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Development and Evaluation of Nanoemulsion Systems for Poorly Soluble Drugs

Snehal M. Sunkare[1], Mayuri G. Zore[2], Ritesh S. Rajput[3], Rahul G. Belokar[4], Raj S. Santre[5], Pavan A. Ghuge[6], Shivam R. Ingle[7]

[1,2]*Lecturer Gawande college of Pharmacy, Sakharkherda*

[3,4,5,6,7]*Student Gawande College of Pharmacy*

***Abstract*— Poor aqueous solubility is among the most persistent challenges in modern pharmaceutics. Nearly seventy percent of newly discovered chemical entities exhibit limited solubility in water, resulting in erratic absorption, low bioavailability, and inconsistent therapeutic response. To overcome these issues, scientists have developed advanced formulation systems capable of increasing dissolution rate and improving systemic delivery. Among these, nanoemulsion technology has emerged as one of the most promising approaches for solubilizing lipophilic molecules. A nanoemulsion is a fine, thermodynamically unstable yet kinetically stable colloidal dispersion of two immiscible liquids stabilized by surfactants and co-surfactants, with droplet sizes typically ranging between 20 and 200 nanometers. Their unique physicochemical characteristics such as large surface area, optical clarity, and the ability to encapsulate both hydrophilic and lipophilic drugs make them highly adaptable for oral, topical, parenteral, and ophthalmic administration. This review provides a detailed, humanized exploration of the formulation principles, preparation techniques, and characterization parameters of nanoemulsions. It also highlights their mechanisms for enhancing solubility and bioavailability, summarizes recent pharmaceutical applications, and discusses future perspectives in drug delivery innovation.**

***Keywords*—Poor aqueous solubility, Chemical entities, Limited solubility, Absorption, Bioavailability, Therapeutic response, Advanced formulation systems, Dissolution rate, Systemic delivery, Nanoemulsion technology, Lipophilic molecules**

I. INTRODUCTION

The success of any pharmaceutical formulation depends primarily on the drug's ability to dissolve and reach systemic circulation in sufficient concentration to exert its pharmacological effect. However, the last two decades have witnessed an unprecedented increase in the number of poorly soluble molecules emerging from drug discovery programs. These compounds often show excellent biological activity in vitro but fail to reach therapeutic levels in vivo because of poor dissolution in gastrointestinal fluids.

According to the Biopharmaceutics Classification System, drugs with high permeability but low solubility (Class II) and those with both low solubility and low permeability (Class IV) constitute the majority of new chemical entities. (1)

For these classes, dissolution rate rather than permeability becomes the limiting step in absorption, leading to sub-therapeutic plasma levels, variability in bioavailability, and reduced patient adherence due to high dosing frequency. Traditional formulation strategies such as micronization, salt formation, solid dispersions, and the use of complexing agents have provided partial solutions, yet they often suffer from limitations including physical instability, recrystallization of the active compound, or incompatibility with excipients. Consequently, the focus of pharmaceutical scientists has shifted toward the development of novel delivery systems that can enhance solubility without compromising stability or safety. Within this framework, nanoemulsions have drawn considerable attention because of their simplicity, versatility, and ability to deliver drugs with widely differing physicochemical properties. Nanoemulsions are isotropic systems composed of oil and water stabilized by a surfactant blend. The size of their dispersed droplets typically lies below 200 nm, giving them a translucent appearance and a high interfacial area for drug dissolution. In contrast to conventional coarse emulsions, nanoemulsions exhibit long-term kinetic stability, low viscosity, and excellent optical transparency. The surfactants reduce interfacial tension between oil and water phases, while co-surfactants further improve flexibility at the interface, allowing spontaneous formation of droplets under mild mechanical conditions. These physicochemical features make nanoemulsions particularly suitable for the solubilization of hydrophobic drugs such as cyclosporine, paclitaxel, curcumin, and celecoxib agents that traditionally display poor oral bioavailability.

The pharmaceutical significance of nanoemulsions extends beyond mere solubility enhancement. Their nanoscale droplet size ensures rapid diffusion and intimate contact with biological membranes, facilitating improved permeability and absorption.

