Nano-Emulsions For Breast Cancer Therapy: A Review

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Abstract : Nano-emulsions (NEs) are kinetically stable dispersions of oil and water stabilized by surfactants, with droplet sizes typically in the 20–200 nm range. Because they markedly improve the solubility, chemical stability, and bioavailability of hydrophobic anticancer agents, NEs have attracted considerable interest as carriers for breast cancer therapy. NEs permit high drug loading, can reduce excipient-related toxicities (e.g., elimination of solvent vehicles required for paclitaxel), and enable alternative administration routes (intravenous, intraductal, topical/dermal, and intranasal) and combinations (drug + chemosensitizer or targeting ligand). Recent preclinical work reports enhanced cellular uptake, improved cytotoxicity against breast cancer cell lines (including drug-resistant lines), and favorable in vivo tumor control with reduced systemic toxicity. Surface functionalization (PEGylation, hyaluronic acid, antibodies, peptides) enables active targeting of receptors overexpressed in breast cancer (EGFR, HER2, CD44), while co-encapsulation of efflux pump inhibitors or siRNA can help reverse multidrug resistance. Major formulation considerations include oil phase and surfactant choice, droplet size and polydispersity, zeta potential, stability (creaming, coalescence), sterilization, and scalable manufacturing (high-pressure homogenization, microfluidization, low-energy spontaneous emulsification). Challenges to clinical translation remain: long-term stability, in vivo fate and immunogenicity, reproducible large-scale manufacturing, rigorous toxicology, and regulatory characterization. Still, the weight of preclinical evidence and improved formulation technologies position nano-emulsions as a promising, near-term platform to improve therapeutic index and overcome resistance in breast cancer.

Keywords ; Nano-Emulsion; Breast Cancer; Drug Delivery; Multidrug Resistance; Formulation; Translational Challenges

1. Introduction

Breast cancer remains a leading cause of cancer morbidity and mortality Breast cancer continues to be one of the most prevalent malignancies and remains a leading cause of cancer-related morbidity and mortality among women worldwide. According to global cancer statistics, it accounts for a significant proportion of new cancer diagnoses and is a major contributor to cancer-related deaths each year. Despite advancements in screening and early detection, the clinical management of breast cancer still poses considerable challenges due to its heterogeneous nature, variable molecular subtypes, and the development of drug resistance.

Conventional chemotherapeutic agents, such as paclitaxel, doxorubicin, and cyclophosphamide, form the backbone of systemic breast cancer therapy. While these drugs have demonstrated substantial efficacy, their therapeutic potential is often hindered by multiple limitations, including poor aqueous solubility, rapid clearance, non-specific biodistribution, dose-limiting toxicities, and the emergence of multidrug

resistance. These drawbacks not only compromise treatment outcomes but also severely impact the quality of life of patients. Moreover, the inability of these drugs to selectively target tumor tissues often leads to undesirable systemic side effects, such as cardiotoxicity and myelosuppression.

In recent years, the field of nanomedicine has gained momentum as a promising strategy to overcome these therapeutic bottlenecks. Nanotechnology-based drug delivery systems have the potential to enhance pharmacokinetic profiles, improve tumor-specific accumulation through enhanced permeability and retention (EPR) effect, reduce systemic toxicity, and provide controlled or sustained release of therapeutic agents. Among the various nanocarrier platforms—such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, and dendrimers—nano-emulsions have emerged as particularly attractive candidates for cancer therapy.

Nano-emulsions are kinetically stable colloidal dispersions consisting of oil-in-water (O/W) or water-in-oil (W/O) droplets stabilized by surfactants and co-surfactants. Due to their small droplet size (typically in the range of 20–200 nm), they exhibit high surface area, excellent solubilization capacity for hydrophobic drugs, and improved stability compared to conventional emulsions. These attributes make nano-emulsions especially suitable for delivering lipophilic anticancer drugs and natural bioactive compounds that otherwise suffer from poor solubility and limited bioavailability. Additionally, nano-emulsions offer the flexibility to incorporate functional excipients for targeted delivery, pH- or enzyme-responsive drug release, and combination therapies, thereby broadening their application in breast cancer management.

