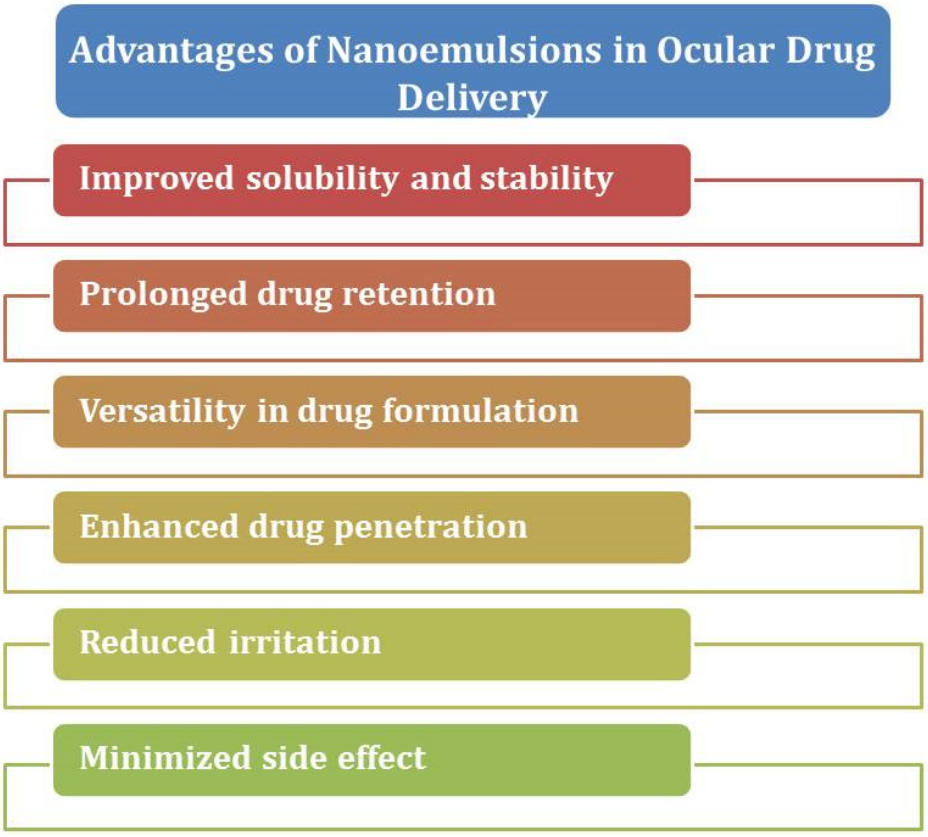

Figure 2: Illustrating the advantages of Nanoemulsion as an Ocular Drug Delivery system.

Table 4: Formulation components, biological activity and key findings for Nanoemulsion intended for pulmonary delivery.

Formulation component	Biological action	Particle size (nm)	Key findings	Reference
Tadalafil	Treating Pediatric Pulmonary Hypertension	25 nm	Nebulization using Tadalafil nanoemulsion via a jet nebulizer was suggested as an alternate method of targeted delivery to the lungs in order to guarantee more efficacies and lessen the systemic negative effects.	120
Palm-based ester and quercetin	Antitumor activity	106 nm	The study proved that developing an aerosol nanoemulsion for pulmonary drug delivery utilizing palm-based ester (POE), with quercetin serving as the model drug for the treatment of lung cancer.	121
Docetaxel	Anticancer activity	90-110 nm	In this investigation, formulating Docetaxel nanoemulsion formulation using biocompatible excipients for pulmonary delivery is one possible way to increase the bioavailability and biocompatibility of this poorly soluble drug in water. Additionally, the study proved that nanoemulsion is an excellent candidate to be used as carrier system.	122
Gemcitabine and Medium-chain triglyceride	Anticancer activity	141 nm	The study exhibited that the developed nanoemulsion containing Gemcitabine induced cytotoxicity towards the investigated cancer cells efficiently.	123
Docetaxel and Curcumin	Lung anticancer activity	up to 190 nm	The present investigation has yielded a perfect nanoemulsion loaded with Docetaxel and Curcumin. The developed nanoemulsion provided a high lung drug content which is necessary for local therapies for lung-related diseases with better efficacy and less damage to normal cells.	124
Tea tree oil	Antimicrobial activity	12.5 nm	The study demonstrated the potential of inhalable nanoemulsion containing tea tree oil as local treatments for bacterial and fungal pneumonia, with no apparent side effects.	125
Rifampicin and oleic acid		40- 60 nm	The study illustrated the potential of rifampicin-oleic acid nanoemulsion for pulmonary delivery. The developed nanoemulsion showed greater cell internalization potential, lower plasma drug concentration and higher lung drug content.	126

needle-free administration.[154] An overview of nanoemulsion' function in vaccine delivery is provided as follow:

