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REVIEW ARTICLE

Development and Therapeutic Applications of Pharmaceutical Nanoemulsions in Modern Drug Delivery

Nikhitha Gajula*[1], Chaitanya B[2]

[1] *UG Scholar, Department of Pharmaceutics, Joginpally BR Pharmacy College, Moinabad, Telangana, India*
[2] *Assistant Professor, Department of Pharmaceutics, Joginpally BR Pharmacy College, Moinabad, Telangana, India*

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Abstract: Nanoemulsions are thermodynamically stable colloidal dispersions with droplet sizes ranging from 20 to 200 nm. These systems improve drug solubility, stability, and bioavailability through their unique physicochemical properties and versatile delivery capabilities. The formulation of nanoemulsions involves careful selection of oils, surfactants, and preparation methods - either high-energy mechanical processes or low-energy spontaneous emulsification techniques. The resulting nanoscale droplets exhibit remarkable stability and can be tailored for various administration routes including oral, parenteral, topical, and ocular delivery. Recent developments show their potential in improving the pharmacokinetic profiles of poorly water-soluble drugs, enabling targeted delivery, and reducing dosing frequency. Nanoemulsions are also used in food technology, cosmetics, and agriculture. Nanoemulsions improves the therapeutic efficacy of anti-cancer drugs, improving ocular drug delivery, and facilitating brain targeting through intranasal administration. Their ability to protect sensitive bioactive compounds while maintaining optimal droplet size distribution makes them particularly valuable for commercial pharmaceutical formulations. Despite these advantages, considerations regarding preparation methods, stability optimization, and regulatory compliance remain crucial for successful implementation in clinical applications.

Keywords: Nanoemulsion; Drug delivery systems; Bioavailability; Colloidal dispersions; Chemotherapy

1. Introduction

Nanoemulsions (NEs) represent a sophisticated class of colloidal drug delivery systems that have revolutionized pharmaceutical formulation science [1]. These thermodynamically stable dispersions, characterized by droplet sizes ranging from 20 to 200 nm, offer unique advantages in drug delivery applications [2]. The nanoscale dimensions of these systems contribute to their exceptional stability against gravitational separation, flocculation, and coalescence, distinguishing them from conventional emulsions [3]. The fundamental classification of nanoemulsions is based on the spatial arrangement of their constituent phases. Oil-in-water (O/W) nanoemulsions consist of oil droplets dispersed in an aqueous continuous phase, while water-in-oil (W/O) systems feature aqueous droplets distributed within an oil continuous phase [4]. More complex architectures include multiple emulsions such as water-in-oil-in-water (W/O/W) and oil-in-water-in-oil (O/W/O) systems, which enable sophisticated drug delivery strategies [5].

The pharmaceutical significance of nanoemulsions stems from their ability to address critical challenges in drug delivery. Their large interfacial area enhances drug solubilization and absorption, while their tunable surface properties facilitate targeted delivery [6]. The versatility of nanoemulsions permits the incorporation of both hydrophilic and lipophilic active pharmaceutical ingredients, making them suitable carriers for diverse therapeutic agents [7]. Recent advances in nanoemulsion technology have expanded their applications beyond traditional pharmaceutical formulations. Their utility extends to various administration routes, including oral, parenteral, topical, and ocular delivery systems [8]. The enhanced permeability of nanoemulsions through biological membranes has particularly benefited the delivery of poorly water-soluble drugs, resulting in improved bioavailability and therapeutic outcomes [9]. The development of nanoemulsion formulations requires careful consideration of various factors including the selection of appropriate oils, surfactants, and preparation methods [10]. The stability and efficacy of these systems depend on the precise control of composition, processing parameters, and environmental conditions during preparation and storage [11].

Nanoemulsions have emerged as crucial tools in addressing contemporary pharmaceutical challenges. Their ability to protect sensitive drug molecules from degradation while maintaining optimal bioavailability has made them invaluable in modern drug formulation strategies [12]. The enhanced penetration capabilities of nanoemulsions through biological barriers have particularly benefited the delivery of therapeutic agents to traditionally challenging sites such as the blood-brain barrier and ocular tissues [13].

