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Review Article:

Nanoemulsions: Synergy Between Intrinsic Antibacterial Activity and Antimicrobial Drug Delivery- A Review

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Abstract

Background: Antimicrobial resistance represents one of the most critical global developmental and public health problems of the modern era. One of the major contributors to multidrug-resistant bacteria (MDR) is biofilm formation, which is the leading cause of chronic infections. Nanoemulsions (NEs)—defined as kinetically stable colloidal dispersions with droplet sizes typically ranging from 20 to 200 nm—have emerged as one of the most versatile platforms for the delivery of antimicrobial drugs over the past two decades. **Aim:** This review critically evaluates the antibacterial mechanisms of both drug-free and drug-loaded NEs, highlighting their dual roles as intrinsic antimicrobial agents and advanced delivery systems that enhance antibiotic efficacy. It further emphasizes the importance of their physicochemical characteristics and underlying mechanisms of action, with particular focus on their potential to address the challenges associated with MDR pathogens. **Methods:** To achieve this aim, a comprehensive search was conducted across the ScienceDirect, Springer, PubMed, National Institute of Health, CrossRef, and Google Scholar, for studies published from 1999 to 2026. The final search was performed on April 3, 2026. **Results:** Evidence indicates that drug-free NEs exert intrinsic antibacterial effects via membrane disruption and biofilm penetration. While drug-loaded NEs serve as advanced delivery platforms that optimize solubility and stability, yielding synergistic therapeutic outcomes. **Conclusion:** NEs represent a significant advancement in antimicrobial therapy due to their dual functionality. They combine inherent antibacterial properties with a high capacity for delivering multiple agents. This ability to load several antibiotics or bioactive substances at once enables powerful synergistic effects that can overcome traditional resistance mechanisms. With their ease of preparation and versatility for co-delivering multiple drugs in various dosage forms, NEs are valuable nanostructured platforms that hold great promise in addressing the global challenge posed by MDR pathogens.

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1. Introduction

Antimicrobial resistance represents one of the most critical global developmental and public health problems of the modern era. The irrational and excessive use of antibiotics has accelerated the emergence and spread of multidrug-resistant (MDR) bacterial strains, resulting in persistent infections, prolonged hospitalization, and increased mortality rates. Alarming, since the 1980s, the discovery and development of new antibiotics have markedly declined and cannot keep pace with the rising rates of antimicrobial resistance, highlighting the urgent demand for advanced drug delivery strategies. Since monotherapy may be insufficient against MDR bacteria,

combination therapy has been used to treat MDR bacterial infections. However, if bacteria show resistance to one antibiotic, resistance may be transmitted to another antibiotic used in such a combination. Moreover, Recent estimates indicate that bacterial MDR infections directly accounted for approximately 1.27 million deaths worldwide in 2019 and contributed to nearly 4.95 million deaths overall (1–5).

One of the major contributors to the development of MDR is biofilm formation, a process in which bacterial communities become embedded within a self-produced extracellular matrix of Extracellular Polymeric Substances (EPS) which help the bacteria to adhere firmly to surfaces, and it is the leading cause of chronic infections, since it act as a barrier against conventional antimicrobial agents (6–8). These biofilms are heterogeneous in nature, and they are usually formed through five main stages, as shown in Figure 1 (9–11).

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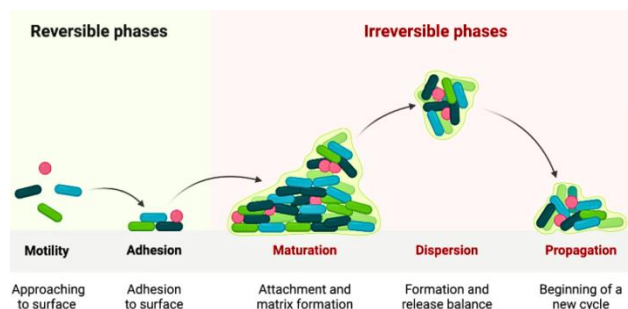


Figure 1. Stages of bacterial biofilm formation

Traditional antibiotics often fail to achieve effective intracellular or biofilm-targeted concentrations due to factors such as poor solubility, enzymatic degradation, and limited permeability through bacterial biofilm layers, thereby promoting the development of resistance. Consequently, higher antibiotic concentrations are often required to eradicate biofilm-associated bacteria, increasing the risk of systemic side effects and toxicity (12,13). In the search for drugs with antimicrobial effects, the secondary metabolites of medicinal plants present a viable option, as they have been reported to possess various biological activities of interest, such as anti-biofilm, anti-inflammatory activities, and can help combat MDR. In fact, most of the available antibiotics have been obtained from medicinal plants or acquired from compounds of natural origin (14,15).

EOs, as secondary metabolites of medicinal plants, possess broad-spectrum biological activities. However, their clinical application is limited by factors such as low solubility, volatility, thermal instability, and susceptibility to oxidation. Nanotechnology-based drug delivery systems have emerged as a promising approach to overcome these limitations by enhancing stability, solubility, and penetration ability, while enabling targeted delivery and

reducing side effects. Nano-drug delivery platforms can be engineered to control their loading, surface characteristics, and droplet size, thereby improving their therapeutic efficacy and overcoming drug resistance (16–19).