Enhanced Antigen Delivery

Antigen Protection: Antigens can be encapsulated within the nanoemulsion to prevent destruction by enzymes or other environmental stimuli.[86] The efficiency of the vaccine is increased because of this protection, which guarantees that the antigen will stay active and intact until it reaches its target. A large number of antigens are hydrophobic and weakly soluble. These hydrophobic antigens can be encapsulated by nanoemulsion, increasing their solubility and guaranteeing more effective delivery. Dendritic cells and macrophages are two types of antigen-presenting cells that can be easily uptake nanoemulsion due to their nanoscale size.[155] Nanoemulsion boosts the delivery of antigens to antigen-presenting cells, which results in a more potent and targeted immune response.

Adjuvant Characteristics

Certain nanoemulsion possess natural adjuvant properties that enable them to activate the immune system without requiring the entrapped antigen.[156] Toll-Like Receptors (TLRs) on immune cells can be activated by nanoemulsion, which trigger the release of cytokines and the activation of the adaptive immune response.[157] Additionally, adjuvants like squalene, or aluminum salts can be added to nanoemulsion to increase the immunogenicity of the vaccine. These adjuvants increase the vaccine's efficacy by enhancing the body's immunological reaction to the antigen.

Thermostability and Storage Benefits

Sustaining the cold chain to keep vaccine efficacy is one of the major issues in vaccine delivery. The thermostability of vaccines can be improved by nanoemulsion, which minimize the requirement for rigorous refrigeration and facilitate vaccine storage and transportation, especially in environments with

limited resources.[158] Moreover, nanoemulsion can increase the shelf life of vaccinations by shielding the antigen from external factors like light, oxygen and temperature changes. This helps to ensure that the shots stay effective for longer.

Controlled Release and Dose Sparing

Antigen can be released gradually and under control using nanoemulsion formulations. This longer release may lessen the need for repeated booster doses by mimicking natural infection processes and resulting in a more robust and effective immune response.[159] Dose sparing, in which less antigen is required to elicit the intended immune response, may be possible due to nanoemulsion' improved transport and adjuvant properties. This is especially helpful in cases where the supply of vaccines is restricted or in pandemic circumstances where a quick scale-up is required.

Applications in Emerging and Pandemic Vaccines

Researchers are investigating the use of nanoemulsion as vaccines against a variety of pathogens, including newly discovered infectious diseases and possible pandemic hazards such as influenza, SARS-CoV-2 (COVID-19) and Ebola. They provide a flexible framework for the development of novel vaccines since they can improve the antigen's delivery and efficacy. Nanoemulsion presents an appealing alternative for quick vaccine development in response to newly developing infectious diseases because of their scalability and ease of formulation.[160] Table 7 confirmed vaccine therapy via numerous investigations that utilized nanoemulsion formulations in their protocol.

Applications of Nanoemulsion beyond Pharmaceuticals

Nanoemulsion find extensive use in other fields ascribed to their special characters, which include large surface area, improved bioavailability and stability.[16] Here are a few noteworthy examples from a range of industries:

Cosmetics and Personal Care

Nanoemulsion can be involved in skin care products.[40] Vitamins, peptides and antioxidants are among the active substances that are better delivered to the skin by nanoemulsion.[166] They improve stability and penetration, making serums, anti-aging treatments and moisturizers more potent. Further, nanoemulsion can aid in improving skin covering uniformity and UV protection in the form of sunscreen. Nanoemulsion make it possible to formulate sunscreens that are less oily or transparent as a result of encapsulating UV filters in nano-sized droplets.[167] Moreover, nanoemulsion can be utilized in hair maintenance.[168] It can be more efficiently transport vitamins, proteins and conditioning ingredients to the hair and scalp in hair care products, increasing their overall effectiveness. Additionally, a specialized area of medicine known as cosmetic ophthalmology is dedicated to improve the appearance of the eyes and surrounding tissues. Nanoemulsion has drawn a lot of attention in this field as they

