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Literature Perspectives on Nanoemulsion Technologies for Drug Delivery Enhancement

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Abstract: With its many benefits over conventional delivery methods, Nano emulsions have become a promising medication delivery mechanism. Nano emulsions, which are distinguished by their nanometer-sized droplets, have special qualities like increased stability, higher bioavailability, and a high solubilization capacity, which make them perfect for administering medications that are poorly soluble. This review examines the types, composition, and preparation techniques of Nano emulsions, emphasizing their use in parenteral, topical, oral, and pulmonary drug delivery applications. Along with the difficulties of stability, scalability, and regulatory considerations, the potential of Nano emulsions in combination therapies, controlled release, and targeted drug administration is also covered. The revolutionary potential of Nano emulsions in personalized medicine is further evidenced by recent developments in functionalization and gene therapy. The goal of this thorough analysis is to give readers a better knowledge of Nano emulsions as a flexible drug delivery platform while highlighting its potential future effects on the healthcare sector.

Keywords: Targeted therapy, controlled release, bioavailability, drug delivery systems, and Nano emulsion.

I.INTRODUCTION

An Overview of Drug Delivery Systems

Drug distribution to the intended location is managed by drug delivery systems (DDS). There are benefits and drawbacks to topical, injectable, and oral pharmaceutical administration. Because of its convenience and patient participation, the oral approach is the most often used. Common issues include absorption variability, first-pass metabolism, and poor bioavailability. Although intravenous and intramuscular injections are painful, invasive, and inconvenient for long-term treatment, they provide rapid and comprehensive drug delivery. Although topical therapies are helpful for targeted treatment, drug penetration is limited by the skin's barrier properties. Poorly water-soluble medications, which include a significant portion of novel therapeutic candidates, are difficult for conventional drug delivery methods to distribute. Many medications need higher dosages to achieve therapeutic levels because of their poor oral bioavailability, which could result in toxicity and adverse effects. Additionally, conventional methods are unable to target particular tissues or cells, which leads to body-wide dispersion. Drug non-specificity increases systemic side effects and reduces therapeutic efficacy. Frequent dosage may reduce patient compliance and increase healthcare costs because of the quick elimination of medications in the bloodstream. Considering these limitations, there is a lot of interest in creating better medication delivery methods that get around current ones. Nano emulsions have attracted attention because of their distinct qualities and wide range of medication delivery uses. [1] [2]

NANO-EMULSIONS:
Oil, water, and surfactants combine to form Nano emulsions, which are emulsions at the Nano scale with droplet sizes usually between 20 and 200 nanometers. [3] Nano emulsions are kinetically stable, which means they may stay in a stable condition for long periods of time without experiencing noticeable phase separation, in contrast to traditional emulsions, which are thermodynamically unstable and have a tendency to phase-separate over time. [4] Because of their stability and tiny droplet size, Nano emulsions have special qualities that make them excellent drug delivery vehicles.

The dispersion of one immiscible liquid into another, supported by surfactants that lower the interfacial tension between the two phases, is the fundamental idea behind Nano emulsions. Because Nano emulsions have a huge surface area due to their small droplet size, hydrophobic medicines are better soluble and easier to absorb through biological membranes. [5] Depending on the drug's characteristics and the intended administration route, Nano emulsions can be made in a number of ways, such as oil-in-water (O/W), water-in-oil (W/O), and bicontinuous structures. [6].

Early in the 20th century, the first reports of emulsions in the pharmaceutical industry marked the beginning of the historical evolution of Nano emulsions. However, Nano emulsions were not widely investigated as drug delivery vehicles until the late 20th and early 21st centuries, when nanotechnology advanced. Nano emulsions are widely used in a variety of industries, such as the food, cosmetics, and pharmaceutical sectors, due to their capacity to precisely control the size and content of the particles and their capacity to encapsulate both hydrophilic and hydrophobic medicines. [7]

Nano emulsions have a number of benefits over traditional medication delivery methods. Because of their small size, they can more easily pass through biological barriers such the skin, blood-brain barrier, and gastrointestinal system, facilitating the more efficient delivery of medicinal substances to their intended locations. [4] Furthermore, Nano emulsions can be designed to release medications in a regulated and sustained manner, which lowers dosage frequency and increases patient compliance. The potential of Nano emulsions to deliver a broad spectrum of therapeutic agents is further expanded by their capacity to combine hydrophilic and lipophilic medicines in a single system [8]

Because of these benefits, Nano emulsions are becoming more widely acknowledged as a flexible and promising drug delivery platform with prospective uses in a range of therapeutic domains. The composition, methods of preparation, benefits, and uses of Nano emulsions in drug delivery will all be covered in this review, along with the difficulties and potential future developments of this cutting-edge technology.