* Corresponding author: Nikhitha Gajula

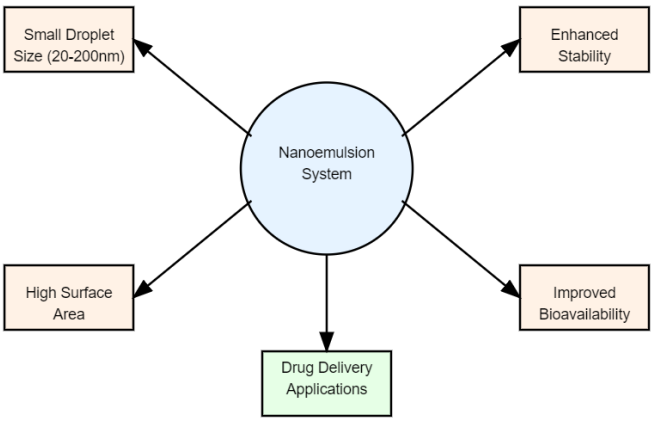

Figure 1. Advantages of Nanoemulsions

2. Types of Nanoemulsions

2.1. Based on Phase Distribution

The organization of dispersed and continuous phases in nanoemulsions determines their fundamental characteristics and applications. The primary classifications include biphasic and multiple phase systems [14].

2.1.1. Biphasic Systems

Oil-in-water (O/W) nanoemulsions represent the most commonly utilized format in pharmaceutical applications. In these systems, oil droplets ranging from 20-200 nm are dispersed throughout an aqueous continuous phase. The stability and characteristics of O/W nanoemulsions depend significantly on the phase volume ratio (Φ) and interfacial properties [15].
Water-in-oil (W/O) nanoemulsions, conversely, comprise nanoscale water droplets dispersed in an oil continuous phase. These systems prove particularly valuable for delivering hydrophilic drugs through lipophilic routes and protecting water-soluble bioactive compounds from degradation [16].

2.1.2. Multiple Emulsion Systems

Multiple emulsions represent more complex architectures designed for sophisticated drug delivery applications. Water-in-oil-in-water (W/O/W) systems consist of primary W/O emulsion droplets dispersed within an external aqueous phase. These structures enable dual drug loading and controlled release profiles [17].
Oil-in-water-in-oil (O/W/O) systems, though less common, offer unique advantages for specific applications, particularly in sustained release formulations and protection of sensitive oil-soluble compounds [18].

Table 1. Classification and Characteristics of Pharmaceutical Nanoemulsions

Type	Droplet Size (nm)	Continuous Phase	Dispersed Phase	Primary Applications
O/W Nanoemulsions	20-200	Water	Oil	Oral and parenteral delivery of lipophilic drugs
W/O Nanoemulsions	20-200	Oil	Water	Delivery of hydrophilic compounds through lipophilic routes
W/O/W Multiple Emulsions	100-200	Water	Oil containing water droplets	Sustained release, protection of sensitive compounds
O/W/O Multiple Emulsions	100-200	Oil	Water containing oil droplets	Complex drug delivery systems, dual release profiles

2.2. Physicochemical Properties

The effectiveness of nanoemulsions in drug delivery depends on several key physicochemical properties:

2.2.1. Interfacial Properties

The oil-water interface in nanoemulsions plays a crucial role in determining stability and drug release characteristics. The interfacial tension, influenced by surfactant type and concentration, affects droplet formation and stability. Lower interfacial tension typically results in smaller droplet sizes and enhanced stability [19].

2.2.2. Droplet Size

The nanoscale dimensions of emulsion droplets contribute significantly to their unique properties. Uniform droplet size distribution, typically achieved through careful formulation and processing, ensures consistent drug loading and release profiles. Modern characterization techniques enable precise control and monitoring of droplet size distributions [20].

2.2.3. Zeta Potential

Surface charge characteristics, quantified by zeta potential measurements, significantly influence the stability and biological interactions of nanoemulsions. Higher absolute zeta potential values (typically >|30| mV) generally indicate better stability against aggregation [21]

3. Methods of Preparation

3.1. Low-Energy Methods

Low-energy emulsification methods utilize the intrinsic physicochemical properties of the system components to form nanoemulsions, offering advantages in terms of energy efficiency and gentler processing conditions [22].

