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REVIEW ARTICLE

Formulation, Characterization, and Applications of Nanoemulsions

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Abstract: Nanoemulsions are kinetically stable isotropic systems with droplet dimensions typically ranging between 20 and 200 nm, representing a transformative approach in pharmaceutical and industrial applications. Composed of oil, water, and stabilizing surfactants, these colloidal dispersions exhibit unique physicochemical properties such as enhanced optical clarity, substantial interfacial area, and robust kinetic stability. Their amalgamation into drug delivery protocols addresses critical challenges associated with the bioavailability of lipophilic compounds, facilitating efficient transport across biological barriers including the blood-brain barrier and dermal layers. The formation of these nanocarriers relies on fundamental principles involving either high-energy dispersion techniques or low-energy phase inversion methods, where the precise selection of oils and surfactant blends determines formulation stability and therapeutic efficacy. A diverse spectrum of administration routes ranging from parenteral and oral to topical and intranasal systems enables targeted therapeutic interventions in oncology, neurology, and dermatology. Apart from pharmaceuticals, the utility of these systems extends to nutraceuticals and cosmeceuticals, although successful commercialization necessitates rigorous long-term stability profiling.

Keywords: Nanoemulsions; Bioavailability; Colloidal Dispersions; Pharmacokinetics; Targeted Delivery

1. Introduction

The pharmaceutical nanotechnology has undergone a significant transformation with the advent of nanoemulsions, advanced colloidal systems that have redefined the delivery of therapeutic agents. Nanoemulsions are defined as kinetically stable, liquid-in-liquid dispersions wherein the dispersed phase takes the form of droplets with diameters typically ranging from 20 to 200 nm. Unlike conventional macroemulsions, which are prone to phase separation and exhibit a milky appearance due to significant light scattering, nanoemulsions are characterized by their optical transparency or translucency. This unique optical property arises because the droplet size is significantly smaller than the wavelength of visible light, rendering them distinct in both appearance and physicochemical behavior. These systems are composed of two immiscible liquids usually an oil phase and an aqueous phase stabilized into a single phase by an interfacial film of surfactants and co-surfactants. This film lowers the interfacial tension, although not to the ultralow levels seen in microemulsions, necessitating energy input for formation [1].

A critical distinction in colloid science lies between nanoemulsions and microemulsions. While both appear visually similar and isotropic, their underlying stability mechanisms differ fundamentally. Microemulsions are thermodynamically stable systems that form spontaneously when the correct components are mixed, representing a state of minimum free energy. In contrast, nanoemulsions are non-equilibrium systems that possess kinetic stability. They are metastable; while they may eventually separate over extended periods, their breakdown processes (such as Ostwald ripening and coalescence) are exceedingly slow, often rendering them stable for years. This kinetic stability is attributed to the steric or electrostatic repulsion provided by the surfactant monolayer, which creates a high energy barrier against droplet aggregation. Moreover, the Brownian motion of the nanometric droplets is sufficient to overcome gravitational forces, thereby preventing phenomena such as sedimentation or creaming that plague conventional coarse emulsions.

The pharmaceutical significance of nanoemulsions is largely driven by the challenges associated with modern drug discovery. A substantial proportion of new chemical entities (NCEs) exhibit poor water solubility, classifying them as Class II or Class IV compounds within the Biopharmaceutics Classification System (BCS). The poor solubility of these lipophilic drugs severely limits their oral bioavailability and therapeutic efficacy. Nanoemulsions address this bottleneck by serving as robust solvent reservoirs. The lipophilic core of the nanoemulsion can solubilize high concentrations of hydrophobic drugs, while the aqueous continuous

