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REVIEW

Nanoemulsions Based Therapeutic Strategies: Enhancing Targeted Drug Delivery against Breast Cancer Cells

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Abstract: Nanoemulsions (NEs), colloidal systems of nanoscale droplets (~100 nm), have emerged as transformative tools in oncology due to their high surface area-to-volume ratio, tunable physicochemical properties, and capacity for targeted drug delivery. While NEs find applications across diverse fields, their urgency in breast cancer therapy stems from critical limitations of conventional treatments, including systemic toxicity, poor bioavailability, and multidrug resistance. Unlike traditional chemotherapeutics, NEs enable precise tumor targeting via passive mechanisms (eg, enhanced permeability and retention effect) and active strategies (eg, ligand-functionalized surfaces), significantly reducing off-target effects. Their ability to encapsulate hydrophobic drugs, improve solubility, and sustain controlled release enhances therapeutic efficacy while overcoming resistance mechanisms prevalent in aggressive breast cancer subtypes, such as triple-negative and HER2-positive tumors. This review comprehensively analyzes NE formulation techniques (eg, ultrasonication, phase inversion temperature, bubble bursting), stability optimization through surfactant dynamics, and predictive modeling of droplet behavior. A focal point is their role in modulating tumor microenvironments, inducing apoptosis, and inhibiting angiogenesis in preclinical breast cancer models. By spotlighting NE-driven advancements in drug accumulation, reduced relapse rates, and adaptable combination therapies, this article underscores their potential to revolutionize oncology. Future research must prioritize clinical translation, scalability, and multifunctional NE designs to address unmet needs in precision breast cancer treatment.

Keywords: nanoemulsions, targeted drug delivery, breast cancer therapy, nanoscale droplets, tumor microenvironment

Introduction

Cancer is one of the most serious diseases threatening human health and remains a leading cause of death worldwide. It significantly reduces life expectancy, making it a major public health and economic burden across all nations.[1] Currently, cancer accounts for nearly 16.8% of all global deaths and contributes to over 22.8% of all mortality cases.[1] Among individuals aged 30–69, it is responsible for 30.3% of premature deaths and ranks as one of the top three causes of mortality in 177 out of 183 countries.[2] Beyond its impact on longevity, cancer imposes substantial macroeconomic and societal costs, varying by type, region, and gender.[3] A 2020 study revealed the significant impact of cancer mortality on women, reporting that nearly one million children lost their mothers to cancer, with breast and cervical cancers being responsible for nearly half of these deaths.[4]

As illustrated in Table 1, more than 60% of new cancer cases and fatalities stem from the ten most prevalent cancer types.[2] Lung cancer ranks as the most diagnosed cancer globally, accounting for 12.4% of cases, followed by breast cancer in women (11.6%), colorectal cancer (9.6%), prostate cancer (7.3%), and stomach cancer (4.9%). In terms of

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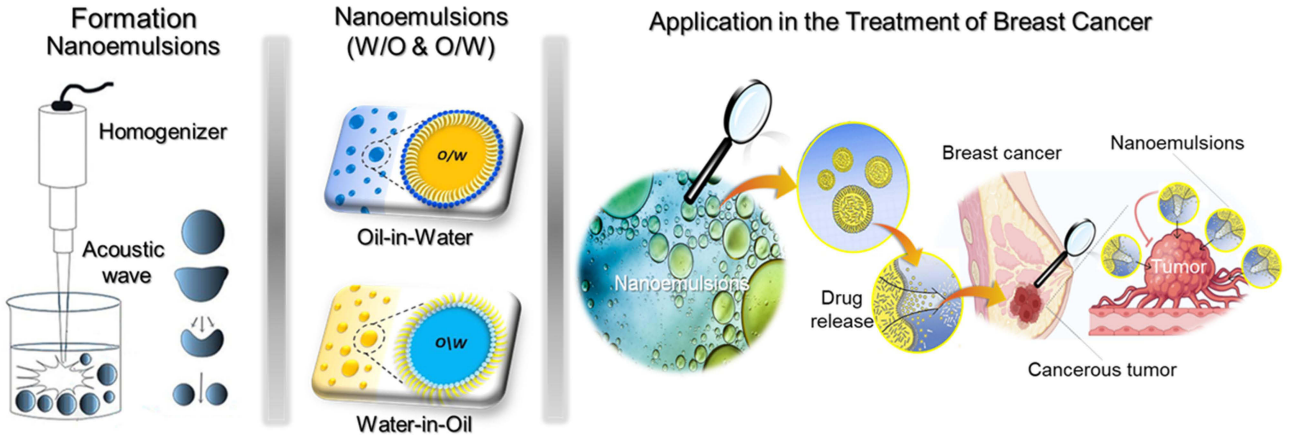
Graphical Abstract



mortality, lung cancer leads with 18.7% of all cancer-related deaths, followed by colorectal (9.3%), liver (7.8%), breast (6.9%), and stomach (6.8%) cancers. In women, breast cancer remains the most commonly diagnosed and the leading cause of death, whereas lung and colorectal cancers follow in both incidence and mortality. For men, lung cancer ranks highest in both cases and fatalities, with prostate and colorectal cancers being the next most frequently diagnosed, and liver and colorectal cancers ranking second and third in mortality.[2]

Nanoemulsions (NEs) play a crucial role in cancer treatment by encapsulating drugs, enhancing solubility, and improving the stability and bioavailability of chemotherapeutic agents.[5] Recent advancements in drug delivery systems have shown promising potential in overcoming limitations of conventional cancer treatments. These technologies enhance drug solubility, bioavailability, and therapeutic efficiency while minimizing toxicity and side effects. Additionally, they offer targeted drug release under tumor conditions, leading to high absorption and cytotoxic effects on cancer cells with minimal impact on healthy tissue.[6]

Breast cancer, the most frequently diagnosed malignancy in women, is a key focus of this discussion. Among its subtypes, Luminal A characterized by hormone receptor positivity and low proliferation rates is associated with favorable outcomes and high responsiveness to hormonal treatments.[5] Another type is Luminal B. It is also receptor-positive but with higher proliferation rates compared to Luminal A; this subtype may require a combination of therapies, including

Table 1 New Cases and Mortality Rates for the Top 10 Leading Cancers in 2022.[2]

Both Sexes			
Incidence		**Mortality**	
Lung	12.4%	Lung	18.7%
Female breast	11.6%	Colon & rectum	9.3%
Colon & rectum	9.6%	Liver	7.8%
Prostate	7.3%	Female breast	6.9%
Melanoma of skin	4.9%	Stomach	6.8%
Liver	4.3%	Pancreas	4.8%
Thyroid	4.1%	Esophagus	4.6%
Cervix uteri	3.3%	Prostate	4.1%
Bladder	3.1%	Cervix uteri	3.6%
Non-Hodgkin lymphoma	2.8%	Leukemia	3.1%
Other cancer	36.6	Other cancer	30.3%

chemotherapy and targeted agents. The next is HER2-positive, characterized by overexpression of the HER2 protein; this subtype may benefit from targeted therapies such as trastuzumab (Herceptin) but may also present aggressive behavior.[2] The last one is triple-negative. This type of breast cancer, lacking hormone receptors (ER and PR) and HER2, is often more challenging to treat and is associated with poorer outcomes, requiring more research into targeted therapies.

To combat cancer, various treatment approaches such as surgery, radiotherapy, and chemotherapy have been implemented. Among these, chemotherapy is widely used due to its straightforward and accessible procedures.[7] Over the past decade, nanotechnology has found applications in multiple fields, including cosmetics, food science, pharmaceuticals, and agricultural pesticides. Within the pharmaceutical sector, various nanocarriers such as nanoparticles, nanocapsules, solid lipid nanoparticles, and NEs have been developed to encapsulate bioactive compounds.[8]

NEs have emerged as a rapidly advancing class of colloidal carriers, facilitating effective and economical applications in diverse fields such as agriculture,[9] food,[10] cosmetics,[11] and pharmaceuticals.[12] Their classification is based on the chemical nature of the dispersed phase. Oil-in-water (O/W) emulsions occur when oil droplets are suspended in water, while water-in-oil (W/O) emulsions are formed when water is dispersed in oil. These are considered single emulsions. More complex systems, such as oil-in-water-in-oil (O/W/O) and water-in-oil-in-water (W/O/W) emulsions, involve a primary emulsion being dispersed in an additional liquid phase.[13] This ability to incorporate different dispersed phases makes NEs ideal for encapsulating a wide range of bioactive compounds. The continual advancement of NEs, incorporating more intricate compositions and internal compartments,[14] has positioned them as multifunctional drug delivery platforms. In medicine, NEs are valuable tools for addressing both existing and emerging health challenges. Their effectiveness in enhancing pharmaceutical compounds has been demonstrated across various therapeutic applications.[15] Specifically, their high surface-area-to-volume ratio promotes efficient drug absorption, while their adjustable interfacial properties allow for targeted delivery of active agents.[16] By modifying their surface to display biomolecules such as antibodies, NEs can achieve precise drug targeting, ensuring optimal doses reach intended sites while minimizing off-target effects.[17] Additionally, encapsulating drugs within NE structures protects them from environmental fluctuations, including enzymatic degradation and pH changes.[18] These attributes contribute to their growing adoption in pharmaceutical research, underlining their potential in healthcare advancements.

In nanocarrier-based drug delivery systems, targeted transport of therapeutic agents is further optimized through a combination of passive and active mechanisms, leveraging the unique properties of nanocarriers.[19] Passive transport exploits the physicochemical traits of nanocarriers and the biological environment of the target tissue.[20] For example, nanomedicines can accumulate at tumor sites through the enhanced permeability and retention (EPR) effect, which takes advantage of the leaky vasculature associated with tumors.[19] Meanwhile, active transport provides precise drug delivery by interacting with specific cellular components, utilizing ligand-receptor binding, pH-sensitive release, or cell-penetrating peptides to ensure efficient drug uptake.[21] Often, these mechanisms work together to maximize drug efficacy, specificity, and safety, particularly when integrated with strategic drug-loading methods.

The advancement of nanotechnology has led to increasing evidence supporting the role of nanocarriers in overcoming drug resistance in cancer chemotherapy.[22] Traditional treatments, while widely used, remain suboptimal, as reflected in high mortality rates, particularly in women affected by certain cancers. Conventional therapies including surgery, radiotherapy, and chemotherapy face challenges such as limited bioavailability, poor cellular uptake, acquired drug resistance, and adverse side effects. In contrast, nanomedicine offers a promising alternative, particularly for breast cancer treatment. Recent breakthroughs in nanomedicine are fostering novel therapeutic applications and innovative healthcare strategies.[23]

This review article aimed to critically synthesize current advancements in NEs as versatile pharmacological carriers, emphasizing their formulation strategies, stability mechanisms, and transformative potential in breast cancer therapy. Key objectives included analyzing innovative synthesis techniques for precise droplet size control, elucidating the role of surfactants and predictive models in optimizing stability, and evaluating the efficacy of NEs in targeted drug delivery, tumor microenvironment modulation, and overcoming multidrug resistance. By consolidating recent research, the review underscores NEs' capacity to enhance therapeutic precision through tumor-specific accumulation, minimized off-target effects, and adaptable delivery systems. The outcomes highlight NEs as promising tools for advancing oncology, bridging gaps between preclinical innovation and clinical translation. Future research should prioritize scalable production, biocompatibility assessments, and multifunctional NE designs to unlock their full potential in precision medicine and broader biomedical applications.

Nanoemulsions

NEs are emulsions characterized by uniformly sized particles ranging from 20 to 200 nm. Prior research has demonstrated the effectiveness of NEs in drug encapsulation for distribution purposes.[24] Due to their minuscule size, some NEs exhibit optical transparency or translucency. These systems comprise nanoscale droplets of one immiscible liquid uniformly distributed in another.[25,26] Industrially, NEs are predominantly formulated as O/W or W/O mixtures (Figure 1). In O/W NEs, oil droplets are dispersed in an aqueous medium, whereas W/O systems feature water droplets suspended in an oil phase.[27] O/W NEs are more widely adopted than W/O variants, with their droplets stabilized by hydrophilic surfactants, while lipophilic surfactants coat droplets in W/O systems.