3.1.1. Spontaneous Emulsification

This method involves the formation of nanoemulsions through the controlled diffusion of components between phases. The process begins with dissolving oil, lipophilic emulsifier, and water-soluble cosolvent in the organic phase. Upon gentle addition to the aqueous phase containing hydrophilic emulsifiers, spontaneous formation of nanodroplets occurs due to interfacial turbulence and diffusion effects [23].

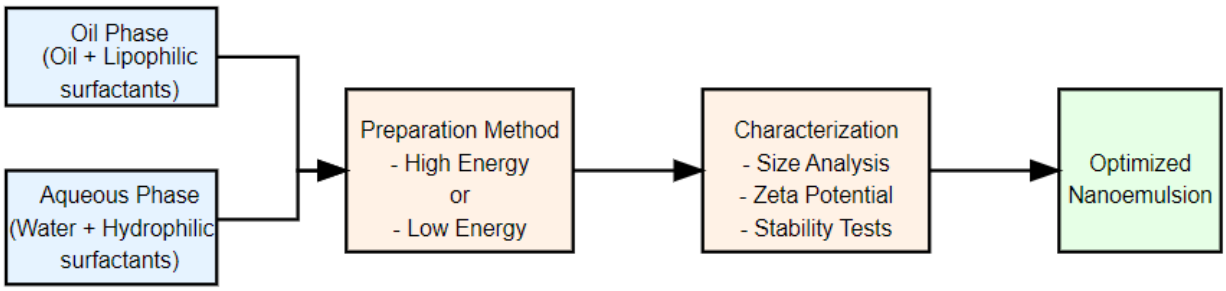

Figure 2. Preparation process for Nanoemulsion

3.1.2. Phase Inversion Temperature (PIT) Method

The PIT method exploits the temperature-dependent solubility characteristics of nonionic surfactants. As temperature changes, the surfactant undergoes a transition in its affinity between oil and water phases. At the phase inversion temperature, minimal interfacial tension facilitates the formation of extremely fine droplets. Careful temperature control during this process results in stable nanoemulsions with uniform droplet size distribution [24].

3.1.3. Phase Inversion Composition (PIC) Method

The PIC method involves gradual addition of the aqueous phase to an oil-surfactant mixture while maintaining constant temperature. This process leads to the formation of nanoemulsions through compositional changes rather than temperature variations. The method typically produces droplets around 50 nm in diameter with high kinetic stability [25].

Table 2. Comparison of Nanoemulsion Preparation Methods

Method	Energy Input	Advantages	Limitations
High-pressure Homogenization	High	Uniform droplet size, Good reproducibility	High energy cost, Heat generation
Ultrasonication	High	Simple operation, Low initial cost	Batch size limitations, Metal contamination
Phase Inversion Temperature	Low	Energy efficient, Gentle process	Temperature sensitive, Limited to specific surfactants
Spontaneous Emulsification	Low	Simple process, No special equipment	Limited to specific compositions

3.2. High-Energy Methods

High-energy methods employ mechanical devices to generate intense disruptive forces for droplet size reduction. These methods offer better control over droplet size distribution but require specialized equipment [26].

3.2.1. High-Pressure Homogenization

This widely used technique involves forcing the coarse emulsion through a narrow gap under high pressure (100-2000 bar). The resulting mechanical stress, cavitation, and turbulent flow conditions break down larger droplets into nanoscale dimensions. Multiple passes through the homogenizer may be required to achieve desired droplet size distributions [27].

3.2.2. Ultrasonication

Ultrasonication employs high-frequency sound waves to generate cavitation forces that break down droplets. The process involves alternating compression and expansion cycles, creating localized regions of intense mechanical stress. While effective for small-scale preparations, scaling up ultrasonication processes presents challenges in maintaining uniform droplet size distribution [28].