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phase allows for compatibility with physiological fluids. Upon administration, the immense interfacial surface area generated by the nanometric size of the droplets provides a vast platform for enzymatic hydrolysis and drug absorption. This results in a rapid onset of action and more predictable pharmacokinetic profiles compared to traditional solid dosage forms or suspensions. Moreover, the versatility of nanoemulsions extends beyond simple solubilization. They are engineered to protect labile drugs, such as peptides and proteins, from hydrolysis and enzymatic degradation within the gastrointestinal tract. Their small size allows for permeation across critical biological barriers, including the skin and the blood-brain barrier, opening new avenues for transdermal and central nervous system (CNS) therapies. The formulation flexibility allows nanoemulsions to be designed as aqueous-based (O/W) systems for encapsulating lipophilic drugs or oil-based (W/O) systems for hydrophilic agents, making them adaptable for oral, parenteral, ophthalmic, and intranasal routes of administration [1].

2. Classification of Nanoemulsions

Nanoemulsions are categorized based on the dispersion of the internal and external phases. This classification is critical as it dictates the physicochemical properties and the suitability of the system for specific drug delivery applications.

2.1. Water-in-Oil (W/O) Nanoemulsions

In Water-in-Oil systems, aqueous droplets are dispersed within a continuous oil phase. These formulations are particularly advantageous for the encapsulation of hydrophilic active ingredients, protecting them from enzymatic degradation and hydrolysis while allowing for sustained release [2].

2.2. Oil-in-Water (O/W) Nanoemulsions

Conversely, Oil-in-Water nanoemulsions consist of oil droplets dispersed throughout a continuous aqueous phase. This type is the most widely utilized in pharmaceutical applications, especially for enhancing the solubility and bioavailability of poorly water-soluble (lipophilic) drugs [3].

2.3. Bicontinuous Nanoemulsions

Bicontinuous systems represent a unique state where microdomains of oil and water are intermingled, often described as sponge-like structures. These can include complex multiple emulsions such as Oil-in-Water-in-Oil (O/W/O) or Water-in-Oil-in-Water (W/O/W), which offer the capability to encapsulate both hydrophilic and hydrophobic substances simultaneously [4].

Table 1. Comparison of Macroemulsions, Nanoemulsions, and Microemulsions

Property	Macroemulsion	Nanoemulsion	Microemulsion
Droplet Size	> 200 nm (up to microns)	20 – 200 nm	10 – 100 nm
Appearance	Milky / Opaque	Transparent / Translucent	Transparent
Thermodynamic Stability	Unstable (Thermodynamically unstable)	Metastable (Kinetically stable)	Stable (Thermodynamically stable)
Preparation Energy	Low to High shear	High energy (usually) or Low energy (specific pathways)	Low energy (Spontaneous)
Polydispersity	High	Low	Very Low (Monodisperse)
Viscosity	High	Low	Low
Formation Mechanism	Non-spontaneous	Non-spontaneous	Spontaneous

3. Advantages and Limitations

The adoption of nanoemulsion technology in drug delivery is driven by several distinct advantages, although it is accompanied by specific limitations that must be addressed during formulation development.

3.1. Advantages of Nanoemulsion Systems

The integration of nanoemulsions into pharmaceutical sciences offers a multitude of benefits over conventional dosage forms:

3.1.1. Enhanced Bioavailability

The reduction of droplet size to the nanometric scale results in a massive increase in the specific surface area. This facilitates rapid dissolution and absorption of lipophilic drugs, adhering to the Noyes-Whitney equation. Consequently, the onset of therapeutic action is accelerated, and the bioavailability of poorly water-soluble compounds is significantly improved [5].

3.1.2. Kinetic Stability

Unlike macroemulsions, nanoemulsions exhibit exceptional resistance to physical instability phenomena such as creaming, sedimentation, and flocculation. The Brownian motion of the nanodroplets dominates over gravitational forces, ensuring the system remains dispersed over extended storage periods.

3.1.3. Versatility in Delivery

Nanoemulsions are adaptable to various routes of administration, including oral, parenteral, topical, and intranasal. Their ability to mask the bitter taste of certain drugs further enhances patient compliance in oral formulations.