These Nanosystems include liposomes, Nanoemulsions (NEs), solid lipid nanoparticles, polymeric nanoparticles, metal nanoparticles, and others, each offering unique advantages for antimicrobial applications (20,21). Among these Nanosystems, NEs have emerged as one of the most versatile platforms for antibacterial drug delivery over the past two decades. NEs are kinetically stable but thermodynamically unstable colloidal dispersions that consist mainly of oil, water, surfactant(s), and/or cosurfactant(s), with droplet sizes typically ranging from 20 to 200 nm (22). This nano-scale size endows it with high surface area, optical transparency, and excellent potential for diverse pharmaceutical and biomedical applications. These systems can be formed by using low-energy methods like the phase-inversion method, but high-energy methods, such as high-speed homogenizers, ultrasonicators, microfluidizers, and high-pressure homogenizers, can still be used for further size reduction of the formed droplets (23–26).

NEs are classified based on their continuous phase. Oil-in-water (O/W) NEs contain oil droplets distributed throughout a continuous aqueous phase, making them ideal for oral and parenteral drug delivery due to their convenient administration and increased patient compliance. Conversely, water-in-oil (W/O) NEs are composed of water droplets dispersed in a continuous oil phase and are mainly used in topical and transdermal formulations. Bicontinuous NEs possess interconnected networks of oil and water stabilized by surfactants, offering improved solubilization for both hydrophilic and lipophilic substances. The fundamental differences between these NE types in addition to Multiple NEs are illustrated in Table 1 (27).

Table 1. Classification of NEs

NE type	Structural characteristics	Dispersed phase	Continuous phase	Pharmaceutical applications
O/W	Oil droplets dispersed within a water phase	Oil	Water	Oral, topical, ocular, and parenteral delivery
W/O	Water droplets dispersed within an oil phase	Water	Oil	Topical formulations and sustained-release systems
Bicontinuous NE	Interconnected water and oil domains forming a continuous network	Both oil and water	Both oil and water	Targeted and controlled drug delivery systems
Multiple NEs (W/O/W or O/W/O)	Droplets encapsulated within larger droplets	Multiple phases	System dependent	For the delivery of peptides, vaccines, and other sensitive agents

NEs systems have stability problems associated with their thermodynamic behavior, so most of these systems are attempted to be stabilized by the addition of surfactant(s), which act to reduce the surface tension at the interface between the two immiscible liquids and prevent droplet coalescence. Compared to conventional emulsions, NEs exhibit superior physical stability, and they require less amount of surfactant than micro-emulsions, making them a practical option as a drug carrier system (28–30). Indeed, the o/w type has gained significant attention as a promising delivery system for antibacterial therapy,

primarily due to its ability to solubilize and encapsulate a large quantity of EOs, protecting them from oxidation, hydrolysis, and evaporation. Moreover, the dispersed oil droplets are readily available to interact with bacterial cell membranes due to their higher surface area, thereby enhancing their stability and biological activity (31–33).

NEs can target MDR bacterial biofilms by interacting with the EPS matrix through methods such as electrostatic attraction, enhanced penetration, and structural disruption. The EPS, which is mainly composed of polysaccharides, proteins, and extracellular DNA (eDNA), typically carries a net negative charge. This allows cationic

NEs to bind effectively to the EPS and accumulate at the biofilm interface. Once attached, the nanosized droplets can penetrate deeply into the biofilm through its hydrated channels. The amphiphilic surfactants present in the NEs disrupt the intermolecular interactions within the EPS, leading to partial destabilization of the matrix and increased permeability. These combined effects enhance the penetration and retention of antimicrobial agents within biofilms, ultimately improving therapeutic efficacy (34–36).

A closely related system to NEs is the self-nanoemulsifying drug delivery system (SNEDDS). These isotropic formulations are made up of oils, surfactants, and co-surfactants, and they spontaneously create fine oil-in-water NEs when diluted in the gastrointestinal environment with mild agitation. SNEDDS are particularly noted for enhancing the aqueous solubility and oral absorption of lipophilic drugs, owing to their high solubilization capacity and superior thermodynamic stability compared to conventional metastable emulsions (Figure 2) (37,38). Although the mechanisms of formation for SNEDDS and NEs differ, both systems are considered in this review due to their overlapping functional applications and shared advantages in improving drug delivery performance.