3.2.3. Microfluidization

Microfluidization utilizes specially designed interaction chambers where two fluid streams collide at high velocity under extreme pressure. This process creates highly uniform nanodroplets through intense shear, cavitation, and impact forces. The technique offers excellent reproducibility and scalability for industrial production [29].

4. Components of Nanoemulsions

4.1. Oil Phase

The selection of appropriate oil phase components significantly influences the stability, drug solubilization capacity, and biological performance of nanoemulsions. Natural oils serve as primary components in many nanoemulsion formulations, offering biocompatibility and enhanced drug solubilization [30]. Medium-chain triglycerides derived from coconut and palm kernel oils demonstrate excellent stability and drug-carrying capacity. Long-chain triglycerides from soybean, safflower, and sesame oils provide additional benefits through their nutritional value and biocompatibility. These oils typically constitute 5-20% of the formulation, though concentrations up to 70% may be used in specific applications [31].

Modified and synthetic oils offer distinct advantages in terms of stability and drug solubilization capacity. Caproyl 90, the Captex series compounds, isopropyl myristate, and ethyl oleate represent commonly used synthetic options. These oils are carefully selected based on their ability to solubilize specific drug molecules and their compatibility with other formulation components [32].

Table 3. Common Components Used in Nanoemulsion Formulations

Excipient Category	Examples	Typical Concentration Range (% w/w)	Function
Natural Oils	MCT, LCT, Essential oils	5-20	Drug solubilization
Synthetic Oils	Captex, Capmul, Labrafac	5-15	Enhanced drug loading
Primary Surfactants	Polysorbates, Lecithin	0.5-10	Emulsion stabilization
Co-surfactants	Propylene glycol, Ethanol	1-5	Interface modification
Stabilizers	HPMC, Xanthan gum	0.1-0.5	Viscosity enhancement
Preservatives	Parabens, Benzalkonium chloride	0.01-0.02	Antimicrobial protection

4.2. Surfactants

Surfactants play crucial roles in nanoemulsion formation and stabilization through interfacial tension reduction and steric stabilization. The selection of appropriate surfactants depends on multiple factors, including their HLB value, regulatory status, and compatibility with other ingredients. Phosphatidylcholine, derived from natural sources such as egg yolk or soybean, demonstrates excellent emulsification properties and biocompatibility. Polysorbates and polyoxyl castor oil derivatives offer robust stabilization capabilities in pharmaceutical formulations. The concentration of primary surfactants typically ranges from 0.5% to 10%, depending on the specific application requirements [33].

4.3. Co-surfactants

Co-surfactants enhance system stability and facilitate nanoemulsion formation through multiple mechanisms. These components reduce interfacial tension, increase interfacial fluidity, and improve overall phase behavior. Short-chain alcohols, ranging from C3 to C8, serve as effective co-surfactants in many formulations. Propylene glycol and medium-chain alcohols provide additional

benefits through their solubilizing properties and ability to modify interface characteristics. Co-surfactants typically comprise 1-5% of the formulation, working synergistically with primary surfactants to achieve optimal stability [34].

4.4. Aqueous Phase

The aqueous phase in nanoemulsions extends beyond simple water inclusion, incorporating various functional additives that enhance stability and performance. Buffer systems play a crucial role in maintaining optimal pH conditions, ensuring both drug stability and physiological compatibility. The selection of appropriate buffer components depends on the intended route of administration and the stability requirements of the incorporated active pharmaceutical ingredients. Common buffer systems include phosphate, citrate, and acetate buffers, carefully selected to maintain pH stability without compromising the overall formulation integrity [35].

Osmotic agents represent another essential category of aqueous phase components, particularly critical for parenteral formulations. Glycerin, sorbitol, and various sugars serve to adjust tonicity, preventing tissue irritation and ensuring physiological compatibility. These agents typically constitute 2-3% of the formulation, though concentrations may vary based on specific requirements. Additionally, preservatives such as benzalkonium chloride or parabens may be incorporated when multiple-dose formulations are desired, typically at concentrations of 0.01-0.02% [36].