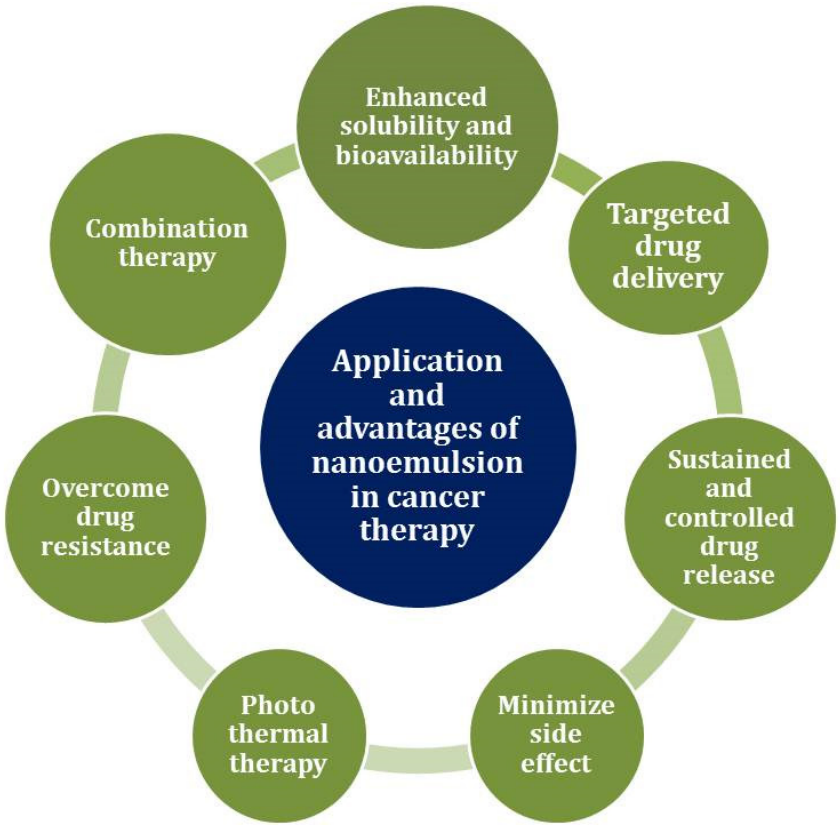

Figure 3: Demonstrating the application and advantages of nanoemulsion in the field of cancer therapy.

Table 5: Formulation components, biological activity and key findings for nanoemulsion developed for ocular drug delivery.

Formulation component	Biological action	Particle size (nm)	Key findings	Reference
Propylene glycol, hydroxypropyl and guar	Treatment of dry eye disease	< 100 nm	The study revealed that the developed propylene glycol/hydroxypropyl-guar-based nanoemulsion could be successfully applied as a lubricant for the management of eye disorders	137
Curcumin, vegetable oil and Alpha-tocopherol acetate.	Treatment of dry eye syndrome	19.3 nm	The study investigated the manufacturing of Curcumin-based nano emulsion eye drop, which proved to be a promising candidate for managing dry eye syndrome	138
Moxifloxacin and ethyl oleate	Antimicrobial activity	29-81 nm	The investigation proved that the therapeutic impact of moxifloxacin loaded nanoemulsion was increased and, as a result, it can be utilized as a safe and reliable delivery method for ocular therapy.	130
Tacrolimus, Castor oil and Soybean oil	Treatment of immune-mediated inflammatory anterior ocular diseases	180 nm	The study proposed that nanoemulsion is a promising ocular drug delivery system for enhancing the bioavailability of Tacrolimus.	139
Lutein and croton oil	Prevention of ocular diseases (Age-related macular degeneration)	10-12 nm	The study formulated the lutein loading nanoemulsion that can be used to treat eye conditions efficiently. It also emphasized that lutein nanoemulsion formulation is a possible substitute for lutein administration systems.	140
Ibuprofen, Miglyol® 812 and lecithin	Treatment of dry eye disease	> 100 nm	The study emphasized that developing ibuprofen-loaded nanoemulsion resulted in a prolonged residence at ocular surfaces, which help in reducing the required dose providing better patient compliance.	141
Ciprofloxacin and Oleic acid	Treatment of bacterial keratitis	121.6 nm	The study developed ciprofloxacin loaded nanoemulsion formulation that showed promise as a drug delivery vehicle for the efficient administration of ciprofloxacin to treat bacterial keratitis and various other bacterial infections of the eyes.	142

can successfully transport cosmetic and therapeutic substances.[169] These benefits include fewer wrinkles, increased skin moisture and an overall improved appearance of the eyes. The application of nanoemulsion in cosmetic ophthalmology include various aspects as an anti-aging treatment, skin lightening and pigmentation correction, dark circles and puffiness reduction, treatment of scars and sun protection.