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In oral delivery, nanoemulsions can promote lymphatic transport, thereby bypassing hepatic first-pass metabolism and increasing systemic bioavailability. In parenteral routes, they provide a stable carrier for intravenous administration of poorly soluble anticancer or anesthetic agents. Topically, they improve drug penetration through the stratum corneum, and in ophthalmic formulations, they offer sustained release with minimal irritation. These diverse applications highlight the broad potential of nanoemulsion systems as a universal platform for challenging drugs.(2)

II. Formulation Principles

The design of a nanoemulsion begins with the careful selection of its components: oil, aqueous medium, surfactant, and co-surfactant. The oil phase serves as the solubilizing reservoir for the hydrophobic drug, while the aqueous phase provides the external environment in which the droplets are dispersed. Surfactants such as polysorbates, sorbitan esters, or polyethylene glycol derivatives stabilize the interface by forming a coherent monolayer around the oil droplets, thus preventing coalescence. Co-surfactants often short-chain alcohols or glycols further reduce interfacial tension and increase fluidity, enabling the formation of nanosized globules with minimal energy input. The ratio among these components is critical; too little surfactant leads to instability, while excessive amounts can cause irritation or toxicity. Therefore, empirical screening and the construction of pseudo-ternary phase diagrams are commonly used to identify the most stable and transparent nanoemulsion region.(3)

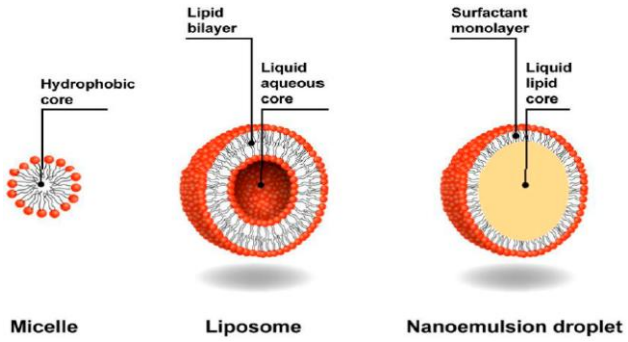

Fig No:- 1) **composition of micelles, liposomes, and nanoemulsion droplets**.

III. Preparation Methods

Several techniques exist for preparing nanoemulsions, broadly classified into high-energy and low-energy methods.

High-energy approaches rely on mechanical devices such as high-pressure homogenizers, ultrasonication probes, or microfluidizers to break down larger droplets into nanoscale sizes. These methods yield highly uniform dispersions with good reproducibility, though they may require costly equipment and temperature control to prevent degradation of sensitive drugs. Low-energy techniques, on the other hand, exploit the physicochemical properties of the system specifically interfacial tension changes during phase inversion or spontaneous emulsification. The phase inversion temperature method* utilizes temperature-induced shifts in surfactant solubility to produce fine droplets, while spontaneous emulsification involves diffusion of the co-solvent from the oil phase to the aqueous phase, resulting in spontaneous formation of nanodroplets. Each method offers advantages depending on the physicochemical nature of the active ingredient and the intended route of administration.(4)

Preparation Methods of Nanoemulsions:-The preparation of nanoemulsions represents a delicate balance between physicochemical optimization and mechanical energy input. Since nanoemulsions are thermodynamically unstable systems, their successful formation depends on the method used to overcome interfacial tension and generate droplets within the nanometric range. Broadly, preparation strategies are classified into high-energy and low-energy techniques. Each approach has distinct advantages, limitations, and areas of application depending on the drug's physicochemical nature, the desired route of administration, and the scalability of the process.

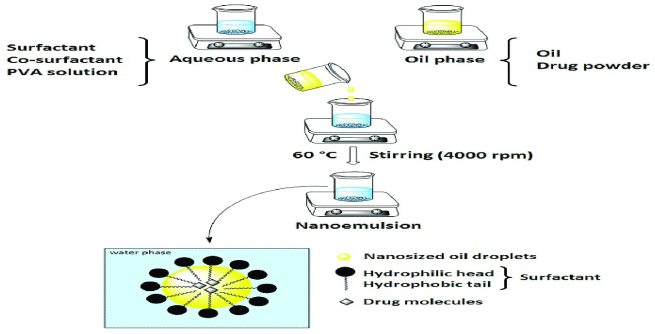

Fig No:- 2) Preparing a Nanoemulsion

3.1 High-Energy Methods

High-energy methods employ external mechanical forces to break down coarse emulsions into nanosized droplets. The goal is to impart sufficient energy to overcome the cohesive forces within the oil phase, enabling formation of stable droplets within the 20–200 nm range.

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These techniques are widely used in both industrial and research settings due to their reproducibility and ability to yield highly uniform dispersions.(5)

3.2. High-Pressure Homogenization

High-pressure homogenization (HPH) is one of the most established techniques for nanoemulsion production. In this method, a pre-emulsion (a coarse mixture of oil, water, and surfactants) is forced through a narrow valve under extremely high pressures ranging from 500 to 2000 bar. The sudden pressure drop, turbulence, and intense shear forces cause the oil droplets to disintegrate into nanoscale globules. This process may be repeated several times (typically 5–10 cycles) to achieve the desired droplet size and polydispersity. HPH is particularly effective for thermally stable drugs and is easily scalable for industrial production, though it requires significant energy input and may not be ideal for heat-sensitive bioactives.(6)

3.3. Ultrasonication

Ultrasonication utilizes acoustic energy generated by a probe or bath sonicator to produce cavitation—rapid formation and collapse of microbubbles in the liquid. The implosion of these bubbles releases localized shockwaves and shear forces that disrupt the oil droplets into nanosized particles. This technique is simple, rapid, and suitable for small-scale formulation screening. Parameters such as sonication time, amplitude, and temperature control are critical to maintain droplet uniformity and prevent degradation of sensitive compounds. Although scalable to some extent, continuous large-batch production using ultrasonication remains challenging due to equipment limitations and localized heating.