3.1.4. Protection of Labile Active Ingredients

The oil core of the nanoemulsion can encapsulate and shield sensitive active pharmaceutical ingredients (APIs), such as peptides and antioxidants, from enzymatic degradation and hydrolysis in the biological environment.

3.1.5. Reduced Tissue Irritation

Compared to co-solvent systems or microemulsions that may require high concentrations of surfactants, nanoemulsions can often be formulated with biocompatible surfactants, minimizing toxicity and tissue irritation upon application.

3.2. Limitations and Challenges

Despite their promising attributes, the development and commercialization of nanoemulsions face specific hurdles:

3.2.1. Manufacturing and Equipment Costs

The production of nanoemulsions, particularly through high-energy methods like high-pressure homogenization, requires sophisticated and expensive machinery. The energy input required to overcome the Laplace pressure and reduce droplet size can be substantial, impacting the cost-effectiveness of the manufacturing process [5].

3.2.2. Ostwald Ripening

While resistant to gravitational separation, nanoemulsions are thermodynamically unstable and susceptible to Ostwald ripening. This phenomenon involves the diffusion of the oil phase from smaller to larger droplets through the continuous phase, leading to droplet growth and eventual phase separation over time.

3.2.3. Scale-Up

Transitioning from laboratory-scale preparation to industrial-scale production poses engineering challenges. Ensuring batch-to-batch consistency in droplet size distribution and stability during large-scale processing requires rigorous optimization of process parameters.

3.2.4. Surfactant Safety

Although generally safer than some alternatives, the need for surfactants to stabilize the interface requires careful selection to avoid toxicity, especially for parenteral administration where high surfactant loads can be problematic.

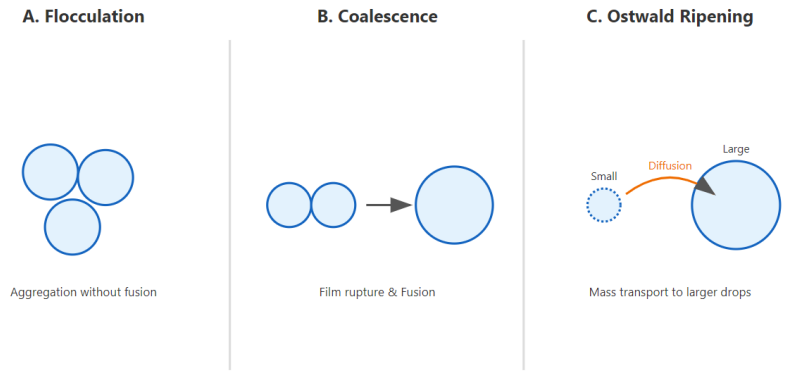

Figure 1. Mechanisms of Physical Instability

4. Components of Nanoemulsion Formulation

The successful formulation of a nanoemulsion relies heavily on the careful selection of its three primary constituents: the oil phase, the aqueous phase, and the surfactant/co-surfactant system [6].

4.1. Oil Phase

The oil phase serves as the fundamental solvent for lipophilic drugs and plays a critical role in determining the solubility and subsequent bioavailability of the active pharmaceutical ingredient (API). The selection of the oil is paramount; it must possess the capacity to solubilize the drug at the desired therapeutic dose. Oils can facilitate drug transport through the systemic circulation and enhance absorption within the gastrointestinal tract via the lymphatic system [7]. Typically, oil/lipid nanosized droplets constitute 5–20% of an O/W nanoemulsion, although concentrations can reach up to 70% in specific formulations. Common oils utilized include corn oil, soybean oil, rice bran oil, and essential oils like clove and thyme oil. The physicochemical nature of the oil also influences the susceptibility of the formulation to Ostwald ripening [8, 9].