Engineers can design complex architectures like W/O/W or O/W/O NEs using these colloids as foundational units.[28] Fabrication typically involves a dual-step process: for instance, creating W/O/W NEs requires first homogenizing an aqueous phase with an oil phase containing oil-soluble surfactants, followed by emulsification with a water phase containing hydrophilic surfactants. Building these systems can be challenging due to the requirement for extremely small droplet sizes in the internal and external droplets of parenteral double NEs, often less than 100 nm, driven by surfactant limitations in parenteral administration.[29] Moreover, altering the internal droplet size significantly affects the oil phase's characteristics.[30] Different NEs offer advantages for specific applications, such as shielding hydrophilic substances from the external water phase, regulating the release of hydrophilic substances, reducing undesirable flavors, or minimizing overall fat content in the system.[31–34] NE formulations, being non-toxic and non-irritating, are suitable for therapeutic use in humans and animals, without harmful effects on cells.[35] These attributes find applications in drug delivery, biological agents, and diagnostic agents.

Nanocarriers can be differentiated by their unique physicochemical properties. A critical classification criterion lies in their biocompatibility and toxicity profiles, which serve as central factors defining their functional identity.[17] The NEs for instance, are promising vehicles for drug delivery and pharmaceutical applications due to their tailored size, morphology, and biocompatibility.[36] Standard preclinical evaluations of NEs often assess their interactions with red blood cells (RBCs) and platelets which are key components in blood clotting processes. The NP's safety and biocompatibility are further validated through cytotoxicity testing across cell lines, histopathology, and serum biomarker analysis.[17] The NE system preserves fragile drugs, enhances solubility, controls drug release, increases bioavailability, and reduces patient variability. For nearly four decades, NEs have been employed in the medical industry, particularly in the formulation of parenteral nutrition liquids.

The creation of NEs involves various manufacturing approaches, broadly categorized into low-energy approaches and high-energy approaches.[25,37–39] In industrial applications, high-energy methods are predominantly employed, demanding a substantial energy input (~10^8–10^{10} W/kg) to generate microscopic droplets. Common mechanical devices for NE production include high-pressure control device homogenization, micro fluidization, Rotor stator emulsification method and sonication. These techniques use specially designed mechanical equipment to break and blend the oil and water phases by creating significant shear, turbulent, and cavitation flow profiles.[26,40] In contrast, low-energy approaches leverage specific system characteristics to create microscopic droplets while conserving energy (around 10^3 W/kg).

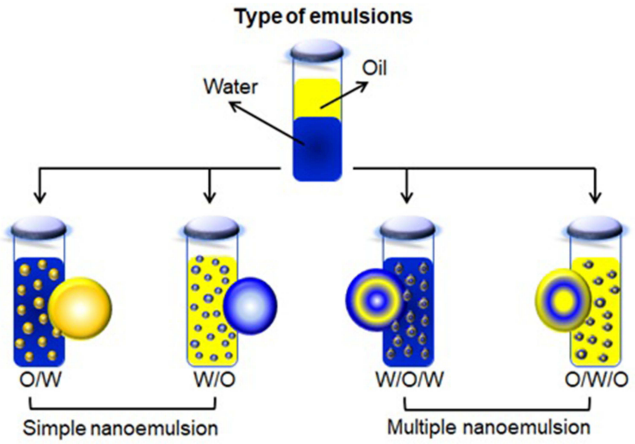


Figure 1 The structural variations of NEs depend on the relative positioning of the oil and aqueous phases.

The rotor-stator technique is a predominant emulsification method in food industries and is increasingly adapted for NE synthesis.[41] Its advantages include simple installation, cost-effectiveness, compatibility with viscous systems, and large-scale emulsion production. However, it is unsuitable for single-step NE generation due to challenges in achieving submicron droplet sizes (<1 μm). Common strategies to reduce droplet dimensions involve rotor redesign, gap minimization, increased rotational speed, and extended disruption zone residence time. High-pressure homogenization (HPH) is favored industrially for its scalability and flexibility.[42] While efficient, most HPH systems struggle to produce droplets in the ~1 nm range. This method involves propelling liquid mixtures (oil, water, surfactants) through micro-orifices at pressures of 500–5,000.[43] Though effective, HPH demands significant energy, risks thermal degradation, and is limited to O/W systems with <20% oil content.[44] Excess surfactants mitigate coalescence, though post-dilution is often required. Microfluidization employs microchannels (50–300 μm) to fragment emulsions under pressure, differing from HPH in channel geometry.[42] Ultrasonication, widely used in labs, reduces droplet size via acoustic cavitation by modulating sonication duration, power intensity, and surfactant concentration.

Ultrasonication serves as a homogenization technique for generating kinetically stable NEs,[45] widely employed in research settings. This method generates acoustic pressure waves through electrical energy, which diminish droplet dimensions by adjusting sonication duration, power intensity, and emulsifier concentration. The process relies on high-frequency sound waves (≥20 kHz), where inertial cavitation induced by the ultrasonic probe provides the energy required to fragment droplets. A piezoelectric transducer converts electrical voltage into mechanical vibrations, generating these sound waves. Such low-energy approaches depend on the spontaneous generation of nanoscale droplets in surfactant-oil-water systems, driven by inherent structural properties or external stimuli like temperature shifts.[46] Common low-energy strategies encompass spontaneous emulsification, phase inversion temperature (PIT), and emulsion inversion point techniques.

The spontaneous emulsification technique blends an organic phase (eg, oil and surfactants) with an aqueous phase containing co-surfactants and water, enabling the mobilization of water-soluble components like solvents and surfactants across phases.[46] This diffusion of hydrophilic elements into the aqueous medium heightens interfacial instability at the oil-water boundary, enlarging the contact area. Disintegration of the transitional microemulsion structure triggers the autonomous generation of nanoscale oil droplets. Known as the Ouzo effect, this phenomenon can be expedited using solvents, regardless of surfactant presence.[46] The method yields nano- or microemulsions irrespective of kinetic parameters. Although still in its early stages of industrial application, it demonstrates cost-efficiency, producing droplets as small as 10 nm.[47]

The phase inversion method refers to the reversible transition between O/W and W/O emulsions during emulsification and is a strategic process driven by surfactant behavior and phase dynamics.[45] This transition arises from shifts in the surfactant's spontaneous curvature, which can be modulated by temperature adjustments (for non-ionic surfactants) or compositional changes.[45] The phase inversion composition (PIC) technique modifies the hydrophilic-lipophilic balance (HLB) of emulsifiers by altering ingredient ratios. For example, introducing salt to ionic-stabilized O/W NEs disrupts surfactant charge, inverting the system to W/O.[48] Similarly, diluting W/O systems with water induces inversion to O/W. However, this method is less effective for hydrophobic compounds. Successful PIC implementation requires incremental water addition to the oil phase, gradually increasing aqueous content.

The PIT method involves a temperature-dependent transition between O/W and W/O emulsions, driven by molecular migration and temperature-modulated shifts in emulsifier hydrophilicity/lipophilicity at fixed composition.[48] This approach generates NEs with minimal energy input, avoiding mechanical shear. PIT relies on transitional inversion in emulsions, governed by temperature-induced modifications to the HLB of surfactants.[47] Membrane emulsification, often misclassified as high-energy, operates mechanically with low energy demands. The choice of the NE production method depends on component properties (eg, surfactant/oil phases) and target product features, including stability, optical/rheological behavior, release kinetics, and functionality. Table 2 summarizes the pros and cons of these techniques.

Preparation of Nanoemulsions

Nanosized emulsions can be produced using various methods, each of which influences the properties of the resulting NE, making the choice of method a crucial factor in NE creation. The energy required for creating O/W NEs can vary, ranging from high-energy to low-energy techniques.[38,49] High-energy methods, such as ultrasound and HPH, rely on mechanical forces to break down the dispersed phase into small oil droplets.[26,50] Ultrasonication is commonly used in

Table 2 Preparation Method of Nanoemulsion Formulation With Advantages and Disadvantages

Methods of nanoemulsion formulation		Advantages	Disadvantages
Low energy	Phase inversion composition	• Low energy process • Flexibility in path • Liquid ratio variation Mixed surfactant Electrolyte change • Heat requirement not compulsory • Low cost	• Prone to Ostwald ripening • Oleic and aqueous phase solubility must be good • Limitation in type of surfactants • Limitation in range of compositions compared to high energy methods
	Phase inversion temperature	• Low energy process • Low cost	• Prone to Ostwald ripening • Oleic and aqueous phase solubility must be good • Limitation to temperature and sensitive surfactants • Heat energy input requirement • Stable range of T is limited
High energy	High pressure homogenization	• Fast and easy way of preparation • Shear force and composition both control the droplet size distribution • Suitable for extensive array of compositions • Very large scale production capability	• In comparison to low energy methods, it requires a great energy input • Requires an initial significant investment • Considerable loss of energy in the form of heat
	Ultrasonication	• Fast and easy way of preparation • Shear force and composition both control the droplet size distribution • Suitable for extensive array of compositions • Very large scale production capability	
	Rotor stator emulsification	• Easy installation • Low cost investment • Viscous system compatibility • Large emulsion volume preparation	• Highly challenging to reduce the drop size

laboratory settings, while high-pressure homogenizers are favored for industrial applications. In contrast, low-energy techniques exploit the compositional properties of ENs (ie, combinations of oil, water, and emulsifiers) to reduce interfacial tension and promote spontaneous emulsification through temperature changes. The PIT and spontaneous or self-emulsification processes are common low-energy approaches.[51,52]

The creation of nano-sized emulsions by high-energy methods depends on the composition of the NEs and the energy input required. These techniques involve the application of substantial shear forces through great kinetic energy to generate small droplets, overcoming energy barriers between the designated oil and aqueous phases. The addition of surfactants and co-surfactants is employed to stabilize the NEs and reduce the interfacial tension. Lower interfacial tension reduces the external energy required to break up the NE droplets.[53] For instance, by adjusting parameters such as ultrasonic wave frequency, energy input, plus duration, one can create NEs with specific characteristics such as size control, biodegradability, biocompatibility, the ability to overcome challenges related to drug loading and resistance, and controlled drug delivery. Consistent energy input and the oil phase's residence time within the disruption zone (sonication waves) significantly affects droplet size and distribution.[49,54] Increasing the sonication duration to a specific threshold, for example, leads to smaller NE droplets.[55] Hence, when producing NEs for in vitro as well as in vivo applications, it's essential to consider factors affecting physical stability and morphology. HPH is a scalable technique for industrial NE research, particularly in food production. However, it faces challenges related to high energy consumption as well as temperature increase.