COMPOSITION TYPES OF NANOEMULSIONS AND NANOEMULSIONS:

Colloidal dispersions known as Nano emulsions are made up of two or more immiscible liquids, usually water and oil, and are held together by an interfacial layer of surfactants, frequently co-surfactants. Nano emulsions have special qualities due to their small droplet size, which is typically between 20 and 200 nanometers. This makes them ideal for drug delivery applications. [3] The elements, varieties, and techniques of preparation of Nano emulsions are covered in detail in this section. The general composition of the Nano emulsion is shown in Figure 1.

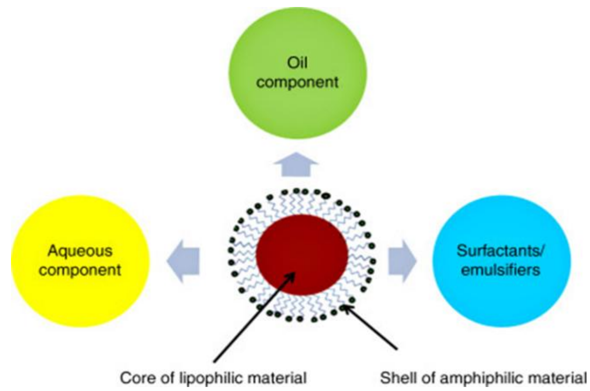

Fig 1: Composition of Nano emulsion

NANOEMULSION COMPONENTS:

Four essential ingredients are usually used in the formulation of a Nano emulsion: the oil phase, the aqueous phase, surfactants, and co-surfactants. [9] [10] [11]

a. Oil Phase: Lipophilic medications, which are otherwise poorly soluble in water, are greatly aided by the oil phase. Medium-chain triglycerides (like caprylic/capric triglycerides), long-chain triglycerides (like soybean oil), and non-ionic surfactant oils (like isopropyl myristate) are among the frequently used oils. The solubility of the medication, the intended release profile, and the application method all influence the oil selection. The oil phase has an impact on the drug loading capacity and release kinetics in addition to the droplet size and stability of the Nano emulsion. [12]

b. Aqueous Phase: Usually made up of purified water, the aqueous phase functions as the dispersed phase in water-in-oil (W/O) Nano emulsions or as the continuous phase in oil-in-water (O/W) Nano emulsions. Certain formulations may contain buffers or electrolytes in the aqueous phase to preserve osmolarity and pH stability, which is crucial for parenteral and ophthalmic uses. The stability of the Nano emulsion and droplet formation can be strongly impacted by the aqueous phase's composition. [13] [14]

c. Surfactants: These amphiphilic compounds stabilize the Nano emulsion by lowering the interfacial tension between the water and oil phases. Ionic surfactants like sodium dodecyl sulfate (SDS) and non-ionic surfactants like polysorbates (like Tween 80) and sorbitan esters (like Span 80) are frequently utilized in Nano emulsion formulations. The stability, toxicity, and droplet size of the Nano emulsion are all impacted by the surfactant selection. Because they have a reduced potential for toxicity and irritation than ionic surfactants, non-ionic surfactants are frequently chosen. [15] [16]

d. Co-surfactants: These substances, which include alcohols (like ethanol and propylene glycol) and glycols (like polyethylene glycol), are frequently added to improve the interfacial film's flexibility and lower interfacial tension even more. This stabilizes the Nano emulsion and permits the production of smaller droplets. Additionally, co-surfactants have the ability to alter the formulation's viscosity, which is essential for topical and transdermal applications. [17] The nature and stability of the Nano emulsion are mostly determined by the ratio of surfactant to cosurfactant and the HLB (hydrophilic-lipophilic balance) value. [18] [19]