4.5. Stabilizing Agents

Stabilizing agents enhance the long-term stability of nanoemulsions through various mechanisms. Thickening agents such as xanthan gum and hydroxypropyl methylcellulose modify the rheological properties of the continuous phase, reducing droplet mobility and preventing coalescence. These agents typically comprise 0.1-0.5% of the formulation, carefully balanced to enhance stability without significantly affecting drug release characteristics [37].

Antioxidants represent another crucial category of stabilizing agents, particularly important for formulations containing oxidation-sensitive components. Alpha-tocopherol, butylated hydroxytoluene, and ascorbic acid protect both the oil phase and incorporated drugs from oxidative degradation. The selection and concentration of antioxidants depend on the specific stability requirements of the formulation components and the intended shelf life of the product [38].

5. Characterization of Nanoemulsions

5.1. Physical Characterization

Dynamic light scattering (DLS) serves as the primary method for determining droplet size distribution and polydispersity index. This technique provides detailed information about particle size populations and their distribution patterns, crucial for understanding formulation stability and performance [39].

Microscopic techniques, including transmission electron microscopy (TEM) and cryo-electron microscopy, offer valuable insights into droplet morphology and internal structure. These methods provide direct visualization of nanoemulsion droplets, confirming size measurements obtained through other techniques and revealing important structural details about the interface and internal organization [40].

Table 4. Characterization Methods for Nanoemulsions

Properties	Analytical Technique	Evaluation Parameter
Particle Size	Dynamic Light Scattering	Size distribution, PDI
Morphology	TEM, Cryo-EM	Droplet structure, Shape
Surface Charge	Zeta Potential	Electrical properties, Stability
Drug Content	HPLC, UV Spectroscopy	Drug loading, Encapsulation efficiency
Stability	Multiple methods	Physical/chemical stability

5.2. Chemical Characterization

Chemical characterization of nanoemulsions involves sophisticated analytical techniques to evaluate composition, purity, and molecular interactions between components. Nuclear magnetic resonance (NMR) spectroscopy provides detailed information about the chemical environment of components, particularly useful for understanding surfactant orientation at interfaces and drug-excipient interactions. Both proton and carbon-13 NMR offer valuable insights into the spatial arrangement of molecules within the system [41].

Fourier transform infrared spectroscopy (FTIR) enables the identification of functional groups and molecular interactions within nanoemulsion systems. This technique proves particularly valuable in detecting chemical changes during storage and evaluating the stability of incorporated active pharmaceutical ingredients. The analysis of characteristic absorption bands provides evidence of successful drug incorporation and potential molecular interactions between formulation components [42].

5.3. Stability Assessment

Stability evaluation of nanoemulsions encompasses multiple parameters monitored over extended periods under various environmental conditions. Thermodynamic stability studies involve exposure to temperature cycling, centrifugation, and freeze-thaw stress conditions. These tests provide crucial information about the system's resistance to physical destabilization mechanisms including creaming, coalescence, and phase separation [43].

Accelerated stability studies conducted at elevated temperatures and humidity levels help predict long-term stability behavior. Regular monitoring of droplet size distribution, zeta potential, and drug content provides quantitative measures of formulation stability. Changes in these parameters over time indicate potential destabilization mechanisms and guide formulation optimization efforts [44].