Table 2. Common Excipients Utilized in Nanoemulsion Formulations

Component Category	Function	Common Examples
Oils (Lipid Phase)	Solubilizes lipophilic drugs; enhances lymphatic transport.	Long-chain triglycerides (LCT): Corn oil, Soybean oil, Olive oil, Safflower oil. Medium-chain triglycerides (MCT): Caprylic/Capric triglycerides (Miglyol®). Essential oils: Eucalyptus oil, Peppermint oil.
Surfactants	Reduces interfacial tension; creates steric/electrostatic barrier.	Non-ionic: Polysorbate 80 (Tween 80), Polysorbate 20, Sorbitan monooleate (Span 80), Cremophor EL. Phospholipids: Egg lecithin, Soy lecithin.
Co-surfactants	Increases flexibility of the interfacial film; reduces bending stress.	Alcohols: Ethanol, Isopropyl alcohol. Glycols: Propylene glycol, Polyethylene glycol (PEG 400). Others: Transcutol® P.
Aqueous Phase	Continuous medium; determines pH and osmolarity.	Distilled water, Phosphate Buffer Saline (PBS), Simulated Gastric Fluid (SGF), Simulated Intestinal Fluid (SIF).

4.2. Aqueous Phase

The aqueous phase forms the continuous medium in O/W nanoemulsions and influences the droplet size and stability through parameters such as pH, ionic strength, and polarity. The selection of the aqueous phase depends on the intended route of administration and the physicochemical properties of the drug. Options range from simple distilled water (pH 7.0) to physiological buffers like Phosphate-Buffered Saline (pH 7.4), Simulated Gastric Fluid (pH 1.2), and Simulated Intestinal Fluid (pH 6.8) [10-13].

4.3. Surfactants

Surfactants are amphiphilic molecules essential for reducing the interfacial tension between the oil and water phases to near-zero values, facilitating the dispersion of droplets. They form a protective interfacial film that prevents droplet coalescence and maintains the nanoscale dimensions of the dispersed phase. The choice of surfactant is governed by its Hydrophilic-Lipophilic Balance (HLB) value, toxicity profile, and ability to achieve the desired viscosity and zeta potential [14]. Ideal surfactants should be effective at low concentrations to minimize potential toxicity and should promote rapid absorption of the drug [15].

4.4. Co-surfactants

Single-chain surfactants alone are often insufficient to reduce the interfacial tension required for nanoemulsion formation. Co-surfactants are employed to interpenetrate the surfactant monolayer, disrupting the rigid crystalline or gel structures at the interface. This increases the fluidity of the interfacial film and further lowers the interfacial tension, thereby facilitating the spontaneous formation of nanoemulsions and enhancing their thermodynamic stability [7, 9, 14].

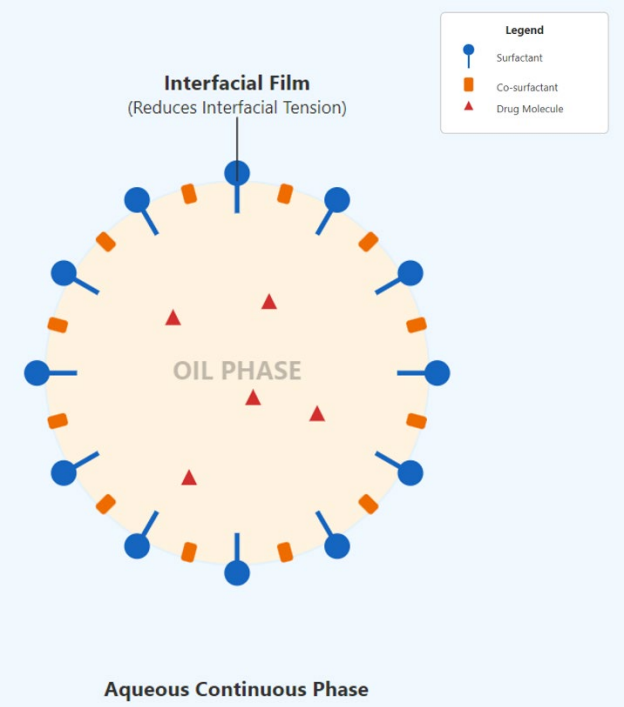

Figure 2. Structure of an Oil-in-Water Nanoemulsion Droplet

5. Preparation Techniques

The fabrication of nanoemulsions is broadly classified into high-energy and low-energy methods.