II.NANOEMULSION TYPES

Depending on the characteristics of the continuous and scattered phases, Nano emulsions can be divided into three primary categories. [20] [21] [22]

a. Nano emulsions of Oil in Water (O/W):

Within the continuous aqueous phase of O/W Nano emulsions, the oil phase is distributed as tiny droplets. These formulations are very helpful for topically, parenterally, or orally administering lipophilic medications. O/W Nano emulsions can offer a controlled release profile, increase absorption, and improve the solubility and bioavailability of medications that are poorly soluble in water. Because of their stability and simplicity of formulation, they are extensively utilized in the food, cosmetic, and pharmaceutical industries.

b. Nano emulsions of water and oil (W/O):

Water droplets scattered across an oil phase make up W/O Nano emulsions. Although less prevalent, they are useful for topical or transdermal delivery of hydrophilic medicines, where the oil phase can function as a barrier to regulate drug release. By rupturing the stratum corneum and producing a reservoir effect, W/O Nano emulsions are very helpful in improving the penetration of active substances through the skin. They are typically less stable than O/W Nano emulsions, though, and stability may need to be maintained by carefully choosing the surfactants.

c. Bicontinuous Nano emulsions:.

Both the water and oil phases are distributed over a continuous network in bicontinuous Nano emulsions; there are no noticeable droplets. These intricate structures can be utilized to deliver both hydrophilic and lipophilic medications at the same time since they are stabilized by a mixture of surfactants and co-surfactants. Since bicontinuous Nano emulsions may be designed to react to environmental cues like pH or temperature, they are especially intriguing for their potential in targeted delivery and controlled medication release. They are more difficult to formulate and maintain than O/W and W/O Nano emulsions, though.

III.PREPARATION METHODS

to ensure stability and the best possible drug delivery, Nano emulsion preparation calls for methods that can create tiny, homogeneous droplets. The techniques employed can be broadly divided into two categories: low-energy and high-energy.

HIGH-ENERGY METHOD:

These techniques convert bigger droplets into nanoparticles by using external energy sources.

a. High Pressure Homogenization:

One of the most widely used methods involves forcing the emulsion through a small opening at high pressure, which causes shear forces, cavitation, and turbulence to generate tiny droplets. High-pressure homogenizers are frequently employed in both laboratory and industrial settings to produce Nano emulsions, with droplet sizes ranging from 50 to 200 nm. For the production of stable O/W Nano emulsions for parenteral and oral drug delivery, this technique works especially well. [23] [24]

b. Ultra sonication:

Using this technique, the emulsion is exposed to high-frequency sound waves, which create cavitation and cause the droplets to split into Nano scale pieces. Ultra sonication is frequently employed for small-scale formulations because it works well for creating Nano emulsions with limited size distributions. However, because of the heat produced during the process, it could not be as scalable as high pressure homogenization and could cause sensitive medications to degrade. [25] [26]

c. Microfluidization:

The emulsion is run through microchannels at high speeds using a microfluidizer in this procedure, which causes shear and impact forces to generate tiny droplets. Microfluidization can be used in both laboratory and industrial settings to create Nano emulsions with consistent droplet sizes. It is especially beneficial. [27] [28]

LOW-ENERGY METHODS:

These techniques create Nano emulsions without requiring an external energy source by utilizing the system's physicochemical characteristics, such as phase transitions.

a. Method of Phase Inversion Temperature (PIT):

Using this technique, the emulsion solution is heated to a point where phase inversion and the creation of nanoparticles occur due to a shift in the surfactant's affinity for the water and oil phases. A stable Nano emulsion is created when it cools. The PIT approach has the advantage of producing Nano emulsions with extremely small droplet sizes while using less energy than high energy methods. It can be difficult to get regular results, though, because it is quite sensitive to the kind and concentration of surfactants used. [29] [30]

b. Emulsification That Occurs Naturally:

This method entails quickly combining the aqueous phase with the oil phase, which contains a surfactant and a solvent that are water soluble. Nano-sized droplets form spontaneously as a result of the solvent's quick diffusion into the aqueous phase. Because spontaneous emulsification is easy to use and doesn't require sophisticated equipment, it can be used in lab-scale formulations. The resulting Nano emulsions might have wider size distributions than those made using high-energy techniques, and the process might not be readily scalable. [31] [32]

IV.ADVANTAGES OF NANO EMULSIONS IN DRUG DELIVERY

Nano emulsions improve the therapeutic efficacy and safety of a variety of medications by providing a number of noteworthy benefits in drug delivery. The advantages of Nano emulsions in terms of bioavailability, controlled release, drug protection, and patient compliance are examined in detail in this section.

a. Increased Bioavailability:

Enhancing the bioavailability of medications that are poorly soluble is one of the most prominent benefits of Nano emulsions. By dispersing lipophilic medications in an aqueous phase that is nanometers in size, Nano emulsions increase their solubility. The pace and extent of medication absorption are greatly increased by the larger surface area accessible for dissolution caused by the smaller droplet size. [33] [34] For example, medications with low water solubility, such as paclitaxel, have demonstrated enhanced bioavailability when prepared as Nano emulsions [35] [36]. Better therapeutic results result from the quicker disintegration and absorption of these medications in the gastrointestinal tract made possible by the high surface area to volume ratio of Nano emulsion droplets. [37] Nano emulsions frequently enable the use of lower dosages of the medication by improving solubility and bioavailability, which can lessen the risk of toxicity and adverse effects. This is particularly advantageous for medications with narrow therapeutic windows or those that have severe side effects at higher doses. [38] Better patient adherence can also result from increased bioavailability, which can help achieve effective therapeutic levels of the medication with fewer doses.

b. Controlled and targeted drug release:

Drug release can be targeted and controlled by Nano emulsions, which can improve therapeutic efficacy and lessen adverse effects. It is possible to design Nano emulsions to release their active chemicals in a regulated way. This is accomplished by adjusting formulation characteristics such the kind of oil used, droplet size, and surfactant content. [39] A number of processes, including as drug diffusion through the emulsion matrix, emulsion breakdown over time, or modifications to the environment (such as pH or temperature), might result in controlled release. [40] [41] For chronic illnesses that necessitate long-term medicine, Nano emulsions, for instance, can be engineered to deliver sustained drug release over prolonged periods of time. Additionally, by tailoring Nano emulsions to target particular tissues or cells, systemic side effects can be reduced and therapeutic efficacy increased. This can be accomplished by adding targeted ligands or altering the Nano emulsion droplets' surface characteristics to improve their ability to engage with particular tissues or cellular receptors. [42] [15] In cancer, targeted Nano emulsions have demonstrated potential in delivering chemotherapeutic drugs straight to tumor cells, protecting healthy tissues and lowering overall toxicity.

c. Drug Encapsulation Protection:

One more significant benefit of Nano emulsions is the protection of active pharmaceutical ingredients (APIs). Sensitive medications can be shielded from enzymatic and hydrolytic breakdown using Nano emulsions. The medicine may be protected from environmental elements that could otherwise cause degradation by the barrier formed by the Nano-sized droplets. [43] [44] For instance, medications that are prone to oxidative deterioration can be successfully shielded in a nanoemulsion's oil phase, increasing their efficacy and shelf life. [45] [46] For biologics and other medications that are prone to instability under typical storage conditions, this is very helpful. The medicine can be protected from environmental elements including light, heat, and moisture—all of which can exacerbate chemical instability—by being encapsulated in a Nano emulsion. The medication's effectiveness is preserved for the duration of its shelf life thanks to this additional protection. Additionally, Nano emulsions can be made to release the medication gradually, which lowers the possibility of abrupt degradation that rapid release systems may experience.

d. Improved patient compliance:

Nano emulsions are a popular option for a range of medication delivery applications since they also provide advantages in terms of patient compliance. Comparing Nano emulsions to traditional formulations, the former are frequently simpler to give. To meet the demands of various patients, they can be made into a range of dosage forms, such as injectable solutions, topical gels, and oral liquids. [8] [47] Because of its small droplet size, Nano emulsions frequently provide more aesthetically beautiful formulations that are simpler to administer or swallow, which increases patient acceptance. Extended dosage intervals are frequently made possible by the controlled release characteristics of Nano emulsions. This can greatly increase adherence to treatment regimens by reducing the frequency with which patients must take their medications. [48]Patients with chronic diseases who need long-term therapy benefit most from reduced dose frequency since it lessens the strain of frequent medication ingestion and aids in maintaining stable drug levels.