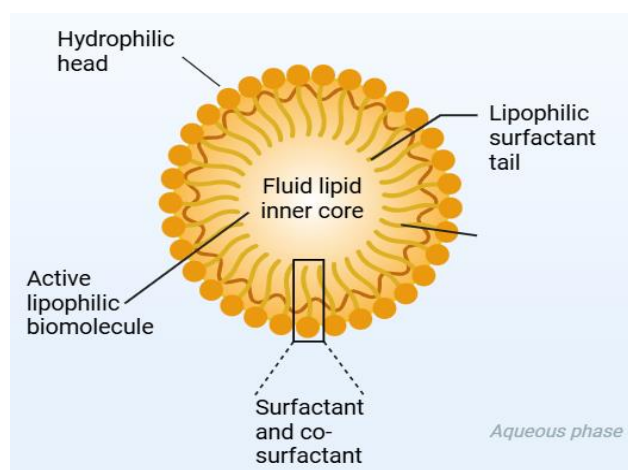


Figure 2. Components of SNEDDS

2. Methodology

A comprehensive search was conducted across several databases, including ScienceDirect, Springer, PubMed, the National Institutes of Health, CrossRef, and Google Scholar, for studies published from 1999 to 2026. The final search was performed on April 3, 2026. Only primary peer-reviewed articles published in English were included in the review. The following search terms were used to identify relevant studies: "nanoemulsion with intrinsic antibacterial activity," "Essential oils-based nanoemulsion for antibacterial activity," "natural substance-loaded nanoemulsion for antibacterial activity," "nanoemulsion loaded with conventional antibiotics," and "dual-loaded nanoemulsion for enhancing antibacterial activity." To be included, a study had to be connected to "nanoemulsion with antibacterial activity" and provide scientifically valid findings with credible references. Studies published in languages other than English were excluded, as were those that did not delve deeply enough into the condition or its formulations. Overall, this review encompasses 35 studies,

including 35 *in vitro* investigations, 10 *in vivo* studies, and one *in silico* study.

3. Research outcomes regarding the role of NEs in antibacterial therapy

In the following sections, we critically integrated major contributions in NEs-based antibacterial strategies, focusing on mechanisms, formulations, experimental outcomes, prevailing constraints, and limitations across various studies conducted until now. Numerous experimental studies have demonstrated that NEs possess intrinsic antimicrobial and/or antibacterial properties even in the absence of conventional antibiotics or natural bioactive payloads. This inherent activity is primarily driven by the electrostatic interaction between the cationic charged NE droplets and the negative charge of the bacterial surface (39). In addition to its small droplet size, which results in a greater surface area available for interaction with targets in the bacterial cell (40). Moreover, surfactants used in their emulsification significantly augment their antibacterial efficacy by facilitating close interaction with bacterial cell membranes, improving droplet dispersion, and permeability. In the case of ionic surfactants, they can directly disrupt membrane integrity and cause leakage of intracellular components, resulting in superior anti-biofilm activity (Figure 3) (40,41).

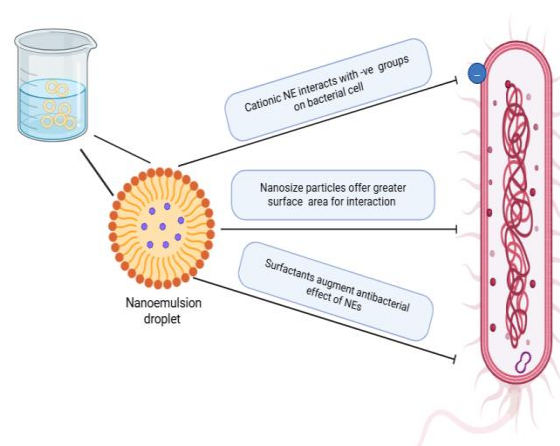


Figure 3. Illustrates intrinsic antibacterial activities of NEs

The concept that NEs can exhibit intrinsic antimicrobial activity, independent of any encapsulated antibiotic or natural compound, emerged from pioneering studies by Hamouda and coworkers, who published a landmark study demonstrating the sporicidal activity of a novel surfactant-based NEs against *Bacillus anthracis*. Their formulation consisted of a lipid-surfactant mixture forming small droplets within the nano-range, which acted not as carriers but as the active agent. The NE was shown to inactivate spores rapidly and effectively, without requiring elevated temperature or harsh chemical concentrations. The mechanism was attributed to the NE's ability to penetrate the spore coat and disrupt its structural integrity, thereby preventing its viability. This study was among the first to highlight the potential of NEs for antimicrobial applications (41).

Subsequent work by Donovan et al. investigated the prevention of influenza A virus pneumonitis using two surfactant-based NE formulations, made from soybean oil,

tributyl phosphate, and Triton X-100, which were tested *in vivo*. Their results extended the antimicrobial mechanism from bacteria to enveloped viruses. Mice treated intranasally with the NEs exhibited complete protection from lethal viral effects, with reduced pulmonary pathology and viral titers. Importantly, no irritation or cytotoxicity was observed, supporting the mucosal safety of the formulations and highlighting their potential use as both antiviral prophylactic and vaccine adjuvant (42).

In the same year, Hamouda and Baker investigated the mechanisms underlying the antimicrobial action of two surfactant-lipid preparations; the first was a w/o emulsion, and the second was a liposomal preparation. Both formulations demonstrated potent bactericidal activity against gram-positive and non-enteric gram-negative species. Interestingly, when EDTA and Tris buffer were added, a marked enhancement in bactericidal activity against gram-negative bacilli was observed. This enhancement was attributed to EDTA-induced disruption of the bacterial outer membrane through chelation of divalent cations, which destabilize lipopolysaccharide layers. Moreover, the addition of excess calcium ions inhibited this effect, confirming the role of cation removal in the antimicrobial mechanism (43).