Thus, the integration of nano-emulsion technology into breast cancer therapeutics holds great promise for enhancing drug delivery efficiency, overcoming resistance mechanisms, and improving patient outcomes. This review aims to highlight the potential of nano-emulsion-based formulations in breast cancer therapy by discussing their formulation strategies, pharmacological advantages, preclinical evidence, and future prospects.

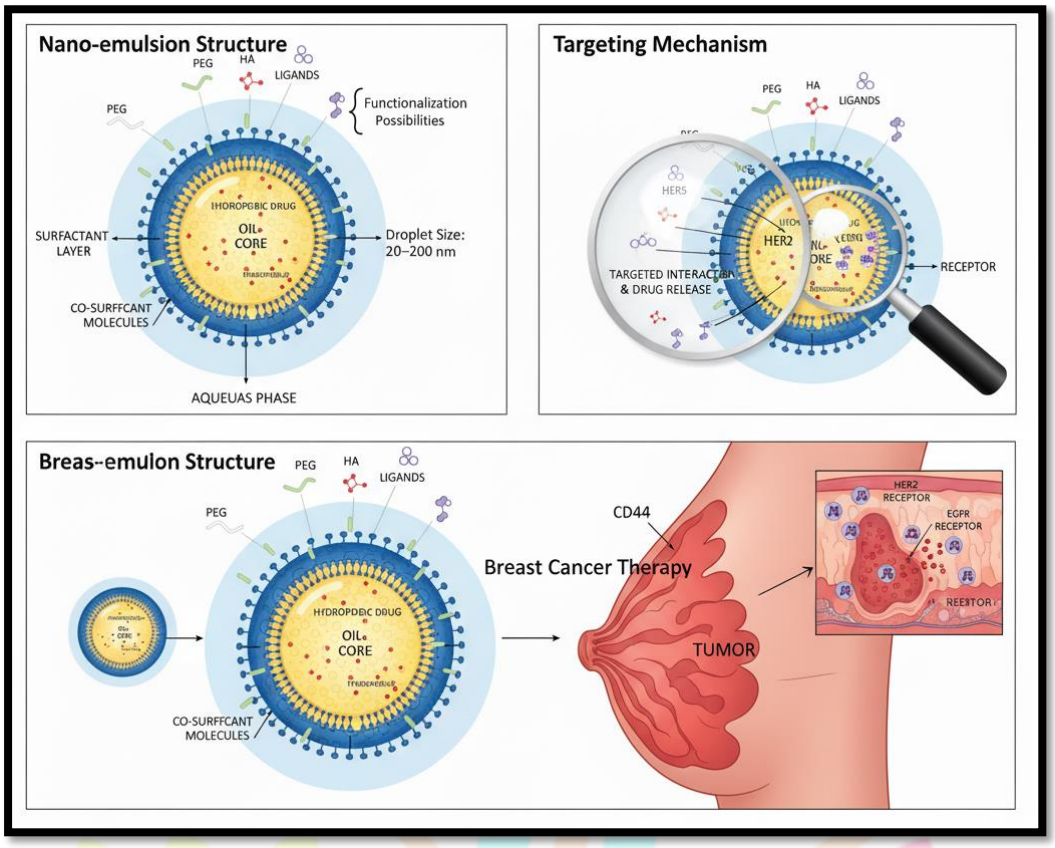

Figure 1 : Schematic representation of nano-emulsion structure and mechanisms in breast cancer therapy — showing oil core encapsulation, surfactant layer, and targeted receptor interactions (HER2, EGFR, CD44).

2. Composition & types of nano-emulsions

. Nano-emulsions (NEs) are colloidal dispersions with droplet sizes typically in the range of 20–200 nm, characterized by high kinetic stability, optical transparency or translucency, and superior solubilization capacity for hydrophobic molecules. Their therapeutic potential in drug delivery, especially for anticancer applications, depends largely on their composition and structural design. The fundamental components, classification, and surface functionalization strategies of nano-emulsions are outlined below.