For the duration of homogenization, NE mixtures flow under high pressure through a valve chamber, resulting in shearing energy that breaks the oil core into a nano-scale size.[56] Parameters (for instance the type of homogenizer, sample composition, and operating settings (eg, duration, energy intensity, and temperature)) all influence droplet size

during homogenization.[57,58] The intensity of homogenization can influence droplet formation, however, the homogenization pressure levels (MPa) used should be appropriate for the NE composition, including the chemical nature of the oil core and the surfactant type. Recent research emphasizes the importance of investigating the effect of homogenization pressure on NE composition, stability, and encapsulation efficiency (EE), indicating that increasing homogenization pressure up to a certain level, such as 120 MPa, improves EE, but exceeding this threshold may have negative effects on the vehicle's structure, such as soy protein isolate.[59] Surfactant kind and concentration, oil proportion, and pressure homogenization conditions all have an impact on the physical stability of NEs.[60]

The selection of the NE production method has a significant impact on the physicochemical characteristics of NEs, including their rheology, stability, and payload release properties. Viscosity influences droplet shearing during emulsification, highlighting the importance of a thorough understanding of diverse NE formulation procedures, compositions, and intended pharmaceutical uses in order to produce NEs with desirable properties. In downstream applications like vaccines, it is critical to separate free and excess surfactants or polymer molecules from the NEs created. While centrifugation is commonly used to assess NE stability against phase separation, it may not effectively remove extraneous components from NE formulations. Instead, dialysis bags or chromatography-based separation techniques are employed to eliminate excess dyes, surfactants, and polymers like polyethylene glycol, with minimal impact on the physical characteristics of NEs.[61]

Characterization Methods for Nanoemulsions

Viscosity influences droplet shearing during emulsification, highlighting the importance of a thorough understanding of diverse NE formulation procedures, compositions, and intended pharmaceutical uses in order to produce NEs with desirable properties. In downstream applications like vaccines, it is critical to separate free and excess surfactants or polymer molecules from the created NEs. A widely used characterization method for NEs is dynamic light scattering (DLS), which relies on the principles of Brownian motion to determine droplet size. DLS exposes moving oil droplets to light, resulting in scattered light with varying intensities, which are quantified using the Stokes-Einstein equation. Key variables, such as the polydispersity index (PDI) and mean droplet diameter, are essential in describing the functional attributes of NEs, particularly their stability and dispersibility. Hence, it is imperative to continuously monitor these variables. Physically stable NEs exhibit properties that remain consistent over time.[62,63]

While DLS is a straight forward and rapid tool for the continuous monitoring of nanomaterial stability profiles, it may fall short in cases where test materials contain low proportions of droplet populations. In such cases, combining DLS data with other techniques, such as microscopic investigation, is advantageous. Electron microscopy allows for more detailed examinations into droplet structure and size.[64] Transmission electron microscopy (TEM) is used to investigate the internal structure of the dispersed phase, whereas scanning electron microscopy (SEM) offers topographical information.[65] Cryo electron microscopy, in addition to traditional TEM and SEM, is gaining popularity for several reasons. Cryo TEM, for example, allows for the direct examination of NEs as frozen hydrated droplets while preserving their original structural features.[66] As a result, cryo-TEM is employed to study the internal structure and scattered phase of NEs in their native condition.[67] While cryo TEM allows artifact-free inspection by distinguishing oil droplets from other structures,[68] it may face difficulties when recognizing droplets with high oil content or viscosity. This constraint is overcome by studying the surface microstructure of NE droplet aggregates with cryo SEM, which can investigate larger sample regions and is the preferable method for determining overall NE structure and dispersity.[69]

Atomic force microscopy (AFM) serves as a tool for analyzing the surface structure of NEs. Although AFM offers critical insights into NE morphology, uniformity, and stability, its laborious and time-intensive workflow limits practicality. Consequently, DLS is frequently preferred for assessing long-term stability. Cryopreparation methods paired with electron energy loss spectroscopy enable chemical profiling of NEs. Additional characterization techniques encompass differential scanning calorimetry, isothermal titration calorimetry, small-angle X-ray scattering, and X-ray spectroscopy.[69] The NEs provide a critical advantage in drug delivery by encapsulating diverse hydrophobic agents such as vitamins,[70] essential oils (EOs),[71] flavor compounds,[72] fluorophores,[73] and therapeutic drugs.[74] This encapsulation safeguards cargo integrity against degradation, enhances bioavailability, and enables controlled release at target sites.[75,76] The EE tests quantify retention within the NE's hydrophobic core,[77] with results influenced by formulation

parameters, NE composition, physicochemical drug properties (eg, oil-phase solubility), and system stability. The EE of NEs is quantified using multiple analytical methods, including ultracentrifugation, dialysis, gel filtration, ultrafiltration, and microfiltration. Ultracentrifugation employs size-selective membranes to isolate unencapsulated molecules from NEs. The dialysis method relies on semipermeable membranes to differentiate NEs from unbound drugs through diffusion gradients. Gel filtration separates NEs by molecular mass using porous gel matrices.[78] To enhance biocompatibility for in vivo applications, eukaryotic L-amino acid peptides are integrated into NPs design, leveraging their innate biodegradability, non-toxicity, and biocompatibility. The safety and biocompatibility of NPs can be evaluated using an MTT assay across diverse cell lines, where decreased cell viability post-NP exposure inversely correlates with the biocompatibility of the NP's constituent materials. In vitro analyses include cell viability assays, cytotoxicity tests (eg, oxidative stress detection), and stress response evaluations (eg, gene expression profiling). These in vitro methodologies are widely adopted in cytotoxicity research, differing in their mechanisms for identifying cell death pathways. Commonly employed assays include the MTT test, trypan blue exclusion assay, Comet assay (for DNA damage), and 2′,7′-dichlorofluorescein diacetate assay.

Nanoemulsion Stability

Stability in the context of NEs refers to their thermodynamic instability, where over time, these systems naturally tend to separate into two distinct phases. However, the introduction of surfactants can effectively prolong this process, rendering emulsions kinetically stable This extension of stability is crucial, particularly in applications like emulsion nanomedicine, where the alteration of a formulation over time can have significant implications for patient health and product quality, allowing NEs to maintain their original properties for extended periods, even months or years. To ensure the proper creation and preservation of NEs, it is essential to comprehend the mechanisms behind emulsion instability and stabilization. The DLVO theory, developed by Derjaguin, Landau, Verwey, and Overbeek, serves as a widely recognized model for predicting emulsion stability. This framework attributes colloidal stability to the balance between two opposing forces: van der Waals attraction and electrostatic repulsion from double-layer interactions. According to DLVO principles, these forces are assumed to act independently, permitting the total energy of contact (FT) to be calculated by summing the individual contributions of FA (attractive) and FR (repulsive) at varying distances. This approach offers a reliable approximation of colloidal stability, particularly at separation distances near 5 nm (Eq. 1).[79]

$$FT = FA + FR \quad (1)$$

At larger inter-droplet distances, repulsive forces govern interaction energies, maintaining dispersion stability. However, as droplets approach, attractive forces prevail, destabilizing the system. Per the DLVO framework, colloidal instability arises when attraction dominates, manifesting through four primary instability mechanisms: coalescence, flocculation, creaming/sedimentation, and Ostwald ripening (Figure 2). [80] Coalescence involves the fusion of smaller droplets into a larger droplet. During collisions, interfacial distortion leads to the formation of a thin interfacial film. Film thickness is governed by the transport of the continuous phase and surfactants across the film. Critical thinning induces rupture due to thickness variations.[81,82] The Marangoni effect, which drives mass transfer along interfaces due to tension gradients, contributes to film thinning.[82] Droplet coalescence reduces the system's total interfacial area, decreasing interfacial energy and Gibbs free energy. Flocculation involves the aggregation of dispersed droplets into clusters separated by thin continuous-phase films. While electrostatic repulsion delays coalescence, flocculation stability differs, as emulsions may rapidly aggregate before slowly coalescing.[83] Flocculation reversibility depends on the strength of inter-droplet attraction forces.[82] Proximity of droplets post-flocculation increases coalescence risk. Creaming/sedimentation occurs when buoyancy-driven separation positions droplets (based on density differences) at the top or bottom of the dispersion.[84] Creaming and sedimentation elevate the risk of droplet coalescence by enhancing droplet proximity. Managing these processes is crucial for the food industry, which incurs significant annual costs, often mitigated by incorporating viscous polysaccharides to slow separation.[85] Creaming can also result from droplet aggregation into expansive floc networks, either spontaneously or via polysaccharide bridging, which accelerates phase separation kinetics.[85] Ostwald ripening describes the growth of larger droplets through the diffusion of the dispersed phase from smaller to larger droplets in the continuous medium.[86] Ostwald ripening is driven by the Kelvin effect, which posits that

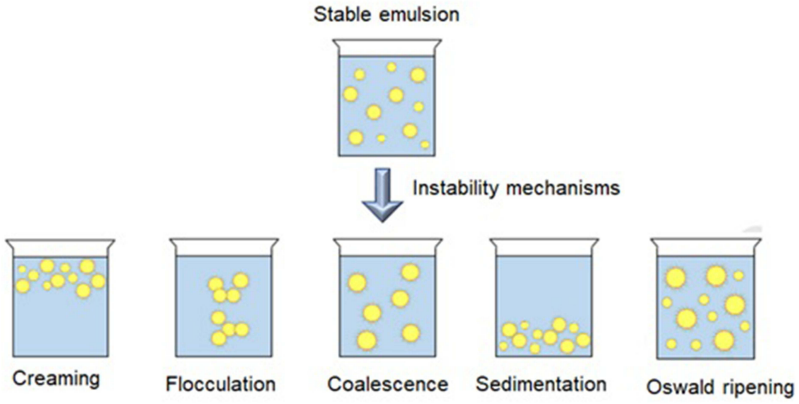


Figure 2 Different mechanisms of emulsion instability. Reprinted with permission from Shao P, Feng J, Sun P, Xiang N, Lu B, Qiu D. Recent advances in improving stability of food emulsion by plant polysaccharides. Food Res Int. 2020;137:109376. Copyright (2020), withpermission from Elsevier..[80]

smaller droplets exhibit higher solubility in the continuous phase. This reduces the total interfacial area of the dispersed phase, lowering the system's Gibbs free energy.[12]

To counteract this phenomenon, employing a dispersed phase with minimal solubility in the continuous medium and ensuring a narrow droplet size distribution are effective preventive measures.[87] The DLVO framework proposes two mechanisms for stabilizing emulsions: preventing droplet aggregation to inhibit destabilization pathways. The first, electrostatic repulsion, arises when similarly charged droplets generate mutual repulsion upon approach. The second, steric stabilization, occurs when a dense interfacial coating physically blocks droplet contact, creating an energy barrier against coalescence. Ionic surfactants stabilize emulsions by drawing counterions from the medium, forming an electrical double layer that enhances electrostatic repulsion (Figure 3). [88,89] An electrical double layer comprises the charged droplet surface, a Stern layer of closely associated counterions, and a diffuse layer of mobile ions.[90] The slip plane defines the boundary where the diffuse layer ceases to move with the droplets.[91] Zeta potential, measured at this plane, reflects emulsion stability higher magnitudes (positive or negative) correlate with enhanced colloidal resistance to aggregation.[92] Steric stabilization creates a thermodynamic barrier to droplet contact, a prerequisite for destabilization under DLVO theory.[93] Nonionic surfactants with extended chains, Pickering particles, or surface-adsorbed polymers enhance stability.[94] As droplets approach, interdigitating of these molecules elevates Gibbs free energy, counteracting van der Waals attraction.[95]

Pharmaceutical Applications

Advances in technology have transformed pharmaceutical formulations, evolving from basic systems to highly complex platforms termed advanced drug delivery systems. In pharmaceutical applications, NEs utilize colloidal dispersions of oil and aqueous phases, with droplet diameters averaging 50–500 nm.[31,32] The NEs primarily exist in two configurations: O/W or W/O,

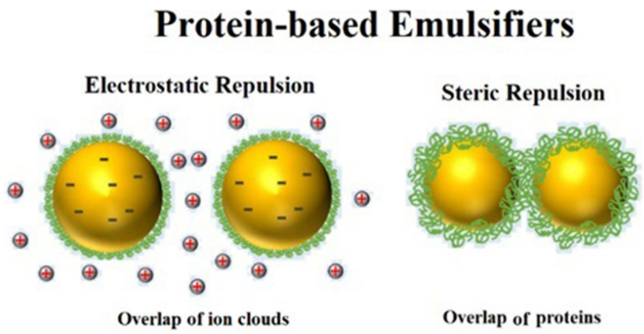


Figure 3 Protein-based emulsifiers prevent oil droplets from clumping together by using steric and electrostatic forces, which rely on the thickness, arrangement, and charge of the attached molecules. Reprinted with permission from McClements DJ, Lu J, Grossmann L. Proposed methods for testing and comparing the emulsifying properties of proteins from animal, plant, and alternative sources. Colloids Interfaces. 2022;6(2):19. © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).[89]

https://doi.org/10.2147/IJN.S488545

where droplets encapsulate either oil or aqueous components.[96] To stabilize NEs, pharmaceutical-grade surfactants designated as Generally Recognized as Safe (GRAS) are employed as emulsifying agents.[97] NEs offer unique advantages as drug carriers, efficiently solubilizing hydrophobic therapeutics and shielding active ingredients from degradation. Key benefits include enhanced drug payload capacity, solubility optimization, bioavailability enhancement, controlled release profiles, and protection against enzymatic/chemical breakdown. The nanoscale droplet size minimizes aggregation and gravitational separation compared to conventional emulsions, extending product shelf-life. Additionally, the high surface-area-to-volume ratio inherent to NEs may enhance targeted delivery of bioactive molecules.[98] The nanoscale droplets in NEs demonstrate distinctive physicochemical properties, including exceptional optical clarity and novel viscoelastic characteristics. These systems display varied optical attributes, transitioning from opaque to translucent, alongside rheological behaviors that vary between fluid and gel-like states. It is essential to recognize that diverse colloidal systems comprising oil, water, and surfactants possess both shared and unique functional properties. Colloidal systems are categorized into three groups based on droplet size and thermodynamic stability: microemulsions (thermodynamically stable, optically isotropic dispersions with droplets 20–100 nm), NEs (kinetically stable systems with droplets <200 nm), and conventional emulsions (metastable systems with droplets ≥200 nm to micrometers).[25] This review prioritizes NEs, which serve as versatile platforms for drug delivery via oral, transdermal, intranasal, or ocular routes. This analysis emphasizes recent advancements in NE-mediated therapeutic delivery.