Following their exploration of surfactant lipid preparations, Hamouda and his colleagues expanded upon these foundational findings by evaluating the broad-spectrum antimicrobial and antiviral efficacy of their optimized surfactant-based NE formulations. In this study, a specific NE formula was prepared as described previously by Hamouda et al. 1999. Briefly, an oil phase was made by mixing different volumes of tributyl phosphate, soybean oil, and Triton X-100, formulated as an O/W NE system within the nano-range. The resulting formula produced rapid bactericidal activity within 15 minutes against many gram-positive species; by contrast, most enteric gram-negative bacteria displayed resistance to the formula under the same conditions. The formulation also displayed remarkable activity against enveloped viruses and fungi. Importantly, the authors demonstrated low toxicity in animal models at bactericidal concentrations, supporting the feasibility of topical application (44).

Collectively, these findings provide clinical mechanistic insights into surfactant-mediated biocidal activity, laying out the foundation for the rational design of next-generation NE-based antimicrobials with broader and more predictable spectra of action. In a landmark study conducted in the year 2000, Al-Adham and colleagues established foundational evidence for the intrinsic antimicrobial activity of both nano- and micro-emulsions. The team formulated an O/W micro-emulsion system of ethyl oleate emulsified by Tween 80 and n-pentanol and demonstrated its remarkable antimicrobial potency. The formulation achieved a 5-log reduction of *Staphylococcus aureus* and *Pseudomonas aeruginosa* populations within just 45 seconds, and approximately 90% microbial reduction in only 15 seconds (45).

In a subsequent study, the same authors reported that this micro-emulsion also exhibited strong anti-biofilm activity against *Pseudomonas aeruginosa*, effectively disrupting established biofilm structures and reducing viable cell counts (46). In a later work, Teixeira et al. evaluated the intrinsic antimicrobial properties of both micro-emulsions and NEs against various foodborne pathogens. In this study, two fine emulsion systems were prepared; the first was an O/W NE of soybean oil and tri-n-butyl phosphate emulsified with Triton X-100, while the second was a micro-emulsion of ethyl oleate with Tween 80 and n-pentanol as an emulsifier and a co-emulsifier, respectively.

Both formulations were assessed for their capacity to disrupt preformed biofilms, and they showed enhanced antibacterial activity with some variability. These findings underscore the broad biocidal potential of surfactant-stabilized nano- and micro-emulsions, highlighting that their physicochemical properties, particularly surfactant type, oil composition, and droplet size, play crucial roles in determining their spectrum of antimicrobial and anti-biofilm activity (47).

3.1. EO-based NEs for antibacterial activity

The following studies increasingly focus on incorporating EOs into NEs. EOs contain diverse bioactive constituents known for their broad-spectrum antimicrobial and antibiofilm activity. Incorporating EOs in NEs not only enhances their aqueous solubility and chemical stability but also improves their bioavailability, cellular interaction, and biofilm penetration (48,49). A notable contribution to the construction of EO-based NEs is the work of Zhao and his colleagues, who prepared a SNEDDS to enhance the oral delivery of Zedoary turmeric oil (ZTO), an EO with antibacterial activities. The optimized formula allowed for a high loading of (30%) ZTO, produced highly stable NE, with enhanced aqueous solubility, and oral bioavailability of ZTO, features that boost their antibacterial activities (50). Cinnamon oil NE was formulated by Ghosh and his colleagues using Tween 80 and water via ultrasonic emulsification. The formulation was optimized by adjusting surfactant concentration, oil-to-surfactant ratio, and emulsification time. An inverse relationship was observed between surfactant concentration and droplet size, while stability improved with increasing surfactant levels. Prolonged sonication reduced droplet diameter, yielding an optimized NE with a mean size of approximately 65 nm. This optimized formulation demonstrated significant bactericidal activity against *Bacillus cereus*, exhibiting time- and concentration-dependent killing effects. These results highlight the strong antimicrobial potential of cinnamon oil NE for various antimicrobial applications (51). Anwer and his colleagues employed a pseudo-ternary phase diagram by the aqueous titration method to identify NE regions. By using triacetin oil to which clove oil was added, and tween 80 and labrasol as surfactant and co-surfactant, respectively, a clove oil NE was constructed whose activity was higher relative to pure clove oil across all tested bacterial strains and showed a comparable efficacy to amikacin (52).

Research by Li et al. focused on the development of Finger citron EO into NE to enhance its antimicrobial effect. Using different surfactants and co-surfactants to formulate five different NE formulations, followed by physicochemical characterization. Antimicrobial investigation suggested enhanced antibacterial activity, especially formulations containing Cremophor, but antifungal activity was weak for NE formulations. These results suggest the potential use of Finger citron-based NEs for antibacterial applications (53). Roya Moghimi and his colleagues tested the antibacterial and antibiofilm activity of Thymus daenensis EO, as a NE formula, and as pure oil against MDR bacteria *A. baumannii*. The stable NE of the EO was prepared using Tween 80 and lecithin as a surfactant and co-surfactant, respectively. The resulting NE particles were within the nano-range and had a spherical, monodispersed, and uniform structure. Overall, antibacterial results indicated that the NE formula of *T. daenensis* EO showed enhanced activity against many *A. baumannii* isolates, with a notable

anti-biofilm performance that exceeds that of several commonly used conventional antibiotics (54).