Table 1 : Comparative Summary of Nano-emulsion Formulation Components

Component	Common Examples	Role in Formulation	Key Advantages
Oil Phase	Soybean oil, MCT, Labrafac®	Solubilizes lipophilic drugs	Improves loading & lymphatic transport
Surfactant	Tween 80, Poloxamer 188, Lecithin	Stabilizes droplets	Enhances dispersion & biocompatibility
Co-surfactant	Ethanol, PEG-400, Propylene glycol	Reduces interfacial tension	Promotes fine droplet formation
Aqueous Phase	Purified water, buffers	Continuous phase	Ensures physiological compatibility

2.1 Core Components of Nano-emulsions

1. **Oil Phase**

- The oil phase serves as the reservoir for lipophilic drugs or natural bioactive compounds. Its selection influences solubilization capacity, stability, and biocompatibility.

Commonly used oils include:

- Natural oils: e.g., soybean oil, olive oil, sesame oil – provide biocompatibility and nutritional value.
- Medium-chain triglycerides (MCTs): e.g., caprylic/capric triglycerides – widely used for their excellent solubilization ability and metabolic safety.
- Semi-synthetic oils: e.g., Labrafac®, Maisine®, Miglyol® – enhance drug loading and promote lymphatic transport.
- Perfluorocarbons: e.g., perfluorodecalin, perfluorohexane – unique for oxygen-carrying capacity and imaging applications.

2. **Surfactants**

- Surfactants reduce interfacial tension between oil and water, stabilizing the nano-sized droplets.
- Nonionic surfactants are most preferred due to low toxicity and high biocompatibility. Examples include:

3. **Co-surfactants**

- Co-surfactants enhance interfacial fluidity and reduce droplet size, improving stability.
- Commonly used examples include:
  - ✓ Short-chain alcohols (ethanol, propylene glycol, glycerol).
  - ✓ PEG derivatives (e.g., PEG-400, poloxamers).
- They facilitate spontaneous emulsification during preparation.

4. **Aqueous Phase**

- The continuous phase of most nano-emulsions, typically composed of purified/deionized water.
- May contain stabilizing agents, buffers, or cryoprotectants (for freeze-dried formulations).

2.2 Types of Nano-emulsions

Nano-emulsions can be broadly classified based on droplet orientation, internal structure, and application purpose:

1. **Oil-in-Water (O/W) Nano-emulsions**

- Oil droplets dispersed in a continuous aqueous phase.
- Widely used for oral, intravenous, and topical delivery of hydrophobic drugs.
- Preferred in cancer therapy due to their ability to solubilize poorly water-soluble drugs and ensure systemic compatibility.

2. **Water-in-Oil (W/O) Nano-emulsions**

- Water droplets dispersed in a continuous oil phase.
- Suitable for encapsulating hydrophilic drugs, peptides, or proteins.
- Often applied in vaccine delivery or depot drug formulations.

3. **Multiple Emulsions (e.g., W/O/W, O/W/O)**

- Complex systems where droplets of one type of emulsion are further dispersed into another.
- Useful for controlled or sustained release, protection of sensitive molecules, and dual drug delivery systems.

4. **Perfluorocarbon-core Nano-emulsions**

- Contain perfluorocarbon oils (e.g., perfluorodecalin) in the core.
- Specially designed for imaging, theranostics, and oxygen delivery.
- Can be combined with targeting ligands for dual imaging and therapy.

2.3 Functionalization of Nano-emulsions

Surface engineering of nano-emulsions enhances their biological performance, stability, and tumor-targeting potential:

- **PEGylation (Polyethylene Glycol coating)**
  - ✓ Increases circulation half-life by providing steric hindrance.
  - ✓ Reduces opsonization and clearance by the reticuloendothelial system (RES).
- **Hyaluronic Acid (HA) Coating**
  - ✓ Provides active targeting by binding to CD44 receptors, which are overexpressed in many breast cancer cells.
  - ✓ Also improves biocompatibility and mucoadhesion.
- **Ligand or Antibody Conjugation**
  - ✓ Functionalization with ligands (e.g., folic acid, peptides) or monoclonal antibodies enables receptor-mediated endocytosis.
  - ✓ Ensures selective accumulation in tumor tissues, improving therapeutic index.