5.1. High-Energy Methods

High-energy techniques utilize mechanical devices to generate intense disruptive forces that break down macroscopic droplets into nanometric sizes [16].

5.1.1. High-Pressure Homogenization

This technique involves forcing the mixture of oil and water through a narrow orifice under extremely high pressure (500–5000 psi). The fluid undergoes intense hydraulic shear, turbulence, and cavitation, resulting in the formation of fine emulsion droplets with a monomolecular surfactant layer. While highly efficient in producing droplets between 10 and 100 nm, this method is energy-intensive and can induce temperature spikes that may degrade heat-sensitive compounds [17-19].

5.1.2. Ultrasonication

Ultrasonication employs high-frequency sound waves (typically 20 kHz) to generate cavitation bubbles within the liquid. The collapse of these bubbles produces shock waves that disrupt the droplets. This method is capable of reducing droplet sizes to below 0.2 microns and is particularly useful for laboratory-scale preparations. For instance, emodin-loaded nanoemulsions with diameters of 10–30 nm have been successfully prepared using this technique [20].

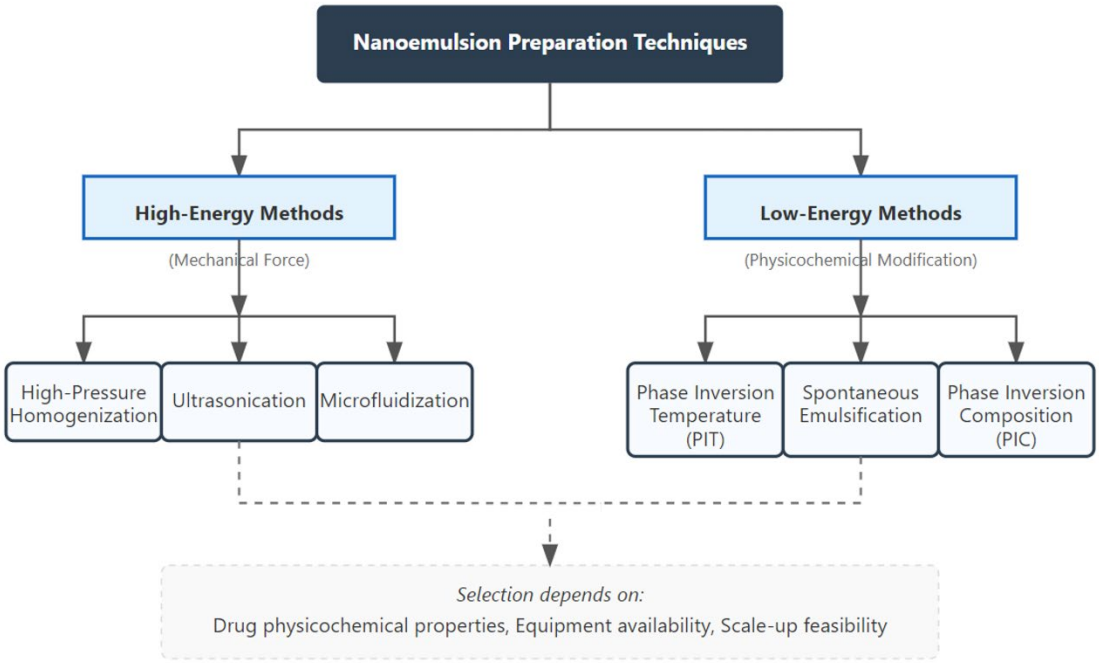

Figure 3. Preparation Techniques for Nanoemulsions

Table 3. Comparison of High-Energy and Low-Energy Preparation Techniques

Method Type	Technique	Mechanism of Action	Advantages	Limitations
High-Energy	High-Pressure Homogenization	Intense hydraulic shear and turbulence break droplets.	Produces uniform, small droplets; industrially scalable.	High energy consumption; potential degradation of heat-sensitive drugs.
	Ultrasonication	Acoustic cavitation generates shockwaves that disrupt phases.	Ideal for small batches; effective size reduction.	Risk of metal contamination (probe); difficult to scale up.
	Microfluidization	Interaction chamber creates high shear and impact forces.	Very narrow size distribution.	High equipment cost; clogging risk.
Low-Energy	Phase Inversion Temperature (PIT)	Temperature change alters surfactant curvature (hydrophilic/lipophilic).	Low energy cost; simple setup.	Limited to ethoxylated non-ionic surfactants; requires precise thermal control.
	Spontaneous Emulsification	Rapid diffusion of solvent/surfactant across interface causes turbulence (Marangoni effect).	No specialized equipment needed; useful for thermolabile drugs.	Requires high solvent/surfactant ratios; solvent removal step often needed.

5.2. Low-Energy Methods

Low-energy methods exploit the physicochemical properties of the system to generate nanoemulsions through phase transitions, offering a more energy-efficient alternative [17, 18].

5.2.1. Phase Inversion Temperature (PIT)