Drug Delivery Applications

NEs have found extensive applications in the delivery of medications and various active compounds across multiple domains. They play a pivotal role in the pharmaceutical and medical sectors, offering a versatile solution for enhancing drug effectiveness and patient care. NEs are employed in diverse fields, including pharmaceuticals, cancer treatment, nutraceuticals, vaccine administration, ocular drug delivery, dermatological treatments, intranasal therapy, gene therapy, anti-inflammatory agents, antibiotics, central nervous system drug delivery, antiviral medications, gastrointestinal drug administration, and pulmonary drug delivery. Their ability to encapsulate and deliver a broad spectrum of drugs and bioactive substances makes them a valuable asset in the realm of healthcare and medicine (Figure 4). [99]

Oral Delivery

One of the primary methods for delivering drugs is orally, which is also one of the most widely used dose forms by patients. The oral delivery of proteins, vaccines, anti-cancer medications, and other medications has very poor bioavailability and is restricted, even with high patient compliance. For oral administration to be effective and sustained, it must overcome physiological hurdles such as limited solubility, permeability, and early breakdown. Through study, scientists attempt to address the physiological obstacles to oral drug distribution and explore technological solutions, including prodrugs, hydrogels, NPs, microemulsions, 3D printing, and other technical approaches. Oral medications have progressively transitioned from traditional to ultra-long-lasting drug administration because of these technological advancements (Figure 5). [100]

Because the oral route is the most convenient, simplest, and cost-effective method for non-invasive medication administration, drug delivery systems based on this premise now dominate the pharmaceutical industry. Furthermore, enhanced patient compliance makes it the best method for attaining treatment goals. This method of administration, however, has limits in terms of elderly, pediatric, and perhaps trauma epileptic patients, where patient participation is a key constraint. Furthermore, several medications are intrinsically difficult to administer orally due to non-conducive physiochemical characteristics. Poorly soluble medications delivered orally have major issues with solubility, stability, and absorption in the gastrointestinal tract (GIT).[101] Hydrolysis and enzymatic degradation of peptide medicines are known to impede their intestinal absorption and bioactivity. Additional downsides may include the restricted capacity of some medications to penetrate the epithelium cell wall. Micronization/nanonization,[102] solid dispersions,[103,104] complexation with cyclodextrins,[105] amorphization,[106] and use of particulate delivery systems that are dispersible in aqueous environments,[107,108] are some of the methods that have been proposed to increase overall bioavailability of drugs.

NE technology has improved the oral bioavailability of poorly soluble and hydrophobic medicines significantly in the last decade, according to many research groups. When poorly soluble medicines were given via NEs, numerous researchers saw significant improvements in C_{max} and the area under the curve (AUC). The most essential structural components of gut-associated lymphoid tissue are Peyer's patches, which are specialized for

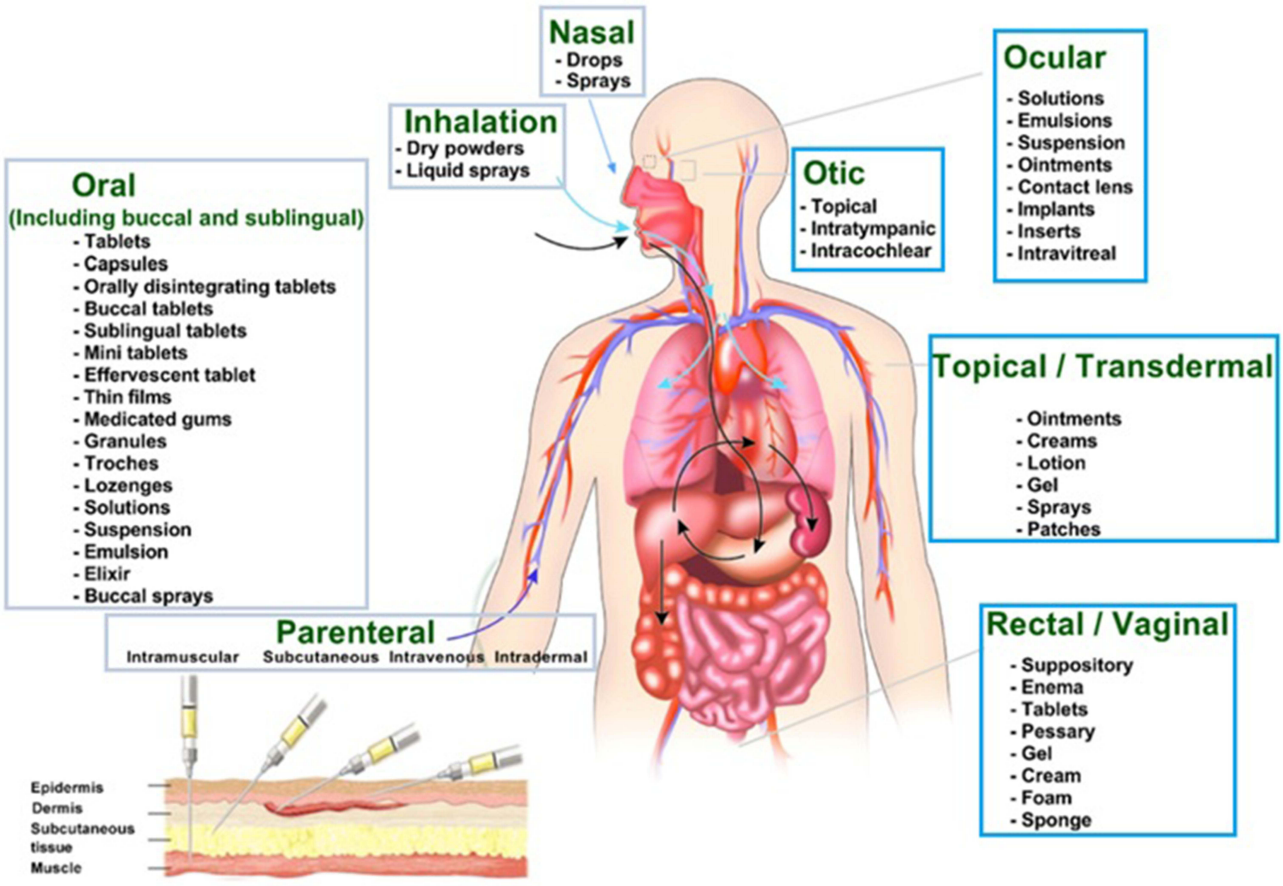


Figure 4 Routes of drug administration and associated dosage forms. Reprinted with permission from Khan MS, Roberts MS. Challenges and innovations of drug delivery in older age. Adv Drug Delivery Rev. 2018;135:3–38. Copyright (2018), withpermission from Elsevier.[99]

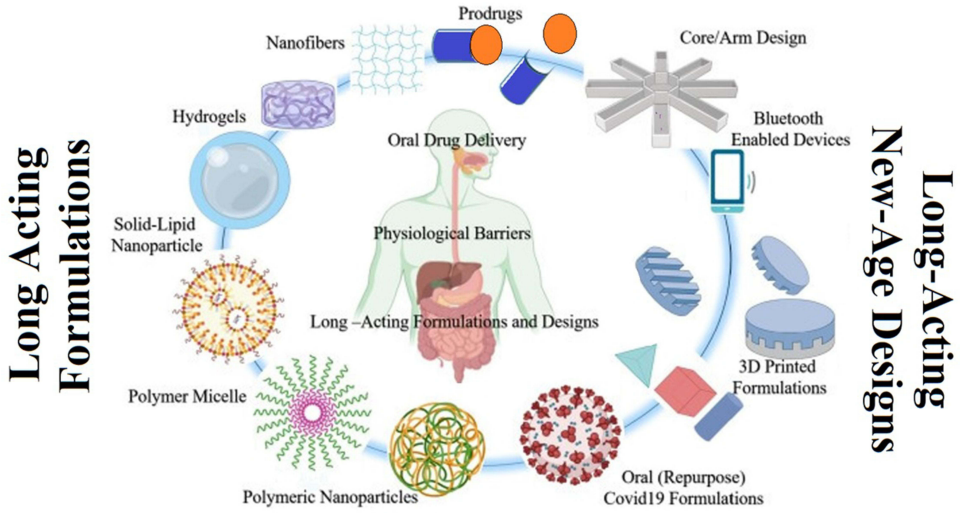


Figure 5 Challenges of oral drug delivery and technical design to overcome these challenges. Reprinted with permission from Majumdar. S. Oral drug delivery: conventional to long acting new-age designs. 2021. Copyright (2021), withpermission from Elsevier.[100]

endocytosis and transit into intraepithelial gaps. The M-cells ingest the NPs, which are quickly absorbed and "shuttled" to the lymphocytes.[109] The advantage of lymphatic absorption over portal blood absorption is that it circumvents the liver's presystemic processing of a medicine. Lymphatic targeting of NEs can facilitate the

following: translocation of antineoplastic drugs for the treatment of lymphomas; sustained/controlled drug release; reduction of drug-related mucosal irritation; avoidance of the hepatic first-pass effect; oral delivery of vaccine antigens to gut-associated lymphoid tissue; and oral delivery of labile drugs protected by the carrier (Figure 6). [66]

Lipids are successfully absorbed in the GIT by a variety of methods. As a result, one of the viable techniques for increasing medication absorption (particularly protein medicines) is to pack them inside lipids, resulting in a large increase in drug absorption as well as lipid absorption. The idea is to load medications with lipids, which are components of NEs, resulting in greater drug absorption in the GIT. It has been demonstrated that using NEs as oral drug delivery systems increases the medication's efficacy at the target location.[110,111] Increased penetration of flavonoids and iridoids from Vitex Agnus-castus extract-loaded NEs has been shown in in vitro transport tests (PAMPA and Caco-2 models) using triacetin as an oil phase and labrasol and cremophor EL as the surfactant and co-surfactant, respectively.[112] Using a novel delivery method for NEs, Elkadi et al (2017) created self-nano emulsifying tablets to improve the solubility of simvastatin.[113]

Parenteral Delivery

Parenteral administration is a prevalent and effective method for delivering drugs characterized by a narrow therapeutic window and poor bioavailability.[114,115] Parenteral drug delivery is a medical intervention that administers a drug directly into the bloodstream, bypassing the gastrointestinal tract.[116] However, this route presents challenges for hydrophobic therapeutics. Current strategies outlined in research such as adjusting vehicular pH, incorporating co-solvents, or cyclodextrin complexation,[101] face constraints such as adjuvant toxicity, injection-site discomfort, and post-administration drug crystallization. Nanostructured carriers have emerged as promising alternatives to address these limitations. Lipid-based emulsions have proven effective for decades in clinical settings requiring intravenous nutrition.[117] Their viability stems from the biological compatibility of core components phospholipids and naturally derived or semi-synthetic oils enabling safe delivery of therapeutic and nutritional agents. Ensuring optimal parenteral