3 Methods of Preparation and Scale-up Considerations

The method of preparation plays a critical role in determining the physicochemical properties, stability, and scalability of nano-emulsions (NEs). Selection of the appropriate technique depends on drug solubility, desired droplet size, formulation stability, and industrial feasibility. Broadly, nano-emulsion preparation techniques are classified into **high-energy** and **low-energy** methods, each with its own advantages and limitations. For successful clinical translation, scale-up considerations, reproducibility, and quality assurance must be carefully addressed.

3.1 High-energy Methods

High-energy methods utilize mechanical devices to apply strong disruptive forces (shear, cavitation, turbulence, or impact) to reduce droplet size into the nanometer range. These techniques are widely applied in pharmaceutical and industrial settings due to their reproducibility and scalability.

1. **High-Pressure Homogenization (HPH)**

   - Involves forcing coarse emulsions through a narrow gap at very high pressure (500–2000 bar), generating intense shear and cavitation forces.
   - Produces uniform droplets with sizes typically between 50–200 nm.
   - Suitable for both **oil-in-water** and **water-in-oil** nano-emulsions.
   - Highly scalable and GMP-compliant, making it the most common industrial method.

2. **Microfluidization**

   - Uses microchannels and interaction chambers where two fluid streams collide under high pressure, breaking down droplets.
   - Provides **highly reproducible droplet size distribution with narrow polydispersity index (PDI)**.
   - Ideal for thermolabile drugs due to shorter processing times.

3. **Ultrasonication**

   - Applies high-frequency ultrasound waves to induce acoustic cavitation, leading to droplet disruption.
   - Effective for lab-scale production but limited for large-scale manufacturing due to heat generation and lower reproducibility.
   - Often combined with HPH or microfluidization for fine-tuning particle size.

3.2 Low-energy Methods

Low-energy methods rely on the **intrinsic physicochemical properties** of the oil–water–surfactant system to achieve spontaneous nano-emulsion formation. They are cost-effective and require less sophisticated equipment but are highly formulation-sensitive.

1. **Spontaneous Emulsification (Self-emulsification)**

   - Achieved by mixing oil, surfactant, co-surfactant, and water under mild agitation.
   - Relies on differences in chemical potential between phases, leading to spontaneous droplet formation.
   - Useful for **self-emulsifying drug delivery systems (SEDDS/SMEDDS)**.

2. **Phase Inversion Method**

- Based on altering parameters such as temperature (Phase Inversion Temperature, PIT) or composition (Phase Inversion Composition, PIC).
- Heating and cooling cycles change surfactant curvature, enabling transition between W/O and O/W emulsions.
- Particularly suitable for thermally stable drugs and small-scale formulations.

3.3 Quality Parameters and Characterization

The quality and stability of nano-emulsions are evaluated using physicochemical and biological parameters:

- **Droplet Size and Polydispersity Index (PDI):** Measured by **Dynamic Light Scattering (DLS)**; optimal values are <200 nm (droplet size) and <0.3 (PDI) for uniformity.
- **Zeta Potential:** Indicates surface charge and colloidal stability; typically ±30 mV is considered stable.
- **Encapsulation Efficiency (EE%):** Reflects the percentage of drug successfully loaded within the emulsion droplets.
- **pH and Osmolarity:** Important for physiological compatibility, especially in parenteral formulations.
- **Rheological Properties:** Assess flow behavior (Newtonian vs. non-Newtonian) relevant to injectability and topical application.
- **Stability Studies:** Include centrifugation, heating-cooling cycles, freeze–thaw testing, and long-term storage stability.
- **Sterility Assurance:** Essential for parenteral and ophthalmic applications, requiring aseptic processing or terminal sterilization.