V.APPLICATIONS OF NANOEMULSIONS IN DRUG DELIVERY

Nano emulsions have emerged as versatile carriers in drug delivery systems, with applications across various routes of administration. Their unique properties, including small droplet size and enhanced stability, make them suitable for a range of therapeutic applications.

a. Oral Drug Delivery:

For oral drug delivery, Nano emulsions are very advantageous, especially for medications with low water solubility. The effectiveness of Nano emulsions in enhancing the bioavailability of oral drugs has been shown in numerous research. For instance, the oral bioavailability and therapeutic efficacy of poorly soluble medications such as celecoxib and curcumin have been significantly improved by Nano emulsion formulations. [49] [50] Comparing these formulations to traditional oral dosage forms, clinical trials have shown better absorption and a quicker beginning of effect. Oral delivery of unpleasant medications can be made more appealing by using Nano emulsions to cover up their flavor. Their capacity to improve solubility and simplify absorption is especially helpful in the treatment of diseases like cancer or chronic inflammation that call for high dosages of lipophilic medications. Clinical experiments using the Nano emulsion formulation of the anti-inflammatory medication diclofenac have demonstrated better absorption and less gastrointestinal irritation when compared to conventional formulations. [51] [52] Another illustration is the application of Nano emulsions to administer antifungal medications, such as itraconazole, where the Nano emulsion has shown improved effectiveness in treating fungal infections. [53] [54]

b. Topical Drug Delivery:

Because Nano emulsions can improve therapeutic efficacy and skin penetration, they are a great asset for topical drug delivery. By rupturing the stratum corneum and enhancing the drug's solubility in the lipid-rich layers of the skin, Nano emulsions can enhance the penetration of active substances through the skin. [55] More effective therapies for dermatological disorders including psoriasis, eczema, and acne may result from this improved penetration. Research has demonstrated that, in comparison to traditional topical formulations, anti-inflammatory medication Nano emulsions, including hydrocortisone, can offer superior therapeutic results with fewer side effects. Anti-aging drug Nano emulsions, like retinoids, have been created to increase skin penetration and effectiveness while reducing irritation. [56]

c. Parenteral Drug Delivery:

Additionally, parenteral drug administration via intravenous (IV) and intramuscular (IM) methods uses Nano emulsions. Because of its small droplet size and improved stability, Nano emulsions can be used to deliver medications via IV and IM routes, offering prefilled syringes a number of advantages. [57] Nano emulsions can increase the solubility of medications such as paclitaxel, which is used in chemotherapy, for intravenous administration. [58] [59] These medications' sustained effectiveness during the infusion time is guaranteed by Nano emulsions' capacity to encapsulate and stabilize them. Nano emulsions injected intramuscularly can also improve the drug's release profile by offering a regulated, prolonged release that can lessen the need for repeated injections. Formulations of Nano emulsions of Vancomycin and other antibiotics have been used to attain greater plasma concentrations while minimizing adverse impacts. [60]

d. Nasal and Pulmonary Delivery:

Nano emulsions are being investigated more and more for medication delivery in the lungs and nose, where their small size and capacity to generate minute aerosols make them appropriate for nasal sprays and inhalation. Drugs can be aerosolized from Nano emulsions for pulmonary administration, which is advantageous for the treatment of respiratory disorders like asthma and chronic obstructive pulmonary disease (COPD). [61] [17] Nasal sprays containing Nano emulsions can improve drug absorption via the nasal mucosa, effectively treating ailments like migraines and rhinitis. Nano emulsions' large surface area and tiny droplet size enhance medication absorption and deposition in the nasal cavity and lungs. Corticosteroid inhalation treatments based on Nano emulsions have demonstrated enhanced delivery and beneficial outcomes in asthma. (Raja, 2014) Analgesic and anti-inflammatory nasal Nano emulsion sprays are being developed for their quick start of effect and enhanced patient compliance.