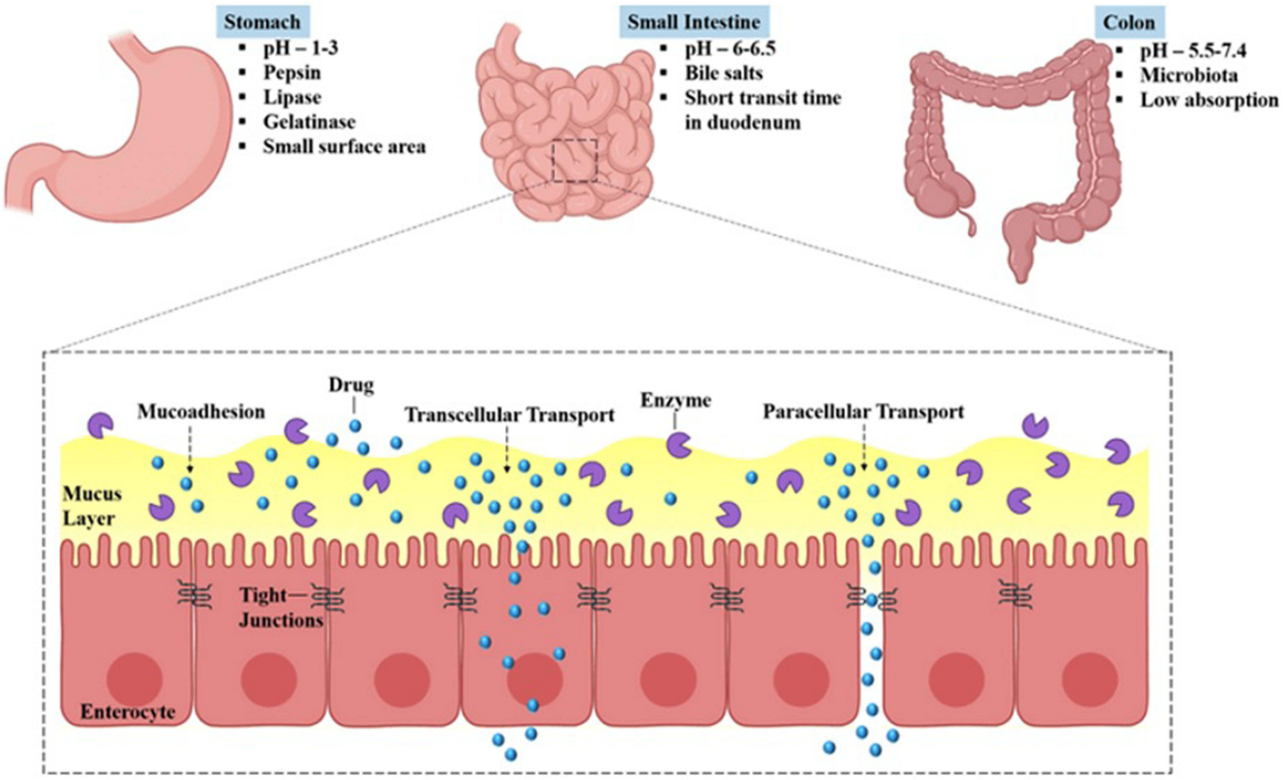


Figure 6 Physiological barriers to oral drug delivery. Reprinted with permission from Majumdar. S. Oral drug delivery: conventional to long acting new-age designs. 2021. Copyright (2021), withpermission from Elsevier.[100]

delivery and system stability requires meticulous regulation of compositional design, structural integrity, and manufacturing parameters. Stability is critically influenced by factors such as formulation chemistry, production protocols, and storage conditions.[118,119] The NEs are effective carriers for parenteral drug delivery due to their high solubilization capacity for hydrophobic bioactives, biocompatibility, and ability to protect therapeutics from chemical/enzymatic degradation.[117,120] Stabilizing NEs for this route requires emulsifiers capable of forming monolayers or multilayers around oil droplets. Common emulsifiers include natural phospholipids (eg, lecithins) and semisynthetic derivatives like dioleoylphosphatidylethanolamine (DOPE) or distearoylphosphatidylcholine (DSPC). Lecithins, sourced from animal or plant origins, are inherently biocompatible and biodegradable. A significant proportion of lecithin phospholipids feature charged polar head groups, such as phosphatidylserine, phosphatidylglycerol, and phosphatidic acid, which confer a strong negative surface charge to droplets. This charge induces electrostatic repulsion, enhancing colloidal stability over time. While natural surfactants are favored for emulsification, formulations are often supplemented with auxiliary emulsifiers to improve stability. Nonionic surfactants, like poloxamers and polyoxyethylene sorbitan derivatives (eg, Tweens), demonstrate synergistic stabilization when combined with phospholipids, forming dense interfacial films that enhance formulation robustness. The hemolytic potential and post-autoclaving droplet size instability associated with Tween 80 limit its applicability in nanoemulsion (NE) formulations. Despite risks of toxicity and hemolysis linked to certain derivatives, polyoxyethylated castor oil variants remain under investigation for parenteral drug delivery.[121,122] Lipophilic drugs delivered via NEs typically exhibit higher plasma levels post-parenteral administration compared to conventional solutions. This is attributed to enhanced distribution volume and reduced clearance rates, which collectively prolong elimination half-life.[123] The sustained and controlled drug release from NEs minimizes injection frequency and dosage requirements throughout treatment regimens. Additionally, their reduced propensity for droplet coalescence or phase separation offers stability advantages over traditional emulsion systems.

Transdermal and Topical Delivery

For some clinical circumstances, systemic medication distribution via the skin is extremely convenient.[124,125] Transdermal delivery methods are especially attractive because they offer the advantage of steady-state controlled drug delivery with self-administration, which may not be possible with the parenteral route.[126] By taking off the transdermal patch, the patient can cease receiving medicine at any time. The skin's ability to obstruct effective bioactive penetration is a significant limitation that now limits the application of this mode of administration for several uses. Drugs applied transdermally have the potential to enter the bloodstream through the stratum corneum, sweat ducts, or hair follicles. The stratum corneum, on the other hand, hinders their absorption and so reduces their bioavailability. The principal skin barriers must be addressed in order to optimize medication pharmacokinetics and targeting.[86] NE droplets may readily penetrate the skin's pores and enter the systemic circulation, where they are channeled for optimal distribution. The penetration of pharmaceuticals through the skin may be improved in a variety of ways by optimizing drug and vehicle characteristics. For example, the greatest penetration is frequently observed when the drug is at its highest thermodynamic activity, as in supersaturated solutions. Betamethasone,[127] clobetasol,[88] corticosterone,[128] flufenamic acid,[129] flurbiprofen,[130] tocopheryl acetate,[131] tolterodine tartrate,[132] and amlodipine[133] are only a few of the medicinal molecules that have been administered to or through the skin using nanoformulations.

Intranasal Delivery

Intranasal drug delivery is another safe and effective way to provide some medications. Indeed, the nasal mucosa has emerged as a therapeutically feasible conduit for the delivery of systemic medications, as well as a promising means of circumventing the barriers to direct drug entrance to the target site. Since ancient times, this approach has been acknowledged in the Ayurvedic system of Indian medicine, and it has lately been recommended over oral administration of medications because it leads to improved systemic bioavailability, probably by bypassing drug metabolism in the gastrointestinal tract.[134] Additionally, intranasal delivery is generally tolerated, painless, and noninvasive. Targeting the brain with medicines presents a number of challenges, especially with hydrophilic and high-molecular-weight molecules.[135] This is because the endothelium, which divides the brain from the systemic circulation, is impermeable across the blood-brain barrier.[136] The olfactory region of the nasal mucosa acts as a direct conduit between the nose and the brain.

The NEs encapsulating therapeutic agents have demonstrated clinical utility across diverse therapeutic areas, including osteoporosis (raloxifene), schizophrenia (olanzapine), motion sickness (metoclopramide), endometriosis (nafarelin), hormone replacement (estradiol), smoking cessation (nicotine), and enuresis (desmopressin).[96]

The potential of nasal administration for central nervous system (CNS) distribution of polar medications for the treatment of chronic CNS illnesses, like Parkinson's or Alzheimer's disease, has been investigated.[137] Because the brain is thought to be one of HIV's safe havens, saquinavir has been effectively used as an intranasal NE drug to target the brain to treat this problem.[138] Vaccines can also be given as NEs via the intranasal route (described later in this review), which has several benefits over the oral and parenteral approaches. However, nasal medication delivery is limited by its capacity, the challenge of attaining exact dose measurements, and the consistency of delivery. The administration strategy, formulation, and delivery mechanism all affect permeability, duration of residence, and metabolism in the nasal cavity, which in turn affects drug distribution in the nasal cavity.

Ocular Delivery

Most ocular medications are administered as aqueous eye drops applied to the lower conjunctival.[139] Key limitations of this approach include short ocular retention, inefficiency in delivering lipophilic/insoluble drugs, and susceptibility to rapid clearance from blinking and tear turnover. Less than 20% of the topical dose persists in the ocular cavity due to enzymatic degradation, absorption barriers, phagocytic activity, and systemic uptake via adjacent tissues.[50] In topical ocular drug delivery, rapid clearance is a critical challenge, with <1% of the applied dose penetrating ocular tissues. Retinal delivery faces even greater inefficiency due to compounding barriers such as anatomical obstructions, aqueous humor dynamics, intraocular metabolism, pigment tissue binding, and non-targeted phagocytosis by resident cells.[140] Developing effective ocular drug formulations presents major hurdles for the pharmaceutical industry, requiring prolonged ocular retention, sustained therapeutic concentrations, and regulatory compliance while accommodating diverse active ingredients. The NEs offer a potential solution, combining sustained release with enhanced permeation into ocular tissues and th aqueous humor.[141] Cationic NEs, leveraging bioadhesive properties, outperform traditional eye drops by improving bioavailability and ensuring targeted delivery of therapeutics to ocular structures.[142] The bioadhesive nature of NEs originates from electrostatic interactions between charged droplets and ocular surfaces, extending nanoscale oil droplet retention. Commercial systems like Novasorb utilize cationic droplets to electrostatically bind negatively charged ocular epithelia, enhancing therapeutic residence time.[143] At physiological pH, the ocular surface including its glycosylaminoglycan-rich mucus layer, corneal/conjunctival cells carries a negative charge. A positively charged formulation applied topically induces electrostatic attraction, extending its ocular residence time. Additionally, nanoscale oil droplets may enhance absorption efficiency.