EO from the *Alhagi maurorum* plant was extracted by Hassanshahian et al. and formulated as a NE to which chitosan was incorporated as a nano-carrier. Antibacterial studies against six MDR bacterial strains showed enhanced effect as compared to free EO, indicating anti-biofilm activity of the resulting NEs. Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration for Biofilm (MBCB) were also examined and showed the highest MIC result against *A. baumannii* and the lowest for *E. coli*. Importantly, these NEs showed a better ability to cure and eliminate the R-plasmid of three MDR bacteria (55). The self-nanoemulsifying technique was used to formulate a nanoemulgel of coriander sativum oil by Ahmad M. Eid and his colleagues. The nano-system was first prepared by using a mixture of Tween-80 and Span-80, then the hydrogel Carbopol 940 was incorporated and mixed with the nano-system to make the final formulation. Antimicrobial assay showed enhanced activity against *P. aeruginosa*, *K. pneumoniae*, and MRSA. In addition to anticancer effects against breast cancer cells in humans. As compared to crude oil, *C. sativum* oil nanoemulgel had a better bioactive profile, suggesting a promising preparation for various pharmaceutical applications (56).

Eugenol-based NEs were formulated by Fu et al. to overcome their low water solubility and high volatility. NEs were prepared by a high-speed homogenizer, and an optimized formula was selected based on visual inspection, dynamic light scattering, and a laser scanning microscope. The resulting NEs exhibited strong antibacterial activity against *S. aureus* and *E. coli*, as observed by scanning electron microscopy (SEM). Further mechanistic assays revealed that NEs exposure induced elevated reactive oxygen species (ROS) and triggered lipid peroxidation. Importantly, cytotoxicity assays indicated minimal effects on cell viability, proliferation, and apoptosis, demonstrating good biocompatibility of the formulation, highlighting its promise as a therapeutic candidate for wound healing and other medical uses (57).

3.2. Natural substances loaded NEs for antibacterial activity

Natural bioactive compounds, including bee propolis (BP), are well known for their anti-microbial, anti-inflammatory, and antioxidant properties. BP is rich in phenolics, flavonoids, and aromatic metabolites that confer strong antibacterial and antibiofilm properties (58,59). Multiple recent studies have confirmed that encapsulating BP in the NE system significantly improves its antibacterial activity against a broad spectrum of pathogens when compared with crude propolis extracts. For example, an Indonesian propolis extract-loaded-SNEDDS showed enhanced antibacterial activity against *E. coli* and *S. aureus* as compared to that of BP alone (60). And propolis extract NE developed through the phase-inversion method from Brazilian propolis maintained its antimicrobial and antioxidant activity under thermal stress and centrifugation, demonstrating stability and potential for food preservative use (61). On the other hand, Maroof and coworkers aimed to enhance the oral delivery and palatability of BP by encapsulating it in a micro-emulsion using the water titration method. Overall, a stable and orally effective system that maintained antimicrobial activity was achieved (62). Propolis NEs also showed a promising combination with conventional antibiotics. Kazemi et al. reported that a propolis NE enhanced activity

against MDR *P. aeruginosa* and acted synergistically with ciprofloxacin antibiotic to reduce viable count and biofilm biomass compared with either agent alone (63).

Beyond BP, numerous natural compounds have been successfully incorporated into NEs to enhance their antibacterial activity. Donsi et al. constructed multiple O/W NEs of carvacrol, limonene, and cinnamaldehyde in sunflower oil droplets. NEs were prepared using a high-pressure homogenizer to make four different formulations by utilizing different emulsifiers. The resulting NEs showed an enhanced antimicrobial activity, which was attributed to increased aqueous solubility, suggesting that a higher dissolved concentration of the active compound in aqueous media is directly correlated with the active compound's increased ability to interact with the cell membrane in a partitioning-dependent manner (64).

More recently, Confessor et al. aimed to overcome poor aqueous solubility and low bioavailability of curcumin by entrapping curcumin within an olive-oil-based NE to enhance its antimicrobial efficacy against MDR bacteria. These NEs, produced via ultrasonication, contain olive oil and the surfactants tween 80 and span 80, and water, and were stable for 120 days. These curcumin-NEs exhibited strong antibacterial activity, and the interaction between these NEs and ceftazidime displayed synergistic effects against *Klebsiella pneumoniae* isolates (65).

3.3. Antibiotic-loaded NEs

A large body of research has focused on utilizing NEs as a carrier to improve the pharmacological performance of conventional antibiotics. One of the most clinically relevant applications is the eradication of *H. pylori*, since treatment by conventional antibiotics is limited due to inadequate gastric residence time and poor basolateral absorption, factors that limit reaching therapeutic levels at the infection site. Lin et al formulated positively charged NEs particles of amoxicillin, chitosan, and heparin by using an O/W emulsification method. By optimizing the surfactant combination (span-20 and tween-20), spherical NE particles were prepared that are capable of effectively encapsulating hydrophilic amoxicillin. The developed NE exhibited stability at PH 1.2, enabling sustained release of amoxicillin in simulated gastrointestinal fluid. Cellular localization analyses demonstrated that the NE system preferentially accumulated at intercellular junctions and within the cytoplasm, corresponding to the typical colonization sites of *H. pylori*. *In vitro* investigations revealed significant inhibition in bacterial growth when compared to the free antibiotic. Furthermore, *in vivo* studies showed that the NE-loaded amoxicillin achieved markedly greater *H. pylori* clearance in infected mice than the conventional drug, underscoring its promise for improved therapeutic efficacy and targeted drug delivery (66).