3.4 Scale-up and Clinical Translation

For successful industrial production and clinical application, the following considerations are critical:

- **Reproducibility:** Maintaining consistent droplet size, PDI, and encapsulation efficiency across multiple batches.
- **Scalability:** High-pressure homogenization and microfluidization are the most suitable techniques for industrial scale-up due to robustness and regulatory acceptance.
- **Sterility and Safety:** Parenteral formulations must meet pharmacopeial sterility standards, often requiring sterile filtration or aseptic production.
- **Regulatory Compliance:** Scale-up processes must adhere to **Good Manufacturing Practices (GMP)** with validated equipment and in-process controls.
- **Cost-effectiveness:** Minimizing energy input, raw material costs, and processing time is vital for commercial viability.

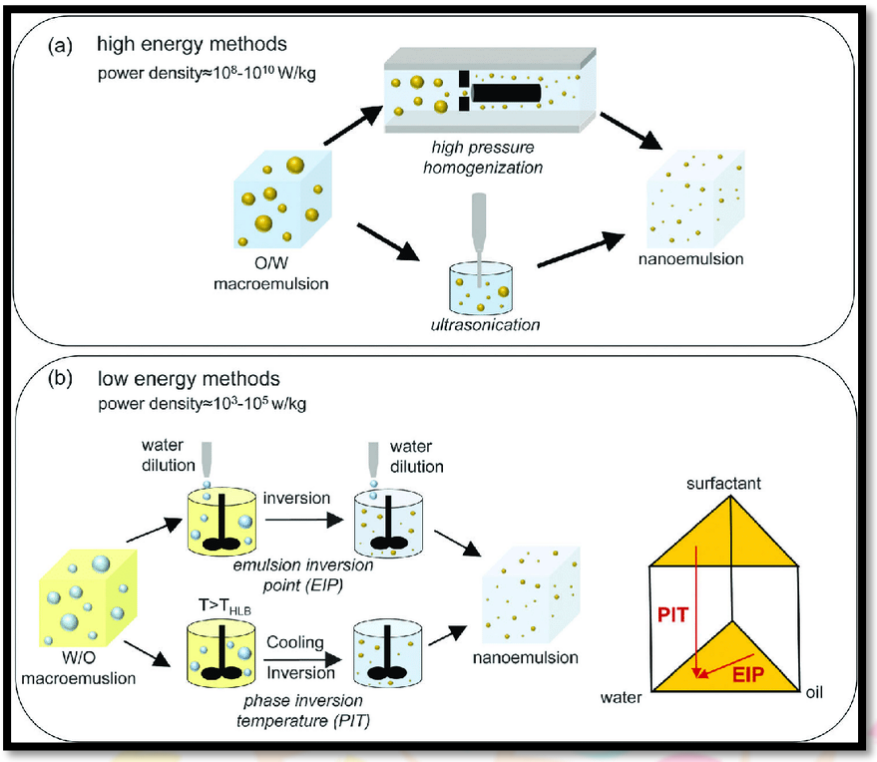

Figure 2 : Methods of Nano-emulsion Preparation and Scale-up

4 Mechanisms by which NEs improve anticancer therapy

1. **Increased solubility & bioavailability** of hydrophobic drugs, avoiding toxic solvents.
2. **Enhanced cellular uptake** via endocytosis, surfactant-mediated membrane interaction, or receptor-mediated uptake when surface ligands are present.
3. **Altered pharmacokinetics:** prolonged circulation (with PEGylation), enhanced permeability and retention (EPR) effect in tumors.
4. **Combination strategies:** co-delivery of chemotherapeutics + efflux pump inhibitors (e.g., elacridar), siRNA, or immunomodulators to overcome resistance. Recent studies show improved cytotoxicity and reversal of drug resistance in vitro/in vivo.

4.1 Pharmacology of Nano-emulsions in Breast Cancer

Nano-emulsions (NEs) influence the pharmacological profile of anticancer drugs by modifying their pharmacokinetics (PK), pharmacodynamics (PD), interaction potential, and immune-related responses. Their nanostructured architecture, surface functionalization, and compositional flexibility allow them to overcome limitations of conventional formulations, leading to improved therapeutic index in breast cancer treatment.