Food and Beverage Industry

Flavors, vitamins and other nutrients can be encapsulated in nanoemulsion to improve their stability and bioavailability.[16] This is especially helpful for functional foods and drinks when it's important to distribute nutrients consistently. Food products can be made more stable by using nanoemulsion, which prolong shelf life and prevent ingredient separation.[57]

Agriculture and Agrochemicals

Nanoemulsion can improve the efficiency of pesticides by enhancing their dispersion, adhesion and penetration into plant tissues.[46,170] They also assist in lowering the required concentration of the active component. Nanoemulsion can aid in the delivery of fertilizer by encapsulating nutrients and releasing them gradually.[171]

Environmental and Industrial Applications

Oil spills can be cleaned up with nanoemulsion. They aid in the breakdown of oil into tiny droplets that are simpler for microbes to remove or break down. By increasing the solubilization of oils and fats, nanoemulsion in industrial cleansers and detergents can increase the removal of grease and pollutants.[172]

Health and Wellness

Concerning with nutraceuticals, nanoemulsion can improve the bioavailability and efficacy of functional elements like omega-3 fatty acids, which are frequently poorly absorbed in their normal forms, as well as health supplements. Beyond medicines, nanoemulsion can be applied to improve the delivery of active substances to the affected areas of over-the-counter topical therapies for disorders like eczema or acne.[12]

Textiles and Materials

Nanoemulsion can improve the performance and durability of textiles through the addition of certain characteristics like stain resistance, water repellency, or antimicrobial activity.[173] Nanoemulsion can enhance adhesion, durability and gloss in paints and coatings. Additionally, they make it possible to create coatings with specific qualities like self-cleaning or anti-corrosive qualities.

Electronics and Nanotechnology

Since nanoemulsion have a high thermal conductivity and stability, they can be employed as coolants in electronics to aid in effective heat dissipation,[174] Nanoemulsion is templates or precursors in the field of nanotechnology that can be utilized to create nanostructured materials with particular features for a variety of purposes.[175]

Limitations of nanoemulsion

Although the great importance and applications of nanoemulsion in various ways, yet they can show certain obstacles that limit their manufacturing.[16] High cost of nanoemulsion preparation may represent a great hindrance in its manufacturing. Sometimes improper manufacturing for nanoemulsion may prone it to instability issues since it showed phase separation, coalescence or creaming. Moreover, safety concerns should be considered while using surfactants to avoid their toxicity. Accordingly, surfactants used should categorize as Generally Recognized as Safe (GRAS), which is designated by a United States Food and Drug Administration (FDA).[176]

Nanoemulsion in Clinical trials

In clinical trials, nanoemulsion shows promise for a number of applications, most notably in drug delivery and therapeutic interventions. Some clinical trials have been stated using nanoemulsion in order to assure safety and efficacy of this nanocarrier (86). Some of these clinical trials were conducted using formulated nanoemulsion for topical application documented as Clinical Trial ID; (NCT04110860) and (NCT04110834).[177,178] Additionally, intranasal nanoemulsion was studied for their influence on pandemic flu vaccine in healthy adults with clinical trial ID (NCT05397119).[179]

Table 6: Formulation components, type of cancer and key findings for Nanoemulsion developed for Cancer Therapy.

Formulation component	Type of cancer	Particle size (nm)	Therapeutic effect and key findings	Reference
Testosterone	Prostate cancer	232 nm	The study investigated the formulation of Testosterone nanoemulsion that decreases the viability of cancer cells. It was verified that the developed formulation might be an interesting strategy for prostate cancer treatment in diagnosed patients.	147
Pequi oil and egg lecithin	Breast cancer	123 nm	The study demonstrated the potential of pequi oil-based nanoemulsion as a nanosized platform to be used as an adjuvant treatment for breast cancer.	148
Neobavaisoflavone and pequi oil	Lung cancer	110 nm	Developing Neobavaisoflavone nanoemulsion proved as novel and effective strategy in treating lung cancer	149
5-Fluorocuracil and castor oil	Colorectal cancer	51.64 nm	The target of the study is to enhance the bioavailability of 5-Fluorocuracil via loading it into a unique nanoemulsion formulation that successfully improved its colorectal targeting.	150
Pyridoclax and Labrafac®	Ovarian cancer	105.8 nm	The study verified that Pyridoclax-loaded nanoemulsion exhibited 2.5 times more efficacies against ovarian cancer cells compared to free Pyridoclax.	151
α-Tocopherol Succinate and Dequalinium	Leukemia	150-170 nm	The study aimed to develop mitochondria-targeting emulsion using α-Tocopherol Succinate and Dequalinium that resulted in promising potential for cancer treatment	152
Norcantharidin and Almond oil,	Melanoma	94- 243 nm	The study could incorporate adequate amount of Norcantharidin into Nanoemulsion formulation and emphasized its safety and efficacy in melanoma treatment	153

Table 7: Formulation components, biological action and key findings for Nanoemulsion developed for vaccine therapy.