3.4.Microfluidization

Microfluidization is a more advanced high-energy method that employs a microfluidizer equipped with an interaction chamber. The pre-emulsion is forced through microchannels at very high velocities under pressures up to 2500 bar. The collision of fluid streams within the chamber generates intense shear, turbulence, and cavitation, breaking down droplets to the nanoscale. This technique ensures excellent droplet size uniformity and narrow distribution (low polydispersity index), making it ideal for parenteral or ophthalmic formulations where consistency is critical. Microfluidization is, however, capital intensive and demands careful maintenance of temperature and pressure to ensure reproducibility.(6)

4.5. High-Shear Mixing

High-shear mixers operate by rotating a rotor at high speeds (typically 10,000–25,000 rpm), which subjects the system to strong shear stress and turbulence. Although this technique generally produces larger droplets than high-pressure homogenization or microfluidization, it serves as a valuable pre-emulsification step before fine homogenization. High-shear mixing is often used when developing thermolabile formulations, as it generates less heat compared with other high-energy techniques.

3.6 Low-Energy Methods

Low-energy methods rely on the intrinsic physicochemical properties of the surfactant–oil–water system rather than mechanical disruption. These techniques are energy-efficient and particularly suitable for heat- or shear-sensitive drugs, though they may require careful optimization of formulation parameters to ensure reproducibility.(7)

3.7. Phase Inversion Temperature (PIT) Method

The phase inversion temperature method exploits the temperature-dependent solubility of nonionic surfactants, especially those based on polyoxyethylene chains. At lower temperatures, these surfactants are more hydrophilic and tend to form oil-in-water (O/W) emulsions. As temperature increases, the hydrophilic polyoxyethylene groups dehydrate, making the surfactant more lipophilic and promoting water-in-oil (W/O) emulsions. When the temperature reaches a specific point known as the phase inversion temperature the interfacial tension becomes minimal, enabling spontaneous formation of nanometric droplets. Rapid cooling at this point “freezes” the nanoemulsion structure, resulting in a kinetically stable dispersion. The PIT method is advantageous for thermally stable drugs and offers excellent control over droplet size without requiring expensive equipment.(8)

3.8 Spontaneous Emulsification (Self-Emulsification)

In spontaneous emulsification, the nanoemulsion forms spontaneously when the organic phase containing oil, surfactant, and co-surfactant is mixed with an aqueous phase under gentle stirring. The driving force for droplet formation arises from the diffusion of the co-solvent and surfactant between phases, which reduces interfacial tension and facilitates dispersion. This method is highly versatile and forms the basis of self-nanoemulsifying drug delivery systems (SNEDDS) used in oral formulations.

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The technique is simple, scalable, and does not require sophisticated equipment; however, precise control over component ratios is essential to avoid instability or phase separation.

3.9.Phase Inversion Composition (PIC) Method

In the phase inversion composition technique, the relative proportion of oil, water, and surfactant is gradually altered, causing the system to undergo a phase transition from W/O to O/W. During this inversion, ultra-low interfacial tension conditions are momentarily achieved, enabling the formation of nanosized droplets. The PIC method allows precise control over nanoemulsion droplet size and is useful in situations where temperature control(as in PIT) is not feasible.(9)

3.10 Solvent Evaporation and Solvent Displacement Techniques

Solvent-based low-energy methods involve dissolving the drug and oil phase in a volatile organic solvent such as ethanol, acetone, or ethyl acetate, followed by its diffusion or evaporation in the aqueous phase. The interfacial turbulence created during solvent displacement leads to formation of nanometric droplets. The solvent is then removed under reduced pressure or continuous stirring, yielding a stable nanoemulsion. These techniques are particularly valuable for encapsulating lipophilic drugs that dissolve readily in organic media, but complete solvent removal is essential to ensure safety and regulatory compliance.