The PIT method relies on the temperature-dependent solubility of polyoxyethylene-type nonionic surfactants. As temperature increases, the surfactant becomes more lipophilic due to the dehydration of its polymer chain. By manipulating the temperature, the system undergoes a phase inversion from O/W to W/O (or vice versa). Near the phase inversion temperature, the interfacial tension is minimal, allowing for the formation of finely dispersed droplets [21].

5.2.2. Spontaneous Emulsification

This method involves the rapid diffusion of a water-miscible organic solvent (containing oil and surfactant) into an aqueous phase. The movement of the solvent across the interface induces turbulence and interfacial instability, leading to the spontaneous formation of nanodroplets. Subsequent evaporation of the organic solvent leaves behind a stable nanoemulsion. This technique has been effectively used to create stable essential oil nanoemulsions with droplet sizes of 50–100 nm [22].

6. Physicochemical Characterization

The rigorous characterization of nanoemulsions is indispensable for validating their formulation quality, stability, and therapeutic potential. This process involves a suite of analytical techniques designed to probe the structural, electrical, and rheological properties of the colloidal system.

6.1. Droplet Size Analysis and Polydispersity

The efficacy of a nanoemulsion is intrinsically linked to its mean droplet diameter. Droplet size analysis is paramount, as it directly influences the rate of drug release, extent of absorption, and physical stability. Smaller droplets provide an exponentially larger specific surface area for interaction with biological membranes, thereby facilitating permeation and bioavailability [23, 24]. Dynamic Light Scattering (DLS), also known as Photon Correlation Spectroscopy (PCS), is the standard technique for determining the Z-average diameter and the Polydispersity Index (PDI). A PDI value below 0.2 typically indicates a monodisperse and uniform population of droplets, which is desirable for predictable pharmacokinetic behavior [25].

Table 4. Characterization Techniques for Nanoemulsions

Parameter	Technique	Information Obtained	Significance
Droplet Size & Distribution	Dynamic Light Scattering (DLS) / Photon Correlation Spectroscopy (PCS)	Mean droplet diameter (Z-average) and Polydispersity Index (PDI).	Determines absorption rate and physical stability (PDI < 0.2 indicates uniformity).
Surface Charge	Zeta Potential Measurement	Electrical potential at the slipping plane.	Indicates colloidal stability; values > ±30 mV suggest high stability against aggregation.
Morphology	Transmission Electron Microscopy (TEM) / Scanning Electron Microscopy (SEM)	Shape and surface structure of droplets.	Confirms spherical nature and detects aggregation.
Rheology	Viscometry / Rheometry	Viscosity and flow behavior.	Affects injectability, spreadability (topical), and flow properties.
Drug Encapsulation	UV-Visible Spectrophotometry / HPLC	Percent Entrapment Efficiency (%EE).	Determines the amount of drug successfully loaded into the oil phase.