Another contribution to antibiotic-loaded NE was by Vatsraj et al. and coworkers, who developed an O/W NE system to enhance the solubility and bioavailability of clarithromycin. By combining Tween 80 and olive oil, researchers achieved a therapeutic drug concentration of the loaded antibiotic. Antibacterial testing showed that the optimized formulation produced a significantly larger inhibition zone than free clarithromycin, attributed to improved solubility and bioavailability. These findings

highlight the NEs' promise as an effective carrier for poorly soluble antibiotics (67).

Mennatallah A. Mohamed et al., addressed the emergence of antibiotic resistance to conventional antibiotics like linezolid, doxycycline, and clindamycin by formulating them as NEs and examined their antimicrobial and cytotoxic activities against *Staphylococci*. As compared to free antibiotics, doxycycline and linezolid NEs exhibited enhanced antibacterial activities. By contrast, clindamycin, when encapsulated as NE, showed poor antibacterial activity toward bacterial isolates. This study manifested that when antibiotics are formulated as NEs, they show lower cytotoxicity and higher antimicrobial activity (68).

A key advancement in antibiotic-loaded NEs is their application in ocular drug delivery for bacterial keratitis. Mehanna et al. developed a levofloxacin-loaded limonene-based *situ* nano-emulgel, formulated with limonene, tween 80, and propylene glycol. The optimized formula exhibited superior eradication of MRSA biofilms and a high safety profile when compared to saline controls (69). Bacterial keratitis was also addressed by Youssef et al., who developed a ciprofloxacin-loaded NEs to overcome the low solubility of the antibiotic at physiological PH. By using hot homogenization and ultrasonication, with oleic acid or Labrafac as the oil phase, the optimized formula exhibited favorable properties and provided sustained drug release with a 2.1-fold increase in trans-corneal permeation as compared with commercial ciprofloxacin. These studies suggest the potential of antibiotic-loaded NEs for treating bacterial keratitis with enhanced biological activities (70).

On the other hand, Anwer and coworkers tried to solve the poor solubility and oral bioavailability of the newly potent and broad-spectrum fluoroquinolone antibiotic, delafloxacin by formulating it as SNEDDS. In this research four different formulations were prepared and fully characterized; among them, only one emerged as the ideal formula due to having optimum features. Microbiological studies showed enhanced antibacterial activity against both gram-positive and gram-negative species, with no signs of resistance (71).

The application of NEs was markedly used to enhance the therapeutic potential of Levofloxacin, as demonstrated previously by Mehanna and coworkers. A comparable work was conducted by Razdan et al., who formulated a levofloxacin-loaded clove-oil NE, which represents a strategic designation that encompasses both the pharmacological action of levofloxacin and the well-documented antibiofilm activity of clove oil. Pseudo-ternary phase diagrams were developed using the aqueous titration method to identify the optimized NE areas. Solubility studies of levofloxacin guided the selection of Tween-80 as the surfactant and PEG-300 as the co-surfactant. The incorporation of levofloxacin into NE improved its solubility and stability while markedly boosted antibacterial activity against key wound pathogens. In addition, the formulation effectively disrupted *P. aeruginosa* biofilms and suppressed quorum-sensing pathways, demonstrating both antimicrobial and anti-virulence effects (72).

Ofloxacin-loaded castor oil-based NE was fabricated by using mechano-chemical procedures and comprehensively characterized. Antimicrobial study against *P. aeruginosa* showed that the ofloxacin-loaded NE had an enhanced antibacterial effect when compared to the free antibiotic, as demonstrated by larger zones of inhibition. Pharmacokinetic studies were also conducted and revealed a controlled release pattern with maximum concentration achieved at 150 min (73). Building on this concept, the same author formulated a PEGylated NE by using sesame oil as the dispersed phase. Their formulation, prepared via

spontaneous emulsification, produced a non-drug-loaded NE and ciprofloxacin-loaded NE formulations. Antimicrobial assays revealed that the ciprofloxacin-loaded sesame oil NE produced larger inhibition zones and lower MIC than the free antibiotic at comparable concentrations. Moreover, dermal and systemic toxicity studies showed no significant adverse effects in Wistar rats (74).

On the other hand, Elabed et al. formulated amoxicillin-loaded oleic-acid-based NE by utilizing a modified spontaneous emulsification process mixed with ultrasonication. Oleic acid as the organic phase was added in dropwise to the aqueous phase, which contained amoxicillin dissolved in deionized water and tween-80, and mixed using a magnetic stirrer, followed by ultrasonication and filtration, producing stable, semispherical particles within the nano-range. *In vitro* assay against MDR *S. typhimurium* demonstrated a 2.3-fold improvement in antibacterial activity; computational methods, including molecular docking and molecular dynamics simulation, revealed a stable and high-affinity binding of the resulting formula with the target pocket of penicillin-binding protein. Furthermore, *in silico* analyses showed enhanced intestinal absorption and reduced hepatotoxicity. These results provide compelling mechanistically informed rationales for employing oleic acid-based NEs to overcome bacterial resistance (75).