3.11Emerging and Hybrid Techniques

Recent innovations have combined elements of both high- and low-energy methods to achieve enhanced efficiency and reproducibility. Ultrasound-assisted microfluidization, for instance, integrates cavitation from ultrasonication with shear from microfluidization to minimize energy consumption while ensuring narrow droplet distribution. Similarly, membrane emulsification utilizes porous membranes to control droplet formation, producing nanoemulsions with exceptional uniformity at relatively low pressures. High-energy premix membrane emulsification and electrospray-based methods are also gaining traction for their ability to fabricate thermally sensitive formulations with high encapsulation efficiency. In addition, continuous manufacturing processes are being developed using microreactors, allowing real-time control over droplet formation, size, and stability.(10)

IV. Characterization Of Nanoemulsions

The evaluation of nanoemulsion quality requires an array of analytical techniques to ensure uniformity, stability, and reproducibility. The most fundamental parameter is droplet size distribution, which is typically measured using dynamic light scattering. Uniform nanosized droplets enhance optical clarity and stability by minimizing gravitational separation and coalescence. Zeta potential measurements provide insight into surface charge and electrostatic repulsion between droplets; high absolute values indicate good physical stability. Transmission electron microscopy offers visual confirmation of droplet morphology, revealing spherical or occasionally ellipsoidal structures surrounded by surfactant layers. Other critical tests include viscosity analysis using rheometers, refractive index measurement, drug loading and entrapment efficiency determination by HPLC or UV spectroscopy, and accelerated stability studies under varying temperature and centrifugation conditions. Collectively, these parameters define the robustness and quality of the formulation.(11)

The successful development of a nanoemulsion formulation does not end at its preparation. Its stability, therapeutic efficiency, and reproducibility are governed by a range of physicochemical parameters that must be thoroughly evaluated. Characterization is therefore a critical stage in nanoemulsion development, serving not only to confirm nanoscale droplet size but also to assess homogeneity, interfacial properties, drug distribution, and long-term behavior under different environmental conditions. Since nanoemulsions are thermodynamically unstable but kinetically stabilized systems, even minor variations in formulation or processing conditions can significantly influence their properties.

A comprehensive characterization ensures that the formulation meets desired specifications for bioavailability, safety, and efficacy. The major characterization parameters include droplet size and distribution, zeta potential, morphology, viscosity, refractive index, pH, drug content, stability, and thermodynamic behavior. Each parameter provides unique insights into the formulation's quality and performance.(12)

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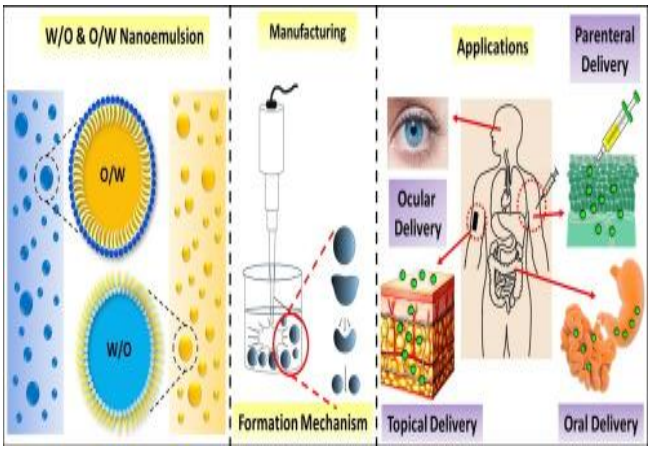

Fig No:- 3) W/O (water-in-oil) and O/W (oil-in-water) Nanoemulsions.

5.1 Droplet Size and Polydispersity Index (PDI)

The most fundamental characteristic of a nanoemulsion is its droplet size distribution. Droplet size directly influences optical clarity, stability, and the rate of drug release and absorption. Smaller droplets provide a larger surface area for solubilization, leading to enhanced dissolution and bioavailability. Droplet size and distribution are typically measured using Dynamic Light Scattering (DLS), also known as Photon Correlation Spectroscopy (PCS). This technique analyzes the fluctuations in light intensity scattered by particles undergoing Brownian motion.

The polydispersity index (PDI) provides information on the uniformity of the droplet population. A lower PDI (below 0.3) indicates a homogeneous nanoemulsion with uniform droplets, while higher values suggest the presence of aggregates or multiple droplet populations. In general, nanoemulsions with droplet sizes between 20–200 nm and a PDI below 0.25are considered optimal for pharmaceutical use. Advanced instruments like Nanoparticle Tracking Analysis (NTA) and Laser Diffraction (LD) can provide complementary size distribution data and concentration profiles, offering deeper insight into droplet behavior under physiological conditions.

5.2 Zeta Potential

Zeta potential is another critical indicator of nanoemulsion stability. It represents the electrical potential at the interface between the dispersed droplet and the surrounding continuous phase. Measured using electrophoretic light scattering, zeta potential reflects the degree of electrostatic repulsion between adjacent droplets.