6.2. Zeta Potential and Colloidal Stability

Zeta potential is a critical parameter that measures the electrokinetic potential at the slipping plane of the dispersed droplets. It serves as a primary indicator of long-term colloidal stability. A high absolute zeta potential value (typically exceeding ±30 mV) suggests strong electrostatic repulsion between adjacent droplets. This repulsive force acts as an energy barrier, effectively preventing droplet aggregation, flocculation, and coalescence, which are precursors to phase separation [25]. The magnitude of the zeta potential is influenced by the choice of surfactant, pH of the medium, and the presence of electrolytes.

6.3. Morphological Assessment

While DLS provides hydrodynamic data, direct visualization is required to confirm the structural integrity and shape of the nanoemulsion droplets. Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) are employed to capture high-resolution images of the dispersed phase. These techniques allow researchers to verify the spherical nature of the droplets and detect any signs of aggregation or precipitation that may not be apparent from light scattering data alone. Cryo-TEM is particularly valuable as it preserves the native state of the liquid droplets without the artifacts introduced by drying or staining [26,27].

6.4. Chemical and Thermodynamic Compatibility

Ensuring the chemical stability of the drug within the formulation is as crucial as maintaining physical stability. Differential Scanning Calorimetry (DSC) is utilized to assess the thermal behavior of the formulation components. It can determine whether the encapsulated drug exists in a crystalline or amorphous state, which impacts solubility. Moreover, Fourier-Transform Infrared Spectroscopy (FTIR) is employed to examine molecular interactions between the drug and excipients. Shifts in characteristic absorption bands can reveal hydrogen bonding or other chemical interactions, ensuring that the drug has not undergone degradation or incompatible reaction during the formulation process [28, 29].

7. Biomedical and Pharmaceutical Applications

7.1. Drug Delivery and Therapeutics

7.1.1. Skin and Transdermal Delivery

Nanoemulsions have garnered significant attention for topical and transdermal applications due to their ability to enhance the permeation of drugs through the stratum corneum. The fluid nature of the nanoemulsion allows it to penetrate the skin's lipid bilayers more effectively than conventional creams. Formulations containing drugs like Clobetasol, Metronidazole, and Domperidone have demonstrated improved therapeutic outcomes and targeted delivery when incorporated into nanoemulsion bases [30-32].

7.1.2. Central Nervous System (CNS) Targeting

Delivering therapeutic agents to the brain is a formidable challenge due to the Blood-Brain Barrier (BBB). Nanoemulsions offer a potential solution by facilitating the transport of lipophilic drugs across the BBB via receptor-mediated endocytosis or by increasing the retention time in the nasal cavity for intranasal delivery. Studies involving intranasal administration of donepezil nanoemulsions for Alzheimer's disease have shown promising results in enhancing brain uptake [33, 34].

Table 5. Therapeutic Applications by Route of Administration

Route of Administration	Target / Condition	Therapeutic Benefit of Nanoemulsion	Example Drugs/Active Agents
Transdermal / Topical	Psoriasis, Dermatitis, Fungal Infections	Enhances permeation through stratum corneum; reduces skin irritation; controlled release.	Clobetasol, Metronidazole, Aceclofenac, Amphotericin B.
Oral	Systemic Infections, Hypertension, Oncology	Improves oral bioavailability of BCS Class II/IV drugs; bypasses hepatic first-pass metabolism via lymphatic transport.	Cyclosporine, Ramipril, Paclitaxel, Curcumin.
Parenteral (IV)	Anesthesia, Nutrition, Cancer	Solubilizes hydrophobic drugs without toxic solvents; reduces pain on injection; potential for passive targeting (EPR effect).	Propofol, Dexamethasone, Doxorubicin.
Intranasal	Alzheimer's, Migraine, CNS Disorders	Direct nose-to-brain delivery bypassing Blood-Brain Barrier (BBB); rapid onset.	Donepezil, Zolmitriptan, Risperidone.
Ophthalmic	Glaucoma, Eye Infections	Increases corneal residence time; enhances ocular penetration; reduces blurring compared to ointments.	Timolol, Dorzolamide.