A) Pharmacokinetics (PK)

Nano-emulsions alter the absorption, distribution, metabolism, and excretion (ADME) of drugs, thereby enhancing bioavailability and therapeutic efficiency:

- **Absorption**
  - Oral administration of hydrophobic drugs is limited by poor water solubility and gastrointestinal instability. NEs improve solubilization, leading to enhanced absorption through enterocytes and lymphatic transport pathways.
  - Several studies report 2–5 fold increases in oral bioavailability of poorly soluble anticancer agents when formulated as NEs.
  - For intravenous (IV) formulations, the small droplet size (~50–200 nm) allows better circulation, tissue penetration, and selective tumor accumulation via the Enhanced Permeability and Retention (EPR) effect.

- **Distribution**
  - ✓ Surface modifications significantly influence biodistribution:
    - ✓ PEGylation reduces uptake by the reticuloendothelial system (RES), prolonging systemic circulation.
    - ✓ Ligand conjugation (e.g., folic acid, hyaluronic acid, antibodies) directs NEs towards overexpressed receptors on breast cancer cells (HER2, EGFR, CD44).
  - ✓ This results in increased tumor targeting and reduced off-target toxicity compared to free drugs.
- **Metabolism**
  - ✓ Oils and surfactants used in NEs can modulate cytochrome P450 (CYP450) enzyme activity, influencing drug metabolism.
  - ✓ Certain formulations enable bypassing of first-pass metabolism (e.g., via lymphatic uptake in oral NEs or intranasal delivery), thereby increasing systemic drug exposure.
  - ✓ This is particularly valuable for natural products (e.g., curcumin, resveratrol) that undergo extensive hepatic metabolism.

- **Excretion**
  - ✓ Sustained release properties of NEs may slow drug clearance, prolonging therapeutic effects.
  - ✓ Lipophilic drugs incorporated in NEs are predominantly eliminated through biliary and fecal excretion, while hydrophilic excipients are cleared renally.

Table 2 : Pharmacological Advantages of Nano-emulsions in Breast Cancer Therapy

Pharmacological Aspect	Effect of Nano-emulsions	Outcome
Absorption	Enhanced solubilization and lymphatic uptake	Increased bioavailability
Distribution	Receptor-targeted delivery (HER2, CD44)	Higher tumor accumulation
Metabolism	Bypass of first-pass metabolism	Improved systemic exposure
Excretion	Sustained release kinetics	Prolonged therapeutic effect
Pharmacodynamics	Increased intracellular concentration	Enhanced cytotoxicity and reduced MDR

B) Pharmacodynamics (PD)

Nano-emulsions enhance drug action at the cellular and molecular levels by influencing drug delivery, intracellular accumulation, and signaling pathway modulation:

- **Enhanced Intracellular Drug Concentration**
  - NEs facilitate uptake via endocytosis or membrane fusion, delivering higher intracellular drug concentrations, which increases apoptosis and induces cell cycle arrest in breast cancer cells.
- **Overcoming Drug Resistance**
  - Co-delivery of chemotherapeutics with efflux pump inhibitors (e.g., verapamil or surfactants that inhibit P-glycoprotein) modifies PD by reversing multidrug resistance (MDR).
  - This results in greater cytotoxicity against resistant breast cancer cells**.**
- **Receptor-mediated Pharmacodynamics**
  - Targeted NEs (e.g., HER2-antibody conjugated systems) enhance selective receptor blockade and downstream signaling inhibition (HER2, EGFR, PI3K/Akt, MAPK pathways).
  - Such receptor-specific PD effects improve efficacy while minimizing systemic toxicity.