A high magnitude of zeta potential (either positive or negative, typically above ±30 mV) prevents coalescence and aggregation due to repulsive forces, thereby improving stability.For oil-in-water nanoemulsions stabilized with nonionic surfactants, zeta potential values are generally low, but steric stabilization by the surfactant layer compensates for the lack of charge. Conversely, ionic surfactants contribute both electrostatic and steric stability. Monitoring zeta potential over time also helps predict formulation longevity; significant changes may indicate surfactant desorption, droplet flocculation, or pH-driven instability.

5.3 Morphology and Structural Analysis

The morphology and internal structure of nanoemulsion droplets reveal important details about the formulation's stability and encapsulation behavior. Imaging techniques such as Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM) , and Atomic Force Microscopy (AFM) are commonly employed. TEM provides high-resolution images of droplet size and shape, confirming spherical morphology and uniform distribution. SEM, while typically used for solid surfaces, can visualize the dried form of nanoemulsions when converted into films or gels. AFM allows for three-dimensional surface mapping under near-physiological conditions, providing valuable information about surface roughness and particle aggregation tendencies.(13)

Cryo-TEM, a variation of TEM where samples are frozen rapidly in liquid nitrogen, is particularly useful for visualizing nanoemulsions in their native hydrated state without structural artifacts. These imaging techniques collectively validate the physical uniformity and nano-dimensionality of the formulation, corroborating data obtained from DLS.

5.4 Viscosity and Rheological Behavior

The viscosity of a nanoemulsion influences its stability, drug release profile, and application performance. Rheological measurements determine how the formulation flows under different shear conditions. Nanoemulsions typically exhibit Newtonian flow behavior at low oil and surfactant concentrations, but higher concentrations can result in non-Newtonian or pseudoplasticbehavior. This is particularly important for topical or parenteral applications, where viscosity must be optimized for syringeability or spreadability.(14)

Viscosity is measured using rotational viscometers or rheometers under controlled temperature conditions. A moderate increase in viscosity generally enhances kinetic stability by slowing droplet movement and coalescence.

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However, excessively high viscosity can reduce drug diffusion and hinder absorption, so a balance must be achieved during formulation design.(15)

5.5 Refractive Index and Optical Transparency

Optical clarity is a distinguishing feature of nanoemulsions, resulting from droplet sizes smaller than the wavelength of visible light. Measurement of refractive index (RI) using an Abbe refractometer provides information about the isotropic nature and homogeneity of the system. The RI of a nanoemulsion should ideally fall between those of the oil and aqueous phases, indicating uniform dispersion. Visual transparency can also serve as a qualitative indicator of droplet size uniformity. Cloudiness or phase separation may indicate coalescence or instability, necessitating reformulation or optimization of surfactant concentration. (16)

VI. Mechanism Of Solubility Enhancement

The ability of nanoemulsions to improve solubility arises from their large interfacial area and efficient drug partitioning. The small droplet size dramatically increases the surface available for drug diffusion into the aqueous phase. Moreover, surfactants create a microenvironment that enhances wettability and dispersion of hydrophobic molecules. Many surfactants also act as permeability enhancers, transiently disrupting lipid bilayers to facilitate transcellular transport. Additionally, the lipidic nature of the oil phase can stimulate lymphatic uptake, particularly for highly lipophilic drugs, enabling bypass of hepatic metabolism and prolonged systemic exposure. Together, these mechanisms produce a significant improvement in oral and parenteral bioavailability compared with conventional formulations.

This multifaceted mechanism involves several overlapping phenomena: reduction of particle size, increase in surface area, interfacial stabilization by surfactants, modification of thermodynamic activity, improved wetting and dispersion, and enhancement of permeability and lymphatic transport. Each mechanism plays a distinct yet synergistic role in ensuring that the drug remains in a solubilized, bioavailable form from formulation to absorption.(17)

6.1 Reduction of Particle Size and Increase in Surface Area

At the core of nanoemulsion-mediated solubilizationlies the dramatic reduction of droplet size to the nanometer range (typically 20–200 nm). According to the Noyes–Whitney equation, the dissolution rate of a solute is directly proportional to its surface area.

When droplet size decreases, the surface area available for dissolution increases exponentially, facilitating a faster transfer of drug molecules from the dispersed phase to the surrounding aqueous medium. The nanoscale dimensions also ensure that the drug remains molecularly dispersed or in a quasi-solubilized state within the oil droplets, reducing the risk of crystallization or precipitation. The enormous surface-to-volume ratio of nanoemulsion droplets further enhances thermodynamic activity, ensuring that a larger proportion of the drug remains in a readily diffusible form.(18)

6.2 Solubilization Within the Oil Phase

Nanoemulsions act as reservoirs that solubilize lipophilic drugs in their internal oil phase. The selection of a suitable oil is critical, as the solubilization capacity directly depends on the oil's molecular affinity with the drug. Medium-chain triglycerides, oleic acid, isopropyl myristate, and ethyl oleate are commonly used oils that provide an optimal environment for dissolving nonpolar drugs. The high solubilization potential of the oil phase prevents drug precipitation even after dilution in gastrointestinal fluids, which is particularly advantageous for oral delivery systems.