Nanoemulsions for Vaccine Delivery

In pharmaceutical applications, the surface properties of NEs play a crucial role in their physical stability and interactions within the body. These characteristics include the type, concentration, shape, and surface charge of the surfactant, coating material type, thickness, size, and architecture, as well as the nature of targeting ligands. Bioconjugation techniques are used to customize these surface characteristics in order to get the required pharmacological activity and physical stability (Figure 7). For instance, steric hindrance can be introduced at the O/W interface by the addition or presentation of polymers, such as polyethylene glycol (PEG), which will change the thickness and surface architecture of the NEs. This PEG shielding also mitigates surface charge, preventing unwanted electrostatic interactions with plasma proteins, which can lead to opsonization and rapid clearance. These positive surface modifications significantly influence the stability and biological interactions of NEs, enhancing their potential in drug delivery applications. However, surface functionalization must also be practical, cost-effective, and favorable for the encapsulated compounds during downstream processing (Figure 7).[50]

Most of the current research on NEs vaccine delivery primarily focuses on intranasal mucosal techniques.[144] In contrast to conventional vaccination methods, intranasal mucosal vaccination involves the introduction of an oil-based emulsion into the nostrils. This approach is preferred due to its ease of administration and the reduced amount of antigen required to trigger an immune response. Although the exact mechanism by which vaccination adjuvants enhance the immune response is not fully understood, it is believed that they promote enhanced antigen distribution and activate

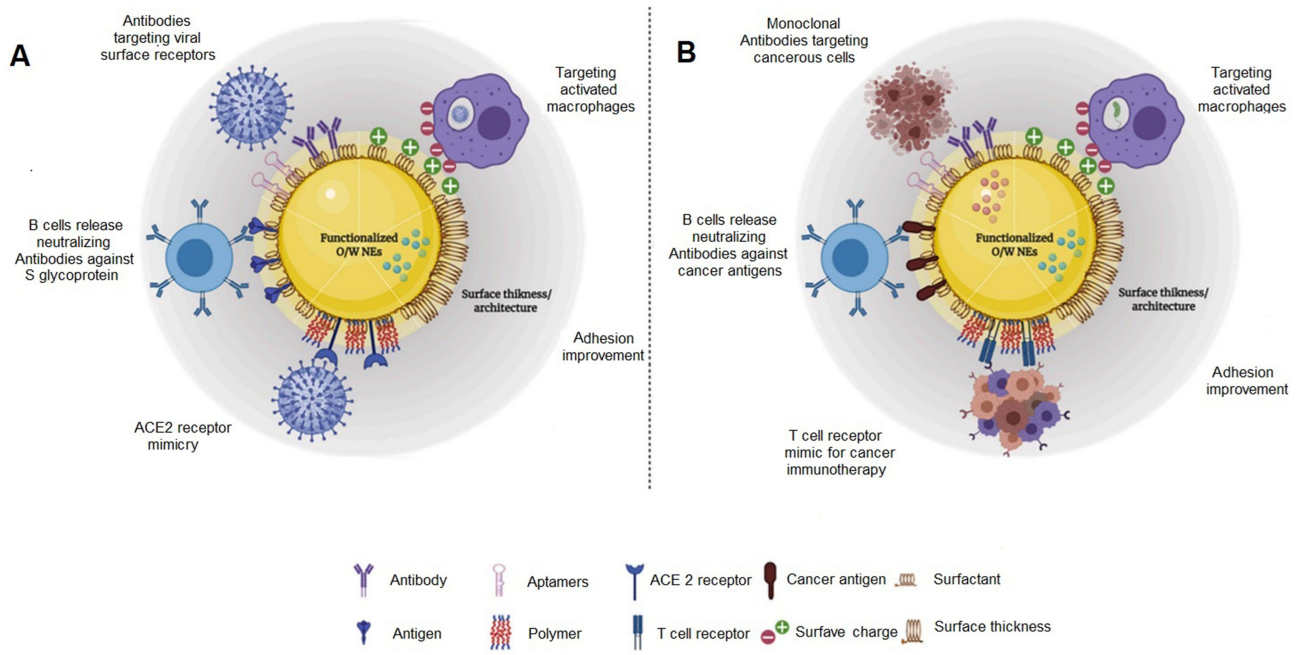


Figure 7 Surface features of O/W NEs play a crucial role in medicinal applications: (**A**) Biomolecules enhance O/W NEs for drug delivery, immune response, viral neutralization, and targeted infection treatment. (**B**) Customizable surfaces enable diverse strategies, including macrophage targeting, cancer cell recognition, immune activation, and T-cell receptor presentation. Reprinted with permission from Gassmann P, List M, Schweitzer A, Sucker H. Hydrosols: alternatives for the parenteral application of poorly water soluble drugs. Eur J Pharm Biopharm. 1994;40(2):64–72. © 2021 The Authors. Published by Elsevier B.V.[114]

innate immune responses as potential pathways. NE-based vaccination adjuvants function by increasing the absorption of antigens by dendritic cells (DCs) and activating Toll-like receptors 2 and 4 (TLR 2 and 4). This, in turn, enhances both humoral and cell-mediated immune responses, particularly Th1 and Th17 responses.[145] Moreover, NE-based mucosal adjuvants have demonstrated safety and tolerability in early-stage human clinical trials, with no harm to the mucosal epithelium.[146] Given that HIV can target the mucosal immune system, there is a suggestion that bolstering mucosal immunity through the use of NEs could be a viable strategy for HIV prevention.[143] Additionally, intranasal vaccinations have shown the ability to confer immunity to the vaginal mucosa.[147] Adjuvants like NEs are currently being employed to deliver attenuated organisms to mucosal surfaces to provoke the appropriate immune response. For example, an intranasally administered NE-adjuvanted inactivated influenza vaccine, with a 1:6 ratio of cationic-to-nonionic surfactants, resulted in a robust mucosal influenza-specific IgA response, offering a notable advantage over responses generated by traditional parenteral immunization.[148] Studies suggest that NEs are effective mucosal adjuvants for recombinant Bacillus anthracis protective antigen anthrax vaccines, as they induce long-lasting, robust, and specific humoral and cellular responses while maintaining antigen stability, all with no adverse effects.[149]

Nanoemulsions for Gene Delivery

Gene delivery is a fundamental concept aimed at introducing genes into a patient's somatic cells to correct genetic defects or create new cellular functions. The excellent adhesion of liposomes to cell surfaces has led to their use as non-viral vectors for gene delivery.[150,151] Although viral gene delivery techniques offer superior transfection capabilities, their higher toxicity limits their utility. This drawback has led researchers to explore non-viral methods, such as cationic NEs. These NEs, containing cationic surfactants, can interact electrostatically with negatively charged DNA, compacting it into nanocomplexes.[152] Stearylamine, a cationic lipid, has been proposed as an effective surfactant for gene transport. Electrophoresis studies revealed that cationic NEs having a zeta potential greater than +30 mV and droplet diameters less than 200 nm, containing stearylamine, efficiently complexed with the model plasmid PIRES2-EGFP.[153] Cationic NEs have also been used for intranasal delivery of TNF siRNA, demonstrating effectiveness in protecting against neuroinflammation in an LPS-induced model.[154] Positive-strand RNA virus self-amplifying messenger RNA (mRNA) has emerged as a potential

non-viral vector for creating vaccine antigens in situ.[155] It has been demonstrated that cell-penetrating peptides improve the absorption of plasmid DNA (pDNA) by mucosal epithelial cells in self-nano emulsifying drug delivery systems (SNEDDS) for oral gene transfer.[156] While liposomes are commonly used for gene transport, NEs offer an advantage in terms of physical stability. Unlike most liposomal preparations, which tend to aggregate upon contact with DNA, potentially causing an embolism when administered systemically,[157] NE-based delivery systems are expected to mitigate this issue.

Nanoemulsions for Breast Cancer Treatment

Nanotechnology has emerged as a promising approach in cancer treatment, with significant research focus on addressing diverse malignancies. This discussion emphasizes prevalent cancer types, particularly breast cancer, which predominantly manifests as carcinomas originating in the milk-producing lobules (lobular carcinoma) or the epithelial lining of the milk ducts (ductal carcinoma). Metastatic progression often occurs via the bloodstream and lymphatic system, commonly affecting the brain, liver, lungs, and skeletal structures.[158] Breast cancer pathogenesis is driven by disruptions in both genetic stability and epigenetic regulation. Mutations in high-penetrance genes such as p53, BRCA1, BRCA2, and PTEN (phosphatase and tensin homolog) frequently elevate susceptibility to hereditary breast cancer. Dysregulation in key signaling cascades including PI3K/Akt/mTOR, Ras/MAPK, NOTCH, and estrogen receptor (ER) pathways is also implicated in tumor cell proliferation and survival.[159] Gene expression profiling revolutionized breast cancer biology and therapeutic strategies by uncovering its heterogeneous transcriptional landscape. These diverse molecular profiles correlate with variations in histological features, metastasis patterns, clinical outcomes, and treatment efficacy, underscoring the disease's inherent complexity. Breast cancer subtypes are classified based on receptor expression: HER2-enriched (ER−, PR−, HER2+), luminal A (ER+/PR+, HER2−, Ki-67 <14%), normal-like (ER+/PR+, HER2−, low Ki-67), luminal B (ER+/PR+, HER2−, Ki-67 ≥14% or HER2+), and basal-like (triple-negative) (ER−, PR−, HER2−, CK5/6 + and/or EGFR+). Luminal and normal-like breast cancers generally exhibit favorable prognoses, whereas basal-like subtypes are associated with poorer outcomes compared to other variants.[160] Although the exact causes of breast cancer remain unclear, certain modifiable risk factors elevate its likelihood. Breast cancer risk factors span multiple categories: hereditary (family history, genetic predisposition, etc)., demographic (age, female, sex, etc)., breast-specific (reduced lactation periods, benign breast conditions), environmental exposures, hormonal influences (hormone replacement therapy, fertility medications, oral contraceptives, etc)., and lifestyle-related (obesity, smoking, poor diet, vitamin D deficiency, sedentary behavior, alcohol use, and shift work).[161] Breast cancer was the most frequently diagnosed cancer among women, accounting for 11.7% of all global cancer cases reported in 2018.[162] In 2020, cancer led to 10 million deaths worldwide, with 19.3 million new cases (18.1 million excluding non-melanoma skin cancer and basal cell carcinoma, and 9.9 million when non-melanoma skin cancers excluding basal cell carcinoma were omitted). The accessibility of chemotherapeutic agents remains restricted due to their lower tumor concentrations compared to other organs, which contributes to heightened toxic effects. The effectiveness of chemotherapeutic drugs is hindered by their limited tumor-specific accumulation, resulting in unintended drug distribution and increased systemic toxicity. To enhance treatment outcomes, various strategies have been explored. Natural enantiomers, like the one formulated by Periasamy et al using Nigella sativa L. essential oil, have shown potential as a breast cancer therapy.[163] This NE demonstrates anti-cancer effects by triggering apoptosis in MCF-7 breast cancer cells in vitro. Additionally, NE can encapsulate active breast cancer medications.[164] Treatment approaches have also incorporated local drug delivery alongside advancements in C6 ceramide NEs. Scientists utilize NE-based drug delivery and local administration to target tumors and pre-tumor lesions while reducing systemic side effects. To enhance treatment, researchers have developed bioadhesive ceramide-loaded NEs coated with chitosan. Nanoencapsulation of C6 ceramide significantly improved its potency, lowering the concentration needed to reduce MCF-7 cell viability by 50% (EC50) by 4.5 times compared to its solution form. Additionally, incorporating tributyrin, a butyric acid pro-drug, into the NE's oil phase further reduced the required concentration by 2.6 times. Compared to its solution form, intraductal administration of the NE prolonged drug retention in mammary tissue for over 120 hours.[165] Natesan and colleagues also utilized chitosan to develop NEs, encapsulating camptothecin and evaluating its effectiveness both in vitro and in vivo, comparing the NE formulation with the free drug.[166] Ongoing advancements in breast cancer treatment using NE-based drug delivery are outlined in Table 3.

Clinically Approved Nanomedicines for the Treatment of Breast Cancer

Nanodrug formulations loaded with NEs are increasingly prominent in global cancer therapy markets. Notably, Abraxane, utilizing albumin-bound paclitaxel, commands a significant share due to its proven clinical efficacy and safety. Doxil and Myocet, leveraging liposomal NEs for doxorubicin delivery, also feature prominently in breast cancer treatment. These drugs are globally accessible and favored for their enhanced therapeutic outcomes. Ongoing research is geared towards refining these drugs and broadening their applications in different cancer types. Clinical trials and studies aim to optimize drug delivery, minimize side effects, and enhance treatment efficacy. Nano drug formulations, which reduce toxicity and improve drug solubility, are set to play an expanding role in personalized cancer therapy, catering to individual patient profiles. While Abraxane, Doxil, and Myocet are established leaders, newer entrants like Onivyde, Nanoxel, NANOXEL-E, and Paclitaxel are making significant inroads. These formulations offer innovative features such as sustained drug release kinetics and reduced cytotoxicity, adding diversity to NEs-based cancer therapy. As research progresses, market shares may shift, reflecting the dynamic landscape of cancer treatment and personalized approaches. The Table 4 provides a comprehensive overview of various nano-drug formulations loaded with NEs for breast cancer therapy, highlighting their nanomedicine characteristics, therapeutic and nanotheranostic applications, years of FDA approval, clinical efficacy, safety profiles, and mechanisms of action on cancer cells.