3.4. Dual-and-multiple loaded NEs for antibacterial activity

NEs, being a biphasic system, inherently bear the ability to occupy diverse compounds either in oil and/or aqueous phases. Utilizing these unique advantages inspires researchers to focus on loading the NE with multiple agents with potential synergistic action on bacterial biofilm and/or combating bacterial resistance. Nabawy et al. Introduced biodegradable polymeric O/W NE co-encapsulating two hydrophobic antimicrobials, eugenol and triclosan, as a dual-loaded therapeutic strategy for chronic wound management caused by biofilm-forming MDR bacteria. He constructed an NE with a cationic charge for effective penetration and accumulation within MDR bacterial biofilm. This NE system showed high biocompatibility and notably delayed the emergence of triclosan resistance. In-vivo study on murine models of established MDR wound biofilm infections demonstrated a 99% reduction in bacterial population (76).

Similarly, Zhang et al. created a SNEDDS co-encapsulating Colistin antibiotic with Niclosamide, an old FDA-approved anthelmintic. The SNEDDS produced very small droplets that greatly improved Niclosamide solubility. *In vitro*, Colistin in the dual-loaded SNEDDS showed 16-128-fold enhanced activity against Colistin-resistant *Salmonella* isolates, as compared with free Colistin. The dual-loaded system exhibited significant therapeutic efficacy in a murine intraperitoneal infection model involving colistin-resistant *Salmonella*. Collectively, these results suggest a promising synergy between Niclosamide and Colistin for the treatment of Colistin-resistant *Salmonella* infections (77).

NEs not only improve the performance of single or dual-loaded formulations but also potentiate complex mixtures; a concept that was proven by Soulaïmani and coworkers in their 2022 study, who evaluated the synergism of an EOs mixture of *Ammodaucus leucotrichus* Cosson, *Thymus vulgaris* L., and *Lavandula maroccana*. The three EOs were mixed and formulated as O/W NEs and produced a strong synergistic effect against MDR bacteria. Moreover, when

conventional antibiotics like gentamycin and amoxicillin were combined with this NEs mixture, a markedly stronger antibacterial effect and a significant decrease in MICs of both antibiotics were observed (78).

Combinational delivery of both hydrophobic and hydrophilic first-line anti-TB drugs rifampicin, isoniazid, pyrazinamide, and ethambutol was formulated by Menon and colleagues as a multi-drug-loaded eugenol-based O/W NE to improve efficacy against *Mycobacterium tuberculosis*. The formulation of NE was performed by constructing a pseudo-ternary diagram, then the formulations were systemically optimized by using a highly complex computational method and were subsequently used as carriers for drug loading. Rifampicin (1 mg/mL), as a hydrophobic drug, was incorporated into the oil phase, whereas the hydrophilic drugs—ethambutol, isoniazid, and pyrazinamide (each at 1 mg/mL)—were dissolved in the aqueous phase. The drug-containing oil and aqueous phases were then emulsified to obtain the final drug-loaded NEs, which achieved synergistic inhibition against resistant *Mycobacterium tuberculosis* strains, while demonstrating good stability and controlled release (79).

4. Challenges, limitations and summary

Despite their therapeutic potential, the widespread application of NEs is constrained by key challenges, including long-term stability, safety concerns related to surfactants, scalability of production, and unresolved regulatory considerations. For the former one, NEs may show kinetic stability, but they are thermodynamically metastable. This inherent instability makes them prone to various destabilization pathways over time, including coalescence, flocculation, creaming, and Ostwald ripening, which can ultimately result in phase separation. Furthermore, chemical instability presents a significant challenge, particularly for labile drugs prone to hydrolysis or oxidation within the NE's dispersed phase. To maintain long-term stability, it is essential to rigorously optimize the formulation, specifically through the strategic selection of surfactants, co-surfactants, and antioxidants to protect sensitive payloads from environmental degradation (80,81). Another significant challenge is the dose-dependent toxicity resulting from the high concentrations of surfactants and cosurfactants needed to stabilize nanoemulsions. While these components, such as polysorbates and polyethylene glycol (PEG) derivatives, are essential for maintaining the interface, they can induce cytotoxicity, hemolysis, and localized irritation when their levels exceed certain thresholds (82). The industrial scalability of NEs remains a major challenge due to trade-offs between manufacturing approaches. High-energy techniques, such as high-pressure homogenization and ultrasonication, enable precise control of droplet size but are associated with high costs, significant energy requirements, and difficulties in maintaining batch-to-batch consistency at large scale. In contrast, low-energy methods, like spontaneous emulsification, are more cost-effective and scalable but often provide limited formulation flexibility and reduced long-term stability. Consequently, successful scale-up necessitates stringent process control and extensive optimization to ensure consistent product quality (83).