The oil droplets essentially serve as microscopic "solvent compartments" that carry the drug in a dissolved form, maintaining its concentration gradient across the gastrointestinal mucosa and facilitating passive diffusion into systemic circulation.(19)

6.3 Surfactant-Mediated Interfacial Solubilization

Surfactants are amphiphilic molecules that play a pivotal role in nanoemulsion formation and stability. Their hydrophilic and lipophilic segments arrange themselves at the oil–water interface, reducing interfacial tension and creating a stable monolayer around the dispersed droplets.

This interfacial layer serves as a microenvironment that can accommodate drugs with varying polarity. For example, drugs that are moderately lipophilic may partition preferentially within the interfacial film rather than the core of the oil droplet. The surfactant molecules also form micellar or mixed-micellar structures upon dilution, which continue to solubilize the drug in gastrointestinal fluids, ensuring sustained supersaturation and preventing precipitation.(20)

In addition, surfactants such as polysorbates and polyethylene glycol esters can enhance drug permeability by interacting with epithelial cell membranes or modulating tight junctions, allowing greater drug transport across biological barriers.

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6.4 Increased Thermodynamic Activity and Supersaturation

From a thermodynamic perspective, nanoemulsions maintain drugs in a high-energy, solubilized state. The nanoscale droplet size leads to elevated curvature at the oil–water interface, increasing the system's interfacial energy. This heightened energy translates into greater thermodynamic activity of the solubilized drug, meaning it possesses a higher "escaping tendency" to move from the dispersed phase into the surrounding medium.Upon dilution in biological fluids, the concentration of the solubilized drug may temporarily exceed its equilibrium solubility, resulting in a supersaturated state. Such a state provides a strong driving force for passive diffusion across biological membranes before precipitation can occur. To stabilize this transient supersaturation, polymers or surfactant combinations are often included to inhibit crystallization, allowing prolonged absorption.

6.5 Improved Wetting and Dispersion

One of the major limitations of poorly soluble drugs is their hydrophobic surface, which resists wetting by aqueous fluids. Nanoemulsions overcome this problem through the presence of surfactants and co-surfactants that drastically reduce surface and interfacial tension. The surfactant molecules adsorb onto the hydrophobic surface of the drug particles, improving their wettability and dispersion in aqueous environments.This enhanced wetting facilitates intimate contact between the drug and the dissolution medium, accelerating solubilization. Additionally, during oral administration, the surfactants in nanoemulsions can interact with bile salts and phospholipids in the gastrointestinal tract, forming mixed micelles that further promote solubilization and transport of hydrophobic drugs.

VII. Applications In Drug Delivery

Nanoemulsions have found applications across nearly every major route of drug administration. In oral formulations, they improve solubility and absorption of compounds such as curcumin, silymarin, and itraconazole. Intravenous nanoemulsions like propofol injection exemplify their safety and efficacy for parenteral use. In dermatology, nanoemulsions enhance penetration of antifungal and anti-inflammatory agents through the skin barrier. Ophthalmic nanoemulsions have been developed for drugs like cyclosporine to provide sustained release and improved ocular tolerability. Nasal and pulmonary nanoemulsions are being explored for rapid systemic absorption and brain-targeted delivery.

Their versatility, combined with the ability to encapsulate both small molecules and biologicals, positions nanoemulsions as one of the most adaptable delivery systems in modern pharmaceutics.

7.1 Oral Drug Delivery

The oral route remains the most preferred and convenient method of drug administration due to its simplicity, patient compliance, and cost-effectiveness. However, the poor aqueous solubility and extensive first-pass metabolism of many drugs severely limit their bioavailability. Nanoemulsions have successfully addressed these challenges by improving solubility, dissolution rate, and intestinal permeability.Upon oral administration, the nanoemulsion undergoes dispersion in gastrointestinal fluids, forming fine oil droplets stabilized by surfactants and co-surfactants. These droplets can solubilize hydrophobic drugs within the oil core and maintain a high concentration gradient across the intestinal epithelium, promoting passive diffusion. The presence of surfactants such as polysorbates, polyethylene glycol esters, or Labrasol further enhances permeability by transiently loosening tight junctions between epithelial cells. Additionally, the lipid components of nanoemulsions stimulate bile secretion and chylomicron formation, facilitating lymphatic uptake of the drug and bypassing hepatic first-pass metabolism.