These NEs offer enhanced drug delivery, reducing toxicity while improving treatment outcomes. In a study, researchers developed a nanocomposite by crosslinking chitosan and agarose to form a polymeric hydrogel, incorporating γ-alumina NPs within the hydrogel for 5-FU delivery. This nanocomposite was encapsulated in a W/O/W NE system. Experiments with MCF-7 breast cancer cells revealed that the 5-FU-loaded NE was more effective in eliminating cancer cells than crude 5-FU.[192] Another study focused on the design and characterization of a pequi oil-based NE with anticancer properties. The NE, made with lecithin as a surfactant, showed excellent physicochemical stability under stress and during long-term storage. It demonstrated significant dose- and time-dependent antitumoral effects against 4T1 breast cancer cells and exhibited lower cytotoxicity toward non-cancerous NIH/3T3 cells. Pequi oil served as both a structural element and a cytotoxic agent. Overall, the pequi oil-based NE shows great potential as a therapeutic platform for breast cancer treatment.[179]

Therapeutic Potential and Hurdles

NEs offer several key benefits as drug delivery systems, particularly for breast cancer treatment. Their ultra-small droplet sizes (usually between 20 and 200 nm) provide a high surface area-to-volume ratio, improving the solubility and bioavailability of poorly soluble drugs.[193] Additionally, NEs can encapsulate both hydrophobic and hydrophilic compounds, enabling the co-delivery of various therapeutic agents, including chemotherapeutics and immunomodulatory drugs. This bimodal approach can facilitate enhanced therapeutic effectiveness while potentially mitigating systemic toxicity. Additionally, the stability of NEs under various environmental stressors (eg, temperature fluctuations, pH changes, etc) allows for prolonged shelf life and ease of formulation, which are crucial for clinical applications. The capacity for surface modification using various surfactants and targeting ligands affords NEs the ability to achieve site-specific delivery, thereby minimizing off-target effects and enhancing localized therapeutic efficacy against breast cancer cells.[194] Despite these advantages, several challenges hinder the widespread clinical adoption of NEs. One prominent issue is the formulation scalability and reproducibility, which can pose significant hurdles when transitioning from laboratory to industrial production. The production processes often involve complex methodologies (eg, HPH or ultrasonication), which can require specialized equipment and may lead to variations in droplet size distribution that impact therapeutic outcomes. Moreover, NEs could exhibit potential immunogenicity or toxicity due to their surfactants or any active pharmaceutical ingredients they carry. The long-term safety of repeated administration of NEs remains an area of concern and requires thorough clinical evaluation, especially considering the particularly sensitive population of breast cancer patients. Furthermore, understanding the pharmacokinetics and dynamics of NEs within the biological system is still in its infancy. Factors such as biological barriers, enzyme interactions, and patient variability can significantly influence the performance of NEs, leading to unpredictable therapeutic responses. To overcome these hurdles, future strategies must focus on several key areas: Developing more streamlined and reproducible production

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Table 3 Breast Cancer Treatment Summary Using NE Drug Delivery

Drugs loaded	Method & Types of NEs	Cell line	Comment	Ref
Docetaxel and thymoquinone	Ultrasonication & O/W	MCF-7 and MDA-MB-231 cells	The DTX and TQ formulation in the B-NE system aims to lower the effective dose of DTX to prevent toxicity. It is more effective at inhibiting MCF-7 and MDA-MB -231 cells than the free drugs. The formulation also shows a synergistic effect in inducing autophagy and apoptosis, making it a promising candidate for breast cancer combination therapy by potentially reducing the required drug dose.	167
2-carene	Self-emulsifying and O/W	MDA-MB-231 breast cell lines and HMEpC	Computational analysis revealed significant interactions between 2-carene and breast cancer target proteins. Docking studies found that HER2 had the highest binding affinity with 2-carene. The nanoemulsion showed strong and sustained in vitro anticancer activity against breast cancer cell lines, as demonstrated by the MTT assay.	168
Lapachol (LAP)	Hot homogenization and O/W	4T1 cells	NE-LAP was successfully prepared and characterized for intravenous administration. It remained stable for 30 days at 0.5 mg/mL and showed a sustained drug release profile. Biodistribution and blood clearance studies indicated increased blood circulation time and preferential tumor uptake, leading to higher antitumor activity compared to LAP alone. The absence of toxicity suggests NE-LAP as an effective cancer treatment strategy.	169
Paclitaxel and erucin	Heating and sonication and O/W	Human epithelial breast cancer cells (T-47D) and normal mouse fibroblasts (L929)	Paclitaxel and erucin-based oil-in-water nanoemulsions (EPNE) were developed to target breast cancer, showing potent cytotoxic activity against paclitaxel-resistant T-47D breast cancer cells. EPNE improved the pharmacokinetic profile and bioavailability of both drugs, reducing potency, dosing frequency, and enhancing patient compliance. In vivo assessments showed EPNE could restore cancerous breast tissue to normal tissue, improve biochemical parameters, promote antioxidant defenses, and reduce inflammatory cytokines. Overall, EPNE shows promise as a viable option for combinatorial drug delivery.	170
Myricetin	Spontaneous emulsification and O/W	Triple-negative breast cancer cells (MDA-MB-231)	Nano-emulsified Myricetin exhibited efficient inhibition of cell proliferation, clonogenicity, and increased apoptosis with an IC50 value of 37 μM, a dose ~2.5 fold lower than native Myricetin. Mechanistic insights revealed that Myr-NE induced more ROS generation and considerably inhibited AKT and mTOR activation, leading to enhanced anticancer activity.	171
L-fucoside from lapachol	High-energy and O/W	4T1 and MDA-MB231 cells	In vivo assays showed NE-F-LapA, with over 98% drug encapsulation, remained stable for over 6 months. In vitro, it exhibited high toxicity against 4T1 and MDA-MB-231 cells, enhancing breast cancer cell uptake and selectivity. Systemic toxicity in mice showed no concerning changes. In a 4T1 breast tumor model, NE-F-LapA significantly inhibited tumor growth and reduced lung metastases. It enabled effective intravenous administration and improved efficacy over the free drug.	172
D-a-Tocopherol Polyethylene Glycol 1000 succinate, curcumin and resveratrol	High energy ultrasonication and O/W	MDA MB 231 and Hep G2 cells	NEs of curcumin and resveratrol (58–68 nm) exhibited synergistic anti-tumor effects, sustained release (22% curcumin, 89% resveratrol), and efficient loading (99.87% curcumin, 99.38% resveratrol).	173
Chloroaluminum phthalocyanine (NE-Pc), Doxorubicin (Dox)	Spontaneous emulsification based on the modified method; Low energy method and O/W	Murine BC cell line (4 T1)	Combination treatment (NE-PcDoxo + PDT) reduced breast cancer in mice, lowering VEGF, increasing Caspase-3, inducing apoptosis, and down-regulating cancer drug target genes, promising anti-tumor therapy.	174
Lapachol	Hot homogenization method, Low energy method and O/W	MDA-MB-231 and 4T1 cells	The NEs (170 nm, zeta potential ~20 mV) achieved >85% encapsulation without affecting Lapachol cytotoxicity. Radiolabeled 99mTc-NE-LAP demonstrated prolonged circulation, and NE-LAP showed superior antitumor activity.	169

Benzyl Isothiocyanate (BITC)	Emulsified with an ultrasonic process; High energy method and O/W	MDA-MB 231 cells	When applied to MDA MB 231 breast cancer cells, BITC NEs exhibited more cytotoxicity than BITC alone. Complete BITC encapsulation in the nanocarrier was confirmed by uptake assays employing flow cytometry and confocal spectroscopy, demonstrating the efficiency and compatibility of the device.	175
Paclitaxel (PTX)	High pressure homogenizer; high energy emulsification method and W/O	MCF-7 cells	NE had 97.81% PTX encapsulation with sustained release. PTX-loaded NEs showed superior cytotoxicity to breast cancer cells. Vitamin E enhanced antiproliferative effects and immune responses.	176
Curcumin	Spontaneous nanoemulsification, low energy method and O/W	MCF-7 cells	Empty NE is an excellent drug delivery system. Curcumin-NEs, activated at 440 nm, shows high phototoxicity, reducing viable tumor cells to 10% after two irradiations, increasing ROS production. Combined with photodynamic therapy, it enhances caspase 3/7 activity, indicating cellular apoptosis. Curcumin-NE is an effective photosensitizing agent.	177
Zataria multiflora essential oil and chitosan biopolymer	Low energy method and O/W	MDA-MB-231, T47D and MCF-7 and L929 cells	Induced ROS generation in the mitochondria of MDA-MB-231 cells by CS/ZEONE results in intrinsic apoptosis. This indicates that ZEO may be more stable and have stronger anticancer effects in vitro when combined with CSNE nanocarriers. It also shows apoptotic potential against breast adenocarcinoma cells.	178
Pequi oil (Caryocar brasiliense Cambess	Low energy method and O/W	4T1-luciferase and NIH-3T3 cells	Stable pequi oil NEs with a PDI of 0.23, size of 123 nm, and zeta potential of 15 mV endured 200 days of storage at various temperatures. They demonstrated dose- and time-dependent antitumoral effects on 4T1 breast cancer cells, with lower cytotoxicity to NIH/3T3 non-tumoral cells. Pequi oil served as both a structural component and a cytotoxic agent in the formulation.	179
Celecoxib and endoxifen	Low-energy method and transdermal drug delivery, W/O	MCF-7 cells	In the HET-CAM model, 5% oleic acid in NLP improved drug penetration without irritation. Although it led to larger droplets, distribution was more uniform (lower PDI) with a more negative zeta potential. CLX and EDX nanoencapsulation increased in vitro cytotoxicity in breast cancer cells, showing synergy in co-delivery.	180
Docetaxel	Self-nanoemulsifying, Low energy method and oral bioavailability of poorly-bioavailable drugs	MDA-MB 231 cells	Reconstituted self-nanoemulsifying drug delivery system (SNEDDS) featured a 121.50 nm droplet size, PDI of 0.338, and 12.3 mV zeta potential. In vitro, it enabled faster DTX release, following Higuchi kinetics. Cytotoxicity tests on MDA-MB 231 cells demonstrated enhanced DTX effectiveness, suggesting its superiority for oral breast cancer treatment.	181
5-fluorouracil, (5-FU)	Green synthesizing method	MCF-7 cells	Curcumin loaded in chitosan/agarose nanocomposites had a 85.6% loading and 79.2% entrapment. pH-sensitive drug release showed promise for targeted cancer treatment in MCF-7 cells.	182
Doxorubicin (DOX)	Low energy method and O/W	MCF-7 and HFS	Varying surfactant-to-oil ratios affected droplet sizes. DOX-loaded NEs enhanced effectiveness, reducing toxicity, with superior MCF-7 growth inhibition and minimal hand-foot syndrome cytotoxicity.	183

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Table 4 Clinically Approved Nanomedicine Drugs