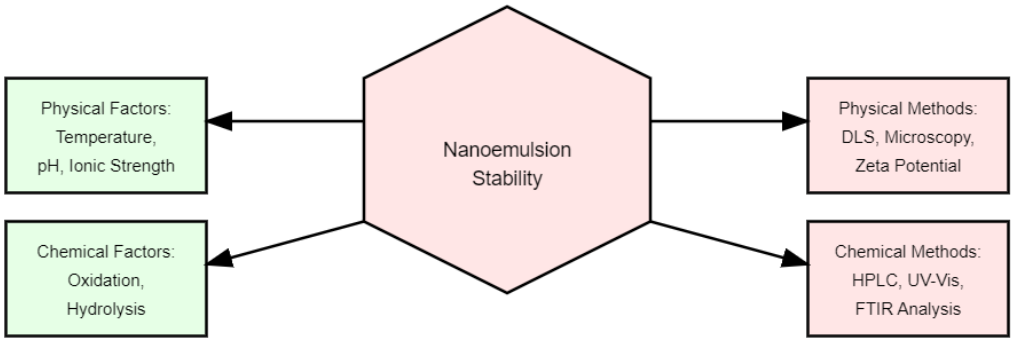

Figure 3. Factors affecting Nanoemulsion Stability and its evaluation

6. Applications in Drug Delivery

6.1. Oral Delivery Systems

Nanoemulsions have revolutionized oral drug delivery by addressing bioavailability challenges associated with poorly water-soluble drugs. The enhanced solubilization capacity combined with improved membrane permeability results in superior absorption profiles compared to conventional formulations. The incorporation of lipophilic drugs into nanoemulsion carriers protects them from degradation in the harsh gastrointestinal environment while facilitating lymphatic uptake, thereby bypassing first-pass hepatic metabolism [45].

6.2. Parenteral Drug Delivery

In parenteral delivery, nanoemulsions offer unique advantages for the administration of hydrophobic drugs. Their small droplet size prevents capillary blockage, while their composition can be tailored to minimize injection site reactions. The ability to sterilize these systems through various methods, including filtration and autoclaving, makes them particularly suitable for intravenous administration. Additionally, the incorporation of targeting ligands enables site-specific drug delivery, enhancing therapeutic efficacy while reducing systemic side effects [46]

6.3. Topical and Transdermal Delivery

Nanoemulsions demonstrate remarkable efficacy in topical and transdermal drug delivery applications due to their unique physicochemical properties. The nanoscale dimensions of droplets facilitate enhanced skin penetration through various pathways, including intercellular, transcellular, and follicular routes. The high surface area to volume ratio combined with excellent spreading properties results in improved contact with the skin surface, enhancing drug permeation [47].

The incorporation of penetration enhancers within the oil phase of nanoemulsions further promotes drug transport across the stratum corneum. These systems have shown particular promise in the delivery of anti-inflammatory agents, antifungal compounds, and various cosmeceuticals. The ability to incorporate both hydrophilic and lipophilic active ingredients makes them versatile platforms for dermatological applications [48].

6.4. Ocular Drug Delivery

Nanoemulsions have addressed significant challenges in ocular drug delivery by improving precorneal retention and enhancing corneal permeation. Their mucoadhesive properties, achieved through careful selection of surfactant systems, prolong contact time with the ocular surface. The small droplet size minimizes blur and irritation commonly associated with conventional eye drops, improving patient compliance [49].

These systems have demonstrated particular success in delivering poorly water-soluble drugs for both anterior and posterior segment disorders. The incorporation of charged surfactants can enhance interaction with the corneal surface, further improving drug bioavailability. Advanced formulations incorporating polymeric additives provide sustained release profiles, reducing dosing frequency [50].

Table 5. Therapeutic Applications and Route-Specific Considerations

Route	Advantages	Challenges	Parameters
Oral	Enhanced bioavailability, Reduced food effect	GI stability, First-pass metabolism	Droplet size, Surfactant selection
Parenteral	Direct systemic delivery, Controlled release	Sterility, Pyrogenicity	Particle size uniformity, Osmolality
Topical	Enhanced penetration, Reduced irritation	Skin barrier, Stability	Viscosity, Penetration enhancers
Ocular	Improved retention, Better corneal contact	Blurred vision, Drainage	Mucoadhesion, Tonicity
Pulmonary	Rapid absorption, Local/systemic delivery	Droplet size control, Irritation	Aerodynamic properties, Safety

7. Conclusion

Nanoemulsions provide unique advantages through their thermodynamically stable, optically transparent, and kinetically stable characteristics with droplet sizes typically ranging from 20-200 nm. Their versatility in loading both hydrophilic and lipophilic drugs, combined with enhanced bioavailability, improved stability, and controlled drug release properties, makes them particularly attractive for pharmaceutical applications across various administration routes. Although they are promising, challenges remain in scale-up manufacturing, optimization of preparation methods, and long-term stability, necessitating continued research in formulation methods and characterization techniques.

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