VI.CHALLENGES AND LIMITATIONS

Notwithstanding their benefits, there are a number of issues and restrictions with Nano emulsions that must be resolved before they can be successfully used in medication delivery systems.

a. Stability Problems:

Physical instability, such as phase separation, flocculation, and coalescence, can occur in Nano emulsions. Nano emulsions are susceptible to instability over time due to their large surface area and tiny droplet size. [62] Chemical stability may also be an issue, especially for delicate medications that could oxidize or hydrolyze in the emulsion. Careful formulation and the application of stabilizers that can avert these problems are necessary to ensure long-term stability.

b. Manufacturing and Scalability:

Because exact control over formulation parameters and manufacturing conditions is required, scaling up the production of Nano emulsions from laboratory to industrial scale can be difficult. Although high-energy techniques like high-pressure homogenization are frequently employed in manufacturing, they can be expensive and call for specialized tools. Despite being easier, low-energy techniques could have trouble producing consistent quality on a bigger scale. In order to retain the nanoemulsion's quality and performance during the switch from bench-scale to pilot-scale manufacturing, considerable optimization is frequently needed.

VII.CURRENT DEVELOPMENTS AND INNOVATIONS

Functionalization, combination therapies, and gene therapy are some of the new medication delivery options made possible by recent developments in Nano emulsion technology.

a. Nano emulsion Functionalization:

The functionalization of Nano emulsions to improve their therapeutic efficacy and targeting capabilities is one recent invention. To deliver medications to particular cells or tissues, surface modification approaches entail affixing targeted ligands or antibodies to the Nano emulsion particles. This focused strategy lessens off-target effects and increases drug delivery precision.

b. Combination therapies:

In order to produce synergistic effects and better treatment outcomes, combination treatments give several medications or therapeutic agents at the same time. Because Nano emulsions may encapsulate and transport numerous medications in a single formulation, they are being employed more and more in combination therapy. This strategy enables synergistic effects and coordinated administration, which can improve treatment efficacy and lower the likelihood of drug resistance.

c. Gene therapy using Nano emulsions:

Through the introduction of genetic material into a patient's cells, gene therapy seeks to treat or prevent diseases. Because Nano emulsions may encapsulate and shield nucleic acids like DNA, RNA, and siRNA from degradation, they are being investigated as carriers for gene therapy applications. [63].

VIII.FUTURE PERSPECTIVE

Given that continuous research is showing that Nano emulsions have promise in customized medicine, their future in medication delivery appears bright. Nano emulsions are anticipated to improve therapeutic efficacy and reduce adverse effects by enabling personalized treatments based on the genetic, environmental, and lifestyle characteristics of each patient. These customized formulations are being made possible by developments in biomaterials and nanotechnology. By improving drug solubility, stability, and targeting, Nano emulsions have the potential to revolutionize healthcare and result in improved treatments for conditions like infections, cancer, and neurological disorders. But there are still difficulties, such as problems with safety, scalability, stability, and regulatory compliance. In order to increase their use in medication delivery, future research must concentrate on creating reliable production procedures, enhancing long-term stability, and resolving safety and regulatory issues. It should also look into novel uses.

IX.CONCLUSIONS

With continuous research and advancements extending their uses and advantages, Nano emulsions have enormous potential as sophisticated drug delivery systems. Improved bioavailability, targeted and controlled release, protection of encapsulated medications, and increased patient compliance are just a few of the many benefits that Nano emulsions provide in drug delivery. They can be administered orally, topically, parenterally, or pulmonary, among other ways, which makes them adaptable and efficient delivery systems for a variety of medicinal substances. The potential of Nano emulsions to solve intricate medical issues and enhance treatment outcomes is further highlighted by recent developments in functionalization, combination treatments, and gene therapy. With continued research spurring advancements and broadening their potential uses, Nano emulsions in medication delivery appear to have a bright future. Nano emulsions are anticipated to be essential in determining the direction of medication delivery and personalized treatment in the future as technology develops and new problems are solved. Realizing the full potential of Nano emulsions and revolutionizing healthcare will require ongoing research and development.

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