C) Drug–Drug and Drug–Excipient Interactions

Drug interactions are critical for combination therapies and clinical safety evaluation of NEs:

- **Drug–Excipient Interactions**
  - Surfactants such as Tween 80 or Cremophor EL substitutes can inhibit P-glycoprotein (P-gp) and certain CYP enzymes, leading to altered drug metabolism and bioavailability.
  - While beneficial in overcoming efflux-mediated resistance, these effects require careful monitoring**.**
- **Drug–Drug Interactions**
  - Nano-emulsions can be engineered for co-delivery systems (e.g., paclitaxel + siRNA, doxorubicin + phytochemicals like curcumin).
  - Such formulations often display synergistic or additive pharmacodynamic effects, improving tumor regression while reducing required drug doses.
  - However, unintended PK/PD interactions may occur, necessitating preclinical evaluation of safety profiles.

5. Safety, toxicity & immunological considerations

Safety assessment of nano-emulsions is a critical step before their translation into clinical use for breast cancer therapy. Although NEs are generally composed of biocompatible oils, surfactants, and co-surfactants, their nanoscale size, surface properties, and repeated administration raise unique toxicological and immunological challenges.

5.1 Surfactant and Oil Component Toxicity

- The choice of surfactant strongly influences tolerability. Conventional solubilizers like Cremophor EL have been associated with hypersensitivity reactions, anaphylaxis, and peripheral neuropathy, limiting their clinical utility.
- NEs allow the substitution of such surfactants with milder, FDA-approved excipients (e.g., polysorbates, lecithin, PEGylated surfactants), thereby reducing hypersensitivity risks.
- The oil phase (medium-chain triglycerides, essential oils, perfluorocarbons) must be carefully selected to balance drug solubility, metabolic compatibility, and minimal local irritation.

5.2 Systemic Toxicity and Off-Target Accumulation

- Due to their nanoscale size and prolonged circulation, NEs may accumulate in liver, spleen, and kidneys, leading to potential hepatic or renal burden.
- Long-term repeated dosing requires evaluation of organ toxicity, metabolic by-products, and oxidative stress induction.
- Parameters such as droplet size, zeta potential, and surface coating significantly influence biodistribution and should be optimized to minimize off-target exposure.

5.3 Immunological Interactions

- NEs can trigger immune recognition through opsonization and complement activation-related pseudoallergy (CARPA), a concern particularly with cationic surfactants or non-PEGylated formulations.
- Surface modifications like PEGylation reduce immune detection but may paradoxically induce the accelerated blood clearance (ABC) phenomenon upon repeated dosing.
- Immuno-stimulatory vs. immuno-evasive effects must be balanced depending on therapeutic intent (e.g., chemotherapy vs. immunotherapy combinations).

5.4 Long-Term Biocompatibility and Repeated Dosing

- While single-dose safety is often demonstrated in preclinical studies, long-term GLP toxicology studies (repeated-dose, toxicokinetics, immunotoxicity) are essential for regulatory approval.
- Chronic use raises concerns of cumulative surfactant toxicity, oxidative stress, or immune dysregulation, especially in adjuvant or maintenance therapy settings.
- Rigorous evaluation of sterility, pyrogenicity, and endotoxin contamination is mandatory for parenteral products

6. Advantages & limitations

6.1 Advantages and Limitations of Nano-emulsions

Nano-emulsions (NEs) offer several advantages as drug delivery systems in breast cancer therapy, but they are also associated with notable challenges that must be addressed for successful clinical translation**.**

A) Advantages

1. Improved Solubility and Bioavailability

NEs enhance solubilization of hydrophobic and poorly water-soluble anticancer agents (e.g., paclitaxel, curcumin), improving oral absorption and systemic exposure.

2. Higher Drug Loading Capacity

Due to their oil core, NEs can encapsulate large amounts of lipophilic drugs and bioactive natural products, minimizing the need for toxic solvents.

3. Co-delivery Potential

NEs can simultaneously carry multiple therapeutic agents such as chemotherapeutics, efflux pump inhibitors, siRNA, or immunomodulators, enabling synergistic effects and overcoming resistance.

4. Versatile Routes of Administration

Suitable for oral, intravenous, transdermal, intranasal, and topical delivery, allowing flexibility in breast cancer management strategies.

5. Low-cost and Biocompatible Components

Most oils, surfactants, and co-surfactants are FDA-approved, inexpensive, and safe for parenteral use, making NEs cost-effective compared to other nanocarriers.