For example, oral nanoemulsion formulations of drugs like Cyclosporine AFenofibrateCurcumin, and Itraconazole have demonstrated significant improvements in bioavailability—sometimes exceeding tenfold compared to conventional suspensions. The ability to maintain supersaturated states in the intestinal milieu also ensures prolonged absorption and reduced variability among patients. These properties make nanoemulsions an indispensable tool in oral delivery of BCS Class II and IV drugs.(21)

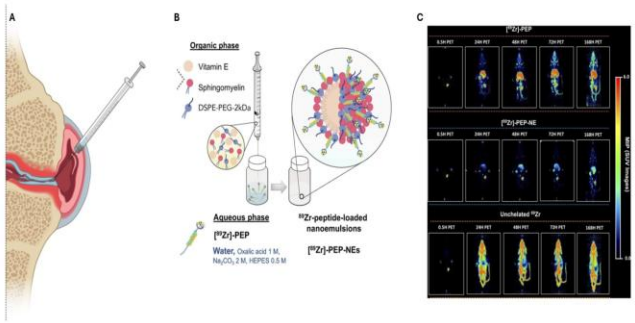

Fig No:- 4) Advance in nanoemulsion-Based Drug Delivery Across

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Nanoemulsion-Based Drug Delivery Across Different Administration Routes

7.2 Parenteral and Intravenous Delivery

Parenteral nanoemulsions have attracted considerable interest for the delivery of drugs that require rapid onset of action or systemic targeting. The fine droplet size (<200 nm) allows intravenous administration without the risk of embolism or vascular irritation. Moreover, the isotropic and sterile nature of nanoemulsions ensures compatibility with physiological fluids and blood components. Nanoemulsion-based injectable systems provide several advantages: they bypass the gastrointestinal tract, avoid enzymatic degradation, and deliver drugs directly into systemic circulation. Lipophilic drugs are solubilized within the oil phase, while surfactants stabilize the dispersion, allowing controlled release at the target site. This approach is widely used for anesthetics such as Propofol, which is formulated as a lipid nanoemulsion to provide rapid induction and smooth recovery with minimal toxicity. Similarly, anticancer drugs like Paclitaxel and Docetaxel have been successfully incorporated into parenteral nanoemulsions, offering enhanced solubility, reduced side effects, and improved tumor targeting.

In targeted drug delivery, surface modification of nanoemulsions with ligands such as folic acid, antibodies, or peptides allows site-specific accumulation via receptor-mediated endocytosis. This strategy is particularly effective in cancer therapy and in delivering peptides, proteins, and vaccines, where controlled biodistribution is crucial.

7.3 Topical and Dermal Delivery

Nanoemulsions have shown tremendous potential in dermatological and cosmetic applications due to their ability to enhance skin permeation, hydration, and drug retention in deeper layers. The small droplet size enables close contact with the stratum corneum, facilitating diffusion through lipid bilayers. Moreover, surfactants in the formulation can temporarily disrupt the stratum corneum's lipid organization, increasing permeability without causing irritation. Topically applied nanoemulsions exhibit non-greasy texture, rapid absorption, and high spreadability, making them ideal for creams, gels, and lotions. They are capable of delivering both hydrophilic and lipophilic drugs in a controlled manner, providing localized action with minimal systemic exposure. Drugs such as Clotrimazole, Ketoconazole, Diclofenac, Ibuprofen, and Vitamin E have been successfully formulated into nanoemulsion-based topical systems for treatment of fungal infections, inflammation, and skin disorders.(22)

Additionally, nanoemulsions are increasingly used in cosmeceuticals for the delivery of antioxidants, anti-aging agents, and photoprotective compounds like Retinol, Coenzyme Q10, and Curcumin. Their ability to improve skin penetration and provide controlled release ensures longer-lasting effects with improved consumer satisfaction.

7.4 Transdermal Delivery

Transdermal nanoemulsions offer a non-invasive and controlled drug delivery approach that circumvents hepatic metabolism and provides sustained plasma levels. Their formulation allows the drug to cross the stratum corneum barrier, primarily through intercellular lipid pathways. The inclusion of penetration enhancers such as oleic acid, isopropyl myristate, or ethanol in nanoemulsions further augments drug flux across the skin. The system provides steady-state release, ensuring prolonged therapeutic action with minimal fluctuations in plasma concentration. Transdermal nanoemulsions are particularly useful for chronic conditions requiring long-term drug administration, such as hormone therapy, pain management, and cardiovascular diseases. Drugs like Nimodipine, Lidocaine, and Nicotine have been formulated into nanoemulsion-based transdermal patches or gels with superior efficacy and reduced side effects compared to conventional systems. Their biocompatibility and ease of application also make nanoemulsions suitable candidates for personalized drug delivery and combination therapies.