Finally, regulatory constraints remain a significant barrier to the clinical translation of NE-based delivery platforms. The absence of global regulatory authority and standardized analytical protocols makes it difficult to objectively assess their safety, therapeutic efficacy, and pharmaceutical quality. Additionally, obtaining regulatory

approval requires rigorous empirical evidence demonstrating excipient biocompatibility, long-term physicochemical stability, and batch-to-batch reproducibility. These factors are essential to meet the stringent criteria for clinical approval (84). Overall studies discussed in this review are summarized in Table 2, which outlines the advantages and limitations of each included study individually. Focusing on the ability to occupy active materials, together with the stability of the formulation, and the enhancement of antibacterial activity, in addition to study type, bacterial strains, and assay methods. **This table is uploaded as a Supplementary Materials file.**

5. Conclusion

NEs represent a significant advancement in antimicrobial therapy due to their dual-functional characteristics. They not only serve as versatile carriers that improve the solubility and targeted delivery of antimicrobial agents, but they also possess substantial intrinsic antibacterial activity derived from their structural nature. This inherent antibacterial potency, especially when combined with EOs, helps to overcome traditional resistance mechanisms through various synergistic effects. Furthermore, the incorporation of natural or synthetic antimicrobial agents into the droplets of NE significantly improves their effectiveness against MDR pathogens by enhancing their ability to disrupt bacterial biofilms. One of the key benefits of NEs is their capacity to co-encapsulate multiple antibiotics or bioactive agents, facilitating synergistic interactions that further potentiate antimicrobial activity and broaden the spectrum of action. With their ease of preparation, ability to co-deliver multiple drugs, and adaptability to various dosage forms, NEs are positioned to become valuable nanostructured platforms that could help address the global challenge of antibiotic resistance.

The authors highlight a significant advancement in the field with the shift towards utilizing NEs as both intrinsic antibacterial agents and advanced drug delivery systems. Notably, the ability to create dual- or multi-loaded NEs holds great potential for enhancing antimicrobial effectiveness against MDR bacteria. This approach can also allow for dose reduction through synergistic effects. By co-delivering agents with complementary mechanisms, these systems can improve therapeutic outcomes and reduce the risk of developing resistance. However, this approach comes with additional complexities, such as challenges related to formulation stability, potential drug-drug interactions, and reproducibility of performance. Therefore, while multi-loaded NEs show promise as a strategy, their clinical relevance will depend on careful optimization, validation of the underlying mechanisms, and thorough safety evaluations.

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المستحلبات النانوية: التآزر بين النشاط المضاد للبكتيريا الذاتي وإيصال الأدوية المضادة للميكروبات - مراجعة

الخلاصة:

المقدمة: تُعد مقاومة المضادات الحيوية من أخطر المشكلات التنموية والصحية العامة على مستوى العالم في العصر الحديث. ويُعدّ تكوّن الأغشية الحيوية أحد العوامل الرئيسية المساهمة في ظهور البكتيريا المقاومة للأدوية المتعددة، وهو السبب الرئيسي للعدوى المزمنة. وقد برزت المستحلبات النانوية - التي تُعرّف بأنها تشتتات غروائية مستقرة حركياً، يتراوح حجم قطراتها عادةً بين 20 و200 نانومتر - كإحدى أكثر المنصات تنوعاً لإيصال الأدوية المضادة للميكروبات خلال العقود الماضية. **الهدف:** تُقيم هذه المراجعة بشكل نقدي الآليات المضادة للبكتيريا لكل من المستحلبات النانوية الخالية من الأدوية والمحملة بها، مُسلطة الضوء على دورها المزدوج كعوامل مضادة للميكروبات ذاتية وأنظمة إيصال متطورة تُعزز فعالية المضادات الحيوية. كما تُؤكد على أهمية خصائصها الفيزيائية والكيميائية وآليات عملها الأساسية، مع التركيز بشكل خاص على قدرتها على مواجهة التحديات المرتبطة بمسببات الأمراض المقاومة للأدوية المتعددة. **الأساليب:** لتحقيق هذا الهدف، أُجري بحث شامل في قواعد بيانات ScienceDirect و Springer و PubMed والمعاهد الوطنية للصحة و CrossRef و Google Scholar، للدراسات المنشورة بين عامي 1999 و2026. أُجري البحث النهائي في 3 أبريل 2026. **النتائج:** تشير الأدلة إلى أن الجسيمات النانوية الخالية من الأدوية تُظهر تأثيرات مضادة للبكتيريا جوهريّة من خلال تعطيل الأغشية واختراق الأغشية الحيوية. بينما تعمل الجسيمات النانوية المحملة بالأدوية كمنصات توصيل متطورة تُحسن الذوبان والاستقرار، مما يؤدي إلى نتائج علاجية تآزرية. **الاستنتاج:** تُمثّل الجسيمات النانوية تقدماً كبيراً في العلاج المضاد للميكروبات نظراً لوظيفتها المزدوجة. فهي تجمع بين خصائص مضادة للبكتيريا متصلة وقدرة عالية على توصيل عوامل متعددة. تُمكن هذه القدرة على تحميل العديد من المضادات الحيوية أو المواد النشطة بيولوجياً في أن واحد من تحقيق تأثيرات تآزرية قوية قادرة على التغلب على آليات المقاومة التقليدية. بفضل سهولة تحضيرها وتعدد استخداماتها في توصيل أدوية متعددة بأشكال جرعات مختلفة، تُعدّ الجسيمات النانوية منصات قيمة ذات بنية نانوية واعدة في مواجهة التحدي العالمي الذي تُشكّله مسببات الأمراض المقاومة للأدوية المتعددة.

الكلمات المفتاحية: المضادات الحيوية، التحميل المزدوج، الزيوت العطرية، مقاومة الأدوية المتعددة، التآزر