Nanodrug Name	Nanomedicine Characteristics	Therapeutic and Nanotheranostic Applications	Years of Approval / FDA Indications / Clinical Efficacy and Safety Profile	Mechanism of Action on Cancer Cells	Ref
Abraxane (Albumin-bound Paclitaxel)	Abraxane is a nanoformulation of paclitaxel with albumin nanoparticles, enhancing drug solubility and cancer cell targeting. It exhibits release percentages of 94% in vitro and 96% in vivo, following the Higuchi kinetic model. Minimal toxicity (≤5%) and cytotoxicity (≤15%) on cancer cells are reported.	NEs-based drug delivery improves solubility and targeting in cancer therapy. Abraxane can serve as a nanotheranostic agent, combining paclitaxel and imaging agents (eg, iron oxide nanoparticles).	Approval: 2005. Indications: Metastatic and locally advanced breast cancer. Clinical Efficacy: Abraxane demonstrates high efficacy in treating breast cancer with a favorable safety profile.	Abraxane binds to tubulin in cancer cells, stabilizing microtubules, inhibiting cell division, and induces apoptosis.	184,185
Doxil (Liposomal Doxorubicin)	Doxil utilizes liposomal NEs for doxorubicin delivery, enhancing efficacy while minimizing side effects. It releases up to 87% with a biphasic kinetic model. Minimal toxicity (≤5%) and cytotoxicity (≤10%) on cancer cells are reported.	Liposomal NEs reduce side effects and improve drug delivery. Doxil can serve as a nanotheranostic agent, combining doxorubicin and imaging agents (eg, gadolinium-based contrast agents).	Approval: 1995. Indications: Breast cancer (among others). Clinical Efficacy: Doxil demonstrates efficacy in breast cancer and various malignancies with a well-established safety profile.	Doxil-loaded liposomes bind to cancer cell membranes, facilitating drug uptake, and doxorubicin intercalates with DNA, inhibiting replication and causing cell death.	186
Myocet (Liposomal Doxorubicin)	Myocet minimizes doxorubicin-induced cardiotoxicity using liposomal NEs. It releases up to 88% with a biphasic kinetic model. Minimal toxicity (≤5%) and cytotoxicity (≤12%) on cancer cells are reported.	Liposomal NEs enhance drug delivery while reducing cardiotoxicity. Myocet can function as a nanotheranostic agent, combining doxorubicin and imaging agents (eg, quantum dots).	Approval: 1999. Indications: Breast cancer (among others). Clinical Efficacy: Myocet exhibits clinical efficacy in breast cancer treatment with reduced cardiotoxicity, ensuring patient safety.	Myocet-loaded liposomes bind to cancer cell membranes, facilitating drug uptake, and doxorubicin intercalates with DNA, inhibiting replication and causes cell death.	187
Onivyde (Irinotecan Liposome Injection)	Onivyde employs liposomal NEs for irinotecan delivery in cancer research. It releases up to 75% with sustained kinetics. It extends beyond breast cancer treatments.	Liposomal NEs offer versatile cancer therapy options, with potential as a nanotheranostic agent using irinotecan and imaging agents (eg, fluorescent dyes).	Approval: 2015. Indications: Not specific to breast cancer but of interest in breast cancer research. Clinical Efficacy: Onivyde exhibits promising clinical efficacy in various cancers, particularly in combination therapies.	Onivyde-loaded liposomes release irinotecan, which inhibits topoisomerase I, leading to DNA damage and apoptosis in cancer cells.	188
Nanoxel (Paclitaxel-Loaded Liposome)	Nanoxel is authorized for breast cancer and other malignancies. It uses liposomal NEs for targeted paclitaxel delivery. Releases up to 94% following Higuchi kinetics. Minimal toxicity (≤6%) and cytotoxicity (≤14%) on cancer cells are reported.	Liposomal NEs enhances therapy, minimizing side effects. Nanoxel can be a nanotheranostic agent, combining paclitaxel and imaging agents (eg, fluorescent markers).	Approval: Various. Indications: Breast cancer and other malignancies. Clinical Efficacy: Nanoxel demonstrates clinical efficacy in breast cancer therapy with a favorable safety profile.	Nanoxel-loaded liposomes bind to cancer cell membranes, facilitating paclitaxel uptake, which disrupts microtubules, inhibiting cell division and induces apoptosis.	189

NANOXEL-E (Paclitaxel-Loaded Liposome)	NANOXEL-E is authorized for breast cancer and other malignancies. It uses liposomal NEs for targeted paclitaxel delivery. Releases up to 92% following Higuchi kinetics. Minimal toxicity (≤7%) and cytotoxicity (≤16%) on cancer cells are reported.	Liposomal NEs-based drug delivery in NANOXEL-E improves therapy, minimizing systemic toxicity. NANOXEL-E can be a nanotheranostic agent, combining paclitaxel and imaging agents (eg, magnetic nanoparticles).	Approval: Various. Indications: Breast cancer and other malignancies. Clinical Efficacy: NANOXEL-E exhibits clinical efficacy in breast cancer treatment, maintaining patient safety.	NANOXEL-E-loaded liposomes bind to cancer cell membranes, facilitating paclitaxel uptake, which disrupts microtubules, inhibiting cell division and induces apoptosis.	[190]
Paclitaxel (Paclitaxel-Loaded Liposome)	OncoPaclitaxel is authorized for breast cancer and other malignancies. It uses liposomal NEs for targeted paclitaxel delivery. Releases up to 91% following Higuchi kinetics. Minimal toxicity (≤8%) and cytotoxicity (≤18%) on cancer cells are reported.	Liposomal NEs-based drug delivery enhances therapy, minimizing side effects. OncoPaclitaxel can be a nanotheranostic agent, combining paclitaxel and imaging agents (eg, gold nanoparticles).	Approval: Various. Indications: Breast cancer and other malignancies. Clinical Efficacy: OncoPaclitaxel exhibits clinical efficacy in breast cancer therapy, ensuring patient safety.	OncoPaclitaxel-loaded liposomes bind to cancer cell membranes, facilitating paclitaxel uptake, which disrupts microtubules, inhibiting cell division and induces apoptosis.	[191]

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methods will be vital. This could include the integration of continuous flow methods or microfluidics to ensure uniformity in droplet size and improve manufacturability while minimizing energy consumption. Research efforts should investigate novel surfactants and co-surfactants that are more biocompatible and possess lower toxicity profiles.[195]

Exploring natural surfactants could offer safer alternatives while preserving the effective drug delivery properties of NEs. To improve the targeting of NEs to tumor sites, research should focus on attaching ligands to NEs that specifically recognize tumor markers or developing stimulus-responsive systems that release drugs in response to specific triggers like pH or temperature changes in the tumor microenvironment. Future research might also utilize advancements in AI and machine learning to create predictive models that customize NE formulations and treatment protocols based on individual patient profiles, optimizing therapeutic outcomes while minimizing side effects. Long-term, comprehensive studies are crucial to assess the safety of NEs with repeated systemic administration. This includes assessing potential immune responses, cytotoxic effects on non-tumoral tissues, and any implications from cumulative exposure to formulation components. By addressing these current disadvantages and leveraging their unique advantages, NEs can transform into a robust platform for breast cancer therapy, paving the way for more effective, targeted, and patient-centric treatment modalities. There is a lack of comprehensive research detailing the in vivo mechanisms governing drug release and bio-distribution of NEs. Understanding how NEs interact within the biological environment, including their absorption, distribution, metabolism, and excretion, is crucial for predicting therapeutic outcomes and potential side effects. Current studies often focus more on formulation and preliminary efficacy rather than these essential pharmacokinetic properties. Many of the formulation approaches remain empirical and may vary significantly between studies. This unpredictability can result in inconsistencies in droplet size, zeta potential, and stability, affecting the overall therapeutic effectiveness of NEs. Additionally, the lack of standardized protocols for production and characterization further complicates the comparative assessment of different NE formulation. The long-term safety of repeated NE administration has not been adequately addressed.[196] Potential cytotoxicity and immunogenic responses to NEs and their components need thorough investigation, particularly given the recurring nature of breast cancer treatments. Current studies often do not account for inter-patient variability in terms of genetics, disease stage, and prior treatments. This variability can significantly impact the effectiveness and safety of NEs, highlighting the need for personalized therapy approaches that have yet to be significantly explored in the context of NEs. Many research labs may lack the necessary funding, infrastructure, or technical expertise to perform extensive pharmacokinetic studies or to develop large-scale production methods that ensure uniformity and quality in NE formulation. The intricate nature of biological systems makes it challenging to predict how NEs will behave within different patient populations. This complexity may discourage researchers from pursuing these avenues due to the uncertain outcomes and high costs associated with advanced studies. A significant emphasis in current research is placed on the initial efficacy of NEs against specific cancer cell lines.[197] While this is critical for establishing the potential of NEs, it often overshadows the longer-term considerations such as safety, pharmacokinetics, and individualized treatment approaches.

There are a few possible ways to overcome these issues. Future studies should adopt an integrative approach that encompasses formulation, pharmacokinetics, and safety assessments from the outset.[197] This includes collaboration between formulation scientists, pharmacologists, and clinicians to create a more holistic view of how NEs will perform in clinical settings. Establishing standardized protocols for both NE production and characterization can improve reproducibility and comparability across studies, thus fostering a more systematic evaluation of their potential clinical applications. Prioritizing long-term safety studies that could utilize in vivo models to assess potential immune responses and cytotoxicity associated with repeated NE administration is crucial. Such studies would provide critical data necessary for regulatory approvals and clinical trials. Emphasizing personalized approaches could enhance treatment effectiveness. This may involve high-throughput screening of patient-derived models to understand how individual tumor profiles respond to various NE formulations, leading to tailored treatment regimens that consider the unique characteristics of each patient's cancer. By rigorously addressing these caveats, the translation of NE technology into effective clinical therapies for breast cancer could be significantly enhanced, ultimately leading to improved patient outcomes.

Future Research and Development

In the realm of utilizing NEs as carriers for the pharmacological treatment of breast cancer, there are notable challenges that forthcoming research must confront. These challenges encompass the development of multifunctional NEs capable of concurrently delivering chemotherapeutic agents, gene therapy vectors, and immunomodulatory agents. Special attention should be given to the design of NEs that exhibit superior targeting precision, heightened bioavailability, and reduced toxicity. It is also imperative to delve into the synergistic effects of combination therapies delivered through NEs and comprehend the in vivo mechanisms governing drug release for optimal therapeutic outcomes. A crucial aspect of this research is the investigation of the long-term safety and immunological implications associated with repeated NEs-based treatments for breast cancer patients. Furthermore, the integration of artificial intelligence and machine learning for predictive modeling of patient responses holds substantial promise in tailoring treatment regimens to individual patients. Subsequent studies may extend their focus to the application of multifunctional NEs in the context of breast cancer treatment, leveraging advanced analytical techniques and patient-derived models to enable highly personalized therapeutic approaches.

Conclusion

This review highlights the considerable potential of NEs as versatile drug carriers in breast cancer treatment. The unique physicochemical properties of NEs, such as their high surface area, stability, and customizable characteristics, make them strong candidates for improving drug delivery systems. By encapsulating a variety of therapeutic agents, NEs can enhance bioavailability and treatment efficacy while reducing systemic toxicity, a major issue in traditional breast cancer treatments. However, despite promising results, significant challenges remain in optimizing the clinical use of NEs. Future research should focus on developing multifunctional NEs that can deliver a combination of chemotherapeutics, gene therapies, and immunomodulatory agents, while improving targeting accuracy and minimizing off-target effects. Investigating the long-term safety and immunological consequences of repeated NE administration is also critical to ensure that treatments remain both effective and safe for patients. Additionally, the integration of artificial intelligence and machine learning could play a crucial role in personalizing treatment regimens based on individual patient characteristics and tumor profiles. As research in this field advances, standardizing NE formulation and characterization methods will be essential to ensure reproducibility and comparability across studies. Ultimately, the progress of NE technology has the potential to transform breast cancer therapy. With ongoing research and a focus on personalized medicine, NEs could lead to more effective and targeted treatments, improving both patient outcomes and quality of life.

Highlights

- Nanoemulsions (NEs) were synthesized using various homogenization techniques to achieve sub-100 nm droplet sizes.
- Surfactants and predictive models enhanced NE stability, preventing coalescence and extending shelf-life.
- NEs demonstrated targeted drug delivery to breast cancer tumors, reducing systemic toxicity and improving therapeutic efficacy.
- Dual O/W and W/O nanoemulsions systems disrupted tumor microenvironments by inducing apoptosis and inhibiting angiogenesis in preclinical models.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

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