VIII. Safety And Stability Considerations

Despite their advantages, the long-term stability and safety of nanoemulsions require careful evaluation. Because they are thermodynamically unstable systems, changes in temperature, pH, or ionic strength can cause phase separation, Ostwald ripening, or coalescence. The choice of surfactant and its concentration largely determine these outcomes. From a toxicological perspective, surfactants and co-solvents must be non-irritant and biocompatible; therefore, pharmaceutical-grade excipients such as Tween 80 or PEG 400 are preferred. In vivo studies have shown that most well-formulated nanoemulsions are safe for both short- and long-term use, provided that droplet size remains below 200 nm and excipient levels fall within regulatory limits.(23)

Safety and stability are fundamental parameters in determining the clinical applicability and regulatory acceptance of nanoemulsion-based drug delivery systems.

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Although nanoemulsions offer remarkable advantages in solubility and bioavailability, their formulation complexity demands careful evaluation of physicochemical stability, biocompatibility, and potential toxicity before therapeutic use. From a safety perspective, nanoemulsions are generally regarded as biocompatible due to their composition typically oils, surfactants, and co-surfactants that are pharmaceutically approved and metabolizable. However, the selection of these excipients plays a pivotal role. Nonionic surfactants such as polysorbates, polyethylene glycol derivatives, and sorbitan esters are preferred for their low toxicity and minimal irritation potential. Excessive concentrations of surfactants or co-solvents, however, may cause membrane disruption or cytotoxicity, especially in parenteral or ocular applications. Therefore, optimizing surfactant ratios is essential to balance emulsification efficiency and safety.(24)

Stability remains another major challenge for nanoemulsion formulations. As thermodynamically unstable systems, they are prone to physical changes such as creaming, flocculation, coalescence, and phase separation during storage or under stress conditions. Ensuring long-term stability requires the appropriate selection of oils with low interfacial tension, surfactant systems that provide both steric and electrostatic stabilization, and controlled processing conditions. (25)

The use of antioxidants (like tocopherol or BHT) helps protect lipid components from oxidative degradation, especially in light- or oxygen-sensitive formulations. Temperature and pH variations can also impact droplet integrity and drug solubility. Stability studies under accelerated ICH conditions (e.g., 40°C ± 2°C, 75% RH ± 5%) are therefore conducted to predict shelf life. Parameters such as droplet size, zeta potential, pH, viscosity, and drug content are routinely monitored to confirm formulation robustness over time. A stable nanoemulsion should maintain consistent droplet size distribution, minimal phase separation, and no drug precipitation throughout its intended shelf life. Toxicological studies in animal models and cell cultures further confirm safety by assessing hemocompatibility, irritation potential, and systemic toxicity. Most reports indicate that nanoemulsions composed of physiological lipids and mild surfactants exhibit excellent tolerance and biodegradability. Nonetheless, thorough preclinical testing and regulatory validation remain mandatory to ensure safe human use.(27)

IX. Future Perspectives And Development

With advances in nanotechnology, nanoemulsion research is rapidly moving toward multifunctional and targeted systems. Emerging studies incorporate polymers, peptides, or ligands onto droplet surfaces to achieve site-specific delivery. Nanocarriers that respond to stimuli such as pH, temperature, or redox environment are under development to release drugs selectively at diseased sites. Additionally, the integration of nanoemulsions with solid carriers resulting in solid nanoemulsions or nanoemulsion-based gels offers improved shelf stability and controlled release characteristics. The combination of experimental research with computational modeling now allows better prediction of formulation behavior, reducing development time and cost. Overall, nanoemulsions are poised to play a central role in next-generation pharmaceutical design, particularly for poorly soluble and biologically complex molecules.(28)

X. Conclusion

Nanoemulsion technology represents a sophisticated yet practical approach to solving one of the most enduring problems in pharmaceutical science—poor solubility of therapeutic agents. By transforming insoluble drugs into kinetically stable nanoscale dispersions, nanoemulsions improve dissolution, enhance bioavailability, and provide flexible routes of administration. Their adaptability, coupled with advances in analytical characterization and formulation science, ensures their continuing evolution as a leading platform for drug delivery innovation. Continued interdisciplinary research will further refine their design, ensuring that nanoemulsions move from laboratory promise to clinical and industrial reality.The intrinsic advantages of nanoemulsions stem from their unique physicochemical architecture. The presence of surfactant and co-surfactant molecules not only reduces interfacial tension but also creates a dynamic interfacial layer that stabilizes droplets and prevents coalescence. This balance of interfacial energy and thermodynamic activity contributes to the remarkable solubilizing capacity of nanoemulsions. When carefully formulated using pharmaceutically acceptable excipients, they demonstrate excellent safety, biocompatibility, and patient tolerability, as evidenced by numerous preclinical and clinical studies.

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