7.1.3. Oncology

In cancer therapeutics, nanoemulsions serve as effective carriers for poorly soluble cytotoxic agents. They can be engineered to accumulate in tumor tissues via the Enhanced Permeability and Retention (EPR) effect or functionalized with ligands for active targeting. This approach enhances the intracellular concentration of the drug in cancer cells while minimizing systemic toxicity [35-37]. Research into multifunctional nanoemulsions has also paved the way for "theranostic" applications, where the system is used simultaneously for imaging (diagnosis) and therapy [38].

7.1.4. Gene Delivery

Beyond small molecules, nanoemulsions are being investigated for the delivery of genetic material. Encapsulation of agents such as doxorubicin alongside genetic components has been explored to facilitate transport across cellular membranes, suggesting a role in gene therapy protocols [36].

7.2. Nutraceuticals and Cosmeceuticals

In the food industry, nanoemulsions act as vehicles for bioactive compounds, improving the stability and bioavailability of nutrients and preservatives. They protect sensitive ingredients from oxidation and degradation, thereby extending the shelf life of food products [39, 40]. Similarly, in cosmeceuticals, nanoemulsions enhance the dermal penetration of active ingredients in anti-aging and moisturizing products, offering superior aesthetic qualities and therapeutic benefits compared to traditional formulations [41].

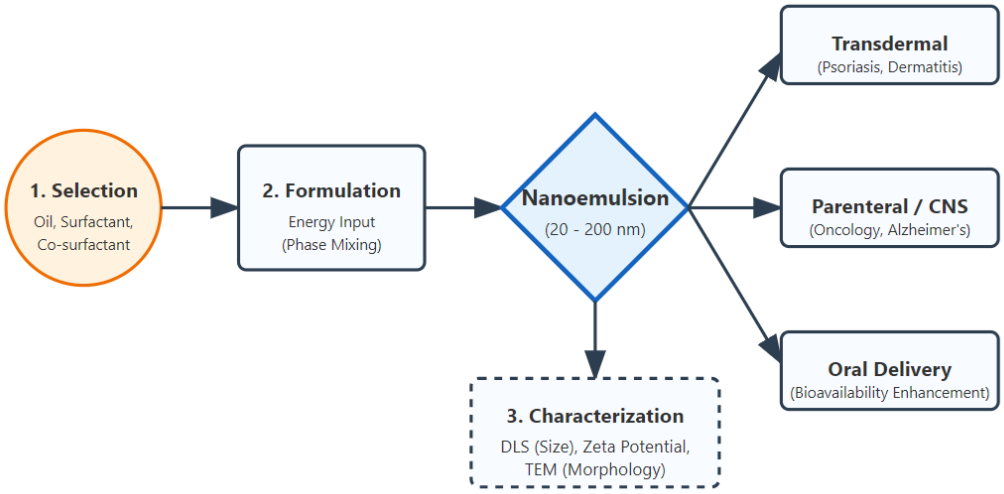

Figure 4. Development and Application of Nanoemulsions

8. Conclusion

Nanoemulsions serve as a versatile and robust platform for drug delivery and industrial formulation. Their unique physicochemical properties, including high surface area and kinetic stability, enable the efficient delivery of hydrophobic drugs, improvement of bioavailability, and targeted therapy. From oncology to cosmeceuticals, the applications of nanoemulsions are vast and expanding. Continued research into their long-term stability, safety profiles, and scale-up manufacturing will be essential to fully realize their potential and transition these innovative systems from laboratory settings to widespread clinical and commercial use.

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