Formulation component	Biological action	Particle size (nm)	Key findings	Reference
Epitope peptide and Isopropyl myristate	Treating *Helicobacter pylori* infection	23.4-64.0 nm	The study highlights the potential of developing unique nanoemulsion system for intranasal delivery of a vaccination against the Helicobacter pylori epitope.	161
DOTAP (1,2-dioleoyl-3-trimethylammonium-propane, chloride salt), DOPE (1,2-dioleoyl-sn-glycerol-3-phos phoethanolamine and Vitamin E	Nasal vaccination	120 nm	The study highlights the potential of polymeric nanoemulsion in promoting the development of mRNA vaccines to fight infectious illnesses.	154
MRSA252 strains and isopropyl myristate	Enhancing intramuscular systemic and nasal mucosal immune responses	Exceeding 160 nm	A novel and strong nanoemulsion adjuvant vaccine using MRSA subunit recombination protein vaccines was developed and proved to be stable and efficient.	162
PEG-b-PLACL, Span85 and squalane oil	Intranasal vaccination	~200 nm	Squalene-based nanoemulsion could enhance the effectiveness of tumor-associated antigen treatment against both *in situ* and metastatic tumors.	163
Bioresorbable polymer, Span®85 and squalene	Influenza pandemic vaccine	200- 400 nm	The study provides an approach for developing prophylactic and therapeutic vaccination. A novel nanoemulsion was prepared forming a ready-to-use adjuvant, called PELC and proved to have big role in influenza pandemic.	164
Squalane and Montanide mineral oil	Vaccine for foot-and-mouth disease	100 nm	The study developed effective and safe squalane nanoemulsion adjuvant that paired with foot-and-mouth disease virus-like particles to facilitate a better immune response	158
PBS-diluted ovalbumin-nanomeulsion mixtures	Nasopharyngeal vaccine adjuvants	200- 600 nm	The investigation developed nanoemulsion-based vaccines, which has thermal stability, potency and being efficient in dispensing the vaccines to the nasal mucosa.	165

Future trend of nanoemulsion

In the upcoming years, it is anticipated that the preparation and application of nanoemulsion would undergo significant change. Some important trends to be aware of; is the improvement in strategy of targeting. Nanoemulsion may be utilized more frequently in combination therapy with other treatments mostly in oncology, such as gene or immunotherapies, to improve overall therapeutic results. Nanoemulsion may also fulfill other medical needs in other fields including neurology, cardiology and chronic disease management. More sustainable approaches for developing nanoemulsion with eco-friendly components will probably be promoted. Accordingly, using nanoemulsion in the medical field has a bright future since they may improve patient outcomes and therapeutic efficacy.

CONCLUSION

To sum up, nanoemulsion is a very adaptable and promising drug delivery system that could completely change a range of therapeutic applications. Their distinct physicochemical characteristics, mainly; their huge surface area, small droplet size and increased stability, allow for better drug solubility, bioavailability and controlled release. Their versatility in meeting wide range of medical needs is further demonstrated by their capacity to encapsulate both hydrophobic and hydrophilic drugs.

Nanoemulsion is being used in different fields owing to ongoing innovation in their formulation processes and understanding of their behavior. In spite of these benefits, some obstacles such as scalability, long-term stability and probable toxicity should be investigated to fully understand their potential. Ongoing research is essential for improving nanoemulsion, converting successful laboratory work into clinical applications. Overall, in the technology of drug delivery, nanoemulsion stand at the front position, providing great opportunities for improving therapeutic effectiveness and patient outcomes. Ultimately, it is predictable that nanoemulsion will exhibit a progressively vital role in modern medicine.

ABBREVIATIONS

PDI: polydispersability index; **API:** Active pharmaceutical Ingredient; **EPR:** Enhanced Permeability and Retention; **COPD:** Chronic Obstructive Pulmonary Disease; **IV:** Intravenous; **IOP:** Intraocular Pressure; **AMD:** Age-related Macular Degeneration; **TLR:** Toll-Like Receptors; **GRAS:** Generally Recognized as Safe; **FDA:** Food and Drug Administration

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

The review focuses on the emerging role of nanoemulsion in improving the efficacy of drug delivery systems. It starts with describing nanoemulsion and highlighting their distinctive characteristics, including; small droplet size and enhanced stability that could affect their bioavailability and therapeutic efficacy. The utilization of nanoemulsion for targeted drug delivery and their application in different route of administrations (oral, intravenous and transdermal) are some of the current trends that are studied. The article discusses current clinical applications that show how nanoemulsion can be used effectively in drug formulations.

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