6. Amenable to Imaging and Theranostics

Functionalized NEs (e.g., with perfluorocarbon cores or contrast agents) can be engineered for dual imaging and therapy, offering theranostic applications in cancer diagnosis and monitoring**.**

B) Limitations

1. **Physical Stability Issues**
   - NEs are thermodynamically unstable systems, prone to droplet coalescence, Ostwald ripening, and phase separation under stress conditions (temperature, pH, ionic strength).
2. **Formulation Sensitivity**
   - Stability and performance are highly dependent on the choice of oil, surfactant, and co-surfactant; small changes in composition can significantly alter pharmacological behavior.
3. **Potential Surfactant-related Toxicity**
   - Some surfactants (e.g., Cremophor EL, high concentrations of polysorbates) may cause hypersensitivity reactions, hemolysis, or enzyme inhibition, requiring safer alternatives.

4. **Opsonization and Rapid Clearance**
    - Unmodified NEs are susceptible to protein corona formation and uptake by the reticuloendothelial system (RES), reducing circulation time. PEGylation can mitigate this, but may induce "accelerated blood clearance" (ABC) upon repeated dosing.

5. **Variable Tumor EPR Effect in Humans**
    - While the Enhanced Permeability and Retention (EPR) effect is significant in preclinical models, its heterogeneity in human tumors reduces predictability of passive targeting.

7. Future Directions

Despite promising preclinical outcomes, the clinical translation of nano-emulsions (NEs) in breast cancer therapy is still limited. To bridge the gap between bench and bedside, future research must integrate pharmacological, technological, and regulatory considerations. The following strategies are proposed:

7.1 Prioritize Clinically Relevant Endpoints in Preclinical Models

- ✓ Most studies emphasize cytotoxicity and tumor regression; however, for regulatory acceptance, toxicokinetics, immunotoxicity, repeated-dose safety, and GLP-compliant studies are essential.
- ✓ Comprehensive assessment of long-term stability, biodistribution, and immunogenicity in animal models will provide translational relevance.

7.2 Scalable and Regulatory-friendly Formulations

1. To ensure industrial feasibility, focus should shift toward **manufacturing-friendly processes** (e.g., high-pressure homogenization, microfluidization) that are already adaptable to GMP environments.
2. Utilization of **excipients already approved for parenteral products** (e.g., FDA/EMA-listed oils, surfactants, and PEG derivatives) will streamline regulatory approval and reduce safety concerns.

7.3 Integration with Molecular Resistance-modulating Strategies

- Combination approaches hold strong promise:
    - ✓ **NEs co-delivered with siRNA, CRISPR payloads, or efflux pump inhibitors** can address multidrug resistance (MDR).
    - ✓ Development of **theranostic NEs** that combine therapy with imaging will aid in monitoring treatment response.

- Companion diagnostics should be developed to **identify patient subgroups** most likely to benefit (e.g., HER2+, triple-negative breast cancer).

7.4 Early-phase Clinical Trials with Strong Translational Packages

- Promising NE candidates should progress to Phase I/II clinical trials with robust Chemistry, Manufacturing, and Controls (CMC) documentation, ensuring reproducibility and safety.
- Clinical trial design should incorporate biomarker-driven endpoints (circulating tumor DNA, receptor expression, immune markers) to establish precision medicine approaches.
- Long-term follow-up for safety, immunogenicity, and therapeutic durability will be critical to clinical acceptance.

8. Conclusion

Nano-emulsions offer a versatile and practical platform to improve delivery of hydrophobic anticancer drugs and phytocompounds for breast cancer therapy. Preclinical evidence supports their capacity to enhance solubility, increase tumor uptake, and overcome certain resistance mechanisms. The principal barriers to clinical translation are manufacturing, long-term stability, comprehensive toxicology, and regulatory characterization. With targeted efforts on scalable, clinically-acceptable formulations and early translational studies with biomarker-guided designs, NEs are well positioned to enter clinical oncology pipelines in the coming years.

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